Oral Formulation of Rigosertib (ON 01910.Na) in Patients with Myelodysplastic Syndrome (MDS) – Phase I Study Results

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Abstract

Background: Rigosertib (ON 01910.Na) is a multi-kinase inhibitor that selectively induces mitotic arrest leading to apoptosis in cancer cells and myeloblasts, while non-toxic to normal cells. Biological activity of the intravenous formulation has been demonstrated in myelodysplastic syndromes (MDS), including an ongoing randomized clinical trial in patients with refractory anemia and excess blasts failing azanucleosides. We report the preliminary results of a safety and efficacy study of a novel oral formulation of rigosertib .

Methods: The trial is a 3 part phase I dose escalation study. The first part addressed bioavailability and tolerability of single oral dosing administered on a weekly basis for 5 weeks, the second included dose escalation, the third represented a dose expansion of the recommended phase 2 dose (RP2D) with absolute biavailability and food/fasting bioavailability studies. Eligibility included any International prognostic Scoring System (IPSS) MDS risk group with at least one cytopenia, failure to respond to at least one prior standard treatment, good performance status (ECOGs 2), adequate kidney and liver functions. Key exclusions included hypoplastic MDS (< 10% cellularity), ascites, history of seizures, uncontrolled hypertension, and history of HIV. Dose limiting toxicity (DLT) was defined as grade 3 or greater non-hematological drug related toxicity or delay in blood count recovery for more than 30 days in the absence of response. Rigosertib dose was escalated based on a defined escalation dose schema (70, 140, 280, 560, and 700 mg). The drug was administered orally twice a day for 14 days of a 21 day cycle.

Results: Between January 2010 and August 2011, 37 MDS patients were enrolled in an ongoing phase I dose escalating study. Pharmacokinetic dose proportionality was established in the 70-700 mg single dose range in the first 3 patients, and pharmacodynamically active concentrations were reached. A subsequent escalation phase enrolled 15 patients who were treated with 70 to 700 mg doses of rigosertib capsules bid for 2 weeks of a 3 week cycle (70mg: N=3; 140 mg: N=2; 280mg: N=2; 560: N=2; 700mg: N=6). The formulation was well tolerated. One patient experienced DLT at the 700mg dose level during the first 3-week cycle (dysuria and shortness of breath). Another patient at this dose level had grade 3 dysuria during cycle 2. The RP2D was identified as 560 mg bid and 22 patients were enrolled in the expansion cohort (part 3). Up to 12 patients in this cohort are undergoing full pharmacokinetic evaluation (absolute bioavailability vs. the IV formulation and food effect). Encouraging signs of activity have been observed, including two marrow CR responses at the 140 and 560 mg dose levels; erythroid response (reduction of at least 4 units of RBC transfusions over 56 days) in four Low/Int-1 risk transfusion dependent MDS patients (3 at 560mg and 1 at 700 mg dose levels). Full PK results as well as clinical activity and tolerability at the RP2D dose level will be presented.

Conclusion: Oral rigosertib is bioavailable and well tolerated. The RP2D was 560 mg bid for 2 weeks of a 3 week with a DLT of dysuria. Early encouraging responses are being confirmed in the expansion phase of the study.

Methods

Rigosertib Background

- Multi-kinase inhibitor
  - Does not affect ATP binding site
  - Inhibits PLK-1 pathway
    - Induces spindle abnormalities and polynumeric centrosomes, resulting in chromosomal catastrophe and apoptosis
  - Inhibits α and β isoforms of PI3 kinase
    - Reduction of Cyclin D1 and Akt phosphorylation correlates with activity of the drug
  - Inhibits activation of anti-apoptotic proteins including Mcl-1
    - Rapid, cycle-dependent induction of apoptosis
- High activity of IV formulation in decreasing BM blasts in higher risk MDS patients
- Development of an oral formulation to facilitate administration

Phase I Trial Methods

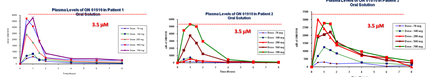
- Phase I dose escalating (70 to 700 mg oral fasting rigosertib dosing bid for 2 out of 3 weeks) study in MDS patients refractory to ESA, lenalinomide or hypomethylating agents
- ESA allowed as concomitant medication
- Escalation to next dose in the absence of drug-related ≥ grade 2 toxicity in either one of the two patients treated for a 21-day first cycle, otherwise, enrollment of 3 to 6 patients per cohort and dose escalation if no more than one dose limiting toxicity (DLT) out of 6 patients
- DLT at least possibly attributable to ON 01910.Na and defined as:
  - Grade 3 non-hematological toxicity other than nausea, vomiting, diarrhea, fever, esophagitis/dysphagia
  - Grade 3 nausea and vomiting uncontrolled by antiemetics; grade 3 diarrhea uncontrolled by antidiarrheal agents; grade 3 drug-induced fever uncontrolled by antipyretics
  - Grade 3 stomatitis and/or esophagitis/dysphagia lasting > 3 days
  - Delay in recovery to baseline blood counts below pre-treatment baseline (>20% difference) of more than 30 days in the absence of a response
- Determination of PK profile (absolute bioavailability and food effect) in a subset of 12 patients treated at MTD level

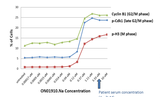
Patient Demographics and Duration of Treatment

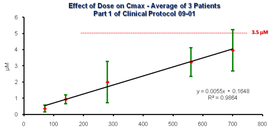
		Rigosertib BID Dosing (mg) for 2 out of 3 weeks					Total
		70	140	280	560	700	
	# Patients	3	2	2	24	6	37
	Sex	3F	1M/1F	2M	15M/9F	5M/1F	21M/14F
	Age (range)	64-82	74-84	73-76	56-89	53-82	53-89
	Duration of Treatment (wks)	4-18	9-34	11-31	1-31+	5-17	1-31+
IPSS	Low-Int-1 non Tx dependent	1	1	0	4	1	7
	Low-Int-1 Tx dependent	0	0	0	12	4	16
	Int-2 High risk	2	1	2	8	1	14
FAB/WHO	RCMD	1	1	0	15	5	22
	RAEB-1	2	1	0	3	0	6
	RAEB-2	0	0	2	6	1	9
Prior Azacitidine/Decitabine Treatment		3	2	2	14	5	26

Pharmacokinetic/Pharmacodynamic Results

Absolute bioavailability vs IV formulation approx. 30% (preliminary results) In 11 patients treated at 560 mg dose level and large food effect (better availability in fasting conditions)

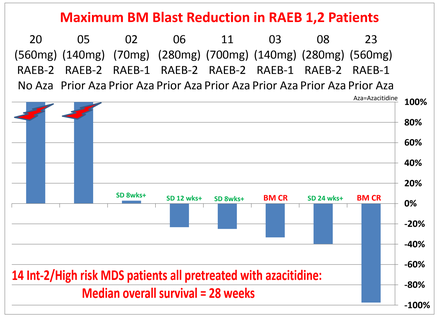






Rigosertib Activity

Maximum BM Blast Reduction in RAEB 1,2 Patients



14 Int-2/High risk MDS patients all pretreated with azacitidine:
Median overall survival = 28 weeks

Transfusion Analysis

- 16 MDS Low-Int-1 Risk Transfusion Dependent Patients Treated at 560 (N=12) or 700 mg bid (N=4)
- 11 Males/5 Females, 54-85 ys (median=72ys)
- 8 patients still ongoing
- 12 evaluable patients treated for at least 8 weeks
- Transfusion dependence defined by at least 2 URBC in the prior 8 weeks
- Transfusion independence (TI) defined by absence of RBC transfusion for at least 8 consecutive weeks
- Erythroid Response (ER) defined by reduction of at least 4 RBC transfusions/8 weeks compared to pretreatment transfusion number in the previous 8 weeks (RBC Tx for Hb ≤ 9.0 g/dL)

Patient Characteristics

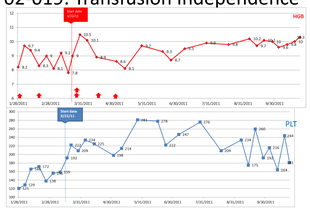
PID	Age	Sex	Cytog	Prior Aza/Dec	Prior Lenalinomide	DOT (wks)	Ongoing	IPSS	Dose (mg)
10	66	M	+mar3	Yes		6.5	N	1	560
12	73	M	-7	Yes		5	N	1	700
16	54	M	Normal	Yes		11	N	1	700
31	81	M	Normal	Yes		2	N	1	560
13	80	M	Complex	Yes		13	N	1	700
14	64	F	Complex	No		5	N	Low	700
18	81	M	Complex	Yes	Yes	19	N	Low	560
19	73	M	Normal	No	Yes	31	Y	Low	560
21	72	F	Normal	Unk		29	Y	Low	560
24	58	F	Normal	No	No	22	Y	1	560
27	76	M	Normal	Yes		9	N	1	560
29	85	M	Not Done	Yes	Yes	18	Y	1	560
34	57	F	Normal	No	Yes	16	Y	Low	560
35	58	M	Normal	No		16	Y	1	560
36	80	M	Normal	No		15	Y	1	560
39	64	F	3 Trans	No		11	Y	1	560

Transfusion Independence and Erythroid Response

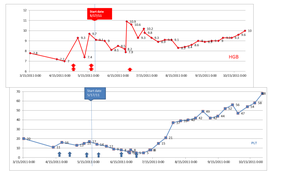
PID	TX response	Concomitant ESA	# Units pre 56ds	# Units during Trt	# Units/56ds Trt	Onset Tx indep week	Duration Tx indep	Red RBC Units	% Reduction
10	NE*		6	4	4.9			-1.1	-18%
12	NE		6	4	6.4			0.4	7%
16	No		12	16	11.6			-0.4	-3%
31	NE		4	2	8.0			4.0	100%
13	No	Yes	6	17	10.5			4.5	74%
14	NE		10	2	3.2			-6.8	-68%
18	TI	Yes	6	10	3.1	10	16	-2.9	-49%
19	TI	Yes	4	2	0.5	7	24	-3.5	-87%
21	No	Yes	8	16	4.4			-3.6	-45%
24	TI	Yes	6	2	0.7	6	16	-5.3	-88%
27	No	Yes	8	13	11.6			3.6	44%
29	ER	Yes	12	16	7.1			-4.9	-41%
34	TI	Yes	4	4	2.0	3	8	-2.0	-50%
35	No	Yes	10	21	10.5			0.5	5%
36	No	Yes	6	8	4.3			-1.7	-29%
39	No	Yes	6	4	2.9			-3.1	-52%

* at least 8 wks Trt

02-019: Transfusion Independence



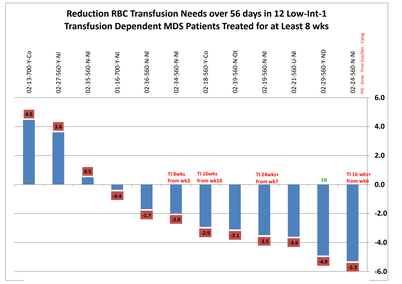
02-024: Transfusion Independence and Platelet Response

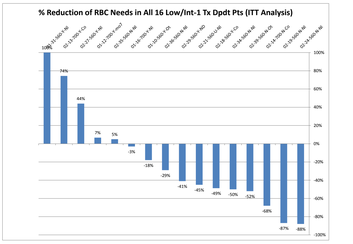


Response Summary

IPSS	N Patients 560 mg bid	Transfusion Independence	HI-E	SD	BM CR	Overall Response
Low-Int-1	16	4 (including 2 HI-N and 1 HI-P)	1	6		69%
Int-2 High	8			1	1	25%
Total	24	4	1	7	1	54%

		560 mg bid			700 mg bid			
	Total Patients	Low risk 4	Int-1 8	All 12	Low risk 1	Int-1 3	All 4	Total 16
Evaluable	Yes	4	6	10	0	2	2	12
	No	0	2	2	1	1	2	4
Tx response (TI+ER) in Evaluable pts	Yes	3	2	5	NE	0	0	5
	No	1	4	5	NE	2	2	7
% Tx response (ITT)		75%	25%	**42%**	NE	0%	**0%**	**31%**





Rigosertib Safety

Grade 2+ Drug Related Adverse Events (SAEs)

	560mg (N=24)		700mg (N=6)	
	Grade 2	Grade 3	Grade 2	Grade 3
Dysuria	4	1	3	1 (DLT)
Hematuria (onset 5 wks)	4 (1)	1	1	1
Urinary Frequency	0	1	0	0
Nocturia	0	0	1	0
Cystitis	0	0	1	0
Diarrhea	1	1	0	0
Abdominal pain (onset 8 wks)	0	1	0	0
Hypotension, syncope (onset 10 wks)	0	0	0	1
Shortness of breath	0	0	0	1 (DLT)
Fatigue	1	1	0	0

Gr 2+ Urinary Symptoms (dysuria, hematuria, nocturia, urinary frequency, cystitis)

Rigosertib BID Dosing	560 mg	700 mg
Incidence (%)	7/24 (29%)	5/6 (83%)
Onset week median [range]	5, [3,10]	3, [2,15]
Hold/Dose reduction	4	2
Dc'd Rigosertib	3	3

Additional Safety Review:

- No myelotoxicity (ANC, WBC, Platelet, Hb)
- No renal (creatinine) or liver (ALT, bilirubin toxicity
- No hypokalemia or hyponatremia
- No change of glucose, calcium/phosphorus
- No variation of urinary pH
- No change in vital signs (temperature, blood pressure, pulse)

Conclusions

Oral rigosertib is bioavailable, active and well tolerated

- 2 BM CR in RAEB-1 pts previously treated with Azacitidine
- 1 Platelet and 1 ANC responses
- 4 cases of transfusion independences and 1 erythroid response in Low/Int-1 Tx dependent evaluable MDS patients treated with rigosertib 560 mg bid 2 out of 3 weeks
  - 1 with complex, 3 with normal cytogenetics, 1 ND
  - Pretreatment Hb (median)= 8.3 g/dL and Maximum Hb (median) = 10.3 g/dL
  - Pretreatment with Lenalinomide in 4 patients (stop dates before starting rigosertib at -30, -10, -9 and -9 weeks)
- Bladder only clinically significant toxicity (dysuria, hematuria)

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