Leukemia insights

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Making Cancer History®

*In this month's Leukemia Insights newsletter, written by Guillermo Garcia-Manero, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we describe clinical trials available at our institution for patients with ALL, including Philadelphia chromosome (Ph)-negative and positive disease, and in both the frontline and salvage settings. Learn more about our Leukemia program.*

# Progress in myelodysplastic syndromes at MD Anderson

## Introduction

The section of myelodysplastic syndrome (MDS) at MD Anderson Cancer Center is the largest program of its class in the world. Despite travel restrictions due to the COVID-19 pandemic, more than 300 new patients with MDS were evaluated at MD Anderson in 2021. Reasons for these visits included confirmation of diagnosis, treatment, or evaluation for allogeneic stem cell transplantation (alloSCT). A majority of patients referred here are eventually enrolled in a clinical trial. Patients are evaluated by a multidisciplinary team that includes leukemia physicians, hematopathologists, stem cell transplant experts, pharmacists, advanced practice providers and research nurses. The MDS program also performs extensive translational and basic research and is supported in part by MD Anderson's Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) Moon Shot® Program.

In the past few years, we have witnessed an explosion in our understanding of MDS. This resulted in the approval in 2020 of two agents: luspatercept (1) and the oral hypomethylating agent (HMA) decitabine/cedazuridine (2). MD Anderson was a leader of the trials that resulted in their approval. This reinforces the importance of referring patients to our center for clinical trials. Despite this progress, prognosis of our patients still is poor, and we are in need of more advanced treatment options. Below, we provide a summary of our approach to patients with MDS and list active clinical trials.

## Current Conceptual Framework for the Therapy of MDS

Patients with MDS are stratified according to the IPSS and IPSS-R scoring systems. Using IPSS and IPSS-R, patients

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with MDS are divided in two broad subgroups: lower- and higher-risk disease. Several other important data points are needed when making treatment decisions: age; type and severity of comorbidities; number and degree of cytopenias; transfusion needs; presence of specific genomic alterations; percentage of bone marrow blasts; cytogenetic profile; potential for alloSCT; and, importantly, prior treatment with an HMA. First is the subset of patients without a morphologic diagnosis of MDS who instead have diagnoses that include idiopathic cytopenia of unknown significance (ICUS), clonal hematopoiesis of indetermined potential (CHIP), and clonal cytopenia of unknown significance (CCUS). Next, we divide patients with MDS into lower or higher risk, and then further subdivide them based on whether they have been exposed to an HMA. Figure 1 summarizes our current approach to treatment.

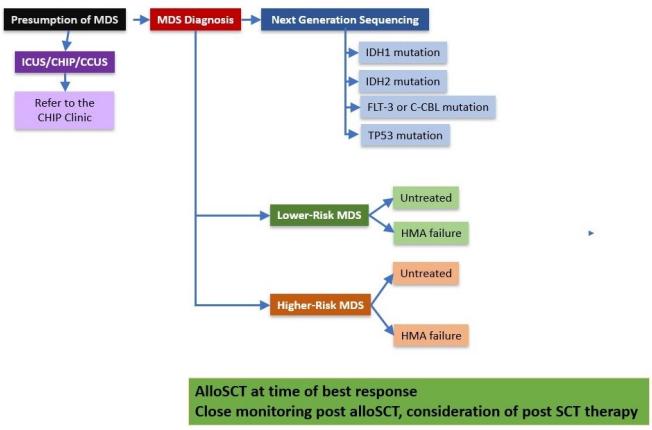


**Figure 1: Investigational treatment approaches in MDS at MD Anderson**. Expand image.

## Clinical Trials for Lower-Risk MDS Including ICUS/CHIP/CCUS

*Treatment of ICUS/CHIP/CCUS:* Individuals with ICUS have no genomic or cytogenetic alterations and likely have a very low risk of progressing to MDS or other myeloid malignancy. Patients with CHIP or CCUS have molecular alterations, in particular in the context of cytopenias (CCUS). We are developing a "CHIP Clinic" to follow such patients and to develop guidelines of care. An important finding associated with CHIP/CCUS is not only the increased risk of transformation to MDS/AML/MPN but also the collateral risk of associated comorbidities. Therapies directed towards those comorbidities, i.e. cardiovascular disease, are warranted. We are interested in evaluating patients with of ICUS/CHIP/CCUS in our center. Work by Simona Colla, Ph.D., and her group at MD Anderson has identified IL-1 as potential target in both CHIP/CCUS and lower-risk MDS. This work has received funding by the E.P. Evans Foundation. A study of canakinumab, an IL-1 inhibitor, is currently open at MD Anderson.

*Targeting IL-1 in Patients with Lower Risk MDS: A Phase I-II Trial of Canakinumab for Patients with Lower-Risk MDS.* Our group has extensively documented the role of altered innate immune signaling in MDS (3). One key cytokine is IL-1. Canakinumab is a potent inhibitor of IL-1 that is currently approved for rare inflammatory disorders. This study is first accruing patients already treated with an HMA. This is an important study because this agent not only targets MDS but also can impact concomitant comorbidities known to affect outcomes in MDS. In addition, MD Anderson is participating on a trial of the combinations of MBG453, NIS793, and canakinumab in this patient population.

*Front-line treatment of Isolated Anemia in Lower-Risk MDS: The COMMANDS Trial.* This is a trial of luspatercept versus erythropoiesis stimulating agent (ESA) for red cell transfusion-dependent lower-risk MDS. Luspatercept is a TGF-b modulator approved in 2020 for patients with refractory anemia with ringed sideroblasts (RARS) who had already been treated with an ESA (1). This drug is not approved for other types of MDS. COMMANDS could serve as the registration trial of luspatercept for all patients with lower-risk MDS.

*Targeting Lower-Risk MDS with Oral Hypomethylating Agents: ASTX727 and ASTX030.* One of the major developments in 2020 was the approval of ASTX727 (decitabine/cedazuridine), an oral form of decitabine, for patients with MDS (4). Our

group has pioneered the use of attenuated schedules of HMAs in lower-risk MDS. At ASH 2021, we presented data with the initial results of ASTX727 in lower-risk MDS. The ORR was 56%, rates of transfusion independence were 66% to 48% and survival had not being reached with a median follow up of 32 months. Early mortality was 0%. We are currently studying a shortened, three-day schedule of ASTX727. ASTX030, discussed below, is a combination of cedazuridine and azacitidine.

*Targeting ALK2 in Lower-Risk MDS*. ALK2 is a kinase that regulates hepcidin, a key molecule in hemoglobin regulation. We are investigating INCB000928, an ALK2 inhibitor, for patients with lower-risk MDS. This study is a phase 1 trial open to patients who have failed other options for anemia such as growth factors, luspatercept or other investigational agents.

*Fostamatinib in Lower-Risk MDS.* Fostamatinib is a spleen tyrosine kinase inhibitor approved for patients with ITP. Work performed at MD Anderson by Yue Wei, Ph.D., and others has suggested that this pathway could also be important in patients with anemia and thrombocytopenia. Our study is exploring the safety and clinical activity of fostamatinib in this group of patients.
Other agents being studied in lower-risk MDS include: roxadustat, the antiCD47 antibody magrolimab and the BRG1/BRM inhibitor FHD-286.

## Clinical Trials for Previously Treated Higher-Risk MDS

The standard of care for a majority of patients with higher-risk MDS still is single-agent HMA. A number of clinical trials are challenging this concept.

*New Oral HMA: ASTX030 (Oral Azacitidine + Cedazuridine).* In addition to the recent development of ASTX727, described above, ASTX030 is a combination of azacitidine and the cytidine deaminase inhibitor cedazuridine. The goal of this study is to develop an oral HMA pharmacokinetically identical to standard parenteral azacitidine. Such an agent will be transformative in MDS.

*Incorporating Immune Checkpoint Inhibitors in Higher-Risk MDS: Targeting TIM-3.* TIM-3 is a checkpoint inhibitor present both in T cells and leukemia stem cells. MBG453, or sabatolimab, is a TIM-3 inhibitor being studied in several trials internationally. MD Anderson is actively participating in these studies. Preliminary data presented at ASH in 2021, indicated an ORR of 57% with a complete remission duration of 19 months and an excellent toxicity profile.

*Targeting BCL-2 in MDS:* The addition of venetoclax, a BCL-2 inhibitor, to an HMA has transformed the care of patients with AML. Several studies are evaluating combinations of venetoclax in MDS. This is an area of significant interest at MD Anderson. Data to be published in Nature Medicine by Simona Colla, Ph.D., and her colleagues identifies subsets of patients that may benefit from this combination. This is being prospectively studied in our center and is supported by the MDAS/AML Moon Shot. MD Anderson is participating in the Verona trial. This is the pivotal registration trial of azacitidine with or without venetoclax in front-line, higher-risk MDS. In addition, MD Anderson is studying total oral combinations of decitabine/cedazuridine with venetoclax and also in a phase 1 trial of azacitidine and venetoclax. These last 2 studies were presented at ASH 2021 and showed ORR from 90% to 100% with OS not reached at the time of presentation.

*Targeting CD47 in MDS.* Investigators at Stanford identified CD47 as a key molecule controlling phagocytic activity of macrophages. A number of monoclonal antibodies are targeting CD47 in MDS. MD Anderson is a part of the ENHANCE trial, a phase 3 randomized study of azacitidine +/- magrolimab in higher risk MDS. Early data with magrolimab in MDS was very encouraging. In addition, we are also testing second-generation antiCD47 antibodies

such as ALX-148. Data presented at ASH in 2021 indicated a safe profile and activity in patients with poor-risk disease.

Other studies in front-line, higher-risk MDS include combinations with cladribine, fludarabine and venetoclax, as well as combinations with decitabine. Another combination includes oral decitabine with the nuclear transport inhibitor eltanexor.

**Clinical Trials for Patients with Higher-Risk MDS Previously Treated with an HMA**

The prognosis of patients with HMA-failure MDS is poor. No drug is approved for these patients. This critical area of research is a high priority at to MD Anderson and is supported by the MDS/AML Moon Shot.

*Targeting BCL-2 in HMA Failure MDS:* One common question is the potential addition of venetoclax in HMA failure. We have two studies evaluating this concept. Data presented at ASH 2021 indicated a high rate of response but rare complete responses. Range of OS was 8.5 to 10.5 months, which could be better than previously reported data in front-line randomized studies (5).

*Role of Chemotherapy in HMA Failure HR MDS: Role of Lower Doses of CPX-351.* Our group reported that a specific subset of patients with HR MDS HMA failure with diploid cytogenetics can benefit from lower doses of conventional AML-like therapy (6). CPX-351 is approved for patients with AML. In this phase 1 study, we are investigating attenuated schedules of this active compound in diploid patients with HR MDS already treated with an HMA.

Other studies include strategies targeting CD70, single agent eltanexor for HMA failure and combination of the LSD1 inhibitor seclidemstat. In addition, patients may be candidates for multiple phase 1 trials. One trial of interest is the study of the IRAK4 inhibitor CA-4948. This drug also has activity in Flt-3 mutated disease. Data presented at EHA 2021 indicated that this agent has significant clinical activity. We are now combining this agent with azacitidine and venetoclax.

**Incorporating Precision Medicine in MDS**

One of the major advances in research in MDS has been the incorporation of next generation sequencing assays in the clinic. This data not only allows better understanding and prognostication of the disease but also better design of targeted approaches for patients with MDS. Genes of interest include IDH2, IDH1, Flt-3, C-CBL and p53 (see Figure 1).

*Targeting IDH1.* IDH1 and IDH2 are mutated in MDS in 5% to 15% of patients, respectively. Initial data in AML studies that included a small group of patients with MDS suggested significant activity of IDH inhibitors. A multicenter Phase 2 trial of the IDH2 inhibitor with or without azacitidine led by MD Anderson showed significant activity of enasidenib in MDS, both in front line and relapsed disease (Venugopal EHA 2021). We are now studying combinations of ivosidenib and CPX-351 in higherrisk, IDH1-mutated disease.

*Targeting Flt3 in MDS:* Despite the fact that Flt-3 mutations are rare in patients with MDS, they have been shown to occur in 15% to 30% of patients with HMA failure. Those patients tend to have leukocytosis. Data from an add-back study indicated significant activity with the addition of the Flt-3 inhibitor sorafenib to azacitidine in patients with HMA failure. We are now expanding this observation with a study combining azacitidine and quizartinib. Of note, this drug also targets mutations in the *C-CBL* gene. Initial results presented by Dr. Guillermo Montalban-Bravo at ASH 2021 indicated a high level of activity with this combination in relapsed Flt-3 + disease. Other studies include the combination of decitabine, venetoclax and quizartinib.

*Targeting P53.* Mutations of the p53 gene have been reported in close to 10% of patients with

MDS, most of whom have therapy-related disease, complex cytogenetics and, therefore, a poor prognosis. These patients tend to be resistant to conventional chemotherapy and, although sensitive to HMA-based therapy, responses are short and the prognosis still dismal. At MD Anderson, this group of patients constitutes close to 30% of our referrals. We had studied the compound APR-246 all the way to phase 3 trials. We are now exploring an oral version of this compound knowns as APR-548.

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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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