LETTER TO THE EDITOR

FLT3 inhibitors potentially improve response rates in acute myeloid leukemia harboring t(6;9)(*DEK::NUP214*): the Mayo Clinic experience

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Supplemental Data for:

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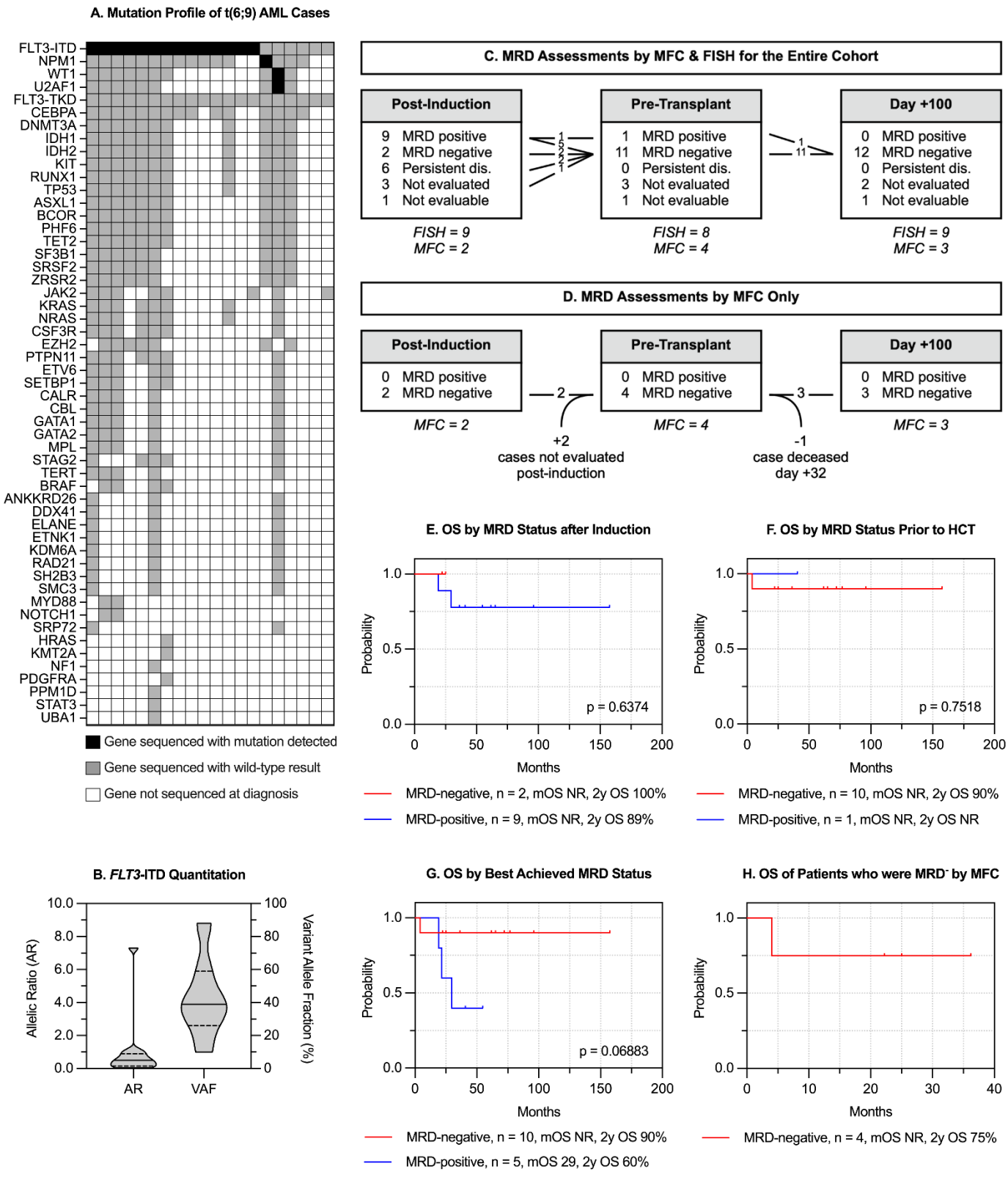

Figure 1. Mutation Profile and MRD Assessment of Evaluable Cases of t(6;9) AML. (A) Of the 21 patients identified retrospectively, 20 had evaluable mutation sequencing at the time of diagnosis or referral. Each column depicts a single case. Black cells represent detected mutations, gray cells represent sequenced genes with wild type results, and white cells represent genes for which sequencing data from the time of diagnosis were unavailable. The number (frequency) of detected mutations was 14 (70%) for *FLT3*-ITD, 1 (6%) for *NPM1*, 1

(11%) for *U2AF1*, and 1 for (10%) *WT1*. **(B)** Of n = 13 evaluable cases, the median *FLT3*-ITD allelic ratio was 0.5 (range 0.05 – 7.3) at the time of diagnosis or presentation. Of n = 7 cases where next generation sequencing (NGS) was available, the median *FLT3*-ITD variant allele fraction (VAF) was 39% (range 10 – 88%). In both violin plots, the solid bars depict the median while dashed bars depict the upper and lower quartiles. **(C)** MRD was assessed by either multiparameter flow cytometry (MFC) or fluorescence *in situ* hybridization (FISH) of at least 500 nuclei at three time points: within 60 days of induction, prior to allogeneic hematopoietic cell transplantation (alloHCT), or on post-HCT day +100. **(D)** The small group (n = 4) of patients whose MRD status was assessed by contemporary methods only (i.e., MFC). Kaplan-Meier plots depict the median OS (mOS) of patients stratified by MRD status **(E)** after induction therapy, **(F)** prior to alloHCT, **(G)** the best MRD status achieved at any time, or **(H)** as assessed by contemporary MFC. In most subgroups, mOS was not reached (NR); otherwise, mOS is depicted in months. No survival comparisons are statistically significant.

Table S1. Overview of t(6;9) AML Patient Treatment and Outcomes by Case

Age / Gender	Sequential Lines of Treatment	HCT Parameters	Best Response	Status at Last Follow Up	Cause of Death
46 F	Cytarabine + idarubicin HiDAC consolidation Allogeneic HCT	MRD Bu/Cy PBSCT	CR	Deceased	Mesenteric thrombosis with bowel necrosis
19 F	Cytarabine + daunorubicin + midostaurin HiDAC + midostaurin consolidation Allogeneic HCT	Haplo Flu/Bu/Thiotepa PBSCT	CR	Alive	
42 M	Cytarabine + daunorubicin HiDAC consolidation Allogeneic HCT	MRD Bu/Cy BMT	CR	Alive	
67 M	Venetoclax + azacitidine + gilteritinib		NR	Deceased	r/r AML
42 M	Cytarabine + daunorubicin + midostaurin HiDAC + midostaurin Allogeneic HCT	MRD Bu/Flu PBSCT	CR	Alive	
20 F	Cytarabine + idarubicin (7+3) x2 HiDAC consolidation Allogeneic HCT	mMUD Flu/Cy/TBI DUCBT	CR	Alive	
27 F	Cytarabine + idarubicin x2 MEC salvage FLT3i trial (AC220) Azacitidine Decitabine + sorafenib Quizartinib Crenolanib Hydroxyurea		NR	Deceased	r/r AML
32 F	Cytarabine + daunorubicin x2 Allogeneic HCT	MUD Bu/Cy PBSCT	CR	Alive	
54 F	Cytarabine + daunorubicin + midostaurin HiDAC + midostaurin consolidation Allogeneic HCT	MUD Bu/Flu PBSCT	CR	Alive	
39 M	Cytarabine + idarubicin HiDAC consolidation Allogeneic HCT CLAG-M	MRD Bu/Flu PBSCT		Deceased	r/r AML
57 M	Azacitidine Cytarabine + idarubicin HiDAC consolidation FLT3i trial (AC220)		CRh	Deceased	r/r AML
52 F	Cytarabine + idarubicin HiDAC consolidation Allogeneic HCT	MUD Bu/Cy PBSCT	CR	Alive	

60 F	Cytarabine + idarubicin CLAG-M salvage HiDAC consolidation Anti-CD47 antibody trial (TT1-621)		CRi	Deceased	r/r AML
63 M	Cytarabine + daunorubicin HiDAC consolidation Allogeneic HCT	MUD Flu/Mel PBSCT	CR	Alive	
41 F	Cytarabine + anthracycline x2 CLAG-M salvage Allogeneic HCT	MUD Flu/Mel PBSCT	CR	Alive	
29 M	Cytarabine + idarubicin HiDAC salvage HiDAC consolidation Allogeneic HCT	MUD Bu/Flu PBSCT	CR	Alive	
39 M	Cytarabine + idarubicin MEC salvage Allogeneic HCT	Haplo Bu/Flu PBSCT	CR	Alive	
36 F	Cytarabine + daunorubicin + midostaurin HiDAC consolidation Allogeneic HCT	MUD Bu/Cy PBSCT	CR	Alive	
23 M	Cytarabine + idarubicin + etoposide ADE + midostaurin consolidation Allogeneic HCT	Haplo Flu/TBI PBSCT	CRh	Deceased	Post-transplant SOS with multiorgan failure (deceased day +32)
19 F	Cytarabine + daunorubicin + midostaurin + GO HiDAC + midostaurin consolidation Allogeneic HCT Gilteritinib maintenance	Haplo Flu/TBI PBSCT	CR	Alive	
16 F	Cytarabine + idarubicin Venetoclax + azacitidine FLAG-Ida Decitabine + vorinostat-FLAG Venetoclax + gilteritinib + daratumumab Mitoxantrone + etoposide + GO Vyxeos + decitabine + vorinostat Imatinib + sirolimus		NR	Deceased	r/r AML

Abbreviations not defined elsewhere: F, female; M, male; ADE, cytarabine, daunorubicin, and etoposide; CLAG-M, cladribine, cytarabine, granulocyte colony stimulating factor (G-CSF), and mitoxantrone; FLAG-Ida, fludarabine, cytarabine, G-CSF, and idarubicin; GO, gemtuzumab ozogamicin; HiDAC, high-dose cytarabine; MEC, mitoxantrone, etoposide, and cytarabine; MUD, matched unrelated donor; MRD, matched related donor; mMUD, mismatched unrelated donor; Haplo, haploidentical donor; Bu, busulfan; Cy, cyclophosphamide; Flu, fludarabine; Mel, melphalan; TBI, total body irradiation; BMT, bone marrow harvest transplantation; DUCBT, double umbilical cord blood transplantation; PBSCT, peripheral blood stem cell transplantation; NR, no response; r/r, relapsed/refractory; SOS, sinusoidal obstruction syndrome.

Table S2. Demographics of the Comparison Cohort.

Characteristic	Non-t(6;9) Cohort	ELN Favorable	ELN Intermediate	ELN Adverse
n	160	17	61	82
Demographics				
Age, years	65 (18 – 86)	59 (19 – 78)	63 (19 – 86)	68 (18 – 86)
Male	87 (54%)	7 (41%)	28 (46%)	52 (63%)
Female	73 (46%)	10 (59%)	33 (54%)	30 (37%)
Cytogenetics				
Normal karyotype	92 (58%)	11 (65%)	46 (75%)	35 (43%)
Complex karyotype	23 (14%)	0 (0%)	0 (0%)	23 (28%)
Mutations				
Number of mutated genes	2 (0 – 7)	3 (0 – 5)	2 (0 – 6)	3 (0 – 7)
ASXL1	27 (17%)	1 (6%)	4 (7%)	22 (27%)
BCOR	11 (7%)	0 (0%)	2 (3%)	9 (11%)
CALR	1 (1%)	0 (0%)	0 (0%)	1 (1%)
CBL	4 (3%)	0 (0%)	2 (3%)	2 (2%)
CEBPA	8 (5%)	1 (6%)	2 (3%)	5 (6%)
CSF3R	2 (1%)	0 (0%)	1 (2%)	1 (1%)
DNMT3A	38 (24%)	4 (24%)	18 (30%)	16 (20%)
EZH2	6 (4%)	0 (0%)	0 (0%)	6 (7%)
FLT3 (Any)	28 (18%)	5 (29%)	17 (28%)	6 (7%)
FLT3-ITD	23 (14%)	2 (12%)	16 (26%)	5 (6%)
FLT3-TKD	6 (4%)	3 (18%)	1 (2%)	2 (2%)
GATA2	5 (3%)	0 (0%)	2 (3%)	3 (4%)
IDH1	8 (5%)	1 (6%)	4 (7%)	3 (4%)
IDH2	26 (16%)	4 (24%)	9 (15%)	13 (16%)
JAK2	9 (6%)	0 (0%)	1 (2%)	8 (10%)
KIT	6 (4%)	1 (6%)	4 (7%)	1 (1%)
KRAS	6 (4%)	2 (12%)	1 (2%)	3 (4%)
MPL	2 (1%)	0 (0%)	1 (2%)	1 (1%)
NOTCH1	1 (1%)	0 (0%)	1 (2%)	0 (0%)
NPM1	19 (12%)	12 (71%)	6 (10%)	1 (1%)
NRAS	15 (9%)	3 (18%)	6 (10%)	6 (7%)
PHF6	5 (3%)	0 (0%)	2 (3%)	3 (4%)
PTPN11	5 (3%)	2 (12%)	2 (3%)	1 (1%)
RUNX1	29 (18%)	0 (0%)	5 (8%)	24 (29%)
SETBP1	4 (3%)	0 (0%)	1 (2%)	3 (4%)
SF3B1	7 (4%)	0 (0%)	0 (0%)	7 (9%)
SRSF2	23 (14%)	2 (12%)	7 (11%)	13 (16%)
TET2	31 (19%)	3 (18%)	14 (23%)	14 (17%)
TP53	29 (18%)	0 (0%)	0 (0%)	29 (35%)
U2AF1	15 (9%)	1 (6%)	3 (5%)	11 (13%)
WT1	20 (13%)	6 (35%)	6 (10%)	8 (10%)
ZRSR2	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Outcomes				
Allogeneic HCT	47 (29%)	7 (41%)	24 (39%)	16 (20%)
Death	114 (71%)	9 (53%)	38 (62%)	67 (82%)

Data are presented as median (range) or n (%), as appropriate. Abbreviations and units are as defined in the main text.