P – 320 Pilot trial of YIV-906 with neoadjuvant chemoradiotherapy (CRT) in patients with locally advanced rectal cancer

K Johung[1], B Kann[1], J Lacy[2], S Stein[3], J Kortmansky[1], W Zaheer[1], Y Cheng[1], W Lam[1], S Liu[1], R Decker[1], H Hochster[4], S Higgins[1]

[1]Yale University School of Medicine, New Haven, Connecticut, USA, [2]Yale Cancer Center, New Haven, Connecticut, USA, [3]Yale University Cancer Center, New Haven, Connecticut, USA, [4]Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, USA

Introduction: Neoadjuvant CRT is the standard of care for clinical stage T3-4 or node positive rectal adenocarcinoma, but it is associated with a 12% rate of acute grade 3-4 diarrhea and 9% rate of longterm gastrointestinal (GI) toxicities1. Furthermore, the rate of complete pathologic responses to neoadjuvant therapy is low in historic studies (8%)1. Reducing GI toxicity is important because these side effects can lead to delayed or incomplete treatment, which may compromise patient outcomes. Novel agents which may improve pathologic response are of interest, as pCR is associated with improved local control and survival. YIV-906 is derived from Huang-Qin-Tang, a traditional Chinese medicine used to treat GI ailments. YIV-906 is a standardized pharmaceutical subjected to quality-control measures including chemical fingerprinting, individual target bioassays, and genomic bioresponse profiling. Phase I/II clinical trials demonstrated the safety of YIV-906 in combination with irinotecan- and capecitabine-based chemotherapy and a reduction in GI side effects. In addition, these studies suggest that YIV-906 may enhance the tumor response to chemotherapy by altering the expression of pro-inflammatory cytokines. In a preclinical study, YIV-906 selectively decreased intestinal injury from abdominal radiation (RT) without compromising tumor control. Therefore, a pilot phase I trial was launched to evaluate the novel combination of YIV-906 with neoadjuvant CRT for rectal cancer.

Methods: A total of 22 patients with clinical stage T3-T4 and N0-N2 rectal adenocarcinoma have enrolled out of a goal accrual of 24 patients. To date, 19 patients have completed the treatment protocol which consists of 3D-conformal pelvic RT to 50.4 Gy in 1.8 Gy fractions with capecitabine (825mg twice daily on days 1-5 of RT each week) and YIV-906 (800mg PO twice daily on days 1-4 of RT each week). The primary endpoint is grade 3-4 GI toxicity by CTCAE v4.0 assessed weekly during RT, and until at least 30 days after RT, with a goal of $\leq$ 10% grade 3-4 acute GI toxicity. The secondary endpoint is pathologic response.

Results: Of the 19 patients who have completed the protocol, 1 patient (5.3%) developed grade 3 diarrhea. There were no other grade 3-4 GI toxicities, and no toxicities attributed to YIV-906. Rates of grade 1-2 GI toxicities were as follows: 84% anorectal pain, 68% diarrhea, 58% nausea, 42% constipation, 21% emesis, and 5% dyspepsia. Three patients (15.8%) had a complete pathologic response at the time of surgery, while 1 had a near complete response, 13 had a moderate response, 1 had a minimal response, and 1 had no definite response. At a median follow up of 18.3 months, 1 patient developed a local recurrence, and 3 patients developed metastatic disease.

Conclusion: This is the first clinical trial to evaluate YIV-906 in combination with RT. Preliminary results demonstrate the safety of YIV-906 with chemoradiation for locally advanced rectal cancer. The rate of GI toxicities and pathologic response are favorable compared to historical controls. Thus YIV-906 is a promising adjunct to pelvic chemoradiation that warrants further evaluation. 1Sauer R, Becker H, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731-40.