Predictors of Response to Rigosertib 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 small molecule anti-cancer agent which inhibits the PI-3K and PLK pathways, promotes G2/M arrest, and selectively induces apoptosis in cancer cells. We have previously reported results of a phase I/II study of rigosertib in patients (pts) with MDS and AML who had relapsed or were refractory to hypomethylating agents (HMA), a population for which there are currently no approved second line therapies. Rigosertib appeared to be well tolerated in this pt population and to have biologic activity with reduction or stabilization of bone marrow (BM) blasts and improvement in the peripheral blood (PB) counts in few treated pts. Reduction in BM blasts by rigosertib was associated with increased survival. In the current analysis, we evaluate pt characteristics that may predict for response.

Methods: We analyzed the results of a phase I/II study of Rigosertib that was conducted in pts with MDS and AML. 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) administered for 72 to 144 hours. A MTD 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. BMs were performed at baseline, week 4, 8, and then q3 months.

Results: Twenty-two pts with MDS or AML refractory or relapsing to a HMA have been treated with rigosertib. The study cohort comprised pts with a diagnosis of int-2 MDS (2), high risk MDS (6), CMMOL (1), and AML (13 pts all with antecedent MDS). Responses according to IWG 2006 criteria were observed in the BM and PB: marrow CR (4), marrow PR (2). Two pts also had hematologic improvement of the erythroid (1) and platelet (1) lineages. Four pts had stable disease (SD) after treatment but their courses were complicated by infections requiring hospitalization and removal from study. Three pts were deemed to be inevaluable because they received < 2 cycles of treatment or did not have a follow-up BM evaluation. Thus, 10/19 evaluable pts (53%) demonstrated either a BM/PB response (6) or SD (4). The median overall survival (OS) of pts with marrow CR+PR (n=6) was 12 months versus 1.8 months for those without a BM response (n=9) (p=0.0159, log-rank test). Age was not a predictor of response. 1 out of 6 responders had a major elimination in the size of the clonal population. Non-responders did not have a change in the magnitude of the clone. Prior response to HMA was not a predictor for response to rigosertib. Those who did have a marrow CR or PR responded early with median time to response of 2-4 cycles. Those with higher blast counts were less likely to respond. At study entry, the median blast percentage of responders was 16% versus 44% for non-responders. Less than 20% blasts at study entry was a positive predictor of response (p=0.047). Of those pts who did not respond or were inevaluable, the majority (75%) had AML, many with a proliferative course. Nine of 19 pts developed cystitis manifested by dysuria and/or hematuria as a side-effect of therapy. Among responding patients, 5 of 6 had cystitis [grade (GR) 1 (2); GR 2 (1); GR 3 (2)] compared with 3 of 9 non-responders [GR 1(1); GR 2 (1); GR 3(1)] (p=0.08). In one responding pt with grade 3 cystitis, a cystoscopy was performed which revealed polypoid inflammatory changes of the mucosa with hemorrhage. Biopsy showed neutrophilic inflammation without malignant cells. Upon resolution of symptoms, treatment was restarted at 50% of the original dose without complications. Pts who developed symptomatic cystitis were treated with sodium bicarbonate with improvement. The relationship between cystitis and response is being investigated.

Conclusions: Rigosertib appears to have biologic activity with reduction in BM blasts associated with increased survival and improvement in the PB counts in a subset of treated pts. Pts with <20% blasts at study entry had a greater likelihood of response. Pts with proliferative disease with rapidly rising or high wbc did not respond. Age, cytogenetic profiles, and response to prior therapy were not predictors of response. Cystitis may be a response related biomarker and requires further analysis. A phase III multicenter randomized trial is underway to compare rigosertib to best supportive care with a primary endpoint of OS in pts with higher risk MDS who have failed, progressed, or relapsed after treatment with HMA, and can be used to validate the observations reported here in a larger study.

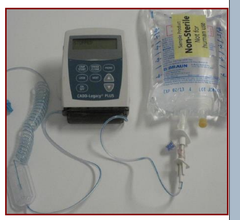
Background

- Novel Benzyl styryl sulfone derivative, water soluble
- Rigosertib is an inhibitor of two important cellular pathways, PLK-1 and PI3 kinase
  - promotes G2/M arrest and selectively induces apoptosis in cancer cells without affecting normal cells (reversibly arrested at G1 phase)
- MDS Patients who have failed treatment with hypomethylating based therapies have a poor prognosis. There are no effective or approved second line treatments, for these patients underlining the need for new agents
- Rigosertib has biologic activity with reduction or stabilization of bone marrow blasts, which is associated with increased survival

Rigosertib Intravenous Infusion Set-Up

Patient wearing Ambulatory Pump

Infusion Set



Methods

- Phase I/II study of conducted in pts with MDS and AML
- Pts with higher-risk MDS/AML 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
- A maximum tolerated dose of 1375 mg/m^2 was identified for the phase II component, and subsequent patients were treated with this dose as a CIV for 72 hours. Eighteen of 22 treated patients received this or higher dose.
- Bone marrows were performed at baseline and weeks 4, 8, and then q3 months thereafter

Patient Disposition

- Twenty-two pts with MDS or AML who had failed treatment with hypomethylating agents were treated with Rigosertib
- Study cohort comprised pts with a diagnosis of
  - Intermediate-2 MDS (2 pts)
  - High-risk MDS (6 pts)
  - Chronic myelomonocytic leukemia (1 pt)
  - AML (13 pts)

Overall Efficacy

- Responses according to IWG 2006 criteria observed in the BM and peripheral blood:
  - Marrow Complete Response (4)
    - Survival of these pts was 12, 15.7, 16.4, and 19.5 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%
- 10/19 evaluable pts (53%) demonstrated a bone marrow/peripheral blood response (6) or stable disease (4)

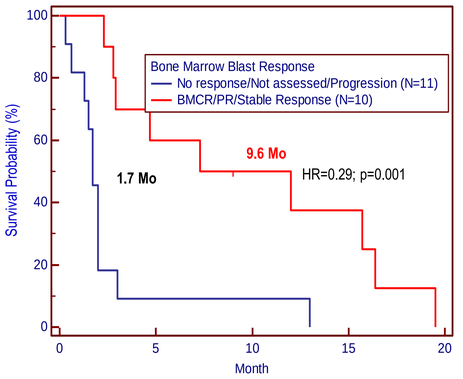
Predictors of Response

- Early bone marrow response at 4-8 weeks correlates with improvement in overall survival
- Patients who did have a marrow complete or partial response responded early with a median time to response of 2-4 cycles
- Less than 20% blasts at study entry was a positive predictor of response (p=0.047). All 8 MDS pts in the study had <20%.
- Patients with proliferative disease with rapidly rising or high white blood cell counts did not respond
- Age, cytogenetic profile, prior response to hypomethylating agents were not predictors of response

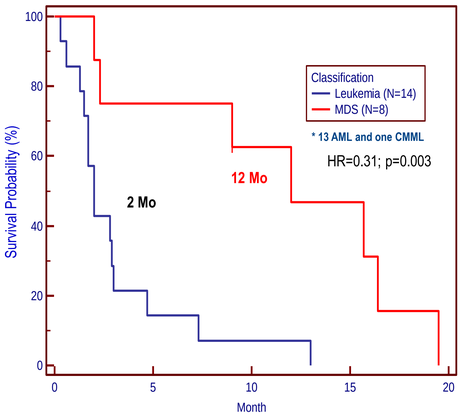
Cystitis Data

- Nine of 19 patients developed cystitis manifested by dysuria and/or hematuria
- Among responding patients, 5 of 6 had cystitis [grade 1 (2); grade 2 (1); grade 3 (2)] compared with 3 of 9 non-responders [grade 1 (1); grade 2 (1); grade 3 (1)] (p=0.08)
- In one responding patient with grade 3 cystitis, a cystoscopy revealed polypoid inflammatory changes of the mucosa with hemorrhage. Biopsy showed neutrophilic inflammation without malignant cells
- Timing of cystitis was variable but often occurred by cycle 2-3
- Patients were managed with sodium bicarbonate tablets with improvement in symptoms

Relation Between Bone Marrow Early Response at 4-8 Weeks and Overall Survival



Overall Survival in Patients with MDS vs AML



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+ vorinostat	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/High	AzaC & decitabine	20	NR	1375	3	1.4	2
014	Int-2/High	AzaC	11	IE	1375	2	0.7	9
015	Int-2/Int-2	Decitabine + ATRA	10	CR	1375	23	19.5	19.5
016	Int-1/AML	AzaC	86	IE	1375	2	0.6	0.6
017	Int-2/AML	AzaC + vorinostat	24	NR	1375	4	2	13
018	AML/AML	AzaC	67	SD	1375	3	1.3	2
019	Int-2/AML	AzaC	54	IE	1375	1	0.3	0.3
020	AML/AML	AzaC + vorinostat	51	SD	1375	4	2.4	3
021	Int-2/AML	Decitabine + ATRA	27	NR	1375	4	1.5	2.8
022	Int-2/High	AzaC + vorinostat	13	NR	1375	4	2.4	9+

Conclusions

- Rigosertib has biologic activity with reduction in BM blasts associated with increased survival and improvement in peripheral blood counts in a subset of patients with MDS and AML who failed prior treatment with hypomethylating agents
- Patients with <20% blasts at study entry have a greater likelihood of response to rigosertib
- Early bone marrow response at 4-8 weeks in patients treated with rigosertib correlates with improvement in overall survival
- Combination studies with other agents, such as azacitidine, are ongoing

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