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POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Risk Stratified Treatment for Patients with Newly Diagnosed Juvenile Myelomonocytic Leukemia: A Phase 1/2 Non-Randomized Study of Trametinib and Azacitidine with or without Chemotherapy

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Background: Juvenile myelomonocytic leukemia (JMML) is an aggressive myeloproliferative disorder of childhood. The biochemical hallmark of JMML is aberrant signaling through the Ras pathway caused by initiating mutations in *NF1, NRAS, KRAS, RRAS, RRAS2, SH2B3, PTPN11*,or *CBL*. While hematopoietic stem cell transplantation (HSCT) can be curative, 5-year event-free survival of children with JMML after HSCT is only ~50%. Recently, several studies have identified mutational burden and DNA methylation as predictive of clinical outcomes in patients with JMML. In the T2020-004 phase 1/2 clinical trial, we will define lower-risk patients as those with one somatic alteration and low DNA methylation and high-risk patients as those with more than one somatic alteration or intermediate/high DNA methylation. Trametinib is an orally bioavailable, reversible, highly selective allosteric inhibitor of MEK1/2 in the Ras/MAPK signaling pathway. Trametinib is FDA-approved for the treatment of adults with advanced melanoma with *BRAF* V600E or V600K mutations and in children with Ras-mutant solid tumors in combination with dabrafenib. Clinical investigation of trametinib monotherapy via the Children's Oncology Group ADVL1521 phase 2 trial (NCT03190915) showed efficacy in children with relapsed/refractory JMML. Phase 2 clinical trial evaluation of azacitidine in children with newly-diagnosed JMML was also efficacious and led to its FDA approval. In this trial, trametinib will be tested in combination with azacitidine in lower-risk patients and in combination with azacitidine and chemotherapy for high-risk patients.
Study Design and Methods: This is a non-randomized, risk stratified, Phase 1/2 study for patients with newly-diagnosed JMML (NCT05849662) conducted via the Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) Consortium with safety and efficacy phases for both lower-risk and high-risk cohorts. Lower-risk patients will receive trametinib once-daily for 28 days in combination with azacitidine administered daily for five days per cycle. Lower-risk patients can receive up to 12 cycles and will proceed to HSCT only if they experience progressive disease or relapse. High-risk patients will receive trametinib administered once-daily for 28 days in combination with azacitidine, fludarabine, and cytarabine (aza/FLA) administered daily for five days per cycle. High-risk patients will receive up to two cycles of therapy before proceeding to HSCT off protocol.
Key Eligibility: Patients aged 1 month to 21 years who meet World Health Organization criteria for JMML will be eligible.
Objectives: The primary safety objectives are to determine the safety of combining trametinib with azacitidine for lower-risk patients and combining trametinib with aza/FLA for high-risk patients. The secondary efficacy objectives are to determine the event-free survival for lower-risk patients in the absence of HSCT and the molecular response rates pre-HSCT for high-risk patients.
Sample Size and Statistical Design: A rolling 6 trial design will be used during Phase 1 of the study to determine the recommended phase II dose (RP2D) of trametinib for lower-risk and high-risk patients in combination with their respective therapies. Starting trametinib dose is 0.032mg/kg daily if less than 6 years of age, or 0.025mg/kg daily if 6 years or older, with one dose level de-escalation if indicated. Phase II of the study involves lower-risk and high-risk cohort expansions at the RP2D

of trametinib. Target accrual is 22 patients in the lower-risk arm and 42 patients in the high-risk arm. The study is open to accrual at all TACL consortium sites.

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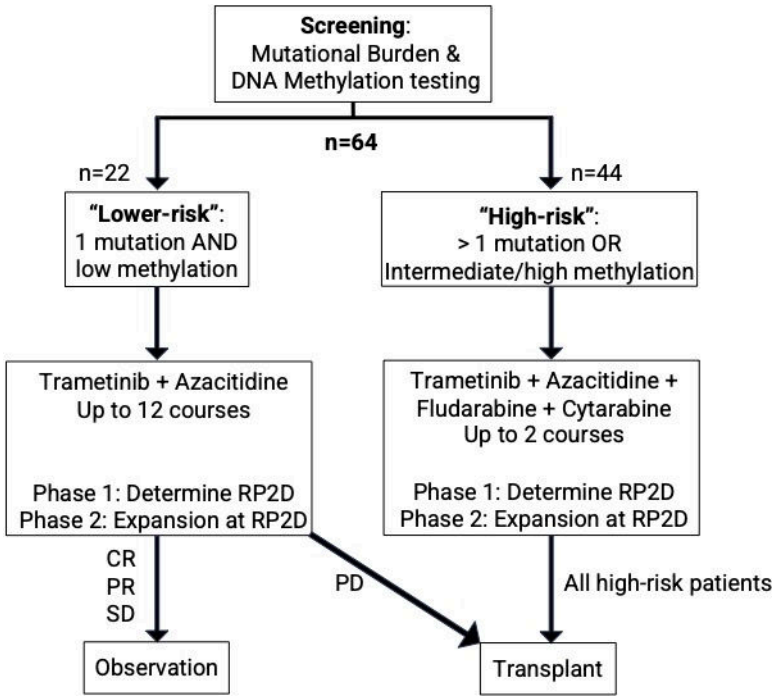

Figure 1

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