

Date of request: September 18, 2017

NCCN Guidelines Panel: Acute Lymphoblastic Leukemia (ALL)

Requests for Guideline Review in Relapsed/Refractory Philadelphia Chromosome-Positive ALL

On behalf of Amgen, I respectfully submit for consideration by the panel, that the NCCN Clinical Practice Guidelines for Relapsed/Refractory Philadelphia Chromosome Positive ALL be updated to reflect that blinatumomab may be used to treat patients who have failed a 2nd generation TKI, in accordance with the FDA approved label for blinatumomab (updated by the FDA on July 11, 2017). This is in contrast to the current NCCN guideline recommendation for the use of blinatumomab after the failure of two TKIs.

Additionally, I respectfully submit for consideration by the panel, that the order of the guidelines for Relapsed/Refractory Philadelphia Chromosome-Negative ALL be updated to prioritize blinatumomab (category 1) above chemotherapy, as blinatumomab has demonstrated statistically superior efficacy with regard to overall survival.

Clinical Data – ALCANTARA (Ph+ R/R ALL)

The Phase 2 ALCANTARA study was a single-arm, multicenter trial that evaluated the efficacy of the bispecific T-cell engager (BiTE) antibody blinatumomab in adult subjects with relapsed/refractory Philadelphia chromosome positive B-cell precursor ALL. Patients enrolled in this trial were either [A] relapsed/refractory to at least one second generation TKI, **OR** [B] intolerant to at least one 2nd generation TKI and intolerant/refractory to imatinib. The primary endpoint was the rate of complete remission/complete remission with partial hematological recovery (CR/CRh) within 2 cycles of blinatumomab.

Blinatumomab was administered in 28-day cycles by continuous intravenous infusion. Pre-dose dexamethasone was administered to help prevent cytokine release syndrome (CRS).

Of 45 patients, 7 (16%) received one prior TKI treatment, 21 (47%) received 2 prior TKI treatments and 17 (38%) received greater than or equal to three prior TKI treatments. Of 45 patients, 31 (62%) received prior salvage therapy and 20 (44%) received prior allogeneic hematopoietic stem-cell transplantation (alloHSCT).

Of 45 patients, 16 (36%; 95% CI, 22% to 51%) achieved CR/CRh during the first two cycles, including four of 10 patients with the T315I mutation; and 88% of CR/CRh responders achieved a complete minimal residual disease response. Seven responders (44%) proceeded to alloHSCT, including 55% (six of 11) of transplantation-naïve responders. Median relapse-free survival and overall survival were 6.7 and 7.1 months, respectively.

The most frequent AEs were pyrexia (58%), febrile neutropenia (40%), and headache (31%). Three patients had cytokine release syndrome (all grade 1 or 2), and three patients had grade 3 neurologic events, one of which (aphasia) required temporary treatment interruption. There were no grade 4 or 5 neurologic events.

In short, single-agent blinatumomab showed significant anti-leukemic activity in high-risk patients with Ph+ ALL who had relapsed after TKI therapy or were refractory to TKI therapy. AEs were consistent with those seen in studies of blinatumomab in Ph- ALL.

Clinical Data – TOWER (Ph- R/R ALL)

In the Phase 3 TOWER study, BLINCYTO demonstrated superior clinical efficacy over chemotherapy. It was a prospective, randomized, open-label study that investigated the effect of blinatumomab compared to standard-of-care (SOC) chemotherapy in heavily pretreated patients with R/R Ph- B-CP ALL (refractory to primary induction

therapy or to salvage with intensive combination chemotherapy, first relapse < 12 months after first remission, 2 or more relapses, or relapse at anytime after allo HSCT). The primary endpoint was overall survival. Adult patients were randomized in a 2:1 ratio to receive blinatumomab or to 1 of 4 SOC chemotherapy regimens, at the discretion of the investigator. In the SOC group, the investigator chose one of four backbones: FLAG ± anthracycline; high-dose ara-C (HiDAC)-based; high-dose methotrexate-based; or clofarabine-based.

Blinatumomab was administered as a continuous intravenous infusion in the study in 6-week cycles of 4 weeks on 9 µg/day on Days 1 – 7, then 28 µg/day on Days 8 – 28 for cycle 1, followed by no therapy for two weeks. Pre-dose dexamethasone was administered to help prevent cytokine release syndrome (CRS). The primary endpoint was overall survival (OS) and secondary endpoints included complete remission (CR) and combined CR with partial or incomplete hematologic recovery (CR/CRh/CRi).

In the TOWER study, 405 patients were randomized to blinatumomab (n = 271) or SOC (n = 134) and analyzed for efficacy. Patients randomized to blinatumomab had significantly longer OS compared to those that received chemotherapy. The median OS was 7.7 months (95% CI, 5.6 – 9.6) for blinatumomab and 4.0 months (95% CI, 2.9 – 5.3) for SOC (hazard ratio for death, 0.71; 95% CI, 0.55 – 0.93), with a median duration of follow-up of 11.7 and 11.8 months, respectively. Estimated survival at 6 months was 54% in the blinatumomab group and 39% in the SOC group. Improvements in overall survival in the blinatumomab group were observed in the stratified subgroups. The largest difference in OS benefit within sub-groups was observed in early relapsing first-salvage patients. Median survival in first salvage was 11.1 months with blinatumomab and 5.3 months with SOC (HR, 0.60, 95% CI, 0.39 to 0.91).

Patients that received blinatumomab exhibited higher remission rates versus SOC, including CR (33.6% vs 15.7%; p<.001) and CR/CRh/CRi (43.9% vs 24.6%; p<.001). Additionally, among patients that had CR/CRh/CRi responses, 76% in the blinatumomab group and 48% in the chemotherapy group achieved a negative status for minimal residual disease. The rate of event-free survival was higher with blinatumomab treatment compared with chemotherapy (6-month estimates, 31% vs 12%) and the blinatumomab arm demonstrated a longer median duration of remission (7.3 vs 4.6 months).

A total of 376 patients had received at least one dose of blinatumomab (N=267) or SOC (N=109; 49 FLAG ± anthracycline, 19 HiDAC-based; 22 high-dose methotrexate-based, and 19 clofarabine-based regimens) and were analyzed for safety. The median number of treatment cycles was 2 (range, 1 – 9) in the blinatumomab group and 1 (range, 1 – 4) in the chemotherapy group.

The adverse events in the blinatumomab group were consistent with previous studies. Serious adverse events were reported in 62% of the patients in the blinatumomab group and 45% in the chemotherapy group. The most commonly reported grade ≥ 3 adverse events for the blinatumomab and chemotherapy groups, included neutropenia (38%, 58%), infection (34%, 52.3), elevated liver enzymes (13%, 15%), neurologic event (9.4%, 8.3%) and cytokine release syndrome (4.9%, 0%), respectively

Supporting Documentation

Please find the following publication submitted in support of this request.

1. Martinelli G, Boissel N, Chevallier P, *et al.* Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome–Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. *J Clin Oncol* 2017; 35: 1795-1802.
2. BLINCYTO® US Prescribing Information (Section 14, Tables 12 and 13)
3. Kantarjian H, Stein A, Gökbuget N, *et al.* Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med.* 2017; 376: 836-847



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Sincerely,

A handwritten signature in black ink, appearing to be "D. Cohan", is written over the printed name and title.

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Medical Director

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