ORAL RIGOSERTIB COMBINED WITH AZACITIDINE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML)

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BACKGROUND

AML in the elderly is associated with a dismal prognosis (5 yr survival <5%). Intensive chemotherapy is generally ineffective and there is a high unmet medical need for novel approaches to treat AML in patients ≥65 yrs.

Rigosertib (RIG) interferes with the Ras-binding domains of RAF kinases and inhibits the RAF-RAF-MEK and the PI3K pathways.1 In vitro, the combination of RIG with AZA synergistically inhibits growth and induces apoptosis of leukemic cells in a sequence-dependent manner.2 RIG’s effective inhibition of human hematopoietic tumor cell lines in vitro, favorable clinical adverse event (AE) profile, and its synergy with AZA suggests the potential value of combination treatment in elderly patients with AML who are ineligible for induction chemotherapy and SCT.

METHODS

Results are presented for pts with AML.1 Oral RIG was administered twice daily on Day 1-21 of a 28-day cycle in escalating cohorts and then at the recommended Phase II dose (560 mg qAM and 280 mg qPM). Two expansion cohorts of 1120 mg/day (560 mg twice a day and 840 mg qAM and 280 mg qPM) were added later. AZA 75 mg/m2/d SC or IV was administered for 7 days starting on Day 8. A CBC was performed weekly, and a bone marrow aspirate/biopsy was performed at baseline, D29, and then every 8 weeks thereafter. Response was determined by IWG criteria for AML (2003). We report on the combination of oral RIG and AZA administered to 17 pts with AML (11 patients identified as AML by investigator and 6 patients defined as MDS RAEB-t per FAB, with >20% blasts at baseline).

RESULTS

Median age was 73 years; 53% of pts were male, and ECOG performance status was 0-1 in 88% of pts. Pts received 1-11 cycles of treatment (median, 3 cycles), with a median duration of treatment of 13.9 weeks (range 5.0 – 74.1 weeks).

The most common treatment-emergent adverse events (TEAEs) were fatigue (53%), diarrhea (53%), nausea (53%), constipation (47%), back pain (41%), pyrexia (41%) and pneumonia (35%), and TEAEs Grade 3-4 were pneumonia (12%), anemia (24%).

PATIENT CHARACTERISTICS

N=17 Number of patients [%]

Gender
Female 9 (53)
Male 8 (47)
Race
White 9 (53)
Black 2 (12)
Hispanic 2 (12)
Asian 1 (6)
Median age 73
Range 57-80
ECOG performance status
0 1 (6)
1 14 (82)
2 2 (12)
Prior treatment regimens
None 2 (12)
1 2 (12)
2 9 (53)
3 5 (29)
3-4 1 (6)
Loss to follow-up

treatment
Prior therapy to study entry include Acizidaine 5 (29%), Decitabine 4 (24%) Cytarabine/Idarubicin 2 (12%), Trametinib/Uprosertib 1 (6%) and ESAs 3 (18%). Twelve pts were evaluable for response. There were 8 pts reported as none, Morphologic complete remission in 1 patient, and Morphologic leukemia-free state in 2 pts. Additional patients in both second- and refractory AML. Of the 12 evaluable patients for response, 6% patients had a greater than 50% decrease of blasts from pretreatment values. Of the 12 patients who met the criteria for RBC transfusion dependence at study entry, 1 patient became transfusion dependence in 1 patient and another had a decrease in more than 4 units on treatment from pretreatment transfusions.

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PATIENT DISPOSITION

N=17 Number of patients [%]

Discontinued study treatment 15 (88)
Primary reason
Progressive Disease 5 (29)
Death 3 (18)
Toxicity / Adverse Event 4 (24)
No hematologic response 1 (6)
Investigator Decision 1 (6)

DISEASE RESPONSE

N=17 Number of patients [%]

Investigator Decision 1 (6)
Response status after the last treatment
Morphologic complete remission 1 (6)
Morphologic leukemia-free state 3 (18)
Partial remission 2 (12)
Failure/Resistant disease 5 (29)
Failure/Indeterminate cause 1 (6)
Not evaluable 5 (29)
RBC transfusion status
Transfusion dependent at entry* 11 (65)No transfusion for 8 weeks after entry 1 (9)
24 units decrease from pretreatment 1 (9)

*early AM/mid-afternoon PM

COMBINATION DOSE ADMINISTRATION

ORAL RIGOSERTIB 840 MG IN DIVIDED DOSES

Week 1: oral rigosertib twice daily* Week 2: oral rigosertib twice daily* + azacitidine (75 mg/m2/d SC or IV)

Week 3: oral rigosertib twice daily* Week 4: No treatment

*early AM/mid-afternoon PM

REFERENCES/ACKNOWLEDGEMENTS


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CONCLUSIONS

The combination of oral RIG and standard-dose AZA was well tolerated in repetitive cycles in elderly pts with AML. In this population of AML pts, responses were seen in 50% of evaluable pts. In total 17 AML patients were treated in Phase 1/2 studies with the combination. Post hoc analyses of other studies are ongoing in pts with AML and MDS with elevated blast count who have received IV rigosertib. Further study of the combination in elderly patients with AML is warranted.

REFERENCES/ACKNOWLEDGEMENTS

