An emerging triplet option for newly diagnosed *FLT3*-mutated acute myeloid leukemia

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FLT3 inhibitors represent a critical component of intensive induction chemotherapy regimens for newly diagnosed *FLT3*-mutated acute myeloid leukemia (AML).[1,2] However, there is currently no clear standard of care for older and unfit patients with *FLT3*-mutated AML. The phase III RATIFY trial, which established midostaurin plus standard chemotherapy as first-line treatment for AML with *FLT3* mutations, did not include patients 60 years or older.[2] In the phase III QuANTUM-First trial, which evaluated quizartinib plus standard chemotherapy in patients up to the age of 75 years with *FLT3*-internal tandem duplication (ITD)-mutated AML, the survival benefit conferred by addition of quizartinib was not observed in those aged 60-75 years in subgroup analysis.[1] In light of this, the optimal therapeutic approach in older and unfit patients with *FLT3*-mutated AML warrants further investigation.

The hypomethylating agent (HMA) azacitidine plus venetoclax confers high initial rates of remission in older and unfit patients with newly diagnosed *FLT3*-mutated AML.[3] However, *FLT3*-ITD mutations represent a major mechanism of adaptive resistance, with *FLT3*-ITD clonal expansion leading to shorter response duration and inferior overall survival (OS).[4] The median OS of AML patients with *FLT3*-ITD mutations treated with a HMA and venetoclax is 9.9 months compared with 14.7 months among *FLT3* wild-type patients.[5] Due to this decreased durability of remission, the European LeukemiaNet (ELN) 2024 genetic risk classification for AML patients treated with non-intensive therapy categorizes *FLT3*-ITD mutations as intermediate risk.[6] *FLT3* mutations lead to MCL-1 and BCL-xL overexpression, decreasing the efficacy of venetoclax-mediated BCL-2 inhibition. Preclinical data suggest that this adverse impact of *FLT3* mutations may be overcome by the combination of FLT3 inhibitors and BCL-2 inhibitors.[7,8] Recent phase I/II clinical studies have shown remarkably high (>90%) rates of remission in *FLT3*-mutated AML treated with frontline HMA, venetoclax, and FLT3 inhibitors, but interpretation of these studies has been limited by relatively short follow-up.[9,10]

In this issue of *Haematologica*, Short *et al*. provide a retrospective analysis of long-term outcomes of AML patients with *FLT3* mutations treated with frontline HMA, venetoclax, and FLT3 inhibitor triplets.[11] Given the very high initial remission rates seen with these combinations, long-term outcome data have been urgently awaited to assess the response durability (Table 1). The median age of the patient population studied is 70 years, with 36% of patients ≥75 years old, making the work highly relevant for patients with AML in whom the median age at diagnosis is 68 years. Here, Short *et al*. demonstrate encouraging 3-year relapse-free survival (RFS) and OS outcomes with HMA, venetoclax, and FLT3 inhibitors, particularly in patients with *FLT3*-tyrosine kinase domain (TKD) mutations in whom 3-year RFS and OS rates were high at 76%. *FLT3*-ITD-mutated patients had less durable responses with 3-year RFS and OS rates of 38% and 45%, respectively, as well as shorter median OS compared to *FLT3*-TKD-mutated AML (28.1 *vs*. 39.3 months). While allogeneic stem cell transplant (SCT) in first remission improves survival in *FLT3*-mutated AML and is recom-

Table 1. Summary of clinical outcomes with hypomethylating agent, venetoclax, and FLT3-inhibitor triplet regimens in the overall, *FLT3*-ITD, and *FLT3*-TKD mutated cohorts.

Outcome	Overall		
CR/CRi, %	93		
ORR (CR, CRi, MLFS), %	99		
MRD-negative by MFC, %	81		
	Overall	***FLT3*-ITD**	***FLT3*-TKD**
Median RFS, months	28.8	16.7	36.6
Median OS, months	38.5	28.1	39.3

CR: complete remission; CRi: complete remission with incomplete count recovery; ORR: overall response rate; MLFS: morphological leukemia-free state; MRD: measurable residual disease; MFC: multiparameter flow cytometry; ITD: internal tandem duplication; TKD: tyrosine kinase domain; RFS: relapse-free survival; OS: overall survival.

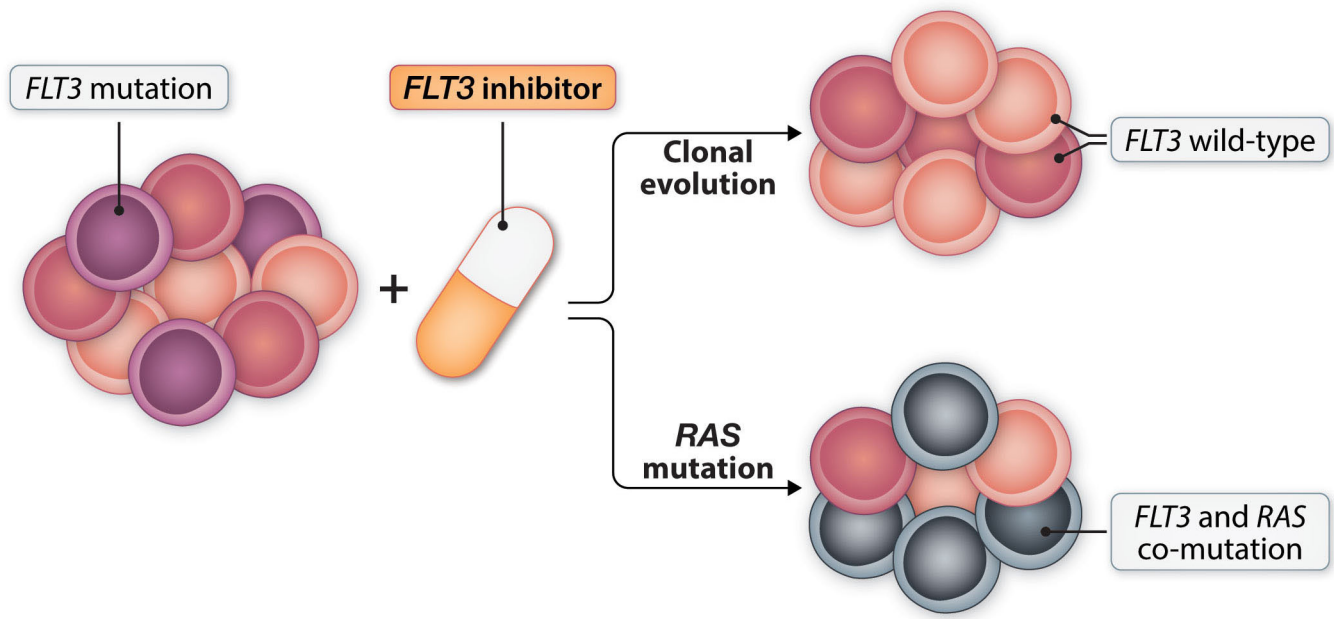

Figure 1. Mechanisms of resistance to FLT3-inhibitor regimens. Clonal evolution and progression with *FLT3* wild-type disease is an important mechanism of resistance to therapy. Further, development of *RAS* pathway mutations mediates resistance to FLT3-inhibitor monotherapy as well as venetoclax-based regimens.

mended for fit patients, allogeneic SCT in first remission did not significantly affect OS in this study population.[6] Despite patients undergoing allogeneic SCT in first remission being significantly younger than those who did not undergo transplantation (median age: 67 years *vs*. 72 years; *P*=0.001), 3-year OS was comparable (55% *vs*. 61%; *P*=0.49), as was relapse rate (20% *vs*. 28%; *P*=0.45). Allogeneic SCT similarly did not improve survival in patients <75 years old, *FLT3*-ITD-mutated AML, or ELN 2022 adverse-risk disease. While these findings may reflect higher rates of transplant-related mortality in this older population, allogeneic SCT can still be considered for select patients, potentially informed by measurable residual disease (MRD) evaluation and future randomized studies.

Short *et al*. demonstrate that *FLT3*-ITD MRD retains its prognostic importance in triplet-treated patients. Patients with *FLT3*-ITD MRD positivity (MRD$^+$) by next-generation sequencing by cycle 4 had significantly poorer 2-year RFS and OS compared to those who were MRD-negative (MRD$^-$) (RFS 62% *vs*. 20%; OS 73% *vs*. 40%). This is similar in concept to work done characterizing the prognostic significance of *NPM1* molecular MRD for patients treated with HMA plus venetoclax or low-dose cytarabine plus venetoclax, among whom patients with bone marrow MRD$^-$ for *NPM1* by reverse transcription quantitative polymerase chain testing by the end of cycle 4 had a 2-year OS of 84% compared with 46% if MRD$^+$.[12]

Notably, the work by Short *et al*. also highlights mechanisms of resistance to HMA, venetoclax, and FLT3 inhibitor triplets (Figure 1). Specifically, *RAS* pathway mutations were associated with decreased duration of response, just as they serve as a mechanism of resistance when FLT3 inhibitors are given as monotherapy and in venetoclax-based regimens.[13,14] Indeed, 3-year OS among those with baseline *RAS* pathway mutations was 22% compared to 63% among those without *RAS* pathway mutations. Furthermore, clonal evolution and progression with *FLT3* wild-type disease serves as another mechanism of therapeutic resistance, with 65% of relapses in this study driven by outgrowth of *FLT3* wild-type clones.

Although the long-term data presented by Short *et al*. are encouraging, the true impact of adding a FLT3 inhibitor to HMA and venetoclax will only be shown in randomized studies. Notably, the phase III LACEWING trial of gilteritinib plus azacitidine *versus* azacitidine for patients with newly diagnosed *FLT3*-mutant AML ineligible for intensive chemotherapy failed to show an OS benefit.[15] Randomized data are needed to prospectively compare outcomes for *FLT3*-mutated AML treated with HMA, venetoclax, and FLT3 inhibitor triplet therapy *versus* HMA and venetoclax doublet therapy to further characterize responses, survival, and the impact of MRD and allogeneic SCT. Triplet regimens are notably myelosuppressive, and future studies will also need to optimize dosing schedules including the duration of venetoclax and FLT3 inhibitors with each cycle, and the use of growth factors. In the study by Short *et al*., granulocyte colony-stimulating factor was given to 58% of responders (42/72) in cycle 1. Ongoing randomized trials include a phase II NCI-sponsored MyeloMATCH study of azacitidine and venetoclax *versus* azacitidine, venetoclax and gilteritinib in older and unfit patients with newly diagnosed *FLT3*-mutated AML (NCT06317649), as well as a phase I/II randomized dose-ranging and expansion study of azacitidine, venetoclax and gilteritinib in patients with newly diagnosed *FLT3*-mutated AML ineligible for intensive chemotherapy (NCT05520567).

Disclosures

ADG has participated in advisory boards and/or provided consultancy services for AbbVie, Astellas Pharma, Bristol-Myers

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Contributions

LB and ADG co-wrote the editorial.

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