A phase Ib dose escalation study of oral monotherapy with KX2-391 in elderly patients with acute myeloid leukemia

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Background

Treatment of elderly patients with acute myeloid leukemia (AML) is complicated by poor tolerance to standard therapies, poor-risk cytogenetics, and multi-drug resistance [1, 2]. Recent advances have brought improvements in outcomes among this population. The addition of venetoclax (BCL2 inhibitor) to a hypomethylating agent has become standard of care among elderly patients unable to receive intensive induction chemotherapy and has contributed to an improvement in composite remission rates from about 30% to 66% [3]. The development of IDH1, IDH2, and FLT3 inhibitors has further broadened the therapeutic options, particularly in the relapsed and refractory setting [4–6]. But despite these advances, only a limited group of patients have the targetable mutations needed to make them candidates for IDH1/2 or FLT3 inhibitors, and the median overall survival remains under two years [3–6]. Because AML is largely a disease of the elderly [7, 8], it remains crucial to explore novel agents that both are tolerable and target alternative pathways.

A potential therapeutic target are the Src family kinases (SFKs). SFKs are activated in most AML cell lines regardless of cytogenetics, and there is evidence in mouse studies that...
Src inhibitors impair leukemia-initiating cells [9–11]. KX2-391 (tirbanibulin, KX01, KX-01, Athenex Pharmaceuticals) is a synthetic, orally active, highly selective inhibitor of both Src tyrosine kinase and tubulin polymerization [12]. Unlike other Src inhibitors, KX2-391 uniquely targets the peptide substrate-binding domain instead of the ATP-binding site. It selectively inhibits the Src-catalyzed transphosphorylation of focal adhesion kinase, Shc, paxillin, and Src kinase autophosphorylation with a half-maximal inhibitory concentration (IC$_{50}$) around 20 nM [12]. These Src-related tumor cell activities lead to the induction of p53, caspase-3 cleavage, and PARP cleavage, resulting in tumor cell apoptosis [12]. KX2-391 has a dual mechanism of action as it also inhibits tubulin polymerization by binding to a novel binding site on tubulin [12].

The half-maximal inhibitory concentration (IC$_{50}$) for Src inhibition by KX2-391 in human tumor cells in the presence of plasma was determined to be about 100 nM. However, the IC$_{50}$ to achieve tubulin polymerization inhibition in human tumor cells in the presence of plasma is about 500 nM. A KX2-391 concentration of 500 nM corresponds to a plasma concentration of 216 ng/mL [12, 13]. In solid tumor patients, analysis has shown that plasma levels of KX2-391 would likely only need to be above 142 ng/mL in order to engage the tubulin [12, 13]. Those plasma levels were achieved at 80 mg doses based on phase I pharmacokinetic data [14]. This is due to the fact that KX2-391 partitions into tumor tissue versus plasma at a ratio of 1.52, thereby reducing the required plasma concentration [12, 13].

In vitro and in vivo studies have demonstrated that KX2-391 has potent antitumor activity against a wide range of leukemia and solid tumor cell lines, including those that are resistant to commonly used cancer therapies such as dasatinib and imatinib [12, 15]. This includes three different human AML cell lines: KG-1, HL-60, and MV-4-11. The KX2-391 concentration causing 50 percent cell growth inhibition (GI$_{50}$) was 16 nM, 10 nM, and 21 nM in the three AML cell lines, respectively. In vitro, KX2-391 has a broader spectrum of activity and stronger potency than the ATP-binding Src inhibitor dasatinib [12]. In previous phase I trials, KX2-391 has been associated with the dose-limiting toxicity (DLT) of neutropenia, suggesting it should be clinically valuable against myeloid malignancies [14]. KX2-391’s highly selective mechanism of actions may lead to a better safety profile. It does not inhibit PDGFR, EGFR, JAK1, JAK2, LCK, or ZAP70. Unlike other tyrosine kinase inhibitors, toxicity studies have revealed no evidence of cardiomyopathy, peripheral edema, or pleural effusion suggestive of cardiac damage. This may be a result of the less potent inhibition of BCR-ABL and LYN. Peripheral neuropathy, commonly associated with tubulin inhibiting drugs, was also not seen with KX2-391 [12].

We conducted a phase I open-label safety, tolerability, and activity study to analyze KX2-391 in elderly patients with AML who have refractory or relapsed disease, or who have declined standard chemotherapy.

**Methods**

**Study design**

This phase Ib open-label, single arm study (NCT01397799) was conducted in three centers in the United States. The primary objective was to determine the maximum tolerated dose (MTD) of KX2-391 associated with approximately one-third (33.3%) dose-limiting toxicity rate during the first 28-day treatment cycle in elderly patients with AML who have relapsed or refractory disease, or who have declined standard chemotherapy. Secondary objectives included response rate, survival, pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability. DLT was defined as grade 3 or higher non-hematologic drug-related toxicity according to National Cancer Institute Common Terminology Criteria (CTCAE) version 4.0.3. Activity against AML was assessed through hematologic and bone marrow response according to International Working Group AML criteria [16] and by overall survival.

The enrollment of patients was based on Storer’s two-stage design [17]. In Stage 1, successive cohorts of patients received fixed (within each dose) and escalating (between cohorts) doses of KX2-391 along with a fixed dose of fluconazole 400 mg daily. Fluconazole was administered during the first 28 days of treatment to assess effects of antifungal therapy on PK and PD parameters. After cycle 1, antifungal prophylaxis was given at the discretion of the treating physician. KX2-391 oral solution or capsule (which demonstrated similar PK profiles) was dosed between 40 and 160 mg once daily for 28 days based on dose cohort and tolerance. Patients were observed for any DLT during that 28-day cycle. If no DLT was observed, the patient was given the opportunity to enroll in the extension cohort and continue on treatment at their current dose until disease progression, toxicity, or withdrawal of consent. The next patient was then enrolled on the next dose level (e.g. 40 mg dose increase). Escalation was continued until DLT was reached during cycle 1 at any dose level, at which point Stage 2 would begin.

In Stage 2, four successive cohorts of three subjects were enrolled in order to estimate the dose at which DLTs were observed in one-third (33.3%) of the patient population. In order to generate these data, the dose for each cohort of three patients was determined by the rate of DLT observed in the previous cohort. The dose of KX2-391 for the first cohort of three subjects in Stage 2 was 20 mg less than the
dose at which the first DLT was observed in Stage 1. Each cohort was evaluated individually in order to determine the dose level for the next cohort. Dose adjustments in 20 mg increments up or down were made depending on the prior cohort’s response. As in Stage 1, all patients received a fixed dose of fluconazole 400 mg for the first 28-day treatment cycle. Once all four cohorts completed assessments for DLT, the frequency of DLT at each dose level was used to determine the MTD, resulting in a 33.3% DLT rate.

The study was conducted in accordance with the Declaration of Helsinki and the International Council on Harmonization Good Clinical Practice Guideline. The study was approved by the institutional review board at all participating institutions. Written informed consent was obtained from all participating patients prior to inclusion.

Patients

Patients were eligible to enroll if they were between the ages of 60–80, had either de novo or secondary AML by 2008 World Health Organization classification [18] as documented by bone marrow biopsy with aspirate within 14 days of enrollment, had an Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2, had adequate liver and renal function, had a normal QTc, and had a life expectancy of at least six weeks.

Exclusion criteria included the following: more than two previous courses of AML remission-induction chemotherapy, acute promyelocytic or chronic myelogenous leukemia, persistent grade 2 or higher toxicity other than hematologic toxicities or alopecia from recent chemotherapy, recent investigational agent prior to starting KX2-391, central nervous system (CNS) involvement of AML or other malignancy, history of gastrointestinal malabsorption, inflammatory bowel disease, or upper gastrointestinal surgery, uncontrolled hypertension at time of dosing, history of hepatitis B or C, HIV, active uncontrolled systemic infection, concurrent active malignancy, significant cardiac disease, need for continued concurrent use of cytochrome P450 3A4 modulating medications other than fluconazole, active pregnancy, and inability to comply with the trial protocol.

Safety and response

Adverse events (AE) were graded according to CTCAE 4.0.3. In determining MTD, DLTs were assessed during the first 28-day cycle and consisted of any grade 3–4 non-hematologic toxicity. Response assessments included morphologic complete remission (CR), cyogenic CR, molecular CR, and partial remission (PR) based on bone marrow aspirate and biopsy, as well as survival duration. Plasma concentrations of KX2-391 were used to assess PK parameters, which included area under the concentration–time curve (AUC), maximum serum concentration (C_{max}), time to peak concentration (T_{max}), minimum concentration (C_{min}) and terminal half-life (t_{1/2}). PD parameters were assessed by blast reductions in the bone marrow. Peripheral blood was drawn for analysis of PK parameters on cycle 1 day 15 at pre-dose and at 1, 2, 4, and 6 h post-dose, as well as at the time of any change in dosing regimen. Bone marrow biopsies with aspiration were performed at screening and then on day 1 of cycle 2, day 1 of cycle 4, and day 1 of every fourth cycle thereafter. Safety was assessed by monitoring all AEs including serious AEs, with routine physical exams, blood counts, chemistry, urinalysis, and bone marrow biopsies.

Statistical analysis

Efficacy and safety data analyses were conducted on all patients who received at least one dose of KX2-391. Response, AEs, and PK and PD parameters were summarized with tables, figures, and data listings. Continuous variables were summarized using mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized by counts and percentage of patients in corresponding categories. Response was assessed by dose cohort. Individual PKs were graphed by serum concentration–time profiles. PD parameters were derived by bone marrow mononuclear cells obtained. PK parameters were generated to correlate with leukocyte count. Adverse events were summarized by type, grade, and associated dose.

Results

Patient characteristics

Twenty-four patients were enrolled from three institutions with an average age of 74 years (range 63–86). Eighteen patients were male, and six patients were female (Table 1). Seventeen patients (71%) were previously treated with hypomethylating agents.

Safety and tolerability

Five dosing levels were tested: 40 mg (n = 1, 4%), 80 mg (n = 2, 8%), 120 mg (n = 8, 33%), 140 mg (n = 12, 50%), and 160 mg (n = 1, 4%). The treatment durations were as follows: seven (29%) patients were on treatment for 12 days or less, nine (38%) for 15–29 days, five (21%) for 33–58 days, and three (15%) for 77 to 165 days. DLTs occurred in eight patients at the specified dosages: 120 mg (transaminitis, elevated bilirubin), 140 mg (mucositis, allergic reaction, transaminitis, acute kidney injury), and 160 mg (mucositis) (Table 2).
The most common (over 25%) treatment-related AEs were: nausea, vomiting, diarrhea, anorexia, fatigue, weakness, transaminitis, hypokalemia, hypotension, febrile neutropenia, dyspnea, abdominal pain, constipation, and dizziness (Table S1). The MTD for KX2-391 was determined to be 120 mg administered once daily.

### Table 1 Patient Demographics

| Daily Dose KX2-391 | 40 mg (N=1) | 80 mg (N=2) | 120 mg (N=8) | 140 mg (N=12) | 160 mg (N=1) | Total (N=24) |
|-------------------|-------------|-------------|--------------|---------------|--------------|--------------|
|                   | n (%)       | n (%)       | n (%)        | n (%)         | n (%)        | n (%)        |
| Sex               |             |             |              |               |              |              |
| Male              | 1 (100.0)   | 2 (100.0)   | 6 (75.0)     | 8 (66.7)      | 1 (100.0)    | 18 (75.0)    |
| Female            | 0           | 0           | 2 (25.0)     | 4 (33.3)      | 0            | 6 (25.0)     |
| Age               |             |             |              |               |              |              |
| <65               | 0           | 0           | 1 (12.5)     | 1 (8.3)       | 0            | 2 (8.3)      |
| ≥65               | 1 (100.0)   | 2 (100.0)   | 7 (87.5)     | 11 (91.7)     | 1 (100.0)    | 22 (91.7)    |
| Mean (Min–Max)    | 80          | 79.5        | 71.0         | 74.1          | 82           | 74.1         |
| Race              |             |             |              |               |              |              |
| Black or African American | 0   | 1 (50.0)    | 0            | 2 (16.7)      | 0            | 3 (12.5)     |
| White             | 1 (100.0)   | 1 (50.0)    | 7 (87.5)     | 10 (83.3)     | 1 (100.0)    | 20 (83.3)    |
| Other             | 0           | 0           | 1 (12.5)     | 0             | 0            | 1 (4.2)      |
| Days on Treatment |             |             |              |               |              |              |
| 0 to 15           | 0           | 1 (50.0)    | 3 (37.5)     | 4 (33.3)      | 1 (100.0)    | 9 (37.5)     |
| 16 to 30          | 0           | 0           | 2 (25.0)     | 5 (41.7)      | 0            | 7 (29.2)     |
| 31 to 60          | 1 (100.0)   | 1 (50.0)    | 1 (12.5)     | 2 (16.7)      | 0            | 5 (20.8)     |
| ≥61               | 0           | 0           | 2 (25.0)     | 1 (8.3)       | 0            | 3 (12.5)     |
| Mean (Min–Max)    | 35          | 34.5        | 55.4         | 26.6          | 12           | 36.6         |
| Primary Diagnosis |             |             |              |               |              |              |
| AML with myelodysplasia-related changes | 0 | 2 (100.0) | 6 (75.0) | 6 (50.0) | 1 (100.0) | 15 (62.5) |
| AML with minimal differentiation | 1 (100.0) | 0 | 1 (12.5) | 3 (25.0) | 0 | 5 (20.8) |
| AML without maturation | 0 | 0 | 1 (12.5) | 2 (16.7) | 0 | 3 (12.5) |
| AML with maturation | 0 | 0 | 0 | 1 (8.3) | 0 | 1 (4.2) |

Min Minimum Max Maximum AML Acute myeloid leukemia

The most common (over 25%) treatment-related AEs were: nausea, vomiting, diarrhea, anorexia, fatigue, weakness, transaminitis, hypokalemia, hypotension, febrile neutropenia, dyspnea, abdominal pain, constipation, and dizziness (Table S1). The MTD for KX2-391 was determined to be 120 mg administered once daily.

### Table 2 Summary of Dose-Limiting Toxicities

| Daily Dose KX2-391 | 40 mg (N=1) | 80 mg (N=2) | 120 mg (N=8) | 140 mg (N=12) | 160 mg (N=1) | Total (N=24) |
|-------------------|-------------|-------------|--------------|---------------|--------------|--------------|
|                   | n (%)       | n (%)       | n (%)        | n (%)         | n (%)        | n (%)        |
| Subjects experiencing a DLT DLT | 0 | 0 | 2 (25) | 5 (41.7) | 1 (100.0) | 8 (33.3) |
| Adverse event     |             |             |              |               |              |              |
| Mucositis         | 0           | 0           | 0            | 1 (8.3)       | 1 (100.0)    | 2 (8.3)      |
| Allergic reaction to drug | 0 | 0 | 0 | 1 (8.3) | 0 | 1 (4.2) |
| Acute kidney injury | 0 | 0 | 0 | 1 (8.3) | 0 | 1 (4.2) |
| Laboratory abnormalities | | | | | | |
| ALT increased     | 0           | 0           | 1 (12.5)     | 1 (8.3)       | 0            | 2 (8.3)      |
| AST increased     | 0           | 0           | 1 (12.5)     | 1 (8.3)       | 0            | 2 (8.3)      |
| Bilirubin increased | 0 | 0 | 1 (12.5) | 0 | 0 | 1 (4.2) |

DLT Dose-limiting toxicity ALT Alanine aminotransferase AST Aspartate aminotransferase

*One subject had grade 3 DLTs of increases in AST and ALT. The dose was reduced to 100 mg, and the adverse events resolved.*
Pharmacokinetics

Following once daily dosing, the median KX2-391 plasma C\textsubscript{max} values achieved following 120 mg and 140 mg doses were 218 ng/mL (range 138–292 ng/mL) and 299 ng/mL (range 120–568 ng/mL), respectively. The median plasma AUC values were 561.95 ng*hr/mL (range 513.99–1006.49 ng*hr/mL) and 855 ng*hr/mL (range 444.73–1238 ng*hr/mL). Pharmacokinetic data for 40 mg and 80 mg doses were limited with only one subject per group (Table 3, Fig. S1).

The KX2-391 concentrations in the bone marrow aspirate were roughly similar to those in the plasma at the closest available time points (Fig. 1). Plasma concentrations of KX2-391 appear to follow a monoexponential decay following once daily oral dosing (Fig. S1).

| Dose (mg) | Cycle | Day | Formulation | Tissue | Subject | T\textsubscript{1/2} (hr) | C\textsubscript{max} (ng/mL) | AUC (ng*hr/mL) | Vz/F (L) | Cl/F (L/hr) |
|-----------|-------|-----|-------------|--------|---------|----------------|----------------|----------------|---------|------------|
| 40        | 1     | 15  | Solution    | Plasma | 009–02  | NA             | 53.90          | 183.56         | NA      | NA         |
| 80        | 1     | 15  | Solution    | Plasma | 009–03  | 3.11           | 212.00          | 568.27         | 441.39  | 98.45      |
| 120       | 1     | 15  | Capsule     | Plasma | 010–16  | NA             | 257.00          | 1006.49        | NA      | NA         |
| 120       | 1     | 15  | Solution    | Plasma | 010–17  | NA             | 138.00          | 513.99         | NA      | NA         |
|           |       |     |             |        | 011–12  | 3.36           | 218.00          | 781.34         | 532.62  | 110.02     |
|           |       |     |             |        | 011–13  | 1.41           | 292.00          | 558.66         | 410.78  | 202.52     |
|           |       |     |             |        | 011–14  | 1.67           | 213.00          | 561.95         | 455.39  | 188.66     |
| 120       | 1     | 15  | Solution    | Plasma | 010–04  | 2.08           | 177.00          | 478.46         | 635.68  | 211.48     |
| 140       | 1     | 15  | Capsule     | Plasma | 010–06  | NA             | 241.00          | 723.15         | NA      | NA         |
|           |       |     |             |        | 010–09  | 1.87           | 240.00          | 660.10         | 498.06  | 184.70     |
|           |       |     |             |        | 010–11  | 1.95           | 269.00          | 915.91         | 366.01  | 130.36     |
|           |       |     |             |        | 011–01  | 1.88           | 568.00          | 1127.28        | 297.74  | 109.67     |
|           |       |     |             |        | 011–02  | NA             | 350.00          | 795.95         | NA      | NA         |
|           |       |     |             |        | 011–03  | NA             | 120.00          | 444.73         | NA      | NA         |
|           |       |     |             |        | 011–04  | NA             | 329.00          | 1125.55        | NA      | NA         |
|           |       |     |             |        | 011–08  | 1.56           | 446.00          | 1238.00        | 229.22  | 101.88     |
| 120       | 2     | 1   | Capsule     | Plasma | 010–18  | 1.74           | 204.00          | 688.30         | 317.26  | 126.48     |
| 120       | 2     | 1   | Capsule     | Plasma | 011–02  | NA             | 114.00          | 386.40         | NA      | NA         |

\( T_{1/2} \) Terminal elimination half-life, \( C_{\text{max}} \) Maximum serum concentration, AUC Area under the concentration–time curve, Vz/F Volume of distribution relative to the fraction of the dose absorbed based on terminal phase, Cl/F Clearance relative to the fraction of the dose absorbed, NA Not applicable, Pharmacokinetic parameter could not be determined due to the lack of time points in the terminal phase, SD Standard Deviation, Min Minimum, Max Maximum
Antitumor activity

One patient receiving 120 mg of KX2-391 was treated for 154 days until developing disease progression. A second patient receiving 120 mg was treated for 165 days until disease progression. This patient had a reduction in splenomegaly from 16 to 4 cm below the costal margin. In addition, the patient had an increase in platelets from 61,000 to 78,000/μL and a decrease in blasts detected in bone marrow aspirate from 43 to 15% after initiation of KX2-391. This patient had a Cmax of 213 ng/mL on cycle 1 day 15. This patient survived 373 days. One patient treated at 160 mg for 12 days survived 564 days from KX2-391 initiation and 552 days from the last dose of study drug. This patient was treatment-free for about 18 months.

Discussion

Low treatment rates compounded by poor response due to unfavorable cytogenetics and multi-drug resistance calls for novel agents and treatment approaches for elderly patients with AML. SFKs are a potential therapeutic target given their activation in most AML cell lines despite the heterogeneity in this disease. However, the tyrosine kinase inhibitors have been limited by their lack of selectivity [11]. KX2-391 is a synthetic, orally available, small molecule that has a dual mechanism of action as a highly selective Src kinase inhibitor and tubulin polymerization inhibitor. Compared to other Src kinase inhibitors, it is unique in that it targets the peptide substrate-binding domain instead of the ATP-binding site. KX2-391 has been shown to have potent activity against several drug-resistant solid and liquid cancer cell lines, as well as in a mouse model of chronic myeloid leukemia [12]. This is the first phase I trial to evaluate KX2-391 in elderly patients with relapsed or refractory AML, or who have declined standard chemotherapy. In the current trial, the MTD of KX2-391 was established to be 120 mg once daily. Overall, KX2-391 was well tolerated. The most common DLTs were grade 3 liver toxicity and mucositis, with one patient having grade 4 kidney injury. These occurred between 120–160 mg dosing and were not consistently observed between patients. This raises the question of whether there may be a higher MTD in healthier patients.

The plasma concentration achieved with the 120 mg daily dose level exceeds the IC50 target of 142 ng/mL needed to achieve microtubule interruption as established in solid tumors [13]. However, it just reaches the goal of 216 ng/mL for a short time, which is needed to achieve microtubule interruption in liquid tumors [12]. Unlike in solid tumors, where the concentration of KX2-391 was found to be higher in tumor tissue compared to plasma, the concentration of KX2-391 is not increased in the bone marrow. Instead, it was roughly comparable to the nearest time relevant plasma concentrations. Despite this, looking at the potential efficacy of KX2-391, there was an approximate linear correlation between both the KX2-391 AUC and Cmax and the percent change in blasts in the bone marrow aspirate (Fig. 2).

In our study, one patient receiving 120 mg was treated for 154 days prior to disease progression. This patient had previously been treated with azacitidine. Another patient receiving 120 mg was treated for 165 days prior to disease progression. This patient had previously been treated with decitabine, as well as cytarabine and daunorubicin. Following initiation of KX2-391, this patient had a 75% reduction in spleen size. The patient had an over 50% decrease in blasts detected in bone marrow aspirate and an increase in platelet count to 78,000/μL, with an absolute neutrophil count of 1220/μL. Although the platelet count did not reach the 100,000/μL threshold, the change in bone marrow blast percentage of over 50% and the absolute neutrophil count greater than 1000/μL meet hematologic criteria for partial remission [16]. This patient survived for 373 days, specifically 208 days after the last dose of KX2-391.
Interestingly, one trial patient was treated with 160 mg daily for only 12 days, after which KX2-391 was stopped due to Grade 3 mucositis. This patient, who had previously been treated with azacitidine, survived for 564 days from treatment initiation with KX2-391 and remained treatment-free for about 18 months. Based on these findings, higher single daily doses may be more effective in AML. Further investigation of alternate dosing regimens, including shorter courses with higher doses or intermittent dosing with drug free days would be of interest to optimize efficacy. These types of regimens may allow for an ideal balance between limiting toxicities and maximizing efficacy. Nevertheless, even among patients who previously received standard AML therapies, KX2-391 shows early evidence of antileukemic activity as an oral monotherapy. These considerations are especially important in elderly patients with AML whose treatment is often complicated by medical comorbidities and attempts to minimize hospitalizations, in addition to multi-drug resistance and poor-risk cytogenetics. In conclusion, KX2-391 is overall well tolerated among elderly patients with AML at a MTD of 120 mg daily. KX2-391 demonstrates preliminary evidence of antitumor activity warranting further research.

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Data availability The datasets generated during the current study are available from the corresponding author on request.

Declarations

Ethics approval The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki, the International Council on Harmonization Good Clinical Practice Guideline, the US Code of Federal Regulations dealing with clinical studies, as well as the ethical standards of the participating institutional committees.

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Consent to publish Not Applicable.

Competing interests Douglas Kramer and David G. Hanguer were employed at Athenex Pharmaceuticals. All remaining authors declare no financial or non-financial competing interests.

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