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FLT3 Testing and Clonal Evolution in Patients with Acute Myeloid Leukemia: A Retrospective Cohort Study in Taiwan

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INTRODUCTION:
Mutation of the FMS-like tyrosine kinase 3 (*FLT3*) gene is one of the most common genetic alterations in acute myeloid leukemia (AML), while *FLT3* internal tandem duplication (ITD) is a predictor of poor disease prognosis in patients. Timing of *FLT3* mutation testing and the pattern of *FLT3* clonal evolution are critical issues for ensuring that patients with *FLT3* mutation-positive AML receive targeted therapy promptly, but data from real-world clinical practice are limited.

AIM:
This retrospective cohort study aimed to assess the turnaround time of *FLT3* testing in two patient cohorts with non-M3 primary AML: newly diagnosed (ND) patients and those with relapsed or refractory disease (R/R). A further aim in the R/R cohort was to assess the pattern of *FLT3* clonal evolution.

METHODS:
Eligible adult patients had evidence of new diagnosis of AML or R/R AML between 1 January 2009 and 31 December 2019 and had undergone at least one *FLT3* test at National Taiwan University Hospital. Patients were followed up until either the end of the data period, loss to follow up (no records for 6 months), or death. We analyzed the time from the date of ordering *FLT3* test to receipt of results (both cohorts) and the acquisition (negative at diagnosis, positive at R/R), loss (positive at diagnosis, negative at R/R), or maintenance (no change in status) of *FLT3* mutation at R/R compared with status at diagnosis. We also explored the association between acquisition/loss/maintenance of *FLT3* mutation at R/R and overall survival (OS) in the R/R cohort.

RESULTS:
From a total AML dataset of 1,789 patients, 659 and 223 were included in the ND and R/R cohorts, respectively (**Table 1**). Demographics and clinical characteristics of the ND and R/R cohorts were similar. The most common type of AML was recurrent genetic abnormalities in both ND and R/R cohorts (50.7% and 67.7%, respectively); 45.8% and 48.0% of patients, respectively, had a normal karyotype; and *NPM1* (21.1% and 16.6%, respectively), and *IDH1/ IDH2* (18.5% and 15.2%, respectively) were the most common types of co-mutations detected. There was no difference in the turnaround time of *FLT3* testing between the ND and R/R cohorts (**Table 1**). Since 2020, *FLT3* testing protocols have been further optimized to meet a 7-day turnaround time; additionally, almost all chemotherapy-fit patients with *FLT3* mutation receive midostaurin in combination with 3+7 chemotherapy after reimbursement of midostaurin was implemented in Taiwan in February 2020.
Of 164 patients with *FLT3* tests at both diagnosis and R/R, most (75.6%, n=124) were *FLT3* mutation-negative at diagnosis (**Table 1**). At R/R, 27/124 (21.8%) acquired an *FLT3* mutation and 12/40 (30.0%) patients lost their *FLT3* mutation (**Table 1**). Risk of mortality was increased in patients who acquired an *FLT3* mutation (HR [95% CI] 1.59 [0.97, 2.62]), maintained their *FLT3* mutation (1.52 [0.58, 2.56]), or lost their *FLT3* mutation (1.22 [0.58, 2.56]), compared with those who were *FLT3*-mutation negative at both diagnosis and R/R (**Figure 1**).

CONCLUSIONS:

This study provided information on the real-world landscape of *FLT3* testing among patients with AML in Taiwan. The turnaround time of *FLT3* testing in the current study was longer than the time reported in clinical trials, likely owing to different procedures in sampling arrangement and report delivery between real world and clinical trial settings.
The distribution of *FLT3* mutation and pattern of clonal evolution were largely consistent with previously published clinical studies. The higher prevalence of *FLT3* mutation in the R/R cohort versus the ND cohort is in accordance with previous research showing that *FLT3*-ITD mutation is predictive of relapse. Patients with *FLT3* mutation at R/R had a shorter OS, which indicates the importance of *FLT3* testing at R/R diagnosis to optimize outcomes through targeted therapy.

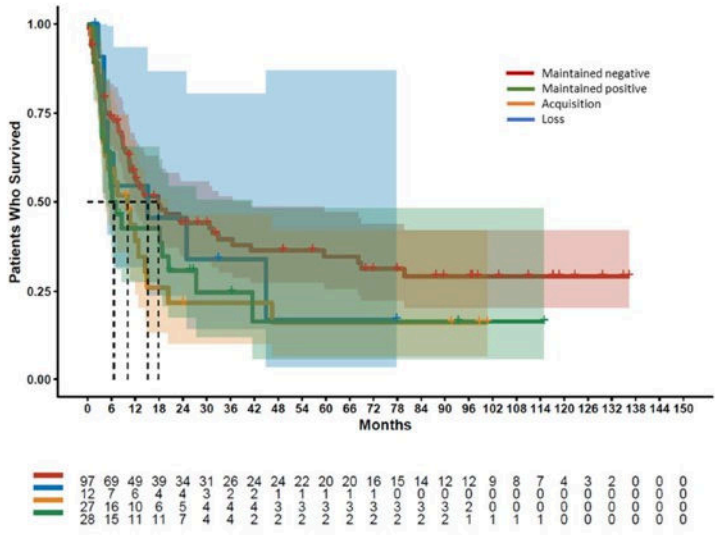
Disclosures Krishnan: *Astellas Pharma Ltd:* Current Employment. **Tai:** *Astellas Pharma Ltd:* Current Employment. **Hou:** *Astellas Pharma Ltd:* Current Employment.

TABLE 1. Turnaround time of *FLT3* testing (ND and R/R AML cohorts), and pattern of *FLT3* clonal evolution in the R/R cohort

	***FLT3* mutation test turnaround time**	
	ND (n=659)	**R/R (n=223)**
Time elapsed, days		
Mean (SD)	17.3 (10.4)	17.3 (10.4)
Median (min, max)	19.1 (4.2, 45.9)	19.1 (4.2, 45.9)
	***FLT3* clonal evolution at R/R (n=164)**	
	Positive (n=55)	**Negative (n=109)**
FLT3 status at AML diagnosis		
Positive (n=40)	28	12
Negative (n=124)	27	97

AML, acute myeloid leukemia; ND, newly diagnosed; *FLT3*, *FMS*-like tyrosine kinase 3; R/R, relapsed or refractory; SD, standard deviation

FIGURE 1. Kaplan–Meier plot of *FLT3* clonal evolution and overall survival in the R/R cohort



FLT3, *FMS*-like tyrosine kinase 3; R/R, relapsed or refractory

Figure 1

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