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.

Progress with FLT3 Inhibitors in Acute Myeloid Leukemia (AML)

The second-generation FLT3 inhibitors gilteritinib and quizartinib have demonstrated encouraging single-agent response rates (40%-55%) in randomized Phase III trials in patients with relapsed/refractory FLT3-mutated AML, but. the 2-year survival rate is less than 20%, with durable responses achieved only in the small subset of patients who are able to undergo allogeneic stem cell transplant (SCT). Similarly, the prognosis remains poor for newly diagnosed older adults with FLT3-ITD mutated AML, with a median overall survival of approximately 12 months with standard-of-care low-intensity regimens, such as azacitidine plus venetoclax. Synergy between FLT3 inhibitors, conventional chemotherapeutic agents, hypomethylating agents (HMAs), and BCL2 inhibitors is supported by accumulating preclinical and clinical evidence. At MD Anderson, we are developing novel combinations to improve outcomes for both frontline and relapsed/refractory FLT3 mutated AML. The available clinical trials are listed below.

Unfit for Intensive Chemotherapy

1. Triplet Combinations

Decitabine + Venetoclax + Quizartinib (NCT03661307): Quizartinib is a potent, selective second-generation FLT3 inhibitor. In early clinical trials, single-agent quizartinib produced a 50% composite complete remission (CRc) rate in relapsed/refractory FLT3+ AML. Venetoclax is a potent BCL2 inhibitor approved by the 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, in addition to inhibiting FLT3, also down-regulate MCL-1, thereby reducing or delaying

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resistance to BCL2 inhibitors like venetoclax. 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 decitabinef in patients with newly diagnosed or relapsed AML (Phase I/II). During induction, patients receive 10 days of decitabine with venetoclax and quizartinib for 14 days. In subsequent cycles, responders receive consolidation with 5 days of decitabine and 14 days or less of venetoclax and quizartinib (duration based on the time to count recovery in previous cycle). Patients in complete remission (CR) can proceed to allogeneic SCT, and those with no transplant option may continue therapy for 12 cycles (or more if clinical benefit) barring disease progression or clinically significant toxicity. Preliminary results of this study (Yilmaz et al, EHA 2022) showed that the triplet was safe and effective, with 78% CRc rates in the relapsed/refractory setting and no early mortality. All five patients treated in the frontline setting achieved CRc and MRD-clearance with good tolerability of the regimen. The study continues to accrue relapsed/refractory and frontline FLT3-ITD mutated patients.

Azacitidine + Venetoclax + Gilteritinib (NCT04140487): Gilteritinib, a second-generation FLT3 inhibitor, has been approved by the FDA as single-agent therapy for the treatment of patients with R/R FLT3-mutated AML. It also has demonstrated potent synergy with venetoclax in preclinical cell lines and PDX models. As a type I FLT3 inhibitor, gilteritinib targets FLT3-TKD (D835) mutations as well, unlike the type II FLT3 inhibitors sorafenib and quizartinib that only target the FLT3-ITD. This is the first study of this triplet, and the goal is to evaluate the clinical efficacy and identify the optimal dosing regimen and duration of venetoclax and gilteritinib in patients with newly diagnosed or R/R FLT3-mutated (ITD or TKD) disease to enhance efficacy while avoiding prolonged myelosuppression. In a preliminary report (Short N et al ASH 2022), we treated 21 older adult patients with newly diagnosed FLT3-mutated AML, and 20 (95%) achieved complete remission (CR) and 1 (5%) achieved morphologic leukemia-free state (MLFS). Seventeen pts (81%) achieved flow MRD negativity, and 19 pts (90%) cleared the FLT3 mutation using a PCR assay. The median overall survival was not reached, with a median follow-up of 12 months. These data are encouraging and appear better in terms of response, MRD clearance and overall survival (OS), than what was achieved with the azacitidine/venetoclax doublet in frontline FLT3-mutated patients in the VIALE-A study. This trial continues to accrue.

ASTX727 + Venetoclax + Gilteritinib (NCT05010122)

ASTX727 is an oral fixed-dose combination of decitabine (35 mg) and cedazuridine (a cytidine deaminase inhibitor; 100 mg) approved for treating patients with myelodysplastic syndrome. We are evaluating the safety and efficacy of an all-oral combination of ASTX727, gilteritinib, and venetoclax in patients with relapsed or refractory FLT3-mutated AML, and older/unfit pts unable to receive chemotherapy. This could be an attractive three-drug oral combination for newly diagnosed older/unfit FLT3-mutated AML.

2. Novel Treatments Other Than Triplets

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 is also unique in that it targets FLT3 691 (gatekeeper mutation) that may not be targeted by many other FLT3 inhibitors. This is an open-label, multicenter, first-in-human, Phase I/II trial enrolling adult patient with AML who relapsed or have refractory disease after at least one line of therapy. The study has recently been amended to include 2 arms: a single-agent

HM43239 arm for patients previously exposed to prior FLT3 inhibitors, and a combination HM43239 + venetoclax arm for patients previously exposed or naïve to prior FLT3 inhibitors.

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.

Iadademstat + Gilteritinib (NCT05546580): Iadademstat is a selective, small molecule that covalently binds the FAD-cofactor in complex with the Lysine Specific Demethylase 1 (LSD1, also known as KDM1A) and inhibits its biological activity. LSD1 sustains the oncogenic transformation, proliferation and the maintenance of the undifferentiated state in leukemia. Preclinical data show that FLT3-ITD mutated AML cell lines treated with iadademstat display reduction in metabolic activity and colony formation. This study evaluates the safety and tolerability of iadademstat in combination with gilteritinib in patients with FLT3-mutated R/R AML.

Fit for Intensive Chemotherapy

1. Liposomal Cytarabine and Daunorubicin (CPX-351) and Quizartinib (NCT04128748): Approximately 18% of older adults with AML harbor FLT3 mutations, and CPX-351 alone may not be the best treatment strategy given the potent driver activity of the FLT3 mutation. 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. This is an attractive regimen for patients with therapy-related AML, AML from prior MDS or MDS/MPN, or AML with MDS-related cytogenetic changes who are also found to have a FLT3-ITD mutation.

2. 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, and incorporation of the purine analog and higher-dose cytarabine in induction was shown to have a preferential activity over traditional anthracycline + cytarabine (3+7) in newly diagnosed FLT3-mutated AML in the Polish randomized phase 3 study (Holowiecki et al, JCO 2012). Based on these data and our previously published data incorporating purine analogs with induction, CLIA has become our 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 on day 6 of induction for 14 days. It is given continuously during consolidation cycles. Upon completion of induction/consolidation cycles, patients start maintenance quizartinib for up to 12 months. Eligible patients may receive allogeneic SCT in first remission.

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

Quizartinib for Patients With FLT3 Wild-Type AML

Quizartinib was primarily developed to treat FLT3-mutated AML. However, early clinical studies also enrolled patients with FLT3 wild-type (WT) 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.

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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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