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The Impact Of Yiv-906 On Progression-Free Survival, Health-Related Quality Of Life And Metabolites Of Patients With Metastatic Colorectal Cancer

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Table of Contents

Table of Figures

Table of Tables

Abstract

Cancer is one of the leading causes of death in the world, and chemotherapy plays an important role in cancer treatment. However, serious adverse effects of chemotherapy could jeopardize the efficacy of the treatment as well as patients' quality of life. In order to remit this problem, a well-characterized herbal medicine, YIV-906 (KD018/PHY906), was developed as a combination therapy with chemotherapy. It is based on a traditional Chinese herbal formulation (Huang-Qin-Tang) that treats diseases related to gastrointestinal disorders and was investigated in a two-arm clinical trial for metastatic colorectal cancer (mCRC). A previous analysis done by Sun et al. showed significantly improved progression-free survival (PFS) in YIV-906 adjuvant group for mCRC patients who completed at least three cycles of treatment. This study confirmed these results using data from the same clinical trial and evaluated differences in health-related quality of life (HR-QoL) and metabolite profiles between experimental and control groups. The health-related quality of life was not significantly different between groups within four cycles, whereas from 5 to 8 cycles, patients in the YIV-906 group had significantly greater HR-QoL compared to those in the control group. To explore the mechanism of YIV-906's impact on PFS or HR-QoL, expression levels of 72 metabolites were collected, and 4 out of these 72 metabolites were significantly impacted by YIV-906. In the future, analyses should confirm these results in larger clinical trials and should explore whether the metabolites identified here are related to improved PFS and HR-QoL in the YIV-906 group.

Keywords: *YIV-906, PFS, health-related quality of life, metabolites.*

1. Introduction

Due to various factors such as population growth and aging, the global burden of cancer has been increasing over time. According to the World Health Organization (WHO), the cancer burden has risen to 18.1 million new cases and 9.6 million deaths in 2018 worldwide [1]. Colorectal cancer (CRC) is the fourth leading cause of death in the world, and metastases (mCRC) are the major cause of mortality in this cancer patients population [2, 3]. According to data from 2008-2014 obtained from the Surveillance, Epidemiology, and End Results Program (SEER), 21% of colorectal cancer cases were diagnosed as distant metastatic disease, for which the 5-year survival is only 13.8% [4]. Chemotherapy plays an important role in treating patients with CRC. Currently, the first-line modern chemotherapy for mCRC is fluorouracil plus leucovorin in combination with oxaliplatin (FOLFOX), while FOLFIRI (5-fluorouracil + leucovorin + irinotecan) is the second most effective chemotherapy [5]. Combinations based on irinotecan (CPT-11) are more effective than CPT-11 alone, and monoclonal antibodies (bevacizumab, cetuximab, and panitumumab) are usually used as adjuvants in mCRC treatment [2].

However, chemotherapy is usually associated with serious adverse effects, such as diarrhea, nausea, and vomiting [6], which could undermine the effect of the therapy by preventing patients from escalating doses or additional courses of the treatment. Other than the efficacy of the treatment, patients' quality of life would be largely lowered. Therefore, medications that can ameliorate these adverse effects without compromising anti-tumor efficacy of the treatment could not only make cancer therapy more effective and efficient, but also improve patients' quality of life during treatment [7].

YIV-906 (KD018 / PHY906) is currently being developed to be an adjuvant for chemotherapy aiming to reduce the side effects associated with cancer chemotherapy and improve the effectiveness of the treatment as well as patients' quality of life. YIV-906 is based on a traditional Chinese herbal formulation, Huang-Qin-Tang (HQT), which consists of four herbs --- *Glycyrrhiza uralensis Fisch, Paeonia lactiflora Pall, Scutellaria baicalensis Georgi, and Ziziphus jujuba Mill.* HQT has been documented for nearly 1800 years for treating common gastrointestinal diseases, like diarrhea, abdominal spasms, fever, headache, vomiting, nausea, and other symptoms. YIV-906 is a pharmaceutical grade of HQT, whose raw herbal ingredients are strictly picked by experienced herbalists and manufactured according to current Good Manufacturing Practice (cGMP) [8]. It has not only been tested in several different animal cancer models in the laboratory, but also in six phase I/II and one phase II clinical trials for multiple types of cancers, such as metastatic colorectal cancer [9, 10], advanced hepatocellular carcinoma [11], advanced pancreatic cancers [12,13] and rectal cancer [14].

Some analyses have been done previously on the difference of progression-free survival (PFS) between patients who did and did not take YIV-906 with CPT-11, and the results showed that, among patients who finished at least 3 cycles of the treatment, YIV-906 adjuvanted chemotherapy could improve patients' PFS significantly compared to chemotherapy alone [credit to Dr. Jiehuan Sun and Peidrin Cheng, et al.]. To confirm this result, we performed survival analysis using the same data source the impact of YIV-906 on health-related quality of life (HR-QoL) was also examined to test if YIV-906 could alleviate adverse events associated with chemotherapy and improve patients' lives during cancer treatment. Furthermore, we analyzed the metabolomic profiles with the intention to

find metabolites correlated to HR-QoL or PFS and seek clues for potential explanations of HR-QoL changes and methods of PFS prediction for mCRC patients treated by chemotherapy.

The data used in this study were obtained from a phase II colorectal trial of YIV-906 named "A Phase II Multi-Center, Randomized, Placebo-Controlled, Double-Blinded Clinical Study of KD018 (PHY906) as a Modulator of Irinotecan Chemotherapy in Patients with Metastatic Colorectal Cancer". It included two clinical sites, University of Pittsburgh Cancer Institute and Yale Cancer Center. All patients recruited into the trial received the combination of irinotecan plus bevacizumab and were randomized to taking either YIV-906 (experimental group) or placebo (control group). Each cycle of therapy was defined as 2 weeks, and patients would continue to be treated until cancer progressed or unacceptable toxicity occurred. The original study planned to recruit up to 108 patients with 54 patients being randomized to each treatment arms. However, due to the change of the protocol for the mCRC first line treatment, the study was forced to stop after obtaining 26 subjects (1:1). [15]

Progression-free survival (PFS) was one of the endpoints of this study, and information of hundreds of different biomarkers was collected at the beginning of every treatment cycle, including metabolites, cytokines, and gene mutations. Prospective evaluation of the effect of YIV-906 on health-related quality of life (HR-QoL) was recorded at each cycle as well. The detailed HR-QoL instruments used in the study, such as Symptom Distress Scale (SDS), Emotional Distress Thermometer (EDT), and Diarrhea subscale, and score interpretation for each of them are attached as in Appendix A. Trial Outcome Index (TOI)

was calculated using some of those instruments mentioned above and was taken as the overall indicator of HR-QoL in the study (higher score indicates better HR-QoL).

2. Methods

2.1 Data Sets

All information used in this study was obtained from the clinical trial "A Phase II Multi-Center, Randomized, Placebo-Controlled, Double-Blinded Clinical Study of KD018 (YIV-906) as a Modulator of Irinotecan Chemotherapy in Patients with Metastatic Colorectal Cancer". In the study, one patient was excluded due to compliance issues, and only patients who completed at least three cycles of treatment (PFS > 42 days) were included in the analysis. The total number of patients involved in this study is 21 (12 in CPT-11 arm; 9 in CPT-11/YIV-906 arm), but it may change slightly in each different analysis due to missing data, which are specified in each section below.

2.2 Survival Analysis

Progression-free survival time was one of the endpoints of the trial, which was defined as the time from the beginning of cycle 1 to cancer progression. All 21 patients were included in the survival analysis. The Kaplan-Meier survival curves were plotted followed by the log rank test to compare differences in the survival experience across two treatment groups overall as well as in each gender group. The Kaplan-Meier survival curves and log rank test were generated using SAS 9.4.

2.3 Health Related Quality of Life

The trial outcome index which reflected overall well-being was chosen for the analysis of HR-QoL. Due to incomplete data collection, HR-QoL information of 2 patients in CPT-

11/YIV-906 arm (both completed more than 10 cycles treatment) and 1 patient in the CPT-11 arm (completed 6 cycles treatment) was missing. Thus, the total sample size of HR-QoL comparison analysis is 18 individuals (11 in CPT-11 arm; 7 in CPT-11/YIV-906 arm). As the treatment cycle increased, the number of patients staying in the study decreased because of cancer progression or missing data (see Table 3-2-1).

The TOI scores for each patient in two treatments were plotted in SAS 9.4. The mean TOI scores of two groups at each cycle were also plotted to compare the overall trend of changes. Student's t-test was used to conduct point comparison for two groups at the cycles that had events (cancer progression) happened and the total patient number was no less than 10.

2.4 Metabolites

In order to assess the metabolomic profiles associated with CPT-11 and YIV-906 treatment, the levels of hundreds of metabolites were collected at the beginning of each treatment cycle. After cleaning out missing data, the information of 72 different metabolites from 21 individuals (12 in CPT-11 arm; 9 in CPT-11/YIV-906 arm) was analyzed for the metabolomic profile evaluation.

For each metabolite, the mean for each group at different cycles was plotted and repeated-measures ANOVA was conducted to compare the difference of the means between two groups over cycles. Due to the large number of metabolites and small sample size, False Discovery Rate (FDR) was used to avoid increased false positive rate when pursuing multiple inferences. [16] The analyses of metabolites were performed using the R programming platform (R 3.5.1).

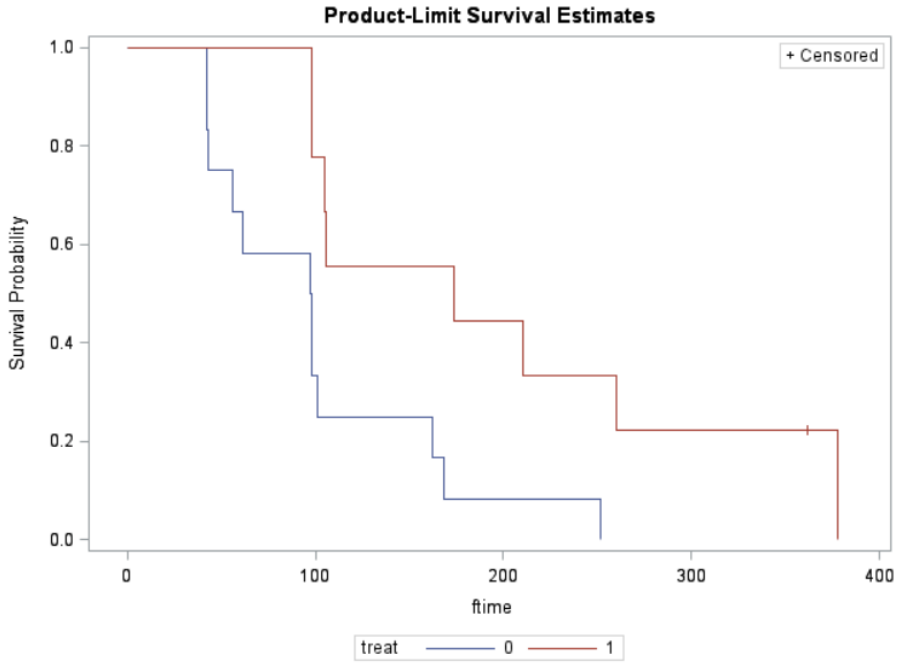
3. Results

3.1 Survival Analysis

Of the 21 patients who were included in the survival analysis, one patient in the CPT-11/YIV-906 treatment group did not show cancer progression at the end of the trial (8/9) while all the patients in the control group had disease progression (12/12). According to the overall Kaplan-Meier curve (Figure 3.1.1), the progression-free survival (PFS) curves of two treatment group were completely separated, and the progression-free survival experiences were statistically significantly better in the CPT-11/YIV-906 group [174 days median PFS; 95% CI (confidence interval): 98 to 378 days] compared to the CPT-11 group [97.5 days median PFS; 95% CI: 42 to 162 days] ($p = 0.0096$). This result was consistent with the results obtained from the previous analyze concluded by Dr. Jiehuan Sun and Peidrin Cheng [unpublished results].

To determine if the differences in PFS was influenced by gender, stratified Kaplan-Meier curves were plotted (Figure 3.1.2). Within this sample, 33.33% (7 individuals) were males and females account for 66.67% (14 individuals). According to the plots, patients in the CPT-11/YIV-906 treatment group had significantly better progression-free survival experience among both males and females with stratified log rank test p-value of 0.0067.

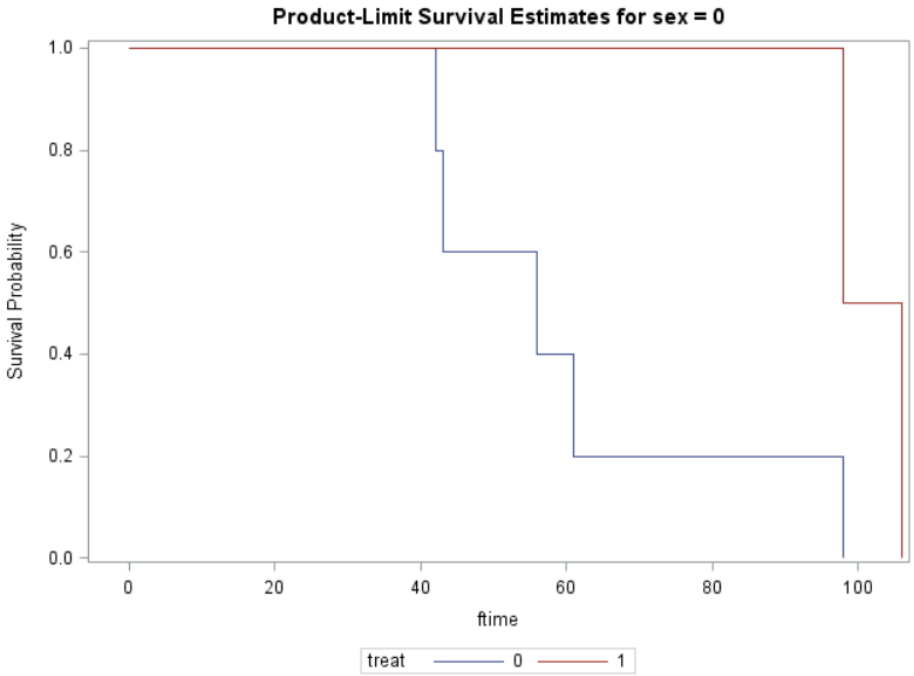
Figure 3.1.1 Overall Kaplan-Meier curves for two treatment groups



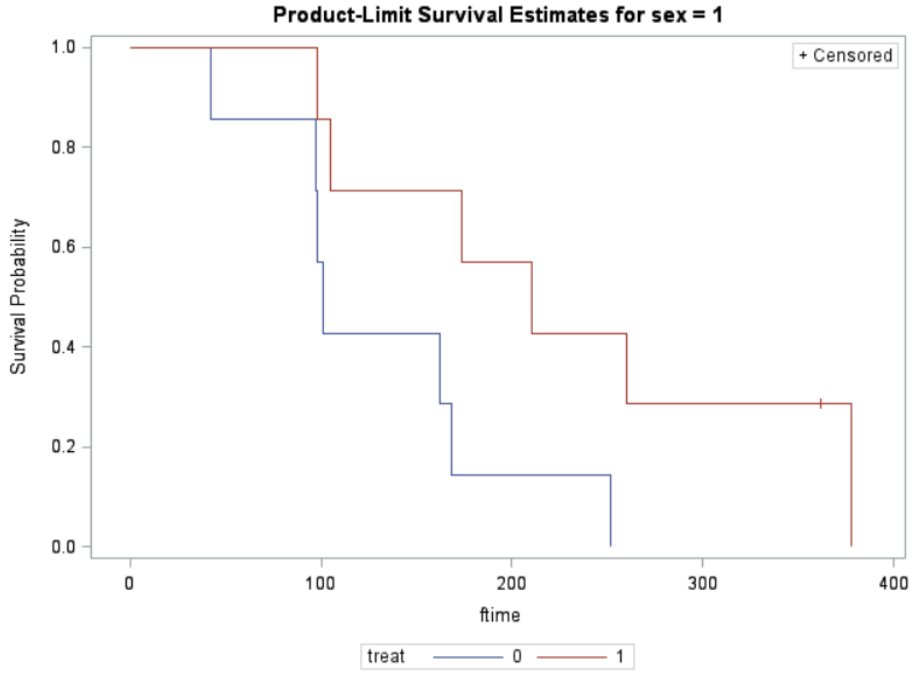
*treat: 0 --- CPT11; 1 --- CPT11/YIV-906

Figure 3.1.2 Stratified Kaplan-Meier curves by gender for two treatment groups

For females:



For males:



*treat: 0 --- CPT11; 1 --- CPT11/YIV-906

3.2 Health Related Quality of Life

In the CPT-11 group, the trial outcome index (TOI) scores of the 11 patients differed from 50 to 100 and most of them were within 60-80, while 6 out of the 7 patients in the CPT-11/YIV-906 group had their TOI score higher than 70 most of the time during the treatment. Within the first 4 cycles of treatment, most of the patients in both groups had a relatively stable health-related quality of life (HR-QoL) except patient 15 in the control group and patient 4 in the experimental groups who experienced a decrease by almost 20 points. After cycle 5, the HR-QoL of most of the patients in the experimental group stayed steadily above 60. The TOI score for patient 19 increased by almost 20 points after 6 cycles of CPT-11/YIV-906 treatment. However, there were large variations in HR-QoL trends for each patient in the CPT-11 group. Three out of 6 patients' HR-QoL became worse as the treatment went on. For the rest of the 3 patients, HR-QoL stayed stable or went up slightly. The data for patient 14 from cycle 2 to cycle 11 was missing but according to the TOI score of cycle 1 and cycle 12-19, he/she seemed to have a relatively stable HR-QoL. The trend for the TOI scores of each patient in two arms of the clinical mentioned above is displayed in Figure 3.2.1.

The two-group comparison for the trend of TOI mean scores over cycles was only made from cycle 1 to cycle 8 (Figure 3.2.2) since fewer patients remained in the study over time and several patients' data were missing completely. The total number of patients (listed in Table 3-2-1) declined to 6 in cycle 9, which was too small to disregard the variance of individuals within each group. As shown in Figure 3.2.2 (b), there was a slightly upward trend for the mean score of TOI in the experimental group, while in the control group, the mean score went down dramatically between cycle 4 and cycle 8. P-values of the t-test (see

in Table 3-2-1) also suggests that at cycle 1 and cycle 4, there was no significant difference between the TOI means of two groups while at cycle 5, 6, 7, and 8 (p-value $\approx$ 0.05) the difference became significant.

Figure 3.2.1 The TOI scores for each patient

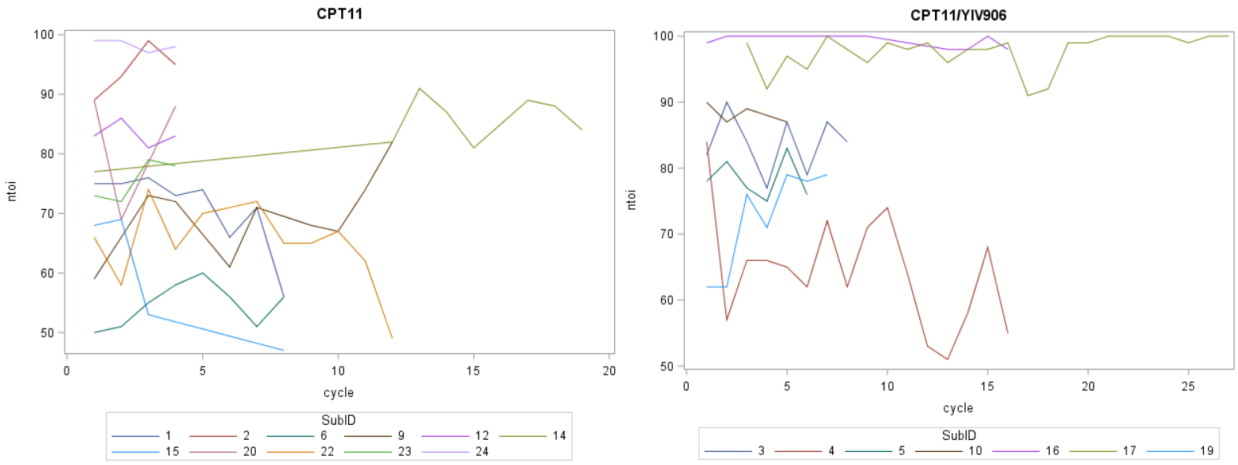
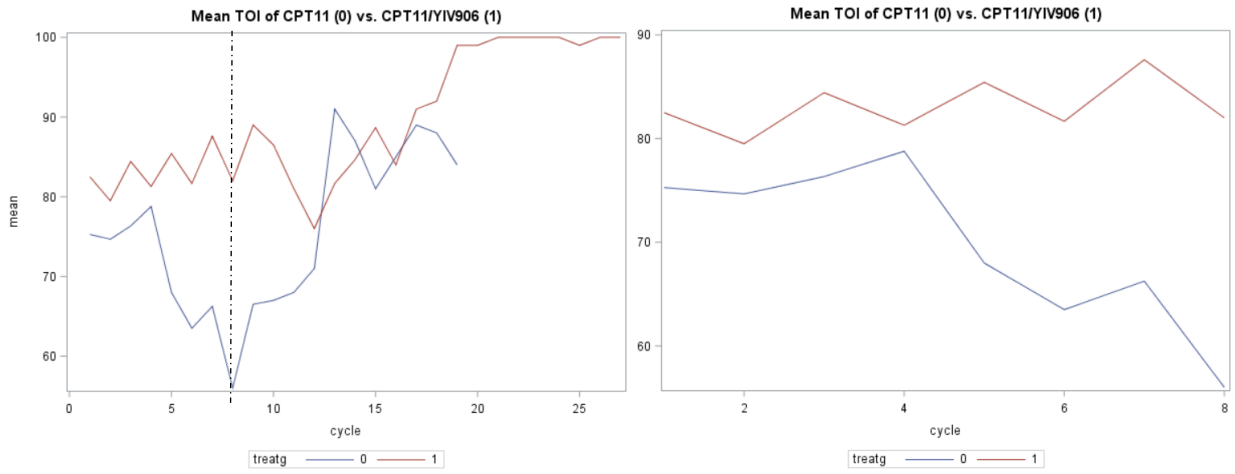


Figure 3.2.2 The means of TOI scores of two treatment groups at each cycle



(a) (b)

Table 3-2-1 The number of patients at each cycle when cancer progression happened and the p-value of the Student's t-test comparing mean TOI between two groups at different cycles.

No. of patients	cycle 1	cycle 4	cycle 5	cycle 6	cycle 7	cycle 8	cycle 9+
CPT-11	11	11	6	6	6	6	3
CPT-11/YIV-906	6	7	7	6	5	4	3
p-value of mean TOI comparison	0.3156	0.7080	0.0463	0.0416	0.0284	0.0512	---

*TOI score for patient 17 in CPT-11/YIV-906 arm was missing.

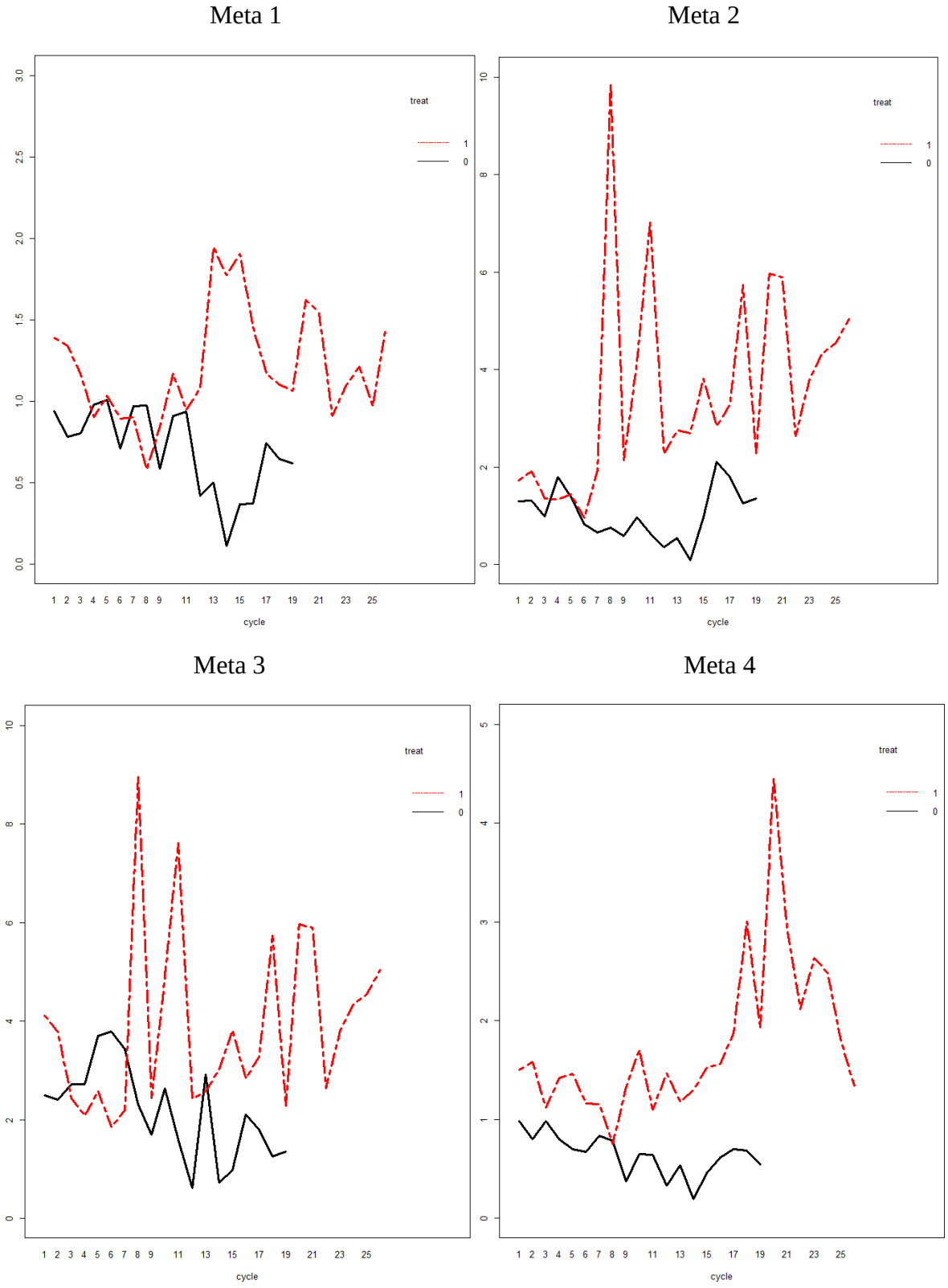
3.3 Metabolites

Of the 72 metabolites, four types of metabolites, referred as Meta 1, Meta 2, Meta 3 and Meta 4 (as a future potential patent candidate), were significantly ($p < 0.05$) affected by YIV-906 intake (Figure 3.3.1).

According to the graphs, for the CPT-11/YIV-906 treatment group, the trends of the means of all 4 metabolites stayed relatively horizontal or went up slightly over cycles. In comparison, the means of these metabolites for patients in CPT-11 group tended to decrease over cycles, some of which even dropped down to 0 at the end. However, these metabolites fluctuated more among patients who took YIV-906, especially Meta 2, 3, and 4.

The FDR-adjusted p-values of the ANOVA comparison between two treatment groups for these 4 metabolites are shown in Table 3-3-1.

Figure 3.3.1 Four metabolites that were significantly affected by YIV-906 at α=0.05



*treat: 0 --- CPT11; 1 --- CPT11/PHY906

Table 3-3-1 Row p-value and FDR-adjusted p-value for repeated-measures ANOVA comparison

Number of Meta	Row P-value	FDR Adjusted P-value
Meta 1**	0.000376	0.016789
Meta 2**	0.000466	0.016789
Meta 3**	0.001243	0.023527
Meta 4**	0.001732	0.023527

** significant at level of type I error α=0.05

4. Discussion

The analysis in our study suggests that the botanical formulation YIV-906 could significantly improve progression-free survival for mCRC patients completing at least three cycles of irinotecan plus bevacizumab (CPT-11) treatment without cancer deterioration. YIV-906 also has a great potential to benefit patients' overall HR-QoL after first a few cycles of treatment. YIV-906 might be able to prevent the HR-QoL from reclining due to chemotherapy in the long term, which allows patients to receive proper doses and duration of the treatment (Figure 3.2.2).

Similar to HR-QoL, the trend of the metabolite levels for two groups also showed that YIV-906 might have greater effect in the long term. There is no obvious separation of the metabolite levels at the early stage of the treatment. However, the group of patients taking YIV-906 in addition to CPT-11 sustains their metabolite profile at the later stage.

Each of these 4 metabolites plays their own role in metabolism. Meta 1 is a very important element in angiogenesis, methyl donation, and antioxidative effects especially in guts and livers. Meta 2 and Meta 3 are both known to promote diuresis, and Meta 4 is one of the fundamental components in metabolism.

Further studies are needed to explore the relationship between the change of these 4 metabolites and PFS or HR-QoL using more comprehensive data. It may not only be able to explain the metabolic mechanism of YIV-906's impact on the quality of life, but also allow us to screen patients who would not respond to a certain cancer treatment before it starts or to predict cancer progression during the treatment using biomarkers. Since the clinical trials of YIV-906 had been designed for cancers at different sites, it would also be interesting to see if there are any biomarkers that could predict the response result for multiple types of cancer. However, in order to make a precise prediction, different kinds of biomarkers, like cytokines, genotypes, and metabolites, should be analyzed comprehensively in the future.

Nevertheless, the biggest limitations of this study are the small sample size and incomplete data collection due to the unexpected early close of the clinical trial, especially for HR-QoL analysis. Some patients who have a relatively long PFS (more than 160 days) did not have their HR-QoL recorded at some cycles or at all, which made the analysis hard to perform. In addition, the follow-up information for HR-QoL as well as metabolites after cancer progressed should also be collected and evaluated to monitor the changes after the drug intake stops, which might provide more clues for understanding the role that YIV-906 plays in cancer treatment. Thus, further analysis for the influence YIV-906 on patients' HR-QoL, metabolites, and the correlation between them should be performed using additional data from future clinical trials of YIV-906 with proper sample size.

5. Acknowledgments

The author thanks Dr. Hongyu Zhao for advice on data analysis and Dr. Yung-Chi Cheng for data sources and all the suggestions for the thesis. Thanks to Dr. Jiehuan Sun and Peidrin Cheng for their previous analysis on PFS.

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Appendix A:

Abbrevaitions	Instrument	Score Interpretation
SDS (higher=worse)	Symptom Distress Scale	higher score indicates higher level of symptom distress
EDT (higher=worse)	Emotional Distress Thermometer	higher score indicates higher level of emotional distress
fatigue (higher=better)	Functional Assessment of Chronic Illness Therapy-Fatigue	higher score indicates higher level of quality of life, i.e. lower level of fatigue
FACIT-D (higher=better)	the Functional Assessment of Chronic Illness Therapy-Diarrhea	higher score indicates higher level of quality of life
FACT-C (higher=better)	Functional Assessment of Cancer Therapy-Colorectal	higher score indicates higher level of quality of life
PWB (higher=better)	Physical well-being (subscale)	high score indicates higher level of physical well-being
SWB (higher=better)	Social/family well-being (subscale)	high score indicates higher level of social/family well-being
EWB (higher=better)	Emotional well-being (subscale)	high score indicates higher level of emotional well-being
FWB (higher=better)	Functional well-being (subscale)	high score indicates higher level of functional well-being
CCS (higher=better)	Colorectal Cancer Subscale	higher score indicates higher level of quality of life with respect to the colorectal specific concerns
DS (higher=better)	Diarrhea subscale	higher score indicates higher level of quality of life with respect to the diarrhea-related concerns
FACT-G (higher=better)	Functional Assessment of Chronic Illness Therapy-General	higher score indicates higher level of quality of life
TOI (higher=better)	Trial Outcome Index	higher score indicates higher level of quality of life (sum of PWB, FWB and additional concerns of DS in the FACIT-D/ or CCS in the FACT-C)