Phase I Study of a Bispecific Ligand-Directed Toxin Targeting CD22 and CD19 (DT2219) for Refractory B-cell Malignancies

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Abstract

Purpose: The novel bispecific ligand-directed toxin (BLT) DT2219 consists of a recombinant fusion between the catalytic and translocation enhancing domain of diphtheria toxin (DT) and bispecific single-chain variable fragments (scFV) of antibodies targeting human CD19 and CD22. We conducted a phase I dose-escalation study to assess the safety, maximum tolerated dose, and preliminary efficacy of DT2219 in patients with relapsed/refractory B-cell lymphoma or leukemia.

Experimental Design: DT2219 was administered intravenously over 2 hours every other day for 4 total doses. Dose was escalated from 0.5 μg/kg/day to 80 μg/kg/day in nine dose cohorts until a dose-limiting toxicity (DLT) was observed.

Results: Twenty-five patients with mature or precursor B-cell lymphoblastic leukemia or leukemia expressing CD19 and/or CD22 enrolled to the study. Patients received median 3 prior lines of chemotherapy and 8 failed hematopoietic transplantation. All patients received a single course of DT2219; one patient was retreated. The most common adverse events, including weight gain, low albumin, transaminitis, and fever were transient grade 1–2 and occurred in patients in higher dose cohorts (≥40 μg/kg/day). Two subjects experienced DLT at dose levels 40 and 60 μg/kg. Durable objective responses occurred in 2 patients; one was complete remission after 2 cycles. Correlative studies showed a surprisingly low incidence of neutralizing antibody (30%).

Conclusions: We have determined the safety of a novel immunotoxin DT2219 and established its biologically active dose between 40 and 80 μg/kg/day × 4. A phase II study exploring repetitive courses of DT2219 is planned.

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Introduction

DT2219, a recombinant fusion protein, contains the catalytic and translocation enhancing domain of diphtheria toxin (DT390) fused with bispecific single-chain variable fragments (scFV) of antibodies targeting human CD19 and CD22 cell surface receptors (1). The protein is engineered so that the native binding region of diphtheria toxin (DT) is replaced by the more avidly bound scFV. After binding, CD19 and CD22 readily internalize (2, 3) to promote toxin entry into the cytosol, inhibition of protein synthesis, and subsequent apoptotic cell death (4). Notably, previous preclinical studies showed that the combination of two different scFVs and a toxin on the same single-chain molecule resulted in greater anticancer activity compared with monomeric anti-CD19 or anti-CD22 connected with truncated DT (5). In addition, xenograft studies demonstrated significant inhibition of CD22⁺CD19⁺ Raji tumor growth and an enhanced therapeutic effect with repetitive dosing in vivo (1).

CD19, a 95-kDa membrane glycoprotein, is ubiquitously present on the surface of all stages of B lymphocyte development and is also expressed on most B-cell mature lymphoma cells and leukemia cells (6). CD22 is a 135-kDa glycoprotein expressed on B-lineage lymphoid precursors, including precursor B acute lymphoblastic leukemia, and often is coexpressed with CD19 on mature B-cell malignancies (7). DT mediates potent cell-cycle-independent cell death and therefore can be particularly effective as an alternative therapy for chemotherapy-refractory malignancies (8). We conducted a phase I dose-escalation study to assess safety, maximum tolerated dose (MTD), and preliminary efficacy in patients with chemorefractory B-cell lymphoma or leukemia expressing CD19 and/or CD22.

Patients and Methods

Patients

All patients gave written informed consent to treatment on the Institutional review board (IRB)-approved treatment protocol in accordance with Declaration of Helsinki. This clinical trial was registered at clinicaltrials.gov (NCT 00889408). DT2219 was cGMP manufactured at the University of Minnesota under FDA IND-application (IND number 1000780). Inclusion criteria included: age >12 years, CD19 and/or CD22 expressing B-cell lymphoma or leukemia refractory to conventional therapy, and
adequate performance and organ function [creatinine ≤ 1.5 upper limit of normal (ULN), liver function tests < 2.5 × ULN; serum albumin ≥ 3 g/dL, left ventricular ejection fraction ≥ 40%]. We excluded patients with active infections, serious concurrent medical problems, history of penicillin allergy, and more recently amended the protocol to also exclude patients with history of central nervous malignancy. Patients were treated at the Scott and White Medical Center, MD Anderson Cancer Center, and Masonic Cancer Center, University of Minnesota.

**Treatment plan**

In this phase 1 study, patients received DT2219 in a single course at doses ranging from 0.5 μg/kg/day (1/500th of the MTD in rabbits) to 80 μg/kg/day i.v. over 2 hours (4 hours for the first dose) every other day for 4 total doses (days 1, 3, 5, and 8). The dose was escalated in 9 cohorts until a dose-limiting toxicity (DLT) was observed (Table 2). The first 15 patients were treated by rapid escalation design (dose cohorts 1–3) or by standard 3+3 dose escalation design (cohorts 4–6). We applied continual reassessment method (9) to the last 10 patients (dose cohorts 8, 9) with the goal to identify the dose level that corresponds to a desired toxicity rate of 33% or less using grade 3 or greater dose-limiting toxicity. DT2219 will be further developed for therapy of mature or precursor B-cell lymphoid malignancies. In the future, DT2219 can be used in combination with other targeted agents providing a safer and nongenotoxic alternative to chemotherapy.

**Disease reassessment and correlative studies**

Disease assessment included physical examination for lymph node and spleen weekly; blood and marrow evaluation including flow cytometry assessment for CD19 and CD22 expression and assessment for minimal residual disease, and computerized tomography (CT) scan 21–28 days after treatment using Chesson criteria for lymphoma and leukemia staging (10, 11). Adverse event collection focused on targeted and unexpected adverse events (AE) before and after each dose at the following time points: 1–4 hours, 24 hours, and days 9, 15, 22, and 29 of the cycle.

**Statistical analysis**

Patients and disease characteristics were summarized using descriptive statistics. For binary endpoints such as toxicity and clinical response, frequencies and proportions were calculated. For continuous endpoints such as area under the curve (AUC), summary statistic including median and range (minimum and maximum) were used. All statistical analyses were performed with Statistical Analysis System software version 9.3 (SAS Institute, Inc.).

**Results**

**Patients and toxicities**

We enrolled 25 patients with a median age of 55 years (range, 34–78 years). Patient and disease characteristics are detailed in Table 1. All patients were evaluable for safety and efficacy. Ten patients had pre-B acute lymphoblastic leukemia, 5 had chronic lymphocytic leukemia (CLL), and 10 had non-Hodgkin lymphoma. All patients were chemo-refractory with a median of 3 (range, 2–5) prior therapies. Most patients received prior monoclonal antibody (rituximab, ofatumumab, inotuzumab), none of the patients received blinatumomab, and eight failed prior hematopoietic cell transplantation (5 autologous and 3 allogeneic). All tumors were biopsy-confirmed to express CD19 and/or CD22 in at least 20% of malignant cells. Most tumors (89%) had over 60% malignant cells CD19+ and/or CD22+ and 13 expressed both CD19 and CD22 targets.

All 25 patients received a single course of therapy. One patient attained partial response after the first cycle and received an additional 4 dose course after the protocol was amended with FDA and IRB approval. Twelve patients treated at doses ranging from 0.5 μg/kg/day to 20 μg/kg/day exhibited no or minimal adverse reactions (Table 2). All 13 patients treated at dose levels ≥ 40 μg/kg/every other day × 4 experienced AE attributed to drug treatment. No infusion toxicity was observed. The most common transient grade 1–2 AEs included weight gain (range, 5%–14% of
underlying lymphoma or leukemia often contributed to cytopenias. Whereas lactate dehydrogenase (2–2.3-fold) transiently increased in 4 patients after the first dose, clinical tumor lysis or acute cytokine release syndrome did not occur. Most AEs were recognized during routine monitoring before the second or third dose of DT2219. All AEs were brief and resolved completely within one week. Two patients experienced DLTs: the first DLT occurred at the 40 μg/kg dose level in a 71-year-old patient with ALL who developed back pain along with acute lower extremity weakness after the third dose of study drug. While the patient had a recent history of CNS leukemia before enrollment, brain MRI and cerebrospinal fluid studies at the time of AE were negative for leukemic CNS involvement. This patient died of rapidly progressive disease. No neurologic adverse effects of any grade occurred in the next 10 patients treated at this or higher doses (40–80 μg/kg). The second DLT event occurred at the 60 μg/kg dose level in a 55-year-old patient who developed grade 3 capillary leak and manifested as hypoxemia, hypotension, pulmonary edema, and hypoalbuminemia in combination with febrile neutropenia. The patient was hospitalized and treated with oxygen, intravenous antibiotics, hydration, and diuresis. Her symptoms improved with supportive care to grade 2 after 2–3 days and completely resolved in 10 days.

**Pharmacologic and immunologic studies**

At the time of enrollment, most patients exhibited low peripheral blood B-cell counts [median B-cell count 3.5% (<0.1 × 10⁸ cells/μL); range, 0%–52%; n = 10] often associated with prior rituximab, corticosteroids, and chemotherapy. The effect of DT2219 on B lymphocytes in a patient with an extramedullary ALL relapse shortly after allogeneic HCT was observed with gradual decline in number of peripheral blood CD19- and CD22-expressing cells after 4 doses of DT2219 (Fig. 1A). The possibility that DT2219 may interfere with fluorochrome-labeled anti-CD19 and anti-CD22 was excluded by examining CD20⁺ baseline), peripheral edema, and hypoalbuminemia consistent with capillary leak syndrome, grade 1–2 fever, and fatigue (Table 2). Seven patients experienced isolated mild elevation of liver function tests (1.1–2.1×ULN) without hyperbilirubinemia, which resolved within 3 to 7 days. Thrombocytopenia and anemia occurred in 5 patients; however, marrow involvement by

### Table 1. Patients and disease characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of subjects (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (range)</td>
<td>74 (34–78)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>13/12</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>20</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
</tr>
<tr>
<td>Black</td>
<td>2</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>10</td>
</tr>
<tr>
<td>CLL</td>
<td>5</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
</tr>
<tr>
<td>Primary refractory</td>
<td>11</td>
</tr>
<tr>
<td>Relapsed refractory</td>
<td>14</td>
</tr>
<tr>
<td>Site of disease</td>
<td></td>
</tr>
<tr>
<td>Marrow</td>
<td>13</td>
</tr>
<tr>
<td>Extramedullary ALL</td>
<td>1</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>15</td>
</tr>
<tr>
<td>Extra lymphatic sites</td>
<td>3</td>
</tr>
<tr>
<td>CD19 and CD22 expression on tumor</td>
<td></td>
</tr>
<tr>
<td>CD19 only</td>
<td>11</td>
</tr>
<tr>
<td>CD22 only</td>
<td>1</td>
</tr>
<tr>
<td>CD19 and CD22 both</td>
<td>13</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
</tr>
<tr>
<td>Lines median (range)</td>
<td>5 (1–5)</td>
</tr>
<tr>
<td>Rituximab</td>
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<td>Ofatumumab</td>
<td>1</td>
</tr>
<tr>
<td>Inotuzumab</td>
<td>1</td>
</tr>
<tr>
<td>Autologous hematopoietic cell transplantation</td>
<td>3</td>
</tr>
<tr>
<td>Allogenic hematopoietic cell transplantation</td>
<td>5</td>
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</table>

### Table 2. Treatment detail and AEs

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Escalation detail</th>
<th>DT2219 dose μg/kg/day</th>
<th>Doses received</th>
<th>Total dose per cycle in μg</th>
<th>N</th>
<th>Drug-related AEs (CTCAE v4.03 toxicity grade)</th>
<th>DLT</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Rapid escalation</td>
<td>0.5</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>1.25</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>10</td>
<td>1</td>
<td>Grade 1 fever (n = 1)</td>
<td></td>
<td>Grade 1 ALT elevation (n = 1)</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Standard escalation</td>
<td>5.0</td>
<td>4</td>
<td>20</td>
<td>3</td>
<td>Grade 1 AST, Grade 2 hypoalbuminemia (n = 1)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10.0</td>
<td>4</td>
<td>40</td>
<td></td>
<td>4</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>20.0</td>
<td>4</td>
<td>80</td>
<td></td>
<td>3</td>
<td>Grade 1 ALT elevation (n = 1) Grade 2 ALT, AST elevation (n = 1)</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Continual Reassessment</td>
<td>40.0</td>
<td>4e</td>
<td>160</td>
<td></td>
<td>Grade 1 AST, Grade 2 hypoalbuminemia (n = 1)</td>
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</tr>
<tr>
<td>8</td>
<td>60.0</td>
<td>4e,c,4</td>
<td>240</td>
<td></td>
<td>5</td>
<td>Grade 1-2 capillary leak syndrome (n = 1) Grade 2 capillary leak syndrome (n = 1) Grade 1 capillary leak syndrome (n = 1)</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>80.0</td>
<td>4</td>
<td>320</td>
<td></td>
<td>3</td>
<td>Grade 1 hypokalemia (n = 1) Grade 2-1 capillary leak syndrome (n = 2) Grade 2 hypokalemia (n = 1)</td>
<td>No</td>
</tr>
</tbody>
</table>

*One patient at the 10 μg/kg/day was less than 12 years old and enrolled after receiving permission from the local IRB.
*Patient with DLT received 3 doses of DT2219.
*One patient at the 60 μg/kg/day was retreated 8 weeks later with second cycle at dose 40 μg/kg/day.
*One patient was dose reduced for fourth injection to 40 μg/kg/day due to capillary leak syndrome.
cells, which also declined over time. The B-cell depletion was specific as CD3+ T-cell levels remained constant during the testing interval.

We also measured the circulating concentration of DT2219 in a functional pharmacokinetic bioassay (Fig. 1B). Patients treated at dose levels 0.5–20 µg/kg/day had no detectable drug in serum when sampled on day 1 and 8 at 15, 30, 45, 60, and 120 minutes postinfusion. All evaluable patients at the University of Minnesota treated with ≥40 µg/kg/dose (n = 10) demonstrated detectable levels of DT2219 with the exception of one (Fig. 1C) with preexisting antibodies to DT (Fig. 1D). The AUC after the first dose (4-hour infusion) was lower at a median of 285 µg/mL × minutes (range, 0–2,020; n = 8) compared with drug levels after the fourth dose (2 hours infusion; AUC median 1,249 µg/mL × minutes; range, 0–1,692; n = 7). A representative AUC is shown in Fig. 1B. The drug half-life ranged from 59 to 110 minutes (n = 4).

Because the recombinant immunotoxin contains a bacterial toxin, immunogenicity is expected and can be a major barrier to
the potential activity of bacterial toxin-based drugs. We measured serum neutralizing antibodies in all patients treated with ≥40 µg/kg/dose at days 1, 8, 15, 29, 35, and 42 (n = 9). Neutralizing antibodies developed in 3 evaluable patients (30%) at dose levels between 40 and 80 µg/kg at median of one week (range, 1–2 weeks) after the first dose of DT2219. One patient had pre-formed anti-DT antibody that we detected at screening and attributed to prior DT immunization. In some patients, the presence of neutralizing antibodies inversely correlated with the serum concentration of DT2219 (Fig. 1C); however, no consistent pattern was recognized.

Clinical responses
Twenty-five patients were evaluable for response, recognizing that only 9 patients in the highest dose cohorts had measurable drug levels. Three patients had biopsy performed at the time of progression and all 3 demonstrated persistence of one or both CD19/CD22 antigens. Treatment produced an objective tumor response in two of these patients. After a single course of DT2219 at dose level 40 µg/kg/day × 4, a 77-year-old patient with chemotherapy-refractory CD19+/CD22+ CLL experienced a 40% reduction in cervical and axillary adenopathy with decrease of an abdominal tumor mass at day 28 after treatment, which was sustained for 2 months. (Fig. 2A) Patient was in continuous complete remission at day 28 after therapy. Another patient with relapsed CD19+/CD22+ diffuse large B cell lymphoma (dose level 60 µg/kg) who experienced a 75% reduction in size of lymphoma lesion after a single course complicated by a grade 3 capillary leak syndrome. Eight weeks later, after FDA approval, this patient received a second DT2219 course at a reduced dose of 40 µg/kg/dose × 4, which resulted in a complete resolution of a subcutaneous mass and pelvic lymphadenopathy (Fig. 2B). Second patient is alive and in complete remission with no neutralizing antibodies (Fig. 1F), currently at 8 months after therapy. We observed no correlation between CD19 and CD22 target expression and clinical activity in this small cohort.

Discussion
We have established the safety and dosing feasibility of a novel CD19/CD22 bispecific ligand-directed toxin DT2219. We also demonstrated that the current dosing schedule and route of administration achieves drug levels capable of biologic and clinical response against CD19/22-expressing lymphoid malignancies refractory to standard therapies with a surprisingly low incidence of neutralizing antibody responses. The current phase I study shows that although MTD was not reached, the drug can be administered safely up to 80 µg/kg/day at days 1, 3, 5, and 8 for total of 4 doses. The first dose infused over 4 hours as a safety precaution was always well tolerated. All other doses were administered over 2 hours. Interestingly, the AUC measured for the first dose was almost always lower than the AUC measured for the fourth dose suggesting the importance of shorter infusion time for immunotoxins with brief half-life. Early on-target saturation also may play a role in low AUC at the onset of therapy, yet the DT2219 dosing in 4 infusions 1 to 2 days apart resulted to adequate drug levels, biologic effectiveness, and tolerable toxicity. Although clinical responses to DT2219 were observed at doses 40 and 60 µg/kg/day, the 4 doses as administered in this trial maybe inadequate to induce deeper remissions. In one patient who achieved partial remission after 1 cycle, an additional cycle led to complete tumor elimination. The rationale for improved efficacy with repetitive dosing is supported by others who are developing immunotoxin conjugates using bacterial toxins, such as the anti-CD22 monoclonal pasudotox for hairy cell leukemia or SL-401, an IL3 receptor-DT fusion protein for myeloid malignancies (12–14).

In our experience, increasing the number of consecutive doses per cycle is unlikely to be tolerated; however, the treatment schedule with repetitive cycles of four every other day doses at least a week apart should be explored in future studies.

An important observation in this study is the lack of neutralizing antibodies formation in 7 of 10 of the evaluable patients treated at the 3 highest dose cohorts. In other trials involving DT-related immunotoxins in non–B-cell malignancies, neutralizing antibody responses have been frequent. One potential explanation is that prior rituximab therapy and B-cell lymphopenia contributed to a blunted humoral response that can last up to 1 year (4).

As is typical for most immunotoxins, the potential toxicity of greatest concern at higher doses was capillary leak syndrome. The underlying mechanism at least in part involves pinocytosis of the immunotoxin by endothelial cells, which is dose-dependent and thus of a particular concern at higher drug concentrations (15). Drug development strategies to engineer toxins that do not induce
capillary leak syndrome are underway (16, 17). However, despite capillary leak in many patients at the higher dose levels (40–80 
μg/kg/day), this side effect was manageable and fully reversible. In 
contrast to recently approved anti-CD19 targeting bispecific anti-
body blinatumomab, which produced neurotoxicity in 11% of 
patients, DT2219 therapy caused no grade 1–2 neurotoxicity and 
only a single grade 3 paraparesis of an uncertain drug causality. 
(18) Importantly, other complications inherent in the use of 
many experimental immunotherapeutic agents such as infu-
sion-related reactions, pyrexia, tumor lysis, or cytokine release 
syndrome were not observed in this study (19).

In conclusion, we have demonstrated safety, dosing feasibility, 
and preliminary clinical activity of a bispecific ligand-directed 
toxin in chemotherapy refractory B-cell lymphoid malignancies. 
In contrast to cytostatic chemotherapy, DT2219-mediated tumor 
cell killing is cell cycle and p53 independent (8), making it a 
particularly attractive therapy for overcoming resistance to stan-
dard chemotherapeutics in lymphoma.

A phase I/II clinical study designed to administer sequential 
cycles of this unique heterodimeric bispecific antibody toxin 
conjugate is underway.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References
1. Valler DA, Chen H, Sicheneder AR, Panoskaltsis-Mortari A, Taras EP. 
Genetic alteration of a bispecific ligand-directed toxin targeting human 
CD19 and CD22 receptors resulting in improved efficacy against systemic B 
2. Pulczynski S. Antibody-induced modulation and intracellular transport of 
CD10 and CD19 antigens in human malignant B cells. Leuk Lymphoma 
3. Chan CH, Wang J, French RR, Glennie MJ. Internalization of the lympho-
cytic surface protein CD22 is controlled by a novel membrane proximal 
4. Keppler-Hafkemeyer A, Brinkmann U, Pastan I. Role of caspases in immu-
5. Valler DA, Todhunter DA, Kuroki DW, Shu Y, Sicheneder A, Chen H. A 
bispecific recombinant immunotoxin, DT2219, targeting human CD19 
and CD22 receptors in a mouse xenograft model of B-cell leukemia/ 
8. Rodriguez R, Lim HY, Barowski LM, Simons JW. Identification of dipher-
theria toxin via screening as a potent cell cycle and p53-independent 
9. Yuan Y, Yin G. Rayestan hybrid dose-finding design in phase I oncology 
10. Cheson BD. New staging and response criteria for non-hodgkin lymph-
oma and hodgkin lymphoma. Radiol Clin North Am 2008;46: 
213–23.
National cancer institute-sponsored working group guidelines for chronic 
12. Kreitman RJ, Tallman MS, Robak T, Coute S, Wilson WH, Steiter-Steven-
son M, et al. Phase I trial of anti-CD22 recombinant immunotoxin 
monoclonal antibody pasuudotox (CAT-8015 or HA22) in patients with hairy 
13. Frankel AE, Woo YH, Ahn C, Pemmaraju N, Medeiros BC, Carraway HE, 
et al. Activity of SL-401, a targeted therapy directed to interleukin-3 
receptor, in blastic plasmacytoid dendritic cell neoplasm patients. Blood 
14. Kreitman RJ, Pastan I. Antibody fusion proteins: Anti-CD22 recombi-
nant immunotoxin monoclonal antibody pasuudotox. Clin Cancer Res 2011;17: 
6398–405.
cell reconstitution in lymphoma patients undergoing allogeneic HSC. 
An effect of pre-treatment with rituximab? Bone Marrow Transplant 2008;42: 
483–7.
Genetic engineering of an immunotoxin to eliminate pulmonary vascular 
17. Wayne AS, Fitzgerald DJ, Kreitman RJ, Pastan I. Immunotoxins for leuke-
Safety and activity of blinatumomab for adult patients with relapsed or 
refractory B-precursor acute lymphoblastic leukaemia: a multicentre, sin-
targeted T cells rapidly induce molecular remissions in adults with che-
motherapy-refractory acute lymphoblastic leukemia. Sci Transl Med 
2013;5:177ra38.
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