

# Oral Rigosertib (ON 01910.Na) Treatment Produces An Encouraging Rate Of Transfusion Independence In Lower Risk Myelodysplastic Syndromes (MDS) Patients; A Genomic Methylation Profile Is Associated With Responses

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## Abstract (submitted 8/8/13)

**Background:** Rigosertib, a novel orally bioavailable small molecule inhibitor of PI3-Kinase and PLK1 pathways, was tested in a phase II study in lower risk (intermediate-1 or low risk per IPSS classification) transfusion-dependent MDS patients.

**Methods:** This randomized, two-arm study administered rigosertib (560 mg bid) either intermittently (2 out of 3 weeks) or continuously to transfusion-dependent patients (4 units RBC transfusions over 8 weeks). Erythrocyte stimulating agents (ESAs) were allowed on study.

**Results:** Forty eight patients have been enrolled as of August 2<sup>nd</sup>, 2013 and another 12 patients will be enrolled. Continuous dosing was stopped after 9 patients due to a higher urinary toxicity resulting in 39 patients receiving intermittent dosing. Overall the drug was well tolerated, except for reversible grade 3 urinary toxicity (dysuria, hematuria, cystitis, and urinary urgency) in 6/48 (12%) patients while 17/48 (35%) experienced grade 2 urinary toxicity. Notably, no significant treatment emergent myelosuppression was evident in these patients. Dosing has been modified to a total daily dose of 840 mg (560 mg am/280 mg afternoon) to improve urinary tolerability. Other measures to manage urinary symptoms include hydration, sodium bicarbonate and dose reduction or interruption. Of 33 patients (3 with del5q) on intermittent dosing treated for at least 8 consecutive weeks, 15 (45%) achieved transfusion independence (TI) or no RBC transfusion for at least 8 consecutive weeks) lasting 8 to 53+ weeks (median=17 weeks). Intent-to-treat analysis showed 17/48 (35%) patients achieved TI. Twelve of 15 responding patients were refractory to prior treatment with ESAs. Fourteen of 15 responding patients (11 out of 12 ESA refractory) received concomitant ESAs, suggesting an effect of rigosertib on ESA resistance or potential synergy with ESA. These effects are being explored in additional trials now in planning.

There was no obvious correlation of response to karyotype or other classifications. We hypothesized that DNA methylation profiles could help explain the differences between responders and non-responders. Pre-therapy bone marrow mononuclear cells from 32 patients (including 4 from the prior Phase I study previously reported in ASH 2011) were analyzed using the Illumina 450K methylation array platform. Seven had complete response or CR (TI + increase in Hb >2Gm/dL), 10 had partial response or PR (TI without Hb increase) and 15 had no response or NR. Supervised hierarchical clustering by methylation intensity demonstrated a distinct profile associated with complete responders. Bisulfite sequencing (which allows quantification of multiple consecutive CpGs in an amplicon) of several differentially methylated loci confirmed the Illumina 450K data. In general, hypermethylation of a group of genes was associated with responders. Functional annotation of the hypo and hypermethylated genes which best distinguished CRs from NRs showed that the genes most affected by methylation were related to regulation of transcription followed by genes involved in cell-cell adhesion, inflammatory response, apoptosis and proliferation. Additional patient samples are being analyzed to confirm these results. In this interim analysis the observed correlation of hematological response to genomic methylation status suggests the possibility of preselecting patients likely to benefit from treatment with rigosertib.

**Conclusions:** Intermittent dosing of oral rigosertib is well tolerated and active in producing transfusion independence in lower risk MDS patients. A genomic methylation signature, once confirmed in prospective studies, may allow pre-selection of responders.

## Background

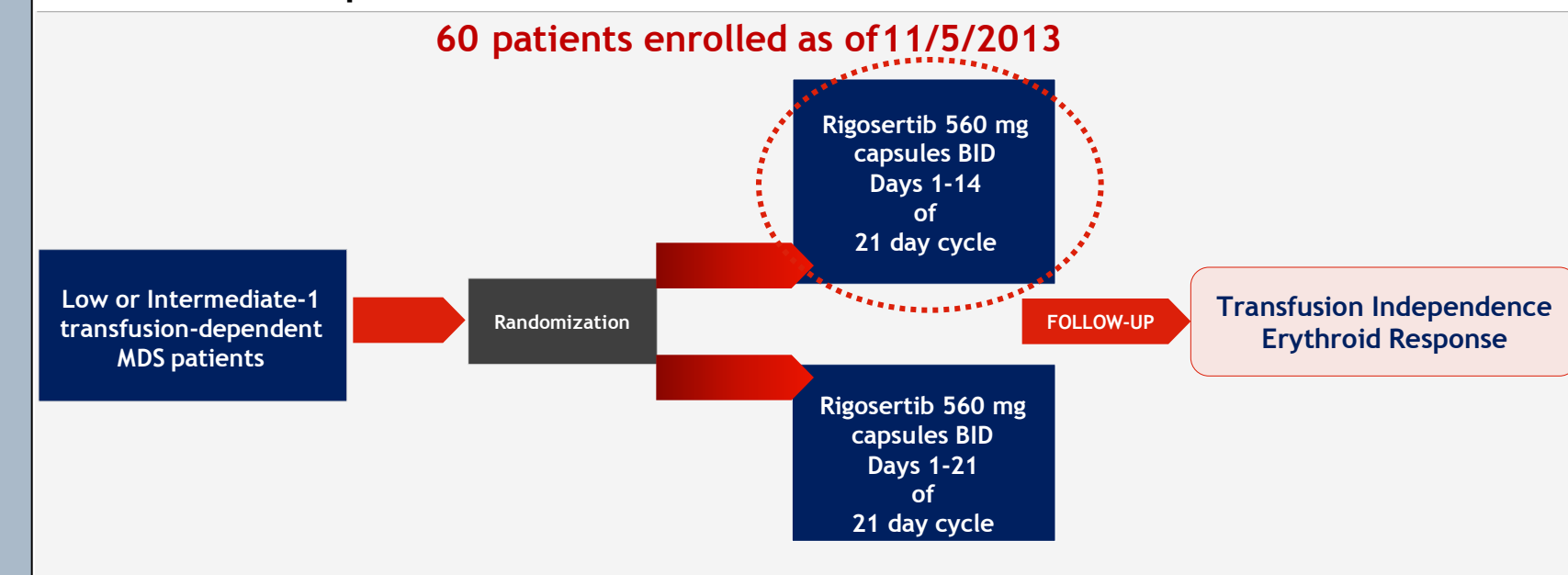
- Rigosertib is an inhibitor of PI 3-Kinase and PLK Pathways
- Intravenous and oral formulations tested in more than 800 patients
  - Phase 3 trial in higher risk MDS completed enrollment
  - MDS patients after Hypomethylating agent treatment
- Three other Phase 3 or Phase 2 trials underway

**Prior Phase I Study of Oral Formulation in 37 MDS patients**  
(Komrokji et al, British Journal of Hematology 2013)

- Absolute bioavailability of oral rigosertib ~35%
- In higher risk MDS patients:
  - Two BM-CR in RAEB-1 patients previously treated with Vidaza
  - One each Platelet and ANC responses
- In lower risk transfusion-dependent MDS patients:
  - Four cases of transfusion independence and
  - One erythroid response
- Key adverse events at 560 mg BID recommended Phase 2 dose:
  - Urinary frequency, dysuria and hematuria
  - AEs addressed by hydration, bicarbonate and dose reduction

## Methods

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



- Total patients enrolled: 60
- Only 9 patients randomized to continuous dosing
- Protocol amended to enroll patients on intermittent dosing (N=51)

### Protocol Objectives

- Identify optimal dose and schedule to
  - minimize urinary adverse events and
  - enhance duration of treatment
- Evaluate activity of rigosertib
  - As a single agent
  - And the role and effects of concomitant ESA
- Identify potential subsets of patients who are likely to respond
  - Genomic methylation analysis of pre-treatment bone marrow

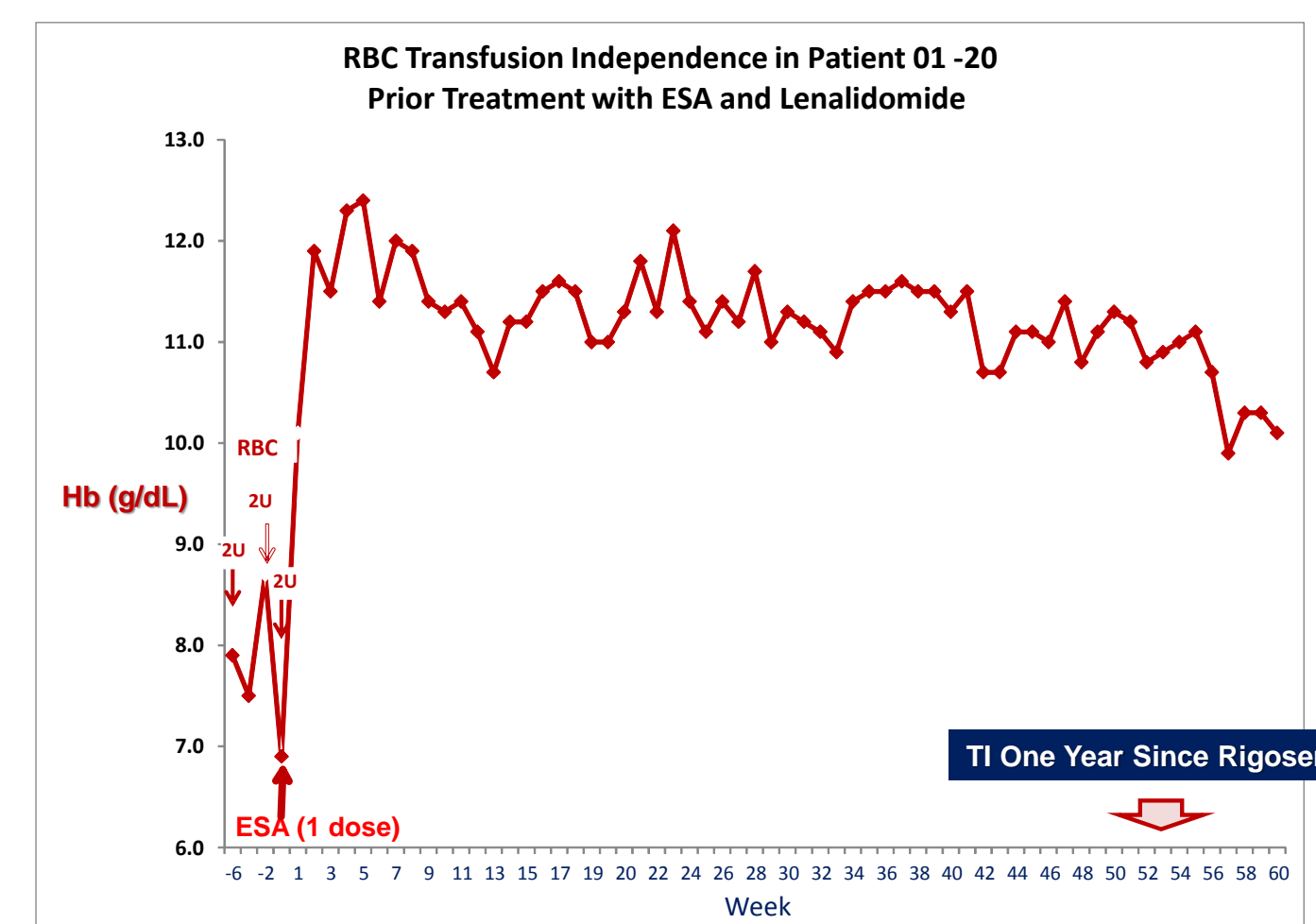
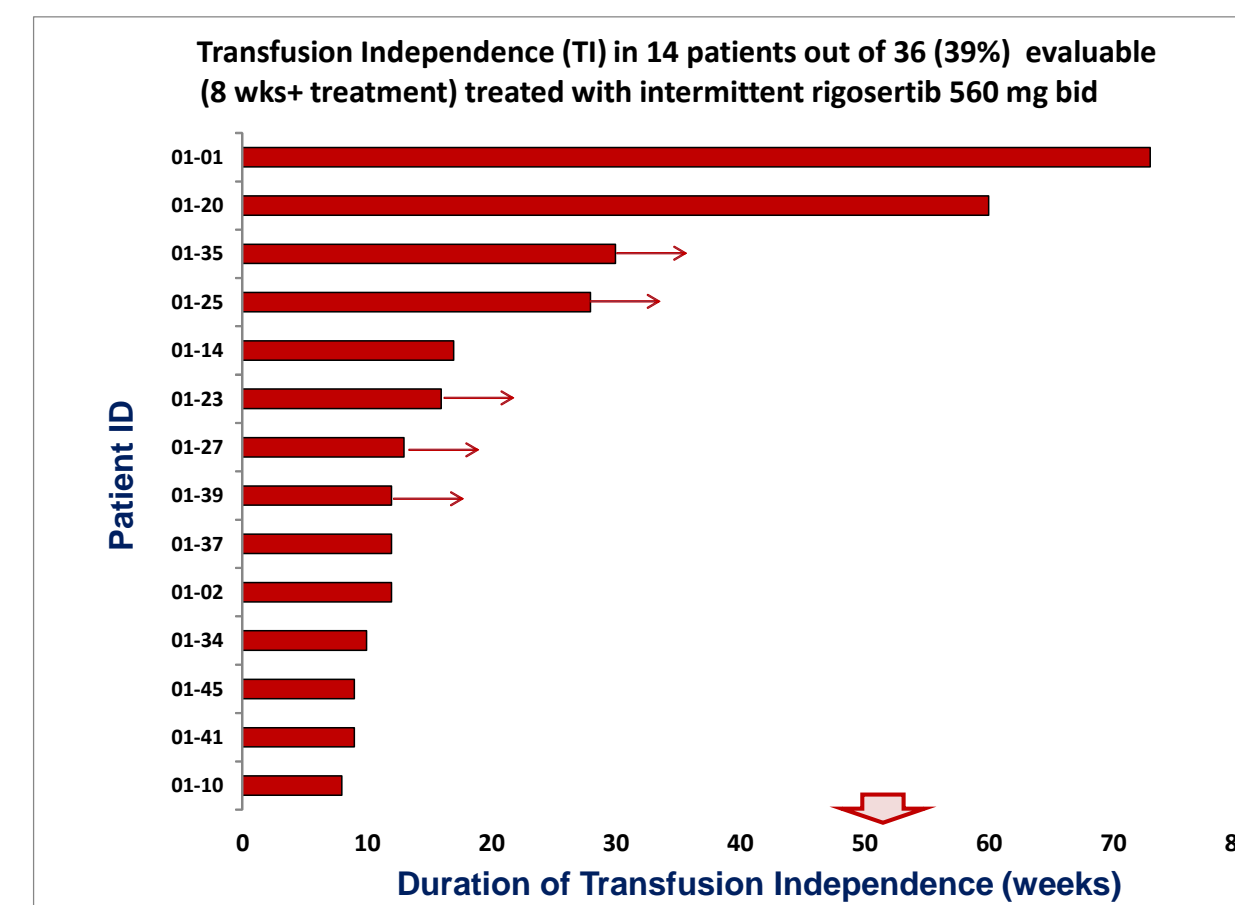
## Patient Demographics

Characteristic	N=60
Median Age, years (range)	74 (54-86)
Male/Female	41/19
Median years from MDS diagnosis (range)	2 (0-12)
Median number prior MDS therapies (range)	2 (0-6)
Prior treatment with HM agents	28
Prior treatment with Lenalidomide	20
Prior treatment with ESAs or EPO>500 mU/mL	46
Median pre-study EPO (mU/mL) (range)	128 (14-11199)
Median# (range) RBC transfusions in 8 weeks prior study	4 (4-11)
# patients with thrombocytopenia grade 3+	16
# patients with neutropenia grade 3+	15
# patients with anemia grade 3+	14
IPSS risk at screen (Low/Int-1/Int-2)	12/46/2
ECOG PS (0/1/2/NR)	41/11/6/2

### FAB/WHO Classification

Refractory Anemia	19
Refractory Cytopenia with Multiple Dysplasia	33
RAEB-1	7
RAEB-2	1
Cytogenetics (Normal/Tri8/del5q/Other)	29/7/3/21

## Rigosertib Efficacy



## Rigosertib Induces Transfusion Independence (TI) Alone or Combined with ESA

ESA Use in Patients		No. of Patients		Transfusion Independent (TI)
Prior ESA	During Rigosertib	Total	TI	
Yes	None	9	3	41%
	Once	5	2	
	2 to up to 12 wks	11	6	
	=>12 weeks	12	4	
	Total	37	15	
No	None	3	0	14%
	Once	1	0	
	2 to up to 12 weeks	3	1	
	= > 12 weeks	0	0	
	Total	7	1	
<b>Total evaluable in the trial</b>		<b>44</b>	<b>16</b>	<b>36%</b>

All patients in continuous or intermittent dosing treated for at least 8 weeks

Regardless of prior ESA therapy:

5/18 (28%) responders in patients who received no more than one dose of ESA  
11/26 (42%) responders in patients who received at least 2 doses of ESA

## Rigosertib Tolerability

BID Dosing	No. of Patients	Incidence of All Urinary Events of All Grades			Percent Incidence
		Grade 1	Grade 2	Grade 3	
3/3 weeks 560	9	0	4	2	67
2/3 weeks 560	35	6	15	4	54
2/3 weeks 560/280	13	2	1	0	8

Urinary symptoms: urinary urgency, dysuria, hematuria, cystitis

New intermittent 560 mg am/280 mg afternoon dosing selected to minimize nocturnal symptoms of urinary urgency.

- Thirteen patients have received this new dosing regimen for a median duration of 6 weeks (range: 1-12 weeks). Only one patient so far developed grade 2 urinary toxicity (urinary tract infection).

### Other Toxicities

- Few other grade 3+ drug related adverse events:
- 3 neutropenia, 1 leucopenia
  - 1 hyponatremia
  - 1 transitional cell carcinoma of the bladder

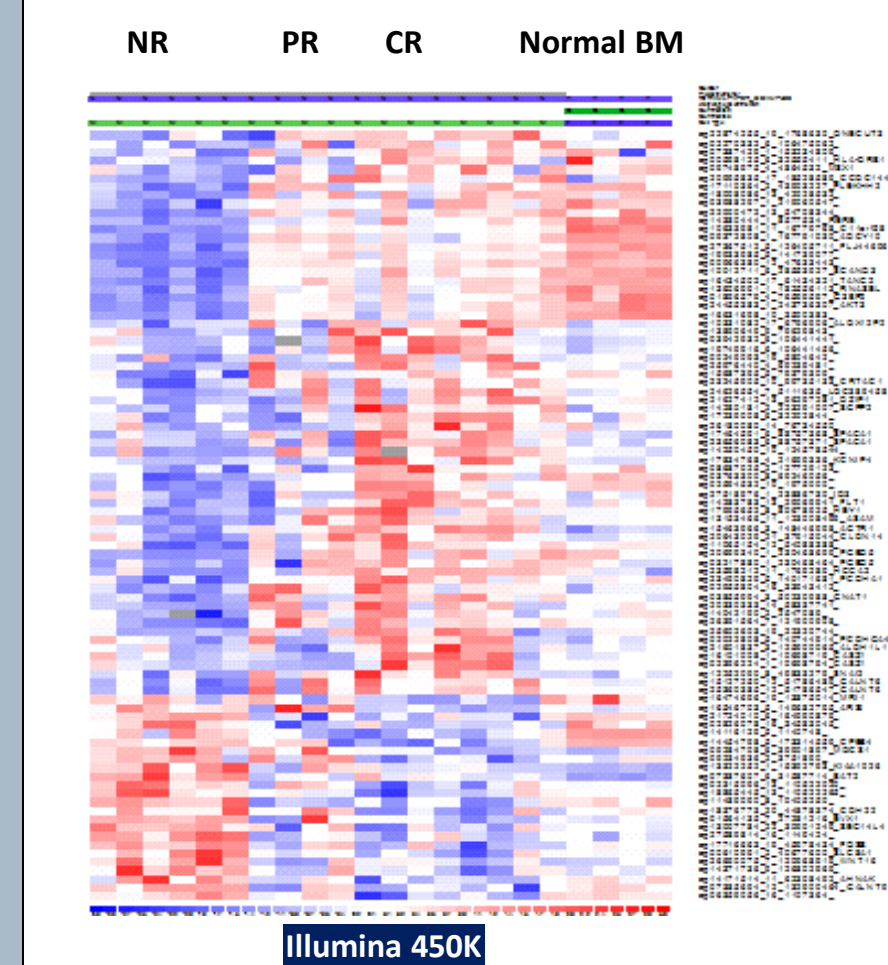
## Predictive Genomic DNA Methylation Signature for Rigosertib Response

- Methylation profile of pre-therapy bone marrow mononuclear cells (BMMNC) was determined by Illumina 450K arrays followed by validation of selected loci by using bisulfite sequencing
- Annotation of hypo- and hyper-methylated loci which best distinguished the Complete Responders (CR) from Non-responders (NR) was carried out

**Annotated Panel of genes loci with differential methylation associated to rigosertib response**

*RRER, CASZ1, KIAA1026, ID3, ADCY10, RNASEL, PGBD5, AKT3, SLC8A1, PLEKHH2, SGPP2, GNAT1, ALDH1L1, AGTR1, MSX1, KCNIP4, G3BP2, FLJ44606, PCDHA1, PCDHGA4, ARSI, CPEB4, SCAND3, BAT2, HLA -DRB1, MOCS1, SPACA1, LOC389458, EVX1, WNT16, SNAI2, HEY1, CRTAC1, HCCA2, C11orf58, AHNAK, ASAM, GALNT6, GALNT9, FLT1, DZIP1, ALOX12P2, CCDC144B, TANC2, ONECUT3, MRI1, FOSB, CDH22, CLDN14 and SEC14L4*

## Genomic Signature



**Genomic Methylation Signature**  
Illumina 450 K Methylation Platform

- Thirty-two samples tested
- Seven had Complete Response (CR)
  - Transfusion independence and
  - Increase in Hemoglobin >2g/ dL
- Ten had Partial Response (PR)
  - Transfusion independence only
- Fifteen were non-responders (NR)
- Key findings:
  - Association between response and methylation status
  - Confirmation of results by bisulfite sequencing
- Evaluation continues

- Functional annotation of hypo and hypermethylated genes which best distinguished CRs from NRs showed that the genes most affected by methylation were related to regulation of transcription followed by genes involved in cell-cell adhesion, inflammatory response, apoptosis and proliferation
- Ongoing work to select small gene panel of best markers to predict response

## Conclusions

- Oral rigosertib active in inducing transfusion independence
  - As a single agent, or
  - When combined with ESA
- Combined response rate (TI + HI + BMCR) of 53%
  - In 36 evaluable patients treated with intermittent dosing
- Intermittent (2/3 wks) better tolerated than continuous dosing
  - Bladder toxicity best managed by hydration, bicarbonate and split dose
    - BID dosing with 560mg AM dose and 280mg PM dose
- Identification of genomic methylation signature
  - Confirmation cohort of 20 patients now being enrolled
  - Potential for patient selection after further confirmation

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