Comprehensive Analysis of Safety: Rigosertib in 557 Patients with Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)

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BACKGROUND

Rigosertib (RIG) is a RAS-mimetic interacting with the RAS-binding domains of RAF kinases, preventing their binding to RAS and inhibiting the RAS-RAF- MEK pathway. (Athuluri-Divakar, et al, Cell 165:643, 2016).). Mutations of RAS are involved in proliferative processes important in neoplastic transformation (Gil-Bazo, et.al, Cancer Biology and Therapy 17:719, 2016).

As of May 2016, 557 patients with MDS or AML received IV (N=335) or oral (N=222) rigosertib. All IV rigosertib was administered as monotherapy. Oral rigosertib was administered as monotherapy (N=168) or in combination with injectable azacitidine (AZA; N=54). Safety results across this rigosertib development program have not been presented.

METHODS / RESULTS

We reviewed all treatment-emergent adverse events (TEAEs among patients with MDS/AML treated with rigosertib IV monotherapy, rigosertib oral monotherapy, or in combination therapy, overall and by grade of severity (Tables 1-3). Due to the unexpected observation of urinary AEs throughout the conduct of clinical trials, including occasional gross hematuria, we analyzed urinary AEs in greater detail.

Table 1: Treatment-emergent Adverse Events Reported in ≥10% of Patients with MDS/AML receiving rigosertib intravenous monotherapy (N = 335)

MedDRA Preferred Term	All Grades	Grade ≥3
Any treatment-emergent adverse event	353 (99)	291 (82)
Fatigue	116 (33)	16 (5)
Nausea	106 (30)	4 (1)
Diarrhoea	97 (27)	6 (2)
Constipation	90 (25)	1 (<1)
Anaemia	85 (24)	74 (21)
Pyrexia	84 (24)	13 (4)
Dyspnoea	66 (19)	14 (4)
Oedema peripheral	56 (16)	2 (1)
Insomnia	55 (15)	3 (1)
Headache	50 (14)	4 (1)
Pneumonia	48 (14)	42 (12)
Abdominal pain	48 (14)	4 (1)
Vomiting	48 (14)	3 (1)
Febrile neutropenia	46 (13)	45 (13)
Cough	46 (13)	0
Dizziness	46 (13)	0
Epistaxis	45 (13)	7 (2)
Thrombocytopenia	41 (12)	38 (11)
Hypokalaemia	41 (12)	11 (3)
Back pain	40 (11)	5 (1)
Urinary tract infection	37 (10)	11 (3)
Haematuria	14(4)*	4(1)

* Adverse Event of Special Interest (AESI)

Table 2: Treatment-emergent Adverse Events Reported in ≥10% of Patients with MDS/AML receiving rigosertib oral monotherapy (N = 168)

MedDRA Preferred Term	All Grades	Grade ≥3
Any treatment-emergent adverse event	163 (97)	105 (63)
Pollakiuria	58 (35)	0
Fatigue	54 (32)	5 (3)
Dysuria	48 (29)	3 (2)
Diarrhoea	43 (26)	1 (1)
Haematuria	41 (24)	6 (4)
Micturition urgency	37 (22)	1 (1)
Urinary tract infection	35 (21)	7 (4)
Anaemia	34 (20)	29 (17)
Urinary tract pain	33 (20)	2 (1)
Nausea	32 (19)	0
Dyspnoea	27 (16)	4 (2)
Oedema peripheral	27 (16)	0
Dizziness	26 (15)	0
Constipation	24 (14)	0
Cough	22 (13)	1 (1)
Decreased appetite	21 (13)	0
Headache	21 (13)	0
Upper respiratory tract infection	20 (12)	0
Abdominal pain	17 (10)	2 (1)
Pain in extremity	17 (10)	0

Table 3: Treatment-emergent Adverse Events Reported in ≥10% of Patients with MDS/AML receiving oral rigosertib combination with AZA (N = 54)

MedDRA Preferred Term	All Grades	Grade ≥3
Any treatment-emergent adverse event	54 (100)	42 (78)
Nausea	22 (41)	0
Fatigue	21 (39)	1 (2)
Diarrhoea	20 (37)	1 (2)
Constipation	20 (37)	0
Dysuria	15 (28)	2 (4)
Decreased appetite	15 (28)	0
Haematuria	14 (26)	3 (6)
Pyrexia	13 (24)	0
Dizziness	12 (22)	0
Thrombocytopenia	11 (20)	11 (20)
Back pain	11 (20)	1 (2)
Dyspnoea	11 (20)	1 (2)
Cough	11 (20)	0
Neutropenia	10 (19)	10 (19)
Pneumonia	10 (19)	9 (17)
Vomiting	10 (19)	0
Epistaxis	9 (17)	0
Pollakiuria	9 (17)	0
Rash	9 (17)	0
Urinary tract infection	8 (15)	4 (7)
Hypokalaemia	8 (15)	2 (4)
Arthralgia	8 (15)	1 (2)
Fall	8 (15)	0
Oedema peripheral	8 (15)	0
Anaemia	7 (13)	6 (11)
Hypotension	7 (13)	2 (4)
Pain	7 (13)	1 (2)
Abdominal pain	7 (13)	0
Contusion	7 (13)	0
Pain in extremity	7 (13)	0
Headache	6 (11)	1 (2)
Upper respiratory tract infection	6 (11)	1 (2)
Dysphagia	6 (11)	0
Gingival bleeding	6 (11)	0
Hypomagnesaemia	6 (11)	0

In patients evaluated for gross hematuria the cause of bleeding was bladder inflammation. Urinary and plasma concentration of RIG were examined to assess dose relationship and to understand the potential cause for bladder inflammation. The pharmacokinetic data revealed that the bladder concentration of RIG, during the sleep cycle (8-24 hour urine collection window) was dose proportional and, approximately 29 and 19 uM for the dose of 560/560 mg and 560/280 mg, respectively. The lower PM dose which led to the lower bladder concentration of RIG at night had a significant impact on reducing Grade 3 urinary toxicity.

According to the azacitidine package insert, the incidence of gross hematuria of any grade with single agent azacitidine is 6.3 % and Grade ≥ 3 of 2.3%.

Evaluations performed of hematuria among 5 studies of oral rigosertib (4 monotherapy & 1 in combination with AZA) in patients with MDS/AML (Table 4).

Table 4: Events of Hematuria in Patients with MDS/AML Treated with Oral Rigosertib as Monotherapy or in Combination Therapy

Number of patients	222
Patients on rigosertib monotherapy*	168
Patients with hematuria	41 (24%)
Patients with Grade 3 hematuria	6 (4%)
Patients with single event	28 (16.6%)
Patients with > 1 event	13 (7.7%)
Patients on combination therapy**	54
Patients with hematuria	14 (26%)
Patients with Grade 3 hematuria	3 (6%)
Patients with single event	10 (18.5%)
Patients with > 1 event	6 (11.1)

*Includes studies 09-01, 09-02, 09-05, and 09-07

**Study 09-08: oral rigosertib in combination with IV/SC AZA

A patient with multiple occurrences of hematuria is counted only once

CONCLUSION

Conclusions: Rigosertib IV or oral formulations or in combination therapy were generally well tolerated in clinical trials in over 500 patients with MDS/AML. Gastrointestinal AEs were most frequently reported with IV rigosertib and genitourinary AEs were seen more often with oral than IV dosing. The greater rate of urinary AEs in the oral than in the IV studies indicates a need for close monitoring of these patients and proactive risk management, such as adequate hydration, timing of administration of the second dose, and bladder emptying prior to sleep to avoid long bladder dwell time. Studies are being designed to optimize dosing and schedule to maximize efficacy and minimize hematuria of oral rigosertib. A randomized trial of oral rigosertib/azacitidine versus azacitidine will be required to optimize the clinical benefit and safety in the management of higher-risk patients with MDS.

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