PHASE II STUDY OF ORAL RIGOSERTIB COMBINED WITH AZACITIDINE IN PATIENTS WITH HIGHER-RISK MYELODYSPLASTIC SYNDROMES (MDS)

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ABSTRACT

Background: Azacitidine based combination trials have not demonstrated improved response or outcome over single agent azacitidine.[1,2] Results of a Phase I/II study in MDS patients demonstrated oral rigosertib and standard-dose azacitidine to be well-tolerated with efficacy in HMA-naive and HMA-failure patients: at 560mg qAM/280mg qPM rigosertib dosing, overall response rate (ORR) was 77%; 88% for HMA-naive group, 60% for HMA-failure group. An increase in genitourinary (GU) adverse events was noted with the combination. Rigosertib at higher doses (1120 mg/day) yielded maximum ORR in lower-risk MDS and was thus investigated in additional cohorts.[3] Risk-mitigation strategies were employed to reduce GU AEs.[4]

Methods: Oral rigosertib was administered twice daily on Day 1-21 of a 28-day cycle (840mg or 1120mg total); parenteral (SC or IV) azacitidine 75mg/m2/day was given for 7 days starting on Day 8 in patients with MDS including both HMA naive and HMA failures. A CBC was performed weekly and a bone marrow aspirate and/or biopsy were performed at baseline, D29, and then every 8 weeks thereafter. Response was determined by IWG criteria for MDS.[6]

Results: Of those patients receiving ≥840mg rigosertib, 55 were evaluable for response. 26 were treated with 840mg rigosertib and 29 were treated with 1120mg.

Median duration of response was 12.2 months (range, 0.1-24.2+) and 10.8 months (range, 0.1-11.8+) for HMA naive and HMA-failure pts, respectively. Median number of cycles to initial/best response was 1/4 and 2/5, respectively.

Responses per IWG 2006 occurred in all IPSS-R subgroups. In low/intermediate (N=17), CR occurred in 4 (24%), PR was 0, mCR was 5 (29%), stable disease was 2 (12%), progression was 0, not evaluable was 3 (18%), HI in 9 (53%). In high risk (N=23), CR occurred in 2 (9%), PR in 1 (4%), mCR was 8 (35%), stable disease was 6 (26%), progression was 1 (4%), not evaluable was 4 (17%), and HI in 7 (30%). In very high risk (N=33), CR occurred in 5 (15%), PR was 0, mCR was 10 (30%), stable disease was 2 (6%), progression was 4 (12%), not evaluable was 11 (33%), and HI in 11 (33%).

Safety-optimization strategies were employed to minimize genitourinary toxicities of hematuria and dysuria.

Conclusions: Oral rigosertib with azacitidine demonstrated efficacy in HMA-naive patients. The combination markedly improved hematopoiesis and reduced blasts in those HMA-failure MDS patients. The combination was well-tolerated in repetitive cycles for 25+ months. Risk mitigation strategies reduced urinary AEs in the expansion cohort. A pivotal Phase 3 trial is planned in an HMA-naive patient population.

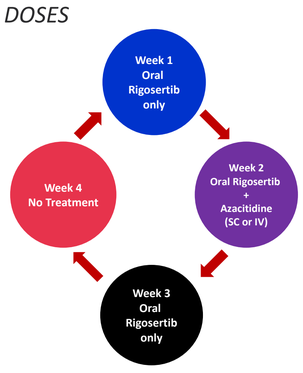
TREATMENT OF HIGHER-RISK MDS

- Azacitidine is standard of care for HR-MDS patients
- Clinical responses in MDS 38-50%[2]
  - CR rate 7-24%
  - Recent studies failed to demonstrate improved clinical benefit with combination therapies compared to single agent AZA
    - (Ades L, et al., #467, ASH 2018)[2]
    - (Sekeres M, et al., Intergroup JCO 2017)[1]
- All patients ultimately relapse or fail to respond; these patients have a poor prognosis, with a median overall survival (OS) of only 4-6 months[4]
- Novel better tolerated combination strategies for patients with MDS are required to improve the clinical outcome

COMBINATION DOSE ADMINISTRATION[4]

ORAL RIGOSERTIB 840 MG OR 1120 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

PATIENT CHARACTERISTICS – HR-MDS ≥ 840 MG/DAY

HMA NAIVE & HMA FAILURE

Number of patients treated		74
Age	Median	69
	Range	42-90
Sex	Male	44 (59%)
	Female	30 (41%)
IPSS classification	Intermediate-1	24 (32%)
	Intermediate-2	26 (35%)
	High	21 (28%)
	Unknown	3 (4%)
IPSS-R classification	Low	3 (4%)
	Intermediate	14 (19%)
	High	23 (31%)
	Very high	33 (45%)
	Unknown	1 (1%)
Prior HMA therapy	Azacitidine	26 (35%)
	Decitabine	6 (8%)
	Both	3 (4%)

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

ONCONOVA THERAPEUTICS

MDS19-0216

HMA NAIVE ≥ 840MG/DAY

EFFICACY

Evaluable for response	29*
Overall response per IWG 2006	26 (90%)
CR+PR	10 (34%)
Complete remission (CR)	10 (34%)
Partial remission (PR)	0
Marrow CR + Hematologic Improvement	5 (17%)
Hematologic Improvement alone	3 (10%)
Marrow CR alone	8 (28%)
Stable disease	3 (10%)
Progression	0
Median duration of response (months)	12.2 (range, 0.1-24.2+)
Median duration of treatment (months)	7.8 (range, 0.7-25.1+)
Median time to initial/best response (cycles)	1/4

** Includes 2 patients treated with non-HMA, chemotherapy*

HMA FAILURE ≥ 840MG/DAY

EFFICACY

Evaluable for response	26*
Overall response per IWG 2006	14 (54%)
CR+PR	2 (8%)
Complete remission (CR)	1 (4%)
Partial remission (PR)	1 (4%)
Marrow CR + Hematologic Improvement	5 (19%)
Hematologic Improvement alone	2 (8%)
Marrow CR alone	5 (19%)
Stable disease	7 (27%)
Progression	5 (19%)
Median duration of response (months)	10.8 (range, 0.1-11.8+)
Median duration of treatment (months)	4.9 (range, 1.1-20.9+)
Median time to initial/best response (cycles)	2/5

** Includes 9 patients treated with non-HMA, chemotherapy in addition to HMA*

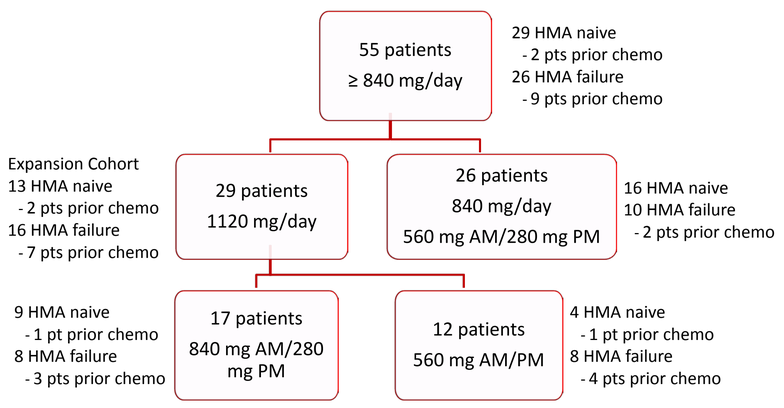
ADVERSE EVENTS

Treatment Emergent Adverse Events (≥30%) in MDS Patients (N = 74)

	Number (%) of Patients			
MedDRA Preferred Term	All grades	Grade 1	Grade 2	Grade ≥3
Any Event	74 (100)	74 (100)	70 (95)	65 (88)
Hematuria	33 (45)	12 (16)	14 (19)	7 (9)
Constipation	32 (43)	19 (26)	13 (18)	-
Diarrhea	31 (42)	22 (30)	5 (7)	4 (5)
Fatigue	31 (42)	6 (8)	22 (30)	3 (4)
Dysuria	28 (38)	15 (20)	6 (8)	7 (9)
Pyrexia	27 (36)	22 (30)	4 (5)	1 (1)
Nausea	26 (35)	21 (28)	5 (7)	-
Neutropenia	23 (31)	2 (3)	1 (1)	20 (27)
Thrombocytopenia	22 (30)	-	3 (4)	19 (26)

PATIENTS WITH HR-MDS EVALUABLE FOR RESPONSE PER RIGOSERTIB TREATMENT GROUP

HMA NAIVE & HMA FAILURE



Rationale for Expansion Cohort at a dose of 1120mg/day:

- Rigosertib as a single agent administered orally at dose of 1120 mg/day yielded the highest response rate of transfusion independence (44%) in lower risk MDS (Raza A, et al., #1689 ASH 2017)
- Pursue Safety Optimization Strategies in additional patients at a higher daily dose

DEFINITION OF EVALUABILITY

- In order for patients to be considered evaluable for response assessment
  - Patients must have been treated with doublet for at least 12 weeks unless
    - Investigator has determined that patient has progressed during the first 12 weeks of treatment
    - Investigator has determined that patient has responded within the first weeks of treatment but terminated treatment before 12 weeks

REASONS FOR DISCONTINUATION

Reason for discontinuation	HMA Naive	HMA Failure
		N=68*
Progressive Disease	7	12
Toxicity / Adverse Event	8	5
Investigator Decision	5	4
Patient Request	7	2
Bone Marrow Transplant	5	3
No hematological response	3	3
Death	0	2
Disease relapse	1	1

** Patient still participating*

SAFETY OPTIMIZATION STRATEGIES

COMPARISON OF RIGOSERTIB DOSING GROUPS

Safety Optimization Strategies			
2nd rigosertib dose must be administered at 3 PM (±1 hour) to avoid a nocturnal bladder dwell time	Oral hydration of at least two liters of fluid daily	Bladder emptying prior to bedtime	Urine pH 2 hours after AM dose. Suggested sodium bicarbonate administration if urine pH < 7.5

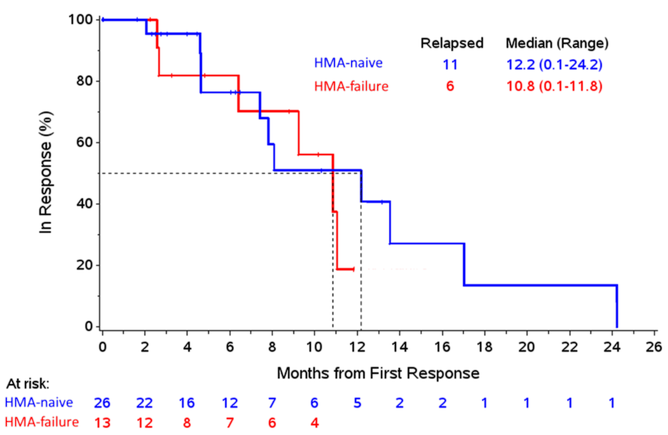
	Rigosertib 840mg	Safety Optimization Strategies Applied Rigosertib 1120mg
	42	43
Patients with hematuria	19 (45%)	17 (40%)
Patients with grade 1 or 2 hematuria only	14 (33%)	15 (35%)
Patients with grade 3 hematuria	5 (12%)	2 (5%)
Patients with dysuria	18 (43%)	13 (30%)
Patients with grade 1 or 2 dysuria only	13 (31%)	10 (23%)
Patients with grade 3 dysuria	5 (12%)	3 (7%)

No GR 4 reported

RESPONSE PER IWG 2006 AMONG MDS IPSS-R SUBGROUPS[6]

Response per IWG 2006	Low/Intermediate N=17	High N=23	Very high N=33	Unknown N=1
Complete remission	4 (24)	2 (9)	5 (15)	0
Partial remission	0	1 (4)	0	0
Marrow CR	5 (29)	8 (35)	10 (30)	0
Stable disease	2 (12)	6 (26)	2 (6)	0
Progression	0	1 (4)	4 (12)	0
Not evaluable	3 (18)	4 (17)	11 (33)	1 (100)
Hematologic improvement	9 (53)	7 (30)	11 (33)	0
Erythroid response	2 (12)	3 (13)	11 (33)	0
Platelet response	6 (35)	6 (26)	10 (30)	0
Neutrophil response	4 (24)	3 (13)	6 (18)	0

DURATION OF THE OVERALL RESPONSE



CONCLUSIONS

- **Oral rigosertib in combination with AZA demonstrated efficacy in both HMA-naive and HMA-refractory MDS patients**
- **In HMA-naive MDS patients oral rigosertib at doses ≥ 840 mg/day administered with AZA is associated with an ORR of 90% and a CR rate of 34%**
- **Oral rigosertib in combination with AZA was well tolerated and administered in repetitive cycles for more than two years**
- **Safety optimization strategies mitigated urinary AEs in the expansion cohort**
- **Based on the safety and efficacy profile of the combination in MDS, a pivotal Phase III trial is planned in an HMA naive population**

REFERENCES/ACKNOWLEDGEMENTS

[1]Sekeres MA, Othus M, List AF, et al. Randomized Phase II Study of Azacitidine Alone or in Combination With Lenalidomide or With Vorinostat in Higher-Risk Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia: North American Intergroup Study SWOG S1117. J Clin Oncol. 2017 Aug 20;35(24):2745-2753. doi: 10.1200/JCO.2015.66.2510. Epub 2017 May 9.

[2]Ades, L., Guerci, A., Laribi, K., Peterlin, P., Vey, N., Thepot, S., Wickenhauser, S., Zerazhi, H., Stamatoullas, A., Wattel, E., Recher, C., Toma, A., Bouabdallah, K., Braun, T., Beyne-Rauzy, O., Gruson, B., Cheze, S., Park, S., Cluzeau, T., Nimubona, S., Bordessoule, D., Benramdane, R., Quesnel, B., Ame, S., De Botton, S., Chermat, F., Lejeune, J., Chevret, S., & Fenaux, P. (2018). A Randomized Phase II Study of Azacitidine (AZA) Alone or with Lenalidomide (LEN), Valproic Acid (VPA) or Idarubicin (IDA) in Higher-Risk MDS: Gfm's 'pick a Winner' Trial. Blood, 132(Suppl 1), 467. Accessed April 10, 2019. https://doi.org/10.1182/blood-2018-99-111756.

[3]Raza, A., Yalçın, C., Cimist, M., Shelton, R., Bilgrami, S. F., Heaney, M. L., & Ali, A. M. (2017). Long Term Responses to Rigosertib in Lower-Risk Myelodysplastic Syndromes (MDS) Patients. Blood, 130(Suppl 1), 5316. Accessed April 10, 2019. Retrieved from http://www.bloodjournal.org/content/130/Suppl_1/5316.

[4]Navada, S. C., Garcia-Manero, G., Atallah, E. L., Rajeh, M. N., Shammo, J. M., Griffiths, E. A., Khaled, S. K., Dakhil, S. R., Young, D. E., Odchimar-Reissig, R., Pemmaraju, N., Alvarado, Y., Ohanian, M. N., John, R. B., Zbyszewski, P. S., Maniar, M., Petrone, M. E., Fruchtman, S. M., & Silverman, L. R. (2018). Phase 2 Expansion Study of Oral Rigosertib Combined with Azacitidine (AZA) in Patients (Pts) with Higher-Risk (HR) Myelodysplastic Syndromes (MDS): Efficacy and Safety Results in HMA Treatment Naïve & Relapsed (Rel)/Refractory (Ref) Patients. Blood, 132(Suppl 1), 230.

[5]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.

[6]Cheson, B. D., Greenberg, P. L., Bennett, J. M., Lowenberg, B., Wijermans, P. W., Nimer, S. D., Pinto, A., Beran, M., de Witte, T. M., Stone, R. M., Mittelman, M., Sanz, G. F., Gore, S. D., Schiffer, C. A., & Kantarjian, H. (2006). Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood,* 108(2), 419-425.