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Continuing Enasidenib Treatment for Patients with Mutant-*IDH2* Relapsed or Refractory Acute Myeloid Leukemia with Stable Disease May Result in Improved Survival and Responses over Time

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BACKGROUND

- Approximately 12% of patients with acute myeloid leukemia (AML) harbor mutations in isocitrate dehydrogenase 2 (*IDH2*) genes. *IDH2* mutations produce the oncometabolite, 2-HG, causing DNA and histone hypermethylation and leading to blocked differentiation of immature cells[1]
- Enasidenib (CC-90007/AG-221) is a novel, small-molecule, oral inhibitor of mutant-IDH2 (mIDH2) proteins, which was recently approved for use in adult patients with m*IDH2* relapsed/refractory (R/R) AML
- The clinical efficacy of enasidenib is derived in part by differentiation of immature leukemic cells[1,2]
- Unlike cytotoxic therapies, differentiating agents can induce first responses months after treatment initiation[3-6]
- Preliminary evidence suggests patients who maintain stable disease (SD) during early treatment with a lower-intensity AML therapy may attain a survival benefit, particularly if accompanied by hematological improvement[7]

OBJECTIVES

- Assess response and survival outcomes for patients with m*IDH2* R/R AML who maintained SD during early enasidenib treatment cycles in the phase 1/2 AG221-C-001 study

METHODS

- Patients included in these *post hoc* analyses:
  - Age ≥18 years
  - Received enasidenib 100 mg daily in continuous 28-day treatment cycles
  - Maintained SD per European LeukemiaNet (ELN) 2017 criteria[8]; ie, had no formal IWG-defined[9] hematologic response and no evidence of progressive disease (PD) for at least 90 days
- All patients who maintained SD for the first 90 days on-study were divided into 3 subgroups:
  - Patients who later attained a hematologic response at any time after day 90 ("SD Late Responders")
  - Patients who continued to maintain persistent SD after day 90 ("SD Only")
  - Patients who experienced disease progression after day 90 ("PD After Day 90")
- Kaplan-Meier estimated median overall survival (OS) and 1-year survival rates are compared among the SD Late Responders, SD Only, and PD After Day 90 groups

RESULTS

Patients

- In all, 214 patients with m*IDH2* R/R AML received enasidenib 100 mg daily; 89 patients (42%) maintained SD for the first 90 days of treatment and comprised the SD cohort (Figure 1)
  - SD Late Responders: n=24 (27%); median treatment duration 250.5 days (range 112-717)
  - SD Only: n=40 (45%); median treatment duration 173 days (range 99-361)
  - PD After Day 90: n=25 (28%); median treatment duration 107 days (range 66-218)
- Baseline demographic and disease characteristics for the SD Late Responders, SD Only, and PD After Day 90 cohorts are shown in Table 1
- The most frequent co-mutations in SD patients with co-mutational data (n=53) were in *SRSF2* (43%), *DNMT3A* (32%), *RUNX1* (26%), and *ASXL1* (23%)

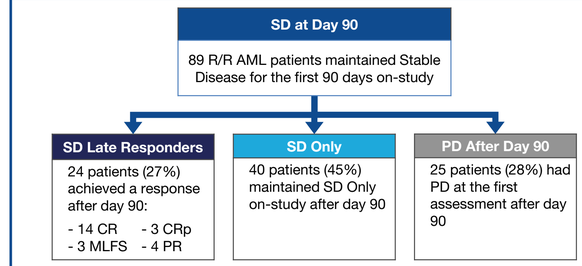
Responses After Day 90

- 24 patients responded after day 90, including 14 who achieved complete remission. Median time to first response was 129.5 days (range 90-336)
  - In univariate analyses, no baseline variable included in Table 1 was significantly predictive of future response/non-response among SD patients
  - Baseline 2-HG level did not appear to influence attainment of later response (Figure 2)
  - SD Late Responders had lower median *IDH2* variant allele frequency (VAF) at baseline than those who did not respond after day 90 (Figure 2), though differences were not statistically significant
  - IDH Differentiation Syndrome was reported for 5 patients in each SD cohort and rarely occurred after day 90
- RBC and platelet transfusion independence rates were ≥80% in SD Late Responders (Figure 3)

Survival Outcomes

- Median OS for all 89 patients who maintained SD for the first 90 days was 9.0 months (95%CI 8.2, 11.4) (Figure 4)
- SD Late Responders:
  - Median OS: 26.7 months (95%CI 10.7, 26.7)
  - Estimated 1-year survival: 61.3% (95%CI 37.9, 84.7)
- SD Only*:*
  - Median OS: 8.8 months (95%CI 7.7, 11.6)
  - Estimated 1-year survival: 26.0% (95%CI 8.1, 43.9)
- PD After Day 90*:*
  - Median OS: 5.8 months (95%CI 5.4, 8.3)
  - Estimated 1-year survival was 0%
- Risk of death was significantly reduced in SD Late Responders by 61% vs the SD Only cohort and by 84% vs the PD After Day 90 cohort (Figure 4)
- In the SD Only cohort, risk of death was significantly reduced by 57% vs the PD After Day 90 cohort (Figure 4)

Figure 1. Stable Disease Patient Subgroups



CR, complete remission; CRp, CR with incomplete platelet count recovery; MLFS, morphologic leukemia-free state; PR, partial remission

Table 1. Baseline Demographic and Disease Characteristics

	SD Late Responders n=24	SD Only n=40	PD After Day 90 n=25
Age (years), median (range)	68.5 (45-81)	67.5 (23-88)	71.0 (34-79)
Gender, % male/female	46/54	52/48	52/48
WHO AML classification, n (%)	n=23	n=37	n=21
Myelodysplasia-related changes	6 (26)	8 (22)	4 (19)
Recurrent genetic abnormalities	6 (26)	5 (14)	3 (14)
Therapy-related myeloid neoplasms	1 (4)	0	0
Not otherwise specified	10 (43)	24 (65)	14 (67)
***IDH2* mutant allele,** n (%)	n=23		
IDH2-R140	14 (61)	31 (78)	20 (80)
IDH2-R172	9 (39)	9 (22)	5 (20)
Co-mutations, n (%)	n=15	n=27	n=11
NPM1	4 (27)	4 (15)	1 (9)
FLT3	0	4 (15)	3 (27)
CEBPA	0	2 (7)	0
Number of mutations, n (%)	n=15	n=27	n=11
0-1	3 (20)	4 (15)	4 (36)
2	2 (13)	6 (22)	1 (9)
≥3	10 (67)	17 (63)	6 (54)
Prior MDS, n (%)			
No	21 (88)	29 (73)	22 (88)
Yes	3 (13)	11 (28)	3 (12)
Prior anti-cancer regimens, n (%)			
1	12 (50)	20 (50)	7 (28)
2	9 (38)	11 (28)	8 (32)
>2	3 (13)	9 (23)	10 (40)
ECOG PS score, n (%)			
0-1	22 (92)	36 (90)	21 (84)
2	2 (8)	4 (10)	4 (16)
Months since diagnosis, median (range)	11.6 (1.8-59.1)	9.0 (1.3-83.1)	12.1 (1.2-54.8)
NCCN Cytogenetic risk, n (%)	n=11	n=33	n=21
Intermediate	8 (73)	21 (64)	12 (57)
Poor	3 (27)	12 (36)	9 (43)
BM blast %*, median (range)	45.0 (1.0-78.0)	50.0 (0-96.0)	66.0 (18.0-95.0)
Hemoglobin (g/dL), median (range)	9.7 (7.0-13.8)	8.9 (7.0-12.7)	8.9 (7.0-12.5)
Platelets (10^9/L), median (range)	44 (4-194)	38 (10-337)	35 (1-372)
WBC (10^9/L), median (range)	1.6 (0.2-20.6)	1.9 (0.3-59.2)	2.7 (0.7-18.2)
ANC (10^9/L), median (range)	0.3 (0-38.0)	0.2 (0-5.4)	0.2 (0-2.6)

*Local assessment
ANC, absolute neutrophil count; BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; MDS, myelodysplastic syndromes; NCCN, National Comprehensive Cancer Network; WBC, white blood cell count; WHO, World Health Organization

Figure 2. 2-HG Concentrations and *IDH2* Variant Allele Frequencies at Baseline

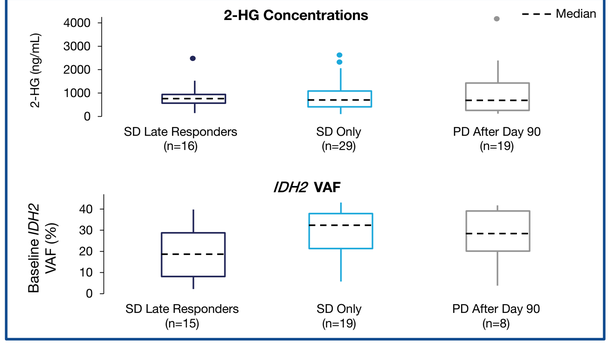
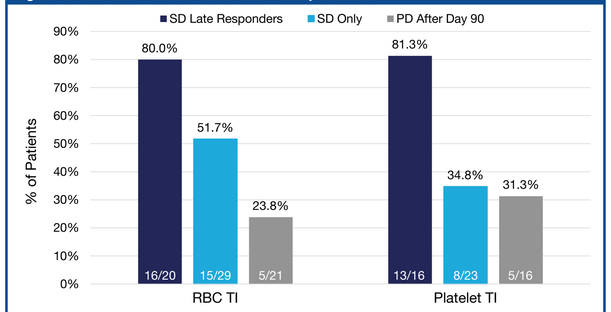
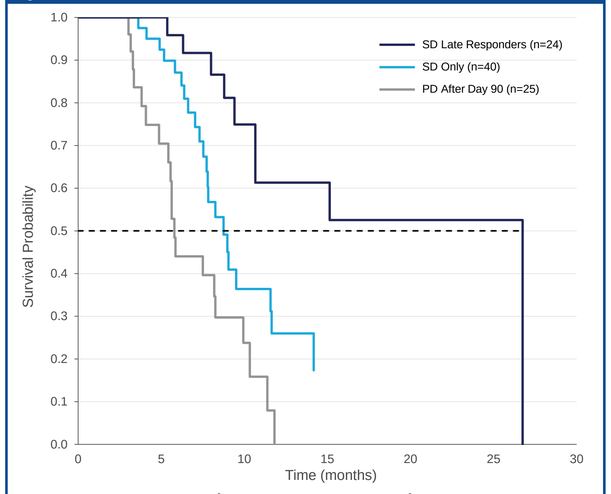


Figure 3. RBC and Platelet Transfusion Independence*



* Among patients who were RBC and/or platelet transfusion-dependent at baseline

Figure 4. Overall Survival



SD Late Responders vs SD Only	SD Late Responders vs PD After Day 90	SD Only vs PD After Day 90
HR 0.39 (95% CI 0.18, 0.85)	HR 0.16 (95% CI 0.07, 0.39)	HR 0.43 (95% CI 0.23, 0.80)

CONCLUSIONS

- SD may represent more controlled proliferation of leukemic blasts and slower differentiation of cells that, in some cases, lead to a later response
- In the first 90 days of treatment with enasidenib 100 mg daily, 42% of patients with m*IDH2* R/R AML maintained SD. Of them, 1 in 4 responded after day 90, with median times to first and best responses of ~4 and ~5 months from treatment initiation
- Among SD patients, those who responded after day 90 had a significant OS benefit compared with those with SD Only (HR 0.39 [61% reduced risk of death]) and those with PD after Day 90 (HR 0.16 [84% reduced risk of death])
  - While no baseline factor was significantly predictive of a response after day 90, results of ongoing longitudinal molecular and translational analyses may elucidate potential reasons for late responses with enasidenib
- R/R AML patients who maintained SD at all response evaluations (SD Only) had a median OS of ~9 months, with a significant 57% reduction in risk of death vs patients with PD After Day 90
- SD during early treatment with enasidenib does not suggest treatment failure, and patients who maintain SD may benefit from continuing enasidenib therapy

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