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NCCN Guidelines Panel: Acute Lymphoblastic Leukemia (ALL)

Change requests for Relapse/Refractory Philadelphia Chromosome-Negative ALL

On behalf of Amgen, I respectfully submit for consideration of the panel, that the NCCN Clinical Practice Guidelines for Acute Lymphoblastic Leukemia are updated to reflect the publication of phase 3 study data that demonstrated immunotherapy product blinatumomab improved overall survival in adult patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (R/R B-CP ALL) compared to chemotherapy.

Clinical Data

The Phase 3 TOWER study 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 with the first remission < 12 months, > 2 relapse 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

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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%) as well as 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 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. Kantarjian H, Stein A, Gökbuget N*, et al*. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med*. 2017; 376: 836-847.

Sincerely,

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