Leukemia insights

DECEMBER 2021

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

In this month's Leukemia Insights newsletter, written by Ghayas Issa, M.D. and Farhad Ravandi, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we discuss menin inhibitors, the latest oral targeted therapy for acute leukemias and five ongoing clinical trials with menin inhibitors at MD Anderson. Learn more about our Leukemia program.

Menin inhibitors: a new class of targeted therapy for treatment of acute leukemia

Introduction

Menin inhibitors are novel targeted agents currently in clinical development for the treatment of genetically defined subsets of acute leukemia. Menin has a tumor suppressor function in endocrine glands. Germline mutations in the gene encoding menin cause the multiple endocrine neoplasia type 1 (MEN1) syndrome, a hereditary condition associated with tumors of the endocrine glands. However, menin is also critical for leukemogenesis in subsets driven by rearrangement of the lysine Methyltransferase 2A (KMT2A) gene, previously known as mixed-lineage leukemia (MLL), which encodes an epigenetic modifier. These seemingly opposing functions of menin can be explained by its various roles in gene regulation.

Leukemias with rearrangement of KMT2A (KMT2Ar) are predicted to respond to menin inhibition with early clinical data validating this proof-of-concept. These leukemias affect infants, children and adults, and lead to adverse outcomes with current standard therapies. Recent studies have identified novel targets in acute leukemia that are susceptible to menin inhibition, such as mutated nucleophosmin 1 (NPM1), the most common genetic alteration in adult acute myeloid leukemia (AML). In addition to these alterations, other leukemia subsets with similar transcriptional dependency could be targeted through menin inhibition. This led to rationally designed clinical studies, investigating small-molecule oral menin inhibitors in relapsed acute leukemias with promising early results.

Leukemia with KMT2Ar

Acute leukemia with KMT2Ar have been recognized for decades as disease-defining abnormalities associated with an adverse prognosis. They are driven by an oncogenic

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 email us at Leukemia@mdanderson.org.

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

CONTACT OUR STAFF

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

fusion of the KMT2A gene, located on chromosome 11q23, with more than 80 different partners identified. These rearrangements occur in 5%–10% of acute leukemias and are the most common cause of infant leukemia (70%–80%). Fusion partners likely influence the leukemia phenotype where t(9;11) (p21;q23) or KMT2A-MLLT3 (also known as AF9) is most common in AML, whereas t(4;11) (q21;q23) or KMT2A-MLLT2 (also known as AFF1 or AF4) is most common in acute lymphoblastic leukemia (ALL). KMT2Ar are detected in up to 70% of therapy-related AML following treatment with a topoisomerase II inhibitor, with a typical short latency to clinical presentation ranging from 6 months to 2 years.

KMT2Ar leukemias are associated with resistance to standard therapies and higher rates of relapse. These leukemias are frequently characterized by hyperleukocytosis, hepatosplenomegaly, and CNS involvement. KMT2Ar can be detected by conventional cytogenetics where translocations involving 11q23 are seen, or by fluorescence in situ hybridization (FISH) with some assays developed for detection of rearrangements regardless of the fusion partner gene (split-signal FISH concept).

KMT2Ar leukemias have a unique, highly distinct gene expression profile characterized by overexpression of the HOX genes along with their co-factor MEIS1. The menin binding site is preserved throughout all KMT2A fusion proteins and is an essential co-factor for binding to HOX gene promoters. In mouse models of KMT2Ar leukemia, genetic ablation of menin reversed aberrant HOX gene expression, leading to abrogation of the differentiation arrest and the oncogenic properties of KMT2A.

NPM1 mutated AML

NPM1 mutations are the most common genetic alterations in adult AML, detected in 20–30% of cases at diagnosis. These mutations are considered leukemia-initiating. They consist of 4 base-pair frameshift insertions or duplications in exon 12, leading to truncation of the protein and disruption of the nuclear shuttling of NPM1. Therefore, mutated NPM1 persists in the cytoplasm which explains why it is exclusively cytoplasmic when mutated. Mutated NPM1 is associated with upregulation of HOX genes, specifically HOXA and MEIS1. The similarity in gene expression profiles between NPM1c and KMT2Ar led to the hypothesis that menin is implicated in this aberrant transcription, and that targeting menin could be also a therapeutic strategy in AML with mutated NPM1. Genetic editing studies confirmed dependency of mutated NPM1 on menin and MEIS1 to exert a leukemogenic function.

Other Leukemia Subtypes Susceptible to Menin Inhibition

The current prevailing model of dependency on menin in acute leukemias is linked to overexpression of HOX genes and their co-factor MEIS1; therefore, this gene expression profile can be used as a biomarker of response to menin inhibition. However, given the current lack of validated assays, leukemia genotypes previously shown to have this gene expression signature could be used as surrogate markers of response. This expression signature is also shared by other genotypes or recurrent cytogenetic abnormalities in AML in addition to mutated NPM1 and KMT2Ar (Table 1). To highlight one example, leukemias with rearrangements involving the Nuclear pore complexes 98 (NUP98), which are rare but associated with an adverse prognosis, have overexpression of HOXA9 in preclinical models and patient samples, with preclinical data demonstrating susceptibility to menin inhibition.

Table 1: Genetic alterations with overexpression of *HOXA* genes predicted to potentially respond to menin inhibitors (Adapted from Issa et al. Leukemia 2021).[1]

Alteration/Mutation	Cytogenetics	Phenotype				References
KMT2Ar	11q23 rearrangements	AML, ALL, MPAL	✓	✓	✓	2-4
KMT2A-PTD	Normal karyotype	AML	✓	✓		2,5
NPM1c	Normal karyotype	AML	✓	✓	✓	2,6
NPM1-MLF1	t(3;5)(q25;q34)	MDS, AML	✓			7,8
NUP98r	11p15 rearrangements	AML, T-ALL, MDS	✓	✓	✓	9-11
SET-NUP214	t(9;9)(q34;q34)	AML, T-ALL, AUL	✓		✓	12
RUNX1-EVI1	t(3;21)(q26;q22)	AML	✓		✓	13
MYST3-CREBBP	t(8;16)(p11;p13)	AML	✓			14
CDX2-ETV6	t(12;13)(p13;q12)	AML		✓		15
CALM-AF10	t(10;11)(p13;q14-21)	T-ALL, AML, MPAL	✓	✓	✓	16-18
MN1-ETV6	t(12;22)(p13;q12)	AML, MDS		✓	✓	19
EZH2	-	MDS, AML	✓			20
IDH1/IDH2	-	MNs			✓	21,22
ASXL1	-	MNs		✓		23
CEBPA	-	AML			✓	24
	Trisomy 8	MNs	✓			25

denotes direct examination of patient samples with the corresponding genotype showing upregulation of *HOXA* genes.

denotes mouse models of the corresponding genotype leading to upregulation of *Hox* genes.

denotes examination of cells lines or other *in vitro* investigations demonstration a role of *HOX* genes or menin inhibition in the corresponding genotype.

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia, MPAL, mixed-phenotype acute leukemia; MDS, myelodysplastic syndrome; AUL, acute leukemia of undifferentiated lineage.

Early Clinical Results with Menin Inhibitors

Identification of the KMT2A binding pocket on menin led to development of potent small-molecule, orally available inhibitors of the menin-KMT2A interaction. Therefore, menin inhibitors disrupt binding of KMT2A to menin, an essential co-factor necessary for binding of the KMT2A complex to promoters of target genes. Pharmacologic inhibition of menin-KMT2A proved to be an effective antileukemic strategy in preclinical models of susceptible leukemias, without affecting normal hematopoiesis, by downregulating the aberrant gene expression profile. This led to release of the differentiation block in these leukemias, with a pronounced increase in markers of myeloid differentiation, and apoptosis.

Given the strong preclinical rationale for use of menin inhibitors as a novel class of targeted therapy in acute leukemias, multiple clinical trials with these agents are ongoing with early results demonstrating clinical activity. Data from the phase I/II clinical trial (AUGMENT-101, NCT04065399) investigating the Syndax menin inhibitor in relapsed or refractory acute leukemia were presented at the 2021 American Society of Hematology (ASH) annual meeting. Of the 45 patients with KMT2Ar or mutated NPM1, the overall response rate was 44% (n=20/45), with 14 of the 20 (70%) responders showing no evidence of minimal residual disease (MRD-). The CR/CRh rate in this population was 22% (n=10/45). This trial included patients with AML, ALL and mixed-phenotype acute leukemia (MPAL) refractory to multiple prior lines of therapy (median of 3 prior lines of therapy), including stem cell transplant and/or venetoclax in approximately half of those enrolled. These results are highly encouraging given the low response rates with standard treatments for KMTAr leukemias. This treatment was overall well tolerated. Major related side effects (≥ grade 3), observed in at least 5% of patients, included QTc prolongation and differentiation syndrome. Detection of differentiation syndrome in this setting justifies the preclinical evidence of a successful reversal of the differentiation block caused by KMT2Ar through menin inhibition. The menin inhibitor SNDX-5613 has been granted an FDA Fast Track Designation for the treatment of relapsed/refractory acute leukemias.

Early data from the KOMET-001 trial (NCT04067336) presented at the 2020 ASH Annual meeting showed potential clinical activity of the oral menin inhibitor KO-539 from Kura Oncology. At the time of that presentation's data cutoff, 12 patients had been enrolled, and 8 were evaluable for response. One patient with KMT2Ar enrolled at the lowest dose level had tumor lysis syndrome, a decrease in hydrea requirements, and stabilization of peripheral blood counts. The preclinical concept of targeting mutated NPM1 though menin inhibition was also validated. There was clinical activity in two patients with NPM1-mutated AML. One patient with NPM1-mutated AML who had previously progressed on seven lines of therapy achieved a complete remission with undetectable MRD. A second patient with mutated NPM1 and FLT3-ITD who had received four prior lines of therapy achieved a morphological leukemia-free state. In addition, there was a complete remission in a patient with relapsed AML and mutations in the RUNX1 and SETD2 genes, therefore justifying investigation of menin inhibition in other susceptible leukemias.

Clinical Trials Investigating Menin Inhibition at MD Anderson

Given the emerging importance of this new class of drugs and the unmet need for patients with these resistant leukemias, there are currently five ongoing clinical trials with menin inhibitors at MD Anderson. Table 2 summarizes major eligibility criteria.

Table 2: Phase I/II clinical trials at MD Anderson investigating menin inhibitors in relapsed/refractory acute leukemias (Adapted from Issa et al. Leukemia 2021)[1].

Clinical trial/ Drug Company	**Drug**	**Dosing**	**Min. age**	**Phase 2 expansion cohorts**
AUGMENT-101 NCT04065399 Syndax	SNDX-5613	PO BID	30 days	A. ALL or MPAL with *KMT2Ar* B. AML with *KMT2Ar* C. AML with *NPM1c*
KOMET-001 NCT04067336 Kura	KO-539	PO daily	18 yrs	A. AML with *KMT2Ar* B. AML with *NPM1c*
NCT04752163 Daiichi Sankyo	DS-1594	PO BID	18 yrs	*A. KMTAr* leukemia: single agent B. AML with *NPM1c*: single agent C. AML with *KMT2Ar* or *NPM1c*: in combination with azacytidine and venetoclax D. ALL with *KMT2Ar*: in combination with mini-HCVD
NCT04811560 Janssen	JNJ-75276617	PO daily	18 yrs	-
NCT05153330 Biomea Fusion	BMF-219	PO daily	18 yrs	-

Status of clinical trials as of November 2021. ALL, acute lymphoblastic leukemia; MPAL, mixed-phenotype acute leukemia; *KMT2Ar,* rearranged *Lysine Methyltransferase 2A;* AML, acute myeloid leukemia; *NPM1c,* mutation of the *Nucleophosmin 1* resulting in a cytoplasmic localization of the protein. Yrs, years. Mini-HCVD, dose reduced combination of cyclophosphamide and dexamethasone, methotrexate, and cytarabine.

Summary

Extraordinary efforts by numerous scientists over the years allowed menin inhibitors to reach investigation in clinic. Though this is only the beginning of clinical investigations of these molecules, early results are encouraging. This new class of drugs has allowed remission in patients with highly resistant leukemias with no other effective therapy.

The immediate next steps, beyond further investigation of the safety and efficacy of menin inhibitors, are to design optimal combination strategies with other effective agents to treat various subtypes of acute leukemia, getting us closer to curing more patients with acute leukemia.

View references

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.

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
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,* Center Medical Director, Bone Marrow Aspiration Clinic	(713) 792-7261
Borthakur, Gautam	*Chief, Section of Developmental Therapeutics*	(713) 563-1586
Daver, Naval	*Director, Leukemia Research Alliance Program*	(713) 794-4392
DiNardo, Courtney D.	*Co-Leader, Section of Acute Myeloid Leukemia (AML), Co-Leader, Section of Developmental Therapeutics Leader, Hereditary Hematologic Malignancy Clinic*	(734) 358-1053
Ferrajoli, Alessandra	*Leukemia Center Associate Medical Director*	(713) 792-2063
Issa, Ghayas “Gus"	*Co-Leader, Section of Chronic Myeloid Leukemia (CML)*	(713) 745-8432
Jabbour, Elias	*Chief, Section of Acute Lymphoblastic Leukemia (ALL)*	(713) 792-4764

Leukemia Faculty Contacts *(continued)*

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.

Jain, Nitin	Director, Cellular Therapy Program	(713) 745-6080
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
Montalban Bravo, Guillermo	*Director, Chronic Myelomonocytic Leukemia (CMML) Program*	*(713) 792-4956*
Pemmaraju, Naveen	*Director, Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) Program*	*(713) 794-3604*
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

Clinical Faculty

Abbas, Hussein	(713) 745-8433
Alvarado, Yesid	(713) 794-4364
Bose, Prithviraj	(713) 792-7747
Burger, Jan	(713) 563-1487
Chien, Kelly	(713) 745-7584
Kornblau, Steven	(713) 794-1568
Maiti, Abhishek	(346) 725-0901
Masarova, Lucia	(832) 750-4211
Montalban Bravo, Guillermo	(713) 794-3604
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
Chang, Kyung Hee	(713) 792-4694
Colla, Simona	(713) 794-5223
Estrov, Zeev	(713) 794-1675
Fiskus, Warren	(713) 563-5901
Ganan_Gomez, Irene	(713)-792-7828
Han, Lina	(713) 792-7640
Ishizawa, Jo	(713) 792-7640
Keating, Michael	(713) 745-2376
Piya, Sujan	(713) 792-7305
Post, Sean	(713) 794-1458
Pourebrahimabadi, Rasoul	(713) 792-7305
Rytting, Michael E.	(713) 792-4855
Wei, Yue	(713) 792-9854
Zeng, Zhinhong	(713) 792-7640
Zhang, Weiguo	(713) 794-4085