Transcriptional Analysis of Colonic Biopsies from Patients with Ulcerative Colitis Treated with Omilancor

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Introduction. Omilancor is an oral, gut-restricted, first-in-class LANCL2 agonist for ulcerative colitis (UC) and Crohn's disease (CD). Through LANCL2 activation, omilancor locally increases the suppressive capacity of regulatory immune cells, including regulatory CD4+ T cells (Tregs), and restores metabolic deficiencies in the intestinal mucosa. Once daily omilancor was well tolerated up to doses of 7500 mg/day for one week in a Phase I study in healthy volunteers.

Methods. In a Phase 2, proof-of-concept, double-blind, parallel-group study, adult patients with Mayo Clinic scores (MCS) of 4 – 10 and endoscopic subscores of 2 or more were randomly assigned to groups given omilancor 440 mg QD, omilancor 880 mg QD or placebo for 12 weeks. Biopsies from a subset of patients pre- and post-treatment were randomly selected for transcriptional analysis. Differentially expressed genes by treatment and remission status were identified by DESeq. Predictive signatures were identified by RandomForest.

Results. Differentially expressed genes upregulated by omilancor relative to baseline and placebo were associated with lipid metabolism and ion balance in addition to known elements of the LANCL2 pathway. Meanwhile, downregulated genes were associated with immune system processes, primarily those in relation to neutrophils and leukocyte trafficking. Predictive modeling of gene expression changes from baseline were able to differentiate patients treated with omilancor from those given placebo with 83% accuracy. Notably, patients treated with omilancor and achieving clinical remission were identified with 100% accuracy. Using baseline gene expression only, a predictive model was generated to classify patients based on likelihood to experience clinical remission following omilancor induction therapy. The 7-gene predictive model was able to classify week 12 remission status with 75% accuracy for both patients who achieved clinical remission and those that did not.

Discussion. Treatment with omilancor results in consistent mechanistic transcriptional changes locally with the colon. Clinical response to omilancor treatment is associated with a baseline gene expression signature with the potential to serve as a companion precision immunology biomarker of response to treatment upon further clinical testing and validation.

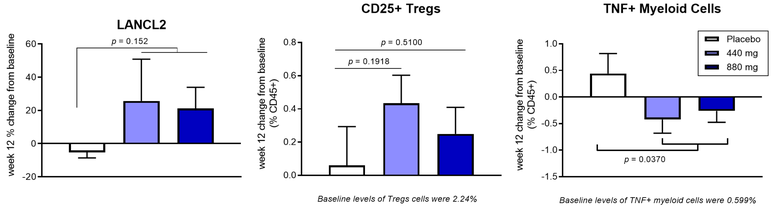

Figure 1. LANCL2 gene expression and colonic flow cytometry

Omilancor treatment at 440 mg or 880 mg provided equal upregulation of LANCL2 gene expression following 12 weeks of oral treatment relative to baseline (**Fig. 1**). LANCL2 expression did not vary in the placebo group. Within colonic biopsies, omilancor treatment notably increased the proportion of CD25^{hi} Tregs and decreased the proportion of TNF+ myeloid cells relative to both baseline and placebo treatment.

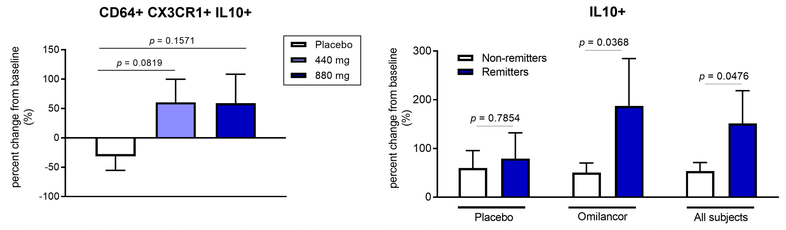

Figure 2. Association of regulatory resident macrophages cells with omilancor

Additionally in colonic biopsies, omilancor treatment increased the proportion of tissue resident regulatory macrophages (**Fig. 2**) and resident memory T cells (**Fig. 3**) relative to baseline. The production of IL10+ from regulatory cells was associated with remission in omilancor treated patients only, while an increase in resident memory T cells was associated with remission across all groups.

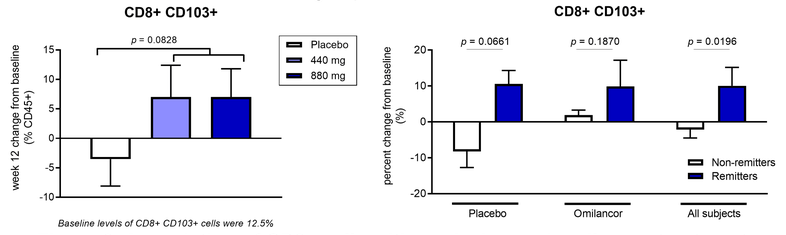

Figure 3. Association of CD8+ cells with remission and omilancor treatment

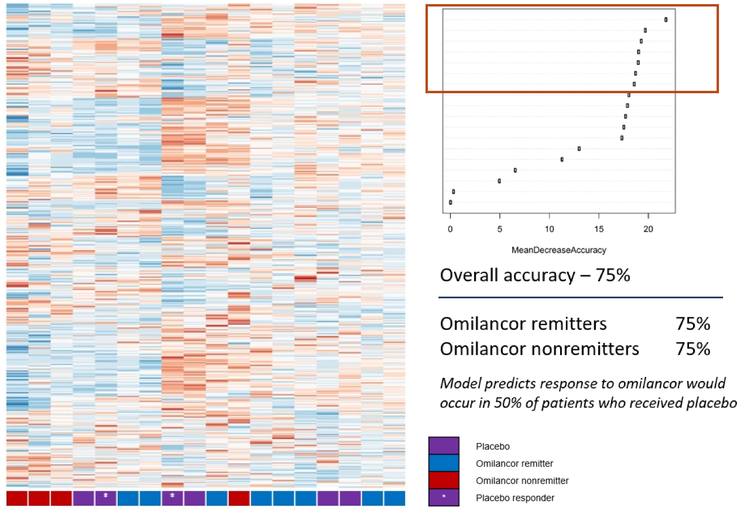

Figure 4. Baseline gene expression

Analysis of gene expression levels at baseline identified a stark contrast between patients who experienced clinical remission after 12 weeks of omilancor treatment and those that did not (**Fig. 4**). When the total differentially expressed gene set was reduced to a panel of 7 genes to create a predictive model, the sensitivity and specificity were 75%. Also, the model had no predictive value in predicting placebo response, suggesting accuracy based upon the mechanisms of the LANCL2 pathway.

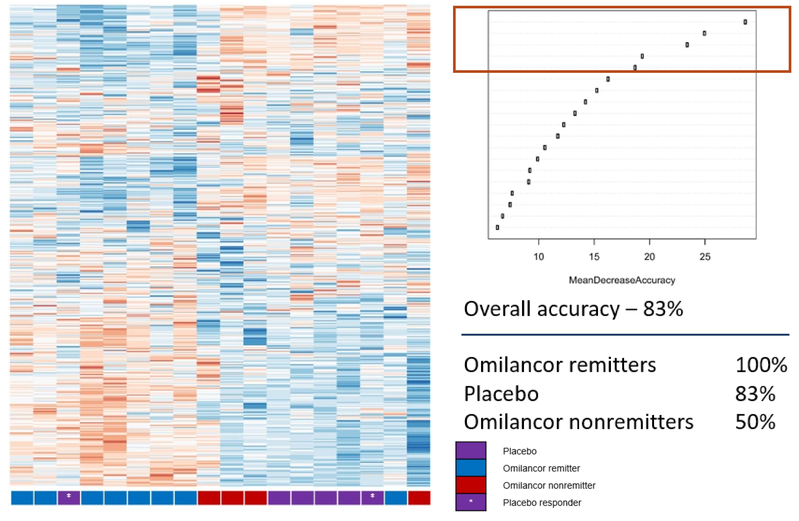

Figure 5. Week 12 change from baseline gene expression

Similarly, the analysis of gene expression trends at week 12 (normalized to expression at baseline) resulted in a division of omilancor responders versus nonresponders and placebo patients (**Fig. 5**). When a predictive model was created from 5 genes, omilancor treated patients who experienced clinical remission at week 12 were identified with 100% accuracy. This observation was validated by PCA (**Fig. 6**), wherein responders were clearly separated from the other groups. Functionally, the differentially expressed genes at Week 12 were associated with key immune system functions including activation, proliferation and recruitment in addition to metabolic and ion transport pathways.

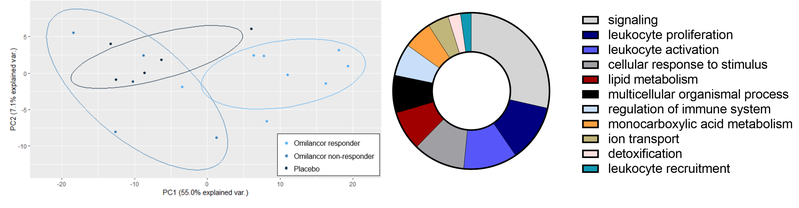

Figure 6. PCA and enrichment of differentially expressed genes by treatment