BACKGROUND INFORMATION

FOR

THE PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING 04 DECEMBER 2012

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
ALL	Acute lymphoblastic leukemia
BiTE®	Bispecific T cell engager
C_{ss}	Steady state serum concentration
CNS	Central nervous system
CR	Complete remission
CRh*	Complete remission with partial hematologic recovery
CRp	Complete remission without platelet recovery
C_{SS}	Steady state serum concentration
DFS	Disease-free survival
E:T	Effector to target
HSCT	Hematopoietic stem cell transplantation
IV	Intravenous
NHL	Non-Hodgkin's Lymphoma
MHC	Major histocompatibility complex
MRD-positive ALL	Minimal residual disease-positive B-cell acute lymphoblastic leukemia
ODAC	Oncologic Drug Advisory Committee
OS	Overall survival
RFS	Relapse-free survival
R/R ALL	Relapsed/refractory B-cell acute lymphoblastic leukemia
TEAE	Treatment-emergent adverse event

1. Executive Summary

Amgen was invited to participate in the 04 December 2012 meeting of the Pediatric Subcommittee of the Oncologic Drug Advisory Committee (ODAC). The purpose of Amgen's participation in the meeting is to discuss issues related to the development of blinatumomab (AMG 103) for pediatric use, and to obtain guidance to facilitate the formulation of a written request for pediatric studies, if appropriate. Requested of Amgen by the FDA, and provided within this briefing package, is the regulatory history of blinatumomab (Section 2), a description of the blinatumomab clinical program in adults and pediatrics (Section 4.1), preclinical data supporting the clinical program (Section 4.1.3), and challenges that have been identified regarding clinical studies in children (Section 4.2).

Blinatumomab has an innovative mechanism of action that utilizes a patient's own cytotoxic T cells to attack CD19-positive malignant cells, including those found in B-cell malignancies. Blinatumomab is a bispecific single chain T cell engager (BiTE®) antibody with dual binding specificities. T cells are bound by its anti-CD3 moiety, whereas B lymphoblasts are bound by the anti-CD19 moiety. This unique feature of blinatumomab allows it to transiently connect malignant cells with T cells, thereby inducing T-cell-mediated killing of the bound malignant cell. In preclinical models, blinatumomab-mediated T-cell activation involves the transient release of inflammatory cytokines and proliferation of T cells. The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T-cell reaction.

Blinatumomab is currently being studied in patients with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R ALL), minimal residual disease (MRD)-positive B-cell ALL (patients in remission according to classic criteria, but with low amounts of malignant cells detectable by molecular methods), and relapsed non-Hodgkin's Lymphoma (NHL). More than 200 patients (predominately adults) have received blinatumomab as a continuous intravenous (IV) infusion at doses ranging from 0.5 to 90 $\mu g/m^2$/day. Blinatumomab is administered as a 4 or 8 week infusion using a portable minipump, followed by a 2-week treatment-free period. Patients are hospitalized for monitoring during the first 3 to 7 days of treatment; thereafter, IV bag changes are performed by a home care provider or practitioner in the outpatient setting.

In adult patients with R/R ALL (the lead indication for Amgen's blinatumomab program), a high incidence of complete remission has been observed with blinatumomab

administered as monotherapy: 72% (26 of 36 patients) had a complete remission or complete remission with partial hematologic recovery (CR + CRh*) and a median CR + CRh* duration of 8.9 months, with 24 of the 26 responders achieving a molecular remission (MRD $<10^{-4}$) (Topp et al, 2012a). In adult patients with MRD-positive ALL, an MRD response rate of 80% (16 out of 20 evaluable patients) was observed; after a median follow up of 33 months, the hematological relapse-free survival (RFS) (all 20 evaluable patients) was 61% (Topp et al, 2011; Topp et al, 2012b). In adult patients with relapsed NHL, patients treated at the target blinatumomab dose of 60 µg/m^2/day had an overall objective response rate of 71% (20 out of 28 evaluable patients, with 10 responses being a complete response or unconfirmed complete response), with a median duration of response of 508 days and ongoing responses in 11 patients, of which one patient has shown a response duration of over 3 years (Goebeler et al, 2011).

The most common treatment-emergent adverse events (TEAEs) observed to date in patients treated with blinatumomab have been flu-like symptoms (pyrexia, chills, headache, and fatigue, which are most likely related to the release of pro-inflammatory cytokines associated with T-cell activation by blinatumomab), tremor, weight increase, hypokalemia, and decrease of blood immunoglobulin. Most of these events were transient in nature, usually occurring during the first cycle. The clinically most important adverse events observed to date in patients treated with blinatumomab have been central nervous system (CNS) events, such as seizure, encephalopathy, tremor, apraxia, speech disorders (aphasia, dysarthria), and disorientation, the majority of which were Grade 1 or 2 in severity. The incidence of patients experiencing CNS events is greatest within the first few days of blinatumomab treatment; these events have been typically reversible within several days either during treatment or after discontinuation of treatment. No long-term effects or sequelae have been observed with blinatumomab-associated CNS events. Infections have been observed and are not unexpected; underlying hematologic malignancies and prior therapies are both known to result in neutropenia that may increase the risk of infection in these patient populations. Additionally, in patients with high blast counts, symptoms that are consistent with tumor lysis syndrome have been reported.

Amgen is in the process of evaluating the dose, safety, and pharmacokinetics (PK) of blinatumomab in the R/R ALL pediatric population in an ongoing, single-arm, phase 1/2 study (Study MT103-205). In this study, the dose selected in the phase 1 part will be

evaluated for safety and efficacy (CR + CRh*) in up to 40 patients (aged <18 years) in the phase 2 part. Assuming a favorable benefit-risk profile, these pediatric data could facilitate blinatumomab access for the pediatric R/R ALL population.

2. Blinatumomab Regulatory History

Ongoing studies in the United States (US) are conducted under a single IND; the sponsorship of this IND was transferred from MedImmune to Micromet on 01 July 2009 and from Micromet to Amgen on 23 March 2012.

Orphan designations have been granted for the following indications in the US (year of orphan designation in parentheses):

- Treatment of acute lymphocytic leukemia (2008)
- Treatment for hairy cell leukemia (2008)
- Treatment of prolymphocytic leukemia (2008)
- Treatment of chronic lymphocytic leukemia (CLL) (2008)
- Treatment of indolent B-cell lymphoma, excluding CLL and NHL with CNS involvement (2006)

The approach to the pediatric evaluation of blinatumomab was previously discussed with FDA as part of a formal meeting in May 2010. It was advised by FDA during the meeting that a dose-finding, PK, and safety study be undertaken to determine an appropriate dose and dosing schedule in pediatric patients aged 0 to <24 months, 2 to 6 years, and 7 to <18 years. FDA also recommended that heterogeneity should be reduced in the pediatric study population in order to adequately assess patients with unmet medical needs or to make comparisons to a historical control population. For a definitive study, FDA strongly recommended a randomized controlled study design.

Amgen intends to seek a globally acceptable pediatric development plan through the future submission of a Pediatric Study Plan in the US and a revised Pediatric Investigational Plan in the European Union (EU).

3. Blinatumomab Mechanism of Action

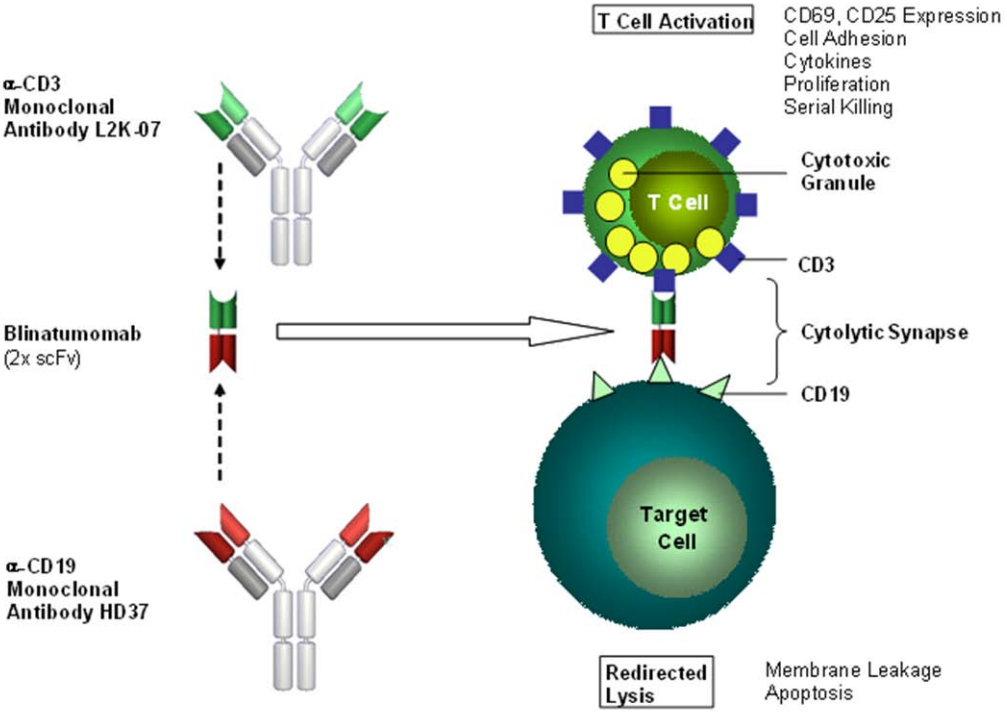
Blinatumomab, a first-in-class bispecific T cell engager (BiTE®) antibody, has dual binding specificities for CD3 and CD19. T cells are bound by its anti-CD3 moiety, whereas malignant and normal B cells are bound by the anti-CD19 moiety. The transient close association of the B cell with the T cell occurs in an antigen independent manner (Kischel et al, 2009), and all circulating T cells are able to participate in T cell mediated lysis through the production of perforin and granzyme B (Figure 1). This close interaction between T and B cells also results in a CD19 dependent polyclonal expansion of T cells and release of cytokines (TNF-α, INF-γ, and IL-2) from the T cells (Brischwein et al, 2007). In vitro, blinatumomab mediated dose-dependent lysis of CD19-positive human B cell precursor leukemia NALM-6 cells at a biological relevant concentration (EC90) of 470 pg/mL (8.5 pM). The lysis by blinatumomab-activated T cells closely resembles a natural cytotoxic T cell reaction (Brandl et al, 2007; Hoffmann et al, 2005; Dreier et al, 2002; Loffler et al, 2000). In the absence of CD19 expressing cells, blinatumomab does not result in activation of T cells.

In the presence of blinatumomab, T cells can eliminate tumor cells even at very low effector-to-target cell (E:T) ratios (1:90), indicating that redirected T cells can repeatedly lyse target cells (Hoffmann et al, 2005). The anti-tumor activity of blinatumomab is polyclonal in nature and is not dependent on T cells bearing a specific T-cell receptor or on peptide antigens presented by cancer cells or the major histocompatibility complex (MHC) class I molecules on target cells. CD8-positive and CD4-positive effector memory T cells have been shown to mediate the majority of BiTE® activity.

Blinatumomab targets malignant B cells highly specifically (affinity of 1.6×10^{-9}M) via CD19, a marker solely expressed by B cells. Then, blinatumomab recruits and activates T cells via a lower affinity interaction with CD3 (8.7×10^{-8}M). In vitro, blinatumomab can induce a half-maximal target cell lysis ranging in vitro between 10 to 100 pg/mL (ie, 0.18-1.8 pM), showing blinatumomab to be a potent molecule (Dreier et al, 2002). The relatively low affinity of blinatumomab for CD3 on T cells may allow fast disengagement of T cells after redirected lysis from target cells and thus support serial lysis by T cells.

Blinatumomab's 2 target antigens, CD3 and CD19, are both expressed in all pediatric age groups during normal development at levels comparable to those in adults (Lewis et al, 2004), and pediatric B-cell malignancies, like those of adults, express CD19. Therefore, blinatumomab is expected to have activity in patients of all ages.

Figure 1. Blinatumomab T Cell-mediated Tumor Cell Lysis



4. Blinatumomab Development Program

Blinatumomab is currently being studied in patients with R/R ALL, MRD-positive ALL, and NHL. More than 200 patients have received blinatumomab as a continuous IV infusion, including 16 patients with R/R ALL aged <18 years. Doses administered to adults have ranged from 0.5 to 90 µg/m^2/day. The maximum dose tested in adults, 90 µg/m^2/day, is 1.5-fold higher than the highest dose planned for evaluation in pediatric patients. The maximum duration of exposure in the adult population has been 140 days. The same formulation and route of administration (ie, continuous IV infusion) used in adult patients is being used in pediatric patients.

A tabular summary of ongoing and planned clinical studies using the continuous IV infusion schedule is provided in Appendix A. Experience with a short-term infusion dosing schedule (for which development was terminated due to adverse events [mainly CNS events] and no efficacy signals) is not presented.

4.1 Relapsed/Refractory ALL

The most advanced program for blinatumomab is treatment of R/R ALL. Three single-arm studies, 2 in adults and 1 in pediatric patients, are currently ongoing (Table 1) and will assess the ability of blinatumomab monotherapy to induce complete remission (Section 4.1.2).

Ongoing pediatric study MT103-205, designed with input from FDA, is an open-label, 2-part, multicenter clinical study. The first part (phase 1) will investigate the PK, safety, and clinical activity of escalating dose levels of blinatumomab in pediatric and adolescent patients with B-precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic hematopoietic stem cell transplantation (HSCT), or refractory to other treatments. Up to 5 different dose levels of blinatumomab will be evaluated. Once a dose has been selected in the phase 1 part, the phase 2 part will assess the safety and efficacy of the recommended dose. This study design combines phase 1 and phase 2 into a single study in order to be efficient due to the limited number of potentially eligible patients and the need for therapeutic options. The eligibility criteria, treatment plan, and assessments are identical for both phases of the study.

Table 1. Blinatumomab Clinical Studies in R/R ALL

Study Number/Description	Patient Population	Dose and schedule	Number of Patients	1º Endpoint	Other Endpoints	Publication
MT103-206 Open-label, multicenter, single arm, exploratory P2 study to evaluate the efficacy, safety, and tolerability of blinatumomab in adult patients with R/R ALL	Adults with B-precursor ALL relapsed after at least induction and consolidation, or having refractory disease; >5% blasts in bone marrow	Up to 5 cycles of blinatumomab cIV, 4 wks on / 2 wks off. Responders: up to 3 additional cycles of treatment or proceed to BMT. Final dose regimen: blinatumomab 5 µg/m²/day (wk 1) followed by 15 µg/m²/day for remaining treatment period.	36	Rate of CR + CRh* within 2 cycles	TTR, RFS, OS; proportion who undergo aHSCT after treatment	Topp et al, 2012a (See Appendix A)
MT103-211 Open-label, multicenter, single arm, P2 study to evaluate the efficacy and safety of blinatumomab in adult patients with R/R ALL	Adults with Ph-negative B-precursor ALL relapsed or refractory with first remission duration ≤12 months in first salvage or after first salvage therapy or within 12 months of aHSCT; 10% or more blasts in bone marrow	Blinatumomab 9 µg/day cIV (corresponding to 5 µg/m²/day) (wk 1, cycle 1) followed by 28 µg/day (corresponding to 15 µg/m²/day) for remaining period. Responders within 2 cycles can receive up to 3 additional cycles or proceed to BMT. Up to 5 cycles of blinatumomab cIV, 4 wks on / 2 wks off.	61 planned	Rate of CR+CRh* within 2 cycles	TTR, RFS, OS; proportion who undergo aHSCT after treatment	Not Available
MT103-205 Single-arm multicenter P2 study preceded by dose evaluation to investigate the efficacy, safety, and tolerability of blinatumomab in pediatric and adolescent patients with R/R ALL	Patients <18 years with Ph-negative B-precursor ALL in second or later bone marrow relapse; any marrow relapse after aHSCT; or refractory to other treatments; >25% blasts in bone marrow.	Phase 1: Blinatumomab 3.75 to 60 µg/m^2/day cIV, 4 wks on / 2 wks off Phase 2: Up to 5 cycles with recommended dose of blinatumomab	Phase 1: up to 48 planned Phase 2: up to 40 evaluable patients	Phase 2 Part: Rate of CR + CRh* within 2 cycles	TTR, RFS, OS, CR duration; proportion who undergo aHSCT after treatment; MRD response (exploratory)	Not Available

BMT = bone marrow transplantation; cIV = continuous intravenous infusion; CR = complete remission; CRh* = complete remission with partial hematologic recovery; aHSCT = allogeneic hematopoietic stem cell transplantation; OS = overall survival; RFS = relapse-free survival; TTR = time to hematological relapse; wks = weeks.

4.1.1 Pediatric Relapsed/Refractory ALL Landscape

Of the approximately 1600 US children and adolescents diagnosed with precursor B-cell ALL each year (based on 2009 SEER data), approximately 25% (400) will experience relapse or fail to achieve remission. The majority (85%) of those in first relapse will achieve a second remission (Ko et al, 2010). Response to chemotherapy decreases with each successive relapse. Approximately 44% of pediatric patients with second marrow relapse of ALL and 27% of those with third marrow relapse achieve a subsequent complete remission (Table 2). Five-year disease-free survival (DFS) rates in patients with second and third remission are reported to be 27% and 15%, respectively (Ko et al, 2010). Two percent of children with ALL who do not achieve a remission are classified as having refractory disease (Pui and Evans, 2006) and suffer a worse prognosis compared to patients with relapsed ALL.

The population targeted in Study MT103-205 includes refractory ALL, second or later bone marrow relapse, or any marrow relapse after allogeneic HSCT. This population has a poor prognosis and few effective standard treatment options (Appendix B and Appendix C). Existing treatment regimens for this disease rely heavily on high-intensity chemotherapy that consists of combinations of a few classes of drugs, eg, antimetabolites, anthracyclines, and alkylating agents. For patients who are refractory after such treatment, or who relapse, not only is there typically cumulative morbidity from the effects of treatment, but there is a higher probability of cross-resistance to available chemotherapeutic agents. Patients who undergo an allogeneic HSCT usually have received very intensive multi-drug treatment regimens for induction/re-induction, consolidation, and additional conditioning followed by allogeneic HSCT, a procedure that is also associated with severe adverse reactions. The prognosis for patients whose ALL relapses after such intensive treatment is particularly poor; the 3-year survival rate for patients who received HSCT from matched sibling, matched related/unrelated, and mismatched donors has been reported to be 21%, 17%, and 6%, respectively (C Peters, unpublished data, February 2012). An effective biologic agent could represent a valuable treatment option for these patients.

Table 2. Benchmark Values Established by the Therapeutic Advances Childhood Leukemia Consortium

Relapse	Response Rate	2-year DFS	5-year DFS
1st relapse	85%	40 ± 4%	27 ± 4%
2nd relapse	44%	31 ± 7%	15 ± 7%
3rd relapse	27%	13 ± 9%	
4th or greater relapse	12%	19 ± 16%	

DFS = disease-free survival

Source: Ko et al, 2010

The most recent FDA approval in the pediatric R/R ALL setting is Clolar® (clofarabine), which was granted an accelerated approval for use as monotherapy on the basis of a single-arm pediatric study (US FDA, 2004). A confirmatory pathway was discussed with FDA as recently as February 2011 (US FDA, 2011). Of the 61 patients with relapsed or refractory disease after 2 or more therapies, the overall rate of remission (CR plus CR without platelet recovery [CRp] (95% CI) was 19.7% (10.6%; 31.8%) (CR = 12% [7 patients]; CRp = 8% [5 patients]), with a median duration of response (CR + CRp) of 10.7 weeks (Clolar® Prescribing Information). Of the 35 patients who were refractory to their immediately preceding induction regimen, 6 (17%) achieved a CR or CRp. Of the 18 patients who had at least 1 prior HSCT, 5 (28%) achieved a CR or CRp.

Many other single agents tested in phase 1 studies in comparable pediatric R/R ALL populations showed CR rates <10%, highlighting the challenge of demonstrating benefit in these patients (Angiolillo et al, 2009; Franklin et al, 2008; Horton et al, 2007a; Horton et al, 2007b; Angiolillo et al, 2006; Wagner-Bohn et al, 2006). In this clinical context, the consensus point estimate for efficacy of interest of a single agent for pediatric patients with second or greater relapse, relapse after allogeneic HSCT, or refractory ALL is a CR + CRh* rate of 10%, which is chosen as the null hypothesis proportion (p_0) for the phase 2 part of Study MT103-205. If the response rate fails to exceed this level, blinatumomab would not be considered an active agent for further development in this indication. Furthermore, the primary efficacy endpoint of this study (CR + CRh* rate within 2 cycles) will be met if the CR + CRh* rate is at least 22.5%, which would suggest a degree of efficacy similar to or higher than that for clofarabine.

For the phase 2 part of the ongoing pediatric Study MT103-205, focusing the key statistical analysis on a subset of patients with the highest need, ie, ALL relapse post allogeneic HSCT or refractory ALL, is being considered. In this regard, it may be necessary to increase the sample size in the respective subsets and to include a prospective analysis component for this approach in the phase 2 part of the study.

For this rare disease population, particularly for patients with relapse after HSCT, current treatment options provide limited efficacy. A high CR + CRh* rate of sufficient improvement relative to currently available therapy should be considered a clinically meaningful endpoint for registration, even when derived from a single-arm study (see Section 4.2).

4.1.2 Efficacy Observed with Blinatumomab

Adult Patients

The goal of the blinatumomab studies in R/R ALL is to demonstrate durable CR, which is associated with clinical benefit in this setting. Apart from the prolongation of survival, which a period of remission often can provide, CR offers disease control and can make patients eligible for HSCT, assuming a suitable donor is available, which is the only curative option for patients in second or later relapse, in relapse after HSCT, or with refractory disease.

Blinatumomab has the potential to demonstrate meaningful clinical benefit in pediatric patients, based on results in adult patients with R/R ALL. Study MT103-206, a phase 2, single-arm study in adults with refractory disease or with relapse after at least induction and consolidation, demonstrated a high incidence of complete remission: 72% had a CR + CRh* (26 of 36 patients; CR = 44% [16 of 36 patients]; CRh* = 28% [10 of 36 patients]) and a median duration (CR + CRh*) of 8.9 months, with 24 of the 26 responders achieving a molecular remission (MRD $<10^{-4}$) (Topp et al, 2012a). These results are encouraging in light of typical results with current salvage multi-chemotherapy regimens in adults (CR + CRh*: 30% to 60%, median DFS: 2.0 to 7.5 months) (Garcia-Manero and Thomas, 2001). The efficacy of blinatumomab in adult R/R ALL is being further characterized in a second single-arm study, MT103-211, which is currently ongoing (Appendix A).

In addition to the efficacy results observed in patients with R/R ALL, there is consistent evidence of blinatumomab's activity in a separate indication in adult ALL. Patients with

MRD ALL in their bone marrow after having achieved a complete remission have a high probability of experiencing an overt relapse (Bassan et al, 2009; Raff et al, 2007). Recent data show that blinatumomab can induce an 80% complete MRD response in these patients (Topp et al, 2011). In a follow-up analysis, it was shown that this translates into a favorable long-term outcome; after a median follow up of 33 months, the hematological RFS (all evaluable patients) was 61% (Topp et al, 2012b). Further support of the efficacy of blinatumomab comes from a phase 1 study in which patients with relapsed NHL were treated with blinatumomab. In that study, patients treated at the target blinatumomab dose of 60 µg/m^2/day had an overall objective response rate of 71% (20 out of 28 evaluable patients, with 10 responses being a complete response or unconfirmed complete response), with a median duration of response of 508 days and ongoing responses in 11 patients, of which one patient has shown a response duration of over 3 years (Goebeler et al, 2011).

Pediatric Patients

Limited experience of blinatumomab in pediatric patients was reported in a Letter to the Editor in *Leukemia* (Handgretinger et al, 2011). In this report, 3 pediatric patients (ages 7, 12, and 15 years at initial diagnosis), with refractory B-precursor ALL after multiple relapses and after allogeneic HSCT, received blinatumomab 15 µg/m²/day as a continuous IV infusion for at least 4 weeks in Germany. All 3 patients showed hematological and molecular CR at 4 weeks of treatment. One patient subsequently received HSCT and was leukemia-free after more than 23 months as of the last available follow-up. The second patient was treated with blinatumomab for 6 weeks and achieved a molecular CR with 100% donor hematopoiesis. A second allogeneic HSCT was not considered due to the high cumulative toxicity from previous chemotherapy regimens. He experienced a hematological relapse 2 weeks after cessation of blinatumomab treatment and died 3 weeks thereafter. The third patient was treated with four 4-week courses of blinatumomab treatment and achieved a molecular CR as well, but he developed a CNS relapse and molecular relapse ($<10^{-4}$) 4 weeks after the fourth treatment course. Blinatumomab caused mild transient and fully reversible side effects including fatigue, mild ataxia, and tremor in the first two patients. No side effects were observed in the third patient.

In Study MT103-205, after a blinatumomab dose has been selected in the phase 1 part, the efficacy of blinatumomab at the recommended dose will be evaluated in up to 40

pediatric patients <18 years of age in the phase 2 part. The dose range (between 5 and 60 μg/m^2/day, continuous IV infusion) was chosen to provide blinatumomab steady state levels within a biologically active range, and within the range that has been tolerable and active in adults with NHL, but below the maximum dose that has been administered to adults (90 μg/m^2/ day). The primary endpoint is rate of CR + CRh* within 2 cycles, but measures of duration and long-term efficacy will also be collected, including time to hematological relapse, CR duration, RFS, overall survival (OS), and proportion of patients who undergo allogeneic HSCT after blinatumomab treatment.

4.1.3 Safety Observed with Blinatumomab

The current understanding of blinatumomab's safety profile is based primarily on clinical data from more than 200 patients (predominately adults) with B-cell malignancies. According to these data, the anticipated clinical benefit of blinatumomab therapy in pediatric patients was considered likely to outweigh safety risks, thereby warranting initiation of the pediatric study, MT103-205. A nonclinical safety program has been conducted using a surrogate molecule because blinatumomab does not cross react in accepted toxicology species. This surrogate induced the expected pharmacological response in the mouse (eg, cytokine release) but did not replicate the clinical adverse event profile (eg, CNS events) observed with blinatumomab.

Adult Patients

The most common TEAEs observed to date in patients treated with blinatumomab have been flu-like symptoms (pyrexia, chills, headache, and fatigue, which are most likely related to the release of pro-inflammatory cytokines associated with T-cell activation by blinatumomab), tremor, weight increase, hypokalemia, and decrease of blood immunoglobulin. Infections have been observed and are not unexpected; underlying hematologic malignancies and prior therapies are both known to result in neutropenia that may increase the risk of infection in these patient populations. Most TEAEs have been early-onset (occurring in cycle 1 at the start of treatment), transient, reversible, easily managed, and have not required discontinuation of blinatumomab treatment. The majority of TEAEs have been Grade 1 or 2 in severity; Grade 3 and 4 TEAEs have included lymphopenia, pyrexia, tremor, and seizure. The clinically most important safety events have been CNS events and cytokine release syndrome.

CNS events have included seizure, encephalopathy, tremor, apraxia, speech disorders (aphasia, dysarthria), and disorientation. In the phase 1 study (Study MT103-104), a

dose schedule (including a step-wise intrapatient dose increase and optimized dexamethasone) and/or early monitoring for CNS issues to limit the risk of CNS events, as well as dexamethasone intervention to manage CNS events, was established for further evaluation in Phase 2 studies. In Study MT103-202, in the first cycle, one patient permanently discontinued treatment due to a grade 3 seizure, which did not recur after cessation of blinatumomab. In Study MT103-206, CNS events were observed in 6 patients (3 with seizures and 3 with encephalopathy). None of these events recurred after treatment interruption. All 6 patients continued treatment at a lower blinatumomab dose of 5 µg/m²/day; 2 patients had recurrence of the event and permanently stopped treatment. In one of these patients, treatment was stopped because of fatal mycotic encephalitis.

Cytokine release syndrome was reported in 3 patients with R/R ALL (Study MT103-206) and required temporary treatment interruption. Of these, 2 patients had a high tumor burden with no cytoreductive prophase, and the third patient had a milder form of cytokine release syndrome.

Four deaths were reported during Study MT103-104: 2 were due to disease progression, one was due to sepsis, and one was due to pneumocystis pneumonia/port sepsis. One death due to mycotic encephalitis was reported in Study MT103-206.

Immunogenicity is being evaluated in all clinical studies. Among 114 patients tested to date, one subject tested positive for anti-blinatumomab antibody at the end of cycle 1. Although the blinatumomab steady state serum concentration (C_{ss}) level was as expected in cycle 1, the drug was not measurable in serum samples from subsequent cycles, possibly due to generation of anti-drug antibody.

Pediatric Patients

Study MT103-205 will permit an evaluation of blinatumomab's safety profile in all pediatric age subsets. The study consists of 2 parts. In the phase 1 (dose-finding) part, which is currently ongoing, safety will be evaluated in up to 48 pediatric patients, including at least 6 patients within each age subset (0 to <2 years; 2 to 7 years; 7 to 18 years). The dose chosen in the phase 1 part will be evaluated in up to 40 patients <18 years old in the phase 2 part. Safety endpoints include the incidence and severity of adverse events, and an assessment of the development of anti-drug antibodies. Patients will be followed for survival for 24 months after the completion of treatment.

Nonclinical Safety

Limited toxicology studies were initially conducted in the chimpanzee to support first-in-human studies (Schlereth et al, 2006). Since blinatumomab does not cross react with a laboratory animal species suitable for repeat dose toxicology studies, mouse surrogate molecules were subsequently developed to aid in the nonclinical safety assessment. The murine surrogate mediated lysis of murine B cells and induced activation and cytokine release by murine T cells analogous to the action of blinatumomab in human cells. Two toxicology studies of 4 weeks duration were conducted in BALB/c mice with the mouse surrogate, one via daily IV bolus dosing and the other via twice daily subcutaneous (SC) injections, at doses of 0.2 to 5 mg/kg. The anticipated pharmacologic changes of decreased lymphocyte counts (B and T cells) and decreased total leukocytes were observed at all dose levels in both studies, associated with decreases in cellularity in lymphoid tissues. These findings were reversible after a 4-week treatment-free period. In contrast to human experience with blinatumomab, where a transient drop in T cells is observed, the mouse surrogate caused a persistent decrease in T cells.

Safety pharmacology studies with IV administration of the murine surrogate did not detect any effect on respiratory function or behavioral parameters. Subsequent to the observation of CNS adverse events in the clinical studies, a pilot study was conducted to assess the effect of the surrogate when administered directly into the cerebral ventricles of mice using a 7-day infusion. No CNS toxicity was observed. Thus, by IV or intracerebral ventricular infusion, evidence of CNS side effects that occurred in humans could not be reproduced in mice using the surrogate molecule. Furthermore, no

changes were observed after histopathological evaluation of the CNS in these animals. Potential animal models continue to be evaluated for assessment of CNS toxicity.

A preliminary embryo-fetal toxicity study has been completed. IV administration of the surrogate molecule to pregnant mice from gestation day 6 to day 15 or 18 was not associated with any adverse effects on maternal clinical condition, pregnancy, or embryo-fetal development.

The key findings in animal studies with the murine surrogate were related to its pharmacological activity (decreases in B and T cells). The toxicity studies in mice were conducted in young adult or adult animals (>8 weeks of age), an age when the immune system is mature in mice and functionally comparable to the human immune system at birth and through early childhood. Based on the available nonclinical data, there is no information to suggest that juvenile animals would exhibit a toxicity profile different from adult animals. No specific juvenile animal toxicology studies are planned. The clinical development plan for pediatrics will use clinical PK and safety data to guide decisions about dosing younger patients (ICH S9, 2009), which is in alignment with perspectives previously communicated by FDA on the program.

4.1.4 Pharmacokinetics and Pharmacodynamics of Blinatumomab

Pharmacokinetics and Pharmacodynamics in Adult Patients

The PK of blinatumomab was assessed over a dose range from 0.5 to 90 µg/m^2/day in adult patients with ALL and NHL. Following continuous intravenous infusion over 4 weeks, the steady state serum concentration (C_{ss}) was achieved within 1 day and remained stable over the dosing period across all dose cohorts. The mean C_{ss} values increased approximately dose proportionally over the dose range tested, and C_{ss} levels in different treatment cycles were comparable.

Published data are available from the MRD-positive ALL setting (Study MT103-202), in which 20 evaluable patients received blinatumomab 15 µg/m²/day (escalation to 30 µg/m²/day after first cycle for nonresponders) by continuous IV infusion (Klinger et al, 2012). The estimated mean (CV%) volume of distribution (V_z) was 1.61 (46.0) L/m^2, the mean clearance (CL) was 0.93 (22.4) L/hr/m^2, and the mean elimination half-life at terminal phase was 1.25 (50.7) hours. Since clinical data suggest that maintaining effective C_{ss} is required for achieving desired pharmacological effect and the drug is eliminated quickly when the infusion is stopped, the continuous IV infusion is considered

to be the viable regimen for blinatumomab. With the continuous IV infusion at 15 µg/m^2/day, the mean (±SD) C_{ss} was 731 ±163 pg/mL.

The kidney may contribute to renal excretion of blinatumomab (MW=55 kDa) in human patients. In bilaterally nephrectomized C57BL/6 mice, systemic exposure (AUC) and the elimination half-life were increased compared with intact animals. However, available clinical data from patients with normal renal function or mild to moderate renal impairment did not show a clinically meaningful difference in blinatumomab exposure.

Pharmacodynamic (PD) effects of blinatumomab were examined in clinical studies in adult patients. Treatment with blinatumomab is associated with a rapid depletion of peripheral B cells, accompanied by T-cell activation, and a transient increase in cytokines.

In in-vitro co-culture experiments, blinatumomab can induce redirected lysis of CD19-positive B lymphocytes and malignant B cell lines. In clinical studies, sustainable depletion of peripheral B cells was observed for the entire treatment cycle and the majority of patients showed the decline of B cells to the limit of detection (1 cell/µL) within one day of infusion.

Upon start of infusion, peripheral T cell counts dropped rapidly but recovered within a few days, and then expanded above baseline counts during treatment. A large proportion of recovering T cells exhibited up-regulation of the activation marker CD69. Months of constant exposure of patients to the globally T cell-activating blinatumomab did not lead to signs of uncontrolled T cell activation (eg, a cytokine storm) or to signs of T cell anergy, as could have been evident from the recovery of target B cell counts under continued treatment.

Cytokine elevation tended to increase with dose, and the inter-patient variability in the extent of cytokine release was large. The cytokine elevation peaked within the first 24 hours after drug administration but declined rapidly within 48 hours in the first cycle. Limited cytokine release was observed in the subsequent cycles. With a stepwise dosing scheme (eg, blinatumomab dose of 5 µg/m^2/day followed by 15 µg/m^2/day), the number of patients with transient cytokine elevation was decreased.

Pharmacokinetics and Pharmacodynamics in Pediatric Patients

In the pediatric study (Study MT103-205), PK and PD data are scheduled to be collected in all patients (<18 years old) during dose escalation from 3.75 up to 60 µg/m^2/day via

continuous IV infusion. Pharmacokinetics in pediatric and adult patients will be characterized jointly by population PK modeling, and factors (eg, demographic and baseline covariates) that may affect the blinatumomab exposure in different age groups will be evaluated. Exposure-efficacy analyses will be performed to identify the efficacious exposure range and corresponding dose range. Exposure-safety analyses will be performed to identify tolerable exposure and dose ranges. The therapeutic window and preferred dose(s) for different age groups will be assessed. The analysis will be used to support the determination of effective pediatric dose(s). The PK/PD characterization supporting dose selection will be based on data from at least 6 patients in each pediatric age group: infants (0 to <2 years), young children (2 to 6 years), and older children/adolescents (7 to 18 years).

4.2 Challenges for the Clinical Development of Blinatumomab in Pediatric Patients

The treatment goal in pediatric patients with R/R ALL, including those who relapse after allogeneic HSCT, is to achieve hematological CR, which offers disease control and/or an opportunity to undergo an additional allogeneic HSCT. The available data from studies in adult patients with R/R ALL and MRD-positive ALL suggest that the blinatumomab treatment will result in a high rate of hematological CR + CRh* that is accompanied by a high rate of molecular remission (MRD $<10^{-4}$). For this orphan disease population (US annual incidence of 400 cases) of high unmet need, particularly in children who relapse after HCST, a high CR + CRh* rate of sufficient improvement relative to currently available therapy, with consideration given to accompanying molecular remission and durability, is considered a clinically meaningful endpoint for registration.

There are several methodological as well as practical challenges of conducting clinical studies in children with R/R ALL. As noted above, the treatment goal in this setting is cure, and children who achieve hematological CR are taken to allogeneic HSCT. In the setting of subsequent HSCT, it becomes challenging to assess duration of response or other clinical benefits of study treatment. HSCT is a heterogeneous treatment modality with respect to types of conditioning regimens and categories of transplant types (eg, matched sibling, matched unrelated, mismatched sibling, mismatched unrelated, cord blood, haplo-matched) that may be used. This heterogeneity has an impact on endpoint assessment. Furthermore, the outcome of children with R/R ALL, depending on the success of “rescue” treatment, is either imminent death or long-term cure, which creates an emotionally charged situation. Once a treatment shows a CR rate that is

considerably better than the available therapy, it will not be possible to conduct a randomized study.

Even if one were able to conduct a randomized study, the analysis of time-dependent endpoints (eg, EFS and OS) for a new re-induction therapy is complicated by the clinical goal to use HSCT as a consolidation therapy after the achievement of remission. While all patients achieving a new remission are not deemed suitable as transplant candidates, for those patients that do meet such criteria, the time to transplant may vary considerably. This variability is based on such factors as the availability of a suitable donor, the satisfactory resolution of intercurrent infections or other health conditions, and even the geographic location of the transplant center relative to the transplant candidate. Therefore, it will not be possible to standardize or control for HSCT. Additionally, in the event that Study MT103-205 demonstrates a high CR rate in pediatric patients with R/R ALL, it may not be feasible to replicate the assessment through randomized studies in the same population. Demand for switching from a control arm to an active crossover treatment arm could be strong, particularly because blinatumomab is administered open-label. High rates of switching and/or a disproportionately high rate of study discontinuation among patients on the control arm could compromise the ability to unequivocally demonstrate clinical benefit.

In summary, the available data suggest that blinatumomab will demonstrate a clinically meaningful rate of remission in the pediatric R/R ALL population. A substantial improvement in efficacy over historical responses with currently available therapy, a reduction in short- and long-term toxicities, or both, would represent an important advance in addressing unmet medical needs for pediatric patients in this setting. Blinatumomab has an innovative mode of action, and the potential to provide clinically meaningful benefit as both a therapy for the attainment of remission and to facilitate towards curative allogeneic HSCT.

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Appendix A. Overview of Clinical Studies with Blinatumomab Continuous Infusion

Study Number/ Key Design Features	Dose, Route, Schedule of Administration	Number of Patients	Status	Summary of Results
Ongoing Studies: Pediatric R/R ALL				
MT103-205 Phase 1/2, single-arm, dose-finding/efficacy study in patients <18 years with B-precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments; > 25% blasts in bone marrow	Phase 1 Part: Blinatumomab up to 60 µg/m^2/day continuous IV, 4 weeks on/ 2 weeks off Phase 2 Part: Up to 5 cycles with recommended dose of blinatumomab	Phase 1 Part: up to 48 planned Phase 2 Part: up to 40 evaluable patients	Phase 1 ongoing	Not available

Study Number/ Key Design Features	Dose, Route, Schedule of Administration	Number of Patients	Status	Summary of Results
Ongoing Studies: Adult R/R ALL				
MT103-206 Phase 2, non-randomized, non-controlled, open-label study in adults with relapsed/ refractory B-precursor ALL; >5% blasts in bone marrow	Up to 5 cycles of blinatumomab continuous IV, 4 weeks on/ 2 weeks off. Responding patients could receive up to 3 additional cycles of treatment or proceed to bone marrow transplantation.	36	Primary analysis 2012; long term follow-up continuing	26 of 36 patients (72%) had hematologic remission (with full or partial hematologic recovery, with 24 of the 26 responders achieving a molecular remission (MRD $<10^{-4}$), within 2 treatment cycles. Sixteen out of 26 responders (62%) showed a CR. Median duration of response was 8.9 months; median overall survival was 9 months. The final dosing regimen was determined to be blinatumomab 5 µg/m²/day in week 1 followed by 15 µg/m²/day for the remaining treatment period. In patients receiving this dosing regimen, the most common TEAEs were pyrexia, headache, tremor, and fatigue; of these, TEAEs with grade ≥ 3 were pyrexia (1 patient) and tremor (2 patients). Fully reversible CNS AEs leading to treatment interruptions were observed in 6 patients (3 with seizures and 3 with encephalopathy), of which 2 patients permanently discontinued. Three patients reported cytokine release syndrome. One patient stopped treatment due to fungal infection (leading to death) (Topp et al, 2012a).
MT103-211 Phase 2, non-randomized, non-controlled, open-label study in adults with Ph^- relapsed/ refractory B-precursor ALL; >10% blasts in bone marrow	Blinatumomab continuous IV infusion	61 planned	Recruiting	Not available

Study Number/ Key Design Features	Dose, Route, Schedule of Administration	Number of Patients	Status	Summary of Results
Ongoing Studies: MRD-positive ALL				
MT103-202 Phase 2, non-randomized, non-controlled, open-label study in adults with B-precursor ALL in complete hematological remission with MRD	Blinatumomab 15 µg/m²/day (escalation to 30 µg/m²/day after first cycle for nonresponders) by continuous IV (4 weeks on, 2 weeks off (10 cycles maximum)	21	Treatment completed; long-term follow-up through 2014	16 of 20 evaluable patients (80%) had complete MRD response (MRD $<10^{-4}$ within 4 cycles.) All responses were shown after 1 cycle. After a median follow up of 33 months, the hematological relapse-free survival of the whole evaluable study cohort of 20 patients is 61% (Kaplan-Meier estimate). The most common TEAEs were pyrexia, chills, decrease of blood immunoglobulin, and hypokalemia. The most common grade 3 and 4 AE was lymphopenia. The majority of TEAEs were transient. In the first cycle, only one patient permanently discontinued treatment due to a grade 3 seizure, which was fully reversible within 1 day after stop of infusion. One patient had syncope with convulsion. No other relevant neurotoxic events were reported in this study. No blinatumomab-related deaths were reported. (Topp et al, 2011; Topp et al, 2012b).
MT103-203 Phase 2, non-randomized, non-controlled, open-label study in adults with pre-B ALL in complete hematological remission with MRD ≥10^{-3} at 2 weeks after last chemotherapy	4 cycles of blinatumomab continuous IV, 4 weeks on / 2 weeks off	Up to 130 planned	Recruiting	Not available.

Study Number/ Key Design Features	Dose, Route, Schedule of Administration	Number of Patients	Status	Summary of Results
Planned Studies: Newly Diagnosed ALL				
E1910 Phase 3, randomized study in adults aged 35 to 70 years with newly diagnosed BCR-ABL-negative B-precursor ALL	Blinatumomab continuous IV for 4 weeks for 2 cycles (2 week break between cycles) in conjunction with chemotherapy versus chemotherapy alone	350 planned	Not Started	Not available

Study Number/ Key Design Features	Dose, Route, Schedule of Administration	Number of Patients	Status	Summary of Results
Ongoing Studies: NHL				
MT103-104 Phase 1, non-randomized, non-controlled, open-label, interpatient dose escalation study in adults with relapsed NHL	Blinatumomab 0.5 to 90.0 µg/m^2/day by continuous IV for 4 or 8 weeks	76	Treatment completed; long-term follow-up continuing	In patients receiving a target dose of blinatumomab 60 µg/m^2/day, a 71% overall objective response rate (using Cheson criteria [Cheson et al, 1999]) was observed (20 out of 28 patients, with 10 responses being CR or CRu) across all NHL subtypes; the median duration of response was 508 days, with ongoing responses in 11 patients, of which one patient has shown a response duration of over 3 years. In patients with relapsed diffuse large B-cell lymphoma (DLBCL) receiving a target dose of blinatumomab 60 µg/m^2/day, a 55% (6/11) response rate was observed. Five out of 6 responses were ongoing, and the median duration of response had not been reached: the median observation time was 216 days (range, 28-505 days). The maximum tolerated dose (MTD) in this study was blinatumomab 60 µg/m^2/day. The most common clinical TEAEs were pyrexia, fatigue, weight increased, headache, weight decreased, chills, and diarrhea. Clinically important adverse events associated with blinatumomab were CNS events, eg, encephalopathy, speech disorders (aphasia, dysarthria, and speech disorder), tremor, apraxia, and disorientation. Four deaths were reported during this study: 2 were due to disease progression, one due to sepsis, and one due to pneumocystis pneumonia/port sepsis. Most TEAEs were early-onset, transient, reversible, easily managed, and did not require treatment discontinuations (Goebeler et al, 2011; Viardot et al, 2011).
20120208 Phase 2, open-label study in adults with relapsed/refractory DLBCL	Blinatumomab continuous IV infusion	25 planned	Recruiting	Not available

Appendix B. ALL Disease State Background

Pediatric patients with ALL are mainly treated within the context of clinical studies conducted by cooperative study groups. Multi-agent chemotherapy regimens are the mainstay of treatment. Treatment is tailored to individual risk factors to ensure that appropriate intensity of treatment is administered to patients with high risk of relapse while avoiding unnecessary toxicity in patients at lower risk (Moricke et al, 2008; Schrappe and Stanulla, 2003). Individual risk factors include age, leukocyte count, genetic features, sites of disease, and response to induction therapy.

While clinical and laboratory features are initially used to stratify patients into different risk groups, prognosis is further assessed after induction treatment based on minimal residual disease (MRD; the presence of a low number of leukemic cells that are not detectable by light microscopy). The degree of MRD is prognostic for response and relapse, with lower MRD translating to better outcomes (Dworzak et al, 2008; Zhou et al, 2007; Bruggemann et al, 2006; Pui and Evans, 2006; Pui et al, 2001; Panzer-Grumayer et al, 2000).

Treatment of B-precursor ALL generally consists of several sequential phases of multiagent chemotherapy treatment, typically at higher intensities in pediatric patients than in adults. The initial phase, induction, typically consists of a 3-drug chemotherapy combination (Pui, 2006a; Pui and Evans, 2006; NCI PDQ®), such as a glucocorticoid (dexamethasone, prednisolone, or prednisone), vincristine, and L-asparaginase and/or an anthracycline (eg, doxorubicin, daunorubicin). Other cytotoxic agents such as cytarabine, cyclophosphamide, or etoposide may also be used. In addition, all patients receive prophylactic intrathecal chemotherapy for possible CNS disease. Cranial radiotherapy may be used in patients with known CNS involvement, or as prophylaxis in patients with higher risk disease.

The attainment of remission alone, however, has been shown to be insufficient for cure, since most patients have residual disease that is undetectable by traditional techniques; without additional therapy, these patients usually relapse. In order to eliminate residual disease, patients in initial remission receive consolidation therapy with 1 or more blocks of intensification/re-induction, accompanied by CNS therapy (prophylactic in patients without CNS infiltration, ongoing for those with CNS disease) (Pui et al, 2008; Pui,

2006b; Pui and Evans, 2006; Conter et al, 2004). Multiple drugs can be used in the consolidation phase:

- In low/standard risk disease, current protocols attempt to limit exposure to drugs associated with late toxic effects (eg, anthracyclines and alkylating agents). Reinduction involves methotrexate or asparaginase and use of a limited cumulative dose of anthracyclines in delayed intensification with an anthracycline-based reinduction and cyclophosphamide reconsolidation.
- In high risk disease, current protocols generally feature blocks of intensified therapy with methotrexate, vincristine, and asparaginase (Aricò et al, 2008; Flohr et al, 2008; NCI PDQ®; ClinicalTrials.gov NCT00430118).

Finally, maintenance therapy is given to prolong remission by preventing the expansion of a drug-resistant clonal population. A typical maintenance regimen for patients in remission consists of daily oral mercaptopurine with weekly oral methotrexate, titrated against WBC and with dose adjustment for thiopurine S-methyltransferase deficiency if indicated (Schrappe and Stanulla, 2003). Maintenance therapy continues until the patient has been in continuous complete remission for 2 to 3 years (Conter et al, 2007; Childhood ALL Collaborative Group, 1996; Bleyer et al, 1991).

Patients with relapsed disease receive additional courses of chemotherapy, with local radiotherapy for extramedullary disease if indicated. Patients who are unlikely to be cured with chemotherapy alone may be candidates for allogeneic HSCT, preferably from a matched related donor. The chances of a cure with HSCT are best for patients who are already in remission following chemotherapy and are MRD-negative. HSCT after first remission may be an appropriate choice for high-risk patients, but typically occurs during second remission or later for lower-risk patients. Additionally, a second HSCT may be a therapeutic option for a patient whose disease relapses following HSCT, particularly if the duration of the first post-HSCT remission was long and/or CR was attained (Schrappe and Stanulla, 2003).

Prognosis of Patients with Relapsed/Refractory Pediatric Acute Lymphoblastic Leukemia

Among children with ALL, more than 95% achieve a complete response with treatment and 75% to 85% remain progression free 5 years from initial diagnosis. However, ALL eventually relapses in up to 25% of patients rendering relapsed ALL to the fourth most common childhood malignancy (Conter et al, 2004).

Prognosis in relapsed patients with ALL depends on timing, extent, and the immunophenotype of relapse (Pui, 2006b). Early relapse is correlated with a poorer prognosis than late relapse (Conter et al, 2004), while bone marrow relapse is associated with a worse outcome compared to extramedullary or combined relapse (Henze and von Stackelberg, 2006).

Approximately 85-90% of ALL pediatric patients with a first marrow relapse achieve a second complete remission and report a median survival of 1.5 years with 5-year disease free survival (DFS) rates of 30-40% (Tallen et al, 2010; Henze et al, 1991).

The ability to achieve remission decreases with each subsequent relapse. Approximately 44% of pediatric patients with second marrow relapse of ALL and 27% of those with third marrow relapse achieve a subsequent complete remission (Table 2). Five-year DFS rates in patients with second and third remission were reported to be 27% and 15%, respectively (Ko et al, 2010).

Fifteen to 20% of children with ALL die from treatment-resistant or recurrent ALL or from the acute and or long-term adverse effects of therapy (Pui, 2006a).

Acute lymphoblastic leukemia is a heterogeneous disease, and there is a clear need for increased efficacy within several poorer-prognosis subgroups, particularly patients with treatment-refractory or relapsed disease, including infants and adolescents. Novel agents are needed that provide a higher response rate or better quality of response than conventional drugs in order to contribute substantially to cure.

Furthermore, existing treatment regimens for all patients rely heavily on cytotoxic agents, which pose several important risks. First, these drugs can cause significant toxicities (eg, suppression of hematopoiesis, gastrointestinal disorders, cardiotoxicity, neurotoxicity) that may be severe and/or cumulative. These toxicities can limit the tolerability of treatment after relapse, and thereby reduce the chances of inducing a second or third remission. Second, the reliance on a limited spectrum of drugs with similar mechanisms of action encourages the proliferation of drug-resistant clones that are less likely to respond to further treatment with drugs of the same class. Third, existing treatments have serious long-term sequelae such as cardiac-late effects, growth impairment, neurophysiologic and endocrinologic deficits, and secondary neoplasms (Mody et al, 2008; Landier et al, 2004). Cognitive deficits and abnormalities in dental,

craniofacial, and skeletal development due to cranial radiotherapy have also been documented (Hudson, 2006). New treatments with an improved safety profile and/or with a different mechanism of action (which could evade acquired drug resistance) would represent an important improvement.

Allogeneic HSCT is life-saving for some children, and currently is the only possibility of cure for those with second relapse or refractory B-precursor ALL. However, the overall impact of this therapy is small because too many children do not achieve durable second remission and relapse or die while waiting for a matching donor. Many children die from transplant-related morbidity or graft-versus-host disease or will ultimately experience subsequent relapse (Gaynon, 2005). The chance of successful HSCT might be improved by drugs that establish higher-quality remission prior to the procedure (for example, converting MRD-positive patients into MRD-negativity); or that extend remission and bridge the waiting time until HSCT when there is no immediate donor available. For patients who are intolerant or do not want to undergo HSCT (as HSCT is related to considerable morbidity and mortality), or in relapsed/refractory patients post HSCT, effective treatments are desperately needed.

Appendix C. Drugs Used in Pediatric R/R ALL

Agent	Approval Date
Methotrexate	1953
6-Mercaptopurine	1953
Cyclophosphamide	1959
Vincristine	1963
Ara-C	1969
Doxorubicin	1974
Daunorubicin	1979
Asparaginase	1994
Clofarabine	2004