A Pilot study of Siltuximab in Large Granular Lymphocytic Leukemia (LGLL) – Trial in Progress

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Background

Large granular lymphocytic leukemia (LGLL) is a rare, indolent malignancy arising from cytotoxic T cells (T-LGLL, ~85%) or NK cells [chronic NK-cell lymphoproliferative disorder (CLPD-NK), ~15%]. Although asymptomatic patients (pts) can be observed, the majority of pts will develop cytopenia and require treatment. Current treatment strategy using immunosuppressive doses of methotrexate, cyclophosphamide, or cyclosporine A has modest efficacy and the responses are usually not durable. Relapsed/refractory pts have limited options. Prospective trials on LGLL are few and no agent has been approved by FDA.

Interleukin-6 (IL-6), a prolinflammatory cytokine, plays an important role in the pathogenesis of LGLL. IL-6 activates JAK/STAT3 pathway via binding to IL-6 receptor (IL-6R), causing resistance to apoptosis and persistent clonal expansion of the LGL cells. Blocking IL-6 *in vitro* decreased activation of STAT3 and resulted in apoptosis of LGLL cells (Teramo A et al. Blood 2013). These effects were independent of the STAT3 mutation status.

Siltuximab is a chimeric mAb against human IL-6. It is currently approved for treatment of idiopathic multicentric Castleman disease (iMCD). We hypothesize that siltuximab, by blocking IL-6, will inhibit intracellular signaling via IL-6R/JAK2/STAT3 activation pathway in LGLL and induce a durable response.

Study Design and Methods

This is a single arm, single center, open label study evaluating the safety and efficacy of siltuximab in LGLL (NCT05316116). Main eligibility criteria include following: adults ≥ 18 YO with a diagnosis of LGLL (either treatment naïve or previously treated) and meeting the prespecified criteria for treatment. Pts with coexisting myelodysplastic syndrome (MDS) are excluded. Up to 20 pts will be enrolled in two stages. Siltuximab will be given at a dose of 11mg/kg (the FDA approved dose for MCD) IV every 3 weeks for up to 12 doses. The primary efficacy endpoint is the overall response rate (ORR) including complete response (CR) and partial response (PR). The main secondary endpoints include the safety of siltuximab in LGLL, duration of response, time to response, CR rate, and progression-free survival (PFS). Correlative studies include STAT3 mutation status, plasma cytokine levels, and whole exome sequencing of sorted malignant LGLs.

Study Progress

Three pts have been enrolled on the study at the time of submission of this report. No new safety signal was observed.

The study is actively recruiting at Moffitt Cancer Center, Tampa, FL.

Contact for trial information or patient referral:

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