Unleashing the clinical power of T cells: CD19/CD3 bi-specific T cell engager (BiTE®) antibody construct blinatumomab as a potential therapy

Zachary Zimmerman, Tapan Maniar and Dirk Nagorsen
Global Development, Amgen Inc., Thousand Oaks, CA 91320, USA

Correspondence to: Z. Zimmerman, One Amgen Center Drive, MS 38-B-A, Thousand Oaks, CA 91320, USA; E-mail: zacharyz@amgen.com

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Abstract

Multi-agent chemotherapy is the standard treatment for most B cell malignancies. Since chemotherapy can be associated with significant toxicity and since relapses resistant to chemotherapy often develop, new therapies are needed. Blinatumomab (AMG 103 or MT103) is a late-stage candidate in clinical development, which belongs to a novel class of antibody constructs termed bi-specific T cell engager antibodies. This antibody construct has dual specificity for CD19 and CD3 and can re-direct polyclonal cytotoxic T lymphocytes toward the tumor. This review focuses on the pre-clinical and clinical development of blinatumomab as a powerful new tool in the treatment of B cell malignancies.

Keywords: BiTE®, bi-specific antibody, immunotherapy, leukemia, lymphoma

Introduction

Chemotherapy is a therapeutic mainstay of hematologic cancers; however, it can have considerable toxicity and relapse frequently develops (1, 2). The therapeutic power of the immune system, and cytotoxic T lymphocytes (CTLs) in particular, has been recognized with the observation of the graft-versus-leukemia/lymphoma effect following allogeneic hematopoietic stem cell transplantation (allo-HSCT) where donor T cells recognize alloantigens on the recipient’s tumor.

Engendering a selective response to the tumor while avoiding off-target toxicity is a major challenge in immunotherapy. Allo-HSCT, for example, is associated with high morbidity and mortality, much of which is due to graft-versus-host disease in which donor T cells infect destructive on recipient tissues (3). Monoclonal antibodies (mAbs) that specifically bind cell-surface antigens represent a more selective approach of immune-mediated tumor therapy. Rituximab, a mAb recognizing the B cell antigen CD20, has become standard in non-Hodgkin lymphoma (NHL) regimens, as an example (4). Rituximab has been shown to be able to lyse target cells through fixation of complement as well as antibody-dependent cellular cytotoxicity in which natural killer (NK) cells are directed to lyse an antibody-coated cell (5). Conventional mAbs such as rituximab, however, are limited in their ability to effectively elicit CTLs as a dominant effector mechanism.

Another challenge is that escape mechanisms can develop that protect a tumor from immune-mediated elimination. Examples include a paucity of strong antigens expressed by the tumor, loss of antigen-presentation machinery such as MHC class I, loss of co-stimulatory molecules, enhanced tumor survival by upregulation of anti-apoptotic proteins and a tumor-associated immunosuppressive microenvironment (6).

One approach that counters many potential routes of immune escape and bridges the exquisite selectivity of mAbs with the therapeutic potential of CTLs is the use of bi-specific antibodies that combine binding sites for different antigens in a single molecule to redirect polyclonal immune effector cells to a pre-defined target (Fig. 1). This review will focus on the development of the most clinically advanced molecule in this class of bi-specific T cell engager (BiTE®) antibody constructs, blinatumomab.

Pre-clinical development of blinatumomab

Bi-specific antibodies have been in development for more than three decades, with many structural iterations (7–9). Despite demonstrating promising pre-clinical activity in eliciting tumor-directed CTL responses, clinical application had been limited, mostly due to issues in clinical-scale production, immunogenicity and adverse reactions (10).

Blinatumomab, derived from B lineage mouse monoclonal antibody, is the most clinically advanced member of a novel class of bi-specific antibody construct termed BiTE® (11). BiTE® antibody constructs are single-chain proteins...
comprising the antigen-binding domains of two different antibodies joined by a non-immunogenic linker that allows for the rotational flexibility to bind two different antigen epitopes on separate cells in close proximity. Blinatumomab contains binding regions for the B cell lineage-specific antigen, CD19 as well as the invariant CD3ε subunit of the TCR present on all T lymphocytes (12).

The selection of CD19 as the target antigen has several advantages. CD19 is expressed on most B-lineage malignancies but is absent on HSCs and plasma cells. Furthermore, it is functionally important as it can enhance Src-family protein tyrosine kinase and PI3K–Akt kinase signaling (13). The PI3K pathway has been implicated in survival and resistance to chemotherapy in hematologic malignancies, and consequently it may be less likely that CD19 is lost under selective pressure of therapy (14, 15).

Several properties of blinatumomab facilitated its clinical development. Because of its single-chain structure, blinatumomab is readily produced in high amounts with a reliable purification strategy yielding a stable monomeric formulation for clinical use (12). Blinatumomab can induce robust T cell proliferation in the presence of CD19+ target cells. Blinatumomab has also been shown to induce the production of proinflammatory cytokines such as IL-2, IFN-γ, TNF-α, IL-4, IL-6 and IL-10 (16). Importantly, blinatumomab induced extremely potent T cell mediated specific lysis with half-maximal activity at a range of 10–100 pg ml⁻¹ (12). Studies using confocal microscopy have demonstrated that BiTE® antibody constructs are capable of inducing a structurally normal immune synapse (17), which is required for physiologic CTL activity.

Both CD4+ and CD8+ T cell subsets are capable of blinatumomab-induced cytotoxicity though the most rapid killing is mediated by the CD8+ population (18). Not surprisingly, the perforin–granzyme pathway is important for this cytotoxicity, as it can be abated by the perforin inhibitor concanamycin A. Other cytotoxic effector pathways seem to be less important as blockade of TNF-family death-inducing ligands such as TNF-α, Fas-ligand and TRAIL has no appreciable effect (12, 19).

Importantly, neither proliferation nor cytotoxicity induced by blinatumomab requires exogenous co-stimulation or IL-2 (20). At this point, we can only speculate why blinatumomab-induced T cell activation seems more robust than previously studied bi-specific antibodies. One hypothesis is that the single-chain design of the construct allows for the necessary flexibility to optimally crosslink the T cell with its cognate antigen-expressing target or the structure may allow for more efficient dimerization of the TCR.

Studies utilizing video-assisted microscopy elucidated another important property: blinatumomab-activated T cells are capable of serial killing even at low effector to target cell ratios. One potential explanation is that the affinity of blinatumomab for CD19 is significantly higher (10⁻⁹ M) compared with the affinity for CD3 (10⁻⁷ M). Since blinatumomab preferentially binds CD19, this may allow for more mobility of the effector T

Fig. 1. Schematic depicting the mechanism of action BiTE®. This figure depicts BiTE® bridging a tumor-associated antigen (TAA) and T cell CD3 to form a TAA–BiTE® complex to induce tumor-directed cytotoxicity characterized by perforin-mediated granzyme entry into the target tumor cell, resulting in caspase activation and apoptosis.
Clinical development of blinatumomab

The first clinical studies of blinatumomab were performed in patients with relapsed/refractory (r/r) NHL (24). Three phase I dose-escalation trials were completed using short-term intravenous infusions of blinatumomab in a total of 21 patients with refractory B cell NHL and one patient with chronic lymphocytic leukemia (CLL). Infusion doses ranging from 0.75 to 13 µg m\(^{-2}\) body surface area (BSA) were administered up to three times weekly. (Table 1 lists all active and completed blinatumomab clinical studies). The most common adverse events (AEs) (pyrexia, rigor and fatigue) were mild to moderate and seemingly related mechanistically to polyclonal T cell activation and/or tumor destruction (24). The production of pro-inflammatory cytokines, in particular, is thought to play a role. Interestingly, the release of pro-inflammatory cytokines appears to be transient and most robust with the onset of treatment and is largely diminished with subsequent cycles (25). This 'first-dose effect' corresponds well to the time during which most AEs have been observed. Interestingly, in vitro studies have suggested that corticosteroids may blunt this immediate cytokine release while sparing the cytotoxic activity of blinatumomab-activated T cells and accordingly steroid pre-treatment has been incorporated into blinatumomab protocols to mitigate any potential cytokine-mediated adverse effects early in the treatment course (16).

Notably, there were also cases of neurologic events such as aphasia, ataxia, disorientation and seizure. These events have thus far been fully reversible but did lead to drug discontinuation in 12 patients. The underlying mechanism is not completely understood, though one hypothesis is that T cells become activated and adhere to the endothelium, potentially transmigrate across the blood–brain barrier (BBB) and enter into the central nervous system (CNS) space (Virchow–Robin space). Activated T cells, upon encountering CD19-expressing B cells in the CNS, potentially cause a local inflammatory phenomenon that results in local cytokine release at the BBB/parenchyma and disturbance of the BBB, possibly leading to neurologic events in some patients. We expect that further exploration of the mechanism of these neurologic events will help refining this hypothesis.

Interestingly, similar neurologic events have been seen with other CD19-directed immunotherapies, such as chimeric antigen receptor (CAR) modified T cells, though it is unclear if the mechanism is related (26). Since the majority

Table 1. All completed and currently active blinatumomab clinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Disease(s)</th>
<th>Dosing</th>
<th>Number of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT103-I/01-2001</td>
<td>I</td>
<td>r/r NHL/CLL</td>
<td>Short-term infusion up to 13 µg m(^{-2}) up to 3 times weekly</td>
<td>22</td>
<td>No objective responses seen</td>
</tr>
<tr>
<td>MT103-I/01-2003</td>
<td>II</td>
<td>r/r NHL/DLBCL</td>
<td>0.5–90 µg m(^{-2}) day(^{-1}) for 4–8 weeks Extension cohort at</td>
<td>76</td>
<td>ORR 76% (55% in DLBCL extension cohort) at doses above 15 µg m(^{-2}) day(^{-1})</td>
</tr>
<tr>
<td>MT103-104 (NCT00274742)</td>
<td>II</td>
<td>r/r NHL/DLBCL</td>
<td>112 µg day(^{-1}) stepwise or continuous dosing 15 µg m(^{-2}) day(^{-1})</td>
<td>Ongoing</td>
<td>ORR 57% in 7 evaluable patients</td>
</tr>
<tr>
<td>MT103-208 (Phase II) (NCT01741792)</td>
<td>II</td>
<td>r/r DLBCL</td>
<td>15 µg m(^{-2}) day(^{-1}) 5 → 15 µg m(^{-2}) day(^{-1})</td>
<td>100–130</td>
<td>MRD- response = 80% Analysis ongoing CR/CRh = 69%, median RFS 7.6 months, median overall survival 9.8 months Analysis ongoing</td>
</tr>
<tr>
<td>MT103-202 (NCT00560794)</td>
<td>II</td>
<td>MRD- ALL</td>
<td>15 µg m(^{-2}) day(^{-1}) stepwise or continuous dosing 15 µg m(^{-2}) day(^{-1})</td>
<td>21</td>
<td>MRD- response = 80% Analysis ongoing CR/CRh = 69%, median RFS 7.6 months, median overall survival 9.8 months Analysis ongoing</td>
</tr>
<tr>
<td>MT103-203 (NCT01207388)</td>
<td>II</td>
<td>MRD- ALL</td>
<td>15 µg m(^{-2}) day(^{-1}) stepwise or continuous dosing 15 µg m(^{-2}) day(^{-1})</td>
<td>36</td>
<td>MRD- response = 80% Analysis ongoing CR/CRh = 69%, median RFS 7.6 months, median overall survival 9.8 months Analysis ongoing</td>
</tr>
<tr>
<td>MT103-206 (NCT01209286)</td>
<td>II</td>
<td>r/r ALL</td>
<td>9 → 28 µg day(^{-1}) stepwise or continuous dosing 15 µg m(^{-2}) day(^{-1})</td>
<td>189</td>
<td>Ongoing</td>
</tr>
<tr>
<td>MT103-211 (NCT01466179)</td>
<td>II</td>
<td>r/r ALL</td>
<td>9 → 28 µg day(^{-1}) stepwise or continuous dosing 15 µg m(^{-2}) day(^{-1})</td>
<td>189</td>
<td>Ongoing</td>
</tr>
<tr>
<td>311 TOWER (NCT02013167)</td>
<td>III</td>
<td>r/r ALL</td>
<td>9 → 28 µg day(^{-1}) stepwise or continuous dosing 15 µg m(^{-2}) day(^{-1})</td>
<td>189</td>
<td>Ongoing</td>
</tr>
<tr>
<td>216 Alcantara (NCT02000427)</td>
<td>II</td>
<td>r/r ALL</td>
<td>9 → 28 µg day(^{-1}) stepwise or continuous dosing 15 µg m(^{-2}) day(^{-1})</td>
<td>189</td>
<td>Ongoing</td>
</tr>
<tr>
<td>ECOG19110 (NCT02003222)</td>
<td>III</td>
<td>ALL</td>
<td>28 µg day(^{-1}) stepwise or continuous dosing 15 µg m(^{-2}) day(^{-1})</td>
<td>28 µg day(^{-1})</td>
<td>Ongoing</td>
</tr>
<tr>
<td>MT103-205 (NCT01471782)</td>
<td>I/II</td>
<td>r/r pediatric ALL</td>
<td>5 → 15 µg m(^{-2}) day(^{-1}) stepwise or continuous dosing 15 µg m(^{-2}) day(^{-1})</td>
<td>Ongoing</td>
<td>Analysis ongoing</td>
</tr>
</tbody>
</table>

→ indicates dose step at 1 week.
Unleashing the power of T cells: blinatumomab

of neurologic events has been reversible, the short half-life of blinatumomab is an advantage as exposure can be rapidly interrupted. Pre-dose steroids along with graduated dosing schedules were implemented in later trials to diminish the risk of the development of neurologic events (16, 24). Further exploration of the mechanism of blinatumomab-induced neurologic events is the subject of ongoing study.

In the single-infusion studies no objective responses (ORs) were seen; however, there was robust evidence of biologic activity such as markers of T cell activation, increases in serum cytokines and diminished CD19+ peripheral B cell numbers (24). Ultimately, these studies were terminated early due to the unfavorable risk/benefit ratio.

Why did these initial studies fail to demonstrate efficacy despite showing biologic activity? One hypothesis was that since the half-life of blinatumomab is relatively short (~2h), perhaps a steady, prolonged exposure is required for clinically meaningful activity. To test this hypothesis, the first study utilizing continuous intravenous infusion (CIV) was begun, designated MT103-104, using a portable pump that allows for continuous drug administration, even in the outpatient setting (27). Patients with r/r NHL on MT103-104 received blinatumomab CIV over a period of 4–8 weeks. As hypothesized, CIV led to steady-state drug levels achieved in one day that were stable over time and treatment cycles. Doses tested ranged from 0.5 to 90 μg m⁻² day⁻¹, with a maximum tolerated dose (MTD) identified at 60 μg m⁻² day⁻¹. Initially only patients with r/r indolent lymphoma were eligible; however, patients with diffuse large B cell lymphoma (DLBCL) were later included.

In total, 76 patients were treated, with the following histologic subtypes: follicular (37%), mantle cell (32%), DLBCL (18%) and other indolent subtypes (13%). The median age was 65 years and most subjects were heavily pre-treated with a median of three prior regimens. The majority of AEs occurred in the first 1–2 days of administration, most commonly lymphopenia, pyrexia, fatigue, weight changes and headache. A similar spectrum of reversible neurologic events also occurred including encephalopathy (8.6%), aphasia (4.3%), tremor (2.9%), disorientation (2.9%) and convulsion (2.9%) (27). In contrast to the single-infusion studies, there were dramatic declines in peripheral B cell numbers, which only recovered upon blinatumomab discontinuation. In subsequent trials using continuous infusion of blinatumomab in patients with acute lymphoblastic leukemia (ALL) (discussed below), B cell depletion has been further characterized. The majority of patients has shown a decline of peripheral B cells within 1 day of treatment initiation and not surprisingly, the development of hypogammaglobulinemia has also been observed in some patients (28). Increased binding of annexin V, suggested that apoptosis rather than redistribution was the predominant mechanism for the decline in peripheral B cell counts suggesting immune mediated clearance. Consistent with this hypothesis, recovery of peripheral B cells only occurs following cessation of the drug (25).

Peripheral T cell numbers also declined, but recovered within 1–2 weeks of therapy commencement often exceeding baseline levels, suggesting re-distribution followed by expansion. The most dramatic expansion was seen in the effector memory T cell population (25).

Clinical responses were seen at doses of 15 μg m⁻² day⁻¹ and higher. At 60 μg m⁻² day⁻¹, the overall response rate (ORR) was 75% across indolent lymphoma subtypes (18 out of 24 patients) with the highest response rate in follicular lymphoma (80%). Additionally, clearance of tumor infiltrate in the bone marrow was seen in five out of six patients with bone marrow involvement. No ORs were seen below the 15 μg m⁻² day⁻¹ dose (27).

Development in DLBCL

DLBCL is the most common lymphoid malignancy in adults and r/r disease has a significant unmet need for new therapies (29). As mentioned previously, 13 patients were treated as part of an extension cohort of trial MT103-104. In this cohort, a ‘double-step’ dosing procedure was tested in which the dose was escalated from 5 to 15 and finally to 60 μg m⁻² day⁻¹ for the treatment duration to reduce the risk of neurologic events. Two steroid-dosing schedules were also compared. Two patients were not eligible for response evaluation as treatment was discontinued prior to reaching the target dose of 60 μg m⁻² day⁻¹; however 6 of the remaining 11 patients responded (55%) and 2 (18%) had stable disease. Four patients had a complete remission (CR) with a median duration of response of 7.8 months and 3 patients were able to go to receive allo-HSCT (30).

In this difficult-to-treat population, these results provided a strong rationale for further development and a phase II study in r/r DLBCL was begun, MT103-208 (31). Patients in this ongoing study were assigned to two different fixed-dosing regimens given that pharmacokinetic analyses showed no impact of BSA for adult patients, either a step-wise dosing of 9, 28 and 112 μg day⁻¹ weekly (cohort I) or 112 μg day⁻¹ throughout (cohort II) (32). After 4 weeks, patients who achieved an OR could have a consolidation cycle. All patients received prophylactic dexamethasone.

As of the most recent analysis, 19 patients had been enrolled in all cohorts and of 16 patients evaluable, 44% had an OR [3 CR, 4 PRs (partial remissions)] (31). The most common AEs were tremor, diarrhea and fatigue. The highest-grade neurologic events seen were grade 3, in five patients. Stepwise dosing (cohort I) had the most favorable risk/benefit ratio and an extension cohort (cohort III) with this dosing regimen has recently completed enrollment.

Development in ALL

Though the prognosis of patients with ALL has improved with high-intensity combination chemotherapy, relapsed disease carries a poor prognosis. Since CD19 is expressed in virtually all cases of precursor B cell ALL, blinatumomab has been studied extensively in this disease.

The first trials were in patients with detectable minimal residual disease (MRD⁺). MRD can be assessed using sensitive quantitative PCR techniques to look for specific genetic aberrations or immunoglobulin rearrangements or by flow cytometry to identify the immunophenotype of leukemic blasts. Numerous studies have demonstrated that patients who remain MRD⁺ after having achieved remission are at an extremely high risk of relapse (33–36).
MT103-202 was a phase II trial to determine whether blinatumomab could induce molecular responses (i.e. responses assessed by molecular/cytometric techniques mentioned above) in MRD+ patients, conducted in collaboration with the German Multicenter Study group for ALL (GMAIL) (28). Adult patients with molecular refractory disease or with a molecular relapse were eligible. Twenty-one patients were enrolled and received a dose of 15 µg m⁻² day⁻¹ for 4 weeks per cycle. Sixteen out of 20 evaluable patients (80%) achieved an MRD response after blinatumomab treatment, all within the first cycle. Twelve of the responders had never achieved MRD negativity at any point with prior therapy indicating molecular refractory disease. Eight patients proceeded to allo-HSCT. Only one neurologic event, a grade 3 seizure, led to discontinuation (28). Importantly, long-term follow-up at a median observation time of 33 months revealed 12 patients still in remission.

The estimated median relapse-free survival (RFS) was 19.1 months in the 16 responders versus 3.2 months in the non-responders (37). Of the 11 patients who did not undergo allo-HSCT, six were in ongoing remission (one patient was censored because of withdrawal of informed consent). Interestingly, of the four patients who did relapse, two relapses were CD19- and two occurred in potentially immunoprivileged sites (CNS and testis), suggesting possible immune escape. A large phase II study, MT103-203, in adult patients with MRD positivity is underway.

Blinatumomab has also been evaluated extensively in patients with grossly r/r disease. Study MT103-206 was a single-arm phase II study which included a dose-finding component followed by an extension cohort in adults with r/r ALL. A total of 36 patients were treated. The dose established in this study was 5 (week 1) to 15 µg m⁻² day⁻¹ (remainder of treatment) which for later trials was converted to 9–28 µg day⁻¹ fixed dosing.

Overall 69% (25 out of 36) of patients achieved a CR/CRh (CRh = CR with partial recovery of peripheral blood counts). Among patients with a prior allo-HSCT the CR/CRh rate was 53% (8 out of 15). Importantly, 88% (22 out of 25) of all responders achieved a molecular remission and most achieved this following the first cycle (38). The median RFS was 7.6 months (7.9 months if patients are censored at transplant). The median overall survival was 9.8 months. The most common AEs were similar to prior studies: pyrexia (81%), fatigue (50%), headache (47%), tremor (36%) and leukopenia (19%). Neurologic events requiring treatment interruption occurred in 17% (6 out of 36) patients. All six patients were re-exposed to blinatumomab and treatment was able to be continued in four patients safely.

These results led to a large pivotal phase II trial MT103-211, in which 189 adults with Philadelphia chromosome (Ph)-r/r B-ALL, were treated with the 9–28 schedule for up to five cycles. A higher-risk, particularly difficult-to-treat patient population was enrolled including primary-refractory disease, early first relapse, multiple relapses and patients who had relapsed soon after allo-HSCT. This study has completed enrollment and results are forthcoming. A randomized phase III trial comparing blinatumomab to standard of care chemotherapy (311 TOWER study) and a phase II trial evaluating blinatumomab in PH+ (216 Alcantara study) are ongoing to confirm and extend these results.

Pediatric patients with ALL have superior outcomes to adults; however, relapse still carries a poor prognosis (39). The initial three pediatric patients with relapsed ALL were treated as part of a compassionate use program at a dose of 15 µg m⁻² day⁻¹ and all three patients achieved a molecular remission (40). A single-institution report described nine pediatric patients with post-transplant relapsed B-precursor ALL with no further standard of care therapy who were treated with blinatumomab on compassionate use (41). Four patients achieved CR after the first cycle of treatment; two patients showed a CR to the second cycle after previous reduction of blast load by chemotherapy. Four patients were successfully re-transplanted in molecular remission from haploidentical donors. After a median follow up of 398 days the probability of hematological event-free survival is 30%. Major AEs were grade 3 seizures in one patient and grade 3 cytokine-release syndrome in two patients.

A phase I/II study is ongoing to evaluate blinatumomab in pediatric patients with treatment-refractory or relapsed ALL in second or more relapse or post-HSCT relapse. The phase I portion has completed enrollment with 41 patients, 25 of whom (61%) had relapsed post-allo-HSCT. Pharmacokinetic parameters were similar to adults and the MTD was established at 5 to 15 µg m⁻² day⁻¹. The main dose-limiting toxicity was cytokine-release syndrome though no cases were seen at the MTD (42). A phase II study in children with r/r ALL is ongoing.

Conclusion

Blinatumomab is the most clinically advanced drug in the new class of bi-specific antibody constructs known as BiTE® antibodies and provides clear proof-of-principle that redirection of CTLs can be a potentially powerful therapeutic modality in hematologic malignancies.

Given the results in ALL and NHL, there has been considerable interest in broader clinical development of blinatumomab. By targeting CD19, blinatumomab may have activity against any B cell malignancy and further studies are clearly needed. The rapid elimination of peripheral B cells following initiation of blinatumomab could also be used in non-malignant conditions such as autoimmune disease where cell-targeted agents such as rituximab are in use, though this remains to be explored.

Further efforts to optimize drug delivery will likely improve the therapeutic index and patient access to blinatumomab. The AEs described in the completed studies are mostly expected from a mechanistic standpoint since blinatumomab is an agent that induces a polyclonal T cell response; however, there remains a need to better understand their pathophysiology. CIV of blinatumomab was a critical step towards improving its therapeutic index. Based on results to date, a number of other strategies could result in significant efficacy gains including higher dosing, resuming therapy after resolution of AEs, prior tumor debulking, combination therapies and use at earlier stages of disease.

B cell malignancies are biologically heterogeneous diseases that can develop resistance to standard therapies. Blinatumomab could become an important therapy that is mechanistically distinct from chemotherapy thereby.
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potentially offering a non-genotoxic option for patients—as monotherapy or even in combination therapies.

Conflict of interest statement: Zachary Zimmerman, Tapan Maniar and Dirk Nagorsen are employees of, and have equity ownership in, Amgen, Inc.

References

of an ongoing phase II trial. ASH Annual Meeting Abstracts 118:252.


