Leukemia insights

ARPIL 2020

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

In this month's Leukemia Insights newsletter, written by Naval Daver, MD, and Musa Yilmaz, MD, and sponsored in part by the Charif Souki Cancer Research Fund, we describe the development of novel combinations using the next generation FLT3 inhibitors.

FLT3 Inhibitors in Acute Myeloid Leukemia

Mutations of the FMS-like tyrosine kinase 3 (FLT3) gene occur in approximately 30-35% of all acute myeloid leukemia (AML) cases, with the internal tandem duplication (ITD) representing the most common type of FLT3 mutation (about 80%). Midostaurin, approved by the U. S. Food and Drug Administration (FDA) in 2017, was the first FLT3 inhibitor to improve overall survival in a randomized trial, when administered in combination with chemotherapy in newly diagnosed patients with FLT3 (ITD and/or tyrosine kinase domain [TKD] mutations). Like most first-generation FLT3 inhibitors, midostaurin has limited single-agent activity in AML. However, next-generation FLT3 inhibitors such as gilteritinib, quizartinib and crenolanib have shown promising single-agent activity in clinical trials. This will likely be further improved by developing rational, safe combinations with standard agents such as azacitidine, induction chemotherapy, venetoclax and others.

At the MD Anderson Leukemia Department, we focus on developing novel combinations using next-generation FLT3 inhibitors and chemotherapy, as there are mounting preclinical and clinical data showing the synergism between FLT3 inhibitors and conventional chemotherapeutics, hypomethylating agents (HMAs) and novel drugs (particularly BCL-2 inhibitors). Below is a list of active clinical trials available for patients with FLT3-mutated or unmutated AML.

1. Older adults, not fit for intensive chemotherapy

1.1 Triplet Combinations

1.1.1 Decitabine + Venetoclax + Quizartinib (NCT03661307): Quizartinib was the first drug developed exclusively as a FLT3 inhibitor. In contrast to the first-generation FLT3 inhibitors, quizartinib is at least 25-times more potent against FLT3 in plasma assays. In early clinical trials, patients with FLT3 positive AML treated with single-agent quizartinib (30 mg or 60 mg daily dose) achieved approximately 50% composite complete remission (CRc) rates. B-cell Lymphoma 2 (BCL-2) overexpression has been implicated in the maintenance and survival of AML cells and has been associated with resistance to chemotherapeutics. Venetoclax is a potent and selective small-molecule inhibitor of BCL-2 that has recently been approved by the FDA for treatment of patients with AML in combination with HMAs. Although the combination of HMA+venetoclax generates high response rates, relapses are common and

ABOUT MyMDAnderson

myMDAnderson is a secure, personalized web site helping community physicians expedite patient referrals, as well as improve continuity of care through information access and streamlined communications.

Physicians who have referred patients to MD Anderson or plan to do so, can utilize the HIPAA compliant features of myMDAnderson to:

- Refer a patient
- View your patient's appointments Access patient reports
- Send and receive secure messages

JOIN THE COVERSATION

Connect with us.

JOIN OUR MAILING LIST

If you would like to receive an electronic issue of the MD Anderson Leukemia Insights e-Newsletter on a monthly basis, please complete the **Subscription Request Form.**

It's the easiest way to stay current with information on the latest leukemia news, research, and resources.

CONTACT OUR STAFF

Mary Alma Welch - Editor
Lisa Palacios - Publishing Editor
Leukemia@mdanderson.org

response durations may be shorter, especially in FLT3-mutated AML. The resistance to venetoclax is frequently driven by the upregulation of MCL-1 and BCL-XL. MCL-1 has been reported as an essential effector of FLT3-ITD-mediated drug resistance, and a number of FLT3 inhibitors down-regulate MCL-1, thereby reducing the propensity to resistance to BCL2 inhibitors. Given strong preclinical evidence showing synergistic activity between venetoclax and quizartinib, we designed this clinical trial to evaluate the efficacy and tolerability of quizartinib added to decitabine and venetoclax in patients with newly diagnosed or relapsed AML (Phase I/II). Patients receive quizartinib daily (continuously), decitabine and venetoclax (14 or 21 days). Patients who are eligible for allogeneic stem cell transplantation may receive transplantation in CR, and those with no transplant option may continue therapy up to 12 cycles (or more) unless there is a significant toxicity or disease progression. Initial tolerability and efficacy appears encouraging.

1.1.2 Azacitidine + Venetoclax + Gilteritinib (NCT04140487): Gilteritinib, a next-generation FLT3 inhibitor, has been recently approved by FDA for the treatment of patients with FLT3-mutated AML. This is the first study of gilteritinib in combination with azacitidine and venetoclax. Based on the rationale for concurrent FLT3-ITD and BCL-2 inhibition in AML, we are evaluating the clinical efficacy of azacitidine and venetoclax in combination with gilteritinib in patients with newly diagnosed or relapsed/ refractory FLT3-mutated disease. In each cycle, patients receive azacitidine for 7 days, gilteritinib continuously, and venetoclax 14 or 21 days, depending on response.
ponatinib), we will reduce treatment-related morbidity and mortality and further increase the cure rate. This regimen is open to patients of all ages with newly diagnosed Ph-positive ALL. Ponatinib and blinatumomab are provided free of charge.

1.2.2 Quizartinib and DS3032b (NCT03552029): DS3032b (milademetan) is a novel, orally bioavailable small molecule inhibitor of mouse double minute 2 homolog (MDM2). More than 90% of AML patients retain wild-type TP53 in the malignant cells, but the p53 protein activity is frequently inhibited by binding of MDM2, resulting in degradation of p53. Pharmacologic inhibition of the interaction between MDM2 and wild-type p53 in tumor cells could restore p53 activity with subsequent antitumor effects from the p53-downstream genes. Combined treatment of quizartinib and DS3032b has shown preclinical synergistic antileukemic activity by targeting 2 distinct cellular pathways: FLT3-ITD signaling pathway and p53 activation pathway. In this Phase I dose-escalation study, patients receive quizartinib (30-60 mg daily) and DS3032b (90-160 mg daily for 7-14 days per cycle) concurrently. Patients with newly diagnosed or relapsed FLT3-ITD mutant AML are eligible. Patients who have received and are relapsed/refractory to prior midostaurin, gilteritinib or sorafenib are eligible. Both drugs are provided free.

1.2.3 Gilteritinib and Azacitidine (NCT02752035): This is a Phase II/III, open-label, 3-arm, randomized study to compare the efficacy and safety of gilteritinib plus azacitidine or azacitidine only. Patients with newly diagnosed FLT3-mutated AML are eligible.

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

1.2.5 SEL24/MEN1703 (NCT03008187): SEL24/MEN1703, a potent PIM and FLT3-ITD dual activity inhibitor, demonstrates significantly broader activity in AML cell lines and primary AML blasts, irrespective of FLT3 status. This is a dose selection and escalation study accruing patients with newly diagnosed or relapsed AML who are not fit for intensive chemotherapy. SEL24/MEN1703 is administered orally once daily for 14 consecutive days over a 21-day treatment cycle.

2. Older adults, fit for intensive chemotherapy

2.1 Liposomal Cytarabine and Daunorubicin (CPX-351) and Quizartinib (NCT04128748): CPX-351 has been approved by the FDA for treatment of older patients with secondary AML. Approximately 15% of this patient population harbors FLT3 mutations, and CPX-351 alone may not be the best treatment strategy for these patients. The CPX-351 and quizartinib protocol enrolls patients (>65 years old) with newly diagnosed or relapsed AML. Quizartinib is given 14 days during induction, then continuously during consolidation cycles. Patients who are not candidates for stem cell transplantation receive single-agent quizartinib as maintenance up to 12 months.

3. Younger adults, fit for intensive chemotherapy

3.1 Cladribine, Idarubicin, Cytarabine (CLIA) + Quizartinib (NCT04047641): We have shown that the addition of cladribine, a purine analogue, to idarubicin and high-dose cytarabine improved outcomes in AML. At our institution, CLIA has become the standard induction and consolidation regimen for patients 65 years old and younger with AML and who are fit for intensive chemotherapy. In this study, patients also will 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. Patients who are eligible may receive allogeneic stem cell transplantation in first remission.

3.2 Cladribine, Idarubicin, Cytarabine (CLIA) + Gilteritinib (NCT02115295): The treatment schedule and eligibility of this protocol are similar to the CLIA plus quizartinib protocol discussed in section 3.1. This study allows both newly diagnosed FLT3-mutated (ITD and/or TKD) patients 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 AML

As a specific FLT3 inhibitor, quizartinib was primarily developed to treat FLT3-mutated AML. However, early clinical studies also enrolled patients with FLT3 wild-type AML. In a Phase II study (Cortes at al. Lancet Oncology 2018), single-agent quizartinib induced 36% and 30% composite CR rates in older (>60 y/o) and younger (age >18 y/o) 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, some of the above quizartinib combination protocols (CPX-351/quizartinib and CLIA/quizartinib) are exploring quizartinib role in patients with FLT3 unmutated AML.

The Leukemia Department welcomes and will facilitate referrals, and would like to work with you to make novel therapies available to your patients. For referrals, please contact any of the Leukemia faculty listed.

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.

Clinical Faculty

Kantarjian, Hagop	*Department Chair*	(713) 792-7026
Garcia-Manero, Guillermo	*Deputy Chair, Chief, Section of Translational Research, Chief, Section of Myelodysplastic Syndromes (MDS), and Director, Leukemia Clinical Fellowship Program*	(713) 745-3428
Konopleva, Marina	*Deputy Chair, and Chief, Section of Leukemia Biology Research*	(713) 794-1628
Wierda, William	*Deputy Chair, Chief, Section of Chronic Lymphocytic Leukemia (CLL), and Leukemia Center Medical Director*	(713) 745-0428
Andreeff, Michael	*Chief, Section of Molecular Hematology and Therapy*	(713) 792-7261
Borthakur, Gautam	*Chief, Section of Developmental Therapeutics*	(713) 563-1586
DiNardo, Courtney D.	*Co-Leader, Section of Acute Myeloid Leukemia (AML), Co-Leader, Section of Developmental Therapeutics*	(734) 358-1053
Ferrajoli, Alessandra	*Leukemia Center Associate Medical Director*	(713) 792-2063
Jabbour, Elias	*Chief, Section of Acute Lymphoblastic Leukemia (ALL)*	(713) 792-4764
Kadia, Tapan	*Co-Leader, Section of Acute Myeloid Leukemia (AML), Co-Leader, Section of Developmental Therapeutics, Co-Leader, Leukemia Clinical Fellowship Program*	(713) 563-3534
Ravandi, Farhad	*Chief, Section of Acute Myeloid Leukemia (AML)*	(281) 216-7806
Sasaki, Koji	*Co-Leader, Section of Chronic Myeloid Leukemia (CML)*	(713) 745-2882
Verstovsek, Srdan	*Chief, Section of Myeloproliferative Neoplasms (MPNs), Director, Clinical Research Center for MPNs*	713) 745-3429

Faculty Contacts

(Continued)

Alvarado, Yesid	(713) 794-4364
Bose, Prithviraj	(713) 792-7747
Burger, Jan	(713) 563-1487
Daver, Naval	(713) 794-4392
Estrov, Zeev	(713) 794-1675
Issa, Ghayas "Gus"	(713) 745-8432
Jain, Nitin	(713) 745-6080
Kornblau, Steven	(713) 794-1568
Masarova, Lucia	(832) 750-4211
Montalban Bravo, Guillermo	(713) 794-3604
Naqvi, Kiran	(713) 745-5073
Ohanian, Maro	(713) 792-0091
Pemmaraju, Naveen	(713) 792-4956
Short, Nicholas	(713) 563-4485
Takahashi, Koichi	(713) 745-4613
Thompson, Philip	(713) 792-7430
Yilmaz, Musa	(713) 745-9945

Research Faculty

Battula, Venkata	(713) 563-2227
Bhalla, Kapil N.	(713) 563-8619
Burks, Jared K.	(713) 792-7640
Carter, Bing Z.	(713) 794-4014
Colla, Simona	(713) 794-5223
Fiskus, Warren	(713) 563-5901
Freireich, Emil	(713) 792-2660
Gandhi, Varsha V.	(713) 792-2989
Han, Lina	(713) 792-7640
Ishizawa, Jo	(713) 792-7640
Keating, Michael	(713) 745-2376
Piya, Sujan	(713) 792-7305
Plunkett, William	(713) 792-3335
Post, Sean	(713) 794-1458
Pourebrahimabadi, Rasoul	(713) 792-7305
Rytting, Michael E.	(713) 792-4855
Ruvolo, Peter	(713) 745-9211
Wei, Yue	(713) 792-9854
Yang, Hui	(713) 792-2558
Zhang, Weiguo	(713) 794-4085