FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland 20993
March 7, 2018

QUESTIONS

BLA 125557/S-013
Blincyto® (blinatumomab)
Applicant: Amgen, Inc.

PROPOSED INDICATION: For the treatment of minimal residual disease (MRD)-positive B-cell precursor acute lymphoblastic leukemia (ALL)

BACKGROUND

Approvals of new therapies for treatment of ALL have been based on measures demonstrating a meaningful rate of achieving and maintaining morphological complete remission. Patients who do not achieve a morphological complete remission after intensive chemotherapy are known to have a short survival.

Study 20120148 was a retrospective cohort study. The patients accrued to the study included 268 adults with Philadelphia chromosome (Ph)-negative B-cell precursor (BCP) ALL in first complete remission (CR1) with minimal residual disease (MRD) detected at a level of ≥ 0.01% (1×10^{-4}) by PCR or ≥ 0.1% (1×10^{-3}) by flow cytometry after at least 3 blocks of intensive chemotherapy. Patients with MRD levels < 0.01% or undetectable were excluded from the study. The table below shows the median relapse-free survival (RFS) of the patients by log-group of MRD at the observational baseline. FDA concluded that patients with ALL in CR1 within the log-groups with MRD ≥ 0.1% had a poor RFS.

Study 20120148 - Summary Descriptive Analysis of RFS by Baseline MRD Level

MRD Level at Observational Baseline	n	Median RFS (months)	95% CI
≥ 10%	15	2.0	1.0, 4.8
1% to < 10%	70	9.7	6.4, 17.3
0.1% to < 1%	108	10.6	7.0, 19.7
0.01% to < 0.1%	75	31.3	13.6, 75.4

Source: FDA analysis

Currently, there are no meta-analyses that demonstrate both trial-level and patient-level surrogacy of MRD for RFS or overall survival (OS) of patients with ALL in CR. Moreover, there are no studies addressing whether conversion from MRD-positive after 3 blocks of

intensive chemotherapy to MRD-negative with additional treatment other than HSCT correlates with clinical benefit.

EFFICACY

Study MT103-203 was a single-arm trial of up to 4 cycles of blinatumomab for treatment of patients with BCP ALL in CR or CR with partial platelet recovery and MRD $\geq$ 0.1%. The primary efficacy endpoint of MT103-203 was complete MRD response (defined as absence of detectable MRD using an assay with a sensitivity < 0.01%) after 1 cycle of blinatumomab. There were 116 patients treated with blinatumomab. From this group, FDA identified 87 patients in CR with hematologic recovery and baseline MRD $\geq$ 0.1%, including 61 patients in CR1, 25 in CR2 and 1 in CR3. A complete MRD response was achieved by 69 patients (79%; 95% CI: 70%, 88%). The estimated median hematological RFS was 22.3 months (25.6 months for patients in CR1 and 11.0 months for patients in CR2 or CR3). A propensity score analysis for the patients in first remission (with or without hematopoietic recovery) in Study MT103-203 and in Study 20120148 demonstrated that the RFS for the patients treated with blinatumomab was significantly greater than in the historical controls ($p<0.0001$ by log-rank; median 35.2 months vs 8.3 months, respectively), but several flaws in the analysis were identified by FDA.

SAFETY

The safety of blinatumomab for treatment of patients with ALL in CR with MRD-positivity was assessed in 137 adults from Study MT103-203 and a second single-arm trial, Study MT103-202. The safety profile of blinatumomab in this patient population was similar to that established for those treated for relapsed or refractory ALL. In the MRD-positive population, 2% had a fatal adverse event. Of the adverse events of special interest, 91% had fever, 69% had a neurologic toxicity, 7% had cytokine release syndrome, and 2% had sepsis. A grade $\geq$ 3 neurologic toxicity occurred in 15% and a grade $\geq$ 3 cytokine release syndrome in 3%.

QUESTIONS

1. **DISCUSSION**: Study MT103-203 included patients with MRD $\geq$ 0.1%. Do the available data support the cut-off of MRD $\geq$ 0.1% as describing a subpopulation of patients with ALL in CR who have a need for pre-emptive therapy?

2. **VOTE:** Do the results of MT103-203 demonstrate that for patients with ALL in CR who have MRD $\geq$ 0.1%, treatment with blinatumomab provides a potential benefit that outweighs the risks from the treatment?