Leukemia insights

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In this month's Leukemia Insights newsletter, written by Naval Daver, M.D., and Jayastu Senapati, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we discuss the TP53-directed treatment approaches in patients with MDS and AML in the Department of Leukemia at The University of Texas MD Anderson Cancer Center. Learn more about our Leukemia program.

TP53-Directed Therapies for AML and MDS

Despite several novel approved therapies for acute myeloid leukemia (AML) and myelodysplastic syndrome (AML), none has significantly altered the prognosis of patients with TP53 aberrations (mutation/loss). The presence of clinically significant *TP53* aberrations predicts for an inferior outcome, and they often are seen in the context of secondary or therapy-related disease and accompanied by complex cytogenetics. Given that standard chemotherapeutic approaches in myeloid leukemias need normal functionality and levels of the p53 protein to mediate apoptosis and differentiation, *TP53* aberrations make leukemic cells chemo-resistant, necessitating alternative approaches. The first step in patients with a *TP53* aberration is to understand the severity of the mutation/loss and whether it is clinically relevant. In general, a TP53 VAF>20% and/or presence of adverse cytogenetics and/or more than one TP53 mutation are considered clinically significant and associated with TP53-driven poor outcomes. Such patients should always be referred for an allogeneic stem cell transplantation, which, despite its limited advantage in myeloid malignancies with *TP53* aberrations, at this time still provides the most significant chance of long-term survival. Finally, given the futility of standard therapies, patients should always be screened for clinical trials that study TP53-directed approaches.

In this issue of Leukemia Insights, we discuss the *TP53*-directed treatment approaches in patients with MDS and AML in the Department of Leukemia at The University of Texas MD Anderson Cancer Center.

1) Anti-CD-47/SIRPα-Based Approaches

The CD47 protein expression on leukemia cells and its subsequent interaction with signal regulating protein alpha (SIRPα) on phagocytes lead to impaired immune

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surveillance and dampening of macrophage anti-tumor activity. This axis, also referred to as the "don't eat me signal," may be a critical innate immune (macrophage) checkpoint in AML and MDS and is therefore a promising target. Several early-phase clinical trials have used this approach in combination with hypomethylating agents +/- other agents, particularly the anti-CD47 antibody magrolimab.

A. Azacitidine + Magrolimab + Venetoclax (NCT04435691)

The phase 2 single-center trial to evaluate of the azaciticine/magrolimab/venetoclax combination has completed enrollment. This trial included patients with newly diagnosed and relapsed/refractory AML and had a cohort for *TP53*-mutated patients. The combination was well tolerated, showed a composite complete response rate of 63% in the newly diagnosed *TP53*-mutated cohort and promising overall survival, as of the last update at the 2022 American Society of Hematology meeting. The final results from this trial will be reported soon.

B. Magrolimab + Azacitidine vs. Venetoclax + Azacitidine or Intensive Chemotherapy in Patients with *TP53*-Mutated, Newly Diagnosed AML (ENHANCE-2) (NCT04778397)

This phase 3, multi-center randomized trial, of which MD Anderson Cancer Center is a pivotal site, is evaluating the combination of magrolimab with low-intensity therapy with azacitidine vs. venetoclax combined with azacitidine or intensive chemotherapy in patients with *TP53*-mutated AML. The ENHANCE-2 trial aims to understand the benefit of magrolimab over venetoclax-azacitidine or intensive chemotherapy (based on age and comorbidities) in adult patients with newly diagnosed, *TP53* mutated AML. Despite the benefit of venetoclax in combination with a hypomethylating agent compared to the hypomethylating agent alone in older/unfit AML, subsequent analysis from the VIALE-A trial and other real-world data showed that the magnitude of survival benefit in the *TP53*-mutated patients was significantly shorter compared with other genomic subgroups. In fact, in the VIALE-A study, the median OS was 5-6 months with azacitidine and venetoclax in the TP53-mutated, frontline AML patients, which was no different than the OS obtained with azacitidine or decitabine alone. Results from the ENHANCE-2 trial will be important to understand whether the combination of azacitidine/magrolimab improves response rates and/or survival compared with standard-of-care therapies. This trial is actively recruiting.

C. Other CD-47/SIRPα-Blocking Approaches.

i. TTI622 + Azacitidine (NCT03530683)
This is a multi-center phase I clinical trial that has a dedicated cohort evaluating the doublet of azacitidine and TTI622 (maplirpacept) in newly diagnosed patients with *TP53*-mutated AML. Given the lack of efficacy and added myelosuppression with the addition of venetoclax in *TP53*-mutated AML, this protocol will omit it. TTI622 is a fusion protein consisting of the CD47-binding domain of human SIRPα linked to the Fc region of human IgG4. The drug is administered intravenous weekly along with azacitidine in 28-day cycles. One of the advantages of targeting SIRPa as opposed to CD47 is the lack of binding to the RBC cytoskeleton, which is hypothesized to mitigate (or avoid) the early anemia seen with CD47 antibodies such as magrolimab. The trial is actively recruiting.

ii. CC95251 +/- Azacitidine +/- Venetoclax (NCT05168202)

This phase I trial studies CC95251 alone or in combination with azacitidine +/-

venetoclax in patients with relapsed/refractory AML or high-risk MDS (newly diagnosed or relapsed/refractory). CC95251 is a fully human anti-SIRPα antibody and has previously shown efficacy in early phase clinical trials in patients with non-Hodgkin lymphoma. This trial will evaluate the safety and establish the maximum tolerated dose of CC95251 as monotherapy and in combination in myeloid leukemias. This trial is actively recruiting.

iii. DSP-107 + Azacitidine (NCT04937166)

Dual signaling protein (DSP) 107 is a bi-functional, trimeric, fusion protein composed of sequences from the extracellular domain of SIRPα and 4-1BBL. The drug is administered intravenously. The SIRPα arm targets CD47 that is overexpressed on leukemia cells and triggers leukemia cell phagocytosis. The trimeric 4-1BBL arm, once cross-presented and immobilized by SIRPα binding to CD47, interacts with 4-1BB expressed on activated immune cells, mainly T- and NK-cells in the tumor microenvironment, and stimulates their proliferation and activation. Therefore, DSP107 triggers both innate and adaptive immune responses. In this phase IB study, the combination of azacitidine and DSP-107 will be studied in patients with relapsed/refractory AML or MDS (or chronic myelomonocytic leukemia) who have failed up to two prior therapies. It includes patients with or without a *TP53* mutation, and patients with or without prior exposure to HMA- and venetoclax-based therapies. In the subsequent dose escalation phase, the plan is to study DSP-107 in combination with azacitidine and venetoclax in relapsed/refractory and frontline AML, including both *TP53*-mutated and *TP53*-wild type patients. The study is actively recruiting.

2. SL401 + Azacitidine +/- Venetoclax (NCT03113643)

SL401 (tagraxofusp) is a recombinant human IL-3 fused to truncated cytotoxic diphtheria toxin and is approved for use in blastic plasmacytoid dendritic cell neoplasm (BPDCN) and targets the CD123 receptor expressed on myeloid leukemia cells. The drug was found to be safe for use in patients with BPDCN and was approved by the FDA as a single agent for the treatment of BPDCN through a registration clinical trial led by Dr. Naveen Pemmaraju at M.D. Anderson. This phase I trial evaluates the combination of SL401 and azacitidine +/- venetoclax in patients with relapsed/refractory AML; newly diagnosed, older/unfit AML; high-risk MDS; and BPDCN. It includes *TP53*-mutated patients. The current phase of the trial aims to establish the maximum tolerated dose and recommended phase 2 dose and is actively recruiting.

3. ONC201 (NCT02392572)

ONC201 is a first-in-class small molecule imipridone that antagonizes G-protein-coupled receptor DRD2, resulting in AKT/ERK inactivation. In preclinical studies, leukemia cells demonstrated sensitivity to ONC201 regardless of their genetic and mutation profiles, including *TP53* aberrations, normal bone marrow cells were spared. The phase I/II trial will study the drug in patients with relapsed/refractory acute leukemia (including AML) and previously untreated MDS in different dose schedules and establish the recommended phase 2 dose. So far, the drug has not shown any concerning safety signal, and the trial is actively recruiting.

D. Other Approaches

A number of cellular therapy trials (KITE 222 CLL1 autoCART, ARCELLX CD123 auto dd-CART, Cellectis CD123 UCART alloCART, NKARTA auto NK-CAR, SANOFI

off-the-shelf NK cells) as well as NK-engagers (Sanofi NK-engager, BMS NK-engager) are being investigated in this patient population. In addition, other agents such as PLK4 inhibitors CDK9 inhibitors are in phase I trials and may be good options for patients with *TP53*-mutated R/R AML and MDS, especially those who are in early salvage status and have a good performance status.

We are recruiting on many of these trials.

Table 1: Table of some of the key clinical trials that are open for patients with *TP53*-mutated AML/MDS

Trial identifier	Drug/Regimen	TP53 status	Target	Principal Investigator	N/D AML	R/R AML	Untreated MDS	R/R MDS
NCT04435691	Magrolimab + Azacitidine + Venetoclax	TP53m or wild type	CD47	Daver	✓	✓		
NCT03530683	TTI-622 + Azacitidine	TP53m or wild type	CD47	Daver	✓			
NCT04937166	CC-95251 + Azacitidine + Venetoclax	TP53m or wild type	CD47/SIRPα	Garcia-Manero		✓	✓	✓
NCT04937166	DSP107 + Azacitidine	TP53m or wild type	(CD47 x 41BB Bispecific)	Daver		✓		✓
NCT03113643	SL401+ Azacitidine + Venetoclax	TP53m	CD123	Pemmaraju	✓	✓	✓	✓
NCT04778397	Magrolimab + Azacitidine vs. Azacitidine + Venetoclax vs. 7+3 intensive chemotherapy	TP53m	CD47/SIRPα	Daver	✓			
NCT02392572	ONC201	TP53m	AKT/ERK	Borthakur		✓	✓	

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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