Phase II study of orally administered rigosertib (ON 01910.Na) in transfusion-dependent lower risk myelodysplastic syndrome (MDS) patients

A. Raza[1], S. Mukherjee[1], A. Eisenberger[1], JG Mears[1], F. Wilhelm[2]

[1]Columbia University Medical Center, New York, NY
[2]Onconova Therapeutics Inc., Newtown, PA

ABSTRACT 7031

Background: Rigosertib, a novel small molecule inhibitor of PI3-Kinase and PLK pathways is currently evaluated (IV infusions) in a Phase III trial in higher risk MDS patients who have failed hypomethylating agents. A previous phase I study found good bioavailability and activity of orally administered rigosertib in transfusion-dependent MDS patients (ASH 2011). Here we report preliminary results from an ongoing phase II study.

Methods: This is a randomized, two-arm study of oral rigosertib (560 mg bid) administered either intermittently (2 out of 3 weeks) or continuously. Transfusion-dependent patients must have received at least 4 units RBC transfusions over 8 weeks before randomization, and can receive transfusions and erythrocyte stimulating agents (ESAs) while on study.

Results: Twenty nine MDS patients (25 intermediate-1 and 4 low risk per IPSS classification) have been randomized as of December 17th, 2012. Overall oral rigosertib was well tolerated except for a high incidence (5 of 9 patients) of grade 2+ urinary side effects (dysuria, hematuria, cystitis, and urinary urgency), in the continuous dosing arm. Accordingly, the protocol was amended to allow all patients to be treated with intermittent dosing, with option of dose interruption/reduction resulting in a much lower frequency of urinary side effects (4/20 patients with urinary grade 2+ toxicity). Fifteen patients (none of them with del5q cytogenetic) have been treated with intermittent dosing for at least 8 weeks. Seven (47%) patients achieved transfusion independence (no RBC transfusion for at least 8 consecutive weeks), which lasted 8 to 27 + weeks. Six of 7 responding patients were refractory to prior treatment with ESAs and 5 of these 7 patients received concomitant ESAs, suggesting an effect of rigosertib on ESA resistance.

Conclusions: Preliminary results of this phase II study indicate that intermittent dosing of rigosertib administered orally is well tolerated and active in producing transfusion independence in approximately 50% transfusion dependent, lower risk MDS patients. The contributing role of rigosertib and ESAs in these transfusion responses is being investigated.

Rigosertib Background

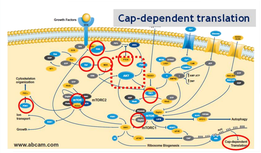
- PLK-1 and PI3 kinase dual-pathway inhibitor
- Promotes G2/M arrest and selectively induces apoptosis in cancer cells without affecting normal cells
- IV and Oral formulations tested in more than 800 patients
  - Phase 3 in higher-risk MDS patients post-hypomethylating agents completely enrolled
  - Three other Phase 2 or 3 trials underway

Prior Phase I Study of Oral Formulation in 37 MDS patients (R Komrokji et al, BJH 2013, in press):

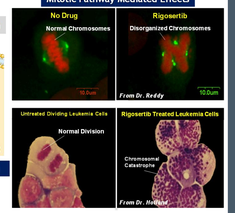
- Absolute bioavailability of oral Rigosertib = 35%
- In High-risk patients
  - 2 BM CR in RAEB-1 pts previously treated with Azacitidine
  - 1 Platelet and 1 ANC responses
- In Low-Int-1 transfusion dependent patients
  - 4 cases of transfusion independence and
  - 1 erythroid response
- Toxicity noted ay 560mg RPTD: urinary frequency, dysuria, hematuria

Two Pathways Inhibited by Rigosertib

PI3-Kinase Mediated Effects



Mitotic Pathway Mediated Effects



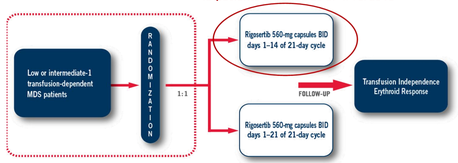
Kinome Profile of Rigosertib (www.kinomescan.com)

Gene Symbol	Assay Mapped Interactions for rigosertib		
	Assay Label	Assay Group	% Ctrl
RIOK1	RIOK1	ATYPICAL	51
PIK3CA(I800L)	PIK3CA (I800L)	MUTANT	54

STUDY DESIGN – PATIENT DEMOGRAPHICS

Study Design of Oral Rigosertib in Lower Risk Transfusion Dependent MDS Patients

43 patients enrolled as of 4/16/2013



Only 9 patients randomized to continuous dosing
Protocol amended to enroll further patients on intermittent dosing (N=34)

Patient Characteristics and Demographics

Characteristic	N=43
Median Age, years (range)	72 (54-84)
Male/Female	25/18
Median years from diagnosis (range)	2 (0-12)
Median prior MDS therapies (range)	1 (0-10)
Prior treatment with HM agents/Lenalidomide	12/10
Prior treatment with ESAs	22
IPSS Risk at Screen (Low/Int-1/Int-2)	7/34/2
ECOG PS (0/1/2)	35/3/5
FAB/WHO Classification	
Refractory Anemia	11
Refractory Cytopenia with Multiple Dysplasia	25
RAEB-1	6
RAEB-2	1
Cytogenetics (Normal/Tri8/del5q/Other)	20/4/2/26

TOLERABILITY – DURATION OF TREATMENT

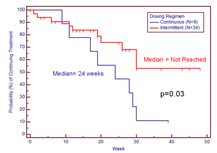
Grade 2/3 Drug Related Adverse Events and SAEs

Symptom	Incidence in 34 Patients Dosed Intermittently		
Severity	*Grade 2*	*Grade 3*	*Total %*
Urinary urgency/frequency (1 SAE)	12	1	38
Dysuria	5	1	18
Hematuria/cystitis (4 SAES in 3 patients)	0	5	15
Fatigue	5	0	15
Nausea	3	0	9
Intermittent Neutropenia	0	1 gr 3; 1 gr 4	6
Hemolytic anemia	1	0	3
Diarrhea	1	0	3
Myalgia	1	0	3
Abdominal pain/discomfort	1	0	3
Insomnia	1	0	3

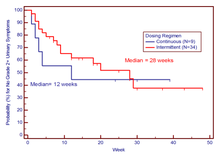
Symptom	Incidence in 9 Patients Dosed Continuously		
Severity	*Grade 2*	*Grade 3*	*Total %*
Hematuria/cystitis/bladder inflammation (1 SAE)	2	3	56
Urinary urgency/frequency	4	0	44
Dysuria	2	0	22

No other drug-related serious adverse event (SAE)

Duration of Treatment



Onset of Grade 2+ Urinary Side Effects



Longer duration of treatment with intermittent vs continuous dosing

Adverse Events Leading to Treatment Discontinuations

PID	Dosing	Adverse Event	Onset week	Drug relationship
01-06	Continuous	Multiple organ failure	11	Unrelated
02-01	Continuous	Upper GI hemorrhage	19	Unrelated
02-03	Intermittent	Myocardial infarction	1	Unrelated
02-04	Intermittent	Shoulder pain	19	Unrelated
01-21	Intermittent	Hemolytic anemia	30	Related
01-14	Intermittent	Urinary symptoms	26	Related
01-31	Intermittent	Urinary symptoms	11	Related
01-33	Intermittent	Urinary symptoms	2	Related
01-34	Intermittent	Urinary symptoms	20	Related

Oral Rigosertib Mediated Urinary Adverse Events: Cause, Effects and Mitigation Plan

Absorption
- Absolute bioavailability 35%
- Absorption best under fasting conditions
- Limited variability; few GI AEs

Excretion
- Excreted with little metabolism
- Urinary and fecal routes
- No effect on renal function

Urinary AEs
- Rigosertib dose related
- Related to time of exposure
- May be affected by pH

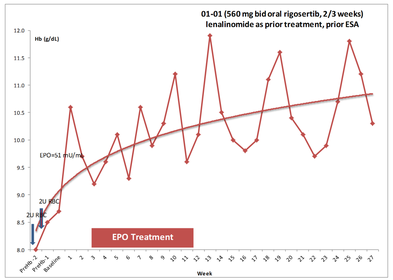
Hypothesis:
Extended residence time of excreted drug(s) in the urinary bladder causes inflammation and cytotoxicity.
Proposed remedy:
Reduce exposure of bladder mucosa by modifying dosing schedule, urinary function and pH

Urinary Toxicity Mitigation Strategy

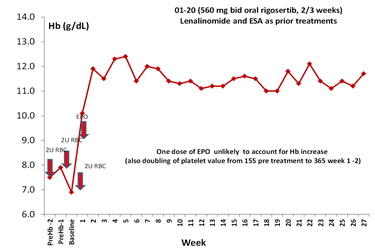
- Switch from continuous to intermittent dosing schedule
- Dose reduction for grade 2+ urinary symptoms
- Replace 560 mg bid dosing with
  - 560 mg am (30 min+ before breakfast) and
  - 280 mg 2hs+ after lunch and 30 min+ before dinner
- Dysuria questionnaire (American Urological Association)
  - to all patients at baseline, 3 weeks and every 3 cycles thereafter
- Recommend vigorous hydration and bicarbonate prn

EFFICACY ON TRANSFUSION INDEPENDENCE

Transfusion Independence for 48+ Weeks



Transfusion Independence for 37+ Weeks

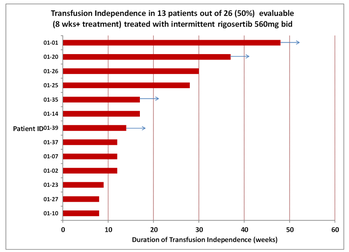


Transfusion Independence Responders - Pre-Treatment Characteristics

PID	IPSS	Cytogenetics	Prior Trt	Prior ESA	EPO mU/mL	Prior RBC*
01-01	0.5	-Y	Len	Yes	51	4
01-02	0.5	18 abn	Len	Yes	35	4
01-07	0.5	Normal	No	Yes	117	4
01-10	0	Normal	No	Yes	32	4
01-14	0.5	Normal	Len	Yes	51	4
01-20	0	Normal	Len	No	128	4
01-23	1	-Y	No	Yes	14	4
01-25	1	Complex	No	No	15	4
01-26	0.5	del20q	Aza	Yes	361	4
01-27	0	Normal	Len	Yes	31	4
01-35	1	+8	Aza	Yes	47	4
01-37	0	Normal	No	Yes	236	4
01-39	0.5	del13q	Aza/Len	Yes	216	4

*Prior RBC = Number of RBC units administered within 8 weeks before baseline

Transfusion Independence in 50% of 26 Evaluable Patients



Transfusion independence defined for at least 8 consecutive weeks without transfusion

Transfusion Independence Responders – Outcomes (weeks)

PID	Response week		ESA Treatment week		
	Onset	*Duration*	*Start*	*Stop*	
01-01	**1**	**48+**	**3**	**12**	Early response
01-02*	4	12	4	4	
01-07*	19	12	5	11	Delayed response
01-10*	13	8	6	10	**> 6months of TR**
01-14	1	17	3	9	
01-20	**1**	**37+**	**1**	**1**	
01-23	1	9	10	22	
01-25	**1**	**28**	**14**	**22**	
01-26	**1**	**30**	**14**	**14**	
01-27*	24	8	21	21	
01-35	14	17+	No	No	
01-37	1	12	9	9	
01-39	1	14+	No	No	

*Potential synergy with ESA

Overall Transfusion Response

Regimen	Responders	Evaluable Patients		ITT Patients	
		Total	*%*	*Total*	*%*
Continuous	2	8	25%	9	22%
Intermittent	13	26	50%	34	38%
Total	**15**	**34**	**44%**	**43**	**35%**

CONCLUSIONS

- Strong signal for transfusion independence
  - 50% of evaluable patients in non-del5q patients
- Possible synergy with ESA
- Intermittent dosing better tolerated
  - 2 weeks of 3 week cycle better than continuous dosing
- Strategy for managing Urinary AEs

Acknowledgments: The authors acknowledge the contributions of Dr A Al-Kali (Mayo Clinic-Rochester, MN), Dr R Tibes (Mayo Clinic Arizona) and Dr G Spitzer (Bon Secours, Greenville, SC) who enrolled patients after December 17, 2012 in this ongoing study