



## The 65th ASH Annual Meeting Abstracts

**ONLINE PUBLICATION ONLY****631.MYELOPROLIFERATIVE SYNDROMES AND CHRONIC MYELOID LEUKEMIA: BASIC AND TRANSLATIONAL****Responses to Combination Chemotherapy with MAPK Pathway Inhibition in Relapsed and Refractory LCH**

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MAPK pathway inhibition (MAPKi) is associated with high response rates in patients with Langerhans cell histiocytosis (LCH), but monotherapy may not be curative and efficacy in LCH-associated neurodegeneration (LCH-ND) is not known. Based on upregulation of Bcl-xL by MAPK activation, we hypothesize that MAPKi may render LCH cells more sensitive to chemotherapy-induced cytotoxicity.

We assessed the safety and efficacy of combination therapy in 10 patients with refractory systemic disease and LCH-ND. Records of patients treated with combination therapy at Texas Children's Hospital from October 2018 to July 2023 were reviewed for clinical responses as well as peripheral blood/tissue BRAFV600E mutation status, ataxia rating scores, and toxicity. The median age at the start of combination therapy was 6.82 years (range, 0.48-20.45 years) with a median of 4 treatments prior to this therapy regimen (range, 1-14). Almost all Clofarabine was administered outpatient (typical starting dose 25 mg/m<sup>2</sup>/day x 5 days). MAPK inhibitors included BRAFV600E inhibitors (50%) and MEK inhibitors (50%). Overall response was 8/10 (80%), with 5/5 (100%) objective response rate (ORR) for systemic disease. Further, 5/6 (83%) demonstrated reduced or extinguished peripheral BRAFV600E+ fraction by the end of combination therapy. Ataxia rating scores were improved in 2/3 (67%) individuals with clinical neurodegeneration. Common toxicities during treatment included fever, skin rash, arthralgia, and cytopenia. Combining therapy was well-tolerated and associated with clinical and molecular improvement in most patients with highly refractory systemic LCH and LCH-ND. Further prospective multi-center trials are required to optimize this approach, determine potential for combination therapy to achieve cure, and compare risks and benefits to chemotherapy or MAPK inhibitor monotherapy.

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