Rigosertib Oral in Transfusion Dependent Lower Risk Myelodysplastic Syndromes (LR-MDS): Optimization of Dose and Rate of Transfusion Independence (TI) or Transfusion Reduction (TR) in a Single-Arm Phase 2 Study

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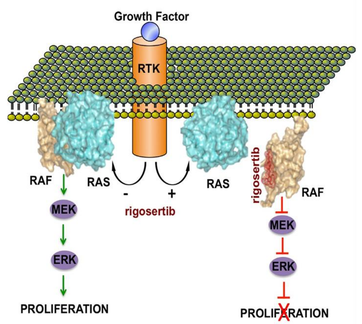
BACKGROUND

Rigosertib, a small molecule, interferes with the RAS-binding domains of RAF kinases and inhibits the RAS-RAF-MEK and the PI3Ks pathways (Athuluri-Divakar SK, Cell 2016;165:643) (Figure 1). Rigosertib IV and oral is currently being tested in clinical trials as a single agent, and in combination in patients MDS. LR-MDS patients have limited treatment options and a large number are transfusion dependent (Raza A, Expert Opinion 2016, 4:9). Erythropoiesis stimulating agents (ESA) are the first line of therapy for LR-MDS patients, but the overall response rate remains low. Thus, novel strategies with the goal of red blood cell (RBC) transfusion reduction (TR) & independence (TI) are required. We expand an earlier report (Raza A, ASH 2013 #2745) on rigosertib oral in LR-MDS with updates on dose optimization on the frequency of TI or TR.

Figure 1. Rigosertib



METHODS

Rigosertib oral was tested in this phase 2 study in LR (intermediate-1 or low risk per IPSS) transfusion-dependent MDS patients. Fifty-four (65.9%) patients had received ESA prior to study. Rigosertib was administered to RBC transfusion-dependent patients; defined as requiring a minimum of 4 packed red blood cell (PRBC) units over 8 weeks. Patients were eligible for efficacy analysis if they received a minimum of 8 weeks of rigosertib in their assigned dosing cohort. Erythrocyte stimulating agents (ESAs) were allowed on study. TI defined as no PRBC transfusions over a period of 8 sequential weeks; TR a reduction in 4 or more RBC units over a period of 8 sequential weeks.

RESULTS

Eighty-two patients with a median age of 70 years (range 54-90) were enrolled between May 2012 and February 2015 (Table 1), at 5 clinical sites, and received a median of 5.4 months (range 0.1-28.8) of oral rigosertib. Of the 82 enrolled patients, 9 patients were treated with 560 mg BID continuously, 7 patients treated with 560 mg in the AM and 280 mg in the PM continuously, 35 patients treated with 560mg BID intermittently (as defined as 2 out of 3 weeks), 31 patients treated with 560mg in the AM and 280mg in the PM intermittently. Sixty patients were treated with ESA and oral rigosertib while on study (Table 2). Continuous rigosertib dosing cohorts were closed early due to higher urinary adverse events & no improvement in efficacy.

EFFICACY

Of the 82 patients, 66 patients received intermittent dosing for at least 8 consecutive weeks; and 20 of 62 evaluable patients (32%) achieved TI lasting 8 to 85+ weeks; with a median of 18 weeks. The highest rate of TI (44%) was observed in the 560 mg BID intermittent cohort: 15 of 34 eligible patients achieved TI lasting 8 to 85+ weeks; with a median of 18 weeks (Table 3). Ninty-three percent (93%) of these 15 patients received rigosertib with continued ESA.

Table 1. Patient Characteristics

Number of patients (%)

	560 mg BID daily N = 9	560 mg BID 2/3 weeks N = 35	560 mg/280 mg 2/3 weeks N = 31	560 mg/280 mg daily N = 7	Total N = 82
Age (years)					
< 65	0	5 (14.3)	4 (12.9)	0	9 (11.0)
65-74	7 (77.8)	15 (42.9)	11 (35.5)	2 (28.6)	35 (42.7)
≥ 75	2 (22.2)	15 (42.9)	16 (51.6)	5 (71.4)	38 (46.3)
Median	70	74	75	78	74
Range	66 - 76	54 - 84	56 - 90	67 - 84	54 - 90
Sex					
Female	4 (44.4)	14 (40.0)	6 (19.4)	3 (42.9)	27 (32.9)
Male	5 (55.6)	21 (60.0)	25 (80.6)	4 (57.1)	55 (67.1)
Race					
Asian	1 (11.1)	0	2 (6.5)	0	3 (3.7)
Black	0	2 (5.7)	1 (3.2)	1 (14.3)	4 (4.9)
Hispanic	0	1 (2.9)	0	1 (14.3)	2 (2.4)
White	8 (88.9)	32 (91.4)	28 (90.3)	5 (71.4)	73 (89.0)
Performance status					
ECOG 0	8 (88.9)	26 (74.3)	18 (58.1)	3 (42.9)	55 (67.1)
ECOG 1	1 (11.1)	4 (11.4)	10 (32.3)	3 (42.9)	18 (22.0)
ECOG 2	0	5 (14.3)	2 (6.5)	1 (14.3)	8 (9.8)
Missing	0	0	1 (3.2)	0	1 (1.2)

Table 2. Patient Disposition

Number of patients (%)

	560 mg BID daily N = 9	560 mg BID 2/3 weeks N = 35	560 mg/280 mg 2/3 weeks N = 31	560 mg/280 mg daily N = 7	Total N = 82
Withdrawn from study	9 (100)	35 (100)	31 (100)	7 (100)	82 (100)
Disease progression	-	4 (11.4)	8 (25.8)	-	12 (14.6)
No Hematologic response	3 (33.3)	5 (14.3)	5 (16.1)	2 (28.6)	15 (18.3)
Death	1 (11.1)	1 (2.9)	-	-	2 (2.4)
Toxicity/Adverse event	1 (11.1)	9 (25.7)	3 (9.7)	2 (28.6)	15 (18.3)
Patient request	2 (22.2)	6 (17.1)	7 (22.6)	-	15 (18.3)
Protocol non-compliance	-	1 (2.9)	-	-	1 (1.2)
Investigator decision	2 (22.2)	9 (25.7)	8 (25.8)	3 (42.9)	22 (26.8)

Table 3. Transfusion Endpoints

	560 mg BID daily N = 9	560 mg BID 2/3 weeks N = 35	560 mg/280 mg 2/3 weeks N = 31	560 mg/280 mg daily N = 7	Total N = 82
RBC transfusion units in 8 wks prior to entry					
Count	9 (100)	35 (100)	31 (100)	7 (100)	82 (100)
Median	4	4	5	4	4
Range	4 - 5	4 - 11	4 - 10	4 - 6	4 - 11
RBC transfusion units in 8 wks after entry					
Count	9 (100)	34 (97.1)	28 (90.3)	7 (100)	78 (95.1)
Median	6	4	6	6	6
Range	2 - 16	0 - 14	0 - 12	4 - 8	0 - 16
8-week change in RBC transfusion units					
Count	9 (100)	34 (97.1)	28 (90.3)	7 (100)	78 (95.1)
Median	1	0	0	2	0
Range	-2 - 12	-6 - 7	-4 - 4	0 - 4	-6 - 12
Transfusion reduction/independence					
Yes	2 (22.2)	17 (48.6)	5 (16.1)	0	24 (29.3)
No	7 (77.8)	17 (48.6)	23 (74.2)	7 (100)	54 (65.9)
Not evaluable	0	1 (2.9)	3 (9.7)	0	4 (4.9)
Rate (%)	22.2	50.0	17.9	0.0	30.8
95% confidence interval	2.8, 60.0	32.4, 67.6	6.1, 36.9	0.0, 41.0	20.8, 42.2
≥8-week Transfusion independence					
Yes	2 (22.2)	15 (42.9)	5 (16.1)	0	22 (26.8)
No	7 (77.8)	19 (54.3)	23 (74.2)	7 (100)	56 (68.3)
Not evaluable	0	1 (2.9)	3 (9.7)	0	4 (4.9)
Rate (%)	22.2	**44.1**	17.9	0	28.2
95% confidence interval	2.8, 60.0	27.2, 62.1	6.1, 36.9	0.0, 41.0	18.6, 39.5

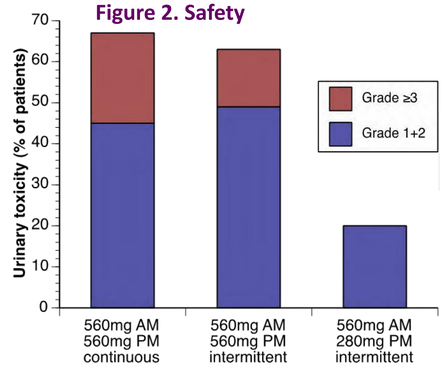
TI = no RBC transfusion over sequential 8 weeks TR = reduction in RBC transfusion of 4 or more units over sequential 8 weeks

SAFETY

The safety assessable population included all patients who received at least one dose of rigosertib (n = 82). All patients received at least 1 week of rigosertib treatment. Continuous rigosertib dosing cohorts were closed early due to higher urinary adverse events (AEs). For all intermittent patients (n=66); the most frequent treatment emergent adverse events observed were urinary with pollakiuria (42.4%), fatigue and micturition urgency (33.3%), urinary tract pain (28.8%), hematuria and dysuria (24.2%). Intermittent and reduced dosing of rigosertib (560 mg AM, 280 mg PM during 14 days of 21-day cycles) was associated with a significantly reduced incidence of urinary toxicity (Figure 2). All AEs were reversible once rigosertib dosing was reduced or discontinued. Strategies are under investigation to ameliorate or manage the urinary AEs:

- Good oral hydration
- Patients should empty their bladder prior to bedtime
- Patients perform AM urinary dipstick
- Sodium bicarbonate tablets: 650 mg orally TID. Further dosing is to be adjusted by the investigator to achieve desired urine pH of 7.5 - 8.5
- Pyridium considered at discretion of clinician.

Figure 2. Safety



Notably, no significant treatment emergent myelosuppression, or other notable AEs were evident in these patients.

CONCLUSION

Oral rigosertib treatment resulted in high rates of TR and TI. Patients administered rigosertib for 2 out of 3 weeks at a dose of 560 mg BID (1120 mg over 24 hours) achieved an impressive TI rate of 44% (15/34). Based on the rate of TI, and the observed urinary AEs, the risk benefit profile of oral intermittent dosing is favorable. Oral rigosertib at a total dose of 1120 mg over 24 hours administered intermittently in HR-MDS pts in combination with azacitidine is now being studied; with further exploration to optimize dose and mitigate urinary AEs.

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