Final Phase I/II Results of Rigosertib (ON 01910.Na) Hematological Effects in Patients with Myelodysplastic Syndrome and Correlation with Overall Survival

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Abstract

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Rigosertib is a multi-kinase inhibitor that selectively induces mitotic arrest leading to apoptosis in cancer cells and blasts, while being non-toxic to normal cells. We analyzed bone marrow (BM) response and overall survival (OS) in 60 patients (pts) with myelodysplastic syndrome (MDS), including 51 patients with refractory anemia and excess blasts (RAEB) and 9 patients with refractory cytopenia and multilineage dysplasia (RCMD) enrolled in 4 independent phase 1/2 clinical trials. These pts were treated with rigosertib administered as a continuous intravenous infusion (CIV) from 2 to 6 days weekly or every other week with BM response initially assessed per protocol by week 4 or 8 and every 8 weeks thereafter. Overall survival (OS) analyses were performed by the method of Kaplan-Meier. OS was related (p=0.04) to FAB/WHO classification (see Table 1) in all MDS pts. Eight pts had hematological improvements. OS was also related to IPSS scoring (p=0.02; Table 2) and to BM blastic response (Table 3; p=0.008) in the 51 RAEB-1,-2,-t pts and in a subset of 38 RAEB-1,-2,-t pts refractory or relapsing after treatment with hypomethylating agents (azacitidine/decitabine) (Table 4; p=0.001). A 49-week OS was found in 15 patients in this last group treated with 3-day rigosertib infusions (1800 mg/day) every other week. Rigosertib infusions were well tolerated without evidence of bone marrow myelotoxicity. These results and the predictive value of BM response to rigosertib for estimating OS survival have led to the initiation of a randomized Phase III survival trial of rigosertib 3-day CIV infusions vs best supportive care in RAEB -1, -2 and-t pts who failed or progressed after receiving hypomethylating agents.

Methods

Rigosertib (ON 01910.Na) Background

- Benzyl styryl sulfone analog, water soluble
- **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 a and b isoforms of PI3 kinase
  - Inhibits activation of anti-apoptotic proteins including Mcl-1: rapid, cycle-dependent induction of apoptosis
- **Reductions of Cyclin D1 and Akt phosphorylation correlate with drug activity in responder patients** (see Abstract #3808: "A Novel Nano-Immunoassay (NIA) Reveals Inhibition of PI3K and MAPK Pathways in CD34+ Bone Marrow Cells of Patients with Myelodysplastic Syndrome (MDS) Treated with the Multi-Kinase Inhibitor ON 01910.Na (Rigosertib)" by AC Fan et al , ASH 2011 and "Treatment of Higher Risk Myelodysplastic Syndrome Patients Unresponsive to Hypomethylating Agents with ON 01910.Na" by M Seetharam et al (J Leukemia Res, 2011 in press)
- Increase of mature CD15-positive myeloid cells (Lack of myelotoxicity) and decrease of immature CD33 cells or CD34 blasts **(Sloand et al. 2007)**

Phase I/II Clinical Trials of Rigosertib in MDS

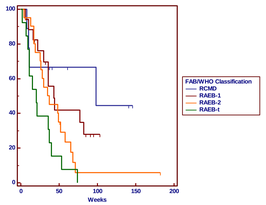
Primary Objectives: Analysis of bone marrow (BM) response and overall survival (OS) in 60 patients with myelodysplastic syndrome (MDS) and WHO/FAB subtypes of refractory cytopenia with multiple dysplasia (RCMD) and refractory anemia with excess blasts (RAEB) -1,- 2 or –t, enrolled in 4 independent clinical trials and treated with rigosertib 2-6 days infusions.

	Study 07-H-0225 (E Sloand/M Olnes)	Study 04-05 (L Silverman)	Study 04-15 (A Raza)	Study 04-17 (P Greenberg)
Population	**Trisomy 8 Refractory AML or MDS**	**MDS/AML Refractory to Azacytidine/ decitabine**	**All Comers MDS/AML**	**Trisomy 8 and Int-2/High Risk Refractory MDS**
Dosing Regimen	800 mg/m^2 given 3-5 days Q2W	650-1700 mg/m^2 given 3-6 days Q2W	800-1500 mg/m^2 given 2 days QW for 3 of 4 weeks; amended to 1800 mg given 3 days Q2W	800 mg/m^2 given 2 days QW for 3 of 4 weeks; amended to 1800 mg given 3 days Q2W
Total Patients (MDS &AML) /MDS patients	14/12	14/7	35/28	13/13

Q2W = every other week; QW = weekly.

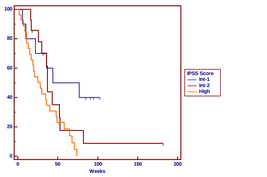
Results

Overall Survival by FAB/WHO Classification in 60 MDS Patients Treated with Rigosertib



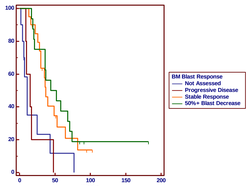
FAB/WHO Classification	RCMD	RAEB-1	RAEB-2	RAEB-t	P-value Logrank
# Patients	9	17	21	13	P =0.01
Median Survival (Weeks)	98	43	37	20	

Overall Survival by IPSS Scoring in 51 RAEB-1, -2, -t MDS Patients Treated with Rigosertib



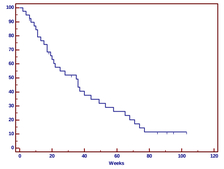
IPSS Scoring	Intermediate-1	Intermediate-2	High	P-value Logrank
# Patients	10	14	27	P =0.03
Median Survival (Weeks)	77	37	28	

Overall Survival by BM Blast Response in 51 RAEB-1, -2, -t MDS Patients Treated with Rigosertib



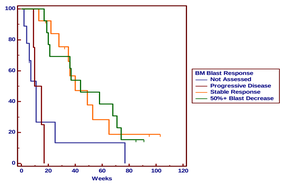
BM Blast Response	≥ 50% Blast Decrease	Stable BM Response	Progressive Disease	Not Assessed	P-value Logrank
# Patients	16	20	5	10	P=0.002
Median Survival (Wks)	48	37	15	11	

Median Overall Survival of 35 Weeks in 39 RAEB-1, -2, -t patients previously treated with HM agents



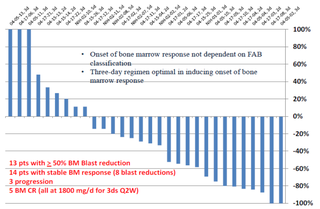
- **Maturity index (# deaths/total # of patients): 32/39 (82%) – mature data set**
- **Median Overall Survival in 7 patients still alive: 85 weeks**
- **47% (7/15) patients alive ≥ 49 wks with pivotal study dosing 1800mg/d 3ds Q2W**
- **Median time between end of HM agents and start of rigosertib: 13 weeks (= 3 months; range: 3-110 weeks, N = 24)**

Overall Survival by BM Blast Response in 39 RAEB-1, -2, -t MDS Rigosertib-Treated Patients Refractory or Relapsing After Azacitidine/Decitabine Treatment

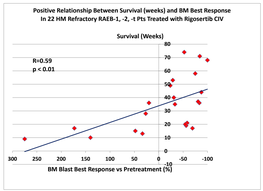


BM Blast Response	≥ 50% Blast Decrease	Stable BM Response	Progressive Disease	Not Assessed	P-value Logrank
# Patients	13	13	4	9	P=0.0005
Median Survival (Weeks)	44	40	12.5	10	

Best BM blast decrease in 30 RAEB-1, -2 –t patients previously treated with hypomethylating agents



Positive relationship between survival (weeks) and BM best response in 22 HM-refractory RAEB-1, -2, -t patients treated with rigosertib CIV who died



Overall Response Rate in the 39 RAEB-1, -2, -t patients previously treated with HM agents

	N	BM Complete Response (HI)	Hematological Improvement	Overall Response Rate
All patients	39	5 (1)	4	9 (23%)
3-day infusion	24	5 (1)	3	8 (33%)
1800 mg/24 hr x 3 ds	15	5 (1)	2	7 (47%)

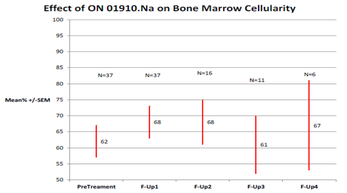
Efficacy Conclusions

- High activity of rigosertib in 39 RAEB-1, -2, -t patients previously treated with HM agents
  - ≥50% BM blast decrease from baseline in 33% (13/39) patients
  - 5 hematological improvements
  - 3-day regimen optimal in inducing BM response
- Of 15 patients previously treated with HM agents who received pivotal dosing regimen (1800 mg/d 3ds Q2W), 47% had ≥50% BM response
- Onset of BM response independent of:
  - Prior treatment with hypomethylating agents
  - Cytogenetics
  - FAB/WHO classification
- Strong correlation between BM blast response and Overall Survival
  - Possible predictive value of BM response to rigosertib for overall survival of higher risk MDS patients

Rigosertib Tolerability

- **Good tolerability, no evidence of cumulative toxicity, no myelotoxicity**
- **2 Deaths/60** (3%) during the **first 4 weeks** of treatment with rigosertib
  - Death due to progressive disease (unrelated to study drug)
  - Death due to pre-existing Grade 4 (CTCAE) thrombocytopenia and intracranial hemorrhage (unrelated to study drug
- **8 Serious Adverse Events/60 (SAEs) related to study drug:**
  - Eye, finger and hip pain at Week 2
  - Urinary frequency at Week 3
  - Dysuria and urinary frequency at Week 5
  - Dysuria and hematuria at Week 2
  - Hematuria at Week 11
  - Grade 3 neutropenia at Week 3
  - Profound fatigue at Week 6

Lack of Myelotoxicity



No change from pre-treatment in BM cellularity over time

Ongoing Pivotal Clinical Trial

RAEB -1, RAEB-2, RAEB-t or chronic myelomonocytic leukemia patients with *de novo* and secondary MDS who progress, relapse after, are refractory to, or are severely intolerant to azacitidine or decitabine

- **No approved therapy for these patients**
- **270 patients randomized 1:2 to two groups**
  - **Best Supportive Care (BSC) alone (N=90)**
  - **BSC + ON 01910.Na 1,800 mg/24 h (N=180)**
    - **infusion on Days 1, 2, and 3 of a 2-week cycle for 16 weeks,**
    - **frequency reduced to every 4 weeks thereafter**
    - **Treatment until progression or death**
  - **Stratification on BM blasts (5-19% vs 20-30%)**
  - **Low dose AraC allowed for BSC, no cross over to ON 01910.Na allowed**
  - **Growth factors, transfusions and hydroxyurea as clinically justified**

Primary end point: survival

- **Secondary end points:**
  - **overall response (complete and partial remission)**
  - **bone marrow response**
  - **hematological improvements**
  - **transition to leukemia**
  - **quality of life**

Disclosures: Drs Raza, Greenberg and Silverman received research funding and drug supply from Onconova. Dr Olnes received drug supply from Onconova. Dr Wilhelm is an Onconova employee