Original Article

A single arm phase 2 clinical trial of YIV-906 with neoadjuvant concurrent chemo-radiation therapy in patients with locally advanced rectal cancer

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Background: Pre-operative chemoradiation for rectal cancer is often associated with severe gastrointestinal (GI) toxicity which can interrupt, delay, and/or lead to termination of treatment. In this study, we evaluated whether the addition of YIV-906, a novel herbal medicine proven to reduce GI toxicity associated with chemotherapy could also reduce GI side effects during standard pre-operative capecitabine and pelvic radiation therapy (RT) in the neoadjuvant setting for the treatment of locally advanced rectal cancer.

Methods: This single arm clinical study enrolled 24 patients between Dec 23, 2014–Sep 17, 2018 at Smilow Cancer Hospital, a comprehensive cancer center at Yale New Haven Hospital. All patients were age ≥18 years, Eastern Cooperative Oncology Group 0–1 and with histologically confirmed T3–T4 and N0–N2, M0 adenocarcinoma of the rectum. Median follow-up was 61.9 months. All patients received concurrent pelvic external beam RT (50.4 Gy in 28 fractions), YIV-906 (taken orally 800 mg twice daily on days 1–4 of RT each week), and oral capecitabine delivered in a neo-adjuvant fashion, followed by definitive surgery. Toxicity was assessed weekly during radiation and until acute symptoms resolved and then at 28 days, 4 months, 7 months and 10 months. Toxicities were graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Results: At the time of surgery, 4 patients (16.7%) had a complete or near-complete response. At a median follow-up of 61.9 months, the mean overall survival (OS) of our patient cohort was 74.9 months [95% confidence interval (CI): 67.3–82.5]. The estimated 5-year OS was 82.0%. We observed 0% acute grade 4 toxicities, and only two cases of acute grade 3 diarrhea (8.3%).

Conclusions: The addition of YIV-906 to capecitabine based chemoradiation for locally advanced rectal cancer led to reduced rates of GI toxicity compared to historical controls, in particular grade 3 or greater diarrhea. These findings suggest YIV-906 should be evaluated in a randomized clinical trial to further assess potential reductions in the toxicity profile of chemoradiation for GI cancers.

Keywords: Neoadjuvant; rectal cancer; toxicity; radiation

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Introduction

The current standard of care for patients with locally advanced rectal cancer (T3–T4 and N0–N2) is pelvic external beam radiation therapy (RT) with concurrent 5-fluorouracil (5-FU) or capecitabine based chemotherapy followed by surgery, either low anterior resection (LAR) or abdominoperineal resection (APR), and FOLFOX chemotherapy either as adjuvant chemotherapy or in the neoadjuvant setting. Total neoadjuvant therapy (TNT) with upfront FOLFOX, followed by pelvic chemoradiotherapy (CRT) and subsequent total mesorectal excision (TME) is increasingly being used for this patient population. Following this multi-disciplinary approach approximately 75% of patients are cured and 80% are successfully treated with sphincter-sparing surgery in modern randomized trials (1-3). Despite high cure rates, pelvic chemoradiation is also commonly associated with short-term and long-term adverse effects which significantly diminish patient's quality of life.

Gastrointestinal (GI) toxicity is most often the dose-limiting toxicity of CRT for locally advanced rectal cancer and typically presents as diarrhea, nausea, and vomiting. Almost all patients experience at least mild to moderate diarrhea during CRT, which has an adverse impact upon quality of life. More severe radiation enteritis and colitis can be potentially life-threatening complications that can interrupt, delay, and/or lead to termination of treatment, leading to adverse outcomes. In addition to acute enteritis, chronic enteropathy, characterized by GI hemorrhage and ulceration, can be a long-term complication of pelvic radiation and lead to reduced bowel motility. Furthermore, there are potentially life-threatening sequelae associated with bowel injury, including fistulas, strictures, and chronic malabsorption (4).

The aim of this study was to investigate whether YIV-906, a standardized and well-characterized Chinese herbal medicine, can be used to reduce GI toxicity associated with CRT for the treatment of rectal cancer. Pre-clinical *in vivo* mouse models with several GI tumor xenografts (colon cancer, pancreatic cancer, and liver cancer) have shown that YIV-906 is able to effectively reduce the severity and incidence of overall toxicity following treatment with a wide range of chemotherapy agents (5-FU, capecitabine, irinotecan, and gemcitabine) by inhibiting the expression of various pro-inflammatory cytokines within the gut mucosa and reducing inflammatory cell infiltration. In addition, YIV-906 may activate the Wnt signaling pathway in GI stem cells, which may help to protect the normal gut epithelium from cytotoxic damage (5). YIV-906 was also shown to reduce the morphological changes associated with radiation induced intestinal injury in mice, including blunting and loss of villi as well as crypt loss and crypt hyperplasia with irregular crypt morphology (6). Prior phase I clinical trials of colorectal and hepatocellular cancer have shown that YIV-906 reduces the incidence of grade ≥3 diarrhea, without altering the pharmacokinetics of the administered chemotherapeutics (7,8). In this study, YIV-906 was administered concomitantly with capecitabine and pelvic RT in the neo-adjuvant setting, with the hypothesis that YIV-906 would reduce the GI side effects, namely diarrhea, secondary to capecitabine plus RT. We present this article in accordance with the TREND reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-23/rc).

Highlight box

Key findings

- The addition of a novel herbal medicine, YIV-906, reduced the gastrointestinal (GI) toxicity associated with preoperative chemoradiation for locally advanced rectal cancer in a prospective phase 2 trial.

What is known and what is new?

- Severe GI toxicity often occurs with neoadjuvant chemoradiation for rectal cancer and can lead to interruption or termination of treatment.
- YIV-906 added to capecitabine-based chemoradiation led to reduced rates of GI toxicity compared to historical controls, in particular grade ≥3 diarrhea.

What is the implication, and what should change now?

- These findings suggest YIV-906 should be evaluated in a randomized trial to further assess potential reductions in the toxicity profile of chemoradiation for rectal cancer, which could impact treatment intensification in the pre-operative setting with total neoadjuvant therapy or watchful waiting strategies. Evaluation of YIV-906 as part of combined modality therapy paradigms for other GI malignancies should also be considered.

Methods

Patient selection

This study was approved by the Yale University Institutional Review Board (approval No. 1404013708). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Twenty-four patients were enrolled from Dec 23, 2014–Sep 17, 2018 in this single arm open label pilot study in the Yale New Haven Hospital System. Informed

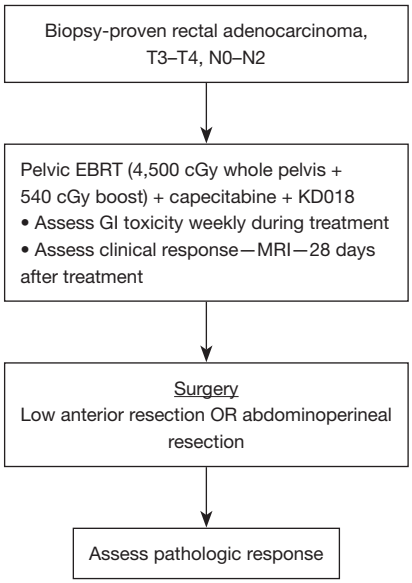

Figure 1 Trial schematic. EBRT, external beam radiation therapy; GI, gastrointestinal; MRI, magnetic resonance imaging.

consent was obtained from all participants in the study. Patients were 18 years of age or older and had histologically confirmed T3–T4 and N0–N2, M0 adenocarcinoma of the rectum with inferior margin within 16 cm from the anal verge. All enrolled patients were deemed eligible for treatment with combined modality therapy (capecitabine and external beam RT) with curative intent and had adequate hematologic parameters as well as adequate renal and hepatic function. Patients with inadequate performance status, life expectancy of less than 6 months, a history of Crohn's disease or inflammatory bowel disease, active collagen vascular disease, history of previous RT to the abdomen or pelvis, contra-indications to chemoradiotherapy, or active human immunodeficiency virus (HIV) or hepatitis were excluded.

Treatment

All patients were treated with a regimen of concurrent pelvic external beam RT, YIV-906, and oral capecitabine delivered in a neo-adjuvant fashion, followed by definitive TME (LAR or APR). A standard course of whole pelvic RT was delivered using 3D conformal techniques, consisting of 45 Gy in 25 fractions to the pelvis and a boost of 5.4 Gy in 3 fractions to a total dose of 50.4 Gy over 28 days at the Yale Department of Therapeutic Radiology. external beam RT was delivered with concomitant capecitabine and YIV-906, and intensity-modulated radiation treatment (IMRT) was not allowed. The radiation boost field was defined as the GTV (gross tumor and nodal volume) plus a minimum of 2.0 cm margin, including the presacral space. A planning target volume (PTV) encompassing the gross tumor target and an adequate margin to account for daily setup variation was defined by the treating physician in the Yale Department of Therapeutic Radiology. The upper border of the field was the L5–S1 interspace, and the lower border of the field was 4 cm below the lowest extent of the gross tumor volume. The planning simulation was performed with a full bladder and with oral contrast to visualize the small bowel in the pelvis.

YIV-906 was taken orally at a dose of 4 capsules (200 mg per capsule) twice daily on days 1–4 of RT each week, for a total daily dose of 1,600 mg. Capecitabine was taken orally at a dose of 825 mg/m^2 twice daily, on days 1–5 of RT each week. Toxicity was assessed weekly during the CRT and at 28-day follow-up after CRT. Assessment of long-term toxicity was done at 4, 7 and 10 months following RT.

Surgery was performed following the completion of all CRT at approximately 8 weeks post neoadjuvant therapy and consisted of an APR or LAR, at the discretion of the surgeon. The study schematic is shown in *Figure 1*.

Outcomes

Tumor response was graded by radiologic and pathologic response. Radiologic evaluation consisted of a pelvic magnetic resonance imaging (MRI) with and without gadolinium, obtained prior to treatment and 28±7 days after treatment. Response or progression of the primary tumor was measured by change in the largest unidimensional measurement on pelvic MRI and evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (9). For pathologic response, the surgical specimen at time of APR or LAR was examined by a pathologist with extensive experience in GI pathology. The dimensions of any grossly visible tumor were recorded at the time of the gross specimen evaluation.

Toxicity was assessed weekly during radiation and until acute symptoms resolved and then at 28 days, 4 months, 7 months and 10 months. Toxicities were graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analyses

Data was analyzed using SPSS, version 25 (IBM). The Kaplan-Meier method was used for analysis of overall survival (OS),

Table 1 Baseline tumor and treatment characteristics of patients treated with chemoradiation and YIV-906

Patient, tumor and treatment characteristics	Value
Age (years)	54.5 [49.5–62]
Gender	
Male	18 (75.0)
Race	
White	19 (79.2)
Nonwhite	5 (20.8)
ECOG	
0	21 (87.5)
1	3 (12.5)
Histology	
Poorly differentiated	3 (12.5)
Moderately differentiated	21 (87.5)
Clinical T stage	
T3	22 (91.7)
T4	2 (8.3)
Clinical N stage	
N0	9 (37.5)
N1	11 (45.8)
N2	4 (16.7)
Tumor location	
Low rectum	9 (37.5)
Mid rectum	10 (41.7)
High rectum	5 (20.8)
Chemotherapy	
Concurrent with RT	1 (4.2)
Concurrent and adjuvant	23 (95.8)
Adjuvant chemotherapy[†]	
Capecitabine	1 (4.2)
FOLFIRI	1 (4.2)
Capecitabine and oxaliplatin	2 (8.3)
FOLFOX	19 (79.2)
Cycles of adjuvant chemotherapy	8 [6–12]
Time from end of RT to surgery (days)	68.5 [61.5–75.5]
Surgery type	
APR	1 (4.2)
LAR	23 (95.8)
Radiation target volumes and dosimetry	
PTV 4,500 (mL)	1,327.5 (1,210.4–1,441.5)
PTV 5,040 (mL)	547.1 (488.3–649.9)
Bladder mean (cGy)	3,900.5 (3,613.5–4,426.5)
Small bowel max DVH 100 mL (cGy)	2,091.8 (1,162.5–4,358.5)
Small bowel max DVH 10 mL (cGy)	4,462.6 (2,968.7–4,777.5)
Large bowel max DVH 135 mL (cGy)	2,400.3 (1,264.8–4,140.4)
Large bowel max DVH 45 mL (cGy)	4,587.5 (3,355.1–4,655.9)

Data are presented as median (interquartile range), median [range] or n (%). [†], one patient did not receive adjuvant chemotherapy. ECOG, Eastern Cooperative Oncology Group; RT, radiation therapy; APR, abdominal perineal resection; LAR, low anterior resection; PTV, planning treatment volume; DVH, dose-volume histogram.

progression-free survival (PFS), local/regional PFS (LRPFS) and distant PFS (DPFS). OS was defined as time from completion of CRT to death. PFS was defined as the time from completion of CRT to progression either within or outside of the treatment field. LRPFS was defined as the time from completion of CRT to progression within the treatment field. DPFS was defined as the time from completion of CRT to progression outside of the treatment field.

Results

Patient and treatment characteristics

The trial schematic is shown in *Figure 1*. Baseline characteristics for the 24 enrolled patients are summarized in *Table 1*. The median age for patients was 54.5 [interquartile range (IQR), 49.5–62] years and 87.5% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 12.5% of patients

were ECOG 1. Clinical staging revealed that 22 of 24 patients (91.7%) had T3 tumors and 2 of 24 patients (8.3%) had T4 tumors. Of the 24 total patients, 9 had N0 disease (37.5%), 11 had N1 disease (45.8%) and 4 had N2 disease (16.7%). Following neo-adjuvant radiation with concurrent chemotherapy, 23 patients underwent LAR and 1 patient underwent APR. Median time from end of radiation to definitive surgery was 68.5 days and 23 of 24 patients received adjuvant chemotherapy following TME, with the majority (79.2%) receiving adjuvant FOLFOX. Median follow-up was 61.9 months.

Dosimetry

Target volume and dosimetry data are summarized in *Table 1*. All patients received 50.4 Gy in 28 fractions. All patients were treated using 3D conformal techniques. The median PTV size for pelvic radiation (4,500 PTV) was 1,327.5 mL (IQR, 1,210.4–1,441.5 mL) and the median PTV size for the boost field (5,040 PTV) was 547.1 mL (IQR, 488.3–649.9 mL). Critical organs at risk were bladder, small bowel, and large bowel. The mean bladder dose was 39 Gy (IQR, 36.1–44.3 Gy). The small bowel maximum DVH for 100 mL was 20.9 Gy (IQR, 11.6–43.6 Gy) and maximum DVH for 10 mL was 44.6 Gy (IQR, 29.7–47.8 Gy). The large bowel maximum DVH for 135 mL was 24 Gy (IQR, 12.6–41.4 Gy) and maximum DVH for 45 mL was 45.9 Gy (IQR, 33.6–46.6 Gy).

Patient outcomes and toxicity

Patient treatment and clinical outcomes are listed in Tables S1,S2. Based on RECIST criteria, 4 patients (19.0%) had a complete clinical response, 11 patients (52.4%) had a partial response, and 6 patients (28.6%) had stable disease after CRT. At the time of surgery, pathologic evaluation revealed that 4 patients (16.7%) had a complete or near-complete response, 15 patients (62.5%) had a moderate response, 4 patients (16.7%) had a minimal response and 1 patient (4.2%) showed no definite response. At a median follow-up of 61.9 months, the mean OS of our patient cohort was 74.9 months [95% confidence interval (CI): 67.3–82.5]. The estimated 3-year and 5-year OS was 91.2% and 82.0%, respectively. The mean PFS was 58.3 months (95% CI: 47.8–68.8). The estimated 3-year and 5-year PFS were 74.6% and 58.5%, respectively. The mean LRPFS was 78.1 months (95% CI: 74.4–81.8). The mean DPFS was 64.2 months (95% CI: 54.4–74.0) (*Table 2*, *Figure 2*).

In our cohort, we observed 0 acute grade 4 toxicities, and only 2 patients (8.3%) with acute grade 3 GI toxicity. The twos cases of grade 3 GI toxicities included 2 patients (8.3%) with grade 3 diarrhea. The case of grade 3 diarrhea was attributed to capecitabine and radiation and resolved without any change or delay in CRT or YIV-906 dosing. Long-term follow-up (4, 7 and 10 months) were recorded for 15 out of the 24 patients and no grade 3 or grade 4 toxicities were observed (*Table 3*, Table S2).

Discussion

Standard of care multimodality treatment for locally advanced rectal cancer is associated with significant GI toxicities. In particular, diarrhea is experienced by the majority of patients undergoing CRT. At a minimum diarrhea can diminish quality of life but if more severe can delay treatment or even cause premature termination of treatment. At its most severe, radiation enteritis can be potentially life threatening. The purpose of this pilot trial was to assess whether YIV-906, which is known to reduce GI side effects with chemotherapy (5), can also reduce GI side effects when it is administered concomitantly with capecitabine and pelvic RT in the neoadjuvant setting for the treatment of locally advanced rectal cancer.

Our cohort of patients for this trial had similar baseline characteristics (T3 *vs.* T4, node positivity, and distance from tumor from anal verge) as prior trials of preoperative CRT for locally advanced rectal cancer, such as the German Rectal Trial (1). Within our cohort we observed reduced rates of acute and long-term GI toxicities. We had no grade 4 or grade 5 GI toxicities, only 2 patients had acute grade 3 GI toxicity (8.3%) and remarkably, only 2 patients in 24 (8.3%) experienced acute grade 3 diarrhea. In contrast, prior trials using CRT with 3D-conformal radiation treatment plans and 5-FU or 5-FU and leucovorin chemotherapy have reported rates of 15–36% for acute grade 3 or greater diarrhea (1,11,12). On long term follow-up we did not observe any grade 3 or 4 GI toxicity, whereas the German Rectal Trial observed a rate of 14% for any grade ≥3 GI toxicity and a 7% rate for grade ≥3 diarrhea (1). While prior phase I/II clinical trials showed reduced GI toxicity when YIV-906 was delivered concurrently with chemotherapy (7,8), our results are the first of our knowledge to demonstrate reduced acute and long-term GI toxicities when YIV-906 is administered concurrently with chemoradiation.

The mechanism underlying the effect of YIV-906 is unknown but preclinical studies suggest that YIV-906 may inhibit the expression of various pro-inflammatory cytokines

Table 2 Summarized data of clinical response to CRT with YIV-906

Variables	Value
Response by MRI after CRT (n=21 total)	
Stable disease	6 (28.6)
Partial response	11 (52.4)
Complete response	4 (19.0)
Pathologic response at time of surgery (n=24 total)	
No definite response	1 (4.2)
Minimal response	4 (16.7)
Moderate response	15 (62.5)
Near complete response	1 (4.2)
Complete response	3 (12.5)
German Rectal Cancer Study Group [Sauer *et al*., 2004 (10)]: complete response (preoperative CRT) (%)	8
Neoadjuvant rectal score (n=24 total)	
0–10	10 (41.7)
10–20	5 (20.8)
>20	9 (37.5)
LRPFS	
Patients with local/regional failure	1 (4.2)
LRPFS (months)	78.1 (74.4–81.8)
German Rectal Cancer Study Group [Sauer *et al*., 2004 (10)]: 5-year local recurrence rate (preoperative CRT) (%)	6
PFS	
Patients with progression of disease	8 (33.3)
PFS (months)	58.3 (47.8–68.8)
3-year PFS (%)	74.6 (65.6–83.6)
5-year PFS (%)	58.5 (45.2–71.8)
German Rectal Cancer Study Group [Sauer *et al*., 2004 (10)]: 5-year PFS (%)	68
DPFS	
Patients with distant failure	5 (20.8)
DPFS (months)	64.2 (54.4–74.0)
German Rectal Cancer Study Group [Sauer *et al*., 2004 (10)]: 5-year distant failure (preoperative CRT) (%)	36
Follow-up (months)	61.9 (56.1–67.6)
OS	
OS (months)	74.9 (67.3–82.5)
5-year OS (%)	82.0 (72.2–91.8)
German Rectal Cancer Study Group [Sauer *et al*., 2004 (10)]: 5-year OS (%)	76

Data are presented as n (%) or mean (95% confidence interval). CRT, chemoradiotherapy; MRI, magnetic resonance imaging; LRPFS, local/regional progression-free survival; PFS, progression-free survival; DPFS, distant progression-free survival; OS, overall survival.

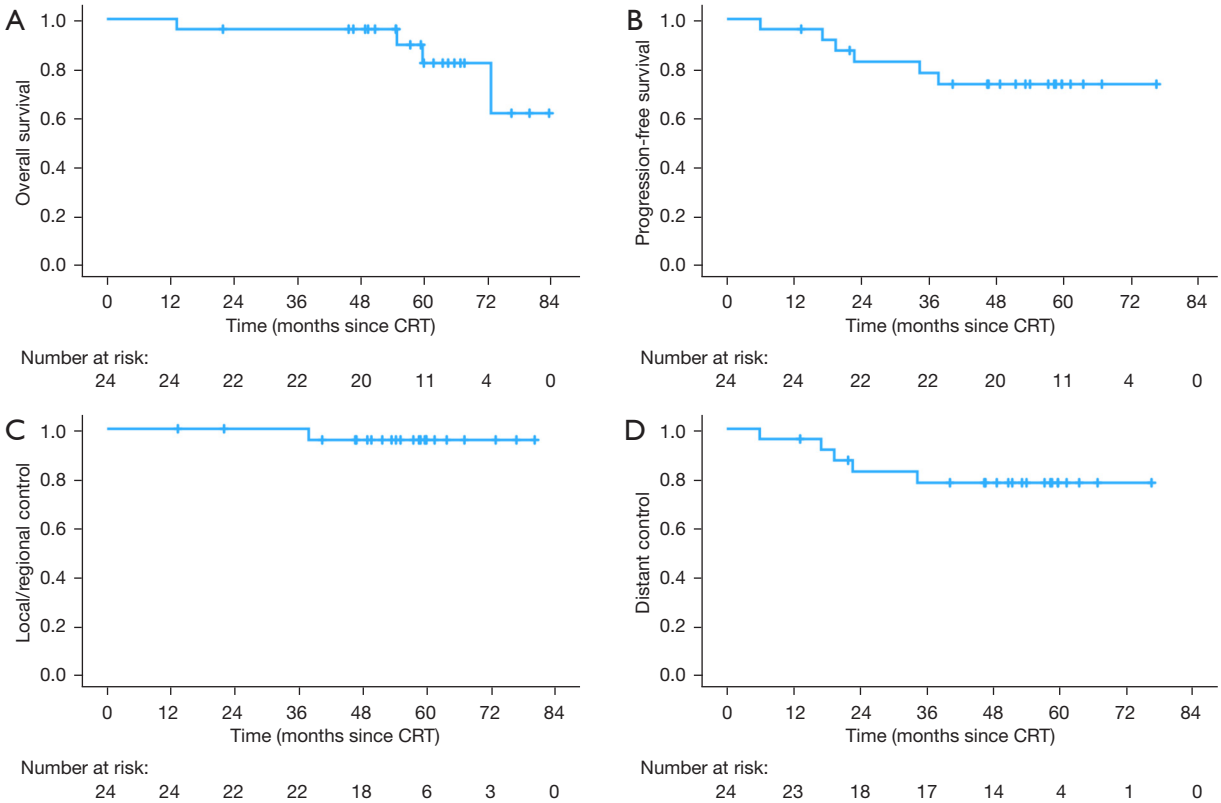

Figure 2 Kaplan-Meier curves. (A) Overall survival; (B) progression-free survival; (C) local/regional progression-free survival; (D) distant progression-free survival. CRT, chemoradiotherapy.

within the gut mucosa and inhibit the infiltration of normal gut mucosa with inflammatory cells leading to a reduction in GI toxicities (5). Preliminary data suggests that YIV-906 may have an anti-tumor effect as well by enhancing the effect of chemotherapy (8). In addition, *in vivo* studies suggest that YIV-906 may act as an immunomodulator by altering the tumor micro-environment to potentiate the effects of immune checkpoint inhibitors (13,14). Further mechanistic evaluation of YIV-906 may allow for advances in oncologic outcomes through reduced treatment related toxicity and increased efficacy of treatment.

Within our trial we observed a radiologic complete response rate of 19.0% and a pathologic complete response rate of 16.7% following CRT. This complete response rate is notably higher than seen in the German Rectal Trial comparing pre-operative *vs.* post-operative chemoradiation, in which 8% of patients in the pre-operative CRT group had a complete pathologic response at time of surgery (1). Our result is more similar to the NSABP R03 and NSABP R04 which observed complete response rates of 15–20% with preoperative CRT (11,15). Recent phase 3 trials have explored a total neoadjuvant approach in which upfront chemotherapy is followed by pre-operative CRT. The rationale for this approach is that it may allow the early treatment of micrometastases, deliver chemotherapy to the primary tumor with intact vasculature, improve patient adherence, and reduce ostomy durations for patients. Two phase 3 trials have shown an improvement of the pathologic response rate with the total neoadjuvant approach when compared to standard of care (28% *vs.* 12–14%). However, this total neoadjuvant approach is also associated with significant grade 3–4 diarrhea (11–17%) (2,3). In this setting of escalating neoadjuvant treatment YIV-906 may be particularly useful for limiting GI toxicities.

This study was limited as a single institution study with a small sample size, which may limit the observation of rarer adverse effects. However, in addition to this clinical trial, approximately 250 patients have participated in clinical trials with YIV-906 in combination with chemo (capecitabine, sorafenib, irinotecan, irinotecan/5-FU/leucovorin) in solid tumors (hepatocellular carcinoma, colorectal, and pancreatic cancers). In those clinical trials,

Table 3 Summarized data of toxicity to CRT with YIV-906

Variables	Value	
	Grade 1–2	Grade 3–4
Toxicity during treatment and at 28-day follow-up		
Total number of patients with short term toxicity recorded	24 (100.0)	
Any grade 3–4 toxicity	7 (29.2)	
Specific toxicity during treatment and at 28-day follow-up		
Constipation	2 (8.3)	0
BM urgency/fecal incontinence	3 (12.5)	0
Diarrhea	17 (70.8)	2 (8.3)
Anorectal pain	15 (62.5)	0
Anorectal hemorrhage	1 (4.2)	0
Nausea/vomiting	14 (58.3)	0
German Rectal Cancer Study Group (Sauer *et al*., 2004)		
Any grade 3–4 acute toxicity (preoperative CRT) (%)	27	
Grade 3–4 acute diarrhea (preoperative CRT) (%)	12	
Toxicity at long-term follow-up (4, 7 and 10 months)		
Total number of patients with long-term toxicity recorded	15 (62.5)	
Any grade 3–4 toxicity	0	0
Specific toxicity at long-term follow-up (4, 7 and 10 months)		
Constipation	2 (13.3)	0
BM urgency/fecal incontinence	1 (6.7)	0
Diarrhea	5 (33.3)	0
Anorectal pain	6 (40.0)	0
Nausea/vomiting	0	0
German Rectal Cancer Study Group (Sauer *et al*., 2004)		
Any grade 3–4 long-term toxicity (preoperative CRT) (%)	14	
Grade 3–4 acute diarrhea (preoperative CRT) (%)	7	

Data are presented as n (%). CRT, chemoradiotherapy; BM, bowel movement.

no additional adverse effects (not seen in the present study) were observed. In addition, this study did not include any patients treated with IMRT. For this reason, we chose to use the German Rectal trial as our historical control to evaluate the benefit of YIV-906, as it also used 3D conformal radiation techniques. A more recent trial comparison would be the RAPIDO trial (3), in which IMRT with standard course CRT with concurrent capecitabine had a rate of grade 3–4 diarrhea of 9.3%, similar to our study; however, within the experimental arm (short-course RT with IMRT followed by chemotherapy) the rate of grade 3–4 diarrhea was increased to 17.6%. IMRT has been increasingly adopted over the years and typically has smaller treatment volumes than the 3D conformal techniques used in this study. Diarrhea due to radiation treatment has been reduced with the use of IMRT and image-guided RT, however 3D conformal RT is still commonly used in the treatment of rectal cancer and diarrhea remains a common and often treatment-limiting side effect with pelvic chemoradiation. We envision many scenarios where YIV-906 may be beneficial in managing GI toxicities during CRT for rectal cancer. For instance, YIV-906 may improve

the therapeutic ratio for patients who have larger treatment volumes, such as T4 tumors. It may enable radiation dose escalation for patients who are not surgical candidates or pursuing organ preservation, and it may ameliorate the often more severe GI toxicity associated with short course radiation treatment which is increasingly being utilized (16). In addition, approximately 4–10% of patients with rectal cancer experience local failure following CRT and surgery (17). Resection of the recurrent tumor is the primary treatment; however, this often requires extensive surgery and is associated with substantial complication and mortality rates. A recent review also found that the overall percentage of positive margins after pelvic resection of locally recurrent rectal cancer was 34.4% (18). An area for future investigation is the potential benefit of YIV-906 as part of the treatment regimen for locally recurrent rectal cancer. YIV-906 may enable completion of chemoradiation without dose reductions or allow intensification of chemotherapy and/or RT for patients who are unable to tolerate salvage surgery or have positive margins following surgery. Our results suggest that YIV-906 may offer utility for a variety of clinical scenarios, as described above, but this will need to be tested further in prospective clinical studies. Finally, for each patient correlative studies on the chemokine and cytokine profile following administration of YIV-906 is currently ongoing and may provide insight into the mechanism by which YIV-906 reduces GI toxicity.

Conclusions

In conclusion, we found that the addition of YIV-906 to capecitabine based chemoradiation for locally advanced rectal cancer led to reduced rates of GI toxicity, in particular grade ≥3 diarrhea, compared to historical controls, and warrants further investigation in the setting of IMRT and the total neoadjuvant treatment approach.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-23/coif). K.L.J. is a member of the National Comprehensive Cancer Network (NCCN) colorectal cancer guidelines panel and NCCN provides reimbursement to travel to meetings at their headquarters to review the guidelines. J.L. has served on the advisory board for Ipsen, Genentech and Bristol Myers Squibb. J.L. has served on leadership for ASCO and editor for SEP. J.L. has consulted for First World, Techspert, Guidepoint, Ipsen, Bristol Myers Squibb, MarketPlus, Equinox, KeyUwest, FirstWord Group, Genentech, AptitudeHealth, Novartis and Deciphera. M.C. is supported by a NCI Mentored Clinical Scientist Research Career Development Award (1K08CA255465-01A1) and has consulted for Daiichi Sankyo, Seattle Genetics, Taiho, Regeneron, Agenus, Elevate Oncology, Loxo@Lilly, I-MAB, Bayer, Macrogenics and Incendia Therapeutics. Y.C.C. is the inventor of YIV-906 (aka PHY906/KD018) for its usage for its usage in cancer treatment. Yale holds the patent. It is licensed to Yiviva which is cofounded with Yale. He did receive funding from the National Foundation of Cancer Research (NFCR) and nominal amount from Yiviva. He received no funding from NIH. Y.C.C. has new drug discovery patent being considered with Yale owning the patent. Y.C.C. serves on the Scientific Advisory Board for Yiviva and serves as a Chair of Consortium for the Globalization of Chinese Medicine. Y.C.C. holds stock or stock options as Cofounder of Yiviva options. W.L. received payments from Yiviva, Inc. as a consultant. S.H.L. is the co-inventor of YIV-906 and is included in the patent that Yale University holds; and is the co-founder and employee of Yiviva Inc. who has licensed the YIV-906 world-wide right from Yale University. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Yale

University Institutional Review Board (approval No. 1404013708). Informed consent was obtained from all participants in the study.

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