Successful Risk-Mitigation Strategies to Reduce the Incidence of Hematuria in Patients (Pts) with Myelodysplastic Syndromes (MDS) Treated with Oral Rigosertib (RIGO) in Combination with Azacitidine (AZA)

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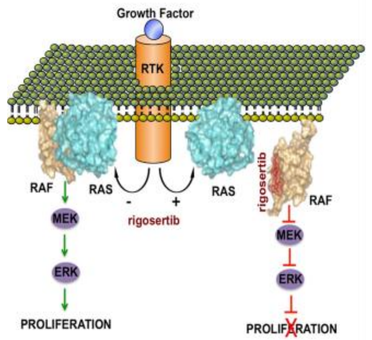
Rigosertib, a small molecule, interferes with the RAS-binding domains of RAF kinases and inhibits the RAS-RAF-MEK and the PI3Ks pathways (Figure 1).[1]

OBJECTIVE

MDS are a rare group of blood cancers that occur as a result of disordered development of blood cells within the bone marrow. MDS occurs most commonly in older adults, with a median age at diagnosis of ≥65 years. Previous studies have demonstrated oral rigosertib at a dose of 560 mg BID in Low-Risk (LR) MDS pts show a transfusion independence rate (IWG2006)[2] criteria of 44%.[3] Oral rigosertib in combination with AZA in pts with Higher-risk (HR) MDS is being studied.[4] In monotherapy & combination trials, oral rigosertib has been associated with an AE of interest, hematuria; shown to be dose & administration scheme.[5] Reported are results of a dose exploration study in HR-MDS[6] pts focusing on impact of risk-mitigation strategies in minimizing incidence of urinary adverse events (UAEs) including hematuria.

Figure 1. Rigosertib



METHODS

Pts with MDS or leukemia (N=168) were given oral rigosertib monotherapy in doses escalating from 70 mg - 700 mg twice daily for either 14 consecutive days per 21-day cycle (intermittent schedule) or for 21 consecutive days per 21-day cycle (continuous schedule). In Part 1 of a combination trial of oral rigosertib with injectable AZA 75 mg/m2/d one week/month starting on Day 8, (N=54) pts were administered rigosertib twice daily on Day 1-21 of a 28-day cycle in escalating cohorts with a previous max dose of 560 mg qAM & 280 mg qPM & AZA administered (total RIGO dose 840 mg; N = 42). In the ongoing Part 2 Study, oral rigosertib at a total dose of 1120 mg in 2 cohorts 560 mg BID or 840mg/280mg is administered with AZA in HR-MDS pts; applying risk-mitigation strategies to minimize hematuria (Table 1).

Table 1: Risk-Mitigation Strategies to Minimize Hematuria

2nd RIGO dose must be administered at 3 PM (±1 hour) at least 2 hours after lunch to avoid a nocturnal bladder dwell time[7]	Oral hydration of at least two liters of fluid per day is encouraged	Mandatory bladder emptying prior to bedtime	Urine pH approximately 2 hrs after AM dose. Sodium bicarbonate suggested administration of 650 TID if pH tests < 7.5

Table 2: Hematuria Comparison Between Rigosertib Monotherapy & Combination Therapy*

Patients on monotherapy	168
Patients with hematuria	37 (22%)
Patients with grade 1 or 2 hematuria	35 (21%)
Patients with grade ≥3 hematuria	6 (3.5%)
All Patients on Combination Part I (Rigosertib 560mg/280mg & Azacitidine)	42
Patients with hematuria	20 (48%)
Patients with grade 1 or 2 hematuria	17 (40%)
Patients with grade ≥3 hematuria	5 (12%)
All Patients on Combination Part 2 with risk mitigation strategy (Rigosertib (1120mg) & Azacitidine	37
Patients with hematuria	4 (11%)
Patients with grade 1 or 2 hematuria	4 (11%)
Patients with grade ≥3 hematuria	0 (0%)

AEs were graded per National Cancer Institute's Common Toxicity Criteria version 4.0 (2009)

RESULTS

In safety-evaluable pts in MDS and leukemia studies with oral rigosertib monotherapy (N = 168) UAEs were identified related to rigosertib at a higher frequency during continuous rigosertib dosing. Due to UAEs, continuous 560 mg BID dosing is no longer being studied. For pts on intermittent rigosertib dosing, the most frequent treatment emergent AEs observed were urinary: pollakiuria (42.4%), micturition urgency (33.3%), urinary tract pain (28.8%), hematuria or dysuria (24.2% each). Incidence of hematuria of any grade with single agent AZA is 6.3 % & Grade ≥3 2.3%.[8] In the combination trial of rigosertib (total dose of 840 mg) & AZA, the incidence of hematuria was 48%, with Grade ≥3 AEs of 12%. In 37 pts studied with oral rigosertib 1120 mg & AZA, & use of risk-mitigating strategies to minimize hematuria, Grade 1 & 2 hematuria = 11%; ≥3 Grade Hematuria = 0 have been seen to date (Table 2).

CONCLUSION

Dose optimization & risk mitigation strategies to minimize UAEs associated with oral rigosertib in combination with AZA have resulted, to date, in a decrease in frequency of hematuria (all grades) from 48% to 11%; with no Gr 3 AEs. Minimization of hematuria permits pts to continue treatment to optimize benefit. Reduction in incidence of hematuria also enables the continued study of oral rigosertib in LR-MDS based on the promising TI Rate previously reported.[3]

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