Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Direct Dial: 800-772-6436
Fax: 866-292-6436

Vadim Romanov, MD, MPhil, FFPM
Medical Director
United States Medical Lead Blincyto® (blinatumomab)
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
vromanov@amgen.com

Date of request: October 3, 2016

NCCN Guidelines Panel: Acute Lymphoblastic Leukemia

Change requests for R/R Ph- ALL

On behalf of Amgen, I respectfully request that the NCCN Clinical Practice Guidelines for Acute Lymphoblastic Leukemia be revised to reflect the availability of phase 3 study data demonstrating that immunotherapy product blinatumomab improved overall survival in patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (R/R B-CP ALL) compared to standard of care i.e. chemotherapy treatment.

Clinical Data

The Phase 3 TOWER study was a randomized, open-label study that investigated the effect of blinatumomab compared to standard of chemotherapy on the overall survival of patients with R/R Ph- B-CPALL. 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 two weeks off therapy. Predose 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). The primary analysis was scheduled to be conducted after 330 deaths had accrued. This prespecified interim analysis by an independent data monitoring committee (DMC) occurred after 248 deaths (75%).

In the TOWER study, 405 patients were randomized to blinatumomab (n = 271) or SOC (n = 134) and analyzed for efficacy. There was a balance of baseline characteristics between the treatment groups (blinatumomab, SOC chemo): median age (37y, 37y); median bone marrow blasts (80%, 79%); prior salvage therapy (56%, 52%); and prior allogeneic stem cell transplant (SCT) (35%, 34%). Based on the DMC analysis, median OS was 7.8 months (95%CI: 5.7, 10.0) for blinatumomab and 4.0 months (95%CI: 2.9, 5.4) for SOC (stratified log-rank test p - .011; hazard ratio – 0.71), that surpassed the prespecified O'Brien-Fleming boundary *p* value of 0.0183. The improvement in OS was consistent between subgroups based on age, prior salvage therapy, and prior alloSCT. Patients that received blinatumomab exhibited higher response rates versus SOC, including CR (39% vs 19%; p<.001) and CR/CRh/CRi (46% vs 28%; p=.001).

A total of 373 patients had received at least one dose of blinatumomab (N=266) or SOC (N=107; 47 FLAG ± anthracycline, 19 HiDAC-based; 22 high-dose methotrexate-based, and 19 clofarabine-based regimens) and were analyzed for safety. At least two cycles of therapy were started in 57% of (blinatumomab treated) and 25% (of SOC chemo treated) patients. Safety outcomes were similar between patients receiving blinatumomab and SOC therapy (table 1).

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Direct Dial: 800-772-6436
Fax: 866-292-6436

	Blinatumomab (N=266)	SOC chemo (N=107)
Any AE, % (per 100 patient-months)	99% (631.3)	99% (764.4)
Any grade 3 AE, %	38%	34%
Any grade 4 AE, %	29%	40%
Any grade 5/fatal AE, %	19%	19%
Grade 5 infection, %	11%	12%
Any serious AE, % (per 100 patient-months)	62% (26.4)	45% (38.1)
Infection, %	28%	31%
Blood/lymphatic, %	14%	16%
Nervous system, %	7%	3%
Cytokine release syndrome, %	3%	0%

Table 1: Incidence Rates of Adverse Events (AE), Regardless of Causality

In addition, the adverse events in the blinatumomab group were consistent with previous studies.

Based on these findings, the DMC recommended that the study be stopped for efficacy before the planned final analysis. Amgen has followed recommendation of DMC and the study was stopped for efficacy in February 2016.The aforementioned results are based on DMC data.

The TOWER study is the first and so far the only randomized controlled study to demonstrate an OS benefit in this difficult-to-treat patient population of R/R Ph- B-Cell precursor ALL patients over current standard of care i.e. chemotherapy.

Please note that the full manuscript describing the aforementioned TOWER study was submitted and accepted for publication. Although, I am unable to supplement this submission with a publication at this time, I do commit to providing this information to the NCCN panel as soon as the publication becomes available.

Supporting Documentation

The following data have been submitted in support of this request.

1. Topp M *et al.* 21st Congress of the European Hematology Association (Release date: May 19, 2016) Abstract S149

Sincerely,

Vadim Romanov, MD, MPhil, FFPM

Medical Director

United States Medical Lead- Blincyto® (blinatumomab)

vromanov@amgen.com