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A RANDOMIZED PHASE II STUDY OF SYSTEMIC THERAPY PLUS WEILESHU (WLS) VERSUS SYSTEMIC THERAPY ALONE IN PATIENTS WITH METASTATIC COLORECTAL CANCER (mCRC)

¹Ruyi Zhang, ¹Xiaoxuan Tu*, ¹Zhou Tong, ¹Hangyu Zhang, ¹Xudong Zhu, ¹Weijia Fang, ²Lanfang Yu, ²Haibo Mou. ¹The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; ²Shulan Hospital, Hangzhou, China

Background In recent years, the role of inflammatory microenvironment induced by gut microbiome in the occurrence and development of CRC has received increased attention across a number of disciplines. WLS is a probiotics product consisted of with 6 billion live probiotics, mainly *Lactobacillus helveticus* and *Bifidobacterium longum*. To further explore the influence of gut microbiome in the anti-tumor efficacy of patients with mCRC, we conducted a randomized controlled trial (NCT04021589).

Methods Patients receiving corresponding systemic therapy were randomly included into the WLS-intervention and the control arms. Fecal samples were collected at baseline and about two months after treatment initiation. Gut microbiota composition was assessed using shotgun metagenomic sequencing. Best clinical response was dichotomized as partial remission (clinical benefit, CB) versus stable disease or disease progression (non-clinical benefit, NCB). Metagenomic analysis across patients with CB and NCB was conducted and random forest model training was employed to predict the efficacy of treatment.

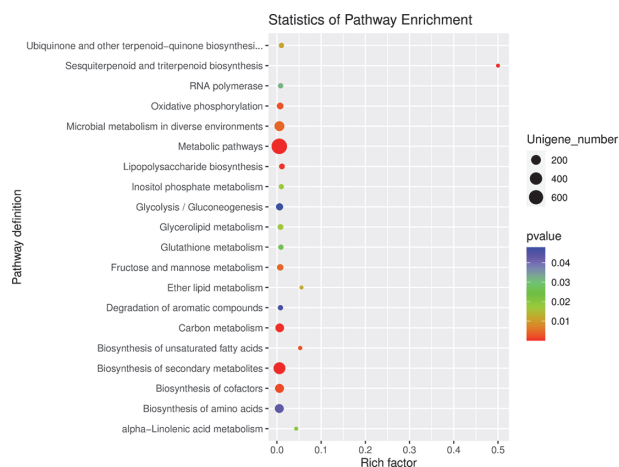
while WLS intervention down-regulated genes related to its synthesis pathway, which may slow the development of CRC. Random forest model showed abundance of *Desulfovibrio vulgaris* and *Parvimonas sp._oral_taxon_393* predominantly discriminated between CB and NCB. They were then used to construct a classifier, which achieved an AUC of 0.95 for efficacy prediction.

Conclusions This prospective randomized pilot study provided insights for influence of the gut microbiome with probiotics in mCRC. WLS could maintain intestinal microecological balance of patients with mCRC by decreasing the degree of abundance of gut microbiome fall after chemotherapy and down-regulating lipopolysaccharide metabolism-related pathway. We established a novel classifier that accurately distinguished between patients with CB and NCB on systemic therapy.

Trial Registration NCT04021589

Ethics Approval This study has been approved by Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. Acceptance number: IIT20200348A-R1

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Abstract 414 Figure 1 Metabolic pathways for differential enrichment. Metabolic pathways for differential enrichment of the gut microbiome genome in microbiota preparation group through KEGG analysis

Results A total of 40 patients with mCRC in two tertiary hospitals were enrolled. Dynamic metagenomic analysis indicated that during systemic treatment, the diversity of the gut microbiome were all decreased in both arms. It has been reported that higher a diversity is associated with a better prognosis, while the degree of decline in WLS-intervention group was a relatively minor change. GO enrichment analysis of differential genes indicated a strong enrichment for genes related to lipid metabolism after WLS intervention (figure 1; $p < 0.01$). Lipopolysaccharide (LPS) could regulate the accumulation of monocyte-like macrophages and promote the inflammatory microenvironment in a chemokine-dependent manner,