**Supplemental Table 1. 2008 World Health Organization criteria for diagnosis of myelodysplastic syndrome/myeloproliferative neoplasm – unclassifiable (MDS/MPN-U).[4]**

(a) Clinical, laboratory and morphological features of one of the categories of MDS (refractory cytopenia with unilineage dysplasia, refractory anemia with ring sideroblasts, refractory cytopenia with multilineage dysplasia, refractory anaemia with excess of blasts) and <20% blasts in the blood and bone marrow, and

(b) prominent myeloproliferative features (platelet count ≥450x$10^9$/L associated with megakaryocytic proliferation, or WBC count ≥13x$10^9$/L, with or without prominent splenomegaly), and

(c) no preceding history of an underlying MPN or of MDS, no history of recent cytotoxic or growth factor therapy and no evidence of *BCR-ABL*, no rearrangement of *PDGFRA, PDGFRB* or *FGFR1*, and no isolated del(5q), t(3;3)(q21;q26) or inv(3)(q21q26), or

in cases of *de novo* disease with mixed myeloproliferative and myelodysplastic features, where sub-classification into an assigned category of MDS, MPN or of MDS/MPN is not possible.

**Supplemental Table 2. Multi-gene panels used at the four participating institutions.**

| **MDACC panel** | | | | | | |
|---|---|---|---|---|---|---|
| *ASXL1* | *BCOR* | *BCOR1* | *BRAF* | *CALR* | *CBL* | *CBLB* |
| *CEBPA* | *CSF3R* | *DNMT3A* | *ETV6* | *EZH2* | *FLT3* | *GATA1* |
| *GATA2* | *GNAS* | *HRAS* | *IDH1* | *IDH2* | *JAK1* | *JAK2* |
| *JAK3* | *KDM6A* | *KIT* | *KMT2A* | *KRAS* | *MEK1* | *MPL* |
| *MYD88* | *NOTCH1* | *NPM1* | *NRAS* | *PHF6* | *PML* | *PTEN* |
| *PTPN11* | *RAD21* | *RUNX1* | *SETBP1* | *SF3B1* | *SMC1A* | *SMC3* |
| *SRSF2* | *STAG2* | *TET2* | *TP53* | *U2AF1* | *WT1* | *ZRSR2* |
| **Cleveland Clinic panel** | | | | | | |
| *APC* | *ASXL1* | *BCOR* | *BCORL1* | *BTRC* | *C7orf55* | *CBL* |
| *CCDC42B* | *CDH23* | *CEBPA* | *CFTR* | *CSF1R* | *CUX1* | *DDX41* |
| *DDX54* | *DHX29* | *DNMT3A* | *EED* | *ERBB4* | *ETV6* | *EZH2* |
| *FLT3* | *GATA2* | *GLI1* | *GLI2* | *GNB1* | *GPR98* | *IDH1* |
| *IDH2* | *IRF4* | *JAK2* | *JAK3* | *KDM6A* | *KIT* | *KRAS* |

| | | | | | | |
|---|---|---|---|---|---|---|
| *MECOM* | *MED12* | *MLL* | *NF1* | *NPM1* | *NRAS* | *OGT* |
| *PHF6* | *PRPF8* | *PTCH1* | *PTPN11* | *RAD21* | *RNF25* | *RUNX1* |
| *SETBP1* | *SF3B1* | *SIMC1* | *SMC3* | *SRSF2* | *STAG2* | *STAT3* |
| *SUZ12* | *TET2* | *TP53* | *U2AF1* | *U2AF2* | *WT1* | *ZRSR2* |
| **Moffitt panel** | | | | | | |
| *FLT3* | *SF3B1* | *SRSF2* | *U2AF1* | *ZRSR2* | *TET2* | *IDH1* |
| *IDH2* | *DNMT3A* | *EZH2* | *ASXL1* | *SETBP1* | *TP53* | *PHF6* |
| *RUNX1* | *ETV6* | *CBL* | *NRAS* | *KIT* | *JAK2* | *MPL* |
| *NPM1* | | | | | | |
| **Vanderbilt panel** | | | | | | |
| *ABL1* | *ASXL1* | *BCOR* | *BCORL1* | *BRAF* | *CALR* | |
| *CBL* | *CDKN2A* | *CSF3R* | *DNMT3A* | *ETV6* | *EZH2* | |
| *FBXW7* | *FLT3* | *GATA2* | *HRAS* | *IDH1* | *IDH2* | |
| *JAK2* | *KIT* | *KRAS* | *MPL* | *MYD88* | *NPM1* | |
| *NRAS* | *PHF6* | *PTEN* | *PTPN11* | *RUNX1* | *SETBP1* | |
| *SF3B1* | *SRSF2* | *TET2* | *TP53* | *U2AF1* | *WT1* | |
| *ZRSR2* | | | | | | |

**Supplemental Table 3. Baseline characteristics of the patients who developed AML.**

| **Patient #** | **Genes mutated*** | **Karyotype** | **IPSS-R cytogenetic category[24]** | **Bone marrow blast percentage** |
|---|---|---|---|---|
| 1 | *SF3B1, TET2, ZRSR2* | Normal | Good | 1 |
| 2 | *ZRSR2* | +8, del(9q) | Intermediate | 15 |
| 3 | *ASXL1, ETV6, EZH2* | Normal | Good | 2 |
| 4 | *None* | Normal | Good | 3 |

| | | | | |
|---|---|---|---|---|
| 5 | *RUNX1, SRSF2, TET2* | Normal | Good | 0 |
| 6 | *NPM1, NRAS* | Normal | Good | 6 |
| 7 | *EZH2, NRAS, SETBP1* | Normal | Good | 2 |
| 8 | *SRSF2* | Normal | Good | 6 |
| 9 | *ASXL1, NRAS, SETBP1, SRSF2* | Normal | Good | 10 |
| 10 | *JAK2, TP53, ZRSR2* | Complex | Very poor | 11 |
| 11 | *None* | Normal | Good | 1 |
| 12 | *ASXL1, RUNX1, SRSF2, TET2* | Normal | Good | 2 |
| 13 | *ASXL1, SRSF2* | del(3q) | Intermediate | 2 |
| 14 | *RUNX1, TET2, ZRSR2* | +8 | Intermediate | 2 |
| 15 | *ASXL1, SRSF2, TET2* | No mitotic activity | Insufficient metaphases | 1 |
| 16 | *NRAS, SETBP1* | Normal | Good | 6 |

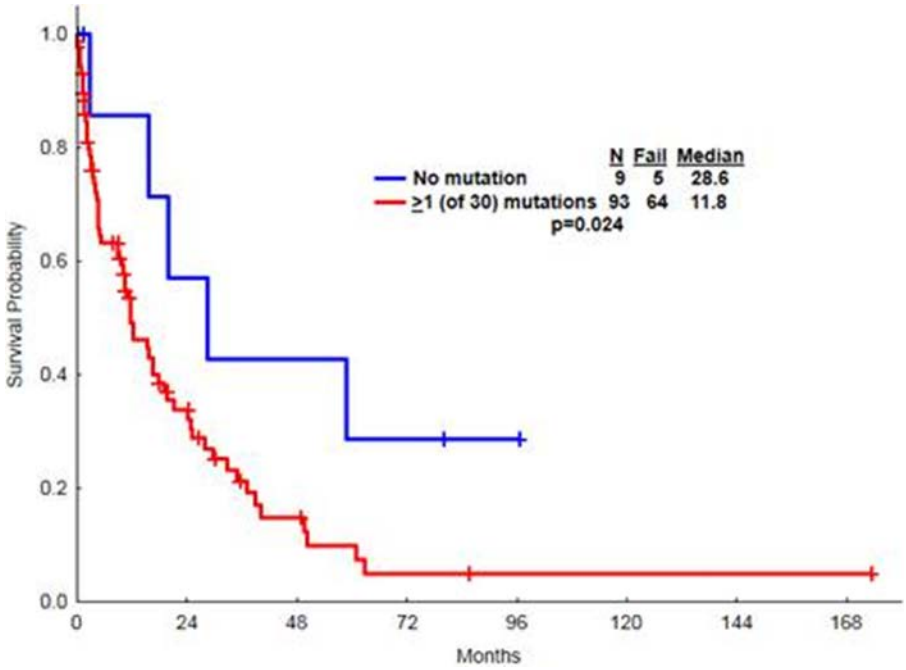
*of the 20 genes sequenced in all 102 patients.

**Supplemental Table 4. Mutational frequencies of selected genes in Cleveland Clinic CMML cohort (n = 40).**

| **Gene** | **Number mutated (%)** |
|---|---|
| *ASXL1* | 9 (23) |
| *CBL* | 5 (13) |
| *DNMT3A* | 1 (3) |
| *ETV6* | 0 (0) |
| *EZH2* | 4 (10) |

| | |
|---|---|
| *IDH1* | 0 (0) |
| *IDH2* | 1 (3) |
| *JAK2* | 1 (3) |
| *KIT* | 0 (0) |
| *NPM1* | 0 (0) |
| *NRAS* | 3 (8) |
| *PHF6* | 1 (3) |
| *RUNX1* | 7 (18) |
| *SETBP1* | 1 (3) |
| *SF3B1* | 2 (5) |
| *SRSF2* | 4 (10) |
| *TET2* | 16 (40) |
| *TP53* | 1 (3) |
| *U2AF1* | 3 (8) |
| *ZRSR2* | 5 (13) |
| *CEBPA* | 0 (0) |
| *FLT3* | 0 (0) |
| *KRAS* | 4 (10) |
| *MLL* | 0 (0) |
| *PTPN11* | 0 (0) |
| *STAG2* | 3 (8) |

**Supplemental Figure 1.** Kaplan-Meier estimates of overall survival (from sample date). The curves represent the survival of patients who had zero versus 1 or more mutations among the 30 genes mentioned in the text. Analysis of just the MDACC patients (n = 48), all of whom had all 30 genes sequenced, confirmed that having ≥1 mutations was associated with inferior survival compared to having none of the 30 genes mutated (p = .02).


1.0
0.8
0.6
0.4
0.2
0.0
Survival Probability
0
24
48
72
96
120
144
168
Months
N Fail Median
No mutation 9 5 28.6
≥1 (of 30) mutations 93 64 11.8
p=0.024