Leukemia insights

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In this month's Leukemia Insights newsletter, written by Jayastu Senapati, M.D., Nicholas Short, M.D., and Tapan Kadia, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we discuss the ongoing maintenance therapy and MRD eradication approaches in AML being investigated at MD Anderson Cancer Center. Learn more about our Leukemia program.

MRD Eradication and Maintenance Strategies in Acute Myeloid Leukemia

Despite attainment of morphologic and even measurable residual disease (MRD) negative remission in acute myeloid leukemia (AML), 5-year relapse-free survival is <50% and allogeneic stem cell transplantation (SCT) remains the best consolidative therapy to reduce risk of relapse. Maintenance therapy with or without SCT can help control disease burden at the level of MRD or below the level of detection of MRD and increase remission duration. Maintenance therapy approaches in AML have evolved over the last 2 decades, and, today, they usually consist of chemotherapy-free regimens with molecularly targeted drugs, hypomethylating agents and checkpoint inhibitors, among others. The main aim of such therapies is to suppress residual disease below level of detection or to eradicate persistent or recurrent MRD after intensive or low-intensity induction/consolidation therapy.

Maintenance therapy is increasingly of interest for patients who are not able to proceed to SCT or in whom the risk of relapse, even after SCT, is high. Additionally, clearance of MRD before SCT has been shown to improve post-SCT outcomes. We encourage all patients with persistent or recurrent MRD to be enrolled on an MRD-directed clinical trial and recommend maintenance approaches for most patients who do not proceed to SCT. Oral azacitidine (CC486, ONUREG) is approved for post-remission maintenance after demonstrating an overall survival (OS) benefit, we are investigating the next generation of maintenance therapy approaches to build on this success. In this issue of Leukemia Insights, we discuss the ongoing maintenance therapy and MRD eradication approaches in AML being investigated at MD Anderson Cancer Center.

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Maintenance strategies in AML:

Ongoing clinical trials and approaches

1.Venetoclax and Azacitidine (NCT04062266)

The VIALE-A trial has established the efficacy of the combination of venetoclax with azacitidine in frontline therapy of older patients with AML. Furthermore, the phase 3 QUAZAR trial demonstrated the efficacy of CC-486 (oral azacitidine, not bioequivalent to parenteral azacitidine) in improving the overall survival of patients with AML in the maintenance setting. In this ongoing phase 2 study, adult patients with AML, not immediately eligible for SCT, who are in first remission after ≥2 cycles of intensive or lower-intensity chemotherapy, or beyond first remission but with persistent MRD, receive low-dose azacitidine (50 mg/m2 intravenous or subcutaneous) on days 1-5 plus venetoclax 400 mg on days 1-14 (doses can be adjusted for cytopenias), every 28 days for up to 24 cycles. Initial results from the trial with close to 2 years of follow up were presented at the American Society of Hematology (ASH) 2022 meeting and show promising safety and activity. The trial is recruiting patients.

2. Oral Decitabine and Genomics-Based Combination Approach (NCT05010772)

In this 5-arm phase 1b/2 study, adult patients with AML in first remission post intensive remission induction therapy and at least one cycle of intensive consolidation therapy, OR post at least two cycles of low-intensity therapy and not candidates for immediate stem cell transplant (SCT) will receive either oral decitabine alone, or oral decitabine in combination with one of 4 orally bioavailable targeted agents based on the baseline genomic drivers of their AML: gilteritinib for FLT3 mutated, enasidenib for IDH2 mutated, or ivosidenib for IDH1 mutated AML. Oral decitabine plus venetoclax is the 5th arm for patients without targetable mutations. The trial plans maintenance for up to 24 months and is enrolling patients.

3. Eltanexor for Post-SCT Maintenance in AML (NCT02649790)

Eltanexor (KPT-8602) is an oral selective inhibitor of nuclear transport (XPO1) and has shown preliminary efficacy in myeloid malignancies. This phase I/II trial includes patients (Part H) with high-risk AML who will be enrolled with/without remission before a planned SCT and will receive the study drug as maintenance while in remission after SCT (to be started within 40-100 days of SCT). The study is recruiting patients.

4. Galinpepimut-S for maintenance therapy in AML in second remission (NCT04229979)

Galinepepimut-S (GPS) is a multivalent Wilms' tumor 1 (WT1) peptide vaccine. Vaccines directed against WT1 in AML have shown efficacy as maintenance agents to prolong relapse-free survival. GPS elicits a strong T-cell immune response (both CD8+ and CD4+) against WT1 protein which is a hallmark of AML leukemic stem cells. In this phase 3 multicenter open-label clinical trial, adult patients with AML in second remission and not immediately eligible for SCT, will be randomized to be treated either on the GPS arm or physician's choice of best available therapy (observation or hypomethylating agents and/or venetoclax and/or low-dose cytarabine). The primary objective of the study is to compare the overall survival with these approaches. The trial is recruiting patients.

5.Vibecotamab for MRD-positive AML (NCT05285813)

Vibecotamab (XmAb14045) is a bi-specific T-cell engager monoclonal antibody which contains a CD123 tumor binding domain and a CD3 T-cell binding domain. This agent has previously showed activity in low blast relapsed/refractory AML and is now being explored in MRD positive AML. This phase II clinical trial includes patients ≥ 18 years of age with AML in first or second morphologic remission who received at least one course of intensive chemotherapy or at least 2 courses

of lower-intensity therapy and have persistent or recurrent MRD positive (by multiparameter flow cytometry of ≥0.1%) with CD123 expression on blasts at ≥20%. The trial is recruiting patients, and preliminary efficacy data are encouraging.

Upcoming clinical trials

1. INTERCEPT (Investigating Novel Therapy to Target Early Relapse and Clonal Evolution as Pre-emptive Therapy in AML)

This is a multicenter phase 1b/2 clinical trial that will include an arm on which patients with AML who have MRD progression will be treated with genomically guided combination approaches for MRD eradication as follows: gilteritinib + venetoclax; low dose cytarabine + venetoclax; ivosidenib + venetoclax; oral decitabine (ASTX727) + venetoclax. This trial will open soon.

Please contact Dr. Tapan Kadia, Dr. Nicholas Short, Dr. Farhad Ravandi or any leukemia faculty for discussion of trials and potential participation of eligible patients.

***Table 1**: Ongoing clinical trials exploring maintenance regimens and MRD eradication strategies in AML at MD Anderson Cancer Center*

Clinical trial identifier and site	Experimental drug/combination	Setting
NCT04062266/ MD Anderson Cancer Center, Houston (Phase II)	▪ Venetoclax and azacitidine	• Adult patients (≥18 years of age) • Not immediately eligible for SCT • In first CR/CRi after ≥2 cycles of intensive chemotherapy or lower-intensity chemotherapy • ≥ second remission with persistent MRD
NCT 05010772/ MD Anderson Cancer Center, Houston (Phase Ib)	▪ Oral decitabine ▪ Oral decitabine + enasidenib ▪ Oral decitabine + gilteritinib ▪ Oral decitabine + ivosidenib ▪ Oral decitabine + venetoclax	• Adult patients (≥18 years of age) • Not immediately eligible for SCT • In first CR/CRi after ≥2 cycles of intensive chemotherapy, within 2 months of last consolidation cycle • In first CR/CRi after ≥2 cycles lower-intensity therapy
NCT02649790/ Multicenter (Phase Ib/II) [Experimental arm Part H]	▪ Eltanexor (KPT-8602):	• Adult patients (≥18 years of age) • Therapy initiation 40-100 days post SCT • CR/CRi at time of enrollment post-SCT with any of the following: a) MRD positive b) Evidence of morphological disease or MRD before SCT c) ≥CR2 before SCT, irrespective of disease status d) Adverse cytogenetics at AML diagnosis (as per ELN 2017 criteria)
NCT04229979/ Multicenter Randomized Open Label (Phase III) [REGAL trial]	▪ Galinpepimut-S *versus* ▪ Physician's choice of best available therapy: Observation (whereby palliative management with hydroxyurea is allowed), or HMA (decitabine or azacitidine), and/or Venetoclax, and/or LDAC	• Adult patients (≥18 years of age) • Not immediately eligible for SCT • In second CR/CRp (irrespective of MRD) a) Platelet> 20,000/ul b) Lymphocytes >300cells/ul c) ECOG 0-3
NCT05285813/ MD Anderson Cancer Center, Houston (Phase II) [AML MRD cohort]	• Vibecotamab (XmAb14045)	• Adult patients (≥18 years of age) • First or second morphological remission after at ≥ 1 course of intensive chemotherapy course or ≥ 2 courses of lower-intensity therapy • MRD positive by MFC at ≥0.1% • CD123 expression at ≥0.1%

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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