Evaluation of Underlying Cause of Genitourinary (GU) Adverse Events (AEs) in Patients with Myelodysplastic Syndromes upon Oral Administration of Rigosertib: Safety and Pharmacokinetic Analysis of Rigosertib across Three Clinical Trials

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INTRODUCTION

Rigosertib

- Oncogenic mutations of Ras genes have been implicated in number of human cancers[1].
- Rigosertib is a small molecule that inhibits cellular signaling in cancer cells by acting as a Ras mimetic[2].
- Rigosertib, as a single agent or in combination, has been evaluated in several clinical trials using various routes of administration.

Clinical Trials of Rigosertib

- As a single agent, Rigosertib was evaluated in a Phase III clinical trial in refractory MDS patients where the drug was administered as a 3 day continuous IV infusion every other week (NCT01241500).
- Rigosertib has also been evaluated in Phase I/II trials via oral route of administration in patients with solid malignancies (NCT01168011); and with myelodysplastic syndromes (NCT01926587).

Pharmacokinetic and Safety analysis was conducted across three clinical trials to evaluate the underlying cause of GU adverse events.

METHODS

Pharmacokinetic analysis of 253 patients was performed as follows

- Study NCT01241500 was conducted with MDS patients (N=184) who were administered Rigosertib by continuous IV infusion (1800 mg/day for 72 hours) every 2 weeks. Blood samples were collected at 6, 24, 30, 48, 56 and 72 hours after infusion initiation.
- In Study NCT01168011, patients with advanced solid tumors (N=33) received oral Rigosertib (560 mg) Q12 hours for 21 days of a 21-day cycle.
- Study NCT01926587, conducted in high risk MDS patients (N=36) with oral administration of Rigosertib in combination with parenteral Azacitidine, evaluated the same AM dose (560 mg) but a lower 280 mg PM dose.
- In study NCT01168011 and NCT01926587, blood samples were collected predose and 0.5, 1, 1.5, 2, 4, 6 and 8 hours after administration of the morning dose of 560 mg.
- For Study NCT01168011, urine was collected for 24 hours (0-4, 4-8 and 8-24 hrs) to determine the percent of dose excreted in urine.
- Rigosertib pharmacokinetic parameters were estimated using non-compartmental analysis.
- The drug concentrations in plasma and urine was determined through multiple reaction monitoring (MRM) by a validated LC-MS/MS assay.

Safety Analysis

- Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 and summarized by system organ class (SOC), preferred term (PT), and worst CTCAE grade per patient.
- Adverse events were summarized by patient, not event.

RESULTS

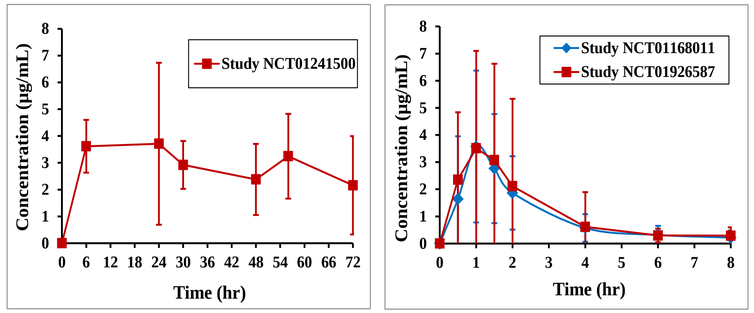

Figure 1. Plasma Concentration of Rigosertib after IV Infusion 1800 mg/day for 3 days (left panel) and oral administration (560 mg) of the morning dose (C1D1) of twice daily (Q12hr) schedule (right panel).

Table 1. Summary of Rigosertib Pharmacokinetic Parameters and Urinary Adverse Events in Two Patient Populations Following Oral Administration

Pharmacokinetic Parameter[a]	Study NCT01168011 (Solid Tumor Patients; N=33)	Study NCT01926587 (High Risk MDS Patients; N=36)
Route of Administration	Oral	Oral
Dose / Dosing Regimen	560 mg bid Q12 hours; Continuous 21 day cycle	560 mg AM/280 mg PM Q12 hours; 3 out of 4 weeks
C_{max} (µg/mL)	3.94 ± 2.98	4.24 ± 3.92
T_{max} (hr)	1.00	1.00
$AUC_{0-\infty}$ (µg-hr/mL)	9.20 ± 6.92	11.6 ± 11.9
Cl/F (L/hr)	94.3 ± 67.4	82.5 ± 56.1
Vss/F (L)	339 ± 324	305 ± 284
$t_{1/2}$ (hr)	2.59 ± 1.06	2.38 ± 1.40
Patients with Urinary Adverse Events		
≥Grade 2	17 of 33 (52%)	17 of 36 (47%)

[a]data presented as mean ± SD except T_{max} (median value reported) following oral administration of 560 mg Rigosertib (C1D1).

- The plasma concentration-time profiles were super imposable (**Figure 1** right panel) for the patients with either solid malignancies or MDS treated with orally administered Rigosertib.
- There was no difference in Rigosertib pharmacokinetic parameters between patient populations (**Table 1**) upon oral administration.

Table 2. Summary of Rigosertib Pharmacokinetic Parameters (week 1; data presented as mean ± SD) and Urinary Adverse Events Following IV Administration.

Pharmacokinetic Parameter	Study NCT01241500 (High Risk MDS Patients; N=184)
Route of Administration	IV Infusion
Dose /Dosing Regimen	1800 mg/day for 3 days; every two weeks
C_{ss} (µg/mL)	3.55 ± 2.36
AUC_{0-24} (µg-hr/mL)	85.1 ± 56.9
Cl (L/hr)	28.0 ± 18.6
Patients with Urinary Adverse Events	
≥Grade 2	19 of 184 (10.0%)

- Approximately 2% of the orally administered dose was recovered in the urine.
- The incidence of grade ≥2 GU adverse events observed with oral dosing was 17 of 33 (52%) and 17 of 36 (47%) in studies NCT01168011 and NCT01926587, respectively.
- The incidence of GU AE's in both the studies was comparable (**Table 1**) even though the PM dose was lower (560 mg vs 280mg).
- Compared to oral dosing, the incidences of GU AE's were dramatically lower (10%) following IV infusion despite 8-fold higher and more prolonged systemic exposure (**Table 2**).

CONCLUSIONS

- Rigosertib displays differential GU adverse events which is probably related to the route of administration and dosing regimen.
- The GU adverse events are independent of the underlying disease state.
- GU AE's are significantly lower when Rigosertib is administered by IV infusion despite of 8 fold higher exposure. This is probably due to the short half-life of drug and dosing holiday of 12 days between two doses.
- The observed incidence of GU AE's upon oral administration is likely related to the dwell time of high concentration of drug in the bladder at night.
- High drug concentration during dwell time could potentially be addressed by deploying a novel dosing regimen derived through pharmacokinetic modeling and simulation[3].

REFERENCES/ACKNOWLEDGEMENTS

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