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Date of request: December 10, 2020
NCCN Guidelines Panel: Acute Lymphoblastic Leukemia (ALL)

To Whom It May Concern:

On behalf of Amgen, I respectfully request the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia Panel review the enclosed updated data for BLINCYTO® (blinatumomab) pertaining to use in adult patients with Philadelphia chromosome-positive (Ph+) B-cell precursor acute lymphoblastic leukemia (B-ALL) and consider updating the guideline recommendations accordingly. This submission request has been updated since the prior request submitted in April 2020 and is based on a recent publication of the previously submitted D-ALBA study data in the New England Journal of Medicine.

Specific Changes:

Taking this newly published data into account, please consider (1) adding a recommendation for the use of blinatumomab in combination with a tyrosine kinase inhibitor (TKI) as consolidation therapy in adolescent and young adult (AYA) and adult patients with newly diagnosed (ND) Ph+ B-ALL, and (2) adding a recommendation for the use of blinatumomab in combination with a TKI for AYA and adult patients with relapsed or refractory (R/R) Ph+ B-ALL.

FDA-Approved Indications:

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

- B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) ≥ 0.1%
- R/R B-cell precursor ALL

Rationale:

This updated submission is based on recent data published in the New England Journal of Medicine from a Phase 2 study in newly diagnosed adult patients (range: 24 to 82 years of age) with Ph+ B-ALL and summarized results of existing published medical literature in the R/R setting demonstrating efficacy and safety of blinatumomab in combination with a TKI.[1-6]

Newly Diagnosed Ph+ B-ALL

The GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) cooperative trial group has adopted a chemotherapy-free treatment induction of TKI plus steroids for patients with ND Ph+ ALL, which has resulted in CR rates of up to 100%.[1]

GIMEMA LAL2116 D-ALBA was a multicenter phase 2 study that evaluated the efficacy and safety of combining blinatumomab with dasatinib as consolidation therapy following this chemotherapy-free treatment induction with the aim of inducing a deeper and more durable response through molecular remission.[1]

The primary objective was to evaluate the rate of patients who achieved complete molecular remission (CMR) or positive non-quantifiable (PNQ) disease after a minimum of two cycles of blinatumomab. Other endpoints included overall survival (OS), disease-free survival (DFS), cumulative incidence or relapse (CIR), and safety.[1]

Sixty-three patients were enrolled, with a median follow-up of 18 months (range: 1 - 25). At the end of the induction period, and prior to blinatumomab initiation, 17 of 59 (29%) patients had a molecular response. At the end of Cycle 2 of blinatumomab, the primary endpoint, the molecular response rate increased to 60%, and continued to increase with subsequent cycles of blinatumomab (Table 1). With the median follow-up of 18 months, OS was 95% (95% CI: 90 - 100) and

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DFS was 88% (95% CI: 80 - 97). Blinatumomab cleared all *ABL1* mutations (including T315I) that occurred during induction, which are known to be associated with TKI resistance.[1]

Table 1. Molecular Responses[1]

	CMR (%)	PNQ (%)	CMR and PNQ (%)
Day +85 (post induction)	6 (10)	11 (19)	17 (29)
Post Cycle 1	19 (36)	16 (29)	35 (64)
Post Cycle 2 (primary endpoint)	23 (42)	10 (18)	33 (60)
Post Cycle 3	20 (50)	8 (20)	28 (70)
Post Cycle 4	17 (47)	12 (33)	29 (81)
Post Cycle 5	16 (55)	5 (17)	21 (72)

There were four study deaths, one during induction, two during complete hematologic response (CHR), and one patient after disease progression after allogeneic stem-cell transplantation (HSCT). Six relapses occurred. Overall, 60 adverse events were reported in 28 patients. Adverse events of grade 3 or higher included: cytomegalovirus (CMV) reactivation or infection, n=6; neutropenia, n = 4; persistent fever, n = 2; pleural effusion, n= 1; pulmonary hypertension, n = 1; neurologic disorder, n = 1.[1]

Relapsed/Refractory Ph+ B-ALL

Data from studies investigating blinatumomab in combination with TKIs in adult patients with R/R Ph+ ALL have been published in the literature. The efficacy and safety results are summarized in Table 2. Overall, the authors concluded the combination of blinatumomab and TKI was a safe and effective strategy for treating patients with R/R Ph+ ALL.[2-6]

Table 2. Blinatumomab in Combination with TKI in R/R Ph+ ALL Outcomes

Study (N)	Safety Outcomes	Efficacy Outcomes
Sokolov et al (N = 11)[2]	Gr2 neurotoxicity, n = 2	9/11 patients achieved molecular CR
Assi et al (N = 12)[3]	Gr 2 CRS, n = 2; Blinatumomab-related Gr 3 neurotoxicity, n =2	9/12 patients achieved molecular response
Hanif et al (N = 5)[4]	No evidence of CRS or neurotoxicity	3/5 patients achieved CMR
King et al (N=11)[5]	G1 CRS, n = 3; Neurotoxicity, n = 1	8/9 patients achieved CMR
Couturier et al (N=23)[6]	6 deaths (2 bacterial infections, 2 fungal infection, 1 secondary cancer and 1 ALL relapse)	20/22 patients achieved CMR

Supporting Documentation

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

1. Foà R, Bassan R, Vitale A, et al. Dasatinib-blinatumomab for ph-positive acute lymphoblastic leukemia in adults. *N Engl J Med*. 2020;383(17):1613-1623.
2. Sokolov AN, Parovichnikova EN, Troitskaya VV, et al. Blinatumomab + tyrosine kinase inhibitors with no chemotherapy in BCR-ABL-positive or IKZF1-deleted or FLT3-ITD-positive relapsed/refractory acute lymphoblastic leukemia patients: high molecular remission rate and toxicity profile. *Blood*. 2017;130:3884.
3. Assi R, Kantarjian H, Short NJ, et al. Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed philadelphia chromosome-positive leukemia. *Clin Lymphoma Myeloma Leuk*. 2017;17:897-901.
4. Hanif A, Wang ES, Thompson JE, et al. Combining blinatumomab with targeted therapy for BCR-ABL mutant relapsed/refractory acute lymphoblastic leukemia. *Leuk Lymphoma*. 2018;59(8):2011-2013.
5. King AC, Pappacena J, Tallman MS, et al. Blinatumomab administered concurrently with oral tyrosine kinase inhibitor therapy is a well-tolerated consolidation strategy and eradicates measurable residual disease in adults with philadelphia chromosome positive acute lymphoblastic leukemia. *Leukemia Research*. 2019;79:27–33.
6. Couturier M-A, Thomas X, Huguet F, et al. Blinatumomab + ponatinib for relapsed Ph1-positive acute lymphoblastic leukemia: the French experience. *Blood*. 2019;267247:PS946.

Sincerely,

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