Title: Long-term follow-up of adult Philadelphia chromosome negative acute lymphoblastic leukemia relapsed refractory patients enrolled in Study 00103311

Amgen Protocol Number Blinatumomab 20180138

Study Sponsor:	Amgen Inc One Amgen Center Drive Thousand Oaks, California 91320 United States Phone: +1-805-447-1000 Fax: +1-805-480-4978
Department:	Center for Observational Research
Therapeutic Area:	Oncology
Key Sponsor Contact:	PPD [redacted] Amgen, Inc Phone: PPD [redacted] Email: PPD [redacted]
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1. BACKGROUND AND RATIONALE

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by the proliferation of immature and abnormal lymphoid cells in the bone marrow and peripheral blood. B-precursor ALL is an aggressive malignant disease. Blinatumomab (Blincyto®) belongs to a class of bispecific antibody constructs called bispecific T cell engagers (BITE®). This T cell–mediated target-specific killing is the therapeutic mechanism of action of blinatumomab (Löffler et al, 2000; Wolf et al, 2005). Blinatumomab specifically targets cells that express CD19, a marker solely expressed by B cells, including B-precursor ALL cells. Due to its unique ability to redirect T cells via CD3 towards a $CD19^+$ tumor cell lysis, blinatumomab can elicit repeated target cell elimination by cytotoxic T cells and a polyclonal response of previously primed $CD4^+$ and $C8^+$ T cells.

Blinatumomab received accelerated approval from the Food and Drugs Agency (FDA) for the treatments of adults and children with relapsed/refractory Philadelphia chromosome negative (Ph-) B-cell ALL in 2014: this was converted to full approval in 2017.The European Medicines Agency (EMA) granted conditional approval to blinatumomab for the treatment of adults with relapsed/refractory Ph- B-cell ALL in November 2015, with conditional approval converted to full approval in June 2018 based on the results of a Phase III randomized trial that demonstrated longer median overall survival (OS: 7.7 months versus 4.0 months) in patients treated with blinatumomab compared to standard of care chemotherapy (Kantarjain et al 2017). This Phase III study was terminated early due to efficacy of meeting the primary endpoint of OS.
As a part of the approval of the relapsed/refractory indication in the EU, the PRAC requested Amgen conduct an additional final overall survival assessment of patients that were alive at last follow-up in the Phase III trial.

The purpose of this study (20180138) is to conduct a one-time vital assessment on patients that were alive at last follow-up in the Phase III study 00103311. At the last follow-up, there were approximately 108 patients alive. The data collection/source for collecting vital status to be utilized will be the sites/patients from existing blinatumomab study number 00103311. The single output from this study effort will be to generate an updated overall survival Kaplan-Meier probability estimates and Kaplan-Meier plot. These results will be subject of a brief updated study report to be sent to the EMA PRAC.

2. OBJECTIVES

The objective of this study is to update the overall survival (OS) Kaplan-Meier probability estimates and the plot last reported in the randomized Phase 3 blinatumomab 00103311 study.

3. STUDY POPULATION/SAMPLE SIZE/STATISTICAL ANALYSES PLANS

3.1 STUDY POPULATION AND METHODS

The population in this study will be the patients who were enrolled originally in the 00103311 trial (A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)). This study will be a single additional vital status follow-up on patients that were alive at the end of the 00103311 study results being reported.
A final follow-up will occur on the remaining alive patients at last follow-up. At least three attempts to contact subjects will be made by the sites from which the subjects were enrolled, and a vital status will be ascertained from medical chart, patient contact, next of kin contact, or national death registry. The vital status of each patient will be assessed as either alive or deceased with corresponding date of vital check or death, as applicable. For subjects where vital status cannot be ascertained beyond the date of last follow-up from the 00103311 study, subject will be marked as lost to follow-up at last follow-up date if no response at least 1 month from last contact.

3.2 SAMPLE SIZE

The number of patients alive at the last follow-up in the 00103311 study was 108 subjects. An earnest effort to ascertain vital status on all subjects will be made. It is unknown how many subjects will have additional follow-up.

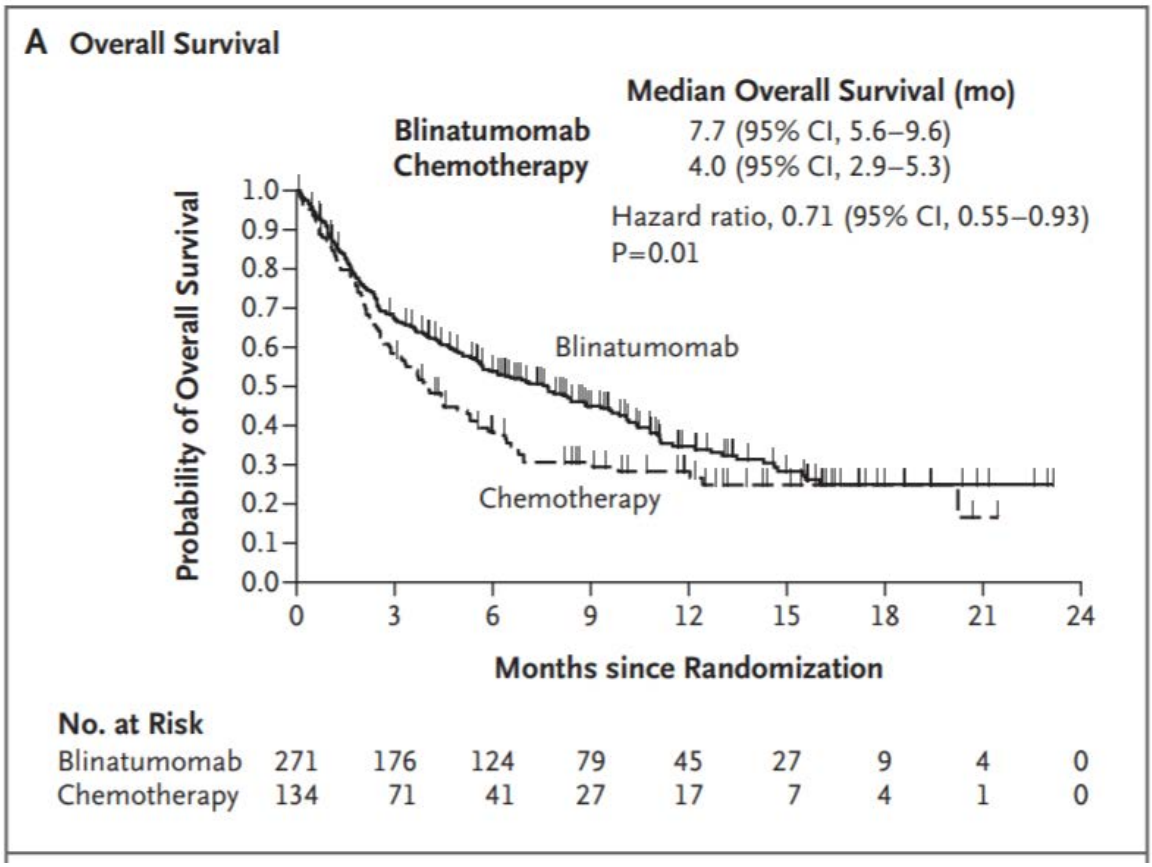
3.3 STATISTICAL ANALYSIS

The endpoint in this study is overall survival. Overall survival is defined as time from randomization of blinatumomab or investigator choice chemotherapy (the two treatment arms in the 00103311 trial) until the event of death or censoring at end of follow-up.

For the analysis, overall survival Kaplan-Meier probabilities and plot last reported in the 00103311 study will be updated to provide a final table of survival probabilities at defined time points (3 months, 6 months, 12 months, 18 months, 24 months, 36 months, 60 months) with relevant 95% confidence intervals and a final plot which also adds an

elongated x-axis of up to 60 months. For reference, the overall survival plot presented in the published study (Kantarjain et al 2017) is presented below:

Figure 1. Probability of overall survival in the two groups (blinatumomab or chemotherapy). Overall survival was calculated as the time from randomization to death from any cause. The median duration of follow-up for overall survival was 11.7 months in the blinatumomab group and 11.8 months in the chemotherapy group.



4. COLLECTION, RECORDING, AND REPORTING OF SAFETY INFORMATION AND PRODUCT COMPLAINTS

This study is analyzing secondary data from medical charts and the only objective is to assess vital status/survival. No safety data will be collected or reported.

5. SUBJECT CONFIDENTIALITY

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur beyond vital status assessment by the sites. Study results will be in tabular form and aggregate analyses that omits subject identification. Any publications and reports will not include subject identifiers.

6. PUBLICATION INTENT

Results of this study is intended to be submitted to regulatory agency EMA PRAC to fulfill a commitment as part of approval for blinatumomab in EU countries.

There are no additional plans to publish these data.

7. References

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