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

Shyamala C. Navada, MD[1], Guillermo Garcia-Manero, MD[2], Katherine Hearn, RN[2], Rosalie Odchimar-Reissig, RN[1], Erin P. Demakos, RN[1], Pierre Fenaux, MD, PhD[4], Michael E. Petrone, MD, MPH[3], Patrick S. Zbyszewski, MBA[3], Richard C. Woodman, MD[3], Steven M Fruchtman, MD[3], Lewis R. Silverman, MD[1]

[1]Tisch Cancer Institute, Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, [2]MD Anderson Cancer Center, Houston, TX;[3]Onconova Therapeutics, Inc., Newtown, PA; [4]Hopital St Louis, Paris, France

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 RAS-RAF-MEK and the PI3Ks 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.[3] 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 $\geq$ 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).

Last therapies prior to study entry include Azacitidine 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 6 responses seen, Morphologic complete remission in 1 patient, and Morphologic leukemia-free state in 3 pts and Partial remission in 2 patients for an ORR of 50%, with responses in both secondary and refractory AML. Of the 12 patients evaluable for response, 6 (50%) patients had a greater than 50% reduction of blasts from pretreatment values. Of the 11 patients who met the criteria for RBC transfusion dependence at study entry, 1 patient became transfusion independent and another had a decrease in more than 4 units on treatment from pretreatment transfusions.

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 were pneumonia (35%), anemia (24%).

PATIENT CHARACTERISTICS

N=17	Number of patients (%)
Gender	
Female	9 (53)
Male	8 (47)
Race	
Asian	2 (12)
Black	4 (24)
Hispanic	2 (12)
White	9 (53)
Age (year)	
Median	73
Range	57 - 80
ECOG performance status	
0	1 (6)
1	14 (82)
2	2 (12)
Prior treatment regimens	
None	2 (12)
1	9 (53)
2	5 (29)
3	1 (6)
Last therapy prior to study entry	
Azacitidine	5 (29)
Decitabine	4 (24)
Cytarabine/Idarubicin	2 (12)
Trametinib/Uprosertib	1 (6)
Erythropoiesis stimulating agents	3 (18)
None reported	2 (12)
Response status after the last therapy	
Relapse	6 (35)
Refractory	9 (53)
Not applicable	2 (12)

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)
Patient Request	1 (6)
Investigator Decision	1 (6)

DISEASE RESPONSE

N=17	Number of patients (%)
IWG 2003 Response	
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)
≥4 units decrease from pretreatment	1 (9)

* ≥2 units of RBC within 8 weeks of the first study treatment

COMBINATION DOSE ADMINISTRATION

ORAL RIGOSERTIB 840 MG IN DIVIDED DOSES

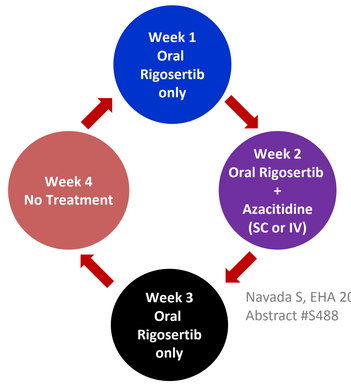
Week 1: Oral rigosertib twice daily*

Week 2: Oral rigosertib twice daily* + azacitidine (75 mg/m^2/day SC or IV)

Week 3: Oral rigosertib twice daily*

Week 4: No treatment

*early AM/mid-afternoon PM



Navada S, EHA 2017 Abstract #S488

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 have been 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 rigosertib in elderly patients with AML is warranted.

REFERENCES/ACKNOWLEDGEMENTS

[1]Athuluri-Divakar SK, Vasquez-Del Carpio R, Dutta K, et al. A Small Molecule RAS-Mimetic Disrupts RAS Association with Effector Proteins to Block Signaling. Cell. 2016;165(3):643–655. doi:10.1016/j.cell.2016.03.045

[2]Skidan I, Zinzar S, Holland J, Reddy R, Reddy EP, Silverman L. Toxicology of a novel small molecule ON01910Na on human bone marrow and leukemic cells in vitro. AACR Meeting Abstracts, Apr 2006; 2006:309.

[3]Vardiman, J. W., Harris, N. L., & Brunning, R. D. (2002). The World Health Organization (WHO) classification of the myeloid neoplasms. Blood, 100(7), 2292-2302. Accessed April 09, 2019. https://doi.org/10.1182/blood-2002-04-1199.

The authors gratefully appreciate the contributions of clinical investigators, study personnel, and, above all, the patients who participated in the trial.

ONCONOVA THERAPEUTICS