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NCCN Guidelines Panel: Pediatric Acute Lymphoblastic Leukemia (ALL)

Request for Guideline Review in Relapsed/Refractory Pediatric ALL

On behalf of Amgen, I respectfully submit for consideration of the panel, that the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia be updated to include data from the Children's Oncology Group (COG) AALL1331 study that demonstrated superior efficacy and tolerability of blinatumomab as post-induction consolidation in high- and intermediate-risk (HR/IR) patients with B-cell precursor acute lymphoblastic leukemia (B-ALL) in first relapse compared with standard of care chemotherapy. This is different and complementary to the current recommendation for the use of blinatumomab in first relapse patients (induction for first relapse following allogeneic hematopoietic stem cell transplantation [HSCT], and consolidation for minimal residual disease [MRD] positive complete response).

FDA Approved Indications

BLINCYTO® (blinatumomab) is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with:

- B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%
- Relapsed or refractory B-cell precursor acute lymphoblastic leukemia

Clinical Data

COG AALL1331 is a randomized phase 3 trial comparing blinatumomab versus chemotherapy as post-reinduction therapy in first relapse of B-ALL in children and adolescents and young adults (AYA). Any B-ALL patient between age 1-30 years in first relapse was eligible to enroll. All patients initially enrolled received one uniform reinduction block of standard of care chemotherapy (UKALLR3). Patients were then randomized into one of four treatment arms based on risk as follows: treatment failure, high risk, intermediate risk, and low risk. Risk stratification was determined by time to relapse, site of relapse, and end of induction MRD (for intermediate and low risk groups). Intermediate risk (IR) and high risk (HR) patients were grouped together as prior studies have shown similar survival. Data are only available for the HR/IR group to date. The HR/IR group were randomized 1:1 to a control chemotherapy arm A or experimental arm B. The primary endpoint was disease free survival (DFS). Key secondary endpoints included overall survival, MRD response, and the ability to proceed to HSCT.

Arm A included two additional blocks of consolidation chemotherapy based on the UKALLR3 regimen followed by HSCT. The experimental treatment arm B included two blocks (cycles) of blinatumomab followed by HSCT. Blinatumomab was administered at a dose of 15 mcg/m^2/day via continuous IV infusion for 28 days followed by a 7-day treatment free interval. Pre-dose dexamethasone was administered to help prevent cytokine release syndrome (CRS).

Early closure of accrual in the HR/IR group and immediate crossover to blinatumomab for patients receiving chemotherapy was recommended by the data safety monitoring committee (DSMC) at a scheduled review in September 2019, although the monitoring threshold of expected events for DFS had not been crossed. This recommendation was based on the clinically and statistically significant difference in toxicity between treatment arms favoring blinatumomab, the significantly higher difference in MRD clearance of blinatumomab compared with control, and DFS and OS results supporting blinatumomab.

In total, 208 HR/IR patients were randomized (chemotherapy arm A: 103, blinatumomab arm B: 105). With a median follow up of 1.5 years, the intent-to-treat (ITT) 2-year DFS (% ± standard error) was 59.3±5.4% in the blinatumomab

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arm versus 41.0±6.2% for the chemotherapy arm (p=0.050, one-sided pre-specified statistical plan). The ITT 2-year OS in the blinatumomab arm was 79.4±4.5% compared to 59.2±6.0% in the chemotherapy arm (p=0.005, one-sided pre-specified statistical plan).

MRD clearance was evaluated among patients with detectable MRD (≥0.1%) at the end of the first chemotherapy block. At the end of cycle 1/block 2, 76% of patients that received blinatumomab had undetectable MRD (<0.01%) compared with 29% of patients on the chemotherapy arm (p<0.0001). The rate at which patients successfully proceeded to HSCT following randomization varied significantly between the two treatment groups. In the blinatumomab arm, 73% of patients proceeded to HSCT while 45% of patients on the chemotherapy arm proceeded to HSCT (p<0.0001).

Rates of CTCAEv4 grade ≥3 febrile neutropenia, infection, sepsis, and mucositis were significantly higher in the chemotherapy arm (block 2/3) compared to the blinatumomab arm (cycle 1/2), (p<0.001 for all comparisons except mucositis chemotherapy block 3 vs. blinatumomab cycle 2, p=0.16) (Table1). Four patients in the chemotherapy arm died post-induction (all due to infection), with no deaths reported in the blinatumomab arm (p=0.05). Blinatumomab related adverse events (AEs) included CRS, neurotoxicity, seizure, and other encephalopathic AEs (Table 2). Blinatumomab related AEs fully resolved.

Table 1. Rate of CTCAEv4 Grade ≥3 Adverse Events

Rate of CTCAEv4 Grade ≥3 Adverse Events				
	Chemotherapy Block 2 (%)	Chemotherapy Block 3 (%)	Blinatumomab Cycle 1 (%)	Blinatumomab Cycle 2 (%)
Febrile Neutropenia	44	46	4	0
Infection	41	61	10	11
Sepsis	14	21	1	2
Mucositis	25	7	0	1

Table 2. Rate of Blinatumomab Related Adverse Events

Rate of Blinatumomab Related Adverse Events				
	Blinatumomab Cycle 1		Blinatumomab Cycle 2	
	Any Grade (%)	Grade 3-4 (%)	Any Grade (%)	Grade 3-4 (%)
CRS	22	1	1	0
Neurotoxicity	18	3	11	2
Seizure	4	1	0	0
Other (Encephalopathic)	14	2	11	2

In short, blinatumomab demonstrated superiority to standard of care chemotherapy as a post induction consolidation therapy in children and AYA patients with HR/IR first relapse of B-ALL.

Supporting Documentation

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

- Brown P, Ji L, Xu X, et al. Slides presented at the 61st Annual Meeting and Exposition of the American Society of Hematology; December 7-10, 2019; Orlando, FL. Abstract #LBA-1
- Brown P, Ji L, Xu X, et al. A randomized phase 3 trial of blinatumomab vs chemotherapy as post-reinduction therapy in high and intermediate risk (HR/IR) first relapse of B-acute lymphoblastic leukemia (B-ALL) in children and adolescents (AYAs) demonstrates superior efficacy and tolerability of blinatumomab. A report from Children's Oncology Group Study AALL 1331. *Blood*. 2019;134(suppl 2):LBA-1.

Sincerely,

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