# Rigosertib Activity In Patients with a Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) Relapsed or Refractory to Hypomethylating Agents

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## ABSTRACT

Background
Rigosertib is a multi-kinase/PI3 kinase inhibitor that promotes G2/M arrest and selectively induces apoptosis in cancer cells. Leukemic cells are more sensitive to rigosertib compared to normal marrow progenitors with increasing cytotoxicity upon prolonged, repetitive exposure (Chen AACR 2008).

Introduction
Pts relapsed or refractory to hypomethylating agents (HMA) have a median survival of 4 to 6 months (Jabbour 2010, Prebet 2011). There is no standard of care for this patient population.

Purpose
Conduct a phase I/II study of rigosertib in pts with MDS and AML.

Materials and Methods
In the phase I component, pts were entered in cohorts of escalating doses in a 3+3 design ranging from 650 up to 1700 mg/m$^2$/d continuous IV infusion (CIV) from 72 to 144 hours every 2 weeks (1 cycle) for 4 cycles during the induction phase. Subsequent treatments were administered every 3 to 4 weeks. A maximum tolerated dose of 1375 mg/m$^2$ was identified for the phase II component, and pts were treated with this dose as a CIV for 72 hours.

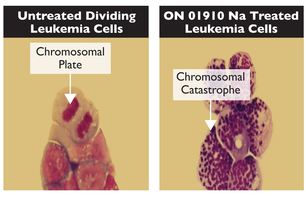
Results
21 patients with MDS or AML refractory/ relapsed to a HMA have been treated: int-2 MDS (2 pts), high risk MDS (5 pts), CMMOL (1 pt), and AML (13 pts) (all had antecedent MDS); Median age 79 years, 86% were male. Patients received between 1-19 cycles of treatment. Responses according to IWG 2006 criteria were observed in the BM and peripheral blood: marrow CR (4), marrow PR (2), hematologic improvement (HI) (2); erythroid (1) platelet (1), stable disease (3), inevaluable (3). Time to response was 2-4 cycles. An additional 2 pts had a >50% BM blast decrease from baseline but not to < 5% PR). Thus, 9/18 evaluable pts (50%) demonstrated either a bone marrow/peripheral blood response (6) or stable disease (3). The median overall survival of those with marrow CR+PR was 10.1 months versus 2 months for those without a bone marrow response (p=0.0011, log-rank test). The most frequent grade 1-2 side-effects included dysuria, hematuria, fatigue, anorexia, nausea, and diarrhea. Cystitis occurred in 6/21 pts; 5/9 among responders, 1/12 nonresponders. Symptoms responded to sodium bicarbonate.

Conclusions
Rigosertib appears to be safe and well tolerated in patients with refractory or relapsed MDS and AML. It has biologic activity with reduction in BM blasts and improvement in the peripheral blood counts in a subset of treated pts, and these effects are associated with increased survival. A phase III multicenter randomized trial is underway to compare rigosertib to best supportive care.

## BACKGROUND

Rigosertib Background
- Novel Benzyl styryl sulfone derivative, water soluble
- Multi-kinase/PLK-1 and PI3 kinase pathway inhibitor
  - promotes G2/M arrest and selectively induces apoptosis in cancer cells without affecting normal cells (reversibly arrested at G1 interface)
- Leukemic cells exhibit significantly higher levels of sensitivity to Rigosertib compared to normal marrow progenitors and increasing cytotoxicity upon prolonged and repetitive exposure (Skidan Proc AACR 2006; Chen Proc AACR 2008).
- Pts relapsed or refractory to hypomethylating based therapies have a poor prognosis and there are no accepted effective second line treatments, thus a need for new agents.

## CHROMOSOMAL CATASTROPHE IN CANCER CELLS TREATED WITH RIGOSERTIB.




## METHODS

- Phase I/II study of Rigosertib being conducted in pts with MDS and AML
- Pts with higher-risk MDS disease had to have failed a hypomethylating agent
- In the phase I component pts entered in cohorts of escalating doses in a classic 3+3 design in doses ranging from 650 up to 1700 mg/m2/d continuous IV infusion (CIV) for durations from 72 hours up to 144 hours every 2 weeks (1 cycle) for 4 cycles of treatment during the induction phase
- Subsequent treatments administered every 3 to 4 weeks
- CBC performed weekly and a bone marrow (BM) is performed at baseline and weeks 4, 8, and then q3 months thereafter

## PATIENT DISPOSITION

- Twenty-one pts with MDS or AML relapsed/refractory to a hypomethylating agent have been treated with Rigosertib thus far

- Study cohort (median age of 79 years) comprised pts with a diagnosis of
  - Intermediate-2 MDS(2 pts)
  - High-risk MDS (5 pt)
  - Chronic myelomonocytic leukemia (1 pt)
  - AML (13 pts)

- Recurrent Cytogenetic abnormalities:
  - 5 pts with normal cytogenetics
  - 2 pts with trisomy 8
  - 4 pts with monosomy 7
  - 5 pts with complex karyotype

- Patients received between 1 – 21 cycles of treatment

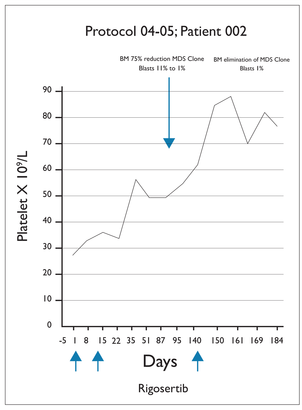
## OVERALL EFFICACY

- Responses according to IWG 2006 criteria observed in the BM and peripheral blood:
  - Marrow CR (4)
    - Survival of these pts was 12, 15.7, 16+, and 16.4 months
  - Hematologic improvement (HI) (2); erythroid (1) platelet (1)
  - An additional 2 pts had a >50% BM blast decrease from baseline but not to < 5%
- 9/18 evaluable pts (50%) demonstrated a bone marrow/peripheral blood response (6) or stable disease (3)
- Five of the six responders had MDS at the initiation of treatment:
  - High-Risk (2)
  - Int-2 (1)
  - CMMoL (1)
  - AML (1)
- Responders had monosomy 7 (2), trisomy 8 (1), normal (1) and complex cytogenetics (2)
- One pt had an elimination of the MDS clone and the others had persistence of the abnormal karyotype throughout their treatment course.
- 83% of non-responders or inevaluable pts had AML; many with a proliferative course.
  - These latter received <1 (1), 2 (3), 3 (4), or 4 (1) cycles before succumbing to disease related infectious complications.
  - Survival for these patients ranged from 0.6 – 2.8 months with a median duration on study of 1.4 months

## OVERALL RESULTS

| PT ID | INITIAL DX/ ON STUDY DX | PRIOR THERAPY | ON STUDY % BM BLASTS | MAX BM RESPONSE (IWG 2006 CRITERIA) | DOSING COHORTS MG/M2/D CIV | # CYCLES | DURATION ON STUDY (MO) | OS(MO) |
|---|---|---|---|---|---|---|---|---|
| 001 | High/AML | AzaC | 80 | PR | 650 | 10 | 7 | 7.3 |
| 002 | Int-1MF/High | AzaC | 11 | CR | 1050 | 14 | 15.7 | 15.7 |
| 003 | AML/AML | AzaC + vorinostat | 45 | NR | 1050 | 2 | 1.6 | 2 |
| 004 | High/High | AzaC | 17 | CR | 1050 | 19 | 16.4 | 16.4 |
| 005 | Int-2/AML | AzaC | 91 | NR | 1375 | 2 | 1.2 | 1.5 |
| 006 | CMMoL/ CMMoL | Decitabine | 22 | PR | 1375 | 4 | 1.6 | 4.7 |
| 007 | Int-2/AML | AzaC | 66 | NR | 1375 | 3 | 1.4 | 1.7 |
| 008 | Int-1/AML | AzaC | 44 | NR | 1700 | 3 | 1.4 | 1.7 |
| 009 | MDS-MF; AML/AML | Decitabine | 51 | NR | 1700 | 3 | 1.2 | 1.3 |
| 010 | Int-2/High | AzaC & Decitabine | 15 | CR | 1375 | 7 | 5 | 12 |
| 011 | Int-1/Int-2 | AzaC & Decitabine | N/A | SD | 1375 | 3 | 1.7 | 2.3 |
| 012 | Int-1/AML | AzaC | 30 | SD | 1375 | 3 | 1 | 2.9 |
| 013 | Int-2/AML | AzaC & Decitabine | 20 | NR | 1375 | 3 | 1.4 | 2 |
| 014 | Int-2/AML | AzaC | 11 | IE | 1375 | 2 | 0.7 | 9 |
| 015 | Int-2/Int-2 | Decitabine ATRA | 10 | CR | 1375 | 21 | 16+ | 16+ |
| 016 | Int-1/AML | AzaC | 86 | IE | 1375 | 2 | 0.6 | 0.6 |
| 017 | Int-2/High | AzaC + vorinostat | 24 | NR | 1375 | 4 | 2 | 0.6 |
| 018 | AML/AML | AzaC | 70 | SD | 1375 | 3 | 1.3 | 2 |
| 019 | Int-2/AML | AzaC | 54 | IE | 1375 | 1 | <1 | <1 |
| 020 | AML/AML | AzaC + vorinostat | 51 | NR | 1375 | 4 | 2.4 | 3 |
| 021 | Int-2/High | Decitabine + ATRA | 27 | NR | 1375 | 4 | 1.5 | 2.8 |

## DURABLE RESPONSE IN A VIDAZA REFRACTORY PATIENT

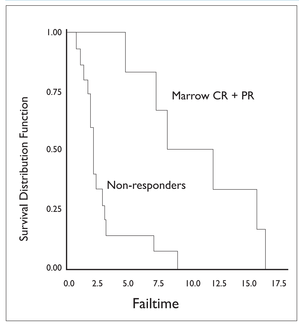



## RIGOSERTIB TOLERABILITY

- Most frequent side effects grade 2+ for all pts receiving extended duration infusions included
  - Fatigue
  - Anorexia
  - Nausea
  - Dysuria

- Five out of 9 responding/stable pts had cystitis compared with 1 of 11 non-responders. The relationship between dysuria and/or cystitis and response is being investigated.

## OVERALL SURVIVAL




The median overall survival of those with marrow CR + PR was 10.1 months versus 2 months for those withtout a bone marrow response (p=0.0011)

## CONCLUSIONS

- Rigosertib appears to be safe and well tolerated in patients with MDS and AML refractory or relapsing after treatment with hypomethylating agents
- Rigosertib has biologic activity with reduction in BM blasts, eradication of the MDS clone and improvement in the peripheral blood counts in some pts
- These effects are associated with increased survival albeit in limited numbers of pts treated thus far
- Dysuria/cystitis may be a response related biomarker and requires further analysis

**Disclosures: Reddy, Holland, Silverman: Onconova: Research Funding. Wilhelm: Onconova: Employment, Equity Ownership. Navada and Odchimar-Reissig: No relevant conflicts of interest to disclose**