

Phase 1 study of rogocekib in patients with relapsed or refractory hematologic malignancies

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Key Points

- Rogocekib (CTX-712), a pan-CDC2-like kinase inhibitor, showed tolerable safety in relapsed/refractory AML and higher-risk MDS.
- The overall response rate was 42.9%, with promising activity in patients, including those with splicing factor mutations.

Rogocekib (development name CTX-712) is a first-in-class, orally available, highly potent, and selective small-molecule inhibitor of CDC2-like kinase, a key regulator of the RNA splicing process. Preclinical studies demonstrated antiproliferative activity on various in vitro and in vivo models of hematologic malignancies. Based on these findings, a phase 1 study of rogocekib was conducted to evaluate the safety and preliminary efficacy in patients with relapsed or refractory acute myeloid leukemia (AML) and higher-risk myelodysplastic syndrome (MDS). Using a 3+3 design informed by previous solid tumor safety data, patients received 70 mg or 105 mg twice a week in capsule form. One dose-limiting toxicity of grade 4 pneumonia was observed in the 105 mg twice a week cohort. Among 12 patients with AML, complete remission (CR) was observed in 3 patients (25.0%), and CR with incomplete hematologic recovery was observed in 1 patient (8.3%). In patients with MDS (n = 2), CR was observed in 1 patient (50.0%). Pharmacokinetics analyses showed higher mean maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to 24 hours post dose (AUC_{0-24}) of rogocekib at 105 mg compared with 70 mg. Pharmacodynamics analysis showed that the relative magnitude of exon skipping in peripheral blood cells increased with exposure to rogocekib. Rogocekib demonstrated a manageable and tolerable safety profile in patients with hematologic malignancies. Currently, a phase 1/2 study of rogocekib in relapsed/refractory AML and higher risk MDS is ongoing in the United States ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05732103) identifier: NCT05732103). This trial was registered at the Japan Registry of Clinical Trials as jRCT2080224127.

Introduction

RNA splicing is a major mechanism and essential part of gene transcription. RNA splicing processes immature pre-messenger RNA (pre-mRNA) transcripts by removing unnecessary introns and producing mature mRNA. This process is highly coordinated and mediated through the spliceosome

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Chordia Therapeutics supports responsible data transparency to advance scientific understanding while safeguarding participant confidentiality. The study protocol is included in this publication and its supplemental materials. Additional anonymized data may be made available to qualified researchers upon request, after completion of all planned analyses and regulatory approval of the indication. Requests will be reviewed for scientific merit and feasibility, and access will be granted upon execution

of a data use agreement. For inquiries, please contact Chordia Therapeutics at <https://www.chorditherapeutics.com/en/contact.html>.

The full-text version of this article contains a data supplement.

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complex comprising 5 small nuclear ribonucleoproteins. Somatic mutations of proteins within these components of the spliceosome complex are highly recurrent in myeloid neoplasms such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).^{1,2} Among these mutations, the mutated genes most commonly seen in AML/MDS are in the splicing factors *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, etc. Mutations in these genes have been shown to induce aberrant splicing changes and have been shown to confer worse overall survival (OS) and dismal outcomes for patients with myeloid neoplasms.^{3,4} As such, these mutations have recently been defined as “adverse” risk mutations by the European LeukemiaNet (ELN) 2022 guidelines.⁵ To date, there are no approved medications that specifically target splicing factor mutations (SFms).

Rogocekib (developmental name CTX-712) is an orally available, potent, and selective small-molecule inhibitor of CDC2-like kinase (CLK) family. Rogocekib dephosphorylates serine/arginine-rich proteins that are targeted by CLK and induces additional aberrant RNA deregulation stress by producing primarily exon-skipped splicing changes. This global increase in splicing changes may lead to cell death in cancer cells that are already exposed to elevated stress. Through this mechanism, rogocekib has shown significant in vitro and in vivo antileukemia activity in preclinical AML cell models, including patient-derived xenograft (PDX) AML models harboring SFms.⁶ These preclinical data also showed a positive correlation between splicing inhibition and increased antitumor efficacy.⁶ Altogether, the mechanistic and efficacy data from preclinical models support the clinical evaluation of rogocekib in hematologic malignancies.

Based on the preclinical efficacy and safety data, a phase 1 trial of rogocekib in malignant tumors was initiated in Japan. From the initial safety data in solid tumors, dose-escalation cohorts in hematologic malignancies were initiated at 2 dose levels to assess the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT), and to determine the recommended dose for the next phase. Here, we report the final results from the phase 1 study including the safety, tolerability, pharmacokinetics, pharmacodynamics, genetic analysis, and efficacy of rogocekib in relapsed or refractory AML and MDS.

Methods

Study design

This was a first-in-human, open-label, multicenter, phase 1 clinical study conducted in Japan in patients with advanced, relapsed, or refractory hematologic malignancies. The primary objectives of this trial were to assess the MTD and the DLT to determine the recommended dose. The secondary objectives evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics, and preliminarily evaluated the antitumor efficacy of rogocekib. In addition, to preliminarily evaluate the efficacy of the study drug in patients with AML or MDS, OS, relapse-free survival, event-free survival (EFS), and response rate were assessed as efficacy end points. The adverse events of rogocekib were assessed in accordance with the National Cancer Institute common terminology criteria for adverse events, version 5.0 translated into Japanese. Patients were assessed for response at cycle 2 day 1, cycle 3 day 1, and every subsequent odd numbered cycle on day 1 based on the ELN 2017 guidelines for patients with AML or the International Working Group 2006 guidelines for MDS.^{7,8}

Patients

Patients aged ≥ 20 years who were diagnosed with MDS, chronic myelomonocytic leukemia (CMML), or AML (excluding acute promyelocytic leukemia) according to the World Health Organization classification revised fourth edition and Eastern Cooperative Oncology Group performance status of 0 or 1 were considered eligible for the trial if they had been unresponsive to standard therapies or ineligible for appropriate standard therapies. For patients with MDS, patients with a revised International Prognostic Scoring System⁹ risk category of intermediate or higher were eligible. Patients with transformation from MDS or CMML to AML were eligible for treatment, provided that they had been treated with standard therapies for MDS or CMML. Patients were ineligible for treatment if they had symptomatic central nervous system involvement that required treatment. Patients who had multiple cancers were also ineligible for treatment except for those who did not require any treatment.

Treatment

Dose escalation cohorts in hematologic malignancies were conducted using safety information from dose escalation cohorts conducted in patients with solid tumors. From the solid tumors cohorts, the MTD was initially determined to be 140 mg twice a week after careful discussion with the safety monitoring committee members.¹⁰ For this trial, because the patient population was expected to include older adult patients, a 3+3 dose escalation design was started with a starting dose of 105 mg twice a week and included a dose range not exceeding the MTD. For this hematologic malignancies cohort, 2 dose levels were assessed and administered orally using a capsule formulation of rogocekib. Dosing was performed over a 28-day cycle at either 70 mg or 105 mg (twice a week). To mitigate gastrointestinal (GI)-related toxicities, prophylactic antiemetics was encouraged with selection of proper medication chosen at the discretion of the treating physician.

The DLT evaluation period was 28 days from the first dose of rogocekib (the duration of the first cycle), during which patients were hospitalized and monitored for safety carefully. Patients were allowed to continue treatment until withdrawal due to an adverse event, physician decision, or progression of the primary disease. If study treatment was discontinued before disease progression, tumor assessment was continued until confirmation of disease progression, start of posttreatment therapy, or death, whichever occurred first.

Pharmacokinetics and Pharmacodynamics

For pharmacokinetic analyses, venous blood samples were collected before dosing, and after dosing at 0.5, 1, 2, 4, 6, 8, and 24 hours of days 1 and 18, before dosing of cycle 1 days 4, 11, and 25 in cycle 1; before dosing on day 1 in cycle 2, and day 1 of even numbered cycle thereafter. Plasma concentration of rogocekib was assayed with liquid chromatography–tandem mass spectrometry. For pharmacodynamic analyses, peripheral blood samples were collected before dosing, and after dosing at 0.5, 1, 2, 4, 6, 8, and 24 hours of day 1 in cycle 1 followed by RNA extraction. The relative magnitude of exon skipping in *S6K* (alias of *RPS6KB1*) and *THAP9-AS1* was calculated as fold change using real-time polymerase chain reaction (PCR). The details of the calculation method are provided in the supplemental Methods.

Exploratory genetic biomarkers

To assess potential biomarkers for patient stratification, bone marrow aspiration or biopsy samples were collected from patients at screening. Patients had genetic results analyzed using Qiagen Comprehensive Cancer Panel (Qiagen N.V., Venlo, The Netherlands), which covered 275 cancer-related genes, including splicing factors and other adverse defining genes such as *ASXL1*, *RUNX1*, and *TP53*.

Statistical analyses

Safety analyses included patients who received at least 1 dose of rogocekib. Efficacy, pharmacokinetic, and pharmacodynamic analyses were performed on patients who received at least 1 dose of rogocekib and who had available data for these assessments. The Kaplan-Meier method was used for the assessment of OS and EFS. For EFS analysis, survival was calculated from the first day of administration to the date of death or date of disease progression (including relapse). Data were analyzed per dose level and for all patients. Pharmacokinetic and pharmacodynamic parameters were assessed using a noncompartmental approach. Exploratory biomarkers were analyzed using descriptive statistics.

The study was conducted in accordance with guidelines for good clinical practice and the study protocol was approved by all institutional review boards at each of the participating sites. Written informed consent was provided by all patients before screening and enrollment. The study sponsor analyzed the data and conducted the statistical analyses. All authors had access to the primary clinical trial data on request. A safety monitoring committee oversaw the conduct and safety of the trial.

Results

Patient characteristics

A total of 15 patients were enrolled, and 14 patients were administered rogocekib in this phase 1 study (13 males, and 1 female). The characteristics of patients administered with rogocekib at each dose level (70 mg and 105 mg twice a week) are shown in [Table 1](#). The median age of patients was 71.0 years (range, 67-78). A total of 12 patients (85.7%) were diagnosed with AML, including 5 patients (41.7%) with de novo AML and 7 patients (58.3%) with secondary AML. All patients had undergone at least 1 previous line of therapy, with most having been previously treated with azacitidine alone or a combination of venetoclax and azacitidine (92.9%). With regard to previous therapies, 8 patients had only 1 previous line of therapy. Regarding the karyotype of the patients, 4 patients had normal karyotypes, 6 patients had a complex karyotype, 1 patient had a 7q deletion, and 3 patients had other chromosomal abnormalities. Among patients with AML, 10 patients were at adverse risk based on ELN 2017⁷ recommendations. The remaining 2 patients were at intermediate risk. Both patients with MDS were classified as "very high" risk according to the revised International Prognostic Scoring System.⁹

Safety

A total of 15 patients were enrolled, and rogocekib was administered to a total of 14 patients; 1 patient with AML enrolled in the 70 mg cohort discontinued before treatment initiation due to a rapid increase in peripheral blasts. All patients eventually

discontinued treatment. The reasons for discontinuation included physician decision in 5 patients and progression of primary cancer in 3 patients in the 70 mg cohort, and progression of primary cancer in 3 patients, poor tolerability in 2 patients, and physician decision in 1 patient in the 105 mg cohort. The median total treatment duration was 65.5 days (range, 15-406) at 70 mg and 130.0 days (range, 15-974) at 105 mg. At least 1 dose reduction during the dosing period was observed in 2 patients at 105 mg. Dose interruption occurring at least once during the treatment period was observed in 5 patients each at 70 mg and 105 mg.

Among all patients, the most common adverse drug reactions (ADRs; judged as treatment-related events that occurred in >25% of all patients) were diarrhea (57%), nausea (43%), tumor lysis syndrome (TLS; 29%), and hypotension (29%). The main GI-related toxicities of diarrhea, nausea, and vomiting (21%) were all grade ≤2 except for 1 case of grade 3 diarrhea and were manageable with concomitant antiemetic treatment. Across all patients, the most common grade ≥3 ADRs were TLS and white blood cell count decreased, which were observed in 2 patients each (14.3%). [Table 2](#) lists all ADRs occurring in ≥10% of patients in this cohort.

In the 105 mg cohort, 3 of 6 patients were DLT evaluable. Two patients who were DLT-unevaluable developed TLS after the first administration and subsequently had their dose reduced from 105 mg to 70 mg. The other patient had rapid tumor progression that led to early drug interruption in the first cycle. Off DLT-evaluable patients, 1 patient experienced a DLT of grade 4 pneumonia. In the 70 mg twice a week group, 6 of 8 total patients were DLT evaluable. One of the DLT unevaluable patients had rapid tumor progression that led to early drug interruption in the first cycle, whereas the other patient developed signs of potential infection, renal function, and hematologic abnormalities, which led to drug interruption. Of the DLT-evaluable patients, no DLTs were observed. Treatment-related adverse events leading to discontinuation were observed in 2 patients at 105 mg (1 patient experienced grade 3 malaise and decreased appetite, whereas the other patient had grade 4 pneumonia). Among all 14 patients, no treatment-related deaths were observed.

Pharmacokinetics and Pharmacodynamics

Rogocekib was rapidly absorbed with a median time to reach maximum plasma concentration (T_{max}) of 2.0 hours for 70 mg, and 3.0 hours for 105 mg; rogocekib was gradually eliminated with a mean elimination half-life ($T_{1/2}$) of 4.89 hours for 70 mg, and 5.23 hours for 105 mg over a period of 24 hours ([Figure 1A](#)). The mean maximum plasma concentration (C_{max}) of rogocekib was 714.1 ng/mL and 1052.0 ng/mL and the mean area under the plasma concentration-time curve from time 0 to 24 hours post dose (AUC_{0-24}) was 5773.1 h·ng/mL and 9547.9 h·ng/mL for 70 mg and 105 mg, respectively. Trough concentrations after repeated doses did not increase, suggesting that no accumulation was observed.

In addition to pharmacokinetic analyses, peripheral blood samples were drawn and examined for pharmacodynamic using real-time PCR. *THAP9-AS1* and *S6K* were chosen as pharmacodynamic markers for target engagement. The relative magnitude of exon skipping in *THAP9-AS1* and *S6K* was assayed by real-time PCR as fold change ([Figure 1B-C](#)). The median maximum folding difference (E_{max}) for both *THAP9-AS1* and *S6K* was 1321.5 and 30.9, respectively, for 70 mg and 1366.2 and 35.8, respectively,

Table 1. Baseline patient characteristics

Characteristics	Hematologic malignancies cohort: 70 mg		Hematologic malignancies cohort: 105 mg	
	N = 8		N = 6	
	n (%)		n (%)	
Sex				
Male	7 (87.5)		6 (100.0)	
Female	1 (12.5)		0 (0.0)	
Age, y				
N	8		6	
Mean (SD)	71.1 (3.6)		70.5 (2.4)	
Median	71.5		70.5	
IQR (Q1-Q3)	(68-73)		(69-72)	
Range (min-max)	(67-78)		(67-74)	
Age category, y				
<65	0 (0.0)		0 (0.0)	
≥65	8 (100.0)		6 (100.0)	
ECOG performance status at baseline				
0	5		4	
1	3		2	
2	0		0	
3	0		0	
4	0		0	
Diagnosis				
MDS	1	(12.5)	1	(16.7)
De novo*	1	(100.0)	1	(100.0)
Secondary*	0	(0.0)	0	(0.0)
IPSS-R risk category*				
Intermediate	0	(0.0)	0	(0.0)
High	0	(0.0)	0	(0.0)
Very high	1	(100.0)	1	(100.0)
CMMML	0	(0.0)	0	(0.0)
AML	7	(87.5)	5	(83.3)
De novo†	3	(42.9)	2	(40.0)
Secondary†	4	(57.1)	3	(60.0)
Previous systemic therapy				
No	0	(0.0)	0	(0.0)
Yes	8	(100.0)	6	(100.0)
Reason for previous systemic therapy				
Advanced or recurrent	5		4	
Induction	4		2	
Consolidation	1		0	
Maintenance	1		0	
Number of regimens				
0	0	(0.0)	0	(0.0)
1	3	(37.5)	5	(83.3)
2	3	(37.5)	1	(16.7)
3	1	(12.5)	0	(0.0)
≥ 4	1	(12.5)	0	(0.0)

ECOG, Eastern Cooperative Oncology Group; IPSS-R, revised International Prognostic Scoring System; IQR, interquartile range; max, maximum; min, minimum; SD, standard deviation; Q1/3, quartile 1/3.

*The denominator is the number of patients diagnosed with MDS.

†The denominator is the number of patients diagnosed with AML.

Table 1 (continued)

	Hematologic malignancies cohort: 70 mg		Hematologic malignancies cohort: 105 mg	
	N = 8		N = 6	
Characteristics	n (%)		n (%)	
Previous radiation therapy				
No	8	(100.0)	6	(100.0)
Yes	0	(0.0)	0	(0.0)
Procedure/surgery/stem cell transplant history				
No	8	(100.0)	6	(100.0)
Yes	0	(0.0)	0	(0.0)

ECOG, Eastern Cooperative Oncology Group; IPSS-R, revised International Prognostic Scoring System; IQR, interquartile range; max, maximum; min, minimum; SD, standard deviation; Q1/3, quartile 1/3.

*The denominator is the number of patients diagnosed with MDS.

†The denominator is the number of patients diagnosed with AML.

for 105 mg whereas the median area under the folding difference from time 0 to 8 hours post dose (AUE_{0-8}) for *THAP9-AS1* and *S6K* was 4096.5 and 123.9, respectively, for 70 mg and 3357.8 and 117.6, respectively, for 105 mg.

Efficacy

Response. Among 12 patients with AML, 3 complete remissions (CRs), 1 CR with incomplete hematologic recovery (CRI), and 1 morphologic leukemia-free state (MLFS) were observed based on ELN 2017 criteria. Of 2 patients with MDS, 1 patient achieved CR

based on 2006 International Working Group guidelines. The overall response rate (ORR; CR plus marrow CR plus partial remission for patients with MDS, and CR + CRI + MLFS plus partial remission for patients with AML) across all 14 patients was 42.9% (Table 3). The median time to remission was 56 days (range, 28-77), and the median duration of response among responding patients was 164 days (range, 14-924), with the longest responding patient having a response for >2 years (Figure 2).

For survival analyses, long-term follow-up was conducted every 6 months from the date of the last administration of rogocekib until

Table 2. All ADRs occurring in ≥10% of patients with hematologic malignancies

Adverse Drug Reaction Term	Hematologic malignancies cohort (N = 14)									
	ADRs									
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
Preferred term	n (%)*		n (%)*		n (%)*		n (%)*		n (%)*	
Any events	1	(7.1)	7	(50.0)	4	(28.6)	2	(14.3)	0	(0.0)
Diarrhea	1	(7.1)	6	(42.9)	1	(7.1)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	6	(42.9)	0	(0.0)	0	(0.0)	0	(0.0)
TLS	1	(7.1)	1	(7.1)	2	(14.3)	0	(0.0)	0	(0.0)
Hypotension	1	(7.1)	2	(14.3)	1	(7.1)	0	(0.0)	0	(0.0)
Stomatitis	3	(21.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(7.1)	2	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	2	(14.3)	0	(0.0)	1	(7.1)	0	(0.0)	0	(0.0)
Hyponatremia	1	(7.1)	2	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	1	(7.1)	1	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pyrexia	1	(7.1)	1	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Amylase increased	0	(0.0)	1	(7.1)	1	(7.1)	0	(0.0)	0	(0.0)
Blood creatinine increased	1	(7.1)	1	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
White blood cell count decreased	0	(0.0)	0	(0.0)	1	(7.1)	1	(7.1)	0	(0.0)
Dehydration	0	(0.0)	2	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
Dysgeusia	1	(7.1)	1	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Taste disorder	1	(7.1)	1	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)
Nail discoloration	2	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

*If a patient is reported to have the same event more than once, then the event with the most severe grade is counted once.

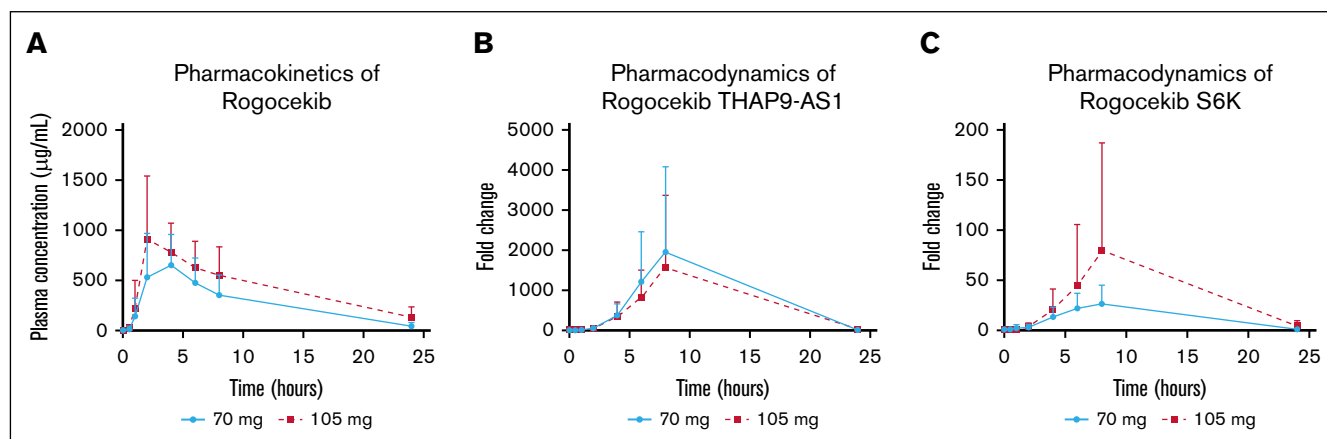


Figure 1. Pharmacokinetic and pharmacodynamic profiles of rogocekib. (A) Pharmacokinetic profile of rogocekib from plasma collected on cycle 1 day 1 of administration. The changes in the mean concentration in plasma of rogocekib was plotted over time. Rogocekib had increased systemic exposure for 105 mg ($n = 6$) compared with 70 mg ($n = 8$). It was rapidly absorbed, and gradually decreased in plasma concentration with a mean $T_{1/2}$ of 4.89 and 5.23 hours for 70 and 105 mg, respectively. (B-C) Pharmacodynamic profiles of rogocekib from plasma collected at cycle 1 day 1 of administration. Based on the pharmacodynamic analysis data, changes in the means and standard deviations of fold changes at 105 mg ($n = 6$) and 70 mg ($n = 8$), reflecting the relative magnitude of exon skipping in *THAP9-AS1* and *S6K* in peripheral blood cells, were plotted over time.

death of the patient, completion of the study period, or 1 year from the date of the start of administration of rogocekib, whichever occurred first. If the administration period was longer than a year, long-term follow-up was not conducted. The median OS across all patients in the hematologic malignancies cohort was 10.40 months (95% confidence interval [CI], 2.99 to not reached [NR]) and the median EFS was 5.55 months (95% CI, 1.71-10.61; Figure 3).

Genetic analysis. Among 14 total patients, 11 patients had genetic analysis samples obtained and assayed for various mutations (Figure 4). Among the patients from whom genetic samples

were obtained, 4 patients were found to have SFMs in *SRSF2* (3 patients) and *U2AF1* (1 patient). Patients with *SRSF2* mutations had either P95L or P95H mutations, whereas the patient with a mutation in *U2AF1* had the S34F polymorphism. All patients with SFMs had AML, and none of the patients with MDS had SFMs. In addition, gene mutations were found in *ASXL1* (3 patients), *TP53* (3 patients), and *RUNX1* (2 patients), which are all classified by the ELN 2017 guidelines as adverse-defining genes; all patients were patients with AML, except for 1 patient with a *TP53* mutation who had MDS.

For patients whose genetic mutation status was confirmed, the ORR was 75.0% in 4 patients with adverse-defining SFMs (1 CR,

Table 3. ORR in patients who received rogocekib

Response	Hematologic malignancies cohort*					
	All patients		SFm-positive†		SFm-negative‡	
	N = 14		N = 4		N = 7	
Best overall response	n (%)	95% CI‡	n (%)	95% CI‡	n (%)	95% CI‡
CR	4 (28.6)	(8.4-58.1)	1 (25.0)	(0.6-80.6)	3 (42.9)	(9.9-81.6)
CRi	1 (7.1)	(0.2-33.9)	1 (25.0)	(0.6-80.6)	0 (0.0)	(0.0-41.0)
mCR	0 (0.0)	(0.0-23.2)	0 (0.0)	(0.0-60.2)	0 (0.0)	(0.0-41.0)
MLFS	1 (7.1)	(0.2-33.9)	1 (25.0)	(0.6-80.6)	0 (0.0)	(0.0-41.0)
PR	0 (0.0)	(0.0-23.2)	0 (0.0)	(0.0-60.2)	0 (0.0)	(0.0-41.0)
SD	3 (21.4)	(4.7-50.8)	1 (25.0)	(0.6-80.6)	1 (14.3)	(0.4-57.9)
PD	2 (14.3)	(1.8-42.8)	0 (0.0)	(0.0-60.2)	1 (14.3)	(0.4-57.9)
NE	3 (21.4)	(4.7-50.8)	0 (0.0)	(0.0-60.2)	2 (28.6)	(3.7-71.0)
ORR§	6 (42.9)	(17.7-71.1)	3 (75.0)	(19.4-99.4)	3 (42.9)	(9.9-81.6)

mCR, marrow CR; NE, not evaluable; PD, progressive disease; PR, partial remission; SD, stable disease.

*Patients with MDS are included.

†Only patients analyzed for biomarker assay (excluding patients from whom samples were not collected or consent for a biomarker assay was not obtained).

‡Clopper-Pearson exact method.

§SORR is defined as the rate of patients whose best overall response is CR or CRi or mCR or MLFS or PR.

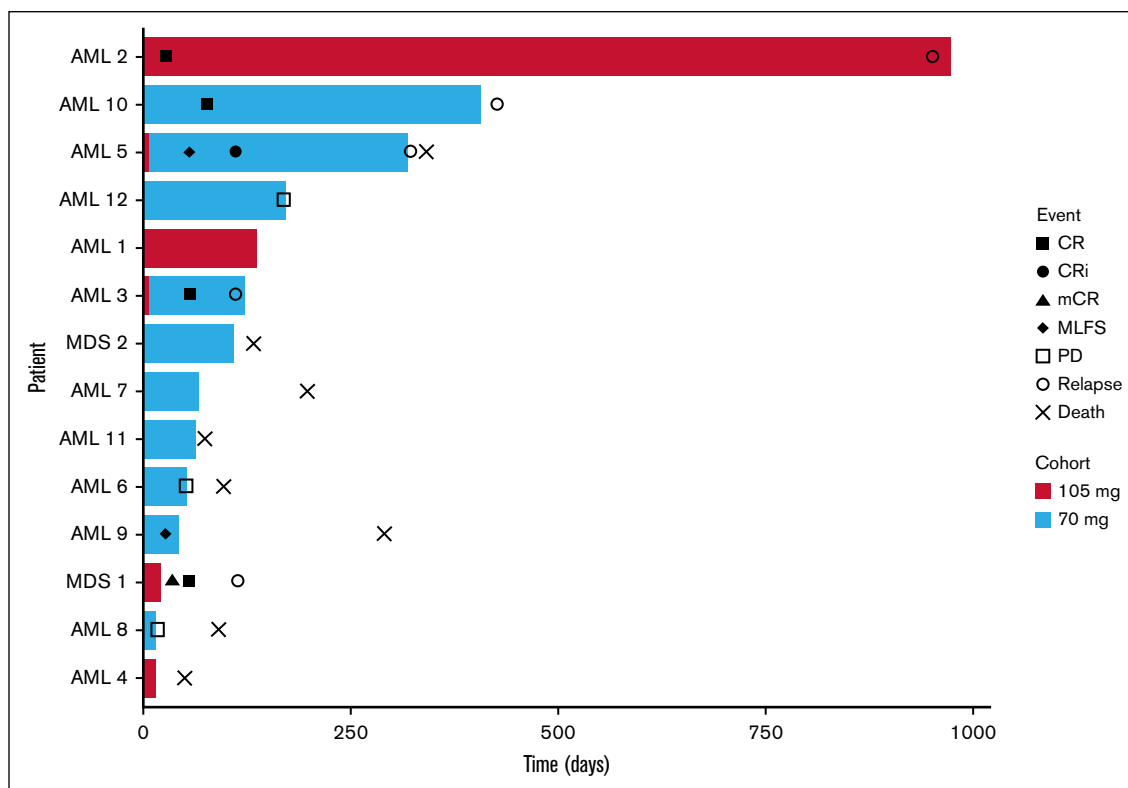


Figure 2. Swimmer plot of responses to rogocekib for all patients. The median treatment duration for this study was 88 days (range, 15-974) and a median duration of response of 164 days (range, 14-924). mCR, marrow CR; PD, progressive disease.

1 CRi, 1 MLFS). In 7 patients without SFms, the ORR was still 42.9% (3 CR). Table 3 shows the best overall response in patients with and without SFms. The median OS for patients with SFms was NR (95% CI, 9.56 to NR) whereas the median OS for patients without SFms was 4.37 months (95% CI, 1.64 to NR; Figure 3A). The median EFS for patients with SFms was 14.06 months (95% CI, 10.61 to NR) whereas the median EFS for patients without SFms was 3.71 months (95% CI, 0.56 to NR; Figure 3B).

Discussion

This was a first-in-human trial assessing the safety and efficacy of rogocekib, a novel pan-CLK inhibitor, in the treatment of relapsed and refractory AML and MDS. Previous attempts were made at inhibiting the splicing mechanism in hematologic malignancies in a clinical setting; H3B-8800, a selective inhibitor of SF3b components in the splicing mechanism, previously showed promise in preclinical models; however, in clinical trials no CR or partial remissions were observed.¹¹ Additionally, E7107, a pre-mRNA spliceosome inhibitor was discontinued early in clinical development due to high toxicity observed in patients.¹² Although rogocekib shares similarities to previously tested compounds in that it induces changes in RNA splicing by the spliceosome through CLK inhibition, the pan-CLK and selective inhibitory mode of rogocekib may provide higher efficacy, more robust anticancer efficacy, and superior safety compared with previous splicing factor modulators. Notably, although no CRs were neither observed for H3B-8800 in patients with hematologic malignancy (0% combined CR rate) nor E7107 in patients with solid tumors, in this trial, rogocekib had a

combined CR rate of 35.7% (4 CR and 1 CRi) among a total of 14 total patients with AML and MDS.

In this phase 1 study, the adverse events that occurred from rogocekib treatment were manageable and tolerable. This safety profile is comparable with the safety information from patients with solid tumors.¹⁰ The most common ADRs were diarrhea (57%), nausea (43%), TLS (29%), and hypotension (29%). Although diarrhea and nausea were common ADRs, all cases were grade ≤ 2 , with only 1 case of grade 3 diarrhea. Furthermore, concomitant administration of rogocekib with antiemetic medication enabled these GI toxicities to be brought to a tolerable state. TLS has previously been reported in patients receiving hypomethylating agents and venetoclax¹³ as well as in other targeted medications such as FMS-like tyrosine kinase 3 (FLT3)¹⁴ and isocitrate dehydrogenase 1 and 2 (IDH1/2)^{15,16} inhibitors. Although TLS was observed in this trial, all cases were manageable with supportive treatment such as hydration and allopurinol. Administration of rogocekib presented no cases of corrected QT interval prolongation or other cardiac-related toxicities. Additionally, there were no cases of vision loss in our trial, which was a main factor for the discontinuation of the clinical trial for the splicing modulator E7107.^{12,17} Altogether, these results have confirmed the tolerability and safety of rogocekib at 70 mg twice a week in patients with AML and MDS. Further investigation at 105 mg twice a week was considered, but due to a change in formulation from capsules to tablets, a new clinical trial was initiated in the United States to confirm the safety of rogocekib in this patient population.¹⁸

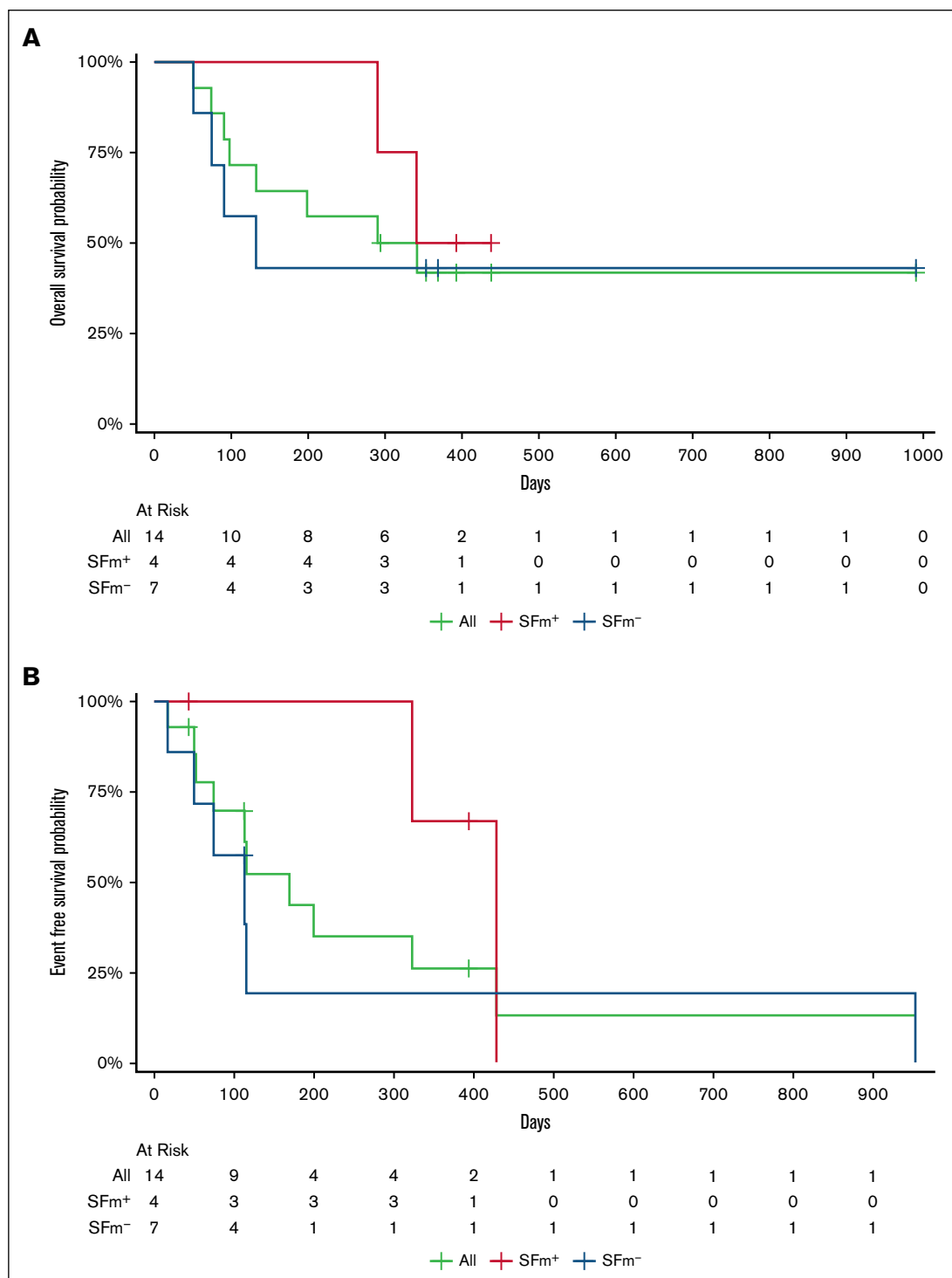


Figure 3. OS and EFS of patients who received rogocekib dose. (A-B) The median OS among all patients in the hematologic malignancies cohort was 10.40 months whereas the median EFS was 5.55 months. For patients harboring SFms, the median OS was NR whereas the median OS for patients without SFms was 4.37 months. The median EFS for patients with SFms was 14.06 months whereas the median EFS for patients without SFms was 3.71 months. Genetic information was not obtained for 3 patients.

Preclinical investigation of rogocekib demonstrated that increasing doses of rogocekib increased the effect of CLK inhibition. Western blotting showed that serine/arginine-rich proteins (the main target of

CLK) have dose-dependent decreases in phosphorylation levels as the concentration of rogocekib was increased. Rogocekib demonstrated strong anticancer effects in a variety of cancers including

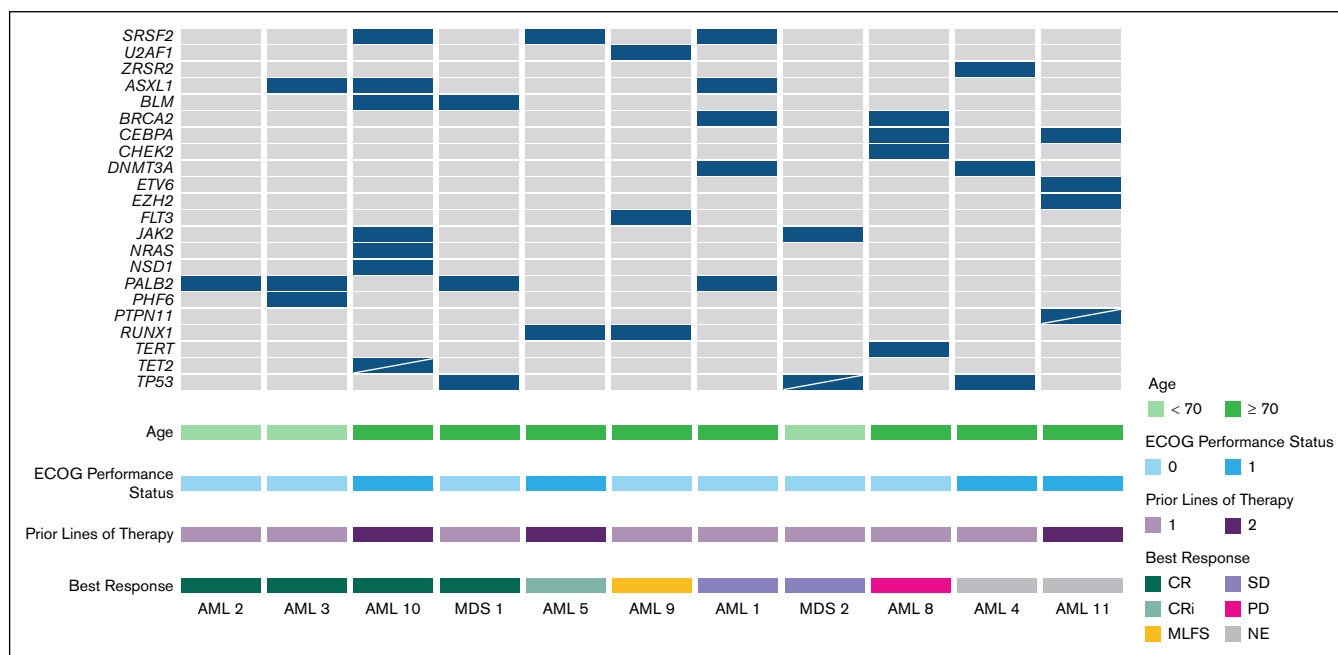


Figure 4. Comutation plot of patients treated with rogocekib. The genetic and clinical profiles of 11 patients from whom samples were obtained for mutational analysis were graphed on a comutation plot. The top panel displays gene mutations across a range of genes including *SRSF2*, *U2AF1*, *ASXL1*, *TP53*, *RUNX1*, and other gene mutation. Double-hit mutations occurring within the same gene are denoted with a diagonal slash. Clinical annotations include age, ECOG performance status, previous lines of therapy, and best treatment response. Each column represents an individual patient, labeled by disease type and sample number. Full details on genetic mutations can be found in the Supplemental Table S2. ECOG, Eastern Cooperative Oncology Group; NE, not evaluable; PD, progressive disease; SD, stable disease.

AML cell models and mouse models.⁶ Results from these studies suggested that CLK inhibition is a potential new strategy for hematologic malignancies and warranted further clinical investigation. Investigation of the mechanism of CLK inhibition revealed that inhibition of the components in the spliceosome module led to an increase in RNA missplicing events, primarily in exon skipping. Pharmacokinetic results from this study showed that the C_{max} and AUC_{0-24} of rogocekib increased at 105 mg compared with 70 mg. At the same time, the median E_{max} also increased with higher exposure of rogocekib in pharmacodynamic analyses, which measured the relative magnitude of exon skipping in *S6K* and *THAP9-AS1* in peripheral blood cells, whereas the median AUE_{0-8} was higher at 70 mg. These results confirm the target engagement of rogocekib and its ability to affect splicing mechanisms in humans.

SFms are reported to be highly recurrent in hematologic malignancies. Patients with SFms continue to have dismal outcomes.^{4,19} As such, these SFms have been classified as adverse-defining gene mutations. To date, there are no therapies that specifically target this vulnerable patient population. Preclinical data of rogocekib demonstrated that in PDX AML mouse models, administration of rogocekib demonstrated strong antitumor activity including in 1 PDX model that harbored an *SRSF2* P95H SFm and showed increased survival benefit in a dose-dependent manner.²⁰ The preliminary efficacy results in our clinical trial demonstrate an ORR of 75% in a subgroup of patients harboring SFms (specifically *SRSF2* and *U2AF1* mutations). Because there are no treatments that specifically target SFms, these results suggest a potential breakthrough therapy for patients with SFms. However,

because the number of patients with SFms was low ($n = 4$), to confirm the efficacy in this population, further enrollment of patients with *SRSF2* and *U2AF1* including *SF3B1* and *ZRSR2* mutations is necessary in further clinical trials. Additionally, response was observed in patients with other adverse-defining genetic mutations such as *RUNX1*, *ASXL1*, and *TP53*. Three patients in this trial had *TP53* mutations, and a response was observed in 1 patient with MDS (1 CR), suggesting the potential efficacy of rogocekib in patients with *TP53* mutations.

Overall, these results suggest that rogocekib possesses a tolerable safety profile and preliminary efficacy in patients with relapsed or refractory AML or higher-risk MDS. Additionally, preliminary efficacy in patients with SFms suggest a potential indication for this vulnerable group of patients. However, because of the limited number of patients with SFms, more investigation is necessary to confirm the efficacy in this patient population. Regardless, the observation of clinical response in both patients with AML and those with MDS irrespective of SFm status prompts the need for further investigation into the safety and efficacy of rogocekib for patients with hematologic malignancies. Recently reported preclinical results have suggested that CLK inhibition may also have a synergistic effect with other currently approved targeted agents such as B-cell lymphoma 2 inhibitors and opens up the possibility for future combination treatment strategies.²¹ Currently, a phase 1/2 study of a tablet formulation of rogocekib as a monotherapy is ongoing in the United States in patients with relapsed or refractory AML or MDS (ClinicalTrials.gov identifier: NCT05732103).¹⁸

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References

1. Yoshida K, Sanada M, Shiraishi Y, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature*. 2011;478(7367):64-69.
2. Chen S, Benbarche S, Abdel-Wahab O. Splicing factor mutations in hematologic malignancies. *Blood*. 2021;138(8):599-612.
3. Saez B, Walter MJ, Graubert TA. Splicing factor gene mutations in hematologic malignancies. *Blood*. 2017;129(10):1260-1269.
4. van der Werf I, Wojtuszkiewicz A, Meggendorfer M, et al. Splicing factor gene mutations in acute myeloid leukemia offer additive value if incorporated in current risk classification. *Blood Adv*. 2021;5(17):3254-3265.
5. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377.
6. Yoda A, Morishita D, Ochi Y, et al. CTX-712, a novel splicing modulator targeting myeloid neoplasms. *Blood*. 2022;140(suppl 1):489-490.
7. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
8. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108(2):419-425.
9. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. *Blood*. 2012;120(12):2454-2465.

10. Yamamoto N, Koyama T, Katsuya Y, et al. A first-in-human phase I study of CTX-712 in patients with advanced, relapsed or refractory malignant tumors (CTX-712-CL-01 study): efficacy and safety in solid tumor cohorts [abstract]. *Cancer Res.* 2024;84(7 suppl). Abstract CT110.
11. Steensma DP, Wermke M, Klimek VM, et al. Phase I first-in-human dose escalation study of the oral SF3B1 modulator H3B-8800 in myeloid neoplasms. *Leukemia.* 2021;35(12):3542-3550.
12. Hong DS, Kurzrock R, Naing A, et al. A phase I, open-label, single-arm, dose-escalation study of E7107, a precursor messenger ribonucleic acid (pre-mRNA) spliceosome inhibitor administered intravenously on days 1 and 8 every 21 days to patients with solid tumors. *Invest New Drugs.* 2014;32(3):436-444.
13. Huang JQ, Academia E, Pollyea DA, et al. Tumor lysis syndrome (TLS) in acute myeloid leukemia (AML) patients treated with azacitidine (AZA) and venetoclax (VEN). *JCO.* 2020;38(15 suppl):e19507.
14. Zhao J, Song Y, Liu D. Gilteritinib: a novel FLT3 inhibitor for acute myeloid leukemia. *Biomark Res.* 2019;7:19.
15. Marvin-Peek J, Garcia JS, Borthakur G, et al. A phase Ib/II study of ivosidenib with venetoclax $\pm$ azacitidine in IDH1-mutated hematologic malignancies: a 2024 update. *Blood.* 2024;144(suppl 1):219.
16. Pollyea DA, Tallman MS, de Botton S, et al. Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia. *Leukemia.* 2019;33(11):2575-2584.
17. Eskens FALM, Ramos FJ, Burger H, et al. Phase I pharmacokinetic and pharmacodynamic study of the first-in-class spliceosome inhibitor E7107 in patients with advanced solid tumors. *Clin Cancer Res.* 2013;19(22):6296-6304.
18. Al-Kali A, Saliba A, Arana Yi CY, et al. Phase 1/2 multicenter, open-label study of CTX-712 in patients with relapsed/refractory acute myeloid leukemia and higher risk myelodysplastic syndromes. *Blood.* 2023;142(suppl 1):3249.
19. Pellagatti A, Armstrong RN, Steeples V, et al. Impact of spliceosome mutations on RNA splicing in myelodysplasia: dysregulated genes/pathways and clinical associations. *Blood.* 2018;132(12):1225-1240.
20. Yoda A, Morishita D, Mizutani A, et al. CTX-712, a novel Clk inhibitor targeting myeloid neoplasms with *SRSF2* mutation. *Blood.* 2019;134(suppl 1):404.
21. Wang E, Pineda JMB, Kim WJ, et al. Modulation of RNA splicing enhances response to BCL2 inhibition in leukemia. *Cancer Cell.* 2023;41(1):164.e8–180.e8.