

## MCGRAW TRIAL: EVALUATION OF THE SAFETY AND EFFICACY OF AN ORAL MICROBIOME INTERVENTION (SER-401) IN COMBINATION WITH NIVOLUMAB IN FIRST LINE METASTATIC MELANOMA PATIENTS

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**Background** While anti-PD-based therapy is an approved first-line treatment for patients with advanced, surgically unresectable metastatic melanoma (MM), many do not benefit. Abundance of *Ruminococcaceae* and other microbes in cancer patients' gut microbiome has been associated with improved anti-PD1 efficacy. Thus, combination approaches to overcome anti-PD1 primary resistance with gut microbiome modulation are being explored. In this trial, SER-401, an investigational microbiome therapeutic enriched in *Ruminococcaceae* and other spore-forming microbes, was evaluated in combination with nivolumab in first line MM patients.

**Methods** MCGRAW is a multi-center, randomized, blinded, and placebo-controlled phase 1b study in patients with advanced melanoma. Patients were randomized 2:1 to the SER-401 active or placebo arm, respectively, and stratified by baseline stool *Ruminococcaceae* abundance. Patients received an oral vancomycin preparative regimen+SER-401 (active arm), versus no antibiotics+placebo (placebo arm). One week later, all patients received nivolumab 480 mg Q4W. The primary endpoint was safety. Secondary endpoints were SER-401 microbiome engraftment, ORR, DCR, PFS, and change in frequency of tumoral CD8+ T cells on-treatment. The study was not powered for comparison between arms. Baseline and on-treatment stool samples were collected for microbiome analysis, tumor and blood samples were collected for exploratory biomarker analysis.

**Results** Fourteen patients were randomized (N=8 active, N=6 placebo). Grade 3-4 TRAEs were observed in 0 and 1 (17%) participants in the SER-401/nivolumab and placebo/nivolumab arms, respectively. In the vancomycin+SER-401/nivolumab arm, ORR was 25.0% (95% CI: 3-65) and DCR was 37.5% (95% CI: 9-76). In the no antibiotics+placebo/nivolumab arm, ORR was 66.7% (95% CI: 22-96) and DCR was 83.3% (95% CI: 36-99). Overall, microbiome engraftment was observed in the active arm but did not reach optimal kinetics or magnitude in many patients. Differences in the fecal microbial and metabolic profiles of responders and non-responders were observed to be prior to initial nivolumab administration. Additional orthogonal biomarker analyses revealed further differences between the responders and non-responders, with the CR patient in the active arm having a distinct profile both at screening and on-treatment.

**Conclusions** This study demonstrated that SER-401 and anti-PD1 are a safe combination in MM patients, however DCR was lower in the active arm versus control, perhaps related to the antibiotic preparative regimen. Enrollment challenges and sub-optimal SER-401 engraftment resulted in early termination of the study. Despite these limitations, our integrative clinical

and biomarker analysis provides information regarding the link between the gut microbiome, peripheral immune cell populations, and the tumor microenvironment during nivolumab therapy with or without SER-401.

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**Trial Registration** ClinicalTrials.gov (NCT03817125)

**Ethics Approval** The MCGRAW study was approved by WCG IRB (previously known as WIRB) protocol # 20182747

**Consent** All participants provided written informed consent before enrollment

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