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ORAL ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Efficacy of the Allosteric MEK Inhibitor Trametinib in Relapsed and Refractory Juvenile Myelomonocytic Leukemia: A Report from the Children's Oncology Group

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Background: Juvenile myelomonocytic leukemia (JMML) is an aggressive myeloproliferative neoplasm of infants and toddlers. Upfront therapies typically include high-dose cytarabine or azacitidine, but the only definitive treatment is hematopoietic stem cell transplantation (HSCT). While HSCT cures ~50% of patients, the prognosis is dismal for those who relapse. In the absence of a second HSCT, patients who relapse have a 2-year overall survival of ~10%. JMML is initiated by germline and somatic driver mutations in *NF1, KRAS, NRAS, PTPN11, and CBL*. These mutations converge on Ras signaling, leading to elevated levels of active Ras-GTP in specific cell lineages. Genetically engineered mouse (GEM) models accurately model key molecular, biologic, and biochemical features of JMML. Preclinical trials of the allosteric MEK inhibitors in *Kras* and *Nf1* mutant mice demonstrated dramatic phenotypic responses with reduction in white blood cell counts, resolution of splenomegaly, and reversion to normal erythropoiesis. Based on the promising efficacy signal in GEM models, we evaluated trametinib, an orally bioavailable allosteric inhibitor of MEK1/2, in a prospective clinical trial in children with relapsed or refractory JMML to determine the overall response rate to trametinib.
Results: Ten infants and children with JMML (median age 23.6 months) were enrolled and all were evaluable for safety and efficacy. Patients received age-adjusted dosing of trametinib for 28-day cycles and could remain on study for up to 12 cycles in the absence of disease progression or toxicity. A clonal Ras pathway mutation was confirmed in the blood and/or bone marrow of all patients. The objective response rate was 50% (two complete and three partial clinical responses). Four patients proceeded to HSCT after receiving protocol therapy and remain alive in complete remission with undetectable levels of the Ras pathway mutation identified at enrollment. Three additional patients completed 12 cycles of trametinib and continue to receive off-protocol therapy 6-24 months later with no change in the variant allele frequency of the underlying Ras pathway mutation. The remaining three patients had progressive disease with two demonstrating molecular evolution by the end of cycle 2. Paired pre- and post-trametinib RNASeq and proteomic analyses confirmed on-target biochemical effects of trametinib with down-regulation of both Ras/MAPK pathway related gene expression and MEK1/2 kinase activity, respectively. To gain deeper insight into how trametinib might affect distinct populations of hematopoietic cells, we generated single cell RNASeq data before and after treatment. The most prominent finding was a reduction in the proportions of classical and non-classical monocytes and broad downregulation of immune-related pathways in all cell populations. However, the down-regulation of MAPK signaling genes was confined to specific cell types including, macrophages, classical monocytes, and granulocyte-monocyte progenitors, which uniquely displayed downregulated KRAS-related signatures following treatment. High DNA methylation and the presence of >1 mutation at enrollment correlated with lack of response to trametinib.
Conclusions: We conducted an open label, phase 2 trial of trametinib in children with relapsed or refractory JMML. This is the first completed study of a MEK inhibitor in any hematologic malignancy in children. The trial met its primary objective and

demonstrated a 50% objective response rate with 70% of patients bridging to a successful HSCT or completing the maximum 12 cycles permitted on study. The three patients who completed 12 cycles continue to receive trametinib off study for as long as 2 years. Although limited by a small number of patients, the long-term survival, and correlative molecular analyses from this trial raise provocative questions about whether certain patients with JMML might be spared the long-term adverse health risks of genotoxic HSCT conditioning regimens based on favorable molecular characteristics at diagnosis. This hypothesis will now be tested in a national, risk-stratified therapeutic trial (NCT05849662) of trametinib in combination with azacitidine in newly diagnosed patients.

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Disclosures No relevant conflicts of interest to declare.

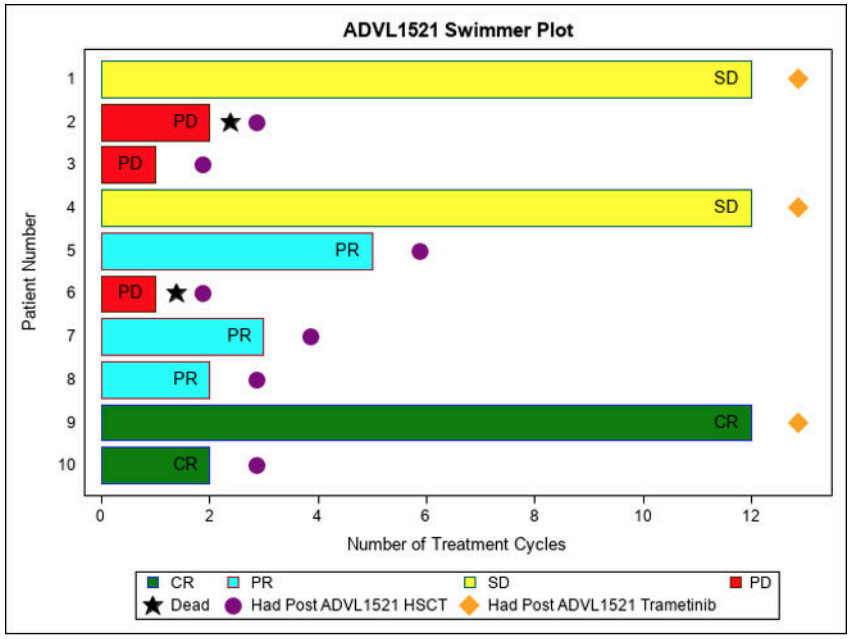

Figure 1. Responses and survival in relapsed/refractory JMML patients treated with trametinib. Swimmer plot demonstrating individual outcomes over time. Each row represents one patient. Outcomes are color-coded based on response as follows: Complete clinical response (CR; green); partial clinical response (PR; teal); stable disease (SD; yellow); and progressive disease (PD; red). Symbols indicate patients who received hematopoietic stem cell transplants (HSCT) after trametinib treatment (purple circles), continued trametinib without HSCT (tan diamonds), and/or died with progressive disease.

Figure 1

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