Correlation Between Mutation Clearance and Clinical Response in Elderly Patients with Acute Myeloid Leukemia (AML) Treated with Azacitidine and Pracinostat

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BACKGROUND

- Older patients with acute myeloid leukemia (AML) have poor prognosis, with a median overall survival (OS) of 5–10 months[1] because:
  - Unfit for intensive induction therapy due to age and/or comorbidities
  - Poor cytogenetic risk and/or molecular mutations associated with disease resistance to standard therapy
- A greater understanding of the genetic abnormalities and their association with patient outcomes, as well as more effective and better-tolerated treatments, are needed for AML
- In a phase 3 study in AML patients aged ≥65 years who were not candidates for intensive therapy and stem cell transplant, the hypomethylating agent azacitidine resulted in a complete-response (CR) rate comparable to that achieved with conventional care regimens (19.5% vs 21.9%) and a trend for better median OS (10.4 months vs 6.5 months) and 1-year OS (46.5% vs 32.4%)[2]
- Pracinostat is an investigational, oral hydroxamic acid-based histone deacetylase (HDAC) inhibitor selective for classes I, II, and IV isoforms
  - HDAC inhibitors and azacitidine have demonstrated synergistic activity in vitro[3]
- In a single-arm phase 2 study in 50 patients aged ≥65 years with previously untreated AML who were not eligible for intensive induction chemotherapy, pracinostat and azacitidine led to 42% CR rate and a median OS of 19.1 months (**Table 1**)[4]
  - CR rate and OS were favorable across patient subsets (**Table 1**)

Table 1: Previously Reported Primary Efficacy Results by Patient Subsets

Population	CR+CRi+ MLFS (%)	Median OS (months)
Age		
66–74 years	45.8	22.8
≥75 years	57.7	13.5
AML type		
De novo	51.5	13.0
Secondary	52.9	29.6
ECOG performance status		
0–1	50.0	19.1
2	62.5	13.0
Cytogenetic risk group		
Intermediate	59.3	24.1
High	47.6	13.5

CR, complete response; CRi, complete response with incomplete blood recovery; MLFS, morphologic leukemia-free state.

OBJECTIVE

- This *post-hoc* analysis of the phase 2 study was conducted to characterize somatic mutations profile in patients enrolled in this trial and investigate the impact of somatic mutations and their clearance on disease response and patient outcomes

METHODS

Study Design

- The phase 2 study evaluated the combination of pracinostat and azacitidine in 50 AML patients aged ≥65 years
  - Pracinostat 60 mg administered orally 3 days/week (eg, Monday, Wednesday, Friday) for 3 weeks, and azacitidine 75 mg/m^2 administered daily intravenously/subcutaneously for 7 days. Treatment cycles were repeated every 28 days
- Primary endpoint: CR+CRi (CR with incomplete blood count recovery)+morphologic leukemia-free state (ie, marrow CR)
  - Responses were assessed at the end of Cycle 2, 4, and 6, and then every 3 cycles until CR achieved or if there was a suspicion of progressive disease
- Secondary endpoints: Overall response rate (ORR); cytogenetic CR; duration of response; progression-free survival; OS; safety and tolerability profile

Patient Population

- Key inclusion criteria: Age ≥65 years; newly diagnosed *de novo*, secondary, or treatment-related AML; intermediate or unfavorable-risk cytogenetics by US Southwest Oncology Group criteria; ≥20% bone marrow blasts; Eastern Cooperative Oncology Group (ECOG) performance score 0–2
- Key exclusion criteria: Acute promyelocytic leukemia (FAB M3); good risk cytogenetics defined as t(15;17), t(8;21), t(16;16), del(16q), or inv(16) karyotype; candidate for intensive chemotherapy (induction chemotherapy, bone marrow, or stem cell transplant) within the next 4 months; received more than 1 cycle of hypomethylating agent, previous bone marrow transplant, or other intensive chemotherapy for either an antecedent hematologic disorder or AML; received prior HDAC inhibitor or deacetylase inhibitor; active central nervous system disease

Molecular Mutation Analyses

- 41 of 50 patients had a pre-treatment bone marrow sample available for analyses and 19 of these 41 patients had serial bone marrow samples (median=3) obtained while on therapy
- A total of 88 samples were sequenced
- Mutations were assayed by SureSelect targeted capture exon sequencing (Agilent) of 295 genes that are recurrently mutated in hematologic malignancies
- High-confidence somatic mutations were called using modified version of Mutect and Pindel algorithm
- Longitudinal mutation clearance was analyzed by plotting variant allele frequency (VAF) over time
- Association with mutations and treatment response was analyzed by Fisher exact test or Chi-square test, whichever is appropriate
- Survival was analyzed by Kaplan-Meier method, and difference in survival based on mutations was tested by log-rank test

RESULTS

- Demographics and disease characteristics were comparable in the total study population and the gene sequencing population as shown in **Table 2**

Table 2. Baseline Demographics and Disease Characteristics

	Total Study Population N=50	Gene Sequencing Population (n=41)
Age		
Median (range), years	75 (66–84)	74 (66–84)
No. (%) age ≥ 75 years	26 (52%)	20 (49%)
Bone Marrow Blasts		
Median (range)	40% (20–89%)	40% (20–84%)
Gender, Male	29 (58%)	24 (59%)
ECOG Performance Status 0–1	42 (84%)	37 (90%)
AML Presentation		
De novo	33 (66%)	26 (63%)
Secondary to MDS, MPN, or prior chemo/radiotherapy	17 (34%)	15 (37%)
Cytogenetic Risk Group		
Intermediate	27 (54%)	23 (56%)
Cytogenetically normal	21 (42%)	17 (41%)
Cytogenetically abnormal	6 (12%)	6 (15%)
Poor*	21 (42%)	16 (39%)
Not classified	2 (4%)	2 (5%)

*Poor risk defined using SWOG definition, and included: Del(5q)/−5, −7/del(7q), abnormal 3q, 9q, 20q, 17p, t(6;9), t(9;22) and complex karyotypes (≥3 unrelated abnormalities)

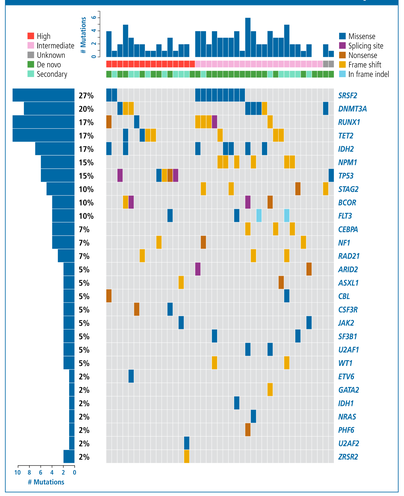
- At baseline, 96 mutations in 28 genes were detected in 38 patients (**Figure 1**)
  - The most frequent mutations were in *SRSF2* (27%), *DNMT3A* (20%), *IDH2* (17%), *RUNX1* (17%), and *TET2* (17%)
  - Distribution of mutations is in marked contrast with young *de novo* AML patients[1] and represents the unique features of elderly AML population
  - Frequent mutations that are related to secondary AML[5] and clonal hematopoiesis of indeterminate potential (CHIP)
  - The mutation profile appeared to be generally typical of an older population with AML[1] and are also common in myelodysplastic syndrome[6]
- Gene mutation associations with CR are shown in **Table 3**

Table 3. CR Rate by Mutation Status of Specific Genes*

	CR Rate (%)		
Gene; n (%)	**Mutated**	**Wild-type**	***P* value**
DNA methylation pathway†; 15 (37)	60	22	0.027
***SRSF2*; 11 (27)**	22	46	0.204
***RUNX1*; 7 (17)**	17	44	0.217
***NPM1*; 6 (15)**	83	30	0.025
***TP53*; 5 (12)**	0	46	0.065
***BCOR*; 4 (10)**	75	35	0.157
***FLT3*; 4 (10)**	67	37	0.338
***STAG2*; 4 (10)**	0	45	0.118
***CEBPA*; 3 (7)**	100	33	0.052
***RAD21*; 3 (7)**	100	33	0.052
***NF1*; 3 (7)**	0	41	0.606

*n≥3 patients ; †*DNMT3A*, *IDH1*, *IDH2*, or *TET2*

Figure 1. Landscape of High-Confidence Somatic Mutations Detected at Pre-Treatment Samples



- Gene mutation associations with OS are shown in **Table 4** and **Figure 2**, and median OS was 17.7 months in 20 patients with mutations typically associated with secondary AML[5] and 18.1 months in 18 patients with mutations typically associated with *de novo* AML[5]

Table 4. OS by Mutation Status of Specific Genes*

	Median OS (months)		
Gene; n (%)	**Mutated**	**Wild-type**	***P* value**
***SRSF2*; 11 (27)**	10.7	19.1	0.230
***DNMT3A*; 8 (20)**	13.5	19.1	0.874
***IDH2*; 7 (17)**	Not reached	14.9	0.209
***RUNX1*; 7 (17)**	8.0	18.2	0.078
***NPM1*; 6 (15)**	Not reached	14.9	0.133
***TET2*; 5 (12)**	20.1	17.8	0.786
***TP53*; 5 (12)**	7.6	19.1	0.668
***BCOR*; 4 (10)**	19.1	17.8	0.382
***FLT3*; 4 (10)**	7.6	18.2	0.939
***STAG2*; 4 (10)**	8.0	19.1	0.768
***CEBPA*; 3 (7)**	Not reached	14.9	0.061
***RAD21*; 3 (7)**	22.9	14.9	0.626
***NF1*; 3 (7)**	3.0	19.1	0.005

*n≥3 patients

- A CR was achieved in 10/19 patients who had longitudinal sequencing analysis and at the time of CR, 9 (90%) had persistently detectable mutations in their bone marrow
  - In 7 of the 10 patients, continued exposure to pracinostat and azacitidine lowered the VAF or cleared residual mutations (**Figure 3A**)
  - In 2 of the 10 patients, samples showed re-expansion of the founder clone (**Figure 3B**)
  - Expansion of a new clone occurred in 1 patient (*RAD21*; **Figure 3C**)

Figure 2. OS for Specific Genes With Mutations

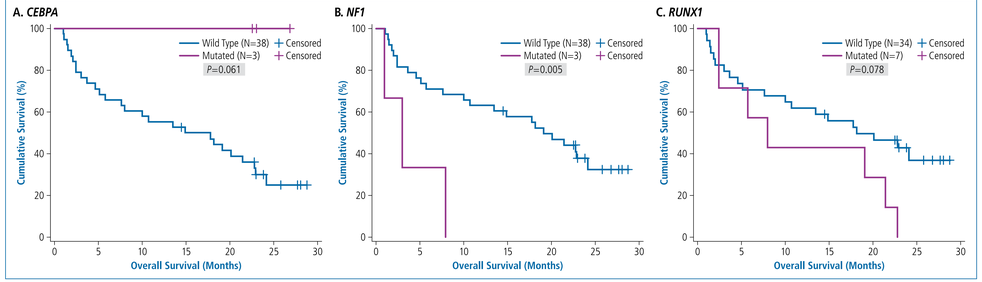
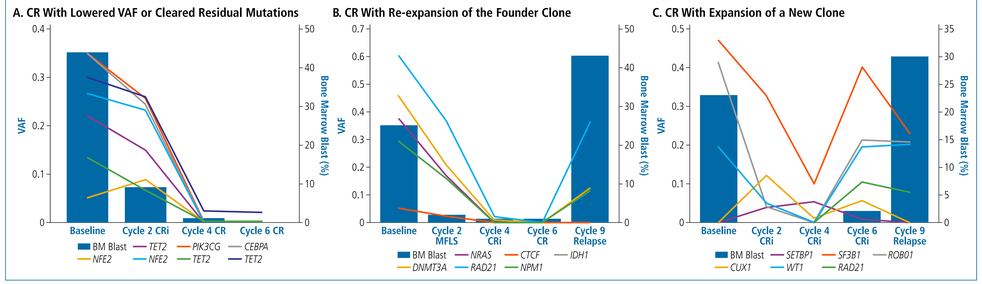


Figure 3. Longitudinal Sequencing Analyses (Each Panel Shows Data for One Patient)



CONCLUSIONS

- Mutations in *NPM1* and the DNA methylation pathway were common in the study population and associated with a better response to pracinostat and azacitidine, while *TP53* mutation was associated with a poor response
  - Mutations that respond to pracinostat and azacitidine may be an important factor in the favorable CR and OS findings in the overall study
- Persistent mutation at the time of CR suggests residual leukemic clonal hematopoiesis
- Continued treatment increases the rate of minimal residual disease clearance as by continued decline of mutation VAF after achieving CR

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