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Intergroup LEAP Trial (S1612): A Randomized Phase 2/3 Platform Trial to Test Novel Therapeutics in Medically Less Fit Older Adults with Acute Myeloid Leukemia

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AUTHORS CONTRIBUTION

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DISCLOSURE STATEMENT

The authors declare no competing financial interests.

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TO THE EDITOR

Therapeutic resistance and reduced chemotherapy tolerance offer challenges in older adults with acute myeloid leukemia (AML) [1, 2]. Such patients may receive low-dose cytarabine or DNA methyltransferase inhibitors ("hypomethylating agents") but unimpressive complete remission (CR) rates and modest survival improvement compared to supportive care alone [3–5] highlight the need for new, effective therapies. With a rapidly increasing number of drug candidates entering the clinic, their timely identification and validation is critically important.

Evaluating new AML therapies has well-recognized limitations particularly if relying on "promising results" from early-phase, single-arm studies as the foundation of late-phase randomized studies. These, in turn, are often non-confirmatory [6]. This drug testing paradigm is particularly inefficient when therapies need to be tailored to patient subsets, now commonly considered in AML [7]. Platform trials have been developed as a long-lived, versatile screening tool to accelerate drug testing and limit patients' exposure to inactive or harmful therapies [8]. To develop such a trial for medically less-fit older adults with AML, a working group was established with permanent representation from the Network Groups of the U.S. National Cancer Institute (NCI) National Clinical Trials Network (NCTN) conducting trials in adult leukemia (ALLIANCE, ECOG-ACRIN, and SWOG) and the Canadian Cancer Trials Group (CCTG). Chaired by SWOG, this group's efforts led to the Intergroup LEAP (Less Intense AML Therapy Platform) Trial (SWOG-led S1612; ClinicalTrials.gov: NCT03092674).

The aim of the study is to serve as a nimble platform through which to continually test novel agents and combinations in a manner that assesses efficacy and comparative survival benefit in this patient population. To do so, a rolling-arm study similar to the one recently described by Ventz and colleagues [9] was designed with inclusion of one additional feature. Rather than "simply" rolling *arms* in, a meta-unit approach is used with study "cassettes" – a term describing a bundle of curated study arms, including a control. Within any cassette, some arms may be activated only when accrual to other arms is suspended, allowing continued enrollment without pauses for analysis. The first cassette, in phase 2/3 design, includes four arms (three experimental arms plus control). A charter will be used by which new study cassettes will be added under the auspices of the S1612 working group, transparently vetted, and prioritized in concert with the NCTN Leukemia Committees, NCI Leukemia Steering Committee, and NCI Cancer Therapy Evaluation Program (CTEP) and Investigational Drug Branch (IDB). Although led by SWOG, investigators from any group can propose and champion an arm or cassette, making S1612 attractive to investigators across the NCTN.

Reflective of our intent to be as unrestrictive as possible and to provide treatment options for the real-world patient, relaxed inclusion criteria will be used. Any adult aged ≥60 years with previously untreated AML (excluding acute promyelocytic leukemia) or myelodysplastic syndrome with excess blasts-2 [10] will be eligible, regardless of organ function abnormalities, as long as deemed unsuited for intensive chemotherapy. Some patients may be ineligible for certain arms because of experimental arm-specific restrictions. Such patients will only be randomized between the arms for which they are eligible. If assigned to the control arm, these patients will not contribute to the evaluation of the experimental arm(s) for which they are not eligible. All patients must be eligible for at least one experimental arm. In the first cassette, age, performance status, and FLT3 mutation status will be used for randomization stratification. Over time, additional factors may be used as integral biomarkers to refine patient stratification or determine eligibility for individual study arms (e.g. for evaluation of targeted therapies).

By adding this cassette model to the rolling-arms design, we acknowledge the significant challenges related to clinical trial conduct such as regulatory matters, complexity of managing the matching of experimental and control cases when specific arms are temporarily closed, drug supply issues and the like. Additionally, intellectual property agreements can become too complex over the life of an indefinite rolling-arms design. Regulatory pathways for drug approvals require limits on the number of arms in the design. Moreover, utilizing more than four-to-eight arms in a rolling-arms design could become too cumbersome over prolonged trial operation. We believe that introducing new iterations of the trial in a cassette format will allow more ready adaptation to these considerations.

For our first cassette, the primary phase 2 objective is to determine, based on overall survival (OS), which of the experimental regimens, if any, should be tested further against the control regimen. Initially, several surrogates were considered for this purpose, including CR rate and event-free survival (EFS), which have served as endpoints in similar past studies. However, these surrogates were deemed problematic. Two trials conducted by the NCRI/MRC have shown that doubling in CR rates (the improvement of the early surrogate endpoint needed to continue to a full phase 3 trial) does not necessarily translate into improved survival [11, 12]. EFS captures the durability of morphological response, but EFS has not been validated as a surrogate of OS [13, 14]. Moreover, EFS may not be ideal as an endpoint if a large proportion of treated patients will experience disease progression, an event that is poorly defined in AML. Therefore, OS will be the primary phase 2 endpoint. Any and all regimens meeting the phase 2 threshold will move forward to phase 3 testing. The first cassette was design so that, if needed, phase 3 accrual to all experimental arms can occur simultaneously, potentially with arms at different stages of accrual (e.g. because they start at different times) and/or different accrual paces (e.g. because of differences in eligibility criteria). Prior to entering phase 3 testing, all regimens will be discussed with the U.S. Food and Drug Administration (FDA) regarding potential drug registration. The primary phase 3 objective will be to compare OS between the control arm and experimental arm(s) selected in phase 2. Patients accrued during the phase 2 portion of the trial will be used in the phase 3 analysis. Patients will remain on protocol therapy until completion of protocol therapy (if specified for the treatment arm), unacceptable toxicity, disease progression (unless it is felt that remaining on study treatment is in the best interest of the patient), or relapse.

As rolling-arm cassettes are added to, or dropped from, the study, the accrual rates to arms and timing of analyses may vary, and the statistical design for each cassette will be tailored according to the underlying science and logistical context. For example, if a pharmaceutical company partner wishes to participate only in the randomized phase 2 portion of a rolling-arms cassette because they want to lead the phase 3 study, there will be flexibility in planning cassettes to accommodate various stakeholder needs. The effect size of a targeted agent may vary by biology, and the cassettes can have statistical designs tailored to the context. Given the trial's dynamic nature, the prognostic and predictive factors of randomized patients may change over time. To control for this potential drift, only concurrently randomized patients will be evaluated in comparisons between arms. Introduction of new rolling-arms cassettes will also mitigate this problem.

By consensus, the initial control arm will be azacitidine because of its widespread use and general acceptance in the U.S. and Canada in the target patient population. In the future, if another regimen is determined to have improved OS compared to azacitidine, the study design will be modified and the control arm replaced. New cassettes may use a different control regimen as appropriate for the new therapies to be tested. Investigational agents used in the experimental arms will be provided by the NCI/CTEP under a collaborative agreement between the drug manufacturers and the NCI Division of Cancer Treatment and Diagnosis.

S1612 will provide a unique opportunity for laboratory-based correlative research, e.g. aimed at understanding molecular and biological features of AML, clonal evolution with treatment, and how measures of disease burden as assessed by molecular or flow cytometric methods correlate with treatment outcomes and possibly could serve as surrogate endpoints for clinical benefit or to direct therapy. Furthermore, in addition to gathering information about resource utilization, the trial will also evaluate the impact of novel therapies on patient-reported outcomes including global health-related quality-of-life and physical, emotional, social, and cognitive health via questionnaires and geriatric assessments. These investigational tools will serve to describe the baseline variability in these health parameters and evaluate the association between specific patient characteristics and treatment outcomes. While several scores have been developed to identify patients who may not tolerate intensive therapy [2], no existing tools provide an explicit, objective definition of being "medically less-fit" in the context of AML therapy. Data collected during the conduct of S1612 and possibly other trials may enable the development of such a definition, which may then become integral part of the trial's eligibility assessment.

The NCTN LEAP Trial is projected to open for enrollment before the end of 2017. With an estimated accrual of 35–40 patients per month, we anticipate this trial will become an important resource for drug testing in older adults with AML and central tool from the NCTN investigators to hasten the critical evaluation of new therapies for this difficult-to-treat subset of patients.

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