Background: Rigosertib is a small molecule anti-cancer agent which inhibits the cellular mitotic activity by promoting microtubule dysfunction and apoptosis in cancer cells. We have previously reported results at a phase I study of rigosertib in patients with AML and also have investigated it as refractory to hypomethylating agents (RMA), a population for which there are currently no approved second line therapies. Rigosertib appeared to be well tolerated in this population and have biologic activity with reductions in disease burden with a high objective response rate (ORR) seen in patients with refractory myelodysplastic syndromes (MDS). In the current analysis, we evaluate results of patients who entered the rigosertib phase II study and were previously treated with hypomethylating based therapies, we have observed increased survival. In the current analysis, we evaluate results of patients who entered the rigosertib phase II study and were previously treated with hypomethylating based therapies

Methods: We analyzed the results of a phase II study of rigosertib that was conducted in patients who had received at least one previous hypomethylating agent as per the study protocol. Patients were identified in cohorts of escalating doses in a 3+3 design ranging from 580 mg to 1160 mg administered as 4-hour IV infusions every 2 weeks. AMTD of 1375 mg/m² was identified for the phase II cohort, and subsequent pts were treated with this dose in a 2x2 factorial design.

Results: Twenty-two pts with AML or MDS cohort of escalating dosing to a dose of 1375 mg/m² have been treated with rigosertib. The study cohort contained pts with a median age of 70 (range: 55-86), 64% male; 72% with AML, 28% with myelodysplastic syndromes. Responses according to IWG 2006 criteria were observed in the BW (n=8), marrow (FM): 2 PR, 1 NR. The pts had hematologic improvement of the erythroid (1) and platelet (1) lines. Four pts had stable disease (SD) after treatment but their courses were not analyzed further in the study. Those pts were deemed to be evaluable because they received ≥2 cycles of treatment or did not have a follow-up BM evaluation. Therefore, 13 pts could be evaluable pts (55%) determined either by BM response or SD (n=2). The median overall survival (OS) of pts with marrow CR (3) and BMCR (7) was 12 months versus 1.5 months for those without a BM response (n=1) or SD, log rank test: 0.005. Age was not a significant predictor of response in the study. A previous failure of decitabine treatment had a negative impact on survival. There were no deaths in the study. OS of pts was not significantly different among the 3 dose levels of rigosertib. Of the 10 evaluable pts, 53% demonstrated a bone marrow and/or peripheral blood response with (n=4) or stable disease (SD) (n=1). There was a significant decrease in AICM count; 8 of 10 evaluable pts improved (≥25%) in AICM count. There was an improvement in WBC and platelet count, however this was not statistically significant. Five of 10 evaluable pts had an improvement in PR radiograph. Three pts had stable disease (SD) and three pts had no change in the magnitude of the change. Prior response to HA was not a predictor for response to rigosertib. Those who did not have a BMCR or PR responded early with median time to response of 2.4 cycles. Those with higher blast counts were less likely to respond. A study exit, the median blast percentage of responders was 16% versus 44% for non-responders. Less than 20% blasts in study entry was a positive predictor for response. Rigosertib may be a new option for patients who have not responded to decitabine therapy and are deemed to be a refractory population. There were no new safety signals observed in this study.

Conclusions: Rigosertib has a biologic activity with reduction in blood counts and increased survival in patients with MDS. In the cohort of patients with MDS and AML who failed prior treatment with hypomethylating agents, Rigosertib showed a potential benefit in prolonging overall survival. The safety profile of rigosertib was consistent with the prior reports of rigosertib. Of the 19 patients who entered the phase I study, 14 had a documented response (day 1 to day 84), 12 had a decrease in disease burden.

Predictors of Response

Early bone marrow response at 4-8 weeks correlates with improved overall survival. Patients who did have a marrow complete or partial response revealed 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 BM pts in the study had >20% blasts. Patients with proliferative disease with rapidly rising white blood cell counts did not respond.

There was no change in the magnitude of the change. Prior response to HA was not a predictor for response to rigosertib. Those who did not have a BMCR or PR responded early with median time to response of 2.4 cycles. Those with higher blast counts were less likely to respond.

Methods

Phase I/II study of conducted in pts with AML and MDS. Pts with high-risk RMA disease had to have failed hypomethylating agents.

In the phase I component pts entered in cohorts of escalating doses in a series 1+3 design in doses ranging from 650 up to 1700 mg/m²/day continuous IV infusion (CVI) for durations from 72 hours to 14 days. A total of 35 patients were treated with rigosertib for these 2 cohorts. Those pts were treated with sodium bicarbonate with improvement. The relationship between cytogenetics and response is being investigated.

Conclusions: Rigosertib appears to have biologic activity with reduction in bone marrow blasts with increased survival in patients with MDS. In the cohort of patients with MDS and AML who failed prior treatment with hypomethylating agents, Rigosertib showed a potential benefit in prolonging overall survival. The safety profile of rigosertib was consistent with the prior reports of rigosertib. Of the 19 patients who entered the phase I study, 14 had a documented response (day 1 to day 84), 12 had a decrease in disease burden.

Cytisitis Data

- Nine of 19 patients developed cystitis manifested by dysuria and/or hematuria
- Among responding patients, 5 of 6 had cystitis grade 1 (2); 4 grade 2 (6) and 1 grade 3 (1)
- Of the grade 3 cystitis cases, a cystoscopy revealed pyelonephritic changes in the kidney and bilateral cell counts did not respond
- At the time of cystitis was variably associated with occurring cycle 3.
- Patients were managed with sodium bicarbonate tablets with improvement in symptoms

Overall Survival in Patients with MDS vs AML

- 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, Rigosertib showed a potential benefit in prolonging overall survival.

Conclusions

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.