Blinatumomab for the Treatment of Philadelphia Chromosome–Negative, Precursor B-cell Acute Lymphoblastic Leukemia

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Disclosure of Potential Conflicts of Interest

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Abstract

Blinatumomab is a CD19/CD3-bispecific antibody designed to redirect T-cells towards malignant B-cells and induce their lysis. It recently gained accelerated approval by the Food and Drug Administration for the treatment of relapsed or refractory Philadelphia chromosome-negative B-cell ALL (RR-ALL). In the phase II trial that served as the basis for approval, blinatumomab demonstrated significant single agent activity and induced remission (complete remission (CR) and CR with incomplete recovery of peripheral blood counts (CRh)) in 43% of 189 adult patients with RR-ALL; the majority of responders (82%) also attained negative minimal residual disease (MRD-negative) status that did not generally translate into long term remissions in most cases. Additional studies show that blinatumomab can induce high response rates associated with lasting remissions in patients in first remission treated for MRD-positivity suggesting a role for blinatumomab in the upfront, MRD-positive, setting. Blinatumomab infusion follows a predictable immunopharmacologic profile including early cytokine release that can be associated with a clinical syndrome, T-cell expansion and B-cell depletion. Central nervous system toxicities represent a unique toxicity that shares similarities with other T-cell engaging therapies. Further studies are needed in order to clarify the optimal disease setting and timing for blinatumomab therapy. Additional insights into the pathogenesis, risk factors, and prevention of central nervous system toxicities as well as better understanding of the clinical consequences and biological pathways that are associated with drug resistance are needed.
Introduction

Patients with acute lymphoblastic leukemia (ALL) that relapse after achieving remission, or less commonly, that are refractory to induction therapy represent a challenging, high risk, population. These patients have poor survival with currently available chemotherapy approaches and the impact of allogeneic transplant in those selected few that respond to salvage chemotherapy is modest (1-3).

A flurry of targeted therapies have recently been introduced for relapsed or refractory ALL (RR-ALL). Several such approaches are currently under investigation in patients with B-cell precursor ALL (BCP-ALL) and show encouraging results in early phase clinical trials (Table 1). Most of these therapies target epitopes that are commonly expressed on neoplastic B-cells such as CD19, CD20, CD22 and CD52 in order to induce tumor cell lysis via antibody or complement dependent-cytotoxicity, induce apoptosis, or as a means to effectively deliver cytotoxic compounds to the malignant cell. Another class of drugs, T-cell engaging therapies, are designed to induce neoplastic B-cell destruction by activating specific cytotoxic T-cell responses. This can be achieved by creating autologous T-cells with chimeric antigen receptors that have CD19 specificity (CART19) or by the use of blinatumomab, a CD19/CD3-bispescific BiTE® antibody. Blinatumomab (Blincyto®) was the first drug in class to gain accelerated approval by the FDA for patients with relapsed or refractory Philadelphia-negative ALL (4). We herein review the biological, pharmacological and clinical data that led to the approval of this new drug in ALL and discuss the role of blinatumomab in current clinical practice.

CD19 as a Target
CD19 is a 95Kd transmembrane protein that appears early during B cell development and persists throughout B cell differentiation. CD19 is present on virtually all mature B cells in the blood and in secondary lymphoid tissues; its expression declines only during the late stages of B-cell differentiation towards an antibody-producing plasma cell (5, 6). CD19 acts as a costimulatory molecule of the B-cell receptor (BCR) complex and associates with CD21, CD81 and CD225 to decrease the threshold for BCR mediated activation of B-cells (6, 7). Activation of CD19 results in the phosphorylation of several cytoplasmatic tyrosine residues that mediate downstream signaling pathways involved in B cell function (6, 8). In addition, CD19 was reported to operate in a BCR-independent manner to affect B-cell development, differentiation and function (5, 6). Uckun et al. recently reported on the cloning and characterization of a novel high-mobility group (HMG)-box protein as the membrane-associated natural CD19 ligand (CD19-L) (9).

The consequence of CD19 deficiency was previously described in knockout murine models and in humans (10). In one report, a primary immune deficiency syndrome associated with loss of CD19 expression due to homozygous mutations resulting in deletion of the cytoplasmatic domain was described, perhaps pointing to potential toxicities of CD19-targeted therapies. The clinical consequence was of hypogammaglobulinemia and a defective response to antigenic stimuli, albeit with normal composition of the marrow precursor B-cell compartment and peripheral blood B-cell counts (7).

CD19 represents an attractive target in BCP-ALL since it is present on the vast majority BCP-ALL cells (11). Furthermore, CD19 is B-cell lineage specific and thus targeting this protein does not generally compromise other tissues. There is evidence to suggest a role for CD19 in
enhancing malignant pathways (10). For example, high levels of CD19 expression were shown to correlate with Akt activation and over expression of c-Myc (12, 13). Targeting CD19 in vitro seems to confer anti-tumor activity by induction of cell cycle arrest (14), apoptosis (9) and sensitization of neoplastic cells to chemotherapy (15, 16).

**Blinatumomab: Compound, Pharmacology, and Early Preclinical Observations**

Blinatumomab, a CD19/CD3-bispesific BiTE® antibody, is a 55KD fusion protein designed to redirect previously unstimulated T-cells towards malignant B cells and induce their destruction. The fusion antibody is a construct of two single chain antibodies that have CD3 and CD19 specificities, respectively, connected by a 5 amino-acid non-immunogenic linker (17) (Fig. 1).

Initial observations in lymphoma cell lines and later in leukemia and lymphoma murine models demonstrated exceptional efficacy of blinatumomab in eliminating malignant CD19+ B-cells at very low concentrations (10-100 pg/ml) (18-20). Lysis of the malignant cells is independent of antigen presentation or co-stimulation and is primarily mediated by the cytotoxic T-cell proteins perforin and granzyme (17). A continuous mode of administration was chosen for human studies based on the drug’s short half-life, mode of action and disappointing efficacy signals with short term intravenous infusion schedules in early clinical trials (17).

Blinatumomab is reported to have a predictable, linear pharmacokinetic profile that is independent of the underlying diagnosis (21). In one report, patients with molecularly relapsed or refractory adult BCP-ALL (minimal residual disease positive; MRD+) were treated with blinatumomab at a dose of 15mcg/m²/d over a 4 week cycle followed by a 2-week treatment free interval. The mean steady state serum concentration with this treatment regimen was
731 pg/ml (range 492-1050), average elimination half-life \((t_{1/2})\) was 1.25±0.63 hours, average clearance rate was 22.3±5 L/d/m² and volume of distribution was 1.61±0.74 L/m² (22). Steady state concentration did not significantly vary between first and subsequent cycles; no human anti-mouse antibodies were detected. In the relapsed refractory ALL (RR-ALL) setting, steady state concentrations are comparable to those reported above (23); furthermore, similar pharmacokinetic parameters were reported in pediatric patients as compared to adult patients with RR-ALL when body surface area-based dosing was applied (24).

T-cell and B-cell dynamics following administration of blinatumomab are also predictable and well characterized. The initial activation of polyclonal T-cells results in a transient release of cytokines such as IL2, IL6, IL10, IFN\(\gamma\) and TNF\(\alpha\). Cytokine release seems to be confined to the first cycle of therapy, perhaps due to reduction in the number of target cells in subsequent cycles. B-cell counts drop within 2 days of treatment and remain low throughout therapy; T-cells decline to nadir within one day of treatment but promptly re-expand within a few days to more than double the baseline level by 2-3 weeks, mostly attributed to expansion of the effector memory T-cell compartment (CD45RA-/CD197\(^+\)). A large proportion of re-expanding T-cells also exhibit T-cell activation markers such as CD69 (22, 25).

**Blinatumomab for B-cell Precursor ALL**

To date, treatment with blinatumomab has been reported in RR-ALL or in the setting of MRD positivity; the latter is regarded as a high risk feature closely associated with disease resistance/relapse (26, 27) (Table 2).

Topp (28) initially reported on the outcome of 21 adult patients (median age 47 years) with MRD positive disease that were treated with Blinatumomab. MRD positivity was defined
as ≥1X10^4 by PCR for Immunoglobulin or T-cell receptor genes or specific genetic aberrations (MLL, BCR-ABL) documented at any time-point after consolidation therapy was completed.

Fifteen patients had MRD refractory disease and 5 had MRD relapse; 5 patients with Ph+ disease were included in this study. Patients on this phase II trial received 15 mcg/m²/d continuously during 4 weeks of 6 week cycles; responders were treated with up to 4 cycles. The primary end point was defined as the achievement of PCR-based negative MRD by 4 cycles of therapy. MRD negative disease was obtained after one cycle in all 16 of the 20 evaluable responding patients (80%), half of which proceeded to allogeneic transplant. At the time of report all transplanted patients as well as 4 of 7 that were not transplanted maintained their remission translating into a relapse free survival (RFS) of 78% at a median follow up 13.5 months. Four relapses were documented; two were extra medullary relapses and 2 were CD19 negative. The most frequent adverse events (AE’s) were pyrexia, chills, hypogammaglobulinemia and hypokalemia. Grade III or higher AE were documented in 81% of patients, lymphopenia being the most frequent. No early deaths were observed; 2 patients developed central nervous system (CNS) AE’s: seizures in one patient and syncope and convulsions in another. An update of this trial reported at 33 months of follow-up demonstrated hematologic RFS of 61% (65% in those transplanted and 60% for those that were not) (29). The results of a large phase II trial in MRD+ ALL patients were recently reported (BLAST trial) (30). One hundred and sixteen patients over age 18 (median age 45 years) with positive MRD (defined as ≥10^-3 by PCR) were treated with the same dose of blinatumomab described above. Seventy four patients completed planned therapy (4 cycles of blinatumomab or less if the patient went to transplant); 32 patients discontinued therapy due to AE’s, relapse,
or investigator decision. The primary endpoint of MRD negativity after 1 treatment cycle was met in 78% of the 116 patients and further increased to 80% on subsequent treatment cycles. Most frequent AEs (in >20% of patients) were pyrexia, headache, tremor, chills, fatigue, nausea and vomiting. Sixty percent of patients experienced high grade toxicities including aphasia and encephalopathy in 5% each. Two patients died during therapy of subdural hemorrhage and pneumonia.

Blinatumomab was also used in the setting of RR-ALL. In an initial report, Topp et al. (31) reported on 36 adult patients (median age 32 years) treated with blinatumomab for RR-ALL. The study population consisted of high risk patients and included 15 patients that relapsed post-transplant, 8 patients with early relapse or primary refractory disease, patients with Ph+ disease (n=2) and MLL rearranged disease (n=4). Patients were initially treated with the ‘MRD+’ dose of 15 mcg/m²/d for 4 of a 6-week cycle but dosing was later amended due to a grade IV cytokine release syndrome (CRS) in 1 patient to include 1 week of a lower 5 mcg/m²/d dose followed by 15 mcg/m²/d. Dexamethasone or cyclophosphamide pre-treatment were also allowed in order to avoid CRS. The primary end point of this study was defined as the achievement of CR (or CR with incomplete count recovery (CRh)) within 2 treatment cycles and was met in 69% of patients; 88% of responders achieved MRD negative disease. The median OS and RFS were 9.8 and 7.6 months, respectively. Lower CR rates as well as a trend towards lower OS were noted in the post-transplant subgroup. Fifty two percent of responders went on to receive an allograft with considerable transplant related mortality (TRM; 6 of 13 patients). Ten patients relapsed, 3 of which had CD19 negative recurrence. Most patients experienced serious AE’s (SAE’s) including 2 grade IV CRS and 6 patients that required treatment interruption due to
CNS toxicities. Six patients died from infection during active treatment. A subsequent phase II study, the largest prospectively reported experience with blinatumomab to date, enrolled 189 adult patients with Ph-negative RR-ALL (median age 39; one third of patients with post-transplant relapse) to received 28 mcg/d for 4 of 6-week cycles with a run-in dose of 9 mcg/d on the first week of the first cycle and in up to 5 cycles of therapy. Steroid prophase was given to patients with a high burden of disease (>50% blasts in marrow, peripheral blasts >15,000 X10^9/L or elevated LDH per investigator discretion). The primary end point of CR/CRh was achieved in 43% of patients; MRD negativity was observed in 82% of responders. Forty percent of responders went on to receive an allograft with a reported TRM of 11% at 100 days, in contrast to the high TRM in the previous trial. OS and RFS were 6.1 and 5.9 months respectively (Fig. 2); patients that achieved an MRD-negative status tended to have better outcomes (6.9 months vs. 2.3 months for MRD- and MRD+, respectively). Although blinatumomab demonstrated significant single agent activity in this high risk disease setting it should be noted that the overall OS and RFS were far from satisfactory (with or without transplant); Nonetheless, it is reasonable to perform alloSCT in eligible patients who respond to blinatumomab salvage. Ninety-nine percent of patients had an AE of any grade, most frequently (in decreasing order) pyrexia, headache, febrile neutropenia, peripheral edema, nausea, hypokalemia, constipation and anemia. The majority of patients experienced ≥grade III toxicity (68%) most frequently febrile neutropenia, neutropenia and anemia; disseminated intravascular coagulation was noted in 2% of patients. Ten percent of patients required dose reductions due to AE’s. Thirty-four patients permanently discontinued therapy due to AE’s and in 18 patients dose interruptions were deemed treatment-related by the investigator. Twelve
percent of patients (n=23) suffered fatal AE’s, mainly infection. CNS toxicities were noted in half of the patients and were mostly early in therapy and low grade; 13% of patients had grade III or higher CNS events that resolved in most cases (32). A phase III trial comparing blinatumomab to investigator’s choice of chemotherapy in RR-ALL is ongoing (TOWER study; NCT02013167).

Data on the safety and efficacy of blinatumomab in the pediatric population is still accumulating (33, 34). Von Stackelberg et al. recently reported on 41 pediatric patients (<18 years of age) treated with blinatumomab at escalating doses for RR-ALL (5-30 mcg/m²/day). The study population was enriched for patients with high risk features such as post-transplant relapse (63% of patients) or refractory disease (20%). Recommended dose was established at 5 mcg/m²/day for 1 week followed by 15 mcg/m²/day for an additional 3 weeks in 6-week treatment cycles. Across all dose levels explored in this study, 32% of patients achieved CR. Seventy-seven percent of responders rendered MRD negative and 69% of responders went on to receive a transplant. Median OS (for all patients) and RFS (for responders) were 5.7 and 8.3 months, respectively with 1 year of follow-up (24). A subsequent report summarized the initial results of a phase II study in pediatric RR-ALL treated with blinatumomab at the above reported dose (5-15 mcg/m²/day). CR was achieved in 31% of patients during the first 2 cycles of therapy. Five of the responding 12 patients (42%) rendered MRD negative and 6 proceeded to transplant. Median OS (for all patients) and RFS (for responders) were 4.3 and 5.6 months, respectively. CRS was noted in 3 patients (2 of which had ≥grade III AE) (35).

**Blinatumomab for Other CD19+ B-cell Malignancies**

The first pivotal phase I trial to report on the safety and potential efficacy of blinatumomab in blood cancers was published in 2008 and involved 38 adult patients with
various refractory CD19-positive lymphoma, mostly mantle cell lymphoma (38.5%) and follicular lymphoma (41%) (25). Blinatumomab was given via continuous IV infusion over 4-8 weeks at escalating doses from 0.5 mcg/m²/d up to 60 mcg/m²/d. Toxicity was generally similar to that described for the ALL cohort above and included manageable AE’s that appeared early in treatment and were largely reversible. Five patients discontinued therapy due to CNS AE’s. All documented responses occurred at a dose level of ≥15 mcg/m²/d suggesting a dose-response relationship. Eleven of 38 patients (29%) experienced major responses (4 complete and 7 partial remissions). In a follow-up report additional escalation of the dose to 90 mcg/m²/day resulted in 2 documented CNS dose limiting toxicities and authors recommended a dose of 60mcg/m²/day for treatment of lymphoma (36). Results of a phase II study assessing blinatumomab in heavily pre-treated adult patients with relapsed or refractory diffuse large B-cell lymphoma were recently presented. Twenty five patients were treated, most of whom received treatment with stepwise dosing of 9, 28 and 112 mcg/d for 8 weeks (followed by 4 week consolidation in some). At this higher dose, most patients experienced serious AE’s, most frequently infections; two patients died during on-study (progressive disease and pneumonia) and 7 patients suffered grade III neurologic AE’s. The overall response rate was 43% (9 of 21 evaluable patients) and median duration of response was 11.6 months (37).

Toxicity

Much of the toxicity that is associated with blinatumomab therapy appears early during therapy and stems from its mode of action, i.e., polyclonal T cell activation. Indeed, immunopharmacologic studies demonstrate that blinatumomab is associated with a transient release of inflammatory cytokines and with the proliferation of specific T cell populations as
described above (22). Another anticipated drug effect, B-cell depletion, results in significant panhypogammaglobulinemia (HGG) during and after therapy. All 5 responding patients in one report did not recover to baseline immunoglobulin concentrations based on a median follow-up of over 15 months (38). The clinical consequences of prolonged HGG after blinatumomab therapy as well as the role of replacement therapy in such patients remain to be established.

Cytokine release syndrome (CRS) and CNS toxicities deserve special attention as they seem to be a recurrent theme with T-cell engaging therapies and are frequently reported with blinatumomab as well as with CART19 therapies (39, 40).

CRS severity varies among the various reports and can range from mild, low grade toxicities to life threatening fatal occurrences. The risk of developing high grade CRS seems to correlate both with disease burden and initial blinatumomab dosing; the risk of CRS can be significantly reduced with a ‘stepwise’ dosing approach as well as with a steroid-based pre-treatment in patients with high disease burden. In that regard in-vitro studies suggest that co-administration of dexamethasone with blinatumomab blunts the production of inflammatory cytokines without significantly affecting T-cell activation or neoplastic B-cell killing (41). Furthermore ad-hoc analysis from a large phase II trial did not show any appreciable effect of dexamethasone on the achievement of CR/CRh (32). High-grade CRS was not reported in the setting of MRD+ ALL (28). In the initial phase II trial in patients with RR-ALL, 2 of 36 patients had grade IV CRS. Both patients had high burden of disease (approximately 90% blasts in marrow) and one of these patients also had concomitant tumor lysis syndrome. A step-wise dosing approach and pre-treatment with steroids and/or cyclophosphamide resulted in no further ≥grade III CRS (31). In the subsequent larger phase II trial a stepwise dosing approach in the first
cycle and steroid pretreatment for patients with >50% blasts in marrow, peripheral blasts >15,000 X10^9/L or elevated LDH per investigator discretion resulted in only 2% of patient (n=3) experiencing grade III CRS (32). In both trials patients with higher grade CRS seemed to have responded well to therapy (4/5 patients achieved CR). Some investigators observed striking clinical and biological similarities between high grade CRS after T-cell engaging therapy and hemophagocytic lymphohistiocytosis or macrophage activation syndrome. Furthermore anecdotal reports describe dramatic responses to IL6 receptor directed therapy (42), as is the case for CART19 therapies.

In contrast to CRS, CNS toxicity is reported across diagnoses, disease burden and dosing levels. These toxicities tend to appear early in therapy (within the first week) and are largely low grade, reversible and usually do not necessitate treatment interruption or discontinuation. The clinical presentation can be quite variable and includes tremor, dizziness, confusion, encephalopathy, ataxia, aphasia and convulsions. The role of dose adjustments or steroids in prevention or management of CNS toxicities is not clear to date but nonetheless are employed in various reports and in the clinic (32, 36). In the largest prospective trial to date, 52% of 189 patients treated for RR-ALL had neurologic AE’s, most of which were low grade (76%). Twenty patients (11%) and 4 (2%) had grade III and IV CNS toxicity, respectively. All of these toxicities resolved although 3 patients died of apparently unrelated causes after the onset of toxicity. According to dose-modification criteria in this study protocol, blinatumomab was permanently discontinued in patients with grade IV CNS toxicity, those with more than one seizure and those whose therapy was delayed by more than 2 weeks due to toxicity. All other patients with high-grade CNS toxicity were eligible for re-treatment with blinatumomab at the same or lower dose.
with steroid premedication once toxicity resolved to grade I or baseline. Applying these criteria resulted in treatment interruption in 29 patients; 10 of these patients already achieved remission before dose was interrupted. Forty-two percent of the remaining 19 patients achieved remission after treatment was re-started (32).

Clinical and biological markers to aid identifying patients at risk for significant CNS toxicity are lacking. A low peripheral blood B to T cell ratio (e.g., <1:10) was suggested in one retrospective analysis to predict CNS toxicity (43). This approach was later applied in patients with NHL to allocate patients ‘at risk’ for CNS toxicity to a ‘stepwise’ dose escalation approach (36).

Conclusions and Future Directions

Blinatumomab represents an important addition to our therapeutic armamentarium for treating RR-ALL and is hopefully the first of many targeted immunotherapies to enter the clinic. Although blinatumomab demonstrated impressive single agent activity in RR-ALL for which it was approved, current data suggests that responses are generally short-lived and should be followed by allogeneic transplantation if feasible. Unfortunately even those RR-ALL patients in whom MRD negativity was achieved had relatively short relapse free survival (6.9 months vs. 2.3 months for MRD- and MRD+, respectively (32)); possibly reflecting the inherent resistance due to clonal heterogeneity that characterizes heavily pre-treated RR-ALL. In contrast, long term remissions were reported when blinatumomab was administered for MRD+ disease in first remission suggesting that moving blinatumomab into the upfront setting may be an optimal intervention. Indeed, the phase III E1910 study (NCT02003222) is currently randomizing fit patients to blinatumomab in the post induction phase. Another ongoing phase II trial is
assessing the addition of blinatumomab to low dose chemotherapy or to steroids and dasatinib in patients over 65 years with Philadelphia negative or positive ALL, respectively (NCT02143414).

Mechanisms of resistance to blinatumomab therapy are poorly described to date. Loss of CD19 expression is a potential pathway for resistance. Indeed, CD19 negative relapses were reported in trials assessing this drug in RR-ALL (31, 32). Furthermore, recent observations suggest that CD19 negative sub-clones may exist alongside the dominant CD19+ clone and thus may be selected for with CD19 targeted therapy (44).

Finally, the unique toxicity profile of T-cell engaging therapies, specifically CNS toxicity is poorly understood and studies to better describe the ‘at-risk’ population as well as preventive approaches are eagerly anticipated.

References


Table 1. Selected targeted therapies for Ph-negative B-cell precursor acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Class</th>
<th>Target</th>
<th>Compound</th>
<th>Stage of clinical development/activity in capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconjugated antibodies</td>
<td>CD20</td>
<td>Rituximab</td>
<td>FDA approved for various CD20+ malignancies. Phase II trials in newly diagnosed adult CD20+ ALL demonstrate survival benefit in younger adults (45, 46). Phase III trial ongoing (GRALL-2005).</td>
</tr>
<tr>
<td></td>
<td>CD20</td>
<td>Ofatumumab</td>
<td>Ongoing phase II trial in newly diagnosed adult CD20+ ALL (47)*.</td>
</tr>
<tr>
<td></td>
<td>CD22</td>
<td>Epratuzumab</td>
<td>Phase II trials demonstrate the benefit of chemotherapy in combination with epratuzumab in pediatric and adult RR-ALL (48-50). Phase III trial ongoing for pediatric patients with relapsed ALL (NCT01802814).</td>
</tr>
<tr>
<td></td>
<td>CD52</td>
<td>Alemtuzumab</td>
<td>Post remission therapy in newly diagnosed adult ALL resulted in deeper MRD response in a phase I trial (51)*.</td>
</tr>
<tr>
<td>Immuno-conjugates</td>
<td>CD22</td>
<td>Inotuzumab ozogamicin</td>
<td>Significant single agent activity in adults with RR-ALL (52); phase III ongoing and recently reported to have positive results in terms of CR rates (NCT01564784). Ongoing early phase trials of Inotuzumab ozogamicin in combination with chemotherapy in the upfront or RR-ALL setting in adults (53, 54)*.</td>
</tr>
<tr>
<td></td>
<td>CD19</td>
<td>SGN19A</td>
<td>Ongoing phase I study in pediatric and adult patients with RR-ALL/lymphoma (55)*.</td>
</tr>
<tr>
<td>Immuno-toxins</td>
<td>CD22</td>
<td>BL22/HA22</td>
<td>Ongoing phase I trial in pediatric RR-ALL (56)*.</td>
</tr>
<tr>
<td></td>
<td>CD22, CD19</td>
<td>Combotox</td>
<td>Phase I trials in pediatric and adult RR-ALL completed (57, 58); Combotox in combination with cytarabine currently explored in adults.</td>
</tr>
<tr>
<td>T-cell engaging therapies</td>
<td>CD19</td>
<td>Blinatumomab</td>
<td>Accelerated FDA approval for Ph-negative RR-ALL based on phase II trials (31, 32). Effective in eradicating MRD (28-30)*. Several phase II and III trials ongoing (e.g., NCT02003222, NCT02143414, NCT02013167, NCT02000427).</td>
</tr>
<tr>
<td></td>
<td>CD19</td>
<td>CART cells</td>
<td>Significant activity in pediatric and adult RR-ALL (40).</td>
</tr>
<tr>
<td>Kinase inhibitors</td>
<td></td>
<td></td>
<td>Pre-clinical activity; anecdotal reports from the clinic (59).</td>
</tr>
</tbody>
</table>

*Presented in abstract form.*
Abbreviations: CR, complete remission; MRD, minimal residual disease; RR-ALL, relapsed or refractory acute lymphoblastic leukemia.
Table 2. Blinatumomab for acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Context</th>
<th>N</th>
<th>Median age (range)</th>
<th>Remission rate (CR/CRh)</th>
<th>MRD negative rate (among responders)</th>
<th>Survival (median follow-up, months)</th>
<th>Salvaged to transplant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topp et al. (28, 29)</td>
<td>Phase II: MRD-positive adult ALL</td>
<td>21</td>
<td>47 (20-77)</td>
<td>-</td>
<td>80%</td>
<td>RFS 65% (33 months)</td>
<td>50%</td>
</tr>
<tr>
<td>Goekbuget et al. (30)*</td>
<td>Phase II: MRD-positive adult ALL</td>
<td>116</td>
<td>45 (18–76)</td>
<td>-</td>
<td>80%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Topp et al. (31)</td>
<td>Phase II: Adult RR-ALL</td>
<td>36</td>
<td>32 (18-77)</td>
<td>69%</td>
<td>88%</td>
<td>OS 9.8 months (12.1 months)</td>
<td>52%</td>
</tr>
<tr>
<td>Topp et al. (32)</td>
<td>Phase II: Adult RR-ALL</td>
<td>189</td>
<td>39 (18-79)</td>
<td>43%</td>
<td>82%</td>
<td>OS 6.1 months (9.8 months)</td>
<td>40%</td>
</tr>
<tr>
<td>Von Stackelberg et al. (24)*</td>
<td>Phase I: Pediatric RR-ALL</td>
<td>41</td>
<td>&lt;18 years</td>
<td>32%</td>
<td>77%</td>
<td>OS 5.7 months (12.4 months)</td>
<td>69%</td>
</tr>
<tr>
<td>Gore et al. (35)*</td>
<td>Phase I-II: Pediatric RR-ALL</td>
<td>39</td>
<td>9 (2-16)</td>
<td>31%</td>
<td>42%</td>
<td>OS 4.3 months (6 months) RFS 5.6 months</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Presented in abstract form.

Abbreviations: CR, complete remission; CRh, complete remission with partial hematological recovery; MRD, minimal residual disease; OS, overall survival; RR-ALL, relapsed or refractory acute lymphoblastic leukemia; RFS, relapse free survival.
**Figure 1.** Blinatumomab structure and mode of action.

VH, heavy chain variable *domain*; VL, light chain variable *domain*.

**Figure 2.** Relapse-free survival (A), overall survival (B), and overall survival with censoring at achievement of a complete remission (C) in 189 patients with relapsed or refractory BCP-ALL.

Figure 1:

- **Cytokine production**
  - ↑ IL2
  - ↑ IL6
  - ↑ IL10
  - ↑ IFNγ
  - ↑ TNFα

- **T-cell activation and proliferation**
  - ↑ CD69
  - ↑ CD25

- **Perforin and granzymes**

- **Redirected lysis**
  - Apoptosis
Figure 2:

A

Relapse-free survival (%)

Number at risk 82 62 49 26 18 11 6 4 1 0

Time (months)

B

Overall survival (%)

Number at risk 189 139 104 72 44 27 21 14 10 6 0

Time (months)

C

Overall survival (%)

Number at risk 189 139 104 72 44 27 21 10 6 0

Time (months)

Censored at the time of CR or CRh

N Median overall survival (months) 95% CI

No 189 6.1 4.2–7.5

Yes 189 3.5 2.4–3.9

Censored

Not censored at CR or CRh

CCR Drug Updates
Blinatumomab for the Treatment of Philadelphia Chromosome-Negative, Precursor B-cell Acute Lymphoblastic Leukemia

Ofir Wolach and Richard M Stone

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