Leukemia insights

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In this month's Leukemia Insights newsletter, written by Naval Daver, M.D., and Musa Yilmaz, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we cover our clinical trials available for patients with newly diagnosed or relapsed/refractory FLT3-mutated acute myeloid leukemia (AML). Learn more about our Leukemia program.

FLT3 Inhibitors in Acute Myeloid Leukemia

Outcomes remain poor for older adults with FLT3-mutated acute myeloid leukemia (AML) who are not fit for intensive chemotherapy. In the frontline setting, the median overall survival (OS) with standard-of-care low-intensity regimens, such as hypomethylating agents (HMA) plus first-generation FLT3 inhibitors (midostaurin, sorafenib) or venetoclax, is 8-12 months. Next-generation FLT3 inhibitors, such as gilteritinib and quizartinib, have shown promising single-agent response rates (40%-55%) in Phase III clinical trials in patients with relapsed/refractory (R/R) FLT3-mutated AML; however the 2-year survival rate is less than 20%, with durable responses achieved only in the small subset of patients who are able to proceed to allogeneic stem cell transplant. New strategies are needed for this patient population. Mounting preclinical and clinical data show the synergism among FLT3 inhibitors, conventional chemotherapy agents, HMAs and BCL2 inhibitors (venetoclax). At MD Anderson, we are focusing on developing novel combinations using these agents. Following are the clinical trials available for patients with newly diagnosed or relapsed/refractory FLT3-mutated AML.

1. Older adults, not fit for intensive chemotherapy

1.1 Triplet Combinations

1.1.1 Decitabine + Venetoclax + Quizartinib (NCT03661307): Quizartinib is a potent and selective second-generation FLT3 inhibitor. In early clinical trials, single-agent quizartinib produced a 50% composite complete remission (CRc) rate in R/R FLT3+ AML.

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Venetoclax is a potent BCL2 inhibitor approved by the Food and Drug Administration (FDA), in combination with HMAs, for the treatment of newly diagnosed patients with AML not eligible for intensive therapy. Resistance to venetoclax is frequently driven by the upregulation of MCL-1 and BCL-XL. A number of FLT3 inhibitors down-regulatecytotoxic regimens are poor, with less than half of patients achieving a second remission. Remission rates are even lower for patients with multiply refractory disease. Long-term survival rates for patients with R/R ALL are <20%. Novel agents and combinations are needed to induce remission and facilitate the bridge to potentially curative ASCT.

MCL-1, thereby reducing the likelihood of resistance to BCL2 inhibitors. Given strong preclinical evidence showing synergy between venetoclax and quizartinib, we designed this clinical trial to evaluate the efficacy and tolerability of the two oral drugs, combined with decitabine and in patients with newly diagnosed or relapsed AML (Phase I/II). For each cycle, patients receive decitabine intravenously for 10 days, quizartinib orally daily continuously, and venetoclax orally daily for 14 or 21 days. Patients in complete remission (CR) can proceed to allogeneic stem cell transplant, and those with no transplant option may continue therapy for 12 cycles (or more) barring disease progression of any clinically significant toxicity. Preliminary results of this study (Yilmaz et al, ASH 2020) showed that the triplet was safe and effective, with 80% CRc rates in the R/R setting with no early mortality. All 4 patients treated in the frontline settings achieved CRc and MRD-clearance. The study continues to accrue.

1.1.2 Azacitidine + Venetoclax + Gilteritinib (NCT04140487): Gilteritinib, a second-generation FLT3 inhibitor, has been approved by the FDA for treatment of patients with R/R FLT3-mutated AML. Gilteritinib also has demonstrated potent preclinical synergy with venetoclax. Also the FLT3-TKD (D835) mutation is sensitive to it, unlike sorafenib and quizartinib. This is the first study of a triplet of gilteritinib with azacitidine and venetoclax, and the goal is to evaluate the clinical efficacy of the combination in patients with newly diagnosed or R/R FLT3-mutated (ITD or TKD) disease. In each cycle, patients receive azacitidine for 7 days, gilteritinib daily continuously, and venetoclax for 14 or 21 days, depending on response.

1.2 Doublet Combinations

1.2.1 Quizartinib + Venetoclax (NCT03735875), Gilteritinib + Venetoclax (NCT03625505): In addition to the triplets, we are investigating the doublets of venetoclax/quizartinib and venetoclax/gilteritinib in FLT3-positive patients with R/R disease. Both protocols are enrolling patients who have no prior exposure to quizartinib or gilteritinib. Recent results (Daver et al, ASH 2020) demonstrated that the CRc rates with the doublet of gilteritinib and venetoclax were 84%, approximately double the CRc rates seen with gilteritinib alone in R/R FLT3-mutated patients, suggesting the preclinical synergy with gilteritinib and venetoclax translates to the clinic. Molecular clearance was seen in >50% of the responders, indicating deep responses. These combinations are well-tolerated, more convenient since both are oral agents and may be an option for older (>75 year) patients with FLT3-mutated AML for whom the triplet of may be more difficult to tolerate/administer. Venetoclax, gilteritinib and quizartinib are provided free on the respective trials.

1.2.3 Sorafenib and Palbociclib (NCT03132454): FLT3 mutations confer constitutive growth signaling that acts through the cyclin-dependent kinase 4/6 (CDK) pathway. Palbociclib is an orally bioavailable, selective inhibitor of CDK4/6 that has been shown to trigger cell cycle arrest and tumor growth inhibition in AML.

In this study, patients receive sorafenib and palbociclib concurrently daily for 28 days per cycle. This study is accruing patients with relapsed disease.

1.2.4 HM43239 (NCT03850574): HM43239 is a potent FLT3 inhibitor targeting ITD, TKD, and ITD/TKD mutants and other receptor tyrosine kinases including SYK, AXL, PDGFRs and RET. HM43239 showed in vitro antitumor effects in AML cell lines harboring FLT3 mutations and wild-type FLT3 AML cell lines, and this was confirmed in vivo in various mice xenograft models. This agent also appears to target FLT3 691 (gatekeeper mutation) that may not be targeted by other FLT3 inhibitors and is being evaluated in a A Phase I/II Study in Patients with R/R AML. A recent preliminary report showed a CR/CRi in 2 of 6 patients who had received prior therapy with FLT3 inhibitors (Daver N et al, ASH 2020). The dose escalation is ongoing.

2. Older adults, fit for intensive chemotherapy

2.1 Liposomal Cytarabine and Daunorubicin (CPX-351) and Quizartinib (NCT04128748): Approximately 15% of older adults with AML harbor FLT3 mutations, and CPX-351 alone may not be the best treatment strategy. The CPX-351 and quizartinib protocol enrolls patients >65 years with newly diagnosed or relapsed AML. Quizartinib is given 14 days during induction, then continuously during consolidation. Patients who are not eligible for stem cell transplant receive single-agent quizartinib as maintenance for up to 12 months.

3. Younger adults, fit for intensive chemotherapy

3.1 Cladribine, Idarubicin, Cytarabine (CLIA) + Quizartinib: (NCT04047641): The addition of cladribine, a purine analog, to the idarubicin and high-dose cytarabine regimen improves OS in AML. At our institution, CLIA has become the standard induction and consolidation regimen for patients with AML who are age 65 and younger and fit for intensive chemotherapy. In this study, patients start quizartinib daily on day 6 of induction for 14 days. It will be given continuously during consolidation cycles. Upon completion of induction/consolidation cycles, patients will start maintenance quizartinib for up to 12 months. Eligible patients may receive allogeneic stem cell transplant in first remission.

3.2 Cladribine, Idarubicin, Cytarabine (CLIA) + Gilteritinib (NCT02115295): The treatment schedule and eligibility of this protocol are identical to the CLIA plus quizartinib protocol described in section 3.1. This study enrolls patients with newly diagnosed FLT3-mutated AML who are candidates for intensive chemotherapy. Gilteritinib will be given Day 1-14 of cycle 1 and continuously starting in Cycle 2.

4. Use of quizartinib in patients with FLT3 wild-type (WT) AML

Quizartinib was primarily developed to treat FLT3-mutated AML. However, early clinical studies also enrolled patients with FLT3 wild-type disease. In a Phase II study (Cortes at al. Lancet Oncology 2018), single-agent quizartinib induced 36% and 30% composite CR rates in older (>60 years old) and younger (age >18 years old) adults with AML without a detectable FLT3 mutation, respectively. These response rates in patients with FLT3 negative AML were remarkably higher than those with other single-agent FLT3 inhibitors such as midostaurin, sorafenib, gilteritinib (Borthakur et al Hematologica 2011, Perl et al Lancet Oncology 2017, Stone et al Blood 2005). Given these favorable response rates in FLT3 wild-type AML, some of the above quizartinib combination protocols (CPX-351/quizartinib and CLIA/quizartinib) allow patients with FLT3 unmutated AML.

Leukemia Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress. View our faculty roster.

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Announcements

Leukemia Insights Newsletter

Our Leukemia Insights e-newsletter is now available online. Started in 2007 by Hagop Kantarjian, M.D., Leukemia Insights focuses on our various therapy options at MD Anderson Cancer Center. Click here to visit our new website.

Emil J Freireich Hematology Grand Rounds

The MD Anderson Cancer Center Emil J Freireich Hematology Grand Rounds now has a virtual format. This series highlights the incredible research taking place at MD Anderson Cancer Center while showcasing leaders from our research community, in an effort to remain engaged and inspired during the COVID-19 pandemic. Hosted by the Department of Leukemia in collaboration with the Department of Lymphoma/Myeloma, and Department of Stem Cell Transplantation and Cellular Therapy, we aim to strengthen the connections between the scientific and medical community at MD Anderson Cancer Center, our colleagues, patients and friends from around the world. Click here to visit our new website.