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
May 14, 2019

QUESTIONS

NDA 212166
Quizartinib
Applicant: Daiichi-Sankyo, Inc.

PROPOSED INDICATION: Treatment of adults with relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD positive, as detected by an FDA-approved test.

BACKGROUND

Patients with acute myeloid leukemia (AML) that is refractory to or relapsed after a first-line regimen have a poor prognosis. The usual approach to treatment of such patients is with intensive combination cytotoxic chemotherapy or off-label use of low-intensity chemotherapy; gilteritinib is also approved for relapsed or refractory AML with a FLT3 mutation in particular. For patients who achieve a second complete remission (CR), allogeneic stem cell transplantation (HSCT) is considered the optimal approach to extend survival.

EFFICACY

Study AC220-007 was a randomized trial comparing quizartinib to standard-of-care chemotherapy for the treatment of adult patients with FLT3-ITD positive relapsed or refractory AML. Randomization was stratified by the type of preselected chemotherapy (intensive cytotoxic vs low-dose cytarabine) and response to prior therapy. The primary endpoint of the study was OS. Study outcomes were:

Study AC220-007: FDA Analysis of Efficacy Outcomes

	Quizartinib N=245	**Chemotherapy N=122**
Median OS (95% CI)	26.9 weeks (23.1, 31)	20.4 weeks (17, 25.2)
HR (95% CI)	0.77 (0.59, 0.99); p = 0.019	
Median EFS (95% CI)	6.0 weeks (0.1, 8.3)	3.7 weeks (0.4, 6.0)
HR (95% CI)	0.90 (0.71, 1.16); p = 0.114	
CR rate, n (%; 95% CI)	10/245 (4%; 2, 7%)	1/122 (1%; 0.1, 5%)
CR/CRh rate, n (%; 95% CI)	27/245 (11%; 8, 16%)	-
Achieved transfusion independence	26/99 (26%: 19, 36%)	-

ISSUE #1: Although Study AC220-007 was positive (HR 0.77; 95% CI 0.59, 0.99; p=0.019 as calculated by FDA), the significance was marginal, the OS results were not robust, the OS treatment effect appeared to be driven by the stratum of patients preselected for low-intensity chemotherapy, and the OS treatment effect may have been confounded by imbalances in poststudy therapy, including allogeneic HSCT. Additionally, analyses of other efficacy endpoints showed no statistically significant differences.

QUESTIONS (cont.)

SAFETY

The common (> 10%) adverse events during cycle 1 of quizartinib were nausea, anemia, QT prolonged, thrombocytopenia, pyrexia, hypokalemia, febrile neutropenia, vomiting, fatigue, diarrhea, neutropenia, white blood cell count decreased, platelet count decreased, neutrophil count decreased, headache and decreased appetite. There was also a 7% risk of events on the spectrum of differentiation syndrome with or without acute febrile neutrophilic dermatosis. The adverse events of special interest identified by the Applicant included infection, hemorrhage, hepatic disorders, QT prolongation, cardiac arrhythmias, and cardiac failure. In Study AC220-007, 27% of patients experienced at least one event of QT-prolongation. When compared to intensive chemotherapy or LDAC, the risk of cardiac events was substantially higher with quizartinib. Across the quizartinib clinical development program, the risk of on-treatment deaths due to cardiac events was estimated as 1-2%.

ISSUE #2: Quizartinib causes delayed cardiac repolarization by inhibition of IKs, a mechanism unique among non-antiarrhythmic drugs. Potential strategies to manage the risk of life-threatening or fatal cardiac events might include a contra-indication for use with drugs that prolong QT via the complementary IKr channel and a recommendation for administration of beta-blockers to prevent arrythmias.

QUESTIONS

1. **DISCUSSION:** Please discuss whether the results of the OS analysis of Study AC220-007 are persuasive evidence of effectiveness of quizartinib and the reasons for your opinion.

2. **DISCUSSION:** Please discuss the feasibility and adequacy of a) a contra-indication for use with drugs that prolong QT via the complementary IKr channel and b) a recommendation for administration of beta-blockers to prevent arrythmias as means to reduce the risk of life-threatening and fatal cardiac events resulting from IKs blockade if quizartinib is marketed.

3. **VOTE:** Do the results of Study AC220-007 demonstrate that treatment with quizartinib provides for a benefit that outweighs the safety risks for patients with relapsed or refractory FLT3-ITD-positive AML?