BACKGROUND MATERIALS

FOR

THE ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

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SUPPLEMENTAL
BIOLOGICS LICENSE APPLICATION FOR BLINATUMOMAB

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ACS	American Cancer Society
ALCANTARA	Study 20120216 (Study 216)
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATE	average treatment effect
BiTE®	bispecific T-cell engager
BLAST	Study MT103-203 (Study 203)
BSA	body surface area
CD	cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
COG	Children's Oncology Group
CR	complete response/remission
CR1	first complete remission
CR2	second complete remission
CR3	third complete remission
CSR	clinical study report
C_{ss}	steady state concentration
CTCAE	Common Toxicity Criteria for Adverse Events
DCAS	direct comparison analysis set
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EMA/EMEA	European Medicines Agency
ESG-MRD-ALL	European Study Group on MRD detection in ALL
ESMO	European Society for Medical Oncology
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GGT	gamma-glutamyltransferase
GMALL	German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia
HR	high risk

Abbreviation or Term	Definition/Explanation
HSCT	hematopoietic stem cell transplant
Ig	immunoglobulin
IPTW	Inverse Probability of Treatment Weight
IR	intermediate risk
IV	intravenous
Key Sec EP FAS	Key Secondary Endpoint Full Analysis Set
KM	Kaplan-Meier
LR	low risk
mAbs	monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not estimable
NGS	next-generation sequencing
NIH	National Institutes of Health
OS	overall survival
PCR	polymerase chain reaction
Prim EP FAS	Primary Endpoint Full Analysis Set
REMS	Risk Evaluation and Mitigation Strategy
RFS	relapse-free survival
sBLA	supplemental Biologics License Application
sIPTW	stabilized Inverse Probability of Treatment Weight
SMQ	standardized MedDRA Query
TCR	T-cell receptor
TKI	tyrosine kinase inhibitor
TOWER	Study 00103311 (Study 311)
US	United States
WBC	white blood cell

1. EXECUTIVE SUMMARY

Introduction

Blinatumomab (BLINCYTO®) is a bispecific T-cell engager (BiTE®) antibody construct that directs T-cells to CD19-positive cells. CD19 is expressed on blast cells in more than 95% of cases of B-cell precursor acute lymphoblastic leukemia (ALL). Blinatumomab's mechanism of action utilizes a patient's own cytotoxic T-cells to attack malignant B-cells. 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. 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 indicated for the treatment of relapsed or refractory B-cell precursor ALL in adults and children (BLINCYTO® USPI, 2017); dosing is based on patient weight (< 45 kg or ≥ 45 kg). Blinatumomab was granted accelerated approval in December 2014 for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell ALL based upon the results of a large single-arm study (Study 211, N = 189). The primary endpoint was the rate of CR/CRh* (hematologic complete remission with ≤ 5% of blasts in bone marrow, no evidence of disease, and with full or partial peripheral blood count recovery), which is a measure of reduced disease burden, within 2 cycles of blinatumomab. In this study, the CR/CRh* rate for blinatumomab was 41.6% (95% CI: 34.4, 49.1), which was almost double the CR rate of standard of care chemotherapy regimens based on results of a historical comparator study (CR = 24%, 95% CI: 20, 27), which included data from major academic centers and was weighted to account for key subject characteristics in Study 211.

Blinatumomab gained approval for pediatric dosing in 2016 and Philadelphia chromosome-positive disease in 2017. It was at this time (2017) that blinatumomab was also granted full approval, based upon the results of a randomized controlled study in adult relapsed or refractory ALL patients (Study 311, also known as TOWER, N = 405). In this study, the CR/CRh* rate in the blinatumomab arm was 42% (95% CI: 37, 49), which was again more than double the CR/CRh* rate of 20% (95%: 14, 28) in the standard of care chemotherapy arm. A significant overall survival (OS) benefit was also demonstrated for blinatumomab over chemotherapy, with a median OS of 7.7 months

(95% CI: 5.6, 9.6) in the blinatumomab arm compared with 4.0 months (95% CI: 2.9, 5.3) in the standard of care chemotherapy arm (hazard ratio = 0.71 [95% CI: 0.55, 0.93], stratified log-rank test p = 0.012). Thus, results of this randomized controlled study confirmed the ability of blinatumomab to reduce disease burden (measured by CR) and established that this reduction correlated with longer-term clinical benefits predicted by the earlier single-arm study and historical comparisons.

Amgen is now seeking approval of blinatumomab for the treatment of minimal residual disease (MRD)-positive B-cell precursor ALL. The proposed dosing regimen is blinatumomab 28 µg per day administered by continuous intravenous (IV) infusion over 4 weeks followed by a treatment-free period of 2 weeks (1 cycle = 6 weeks) for patients weighing ≥ 45 kg. A treatment course for induction of MRD response consists of 1 cycle of blinatumomab. Patients may receive up to 3 additional cycles as consolidation treatment. This briefing document provides information in support of this indication for the Oncologic Drugs Advisory Committee.

Background on MRD-positive ALL

ALL is a rare aggressive cancer of the bone marrow. Nearly 50% of adult patients and 25% of pediatric patients with B-cell ALL eventually experience relapse or are refractory to initial treatment (Gökbuget et al, 2012b; Bassan and Hoelzer, 2011; Oriol et al, 2010; Gökbuget and Hoelzer, 2009; Conter et al, 2004). The goals of therapy are to induce remission and proceed to allogeneic hematopoietic stem cell transplant (HSCT), or to attain a durable remission with consolidation chemotherapy, each approach with the ultimate goal of preventing relapse and improving OS.

Approximately 30% to 50% of adult and 10% to 20% of pediatric ALL patients who achieve hematologic CR (ie, < 5% blasts in bone marrow by conventional morphologic assessment) following multi-agent therapy (ie, induction or consolidation chemotherapy) are MRD-positive (Gökbuget et al, 2012a; Bassan et al, 2009; Holowiecki et al, 2008; Raff et al, 2007; Brüggemann et al, 2006; van Dongen et al, 1998). The presence of MRD after induction or consolidation chemotherapy is the most important risk factor for hematologic relapse in adult and pediatric patients with ALL (Berry et al, 2017; Jabbour et al, 2017; Lussana et al, 2016; van Dongen et al, 2015; Gökbuget et al, 2012a; Gökbuget and Hoelzer, 2011; Bassan et al, 2009; Brüggemann et al, 2006; van Dongen et al, 1998). Although MRD has been evaluated primarily as a prognostic

factor for relapse in ALL, it differs from other prognostic factors in that it is a direct measure of disease.

Recurrent or resistant ALL exists along a continuum, with MRD (ie, molecular level disease) on one end and overt leukemia on the other end of the spectrum. MRD is submicroscopic levels of residual leukemia, detectable only with very sensitive technologies (such as flow cytometry or polymerase chain reaction [PCR]). After induction or consolidation treatment, patients who are MRD-positive are very unlikely to achieve MRD-negativity with additional rounds of chemotherapy, largely because these patients have already received standard of care chemotherapy regimens for the treatment of ALL, and these submicroscopic leukemia cells have already survived exposure to these treatments. As such, the presence of MRD indicates that a patient has not achieved a true disease-free state. However, there are no approved therapies specifically to treat MRD-positive patients, and there are no effective chemotherapies for these patients. Allogeneic HSCT is the only available treatment option for patients with MRD-positive ALL, but the outcome is far from optimal. Patients with MRD-positive disease may relapse while waiting for HSCT, and those who are MRD-positive prior to HSCT have worse outcomes compared to patients who are MRD-negative prior to HSCT (Bar et al, 2014; Gökbuget et al, 2012a).

Although numerous individual ALL studies have demonstrated the prognostic power of MRD positivity, the use of MRD negativity as a more definitive endpoint in clinical trials has been hampered by heterogeneous testing methods and the lack of a clear correlation with clinical outcomes in randomized trials. This issue has been partially addressed by the results of a meta-analysis based on published reports of 39 MRD studies (16 adult, 20 pediatric, and 3 mixed), comprising a dataset of 13,637 patients with ALL, which provides the strongest evidence to date regarding the prognostic value of MRD in relation to both event-free survival (EFS) and OS across multiple key patient and disease factors (Berry et al, 2017). In this meta-analysis, EFS (which included disease-free, recurrence-free, relapse-free, and event-free survival) at 10 years was approximately 64% for adults with ALL who were MRD-negative and 21% for adults who were MRD-positive. In pediatric patients, EFS was 77% at 10 years for MRD-negative patients versus 32% for MRD-positive patients. The relative benefit in EFS based on hazard ratios was similar regardless of age category (0.28 for adults; 0.23 for pediatrics), and the hazard ratio for OS was 0.28 for both adult and pediatric patients. Results were consistent across many therapy modalities (including conventional chemotherapy,

high-dose chemotherapy, and HSCT), ages, testing methods, and disease factors (Philadelphia-negative or Philadelphia-positive). Results of this meta-analysis confirm that achieving MRD negativity in ALL patients in hematologic CR (representing a further reduction in leukemic tumor burden) is a robust predictor of prolonged relapse-free survival (RFS) and OS and that MRD warrants consideration as an early measure of disease response for evaluating new therapies and accelerating drug development for regulatory approval (Berry et al, 2017).

Given the poor outcome of MRD-positive ALL with or without HSCT and lack of approved drugs specifically to treat MRD-positive patients, there is clearly an unmet need for this disease. In the relapsed/refractory ALL setting, blinatumomab demonstrated that CR as a direct measure of reduced disease burden was a predictor of clinical benefit (ie, prolonged OS). Thus, it is reasonably likely that patients with MRD, which is also a direct measure of disease burden, can achieve long-term benefits from a therapy that dramatically reduces their leukemic tumor burden and converts them to a state of MRD negativity (below the limits of what can be detected). The potential role of blinatumomab to address this need has been recently recognized in the National Comprehensive Cancer Network (NCCN) guidelines, which recommends consideration of blinatumomab treatment for persistent or late clearance MRD-positive ALL (NCCN, 2017). Current NCCN guidelines do not define a specific threshold for MRD positivity but note that MRD positivity can be detected with flow cytometry or PCR methods with a minimum sensitivity of $< 1 \times 10^{-4}$. Blinatumomab, if granted regulatory approval for this indication, would be the first treatment utilizing MRD positivity as a selection criterion and MRD negativity as an endpoint for ALL.

Blinatumomab Clinical Development Program in Adults With MRD-Positive ALL

The pivotal study providing efficacy data for this indication is Study MT103-203 (Study 203; also known as the BLAST study), a phase 2, open-label, single-arm study in adult subjects whose MRD-positive B-cell precursor ALL was in hematologic CR as defined by less than 5% blasts in the bone marrow after at least 3 intense chemotherapy blocks (N = 116). Eligible subjects were required to have MRD at a level of $\geq 1 \times 10^{-3}$ in any assay (PCR or flow cytometry) with a minimum sensitivity of 1×10^{-4}. The primary endpoint was the rate of complete MRD response (defined by the absence of detectible MRD using an assay with a minimum sensitivity of 1×10^{-4}) after 1 cycle of blinatumomab treatment. The key secondary efficacy endpoint was the hematologic

RFS rate at 18 months after initiation of blinatumomab. The intent for this endpoint according to the study protocol was to not include Philadelphia-positive subjects and subjects who received HSCT after blinatumomab treatment. As such, Philadelphia-positive subjects were excluded, and transplanted subjects were censored at the time of HSCT or post-blinatumomab chemotherapy. Such censoring was only implemented for the primary analysis of RFS at 18 months. Other secondary efficacy endpoints were OS, mortality rate within 100 days after allogeneic HSCT, time to hematologic relapse, and duration of complete MRD response. Landmark analyses of RFS and OS were analyzed as important supportive endpoints to evaluate the association between complete MRD response and subsequent RFS and OS.

Further support for the proposed indication is provided by Study MT103-202 (Study 202), a phase 2, open-label, single-arm study in adult subjects whose MRD-positive B-cell precursor ALL was in hematologic CR as defined by less than 5% blasts in the bone marrow (N = 21). Study 202 preceded the 203 study and provided the initial evidence that inspired the larger follow-up study. Eligible subjects in Study 202 were required to have a quantifiable MRD level of $\geq 1 \times 10^{-4}$. The primary endpoint was MRD response rate (defined as bcr/abl and/or t[4;11] genes below the detection limit and/or individual rearrangements of immunoglobulin [Ig] or T-cell receptor [TCR] genes below 1×10^{-4}).

A historical comparator study (Study 20120148, or Study 148) using patient-level data from multiple ALL study groups was conducted to substantiate the relevance of the single-arm trial efficacy data from Study 203 in adult subjects with MRD-positive B-cell precursor ALL. A prospectively planned propensity score analysis was conducted to further investigate the historical data from Study 148 as a comparator to Study 203, controlling for important baseline covariates. In an effort to mimic the effects of randomization and allow for more valid statistical comparisons, propensity score analysis methods are used to balance the historical control population and the clinical study population with respect to potential prognostic factors.

The assessment of safety was based on a broad evaluation of safety data from 843 adult and pediatric subjects treated with blinatumomab in 8 clinical studies of ALL. Of these 843 subjects, 137 subjects from Studies 203 and 202 were included in the "adult MRD-positive ALL population," and 706 subjects from 6 relapsed/refractory ALL studies were included in the "total relapsed/refractory ALL population," which included

528 adult subjects with Philadelphia chromosome-negative relapsed/refractory ALL, referred to as the "adult Philadelphia-negative relapsed/refractory ALL population." The relapsed/refractory ALL populations were included as reference populations for assessing the safety of blinatumomab in adult subjects with MRD-positive ALL.

Efficacy Results

In the pivotal Study 203, blinatumomab induced a complete MRD response after 1 treatment cycle (the primary endpoint) in 77.9% of subjects (88/113 subjects; 95% CI: 69.1, 85.1); 2 additional subjects had a complete MRD response during cycle 2 of treatment, for an overall complete MRD response rate of 79.6% (95% CI: 71.0, 86.6). The complete MRD response rate was consistent across multiple baseline covariates, including age, gender, CR status (ie, first CR [CR1] or second CR [CR2]), Philadelphia chromosome status, and MRD level. The median duration of complete MRD response at cycle 1 was 17.3 months (95% CI: 12.6, 23.3).

The Kaplan-Meier (KM) estimate for hematologic RFS at 18 months, with censoring for HSCT or post-blinatumomab chemotherapy (the key secondary endpoint), was 54% (95% CI: 33, 70). The KM estimate for OS at 18 months was 65% (95% CI: 55, 73); the median OS was 36.5 months (95% CI: 19.2, NE).

In the landmark analysis from day 45 (the day by which all cycle 1 MRD responses had been assessed), the median RFS was 17.9 months longer in subjects who achieved a complete MRD response compared to subjects who did not have a complete MRD response (23.6 months [95% CI: 17.4, NE] versus 5.7 months [95% CI: 1.6, 13.6], respectively). Median OS (from day 45) was 28.4 months longer in subjects who achieved a complete MRD response compared to subjects who did not have a complete MRD response (38.9 months [95% CI: 33.7, NE] versus 10.5 months [95% CI: 3.8, NE], respectively). Although RFS and OS appear prolonged by achieving a complete MRD response, a direct causal relationship cannot be established since there may be baseline factors that contributed to both the ability to achieve a complete MRD response and prolonged RFS and OS. However, baseline factors that would appear to account for both improved complete MRD response rates and prolonged RFS and OS were not found in this study. Routine subgroup analyses of baseline prognostic factors, such as age, gender, CR status (CR1 or second and third CR [CR2/CR3]), MRD level at baseline, white blood cell (WBC) count at first diagnosis, need for salvage therapy for CR, and genetic aberration (t(4;11) translocation and/or MLL-AF4+) showed that CR

status (CR1 versus CR2/CR3) emerged as the most important predictor of RFS and OS. Additional landmark analyses of RFS and OS by MRD response and CR status consistently showed that there is a benefit of achieving a complete MRD response irrespective of CR status.

Based on these results as well as the strong results of published literature correlating MRD negativity with long-term EFS/RFS and OS (Berry et al, 2017) and results of the historical comparisons in matched populations using propensity score analyses (described below), Amgen considers that the magnitude of MRD negativity and prolonged RFS and OS induced by blinatumomab in the landmark analyses provides sufficient evidence that achieving complete MRD response is reasonably likely to predict clinical benefit (ie, prolonged RFS and OS) in subjects with MRD-positive B-cell precursor ALL.

In the supportive dataset from Study 202, 80% of subjects (16/20 evaluable subjects; 95% CI: 56.3, 94.3) achieved an MRD response (the primary endpoint), with all MRD responses achieved within cycle 1 of blinatumomab treatment. The median hematologic RFS had not been reached after a median follow-up time of 50.8 months (> 4 years). Ten subjects (50%) were relapse free after at least 5 years of follow-up (duration of follow-up ranged from 5.0 to 5.9 years). Overall, 5 of the 9 subjects who received HSCT after blinatumomab treatment, and 5 of 11 subjects not transplanted after blinatumomab, remained in continuous hematologic CR at least 5 years after starting blinatumomab treatment. The final RFS estimate was 52.6% at 5.9 years.

Results from the historical comparator Study 148, based on a dataset of 182 subjects with similar inclusion criteria to subjects in the pivotal blinatumomab Study 203, showed that 18-month RFS, censored at HSCT, was 37% (95% CI: 28, 46) and 18-month OS, uncensored at HSCT, was 56% (95% CI: 49, 64), which were lower than the results observed in the pivotal blinatumomab Study 203, which showed 18-month RFS, censored at HSCT or post-blinatumomab chemotherapy, of 54% (95% CI: 33, 70) and 18-month OS, uncensored at HSCT or post-blinatumomab chemotherapy, of 65% (95% CI: 55, 73).

In order to allow for direct comparisons between the historical data from Study 148 and clinical data from Study 203, evaluations were performed with propensity score methods. The use of propensity score adjustments was successful in creating a balanced

population of blinatumomab-treated and control subjects with respect to important baseline covariates (age, gender, time from initial diagnosis to MRD, WBC count at diagnosis, presence of genetic aberrations, country, and type of chemotherapy). This balance allowed for more valid statistical comparisons between the 2 treatment groups. Results of the propensity score analysis showed that blinatumomab was associated with a statistically significant improvement in RFS (hazard ratio = 0.50, 95% CI: 0.32, 0.78), as well as a directional improvement in OS (hazard ratio = 0.76, 95% CI: 0.47, 1.24). Results of the endpoint analyses were largely consistent across analysis sets and sensitivity analyses.

Safety Results

Overall Safety Results

The safety profile for the adult MRD-positive ALL population was consistent with the known safety profile of blinatumomab in relapsed/refractory ALL that is reflected in current prescribing information (BLINCYTO® USPI, 2017). No new adverse drug reactions were identified based on the assessment of safety data in the adult MRD-positive ALL population. Across all of the ALL populations, the most frequently reported adverse event was pyrexia, reported at subject incidences of 90.5% in the adult MRD-positive ALL population, 61.4% in the adult relapsed/refractory Philadelphia-negative ALL population, and 64.6% in the total relapsed/refractory ALL population. Most reports of pyrexia in the adult MRD-positive ALL population were low in severity (grade 1 or 2) and were managed with anti-pyretic medication without interruption of blinatumomab treatment. Other adverse events with a subject incidence of ≥ 20% in the adult MRD-positive ALL population were generally comparable to the subject incidences across the pooled ALL populations (ie, difference in incidence of < 10%) except for tremor, chills, and fatigue, which are known adverse events with blinatumomab in current prescribing information. The subject incidences of anemia and febrile neutropenia, frequently reported adverse events in the relapsed/refractory ALL populations, were lower in the adult MRD-positive ALL population (5.8% and 2.2%, respectively) compared with the adult relapsed/refractory Philadelphia-negative ALL population (22.0% and 24.4%, respectively) and the total relapsed/refractory ALL population (24.9% and 23.7%, respectively).

Two fatal adverse events in the adult MRD-positive ALL population were reported within 30 days of the last dose of blinatumomab treatment: fungal pneumonia following a

grade 3 H1N1 influenza (considered treatment related by the investigator) and a subdural hemorrhage (considered unrelated to treatment by the investigator) that occurred at the site of a prior hemorrhage that was attributed to progressing ALL. In addition, 51 deaths were reported more than 30 days after the last dose of blinatumomab treatment. Overall, the causes of death reported were consistent with those commonly observed in patients with hematologic malignancies and in the transplant setting.

Serious adverse events were reported for 60.6% of subjects in the adult MRD-positive ALL population, which was consistent with the adult relapsed/refractory Philadelphia-negative ALL population (63.4%) and the total relapsed/refractory ALL population (61.5%). In the adult MRD-positive ALL population, the most frequently reported serious adverse event was pyrexia, reported in 12.4% of subjects compared with 6.4% in the adult relapsed/refractory Philadelphia-negative ALL population and 7.2% in the total relapsed/refractory ALL population. Most of the serious pyrexia events in the adult MRD-positive ALL population were managed with anti-pyretic medication without interruption of blinatumomab treatment. None of the serious pyrexia events in the adult MRD-positive ALL population resulted in treatment discontinuation. Serious tremor, reported in $\geq$ 5% of the adult MRD-positive ALL population (5.8%), was reported in 1.7% of the adult relapsed/refractory Philadelphia-negative ALL and total relapsed/refractory ALL populations. The majority of subjects with serious tremor in the adult MRD-positive ALL population continued blinatumomab throughout the events with supportive therapy, and all serious tremor events resolved in the adult MRD-positive ALL population. Serious febrile neutropenia was reported less frequently in the adult MRD-positive ALL population than in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations (1.5% vs 8.5% and 8.2%, respectively). The subject incidence of cytokine release syndrome was lower in the adult MRD-positive ALL population (2.9%; 1.5% grade $\geq$ 3) than in the adult relapsed/refractory Philadelphia-negative ALL population (14.2%; 3.4% grade $\geq$ 3) and the total relapsed/refractory ALL population (14.6%; 3.8% grade $\geq$ 3). (Severity of adverse events was graded using Common Toxicity Criteria for Adverse Events [CTCAE] version 4.03.) In the adult MRD-positive population, all of the cytokine release syndrome events (2 grade 3 events and 2 grade 1 events) occurred early in treatment (on days 1 or 2) and resolved within < 1 to 2 days with supportive therapy. None of these cytokine release syndrome events resulted in treatment discontinuation.

Key Safety Risks

Across the blinatumomab program, key safety risks for blinatumomab are neurologic events, cytokine release syndrome, and medication errors due to the complexity of preparation and administration of blinatumomab. Based on a broad evaluation of safety data from 843 subjects treated with blinatumomab in 8 clinical studies of ALL, including 137 adult subjects MRD-positive ALL, the safety risks observed in the adult MRD-positive ALL population are consistent with the known safety profile established for blinatumomab in patients with relapsed/refractory ALL. Neurologic events and cytokine release syndrome are identified as warnings in current prescribing information. A Risk Evaluation and Mitigation Strategy (REMS) is currently in place to communicate to healthcare providers and pharmacists the risks of neurologic events and cytokine release syndrome, and the potential occurrence of preparation and administration errors. Since the initial approval of blinatumomab for relapsed/refractory ALL, more than 3,000 patients have been treated with blinatumomab in the marketed setting globally. Overall, the safety information received in the postmarketing setting has been consistent with the established safety profile of blinatumomab, with only one significant safety update to the prescribing information to add the risk of pancreatitis.

Conclusion

The impact of MRD on the course of ALL is well recognized. MRD is a direct measure of disease burden, and presence of MRD indicates that a patient has not achieved a true disease-free state despite achieving a morphologic response (ie, CR) following induction or consolidation chemotherapy. Given the especially poor long-term outcomes in patients with MRD-positive ALL with or without HSCT and the lack of approved drugs specifically to treat MRD-positive patients, there is clearly an unmet need for this disease. From a regulatory perspective, in the ALL setting, achieving MRD negativity (ie, complete MRD response) in patients who have been treated for MRD-positive disease has not been used previously as an endpoint or early measure of disease response for evaluating new therapies. In relapsed/refractory ALL, blinatumomab demonstrated that CR as a direct measure of reduced disease burden was a predictor of clinical benefit (ie, prolonged OS). Likewise, it is reasonably likely that patients with MRD, which is also a direct measure of disease burden, can achieve long-term benefits from a therapy that dramatically reduces their leukemic tumor burden and converts them to a state of MRD negativity. Amgen considers that the magnitude of MRD negativity

induced by blinatumomab in Study 203, coupled with RFS and OS that compare favorably to matched populations (using propensity score analyses), provides sufficient evidence that complete MRD response is an endpoint that is reasonably likely to predict long-term clinical benefits (ie, prolonged RFS and OS) in subjects with MRD-positive B-cell precursor ALL.

The safety profile for the adult MRD-positive ALL population is consistent with the known safety profile of blinatumomab in relapsed/refractory ALL and remains distinct from the profile of cytotoxic chemotherapies. Most adverse events occurred within the first few weeks of the first cycle and were mitigated by appropriate measures such as temporary interruption and supportive therapy without negatively affecting therapeutic benefit. The key safety risks associated with blinatumomab (neurologic events, cytokine release syndrome, and medication errors) are well recognized by health care providers who are familiar with managing these conditions in the treatment of patients with ALL, and can be managed effectively through guidance in current prescribing information and the REMS, and the toxicities associated with blinatumomab are unlikely to offset the anticipated benefits for patients with MRD-positive ALL. Blinatumomab, administered as monotherapy, has a favorable benefit-risk profile and represents an important therapeutic option for the treatment of patients with MRD-positive ALL.

2. OVERVIEW OF MRD-POSITIVE ALL

2.1 Disease Background

ALL is a rare aggressive cancer of the bone marrow, with approximately 6,590 new cases diagnosed in the United States (US) each year (American Cancer Society [ACS], 2016). Of these new diagnoses, approximately 2,400 occur among adults (Howlader et al, 2014). In the European Union (EU), more than 7,200 new cases are diagnosed annually (Gatta et al, 2011) with approximately 40% (roughly 3,000 diagnoses) occurring in adults (Inaba et al, 2013). The majority of ALL cases are B-lineage, Philadelphia chromosome-negative ALL (ACS, 2016). The complete prevalence (number of people alive at a given point in time who previously had a diagnosis of the disease) of ALL in the EU in 2008 was 27 per 100,000 persons (Gatta et al, 2011), which is similar to an estimated prevalence of approximately 23 per 100,000 persons for the US in 2010 (Howlader et al, 2014).

Despite the fact that treatment regimens for ALL can induce hematologic CR rates that approach 90%, nearly 50% of adult patients and 25% of pediatric patients with B-cell ALL will eventually experience relapse or are refractory to initial treatment (Gökbuget et al, 2012b; Bassan and Hoelzer, 2011; Oriol et al, 2010; Gökbuget and Hoelzer, 2009; Conter et al, 2004). Patients who achieve hematologic CR by morphologic assessment (ie, < 5% blasts in bone marrow) can still have MRD, which is submicroscopic leukemic cells in the bone marrow below the detection of conventional morphological methods (NCCN, 2017). Approximately 30% to 50% of adult and 10% to 20% of pediatric ALL patients who achieve hematologic CR following multi-agent therapy are MRD-positive (Gökbuget et al, 2012a; Bassan et al, 2009; Holowiecki et al, 2008; Raff et al, 2007; Brüggemann et al, 2006; van Dongen et al, 1998). The persistence of MRD after standard induction or consolidation treatment, or reappearance of MRD after prior achievement of a negative MRD status, is the strongest prognostic factor for hematologic relapse and decreased OS regardless of treatment choice or risk classification system (Lussana et al, 2016; van Dongen et al, 2015; Beldjord et al, 2014; Gökbuget et al, 2012a; Gökbuget and Hoelzer, 2011; Patel et al, 2010; Bassan et al, 2009; Spinelli et al, 2007; Brüggemann et al, 2006). Other prognostic factors for relapse and OS include baseline features such as cytogenetics (particularly the 9;22 translocation), WBC count, age, and duration of initial remission (Oriol et al, 2010; Moorman et al, 2007; Fielding et al, 2007; Thomas et al, 1999; Larson et al, 1995; and

Hoelzer et al, 1988). Although MRD has been evaluated primarily as a prognostic factor for relapse in ALL, it differs from other prognostic factors in that it is a direct measure of disease.

The dominant prognostic role of MRD in ALL was first established in pediatric patients in a landmark study by van Dongen et al, which showed that MRD could not only represent the best indicator for relapse but also be a substantial aid in making treatment decisions (ie, treatment intensification or deintensification) (van Dongen et al, 1998). The value of achieving MRD negativity has been demonstrated subsequently in numerous trials of childhood and adult ALL (Gökbuget et al, 2012a; Bassan et al, 2009; Holowiecki et al, 2008; Raff et al, 2007; Brüggemann et al, 2006; Vora et al, 2014; Vora et al, 2013). The concept of MRD-oriented therapy has gained worldwide consensus in pediatric and adult ALL. Assessment of MRD is commonly used clinically to evaluate the depth of response, categorize the level of risk of relapse, and to aid in treatment decisions (NCCN, 2017; Hoelzer et al, 2016).

MRD is evaluated by multiple methods, most commonly multichannel flow cytometry with immunophenotypic markers, real-time quantitative PCR with oligonucleotide primers that are specific for an identified clonotypic rearrangement, or next-generation sequencing (NGS). Current methods can detect leukemic cells starting at a quantitative sensitivity threshold of 1×10^{-4} (1 leukemic cell in 10,000 cells). The concordance rate for detecting MRD between methods (ie, PCR or multi-color flow cytometry) is generally high (NCCN, 2017). Patients who are highly responsive to induction or consolidation chemotherapy and achieve an MRD level below 1×10^{-4} have a favorable prognosis. Patients are considered to have MRD (ie, MRD-positive) if it is detectable and can be quantified starting from the lower limit of quantitation of 1×10^{-4} in the bone marrow. Clinical outcomes for patients with an MRD level of $\geq 1 \times 10^{-3}$ ($\geq$ 1 leukemic cell in 1,000 cells) have been shown to be worse than outcomes for patients with an MRD level of $\geq 1 \times 10^{-4}$ in both adult and pediatric patients (Gökbuget et al, 2012a; Bader et al, 2009). Regardless of the method used to measure MRD (eg, flow cytometry or PCR), MRD-negative status has been shown to correlate with improved clinical outcomes (Berry et al, 2017).

2.2 Current Treatment Options and Unmet Need

Recurrent or resistant ALL exists along a continuum, with MRD (ie, molecular level disease) on one end and overt leukemia on the other end of the spectrum. As noted

previously, the presence of MRD after induction or consolidation treatment identifies patients with a high risk for relapse among patients achieving hematologic CR (Patel et al, 2010). In a study reported by Gökbuget et al, patients with MRD in first hematologic CR who did not receive HSCT relapsed after a median time of 7.6 months; continuous hematologic CR and survival at 5 years reached only 12% and 33%, respectively (Gökbuget et al, 2012a). In another study, the 5-year disease-free survival (DFS) rates following induction/early consolidation treatment were reported to be 72% in MRD-negative patients compared with 14% in MRD-positive patients, regardless of other clinical risk factors (Bassan et al, 2009). In patients with ALL determined to be of standard risk by conventional methods, the presence of MRD early in treatment further differentiated risk groups (Brüggemann et al, 2006). Ten percent of treated patients achieved MRD < 1×10^{-4} on day 11 and day 24 and were at low risk for relapse, having a 3-year relapse rate of 0%. A high-risk group of patients (23%) was identified to have MRD ≥ 1×10^{-4} at week 16, and had a 3-year relapse rate of 94%. Similarly, an assessment of MRD in patients with Philadelphia chromosome-negative ALL found that MRD ≥ 1×10^{-3} after induction was an independent prognostic indicator for relapse (Holowiecki et al, 2008).

MRD status has been found to be prognostic of outcome when measured before or after allogeneic HSCT. In a large, single-center study in the US, a heterogeneous population of 160 adult patients with relapsed/refractory ALL, including many in second remission and beyond, was evaluated for survival according to MRD status (Bar et al, 2014). Patients with MRD-negative status before allogeneic HSCT were found to have a 3-year relapse rate of 17% and OS of 68% compared with a 3-year relapse rate of 38% and OS of 40% in patients with MRD-positive status before allogeneic HSCT. In an earlier small study, the 3-year OS of patients who underwent transplantation in remission was 80% for MRD-negative patients compared to 49% for MRD-positive patients (Spinelli et al, 2007). Moreover, 3-year relapse rates were 7% for those who were MRD-negative at day 100 after allogeneic HSCT and 80% for those who were MRD-positive at day 100 after allogeneic HSCT (p = 0.0006).

It is known that MRD is a direct measure of disease burden following specific therapeutic interventions, and thus is indicative of therapeutic response (Berry et al, 2017; NCCN, 2017; Hoelzer et al, 2016). Typically, the presence of MRD represents disease that is insensitive to multi-agent therapy used for induction or consolidation, and thus

subsequent rounds of similar therapy will unlikely be efficacious for eliminating MRD. Current therapy has not been satisfactory in eradicating disease.

While the literature provides a growing body of evidence supporting the clinical benefit of treating ALL patients who are MRD-positive (Jabbour et al, 2017; Lussana et al, 2016; van Dongen et al, 2015; Bassan et al, 2009), there are no approved therapies specifically to treat MRD-positive patients and no effective chemotherapies for these patients. Allogeneic HSCT is the only available treatment option for patients with MRD-positive ALL, but the outcome is far from optimal (Bar et al, 2014; Gökbuget et al, 2012a; Spinelli et al, 2007). Therefore, achieving MRD negativity before HSCT is clinically valuable because MRD negativity leads to a more favorable outcome of HSCT. Thus, treatment of patients with ALL in hematologic CR, but with MRD positivity after initial treatments, represents an area of unmet medical need. Given the established prognostic value of MRD, effective alternative therapies targeting MRD could be readily incorporated into existing treatment paradigms. The June 2017 NCCN guidelines for the treatment of ALL, in which consolidation treatment strategies after achievement of hematologic CR are categorized by MRD status, recommend consideration of blinatumomab treatment for persistent or late clearance MRD-positive ALL. The guidelines acknowledge that long-term remission may be achievable with blinatumomab, and also state that allogeneic HSCT should be considered for these patients (NCCN, 2017). In addition, the European Society for Medical Oncology (ESMO) guidelines confirm that blinatumomab treatment is effective in patients with MRD-positive ALL (Hoelzer et al, 2016).

2.3 Clinical Significance of Minimal Residual Disease

As noted in Section 2.2, MRD is a direct measure of disease burden. Numerous individual ALL studies have demonstrated the prognostic power of MRD positivity in ALL, and MRD status has been used to drive treatment decisions for individual patients. The use of MRD negativity as a more definitive endpoint in clinical trials has been hampered by the heterogeneous testing methods and the lack of a clear correlation with clinical outcomes in randomized trials. However, this issue has been partially addressed by the results of a meta-analysis based on published reports of 39 MRD studies (16 adult, 20 pediatric, and 3 mixed), comprising a dataset of 13,637 patients with ALL, which provides the strongest evidence to date regarding the prognostic value of MRD in relation to both EFS and OS across multiple key patient and disease factors

(Berry et al, 2017). In order to account for differences in outcome definitions across studies, a broad definition of EFS was used for the meta-analysis (ie, disease-free, recurrence-free, relapse-free, and event-free survival). Measurements of MRD in the adult studies were by PCR (12 studies), flow cytometry (3 studies), or mixed methods (1 study), with a cutoff for MRD positivity of 1×10^{-3} (7 studies), 1×10^{-4} (7 studies), 5×10^{-4} (1 study), and unspecified (1 study). Assessment of MRD occurred after induction (7 studies), consolidation (4 studies), or at other time points (5 studies).

Results of this meta-analysis confirm that achieving MRD negativity in ALL patients previously in hematologic CR is a robust prognostic factor for both adults and pediatric patients with ALL. The EFS at 10 years was approximately 64% for adult patients with ALL who were MRD-negative and 21% for adults who were MRD-positive. In pediatric patients, EFS was 77% at 10 years for MRD-negative patients versus 32% for MRD-positive patients. The relative benefit in EFS based on hazard ratios was similar regardless of age category (0.28 for adults; 0.23 for pediatrics), and the hazard ratio for OS was 0.28 for both adult and pediatric patients. Study selection for the meta-analysis was based on availability of characteristics relevant to the analysis (ie, study sample size, age, duration of follow-up, details of MRD assessment, ALL phenotype/genotype, and reporting of EFS and OS) and was independent of the treatments administered to the study subjects. Therefore, this meta-analysis demonstrates the prognostic value of MRD across many therapy modalities, including, but not limited to, conventional chemotherapy, high-dose chemotherapy, and HSCT.

Of particular interest in the meta-analysis, the results for EFS and OS were consistent across all subgroups examined (Table 1). Results of the individual studies included in the meta-analysis also showed a consistent prognostic benefit of MRD negativity on EFS. Point estimates of hazard ratios were < 1 for all studies (adult and pediatric) and the upper limit of the 95% CIs were < 1 for 13 of 16 adult studies and 17 of 20 pediatric studies. The uniformity of the results across subgroups and studies further advances the consensus regarding the importance of achieving MRD negativity for all patients, not just those who are not eligible for HSCT, and substantiates that MRD warrants consideration as an early measure of disease response for evaluating new therapies and accelerating drug development for regulatory approval (Berry et al, 2017).

Table 1. Hazard Ratios (95% Bayesian Credible Intervals) of Event-free Survival and Overall Survival for MRD-negative Versus MRD-positive Patients, by Subgroup, Meta-analysis of Adult ALL Studies

Subgroup	Event-free Survival HR (95% BCI)	Overall Survival HR (95% BCI)
Analysis method		
Flow cytometry	0.32 (0.20, 0.51)	0.28 (0.13, 0.61)
PCR	0.24 (0.18, 0.32)	0.29 (0.18, 0.49)
Analysis cutoff		
$\leq 1 \times 10^{-4}$%	0.29 (0.21, 0.39)	0.25 (0.18, 0.35)
$> 1 \times 10^{-4}$%	0.21 (0.14, 0.32)	0.30 (0.18, 0.50)
Period assessed		
Induction	0.33 (0.24, 0.44)	0.54 (0.24, 1.20)
Consolidation	0.25 (0.18, 0.36)	0.27 (0.18, 0.40)
Other	0.18 (0.08, 0.42)	0.20 (0.04, 0.92)
Philadelphia chromosome status		
Negative	0.28 (0.22, 0.37)	0.26 (0.17, 0.40)
Positive	0.34 (0.22, 0.53)	0.38 (0.19, 0.75)
ALL phenotype		
B-cell	0.28 (0.17, 0.46)	-
T-cell	0.31 (0.19, 0.53)	-
Study type		
Randomized controlled trial	0.31 (0.21, 0.45)	-
Database	0.25 (0.18, 0.33)	0.29 (0.19, 0.44)

ALL = acute lymphoblastic leukemia; BCI = Bayesian credible interval; HR = hazard ratio; MRD = minimal residual disease; PCR = polymerase chain reaction

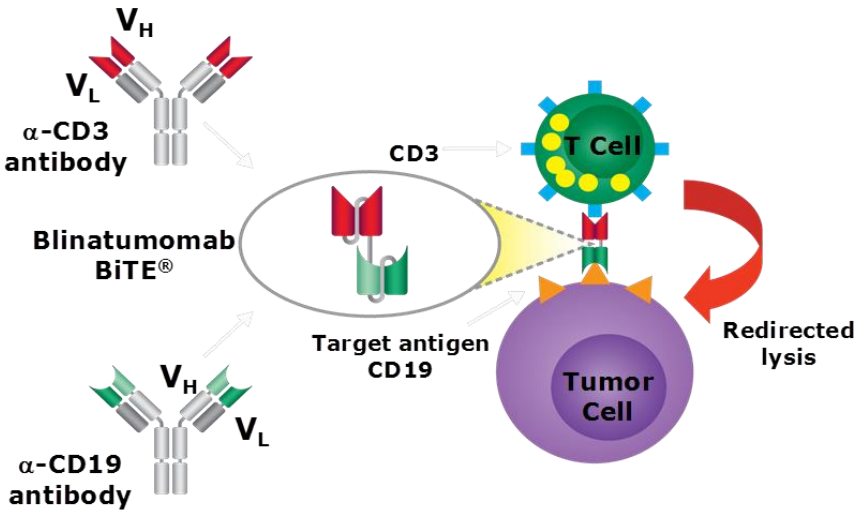
Hazard ratios compare patients who achieved MRD negativity to those who did not; HR < 1 represents longer EFS/OS for those who achieved MRD negativity than for those who did not.

Source: Data for adults were extracted from Figure 3 (EFS) and Figure 4 (OS) in Berry et al, 2017, which presents subgroup data from both adult and pediatric studies.

3. BACKGROUND ON BLINATUMOMAB (BLINCYTO®)

Blinatumomab is a novel single chain antibody construct of the BiTE® class. It was developed by genetic engineering from two distinct parental murine monoclonal antibodies (mAbs): HD37, which recognizes the pan-B-cell antigen CD19; and L2K-07, which specifically binds the T-cell receptor-associated complex, CD3. The targeted CD19 antigen is constitutively expressed on normal B cells throughout a person's lifetime (Smet et al, 2011) and is highly conserved in B-cell malignancies (Tedder, 2009; Wang et al, 2012). B-cell blasts from adult and pediatric patients with B-cell ALL showed comparable, high levels of CD19 expression on all malignant cells examined (Raponi et al, 2011; Ludwig et al, 1994). Blinatumomab's mechanism of action utilizes a patient's own T-cells to kill CD19-positive B-cells, including malignant B-cells. T-cells are bound by its anti-CD3 moiety, whereas malignant and normal B-cells are bound by the anti-CD19 moiety. Blinatumomab is designed to transiently connect CD19-positive cells with T-cells; as part of this action, blinatumomab causes the formation of a cytolytic synapse between the T-cell and the tumor cell (Offner et al, 2006; Figure 1), releasing the pore-forming protein perforin and the apoptosis-inducing proteolytic enzymes granzyme A and B. The subsequent serial lysis of multiple malignant cells by a single T-cell closely resembles a natural cytotoxic T-cell reaction (Hoffmann et al, 2005). Blinatumomab-mediated T-cell activation involves the transient release of inflammatory cytokines and the proliferation of T-cells (Klinger et al, 2012).

Figure 1. T-cell Mediated Tumor Cell Lysis Through Formation of a Cytolytic Immunological Synapse Induced by Blinatumomab



Blinatumomab received full approval by the Food and Drug Administration (FDA) on 11 July 2017 for the treatment of relapsed or refractory B-cell precursor ALL in adults and children. Blinatumomab was granted Breakthrough Therapy designation on 30 June 2014 and accelerated approval on 03 December 2014 for the treatment of patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. Amgen is now seeking approval of blinatumomab for the treatment of MRD-positive B-cell precursor ALL. The proposed dosing regimen is blinatumomab 28 µg per day administered by continuous IV infusion over 4 weeks followed by a treatment-free period of 2 weeks (1 cycle = 6 weeks) for patients weighing ≥ 45 kg. Patients may receive up to 4 cycles of treatment. This briefing document summarizes data included in the supplemental Biologics License Application (sBLA) submitted to the FDA in support of this indication.

3.1 Overview of Clinical Development Program in MRD-positive ALL

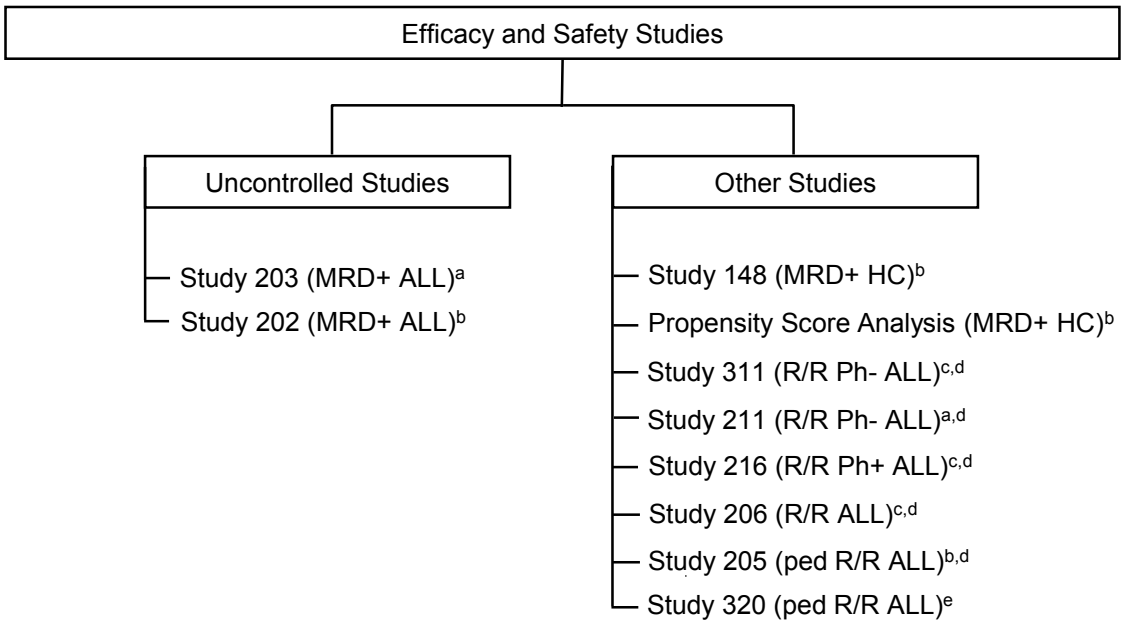
The efficacy of blinatumomab for the treatment of patients with MRD-positive B-cell precursor ALL is based primarily on data from Study 203, a pivotal, phase 2, open-label, single-arm study in adult subjects with MRD-positive B-cell precursor ALL (N = 116). Study 203 was conducted in Europe. Further support for the proposed indication is provided by Study 202, a phase 2, open-label, single-arm study in adult subjects with MRD-positive B-cell precursor ALL (N = 21). Study 202 was conducted in Germany.

A patient-level historical comparator study (Study 148) (based on data from ALL study groups in Europe) and a propensity score analysis were also conducted to substantiate the relevance of the single-arm trial efficacy data from Study 203 in adult subjects with MRD-positive B-cell precursor ALL.

The safety profile of blinatumomab for adult subjects with MRD-positive B-cell precursor ALL is based primarily on pooled data from Studies 203 and 202 (N = 137). An integrated analysis of safety data, pooled by indication and overall, was also performed and included 843 subjects treated with blinatumomab in 8 ongoing and completed studies in adult subjects with Philadelphia chromosome-negative relapsed/refractory ALL (N = 528), pediatric subjects with relapsed/refractory ALL (N = 133), adult subjects with Philadelphia chromosome-positive relapsed/refractory ALL (N = 45), and adult subjects with MRD-positive ALL (N = 137). An overview of clinical studies supporting the efficacy and safety of blinatumomab in the sBLA is provided in Figure 2. A detailed table of studies included in the sBLA is provided in Appendix 1.

Of note, Amgen considers that the data from Studies 203, 202, and 148 are applicable to the US population and US medical practice for the following reasons. In the US and EU, treatment of pediatric and adult ALL includes derivatives of the multiagent chemotherapy regimen originally developed by the Berlin-Frankfurt-Munster Group based in Europe. Thus, treatment of adults and pediatrics with ALL includes chemotherapy regimens that are also similar between the two regions. Patients with Philadelphia-positive ALL also receive tyrosine kinase inhibitors (TKIs) as part of their therapy (NCCN, 2017). In both regions, general ALL treatment phases are grouped into induction, consolidation, and maintenance. There is no one preferred standard therapy regimen in the EU and US. For induction therapy in both regions, most regimens typically include a combination of vincristine, anthracycline, and corticosteroid with or without cyclophosphamide or cytarabine and/or L-asparaginase (NCCN, 2017; Hoelzer et al, 2016). Once in hematologic CR, assessment of MRD is commonly used clinically to evaluate the depth of response, categorize the level of risk of relapse, and aid in further treatment decisions in both the US and EU (NCCN, 2017; Hoelzer et al, 2016). Given that the mechanism of action of blinatumomab is different than chemotherapy and blinatumomab has been shown to be an effective treatment in the relapsed or refractory ALL population in the US and EU, blinatumomab is expected to be an effective treatment option for MRD-positive ALL patients in the US population, because patients would have previous drug exposures from chemotherapy regimens that are identical or similar to those used in the EU.

Figure 2. Overview of Blinatumomab Clinical Studies in the sBLA



ALL = acute lymphoblastic leukemia; HC = historical comparator; MRD+ = minimal residual disease positive; ped = pediatric; Ph- = Philadelphia-chromosome negative; Ph+ = Philadelphia-chromosome positive; R/R = relapsed/refractory; Study 203 also known as BLAST; Study 311 also known as TOWER; Study 216 also known as ALCANTARA; Study 320 also known as RIALTO
Note: Study status is based on study status at time of data cutoff for sBLA.
[a] Primary and secondary analyses completed; long-term efficacy follow-up ongoing
[b] Study completed
[c] Primary analysis completed; long-term efficacy follow-up ongoing
[d] Data were provided in the ISS/SCS for safety comparison.
[e] Study treatment ongoing

Of note, at the time of protocol development for Study 203, Amgen considered potential options for conducting randomized trials specifically in the adult MRD-positive ALL population. In this patient population, randomized controlled trials were considered in the transplant and non-transplant settings: blinatumomab followed by transplantation versus transplantation alone in subjects eligible for transplantation, and blinatumomab versus chemotherapy in subjects not eligible for transplantation. However, due to significant study design issues originating from the lack of standardization in the treatment of adults with MRD-positive ALL in a transplant setting and the lack of a viable comparator treatment in a non-transplant setting, randomized trials in adults that compare blinatumomab to chemotherapy would not provide data that are more robust than currently available data. In addition, some investigators indicated a reluctance to enroll patients in a randomized trial based on the high MRD response rate observed in Study 202.

Two studies sponsored by the National Cancer Institute (NCI), a division of the National Institutes of Health (NIH), are ongoing in other ALL populations (first relapse and newly diagnosed ALL) and can be considered as sources of additional data for the use of blinatumomab for the treatment of MRD-positive ALL: Children's Oncology Group (COG)-AALL1331 (Study AALL1331) and Eastern Cooperative Oncology Group (ECOG)-E1910 (Study E1910). Brief summaries of each study are provided below.

Study AALL1331 is a group wide, risk-stratified, randomized, phase 3 study to test whether incorporation of blinatumomab into the treatment of subjects with childhood B-cell lymphoblastic leukemia at first relapse will improve DFS (the primary endpoint). Eligible subjects (1 to 30 years of age in first relapse) are stratified according to risk category (high risk [HR], intermediate risk [IR], or low risk [LR]) based on site of relapse (marrow versus isolated extramedullary), time to relapse (< 36 or ≥ 36 months for marrow; < 18 or ≥ 18 months for isolated extramedullary), and MRD status (MRD $< 1 \times 10^{-3}$ or $\geq 1 \times 10^{-4}$) following a uniform first block of chemotherapy. Subjects in the HR and IR groups receive 2 additional blocks of chemotherapy followed by HSCT or 2 blocks of blinatumomab followed by HSCT. Subjects in the LR group receive 2 additional blocks of chemotherapy followed by continuation and maintenance chemotherapy, or 1 additional block of chemotherapy, 2 blocks of blinatumomab (each followed by continuation), and a third additional block of blinatumomab followed by maintenance chemotherapy. OS is a key secondary endpoint. MRD response among the HR and IR groups is a supportive endpoint. The estimated enrollment in this study is 598 subjects. The primary analysis results are projected to be available during the first quarter of 2023.

Study E1910 is a randomized, open-label, parallel arm, phase 3 study of combination chemotherapy with or without blinatumomab in subjects with newly diagnosed Philadelphia-negative B-cell lineage ALL. Eligible subjects (30 to 70 years of age) receive induction and intensification chemotherapy using predefined regimens based on subject characteristics. Those who achieve hematologic CR are stratified by age (< 55 versus ≥ 55 years), MRD status (positive versus negative), CD20 status (positive versus negative), rituximab use (yes or no), and intent to receive blood/marrow transplant (yes or no), and then are randomized either to continue consolidation chemotherapy or to receive 2 courses of blinatumomab followed by consolidation chemotherapy. Subjects in either group may undergo allogeneic HSCT or proceed to

maintenance therapy per investigator discretion. The primary objective is to compare the OS of blinatumomab in conjunction with chemotherapy to chemotherapy alone in subjects who are MRD-positive after induction and intensification chemotherapy. If superiority of blinatumomab in the MRD-positive group is shown, the OS of blinatumomab in conjunction with chemotherapy will be compared to chemotherapy alone in subjects who are MRD-negative. If superiority of blinatumomab in the MRD-positive group is not shown, the OS of blinatumomab in conjunction with chemotherapy will be compared to chemotherapy alone in the overall population. RFS is a secondary endpoint. The estimated enrollment in this study is 509 subjects, with approximately 285 subjects randomized. The primary analysis results are projected to be available during the first quarter of 2023.

3.2 Summary of Key Regulatory Interactions

Key interactions with the FDA leading up to the submission of the sBLA are provided in Table 2.

Table 2. Key FDA Regulatory Interactions for Blinatumomab for the MRD-positive ALL Indication

Date	Activity
15 Dec 2010	Submission of Study 203 protocol for FDA feedback
04 Mar 2011	FDA feedback on the Study 203 received (protocol withdrawn)
03 May 2016	Type B pre-sBLA meeting to discuss the clinical aspects of the submission of an sBLA
07 Aug 2017	Type C WRO to discuss administrative aspects of the submission of the MRD-positive ALL sBLA
29 Sept 2017	MRD-positive ALL sBLA submitted

ALL = acute lymphoblastic leukemia; FDA = Food and Drug Administration; MRD = minimal residual disease; sBLA = supplemental Biologics License Application; WRO = Written Response Only

3.3 Measures of Clinical Benefit in the Treatment of MRD-positive ALL

3.3.1 Complete MRD Response Rate

In the pivotal blinatumomab Study 203, complete MRD response rate (defined by the absence of detectible MRD using an assay with a minimum sensitivity of 1×10^{-4}) after 1 cycle of treatment was chosen as the primary endpoint to describe the efficacy of blinatumomab in subjects with MRD-positive B-cell precursor ALL. MRD is very likely to be detected months before clinical relapse becomes overt, and its presence increases

the probability of hematologic relapse (Raff et al, 2007). From a medical perspective, there was evidence in the literature at the time of the Study 203 protocol development that MRD negativity was predictive of a relevant clinical outcome (ie, better RFS and/or OS) (Appelbaum et al, 2007; Bader et al, 2009). More recent data confirm the strong relationship between MRD response and time to relapse (Gökbuget et al, 2012a). The recent meta-analysis by Berry et al confirmed that achieving MRD negativity in patients with hematologic CR (representing a further reduction in leukemic tumor burden) is a robust predictor of prolonged RFS as shown by consistent results across multiple subgroups, including methods for MRD detection (flow cytometry or PCR), MRD analysis cutoff ($\leq 1 \times 10^{-4}$ or 1×10^{-4} to 1×10^{-3}), period assessed (after induction, after consolidation, or other), Philadelphia chromosome status (Philadelphia-positive or Philadelphia-negative), ALL type (B-cell or T-cell), age (pediatric or adult), and study type (randomized trial or database) (Berry et al, 2017).

In the relapsed/refractory ALL setting, blinatumomab demonstrated that CR as a direct measure of reduced disease burden was a predictor of clinical benefit (ie, prolonged OS) (Section 1). Thus, it is reasonable to expect that induction of MRD negativity, which is also a direct measure of reduced disease burden, by treatment with blinatumomab would lead to improved RFS and OS. Methods of MRD evaluation are well established. Currently, MRD is being detected at earlier stages, and assays for detection are more precise and sensitive than those used in hematologic CR.

The data presented herein for blinatumomab and historical comparators provide evidence that MRD status measured after blinatumomab treatment predicts clinical outcome (eg, RFS and OS), thus supporting the use of complete MRD response as an endpoint that is reasonably likely to predict clinical benefit and representing another step forward in diagnosing and treating patients with ALL.

3.3.2 Relapse-free Survival

In blinatumomab Study 203, duration of remission was measured by RFS and time to hematologic relapse. Per agreement with the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), the analysis of RFS was to exclude potential benefits from subjects undergoing an HSCT, as patients who were not eligible for HSCT were considered to have a higher unmet medical need than patients who were eligible for HSCT. Thus, the primary analysis of RFS censored the data at the point where HSCT or further chemotherapy was introduced. Although there

is no perfect method to account for an event such as HSCT that does not occur at a fixed time, this was implemented for the prospectively defined key secondary endpoint by censoring RFS at the time of HSCT. In the context of the MRD-positive ALL studies with blinatumomab, measurement of RFS and calculation of time to hematologic relapse allow for exploration of a correlation between MRD negativity and the established clinical benefit of improvement in RFS. Also, subjects were followed for 18 months from the start of blinatumomab therapy for the analysis of RFS, based on discussions with CHMP.

3.3.3 Overall Survival

Overall survival is the universally accepted direct measure of clinical benefit in ALL and is considered as the most reliable cancer endpoint in oncology studies (US FDA, 2007). As a result, OS was included as a secondary endpoint in Study 203.

4. EFFICACY DATA

4.1 Clinical Studies

4.1.1 Pivotal Study 203

4.1.1.1 Study Design and Statistical Methodology

Study 203 is a pivotal, open-label, multicenter, single-arm, phase 2 study in subjects ≥ 18 years of age whose MRD-positive B-cell precursor ALL was in hematologic CR as defined by less than 5% blasts in the bone marrow after at least 3 intense chemotherapy blocks (ie, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia [GMALL] induction I-II/consolidation I, induction/intensification/consolidation, or 3 blocks of hyper-CVAD [cyclophosphamide, vincristine, doxorubicin, and dexamethasone]). Subjects were required to have MRD at a level of ≥ 1 x 10^{-3} using any assay (PCR or flow cytometry) with a minimum sensitivity of 1 x 10^{-4} after an interval of at least 2 weeks from their last systemic chemotherapy. Important exclusion criteria included the presence of circulating blasts or current active extramedullary disease, history of clinically relevant central nervous system (CNS) pathology, or any prior allogeneic HSCT. The study was conducted at 46 centers in Europe. The primary and secondary analyses for this study are completed; subjects are being followed for long-term efficacy.

Subjects in this study were treated with blinatumomab as a continuous IV infusion at a dose of 15 µg/m^2/day (approximately equivalent to the blinatumomab fixed dose of 28 µg/day) over 4 weeks followed by a treatment-free period of 2 weeks (1 cycle =-6 weeks). Subjects were eligible to receive up to 4 cycles of treatment. Subjects with MRD relapse in the observation period following completion of the initial treatment period with blinatumomab were eligible to receive an additional 2 cycles of blinatumomab retreatment. To ensure subjects' safety, the study protocol was amended to implement a premedication regimen that included a corticosteroid (prednisone 100 mg IV or equivalent) administered within 1 hour prior to the start of treatment on day 1 of each cycle (the original protocol included the corticosteroid premedication regimen before cycle 1 only). No step-dosing was required in this study, because results from the earlier phase 2 Study 202, in which blinatumomab 15 µg/m^2/day was administered since day 1, showed that the dose was well tolerated, and baseline B-cell levels as well as the risk of related cytokine release syndrome events were low in the setting of MRD-positive ALL. (Step-dosing was used in the treatment of patients with

relapsed/refractory B-cell precursor ALL, and is required during the first cycle of blinatumomab to mitigate the first-dose effects of cytokine release syndrome [BLINCYTO® USPI, 2017]). Subjects in this study were hospitalized for at least 3 days after the start of treatment during cycle 1 and for at least 2 days after the start of treatment during subsequent cycles of treatment.

Subjects were assessed for MRD after each treatment cycle (day 29) and at efficacy follow-up visits. The core study period for each subject included the screening period, treatment cycle (including the 2-week treatment-free interval), and the 30-day safety follow up visit. For subjects undergoing allogeneic HSCT, 100-day post-transplant mortality and 2-year efficacy and survival follow-up were assessed. Subjects not eligible for allogeneic HSCT were permitted to receive up to 4 cycles of blinatumomab treatment or until hematologic relapse occurred, whichever occurred first. These subjects were followed for a total of 2 years for efficacy including bone marrow assessments, then for 3 years of survival follow-up.

The primary endpoint was the complete MRD response rate defined by absence of detectible MRD (using an assay with a minimum sensitivity of 1×10^{-4}) after 1 cycle of treatment with blinatumomab. To evaluate the impact of MRD status on clinical outcome, the hematologic RFS rate at 18 months after initiation of blinatumomab was designated as a key secondary efficacy endpoint, with censoring performed at HSCT or post-blinatumomab chemotherapy. Secondary endpoints included OS, mortality rate within 100 days after allogeneic HSCT, time-to-hematologic relapse, duration of complete MRD response, and safety.

The purpose of the primary analysis was to evaluate the primary efficacy endpoint and assess safety. The purpose of the secondary analysis was to evaluate the key secondary endpoint of hematological RFS and other secondary time-to-event efficacy analyses, including an update to the safety analysis. For the secondary analysis of RFS, subjects were followed for at least 18 months. The final analysis will be carried out 5 years after the last subject enrolled into the study.

Key statistical methods for the efficacy endpoints for Study 203 are provided in Table 3. The statistical analyses presented in this document are based on the following prespecified study populations:

- **Primary Endpoint Full Analysis Set (Prim EP FAS)**: All subjects with an Ig TCR PCR MRD assay with the minimum required sensitivity of 1 x 10^{-4} at central lab established at baseline. The Prim EP FAS was used to analyze the primary endpoint of complete MRD response rate achieved after 1 cycle of blinatumomab.
- **Key Secondary Endpoint Full Analysis Set (Key Sec EP FAS)**: All subjects excluding those with Philadelphia-positive ALL who were in hematologic CR when blinatumomab treatment was initiated and excluding transplants (via censoring at the time of HSCT). The Key Sec EP FAS was used to analyze the key secondary endpoint of hematologic RFS rate at 18 months.
- **Full Analysis Set (FAS):** All subjects who received any infusion of blinatumomab (consistent with the intention-to-treat principle in single-arm open-label studies). The FAS was used to analyze OS and safety endpoints.
- **HSCT Secondary Endpoint Full Analysis Set (HSCT Sec EP FAS)**: All subjects from the FAS who underwent HSCT prior to relapse (hematological or extramedullary) excluding Philadelphia-positive subjects. The HSCT Sec EP FAS was used to analyze the secondary endpoint of 100-day mortality after allogeneic HSCT.

Table 3. Study 203: Key Efficacy Endpoint Definitions and Statistical Analysis Methods

Efficacy Endpoint	Definition	Statistical Methods	Censoring
Primary Complete MRD response rate, defined by the absence of MRD after 1 cycle of treatment with blinatumomab Additional analyses were performed after cycles 2, 3, 4, and anytime during the study	Calculated as the number of subjects with complete MRD response after one cycle of treatment in the respective analysis set divided by all subjects in the respective analysis set Evaluated primarily for the Prim EP FAS that included all subjects with an Ig T-cell receptor PCR MRD assay with the minimum required sensitivity of 1×10^{-4} at central lab established at baseline	Response rate and the 2-sided exact 95% CI and by covariates The statistical hypothesis was H_0: $\pi \leq p_0 = 44\%$[a] versus H_1: $\pi \geq p_1 = 61\%$, where π is the true rate of subjects with a complete MRD response. The efficacy of blinatumomab was established if the null hypothesis could be rejected.	NA
Key Secondary Hematologic RFS rate at 18 months	Calculated as the time from the first dose of blinatumomab to the earlier of the first assessment of hematologic or extramedullary relapse, or secondary leukemia, or death due to any cause Evaluated primarily for the Key Sec EP FAS that included all subjects in the FAS who were In hematologic CR at treatment start, excluding Philadelphia-positive subjects and excluding transplants (via censoring at the time of HSCT)	The statistical null hypothesis was that RFS at 18 months is $\leq 28\%$[b] and was only to be tested if the primary endpoint null hypothesis was rejected. The following were provided: 18-month KM estimate and 2-sided 95% CIs. Median, range, Q1 and Q3 with 2-sided 95% CI by KM Sensitivity analysis without censoring for HSCT Landmark analysis to assess impact of MRD response on RFS (subjects with and without MRD response at 45 days after the first dose of blinatumomab, calculating RFS from day 45)	Censored at earliest of: • last hematologic assessment for subjects without an event • HSCT • start of chemotherapy for subjects who received chemotherapy before relapse for persistent MRD or any other reason

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Footnotes are on the last page of this table.

Table 3. Study 203: Key Efficacy Endpoint Definitions and Statistical Analysis Methods

Efficacy Endpoint	Definition	Statistical Methods	Censoring
Other Secondary			
OS	Defined as the time from treatment start with blinatumomab until death due to any cause	Median, range, Q1 and Q3 with 2-sided 95% CI by KM Landmark analysis as described for RFS	Censored at date of last contact
100-day mortality after allogeneic HSCT	Defined as the KM rate of subjects dying within 100 days after the day of the first allogeneic HSCT and included only subjects who had an allogeneic HSCT after start of treatment with blinatumomab	Mortality rate and 95% CI at 100 days by KM estimate	NA
Time to hematologic relapse	Calculated from treatment start with blinatumomab until the time of hematologic or extramedullary relapse	Median, range, Q1 and Q3 with 2-sided 95% CI by KM	Censored at last hematologic assessment prior to death, secondary leukemia, or HSCT or post-blinatumomab chemotherapy (whichever occurred first)
Duration of complete MRD response	Calculated from time from onset of MRD negativity until MRD or hematologic relapse or date of last confirmation of negative MRD status	Median, range, Q1 and Q3 with 2-sided 95% CI by KM	Censored at date of last confirmation of negative MRD status

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FAS = full analysis set; HSCT = hematopoietic stem cell transplantation; Ig = immunoglobulin; Key Sec EP FAS = Key Secondary Endpoint Full Analysis Set; KM = Kaplan-Meier; MRD = minimal residual disease; NA = not applicable; OS = overall survival; PCR = polymerase chain reaction; Prim EP FAS = Primary Endpoint Full Analysis Set; RFS = relapse-free survival

[a] The estimate of 44% refers to the conversion rate by allogeneic HSCT, which is generally accepted to be an appropriate intervention for MRD-positive ALL and was based on results from published literature (Spinelli et al, 2007). In the Spinelli study, a 3 log mean reduction in leukemia burden was confirmed from bone marrow samples of 36 patients; among those who were not in molecular CR prior to transplant (n = 25), 11 (44%) achieved molecular CR after transplant.

[b] The null value of 28% was based on input from external experts: RFS after 1 year was 17.5% (14 out of 80 patients) from historical data. In a conservative manner, RFS at 18 months was estimated by the upper limit of the 95% two-sided CI of this rate.

Source: Appendix 16.1.9 of Study 203 Secondary Analysis CSR

4.1.1.1.1 MRD Measurement Methodology

In Study 203, subjects were screened based on the local site evaluation of MRD at a level of $\geq 1 \times 10^{-3}$ using any assay (PCR or flow cytometry) with a minimum sensitivity of 1×10^{-4}. Subjects were allowed to enroll in the study based on the local results; an aliquot of the bone marrow aspirate was sent to the central laboratory for determination of baseline MRD level using a validated real-time quantitative PCR assay. All tumor response MRD measurements were performed at the central laboratory. The PCR method was performed in the following manner.

Genomic DNA from bone marrow samples obtained from subjects at diagnosis or after relapse were used to identify leukemia-specific clonal gene rearrangements in the junctional regions of different gene loci (complete and incomplete Ig heavy chain, Ig light chain, and TCR beta, TCR gamma, TCR delta, and TCR delta/alpha genes) with standard PCR with consensus primers. Sanger sequencing was performed to identify the clone-specific junctional region sequence (malignant transformation of a lymphoid progenitor will result in the clonal expansion of lymphoid progenitor cells with a clone-specific junctional region sequence). Specific and sensitive real-time quantitative PCR assays were established (hydrolysis probe method used). Specificity of the assay was based on positioning the 3' end of one of the primers in the junctional region of the Ig/TCR gene rearrangement. The junctional region of the Ig/TCR gene is amplified exponentially with each PCR cycle with a sensitivity of at least 1×10^{-4}. In this manner, MRD was quantified in DNA isolated from bone marrow aspirates collected at prespecified time points during treatment. Final interpretation of MRD results followed EuroMRD Consortium (formerly the European Study Group on MRD detection in ALL [ESG-MRD-ALL]) guidelines (van der Velden et al, 2007).

At the time of the initial protocol development for Study 203 in 2010, MRD detection methods included flow cytometry with sensitivity estimated to be in the range of 1×10^{-3} to 1×10^{-4} and real-time quantitative PCR with an assay detection limit of 1×10^{-4}. In Study 203, a conservative definition of MRD positivity, using a level of $\geq 1 \times 10^{-3}$, was chosen as the enrollment MRD requirement to account for the sensitivities of the available assays, and the cutoff of $\geq 1 \times 10^{-3}$ ensured an adequate degree of tumor load reduction to reliably measure response (ie, at least 10-fold tumor load reduction from 10^{-3} to 10^{-4}). Additionally, the literature supported that MRD at 1×10^{-3} identified patients with higher risk. An assessment of MRD in 116 patients with Philadelphia

chromosome-negative ALL found that MRD ≥ 1 x 10^{-3} after induction was an independent prognostic indicator for relapse (Holowiecki et al, 2008). Subsequently, published data supported the assumption of a quantitative relationship between MRD level and time to relapse. Specifically, the median duration of remission decreased from 7.6 months in patients with MRD ≥ 1 x 10^{-4} to 4.9 months in patients with MRD ≥ 1 x 10^{-3} (Gökbuget et al, 2012a), suggesting that the risk of relapse is high at MRD levels ≥ 1 x 10^{-4} and is progressively worse with increasing disease burden (ie, MRD ≥ 1 x 10^{-3}).

The definition of MRD positivity is continually evolving as assessment techniques become more sensitive. The current NCCN guidelines do not define a specific threshold for MRD positivity but note that MRD positivity can be detected with flow cytometry or PCR methods with a minimum sensitivity of < 1 x 10^{-4} (NCCN, 2017). As discussed in Section 2.1, most recent published literature defines MRD positivity as ≥ 1 x 10^{-4}. Amgen considers that MRD positivity at ≥ 1 x 10^{-4} is an appropriate cutoff for identifying an MRD-positive population. Data derived using the 1 x 10^{-3} cutoff in Study 203 are directly relevant for evaluation of patients today identified as MRD-positive using a current 10^{-4} assay. First, most patients who are MRD-positive by a 10^{-4} assay are also MRD-positive using the 10^{-3} cutoff. Data from historical comparator study (Study 148) show that in patients with MRD-positive ALL identified using the current 10^{-4} cutoff, approximately 70% also had MRD levels of at least 1 x 10^{-3} (Appendix 2). Second, risk according to MRD level appears to be a continuous function. Patients with higher baseline MRD levels have shorter median RFS (Dhédin et al, 2015; Gökbuget et al, 2012a). Thus, the 18-month RFS key secondary endpoint was likely to be sufficient to capture meaningful clinical benefit compared to historical data.

4.1.1.2 Demographic and Other Baseline Characteristics

A total of 116 subjects received ≥ 1 infusion of blinatumomab and were included in the FAS. The Prim EP FAS (n = 113) excluded 3 subjects with unevaluable MRD assays at baseline (1 subject had no MRD results and 2 subjects had low MRD assay sensitivity).

The core study included subjects who completed the day 29 visit after 4 cycles for subjects who did not have HSCT, and completion of at least day 29 of cycle 1 for subjects who had HSCT. At the time of the secondary analysis, all 116 subjects in the FAS had ended the core study, including 3 subjects (2.6%) who started retreatment

cycles. Treatment completion was the main reason for ending the core study (71.6%). The median duration of the core study was 2.7 months (range: 0 to 7 months). After completing the core study, subjects were to remain in the study for the long-term follow-up period. Approximately half of the subjects (53.4%) were continuing in the study at the time of the secondary analysis. Of the subjects who ended the study, all died except for 1 subject who withdrew. The median duration on study was 18.3 months (range: 1 to 54 months).

More than half of the subjects in Study 203 were male (58.6%) and most were white (87.9%). The median age was 45.0 years (range: 18 to 76 years) and 12.9% of subjects were ≥ 65 years of age. The protocol targeted subjects who were MRD-positive at baseline; MRD levels ≥ 1 x 10^{-3} were confirmed by the central laboratory for 91.4% of subjects. Five subjects (4.3%) had Philadelphia-positive ALL and 5 subjects (4.3%) had a t(4;11) translocation/MLL-AF4 fusion gene. Overall, 64.7% were in CR1, 33.6% were in CR2, and 1.7% were in CR3.

4.1.1.3 Efficacy Results

4.1.1.3.1 Complete MRD Response

In the Prim EP FAS, complete MRD response was achieved within the first cycle in 77.9% (95% CI: 69.1, 85.1) of subjects (Table 4), which was significantly greater than the null hypothesis threshold of 44% prespecified for the study (as described in Table 3). Beyond cycle 1 of treatment, 2 additional subjects had a complete MRD response (both at cycle 2). Thus, the overall complete MRD response rate for the Prim EP FAS was 79.6% (95% CI: 71.0, 86.6), with a median time to complete MRD response of 29.0 days (range: 5 to 71 days).

Complete MRD response was achieved after 1 cycle for subjects in CR1 (82.2%; 60/73 subjects) as well as those in CR2 (71.1%; 27/38 subjects). The number of subjects in CR3 (n = 2) was too small to provide a reliable estimate of complete MRD response. The primary endpoint of complete MRD response was analyzed by other covariates, including age, gender, incidence rate of neurologic events during cycle 1, Philadelphia chromosome status, and MRD level at baseline. Complete MRD response rates were largely consistent across all subgroups.

Table 4. Study 203: Overall MRD Response at Cycle 1 and MRD Response by CR Status

	Primary Endpoint Full Analysis Set (N = 113)	
MRD assessment cycle 1 (%)	n (%)	95% CI
Evaluable	112 (99.1)	Not Applicable
Not evaluable	1 (0.9)	Not Applicable
MRD response at cycle 1 (%) (95% exact CI)		
Complete MRD response	88 (77.9)	(69.1, 85.1)
MRD nonresponse	25 (22.1)	(14.9, 30.9)
Low-level MRD positivity, non-quantifiable	10 (8.8)	(4.3, 15.7)
Quantifiable MRD positivity	14 (12.4)	(6.9, 19.9)
No MRD response assessment	1 (0.9)	(0.0, 4.8)
MRD level < 1 x 10^{-4}, [a]	98 (86.7)	(79.1, 92.4)
No MRD response assessment	1 (0.9)	(0.0, 4.8)
MRD response by relapse history	n/N (%)	
Subjects in CR1	60/73 (82.2)	(71.5, 90.2)
Subjects in CR2	27/38 (71.1)	(54.1, 84.6)
Subjects in CR3	1/2 (50.0)	(1.3, 98.7)

CR1 = first clinical remission; CR2 = second clinical remission; CR3 = third clinical remission; MRD = minimal residual disease; N = number of subjects in the analysis set
[a] Includes the 88 subjects who had complete MRD response (absence of MRD with an assay with a minimum sensitivity of 1 x 10^{-4}) and the 10 subjects who had non-quantifiable, low-level MRD positivity
Source: Modified from Table 5 of Module 2.7.3 and Table 14-4.1.3 of Study 203 Primary Analysis CSR

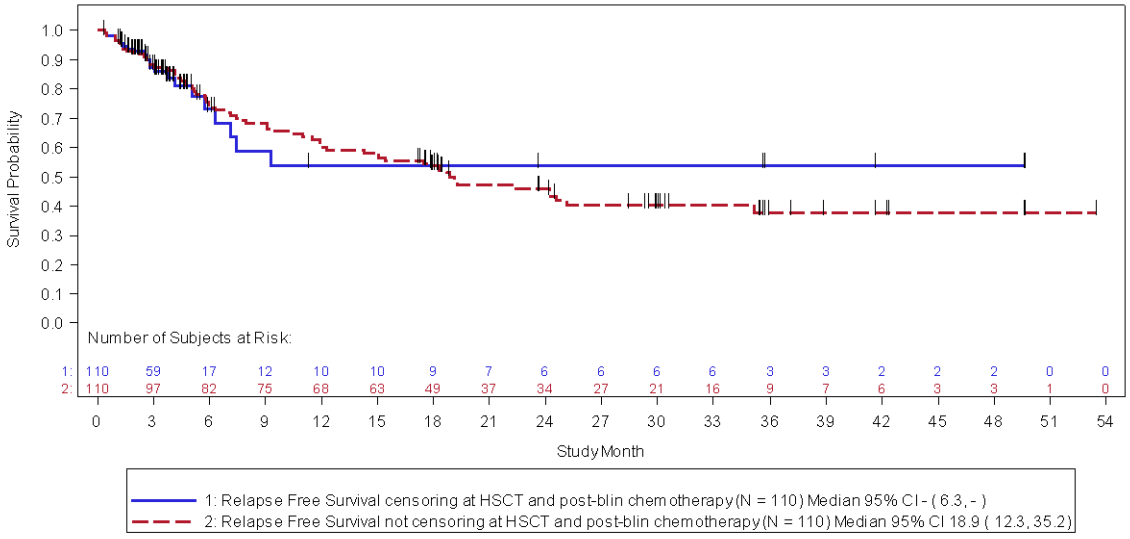
4.1.1.3.2 Relapse-free Survival

A total of 89 (80.9%) of the 110 subjects in the Key Secondary Endpoint Full Analysis Set (Key Sec EP FAS) were in remission and either censored at the time of their last hematologic assessment (10/110 subjects; 9.1%) or censored for HSCT (70/110; 63.6%) or post-blinatumomab chemotherapy (9/110 subjects; 8.2%). A total of 19.1% (21/110) of subjects had a hematologic RFS event: 16.4% had a hematologic relapse, 0.9% had secondary leukemia, and 1.8% had died. The KM-estimated RFS rate at 18 months, censored at HSCT or post-blinatumomab chemotherapy, was 54% (95% CI: 33, 70) (Figure 3).

Of note, per protocol and based on advice from the CHMP, the primary analysis of RFS was censored for HSCT or post-blinatumomab chemotherapy in order to isolate the efficacy of blinatumomab as a monotherapy among those not eligible for HSCT, which was considered an area of particular unmet medical need (Section 3.3.2). The study

was not designed to measure the impact of HSCT on RFS. The comparison of KM curves of RFS, censored with and without HSCT and post-blinatumomab chemotherapy, is not appropriate to evaluate the effect of HSCT on RFS, because the analysis is subject to potential bias due to informative censoring (ie, HSCT and receipt of chemotherapy after blinatumomab are sometimes associated with or triggered by other events, such as MRD relapses, which are also associated with the failure/hematological-relapse time).

Figure 3. Study 203: Kaplan-Meier Curve of Relapse-free Survival (Key Sec EP FAS)



Censor indicated by Vertical Bar

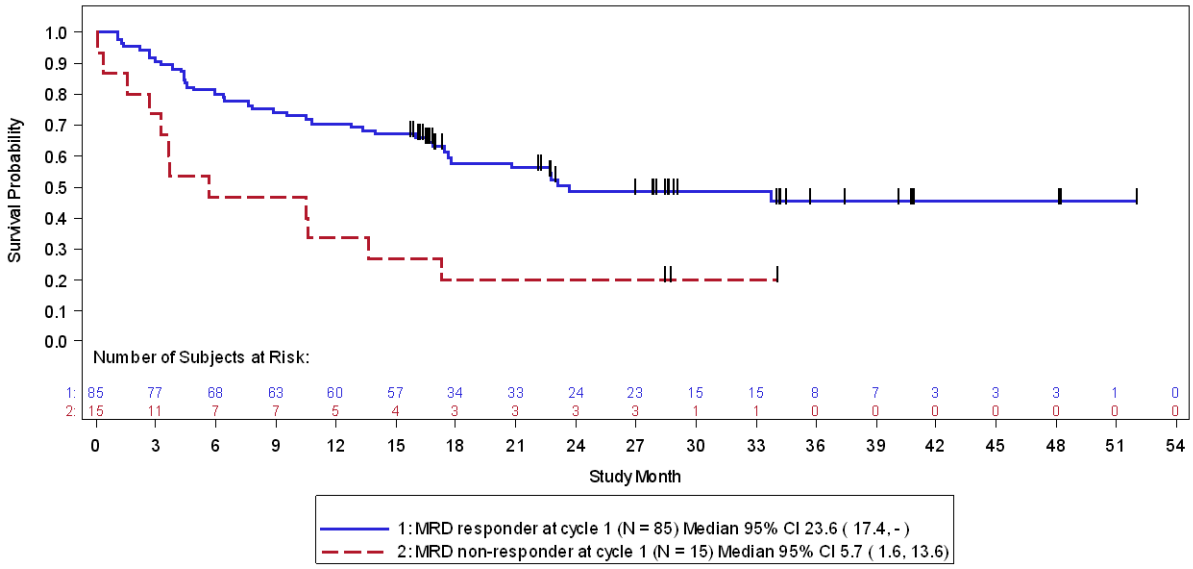
Program: /userdata/stat/amg103/onc/mt103_203/analysis/secondary/figures/program/f-eff-km.sas
Output f14-04-002-001-eff-km-rfs-ksfasfl.rtf (Date Generated: 23NOV15 05:03) Source Data: adam.adsl, adam.adfteeff

HSCT = hematopoietic stem cell transplantation; Key Sec EP FAS = Key Secondary Endpoint Full Analysis Set
All subjects in the FAS in hematologic complete remission at treatment initiation, excluding subjects with Philadelphia-positive acute lymphoblastic leukemia.
The intent of the Kaplan-Meier plot is to show the effect of blinatumomab without HSCT or additional chemotherapy. The plot makes no inferences about the benefit of HSCT.
Source: Figure 2 of Module 2.7.3

The relationship between complete MRD response and RFS was evaluated in 107 subjects from both the Prim EP FAS and Key Sec EP FAS in a landmark analysis starting from day 45 (day by which all cycle 1 MRD responses had been assessed; Figure 4). In the landmark analysis, subjects who relapsed, died, or were censored before day 45 were excluded to correct for immortal time bias. In the subgroup of subjects achieving complete MRD response at cycle 1 (excluding 7 subjects who had an event or were censored before day 45), a total of 52.9% (45/85) subjects were alive

without relapse (censored) at the end of the follow-up period compared to a total of 20.0% (3/15) of subjects who did not have a complete MRD response (100 subjects total). The KM-estimated RFS rate at 18 months (from day 45) was 58% (95% CI: 46, 68) in subjects with complete MRD response at cycle 1 compared to a rate of 20% (95% CI: 5, 42) in subjects who did not have a complete MRD response. The median RFS (from day 45) was 17.9 months longer for subjects who achieved a complete MRD response compared to subjects who did not have a complete MRD response (23.6 months [95% CI: 17.4, NE] versus 5.7 months [95% CI: 1.6, 13.6] in complete MRD responders versus nonresponders, respectively). Although RFS appears prolonged by achieving a complete MRD response, a direct causal relationship cannot be established since there may be baseline factors that contributed to both the ability to achieve a complete MRD response and prolonged RFS. However, baseline factors that would appear to account for both improved complete MRD response rates and prolonged RFS were not found in this study. Routine subgroup analyses of baseline prognostic factors, such as age, gender, CR status (CR1 or CR2/CR3), MRD level at baseline, WBC count at first diagnosis, need for salvage therapy for CR, and genetic aberration (t(4;11) translocation and/or MLL-AF4+) showed that CR status (CR1 versus CR2/CR3) emerged as the most important predictor of RFS (Appendix 3). Additional landmark analyses of RFS by MRD response and CR status consistently showed that there is a benefit of achieving a complete MRD response irrespective of CR status (Appendix 4 and Appendix 5).

Figure 4. Study 203: Kaplan-Meier Curve of Relapse-free Survival Landmark Analysis (from Day 45): Complete MRD Responder Versus MRD Nonresponder (Prim EP FAS and Key Sec EP FAS)



Censor indicated by Vertical Bar

Program: /userdata/stat/amg103/onc/mt103_203/analysis/secondary/figures/program/f-eff-km.sas
Output: f14-04-002-009-eff-km-rfs45-mrd-ksfasfl.rtf (Date Generated: 23NOV15 05:03) Source Data: adam.adsl, adam.adtteeff

Ig = immunoglobulin; Key Sec EP FAS = Key Secondary Endpoint Full Analysis Set (all subjects in the FAS, excluding Philadelphia chromosome-positive subjects in hematologic complete remission from start of treatment); MRD = minimal residual disease; PCR = polymerase chain reaction; Prim EP FAS = Primary Endpoint Full Analysis Set (all subjects with an Ig or T-cell receptor PCR MRD assay with sensitivity of 1×10^{-4} established at baseline by central laboratory)

Subjects who relapsed or died or were censored before day 45 were excluded from the analysis. The time to relapse was recalculated from the landmark analysis.

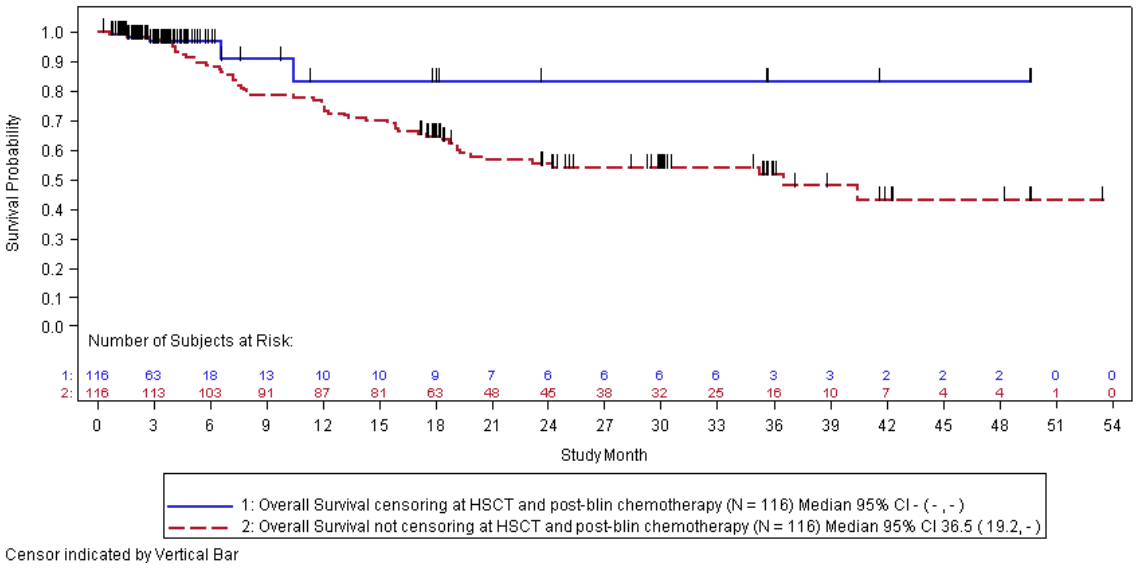
Although RFS appears prolonged by achieving a complete MRD response, a direct causal relationship cannot be established since there may be baseline factors that contributed to both the ability to achieve a complete MRD response and prolonged RFS.

Source: Figure 3 of Module 2.7.3

4.1.1.3.3 Overall Survival

At the time of the secondary analysis, a total of 53 deaths (45.7%, 53/116) were reported in the study and 63 subjects (54.3%; 63/116) were alive. The KM-estimated rate for OS at 18 months was 65% (95% CI: 55, 73), with a median OS of 36.5 months (95% CI: 19.2, NE). When censoring for HSCT or post-blinatumomab chemotherapy, the KM-estimated OS probability at 18 months was 83% (95% CI: 55, 94); the median OS was not estimable (Figure 5).

Figure 5. Study 203: Kaplan-Meier Curve of Overall Survival With and Without Censoring for HSCT and Post-blinatumomab Chemotherapy (Full Analysis Set)

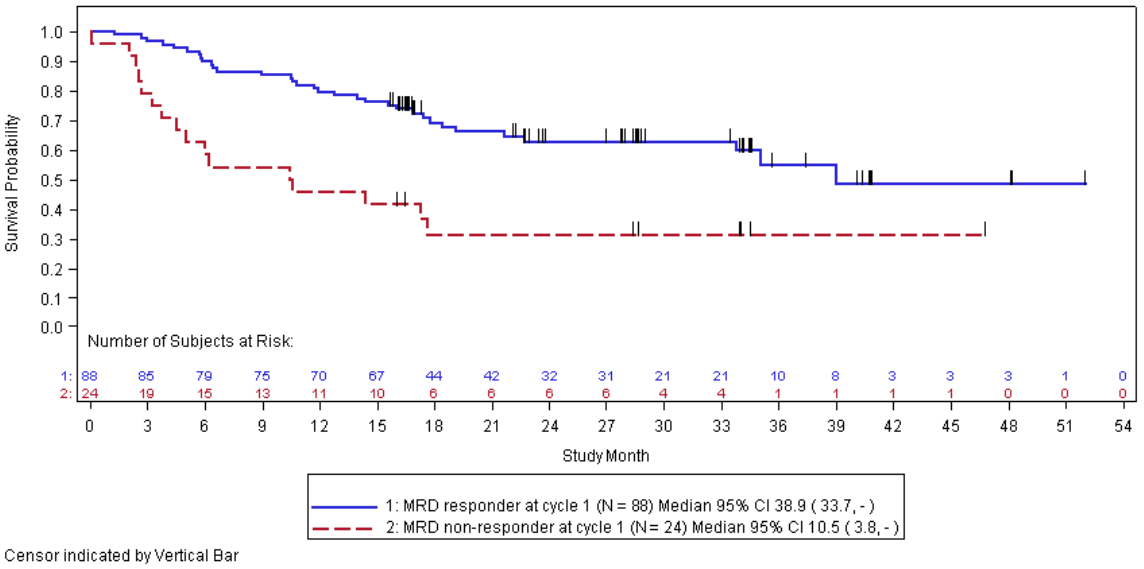


HSCT = hematopoietic stem cell transplantation; post-blin = after blinatumomab chemotherapy
Note: Subjects who died or were censored before day 45 were excluded from the analysis.
The Intent of the Kaplan-Meier plot is to show the effect of blinatumomab without HSCT or additional chemotherapy. The plot makes no inferences about the benefit of HSCT.
Source: Figure 4 of Module 2.7.3

The relationship between complete MRD response and OS was compared in a landmark analysis starting from day 45 in the Prim EP FAS subjects (N = 112). In the subgroup of subjects achieving complete MRD response at cycle 1 (excluding 1 subject who died or was censored before day 45), 62.5% (55/88) of subjects were alive at the end of the follow-up period (and censored) versus 33.3% (8/24) among subjects who did not have a complete MRD response. The KM-estimated OS rate at 18 months (from day 45) was 69% (95% CI: 58, 78) in subjects who had a complete MRD response versus 31% (95% CI: 14, 51) in subjects who did not have a response. The median OS (from day 45) was 28.4 months longer in subjects who achieved a complete MRD response compared to subjects who did not have a response (38.9 months

[95% CI: 33.7, NE] versus 10.5 months [95% CI: 3.8, NE] in complete MRD responders versus MRD nonresponders, respectively), as presented in Figure 6. Although OS appears prolonged by achieving a complete MRD response, a direct causal relationship cannot be established since there may be baseline factors that contributed to both the ability to achieve a complete MRD response and prolonged OS. However, baseline factors that would appear to account for both improved complete MRD response rates and prolonged OS were not found in this study. Routine subgroup analyses of baseline prognostic factors, such as age, gender, disease subtype (Philadelphia negative, Philadelphia positive), relapse history (CR1 or CR2/CR3), MRD level at baseline, WBC count at first diagnosis, need for salvage therapy for CR, and genetic aberration (t(4;11) translocation and/or MLL-AF4+) showed that CR status (CR1 versus CR2/CR3) emerged as the most important predictor of OS (Appendix 6). Philadelphia chromosome status was also a predictor of OS, but the sample size for Philadelphia-positive subjects (N = 5) was small. Additional landmark analyses of OS by MRD response and CR status consistently showed that there is a benefit of achieving a complete MRD response irrespective of CR status (Appendix 7 and Appendix 8).

Figure 6. Study 203: Kaplan-Meier Curve of Overall Survival Landmark Analysis (from Day 45): Complete MRD Responder Versus MRD Nonresponder (Prim EP FAS)



MRD = minimal residual disease; Prim EP FAS = Primary Endpoint Full Analysis Set
Subjects who died or were censored before day 45 were excluded from the analysis.
Although OS appears prolonged by achieving a complete MRD response, a direct causal relationship cannot be established since there may be baseline factors that contributed to both the ability to achieve a complete MRD response and prolonged OS.
Source: Figure 5 of Module 2.7.3

4.1.1.3.4 100-day Mortality After Allogeneic HSCT

The overall subject incidence of HSCT after treatment with blinatumomab was 77.6% (90/116) in the FAS. Of the 90 subjects who had an HSCT, 76 (84.4%) subjects were in continuous hematologic CR at the time of HSCT.

In the HSCT Sec EP FAS (ie, all subjects from the FAS who underwent HSCT prior to hematological or extramedullary relapse excluding Philadelphia-positive subjects; the prespecified study population for this analysis), 74 subjects from the FAS received allogeneic HSCT while in continuous hematologic CR. Of these 74 subjects, 31 (41.9%) subjects died, with 5 deaths occurring during 100 days after allogeneic HSCT. The OS rate at 100 days after allogeneic HSCT was 93% (95% CI: 85, 97). Therefore, the 100-day mortality rate after allogeneic HSCT was 7% (95% CI: 3, 15), which is lower than the published rate of 28% (Bishop et al, 2008).

Among the 5 deaths that occurred during 100 days after allogeneic HSCT, the causes of death were reported as septic multi-organ failure, sepsis and multi-organ failure,

septicemia, features suggestive of veno-occlusive disease, and unknown reason. None of the deaths were reported as being related to blinatumomab treatment.

4.1.1.3.5 Time to Hematologic Relapse

In the Key Sec EP FAS (N = 110), the 18-month KM estimate for time to hematologic relapse (TTHR; defined in Table 3), censored at HSCT or post-blinatumomab chemotherapy, was 55% (95% CI: 34, 72); the median TTHR was not estimable (95% CI: 7.1 months, NE). A total of 82.7% (91/110) of subjects were censored as of the data cutoff, and a total of 17.3% (19/110) subjects had events: 16.4% (18/110) had a relapse and 0.9% (1/110) had secondary leukemia. The 18-month KM estimate for TTHR, not censored for HSCT or post-blinatumomab chemotherapy, was 67% (95% CI: 57, 76), and the median TTHR was not estimable (95% CI: 24.3 months, NE).

4.1.1.3.6 Duration of Complete MRD Response

The median duration of MRD response for the Key Sec EP FAS and Prim EP FAS subjects who had complete MRD response at cycle 1 (N = 85) was 17.3 months (95% CI: 12.6, 23.3) uncensored and 45.0 months (95% CI: 6.5, 45.0) when censored at the time of HSCT or post-blinatumomab chemotherapy. The 18-month KM estimates were 46% (95% CI: 33, 57) and 51% (95% CI: 28, 69), respectively.

4.1.2 Study 202

4.1.2.1 Study Design and Statistical Methodology

Study 202 was an exploratory, proof-of-concept, open-label, multicenter, single-arm, phase 2 study in adult subjects with MRD-positive B-cell precursor ALL, with a dose-finding run in phase. Eligible subjects were ≥ 18 years of age and were in hematologic CR with molecular failure or molecular relapse with quantifiable MRD level of ≥ 1 x 10^{-4} starting at any time point after established standard induction/consolidation therapy of ALL. The study was conducted at 6 centers in Germany. This study is completed.

The study was planned with a Simon's 2-stage design, which is widely used for phase 2 cancer studies, because it allows for the accumulation of data on both therapeutic activity and safety and relies on statistical testing to control both type 1 and type 2 error rates (continue with an ineffective treatment or abandon an effective treatment, respectively) (Porcher and Desseaux 2012; Koyama and Chen, 2008). Stage 1 began

with blinatumomab continuous IV infusion at 15 µg/m^2/day over 4 weeks followed by a treatment-free period of 2 weeks (1 cycle = 6 weeks). After 1 cycle of blinatumomab treatment, a data review committee reviewed the data from these subjects, as prespecified by the protocol. The protocol was amended twice to permit dose escalation of blinatumomab to 30 µg/m^2/day after cycle 1 for subjects who did not achieve MRD response. Subjects who were positive for bcr/abl and received concomitant treatment with a TKI during cycle 1 of blinatumomab treatment and who did not respond received 15 µg/m^2/day of blinatumomab in cycle 2 without a TKI. If the subject did not respond after 2 cycles at 15 µg/m^2/day of blinatumomab, the dose was increased to 30 µg/m^2/day of blinatumomab.

The dosing schedule in this study was based on a phase 1 study (Study 104) in subjects with relapsed or refractory non-Hodgkin lymphoma (NHL), which showed that a maintenance dose of 15 µg/m^2/day blinatumomab for 4 to 8 weeks was well tolerated in 13 subjects. It was also demonstrated that blinatumomab at this dose level exerted clinical efficacy not only in peripheral lymph nodes but also in bone marrow of subjects with NHL. Based on the high efficacy observed (ie, 80% MRD response rate) and manageable safety profile at the 15 µg/m^2/day dose in this phase 2 study 202, the recommended blinatumomab dose for subjects with MRD-positive ALL was determined to be 15 µg/m^2/day (approximately equivalent to the blinatumomab fixed dose of 28 µg/day).

The primary endpoint of the study was MRD response rate, which corresponded to the incidence of MRD negativity/response (bcr/abl and/or t[4;11] genes below the detection limit and/or individual rearrangements of Ig or TCR genes below 1 x 10^{-4}) within 4 cycles of treatment with blinatumomab. Secondary endpoints provided by long-term follow-up included duration of response (as measured by RFS) and other MRD results (eg, MRD response by treatment cycle and overall, MRD relapse, MRD progression, hematologic remission, and duration of MRD response). Safety was also assessed as a secondary endpoint.

Subjects were assessed for MRD after each treatment cycle (day 29) and at efficacy follow-up visits. The core study period for each subject included the screening period, treatment cycle (including the 2-week treatment-free interval), and the 30-day safety follow up visit. After the end of the last treatment cycle, subjects were to be followed-up

in regular intervals until hematological relapse but not longer than 5 years after the subject finished the last treatment cycle with blinatumomab.

Key statistical methods for the efficacy endpoints for Study 202 are provided in Table 5.

Table 5. Study 202: Key Efficacy Endpoint Definitions and Statistical Analysis Methods

Efficacy Endpoint	Definition	Statistical Methods	Censoring
Primary			
MRD response rate, which is the incidence of MRD negativity/response[a] within 4 cycles of treatment with blinatumomab	Responders were defined as subjects with MRD negativity within 4 treatment cycles Based on the FAS (all subjects who completed at least treatment cycle 1 and for whom at least 1 MRD response assessment was available)	The following hypotheses were tested in this study: H_0: $\pi \leq p_0 = 5\%$ vs H_1: $\pi \geq p_1 = 30\%$. The MRD response probability (p_0), which, if true, means that the agent was not worth studying further, was estimated to be not higher than 5%. The future use of blinatumomab would be of considerable interest if the true MRD response probability (π) was 30% or higher (p_1).	NA
Secondary			
Time to hematologic relapse/RFS	Calculated from the start of the first infusion until hematologic relapse or death. Hematologic relapse was defined as ≥ 5% leukemia cells in bone marrow.	Median, range, Q1 and Q3 with 2-sided 95% CI by KM	Censored at: • last available date of bone marrow aspiration/biopsy
Time to MRD progression	Calculated from start of first infusion until MRD progression or hematologic relapse in subjects who did not achieve MRD negativity. MRD progression was defined as an increase in MRD level by 1 log compared with baseline.	Median, range, Q1 and Q3 with 2-sided 95% CI by KM	Same as above

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Table 5. Study 202: Key Efficacy Endpoint Definitions and Statistical Analysis Methods

Efficacy Endpoint	Definition	Statistical Methods	Censoring
Time to MRD relapse/Duration of MRD response	Calculated for subjects from the time of first detection of MRD response until the first detection of MRD relapse was measured.	Median, range, Q1 and Q3 with 2-sided 95% CI by KM	Same as above

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FAS = full analysis set; Ig = immunoglobulin; KM = Kaplan-Meier; MRD = minimal residual disease; NA = not applicable; RFS = relapse-free survival; TCR = T-cell receptor

[a] Negativity/response was defined as bcr/abl and/or t(4;11) translocations that were below the detection limit and/or individual rearrangements of Ig or TCR genes below 1×10^{-4}.

Source: Appendix 16.1.9 of Study 202 Primary Analysis CSR and Appendix 16.1.9 of Study 202 Final Analysis CSR

4.1.2.2 Demographic and Baseline Characteristics

A total of 32 subjects were screened in this study; 20 subjects were included in the FAS, which included all subjects from the safety analysis set (N = 21) who completed at least the first treatment cycle and for whom at least 1 MRD response assessment was available. Most of the subjects in the study (60%, 12/20) were female and all were Caucasian (100%, 20/20). The age distribution of the subjects was as follows: 15% between 20 and 30 years of age; 25% between 31 and 40 years of age, 10% between 51 and 60 years of age; and 45% were over 60 years of age.

4.1.2.3 Efficacy Results

A total of 80% of subjects in the FAS (16/20 evaluable subjects; 95% CI: 56.3, 94.3) achieved an MRD response, with all MRD responses achieved within the first treatment cycle. The null hypothesis for the primary endpoint was rejected, indicating that further examination of blinatumomab for the treatment of MRD-positive ALL was warranted.

Of the 16 subjects who achieved an MRD response, 5 subjects experienced MRD relapse during the long-term follow-up. The median duration of MRD response was 13 months (95% CI: 2.8, NE). The median hematologic RFS had not been reached after a median follow-up time of 50.8 months (> 4 years). Ten subjects (50%) were relapse free after at least 5 years of follow-up (duration of follow-up ranged from 5.0 to 5.9 years). Overall, 5 of the 9 subjects who received HSCT after blinatumomab treatment and 5 of 11 subjects not transplanted after blinatumomab remained in continuous hematologic CR at least 5 years after starting blinatumomab treatment (Gökbuget et al, 2017). The final RFS estimate was 52.6% at 5.9 years.

4.2 Historical Comparator Studies

4.2.1 Study 148

4.2.1.1 Study Design

Study 148 was a retrospective non-interventional cohort study of historical treatment and outcome data from MRD-positive patients with Philadelphia-negative B-cell precursor ALL who had received standard of care treatment according to national study protocols. The primary research objectives were to estimate RFS and OS for patients with MRD-positive B-cell precursor ALL. Assessment of MRD response was not included in the study because of the variability in treatment regimens after documentation of

MRD-positive status (eg, continued chemotherapy, investigational agent, or no intervention) and variable availability of MRD assessments after the qualifying baseline MRD-positive value.

The study population was assembled from patient databases of ALL study groups in Europe that included MRD testing in their protocols. All subjects who were treated at participating study group facilities, diagnosed with ALL in the year 2000 to 2014, and who met the eligibility criteria were included in the study. Subjects ages 15 years or older with Philadelphia-negative B–cell precursor ALL in hematologic CR (defined as < 5% blasts in bone marrow after at least 3 intensive chemotherapy blocks) were included if MRD was detected at a level of $\geq 1 \times 10^{-4}$ by PCR or $\geq 1 \times 10^{-3}$ by flow cytometry at a reference lab; a history of ALL treatment (including response to first therapy, number of prior relapses) was available; and relapse status and disease follow-up after time point of MRD detection was available. Subjects were excluded from the analysis if they had extramedullary disease at the time point of MRD detection, were exposed to blinatumomab within 18 months of MRD detection, or underwent allogeneic HSCT before MRD detection. Subject data were entered into a study-specific electronic case report form to ensure a standardized data collection process across study groups.

4.2.1.2 Methods

Key statistical methods for the efficacy endpoints for Study 148 are provided in Table 6. The FAS is the entire population of Study 148. The direct comparison analysis set (DCAS) was selected to provide an external historical comparison group that most similarly matched the inclusion criteria to subjects enrolled in blinatumomab clinical Study 203. The DCAS was defined as adult subjects ages 18 years or older with Philadelphia-negative B-cell precursor ALL in CR1 with an MRD level of $\geq 1 \times 10^{-3}$ as detected by PCR or flow cytometry, and with a time to relapse greater than 14 days from the date of MRD detection.

Table 6. Study 148: Key Efficacy Endpoint Definitions and Statistical Analysis Methods

Efficacy Endpoint	Definition	Statistical Methods	Censoring
Primary Hematologic RFS	Calculated as the time from first MRD detection following CR1 (after at least 3 blocks of chemotherapy per inclusion criterion) to hematologic relapse or death. Based on FAS (subjects 15 years or older with Philadelphia-negative B-cell precursor ALL in hematologic CR with MRD level of $\geq 1 \times 10^{-4}$ regardless of detection method) or DCAS (adult subjects 18 years or older with Philadelphia-negative B-cell precursor ALL in CR1 with MRD level of $\geq 1 \times 10^{-3}$ as detected by PCR or flow cytometry, with a time to relapse greater than 14 days from the date of MRD detection, and in first relapse).	Median, range, Q1 and Q3 with 2-sided 95% CI by KM KM proportions at select time points Univariate Cox regressions to assess predictors of RFS Multivariate Cox regression with variables selection through forward selection, criterion for entry p-value < 0.10 Mantel-Byar analysis tested the null hypothesis that RFS is the same with or without allogeneic HSCT. It is an unbiased modification of the log-rank test where subjects may dynamically convert from the no-HSCT risk set to the HSCT risk set on the date of the procedure (Lee et al, 1982). Cox proportional hazard model defining allogeneic HSCT as a time-dependent covariate. Subjects who had transplants contributed to the estimation of RFS as subjects who had not received transplants from baseline to the date of allogeneic HSCT, then as subjects who received transplants from allogeneic HSCT to relapse/death or censor.	Censored at last disease assessment for subjects alive without relapse Censored and uncensored at HSCT

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Table 6. Study 148: Key Efficacy Endpoint Definitions and Statistical Analysis Methods

Efficacy Endpoint	Definition	Statistical Methods	Censoring
Secondary			
OS	Calculated as the time from MRD detection to death	Median, range, Q1 and Q3 with 2-sided 95% CI by KM Mantel-Byar analysis, as described for RFS Cox proportional hazard model, as described for RFS with death or censor as ending time	Censored at last disease assessment for subjects alive without relapse Censored and uncensored at HSCT

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ALL = acute lymphoblastic leukemia; CR = complete remission; CR1 = first complete remission; DCAS = direct comparison analysis set; FAS = full analysis set; HSCT = hematopoietic stem cell transplantation; KM = Kaplan-Meier; MRD = minimal residual disease; OS = overall survival; PCR = polymerase chain reaction; RFS = relapse-free survival

Source: Section 1.3.3.2 of Module 2.7.3

4.2.1.3 Results

A total of 287 subjects were included in the FAS; 59% of subjects were male and the median age was 32 years (range: 15 to 65). The initial diagnosis of ALL was made after 2005 for more than 65% of subjects. The time from initial ALL diagnosis until the MRD detection date following complete remission after chemotherapy was less than 6 months for over 80% of subjects. All but 2 subjects in the FAS were in CR1 at the time of baseline MRD. Approximately 27% of subjects had a baseline MRD level of 1×10^{-4} to 1×10^{-3}.

A total of 182 subjects were included in the DCAS; 56% of subjects were male and the median age was 33 years (range: 18 to 65). The initial diagnosis of ALL was made before 2010 for more than 90% of subjects. The time from initial ALL diagnosis until the MRD detection date following complete remission after chemotherapy was less than 6 months for over 78% of subjects. All subjects in the DCAS were in CR1 at the time of baseline MRD. Unlike subjects in the FAS, all subjects had a baseline MRD level of $\geq 1 \times 10^{-3}$. A detailed summary of baseline and disease characteristics is provided in Appendix 2.

The RFS and OS outcomes of the FAS and DCAS were estimated and the following observations were made:

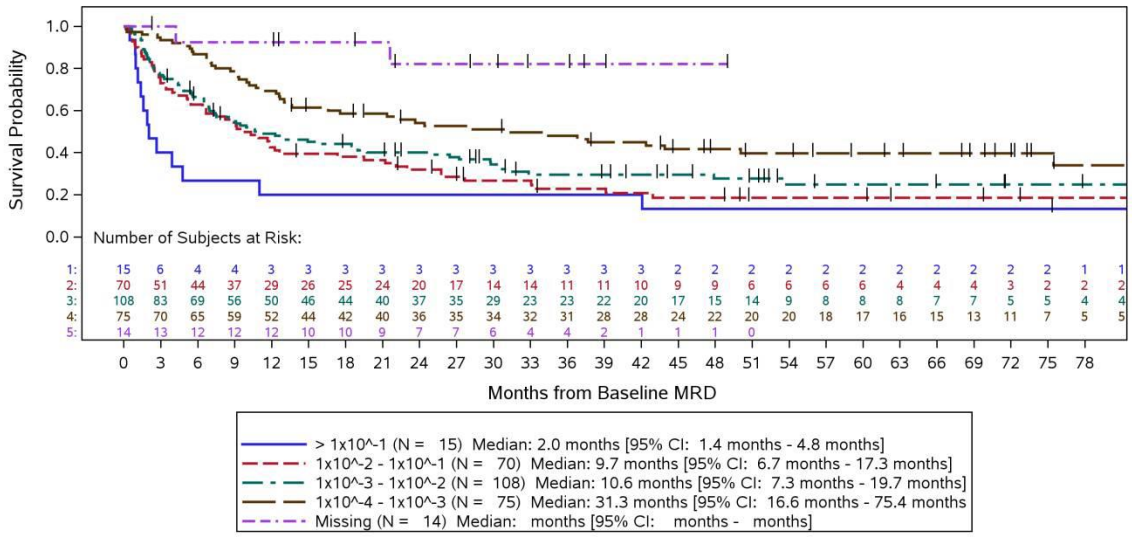
- Median hematologic RFS (censored at HSCT)
  - FAS: 12.7 months (95% CI: 9.4, 21.2) from the baseline MRD assessment; 18-month hematologic RFS (censored at HSCT) was 45% (95% CI: 38, 53)
  - DCAS: 8.5 months (95% CI: 5.6, 12.3) from the baseline MRD assessment; 18-month hematologic RFS (censored at HSCT) was 37% (95% CI: 28, 46) (Appendix 9).
- Median hematologic RFS (uncensored at HSCT)
  - FAS: 12.9 months (95% CI: 10.6, 21.3) from the baseline MRD assessment; 18-month hematologic RFS (uncensored at HSCT) was 47% (95% CI: 41, 53)
  - DCAS: 9.9 months (95% CI: 6.8, 12.9) from the baseline MRD assessment; 18-month hematologic RFS (uncensored at HSCT) was 41% (95% CI: 34, 49) (Appendix 10).
- Median OS (uncensored at HSCT)
  - FAS: 34.7 months (95% CI: 23.3, 50.6) from the baseline MRD assessment; 18-month OS (uncensored at HSCT) was 61% (95% CI: 56, 67)
  - DCAS: 27.6 months (95% CI: 17.3, 39.6) from the baseline MRD assessment; 18-month OS (uncensored at HSCT) was 56% (95% CI: 49, 64) (Appendix 11).

- Median OS (censored at HSCT)
  - FAS: 32.5 months (95% CI: 21.6, 43.6) from the baseline MRD assessment; 18-month OS (censored at HSCT) was 60% (95% CI: 52, 67)
  - DCAS: 18.0 months (95% CI: 13.6, 35.4) from the baseline MRD assessment; 18-month OS (censored at HSCT) was 50% (95% CI: 40, 59) (Appendix 12).
- Improved rates of RFS and OS were achieved in subjects with lower baseline WBC count (< 30 000/µL) and younger age (< 35 years) at diagnosis from the multivariate analyses (Appendix 13 and Appendix 14).
- HSCT was associated with improved RFS and OS (Appendix 15).
- The 100 day-mortality rate after HSCT was 8.2% (95% CI: 3.1, 13.4) in FAS and 8.6% (95% CI: 2.0, 15.2) in DCAS (Appendix 16).

From this pooled analysis of historical data in subjects with MRD-positive disease in hematologic remission, RFS was shown to be relatively short and translated into limited OS.

Of note, in the FAS of all subjects, there was a trend of longer survival with lower MRD level at baseline (Figure 7). Thus, MRD positivity at any level above 1 x 10^{-4} is an indicator of poor prognosis. This result is consistent with published data (Gökbuget et al, 2012a).

Figure 7. Study 148: Kaplan-Meier Plot of Relapse-free Survival by Baseline MRD Level in Historical Control Population (FAS)



Censor indicated by vertical bar |.

Program: TFL Shell Example\t07_02_rf_kmplot_cov.sas
Output: /userdata/cfor/projects/p13_onc_024/output/t07_02_rf_kmplot_cov_004_mrdlevel.rtf (Date Generated: 12AUG14 19:13) Source Data: adtte

FAS = full analysis set; MRD = minimal residual disease
Source: Figure 7 of Study 148 Study Report

4.2.2 Propensity Score Analysis

Propensity score methods are typically used for comparisons involving observational data. The approach provides a way to mimic the effect of randomization by creating a balance between treated and untreated patients with respect to important baseline covariates that determine both the propensity for a patient to be treated (with the treatment under evaluation) and a patient's prognosis, and allows for more valid statistical comparisons (Rosenbaum and Rubin, 1983). More recently, propensity score methods have been used in a regulatory setting when needing to evaluate results from non-randomized studies for regulatory decision making (Levenson and Yue, 2013; Yue, 2007).

4.2.2.1 Study Design and Methods

A prospectively planned propensity score analysis was conducted to compare RFS and OS in subjects treated with blinatumomab in Study 203 to subjects from the historical comparator Study 148. Data from these studies were combined to form the analysis. The following inclusion criteria were used:

- Philadelphia chromosome-negative B–cell precursor ALL in CR1 with complete baseline covariate set (only CR1 was included because all subjects in the DCAS in Study 148 were in CR1)
- MRD-positive at a level of $\geq 1 \times 10^{-3}$ independent of detection method
- Subjects who were at least 18 years old at MRD baseline date (Study 148) or first blinatumomab treatment (Study 203)
- Subjects in Study 148 with time to relapse greater than 14 days from MRD detection (the median time between MRD-positivity assessment and initiation of blinatumomab treatment in Study 203). This restriction was added to mirror what occurred in the clinical study, where potential subjects became screening failures if they experienced a hematologic relapses during the screening period.

Additional sensitivity analysis sets were analyzed restricting MRD detection method to PCR (PCR Analysis Set), and including CR2 and CR3 (FAS).

The following prespecified covariates were identified as potentially important prognostic factors and were considered for the propensity score model. The majority of the covariates were chosen based on prognostic factors that have been identified for ALL in published literature and to account for potential regional differences in treatment practices.

- Age at primary diagnosis (years)
- Sex (male, female)

- Country (Germany, others)
- Presence and type of any cytogenetic and molecular aberrations (t(4;11)MLL-AF4; yes, no/unknown)
- Time from primary diagnosis to MRD baseline date (months)
- Baseline MRD level (-3 = < 1 x 10^{-3}, -2 = ≥ 1 x 10^{-3} and < 1 x 10^{-2}, -1 = ≥ 1 x 10^{-2} and < 1 x 10^{-1}, 0 = ≥ 1 x 10^{-1})
- WBC at diagnosis (≤ 30 000/µL, > 30,000/µL)
- Type of prior chemotherapy (GMALL, other)

For fitting the propensity score model, covariates were selected by a stepwise variable selection algorithm considering all main effects and 2-way interaction terms. Separate propensity score models were completed for each analysis set.

The Inverse Probability of Treatment Weight (IPTW) approach for propensity score adjustment was chosen for this analysis. With time-to-event endpoints, other methods such as stratification and covariate adjustment have been shown to produce biased estimates of marginal and conditional hazard ratios (Austin, 2013; Austin et al, 2007) and the method of propensity score matching usually results in many dropped observations, which was considered prohibitive due to the relatively small sample sizes, particularly from Study 203 (N = 73 in CR1, propensity score primary analysis set).

The propensity score-based weight formula chosen was that for average treatment effects (ATE), which estimates the average treatment effect from moving the entire population from untreated to treated (Imbens, 2004). This approach mirrors the objective of a randomized study.

In order to adjust for instability caused by very large weights, stabilized IPTW (sIPTW; Cole and Hernan, 2004) and trimmed IPTW and trimmed sIPTW were also considered (Lee et al, 2011). For each analysis set, the method that provided the best overall balance with respect to the baseline covariates and the fewest impactful statistical outlying values was chosen as the primary weighting method. This selection was completed prior to the statistical analyst having access to the endpoint results.

RFS and OS were analyzed using a Cox proportional hazards model weighted by the methods described above and including each subject's treatment status as an independent factor and a time varying covariate for HSCT also in the model. Robust variance estimation was used for the calculation of 95% CIs around the resulting hazard ratio for the treatment covariate. An additional sensitivity analysis, excluding the HSCT

time-varying covariate, was also performed to ensure robustness. RFS and OS estimates at specific time-points could only be calculated from the models that did not adjust for HSCT.

4.2.2.2 Results

4.2.2.2.1 Covariate Balance

Covariate balance was assessed before and after weighting, calculating standardized differences between treatment groups, and using univariate models for each covariate with treatment as the predictor. Table 7 shows the covariate balance before and after adjustment according to sIPTW for the primary analysis set. For this analysis, stabilized IPTW provided the best overall balance of baseline covariates, including age at primary diagnosis and the time from primary diagnosis to baseline MRD. All but 1 stabilized IPTW adjusted covariate achieved standardized differences less than 0.2 (the standard acceptance cutoff), with only 1 borderline at 0.2. The overlap in the propensity scores between the 2 treatment groups was considered adequate with the criterion that was prespecified in the statistical analysis plan.

Table 7. Covariate Balance Before and After Propensity Score Adjustments With Stabilized IPTW: Propensity Score Analysis

	Unweighted				Stabilized IPTW			
Characteristic Mean (SD)/n (%)	Control (N=182)	Blin (N=73)	Standard Difference	p-value[a]	Control (N=174.3)	Blin (N=78.5)	Standard Difference	p-value
Age at primary diagnosis (years)	36.3 (13.6)	44.8 (16.6)	**-0.56**	<0.001	37.8 (13.8)	36.5 (16.4)	0.09	0.573
Gender (Female)	80 (44.0)	32 (43.8)	0.00	0.986	76.6 (43.9)	27.0 (34.4)	**0.20**	0.226
Country (Not Germany)	112 (61.5)	35 (47.9)	**0.28**	0.048	143.6 (58.8)	151.6 (55.3)	0.07	0.674
MRD at Baseline (recoded)	-1.5 (0.6)	-1.7 (0.7)	0.16	0.249	-1.6 (0.60)	-1.5 (0.8)	-0.08	0.688
Time from primary diagnosis to MRD baseline date (months)	6.6 (6.1)	12.8 (14.3)	**-0.56**	<.001	7.3 (7.2)	8.1 (9.7)	-0.09	0.463
WBC at diagnosis (>30 000/mm^3)	51 (28.0)	15 (20.5)	0.17	0.220	45.2 (26.0)	19.1 (24.3)	0.04	0.822
WBC at diagnosis (continuous, log10)	4.15 (0.62)	3.98 (0.60)	**0.26**	0.072	4.13 (0.60)	4.07 (0.60)	0.10	0.542
t(4;11)MLL-AF4 mutation (Yes)	15 (8.2)	5 (6.8)	0.05	0.709	14.1 (8.1)	5.6 (7.2)	0.03	0.820
Prior chemotherapy (GMALL)	76 (41.8)	42 (57.5)	**-0.32**	0.023	78.0 (44.7)	39.2 (50.0)	-0.10	0.533

Blin = blinatumomab; GMALL = German Multicenter study Group for Adult Acute Lymphoblastic Leukemia; IPTW = inverse probability of treatment weight; MRD = minimal residual disease; SD = standard deviation; WBC = white blood cell count

Note: Before and after adjustment with stabilized IPTW from propensity score model fitted values. An absolute standard difference of < 0.2 is considered well balanced.

[a] p-value is not related to standard difference, but based on a univariate regression model with covariate as outcome and treatment as predictor.

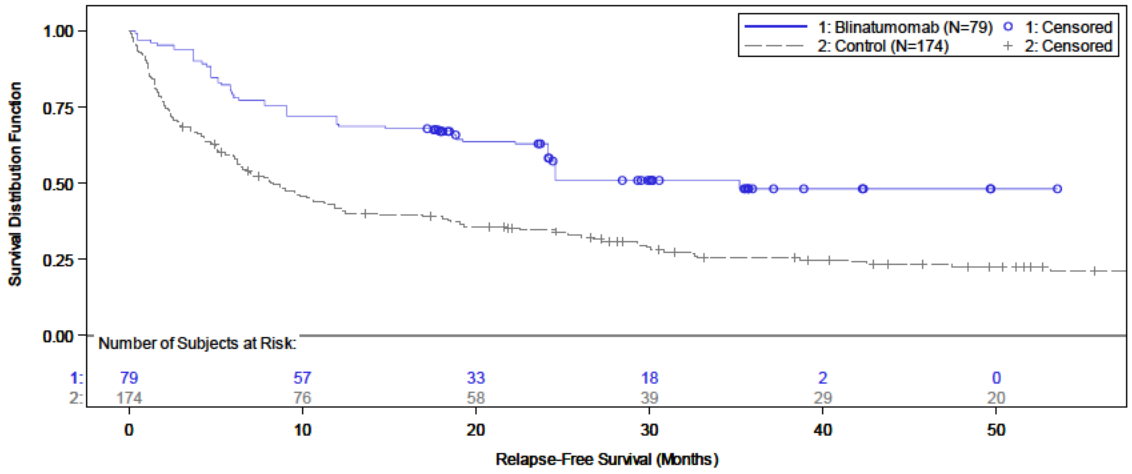
Source: Table 11-2 of Propensity Score Analysis Report

4.2.2.2.2 Relapse-free Survival

For RFS, a statistically significant improvement was associated with blinatumomab (hazard ratio = 0.50, 95% CI: 0.32, 0.78), and this result was consistent across weighting methods and analysis sets (Appendix 17) as well as the exclusion of the HSCT time-varying covariate from the outcome model (Appendix 18). The 18-month RFS estimate, unadjusted for HCST, was 39% (95% CI: 33, 48) for control and 67% (95% CI: 58, 78) for blinatumomab, indicating a 1.7-fold improvement in RFS for blinatumomab at 18 months. The KM-based median RFS, unadjusted for HSCT, was estimated at 8.3 months (95% CI: 6.2, 11.8) for control and 35.2 months (95% CI: 24.2,

NE) for blinatumomab. The KM curves demonstrate a clear separation in RFS over time between the two treatment groups (Figure 8).

Figure 8. Kaplan-Meier Curve of Relapse-free Survival: Propensity Score Analysis (Primary Analysis Set With Stabilized IPTW)



Note: Median overall survival and 95% CI is 35.2 (24.2, -) and 8.3 (6.2, 11.8) for Blinatumomab and Control respectively
Study snapshot data(MT103_203:18SEPT2015; 20120148:28MAY2015)
The number at risk and sample size are rounded from fractional units to the nearest whole number.

Program: /userdata/stat/amg103/meta/mrd_2017/analysis/reg_quest/figures/program/f-propen-mrd-km-round.sas
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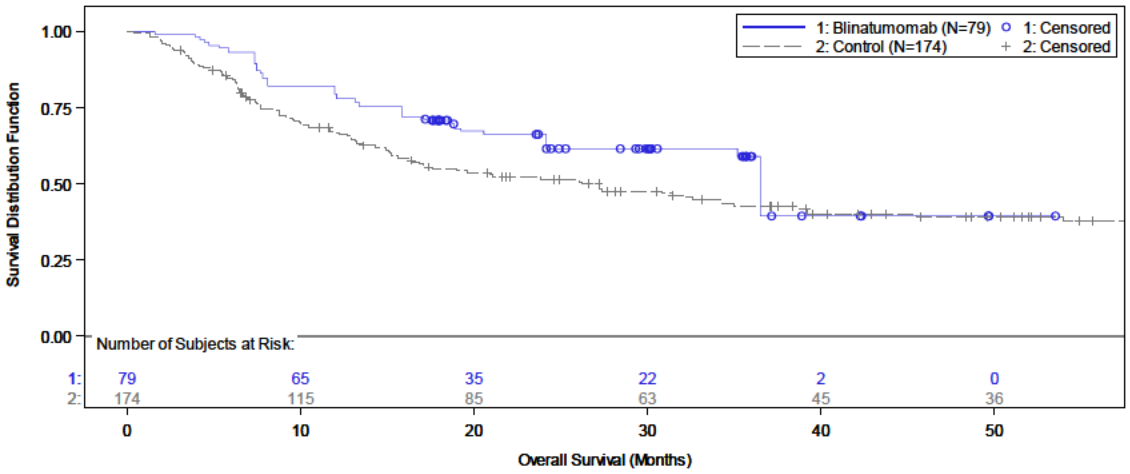
IPTW = inverse probability of treatment weight

4.2.2.2.3 Overall Survival

For OS, a directional improvement was associated with blinatumomab (hazard ratio = 0.76, 95% CI: 0.47, 1.24), and this result was consistent across weighting methods and analysis sets as well as the exclusion of the HSCT time-varying covariate from the outcome model. The 18-month OS, unadjusted for HCST, was estimated at 55% (95% CI: 48, 63) for control and 71% (95% CI: 62, 81) for blinatumomab, showing a 1.3-fold increase in OS for blinatumomab at 18 months. The KM-based median OS, unadjusted for HSCT, was estimated at 27.2 months (95% CI: 16.4, 38.6) for control and 36.5 months (95% CI: 24.2, NE) for blinatumomab (Figure 9).

Figure 9. Kaplan Meier Curve of Overall Survival: Propensity Score Analysis (Primary Analysis Set With Stabilized IPTW)



Note: Median overall survival and 95% CI is 36.5 (24.2, -) and 27.2 (16.4, 38.6) for Blinatumomab and Control respectively
Study snapshot data(MT103_203:18SEPT2015; 20120148:28MAY2015)
The number at risk and sample size are rounded from fractional units to the nearest whole number.

Program: /userdata/stat/amg103/meta/mrd_2017/analysis/reg_quest/figures/program/f-propen-mrd-km-round.sas
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IPTW = inverse probability of treatment weight

4.2.2.3 Conclusions

When comparing demographic and disease characteristics between the historical comparator Study 148 and Study 203, similarities and also differences were noted. While gender, WBC count at baseline, and baseline MRD levels were distributed fairly equally between the 2 studies, patients in the historical comparator study were younger and appeared to have a slightly shorter time period between original ALL diagnosis and detection of MRD positivity compared with those in Study 203. By calendar period, the historical data generally did not overlap with Study 203 data; however, since 2000, few new therapies have been introduced for salvage treatment of relapsed/refractory ALL subjects or for MRD-positive ALL subjects. Furthermore, the historical comparator Study 148 primarily comprised subjects in first hematologic CR, whereas Study 203 had over a third of subjects in CR2 or CR3. Lastly, the proportion of subjects undergoing allogeneic HSCT in the historical comparator Study 148 was much lower (36.8% of the DCAS) compared to Study 203 (77.6%). Factors that may suggest a better prognosis among subjects in the historical data include younger age and the fact that all subjects were in CR1. Factors that may suggest a better prognosis among subjects in Study 203 include a longer period between ALL diagnosis and MRD assessment, as well as a higher rate of HSCT. Thus, any comparison of crude results between the 2 studies should be made with caution. With this understanding, results of the historical data from

Study 148 showed that 18-month RFS, censored at HSCT, was 37% (95% CI: 28, 46) and 18-month OS, uncensored at HSCT, was 56% (95% CI: 49, 64), which were lower than the results observed in the pivotal blinatumomab Study 203, which showed 18-month RFS, censored at HSCT or post-blinatumomab chemotherapy, of 54% (95% CI: 33, 70) and 18-month OS, uncensored at HSCT or post-blinatumomab chemotherapy, of 65% (95% CI: 55, 73).

In order to allow for direct comparisons between these historical data and clinical study 203, evaluations were performed with propensity score methods. The use of propensity score adjustments was successful in creating a more balanced population of blinatumomab-treated and control subjects with respect to important measured baseline covariates. This balance allowed for more valid statistical comparisons between the 2 treatment groups. Results of the propensity score analysis showed that blinatumomab was associated with a statistically significant improvement in RFS (hazard ratio = 0.50, 95% CI: 0.32, 0.78), as well as a directional improvement in OS (hazard ratio = 0.76, 95% CI: 0.47, 1.24). Results of the endpoint analyses were largely consistent across analysis sets and sensitivity analyses.

Although propensity score analysis methods offer a sophisticated and efficient approach to comparing single-arm clinical trial data and historical patient data, there are limitations. In the context of this analysis, the following limitations should be noted. In the propensity score analysis, only measured covariates that are common to both studies can be accounted for in the analysis; the propensity score model does not necessarily balance unmeasured covariates. It also assumes that management and treatment of ALL has not changed since the time period of study. Additionally, the propensity score analyses are, to some extent, post-hoc and exploratory, since they were not prespecified prior to collection of data from Study 203, though the statistical analysis plan was finalized prior to the analysis, and the specified propensity score model selection method was finalized prior to applying propensity score weighting to the outcome models. Due to the limited sample size, the power to detect clinically meaningful differences between the treatment groups is reduced. Finally, the completeness and quality of the historical data is unlikely to be as good as that of the clinical trial data, and especially that of a randomized, controlled trial. Despite these limitations, the propensity score analyses support a clear and robust advantage in RFS, and a trend toward improvement in OS, associated with blinatumomab and support the definitive effects shown on MRD response in Study 203.

5. SAFETY DATA

5.1 Safety Assessment

Safety was evaluated through the collection of all treatment-emergent adverse events (hereafter referred to as adverse events), including severity, relationship to treatment (per the investigator), onset and duration, outcome, changes in laboratory values, vital signs, and physical examination findings.

The safety profile of blinatumomab for adult subjects with MRD-positive B-cell precursor ALL is based primarily on pooled data from Studies 203 and 202 (N = 137). An integrated analysis of safety data, pooled by indication and overall, was also performed and included 843 subjects treated with blinatumomab in 8 ongoing and completed studies in adult subjects with Philadelphia chromosome-negative relapsed/refractory ALL (N = 528), pediatric subjects with relapsed/refractory ALL (N = 133), adult subjects with Philadelphia chromosome-positive relapsed/refractory ALL (N = 45), and adult subjects with MRD-positive ALL (N = 137). This summary presents safety evaluations primarily focused on safety data from the adult MRD-positive ALL population, with summary data from the adult Philadelphia-negative relapsed/refractory ALL population and total relapsed/refractory ALL population included as reference populations. The pooled analyses were performed on the safety analysis set, which included all subjects who received $\geq$ 1 dose of blinatumomab.

5.2 Safety Overview

5.2.1 Exposure

In the adult MRD-positive ALL population, median exposure was 55.50 days (range: 0.7 to 195.7 days), which was greater than median exposure in the total relapsed/refractory ALL population (39.90 days) and the adult relapsed/refractory Philadelphia-negative ALL population (47.95 days).

5.2.2 Baseline and Other Disease Characteristics

The adult MRD-positive ALL population comprised 56.2% male subjects and most subjects (89.8%) were white, which was generally consistent across all populations examined. All subjects in the adult MRD-positive ALL population were from Europe; the majority of subjects in the other populations examined were also from Europe. The median age for the adult MRD-positive ALL population was 45.0 years

(range: 18 to 77 years), which was higher than the adult relapsed/refractory Philadelphia-negative (37.5 years) and total relapsed/refractory ALL populations (32.0 years). Subjects ≥ 65 years of age comprised 15.3% of the adult MRD-positive ALL population, 13.0% of the adult relapsed/refractory Philadelphia-negative ALL population, and 11.4% of the total relapsed/refractory ALL population.

Similar to the other populations examined (except Study 216 in Philadelphia-positive relapsed/refractory ALL subjects, also known as the ALCANTARA study), the majority of subjects in the adult MRD-positive ALL population had Philadelphia-negative ALL at baseline (92.7%). All subjects in the adult MRD-positive ALL population had ECOG performance status at baseline of 0 or 1, as did the majority of subjects in the adult relapsed/refractory ALL populations.

The key difference between the adult MRD-positive ALL population and the other populations examined was the requirement for subjects in Studies 203 and 202 to be in hematologic CR at baseline. This difference was reflected in baseline laboratory values where platelet count, neutrophil count, and WBC count were generally more favorable for the adult MRD-positive ALL population than for other populations. Furthermore, none of the subjects in the adult MRD-positive ALL population had bone marrow blasts based on central and local laboratory assessments at baseline. Across all other populations and in the pooled ALL population, at least 54% of subjects had ≥ 50% bone marrow blasts based on central and local laboratory assessments at baseline. No subjects in the adult MRD-positive ALL population had undergone prior allogeneic HSCT, compared with 34.2% in the adult relapsed/refractory Philadelphia-negative ALL population and 39.0% in the total relapsed/refractory ALL population who had undergone prior allogeneic HSCT.

The majority of subjects across all populations (approximately ≥ 70%) had creatinine clearance (CrCl) ≥ 90 mL/min, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x the upper limit of normal (ULN), and total bilirubin ≤ 1.5 x ULN.

5.2.3 Overview of Adverse Events

Table 8 provides an overview of the adverse event data in the adult MRD-positive ALL and relapsed/refractory ALL populations. Summary data for the adult and pediatric relapsed/refractory ALL populations, total relapsed/refractory ALL population, and overall

ALL population are included for reference. The overall subject incidences of adverse events were consistent across the ALL populations examined (> 99%). The subjects incidences of serious adverse events, adverse events leading to study drug discontinuation, and adverse events leading to study drug interruption were generally similar across the adult MRD-positive ALL population, the adult relapsed/refractory Philadelphia-negative ALL population, and the total relapsed/refractory ALL population. The subject incidences of treatment-related adverse events and serious treatment-related adverse events were higher in the adult MRD-positive ALL population than in the adult relapsed/refractory Philadelphia-negative ALL population and the total relapsed/refractory ALL population. Fatal adverse events and adverse events of grade $\geq$ 3 and grade $\geq$ 4 occurred less frequently in adults with MRD-positive ALL than in the adult relapsed/refractory Philadelphia-negative ALL population and total relapsed/refractory ALL population. This finding is not unexpected, given that subjects in the adult MRD-positive ALL population entered the studies in hematologic CR. Subjects in the relapsed/refractory ALL population had high tumor burden, impaired bone marrow function, and compromised immunity from prior chemotherapy exposure and/or myeloablative HSCT. The higher incidence of treatment-related adverse events appeared to be driven by grade 1 and grade 2 adverse events, as the subject incidence of treatment-related grade $\geq$ 3 and grade $\geq$ 4 adverse events was comparable across the ALL populations.

Table 8. Summary of Treatment-emergent Adverse Events in Any ALL Population (Safety Analysis Set)

	Adult R/R Ph- ALL	Pediatric R/R ALL	Adult R/R Ph+ ALL	R/R ALL	Adult MRD+ ALL	Total
	Study 211 Study 206 Study 311 (Blin arm) (N = 528)	Study 205 Study 320 (N = 133)	Study 216 (N = 45)	Total (N = 706)	Study 202 Study 203 (N = 137)	All Studies (N = 843)
All TEAEs – n (%)	523 (99.1)	132 (99.2)	45 (100.0)	700 (99.2)	137 (100.0)	837 (99.3)
Grade ≥ 3	443 (83.9)	110 (82.7)	37 (82.2)	590 (83.6)	88 (64.2)	678 (80.4)
Grade ≥ 4	251 (47.5)	70 (52.6)	18 (40.0)	339 (48.0)	39 (28.5)	378 (44.8)
Serious	335 (63.4)	71 (53.4)	28 (62.2)	434 (61.5)	83 (60.6)	517 (61.3)
Fatal	91 (17.2)	15 (11.3)	5 (11.1)	111 (15.7)	2 (1.5)	113 (13.4)
Leading to study drug discontinuation	83 (15.7)	13 (9.8)	3 (6.7)	99 (14.0)	23 (16.8)	122 (14.5)
Grade ≥ 3	77 (14.6)	11 (8.3)	3 (6.7)	91 (12.9)	18 (13.1)	109 (12.9)
Grade ≥ 4	45 (8.5)	7 (5.3)	1 (2.2)	53 (7.5)	6 (4.4)	59 (7.0)
Serious	71 (13.4)	12 (9.0)	2 (4.4)	85 (12.0)	17 (12.4)	102 (12.1)
Fatal	26 (4.9)	3 (2.3)	0 (0.0)	29 (4.1)	2 (1.5)	31 (3.7)
Leading to study drug interruption	175 (33.1)	24 (18.0)	16 (35.6)	215 (30.5)	39 (28.5)	254 (30.1)
Grade ≥ 3	119 (22.5)	14 (10.5)	12 (26.7)	145 (20.5)	22 (16.1)	167 (19.8)
Grade ≥ 4	34 (6.4)	4 (3.0)	1 (2.2)	39 (5.5)	8 (5.8)	47 (5.6)
Serious	117 (22.2)	18 (13.5)	12 (26.7)	147 (20.8)	29 (21.2)	176 (20.9)
Fatal	9 (1.7)	0 (0.0)	0 (0.0)	9 (1.3)	0 (0.0)	9 (1.1)

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Footnotes are on the last page of this table.

Table 8. Summary of Treatment-emergent Adverse Events in Any ALL Population (Safety Analysis Set)

	Adult R/R Ph- ALL	Pediatric R/R ALL	Adult R/R Ph+ ALL	R/R ALL	Adult MRD+ ALL	Total
	Study 211 Study 206 Study 311 (Blin arm) (N = 528)	Study 205 Study 320 (N = 133)	Study 216 (N = 45)	Total (N = 706)	Study 202 Study 203 (N = 137)	All Studies (N = 843)
Treatment related TEAEs - n (%)	447 (84.7)	114 (85.7)	41 (91.1)	602 (85.3)	133 (97.1)	735 (87.2)
Grade ≥ 3	290 (54.9)	73 (54.9)	20 (44.4)	383 (54.2)	73 (53.3)	456 (54.1)
Grade ≥ 4	122 (23.1)	35 (26.3)	7 (15.6)	164 (23.2)	32 (23.4)	196 (23.3)
Serious	172 (32.6)	32 (24.1)	12 (26.7)	216 (30.6)	69 (50.4)	285 (33.8)
Fatal	13 (2.5)	1 (0.8)	1 (2.2)	15 (2.1)	1 (0.7)	16 (1.9)
Leading to study drug discontinuation	45 (8.5)	9 (6.8)	2 (4.4)	56 (7.9)	16 (11.7)	72 (8.5)
Grade ≥ 3	39 (7.4)	7 (5.3)	2 (4.4)	48 (6.8)	13 (9.5)	61 (7.2)
Grade ≥ 4	18 (3.4)	5 (3.8)	1 (2.2)	24 (3.4)	4 (2.9)	28 (3.3)
Serious	37 (7.0)	9 (6.8)	1 (2.2)	47 (6.7)	13 (9.5)	60 (7.1)
Fatal	6 (1.1)	1 (0.8)	0 (0.0)	7 (1.0)	1 (0.7)	8 (0.9)
Leading to study drug interruption	121 (22.9)	16 (12.0)	12 (26.7)	149 (21.1)	35 (25.5)	184 (21.8)
Grade ≥ 3	82 (15.5)	9 (6.8)	8 (17.8)	99 (14.0)	20 (14.6)	119 (14.1)
Grade ≥ 4	19 (3.6)	1 (0.8)	1 (2.2)	21 (3.0)	7 (5.1)	28 (3.3)
Serious	75 (14.2)	11 (8.3)	7 (15.6)	93 (13.2)	26 (19.0)	119 (14.1)
Fatal	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.4)

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ALL = acute lymphoblastic leukemia; Blin = blinatumomab; MRD = minimum residual disease; Ph = Philadelphia chromosome; R/R = relapsed/refractory; TEAE =treatment-emergent adverse event
Study 311 is also known as TOWER; Study 216 is also known as ALCANTARA; Study 320 is also known as RIALTO.
Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.
Severity graded using Common Terminology Criteria for Adverse Events version 4.03
Source: Table 14 of Module 2.7.4

5.2.4 Common Adverse Events

In the pooled ALL populations, the subject incidence of adverse events was > 99% across all populations examined. Adverse events (preferred terms) reported for ≥ 20% of subjects in any ALL population are summarized in Table 9. In the adult MRD-positive ALL population, the most frequently reported adverse event was pyrexia (90.5%), which occurred at incidences of 61.4% in the adult relapsed/refractory Philadelphia-negative ALL population and 64.6% in the total relapsed/refractory ALL population. Most events of pyrexia were grade 1 or 2 and were managed with anti-pyretic medication without interruption of blinatumomab treatment. Other adverse events (preferred terms) with a subject incidence of ≥ 20% in the adult MRD-positive ALL population were generally comparable to the subject incidences across the pooled ALL populations (ie, difference in incidence of < 10%) except for tremor, chills, and fatigue, which are known adverse events with blinatumomab in current prescribing information.

The subject incidences of anemia and febrile neutropenia, frequently reported adverse events for the relapsed/refractory ALL populations, were lower for the adult MRD-positive ALL population (5.8% and 2.2%, respectively) compared with the adult relapsed/refractory Philadelphia-negative ALL population (22.0% and 24.4%, respectively) and the total relapsed/refractory ALL population (24.9% and 23.7%, respectively). Of note, the subject incidence of cytokine release syndrome (reported in ≤ 20% of subjects in any ALL population) was lower in the adult MRD-positive ALL population (2.9%) than in the adult relapsed/refractory Philadelphia-negative ALL population (12.9%) and the total relapsed/refractory ALL population (13.3%).

Table 9. Treatment-Emergent Adverse Events by Preferred Term Reported for ≥ 20% of Subjects in Any ALL Population (Safety Analysis Set)

Preferred Term	Adult R/R Ph- ALL Study 211 Study 206 Study 311 (Blin arm) (N = 528) n (%)	Pediatric R/R ALL Study 205 Study 320 (N = 133) n (%)	Adult R/R Ph+ ALL Study 216 (N = 45) n (%)	R/R ALL Total (N = 706) n (%)	Adult MRD+ ALL Study 202 Study 203 (N = 137) n (%)	Total All Studies (N = 843) n (%)
Number of subjects reporting TEAEs	523 (99.1)	132 (99.2)	45 (100.0)	700 (99.2)	137 (100.0)	837 (99.3)
Pyrexia	324 (61.4)	106 (79.7)	26 (57.8)	456 (64.6)	124 (90.5)	580 (68.8)
Headache	172 (32.6)	37 (27.8)	14 (31.1)	223 (31.6)	54 (39.4)	277 (32.9)
Nausea	114 (21.6)	33 (24.8)	7 (15.6)	154 (21.8)	32 (23.4)	186 (22.1)
Anaemia	116 (22.0)	47 (35.3)	13 (28.9)	176 (24.9)	8 (5.8)	184 (21.8)
Febrile neutropenia	129 (24.4)	20 (15.0)	18 (40.0)	167 (23.7)	3 (2.2)	170 (20.2)
Hypokalaemia	104 (19.7)	28 (21.1)	8 (17.8)	140 (19.8)	28 (20.4)	168 (19.9)
Diarrhoea	111 (21.0)	16 (12.0)	9 (20.0)	136 (19.3)	28 (20.4)	164 (19.5)
Fatigue	85 (16.1)	12 (9.0)	6 (13.3)	103 (14.6)	36 (26.3)	139 (16.5)
Vomiting	68 (12.9)	32 (24.1)	6 (13.3)	106 (15.0)	29 (21.2)	135 (16.0)
Oedema peripheral	107 (20.3)	7 (5.3)	8 (17.8)	122 (17.3)	11 (8.0)	133 (15.8)
Tremor	75 (14.2)	9 (6.8)	4 (8.9)	88 (12.5)	40 (29.2)	128 (15.2)
Thrombocytopenia	81 (15.3)	24 (18.0)	10 (22.2)	115 (16.3)	12 (8.8)	127 (15.1)
Chills	60 (11.4)	7 (5.3)	4 (8.9)	71 (10.1)	39 (28.5)	110 (13.0)
Bone pain	55 (10.4)	14 (10.5)	9 (20.0)	78 (11.0)	4 (2.9)	82 (9.7)
Hypertension	40 (7.6)	27 (20.3)	4 (8.9)	71 (10.1)	9 (6.6)	80 (9.5)

ALL = acute lymphoblastic leukemia; Blin = blinatumomab; MRD = minimum residual disease; Ph = Philadelphia chromosome; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event
Study 311 is also known as TOWER; Study 216 is also known as ALCANTARA; Study 320 is also known as RIALTO.
Safety analysis set: All subjects who received at least one infusion of blinatumomab.
Adverse events coded using MedDRA version 18.1
Source: Table iss-06.2.1

5.2.5 Serious Adverse Events

In the adult MRD-positive ALL population, serious adverse events were reported for 60.6% of subjects, which was consistent with the adult relapsed/refractory Philadelphia-negative ALL population (63.4%) and the total relapsed/refractory ALL population (61.5%). For the adult MRD-positive ALL population, the most frequently reported serious adverse event was pyrexia, reported for 12.4% of subjects compared with 6.4% for the adult relapsed/refractory Philadelphia-negative ALL population and 7.2% for the total relapsed/refractory ALL population. Most of the serious pyrexia events in the adult MRD-positive ALL population were managed with anti-pyretic medication without interruption of blinatumomab treatment. None of the serious pyrexia events resulted in treatment discontinuation.

Serious tremor, reported for ≥ 5% of the adult MRD-positive ALL population (8 subjects; 5.8%), was reported for 1.7% of the adult relapsed/refractory Philadelphia-negative ALL and total relapsed/refractory ALL populations. Of the 8 subjects with serious tremor events in the adult MRD-positive ALL population, 2 subjects discontinued blinatumomab treatment, 1 subject interrupted blinatumomab treatment, and 5 subjects continued blinatumomab treatment throughout the events with supportive therapy. The serious tremor events resolved for all subjects.

Serious febrile neutropenia was reported less frequently in the adult MRD-positive ALL population than in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations (1.5% vs 8.5% and 8.2%, respectively). Appendix 19 provides a summary of serious adverse events reported in ≥ 5% of subjects in any population.

5.2.6 Adverse Events of Grade 3 or Higher

In the adult MRD-positive ALL population, the subject incidence of grade ≥ 3 adverse events was lower than that reported for the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations (64.2% vs 83.9% and 83.6%, respectively). The most frequently reported (≥ 10%) grade ≥ 3 adverse event in the adult MRD-positive ALL population was neutropenia (13.1%), which was reported at similar rates in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations (16.3% and 14.7%, respectively). Febrile neutropenia, anemia, and thrombocytopenia, which were each reported for ≥ 10% of the

adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations, were reported for < 5% of subjects in the adult MRD-positive ALL population. Appendix 20 provides a summary of grade ≥ 3 adverse events reported in ≥ 5% of subjects in any population.

5.2.7 Fatal Adverse Events

Consistent with the nature and severity of the background diseases, the subject incidence of fatal adverse events that occurred within 30 days of the last dose of blinatumomab treatment in the adult MRD-positive ALL population (2 subjects; 1.5%) was lower than in all other study populations, including the adult relapsed/refractory Philadelphia-negative ALL population (17.2%), the total relapsed/refractory ALL population (15.7%), and the pooled ALL population (13.4%). The 2 fatal adverse events in the adult MRD-positive ALL population occurred in Study 203 and were fungal pneumonia following grade 3 H1N1 influenza that was considered by the investigator to be related to blinatumomab, and subdural hemorrhage at the site of a prior hemorrhage that was attributed to progressing ALL. In the adult Philadelphia-negative and total relapsed/refractory ALL populations, the most frequently reported fatal adverse event was sepsis (2.7% and 2.3%, respectively). Other fatal adverse events that occurred in ≥ 1% of subjects in either the adult Philadelphia-negative or total relapsed/refractory ALL populations were septic shock (1.5% and 1.3%, respectively), multi-organ failure (0.8% and 1.0%, respectively), and pneumonia (1.1% and 0.8%, respectively). Appendix 21 presents a summary of fatal treatment-emergent adverse events reported by ≥ 1 subject in any population within 30 days of the last dose of blinatumomab treatment.

In addition, 51 deaths were reported more than 30 days after the last dose of blinatumomab treatment. Of these, 32 deaths occurred in subjects with on-study HSCT: 21 subjects died without documented relapse (primarily due to infection) and 11 subjects died after relapse (primarily from disease progression and infection). The remaining 19 deaths occurred in subjects without on-study HSCT: 18 subjects died after relapse (primarily from infection), and 1 subject died without document relapse (the cause of death was not reported and no autopsy was performed). Overall, the causes of death reported were consistent with those commonly observed in patients with hematologic malignancies and in the transplant setting.

5.2.8 Adverse Events Leading to Discontinuation

Treatment Interruptions Due to Adverse Events

In the adult MRD-positive ALL population, adverse events leading to study drug interruption were reported for 28.5% of subjects, which was consistent with the adult relapsed/refractory Philadelphia-negative ALL population (33.1%) and the total relapsed/refractory ALL population (30.5%). The most frequently reported adverse events leading to interruption of study drug (≥ 2% of subjects) in the adult MRD-positive ALL population (preferred terms) were pyrexia (6.6%); overdose, encephalopathy, tremor, and aphasia (2.9% for each); and chills, increased ALT, increased AST, and hypotension (2.2% for each). The subject incidences of these events in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations were < 1% except for pyrexia (2.7% and 3.0%, respectively), encephalopathy (1.7% and 1.4%, respectively), and tremor (1.7% and 1.4%, respectively). Adverse events leading to interruption of study drug that were reported at a lower rate in the adult MRD-positive ALL population than in either the adult relapsed/refractory Philadelphia-negative ALL population or the total relapsed/refractory ALL population (> 1% difference) were cytokine release syndrome (0.7% vs 3.0% and 2.7%, respectively), seizure (0.0% vs 1.9% and 1.8%, respectively), and neutropenia (0.0% vs 1.3% and 1.0%).

Treatment Discontinuations Due to Adverse Events

In the adult MRD-positive ALL population, adverse events leading to discontinuation of study drug were reported for 16.8% of subjects, which was consistent with the adult relapsed/refractory Philadelphia-negative ALL population (15.7%) and the total relapsed/refractory ALL population (14.0%). The most frequently reported adverse events leading to discontinuation of study drug (≥ 2%) in the adult MRD-positive ALL population were tremor (3.6%), seizure (2.9%), and encephalopathy and aphasia (2.2% for each), which were each reported for ≤ 1.3% of subjects in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations. The subject incidence of cytokine release syndrome that led to discontinuation of study drug was higher in the total relapsed/refractory ALL population (1.0%) than in the adult MRD-positive ALL population (0.0%).

5.2.9 Adverse Events of Interest

Across the development program for blinatumomab, the adverse events of interest associated with blinatumomab include neurologic events, cytokine release syndrome, infections, elevated liver enzymes, infusion reactions, tumor lysis syndrome, capillary leak syndrome, medication errors (overdose), decreased immunoglobulins, embolic and thrombotic events (including disseminated intravascular coagulation), leukoencephalopathy (including progressive multifocal leukoencephalopathy), neutropenia and febrile neutropenia, lymphopenia, pancreatitis, and immunogenicity.

Key safety risks for blinatumomab are neurologic events, cytokine release syndrome, and medication errors, which are discussed in detail below. A summary of the other adverse events of interest for blinatumomab is provided in Appendix 22. Appendix 23 provides overall summary tables of the subject incidence rates for all adverse events of interest, including subject incidence rates of serious, grade ≥ 3 or grade ≥ 4, and fatal events of interest, and time to first onset of each event of interest; search strategies for the events of interest are also noted.

No new safety risks were identified based on the analyses of events of interest for adults with MRD-positive ALL or for the pooled ALL populations. The safety risks observed in the adult MRD-positive ALL population are consistent with those reported in current prescribing information. Risk mitigation strategies are discussed in Section 5.2.10.

5.2.9.1 Neurologic Events

In the adult MRD-positive ALL population, neurologic events were reported for 71.5% of subjects (22.6% serious), compared with 66.9% (13.3% serious) in the adult relapsed/refractory Philadelphia-negative ALL population, and 63.7% (12.0% serious) in the total relapsed/refractory ALL population. Grade ≥ 3 and grade ≥ 4 neurologic events, respectively, were reported for 16.1% and 2.2% in the adult MRD-positive ALL population, which was similar to the adult relapsed/refractory Philadelphia-negative ALL population (13.8% and 1.5%) and the total relapsed/refractory ALL population (12.7% and 1.3%). No fatal neurologic events occurred in the adult MRD-positive ALL population.

The most frequently reported neurologic events (preferred terms) in the adult MRD-positive ALL population (≥ 10% of subjects), with subject incidences in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations,

respectively, included for comparison, were headache (39.4% vs 32.6% and 31.6%), tremor (29.2% vs 14.2% and 12.5%), insomnia (16.1% vs 11.6% and 9.6%), aphasia (11.7% vs 3.2% and 3.0%), and dizziness (10.2% vs 9.8% and 8.8%). Of the aphasia events in the adult MRD-positive ALL population, 1 event was grade 3 and all other events were grade 1 or 2. The majority of aphasia events occurred early in treatment (median time to onset of 6 days), and all events resolved, with a median duration of 2 days. Most of the aphasia events did not require treatment interruption or discontinuation. For the one grade 3 aphasia event, blinatumomab was discontinued and the event lasted 2 days.

The most frequently reported grade ≥ 3 neurologic events (subject incidence ≥ 3%) in the adult MRD-positive ALL population , with subject incidences in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations, respectively, included for comparison, were tremor (4.4% vs 0.9% and 0.7%), encephalopathy (3.6% vs 2.7% and 2.0%), and headache (3.6% vs 1.9% and 2.3%). Of the grade ≥ 3 encephalopathy events in the adult MRD-positive ALL population, grade 4 events were reported for 2 subjects and grade 3 events were reported for 3 subjects. The median duration of the events was 2 days, and all of the events resolved. Blinatumomab treatment was interrupted for the grade 3 events and was discontinued for the grade 4 events.

Overall, the median time to first onset of neurologic events was 2.0 days in the adult MRD-positive ALL population and 6.0 days in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations. The median time to first grade ≥ 3 neurologic event was 4.0 days in the adult MRD-positive ALL population, 17.0 days in the adult relapsed/refractory Philadelphia-negative ALL population, and 17.5 days in the total relapsed/refractory ALL population.

In the adult MRD-positive ALL population, the median duration of neurologic events (KM) was shorter (10.0 days; 95% CI: 6.0, 15.0) than in the adult relapsed/refractory Philadelphia-negative ALL population (19.0 days; 95% CI: 13.0, 29.0), and total relapsed/refractory ALL population (14.0 days; 95% CI: 11.0, 19.0). The median duration of grade ≥ 3 neurologic events (KM) was similar across populations: 4.0 days (95% CI: 2.0, 6.0) in the adult MRD-positive ALL population, 3.0 days (95% CI: 3.0, 5.0) in the adult relapsed/refractory Philadelphia-negative ALL population, and 4.0 days (95% CI: 3.0, 5.0) in the total relapsed/refractory ALL population.

In the adult MRD-positive ALL population, neurologic events resolved for 95.9% of subjects with neurologic events of any grade, and in all subjects with any grade ≥ 3 neurologic events. The neurologic events that did not resolve were headache and sleep disorder/insomnia (5 subjects each); tremor (4 subjects); paresthesia and anxiety (2 subjects each); and depression, peripheral sensorimotor neuropathy, and polyneuropathy (1 subject each). All of these events were non-serious, and all were grade 1 and 2 in severity, with the exception of one grade 3 event of depression that was considered not related to treatment per the investigator.

Study drug interruptions and discontinuation for events classified as Nervous System Disorders or Psychiatric Disorders were generally reported for < 10% of subjects regardless of ALL population, indicating that the tolerability profile with respect to neurologic events is similar across ALL populations.

Of note, in Study 203, the protocol was amended to implement a premedication corticosteroid regimen (prednisone 100 mg IV or equivalent) administered within 1 hour prior to the start of treatment on day 1 of each cycle (the original protocol included the corticosteroid premedication regimen before cycle 1 only). A total of 49 subjects were treated with blinatumomab prior to the amendment, and 67 subjects were treated after the amendment. Although the subject incidence of all neurologic events remained similar for subjects treated before (71.4%) and after (73.1%) the protocol amendment, the subject incidence of grade 3 ≥ events was reduced from 26.5% for subjects treated before the amendment to 9.0% for subjects enrolled after the amendment, most notably for grade ≥ 3 events of tremor (10.2% vs. 1.5%), encephalopathy (10.2% vs. 0.0%), and aphasia (2.0% vs. 0.0%). The subject incidence of serious neurologic adverse events was reduced from 36.7% to 16.4%, most notably for serious events of tremor (10.2% vs. 4.5%), encephalopathy (12.2% vs. 0.0%), and aphasia (6.1% vs. 4.5%), and seizure (4.1% vs. 1.5%). Proposed prescribing information for the MRD-positive ALL indication includes a recommendation for premedication with a corticosteroid regimen (prednisone 100 mg IV or equivalent) to be administered within 1 hour prior to the start of treatment on day 1 of each cycle of blinatumomab.

5.2.9.2 Cytokine Release Syndrome

The subject incidence of cytokine release syndrome was lower in the adult MRD-positive ALL population (2.9%; 1.5% grade ≥ 3) than in the adult relapsed/refractory

Philadelphia-negative ALL population (14.2%; 3.4% grade ≥ 3) and the total relapsed/refractory ALL population (14.6%; 3.8% grade ≥ 3). The median time to first onset of a cytokine release syndrome event was 2.0 days for each of the 3 populations. The lower incidence of cytokine release syndrome events in adult MRD-positive ALL subjects may be due to the lower disease burden in the MRD-positive ALL population compared with relapsed/refractory ALL population.

Cytokine release syndrome (preferred term) was the only cytokine release syndrome event reported in the adult MRD-positive ALL population (2.9% of subjects compared with 12.9% and 13.3% of subjects in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations, respectively). All of the cytokine release syndrome events (preferred term) in the adult MRD-positive ALL population (2 grade 3 events and 2 grade 1 events) occurred early in treatment (on days 1 or 2) and resolved within < 1 day to 2 days with supportive treatment. One of the grade 3 events resulted in treatment interruption, and none of the events resulted in treatment discontinuation.

5.2.9.3 Medication Errors

Blinatumomab preparation and administration is a multistep process which, because of its complexity, can lead to an increased likelihood of medication errors. Medication errors that have been observed across the blinatumomab clinical studies include increased flow rate of the infusion pump through malfunction leading to an accidental increase, manipulation of the pump by the subject, infusion rate set incorrectly or an error connecting the infusion line to the pump, or overdose caused by pharmacy preparation errors relating to the calculation of blinatumomab concentration. All medication errors were reported as serious adverse events in blinatumomab studies, per protocol.

In the adult MRD-positive ALL population, medication error events were reported for 4.4% of subjects, compared with 3.8% in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations. No subjects in the adult MRD-positive ALL population had grade ≥ 3 or grade ≥ 4 medication error events; the subject incidences of grade ≥ 3 or grade ≥ 4 medication error events were consistently low across all other populations (< 1% of subjects).

The most frequently reported medication error event in the adult MRD-positive ALL population was overdose, reported for 3.6% of subjects, which was consistent with the

2.7% incidence in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations. Accidental overdose (0.7%, 1 subject) was the only other medication error event reported in the adult MRD-positive ALL population (1.1% and 1.0% of subjects in the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations, respectively). Across all of the ALL studies, the majority of subjects with overdose events reported no adverse events associated with the overdose; the few adverse events reported (fever, tremors, headache, and encephalopathy) were consistent with those reported in prescribing information, and most of the events did not result in treatment interruption or discontinuation.

5.2.10 Pharmacovigilance and Risk Minimization

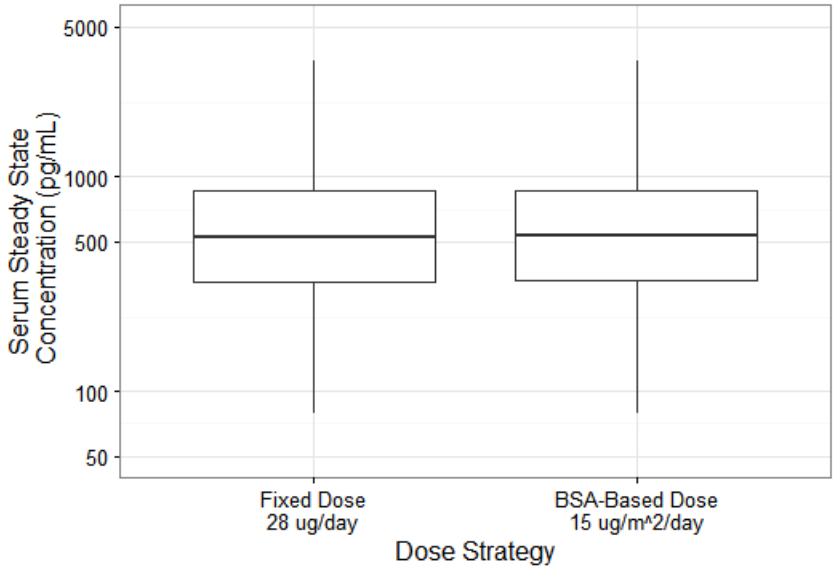
Risk mitigation strategies utilized in the adult MRD-positive ALL studies and all other blinatumomab clinical studies (ie, clinical monitoring, stopping rules, dose modification, premedication treatment with corticosteroids, and appropriate supportive therapy [where applicable]) are consistent with those included in the appropriate sections of prescribing information. Based on the safety data evaluated in clinical studies of adult subjects with MRD-positive ALL, Amgen considers that the risks associated with use of blinatumomab can continue to be managed in the postmarketing setting through routine pharmacovigilance and prescribing information. In addition, a REMS communication plan is currently in place to inform healthcare providers, pharmacists, and nurses about the important serious risks of cytokine release syndrome, neurologic toxicities, and preparation and administration errors associated with use of blinatumomab.

Although blinatumomab is to be prepared and administered in highly specialized settings with sufficient familiarity with cytotoxic drugs, it is also important for pharmacy staff to understand some of the unique aspects of blinatumomab preparation and administration to minimize medication errors. Therefore, prescribing information includes comprehensive instructions for use.

6. CLINICAL DOSE AND REGIMEN FOR THE TREATMENT OF MRD-POSITIVE ALL

The blinatumomab dose evaluated in Studies 202 and 203 in subjects with MRD-positive ALL was 15 µg/m^2/day under continuous IV infusion. Although an equivalent fixed dose of 28 µg/day was not directly tested in the clinical studies for MRD-positive ALL, similar exposure levels were expected with either body surface area (BSA)-based dosing or fixed dosing at an equivalent dose. Similar drug exposure levels were observed at the 28 µg/day fixed dose and 15 µg/m^2/day dose regardless of indication. This finding was further supported with a pharmacokinetic (PK) simulation using a population PK model. In this simulation, the BSA values were pulled from the log normal distribution of all adult subjects (10,000 subjects were simulated). The simulated mean (SD) steady state concentrations (C_{ss}) were 671 (551) pg/mL and 673 (546) pg/mL for the 28 µg/day and 15 µg/m^2/day dosing regimens, respectively. As shown in Figure 10, the simulated C_{ss} values under the 28 µg/day fixed dose and the 15 µg /m^2/day BSA-based dose are comparable. Therefore, the 28 µg/day fixed dosing regimen can be recommended for the treatment of MRD-positive ALL for patients weighing ≥ 45 kg.

Figure 10. Simulated Blinatumomab Steady State Concentrations (C_{ss}) at a 28 µg/day Fixed Dose and a 15 µg/m^2/day BSA-based Dose Under Continuous IV Infusion Using the Population PK Model



BSA = body surface area; IV = intravenous; PK = pharmacokinetic
Source: Figure 6 of Module 2.7.2

From a safety and efficacy perspective, the blinatumomab 15 µg /m^2/day dose was found to be safe and effective for the treatment of MRD-positive ALL in Studies 202 and 203. Unlike in the treatment of relapsed/refractory ALL, step-dosing of blinatumomab is not needed in the treatment of MRD-positive ALL, as baseline B-cell levels and related cytokine release syndrome events were low in the setting of MRD-positive ALL (see Section 4.1.1.1).

7. BENEFITS AND RISKS CONCLUSIONS

7.1 Therapeutic Context

As noted in Section 2.1, ALL is a rare aggressive cancer of the bone marrow, with approximately 6,590 new cases diagnosed in the US each year (ACS, 2016). Of these new diagnoses, approximately 2,400 occur among adults (Howlader et al, 2014). Nearly 50% of adult patients and 25% of pediatric patients with B-cell ALL eventually experience relapse or are refractory to initial treatment (Gökbuget et al, 2012b; Bassan and Hoelzer, 2011; Oriol et al, 2010; Gökbuget and Hoelzer, 2009; Conter et al, 2004). The goals of therapy are to induce remission and proceed to allogeneic HSCT (Hahn et al, 2006), or to attain a durable remission with consolidation chemotherapy, each approach with the ultimate goal of preventing relapse and improving OS.

Approximately 30% to 50% of adult and 10% to 20% of pediatric ALL patients who achieve hematologic CR (ie, < 5% blasts in bone marrow by conventional morphologic assessment) following multi-agent therapy (ie, induction or consolidation chemotherapy) are MRD-positive (Gökbuget et al, 2012a; Bassan et al, 2009; Holowiecki et al, 2008; Raff et al, 2007; Brüggemann et al, 2006; van Dongen et al, 1998). The presence of MRD after induction or consolidation chemotherapy is the most important risk factor for hematologic relapse in patients with ALL (Berry et al, 2017; Jabbour et al, 2017; Lussana et al, 2016; van Dongen et al, 2015; Gökbuget et al, 2012a; Gökbuget and Hoelzer, 2011; Bassan et al, 2009; Brüggemann et al, 2006; van Dongen et al, 1998). Although MRD has been evaluated primarily as a prognostic factor for relapse in ALL, it differs from other prognostic factors in that it is a direct measure of disease.

Resistant or recurrent ALL exists along a continuum, with MRD (ie, molecular level disease) on one end and overt leukemia on the other end of the spectrum. MRD is submicroscopic levels of residual leukemia, detectable only with very sensitive technologies. After induction or consolidation treatment, patients who are MRD-positive are very unlikely to achieve MRD-negativity with additional rounds of chemotherapy, largely because these patients have already received standard of care chemotherapy regimens for the treatment of ALL, and these submicroscopic leukemia cells have already survived exposure to these treatments. As such, the presence of MRD indicates that a patient has not achieved a true disease-free state. However, there are no approved therapies specifically to treat MRD-positive patients, and there are no effective chemotherapies for these patients. Allogeneic HSCT is the only available treatment

option for patients with MRD-positive ALL, but the outcome is far from optimal (Bar et al, 2014; Gökbuget et al, 2012a). Given the especially poor outcome of MRD-positive ALL with or without HSCT and lack of approved drugs specifically to treat MRD-positive patients, there is clearly an unmet need for this disease.

7.2 Benefits

Patients with MRD-positive B-cell ALL following induction or consolidation of frontline treatment, or who become MRD-positive at any time after treatment, have a poor leukemia-free survival (Raff et al, 2007). In patients with B-cell precursor ALL who have achieved hematologic CR, but remain MRD-positive, the key benefits of blinatumomab treatment are achievement of complete MRD response, increased durability of hematologic CR (as measured by RFS), and a trend toward improvement in OS.

The efficacy of blinatumomab for the treatment of patients with MRD-positive B-cell precursor ALL is based primarily on data from 116 adult subjects with MRD-positive ALL in the pivotal, single-arm, phase 2 Study 203, with supportive data from 20 adult subjects with MRD-positive ALL in the phase 2 Study 202. Of the 113 subjects with MRD-positive ALL in Study 203, blinatumomab induced a complete MRD response within 1 treatment cycle in 77.9% of the subjects (95% CI: 69.1, 85.1); 2 additional subjects had a complete MRD response during cycle 2 of treatment, for an overall complete MRD response rate of 79.6% (95% CI: 71.0, 86.6). The median duration of complete MRD response at cycle 1 was 17.3 months (95% CI: 12.6, 23.3). The 18-month KM estimate for RFS, censored at HSCT or post-blinatumomab chemotherapy, was 54% (95% CI: 33, 70). The KM estimate for OS at 18 months was 65% (95% CI: 55, 73); the median OS was 36 months (95% CI: 19.2, NE). In landmark analyses that measured RFS and OS from day 45 (the day by which all cycle 1 MRD responses had been assessed), subjects who achieved a complete MRD response versus those who did not had higher KM-estimated RFS and OS at 18 months and longer median RFS (difference of 17.9 months) and OS (difference of 28.4 months). Although RFS and OS appear prolonged by achieving a complete MRD response in the landmark analyses, a direct causal relationship cannot be established since there may be baseline factors that contributed to both the ability to achieve a complete MRD response and prolonged RFS and OS. However, baseline factors that would appear to account for both improved complete MRD response rates and prolonged RFS and OS were not found in this study. Routine subgroup analyses of baseline prognostic factors, such as age, gender, CR status (CR1 or CR2/CR3),

MRD level at baseline, WBC count at first diagnosis, need for salvage therapy for CR, and genetic aberration (t(4;11) translocation and/or MLL-AF4+) showed that CR status (CR1 versus CR2/CR3) emerged as the most important predictor of RFS and OS. Additional landmark analyses of RFS and OS by MRD response and CR status consistently showed that there is a benefit of achieving a complete MRD response irrespective of CR status.

Efficacy results from the earlier supportive phase 2 Study 202 were consistent with those reported in Study 203. In Study 202, 80% of subjects (16/20 evaluable subjects) achieved an MRD response. The median hematologic RFS had not been reached after a median follow-up time of 50.8 months (> 4 years). Ten subjects (50%) were relapse free after at least 5 years of follow-up (duration of follow-up ranged from 5.0 to 5.9 years). Overall, 5 of the 9 subjects who received HSCT after blinatumomab treatment, and 5 of 11 subjects not transplanted after blinatumomab, remained in continuous hematologic CR at least 5 years after starting blinatumomab treatment.

Recognizing the limitations of the single-arm design of Study 203, Amgen used multiple methods, including a historical comparator study (Study 148), which matched subjects as closely as possibly to the subject population in Study 203, and a propensity score analysis to adjust for key prognostic factors to evaluate magnitude of effects observed with blinatumomab in Study 203 relative to existing treatment regimens. Results from the historical comparator Study 148 showed that 18-month RFS, censored at HSCT, was 37% (95% CI: 28, 46) and 18-month OS, uncensored at HSCT, was 56% (95% CI: 49, 64), which were lower than the results observed in the pivotal blinatumomab Study 203, which showed 18-month RFS, censored at HSCT or post-blinatumomab chemotherapy, of 54% (95% CI: 33, 70) and 18-month OS, uncensored at HSCT or post-blinatumomab chemotherapy, of 65% (95% CI: 55, 73).

Results of Study 148 are further supported by the propensity score analysis in which data from Study 148 and Study 203 were directly compared and showed that blinatumomab was associated with a meaningful and statistically significant improvement in RFS (hazard ratio = 0.50, 95% CI: 0.32, 0.78), as well as a directional improvement in OS (hazard ratio = 0.76, 95% CI: 0.47, 1.24). Results of the endpoint analyses were largely consistent across analyses sets and sensitivity analyses.

Based on the strong results of published literature (Berry et al, 2017) correlating MRD negativity with long-term EFS and OS and results of the historical comparisons in matched populations using propensity score analyses, Amgen considers that the magnitude of MRD negativity and prolonged RFS and potentially OS induced by blinatumomab in Study 203 provides sufficient evidence that achieving complete MRD response is reasonably likely to predict clinical benefit (ie, prolonged RFS and OS) in subjects with MRD-positive B-cell precursor ALL.

7.3 Risks

Across the blinatumomab development program, key risks include neurologic events and cytokine release syndrome. In some cases, these events may be severe and require temporary interruption or permanent discontinuation of blinatumomab treatment. Medication errors is also an important risk because of the unique aspects of blinatumomab preparation and administration; there is a possibility that errors may occur during these steps potentially leading to an overdose of blinatumomab.

The assessment of safety was based on a broad evaluation of safety data from 843 subjects treated with blinatumomab in 8 clinical studies of ALL. Of these 843 subjects, 137 subjects from Studies 203 and 202 were included in the adult MRD-positive ALL population, and 706 subjects from 6 studies were included in the total relapsed/refractory ALL population (which included 528 adult subjects with Philadelphia chromosome-negative relapsed/refractory ALL). Subjects in the adult MRD-positive ALL population entered the studies in hematologic CR. In contrast, subjects in the relapsed/refractory ALL population had high tumor burden, impaired bone marrow function, and compromised immunity from prior chemotherapy exposure and/or myeloablative HSCT. Therefore, for select adverse event categories (eg, fatal events, adverse events of grade $\geq$ 3 and grade $\geq$ 4) and select adverse event preferred terms (eg, anemia, febrile neutropenia) the subject incidence rates in adult MRD-positive ALL population were lower than those observed in the total relapsed/refractory ALL population. Across the pooled blinatumomab ALL studies, no new safety risks were identified based on the analyses of adverse events.

It should also be noted that the adult MRD-positive ALL studies were some of the earlier clinical studies to be conducted with blinatumomab, and the safety profile of blinatumomab was still being established during these studies. Based on clinical experience with blinatumomab in phase 1 and 2 studies (including the adult

MRD-positive ALL studies and earlier relapsed/refractory ALL studies), a premedication regimen with a corticosteroid (prednisone 100 mg IV or equivalent) was implemented during pivotal Study 203 to ensure subjects' safety (the original protocol included the corticosteroid premedication regimen before cycle 1 only). Over the course of the blinatumomab development program (including the MRD-positive ALL studies), risk mitigation strategies, such as clinical monitoring, stopping rules, dose modification for certain adverse events, premedication with corticosteroids, and appropriate supportive therapy, where applicable, were shown to be effective in mitigating adverse events and have been implemented in prescribing information. In addition, a REMS communication plan is currently in place to inform healthcare providers, pharmacists, and nurses about the important safety risks of cytokine release syndrome, neurologic toxicities, and preparation and administration errors associated with use of blinatumomab.

Neurologic Events

The overall subject incidence of neurologic events was generally similar between the adult MRD-positive ALL population and the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations. Grade ≥ 3 neurologic events (including duration of the events) were similar in incidence between the adult MRD-positive ALL population and the adult relapsed/refractory Philadelphia-negative and total relapsed/refractory ALL populations, but appeared earlier in the adult MRD-positive ALL population. In the adult MRD-positive ALL population, neurologic events resolved for 95.9% of subjects with any grade neurologic event, and in all subjects with grade ≥ 3 neurologic events. Of the most common events, tremor was reported more frequently in the adult MRD-positive ALL population. Minor differences in safety results between the adult MRD-positive ALL population and the relapsed/refractory ALL populations can be expected due to the baseline disease characteristics of the study populations (ie, subjects in hematologic CR versus subjects in relapse, higher mean age of MRD-positive ALL subjects compared with relapsed/refractory ALL population). The implementation of a premedication regimen with a corticosteroid (prednisone 100 mg IV or equivalent) in Study 203 reduced the subject incidence of grade ≥ 3 and serious neurologic events. Proposed prescribing information for the MRD-positive ALL indication includes a recommendation for premedication with a corticosteroid regimen (prednisone 100 mg IV or equivalent) to be administered within 1 hour prior to the start of treatment on day 1 of each cycle of

blinatumomab. The results with respect to neurologic events do not indicate any new risks beyond those already identified for blinatumomab.

Cytokine Release Syndrome

The subject incidence of cytokine release syndrome was lower in the adult MRD-positive ALL population (2.9%; 1.5% grade ≥ 3) than in the adult relapsed/refractory Philadelphia-negative ALL population (14.2%; 3.4% grade ≥ 3) and the total relapsed/refractory ALL population (14.6%; 3.8% grade ≥ 3). The median time to first onset of a cytokine release syndrome event was 2.0 days (range: 1 to 254 days) for each of the 3 populations. Based on these results, subjects with MRD-positive ALL appear to be at reduced risk of cytokine release syndrome events compared with the relapsed/refractory ALL population, possibly due to the lower disease burden in MRD-positive ALL subjects. Thus, the safety data in subjects with MRD-positive ALL do not indicate any new risks beyond those already identified for blinatumomab.

Medication Errors

Medication error events were reported in < 5% of subjects across all populations. Per protocol, all of the medication error events were to be reported as serious. No subjects in the MRD-positive ALL population had a grade ≥ 3 or grade ≥ 4 medication error events; the subject incidences of grade ≥ 3 or grade ≥ 4 medication error events were consistently low across all other populations (< 1%).

Overall, the safety risks observed in the MRD-positive ALL population are consistent with the known safety profile established for blinatumomab in patients with relapsed/refractory ALL.

7.4 Benefit-risk Assessment

The presence of MRD is widely accepted as the most important risk factor for relapse after achieving hematologic CR regardless of treatment choice or risk classification system (Lussana et al, 2016; van Dongen et al, 2015; Gökbuget et al, 2012a; Gökbuget and Hoelzer, 2011; Bassan et al, 2009; Brüggemann et al, 2006). A recently published meta-analysis of 39 MRD studies (16 adult, 20 pediatric, and 3 mixed) solidified the association between MRD-negative status and improved clinical outcomes (EFS and OS) that has up to this point been based largely on reports of individual studies with variable sample sizes. Of particular interest, EFS and OS for patients who

were MRD-negative were shown to be remarkably consistent across a variety of subgroups (eg, MRD detection by flow cytometry vs PCR, MRD assessment after induction versus after consolidation, definition of MRD positivity, Philadelphia chromosome status, and B-cell or T-cell phenotype) (Berry et al, 2017).

Blinatumomab induced MRD negativity in a large proportion of subjects (up to 80%) with MRD-positive ALL in the pivotal Study 203 and the supportive Study 202. A thorough evaluation of pooled historical data, in conjunction with the propensity score analysis, show that MRD negativity induced by blinatumomab provides additional clinical benefits by extending RFS and potentially prolonging OS as compared to what might have been expected without such intervention. The biologic significance of this finding is further supported by the strong association between complete MRD response and RFS and survival outcomes in Study 203. In blinatumomab-treated subjects who achieved a complete MRD response versus those who did not achieve a complete MRD response, higher KM-estimated RFS and OS were observed at 18 months, including longer median RFS (difference of 17.9 months) and OS (difference of 28.4 months).

The key risks that have been identified in clinical trials are neurologic events, cytokine release syndrome, and medication errors. Most adverse events occurred within the first few weeks of the first cycle and were mitigated by appropriate measures such as temporary interruption and supportive therapy without negatively affecting therapeutic benefit. These risks are well recognized by health care providers who are familiar with managing these conditions in the treatment of patients with ALL. Since the initial approval of blinatumomab for relapsed/refractory ALL, more than 3,000 patients have been treated with blinatumomab in the marketed setting globally. Overall, the safety information received in the postmarketing setting has been consistent with the established safety profile of blinatumomab, with only one significant safety update to the prescribing information to add the risk of pancreatitis.

In summary, MRD is a direct measure of disease burden, and the impact of MRD on the course of ALL is well recognized. There is a great need for an agent that can provide benefit in patients with MRD-positive ALL. The ability of blinatumomab as a single-agent therapy to induce a high degree of MRD negativity, combined with the persuasive evidence for a correlation between MRD negativity and prolonged RFS, and a trend toward improvement in OS, support a positive benefit-risk profile for blinatumomab and

represents an important therapeutic option for the treatment of patients with MRD-positive ALL.

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9. APPENDICES

Appendix 1. Blinatumomab ALL Studies

Study Number	Study Objectives	Study Design and Type of Control; Study Status	Key Entry Criteria	Test Products; Dosage Regimen; Route of Administration; Duration of Treatment	Number of Subjects
Adult MRD-positive ALL Clinical Studies					
203	Efficacy Safety QTc Evaluation	Phase 2 • Pivotal • Non-randomized • Non-controlled • Open-label • Multicenter Core study completed; long-term efficacy f/u ongoing	Adult subjects in complete hematological remission with MRD-positive ALL	Blin cIV 15 µg/m²/day, 4 wks on / 2 wks off Up to 4 cycles blin cIV	116
202	Efficacy Safety PK/PD	Phase 2 • Non-randomized • Non-controlled • Open-label • Multicenter Study completed	Adult subjects in complete hematological remission with MRD-positive ALL	Blin cIV 15 µg/m²/day (escalation to 30 µg/m²/day after first cycle for non-responders), 4 wks on / 2 wks off Up to 10 cycles blin cIV	21
Adult MRD-positive ALL Historical Comparator Studies					
148	Efficacy	Retrospective, non-interventional pooled analysis of historical data Study completed	Adult subjects in complete hematological remission with MRD-positive ALL	N/A	287 FAS (182 DCAS)
Propensity Score Analysis	Efficacy	Propensity score analysis of RFS and OS among adult patients with MRD-positive ALL Study completed	Adult subjects in complete hematological remission with MRD-positive ALL	N/A	182 (DCAS from Study 148) 73 (blin)

Appendix 1. Blinatumomab ALL Studies

Study Number	Study Objectives	Study Design and Type of Control; Study Status	Key Entry Criteria	Test Products; Dosage Regimen; Route of Administration; Duration of Treatment	Number of Subjects
Relapsed/Refractory ALL Clinical Studies					
311	Efficacy Safety	Phase 3 • Randomized • Controlled • Open-label • Multicenter Study completed	Adults with Ph- B-cell precursor R/R ALL, >5% blasts in bone marrow, and any of the following: refractory to primary induction or salvage therapy, untreated first relapse with first remission duration < 12 months, untreated second or greater relapse, relapse any time after aHSCT	Blin 9 µg/day cIV (wk 1, cycle 1) followed by 28 µg/day for remaining period, 4 wks on/2 wks off 1 of 4 SOC regimens: 1) FLAG-based regimen 2) HiDAC-based regimen 3) HDMTX-based combination regimen 4) clofarabine/ clofarabine-based regimens Up to 9 cycles blin cIV	405 randomized (271 blin; 134 SOC)
211	Efficacy, Safety PK/PD	Phase 2 • Non-randomized • Non-controlled • Open-label • Multicenter Study completed	Adults with Ph- B-cell precursor R/R ALL, ≥10% blasts in bone marrow, and any of the following: refractory or relapsed with first remission duration ≤12 months in first salvage, relapsed or refractory after first salvage therapy, relapsed within 12 months of aHSCT	Blin 9 µg/day cIV (wk 1, cycle 1) followed by 28 µg/day for remaining period, 4 wks on/2 wks off Up to 5 cycles blin cIV	225

Appendix 1. Blinatumomab ALL Studies

Study Number	Study Objectives	Study Design and Type of Control; Study Status	Key Entry Criteria	Test Products; Dosage Regimen; Route of Administration; Duration of Treatment	Number of Subjects
Relapsed/Refractory ALL Clinical Studies					
206	Efficacy Safety QTc evaluation PK/PD	Phase 2 • Non-randomized • Non-controlled • Open-label • Multicenter • Dose ranging Study completed	Adults with B-cell precursor ALL relapsed after at least induction and consolidation, or with refractory disease; >5% blasts in bone marrow	Blin 5/15/30 µg/m^2/day cIV, 4 wks on/2 wks off Up to 5 cycles blin cIV	36
216	Efficacy Safety PK	Phase 2 • Non-randomized • Non-controlled • Open-label • Multicenter Study completed	Adult subjects with R/R Ph+ B-cell precursor ALL, relapsed or refractory to at least 1 second generation or later TKI, or intolerant to second generation TKI, and intolerant or refractory to imatinib mesylate	Blin 9 µg/day cIV (wk 1, cycle 1) followed by 28 µg/day for remaining period, 4 wks on / 2 wks off Up to 5 cycles blin cIV	45
205	Efficacy Safety PK/PD	Phase 1/2 • Non-randomized • Non-controlled • Open-label • Multicenter • Dose finding Study completed	Subjects <18 years with B-cell 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: Blin 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 blin Up to 5 cycles blin cIV (phase 2 portion)	93 (49 in phase 1 and 44 in phase 2)

Appendix 1. Blinatumomab ALL Studies

Study Number	Study Objectives	Study Design and Type of Control; Study Status	Key Entry Criteria	Test Products; Dosage Regimen; Route of Administration; Duration of Treatment	Number of Subjects
Relapsed/Refractory ALL Clinical Studies					
320	Safety Efficacy	Expanded access • Single-arm • Open-label • Multicenter Study ongoing	Subjects > 28 days to < 18 years with B-cell precursor ALL in second or later bone marrow relapse, any marrow relapse after aHSCT; or refractory to other treatments; ≥ 5% blasts in bone marrow	Blin 5/15 µg/m²/day cIV (5 µg/m²/day for wk 1 of cycle 1, 15 µg/m²/day for remaining wks/cycles), 4 wks on 2 wks off Up to 5 cycles blin cIV	Approx. 80

aHSCT = allogeneic hematopoietic stem cell transplantation; ALL = acute lymphoblastic leukemia; blin = blinatumomab; cIV = continuous intravenous infusion; DCAS = direct comparison analysis set; FAS = full analysis set; FLAG = fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor; f/u = follow up; HiDAC = high-dose cytarabine arabinoside; HDMTX = high-dose methotrexate; MRD = minimal residual disease; N/A = not applicable; OS = overall survival; PD = pharmacodynamics; Ph- = Philadelphia-negative; Ph+ = Philadelphia-positive; PK = pharmacokinetics; R/R = relapsed/refractory; RFS = relapse-free survival; SOC = standard of care; TKI = tyrosine kinase inhibitor; wks = weeks

Appendix 2. Demographic and Baseline Disease Characteristics: Historical Comparator Study 148 (FAS and DCAS)

	FAS N = 287 n (%)	DCAS N = 182 n (%)
Sex		
Male	168 (58.5)	102 (56.0)
Female	119 (41.5)	80 (44.0)
Age at primary diagnosis (years)		
Mean	34.79	36.27
SD	13.39	13.65
Median	32.00	33.00
Q1, Q3	23.00, 44.00	24.00, 47.00
Min, Max	15.0, 65.0	18.0, 65.0
Age group at diagnosis, years		
15 to 34[a]	163 (56.8)	98 (53.8)
35 to 54	89 (31.0)	56 (30.8)
55 to 64	34 (11.8)	27 (14.8)
65 and older	1 (0.3)	1 (0.5)
Baseline MRD status[b]		
Persistent	223 (77.7)	138 (75.8)
Relapsed	59 (20.6)	42 (23.1)
Unknown	5 (1.7)	2 (1.1)
MRD level at baseline		
$\geq 10^{-0}$	2 (0.7)	2 (1.1)
$\geq 1 \times 10^{-1}$ to $< 10^{-0}$	13 (4.5)	11 (6.0)
$\geq 1 \times 10^{-2}$ to $< 10^{-1}$	71 (24.7)	65 (35.7)
$\geq 1 \times 10^{-3}$ to $< 10^{-2}$	109 (38.0)	104 (57.1)
$\geq 1 \times 10^{-4}$ to $< 10^{-3}$	77 (26.8)	0 (0.0)
Missing[c]	15 (5.2)	0 (0.0)
Time from initial diagnosis to baseline MRD status group		
< 6 months	230 (80.1)	142 (78.0)
≥ 6 months	55 (19.2)	40 (22.0)
Unknown	2 (0.7)	0 (0.0)
Cytogenetic/molecular aberrations[d]		
Philadelphia chromosome t(9;22)/bcr-abl	0 (0.0)	0 (0.0)
t(4;11)MLL-AF4	20 (7.0)	15 (8.2)
None	229 (79.8)	139 (76.4)
Other	37 (12.9)	27 (14.8)
Unknown	1 (0.3)	1 (0.5)

Appendix 2. Demographic and Baseline Disease Characteristics: Historical Comparator Study 148 (FAS and DCAS)

	FAS N = 287 n (%)	DCAS N = 182 n (%)
WBC at diagnosis		
< 30 000/μL	207 (72.1)	130 (71.4)
≥ 30 000/μL	77 (26.8)	51 (28.0)
Unknown	3 (1.0)	1 (0.5)
Group at study entry – n (%)		
Continuous first CR	284 (99)	182 (100)
Molecular failure[e]	223 (78)	138 (76)
Molecular relapse[f]	59 (21)	42 (23)
Molecular failure after relapse treatment	3 (1)	0 (0)
Year of initial diagnosis – n (%)		
2000 to 2004	99 (34.5)	59 (32.4)
2005 to 2010	158 (55.1)	107 (58.8)
2010 or Later	30 (10.5)	16 (8.8)

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ALL = acute lymphoblastic leukemia; CR = complete remission; DCAS = direct comparison analysis set; FAS = full analysis set; MRD = minimal residual disease; PCR = polymerase chain reaction; WBC = white blood cell count

DCAS = Subjects enrolled in Study 148 who were ≥ 18 years old at the time of original ALL diagnosis, had MRD at a level of at least 1 x 10^{-3} regardless of detection method, time to relapse > 14 days from MRD detection and who were in first remission.

FAS = Subjects were ≥ 15 years old (15 to 17 years old without enrollment in a pediatric trial) with Philadelphia chromosome-negative B-precursor ALL (diagnosis in 2000 or later) in complete remission (minimum MRD 1 x 10^{-4}), and history, relapses status, and disease follow-up was available.

[a] Minimum age in the direct comparison analysis set was 18 years old

[b] Baseline MRD status is the earliest MRD detection date following complete remission after at least 3 blocks of chemotherapy

[c] Subjects had qualitative and PCR-based MRD assessment with a sensitivity of either 1 x 10^{-3} or 1 x 10^{-4}, no exact MRD measurement available

[d] Cytogenetic/molecular aberrations that were considered relevant by the investigators beyond Philadelphia chromosome negativity; categories are not mutually exclusive

[e] Molecular failure is defined as subject never achieved a molecular CRs

[f] Molecular relapse is defined as subject returned to MRD positive status above 10^{-4} after prior achievement of molecular CR.

Source: Table 3, Table 4, and Table 6 of 148 Study Report

Appendix 3. Relapse-free Survival by Covariate Levels (Univariate Analyses) Key Sec EP FAS: Study 203

	Events[a]/Patients	Median (Months)	18 months KM estimate	Hazard Ratio[b] (95% CI)	P-value
Age					0.36
18 - 34	16/33	24.6	0.64	Reference	
35 - 54	23/40	17.9	0.50	1.30 (0.68, 2.45)	
55 - 64	17/23	12.3	0.43	1.76 (0.89, 3.49)	
≥65	6/14	NE	0.57	0.95 (0.37, 2.42)	
Gender					0.45
Male	34/64	22.3	0.56	Reference	
Female	28/46	18.1	0.50	1.21 (0.74, 2.00)	
Patients by t(4;11) translocation and/or MLL-AF4+ ALL hematological remission					0.59
Yes	2/5	NE	0.60	Reference	

Appendix 3. Relapse-free Survival by Covariate Levels (Univariate Analyses) Key Sec EP FAS: Study 203

	Events[a]/Patients	Median (Months)	18 months KM estimate	Hazard Ratio[b] (95% CI)	P-value
No	50/83	18.3	0.50	1.61 (0.39, 6.62)	
Unknown	10/22	24.6	0.64	1.20 (0.26, 5.48)	
Relapse history					0.0044
Patients in 1st CR	36/75	24.6	0.62	Reference	
Patients in 2nd CR and 3rd CR	26/35	11.0	0.34	2.09 (1.26, 3.48)	
MRD level at baseline					0.23
≥10xE-2 and <10xE0	32/51	18.9	0.51	1.37 (0.82, 2.27)	
<10xE-2	28/57	35.2	0.58	Reference	
WBC at first diagnosis					0.70
≤30,000/mm^3	41/74	18.9	0.54	Reference	
>30,000/mm^3	10/17	14.8	0.47	1.15 (0.57, 2.29)	

Appendix 3. Relapse-free Survival by Covariate Levels (Univariate Analyses) Key Sec EP FAS: Study 203

	Events[a]/Patients	Median (Months)	18 months KM estimate	Hazard Ratio[b] (95% CI)	P-value
Need of salvage therapy for CR					0.99
Yes	20/37	18.7	0.54	Reference	
No	41/72	19.2	0.53	1.00 (0.58, 1.70)	

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KM=Kaplan-Meier. CR=Complete remission. CI=Confidence Interval. NE=not estimable. [a] Events are relapses, secondary leukemia and deaths. [b] The hazard and hazard ratio estimates are obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer relapse-free survival compared to the reference group.

Program: /userdata/stat/amg103/onc/mt103_203/analysis/secondary/tables/program/t-eff-covar.sas
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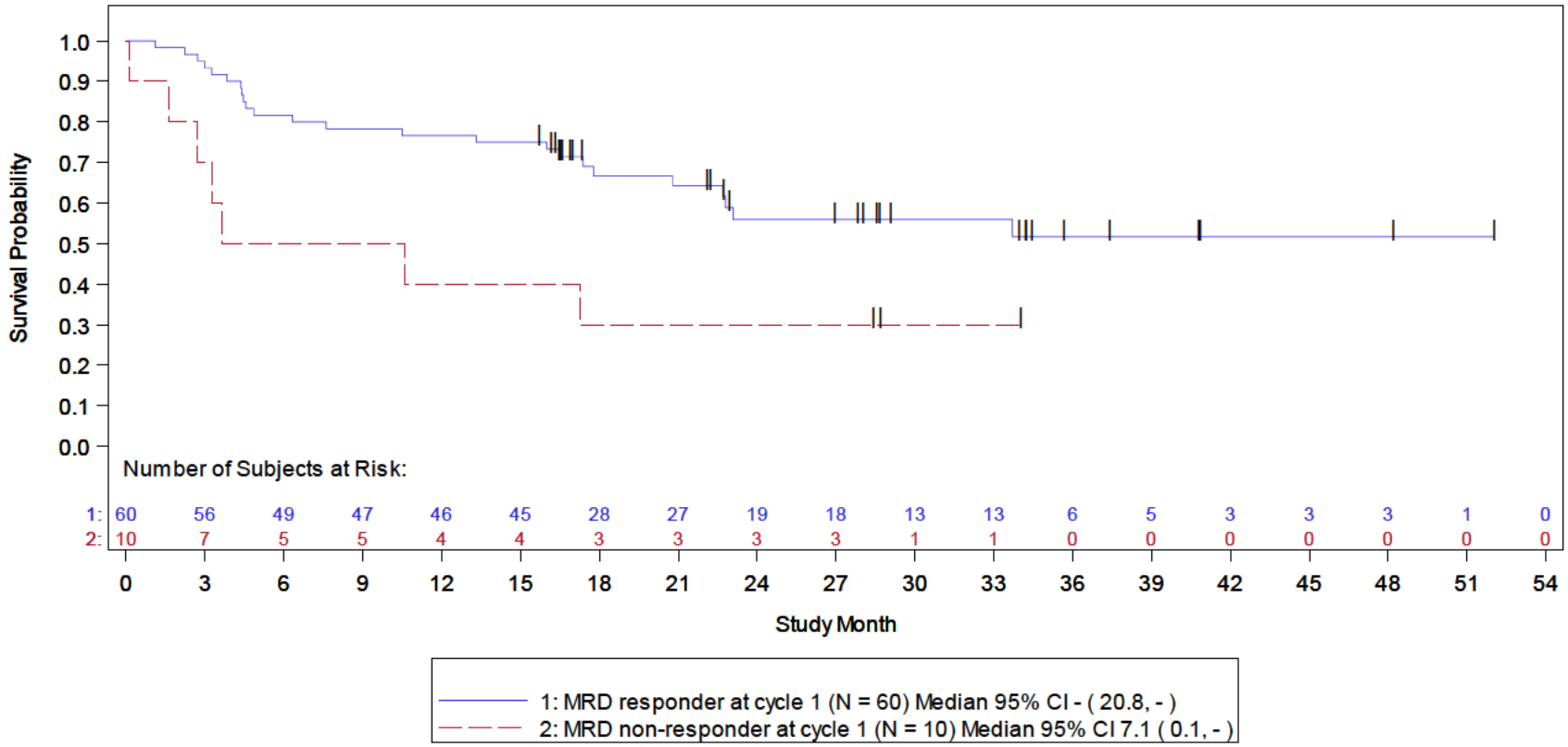
Appendix 4. Relapse-free Survival From Day 45 in MRD Complete Responders Versus Nonresponders for Subjects in CR1 (Prim EP FAS and Key Sec EP FAS): Study 203



Censor indicated by Vertical Bar

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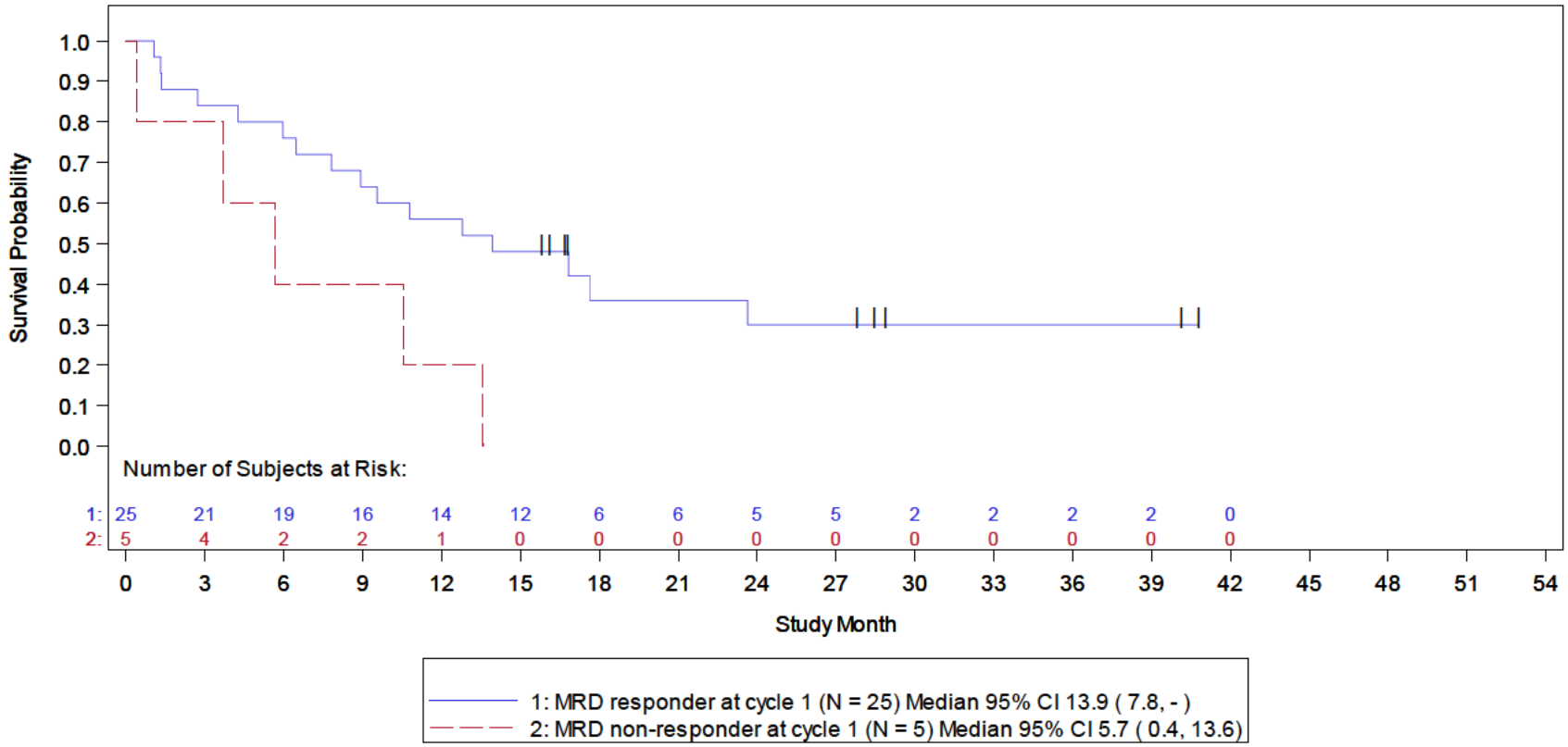
Appendix 5. Relapse-free Survival From Day 45 in MRD Complete Responders Versus Nonresponders for Subjects in CR2 or CR3 (Prim EP FAS and Key Sec EP FAS): Study 203



Censor indicated by Vertical Bar

Program: /userdata/stat/amg103/meta/mrd_2017/analysis/reg_quest/figures/program/f-odac-km-day45.sas
Output: fodac-07-odac-rfs45-second-rem.rtf (Date Generated: 08JAN18 02:25) Source Data: a203.adsl, a203.adtteeff

Appendix 6. Overall Survival by Covariate Levels (Univariate Analyses) FAS: Study 203

	Events[a]/Patients	Median (Months)	18 months KM estimate	Hazard Ratio[b] (95% CI)	P-value
Age					0.48
18 - 34	17/36	36.5	0.64	Reference	
35 - 54	19/41	40.4	0.63	0.96 (0.50, 1.85)	
55 - 64	13/24	19.2	0.58	1.21 (0.59, 2.50)	
≥65	4/15	NE	0.80	0.50 (0.17, 1.48)	
Gender					0.27
Male	28/68	NE	0.68	Reference	
Female	25/48	20.6	0.60	1.36 (0.79, 2.33)	
Philadelphia disease					0.017
Philadelphia positive	4/5	7.2	0.20	3.51 (1.26, 9.83)	
Philadelphia negative	49/111	36.5	0.67	Reference	

Appendix 6. Overall Survival by Covariate Levels (Univariate Analyses) FAS: Study 203

	Events[a]/Patients	Median (Months)	18 months KM estimate	Hazard Ratio[b] (95% CI)	P-value
Patients by t(4;11) translocation and/or MLL-AF4+ ALL hematological remission					0.99
Yes	2/5	NE	0.60	Reference	
No	41/88	40.4	0.64	1.09 (0.26, 4.50)	
Unknown	10/23	36.5	0.70	1.06 (0.23, 4.84)	
Relapse history					0.087
Patients in 1st CR	30/75	36.5	0.69	Reference	
Patients in 2nd CR and 3rd CR	23/41	19.1	0.56	1.61 (0.93, 2.77)	
MRD level at baseline					0.21
≥10xE-2 and <10xE0	28/54	23.1	0.61	1.42 (0.82, 2.44)	
<10xE-2	24/60	NE	0.68	Reference	

Appendix 6. Overall Survival by Covariate Levels (Univariate Analyses) FAS: Study 203

	Events[a]/Patients	Median (Months)	18 months KM estimate	Hazard Ratio[b] (95% CI)	P-value
WBC at first diagnosis					0.95
≤30,000/mm^3	35/78	NE	0.64	Reference	
>30,000/mm^3	9/18	36.5	0.67	1.02 (0.49, 2.13)	
Need of salvage therapy for CR					0.74
Yes	17/38	40.4	0.68	Reference	
No	36/77	36.5	0.62	1.10 (0.62, 1.96)	

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KM=Kaplan-Meier. CR=Complete remission. CI=Confidence Interval. NE=not estimable [a] Events are deaths. [b] The hazard and hazard ratio estimates are obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer overall survival compared to the reference group.

Program: /userdata/stat/amg103/onc/mt103_203/analysis/secondary/tables/program/t-eff-covar.sas
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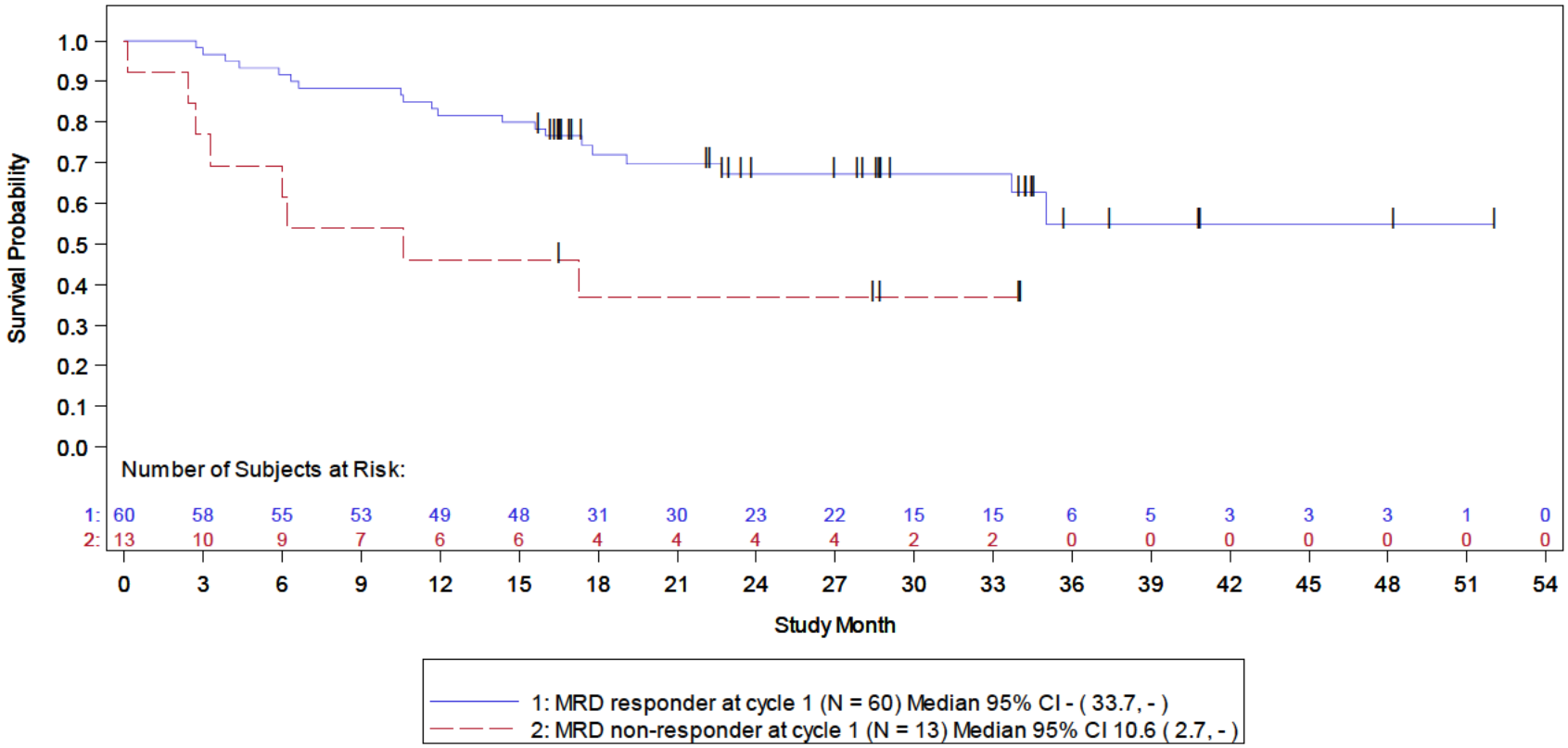
Appendix 7. Overall Survival From Day 45 in MRD Complete Responders Versus Nonresponders for Subjects in First CR (Prim EP FAS): Study 203



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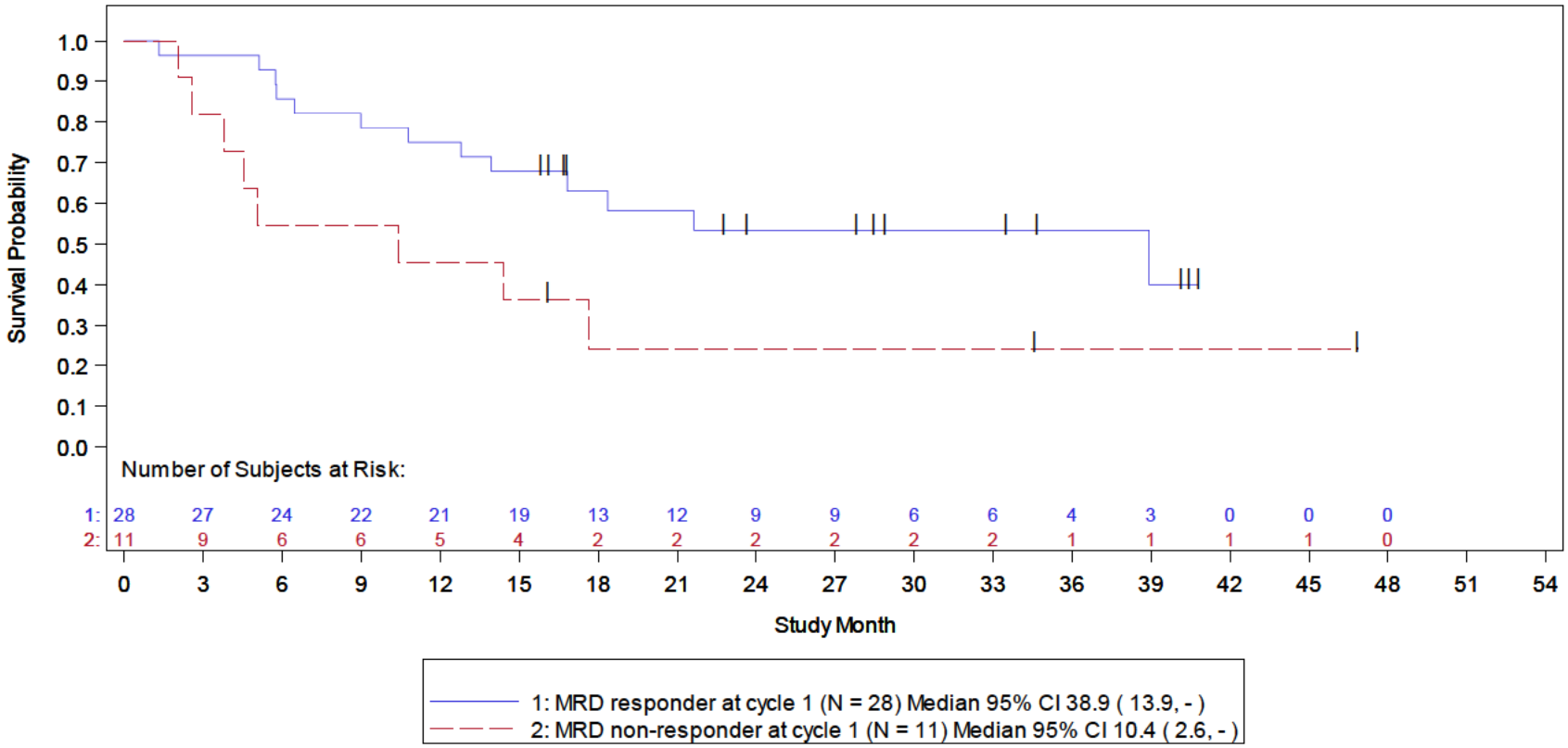
Appendix 8. Overall Survival From Day 45 in MRD Complete Responders Versus Nonresponders for Subjects in CR2 and CR3 (Prim EP FAS): Study 203



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Program: /userdata/stat/amg103/meta/mrd_2017/analysis/reg_quest/figures/program/f-odac-km-day45.sas
Output: fodac-09-odac-os45-second-rem.rtf (Date Generated: 08JAN18 02:25) Source Data: a203.adsl, a203.adtteeff

Appendix 9. Hematologic Relapse-free Survival Analysis Censored at Allogeneic HSCT: Historical Comparator Study 148 (FAS and DCAS)

	FAS Censored at HSCT[a] N = 285	DCAS Censored at HSCT[a] N = 182
Subject Status		
Events - n(%)	133 (46.7)	95 (52.2)
Death in CR	9 (3.2)	5 (2.7)
Relapse	124 (43.5)	90 (49.5)
Censored - n(%)	152 (53.3)	87 (47.8)
Time to Event (months)		
KM Median (95% CI)	12.7 (9.4, 21.2)	8.5 (5.6, 12.3)
KM Quartile 1, Quartile 3	3.9, 53.6	2.5, 30.3
Minimum, Maximum	0.1, 125.2	0.3, 125. 2
KM proportion (95% CI)		
Month 3	0.77 (0.72, 0.82)	0.69 (0.62, 0.76)
Month 6	0.66 (0.60, 0.73)	0.57 (0.49, 0.65)
Month 9	0.60 (0.53, 0.66)	049 (0.40, 0.58)
Month 12	0.52 (0.45, 0.59)	0.42 (0.33, 0.51)
Month 18	0.45 (0.38, 0.53)	0.37 (0.28, 0.46)
Month 24	0.40 (0.32, 0.47)	0.31 (0.22, 0.41)
Month 30	0.36 (0.29, 0.44)	0.26 (0.17, 0.36)
Month 36	0.31 (0.24, 0.39)	0.21 (0.12, 0.30)

ALL = acute lymphoblastic leukemia; CR = complete remission; DCAS = direct comparison analysis set; FAS = full analysis set; HSCT = hematopoietic stem cell transplanation; KM = Kaplan Meier; MRD = minimal residual disease

DCAS = Subjects enrolled in Study 148 who were $\geq$ 18 years old at the time of original ALL diagnosis, had MRD at a level of at least 1×10^{-3} regardless of detection method, time to relapse greater than 14 days from MRD detection and who were in first remission.

FAS = Subjects were at least 15 years old (15 to 17 years old not enrolled in a pediatric trial) with Philadelphia chromosome-negative B-precursor ALL (diagnosis in 2000 or later) in complete remission (minimum MRD 1×10^{-4}), and history, relapse status and disease follow-up were available.

[a] Missing baseline MRD status: N = 2 subjects in FAS

Source: Table 20 of 148 Study Report

Appendix 10. Hematological Relapse-free Survival Analysis Uncensored at Allogeneic HSCT: Historical Comparator Study 148 (FAS and DCAS)

	FAS (N = 285)	DCAS (N=182)
Subject Status		
Events - n(%)	190 (66.67)	131 (71.98)
Death in CR	26 (9.12)	14 (7.69)
Relapse	164 (57.5)	117 (64.3)
Censored - n(%)	95 (33.3)	51 (28.0)
Time to Event(months)		
KM Median (95% CI)	12.9 (10.6, 21.3)	9.9 (6.8, 12.9)
KM Q1, Q3	4.3, .	2.7, 47.9
Min, Max	0.2, 126.5	0.5, 126.5
KM proportion (95% CI)		
Month 3	0.79 (0.74, 0.83)	0.72 (0.65, 0.79)
Month 6	0.69 (0.64, 0.74)	0.61 (0.54, 0.69)
Month 9	0.61 (0.55, 0.66)	0.52 (0.44, 0.59)
Month 12	0.53 (0.47, 0.59)	0.45 (0.38, 0.53)
Month 18	0.47 (0.41, 0.53)	0.41 (0.34, 0.49)
Month 24	0.42 (0.36, 0.48)	0.37 (0.30, 0.44)
Month 30	0.38 (0.32, 0.44)	0.32 (0.25, 0.39)
Month 36	0.34 (0.29, 0.40)	0.28 (0.21, 0.34)

ALL = acute lymphoblastic leukemia; CR = complete remission; DCAS = direct comparison analysis set; FAS = full analysis set; HSCT = hematopoietic stem cell transplanation; KM = Kaplan Meier; MRD = minimal residual disease

DCAS = Subjects enrolled in Study 148 who were $\geq$ 18 years old at the time of original ALL diagnosis, had MRD at a level of at least 1 x 10^{-3} regardless of detection method, time to relapse greater than 14 days from MRD detection and who were in first remission.

FAS = Subjects were at least 15 years old (15 to 17 years old not enrolled in a pediatric trial) with Philadelphia chromosome-negative B-precursor ALL (diagnosis in 2000 or later) in complete remission (minimum MRD 1 x 10^{-4}), and history, relapse status and disease follow-up were available.

Missing baseline MRD status: N = 2 subjects in FAS; N = 0 in DCAS

Source: Table 7 of 148 Study Report

Appendix 11. Overall Survival Analysis Uncensored at Allogeneic HSCT: Historical Comparator Study 148 (FAS and DCAS)

	FAS (N = 285)	DCAS (N = 182)
Subject Status		
Events - n(%)	157 (55.09)	107 (58.79)
Censored - n(%)	128 (44.9)	75 (41.2)
Time to Event(months)		
KM Median (95% CI)	34.7 (24.3, 50.6)	27.6 (17.3, 39.6)
KM Q1, Q3	10.6, 123.9	8.1, 123.9
Min, Max	0.9, 137.8	0.9, 137.8
KM proportion (95% CI)		
Month 3	0.97 (0.95, 0.99)	0.95 (0.92, 0.98)
Month 6	0.88 (0.85, 0.92)	0.86 (0.81, 0.91)
Month 9	0.80 (0.75, 0.84)	0.74 (0.68, 0.81)
Month 12	0.73 (0.68, 0.79)	0.69 (0.62, 0.76)
Month 18	0.61 (0.56, 0.67)	0.56 (0.49, 0.64)
Month 24	0.57 (0.51, 0.63)	0.54 (0.46, 0.61)
Month 30	0.53 (0.47, 0.59)	0.49 (0.42, 0.57)
Month 36	0.48 (0.42, 0.55)	0.44 (0.36, 0.52)

ALL = acute lymphoblastic leukemia; CR = complete remission; DCAS = direct comparison analysis set; FAS = full analysis set; HSCT = hematopoietic stem cell transplanation; KM = Kaplan Meier; MRD = minimal residual disease; DCAS = Subjects enrolled in Study 148 who were $\geq$ 18 years old at the time of original ALL diagnosis, had MRD at a level of at least 1 x 10^{-3} regardless of detection method, time to relapse greater than 14 days from MRD detection and who were in first remission.

FAS = Subjects were at least 15 years old (15 to 17 years old not enrolled in a pediatric trial) with Philadelphia chromosome-negative B-precursor ALL (diagnosis in 2000 or later) in complete remission (minimum MRD 1 x 10^{-4}), and history, relapse status and disease follow-up were available.

Missing baseline MRD status: N = 2 subjects in FAS, N = 0 in DCAS

Source: Table 13 of 148 Study Report

Appendix 12. Overall Survival Analysis Censored at Allogeneic HSCT: Historical Comparator Study 148 (FAS and DCAS)

	FAS Censored at HSCT[a] N = 285	DCAS Censored at HSCT[a] N = 182
Subject Status		
Events - n(%)	102 (35.8)	73 (40.1)
Censored - n(%)	183 (64.2)	109 (59.9)
Time to Event(months)		
KM Median (95% CI)	32.5 (21.6, 43.6)	18.0 (13.6, 35.4)
KM Quartile 1, Quartile 3	9.9, 123.9	7.9, 84.4
Minimum, Maximum	0.1, 137.8	0.3, 137.8
KM proportion (95% CI)		
Month 3	0.97 (0.95, 0.99)	0.96 (0.92, 0.99)
Month 6	0.86 (0.82, 0.91)	0.84 (0.78, 0.90)
Month 9	0.78 (0.72, 0.84)	0.70 (0.62, 0.78)
Month 12	0.72 (0.66, 0.79)	0.63 (0.55, 0.72)
Month 18	0.60 (0.52, 0.67)	0.50 (0.40, 0.59)
Month 24	0.55 (0.47, 0.62)	0.48 (0.39, 0.58)
Month 30	0.51 (0.44, 0.59)	0.45 (0.35, 0.54)
Month 36	0.46 (0.38, 0.54)	0.39 (0.29, 0.40)

ALL = acute lymphoblastic leukemia; DCAS = direct comparison analysis set; FAS = full analysis set; HSCT = hematopoietic stem cell transplantation; KM = Kaplan-Meier; MRD = minimal residual disease

DCAS = Subjects enrolled in Study 148 who were $\geq$ 18 years old at the time of original ALL diagnosis, had MRD at a level of at least 1×10^{-3} regardless of detection method, time to relapse greater than 14 days from MRD detection and who were in first remission.

FAS = Subjects were at least 15 years old (patients 15 to 17 years old not enrolled in a pediatric trial) with Philadelphia chromosome-negative B-precursor ALL (diagnosis in 2000 or later) in complete remission (minimum MRD 1×10^{-4}), and history, relapse status and disease follow-up were available.

[a] Baseline MRD status missing: N = 2 subjects in FAS

Source: Table 22 of 148 Study Report

Appendix 13. Multivariate Model for Baseline Predictors of Hematologic Relapse-free Survival: Historical Comparator Study 148 (FAS and DCAS)

	FAS N = 287			DCAS N = 182		
	HR	95% CI	P-value	HR	95% CI	P-value
Age						
18 to 34 years	0.626	(0.402, 0.973)	0.0767	0.58	(0.36, 0.94)	0.0533
35 to 54 years	0.793	(0.496, 1.268)		0.81	(0.49, 1.36)	
≥ 55 years	1.00	(Reference)		1.00	(Reference)	
WBC count at diagnosis						
< 30 000/μL	0.645	(0.467, 0.892)	0.0079	0.66	(0.45, 0.96)	0.0298
≥ 30 000/μL	1.00	(Reference)		1.00	(Reference)	

ALL = acute lymphoblastic leukemia; CI = confidence interval; DCAS = direct comparison analysis set; FAS = full analysis set; HR = hazard ratio; MRD = minimal residual disease; WBC = white blood cell

DCAS = Subjects enrolled in Study 148 who were ≥ 18 years old at the time of original ALL diagnosis, had MRD at a level of at least 1×10^{-3} regardless of detection method, time to relapse greater than 14 days from MRD detection and who were in first remission.

Note: Factors were included in the multivariate model through forward selections with entry criterion p-value < 0.10.

Source: Table 9 and Table 28 of 148 Study Report

Appendix 14. Multivariate Model of Baseline Predictors of Overall Survival: Historical Comparator Study 148 (FAS and DCAS)

	FAS N = 287			DCAS N = 182		
	HR	95% CI	P-value	HR	95% CI	P-value
Age						
18 to 34 years	0.437	(0.273, 0.699)	0.0003	0.40	(0.23, 0.67)	0.0007
35 to 54 years	0.745	(0.458, 1.213)		0.72	(0.42, 1.24)	
≥ 55 years	1.00	(Reference)		1.00	(Reference)	
WBC count at diagnosis						
< 30,000/µl	0.571	(0.400, 0.814)	0.0020	0.56	(0.37, 0.85)	0.0064
≥ 30,000/µl	1.00	(Reference)		1.00	(Reference)	

ALL = acute lymphoblastic leukemia; CI = confidence interval; DCAS = direct comparison analysis set; FAS = full analysis set; HR = hazard ratio; MRD = minimal residual disease; WBC = white blood cell

DCAS = Subjects enrolled in Study 148 who were ≥ 18 years old at the time of original ALL diagnosis, had MRD at a level of at least 1 x 10^{-3} regardless of detection method, time to relapse greater than 14 days from MRD detection and who were in first remission

Note: Factors were included in the multivariate model through forward selection with entry criterion p-value < 0.10.

Source: Table 15 and Table 30 of 148 Study Report

Appendix 15. Hazard Ratio for the Effect of HSCT on RFS and OS as Assessed Through Time-dependent Cox Model: Historical Comparator Study 148 (FAS and DCAS)

		HR Transplanted/ No Transplant	95% CI	P-value
FAS	Relapse Free Survival			
(N=287)	Unadjusted	0.769	(0.551, 1.073)	0.1224
	Adjusted[a]	0.611	(0.430, 0.869)	0.0061
	Overall Survival			
	Unadjusted	0.812	(0.582, 1.134)	0.2225
	Adjusted[a]	0.819	(0.573, 1.172)	0.2753
DCAS	Relapse Free Survival			
(N=182)	Unadjusted	0.29	(0.20, 0.43)	< 0.0001
	Adjusted[a]	0.24	(0.16, 0.36)	< 0.0001
	Overall Survival			
	Unadjusted	0.42	(0.28, 0.63)	< 0.0001
	Adjusted[a]	0.41	(0.26, 0.63)	< 0.0001

ALL = acute lymphoblastic leukemia; CI = confidence interval; DCAS = direct comparison analysis set; FAS = full analysis set; HR = hazard ratio; HSCT = hematopoietic stem cell transplantation; MRD = minimal residual disease; OS = overall survival; RFS = relapse-free survival

DCAS = subjects enrolled in Study 148 were ≥ 18 years old at the time of original ALL diagnosis, had MRD levels of at least 1 x 10^{-3} regardless of detection method, had time to relapse greater than 14 days from MRD, and were in first remission.

[a] RFS and OS multivariate models were adjusted for the following *a priori* selected factors: age, white blood cell count at diagnosis. OS was adjusted for age, white blood cell count, and year of diagnosis

Source: Table 27 and Table 31 of 148 Study Report

Appendix 16. Hematopoietic Stem Cell Transplantation: Historical Comparator Study 148 (FAS and DCAS)

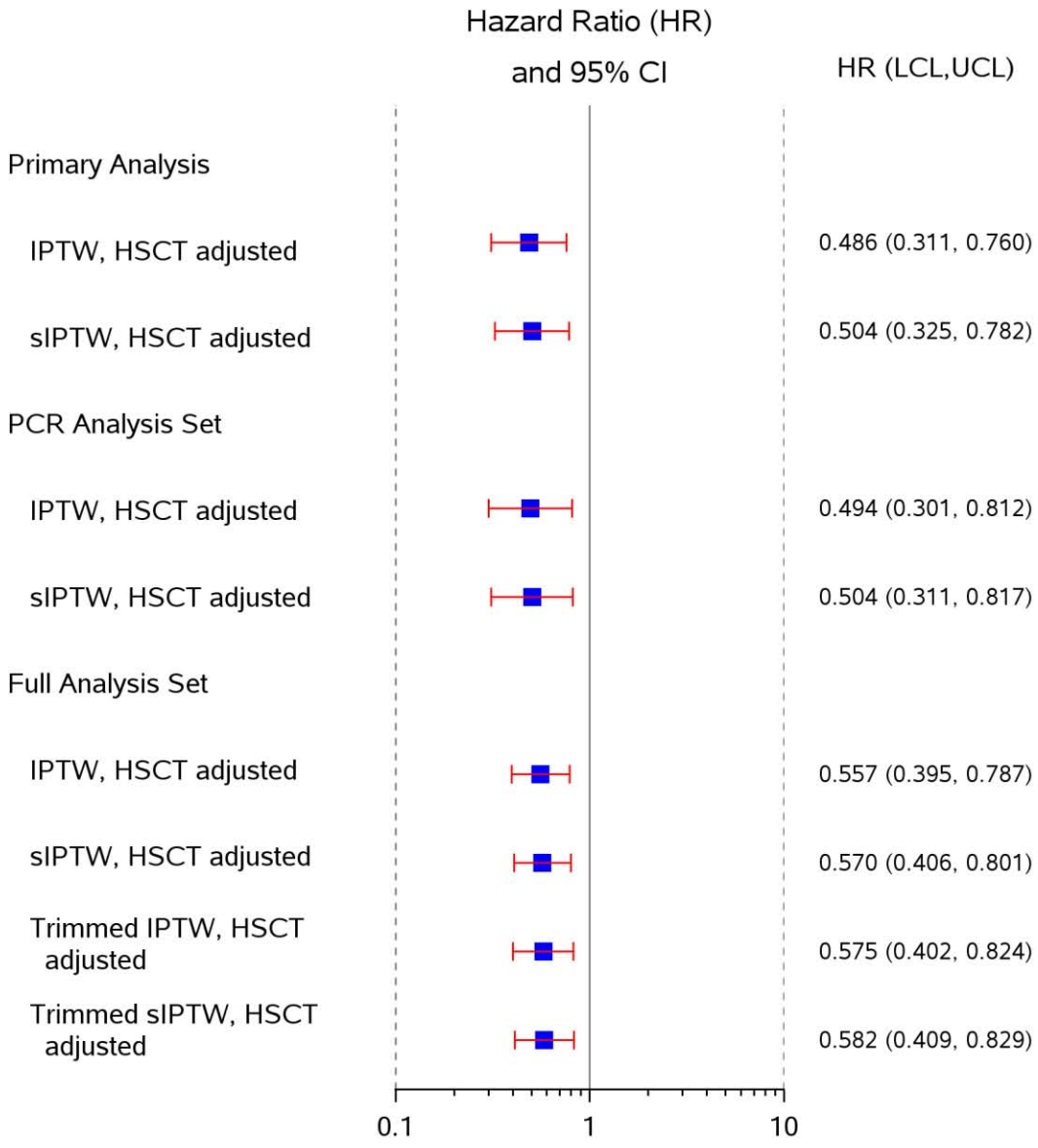
	FAS (N=110)	DCAS (N=70)
Time from baseline MRD status[a] to HSCT (months)		
Mean	5.1	5.6
SD	6.2	6.9
Median	3.4	3.8
Q1, Q3	1.7, 6.3	1.7, 6.8
Min, Max	0.1, 39.8	0.3, 39.8
100-day mortality after HSCT		
KM proportion	0.0821	0.0859
95% confidence interval	(0.0307, 0.1335)	(0.0202, 0.1517)

ALL = acute lymphoblastic leukemia; DCAS = direct comparison analysis set; FAS = full analysis set; HSCT = Hematopoietic stem cell transplantation; KM = Kaplan-Meier; MRD = minimal residual disease; SD = standard deviation

DCAS = Subjects enrolled in Study 148 who were ≥ 18 years old at the time of original ALL diagnosis, had MRD at a level of at least 1×10^{-3} regardless of detection method, time to relapse greater than 14 days from MRD detection and who were in first remission

Source: Table 19 of 148 Study Report

Appendix 17. Forest Plots of Hazard Ratios for Primary and Sensitivity Analyses of Relapse-free Survival, Adjusted for HSCT: Propensity Score Analysis

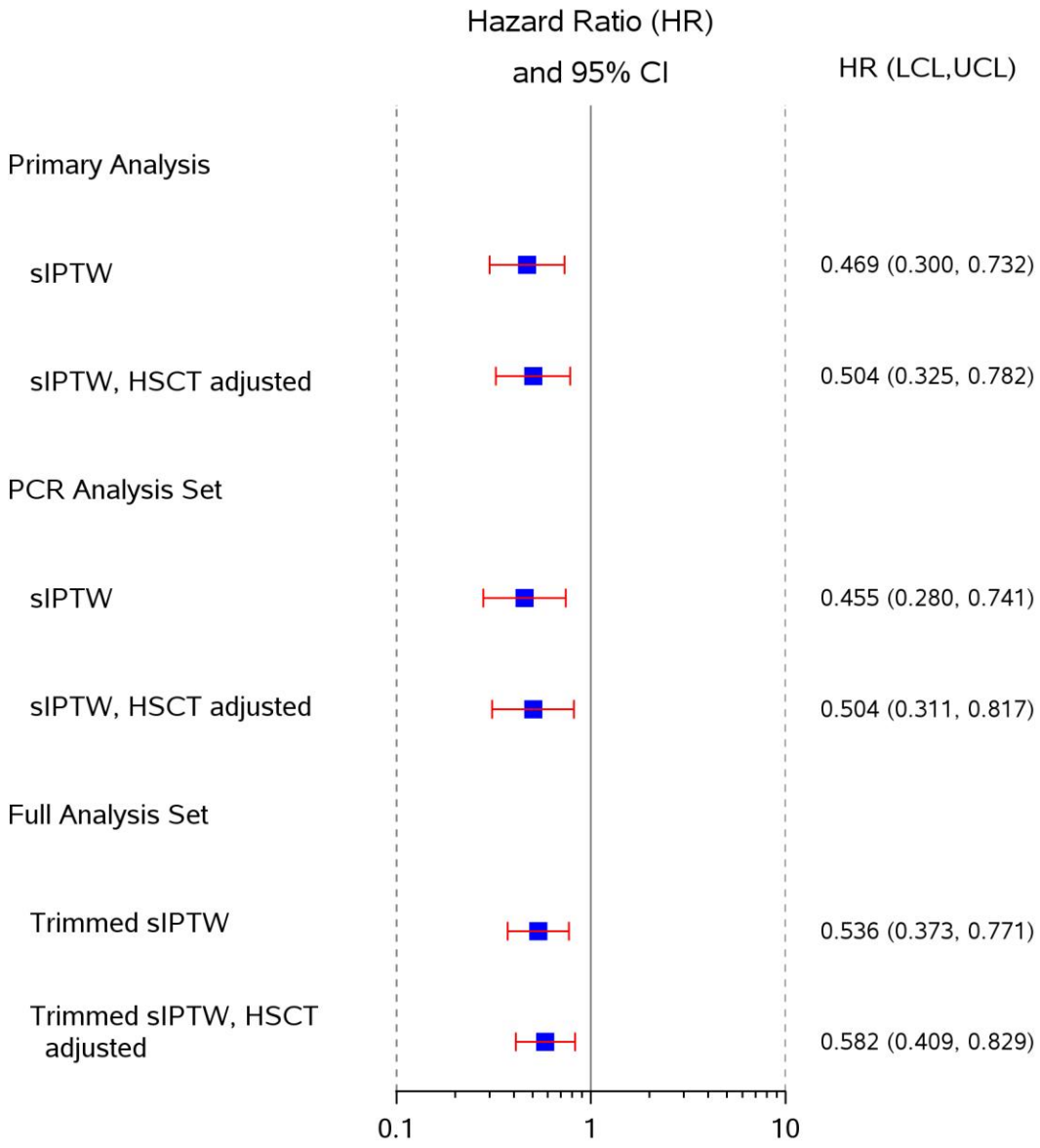


Note: IPTW = Inverse probability of treatment weight. sIPTW = stabilized IPTW
LCL = Lower Confidence Limit, UCL = Upper Confidence Limit
Study snapshot data (MT103_203:18SEPT2015; 20120148:28MAY2015)

Program:
/userdata/stat/amg103/meta/propen/analysis/mrd/figures/program/f-ps-forest-hr.sas
Output: f05-001-ps-forest-hr-rfs-hsct.rtf (Date Generated: 27JAN16 03:21) Source Data: adam.propsc

HSCT = hematopoietic stem cell transplant
Source: Figure 10-12 of Propensity Score Analysis Report

Appendix 18. Forest Plots of Hazard Ratios for Primary Analyses of Relapse-free Survival, Adjusted Versus Unadjusted for HSCT: Propensity Score Analysis



Note: sIPTW = Stabilized inverse probability of treatment weight.
LCL = Lower Confidence Limit, UCL = Upper Confidence Limit
Study snapshot data (MT103_203:18SEPT2015; 20120148:28MAY2015)

Program:
/userdata/stat/amg103/meta/propen/analysis/mrd/figures/program/f-ps-forest-hr.sas
Output: f05-004-ps-forest-hr-rfs-siptw.rtf (Date Generated: 27JAN16 03:21) Source Data: adam.propsc

HSCT = hematopoietic stem cell transplant
Source: Figure 10-13 of Propensity Score Analysis Report

Appendix 19. Serious Treatment-emergent Adverse Events by Preferred Term Reported for ≥ 5% of Subjects in Any Population (Safety Analysis Set)

	Adult R/R Ph- ALL	Pediatric R/R ALL	Adult R/R Ph+ ALL	R/R ALL	Adult MRD+ ALL	Total
Preferred Term	Study 211 Study 206 Study 311 (Blin arm) (N = 528) n (%)	Study 205 Study 320 (N = 133) n (%)	Study 216 (N = 45) n (%)	Total (N = 706) n (%)	Study 202 Study 203 (N = 137) n (%)	All Studies (N = 843) n (%)
No. of subjects reporting serious TEAEs	335 (63.4)	71 (53.4)	28 (62.2)	434 (61.5)	83 (60.6)	517 (61.3)
Pyrexia	34 (6.4)	15 (11.3)	2 (4.4)	51 (7.2)	17 (12.4)	68 (8.1)
Febrile neutropenia	45 (8.5)	9 (6.8)	4 (8.9)	58 (8.2)	2 (1.5)	60 (7.1)
Sepsis	24 (4.5)	6 (4.5)	3 (6.7)	33 (4.7)	1 (0.7)	34 (4.0)
Device related infection	15 (2.8)	3 (2.3)	3 (6.7)	21 (3.0)	4 (2.9)	25 (3.0)
Cytokine release syndrome	12 (2.3)	9 (6.8)	1 (2.2)	22 (3.1)	2 (1.5)	24 (2.8)
Tremor	9 (1.7)	0 (0.0)	3 (6.7)	12 (1.7)	8 (5.8)	20 (2.4)

ALL = acute lymphoblastic leukemia; Blin = blinatumomab; MRD = minimum residual disease; Ph = Philadelphia chromosome; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event
Study 311 is also known as TOWER; Study 216 is also known as ALCANTARA.
Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.
Adverse events coded using Medical Dictionary for Regulatory Activities version 18.1
Source: Table 22 of Module 2.7.4

Appendix 20. Grade 3 or Higher Treatment-emergent Adverse Events by Preferred Term Within System Organ Class Reported for ≥ 5% of Subjects in Any Population (Safety Analysis Set)

System Organ Class Preferred Term	Adult R/R Ph- ALL Study 211 Study 206 Study 311 (Blin arm) (N = 528) n (%)	Pediatric R/R ALL Study 205 Study 320 (N = 133) n (%)	Adult R/R Ph+ ALL Study 216 (N = 45) n (%)	R/R ALL Total (N = 706) n (%)	Adult MRD+ ALL Study 202 Study 203 (N = 137) n (%)	Total All Studies (N = 843) n (%)
Number of subjects reporting grade 3 or higher treatment-emergent adverse events	443 (83.9)	110 (82.7)	37 (82.2)	590 (83.6)	88 (64.2)	678 (80.4)
Blood and lymphatic system disorders	284 (53.8)	62 (46.6)	28 (62.2)	374 (53.0)	37 (27.0)	411 (48.8)
Febrile neutropenia	116 (22.0)	18 (13.5)	12 (26.7)	146 (20.7)	3 (2.2)	149 (17.7)
Anaemia	86 (16.3)	37 (27.8)	7 (15.6)	130 (18.4)	4 (2.9)	134 (15.9)
Neutropenia	86 (16.3)	15 (11.3)	3 (6.7)	104 (14.7)	18 (13.1)	122 (14.5)
Thrombocytopenia	65 (12.3)	24 (18.0)	10 (22.2)	99 (14.0)	6 (4.4)	105 (12.5)
Leukopenia	29 (5.5)	12 (9.0)	2 (4.4)	43 (6.1)	10 (7.3)	53 (6.3)
Lymphopenia	5 (0.9)	2 (1.5)	0 (0.0)	7 (1.0)	9 (6.6)	16 (1.9)
Leukocytosis	8 (1.5)	1 (0.8)	3 (6.7)	12 (1.7)	0 (0.0)	12 (1.4)
General disorders and administration site conditions	91 (17.2)	31 (23.3)	11 (24.4)	133 (18.8)	16 (11.7)	149 (17.7)
Pyrexia	41 (7.8)	24 (18.0)	5 (11.1)	70 (9.9)	9 (6.6)	79 (9.4)
Pain	8 (1.5)	2 (1.5)	4 (8.9)	14 (2.0)	1 (0.7)	15 (1.8)
Immune system disorders	30 (5.7)	10 (7.5)	1 (2.2)	41 (5.8)	5 (3.6)	46 (5.5)
Cytokine release syndrome	13 (2.5)	8 (6.0)	0 (0.0)	21 (3.0)	2 (1.5)	23 (2.7)
Infections and infestations	183 (34.7)	32 (24.1)	11 (24.4)	226 (32.0)	16 (11.7)	242 (28.7)
Pneumonia	33 (6.3)	3 (2.3)	1 (2.2)	37 (5.2)	3 (2.2)	40 (4.7)
Sepsis	27 (5.1)	6 (4.5)	4 (8.9)	37 (5.2)	1 (0.7)	38 (4.5)
Device related infection	21 (4.0)	4 (3.0)	3 (6.7)	28 (4.0)	4 (2.9)	32 (3.8)

Appendix 20. Grade 3 or Higher Treatment-emergent Adverse Events by Preferred Term Within System Organ Class Reported for ≥ 5% of Subjects in Any Population (Safety Analysis Set)

System Organ Class Preferred Term	Adult R/R Ph- ALL Study 211 Study 206 Study 311 (Blin arm) (N = 528) n (%)	Pediatric R/R ALL Study 205 Study 320 (N = 133) n (%)	Adult R/R Ph+ ALL Study 216 (N = 45) n (%)	R/R ALL Total (N = 706) n (%)	Adult MRD+ ALL Study 202 Study 203 (N = 137) n (%)	Total All Studies (N = 843) n (%)
Investigations	129 (24.4)	47 (35.3)	9 (20.0)	185 (26.2)	28 (20.4)	213 (25.3)
Alanine aminotransferase increased	31 (5.9)	16 (12.0)	5 (11.1)	52 (7.4)	7 (5.1)	59 (7.0)
Aspartate aminotransferase increased	20 (3.8)	13 (9.8)	5 (11.1)	38 (5.4)	4 (2.9)	42 (5.0)
White blood cell count decreased	24 (4.5)	13 (9.8)	2 (4.4)	39 (5.5)	3 (2.2)	42 (5.0)
Platelet count decreased	18 (3.4)	19 (14.3)	2 (4.4)	39 (5.5)	2 (1.5)	41 (4.9)
Neutrophil count decreased	20 (3.8)	15 (11.3)	0 (0.0)	35 (5.0)	2 (1.5)	37 (4.4)
Blood bilirubin increased	15 (2.8)	8 (6.0)	1 (2.2)	24 (3.4)	0 (0.0)	24 (2.8)
Metabolism and nutrition disorders	101 (19.1)	30 (22.6)	4 (8.9)	135 (19.1)	6 (4.4)	141 (16.7)
Hypokalaemia	27 (5.1)	21 (15.8)	2 (4.4)	50 (7.1)	3 (2.2)	53 (6.3)
Nervous system disorders	67 (12.7)	11 (8.3)	7 (15.6)	85 (12.0)	19 (13.9)	104 (12.3)
Headache	10 (1.9)	3 (2.3)	3 (6.7)	16 (2.3)	5 (3.6)	21 (2.5)

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ALL = acute lymphoblastic leukemia; Blin = blinatumomab; MRD = minimum residual disease; Ph = Philadelphia chromosome; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event
Study 311 is also known as TOWER; Study 216 is also known as ALCANTARA.
Safety analysis set: All subjects who received at least one infusion of blinatumomab.
Adverse events coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1
Severity graded using Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03
Source: Table iss-06.3.3

Appendix 21. Fatal Treatment-emergent Adverse Events by Preferred Term Reported for ≥ 1 Subject in Any Population (Safety Analysis Set)

Preferred Term	Adult R/R Ph- ALL Study 211 Study 206 Study 311 (Blin arm) (N = 528) n (%)	Pediatric R/R ALL Study 205 Study 320 (N = 133) n (%)	Adult R/R Ph+ ALL Study 216 (N = 45) n (%)	R/R ALL Total (N = 706) n (%)	Adult MRD+ ALL Study 202 Study 203 (N = 137) n (%)	Total All Studies (N = 843) n (%)
Number of subjects reporting fatal TEAEs	91 (17.2)	15 (11.3)	5 (11.1)	111 (15.7)	2 (1.5)	113 (13.4)
Sepsis	14 (2.7)	1 (0.8)	1 (2.2)	16 (2.3)	0 (0.0)	16 (1.9)
Septic shock	8 (1.5)	0 (0.0)	1 (2.2)	9 (1.3)	0 (0.0)	9 (1.1)
Multi-organ failure	4 (0.8)	2 (1.5)	1 (2.2)	7 (1.0)	0 (0.0)	7 (0.8)
Pneumonia	6 (1.1)	0 (0.0)	0 (0.0)	6 (0.8)	0 (0.0)	6 (0.7)
Respiratory failure	2 (0.4)	3 (2.3)	1 (2.2)	6 (0.8)	0 (0.0)	6 (0.7)
Acute lymphoblastic leukaemia	3 (0.6)	2 (1.5)	0 (0.0)	5 (0.7)	0 (0.0)	5 (0.6)
Disease progression	2 (0.4)	2 (1.5)	0 (0.0)	4 (0.6)	0 (0.0)	4 (0.5)
Cerebral haemorrhage	2 (0.4)	0 (0.0)	1 (2.2)	3 (0.4)	0 (0.0)	3 (0.4)
Death	1 (0.2)	1 (0.8)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Bacterial sepsis	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Bronchopulmonary aspergillosis	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Fungal sepsis	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Fusarium infection	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Lung infection	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Neutropenic sepsis	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Pneumonia fungal	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Acute respiratory failure	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)

ALL = acute lymphoblastic leukemia; Blin = blinatumomab; MRD = minimum residual disease; Ph = Philadelphia chromosome; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event
Study 311 is also known as TOWER; Study 216 is also known as ALCANTARA.
Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.
Adverse events coded using Medical Dictionary for Regulatory Activities version 18.1
Source: Table 18 of Module 2.7.4

Appendix 22. Other Adverse Events of Interest for Blinatumomab

Key safety risks for blinatumomab are neurologic events, cytokine release syndrome, and medication errors and are discussed in Section 5.2.9. A summary of the other adverse events of interest for blinatumomab is provided below. Appendix 23 provides overall summary tables of the subject incidence rates for all adverse events of interest, including subject incidence rates of serious, grade ≥ 3 or grade ≥ 4, and fatal events of interest, and time to first onset of each event of interest; search strategies for the events of interest are also noted.

Infusion Reactions

Infusion reactions and cytokine release syndrome can be indistinguishable since blinatumomab is a bispecific single-chain antibody construct derived from murine monoclonal antibodies and the pharmacological mechanism of action may involve cytotoxic T-cells. There may be overlap between infusion reactions and the events observed as part of cytokine release syndrome (eg, fever or hypotension) due to the release of pro-inflammatory cytokines, including interleukin (IL)-10, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-6. Additionally, the timing of infusion reactions may overlap with cytokine release syndrome as both generally occur within close proximity to the start of an infusion (48 hours). Therefore, to capture the most clinically significant infusion reactions associated with treatment within the first 24 to 48 hours of start of blinatumomab infusion, events with a vascular component such as hypotension and circulatory collapse, as well as hypersensitivity reactions (eg, anaphylaxis or allergic reactions) were evaluated. Infusion reaction events were identified using an Amgen-defined MedDRA search strategy with a time restriction (ie, onset of event within 48 hours and no duration restriction).

In the adult MRD-positive ALL population, infusion reaction events were reported for 90.5% of subjects (13.9% serious), which was higher than in the adult relapsed/refractory Philadelphia-negative ALL population (50.8%; 2.5% serious) and the total relapsed/ refractory ALL population (53.5%; 3.3% serious). Grade ≥ 3 and grade ≥ 4 events, respectively, were reported for 10.2% and 0.7% in the adult MRD-positive ALL population, which were consistent with other populations. No fatal infusion reaction events were reported.

In the adult MRD-positive ALL population, the most frequently reported infusion reaction event was pyrexia (85.4%), compared with 40.0% in the adult relapsed/refractory Philadelphia-negative ALL population and 44.2% in the total relapsed/refractory ALL population. The majority of pyrexia events in the adult MRD-positive ALL population were grade 1 and 2 in severity and were managed with anti-pyretic medication and without interruption of blinatumomab treatment. Another frequently reported infusion reaction event was hypotension, reported for 12.4% of subjects in the adult MRD-positive ALL population, and < 5% in the adult relapsed/refractory Philadelphia-negative ALL and total relapsed/refractory ALL populations. The majority of hypotension events in the adult MRD-positive ALL population were grade 1 and 2 in severity, and most subjects continued blinatumomab treatment through the hypotension events without interruption of blinatumomab treatment.

Infections

In the adult MRD-positive ALL population, infection events were reported for 46.7% of subjects (13.1% serious), which was lower than in the adult relapsed/refractory Philadelphia-negative ALL population (64.0%; 29.5% serious) and the total relapsed/refractory ALL population (59.6%; 27.1% serious). Grade $\geq$ 3 and grade $\geq$ 4 events, respectively, were reported in 11.7% and 2.9% of subjects in the adult MRD-positive ALL population, which were similarly lower than in the other populations. The most frequently reported infection event in the adult MRD-positive ALL population was nasopharyngitis (10.9%), which was reported for 4.7% of subjects in the adult relapsed/refractory Philadelphia-negative ALL population and 4.2% of subjects in the total relapsed/refractory ALL population.

Fatal events of infection were reported for 0.7% (1 subject) in the adult MRD-positive ALL population, 10.4% of subjects in the adult relapsed/refractory Philadelphia-negative ALL population, and 8.4% of subjects in the total relapsed/refractory ALL population. The lower rate of deaths in the adult MRD-positive ALL population is not unexpected, as this population is in hematological CR and has a lower disease burden. The fatal event in the adult MRD-positive ALL population was fungal pneumonia following grade 3 H1N1 influenza, which was considered by the investigator to be related to blinatumomab.

Tumor Lysis Syndrome

Tumor lysis syndrome describes a combination of metabolic abnormalities that occur due to the release of nuclear and cytoplasmic degradation products of malignant cells. Characteristic findings of tumor lysis syndrome include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. High tumor burden is an important risk factor for tumor lysis syndrome, and therefore these events are unlikely in subjects with MRD-positive ALL (who are in hematologic CR). In the adult MRD-positive ALL population, no subjects were reported to have events of tumor lysis syndrome.

Capillary Leak Syndrome

Capillary leak syndrome is a disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in subjects who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. Capillary leak syndrome comprises a set of signs and symptoms such as edema, hypoalbuminemia, and hypotension, which can occur at any time while on treatment in patients with hematologic malignancies and can lead to generalized edema and multiple organ failure. No safety signal for blinatumomab consistent with capillary leak syndrome was observed in preclinical studies of blinatumomab.

In the adult MRD-positive ALL population, 1 subject (0.7%) had an event of capillary leak syndrome (nonserious), which compares with 1 subject (0.2%; serious, grade 4 event) in the adult relapsed/refractory Philadelphia-negative ALL population and 7 subjects (1.0%; 3 [0.4%] serious; 3 [0.4%] grade $\geq$ 3) in the total relapsed/refractory ALL population. No fatal events of capillary leak syndrome were reported.

Neutropenia and Febrile Neutropenia

In the adult MRD-positive ALL population, neutropenia and febrile neutropenia events were reported in 16.1% of subjects (5.1% serious), which was lower than in the adult relapsed/refractory Philadelphia-negative ALL population (40.3%; 11.9% serious) and the total relapsed/refractory ALL population (39.5%; 11.0% serious). Grade $\geq$ 3 and grade $\geq$ 4 events, respectively, were reported for 16.1% and 12.4% in the adult MRD-positive ALL population, which was lower than the adult relapsed/refractory Philadelphia-negative ALL population (37.1%; 15.2%) and the total relapsed/refractory

ALL population (36.1%; 15.3%). No fatal events of febrile neutropenia were reported in the adult MRD-positive ALL population.

Lymphopenia

Lymphopenia events were reported for 9 subjects (6.6%) in the adult MRD-positive ALL population, 13 subjects (2.5%) in the adult Philadelphia-negative relapsed/refractory ALL population, and 20 subjects (2.8%) in the total relapsed/refractory ALL population. Serious adverse events of lymphopenia were reported for 6 subjects (4.4%) in the adult MRD-positive ALL population and 1 subject (0.1%) in the Philadelphia-negative relapsed/refractory ALL population. Among the 6 subjects in the adult MRD-positive ALL population with serious adverse events of lymphopenia, all were from Study 202. All of the events were grade 4 in severity and were transient, occurring early in treatment on days 1 to 3 and resolving within 1 to 4 days without supportive treatment. None of the serious events of lymphopenia resulted in treatment interruption or discontinuation.

Per the protocol, in the early adult MRD-positive ALL Study 202, all marked hematological and other laboratory abnormalities were required to be reported as adverse events, and all laboratory abnormalities of grade 4 in severity were required be reported as serious adverse events. In the adult MRD-positive ALL Study 203 and subsequent relapsed/refractory ALL studies, laboratory abnormalities had to be considered clinically relevant to meet the criteria for reporting as an adverse event. Clinically relevant was defined in the 203 protocol and relapsed/refractory ALL protocols as those laboratory abnormalities that resulted in a clinical reaction, such as the addition of a concomitant medication or discontinuation of treatment. Since lymphopenia appeared to be transient (usually occurring and resolving early without supportive treatment), it was unlikely to be considered by the investigator to be clinically relevant in Study 203 or in the relapsed/refractory ALL studies per the protocol definition and therefore was reported less frequently as adverse events in these studies.

Decreased Immunoglobulins

In the adult MRD-positive ALL population, 18.2% of subjects experienced decreased immunoglobulin events, which was higher than all other populations examined, including the adult relapsed/refractory Philadelphia-negative ALL population (11.7%) and the total relapsed/refractory ALL population (11.3%). Grade 3 events occurred in 5.1% of

subjects in the adult MRD-positive ALL population; no grade 4 events were reported. No serious or fatal decreased immunoglobulin events were reported for any population.

The most frequently reported decreased immunoglobulin events occurring in the adult MRD-positive ALL population were blood IgG decreased (13.9%, vs 2.8% in each of the adult relapsed/refractory Philadelphia-negative ALL and the total relapsed/refractory ALL populations); blood IgA decreased (10.2%, vs 1.7% in the adult relapsed/refractory Philadelphia-negative ALL population and 1.4% in the total relapsed/refractory ALL population); and blood IgM decreased (7.3%, vs 1.5% in the adult relapsed/refractory Philadelphia-negative ALL population and 1.4% in the total relapsed/refractory ALL population).

The differences in the subject incidences of decreased immunoglobulins is likely due to the reporting requirements in the study protocols. As noted above in the discussion on lymphopenia, in the early adult MRD-positive ALL Study 202, all marked hematological and other laboratory abnormalities were required to be reported as adverse events per protocol, whereas in the adult MRD-positive ALL Study 203 and subsequent relapsed/refractory ALL studies, they had to be considered clinically relevant to meet the criteria for reporting as an adverse event. Clinically relevant was defined in the 203 protocol and relapsed/refractory ALL protocols as those laboratory abnormalities that resulted in a clinical reaction, such as the addition of a concomitant medication or discontinuation of treatment. In the adult MRD-positive ALL population, 17 of the 25 subjects with decreased immunoglobulin events were in Study 202. The majority of the decreased immunoglobulin events in Study 202 were grade 1 and 2 in severity, most subjects continued blinatumomab treatment through the events with supportive treatment, and none of the events led to treatment interruption or discontinuation.

Elevated Liver Enzymes

In the adult MRD-positive ALL population, elevated liver enzyme events were reported for 12.4% of subjects (3.6% serious), which was lower than all other populations examined, including 22.9% (1.7% serious) in the adult relapsed/refractory Philadelphia-negative ALL population and 22.9% (1.6% serious) in the total relapsed/refractory ALL population. Grade $\geq$ 3 and grade $\geq$ 4 events, respectively, were reported for 8.0% and 4.4% in the adult MRD-positive ALL population, 13.6% and 2.7% in the adult relapsed/refractory Philadelphia -negative ALL population, and 14.3% and

3.3% in the total relapsed/refractory ALL population. No fatal events were reported for any population.

The most frequently reported elevated liver enzyme events across populations were ALT increased and AST increased. In the adult MRD-positive ALL population, the subject incidences of ALT increased and AST increased (8.0% and 4.4%) were lower than in the adult relapsed/refractory Philadelphia-negative ALL population (10.6% and 8.9%) and total relapsed/refractory ALL population (11.5% and 9.8%). The subject incidence of gamma-glutamyltransferase (GGT) increased was generally consistent (≤ 5.7%) across populations. All other preferred terms occurred in ≤ 2 subjects in the adult MRD-positive ALL population, and the incidences were lower than, or consistent with, all other populations examined. The median time to onset to the first elevated liver enzyme event was 2.0 or 3.0 days for all populations (range: 1 to 238 days).

A medical review was performed for potential cases meeting the laboratory criteria for Hy's law (ALT or AST > 3.0 ULN; total bilirubin ≥ 2.0 ULN; alkaline phosphatase < 2.0 ULN) and with no other confounding factors including preexisting or acute liver disease (US FDA, 2009). Across all of the ALL studies, no subjects met the full criteria for Hy's law, since plausible alternative etiologies or other confounding factors were present, such as concurrent cytokine release syndrome, tumor lysis syndrome, macrophage activation syndrome, severe infections, medical history of elevated liver enzymes, hyperbilirubinemia, Gilbert's syndrome, or concomitant medications known to be associated with the elevations in liver enzymes or hepatic dysfunction.

Embolic and Thrombotic Events

In the adult MRD-positive ALL population, embolic and thrombotic events were reported in 5.1% (2.9% serious) of subjects, which compares with 8.0% (2.3% serious) in the adult relapsed/refractory Philadelphia-negative ALL population and 7.9% (2.0% serious) in the total relapsed/refractory ALL population. Grade ≥ 3 and grade ≥ 4 events, respectively, were reported for 3.6% and 1.5% of subjects in the adult MRD-positive ALL population, 2.5% and 0.8% in the adult relapsed/refractory Philadelphia-negative ALL population, and 2.3% and 0.7% in the total relapsed/refractory ALL population. No fatal embolic and thrombotic events were reported in the adult MRD-positive ALL population. The most frequently reported embolic and thrombotic events in the adult MRD-positive ALL population was the preferred term thrombosis in device (2.2%, 3 subjects). One subject (0.7%) in the adult MRD-positive ALL population was reported to have an event

of disseminated intravascular coagulation, compared with 1.1% in the adult relapsed/refractory Philadelphia-negative ALL population and 2.4% in the total relapsed/refractory ALL population.

Leukoencephalopathy

Patients with ALL typically receive CNS-directed therapies including brain irradiation and multiple intrathecal chemotherapies to treat or prevent CNS disease; these treatments can result in clinical or radiologic neurologic findings such as leukoencephalopathy. Data from Amgen safety database were reviewed to identify events reported as leukoencephalopathy, as well an additional review of any serious neurologic events to identify any cases that contained descriptive content on magnetic resonance imaging (MRI) or CT findings that might identify potential cases of leukoencephalopathy, which were not otherwise reported. Diagnostic criteria established for certainty of progressive multifocal leukoencephalopathy (PML) diagnosis include compatible clinical findings, compatible imaging findings, and cerebral spinal fluid (CSF) PCR positive for John Cunningham Virus (JC Virus) (Keene et al, 2011). Across all of the ALL studies, no subject has met the complete diagnostic criteria for PML.

Pancreatitis

Pancreatitis was reported for 1 subject (0.7%, non-serious) in the adult MRD-positive population and 0.4% and 0.3% of subjects in the adult relapsed/refractory Philadelphia-negative ALL and total relapsed/refractory ALL populations, respectively. Grade ≥ 3 events were reported for 2 subjects (0.4%) in the adult relapsed/refractory Philadelphia-negative ALL population. No grade 4 or fatal events of pancreatitis were reported across populations.

Immunogenicity

When administering biologic agents, one concern is that the immune system may mount a response against the foreign antigen and antidrug antibodies have the potential to alter exposure and efficacy of the biologic. To date, development of anti-blinatumomab antibodies has been detected in 9 out of 712 subjects (< 2%) with available samples across all blinatumomab studies, including non-Hodgkin lymphoma studies. Of these 9 subjects, 7 subjects were identified with anti-blinatumomab antibodies that had in-vitro neutralizing activity. Among the 9 cases, 7 subjects achieved clinical response as defined in the respective protocols. Blinatumomab serum concentration levels in 2 out

of 9 subjects were reduced. The impact of immunogenicity on safety was evaluated through medical review and assessment of the type and severity of adverse events, potential infusion reactions, and number of doses received while on study for blinatumomab-treated antibody-positive subjects. In those assessments, no evidence of an altered safety profile was observed for subjects who tested positive for anti-blinatumomab antibodies.

Appendix 23. Summary of Treatment-emergent Events of Interest for Blinatumomab ALL Studies (Safety Analysis Set)

Event of Interest (Search Strategy/Type)	Adult R/R Ph- ALL Study 211 Study 206 Study 311 (Blin arm) (N = 528) n (%)	Pediatric R/R ALL Study 205 Study 320 (N = 133) n (%)	Adult R/R Ph+ ALL Study 216 (N = 45) n (%)	R/R ALL Total (N = 706) n (%)	Adult MRD+ ALL Study 202 Study 203 (N = 137) n (%)	ALL Pooled All Studies (N = 843) n (%)
Neurologic Events (Sponsor defined MedDRA/NA)						
Overall incidence	353 (66.9)	69 (51.9)	28 (62.2)	450 (63.7)	98 (71.5)	548 (65.0)
Time to onset (median)	6.0 days	5.0 days	8.5 days	6.0 days	2.0 days	5.0 days
Grade ≥ 3	73 (13.8)	11 (8.3)	6 (13.3)	90 (12.7)	22 (16.1)	112 (13.3)
Grade ≥ 4	8 (1.5)	1 (0.8)	0 (0.0)	9 (1.3)	3 (2.2)	12 (1.4)
Serious	70 (13.3)	9 (6.8)	6 (13.3)	85 (12.0)	31 (22.6)	116 (13.8)
Fatal	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.4)
Cytokine release syndrome (Sponsor defined MedDRA/Narrow)[a]						
Overall incidence	75 (14.2)	24 (18.0)	4 (8.9)	103 (14.6)	4 (2.9)	107 (12.7)
Time to onset (median)	2.0 days	2.0 days	6.0 days	2.0 days	2.0 days	2.0 days
Grade ≥ 3	18 (3.4)	9 (6.8)	0 (0.0)	27 (3.8)	2 (1.5)	29 (3.4)
Grade ≥ 4	3 (0.6)	4 (3.0)	0 (0.0)	7 (1.0)	0 (0.0)	7 (0.8)
Serious	15 (2.8)	10 (7.5)	1 (2.2)	26 (3.7)	2 (1.5)	28 (3.3)
Infections (Infections and Infestations System Order Class)						
Overall incidence	338 (64.0)	61 (45.9)	22 (48.9)	421 (59.6)	64 (46.7)	485 (57.5)
Time to onset (median)	17.0 days	19.0 days	14.5 days	17.0 days	27.0 days	17.0 days
Grade ≥ 3	183 (34.7)	32 (24.1)	11 (24.4)	226 (32.0)	16 (11.7)	242 (28.7)
Grade ≥ 4	80 (15.2)	7 (5.3)	3 (6.7)	90 (12.7)	4 (2.9)	94 (11.2)
Serious	156 (29.5)	26 (19.5)	9 (20.0)	191 (27.1)	18 (13.1)	209 (24.8)
Fatal	55 (10.4)	2 (1.5)	2 (4.4)	59 (8.4)	1 (0.7)	60 (7.1)
Elevated Liver Enzyme (SMQ Liver related investigations, signs and symptoms/Narrow) [a]						
Overall incidence	121 (22.9)	33 (24.8)	8 (17.8)	162 (22.9)	17 (12.4)	179 (21.2)
Time to onset (median)	3.0 days	2.0 days	2.0 days	3.0 days	3.0 days	3.0 days
Grade ≥ 3	72 (13.6)	23 (17.3)	6 (13.3)	101 (14.3)	11 (8.0)	112 (13.3)
Grade ≥ 4	14 (2.7)	6 (4.5)	3 (6.7)	23 (3.3)	6 (4.4)	29 (3.4)
Serious	9 (1.7)	1 (0.8)	1 (2.2)	11 (1.6)	5 (3.6)	16 (1.9)

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Appendix 23. Summary of Treatment-emergent Events of Interest for Blinatumomab ALL Studies (Safety Analysis Set)

Event of Interest (Search Strategy/Type)	Adult R/R Ph- ALL Study 211 Study 206 Study 311 (Blin arm) (N = 528) n (%)	Pediatric R/R ALL Study 205 Study 320 (N = 133) n (%)	Adult R/R Ph+ ALL Study 216 (N = 45) n (%)	R/R ALL Total (N = 706) n (%)	Adult MRD+ ALL Study 202 Study 203 (N = 137) n (%)	ALL Pooled All Studies (N = 843) n (%)
Infusion reactions (Sponsor defined MedDRA /Narrow) [a]						
Overall incidence	268 (50.8)	88 (66.2)	22 (48.9)	378 (53.5)	124 (90.5)	502 (59.5)
Time to onset (median)	2.0 days	1.0 day	2.0 days	2.0 days	1.0 day	1.0 day
Grade ≥ 3	41 (7.8)	21 (15.8)	3 (6.7)	65 (9.2)	14 (10.2)	79 (9.4)
Grade ≥ 4	2 (0.4)	1 (0.8)	0 (0.0)	3 (0.4)	1 (0.7)	4 (0.5)
Serious	13 (2.5)	9 (6.8)	1 (2.2)	23 (3.3)	19 (13.9)	42 (5.0)
Tumour lysis syndrome (SMQ/Narrow)[a]						
Overall incidence	23 (4.4)	4 (3.0)	0 (0.0)	27 (3.8)	0 (0.0)	27 (3.2)
Time to onset (median)	3.0 days	2.0 days	--	3.0 days	--	3.0 days
Grade ≥ 3	15 (2.8)	3 (2.3)	0 (0.0)	18 (2.5)	0 (0.0)	18 (2.1)
Grade ≥ 4	2 (0.4)	1 (0.8)	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.4)
Serious	5 (0.9)	1 (0.8)	0 (0.0)	6 (0.8)	0 (0.0)	6 (0.7)
Capillary leak syndrome (Sponsor defined MedDRA /Narrow) [a]						
Overall incidence	1 (0.2)	6 (4.5)	0	7 (1.0)	1 (0.7)	8 (0.9)
Time to onset (median)	2.0 days	6.0 days	--	2.0 days	--	2.0 days
Grade ≥ 3	1 (0.2)	2 (1.5)	0	3 (0.4)	0	3 (0.4)
Grade ≥ 4	2 (0.4)	1 (0.8)	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.4)
Serious	1 (0.2)	2 (1.5)	0	3 (0.4)	0	3 (0.4)
Medication errors (Sponsor defined MedDRA/Broad) [a]						
Overall incidence	20 (3.8)	6 (4.5)	1 (2.2)	27 (3.8)	6 (4.4)	33 (3.9)
Time to onset (median)	7.0 days	13.5 days	9.0 days	8.0 days	50.0 days	14.0 days
Grade ≥ 3	4 (0.8)	1 (0.8)	0	5 (0.7)	0	5 (0.6)
Grade ≥ 4	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Serious	20 (3.8)	6 (4.5)	1 (2.2)	27 (3.8)	6 (4.4)	33 (3.9)

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Appendix 23. Summary of Treatment-emergent Events of Interest for Blinatumomab ALL Studies (Safety Analysis Set)

Event of Interest (Search Strategy/Type)	Adult R/R Ph- ALL Study 211 Study 206 Study 311 (Blin arm) (N = 528) n (%)	Pediatric R/R ALL Study 205 Study 320 (N = 133) n (%)	Adult R/R Ph+ ALL Study 216 (N = 45) n (%)	R/R ALL Total (N = 706) n (%)	Adult MRD+ ALL Study 202 Study 203 (N = 137) n (%)	ALL Pooled All Studies (N = 843) n (%)
Decreased immunoglobulins (Sponsor defined MedDRA/Narrow) [a, b]						
Overall incidence	62 (11.7)	14 (10.5)	4 (8.9)	80 (11.3)	25 (18.2)	105 (12.5)
Time to onset (median)	42.0 days	29.0 days	105.5 days	42.0 days	29.0 days	29.0 days
Grade ≥ 3	12 (2.3)	3 (2.3)	0	15 (2.1)	7 (5.1)	22 (2.6)
Grade ≥ 4	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Embolic and Thrombotic Events (including DIC) (SMQ/Narrow)						
Overall incidence	42 (8.0)	11 (8.3)	3 (6.7)	56 (7.9)	7 (5.1)	63 (7.5)
Time to onset (median)	22.0 days	3.0 days	175.0 days	21.0 days	65.0 days	23.0 days
Grade ≥ 3	13 (2.5)	1 (0.8)	2 (4.4)	16 (2.3)	5 (3.6)	21 (2.5)
Grade ≥ 4	4 (0.8)	1 (0.8)	0 (0.0)	5 (0.7)	2 (1.5)	7 (0.8)
Serious	12 (2.3)	1 (0.8)	1 (2.2)	14 (2.0)	4 (2.9)	18 (2.1)
Fatal	2 (0.4)	1 (0.8)	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.4)
Leukoencephalopathy (Sponsor defined MedDRA /Broad) [a]						
Overall incidence	4 (0.8)	2 (1.5)	1 (2.2)	7 (1.0)	1 (0.7)	8 (0.9)
Time to onset (median)	24.0 days	30.0 days	23.0 days	23.0 days	17.0 days	20.5 days
Grade ≥ 3	2 (0.4)	0	0	2 (0.3)	0	2 (0.2)
Grade ≥ 4	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Serious	2 (0.4)	0	0	2 (0.3)	1 (0.7)	3 (0.4)

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Appendix 23. Summary of Treatment-emergent Events of Interest for Blinatumomab ALL Studies (Safety Analysis Set)

Event of Interest (Search Strategy/Type)	Adult R/R Ph- ALL Study 211 Study 206 Study 311 (Blin arm) (N = 528) n (%)	Pediatric R/R ALL Study 205 Study 320 (N = 133) n (%)	Adult R/R Ph+ ALL Study 216 (N = 45) n (%)	R/R ALL Total (N = 706) n (%)	Adult MRD+ ALL Study 202 Study 203 (N = 137) n (%)	ALL Pooled All Studies (N = 843) n (%)
Neutropenia and febrile neutropenia (Sponsor defined MedDRA/Narrow)						
Overall incidence	213 (40.3)	45 (33.8)	21 (46.7)	279 (39.5)	22 (16.1)	301 (35.7)
Time to onset (median)	10.0 days	3.5 days	3.0 days	8.0 days	36.0 days	8.0 days
Grade ≥ 3	196 (37.1)	44 (33.1)	15 (33.3)	255 (36.1)	22 (16.1)	277 (32.9)
Grade ≥ 4	80 (15.2)	25 (18.8)	3 (6.7)	108 (15.3)	17 (12.4)	125 (14.8)
Serious	63 (11.9)	11 (8.3)	4 (8.9)	78 (11.0)	7 (5.1)	85 (10.1)
Fatal	2 (0.4)	0	0	2 (0.3)	0	2 (0.2)
Lymphopenia (Sponsor defined MedDRA/Narrow) [a]						
Overall incidence	13 (2.5)	7 (5.3)	0	20 (2.8)	9 (6.6)	29 (3.4)
Time to onset (median)	2.0 days	2.0 days	--	2.0 days	2.0 days	2.0 days
Grade ≥ 3	11 (2.1)	6 (4.5)	0	17 (2.4)	9 (6.6)	26 (3.1)
Grade ≥ 4	9 (1.7)	5 (3.8)	0 (0.0)	14 (2.0)	8 (5.8)	22 (2.6)
Serious	1 (0.2)	0	0	1 (0.1)	6 (4.4)	7 (0.8)
Pancreatitis (SMQ/Narrow) [a, c]						
Overall incidence	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.7)	3 (0.4)
Time to onset (median)	12.5 days	--	--	12.5 days	4.0 days	4.0 days
Grade ≥ 3	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Serious	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)

ALL = acute lymphoblastic leukemia; Blin = blinatumomab; DIC = disseminated intravascular coagulation; MedDRA = Medical Dictionary for Regulatory Activities; MRD+ = minimum residual disease-positive; NA = not applicable; Ph- = Philadelphia chromosome-negative; Ph+ = Philadelphia chromosome-positive; R/R = relapsed/refractory; SMQ = Standard MedDRA Query

Safety analysis set: All subjects who received at least 1 infusion of blinatumomab. Severity graded using Common Technical Criteria for Adverse Events, version 4.03. Adverse events coded using MedDRA version 18.1.

Time to onset is median time to first onset of event of interest.

[a] No fatal adverse events were reported.

[b] No serious adverse events were reported.

[c] No grade ≥4 adverse events were reported.

Source: Modified from Table 15 of Module 2.7.4, Tower/Ph+ filing and Table 59 of Integrated Summary of Safety, Tower/Ph+ Filing (Table iss-06.6.1; Table iss-06.10.1 to Table iss-06.10.14)