Fms-like tyrosine kinase 3 (FLT3)–mutated acute myeloid leukemia (AML) accounts for approximately 30% of all newly diagnosed AML and generally portends a poor prognosis. The FLT3-internal tandem duplication (ITD) mutation carries a worse prognosis than the FLT3-tyrosine kinase domain (TKD) mutation (1). Multiple tyrosine kinase inhibitors have now demonstrated clinical activity against FLT3-mutated AML. Type I FLT3 inhibitors (FLT3i), which include midostaurin, gilteritinib, and crenolanib, bind to the active gate-keeper domain of FLT3; type II inhibitors, which include quizartinib, sorafenib, and ponatinib, bind to the hydrophobic region of FLT3 in its inactive conformation. Importantly, type II FLT3i do not have activity against TKD mutations, whereas type I inhibitors do (2). Of these agents, midostaurin is now FDA approved for first-line treatment of FLT3-mutated AML, while gilteritinib is approved as a single agent in the relapsed/refractory setting based on the results of large phase III, randomized multicenter studies and continues to be the most used FLT3i in the United States outside of a clinical trial setting (3). Despite these advances, patients nearly always relapse or develop refractory disease after treatment with a FLT3i in combination with chemotherapy or as single agent. Patients who can be bridged to an allogeneic stem cell transplant (AlloHSCT) after FLT3i therapy have a longer overall survival (OS) and more durable remissions (4).

In this issue of Blood Cancer Discovery, Alotaibi and colleagues have elegantly analyzed mutation dynamics in a cohort of patients with FLT3-mutant AML who achieved a complete remission to different types of FLT3i and subsequently relapsed (5). They have also teased out patterns of primary resistance to type 1 FLT3i versus type II FLT3i therapy. Among 67 patients with FLT3-mutant AML who had data from next-generation sequencing (NGS) profiling of bone marrow samples pre- and post-FLT3i therapy, 55% patients developed emergent mutations postrelapse, 26% had on-target FLT3 mutations, 16% had mutations in epigenetic modifiers, 13% had mutations in the RAS/MAPK pathways, 7% had mutations in the WT1 gene, and 7% had mutations in the TP53 gene, respectively. Of the patients who developed emergent mutations after FLT3i therapy, 33% patients were treated with type I FLT3i therapy, and a majority of the patients (29%) had mutations in the RAS/MAPK pathway, whereas in 65% of the patients treated with prior type II FLT3i therapy, the most common mutation was an on-target mutation in FLT3-D835 in 30% of cases, and only 6% had mutations in the RAS/MAPK pathway. A quarter of the cohort (26%) had no detectable FLT3 mutations at relapse. The authors additionally sought to define mechanisms of primary resistance to FLT3i by comparing an additional cohort of 106 patients who were primarily resistant to FLT3i with the original cohort of patients responsive to FLT3i at baseline. They found that more patients with FLT3i primary refractory disease had a RAS mutation with a variant allele frequency >20% compared with initially FLT3i responsive disease, with a trend toward significance ($P = 0.083$). The authors also show that the incidence of certain mutations postrelapse differs based on the combination of FLT3i with either low-intensity therapy (LIT) or conventional cytotoxic therapy (CCT). The combination of type II inhibitors with CCT had lower FLT3-D835 mutations (6% vs. 45%) compared with combination with LIT; however, TP53 mutations were higher in combination with CCT (18% vs. 7%) than with LIT, highlighting a possible role of the combination of therapies used in promoting the selection of therapy-resistant clones (5).

To our knowledge, this article is the first report demonstrating patterns of resistance to type II inhibitors. In addition, it further supports the recent finding that the RAS/MAPK pathway is the dominant pathway involved in secondary resistance after type I FLT3i treatment (6). It is important to understand the patterns of secondary resistance via NGS profiling in patients with AML to help develop
predictive models for sequential therapies after relapse. These data highlight the RAS/MAPK pathway’s importance not only in the postrelapse setting but also in possibly driving primary resistance to FLT3i, hence, posing a new possible preclinical target—concomitant targeting of the RAS/MAPK pathway and FLT3 in FLT3-mutated AML. IDH1 and IDH2 mutations co-occur with FLT3 mutations in newly diagnosed AML in 15% to 27% and 8% to 30% of patients, respectively (7). A totaibi and colleagues also note that emergent mutations in epigenetic modifiers are prominent, found in 16% of patients postrelapse, with IDH1 and IDH2 being the most common occurring mutations in 10% of patients treated with type II FLT3i and in 5% of patients treated with type I FLT3i. Furthermore, they found that responding patients had a higher incidence of IDH2 mutations at baseline, 21% versus 7%, compared with nonresponders (5). Given the frequent co-occurrence of these mutations at diagnosis and the higher incidence in therapy-responsive patients in this study, an approach combining targeted therapies in patients with FLT3-mutant and IDH-mutant AML could perhaps yield better and deeper responses, as demonstrated in a recently reported retrospective study, and should be explored in prospective clinical trials (8).

In the current study, 31% of patients underwent AlloHSCT in remission and then relapsed. The authors do not give detailed information about specific postrelapse mutations in this cohort and the details pertaining to FLT3i in the maintenance setting. In this context, it is important to mention the recent positive data of the SORMAIN trial that showed decreased risk of relapse and death in patients with FLT3-mutant AML who received sorafenib maintenance post-AlloHSCT (85% relapse-free survival at 24 months vs. 53.3% with placebo; ref. 9). Placing patients on a FLT3i for post-AlloHSCT maintenance is beneficial, but we do not know which FLT3i is superior in this setting. Molecular profiling, as well as deep sequencing mutations that emerge post-AlloHSCT, will help us develop the best possible maintenance strategies in these patients with aggressive AML (9).

The recently published Beat AML study applied a precision medicine strategy where patients aged >60 years were matched to a therapeutic approach within 7 days based on a complete genetic and cytogenetic analysis. The study was able to demonstrate feasibility of rapidly utilizing the data from precision molecular approaches toward treatment decisions in elderly patients with AML. Most notably, patients who were treated in a genetically defined subgroup on the Beat AML study had a lower early-death rate (30-day mortality rate of 3.7% vs. 20.4%) and improved OS (median OS, 12.8 vs. 3.9 months) compared with the group that received the standard-of-care treatment approach. A lower frequency of FLT3 mutations was observed in the therapy-eligible patients (18.3%) assigned to these groups compared with the usual rate at baseline, 21%–34%, likely due to the older cohort of patients enrolled on the study (10). Among the patients who had FLT3 mutations, those with FLT3-ITD or FLT3-TKD mutations received treatment with gilteritinib monotherapy or gilteritinib in combination with decitabine. The patients who had concurrent mutations in nucleophosmin 1 + FLT3-ITD were treated with entospletinib (syk inhibitor) with induction (fit) or without induction (unfit). Although specific rates of response to therapy in the FLT3-mutated group cannot be assessed, a safe conclusion from the study was that the precision medicine-based approach was generally beneficial for therapy-eligible patients despite a 7-day delay in treatment imposed by the time required for detailed molecular profiling (10). This further underscores the need for a rapid turnaround time and assessment of the leukemia molecular profile prior to embarking on a therapeutic approach that is a cornerstone of treatment in FLT3-mutated AML where FLT3i are incorporated in induction, in consolidation, as well as increasingly in maintenance therapy. Although receiving the results of genetic profiling data prior to beginning AML therapy is challenging to achieve outside of a clinical trial setting, the results of the Beat AML study underscore the need to strive toward this ideal for every individual patient diagnosed with AML. It clearly suggests that better patient outcomes are likely when information from genetic profiling is incorporated into the therapeutic decision-making process.

To summarize, patients with FLT3-mutated AML have better therapeutic options available compared with before, with the high likelihood of more selective FLT3i becoming FDA approved in the near future. Understanding the patterns of mutations associated with primary resistance and relapse will allow us to design better sequential therapies and combinations with other agents for treatment of FLT3-mutated AML. Future clinical studies should prospectively evaluate upfront combinations of targeted therapies, such IDH inhibitors with FLT3i and RAS/MAPK targeting concurrently with FLT3i in this aggressive malignancy.

Authors’ Disclosures

A. Shastri reports research funding from Kymera Therapeutics, consulting fees from GLG and Guidepoint, and honoraria from OncLave. A. Verma reports research funding from Bristol-Myers Squibb, Janssen, MedPacto, Novartis, Curis, Prelude, and Eli Lilly and Company; compensation as a scientific advisor to Novartis, Stelexis Therapeutics, Acceleron Pharma, and Celgene; and equity ownership in Throws Exception and Stelexis Therapeutics. No disclosures were reported by the other authors.

Published first December 6, 2020.

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Access the most recent version of this article at:
doi: 10.1158/2643-3230.BCD-20-0210

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