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Research paper

Rigosertib in combination with azacitidine in patients with myelodysplastic syndromes or acute myeloid leukemia: Results of a phase 1 study

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ABSTRACT

Phase 1 results from a Phase 1/2 study comprise 18 patients with myelodysplastic syndromes (MDS; $n = 9$), acute myeloid leukemia (AML; $n = 8$), and chronic myelomonocytic leukemia (CMML; $n = 1$) who were either hypomethylating agent naïve ($n = 10$) or relapsed/refractory following prior hypomethylating agent therapy ($n = 8$) (NCT01926587). Patients received oral rigosertib, an inhibitor of Ras-effector pathways, in 3 successive cohorts (140 mg twice daily, 280 mg twice daily, or 840 mg/day [560 mg morning/280 mg evening]) for 3 weeks of a 4-week cycle. Patients received parenteral azacitidine (75 mg/m^2/day × 7 days) during the second week; the cycle repeated every 4 weeks. The combination was well tolerated for a median of 4 (range 1–41) cycles, with 72% of patients experiencing ≥1 serious adverse events. No dose-limiting toxicities were observed. Thus, no maximum tolerated dose was reached. The most frequently reported adverse events were diarrhea (50%), constipation, fatigue, and nausea (each 44%), and pneumonia and back pain (each 33%). Sequential administration demonstrated an overall response rate of 56% in evaluable patients, with responses observed in 7/9 MDS/CMML patients (78%) and 2/7 AML patients (29%). Further clinical studies are warranted to investigate this doublet therapy in patients with myeloid malignancies.

1. Introduction

The myelodysplastic syndromes (MDS) are heterogeneous clonal hematopoietic disorders that affect cell proliferation and differentiation. MDS is characterized by ineffective hematopoiesis leading to bone marrow failure and increased risk of progression to acute myeloid leukemia (AML) [1,2].

Azacitidine is standard of care for higher-risk MDS patients, with clinical responses occurring in up to 50% of patients and a complete remission rate ranging from 7 to 24% [3,4]. However, all responding patients ultimately relapse or progress. Patients failing a hypomethylating agent (HMA) have limited treatment options and a poor prognosis, with a median overall survival of 46 months [5,6]. There are currently no health authority approved therapies after HMA failure. The mechanisms of resistance following HMA failure are poorly understood, but genomic profiling at the time of diagnosis and changes in mutational profiles may provide new insights into the biology of resistance in higher-risk MDS.

Older patients with relapsed/refractory AML also have a dismal prognosis. These patients often cannot tolerate aggressive treatment due to age, frailty or co-morbidities. Thus, azacitidine has been used as a single agent in older patients with AML. In patients with 20–30% blasts, azacitidine significantly prolonged survival compared to conventional care regimens [7]. Azacitidine reduced the risk of death by 31% compared to conventional care regimens in a phase 3 study in older AML patients [8]. The addition of venetoclax, a highly selective oral inhibitor of the B-cell lymphoma 2 protein, to hypomethylating therapy has demonstrated promising clinical activity with improved survival for elderly patients with treatment-naïve AML [9], but prolonged survival has not yet been confirmed in a relapsed/refractory

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Table 1
Preclinical synergy of rigosertib followed by azacitidine.
Source: Skidan et al. [14].

Combination drug	CI	Ratio	Description
Rigosertib* (125 nM) + 5AzaC (2 μM)	0.44	1:62.5	Synergism
Rigosertib (125 nM) + 5AzaC (4 μM)	0.30	1:31.25	Strong synergism
Rigosertib (250 nM) + 5AzaC (2 μM)	0.68	1:125	Synergism
Rigosertib (250 nM) + 5AzaC (4 μM)	0.57	1:62.5	Synergism
Rigosertib (500 nM) + 5 AzaC (2 μM)	0.63	1:250	Synergism
Rigosertib (500 nM) + 5AzaC (4 μM)	0.75	1:125	Moderate synergism

elderly AML population. As such, this patient population would benefit greatly from the continued development of novel agents with the potential to induce greater responses and acceptable safety profiles [10].

Rigosertib is the sodium salt of (*E*)-2,4,6-trimethoxystyryl-e-carboxymethylamino-4-methoxybenzyl sulfone, an unsaturated sulfone kinase inhibitor [11]. It is a small molecule that inhibits cellular signaling by targeting the Ras binding domain with downstream effects on the PI3K/AKT and Raf/PLK pathways [12]. It has demonstrated activity in patients with HMA failure in ongoing studies utilizing the intravenous formulation [13]. The pharmacodynamically effective concentration of 0.175 μg/mL (370 nM) of rigosertib was estimated for MDS based on in vitro studies conducted with various leukemic cell lines [14].

In preclinical studies, the combination of rigosertib and azacitidine demonstrated synergy using azacitidine concentrations that were equivalent to doses administered in the clinical setting. In one study, the effect of the combination on survival of human leukemic cell lines was measured after 72 h of exposure (Table 1) [15]. The combination of rigosertib and azacitidine produced an increase of 1.7- to 2.9-fold in cytotoxicity ($p < 0.05$), and sequential exposure with rigosertib followed by azacitidine achieved maximum synergy. In another study investigating the effects of drug combination treatment on the viability of acute myeloid leukemia cell lines, a synergistic effect was observed when the cells were pretreated with rigosertib before administering azacitidine, in contrast to the additive effect observed when the two treatments were administered simultaneously [16].

To evaluate whether this preclinical synergy could translate into clinical benefit, we conducted a Phase 1/2 study to evaluate the safety and efficacy of the combination of oral rigosertib preceding administration of the approved parenteral azacitidine dosing regimen and to determine the recommended Phase 2 dose (RP2D) of the combination in patients with higher-risk MDS and acute myeloid leukemia.

2. Materials and methods

A Phase 1/2 open-label study was conducted according to the provisions of the Declaration of Helsinki and its current amendments, and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients reviewed and signed informed consent forms approved by site-specific ethics committees prior to undergoing any study procedures. The current report focuses on the results of the Phase 1 dose-finding portion of the study.

2.1. Objectives

The objectives of the Phase 1 dose-escalation portion of the study, conducted between October 2013 to May 2017, were to evaluate the safety, tolerability and efficacy of the novel combination of increasing doses of oral rigosertib and standard-dose parenteral azacitidine in patients with higher-risk MDS, non-proliferative AML, or CMML.

2.2. Study design

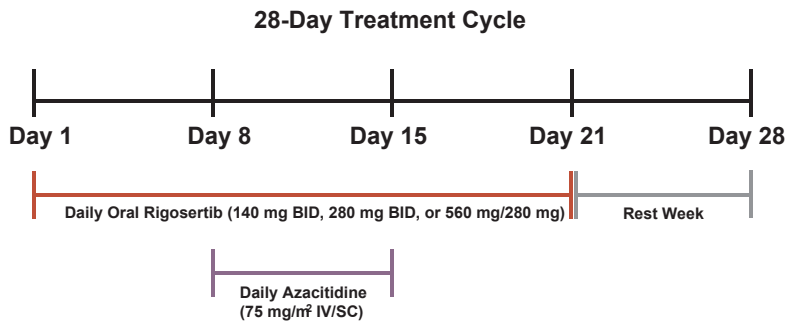
The Phase 1 dose-escalation followed a traditional 3 + 3 design to determine the maximum tolerated dose (MTD) and RP2D of rigosertib. Oral rigosertib was administered in 3 successive cohorts at doses of 140 mg twice daily (BID), 280 mg BID, and 840 mg total daily dose (560 mg in the morning/280 mg in the evening) under fasting conditions for 3 weeks of a 4-week cycle (3-weeks-on/1-week-off regimen) (Fig. 1).

Rigosertib was initiated one week prior to the start of azacitidine based on the aforementioned preclinical synergy of pre-treatment with rigosertib prior to azacitidine exposure. Starting on day 8, standard dose azacitidine was administered either subcutaneously or intravenously, at 75 mg/m^2/day for 7 days of a 28-day (4week) cycle. The intermittent dosing of oral rigosertib with azacitidine was based on an earlier study with oral rigosertib monotherapy in which intermittent administration (2 of 3 weeks) provided the most favorable combination of response and safety [17].

The decision on whether to escalate the dose of oral rigosertib was based on the occurrence and number of dose-limiting toxicities (DLTs) in the first 4-week cycle of treatment. A DLT was defined as an adverse event (AE) that occurred during the first 4-week cycle and was considered possibly, probably, or definitely drug related, including ≥ Grade 2 drug-induced fever (< 39 °C starting within 24 h of rigosertib administration with no other obvious cause); ≥ Grade 3 stomatitis and/or esophagitis/dysphagia lasting > 3 days; or any other > Grade 3 nonhematological toxicity (e.g., uncontrolled ≥ Grade 3 nausea, vomiting, or diarrhea lasting for ≥ 48 h). At least 6 patients must have received a particular dose in order for that dose to be declared the MTD/RP2D.

2.3. Eligibility

Eligible patients had an Eastern Cooperative Oncology Group performance status of 02, baseline serum creatinine ≤ 2.0 mg/dL, and total bilirubin < 2.0 mg/dL unless attributed to hemolysis or ineffective



Abbreviations: BID = twice a day; IV = intravenous; SC = subcutaneous

Fig. 1. Oral rigosertib + azacitidine combination dosing schema.
Abbreviations: BID = twice a day; IV = intravenous; SC = subcutaneous.

Table 2
Patient characteristics.

Number of patients treated		18
Age (years)	Median	70.5
	Range	25–80
Sex – *n* (%)	Male	11 (61)
	Female	7 (39)
ECOG performance status – *n* (%)	0	4 (22)
	1	12 (67)
	2	2 (11)
Prior therapy – *n* (%)	Any prior therapy	15 (83)
	Supportive care	3 (17)
	Intensive chemotherapy	7 (39)
	Immunotherapy	1 (6)
	Hypomethylating agents	8 (44)
	Azacitidine	5 (28)
	Decitabine	3 (17)
Disease – *n* (%)	MDS	9 (50)
	AML	8 (44)
	CMML	1 (6)
Baseline laboratory measurements		
Bone marrow blast (%)	Median	13.5
	Range	0–64.0
Hematocrit (%)	Median	29.8
	Range	19.3–39.0
Hemoglobin (g/dL)	Median	9.7
	Range	6.8–13.4
Platelets ($\times 10^9$/L)	Median	52.5
	Range	9.0–305
Leukocytes ($\times 10^9$/L)	Median	3.0
	Range	0.5–58.8
Neutrophils ($\times 10^9$/L)	Median	0.91
	Range	0.24–24.11
Bilirubin (mg/dL)	Median	0.55
	Range	0.20–1.60
Creatinine (mg/dL)	Median	1.01
	Range	0.72–2.37

Abbreviations: AML = acute myeloid leukemia; CMML = chronic myelomonocytic leukemia; ECOG = Eastern Cooperative Oncology Group; MDS = myelodysplastic syndrome.

erythropoiesis. Patients could have received prior hypomethylating based therapy but could not have received prior rigosertib. Patients diagnosed with MDS must have been classified as intermediate-1, intermediate-2, or high-risk, according to the International Prognostic Scoring System [18]. Patients with AML (20–30% bone marrow blasts) must have received no more than 1 prior salvage therapy and were excluded for a rapidly rising white blood cell count (i.e., count must have been $\leq$ 25,000 $\times$ 10^9/L and stable for $\geq$ 4 weeks without intervention).

2.4. Drug supply

Rigosertib was supplied by Onconova Therapeutics, Inc. as 280 mg and 70 mg capsules and stored between 2 − 8 °C.

Azacitidine was obtained commercially and administered in accordance with local prescribing information as standard of care treatment using the approved dose.

Study treatment was provided primarily in the outpatient setting.

2.5. Methods of evaluation

Safety and complete blood counts were evaluated weekly, and efficacy was assessed via bone marrow examination at baseline, week 4, and every 8 weeks thereafter. Responses were measured according to the International Working Group (IWG) criteria for MDS and AML [19,20]. Patients remained on study until IWG progression criteria were met (i.e., 50% increase of bone marrow blasts or worsening of cytopenias secondary to MDS and not drug toxicity), unacceptable toxicity, or death from any cause.

2.6. Statistical methods

Safety analyses were performed on all patients who received at least 1 dose of rigosertib. Safety assessments included medical history, physical examination, vital signs, weight, Eastern Cooperative Oncology Group performance status, standard 12-lead electrocardiogram, laboratory evaluations, urinalysis, and toxicity and AE assessments. AE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) [21].

The intent-to-treat (ITT) population included all enrolled patients, the per-protocol population included all patients who completed the study without major protocol violations, and the safety population included all patients who received at least 1 dose of rigosertib. To be evaluable for response, a patient must have received 3 cycles of treatment, unless they had a response or progressed before that time point. Duration of response was defined as the time between the first sign of response in any lineage and the time at which responses in all lineages showing response were subsequently lost or the patient had progression of disease. The primary efficacy analysis was based on the ITT population. Subset analyses were also performed in MDS patients who were previously treated with an HMA and those with no prior HMA exposure.

3. Results

3.1. Patient disposition

Eighteen patients were treated with the combination; all have ended participation in the study for the following reasons: progressive disease (5 patients, 28%), death (4 patients, 22%, with death due to pneumonia for 2 patients and subdural hematoma and cardiac arrest for 1 patient each), Investigator decision (3 patients, 17%), AEs (2 patients, 11%), patient request (2 patients, 11%), bone marrow transplant (1 patient, 6%), and lack of hematological response (1 patient, 6%).

3.2. Patient characteristics

Of the 18 treated patients, 9 patients (50%) had MDS, 8 patients (44%) had AML, and 1 patient (6%) had CMML (Table 2). The median age was 70.5 years, 11 patients (61%) were male, and Eastern Cooperative Oncology Group performance status was 0 (4 patients, 22%), 1 (12 patients, 67%), or 2 (2 patients, 11%).Three of 9 patients with MDS had high-risk disease according to the International Prognostic Scoring System [18], 4 patients had intermediate-2 risk, and 2 patients had intermediate-1 risk. Twelve patients (67%; including 6 of 9 MDS patients, the single patient with CMML, and 5 of 8 AML patients) had received red blood cell transfusions within 8 weeks prior to study entry, with a median of 6 units (range 2–12 units) transfused. Seven patients (39%; including 4 of 9 MDS patients and 3 of 8 AML patients) had received platelet transfusions within 8 weeks prior to study entry, with a median of 9 units (range 5–113 units) transfused.

Nearly all patients (15 patients, 83%) had received prior therapy, including 3 patients (17%) treated only with supportive care (2/9 MDS patients and 1/8 AML patients); 8 patients (44%) treated with prior HMAs (3/9 MDS patients, 4/8 AML patients, and the single CMML patient); 7 patients (39%) treated with intensive chemotherapy (1/9 MDS patients and 6/8 AML patients); and 1 patient (6%) with AML treated with MEK/Akt inhibitor therapy. The 3 patients who had not received any prior therapy entered the study between 23 and 64 days after their initial MDS diagnosis.

3.3. Safety

The combination was well tolerated at each dose level, with no DLTs observed. The RP2D was determined to be 840 mg rigosertib/day (560 mg morning/280 mg evening) with standard-dose azacitidine.

Table 3
Overall summary of safety: treatment-emergent adverse events in ≥20% of patients and all serious adverse events.

MedDRA preferred term	Rigosertib 140 mg BID (*N* = 7)		Rigosertib 280 mg BID (*N* = 5)		Rigosertib 560 mg/280 mg (*N* = 6)		All patients (N = 18)	
	Any grade *n* (%)	Grade ≥ 3 *n* (%)	Any grade *n* (%)	Grade ≥ 3 *n* (%)	Any grade *n* (%)	Grade ≥ 3 *n* (%)	Any grade *n* (%)	Grade ≥ 3 *n* (%)
Any TEAE	7 (100)	7 (100)	5 (100)	5 (100)	6 (100)	4 (67)	18 (100)	16 (89)
Diarrhea	2 (29)	–	3 (60)	–	4 (67)	–	9 (50)	–
Constipation	3 (43)	–	3 (60)	–	2 (33)	–	8 (44)	–
Fatigue	1 (14)	–	3 (60)	–	4 (67)	–	8 (44)	–
Nausea	3 (43)	–	2 (40)	–	3 (50)	–	8 (44)	–
Pneumonia	1 (14)	1 (14)	3 (60)	3 (60)	2 (33)	2 (33)	6 (33)	6 (33)
Back pain	1 (14)	–	2 (40)	–	3 (50)	1 (17)	6 (33)	1 (6)
Neutropenia	2 (29)	2 (29)	2 (40)	2 (40)	1 (17)	1 (17)	5 (28)	5 (28)
Decreased appetite	–	–	4 (80)	–	1 (17)	–	5 (28)	–
Oedema peripheral	1 (14)	–	1 (20)	–	3 (50)	–	5 (28)	–
Pyrexia	1 (14)	–	2 (40)	–	2 (33)	–	5 (28)	–
Vomiting	1 (14)	–	3 (60)	–	1 (17)	–	5 (28)	–
Thrombocytopenia	3 (43)	3 (43)	1 (20)	1 (20)	–	–	4 (22)	4 (22)
Chest pain	2 (29)	1 (14)	2 (40)	–	–	–	4 (22)	1 (6)
Dysuria	1 (14)	–	–	–	3 (50)	1 (17)	4 (22)	1 (6)
Headache	2 (29)	–	2 (40)	1 (20)	–	–	4 (22)	1 (6)
Dysphagia	2 (29)	–	1 (20)	–	1 (17)	–	4 (22)	–
Dyspnea	–	–	1 (20)	–	3 (50)	–	4 (22)	–
Hypotension	1 (14)	–	2 (40)	–	1 (17)	–	4 (22)	–
Any SAE	5 (71)	3 (43)	4 (80)	4 (80)	4 (67)	3 (50)	13 (72)	10 (56)
Pneumonia	–	–	1 (20)	1 (20)	2 (33)	2 (33)	3 (17)	3 (17)
Acute myeloid leukemia	2 (29)	1 (14)	–	–	–	–	2 (11)	1 (6)
Back pain	–	–	–	–	1 (17)	1 (17)	1 (6)	1 (6)
Cardiac arrest	–	–	–	–	1 (17)	1 (17)	1 (6)	1 (6)
Cellulitis	–	–	1 (20)	1 (20)	–	–	1 (6)	1 (6)
Embolism	–	–	–	–	1 (17)	1 (17)	1 (6)	1 (6)
Escherichia bacteremia	1 (14)	1 (14)	–	–	–	–	1 (6)	1 (6)
Hemorrhage intracranial	–	–	1 (20)	1 (20)	–	–	1 (6)	1 (6)
Lobar pneumonia	1 (14)	1 (14)	–	–	–	–	1 (6)	1 (6)
Pneumonia fungal	1 (14)	1 (14)	–	–	–	–	1 (6)	1 (6)
Sepsis	–	–	1 (20)	1 (20)	–	–	1 (6)	1 (6)
Subdural hematoma	–	–	1 (20)	1 (20)	–	–	1 (6)	1 (6)
Upper gastrointestinal hemorrhage	–	–	1 (20)	1 (20)	–	–	1 (6)	1 (6)
Atrial fibrillation	–	–	–	–	1 (17)	–	1 (6)	–
Mental status changes	–	–	–	–	1 (17)	–	1 (6)	–
Pyrexia	1 (14)	–	–	–	–	–	1 (6)	–
Transfusion reaction	–	–	1 (20)	–	–	–	1 (6)	–

Abbreviations: BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Patients received between 1 and 41 treatment cycles (median 4 cycles), with a median duration of treatment of 6.4 (range 1.1–41.0) months, and a median relative dose intensity to both study drugs of 80% (range 43–96%). While study treatment was administered for 1–6 cycles among patients with AML, 5 of 9 patients with MDS received > 6 cycles (7, 11, 17, 25, and 41 cycles, respectively) and the median relative dose intensity was slightly higher among patients with MDS (81%) than AML (75%), suggesting that study treatment may have been better tolerated among MDS patients. Study treatment was also administered for a longer duration among patients who received no prior therapy (n = 3; median 7 [range 3–41] cycles) and patients who received prior supportive care only (n = 3; median 6 [range 1–11] cycles) or prior HMAs only (*n* = 5; median 6 [range 3–25] cycles) compared to patients who received prior intensive chemotherapy (*n* = 7) (median 3 [range 1–5] cycles).

All patients experienced > 1 AE, the most frequently reported of which were diarrhea (50%), constipation, fatigue, and nausea (each 44%), and pneumonia and back pain (each 33%) (Table 3). Sixteen patients (89%) experienced ≥ Grade 3 AEs, with the most frequently reported terms including pneumonia (33%), neutropenia (28%), and thrombocytopenia (22%).

Thirteen patients (72%) reported 20 serious AEs (see Table 3; some patients had more than 1 event). Seven patients had serious AEs with fatal outcome, including 2 patients (11%) who died due to pneumonia and 1 patient (6%) each who died due to worsening AML, cardiac arrest, intracranial hemorrhage, sepsis, and subdural hematoma. Of note, 4/7 patients with serious AEs with fatal outcome were counted as death resulting in treatment discontinuation; the other 3 deaths occurred within 30 days after the patients had discontinued study treatment. No serious AEs were considered related to study treatment, and no serious events represented DLTs.

Four patients (22%) experienced AEs that contributed to treatment discontinuation, including 2 patients (11%) at different dose levels who experienced Grade 4 treatment-related thrombocytopenia events, 1 patient (6%) with Grade 1 dysphagia and delirium, and 1 patient (6%) with Grade 3 fungal pneumonia.

Genitourinary AEs have been observed in previous rigosertib studies in up to 70% of patients and have been considered dose limiting at 560 and 700 mg BID of rigosertib monotherapy [17,22]. In the current study, 6 patients (33%) experienced one or more genitourinary AEs, including 4 patients (22%) with dysuria, 3 patients (17%) with pollakiuria, 2 patients (11%) with micturition urgency, and 1 patient (6%) each with bladder spasm, chromaturia, hematuria, urinary incontinence, urinary retention, and urinary tract infection. The majority of genitourinary AEs were Grade 1 or 2 in severity, with 1 patient in the 840 mg/day cohort experiencing Grade 3 genitourinary toxicity. This patient experienced recurrent Grade 1/2 dysuria starting 2 days before the first dose of study treatment that required delay of the second

Table 4
Treatment-related characteristics and response to study treatment.

Patient	Cohort	Diagnosis	Cytogenetics	Prior HMA	BMBL (%) Baseline	BMBL (%) On-study Nadir	Duration of Treatment (weeks)	Best IWG Response [19,20]	Time to Initial Response (months)	Duration of Response (months)	Hematologic Improvement
101−001	140 mg BID	MDS	Complex (> 3 abnormalities)	–	2	0	178.0	CR	8.5	32.6*	HI-E, HI-P
101−004	140 mg BID	MDS	Pseudodiploid clone exhibiting r(7)	–	2	0	17.7	mCR	0.9	1.9*	–
101−006	280 mg BID	CMML	Complex (> 3 abnormalities)	AZA	2	2	19.0	SD	–	–	–
102−001	140 mg BID	MDS	del12p/t12p	–	22	NE	5.0	NE	–	–	–
102−002	140 mg BID	MDS	Normal	AZA	0	0	14.4	SD	–	–	–
102−003	140 mg BID	MDS	del11	–	21	0.65	56.1	mCR	2.8	9.9	HI-E, HI-P
102−004	280 mg BID	MDS	Complex (> 3 abnormalities)	–	1.4	0.4	22.6	mCR	0.9	3.0*	–
102−005	280 mg BID	MDS	Normal	DEC	12	0	120.1	mCR	1.4	27.4	HI-N
102−006	280 mg BID	MDS	del7q/Monosomy7	AZA	4	0	99.0	CR	14.3	6.7	HI-N, HI-P
102−008	560 mg/280 mg	MDS	Normal	–	9	2.1	33.7	mCR	3.3	4.4*	HI-P
101−002	140 mg BID	AML	del20q,t11;16	–	40	0	29.6	MoCR	1.0	5.8	NA
101−003	140 mg BID	AML	Normal	–	59	NE	5.0	NE	–	–	NA
101−005	280 mg BID	AML	Normal	DEC	25	NE	5.0	TF/I	–	–	NA
101−007	560 mg/280 mg	AML	Normal	DEC	7	7	17.0	TF/R	–	–	NA
101−008	560 mg/280 mg	AML	Trisomy 8	–	25	4	9.1	MLFS	1.0	1.0*	NA
101−009	560 mg/280 mg	AML	Normal	–	15	5	25.4	TF/R	–	–	NA
102−007	560 mg/280 mg	AML	del7q/Monosomy7, Trisomy 8, t9;11, 11q23	AZA	47	47	33.0	TF/R	–	–	NA
102−009	560 mg/280 mg	AML	Complex (> 3 abnormalities)	AZA	64	45	13.9	TF/R	–	–	NA

Abbreviations: AML = acute myeloid leukemia; AZA = azacitidine; BID = twice daily; BMBL = bone marrow blast; CMML = chronic myelomonocytic leukemia; CR = complete remission; DEC = decitabine; HI-E = hematologic improvement – erythroid; HIN = hematologic improvement – neutrophil; HI−P = hematologic improvement – platelet; HMA = hypomethylating agent; IWG = International Working Group; NA = not applicable; NE = not evaluable; mCR = marrow complete remission; MDS = myelodysplastic syndrome; MLFS = morphologic leukemia-free state; MoCR = morphologic complete remission; SD = stable disease; TF/I = treatment failure/indeterminate; TF/R = treatment failure/resistant.
*Indicates censoring.

rigosertib dose in Cycle 2 and worsened to Grade 3 for 3 days during Cycle 2 and was reported with concurrent Grade 3 bladder spasm. These events improved to Grade 1/2, and the patient died due to non-treatment-related cardiac arrest approximately 1 week after resolution of the last recurrence of dysuria. No other genitourinary AEs required dose interruption or resulted in dose reduction or permanent discontinuation of study treatment. Genitourinary toxicity was largely isolated to one cycle (3 patients) or two cycles (1 patient), with 2 patients experiencing Grade 1 genitourinary AEs that persisted for the duration of the study (5 and 7 cycles, respectively) but did not limit study dosing. Overall, genitourinary toxicity in this Phase 1 study did not affect study drug tolerability or exposure, with a median duration of treatment that was slightly higher (5.5 cycles, range 3–41 cycles) among the 6 patients experiencing genitourinary events than that of the overall study population (4 cycles, range 1–41 cycles).

3.4. Efficacy

Responses according to IWG were observed in all cohorts (Table 4). Among the 16 patients (89%) evaluable for response evaluation, responses were observed in 9 patients (56%) according to disease-specific IWG criteria [19,20], with a median duration of response of 5.8 (range 1.0–32.6) months. Ten of 18 patients (56%) experienced at least a 50% decrease from baseline in bone marrow blast percentage, and transfusion independence (i.e., not requiring blood products within a 56-day period) was achieved in 5 patients (28%), all of whom were red blood cell transfusion independent for 58–162 days (median 69 days) and 3 of whom were also platelet transfusion independent for 121–162 days (median 133 days).

Of the 9 evaluable patients with MDS/CMML, 7 patients (78%) achieved a response to study treatment, including 2 patients with complete remission and 5 patients with marrow complete remission. Five of the 7 responders were HMA naïve and 2 had received prior HMA therapy. Among 4 MDS patients who had received prior HMA therapy, 2 patients responded (1 complete remission and 1 marrow complete remission with hematologic improvement; best prior response of stable disease to an HMA alone) and 2 patients had stable disease. Hematologic improvement was observed in at least one lineage for 5 of the responding patients.

Of the 7 evaluable patients with AML, 2 patients (29%) achieved a response to study treatment, including 1 patient with morphologic leukemia-free state and 1 patient with morphologic complete remission, both of whom were HMA naïve and had each received 1 prior regimen (supportive care for 1 patient and chemotherapy for 1 patient).

4. Discussion

While azacitidine is the standard of care for higher-risk MDS patients, all responding patients will ultimately relapse or progress, after which survival outcomes are poor due to a lack of effective treatment options following HMA failure [5,6].

Combination therapy strategies have been explored under the hypothesis that clinical activity to HMA therapy may be improved with doublet therapy compared with monotherapy due to possible synergistic mechanisms of action, and the future of the MDS treatment landscape appears to be trending toward novel combination approaches [4,23]. Azacitidine plus vorinostat yielded an objective response rate of 70% in 33 patients with higher-risk MDS [24], and azacitidine plus lenalidomide induced an objective response rate of 72% among 36 patients [25]. While these results are promising, the efficacy of these and other doublet therapies has not yet been confirmed, as response rates have not translated into improved survival outcomes [4]. Many of these combination regimens are also limited by overlapping toxicities induced by each of the combination partners, often resulting in substantial dose modification or discontinuation of one or more investigational agents, which may contribute to the lack of overall efficacy observed with these regimens [4]. Conversely, doublet therapy with standard dose azacitidine and oral rigosertib in this Phase 1 dose escalation exhibited limited overlapping safety profiles, suggesting that repetitive cycles of the combination could be safely administered (up to 3.4 years).

Doublet therapy with sequential oral rigosertib with standard azacitidine (75 mg/m^2/day) is hypothesized to induce clinical benefit while mitigating toxicity due to unique mechanisms of action and synergistic interaction. This novel combination was well tolerated with respect to myelosuppression in the current Phase 1 dose escalation in patients with MDS and AML, with an AE profile that does not differ substantially from that of azacitidine monotherapy. The most frequently observed AEs with the rigosertib/azacitidine combination were diarrhea, constipation, fatigue, and nausea, which are also observed with azacitidine monotherapy, albeit as a slightly lower rate for diarrhea (50% in the combination vs 36% with azacitidine monotherapy), constipation (44% in the combination vs 34% with azacitidine monotherapy), and fatigue (44% in the combination vs 36% with azacitidine monotherapy) [26]. Unique genitourinary toxicities were observed with the combination. Furthermore, the oral administration of rigosertib, which is highly preferable to intravenous dosing for patient comfort and compliance, exhibited sufficient tolerability to enable safe administration every day for 21 days at a median relative dose intensity of 80% in combination with 7 days of standard azacitidine.

Findings from this study were also consistent with preclinical cardiovascular safety studies, which indicated that the human ether-à-go-go related gene potassium ion channel assay was negative and that no electrocardiographic abnormalities or cardiac toxicities were observed in dogs treated with high doses of rigosertib. In the current Phase 1 dose escalation, no severe treatment-related cardiac toxicity was observed and no evidence of prolonged QTc intervals associated with rigosertib treatment was detected. Additionally, no serious infections or bleeding disorders were observed. The absence of these potentially life-threatening AEs are of particular importance for the older MDS and AML populations.

No DLTs were observed up to the maximum dose level tested in the Phase 1 dose-escalation portion of the study (840 mg/day); thus, no MTD could be reached. The initial RP2D was therefore 840 mg/day. However, in a previous Phase 1 dose-escalation study of rigosertib oral monotherapy in 37 patients with MDS, the MTD of rigosertib monotherapy was determined to be 560 BID (1120 mg/day) based on DLTs (2 episodes of Grade 3 dysuria and 1 episode of shortness of breath in 2 patients) observed at 700 mg BID (1400 mg/day) [22]. Thus, Phase 2 studies are also investigating rigosertib at a dose of 1120 mg/day to evaluate whether the monotherapy MTD could also be safety administered in combination with azacitidine.

The majority of patients in the study population will not have any response using the IWG response criteria. Thus, in the current study, the objective response rate of 56% overall (78% in MDS/CMML and 29% in AML) in a relapsed/refractory population where 83% had received prior therapy represents a promising efficacy signal given the paucity of standard therapies for a patient population with such a poor prognosis. Responses in patients who had failed to respond to prior therapy with a single-agent HMA but who responded with the addition of rigosertib to the HMA, is an important observation of the potential to reverse clinical epigenetic resistance and should be explored in further studies. Oral rigosertib and azacitidine combination therapy also induced transfusion independence for approximately one-third of patients during treatment, which is consistent with prior clinical experience with oral rigosertib monotherapy [17].

These Phase 1 findings support further clinical development of the novel sequential combination of oral rigosertib and standard dose azacitidine. Studies are ongoing to determine the role of the mutated Ras pathway for responding patients to the doublet in patients with MDS. The preliminary safety data suggest that overlapping toxicities were not observed with the combination of rigosertib and azacitidine.

This allows for tolerable repetitive administration, which sets this combination apart from other combination regimens that are characterized by cumulative toxicity that limits tolerability and exposure and therefore efficacy in this patient population [4]. Furthermore, the ability to administer rigosertib orally offers a more convenient treatment option for patients, which may improve treatment compliance and result in improved clinical outcomes [27].

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