1. ABSTRACT

- **Title**

An observational study describing the effectiveness and safety of BLINCYTO® in Chinese adults with Philadelphia chromosome-positive relapsed or refractory B-cell precursor Acute Lymphoblastic Leukemia (Ph+ R/R B-cell precursor ALL)

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Authors: [redacted] Center for Observational Research, Amgen Inc.; [redacted] Center for Observational Research, Amgen Inc.

- **Keywords**

Acute lymphoblastic leukemia, B-cell precursor, Philadelphia chromosome-positive, relapsed or refractory, retrospective observational study.

- **Rationale and Background**

The Philadelphia chromosome (Ph), t(9;22), or (BCR-ABL), is present in approximately 25% of adults diagnosed with B-cell precursor acute lymphoblastic leukemia (ALL) (referred to as Ph+ patients) (Liu-Dumlao, 2012; Liu, 2016). Treatment of patients with Ph+ ALL who are resistant to or relapse after first-line therapy remains challenging, which indicates the unmet medical need to develop an effective salvage therapy with limited toxicity, thereby allowing the possibility of achieving a second complete remission (CR) before proceeding to allogeneic haemopoietic stem cell transplant (alloHSCT). Tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL oncogenic protein have been incorporated recently into most treatment regimens. BLINCYTO (blinatumomab) is the first single-agent immunotherapy and the only bispecific T cell engagers (BiTE®) molecule that has been approved in multiple regions for the treatment of B-cell precursor ALL (Ph+ and Ph-) in adults and children. The results from a phase 2 study for the treatment of 45 patients with Ph+ relapsed or refractory (R/R) B-cell precursor ALL (Study 20120216 or ALCANTARA study) provided evidence of the benefit of blinatumomab immunotherapy as a monotherapy for a population of patients with an extremely poor prognosis (Martinelli, 2017).

BLINCYTO (blinatumomab) was approved on 02 December 2020 by the China National Medical Products Administration (NMPA) for the treatment of adult patients with R/R B-cell precursor ALL (Ph+ and Ph-). With the approval of blinatumomab in Mainland China, this observational study investigated the effectiveness and safety of blinatumomab in adult Chinese patients with Ph+ R/R B-cell precursor ALL. This observational study was conducted using medical record review at multiple clinical study sites in Mainland China to provide data on the real-world treatment outcomes of blinatumomab with or without TKIs in patients with Ph+ R/R B-cell precursor ALL.

- **Research Question and Objectives**

Primary Objectives:

- To estimate the percentage of patients with CR/CR with partial hematological recovery (CRh) within 2 cycles of treatment with BLINCYTO in Chinese adults with Ph+ R/R B-cell precursor ALL.
- To estimate the incidence of adverse event of interest (EOI) (recorded within 6 months of first infusion of BLINCYTO).

Secondary Objectives:

- To describe the treatment patterns of BLINCYTO and TKIs in clinical practice.
- To estimate the occurrence of alloHSCT after BLINCYTO treatment.
- To estimate the percentage of patients achieving minimal residual disease (MRD) negative status after CR/CRh.
- To estimate overall survival (OS) at 6 months.
- To estimate relapse free survival (RFS) at 6 months.

- **Study Design**

This was a retrospective observational study in the postmarketing setting using medical record review. The study included adult patients of Chinese descent (≥ 18 years at the initiation of blinatumomab) treated with blinatumomab with or without TKIs for Ph+ R/R B-cell precursor ALL at participating clinical study sites in Mainland China.

- **Setting**

Patient-level data were obtained by abstraction of data from existing medical records at 7 participating clinical study sites in Mainland China. Data abstraction was completed at 1 point in time per patient (at least 6 months from initiation of blinatumomab to capture all primary endpoints) to increase the operational feasibility of the study. Follow-up for objectives began after initiation of blinatumomab treatment. Eligible patients (including deceased) who started blinatumomab treatment a minimum of 6 months before the initiation of data abstraction were included. Treatment was initiated on or after approval of blinatumomab in Mainland China (02 December 2020).

The data collection period was approximately 7 months from the first patient enrolled (20 February 2024) to the last patient enrolled in the study (09 September 2024). End of study was defined as the last chart abstraction for the last patient enrolled, which occurred on 30 September 2024.

- **Patients and Study Size, Including Dropouts**

Medical records of patients treated with blinatumomab with or without TKIs for Ph+ R/R B-cell precursor ALL at participating clinical study sites in Mainland China were eligible for inclusion in the study.

Patients with medical records who met the following criteria were included in the study:

- Adult patients (≥ 18 years at the initiation of blinatumomab) with Ph+ R/R B-Cell precursor ALL confirmed by either cytogenetics or molecular test.
- Patients initiated with blinatumomab with or without TKIs at least 6 months before data abstraction.
- Informed consent provided if required per local regulations.

Note: Medical records of patients participating in clinical studies were included up to the time the patient enrolled into a clinical study; however, patient data after enrollment in a clinical study were not extracted.

Patients with medical records who met any of the following criteria were excluded from the study:

- Medical records of patients with Philadelphia chromosome-negative (Ph-) disease.
- Medical records of patients who received blinatumomab through an expanded access or compassionate use program.

A total of 17 patients initiating blinatumomab treatment for Ph+ R/R B-cell precursor ALL after commercial availability of blinatumomab from the 7 participating clinical study sites in Mainland China were enrolled in the study and included in the full analysis set (FAS).

- **Data Source and Methods**

Source documents were patient medical records, from which the electronic case report forms (eCRFs) data were populated by the study site investigators. These sources included but were not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Patient-level data were obtained by abstraction of data from existing medical records at the 7 participating clinical study sites.

The safety outcomes documented and analyzed in this study were adverse EOIs (adverse EOI is referred as EOI hereafter). The EOIs were defined as cytokine release syndrome (CRS), BLINCYTO-associated neurological adverse event, and infection. Incidence of EOIs within 6 months of first infusion of blinatumomab were recorded.

- **Results**

A total of 17 patients initiating blinatumomab treatment for Ph+ R/R B-cell precursor ALL after commercial availability of blinatumomab from 7 clinical study sites in Mainland China were enrolled in the study and included in the FAS. Of these 17 patients, 14 (82.4%) patients were alive at the end of the study and 3 patients (17.6%) died due to any cause after the end of blinatumomab treatment; none of which were considered related to blinatumomab.

Among the 17 patients in the FAS, 11 (64.7%) were women and 6 (35.3%) were men. At blinatumomab initiation, the median age was 48.0 (range: 22 to 64) years. All 17 blinatumomab-exposed patients were in the 18 to 64 years of age group.

At blinatumomab initiation, 2 patients (11.8%) were primary refractory, 8 patients (47.1%) were in first relapse, 4 patients (23.5%) in second relapse, 2 patients (11.8%) in third relapse, and 1 patient (5.9%) in fourth relapse. Of the 17 patients, 9 patients (52.9%) received only 1 prior line of therapies and 8 patients (47.1%) received $\geq$ 2 prior lines of therapy. The median prior lines of therapies (including TKIs) was 1 (range: 1 to 4). Best MRD response to prior therapies before blinatumomab initiation was MRD negative for 5 patients (29.4%), MRD positive for 4 patients (23.5%), and 8 patients (47.0%) had MRD status reported as unknown or missing. The median number of previous TKI treatments was 2.0 (range: 0 to 4) and the median bone marrow blasts percentage at blinatumomab initiation was 71.25% (range: 0% to 96.0%).

Treatment Patterns

The median number of blinatumomab cycles started was 1 (range: 1 to 3) cycle. Eleven patients (64.7%) started 1 cycle, 5 patients (29.4%) started 2 cycles, and 1 patient (5.9%) started 3 cycles of blinatumomab. The median overall duration of blinatumomab treatment was 14.0 (range: 7 to 88) days. Eleven patients (64.7%) received concomitant treatment with a TKI after initiating blinatumomab; and only 1 patient (5.9%) received blinatumomab as a monotherapy.

Effectiveness

- Eleven patients (64.7%; 95% CI: 38.3, 85.8) achieved CR/CRh within first 2 cycles of blinatumomab treatment.
- Six patients (35.3%; 95% CI: 14.2, 61.7) received alloHSCT after blinatumomab treatment, of which 4 patients (23.5%; 95% CI: 6.8, 49.9) were in remission after having achieved CR/CRh and 2 patients (11.8%; 95% CI: 1.5, 36.4) without achieving CR/CRh.
- Eleven patients achieved CR/CRh within 2 cycles of blinatumomab treatment of which, 9 patients had evaluable MRD. Of the 11 patients who achieved CR/CRh during the first 2 cycles of blinatumomab treatment, 6 patients (54.5%) achieved MRD negative status (3 patients [27.3%; 95% CI: 6.0, 61.0)] each had MRD response and MRD CR), 3 patients (27.3%; 95% CI: 6.0, 61.0) had MRD nonresponse, and 2 patients (18.2%; 95% CI: 2.3, 51.8) had not evaluable MRD.
- Three patients (17.6%) died due to any cause (ie, OS events) and 14 patients (82.4%) were alive (ie, censored) with a median follow-up of 11.7 months. Of the 3 patients, 1 patient each died due to septic shock (at day 503), respiratory circulatory failure (at day 699), and disease progression (at day 355), respectively after blinatumomab initiation. None of the deaths were related to blinatumomab. The 6-month KM estimate for OS was 100% (95% CI: 100, 100).
- Of the 11 patients who achieved CR/CRh during the first 2 cycles of blinatumomab treatment, 2 (18.2%) patients had RFS events, 1 patient each had relapse and death due to any cause. The 6-month KM estimate for RFS was 75.0% (95% CI: 12.8, 96.1).

Safety

Sixteen patients (94.1%) had at least 1 EOI of which 11 (64.7%) had grade 3 EOIs; none of the patients had grade 4 or fatal EOIs. None of the patients required either interruption or discontinuation of blinatumomab due to an EOI.

- *Infection:* Fourteen patients (82.4%) had at least 1 EOI of infection; the most frequently reported (≥ 10% of patients) events of infection by preferred term were pneumonia, COVID-19, and Epstein-Barr virus infection, and sepsis. None of the patients required interruption or discontinuation of blinatumomab due to events of infection. Four patients (23.5%) had serious events of infection and 11 patients (64.7%) had grade 3 events of infection. None of the patients had grade 4 or fatal events of infection. Of the 14 patients (82.4%) who had 29 events of infection (some patients had more than 1 event), most of the events were reported as resolved (10 patients [58.8%] with 16 events). The median duration of any resolved events was 76.5 (range: 13 to 374) days. Nine patients (52.9%) had 13 events with either unknown outcome or events reported as not resolved (of which 8 events in 4 patients were reported with unknown outcome and 5 events in 5 patients had outcome reported as not resolved).
- *Cytokine Release Syndrome:* Nine patients (52.9%) had at least 1 EOI of CRS. One patient (5.9%) had a CRS event which led to interruption of blinatumomab treatment. None of the patients discontinued blinatumomab treatment due to CRS. None of the patients had serious or grade ≥ 3 events of CRS. Among the 9 patients (52.9%) identified with EOIs of CRS, there were 20 CRS events

reported (some patients had more than 1 event). All 20 CRS events were reported as resolved, with a median duration of 3 (range: 1 to 10) days.

- *BLINCYTO-associated Neurologic Events:* None of the patients had an EOI of BLINCYTO-associated neurologic events.

- **Discussion**

This observational study investigated the effectiveness and safety of blinatumomab in adult Chinese patients with Ph+ R/R B-cell precursor ALL on or after the approval of blinatumomab in Mainland China (02 December 2020). Results obtained from medical records of 17 patients who initiated blinatumomab treatment for Ph+ R/R B-cell precursor ALL in Mainland China, were consistent with global studies.

The effectiveness profile, including proportions of patients achieving CR/CRh within first 2 cycles of blinatumomab treatment, patients receiving alloHSCT after blinatumomab treatment, and MRD response were consistent with existing evidence across the most recently published real-world studies (Boissel et al, 2023; Cabannes-Hamy et al, 2022; Badar et al, 2021; Badar et al, 2020). In contrast to the ALCANTARA study, but in line with other recently published real-world studies, patients in this study were younger, more likely to be earlier in their line of treatment, and with fewer prior alloHSCT, further supporting the positive effectiveness profile seen in this study. However, any censored patients before 6 months of follow-up may indicate potential deaths occurring outside of the participating clinical study sites, which may not have been captured from the medical charts and therefore, both OS and RFS estimates were likely overestimated. Furthermore, as EOIs typically occur soon after blinatumomab initiation and given that this study had sufficient follow-up of 6 months, there is unlikely to be ascertainment bias of EOIs.

Overall, the study results for primary endpoints assessed in this study were consistent with the known effectiveness and safety profile of blinatumomab and/or underlying disease (ALL), and no new safety signals were detected from review of the data.

- **Marketing Authorization Holder**

Amgen Inc.

- **Names and Affiliations of Principal Investigators**

Principal investigators of study centers included in this interim analysis report are provided in Section 3 of this report.