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Investigational therapies targeting CD37 for the treatment of B-cell lymphoid malignancies

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ABSTRACT

Introduction: While chemotherapy still remains a cornerstone of oncologic therapy, immunotherapy with monoclonal antibodies has steadily improved the treatment strategy for several hematologic malignancies. New treatment options need to be developed for relapsed and refractory non-Hodgkin lymphoma (NHL) patients. Currently, novel agents targeting specific molecules on the surface of lymphoma cells, such as anti-CD37 antibodies, are under considerable investigation. Here we report on anti-CD37 targeting for the treatment of patients with B-cell NHL.

Areas covered: CD37 seems to be the perfect therapeutic target in patients with NHL. The CD37 antigen is abundantly expressed in B-cells, but is absent on normal stem cells and plasma cells. It is hoped that anti-CD37 monoclonal antibodies will increase the efficacy and reduce toxicity in patients with both newly diagnosed and relapsed and refractory disease. Recent clinical trials have shown promising outcomes for these agents, administered both as monotherapy and in combination with standard chemotherapeutics.

Expert opinion: The development of new therapeutic options might help to avoid cytotoxic chemotherapy entirely in some clinical settings. This article presents the latest state of the art on the new treatment strategies in NHL patients. It also discusses recently approved agents and available clinical trial data.
**Article highlights**

- The understanding of the processes and pathways responsible for NHL-cell proliferation, survival and resistance has recently grown considerably.
- CD37 is a promising target for novel emerging therapeutics used in the treatment of NHL.
- Novel agents targeting CD37, including RIT, offer hope for future treatment in various NHL subtypes.
- The majority of novel mAbs are selective and have mild or unique toxicity profiles.
- Although impressive responses have been observed in NHL, the integration of novel therapies into drug combinations offers the most promise.
1. Introduction

The term non-Hodgkin lymphoma (NHL) is used to describe a heterogeneous group of malignant diseases with widely varying characteristics and clinical outcome. The annual incidence of new cases is 19.5 per 100,000 men and women, and this number has steadily risen over the past three decades [1]. The most common age of diagnosis is around 70 years old [1]. While some aggressive types of NHL can be cured with standard chemotherapeutics combined with immunotherapy, still a large group of patients will continue to relapse or will be refractory from the time of diagnosis [2].

Various strategies involving different targets have been developed, or are currently in the development stage. In recent decades, immunotherapy for NHL has rapidly evolved due to the success of rituximab, a chimeric mouse-human monoclonal antibody (mAb) directed against CD20. As a result, additional therapeutic mAbs have been developed for NHL treatment [3]. NHL conditions are malignant diseases that typically express B-cell antigens, including CD37, and these represent an attractive therapeutic target. The CD37 antigen is abundantly expressed in B-cells, but is absent on normal stem cells and plasma cells. Anti-CD37 mAbs have been recently investigated as monotherapy and in combination with standard of care and emerging therapies, and have been found to have high efficacy in NHL diagnosis.

This article discusses novel therapies using the anti-CD37 mAb with a promising outcome in NHL patients.

2. Biological role of CD37

CD37 is a member of the transmembrane 4 superfamily (TM4SF) of tetraspanin proteins. It consists of four potential membrane-spanning regions, two extracellular loops and short intracytoplasmatic tails [4]. CD37 forms complexes with other tetraspanins, such as CD53, CD81, CD82 and class II glycoprotein, on the surface of B-cells, which might represent an ion channel or transporter [5]; this results in the formation of multiprotein complexes called tetraspanin microdomains, also known as tetraspanin webs, on the cell surface.

CD37 is expressed on developing B-cells from pre-B peripheral mature B-cell stages, but not on plasma cells. T-cells, natural killer (NK) cells and monocytes express CD37 but the level of this antigen is very low. CD37 is not present on erythrocytes and platelets [6]. What is more, the CD37 antigen can be found on B-cell endosomes and exosomes, reflecting possible involvement in intracellular trafficking or antigen presentation [7].

In a healthy organism, CD37 is responsible for interaction with various molecules, including phosphoinositide 3-kinase (PI3K) γ and δ, spleen tyrosine kinase (Syk), tyrosine-protein kinase (Lyn), CD19, CD22, SHP1, Interleukin 6 receptor (IL6R), suppressor of cytokine signaling 3 (SOCS-3),
CD82, major histocompatibility complex (MHC) class II, and different integrins such as integrin $\beta 1$, $\beta 2$, $\beta 3I$ and $\beta 7$ [8]. The exact function of CD37 is still unknown, but it might be involved both in prosurvival and proapoptotic signaling (Figure 1).

CD37-deficient mice present defects in various arms of the immune system, such as impaired antibody responses, increased antigen presenting capacity by dendritic cells and T-cell proliferation [9]. Moreover, CD37 has been observed to play a role in signal transduction pathways responsible for affecting cell development, activation and motility [10]. However, older mice without CD37 expression develop germinal center derived B-cell NHL due to the absence of negative feedback on the interleukin 6 (IL6)/signal transducer and activator of transcription 3(STAT3) signaling pathway [11].

3. Biological effect of inhibiting CD37

After administration, anti-Cd37 mAbs act both to activate the immune system to induce antibody-dependent cell-mediated cytotoxicity (ADCC) against CD37-overexpressing tumor cells and to induce apoptosis in the cancer cells [12]. It was observed that CD37 plays a complex role in T-cell responses. In in vitro studies, it was found that CD37$^{-/-}$ dendritic cells are hyperstimulatory toward T-cells, and that CD37 negatively regulates peptide-MHC presentation [13,14]. What is more, CD37 in T-cells might have a negative regulatory role in T-cell receptor (TCR) signaling. T-cells without CD37 are able to proliferate more rapidly in response to TCR stimulation. However, in vivo studies found that mice without CD37 expression are more susceptible to infection with murine malaria and fail to reject syngeneic cancer cells transfected to express a foreign antigen [15,16]. The differences between the two sets of experiments suggest that CD37-negative dendritic cells might have impaired migratory and adhesion abilities. It is still unknown whether the hyperproliferative phenotype of CD37-negative T-cells is important only in in vitro studies, but mice that are CD37$^{-/-}$ with wildtype dendritic cells did not seem to enhance the number of T-cells that produce interferon gamma (IFN$\gamma$) relative to wildtype mice [17].

4. CD37 in vitro studies

Following the discovery of its expression pattern in NHL, CD37 became one of the first antigens to be investigated as a therapeutic target. The 1980s saw the first clinical studies exploring the 131I MB-1 radioimmunoconjugate [18]. Later, a renewed interest in CD37 resulted in the performance of new studies regarding the development of naked mAb (BI 836826), small modular immunopharmaceuticals (TRU-016/Otltuzumab), antibody drug conjugates (IMGN529 with maytansinoid DM1 and AGS67E with monomethyl auristatin E) and new radioimmunoconjugates (177 Lu Betalutin) [19-22].

4.1. BI 836826
BI 836826 is an Fc-engineered, chimeric immunoglobulin (Ig) G1 anti-CD37 mAb. BI 836826 both activates the immune system to induce an antibody-dependent cell-mediated cytotoxicity (ADCC) and induces apoptosis in cancer cells [23]. It is Fc-engineered to strengthen its ADCC potential and enhance its affinity for the receptor Fc-gamma-RIIIa, which is expressed on human NK cells. BI 836826 has already shown remarkable direct cytotoxicity against isolated chronic lymphocytic leukemia (CLL) cells and has induced potent B-cell depletion from whole blood samples [24]. Moreover, it was observed that in a Ramos mouse model of human B-cell lymphoma, BI 836826 strongly suppressed tumor growth [24].

A *ex vivo* study of the efficacy of BI 836826 in chemoresistant CLL patient samples by Betrian et al [25] found BI 836826 and the PI3K inhibitor idelalisib to be much more cytotoxic when given in combination than when applied singly in fresh peripheral blood mononuclear cells (PBMC) from relapsed CLL patients. BI 836826 is currently under evaluation in clinical studies as a potential new therapeutic option in B-cell malignant diseases according to its *in vitro* and *ex vivo* cytotoxicity.

### 4.2. Otlertuzumab

Otlertuzumab (SMIP-016, TRU-016) is a humanized anti-CD37 specific, single-chain, homodimeric protein built on the ADAPTIR (modular protein technology) platform, consisting of antibody-derived, single-chain variable fragments linked to Ig constant domains [26]. Otlertuzumab triggers direct caspase-independent apoptosis of malignant B-cells and induces ADCC. It does not induce complement activation, but induces apoptosis directly by binding to the CD37 receptor, which upregulates BIM as a result [27]. While otlertuzumab acts by interaction with CD37 rather than with CD20, this agent has the possibility for therapeutic effect if CD20 is absent on the targeted B-cells.

Smolewski et al investigated the therapeutic properties of SMIP-016 in combination with the monoclonal anti-CD20 antibody, ofatumumab in *de novo* CLL cells and in different B-cell neoplasm-derived lines: the Raji line (Burkitt lymphoma (BL) -derived cells), Riva-1 line (derived from diffuse large B-cell lymphoma; DLBCL), and RPMI 8226 line [multiple myeloma (MM) derived cells] [28]. SMIP-016 demonstrated remarkably enhanced cytotoxic activity in the Raji and Riva-1 cell lines when combined with ofatumumab. In addition, both drugs were highly effective at very low concentrations, which suggests that potential adverse events related to the treatment may be avoided by reducing the dose in clinical practice.

Baum et al evaluated the effect of otlertuzumab on various cell lines, alone and in combination with the established therapeutics such as rituximab, doxorubicin, rapamycin and bendamustine [29]. The *in vivo* activity of otlertuzumab was also evaluated in SCID mice. It was observed that otlertuzumab acts synergistically with rituximab, bendamustine and rapamycin, and additively with doxorubicin in NHL cell lines. The findings of *in vivo* studies show that combination therapy based on otlertuzumab
with bendamustine is more effective in a follicular lymphoma (FL) tumor model than monotherapy with either agent used individually.

4.3. AGS67E

Encouraged by the clinical success of brentuximab vedotin in Hodgkin lymphoma (HL) patients, another conjugate with monomethyl auristatin E was discovered [30]. AGS67E is a fully human anti-CD37 IgG2 antibody conjugated to the potent microtubule-disrupting agent monomethyl auristatin E. The activity of AGS67E include apoptosis, cell-cycle alterations, and cytotoxicity in vitro, as well as anticancer in vivo potential. The preclinical efficacy of AGS67E is similar or superior to other CD37 mAbs in similar models of B-cell malignant diseases [31].

In a study by Pereira et al., AGS67E was administered in lymphoma cell lines (BL), mantle cell lymphoma (MCL), FL, DLBCL and xenografts [32]. It was observed that this agent is cytotoxic, induces apoptosis, and alters the cell cycle of cell lines representing NHL in vitro. In addition, AGS67E inhibits the growth of several xenografts representing NHL, and was observed to be effective with every lymphoma xenograft for all tested dosing regimens and schedules. Furthermore, in this work it was reported that CD37 is also expressed in T-cell lymphomas.

Promising results were reported by Heider et al., where AGS67E was found to have a significant ADCC and proapoptotic effect on a BL cell line and in a Ramos mouse model of human B-cell lymphoma [33]. Furthermore, AGS67E demonstrated superior performance to rituximab both in potency and maximal cell lysis, and administration of this agent strongly suppressed tumor growth in a Ramos mouse model of human B-cell lymphoma. The remarkable preclinical pharmacodynamic and antitumor effects of mAb 37.1 therefore warrant clinical development for B-cell malignancies.

4.4. IMGN529

Naratuximab emtansine (IMGN529) is an investigational antibody-drug conjugate consisting of a humanized anti-CD37 antibody conjugated to the maytansine-derived microtubule disruptor, DM1. IMGN529 binds with high affinity and specificity to CD37, which allow for antibody-drug conjugate internalization and processing, and the intracellular release of DM1. As a result of its ability to disrupt microtubule assembly, DM1 subsequently induces cell cycle arrest and apoptosis.

IMGN529 has already shown high anticancer activity in preclinical models of CLL and CD37-positive NHL [34]. Similar results were observed on NHL cell lines. In an in vitro study by Deckert et al, IMGN529 demonstrated significant ADCC activity against lymphoma target cells and B-cell lymphoma cell lines, similar to the ADCC activity shown by rituximab. In addition, the cytotoxic potency induced by IGMN529 was much stronger than that of the naked mAb, with induction of cell death. The agent was also found to have a unique combination of antitumor activities including proapoptotic and immune-effector functions. In addition, a longer tumor-free survival time was observed in a group of
mice with a human B-cell lymphoma cell line which had received IMGN529 in monotherapy compared to those treated with the unconjugated antibody or with rituximab; this confirms that DM1 addition has a positive effect.

4.5. $^{177}$Lu-tetulomab

First attempts with radioimmunotherapy (RIT) with CD37 as target were not very impressive. In vitro and in vivo mouse model studies evaluated the properties of CD37 with a $^{131}$I-labeled murine mAb (MB-1) [35-37]. To improve the effectiveness of RIT against CD37, a novel agent, betalutin, has been designed by attaching the radiolabel $^{177}$Lu to the anti-CD37 antibody HH1-$^{177}$Lu-tetulomab ($^{177}$Lu-betalutin) [38]. $^{177}$Lu-tetulomab showed remarkable results in a study with SCID mice that were intravenously injected to Burkitt's Daudi-cell lymphoma mice [39]. Treatment with this agent resulted in a threefold increase in survival compared to untreated control mice. In addition, RIT was well tolerated at dosages about 10 times above those considered relevant for patients with B-cell NHL.

In a study by Dahle et al $^{177}$Lu-tetulomab was compared to $^{177}$Lu-rituximab [40]. It was observed that $^{177}$Lu-tetulomab was significantly more efficient at inhibiting cell growth. Furthermore, treatment with this agent resulted in significantly increased survival of mice, compared with control groups treated with $^{177}$Lu-tetulomab or saline. In addition, the CD37 epitope recognized by $^{177}$Lu-tetulomab was highly expressed in 216 out of 217 tumor biopsies from patients with B-cell NHL. These two studies give justify further clinical studies of RIT targeting CD37.

According to the preclinical studies mentioned above, $^{177}$Lu-tetulomab successfully binds to lymphoma cell lines and biopsies from NHL patients, and tumors in mice models. It indicates that CD37 can be an excellent target for RIT and this should be investigated in future clinical studies.

5. CD37 in vivo studies

Currently there are only two clinical trials with BI 836826 in NHL patients. All major studies are shown in Table 1. The first one (NCT01403948) is a phase 1 clinical trial evaluating the maximum tolerated dose (MTD), safety, pharmacokinetics and efficacy of BI 836826 in monotherapy in relapsed or refractory NHL patients after at least one prior treatment line. The second study (NCT02624492), compares BI 836826-GemOx with R-GemOx in patients with relapsed and refractory DLBCL. In addition, it establishes MTD and evaluates efficacy and toxicity. However, no data has yet been published for either study and they are still recruiting patients.

While otriltuzumab has already demonstrated promising results in phase 2 clinical studies when given in combination with bendamustine, versus bendamustine alone, in patients with relapsed CLL, data regarding its effect on NHL is still limited [41]. In a phase 1 study by Pagel et al., 16 patients with relapsed and refractory NHL diagnosis were enrolled including eight patients with FL, four with MCL
and four with Waldenström's macroglobulinaemia (WM) [42]. There were only two clinical responses: one partial response (PR), observed in an FL patient with progression free survival (PFS) of 477 days, and one minor response observed in a WM patient (PFS of 420 days). Eleven patients had stable disease (SD) with a median time to progression of 91 days. Otteruzumab was well tolerated in this group; however, its efficacy as monotherapy was not impressive. It is recommended that future studies should be performed to explore the potential of otteruzumab administered in combination.

Another phase 1b study examined the effect of otteruzumab administered in combination with rituximab and bendamustine in relapsed indolent B-cell NHL patients [43]. Among the 12 included patients, nine had FL and three had small lymphocytic lymphoma (SLL). The patients were heavily pretreated with a median number of three prior regimens. The overall response rate (ORR) was 83% for all patients, with 67% in the 10 mg/kg dose group and 100% in the 20 mg/kg dose group. Three patients in the 10 mg/kg cohort and one in the 20 mg/kg cohort had a complete response (CR). All responses were demonstrated after the second treatment cycle. The drug was well tolerated in both doses with only eight grade 3 and 4 adverse events (AEs) observed in five patients. As a result, the combination of otteruzumab with rituximab and bendamustine was well tolerated with predictable and manageable toxicity and showed clinical efficacy in relapsed NHL patients.

No clinical study with otretuzumab is currently ongoing in NHL patients. However, a phase 1b study evaluating safety and efficacy of otretuzumab and rituximab, obinutuzumab (a new class of anti-CD20 mAb), idelalisib, or ibritinib (Bruton’s kinase inhibitor) in CLL patients is currently at the recruitment stage (NCT01644253).

There is only one phase 1 clinical study (NCT 02175433) evaluating AGS67E in monotherapy in relapsed and refractory lymphoid malignancies, including NHL [44]. Although the study is still ongoing and patients are being recruited, the interim results have been published. So far, 50 patients have been enrolled to the study (22 DLBCL, seven FL, four adult cutaneous T-cell lymphoma (CTCL), four mycosis fungoides (MF), three peripheral T-cell lymphoma (PTCL), two MCL and eight with other diagnoses). The safety profile was good with no major nonhematological toxicities. AGS67E demonstrated signs of activity with seven CRs (four in DLBCL diagnosis) and four PR.

Only a single phase 1 clinical trial of IMGN529 has been conducted in patients with relapsed and refractory B-cell NHL [45]. Thirty-one patients have been enrolled to this study (14 DLBCL, 10 FL, five MCL and two marginal zone lymphoma - MZL). The most common treatment-related AEs were neutropenia (30%), fever (27%), asthenia (20%) and fatigue (20%). Four objective responses have been reported (two CR and two PR). This study showed a manageable safety profile and encouraging evidence of efficacy used in monotherapy, particularly in individuals with DLBCL, what resulted in planned phase 2 multicenter clinical study.
177Lu-tetulomab (Betalutin) is currently under investigation in NHL patients under early clinical trials. The first to yield results is a phase 1 study in refractory and relapsed DLBCL patients who are not eligible for autologous stem cell transplantation (NCT02658968). The early findings for 10 patients (nine FL and one MCL) have been published by Kolstad et al [46]. The toxicity profile was tolerable and majority of side effects were hematological. The authors observed grade 3 and 4 AEs in four patients (two thrombocytopenia, one pneumonia and one atrial fibrillation). At a drug dose of 10 MBq/kg, two out of four patients demonstrated PR, and another an SD. At a dose of 20 MBq/kg, two out of three patients had a CR and one had PR. The first patient treated in this study has now been in stable remission with an observation time of 18 months. Most recently, the same group reported the updated results of a phase 1/2 study with 177Lu-tetulomab satetraxetan in patients with different types of relapsed NHL, including FL, MCL and MZL (NCT01796171) [47]. The phase 1 was a dose escalating study to define the maximum tolerable dose of Betalutin, as well as to assess safety, toxicity, pharmacokinetics, biodistribution and efficacy of the drug. Then, a dose was selected for the phase 2 in which response rates and PFS were assessed. Sixty one patients have been enrolled, and 55 of them were evaluable for safety and 55 for efficacy. Thirty patients were enrolled to a phase 2 expansion arm so far. The most common grade 3/4 AEs were hematologic toxicities (neutropenia in 58% and thrombocytopenia in 53%); four patients (7%) had ≥ grade 3 infections. There were no study drug related deaths. The ORR for all evaluable patients was 64% (CR in 24%). For a 177Lu-lilotomab pre-dose of 40 mg, 15 MBq/kg of Betalutin was the recommended phase 2 dose. Among patients evaluable for efficacy assessment the ORR was 69% (CR in 28%). With the median follow-up of 5.8 months, the median PFS was 13.3 months (15 months for those with CR). Additionally, in 7 patients from phase 1, for the drug pre-dose of 100 mg/m² the recommended phase 2 dose of Betalutin was 20 MBq. In those patients the ORR was 43%, with CR in 14% patients.

Another phase 1 study open label, randomized study to assess pharmacokinetics, biodistribution and radiation dosimetry of 177Lu-tetulomab satetraxetan radioimmunotherapy in patients with relapsed non-Hodgkin lymphoma (NCT02657447) in patients with relapsed NHL has been planned [48].

6. Conclusion

The novel drugs targeting CD37 described above have potent activity against a range of malignancies; this finding highlights their therapeutic potential in treating not only CLL but also other B-cell malignant diseases, including different subtypes of NHL. However, several of these agents are in the early phase of development. Therefore reinforcing the need for further current clinical development in multicenter phase 2 and 3 clinical studies. Moreover, special attention should be focused on patients with refractory and relapsed DLBCL diagnosis, where targeting the CD37 with mAbs and RIT can be an excellent option.

7. Expert opinion
The CD37 antigen is almost exclusively expressed on mature human B cells and B-cell–derived lymphoid malignancies; however, its expression appears to be lower on NHL cells than on healthy B-cells [49, 50]. As a result CD37, represents a solid alternative target for NHL therapy and it is an excellent target for immunotherapy.

Interestingly, anti-CD37 mAbs may be very effective when combined with other novel drugs. This is a much more rational approach than using combinations with standard chemotherapeutics or monotherapy with another mAb. In the authors’ opinion, the most promising choice of mAb might be olteltuzumab (TRU-016). This agent has already proven to be efficacious and of low toxicity when given in combination with bendamustine in CLL patients in a randomized phase 2 trial [41]. Olteltuzumab enhances the cytotoxicity of bendamustine without a tolerable safety profile. Moreover, olteltuzumab may demonstrate an enhanced proapoptotic effect when combined with novel drugs such as PI3K pathway inhibitors [51]. These findings suggest that olteltuzumab might be an excellent complement for new biological drugs including ibrutinib and idelalisib.

Various in vitro studies have found that olteltuzumab has an additive cytotoxic effect with mTOR inhibitors, CD20 mAbs, PI3K inhibitors and ibrutinib [52-54]. Currently, this agent is under investigation with different drug combinations in a range of clinical studies against various B-cell malignant diseases. It is under evaluation in CLL and NHL patients in combination with rituximab, obinutuzumab or ibrutinib, and in combination with both rituximab and idelalisib (NCT01644253). The exact role of olteltuzumab in the therapy of NHL is still not defined, but it is changing rapidly on a monthly basis.

While olteltuzumab seems to be the most promising topic for authors, the data from clinical studies with other anti-CD37 mAbs, including RIT, are also awaited. An ideal situation would be if NHL patients could be treated with a combination of modern small molecules such as BCR inhibitors and next-generation immunotherapeutics, for example, mAbs consisting of CD37; this approach will result in less short-term and long-term toxicity. It is important to consider that a closer examination of the mode of action of CD37 mAbs may open a window of opportunity for a new generation of treatment options. Such an approach may pave the way for chemo-free treatment in the near future.

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Declaration of interest

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

• A paper showing effects on the role of CD37 in antigen presentation by dendritic cells


• A paper on influence of CD37 on migratory activity of dendritic cells


•• A study assessing effects of anti-CD37 antibody conjugated with cytotoxic drug on neoplastic B lymphocytes


• A report on the remarkable preclinical pharmacodynamic and antitumor effects of Fc-engineered monoclonal anti-CD37 antibody


•• A study revealing mechanism of CD37SMIP activity against chronic lymphocytic leukemia cells


• A preclinical study showing antitumor activity of TRU-16 in B-cell malignancies


• A review on the role of 131-labeled anti-CD37 antibody in B-cell lymphoma


• A randomized phase 2 clinical trial with otlertuzumab in chronic lymphocytic leukemia patients


• A clinical study showing activity otlertuzumab in patients with resistant/relapsed patients with non-Hodgkin’s lymphoma


• A phase 1 study showing activity otlertuzumab in combination with bendamustine in patients with non-Hodgkin’s lymphoma


• A phase 1/2 study with 177 Lu-Lilotomab in indolent non-Hodgkin’s lymphoma patients


Capture to the Figure

Figure 1. The biological pathway connected CD37. Pro-survival and proapoptotic effects of CD37 are schematically shown. Clustering of α4β1 integrins by CD37 may provide to pro-proliferative PI3K/Akt pathway activation. Linking complexes with PI3Kγ, Lyn, or Syk causes Akt pathway inactivation.

PI3K-phosphoinositide 3-kinase, Akt- protein Kinase B, Lyn- tyrosine-protein kinase, Syk-spleen tyrosine kinase, SOCS-3-suppressor of cytokine signaling 3, IL6-interleukin 6, STAT3- signal transducer and activator of transcription 3.
Table 1. Clinical trials assessing efficacy of CD37 targeting

<table>
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<tr>
<th>Agent</th>
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