A Phase I Study of the IDH2 inhibitor enasidenib as maintenance therapy for *IDH2*-mutant myeloid neoplasms following hematopoietic cell transplantation

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Disclosures

Consulting fees
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Background

- Characterization of molecular alterations in AML has led to development of targeted therapies, including IDH1/2 inhibitors.

- Maintenance therapy following hematopoietic cell transplantation (HCT) and consolidation chemotherapy has shown substantial promise in AML.

- The IDH2 inhibitor enasidenib was associated with impressive rates of response in relapsed/refractory AML and is now FDA-approved for this indication.

- We sought to assess the tolerability and MTD of enasidenib as post-HCT maintenance for *IDH2*-mutated myeloid malignancy.

Methods

- Eligibility included HCT-eligible patients aged ≥ 18 years with AML in remission, or MDS with <5% marrow blasts. Those with prior HCT, active disease, QTc ≥450ms, and active infections were excluded.

- A 2-step registration process was utilized; 1 before HCT and 1 before enasidenib initiation.

- Prior to HCT, normal organ and recovered marrow function (neutrophils > 1000/µL and platelets > 50000/µL) were required.

Methods

- Enasidenib was initiated between days 30 and 90 after HCT, at which time the following were required:

  -Chimerism ≥70% of donor origin among blood/marrow cells

  -No aGVHD requiring ≥0.5mg/kg/day prednisone or equivalent

  -No active disease.

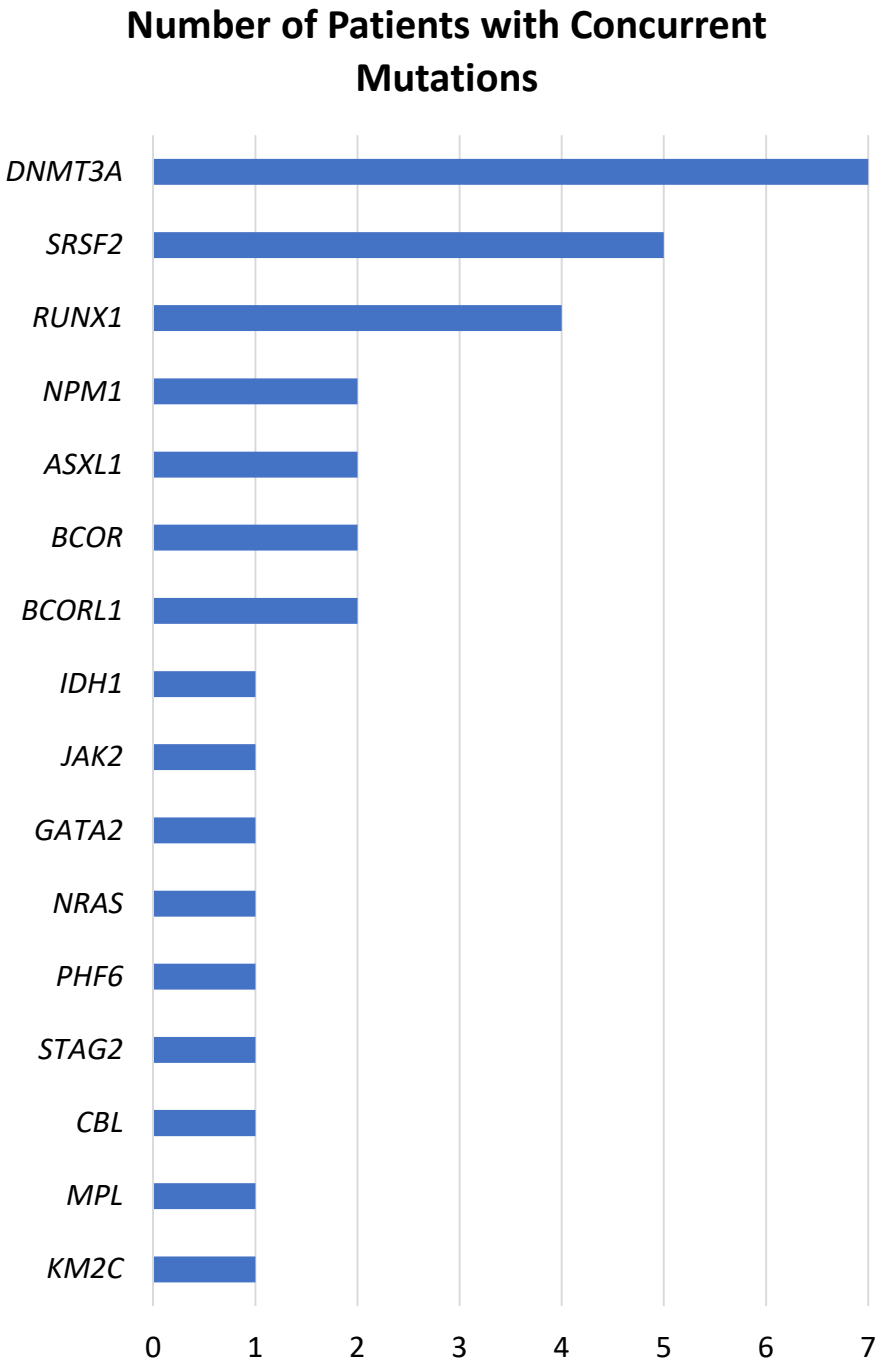
- Enasidenib was taken orally daily in 28-day cycles. The period of DLT evaluation was the first cycle.

	Enasidenib Dose
Dose Level 1	50mg PO Daily
Dose Level 2	100mg PO Daily
Expansion (10 patients)	100mg PO Daily

Patient Characteristics

Number Treated with enasidenib*	16
Mean age (range)	61 (31-76)
Male	12 (75%)
Caucasian	13 (81%)
AML	14 (88%)
MDS-EB2	2 (13%)
AML Patient Data	
AML-MRC	6 (8%)
AML arising from antecedent MPN	2 (13%)
Cytogenetic Risk (15 pts with available data)	
Adverse	4 (27%)
Intermediate	11 (73%)
***IDH2* Mutational subtype (14 pts with available data)**	
IDH2 R140	10 (64%)
IDH2 R172	5 (36%)
Received enasidenib prior to HCT	7 (44%)
Reduced Intensity conditioning	12 (75%)
Myeloablative conditioning	4 (25%)
Matched unrelated donor	9 (56%)
Matched related donor	1 (6%)
Haploidentical donor	6 (38%)

* 19 patients were registered, of which 16 went on to receive post-HCT maintenance



Safety and Tolerability

Dose Level	Enrollment	Dose Limiting Toxicity	Attributable ≥ Grade 3 Adverse Events
1 (50mg QD)	3	No	G3 Anemia
2 (100mg QD)	6	No	G3 Bilirbinemia, G4 Neutropenia
Expansion (100mg QD)	7 (of 10)	NA	

- Six patients (38%) have required dose interruptions lasting a median of 19 days (range 7-25 days).
- Four patients have required a dose reduction to 50mg from 100mg daily.
- In total, 3 patients (18%) have to date discontinued study treatment, one for G3 bilirubinemia, one to pursue another trial for GVHD, and one for relapse.
- Three patients have experienced ≥ G2 acute GVHD, and four patients experienced moderate chronic GVHD.

Patient Disposition

- Median follow-up for surviving patients is at 11.7 months.
- Two pts (13%) have relapsed during follow-up, one at 96 and one at 364 days following HCT.
- Six patients have completed the 12-month follow-up period without relapse.
- Seven patients remain on study treatment.
- 15 of 16 patients remain alive.

Study Status

- The study remains open and recently completed pre-HCT registration accrual.

- Planned data analysis to assess 2-HG measurement and *IDH* mutational MRD, prior to and after treatment, as predictor and prognostic biomarkers.