Evaluation of Rigosertib In Patients with a Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) Relapsed or Refractory to Hypomethylating Agents: A Phase I/II Study

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Abstract

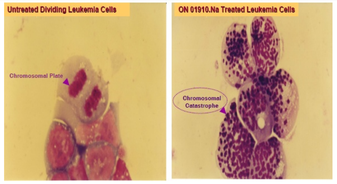
Background: Rigosertib is a small molecule anti-cancer agent with a multi-targeted mechanism of action. It is a multi-kinase/PI3 kinase inhibitor that promotes G2/M arrest and selectively induces apoptosis in cancer cells. Leukemic cells exhibit significantly higher levels of sensitivity to rigosertib compared to normal marrow progenitors and increasing cytotoxicity upon prolonged and repetitive exposure (Chen Proc AACR 2008). Azacitidine is first-line therapy for patients (pts) with higher-risk MDS and produces a response rate of 50%. Pts relapsed or refractory to hypomethylating agents have a short life expectancy of approximately 4 to 6 months (Jabbour 2010, Prebet 2011). There are no approved second line therapies for this patient population. **Methods:** A phase I/II study of Rigosertib is being conducted in pts with MDS and AML. Pts with higher-risk disease had to have failed a hypomethylating agent. In the phase I component, pts were entered in cohorts of escalating doses in a classic 3+3 design ranging from 650 up to 1700 mg/m^2/d continuous IV infusion (CIV) for durations from 72 hours to 144 hours every 2 weeks (1 cycle) for 4 cycles of treatment 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 subsequent pts were treated with this dose as a CIV for 72 hours. A CBC was performed weekly and a bone marrow (BM) was performed at baseline and week 4, 8, and then q3 months afterwards.
Results: Twenty-one patients with MDS or AML refractory/relapsed to a hypomethylating agent have been treated with rigosertib. The study cohort comprised pts with a diagnosis of intermediate-2 MDS (2 pts), high risk MDS (5 pts), chronic myelomonocytic leukemia (1 pt), and AML (13 pts) (all AML had an antecedent MDS). The median age was 79 years. 86% of pts were male. Patients received between 1-19 cycles of treatment. Their cytogenetic profiles were diverse with the most recurrent abnormalities including a complex karyotype (5 pts), normal (5 pts), monosomy 7 (4 pts), and trisomy 8 (2 pts). Responses according to IWG 2006 criteria were observed in the BM and peripheral blood: marrow CR (4), hematologic improvement (HI) (2); erythroid (1) platelet (1). Time to response was 2-4 cycles. An additional 2 pts had a >50% BM blast decrease from baseline but not to < 5%. Three pts had stable disease after treatment but their courses were complicated by infections requiring hospitalization and removal from the study. Three pts were deemed to be inevaluable because they received less than 2 cycles of treatment or did not have a follow-up bone marrow evaluation. 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). Of those pts who did not respond or were inevaluable, the majority (83%) had AML, many with a proliferative course. The most frequent grade 1-2 side-effects included dysuria, hematuria, fatigue, anorexia, nausea, and diarrhea. Possibly related grade 3 side-effects included fatigue, hematuria, and dyspnea, each in one pt. Six of 21 pts developed cystitis manifested by dysuria and/or hematuria. Among responding or stable patients, 5 of 9 had cystitis compared with 1 of 12 non-responders. Patients who developed symptomatic cystitis were treated with sodium bicarbonate with improvement. The relationship between dysuria and/or cystitis and response is being investigated.
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. Dysuria/cystitis may be a response related biomarker and requires further analysis. Data regarding pharmacokinetics and pharmacodynamics will be presented and correlated to response. Given promising initial results, a phase III multicenter randomized trial is underway to compare rigosertib to best supportive care with a primary endpoint of overall survival in patients with higher risk MDS who have failed, progressed, or relapsed after treatment with hypomethylating agents.

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/m^2/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

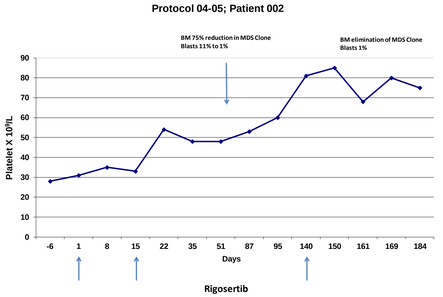
Patient Disposition

- 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 – 19 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, 12.2+, 15.7, and 16.4, and 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

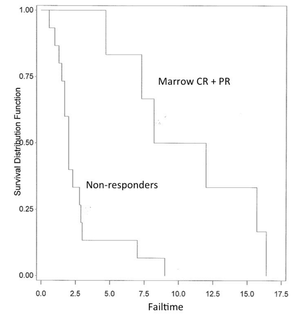
Durable Response in a Vidaza Refractory Patient



RigosertibTolerability

- 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 12 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 without a bone marrow response (p=0.0011)

Overall Results

Pt ID	Initial Dx/ On Study Dx	Prior Therapy	On Study % BM Blasts	Max BM Response (IWG 2006 criteria)	Dosing Cohorts mg/m^2/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	15	12.2+	12.2+
016	Int-1/AML	AzaC	86	IE	1375	2	0.6	0.6
017	Int-2/High	AzaC + vorinostat	24	NR	1375	4	2	11+
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

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