Background: Somatic isocitrate dehydrogenase 1 mutations (IDH1m) convert α-ketoglutarate to the oncogenic metabolite R-2-hydroxylglutarate (2-HG). IDH1m are detected in approximately 13% of intrahepatic cholangiocarcinomas (CCAs). 1 Ivo-sidenib, an oral inhibitor of the IDH1m protein inhibits 2-HG and restores immune response in CCA. 2 We analyzed pre-treatment samples, using machine learning models to quantify histologic features of the CCA tumor microenvironment, enabling identification of correlates of IDH1m status, early disease progression (patients experienced progression or death within 1.54 months), and plasma 2-HG levels (median, 630 ng/ml).

Methods: A set of H&E images, including from ClarIDHy, 3 a phase 3 placebo controlled clinical trial of ivosidenib in IDH1m CCA, were split into training/validation (n=200) and test sets for model development. Whole slide images were annotated by GI pathologists to identify and quantify more than 500 different human interpretable features (HIFs), including cell (cancer cell, lymphocyte, macrophage, plasma cell, fibroblast) and tissue (cancer epithelium, stroma, necrosis) features. Utilizing IDH1m and wild type (WT) screening samples, multivariate logistic regression models were trained to predict IDH1m status. P-values were calculated by univariate logistic regression and corrected for multiple comparisons via adjustment for FDR.

Results: A HIF-based multivariate model discriminated between IDH1m and WT CCA (AUC, 0.83; 95% CI, 0.74-0.92). IDH1m was associated with a lower proportion of lymphocytes throughout the tumor (OR, 0.64; P<0.01; FDR P=0.022), and higher proportion of fibroblasts (OR, 1.8; P<0.01; FDR P=0.023) and lower proportion of plasma cells in the stroma (OR, 0.68; P<0.01; FDR P=0.032 ) (figure 1A). In a subset of samples, CD3 and CD8 staining showed reduced T-lymphocyte infiltration patterns in IDH1m (n=5) samples relative to IDH1 WT (n=19) (figure 1B). Early disease progression of enrolled ClarIDHy patients (ivosidenib n=61, placebo n=38) was associated with a higher proportion of macrophages (OR, 1.70; P<0.01; FDR P=0.08) and a lower proportion of tumor infiltrating lymphocytes (OR, 0.63; P<0.01; FDR P=0.08), (figure 2A). When correcting for treatment effect, the proportion of lymphocytes in the tumor were still associated with improved PFS (P=0.011). Consistent with previously published data2, high 2-HG levels were associated with lower numbers of tumor infiltrating lymphocytes (OR, 0.63; P=0.011; FDR P=0.08) (figure 2B).

Conclusions: Quantitative histologic evaluation suggests that pre-treatment IDH1m CCA samples have a colder tumor microenvironment relative to IDH1 WT CCA, with an immunosuppressive tumor microenvironment being associated with early progression. Results from this analysis support exploration of combination with immune checkpoint inhibitors.

REFERENCES:
Differences in CCA tumor microenvironment. Differences in CCA tumor microenvironment based on early disease progression and pre-treatment plasma 2-HG levels. (A) Pre-treatment screening samples from 99 (ivosidenib cohort n=61, placebo cohort n=38) patients treated on the ClarIDHy study were analyzed for association with early disease progression, defined as experiencing progression or death within 1.54 months (47 days) (PFS<1.54 months). Early disease progression was associated with lower proportions lymphocytes over immune cells in cancer epithelium (Upper Row) and higher proportions of macrophages (Bottom Row) over immune cells in cancer epithelium. (B) Plasma 2-HG levels were available for 100 IDH1m patients, with sample groups separated based on the median plasma 2-HG level (630 ng/ml). Higher plasma 2-HG levels were associated with lower proportions of lymphocytes in CCA tumor. Uncorrected P values are displayed on the Figures (A and B).