

1 Letter

2 ***KRAS* G12 mutations as adverse prognostic factors in *KMT2A*-rearranged acute**
3 **myeloid leukemia**

4 **Running title: *KRAS* G12 mutations in *KMT2A*-rearranged AML**

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74 TO THE EDITOR:

75 Acute myeloid leukemia (AML) is a genetically and clinically heterogeneous disease
76 characterized by uncontrolled proliferation of hematopoietic precursor cells [1]. *KMT2A* (*MLL*)
77 rearrangements are among the most frequent chromosomal abnormalities in AML [2]. The
78 proportion of *KMT2A*-rearrangements is higher in infants/children with AML [3]. *KMT2A*-
79 rearranged (*KMT2A-r*) AML is also heterogeneous, with >60 different fusion partner genes
80 identified [4]. The prognosis of patients with *KMT2A-r* AML varies based on the *KMT2A* fusion
81 pattern [5]. Therefore, some fusion patterns are currently used for risk stratification of AML
82 treatment [6]. In *KMT2A-r* AML, RAS pathway genes are frequently mutated [7,8]. Our recent
83 study identified mutations in the Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene
84 as adverse prognostic factors in *KMT2A-r* AML [9]. However, the effect of the location of
85 *KRAS* mutations on prognosis remains unclear because of the small sample size.

86 In this study, targeted sequencing was performed in samples from patients enrolled in the
87 Japan Children's Cancer Group (JCCG) AML-99/AML-05/AML-12 studies, which was
88 analyzed using the data in the TARGET-AML cohort [3]. Then, we examined the prognostic
89 significance of *KRAS* mutations based on their location in patients with *KMT2A-r* AML
90 (*n* = 225) and non-*KMT2A-r* AML (*n* = 882). For further information on patients and study
91 protocol, DNA sequencing and mutation calling, and statistical analysis, please refer to
92 Supplemental Methods. This study was conducted following the principles defined in the
93 Declaration of Helsinki and approved by the ethics committees of all participating institutions,
94 the Kyoto University Medical Ethics Committee, and the JCCG Research Review Committee
95 (approval numbers: G0361 and 106). All patients, or their parents or guardians, provided
96 written informed consent.

97 Table S1 shows the characteristics of the 225 patients with *KMT2A-r* AML. The median age
98 at diagnosis was 3.5 years (range, 0.0–18.2). *MLLT3* (*n* = 91, 40.4%) was the most frequent

99 fusion partner. Sex, age, FAB classification, and frequency of fusion partners were similar
100 between the JCCG and TARGET cohorts. Table S2 also shows the characteristics of the 882
101 patients with non-*KMT2A*-r AML. The median age at diagnosis was 10.4 years (range, 0.0–
102 29.9), which was higher than that in patients with *KMT2A*-r AML. Among disease subtypes,
103 normal karyotype was the most frequent (n = 244, 27.7%), followed by t(8;21) (n = 206,
104 23.4%), and inv(16) (n = 116, 13.2%).

105 *KRAS* mutations were detected in 58/225 (25.8%) patients with *KMT2A*-r AML and 70/882
106 (7.9%) patients with non-*KMT2A*-r AML (Fig. S1A), with a higher percentage in patients with
107 *KMT2A*-r AML ($P < 0.0001$). This result is interesting because *KMT2A*-r AML is a disease
108 subtype with a lower number of coexisting driver mutations [3]. The high frequency of *KRAS*
109 mutations may suggest that *KRAS* mutations are more crucial in the pathogenesis of *KMT2A*-
110 r AML. Subsequently, the detected mutations were classified by codon and amino acid
111 alteration (Fig. S1B). Figure S1C shows the distribution of *KRAS* mutations. *KRAS* mutations
112 were dominated by single-base missense mutations, and most mutations were clustered at
113 codons 12 (G12) and 13 (G13) in both *KMT2A*-r and non-*KMT2A*-r AML, which is consistent
114 with previous studies on various cancers [10].

115 We examined the prognostic significance of *KRAS* mutations based on their location in
116 patients with *KMT2A*-r AML (n = 225). Patients with *KRAS* G12 mutations had a significantly
117 worse prognosis than *KRAS*-wild-type (WT) patients for both event-free survival (EFS) and
118 overall survival (OS) (Fig. 1A, $P < 0.0001$ for both EFS and OS). Patients with *KRAS* G13 or
119 other *KRAS* mutations showed similar prognoses to patients with *KRAS*-WT (3-year EFS,
120 WT: 57.4%, G12: 15.8%, G13: 43.5%, others: 42.9%; 3-year OS, WT: 74.8%, G12: 35.1%,
121 G13: 56.5%, others: 70.7%). By contrast, in non-*KMT2A*-r AML, the prognosis was not
122 significantly different between groups, including patients with *KRAS* G12 mutations (Fig. 1B).
123 Patients with *KMT2A*-r AML with *KRAS* G12 mutations in both JCCG (n = 120) and TARGET

124 (n = 105) cohorts had worse prognoses (Fig. S2). We also analyzed the prognostic
125 significance of amino acid alterations in patients with *KRAS* G12 mutations in *KMT2A-r* AML.
126 Patients with uncommon *KRAS* G12 mutations (G12A, G12S, and G12C) had a particularly
127 worse prognosis in both EFS and OS compared with those with G12D/G12V (Fig. S3).

128 We compared the patient characteristics to investigate the mechanism of worse prognosis
129 in patients with *KRAS* G12 mutations. Patients with *KRAS* G12 mutations had a higher age
130 (median age, WT: 3.1 years, G12: 8.9 years, G13 and others: 2.9 years) (Table S3).
131 Compared with WT patients, the frequency of *KMT2A-MLLT3* was lower and that of *KMT2A-*
132 *MLLT10/KMT2A-MLLT4* was higher in patients with *KRAS* G12 mutations. Consistent with
133 the previous study [11], patients with *KMT2A-MLLT4* had a higher age (Table S4); therefore,
134 the higher age in patients with *KRAS* G12 mutations may be attributed to the higher frequency
135 of *KMT2A-MLLT4*. Subsequently, coexisting mutations were compared between patients with
136 *KRAS* G12 mutations and those with other *KRAS* mutations in *KMT2A-r* AML (Fig. S4), which
137 showed no significant differences between the groups. Patients with *KRAS* G12 mutation had
138 more coexisting mutations than those with other *KRAS* mutations, but the difference was not
139 significant (mean, 1.24 vs. 0.76, $P=0.13$). Variant allele frequencies (VAFs) were also
140 compared for *KRAS* G12 mutations and other *KRAS* mutations, but the difference was not
141 significant (Fig. S5). Moreover, VAFs of *KRAS* mutations had no significant impact on the
142 prognosis of patients with *KMT2A-r* AML. These results indicate that *KRAS* G12 mutations
143 are worse prognostic factors and are associated with distinct patient characteristics in
144 *KMT2A-r* AML.

145 We then performed survival analysis by classifying patients into risk subgroups. Patients
146 with *KMT2A-MLLT4* fusion or *FLT3*-internal tandem duplication (ITD) were classified as the
147 high-risk group, and the remaining patients were classified as the intermediate-/low-risk
148 group. In both high-risk group (n = 26) and intermediate-/low-risk group (n = 199), patients

149 with *KRAS* G12 mutations had a worse prognosis than those without (Fig. S6).

150 We further investigated whether hematopoietic stem cell transplantation (SCT) can rescue
151 patients with *KRAS* G12 mutations in *KMT2A*-r AML in the first complete remission. Of the 58
152 patients with *KRAS* mutations, 48 patients were analyzed, and three patients with unavailable
153 SCT data and seven patients who were in nonremission were excluded. Of these, 19 patients
154 had *KRAS* G12 mutations. Prognosis was not significantly different between patients with
155 and without SCT in patients with *KRAS* mutations ($n = 48$) (Fig. S7), as well as in those with
156 *KRAS* G12 ($n = 19$) and other *KRAS* mutations ($n = 29$).

157 Finally, we examined whether *KRAS* G12 mutations are independent adverse prognostic
158 factors in *KMT2A*-r AML. We performed a multivariate analysis that included age, *KMT2A*
159 fusion patterns, *FLT3*-ITD, and *KRAS* G12, G13, and other mutations (Table 1). Only the
160 *KRAS* G12 mutation was a prognostic factor predicting worse prognosis in both EFS [hazard
161 ratio (HR), 2.32; 95% CI, 1.38–3.90; $P = 0.002$] and OS (HR, 1.96; 95% CI, 1.05–3.64;
162 $P = 0.03$). In contrast, *KMT2A* fusion patterns, *KRAS* G13 mutations, or other *KRAS*
163 mutations were not statistically significant. These results indicate that *KRAS* G12 mutations
164 are independent worse prognostic factors in patients with *KMT2A*-r AML.

165 The prognostic impact of *KRAS* mutations per codon has been investigated in many
166 cancers. Patients with colorectal cancer with G12 mutations had poor prognosis compared
167 with those with other *KRAS* mutations [12]. However, the results were not always consistent
168 and some studies showed different results in different cancer types. To the best of our
169 knowledge, this is the first study showing that the prognostic impact of *KRAS* mutations may
170 vary by codon in AML, particularly in *KMT2A*-r AML. Multivariate analysis showed that *KRAS*
171 G12 mutations are independent poor prognostic factors in *KMT2A*-r AML, whereas other
172 *KRAS* mutations and *KMT2A* fusions are not significantly associated with prognosis. Thus,
173 *KRAS* G12 mutations may be superior to *KMT2A* fusions as poor prognostic factors and may

174 contribute to better treatment stratification of *KMT2A*-r AML. Because *KMT2A*-r AML is more
175 common in infants and children and rare in adults [3], we were unable to analyze adult
176 patients. Future studies should investigate whether the *KRAS* G12 mutation is also
177 associated with poor prognosis in adult patients with *KMT2A*-r AML.

178 *KRAS* encodes a protein that is a member of the small GTPase superfamily. *KRAS*
179 mutations result in reduced intrinsic GTPase activity, which mediates malignant
180 transformation through the constant activation of the *KRAS* protein and downstream signaling
181 pathways [13]. A study reported a possible molecular mechanism underlying the poor
182 prognosis of patients with *KRAS* G12 mutations: *KRAS* codon 12 mutation is associated with
183 resistance to apoptosis and confers a more aggressive tumor phenotype than other *KRAS*
184 mutations [14]. By contrast, our recent preliminary analysis showed that most *KRAS*
185 mutations detected at diagnosis in *KMT2A*-r AML are lost at relapse [15], indicating that
186 *KRAS* mutations are not the direct cause of relapse but may be associated with relapse
187 through indirect mechanisms. Future studies elucidating the mechanisms by which *KRAS*
188 G12 mutations contribute to poor prognosis may also lead to the development of better
189 therapeutic strategies for *KMT2A*-r AML.

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191 **Data availability**

192 The datasets used in this study are available from the corresponding author upon
193 reasonable request.

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207 **Author contributions**

208 SI, KY, KS, and HMatsuo analyzed the clinical and sequencing data; NI and MT helped
209 with the analysis; YN, GY, ST, NS, and YH performed sequencing; YShiozawa, YShiraishi,
210 KC, AO, HT, and SM developed sequence data processing pipelines; YK, HG, HMoritake,
211 KT, EI, NK, DT, TT, AT, JT, and SA collected clinical samples; KY, MN, SA, SO, and HMatsuo
212 supervised the project. SI, KY, KS, and HMatsuo wrote the manuscript.

213

214 **Competing interests**

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262 10.1097/01.HS9.0000969016.51775.a7

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270 **Figure legends**

271 **Figure 1. *KRAS* G12 mutations as prognostic factors in *KMT2A*-r AML.**

272 (A) Survival analysis for EFS and OS in *KMT2A*-r (n = 225) and non-*KMT2A*-r AML (n = 882)
273 based on the *KRAS* mutation codon.

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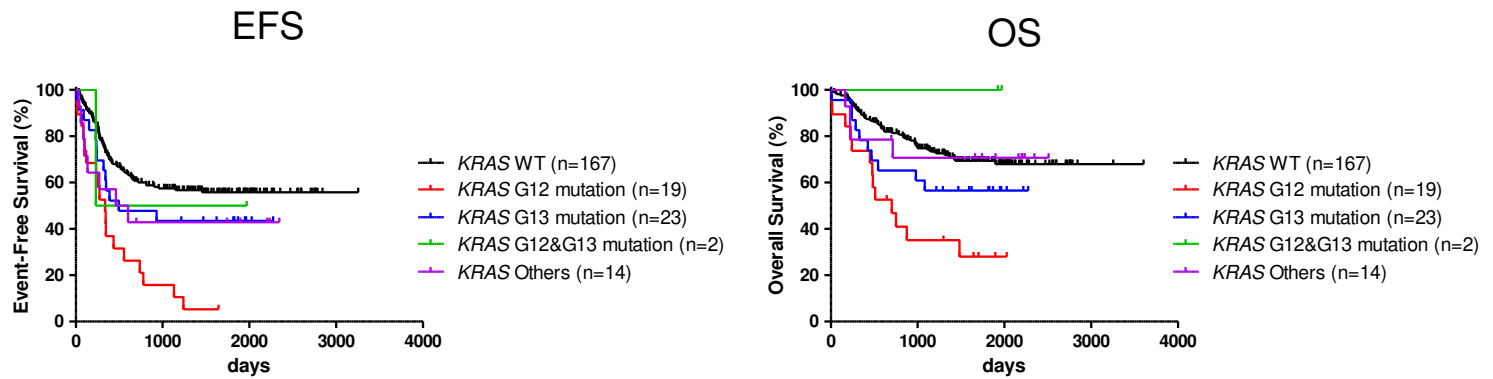
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295 **Table 1. Multivariate analysis of patients with *KMT2A*-r AML.**

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	EFS			OS		
	HR	95%CI	P-value	HR	95%CI	P-value
Age (+1 year)	1.03	0.99–1.06	0.14	1.07	1.02–1.11	0.003
<i>KMT2A-MLLT3</i>	0.72	0.36–1.46	0.36	0.88	0.35–2.21	0.79
<i>KMT2A-MLLT10</i>	1.52	0.75–3.08	0.25	1.74	0.69–4.42	0.24
<i>KMT2A-ELL</i>	0.88	0.37–2.08	0.77	1.37	0.48–3.97	0.56
<i>KMT2A-MLLT4</i>	2.22	0.97–5.09	0.06	2.33	0.85–6.42	0.10
<i>KMT2A-MLLT1</i>	1.46	0.59–3.61	0.41	0.99	0.28–3.45	0.99
<i>FLT3</i> -ITD	2.37	0.99–5.66	0.053	2.18	0.73–6.45	0.16
<i>KRAS</i> G12 mutation	2.32	1.38–3.90	0.002	1.96	1.05–3.64	0.03
<i>KRAS</i> G13 mutation	1.28	0.72–2.27	0.40	1.38	0.70–2.75	0.35
<i>KRAS</i> Others	1.16	0.55–2.44	0.69	0.66	0.23–1.93	0.45

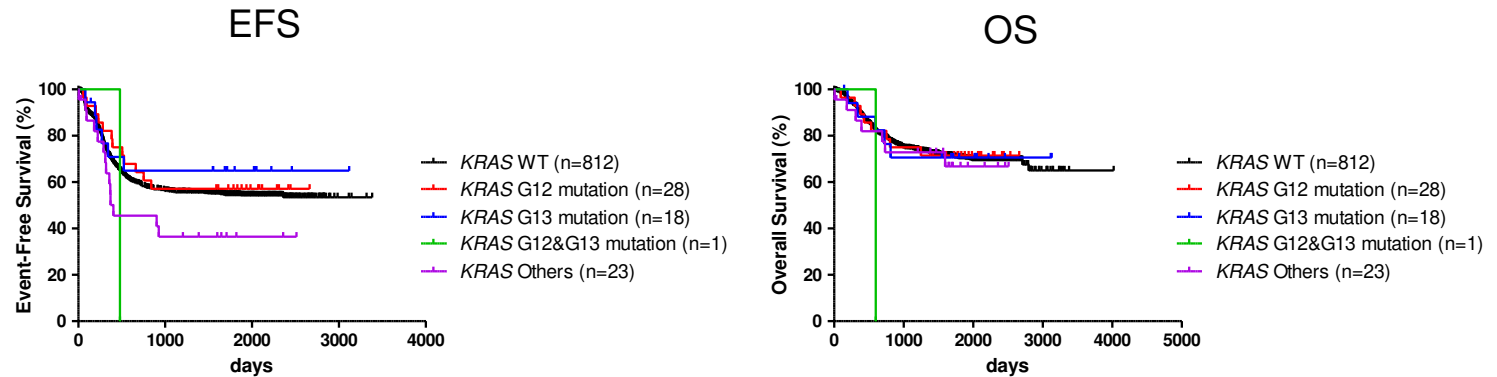
297 EFS, event-free survival; OS, overall survival; CI, confidence interval; *FLT3*-ITD, *FLT3*
 298 internal tandem duplications.

Figure 1**A** *KMT2A*-r AML (n = 225)**Comparison of survival curves**

<i>KRAS</i> mutation pattern		<i>P</i> -value (Bold: <0.05)
WT	vs. G12	<0.0001
WT	vs. G13	0.20
WT	vs. G12&G13	0.78
WT	vs. Others	0.17
G12	vs. G13	0.02
G12	vs. G12&G13	0.29
G12	vs. Others	0.08
G13	vs. G12&G13	0.99
G13	vs. Others	0.81
G12 & G13	vs. Others	0.82

Comparison of survival curves

<i>KRAS</i> mutation pattern		<i>P</i> -value (Bold: <0.05)
WT	vs. G12	<0.0001
WT	vs. G13	0.15
WT	vs. G12&G13	0.38
WT	vs. Others	0.98
G12	vs. G13	0.10
G12	vs. G12&G13	0.12
G12	vs. Others	0.04
G13	vs. G12&G13	0.29
G13	vs. Others	0.49
G12 & G13	vs. Others	0.41

B Non-*KMT2A*-r AML (n = 882)**Comparison of survival curves**

<i>KRAS</i> mutation pattern		<i>P</i> -value (Bold: <0.05)
WT	vs. G12	0.64
WT	vs. G13	0.44
WT	vs. G12&G13	0.38
WT	vs. Others	0.08
G12	vs. G13	0.74
G12	vs. G12&G13	0.21
G12	vs. Others	0.11
G13	vs. G12&G13	0.31
G13	vs. Others	0.12
G12 & G13	vs. Others	0.82

Comparison of survival curves

<i>KRAS</i> mutation pattern		<i>P</i> -value (Bold: <0.05)
WT	vs. G12	0.90
WT	vs. G13	0.93
WT	vs. G12&G13	0.07
WT	vs. Others	0.75
G12	vs. G13	0.96
G12	vs. G12&G13	0.10
G12	vs. Others	0.76
G13	vs. G12&G13	0.07
G13	vs. Others	0.83
G12 & G13	vs. Others	0.11