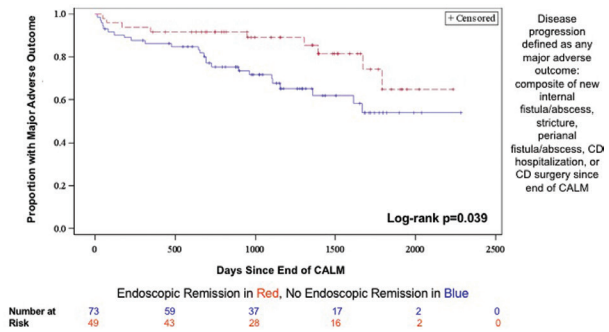
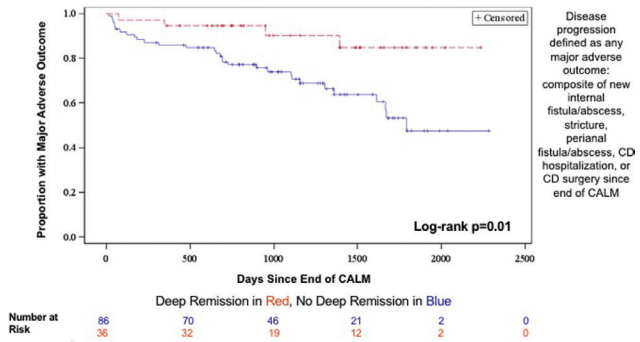


Abstract OP35 – Figure 1. Kaplan–Meier estimates of CD disease progression based on endoscopic remission at 1 year



Abstract OP35 – Figure 2. Kaplan–Meier estimates of CD disease progression based on deep remission at 1 year.

Methods: We analysed medical records from patients with follow-up data since end of CALM. Patients were stratified by outcomes in CALM at 1 year: clinical remission (Crohn's disease activity index, CDAI <150), endoscopic remission (Crohn's disease endoscopic index of severity, CDEIS <4 with no deep ulcerations), and deep remission (CDAI <150, CDEIS <4 with no deep ulcerations, and no steroids for ≥8 weeks). The primary outcome was a composite of major adverse outcomes reflecting CD progression: new internal fistula/abscess, stricture, perianal fistula/abscess, CD hospitalisation, or CD surgery since end of CALM. Kaplan–Meier and Cox regression methods were used to compare composite rates between patients who achieved or did not achieve remission at 1 year. Adjusted hazard ratios (aHR) with 95% confidence intervals (CI) are reported, controlling for randomisation arm and baseline variables significant at $p < 0.2$ level.

Results: One hundred twenty-two patients with median age 29 years (IQR 22.5–37) and median disease duration 0.2 years (IQR 0.1–0.8) were included. Median follow-up time from end of CALM was 3.02 years (range 0.05–6.26 years). Fifty per cent were randomised to the tight control arm. There were no significant differences in baseline characteristics in patients with follow-up data and those lost to follow-up with the exception of a slightly higher CDEIS score in patients lost to follow-up (14.6 vs. 12.9, $p = 0.04$). Thirty-four patients (27.9%) had a major adverse outcome during follow-up. Patients in clinical remission at 1 year did not have significantly lower rates of the composite endpoint (log-rank $p = 0.15$). Patients in endoscopic and deep remission at the end of CALM were significantly less likely to have a major adverse event over time (Figures 1 and 2). After adjusting for age, disease duration, prior surgery, prior stricture, and randomisation arm, endoscopic remission (aHR 0.44, 95% CI 0.20–0.96, $p = 0.038$) and deep remission (aHR 0.25, 95% CI 0.09–0.72, $p = 0.01$) were significantly associated with lower risk of major adverse events.

Conclusions: Early CD patients who achieve endoscopic or deep remission after 1 year of intensive treatment are less likely to have disease progression over a median of 3 years.

OP36

A colonic gene expression signature predicts non-response to anti-inflammatory therapies in inflammatory bowel disease

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Background: The ability to predict response to therapy in inflammatory bowel disease (IBD) is a significant unmet need. We previously described PROgECT, a Phase 2a open-label study of patients with moderate-to-severe ulcerative colitis (UC), which prospectively validated the ability of a molecular profile score (MPS) consisting of a colonic 13-gene expression panel to predict response to TNF-antagonist therapy. Although the MPS had low specificity in predicting responders to therapy, we evaluated whether the MPS could be a useful tool in accurately identifying a subset of non-responder patients to therapy.

Methods: We evaluated the sensitivity and specificity of the MPS in identifying non-responders to therapy in four independent TNF-antagonist trials (ACT1, PURSUIT-SC, PROgECT, PURSUIT-J) and an anti-IL12/23 trial (UNITI). We also characterised the gene expression and microbiome profiles of predicted non-responders by the MPS using microarray and 16S sequencing in the PROgECT cohort.

Results: We report that the MPS can accurately predict non-responders, as defined by lack of mucosal improvement, to TNF-antagonist therapy in UC in four independent clinical trials, with a high negative predictive value (NPV) of 0.78 in ACT1, 0.79 in PURSUIT-SC, 0.89 in PROgECT, and 0.73 in PURSUIT-J. In addition, the MPS could predict non-responders, as defined by lack of endoscopic response, to anti-IL12/23 therapy in Crohn's disease (CD) with an NPV of 0.85. The predicted non-responders by MPS did not differ compared with predicted responders in baseline disease severity as measured by Mayo Score, or baseline inflammatory markers including CRP, faecal calprotectin, or faecal lactoferrin levels. Transcriptomics and microbiome analysis revealed insights into potential ways to treat this predicted non-responder population, as predicted non-responders had 268 differentially expressed genes enriched in inflammatory pathways and also demonstrated significant microbial dysbiosis.

Conclusions: The MPS consistently predicts non-responders to therapy in IBD regardless of ethnicity or whether the therapy targeted TNF or IL12/23 pathways. Clinical parameters and inflammatory markers by themselves lack the granularity to identify this subset of non-responder patients. The MPS is the first prospectively validated predictive biomarker that can accurately identify a discrete subset of non-responder patients to two different anti-inflammatory therapies and may be valuable in identifying subsets of patients in need of treatment with alternative therapies or for patient stratification in clinical trials.

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