Phase 2/3, Multi-Center, International, Randomized, Double-Blind, Placebo Controlled Study of Oral Rigosertib + Injectable Azacitidine (aza) Versus Injectable Azacitidine in Treatment-Naive Patients with Higher-Risk Myelodysplastic Syndrome (HR-MDS)

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Submitted Abstract

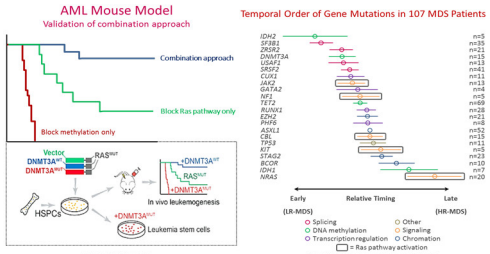
Background
The only approved medications for treatment of first line HR MDS are HMAs (aza & decitabine (DEC) in US, aza only in EU). It is estimated that progression to Acute Myeloid Leukemia (AML) as well as median OS for these pts is <1-3 yrs (Greenberg 2012). Although aza monotherapy demonstrated improvement in OS in HR MDS, clinically meaningful & durable responses continue to be limited to a subset of pts (Silverman 2006). One obvious strategy is to identify a novel drug that can be administered effectively in combo with aza & has minimal overlapping toxicity with aza. Based on this current approach & favorable results of the Ph2 study (Navada EHA 2019) the 1st pivotal Ph3 randomized study of oral rigosertib in combo with aza has been developed as part of an effort to increase overall responses as well as reduce risk of transformation to AML for pts with treatment-naive HR MDS.
Studies have demonstrated that rigosertib binds directly to the Ras-Binding Domains (RBD) found in Ras effector proteins, such as the Raf kinases & PI3K & inhibits the RAS-RAF-MEK & the PI3Ks pathways (Athuluri-Divakar 2016 Cell 2016). In vitro, the combo of rigosertib with aza synergistically inhibits growth & induces apoptosis of leukemic cells in a sequence-dependent fashion. Sequential exposure with rigosertib followed by aza achieved maximum synergy with clinically achievable concentrations (Skiddan AACR 2006, Silverman EHA 2019). In a ph2 study (09-08) oral rigosertib at doses ≥ 840 mg/d administered in combo with aza demonstrated efficacy in HMA-naive MDS pts with an ORR of 90% & a CR rate of 34%. The combo administered in repetitive cycles for more than 2 yrs was well tolerated & the observed GU toxicity was mitigated using specific management guidelines. Based on the efficacy data & favorable safety profile, the pivotal Ph3 trial presented here in treatment-naive HR MDS population has been developed. (Navada et al, EHA 2019).
Study Design & Methods
Ph3, multi-center, international, randomized, double-blind, placebo-controlled study to be conducted in tx-naive pts with HR MDS who will receive oral rigosertib 1120mg/d (560 mg morning & 560 mg afternoon) or placebo in combo with aza 75mg/m2 daily (SC or IV). Pts will take rigosertib/placebo on days 1-21 of a 28-day cycle & starting on Day 8, aza will be administered by SC injection or IV infusion at a 75 mg/m2 daily dose for 7 days of a 28-day cycle according to the approved label. 400 pts are anticipated for enrollment. Major inclusion criteria are shown in Figure 1. Major exclusion criteria are prior treatment with rigosertib or HMA; chronic myelomonocytic leukemia; & prior BMT.
Tx will continue until disease progression as defined by IWG 2006, or unacceptable toxicity. Treatment will continue until PD as defined by IWG 2006 or unacceptable toxicity, after which pts will be followed for survival every 2 mos until death or 3 yrs, whichever occurs first. The primary analysis of all efficacy endpoints will be in the intention-to-treat population. The safety population will include all pts classified according to the protocol treatment they received, regardless of random assignment. Randomized pts who receive no treatment will be excluded. Management guidelines for treatment emergent adverse events requiring dose adjustments, either dose delay or dose modification at time of AE, is provided in protocol.
The final analysis of response rate will be conducted using IWG 2006.
Conclusion
This pivotal Phase 3 trial in tx-naive HR MDS population has been developed based on efficacy data & favorable safety profile from 09-08. The Intergroup randomized ph2 combo study in pts with HR MDS treated with aza + lenalidomide (ORR 49%), or aza + vorinostat (ORR 27%) had a similar ORR to pts treated with aza monotherapy (ORR 38%) (Sekeres 2017). In contrast, the ph2 study of oral rigosertib in combo with aza had an ORR of 90% & a CR rate of 34% (Navada EHA 2019). This proposed study is the 1st ph3 combo study of oral rigosertib with aza & may provide a potential new treatment for first line in a pt population with poor prognosis & limited therapeutic options.

Background

- There are limited therapeutic options for HR MDS and prognosis remains poor. Clinically meaningful & durable responses with azacitidine (aza) monotherapy are limited to a subset (50%) of patients with HR MDS (Silverman 2006). One proposed strategy is to combine aza with other drugs that have novel mechanisms of action in an attempt to improve response rates in HR MDS;
- Rigosertib binds directly to the Ras-Binding Domains (RBD) found in Ras effector proteins and inhibits the RAS-RAF-MEK & the PI3Ks pathways (Athuluri-Divakar 2016 Cell 2016). In vitro, the combination of rigosertib with aza synergistically inhibits growth & induces apoptosis of leukemic cells in a sequence-dependent fashion (Skiddan AACR 2006, Silverman EHA 2019);
- In a single arm phase 1/2 study (09-08), oral rigosertib at daily doses 840 mg or 1120 mg administered in combination with standard dose aza both demonstrated favorable efficacy and safety in HMA-naive HR MDS pts with an ORR of 90% and a CR/PR rate of 34% (Navada et al ASH 2018);
- To evaluate the clinical benefit of novel treatments like rigosertib and improve the efficiency of randomized clinical trials, a variety of adaptive trial designs are increasingly being used in oncology (Sato 2018, Bhatt NEJM 2017). We propose an adaptive seamless phase 2/3 study design to confirm the optimal dose of oral rigosertib for combination with standard dose aza and demonstrate efficacy and safety of this combination therapy in patients with HMA-naive HR MDS (NEJM 2017);

Combination Therapy with Rigosertib + Azacitidine

Preclinical evidence supports synergism of rigosertib + aza combination



Summary of Clinical Benefit of rigosertib/aza in pts w HMA-naive HR MDS

Table 1: Summary of clinical benefit and risk for oral rigosertib in combination with azacitidine

	≥840mg/day	
TOTAL HMA-naive MDS PATIENTS TREATED	39	
Deaths on study	0	
Discontinued d/t PD	7 (18%)	
Discontinued d/t AE	10 (26%)	
CR/PR *	10/29 (34%)	
ORR ***	26/29 (90%)	
TI **	6/20 (30%)	
Pts going on to SCT	5/29 (17%)	
Heme tox	Any Grade	Grade ≥3
Febrile Neutropenia	10 (26%)	9 (23%)
Thrombocytopenia	8 (21%)	8 (21%)
GU tox	Any Grade	Grade ≥3
Hematuria	20 (51%)	6 (15%)
Dysuria	14 (36%)	5 (13%)

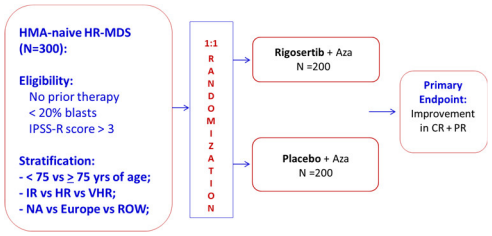
*Response rates are based on IWG criteria and excludes non-evaluable patients. ** Excludes patients who were TI at screening.
***ORR is defined as CR, PR, mCR and hematologic improvement

Response Rates (CR/PR/mCR) in HMA-Naive HR MDS in studies investigating aza combinations

Study	Combination Treatment (ITT) *	RR (%)
Sekeres et al 2017 (Adaptive phase 2/3)	aza monotherapy, n=92	36
	aza + lenalidomide, n=93	34
	aza + vorinostat, n=92	32
Ades et al 2018 (Randomized phase 2)	aza monotherapy, n=81	35.8
	aza + lenalidomide, n=80	31.2
	aza + valproic acid, n=80	36.2
	aza + idarubicin, n=81	35.8
Navada et al 2019 (Single arm phase 1/2)	aza + rigosertib, n=39	59.7

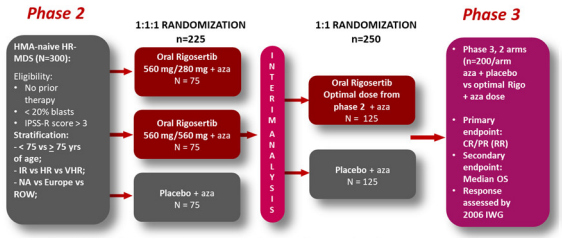
*ITT population would be used for analysis from studies intended for HA submission; mCR is currently not considered a regulatory endpoint
Sekeres et al JCO 35:2745, 2017; Ades et al ASH 2018 abstract #467; Navada et al ASH, 2019 abstract # XXX

Conventional Phase 3 Design for HMA-naive HR MDS



Adaptive Phase 2/3 Study Design for Oral Rigosertib and Aza

(Final study design will require HA review and approval)



- Double blind, placebo- controlled study in both phase 2 and 3 parts of study;
- Cross over is not permitted between treatment arms for any reason;
- The IA and selection of the optimal rigosertib dose will be conducted by an IDMC using pre-defined efficacy and safety criteria;
- Final analysis of phase 3 part of the study will compare placebo + aza arm to optimal rigosertib + aza arm;

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Summary of Seamless Adaptive Phase 2/3 design to evaluate rigosertib and azacitidine combination in HR MDS *

* Adapted from Bhatt et al NEJM 375: 65, 2017

	Phase 2	Phase 3
Objectives	• Identify optimal rigosertib/aza combination arm (based on RR and safety) for phase 3 evaluation vs standard dose aza monotherapy;	• Confirm the efficacy (RR) for the combination of rigosertib/aza compared to standard dose aza; • Demonstrate an improvement in OS with rigosertib/aza combination;
Advantages of study design	• Confirm optimal rigosertib dose to be used with standard dose aza; • Addresses limited sample size from single arm phase 2 study 09-08; • Includes aza monotherapy as control arm;	• Combines data from both phase 2 and 3 for primary endpoint analyses; • Eliminates time between phase 2 and phase 3 parts of the study; • Fewer patients are required (n=475) for the phase 2/3 adaptive design vs separate sequential phase 2 and phase 3 studies (n=625);
Potential limitations of study design	• Rigo dose recommended by IDMC at end of phase 2 study is done using pre-specified criteria and without sponsor involvement;	• Data from the phase 2 and phase 3 randomizations may not be homogeneous; • HA experience is limited compared to conventional phase 3 study designs;

Study conduct and Efficacy analyses

Phase 2 part of study

- Interim analysis to be conducted by IDMC for RR (CR/PR) after all 225 patients have been enrolled into the three arms of the phase 2 study and have completed six 4 week cycles or are withdrawn from study. RR from each of the rigosertib/aza arms will be compared to the aza/placebo arm;
- Criteria for selection of optimal rigosertib dose would be established *apriori* and include both efficacy and safety. The IDMC may recommend one of two options:
  - -select the optimal active rigosertib arm for continuation into the phase 3 portion;
  - - stopping the study due to futility for both rigosertib arms;

Phase 3 part of study

- Primary endpoint: RR will occur after a total of at least 400 patients have completed six 4 week cycles or are withdrawn from study. The primary analysis of all efficacy endpoints will be the ITT population and RR will be conducted using IWG 2006 criteria;
- Key secondary endpoint: final analysis of OS will occur after a total of 300 deaths on both arms are observed;

Dosing

- Ph 2/3, multi-center, international, randomized, double-blind, placebo-controlled study to be conducted in patients with treatment-naive HR MDS who will receive oral rigosertib or placebo in combination with aza 75mg/m2 daily (SC or IV);
- The following two doses of oral rigosertib will be studied in the phase 2 part of the study in combination with aza:
  - 1120 mg/day (560 mg morning & 560 mg afternoon);
  - 840 mg/day (560 mg morning & 280 mg afternoon);
- Patients will receive rigosertib/placebo on days 1-21 of a 28-day cycle & starting on Day 8, aza will be administered by SC injection or IV infusion at a 75 mg/m2 daily dose for 7 days of a 28-day cycle according to the approved label;
- Treatment will continue until disease progression as defined by IWG 2006 or unacceptable toxicity, after which pts will be followed for survival every 2 months until death or 3 years, whichever occurs first;

Conclusions

- Clinical benefit with oral rigosertib at doses ≥ 840 mg/day in combination with standard dose aza for patients with treatment-naive HR MDS has been reported from a single arm phase 1/2 study (09-08) (ASH abstract # 566); (Navada EHA Library 267422);
- An adaptive *seamless* randomized phase 2/3 study design is potentially advantageous for a pivotal study with oral rigosertib in combination with aza to demonstrate the clinical benefit:
  - The phase 2 part of the study will determine the optimal dose of rigosertib as well as demonstrate the incremental benefit of RR (CR/PR) compared to aza monotherapy;
  - The phase 3 part of the study is intended to confirm clinical benefit as measured by RR and OS in a well powered study (n=400);
- It is anticipated that an adaptive phase 2/3 study design will compress study timelines and reduce total number of patients required (N=475), compared to separate phase 2 and 3 studies conducted sequentially (N=625).

References

Greenberg P, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454-65.Silverman 2006
Navada, S, Garcia-Manero G, Atallah E, et al. (2019). Phase 2 Study of Oral Rigosertib Combined with Azacitidine in patients with Higher-Risk Myelodysplastic Syndromes (MDS).EHA Library; 267422; 5839.
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;165:643-55
Skiddan 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.
Silverman, L. et. al. (2019). RIGOSERTIB MODULATES HEMATOPOIESIS GENE SIGNALING PATHWAYS ALONE OR IN SEQUENCED COMBINATION WITH AZACTIDINE ON MDS CELLS IN VITRO. EHA Abstract # PS1332.
Sekeres, M. A., Othus, M., List, A. F., Odenike, O., Stone, R. M., Gore, S. D., ... Erba, H. P. (2017). 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. Journal of Clinical Oncology, 35(24), 2745–2753. doi: 10.1200/jco.2015.66.2510
Bhatt, D. L., & Mehta, C. (2016). Adaptive Designs for Clinical Trials. New England Journal of Medicine, 375(1), 65–74. doi: 10.1056/nejmra1510061
Sato, A., Shimura, M., & Gosho, M. (2017). Practical characteristics of adaptive design in phase 2 and 3 clinical trials. Journal of Clinical Pharmacy and Therapeutics, 43(2), 170–180. doi: 10.1111/jcpt.12617