**IDH1 and IDH2 mutations in myelodysplastic syndromes and role in disease progression**

Courtney D DiNardo¹, Elias Jabbour¹, Farhad Ravandi¹, Koichi Takahashi¹, Naval Daver¹, Mark Routbort², Keyur P Patel², Mark Brandt¹, Sherry Pierce¹, Hagop Kantarjian¹, and Guillermo Garcia-Manero¹

¹Department of Leukemia, the University of Texas MD Anderson Cancer Center, Houston, TX

²Department of Hematopathology, the University of Texas MD Anderson Cancer Center, Houston, TX

**Keywords**

MDS; IDH1; IDH2; outcome; transformation

**Letter to Editor**

Recurrent pathogenic mutations in IDH1 and IDH2 at the conserved amino acid sites IDH1-R132, IDH2-R140 and IDH2-R172 occur in approximately 20% of patients with acute myeloid leukemia (AML).¹ A recent analysis of AML patients at our institution identified IDH1/2 mutations in 20% (n=167) of 826 AML patients, with IDH1/2 mutations occurring most frequently in the setting of diploid karyotype or other intermediate-risk cytogenetics, particularly trisomy 8 (77% vs 53%, p<0.0005). AML patients with IDH1/2 mutations were overall less likely to have a diagnosis of therapy-related AML (8% vs 17%, p=0.003).²

Compared to their frequency in AML, IDH1/2 mutations are less common in myelodysplastic syndromes (MDS), occurring in approximately 5% of MDS patients, although an incidence as high as 12% has been reported.³⁻⁸ While IDH1/2 mutations are thought to represent early “driver” events in leukemogenesis with mutational stability over time, reports of IDH1/2 acquisition at the time of leukemic transformation in patients with myeloproliferative neoplasms and MDS have been described.³⁻⁹⁻¹⁰

The purpose of this analysis is to evaluate the overall prevalence of IDH1/2 mutations in MDS patients treated at our institution, as well as determine the incidence and frequency of IDH1/2 mutations identified at the time of leukemic transformation in MDS patients.
Eligible patients comprised all adults with histologically-confirmed MDS treated at M.D. Anderson Cancer Center from January 2010 to January 2015. A total of 1042 MDS patients with known IDH1 and IDH2 status were included. From January 2010 to September 2012, IDH1/2 molecular analysis was performed by high-resolution melting curve analysis followed by Sanger sequencing confirmation (analytical sensitivity: 10–20%) as has been previously described.\(^{(11)}\) Beginning in September 2012, IDH1/2 testing was performed within a CLIA-certified next-generation sequencing (NGS) platform (analytical sensitivity: 2.5–5%). Statistical analyses were conducted in SAS v9.0 and significance defined as p<0.05. Overall survival (OS) was measured as the time from presentation to date of death or last follow-up, and Progression-free survival (PFS) from presentation to date of death, last follow-up, or date of progression to AML. Informed consent was obtained following institutional guidelines and in accordance with the Declaration of Helsinki.

Of the 1042 MDS patients, 60 patients (5.7%) had IDH1/2 mutations identified. Specifically, 17 patients (1.6%) were IDH1-R132 mutated and 43 patients (4.1%) had IDH2-R140 (n=42) or IDH2-R172 (n=1) mutations, respectively. The clinicopathologic characteristics of patients with and without IDH1/2 mutations are shown in Table 1. Within this cohort, 701 patients (67%) were untreated and 341 (33%) had received systemic MDS therapy prior to presentation. MDS patients with IDH1/2 mutations had a lower ANC count (1.15 × 10^9/L vs 1.71 × 10^9/L, p=0.02), higher bone marrow blast percentage (6% vs 4%, p=0.001), and a trend for higher platelet counts (99 × 10^9/L vs 75 × 10^9/L, p=0.07).

Of the 60 IDH1/2 mutations, 17 (28%) were present in the very low or low-risk IPSS-R groups, 15 (25%) intermediate, and 27 (45%) in the high or very-high IPSS-R prognostic score categories (Table 1). While the distribution of IPSS-R categories among IDH1/2-mutants versus wild-type patients was similar, we identified a conspicuously different underlying pattern of cytogenetics and bone marrow blasts. Consistent with karyotypic patterns in IDH1/2-mutant AML,\(^{(2)}\) the majority of IDH1/2-mutant MDS patients demonstrated favorable or intermediate-risk cytogenetics (93%, n=56), with diploid karyotype in 60%, isolated trisomy 8 in 10%, and other intermediate cytogenetics in 23%; significantly different than the cytogenetic distribution in the IDH1/2 wild-type MDS patients (p=0.023) as per Table 1. Of interest, there were no MDS patients with an IDH1/2-mutation and isolated del(20q), and no IDH1/2-mutated patients with the presence of a del(5q) chromosomal abnormality were identified, as also demonstrated by Papaemmanuil et al.\(^{(12)}\) Only 5% of IDH1/2-mutated patients had chromosome 7 abnormalities or complex cytogenetics, compared to 14% of IDH wild-type patients (Table 1).

At presentation, IDH1/2-mutated patients had higher bone marrow blast percentage than IDH wild-type patients (6% vs 4%, p=0.001) and were more frequently classified as RAEB1 or RAEB2 morphology. By WHO classification, 55% of IDH1/2 mutants were classified as RAEB-1 (32%) or RAEB-2 (23%), compared to 42% IDH wild-type (p =0.051). Additionally, 17% of IDH-mutants were classified as CMML-1 or CMML-2. Interestingly while 10 of the 43 (23%) IDH2-mutations occurred in CMML patients, no IDH1 mutations were detected in CMML patients, suggesting a particular genotype-phenotype correlation with IDH2-mutations and CMML. As SRSF2 mutations, which are not analyzed within our molecular panel, are enriched within CMML patients and also frequently co-occur with

\(Leukemia.\) Author manuscript; available in PMC 2016 May 18.
IDH2 mutations, the IDH2-CMML association may be related to underlying SRSF2 co-
mutations.\(^{13, 14}\) Notably also, no patients with the WHO classification of MDS with refractory anemia (RA) were IDH1/2-mutated, although RA patients comprised 9% of the total MDS cohort.

The frequency of other somatic mutations among IDH1/2-mutated versus wild-type patients is displayed in Table 1. No IDH1/2-mutated MDS patient also had a TP53 mutation at presentation, compared to 17% of the IDH1/2 wild-type MDS cohort \((p=0.006)\). While rare overall, no IDH1/2-mutated patients had concomitant FLT3-ITD or FLT3-D835 mutation \((0\% \text{ vs } 2\%, \ p=0.006)\). Patients with IDH1/2-mutations were also significantly less likely to have a RUNX1 \((13\% \text{ vs } 40\%, \ p=0.015)\), ASXL1 \((21\% \text{ vs } 44\%, \ p=0.039)\), or TET2 mutation \((8\% \text{ vs } 35\%, \ p=0.008)\). While TET2 mutations are frequently thought to be mutually exclusive with IDH1/2 mutations, 2 patients with IDH2-R140 mutations did have concurrent TET2 mutations identified. While the subsets are small, the distribution of KRAS, NRAS, JAK2, NPM1, DNMT3A, EZH2 and CEBPA mutations were similar between IDH1/2-mutated and wild-type patients.

OS among the 701 treatment-naïve MDS patients (including 45 IDH1/2-mutants) was 21.2 months; 22.2 months for IDH1/2-mutated patients and 21.1 months for IDH1/2 wild-type patients \((p=0.67)\). [Figure 1] Within IDH1/2 mutants, survival was not different based on IDH1 vs IDH2 mutation status; 22.2 months for IDH1 and 21.0 months for IDH2 mutants \((p=0.44)\). PFS for treatment-naïve MDS patients was 19.9 months (range 0–47.4 months); 22.2 months for IDH1/2-mutated and 19.7 months for IDH1/2 wild-type \((p=0.77)\). PFS among patients with IDH mutations was similar, 16.9 months in IDH1-mutated patients and 17.4 months IDH2-mutated patients \((p=0.18)\).

Of the 214 treatment-naïve patients receiving HMA therapy for which response assessments are available, 18 (8.4%) had IDH1/2 mutations [Supplemental Table 1]. No significant difference in the rate of responses was seen based on the presence of IDH1/2 mutations, with complete remission (CR) in 7 of 18 IDH1/2-mutant (39%) versus 63 of 196 (32%) IDH wild-type patients \((p=0.56)\). OS was similarly not dependent on IDH1/2 mutation status in this HMA-treated group, with a median OS of 20.0 months in IDH1/2-mutant patients and 15.0 months in IDH1/2 wild-type patients, \(p=0.64\) [Supplementary Figure 1].

During the treatment course of the complete n=1042 cohort, 150 MDS patients transformed to AML. This includes 11 of the 60 patients with IDH1/2 mutation identified at MDS diagnosis (1 IDH1 and 10 IDH2; 18% of IDH1/2-mutated patients), and 138 (14%) IDH1/2 wild-type MDS patients. Additionally, 7 confirmed IDH1/2 wild-type patients at MDS diagnosis had an identified IDH1 or IDH2 mutation at the time of AML transformation \((n=5)\) or progression to RAEB-2 MDS \((n=2); \text{ one subsequently progressed to AML within another 6 weeks}\), with an allelic frequency ranging from 10–37%. Specific details of these 7 patients are provided in Table 2. Of interest, patient #5 had both an IDH1-R132H and IDH2-R140Q mutation at the time of AML transformation. In the patients with apparent IDH1/2 acquisition, IDH1/2-mutations were detected a median of 1.3 years from original presentation, at the time of disease progression. In these 7 patients, OS was universally poor, with 3 month median OS from time of IDH1/2 detection. Thus of the 150 MDS patients

Leukemia. Author manuscript; available in PMC 2016 May 18.
transforming to AML, 17 (11.3%) were identified to have an \textit{IDH1}/2-mutation at the time of AML progression.

We acknowledge several study limitations. Given the limits of sequencing technology, we cannot fully rule out the presence of a small \textit{IDH1}/2 clone in some MDS patients at presentation, undetected at diagnosis which increased in size at the time of progression, thus more accurately representing clonal expansion rather than molecular acquisition. Additionally, selection bias, including more frequent molecular testing among MDS patients with transformation and proliferative disease in this retrospective study may have exaggerated the overall frequency of \textit{IDH1}/2 acquisition. However this is unlikely the case, as only 42 of 150 (28\%) MDS patients transforming to AML had repeat comprehensive molecular sequencing performed within 8 weeks of transformation, and thus the frequency of \textit{IDH1}/2 acquisition or expansion, particularly in MDS patients with diploid or intermediate cytogenetics, may be even higher than reported.

We have previously reported on the dynamic acquisition of \textit{FLT3} and \textit{RAS} mutations in lower-risk patients at the time of MDS disease progression,\(^{15}\) specifically in 20 of 278 IPSS low or intermediate-1 risk MDS patients, of whom 18 (90\%) then transformed to AML. Our findings suggest we can also consider \textit{IDH1}/2-mutations as molecular “drivers” of leukemic transformation in some MDS patients. It will be most interesting to evaluate the efficacy of targeted \textit{IDH}-inhibitors in the secondary/transformed AML setting, specifically whether responding patients revert back to a prior MDS state, or whether complete remissions with full count recovery are attainable. This further advocates a role for rational combination studies of \textit{IDH}-inhibitors with other effective MDS strategies such as hypomethylating agents for these patients.

To conclude, \textit{IDH1}/2 mutations were found in 5.7\% of MDS patients at presentation; 1.6\% \textit{IDH1}-R132 and 4.1\% \textit{IDH2}-mutated. Only one MDS patient with an \textit{IDH2}-R172 mutation was identified, the \textit{IDH2}-R140 mutation comprised all other \textit{IDH2}-mutants. The notable low frequency of \textit{IDH1}-R132 and \textit{IDH2}-R172 mutations is consistent with recent data by Molenaar et al, suggesting \textit{IDH1}-R132 and \textit{IDH2}-R172 mutations are less frequently involved in the ancestral neoplastic clone.\(^{10}\) \textit{IDH1}/2-mutations occurred more frequently in patients with diploid or other intermediate-risk cytogenetics and RAEB classification by WHO, and were less frequent in patients with \textit{TP53}, \textit{RUNX1}, \textit{ASXL1}, or \textit{TET2} mutations. At the time of leukemic transformation/secondary AML, 11.3\% of MDS patients had an \textit{IDH1}/2-mutation identified, suggesting the importance of molecular profiling at the time of progression for optimal characterization and treatment decisions for our patients.

\textbf{Supplementary Material}

Refer to Web version on PubMed Central for supplementary material.

\textbf{Acknowledgments}

This work was supported in part by the MD Anderson Cancer Center Support Grant (CCSG) CA016672 and by the generous philanthropic contributions to MD Anderson’s MDS/AML Moon Shot Program. CDD is also supported by the \textit{Jeanne F. Shelby Scholarship Fund} which has supported her R. Lee Clark Fellow award.
References

1. Im AP, Sehgal AR, Carroll MP, Smith BD, Tefferi A, Johnson DE, et al. DNMT3A and IDH mutations in acute myeloid leukemia and other myeloid malignancies: associations with prognosis and potential treatment strategies. Leukemia: official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2014 Sep; 28(9):1774–83.

2. DiNardo CD, Ravandi F, Agresta S, Konopleva M, Takahashi K, Kadia T, et al. Characteristics, clinical outcome and prognostic significance of IDH mutations in AML. American journal of hematology. 2015 May 27.

3. Pardanani A, Patnaik MM, Lasho TL, Mai M, Knudson RA, Finke C, et al. Recurrent IDH mutations in high-risk myelodysplastic syndrome or acute myeloid leukemia with isolated del(5q). Leukemia: official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2010 Jul; 24(7):1370–2.

4. Kosmider O, Gelsi-Boyer V, Slama L, Dreyfus F, Beyne-Rauzy O, Quesnel B, et al. Mutations of IDH1 and IDH2 genes in early and accelerated phases of myelodysplastic syndromes and MDS/myeloproliferative neoplasms. Leukemia: official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2010 May; 24(5):1094–6.

5. Thol F, Weissinger EM, Krauter J, Wagner K, Damm F, Wichmann M, et al. IDH1 mutations in patients with myelodysplastic syndromes are associated with an unfavorable prognosis. Haematologica. 2010 Oct; 95(10):1668–74. [PubMed: 20949390]

6. Rocquain J, Carbuccia N, Trouplin V, Raynaud S, Murati A, Nezri M, et al. Combined mutations of ASXL1, CBL, FLT3, IDH1, IDH2, JAK2, KRAS, NPM1, NRAS, RUNX1, TET2 and WT1 genes in myelodysplastic syndromes and acute myeloid leukemias. BMC cancer. 2010; 10:401. [PubMed: 20678218]

7. Lin CC, Hou HA, Chou WC, Kuo YY, Liu CY, Chen CY, et al. IDH mutations are closely associated with mutations of DNMT3A, ASXL1 and SRSF2 in patients with myelodysplastic syndromes and are stable during disease evolution. American journal of hematology. 2014 Feb; 89(2):137–44. [PubMed: 24115220]

8. Patnaik MM, Hanson CA, Hodnefield JM, Lasho TL, Finke CM, Knudson RA, et al. Differential prognostic effect of IDH1 versus IDH2 mutations in myelodysplastic syndromes: a Mayo Clinic study of 277 patients. Leukemia: official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2012 Jan; 26(1):101–5.

9. Green A, Beer P. Somatic mutations of IDH1 and IDH2 in the leukemic transformation of myeloproliferative neoplasms. The New England journal of medicine. 2010 Jan 28; 362(4):369–70. [PubMed: 20107228]

10. Molenaar RJ, Thota S, Nagata Y, Patel B, Clemente M, Hirsh C, et al. Clinical and biological implications of ancestral and non-ancestral IDH1 and IDH2 mutations in myeloid neoplasms. Leukemia: official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2015 Apr 3.

11. Patel KP, Ravandi F, Ma D, Paladugu A, Barkoh BA, Medeiros LJ, et al. Acute myeloid leukemia with IDH1 or IDH2 mutation: frequency and clinicopathological features. American journal of clinical pathology. 2011 Jan; 135(1):35–45. Epub 2010/12/22. eng. [PubMed: 21173122]

12. Papaemmanuil E, Gerstung M, Malcovati L, Tauro S, Gundem G, Van Loo P, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013 Nov 21; 122(22):3616–27. quiz 99. [PubMed: 24030381]

13. Meggendorfer M, Roller A, Haferlach T, Eder C, Dicker F, Grossmann V, et al. SRSF2 mutations in 275 cases with chronic myelomonocytic leukemia (CMML). Blood. 2012 Oct 11; 120(15):3080–8. [PubMed: 22919025]

14. Haferlach T, Nagata Y, Grossmann V, Okuno Y, Bacher U, Nagae G, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia: official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2014 Feb; 28(2):241–7.

15. Takahashi K, Jabbour E, Wang X, Luthra R, Bueso-Ramos C, Patel K, et al. Dynamic acquisition of FLT3 or RAS alterations drive a subset of patients with lower risk MDS to secondary AML. Leukemia: official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2013 Oct; 27(10):2081–3.
Figure 1.
a: OS of treatment-naïve MDS patients by IDH1/2-mutant versus wild-type
b: PFS of treatment-naïve MDS patients by IDH1/2-mutant versus wild-type
### Clinicopathologic characteristics of MDS study cohort (n=1042)

| Characteristic     | IDH wild-type [n=982] | IDH-mutated [n=60] | p-value | IDH1 Mutated [n=17] | IDH2-Mutated [n=43] | p-value<sup>2</sup> |
|--------------------|-----------------------|--------------------|---------|----------------------|----------------------|---------------------|
| Median age (range) | 70 (17–90)            | 68 (32–85)         | 0.36    | 68 (57–78)           | 68 (32–85)           | 0.84                |
| Male sex (%)       | 642 (65)              | 44 (73)            | 0.21    | 14 (82)              | 30 (70)              | 0.32                |
| WBC count (×10<sup>9</sup>/L) | 3.6 (0.4 – 223.1) | 2.5 (0.7 – 67.5)  | 0.12    | 2.1 (1.2 – 67.5)     | 3.2 (0.7 – 58.6)     | 0.08                |
| ANC (×10<sup>9</sup>/L)   | 1.71 (0.008–118.3)  | 1.15 (0.064–60.07) | 0.02    | 0.97 (0.098–60.075)  | 1.23 (0.064–33.9)    | 0.31                |
| PLT count (×10<sup>9</sup>/L)  | 76 (3–1552)         | 99 (11–441)        | 0.07    | 99 (30–194)          | 101 (11–441)         | 0.98                |
| BM Blasts (%)      | 4 (0–38)              | 6 (1–18)           | 0.001   | 5 (1–18)             | 7 (1–18)             | 0.41                |
| PB Blasts (%)      | 0 (0–29)              | 0 (0–14)           | 0.12    | 0 (0–3)              | 1 (0–14)             | 0.006               |
| LDH<sup>1</sup>     | 536 (24–9329)         | 550 (278–2321)     | 0.37    | 534 (322–963)        | 580 (278–2321)       | 0.37                |
| Cytogenetics: n (%)| 420 (43)              | 36 (60)            | 10 (59) | 26 (60)              |                      | 0.97                |
| Diploid or –Y      | 420 (43)              | 36 (60)            | 10 (59) | 26 (60)              |                      | 0.97                |
| Isolated del(5q)   | 23 (2)                | 0 (0)              | 0 (0)   | 0 (0)                |                      | 0 (0)               |
| Double del(5q)     | 14 (1)                | 0 (0)              | 0 (0)   | 0 (0)                |                      | 0 (0)               |
| Complex del(5q)    | 56 (6)                | 0 (0)              | 0 (0)   | 0 (0)                |                      | 0 (0)               |
| Trisomy 8          | 73 (7)                | 6 (10)             | 2 (12)  | 4 (9)                |                      | 0.073               |
| ~7/7q or complex   | 135 (14)              | 3 (5)              | 1 (6)   | 2 (5)                |                      | 0.073               |
| Isolated del(20q)  | 29 (3)                | 0 (0)              | 0 (0)   | 0 (0)                |                      | 0 (0)               |
| Other intermediate | 174 (18)              | 14 (23)            | 4 (24)  | 10 (23)              |                      | 0.073               |
| -Not done,Inad.    | 58 (6)                | 1 (2)              | 0 (0)   | 1 (2)                |                      | 0.073               |
| WHO category: n (%)| 5q-                   | 19 (2)             | 0 (0)   | 0 (0)                | 0 (0)                | 0.073               |
| CML Ph-            | 8 (1)                 | 0 (0)              | 0 (0)   | 0 (0)                |                      | 0 (0)               |
| CMML-1             | 100 (10)              | 6 (10)             | 0 (0)   | 6 (14)               |                      | 0 (0)               |
| CMML-2             | 36 (4)                | 4 (7)              | 0 (0)   | 4 (9)                |                      | 0 (0)               |
| Characteristic | IDH wild-type [n=982] | IDH-mutated [n=60] | p-value | IDH1 Mutated [n=17] | IDH2-Mutated [n=43] | p-value<sup>2</sup> |
|---------------|----------------------|-------------------|---------|---------------------|---------------------|--------------------|
| MDS/MPD       | 23 (2)               | 1 (2)             | 1 (6)   | 0 (0)               |                     |                    |
| MDS-U         | 39 (4)               | 1 (2)             | 1 (6)   | 0 (0)               |                     |                    |
| RA            | 88 (9)               | 0 (0)             | 0 (0)   | 0 (0)               |                     |                    |
| RAEB-1        | 215 (22)             | 19 (32)           | 5 (29)  | 14 (33)             |                     |                    |
| RAEB-2        | 199 (20)             | 14 (23)           | 4 (24)  | 10 (23)             |                     |                    |
| RARS          | 35 (4)               | 3 (5)             | 0 (0)   | 3 (7)               |                     |                    |
| RCMD          | 196 (20)             | 11 (18)           | 5 (29)  | 6 (14)              |                     |                    |
| RCMD-RS       | 24 (2)               | 1 (2)             | 1 (6)   | 0 (0)               |                     |                    |
| IPSS-R        |                      | 0.792             |         |                     | 0.334               |                    |
| Very high     | 188 (19)             | 13 (22)           | 4 (24)  | 9 (21)              |                     |                    |
| High          | 195 (20)             | 14 (23)           | 1 (6)   | 13 (30)             |                     |                    |
| Intermediate  | 195 (20)             | 15 (25)           | 6 (35)  | 9 (21)              |                     |                    |
| Low           | 247 (25)             | 12 (20)           | 4 (24)  | 8 (19)              |                     |                    |
| Very low      | 91 (9)               | 5 (8)             | 2 (12)  | 3 (7)               |                     |                    |
| N/A           | 66 (7)               | 1 (2)             | 0 (0)   | 1 (2)               |                     |                    |
| Molecular     |                      |                   |         |                     |                     |                    |
| KRAS/NRAS     | 73 (8)               | 7 (12)            | 0.25    | 1 (6)               | 6 (14)              | 0.37               |
| JAK2          | 25 (3)               | 2 (3)             | 0.76    | 1 (6)               | 1 (2)               | 0.50               |
| FLT3-ITD or D835 | 21 (2)           | 0 (0)             | 0.006   | 0 (0)               | 0 (0)               | n/a                |
| NPM1          | 9 (1)                | 1 (2)             | 0.54    | 0 (0)               | 1 (3)               | 0.54               |
| TP53          | 73 (17)              | 0 (0)             | 0.006   | 0 (0)               | 0 (0)               | n/a                |
| RUNX1         | 24 (40)              | 3 (13)            | 0.015   | 1 (25)              | 2 (10)              | 0.41               |
| ASXL1         | 37 (44)              | 5 (21)            | 0.039   | 2 (50)              | 3 (15)              | 0.12               |
| TET2          | 53 (35)              | 2 (8)             | 0.008   | 0 (0)               | 2 (10)              | 0.51               |
| DNMT3a        | 26 (6)               | 3 (7)             | 0.89    | 1 (7)               | 2 (6)               | 0.93               |
| CEBPA         | 52 (6)               | 4 (8)             | 0.64    | 1 (7)               | 3 (8)               | 0.93               |
| EZH2          | 13 (1)               | 0 (0)             | 0.36    | 0 (0)               | 0 (0)               | n/a                |

<sup>1</sup>Institutional normal reference range for LDH is 313 to 618 IU/L

<sup>2</sup>p-values < 0.1 are depicted in bold font
| # | Age/ Sex | Initial WHO Dx | Cyto | Molecular Testing at Dx | WHO Dx at Progression | Time from Dx to Progression | Genetics at Progression | Status |
|---|----------|----------------|------|-------------------------|----------------------|-----------------------------|-----------------------|--------|
| 1 | 65/M | RAEB-2 (15% blasts) | Diploid | Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2 | AML (67% blasts) | 2.5 years | IDH2-R1420Q (37% AF) FLT3-ITD DNMT3A R882H Same cyto | Died 3.6 mo from AML dx |
| 2 | 70/M | RCMD (6% blasts) | +8 | Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2 | RAEB-2 (15% blasts) | 2.1 years | IDH2-R140Q (30% AF) Same cyto | Died 2.7 mo from RAEB-2 dx |
| 3 | 77/F | RAEB-1 (7% blasts) | Del(5)(q13q33), +6 | Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2 | AML (28% blasts) | 2.3 years | IDH1-R132G (17% AF) TP53-S240R Same cyto | Died 3.0 mo from AML dx |
| 4 | 81/M | RAEB-1 (7% blasts) | Del(12)(p11.2p13), t(7)(p12q11.2) | Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2 | RAEB-2 (10% blasts) (further progressed to AML within 6 wks) | 1 year | IDH2-R140Q (<10% AF) TP53-E339K Also acquired Del(20)(q11.2q13.3) | Died 3.3 mo from RAEB-2 dx |
| 5 | 65/F | CMML-2 (15% blasts) | +21 | Mutant: NPM1 W288fs *, NRAS G12D | AML (60% blasts) | 1.3 years | IDH1-R132H (<10% AF) IDH2-R140Q (12% AF) NPM1 and NRAS still present Same cyto | Died 12 months from AML dx |
| 6 | 60/M | CMML-1 (6% blasts) | Diploid | Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2, DNMT3A | AML (24% blasts) | 6 months | IDH1-R132C (11% AF) JAK2 V617F Same cyto | Died 1.1 mo from AML dx |
| 7 | 63/F | RAEB-1 (7% blasts) | Complex 50,XX, +2, add(5)(q22), −7, +11, +13, −15, +22 | Mutant: TP53 Y243C Wild-type: FLT3, NPM1, RAS, CEBPA, IDH1/2, JAK2, DNMT3A | AML (60% blasts) | 6 months | IDH2-R140Q (18% AF) TP53 Y243C still present Same cyto | Died 2.0 months from AML dx |

*AF = allelic frequency