

## ORIGINAL ARTICLE

The prognostic impact of *FLT3-ITD* and *NPM1* mutations in patients with relapsed acute myeloid leukemia and intermediate-risk cytogeneticsJ How<sup>1</sup>, J Sykes<sup>2</sup>, MD Minden<sup>1</sup>, V Gupta<sup>1</sup>, KWL Yee<sup>1</sup>, AD Schimmer<sup>1</sup>, AC Schuh<sup>1</sup>, S Kamel-Reid<sup>3</sup> and JM Brandwein<sup>1</sup>

Internal tandem duplication of the *fms*-like tyrosine kinase-3 gene (*FLT3-ITD*) and nucleophosmin-1 (*NPM1*) mutations have prognostic importance in acute myeloid leukemia (AML) patients with intermediate-risk karyotype at diagnosis, but less is known about their utility to predict outcomes at relapse. We retrospectively analysed outcomes of 70 patients with relapsed, intermediate-risk karyotype AML who received a uniform reinduction regimen, with respect to *FLT3-ITD* and *NPM1* mutation status and first complete remission (CR1) duration. CR1 duration, but not molecular status, was significantly correlated with CR2 rate. On univariate analysis, patients with mutated *FLT3-ITD* (*FLT3+*) had significantly worse overall survival (OS) compared with those with neither an *NPM1* nor *FLT3-ITD* mutation (*NPM1-/FLT3-*). On multivariate analysis, shorter CR1 duration was significantly correlated with inferior OS at relapse ( $P < 0.0001$ ), while *FLT3* and *NPM1* mutation status and age were not significantly correlated with OS. Patients who subsequently underwent allogeneic stem cell transplant (alloSCT) had a superior OS regardless of CR1 duration, but outcomes were better in patients with CR1 duration  $> 12$  months. In intermediate-risk karyotype AML patients receiving reinduction, CR1 duration remains the most important predictor of OS at relapse; *FLT3-ITD* and *NPM1* status are not independent predictors of survival.

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## INTRODUCTION

In patients with acute myeloid leukemia (AML) and intermediate-risk cytogenetics, nucleophosmin-1 (*NPM1*) mutation status and internal tandem duplication of the *fms*-like tyrosine kinase-3 gene (*FLT3-ITD*) can assist in predicting a patient's risk of relapse and overall survival (OS) with frontline induction and consolidation chemotherapy.<sup>1–4</sup> However, there is a paucity of data elucidating the impact of *NPM1* and *FLT3* status in patients with relapsed disease.

Studies have shown that *NPM1* status remains relatively preserved when comparing bone marrow samples from initial diagnosis to first relapse.<sup>5,6</sup> *FLT3-ITD* status has shown greater variability, with a trend toward increasing mutation levels and the acquisition of new mutations in some patients at relapse.<sup>6,7</sup> Despite this, 75–85% of patients will not show any change in *FLT3* status.<sup>6</sup>

First complete remission (CR1) duration has been demonstrated to be an important predictor of outcome following reinduction therapy.<sup>8,9</sup> However, it is unclear to what extent mutational status influences this, as CR1 duration tends to be shorter in patients with a *FLT3-ITD*. In addition, some physicians may only offer salvage therapy to those patients whom they suspect are likely to benefit from the treatment, yet it has never been shown conclusively that patients with good-prognosis molecular markers at presentation have a superior response to treatment

at relapse. The aim of this study is to clarify whether *NPM1* and *FLT3* status influence response to salvage therapy at relapse.

## PATIENTS AND METHODS

## Patients and treatment

From a database of patients treated at Princess Margaret Hospital between 2002–2010, we identified 97 patients with AML and intermediate-risk cytogenetics based on Southwest Oncology Group criteria<sup>10</sup> who relapsed following a documented CR. All patients had been previously treated with a uniform regimen consisting of induction with daunorubicin and cytarabine followed by two cycles of consolidation, as previously reported.<sup>11</sup> For those patients given reinduction chemotherapy, treatment consisted of a combination of mitoxantrone, etoposide and high-dose cytarabine (NOVE-HiDAC), as previously described.<sup>12</sup>

Molecular testing for *NPM1* and *FLT3-ITD* mutation were performed as previously described.<sup>11</sup> *NPM1* testing was performed at diagnosis, while *FLT3-ITD* testing was performed at relapse if samples were available (57 reinduced patients). For the remaining patients who did not have samples available for testing at relapse, the initial diagnostic *FLT3* result was used. Patients were divided into three molecular subgroups: (1) *NPM1* mutation present but no *FLT3-ITD* (*NPM1+/FLT3-*); (2) neither mutated *NPM1* nor *FLT3-ITD* present (*NPM1-/FLT3-*); (3) *FLT3-ITD* present (*FLT3+*), regardless of *NPM1* status. The sensitivity of the *NPM1* assay was ~1–10%, while *FLT3-ITD* positivity was defined as a percentage of total *FLT3* (mutated + wild-type) of at least 5%.

<sup>1</sup>Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada; <sup>2</sup>Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada and <sup>3</sup>Department of Pathology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada. Correspondence: Dr J Brandwein, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, 610 University Avenue, Rm. 5-109, Toronto, Ontario, Canada M5G 2M9. E-mail: joseph.brandwein@uhn.ca

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## Statistical methods

The primary outcome of interest was OS after relapse and was calculated as the time from patient relapse date to death or last date of follow-up. CR1 duration was calculated as the time from the date of the first complete response to the date of patient relapse. Differences in reinduction or CR2 rates as well as the association between time to relapse and molecular status were compared using the Fisher's exact test or the Mann-Whitney-Wilcoxon test or Kruskal-Wallis test for continuous variables. The Kaplan-Meier method was used to generate survival curves and estimate OS probabilities. Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated using the Cox proportional hazards model. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and the open source statistical software R version 12.2.1 were used to perform all statistical analyses. Two-sided *P*-values of <0.05 were used to determine statistical significance.

## RESULTS

Table 1 summarizes the characteristics of the patients included in the study. Of the 97 patients, 70 (72%) were reinduced with salvage chemotherapy. There were no significant differences between the entire group of relapsed patients and the subset who were reinduced, with the exception that those who were reinduced were younger ( $P < 0.001$ ). Other cytogenetics included +X (1 case) and -12p (1 case). Of the 57 patients who underwent repeat FLT3 testing at relapse, there was a change in 15 cases (26%); 10 changed from negative to positive, and 5 from positive to negative.

The clinical features according to molecular subgroup are summarized in Table 2. The FLT3+ group had a significantly shorter median CR1 duration (7.1 months) than the NPM1-/FLT3- (12.2 months) and NPM1+/FLT3- (11.2 months) groups.

Of the 70 evaluable patients who received reinduction chemotherapy, 42 (60%) achieved a CR2. Of these, 17 underwent allogeneic stem cell transplant (alloSCT) in CR2; 6 of these were FLT3+ (Table 2). At a median follow-up of 10 months from relapse (range 2–53 months), 50 of the reinduced patients (71%) have died. The median OS was 8.2 months (range 6.1–11.4 months) for all 97 patients and 9.7 months (range 7.5–14.7 months) for the 70 patients who were reinduced.

### Analysis of factors influencing CR2 rates

The proportion of patients undergoing reinduction was similar across the three molecular subgroups ( $P = 0.65$ ). As shown in Table 2, among those reinduced, CR2 rates were also not significantly different between molecular subgroups ( $P = 0.29$ ), although CR2 duration was significantly shorter in the FLT3+ subgroup. CR1 duration was, however, a predictor of CR2 rates. Those with a time to relapse <6 months had a CR2 rate of 20%, as compared with 64% for patients with CR1 duration of 6–12 months and 88% for those with CR1 duration  $\geq 12$  months ( $P < 0.0001$ ).

### Univariate analysis for OS

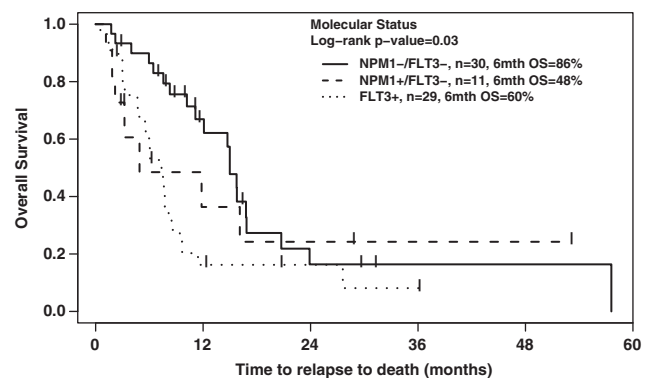
For patients receiving reinduction chemotherapy, there was a significant association between molecular status and OS (log-rank  $P = 0.03$ ), as shown in Figure 1. On pairwise univariate analysis (Table 3), FLT3+ patients had a significantly worse OS than those who were NPM1-/FLT3-. This difference persisted ( $P = 0.022$ ) when restricted to the 64 patients with diploid karyotype. There were no significant differences in OS between the NPM1+/FLT3- cohort and the double-negative group, nor between the FLT3+ group and the NPM1+/FLT3- group. When the patients who underwent alloSCT in CR2 were excluded, there was still a significant association between molecular status and OS ( $P = 0.035$ ), and between the FLT3+ and NPM1-/FLT3- groups (HR: 2.26,  $P = 0.001$ ).

When restricting the analysis to only the 57 patients who were retested for FLT3 at the time of relapse, the pairwise association

**Table 1.** Patient characteristics for all relapsed patients, and those that received reinduction

	Overall	Reinduced
N	97	70
NPM1+ (%)	39 (40)	28 (40)
Sex (%)		
Female	43 (44)	32 (46)
Male	54 (56)	38 (54)
Age at relapse, median (range)	55 (31–76)	52 (31–72)
<60 (%)	63 (65)	54 (77)
$\geq 60$ (%)	34 (35)	16 (23)
WBC $\times 10^9/l$ , median (range)	32 (1–207)	30 (1–207)
Prior disease (%)		
De novo	85 (88)	63 (90)
Secondary	12 (12)	7 (10)
Cytogenetics		
Diploid	89	64
Abn Y	3	3
+8	3	2
Other	2	1
Mutation status (%)		
FLT3-/NPM1+	20 (21)	10 (14)
FLT3-/NPM1-	43 (44)	31 (44)
FLT3+	34 (31)	29 (41)
CR1 duration (months)		
<6	31 (32)	20 (29)
6–12	37 (38)	25 (36)
$\geq 12$	29 (30)	25 (36)
AlloSCT		
None	74 (76)	53 (76)
Prior alloSCT in CR1	4 (4)	0 (0)
AlloSCT in CR2	18 (19)	17 (24)

Abbreviations: alloSCT, allogeneic stem cell transplant; CR, complete remission; FLT3, fms-like tyrosine kinase-3; NPM1, nucleophosmin-1; WBC, white blood cell.



**Figure 1.** OS from time of relapse, according to mutation status, for the 70 patients who underwent reinduction.

with molecular status was no longer significant ( $P = 0.095$ ), possibly due to a reduction in the sample size. However, the OS of FLT3+ group was still significantly inferior to the NPM1-/FLT3- group ( $P = 0.045$ ). Similarly, when the 20 patients with early relapse (CR1 duration <6 months) were excluded, the association between molecular status and OS was not longer significant ( $P = 0.08$ ).

**Table 2.** Clinical characteristics of molecular subgroups

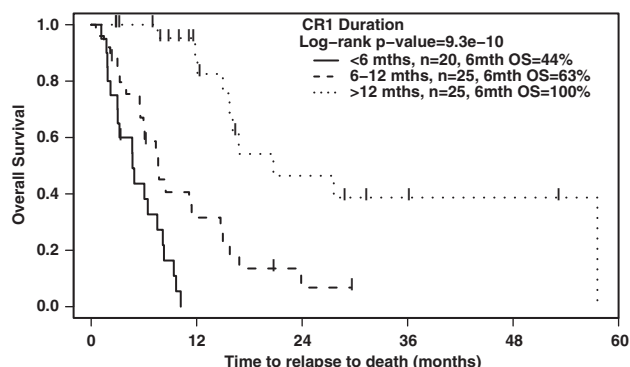
	FLT3-/ NPM1+	FLT3-/ NPM1-	FLT3+	P
Total (% of relapsed patients)	10 (80%)	31 (68%)	29 (74%)	NS
Age (median)	52	54	47	NS
CR1 duration				0.0018
<6 months	3	6	11	
6–12 months	1	9	15	
>12 months	6	16	3	
CR2 rate (%)	6 (60%)	21 (68%)	15 (52%)	NS
AlloSCT in CR2	1	10	6	
CR2 duration, median (months)	13.8	12.2	8.1	0.007

Abbreviations: alloSCT, allogeneic stem cell transplant; CR, complete remission; FLT3, fms-like tyrosine kinase-3; NPM1, nucleophosmin-1; NS, not significant.

**Table 3.** Univariate pairwise comparisons for OS by mutation status and CR1 duration

	HR	95% CI	P-value
<b>Mutation status</b>			<b>0.03</b>
FLT3-/NPM1+ versus FLT3-/NPM1-	1.21	0.48 3.03	0.68
FLT3+ versus FLT3-/NPM1-	2.16	1.17 3.97	<b>0.014</b>
FLT3+ versus FLT3-/NPM1+	1.78	0.72 4.43	0.21
<b>CR1 duration</b>			
6–12 versus <6 months	3.22	1.57 6.62	<b>0.001</b>
≥12 versus <6 months	13.96	5.59 34.91	<b>&lt;0.0001</b>
≥12 versus 6–12 months	4.33	1.96 9.56	<b>0.0003</b>

Abbreviations: CI, confidence interval; CR, complete remission; FLT3, fms-like tyrosine kinase-3; HR, hazard ratio; NPM1, nucleophosmin-1. Bold entries highlight the statistically significant.



**Figure 2.** OS from time of relapse, according to CR1 duration, for the 70 patients who underwent reinduction.

CR1 duration was an important predictor of OS from relapse (see Figure 2). On pairwise comparison, those with CR1 duration of 6 months or less had a significantly worse OS than those with CR1 duration >6 months. Similarly, patients with CR1 duration between 6 and 12 months had a worse OS than patients who relapsed 12 months or more after CR1 (Table 3).

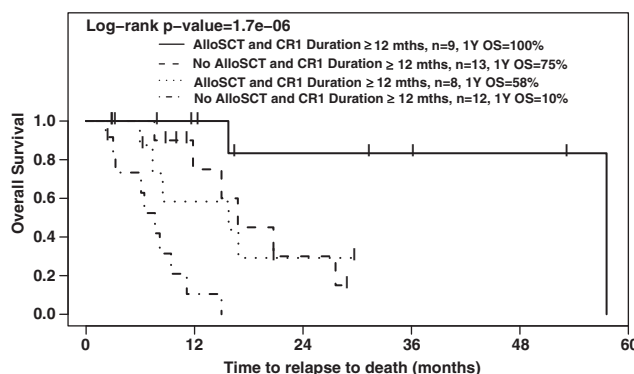
**Multivariate analysis for OS**

A multivariate Cox proportional hazards model was created, using mutation status, age at relapse and CR1 duration. In this model, CR1 duration was a highly significant predictor of OS (Table 4).

**Table 4.** Multivariate analysis for OS, incorporating mutation status, age and CR1 duration

Variable	HR	95% CI	P-value
<b>Molecular status</b>			0.17
NPM1-/FLT3-	1.00	— —	—
NPM1+/FLT3-	2.44	0.86 6.95	0.094
FLT3+	1.57	0.80 3.06	0.19
Age at relapse (continuous)	1.002	0.97 1.03	0.90
<b>CR1 duration</b>			<b>&lt;0.0001</b>
<6 months	15.29	5.67 41.23	<b>&lt;0.001</b>
6–12 months	5.41	2.17 13.50	<b>0.0003</b>
≥12 months	1.00	— —	—

Abbreviations: CI, confidence interval; CR, complete remission; FLT3, fms-like tyrosine kinase-3; HR, hazard ratio; NPM1, nucleophosmin-1. Bold entries highlight the statistically significant.



**Figure 3.** Outcome of the 42 patients who achieved CR2, according to CR1 duration and whether alloSCT was performed in CR2.

After adjusting for CR1 duration, molecular status and age did not have a significant impact on OS. The results were the same when only the 57 patients who were tested for FLT3 at relapse were evaluated (*P*-value for molecular status 0.58, *P*=0.46 for FLT3+).

**Influence of alloSCT in CR2**

Among patients who achieved a CR2, those who subsequently underwent alloSCT had a significantly superior OS (HR: 3.61 (95% CI: 1.39–9.35), *P*=0.0053) than those who did not. Two-year OS rates were 56% and 14%, respectively. This difference was significant for the subset of patients who relapsed at <12 months (HR: 6.20 for patients not receiving an alloSCT compared with those who did (95% CI: 1.75–21.99), *P*=0.005); there was a similar trend seen amongst those who relapsed at ≥12 months, with those not receiving a transplant having worse OS (HR: 7.29 (95% CI: 0.87–60.86), *P*=0.067).

Patients who underwent alloSCT after a CR1 duration ≥12 months had a significantly better OS than those who underwent alloSCT after CR1 duration <12 months (HR: 6.91 (95% CI: 0.81–59.25), *P*=0.041). Figure 3 shows Kaplan–Meier OS curves for patients, stratified by CR1 duration (≥ or <12 months) and by whether or not they received a transplant.

**DISCUSSION**

In our study, neither NPM1 nor FLT3 status predicted for ability to achieve CR2 with salvage chemotherapy. This is in contrast to the frontline setting, where NPM1 positivity is associated with a higher CR rate.<sup>11</sup> In the relapsed setting, CR1 duration appears to be the

more important predictor of CR2; patients with CR1 duration <6 months are particularly resistant to current salvage regimens, as previously described.<sup>13–15</sup>

Our findings on univariate analysis with respect to the adverse impact of *FLT3*-ITD positivity on OS are consistent with those of Ravandi *et al.*<sup>16</sup> However, as patients with *FLT3*-ITD mutations tend to have a shorter CR1 duration,<sup>11</sup> it is important to clarify the influence of molecular status versus CR1 duration on outcome following relapse. We found that the negative prognostic impact of a *FLT3*-ITD mutation disappeared after correcting for CR1 duration on multivariate analysis. Patients with CR1 duration <6 or <12 months had a significantly inferior OS compared with those with longer CR1 duration; the inclusion of molecular status in our multivariate model did not independently influence outcome.

Our findings are in contrast to a French GOELAMS study, which found that both *FLT3*-ITD status and CR1 duration remained important prognostic factors in refractory or relapsed AML.<sup>17</sup> However, that study included patients with primary refractory disease and incorporated favorable and adverse cytogenetic risk groups, while our study was restricted to relapsed patients with intermediate-risk karyotype. In addition, the GOELAMS study used a salvage regimen incorporating gemtuzumab ozogamicin, which may have influenced outcomes. Their study also used only *FLT3*-ITD results at initial diagnosis; some of these may have changed at relapse, as previously described.<sup>6,7</sup>

In contrast to what is seen in the frontline setting, *NPM1*+/*FLT3*- status did not predict for a better OS with salvage chemotherapy in our study, as compared with the other subgroups. The reasons for this are unclear; some cases may have acquired additional mutations, which may have rendered the cells more drug resistant. In contrast to our findings, Chevallier *et al.*<sup>8</sup> reported that *NPM1*+/*FLT3*- patients with a normal karyotype had a higher CR rate and superior 2-year OS following salvage chemotherapy compared with those in other molecular subgroups. However, this latter report did not include a multivariate analysis, and in the subsequent study from this group,<sup>17</sup> *NPM1* status was no longer a significant predictor of survival on either univariate or multivariate analysis.

The high frequency of changes in *FLT3* status at the time of relapse (26%) is consistent with previous reports,<sup>6,7</sup> and supports the need for retesting all relapsed patients for *FLT3* status. This is particularly important with the availability of *FLT3* inhibitors,<sup>18</sup> currently in clinical trials. We also did not measure *FLT3* allele burden, which may also potentially influence results.<sup>19</sup> A limitation in our data is that patients did not have cytogenetics repeated at the time of relapse, and thus we cannot exclude the possibility that some patients may have acquired new cytogenetic abnormalities, placing them into a more unfavorable risk group.

In our study, age at relapse was found not to be a prognostic factor on multivariate analysis, in contrast to what is seen at initial presentation. However, as older patients were less likely to receive salvage chemotherapy, we cannot exclude the possibility of a selection bias that excluded higher-risk elderly patients.

The OS in all subgroups remained poor, and novel treatment approaches therefore need to be considered for all relapsed patients. For patients with *FLT3*-ITD mutations, the addition of the *FLT3* inhibitor CEP-701 to chemotherapy at relapse did not result in any survival benefit in a recent randomized study.<sup>20</sup> However, more promising results in relapsed patients have been shown with the more potent *FLT3* inhibitor, quizartinib<sup>21</sup>. Further studies with this agent, either alone or in combination with chemotherapy, are warranted.

AlloSCT appears to confer a survival advantage to those achieving a CR2, regardless of CR1 duration. It is our opinion that

this should continue to be recommended to all patients who achieve CR2 following relapse. Nevertheless, performing an alloSCT did not completely efface the negative prognostic weight of a shorter CR1 duration, and results remain suboptimal in this subset of patients. Alternative approaches are needed, both to treat relapsed patients with a short CR1 duration but also to provide better frontline therapy for patients identified as being at high risk of early relapse.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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