Phase II Study of the IDH2-Inhibitor Enasidenib (AG-221) in Patients with High-Risk IDH2-Mutated Myelodysplastic Syndromes (MDS)

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Background

- Isocitrate dehydrogenase 2 (IDH2) mutations occur in 5-10% of MDS
- Mutant IDH2 proteins have neomorphic enzymatic activity -> oncometabolite, R-2-hydroxyglutarate -> hypermethylation of DNA and histones and block hematopoietic differentiation
- Enasidenib (AG-221,ENA) is an oral, selective, small molecule inhibitor of mutant IDH2
- Enasidenib : ~40% response rates and a median OS 8.8 months in R/R mIDH2 AML [1]
- ENA in R/R mIDH2 MDS (N=17): 53% response rates and a median OS 16.9 months [2]
- Median OS in post HMA failure setting – 4.5 months in higher risk MDS [3]

Objective

To evaluate the efficacy and tolerability of ENA, as monotherapy or in combination with azacitidine (AZA) in pts with higher-risk IDH2-mutated MDS (NCT03383575)

Materials & Methods

Design & Setting: Multi-institutional open label two arm non-randomized phase II study

Patients & Interventions:

Arm:A - Pts with treatment naïve higher-risk (R-IPSS > 3, or high molecular risk MDS/CMML, or RAEB-T MDS received ENA100 mg orally daily for 14 or 28 d of each 28-d cycle + AZA 75 mg/m2 IV or SC on d 1-7 of each cycle (ENA+AZA). ENA duration was decreased to 14 d of each cycle per amendment to mitigate cytopenias.

Arm:B- Pts with refractory or progressive MDS to prior HMA therapy received ENA alone continuously, in 28-d cycles

Main Outcome Measures: The primary endpoint was overall response rate (ORR) [complete remission (CR), marrow CR (mCR), partial remission (PR) and hematologic improvement (HI)]. Other endpoints include safety, and survival outcomes.

Results

	Total (N = 46)	Arm A (Untreated) AZA + ENA (N = 25)	Arm B (HMA-failure) ENA (N = 21)
Age (years), median [range]	73 [46 – 83]	73 [49 – 83]	73 [46 – 82]
Age ≥ 65 years, n (%)	36 (77)	17 (68)	19 (86)
ECOG performance status 0-1, n (%)	45 (99)	25 (100)	20 (91)
WHO 2017 Diagnosis, n (%)			
MDS-MLD / MDS/MPN-U	14 (30)	7 (28)	7(33)
MDS-EB / AML-MRC	27 (59)	16 (64)	11 (52)
CMML	5 (11)	2 (8)	3 (14)
Baseline transfusion dependence, n (%)			
RBC	14 (30)	3 (12)	11 (52)
Platelets	3 (11)	3 (8)	2 (9)
Bone marrow blasts (%), median [range]	7 [1-22]	8 [1-19]	5 [2-22]
Cytogenetics, n (%)			
Good	23(50)	13 (52)	10 (48)
Intermediate	15 (33)	7 (4)	8 (38)
Poor	8 (17)	5 (20)	3 (14)
IPSS-R risk classification, n (%)			
Low / Intermediate	18(39)	8 (32)	10 (48)
High / Very High	27 (59)	17(68)	11 (52)
Key Mutations *			
ASXL1	17 (47)	10 (55)	7 (38)
SRSF2	20 (55)	13 (72)	7 (38)
RUNX1	8 (22)	5 (27)	3 (16)
TP53	2 (5)	2 (11)	0
NPM1	1 (3)	1 (5)	0

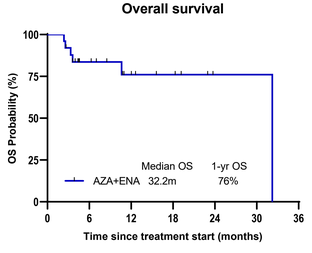
- The median age was 73 years
- 30% had transfusion-dependent anemia.
- 60% categorized as high or very high IPSS-R score. 5 patients in arm A with intermediate IPSS-R score had an ASXL1 mutation as their adverse risk feature.
- Most common co-occurring mutations were ASXL1 (47%) and SRSF2 (55%)

Responses

	Response Evaluable (N = 46)	Arm A (Untreated) AZA + ENA (N = 25)	Arm B (HMA-failure) ENA (N = 21)
Overall response rate (ORR), n (%)	30 (68)	21 (84)	9 (43)
Complete remission (CR)	11 (24)	6 (24)	5 (24)
Partial remission (PR)	3 (7)	2 (8)	1 (5)
Marrow CR (mCR)	12 (26)	11 (44)	1 (5)
Hematological improvement (HI) only	4 (9)	2 (8)	2 (10)
No response (NR), n (%)	16 (35)	4 (16)	12 (57)
Stable disease (SD)	14 (30)	4 (16)	10 (48)
Progressive disease (PD)	2 (4)	0 (0)	2 (10)

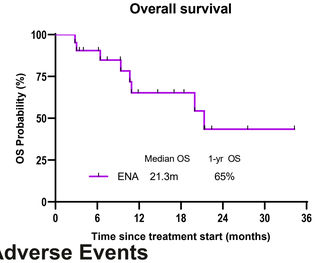
- In HMA-naïve patients treated with enasidenib and azacitidine, the overall response rate was 84%, consisting mostly of mCR or CR.
- In patients with relapsed or refractory disease post HMA, treated with single agent enasidenib, the overall response rate was 43% and 10 pts had stable disease

Survival — Arm A (AZA + ENA) — Untreated patients



With a median follow-up of 10.8 months, the median overall survival was 32.2 mo with 1-year OS rates of 76%

Survival: Arm B (ENA) – R/R MDS post HMA Failure



With a median follow-up of 18.4 months, the median overall survival was 21.3 mo with 1-year OS rate of 65%

Adverse Events

- Grade 1-2 events were primarily GI related
- 3 pts in arm A and 5 in arm B had clinically suspected differentiation syndrome
- 6 patients had grade 3 differentiation syndrome of whom 5 were successfully treated with dexamethasone. 1 patient had leukocytosis and was eventually determined to have AML progression ,was treated with Hydroxyurea
- No deaths occurred as a result of DS.

Discussion

- Enasidenib shows promising efficacy in high risk IDH2-mutated MDS both in combination with azacitidine in treatment naïve and as single agent in post HMA failure setting
- Enasidenib appears to be well tolerated
- DS occurred in 17% of pts, and was manageable

References

1 Stein et al, Blood 2017; 130 (6): 722–731

2. Stein et al, Lancet Haematol 2020;7: e309–19

3. Nazha et al, Blood Cancer J. 2017;7(12):644

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