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A Phase I Trial of Tazemetostat and Venetoclax in Relapsed and Refractory non-Hodgkin Lymphoma

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OBJECTIVES/GOALS: Primary Objective: To evaluate the safety of venetoclax plus tazemetostat in patients with relapsed and refractory (R/R) Follicular lymphoma (FL) or Diffuse large B-cell lymphoma (DLBCL) Secondary Objectives: 1. To evaluate the tolerability of the combination of T+V using patient reported outcomes (PROs) 2. To evaluate the efficacy of T+V METHODS/STUDY POPULATION: Study design: A phase I trial in two parts: Part 1: a single-arm, open-label sequential dose escalation (3+3) of venetoclax in combination with tazemetostat, given at its recommended phase II dose (RP2D) of 800mg BID, to determine the maximum tolerated dose (MTD) of venetoclax. Part 2: two expansion cohorts (R/R DLBCL and R/R FL) to further characterize the safety and tolerability of the combination, and to estimate the preliminary efficacy. We will perform additional exploratory studies to determine if there are biologic features that correlate with responses. Eligibility: up to 38 patients aged >/=18 years old with histologically confirmed diagnosis of FL or DLBCL who have received at least 2 prior lines of therapy for lymphoma with evidence of disease progression and meet inclusion criteria RESULTS/ANTICIPATED RESULTS: Primary Endpoints: 1. Incidence and severity of adverse events as per CTCAEv5 2. Dose-limiting toxicity (DLT) of T+V, and to establish the maximum tolerated dose (MTD) of V plus fixed dose T Secondary Endpoints: 1. Incidence and Severity of toxicity and quality of life as per PRO-CTCAE and FACT-Lym 2. Overall response rate (ORR), complete response (CR) rate, partial response (PR) rate, as per Lugano criteria 3. Duration of response (DOR), progression-free survival (PFS), overall survival (OS)Exploratory Endpoints: 1. Characterization of tumor cells pre-treatment (including EZH2 mutations and BCL2 translocations) 2. Phenotypic analysis (including BCL2 expression) and quantification of the tumor microenvironment in pre-treatment samples (using image mass cytometry)Explorato DISCUSSION/SIGNIFICANCE: There is a need for novel therapeutic approaches to improve the prognosis for patients with R/R NHL. Preclinical data suggests synergism between the pair.5 Importantly, this represents a chemotherapy-free, oral regimen. If well tolerated, this could present an alternative therapeutic option for patients ineligible for more intensive therapies.

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Influence of a Gastrointestinal Infection on Lung Immunity*

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OBJECTIVES/GOALS: We aim to characterize how Heligmosomoides polygyrus bakeri (H. poly) alleviates murine allergic asthma which shares many characteristics of human asthma. This approach of has already identified helminth-produced human immune cell ligand “mimics” that hold great potential for next-generation clinical biologics METHODS/STUDY POPULATION: We examined the lung tissue of C57BL/6 mice infected with H. poly for changes in the pulmonary microenvironment. At ten days post infection, four infected mice and two co-housed uninfected mice were sacrificed, and their lung tissue harvested for examination of RNA via RT-qPCR. This design allows for the comparison between the lung microenvironments of infected and naïve mice. In future experiments, we intend to characterize what small molecules produced by the helminth drive changes in the lung using germ-free models of H. poly infection. RESULTS/ANTICIPATED RESULTS: We found key differences in lung chemokines between mice infected with H. poly and naïve mice. Using a student t-test with naïve correction for variance, we were able to show significant differences in the expression of E cadherin ($p = 0.0355$), CXCL10 ($p = 0.0025$), CX3CL1 ($p = 0.0029$), CCR2 ($p = 0.017$), and IDO1 (0.0078). We also found that differences in the expression of CCL5 bordered on significant with a p-value of 0.066. The expression of most of these markers (CXCL10, CCR2, CCL5, and IDO1) was elevated in the lungs of infected mice compared to naïve controls. In contrast, E cadherin and CX3CL1 showed the opposite trend with naïve mice showing greater expression. These clear differences in lung tissue gene expression underscore the connection between the gastrointestinal and pulmonary mucosal immune compartments. DISCUSSION/SIGNIFICANCE: The changes are unexpected for an infection that has been shown to attenuate allergic inflammation in the lung with increases in the IFN-Y responsive genes IDO1 and CXCL10 and inflammatory lung markers, CCL5 and CCR2. In contrast, there were decreases in inflammatory lung marker CX3CL1 and the tight junction protein E cadherin in infected mice.

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Changes in Lipid Profiles with Progression of Pregnancy in Black Women

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OBJECTIVES/GOALS: Pregnant African American (Black women) have higher rates of adverse pregnancy outcomes compared to other races and routine monitoring of lipid levels is not currently in practice in prenatal care. We hypothesized that lipid profiles would show variation across pregnancy indicative of specific requirements during gestation and fetal development. METHODS/STUDY POPULATION: We used an untargeted lipidome analysis approach to investigate lipid metabolism with the progression of pregnancy. Pregnant Black women were recruited at prenatal clinics in Midwest (Metro Detroit, Michigan and Columbus, Ohio), women under 18 or above 45 years of age were not enrolled due to metabolic changes associated with these age groups. Women signed the consent forms and plasma samples were collected at 8-18 weeks at (T1), 22-29 weeks (T2) and 30-36 weeks (T3) of pregnancy. Samples from sixty-three women (mean age 27.41 ± 5.61 years) who had term birth (completed 37 weeks of pregnancy) were subjected to “shotgun” Orbitrap high resolution/ accurate mass spectrometry. Mixed-effects models were used to quantify systematic changes in relative lipid abundances over time using R lme4 and ggplot2 packages. RESULTS/ANTICIPATED RESULTS: Total lipids and some major lipid classes showed a significant increase with the progression of pregnancy. Phospholipids and glycerolipids exhibited a gradual increase throughout pregnancy, while sphingolipids and total sterol lipids displayed a more pronounced increase at the T3 timepoint. Acylcarnitines, hydroxy acylcarnitines and Lyso phospholipids levels significantly decrease from T1 to T3. One of the interesting finding was that non-esterified fatty acids decreased from T1 to T2 and

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