

Amelioration of Rigosertib Treatment Related Genitourinary Adverse Events in Patients with Myelodysplastic Syndromes: Implementation of Novel Dosing Regimen Derived through Pharmacokinetic Modeling in Phase 2 Study of Oral Rigosertib in Combination with Azacitidine

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INTRODUCTION

Rigosertib

- Small molecule inhibitor of cellular signaling pathways in cancer cells by acting as a Ras mimetic
- Inhibitory effect is mediated by Rigosertib binding to the Ras-binding domain found in many Ras effector proteins¹

Clinical Testing of Oral Rigosertib

- 560 mg BID (q12hr; 2/3 wks) associated with high rates of transfusion independence but with observed genitourinary (GU) adverse events (AEs) in low risk MDS patients²
- Reduction in the PM dose to 280 mg led to a decrease in GU AEs, suggesting a causal relationship with nocturnal bladder drug concentration
- Rigosertib (560/280 mg Q12hrs, 3/4 weeks) + Azacitidine (75mg/m² IV x 7 days q28 days): ORR was 77%; 88% for the HMA naïve group and importantly 60% for the HMA relapsed/refractory group for the high risk MDS patients. However, there was significant GU AE's
- It has been established that GU AE's were unlikely to be related to the higher systemic exposure of the drug³ but attributed to the nocturnal dwell time of drug in the bladder of patients treated with continuous oral administration (3/4 weeks)

OBJECTIVE

The impressive response rate to oral Rigosertib, in the combination treatment, was also associated with significant GU AE's. Hence, it is important to understand the underlying cause and devise ways to maximize response rates with minimization of GU AE's.

This research applied pharmacokinetic modeling and simulation to assess the systemic and bladder exposure of Rigosertib after repeated oral dosing. The aim was to identify an oral dosing regimen for Rigosertib that would maximize systemic exposure with minimized bladder concentration during the sleep cycle, thereby potentially mitigating or eliminating the GU AE's.

METHODS

- A 2-compartment model with 1st order absorption (**Figure 1**) used to generate a virtual population of 100 patients
- Model simulations were then performed to evaluate the steady state systemic (C_{max} , AUC) and urinary exposure (nocturnal bladder concentration) of Rigosertib after BID treatment with different doses (70-840 mg) and dosing times (8hr and 12hr spacing, **Figure 2**)

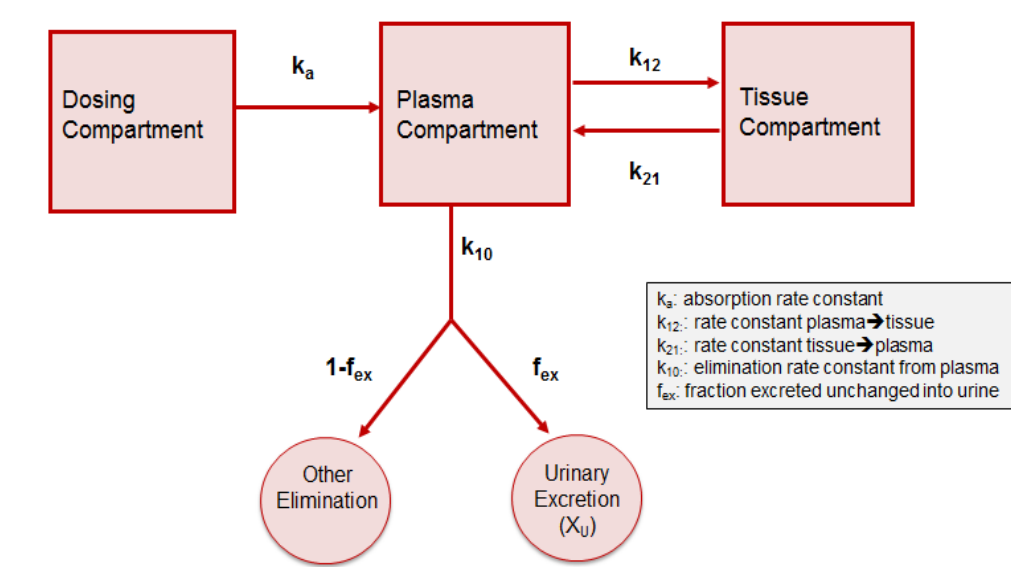


Figure 1. Schematic representation of compartment model of plasma concentration and cumulative urinary excretion of rigosertib following oral administration.

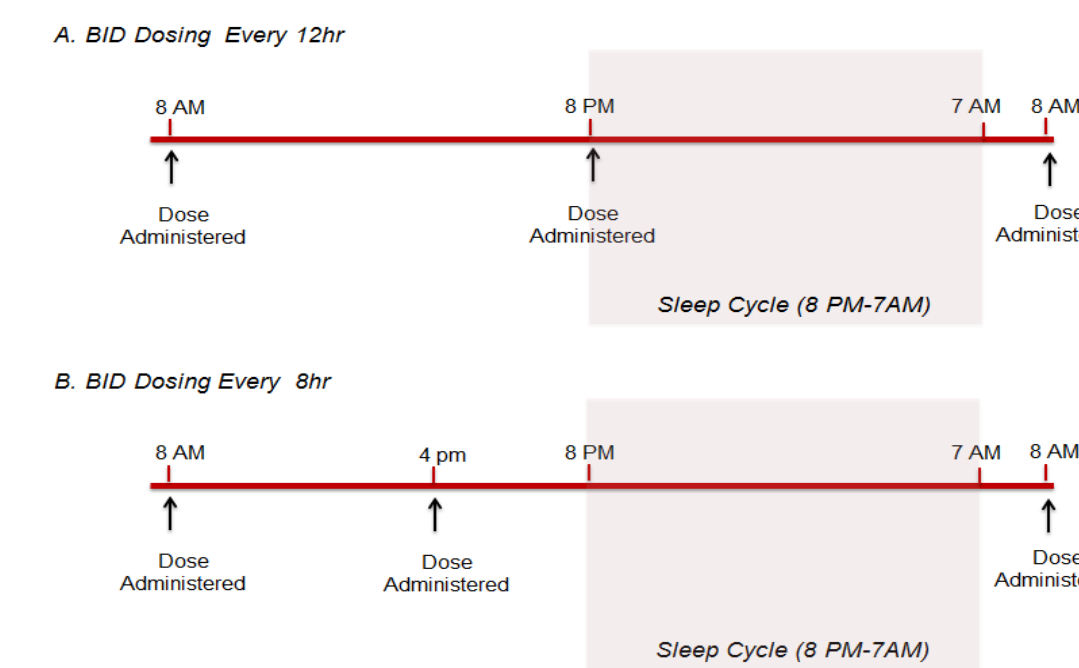


Figure 2. Study designs for 8hr and 12hr dosing regimens

- Optimal dosing regimens were selected for evaluation in an ongoing Phase 2 study in HR-MDS patients in combination with azacitidine
- Model was validated by: 1. comparing the predicted and observed systemic exposure; and 2. comparing GU AE's events from the pre- and post-optimization of dosing regimen
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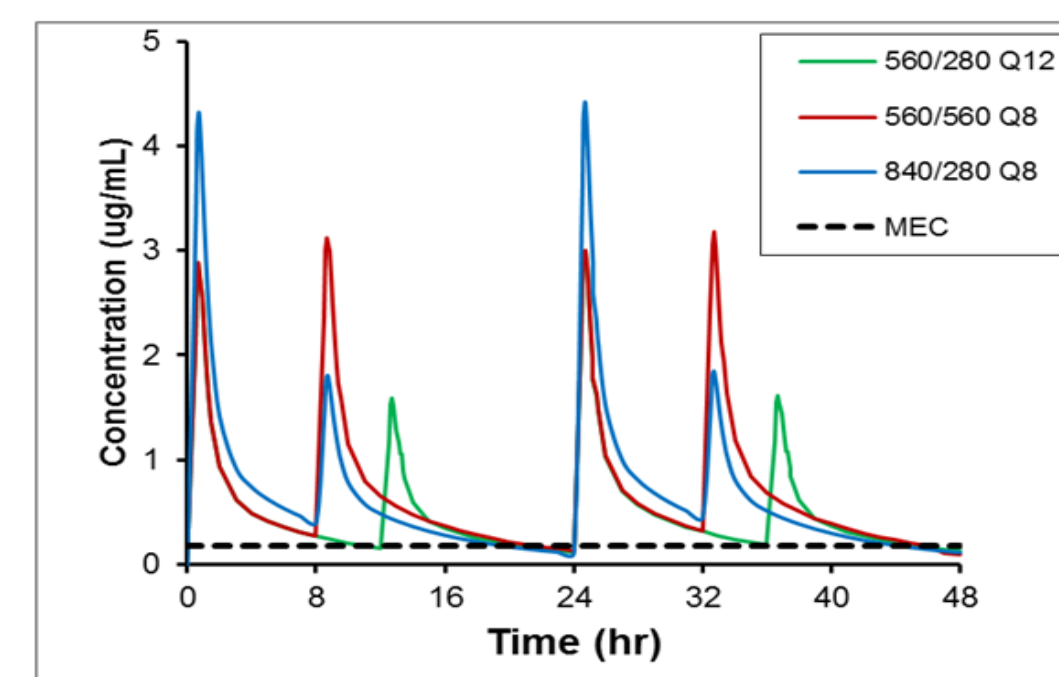


Figure 3. Model simulated rigosertib plasma concentration-time profiles following oral administration of various dosing regimens. Included in the figure is the minimum effective concentration (0.175 ug/mL).

Table 1. Model-Simulated Plasma and Bladder Exposure of Rigosertib for Various Dosing Regimens

PK Parameter	560 mg Q12	560/280 mg 8hr spacing	560/560 mg 8hr spacing	840/280 mg 8hr spacing
C_{max} (ug/mL)	3.31 (1.11)	3.22 (1.02)	3.42 (1.18)	4.78 (1.51)
AUC ₀₋₂₄ (ug-hr/mL)	16.5 (12.3)	12.4 (9.21)	16.5 (12.3)	16.5 (12.3)
Sleep Cycle	29.8	7.37	11.8	8.85
$C_{bladder}$ (ug/mL)	(10.4)	(6.09)	(7.69)	(6.36)

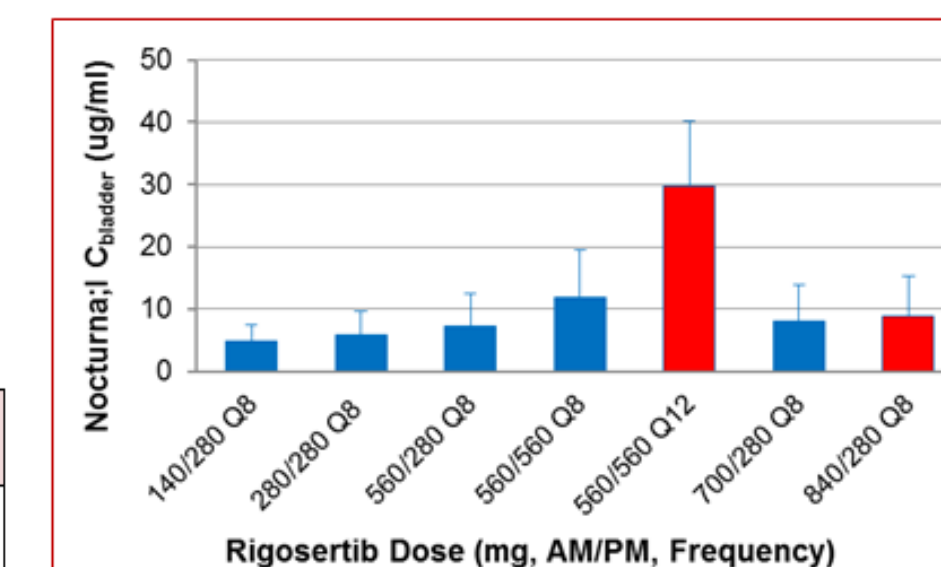
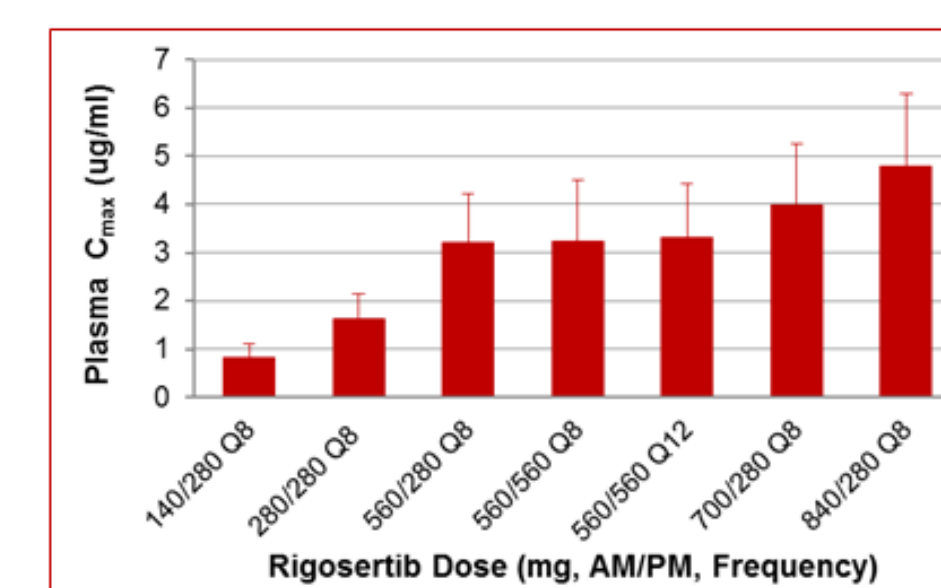


Figure 4. Model simulated plasma C_{max} (upper panel) and nocturnal bladder concentration (lower panel) effect of dose and dosing schedule

RESULTS

- Model simulations demonstrated that duration of plasma exposure above MEC was not changed by varying the dosing regimen (**Figure 3**)
- BID dosing, with the dosing interval of 8 hr, predicted to reduce the bladder concentration by as much as 70% during sleep without compromising systemic drug exposure (**Figure 4, Table 1**)
- Model simulated Rigosertib exposure compared favorably with data from patients treated with the novel twice daily dosing regimens (560mg/560mg and 840 mg/280mg, dosing interval of 8 hours), thereby validating the model (**Table 2**)
- Preliminary safety data (**Table 3**) demonstrates that the Grade 3 GU AEs were significantly reduced (12%) with the optimized dosing regimen compared to the pre-optimized dosing regimen (29%) despite using a higher total dose of drug (1120 mg vs 840 mg)

Table 2. Rigosertib Systemic Exposure Following Oral Dosing to MDS Patients –Comparison to Model Simulations

Dosing Regimen	Observed Data		Model Predicted Data	
	C_{max} (ug/mL)	AUC ₀₋₄ (ug-hr/mL)	C_{max} (ug/mL)	AUC ₀₋₄ (ug-hr/mL)
560/560 mg 8hr spacing (n = 14)	2.93 (1.89)	5.62 (3.78)	3.42 (1.18)	5.07 (2.72)
840/280 mg 8hr spacing (n = 10)	5.87 (3.11)	11.0 (6.56)	4.78 (1.51)	7.3 (3.71)

Table 3. Incidence of Urinary Adverse Events Among High Risk MDS Patients Treated with Different Dosing Schedules of Rigosertib

	Urinary AEs (% of Patients)		
	560 / 280 mg 12 hr spacing Combination with AZA (pre-optimized regimen)	560/560 mg 8hr spacing Combination with AZA	840/280 mg 8hr spacing Combination with AZA
Grade 3	29	0	12
Grade 1/2	71	26	28
N	42	19	18

CONCLUSIONS

Pharmacokinetic modeling can be utilized to design a dosing regimen directed at reducing the incidence of toxicity. The identified dosing regimen, along with mitigation strategies, successfully reduced the risk of Grade 3 GU AEs of Rigosertib without compromising the duration of systemic exposure of Rigosertib above MEC in HR MDS patients.

REFERENCES

1. Athuluri-Divakar SK, et al. *Cell*. 2016 Apr 21;165(3):643-55.
 2. Raza A, et al. *Blood*. 2017; 130:1689
 3. Maniar M, et al. *ASH. 2018; Poster #3106*
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