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International phase II randomized placebo-controlled study investigating the combination of YIV-906 plus sorafenib (SORA) in HBV (+) patients (Pts) with advanced hepatocellular carcinoma.

Ghassan K. Abou-Alfa, Yun Yen, James J. Harding, Jacqueline Whang-Peng, Yuankai Shi, Man Fung Yuen, Xiuhui Li, Shanzhi Gu, Chenghai Liu, Long-Bin Jeng, Chia Jui Yen, Calvin Q Pan, San-Chi Chen, Jason Chia-Hsun Hsieh, M Wasif Saif, Shwu-Huey Liu, Fangyong Li, Wing Lam, Edward Chu, Yung-Chi Tommy Cheng; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, Cornell University; Trinity College Dublin, New York, NY; Taipei Medical University, Taipei City, Taiwan; Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY; Taipei Medical University, Taipei, Taiwan; Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; Queen Mary Hospital, The University of Hong Kong, Hong Kong, Hong Kong; Beijing Youan Hospital, Capital Medical University, Beijing, China; Department of Interventional Radiology, Hunan Cancer Hospital, the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; Shanghai University of Traditional Chinese Medicine Shuguang Hospital, Shanghai, China; Organ Transplantation Center, China Medical University Hospital, Taichung, Taiwan; Department of Oncology, National Cheng Kung University Hospital, Tainan, Taiwan; Calvin Pan. MD Gastroenterology & Hepatology Clinic, New York, NY; Division of Medical Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan; Linkou Chang Gung Memorial Hospital, Taoyuan City, Taiwan; Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI; Yiviva Inc., New York, NY; Yale University, New Haven, CT; Yale University School of Medicine, New Haven, CT; Albert Einstein Cancer Center, Bronx, NY

Background: YIV-906 (formerly PHY906/KD018), inspired by an 1800-year traditional botanical medicine formulation, is being developed under the FDA's botanical drug guidance (IND's 138525 and 62627) for treating gastrointestinal ailments associated with chemotherapeutics or chemoradiation. Multi-targeted tyrosine kinase inhibitors, SORA and Lenvatinib, are first-line systemictreatment options for advanced HCC pts, are limited by high rates of grade ≥ 3 treatment-related adverse events. Preclinical data suggests YIV-906 increases tumor microenvironment inflammation by M1 macrophage activation/proliferation resulting in HCC tumor rejection *in vivo* and reduces SORA-associated toxicity, suggesting improved safety and potential clinical benefit for pts. **Methods:** An international, multicenter, double-blind, placebo-controlled, randomized phase 2 study was conducted examining YIV-906's impact on SORA in advanced HCC pts (NCT04000737), stratified by metastatic status and ECOG Performance Status. The primary endpoint was progression-free survival (PFS). Secondary endpoints were TTP, ORR, and DCR by RECIST1.1; OS, QoL, and safety by CTCAE version 5.0. Per Protocol Set (PPS) analysis exclude patients with misrandomizations and major protocol violations impacting data integrity and quality. Translational correlatives include pharmacokinetics and exploratory soluble biomarkers analysis. **Results:** From 18 Feb 2020 to 03 Jun 2023, 107 pts were screened across 20 study sites in 4 regions (US and Asia). 62 chronic HBV(+) HCC systemic treatment naïve pts with Child-Pugh A liver function were randomized to a 2:1 ratio, (41 pts YIV-906 arm, 20 pts placebo arm). The Investigator-assessed mPFS per RECIST 1.1 was slightly longer in the YIV-906 arm than the placebo arm in ITT group (N = 62). PPS Subgroup analyses indicated: significant improvement in PFS in pts completing at least 2 treatment cycles (N = 49); YIV-906 arm mPFS is 5.6 months (95% CI: 3.6, 7.2) vs. placebo arm 2.3 months (95% CI: 1.9, 3.9) respectively; a 69% reduction in risk of disease progression or death (HR = 0.31 [95% CI: 0.13, 0.72]; p = 0.004). The YIV-906 arm mOS was 14.3 months (95% CI: 8.2, 18.8) vs placebo arm 8.0 months (95% CI: 4.6, 32.1), HR of 0.97 (95% CI: 0.51, 1.84; p = 0.92). In the secondary endpoint ORR, improvement was also observed by the investigator. YIV-906 arm pts tolerated SORA longer, with manageable toxicity profile. No new safety signals in YIV-906 + SORA treated pts were identified compared with sorafenib monotherapy. **Conclusions:** In this limited cohort of patients with confirmed HBV (+) HCC diagnosis, our findings suggest that YIV-906 is effective for increasing SORA's therapeutic index and clinical activity, and supports further studies of YIV-906. Clinical trial information: NCT04000737. Research Sponsor: Yiviva Inc.