Phase1/2 Single Arm Study of Rigosertib (ON 01910.Na) In Patients (Pts) with Relapsed or Refractory Acute Leukemia or Transformed Myeloproliferative Neoplasms

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Abstract

BACKGROUND: Rigosertib (ON01910.Na) is a non-ATP competitive multi-kinase inhibitor which differentially arrests tumor cells in G2-M stages and inhibits polo-like kinase and PI-3 kinase pathways with decreases of Cyclin-D1 and Akt phosphorylation. Earlier clinical studies in advanced solid tumors as well as in myelodysplastic syndrome (MDS) and acute leukemia reported a favorable toxicity profile and showed early evidence of clinical activity. Therefore, we initiated a study in acute myeloid leukemia (AML) investigating alternative schedules to determine the optimal dose and anti-leukemia efficacy. **METHODS**: This phase 1/2 study enrolled pts > 18 years(yrs) of age with relapsed or refractory AML or transformed myeloproliferative neoplasms (MPN). Pts were given rigosertib by continuous IV infusions over 24 hours (hrs) with a fixed dose of 2400mg/day either for 72 hrs or 120 hrs every other week using a standard dose escalation scheme. A blood sample was withdrawn at 6 hrs after the start of infusion during cycle 1 and cycle 2 to assess the plasma concentration of rigosertib. The study was subsequently amended and, after 2 cycles of IV rigosertib (each cycle being 2 weeks) pts could receive rigosertib orally, 560mg twice a day continuously for 20 weeks. The objectives of phase 1 study were to define maximum tolerated dose (MTD), dose limiting toxicities (DLT), identify all toxicities and anti-leukemia activity. Phase 2 primary objective was to determine the clinical efficacy; secondary objectives were to assess time to response or progression, duration of response and overall survival at 6 months. **RESULTS**: 31 pts have been enrolled in study from Sep 2010 to Oct 2012; median age was 67 yrs (range: 32-83 yrs) and 18 of them were males. Twenty five pts were on 72 hrs dose schedule. One of the 6 pts in the 120 hrs dose schedule eventually did not participate. The average plasma levels of rigosertib in pts on week 1 and 3 were 9.20 ± 5.05 and 9.81 ± 6.70 μM, respectively. Thirteen pts were enrolled in phase 2. Diagnosis included: 9 (30%) de novo AML, 15(50%) MDS related AML, 4(13%) treatment related AML and 2 (7%) transformed MPN. Pts had received a median of 2 prior chemolines (range, 1 to 6). There are 13 (27%) pts with primary refractory AML. Nine (30%) pts had a prior allogeneic stem cell transplant and 60% had a adverse karyotype. Pts received a median of 2 cycles (range, 1 to 5). Serious adverse events (SAE) seen were: altered mental status, confusion, delirium(8), febrile neutropenia(12), acute respiratory distress(2) , leukocytosis(3) , sepsis (7), pneumonia(5),urinary tract infection (2),multi organ failure (4), cardiomyopathy (1), fever (2), hypotension (1), hypertension (2), hypokalemia (1),elevated alanine amino transferase (1), pericarditis (1), intracranial hemorrhage (1) and pneumothorax (1). SAE incidence was not related to the duration of infusions (3 or 5 days) and occurred mainly during the first 28 days of treatment. The most common grade1 or 2 adverse events (AE) observed were: hypokalemia , thromboembolic events , hypotension , insomnia and hemorrhoids (2). All the SAEs except altered mental status (AMS) were considered unlikely or not related to the drug. The MTD was determined to be 2400mg over 24 hrs for 3 days. DLT at 2400mg over24 hrs for 5 days was grade 3 transient AMS (including confusion or delirium). Five pts on 120 hrs schedule developed AMS, 2(40%) of them were thought to be related to rigosertib. Three of 20 pts on 72 hrs schedule had transient AMS and 2 (12%) of them were considered to be possibly related to rigosertib. In terms of efficacy, best response noted is stabilization of disease in 7(23%) with same or less marrow blast after 2 cycles. The most common reasons for treatment discontinuation were disease progression, death from disease related complications or no response. The median days patients are on study is 34 (range: 8-80 days). Thirty day mortality is 30% and 60 day mortality is 57%.Study is closed and there are 5 patients who are alive. **CONCLUSIONS**:Analysis of phase 1/2 study of rigosertib shows that it has an acceptable toxicity profile with the main AE being transient AMS. Rigosertib therapy results in stable disease in some pts.

Background

- Rigosertib (ON01910.Na) is a non-ATP competitive multi-kinase inhibitor
- It differentially arrests tumor cells in G2-M stages
- Inhibits polo-like kinase and PI-3 kinase pathways
- Induces a decrease of Cyclin-D1 and Akt phosphorylation
- Clinical studies in advanced solid tumors , myelodysplastic syndrome (MDS) and acute leukemia have reported favorable toxicity profile and early evidence of clinical activity.

Objectives

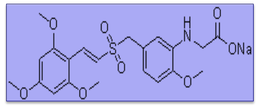
- **Phase 1**:
  - Define the toxicities of ON 01910.Na
  - Define the Maximum Tolerated Dose (MTD)
- **Phase 2** :Determine the clinical response rate

Study Design

- Single center, open label, phase 1/2 study
- Accrue 2 to 34 patients
- Phase 1: Dose escalation done using “3+3” rule.
- Phase 2: Accrual started after completing phase 1.
- Patients treated at the MTD during the Phase 1 portion can be included in the Phase 2
- Total study duration is 30 weeks = 2-week screening phase + 24-week dosing phase + 4-week follow-up phase.

Treatment Plan

- Rigosertib 2400 mg continuous IV infusion over 24 hours for 72 or 120 consecutive hours every 2 weeks for the first 4 weeks
- Per amendment: From week 5 drug given as oral capsule at 560 mg twice-daily taken continuously for 20 weeks.
- Cycles were 2 weeks in length (both IV & oral parts of the trial).



Eligibility

- Patients ≥18 years of age
- Relapsed or refractory acute leukemia
- Bone marrow (BM) blasts >/= 10%
- Performance status < 3
- Adequate organ function
- Declined or not candidates for stem cell transplant or other chemotherapy known to produce remission

Pharmacokinetics

- Average plasma levels of Rigosertib 6 hours after start of 2nd 24 hour infusion in week 1 and 3 were 9.20 ± 5.05 and 9.81 ± 6.70 μM, respectively.

Patient-Leukemia Characteristics

Characteristics	No. (%) or Median [Range]
Sex	Female: Male = 2:3
Age	Median : 67 [32-83]
AML-type	AML-MDS:15, Denovo:9, t-AML:4, AML-MPN:2
Karyotype*	Adverse risk:20, Intermediate risk:10
Molecular Findings	NRAS:7,FLT3- mutation:3, IDH2:3, FLT3-ITD:1,IDH1:1, JAK2:1, NPM:1
Baseline WBC	4.1 [0.1-22.5] x 10^3 /μL
Baseline peripheral blasts	62 [0-99]
Baseline marrow blasts	66 [14-92]
Prior Allogeneic Transplant	9 (30)
Primary Refractory AML	13 (43)
Relapse no. at Rx	Median : 1 [1-3]
No. of prior therapies	Median : 2 [1-6]

AML-MDS: Acute Myeloid Leukemia evolved from MDS , AML-MPN: AML evolved from Myeloproliferative Neoplasm, t-AML: therapy related AML, *Grimwade classification

Results

No. of pts	Phase 1 =17, Phase 2=13
No. of pts	5 day schedule = 5 3 day schedule = 25
No. of cycles	Median : 2 [1-5]
Days on study	Median : 34 [8-80]
Best response	Stable disease=7 pts (marrow blasts at 5 weeks ≤ baseline blasts)
30 Day mortality	9 (30%)
60 Day mortality	17 (57%)
Median survival	8 weeks
No. of pts alive	5 (17%)

Common Adverse Events (AE)

AEs	No. (%)	
	Any grade	Grade ≥3
Sepsis	7 (23)	7 (23)
Alt. mental status	6 (20)	5 (17)
Hypokalemia	5 (17)	5 (17)
Multi organ failure	5 (17)	5 (17)
Pneumonia	5 (17)	5 (17)
Cardiac arrest	3 (10)	3 (10)
Cellulitis	3 (10)	3 (10)
Confusion	3 (10)	2 (7)
Incr. ALT/AST	3 (10)	1 (3)
Weakness	3 (10)	2 (7)
Head ache	3 (10)	1 (3)
Hypertension	3 (10)	1 (3)
Leukocytosis	3 (10)	3 (10)
Resp. failure	3 (10)	3 (10)
Delirium	2 (7)	1 (3)

DLT is transient altered mental status: 2 (40%) in 5 day schedule and 2 (8%) in 3 days schedule

Stable disease (n=7)

Patient No.	1	2	3	4	5	6	7
Baseline marrow blasts	47	60	59	68	80	69	52
Marrow blasts at 5 weeks	47	59	33	39	80	67	50
No. of cycles received	5	3	2	3	5	5	4
Days survived since enrolling	80	43	49	72	78	alive (69)	51

Cause of death

- Disease progression (50%), multi organ failure (13%), sepsis (7%), cardiac arrest (3%), pneumonia (3%) , Intracranial bleed (3%)
- None considered drug-related

Results

- 30/31 patients enrolled received therapy (1 withdrew consent prior to start of treatment)
- MTD is 2400 mg over 24 hrs for 3 days
- DLT was grade 3 transient altered mental status / confusion / delirium
- Five patients on 5-day and three on 3-day schedules developed transient altered mental status
- Two (40%) episodes of altered mental status on 5-day and 2 (8%) on 3-day schedule were thought to be related to drug
- Seven (23%) had stable disease as evidenced by same or lower percent of marrow blasts after a 4 week period
- Four of these 7 patients (57%) had del 5q along with a complex karyotype
- No CR or CRp / CRi
- Study is closed for accrual

Conclusions

- Rigosertib has favorable toxicity profile
- Main adverse event is transient altered mental status
- Therapy with single agent results in stable disease in some patients.
- Combination therapy with Rigosertib is being explored

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Disclosure

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