LB-1

IL-1 Receptor Antagonist in Combination with Pentoxifylline and Zinc for Severe Alcoholic Hepatitis: A Multicenter Randomized Double-Bind Placebo-Controlled Clinical Trial

Dr. Gyongyi Szabo[1], Dr. Mack C. Mitchell[2], Dr. Craig J McClain[3], Dr. Srinivasan Dasarathy[4], Dr. Arthur J. McCullough[4], Laura Nagy[4], Aimee Kroll-Desrosiers[1], Svetlana Radaeva[5] and Bruce Barton[1], (1)University of Massachusetts Medical School, (2)University of Texas Southwestern Medical Center, (3)Department of Medicine Division of GI, Hepatology and Nutrition, Department of Pharmacology & Toxicology, Alcohol Research Center, Hepatobiology & Toxicology Center, University of Louisville, Louisville, KY, Robley Rex Louisville VAMC, University of Louisville, (4)Cleveland Clinic, (5)National Institutes of Health National Institute on Alcohol

Background: Severe alcoholic hepatitis (AH) with MELD > 20 and MDF > 32 is a serious condition with high short-term mortality. This study evaluated the safety and efficacy of the combination of recombinant human interleukin-1 receptor antagonist (anakinra), pentoxifylline (PTX) and zinc (Zn) sulfate in patients with AH. We aimed to target critical pathogenic elements of AH: inflammation (anakinra), protection from cellular injury (PTX) and gut leakiness (Zn). **Methods:** Subjects with clinical diagnosis of severe AH (MELD>20, MDF>32) were randomized to methyl prednisolone (32 mg orally daily for 28 days (PRED) or a combination of anakinra, 100 mg daily subcutaneously for 14 days plus PTX 400 mg orally 3 times daily for 28 days plus Zn 220 mg orally daily for 180 days (IL-1RA). Endpoints included mortality at 30, 90 and 180 days. A Cox proportional regression analysis was used to identify variables associated with mortality. **Results:** A total of 103 patients were enrolled over 4 years at 4 sites. Fifty-three patients were randomized into the IL-1RA and 50 to the PRED arms. At baseline, the mean age was 45.3±10.4 years, 63% were males, 96% white, mean MELD 25.7±3.0 (range 20-40). Baseline characteristics were comparable between treatment groups. Survival probability (Kaplan-Meier estimates) at 180-day post randomization, the primary outcome, was 66.8% in the IL-1RA and 52.8% in the PRED group (HR=0.69; p=0.26). Survival at 30 days was similar between the IL-1RA (83.4%) and PRED groups (81.2%) (HR=0.91, p=0.85). Separation of the survival curves was noted by 90 days (IL-1RA: 69.7%; PRED: 55.8%; HR=0.69, p=0.28). Five subjects were lost to follow-up (IL-1RA:3; PRED:2). In Cox regression analysis, higher baseline MELD score was independently associated with mortality (p=0.003). No unexpected treatment-related severe adverse events were noted in either group. The incidence of infection was comparable in both groups. Survival at 180 days in subjects with initial MELD 20-25 (72.6%) was significantly higher than those with initial MELD 26-31 (45.2%) (HR=2.9, p=0.003). Both MELD strata (MELD 21-25; MELD 26-31) showed non-significant treatment effects in favor of IL-1RA. **Conclusion:** A combination of anakinra, PTX and Zn provides comparable short-term and may provide long-term survival benefits compared to currently used PRED therapy in severe AH. Initial MELD is an important predictor of survival at 30, 90 and 180 days.

Disclosures:

Gyongyi Szabo – Novartis: Consulting; Carlos Foundation: Advisory Committee or Review Panel; Glympse Bio: Consulting; Trek Therapeutics: Consulting; Jannsen Research and Development: Consulting; Orbimed: Consulting; Roviant: Consulting; Salix: Consulting; Tobira: Consulting; Allergan: Consulting; Hepatology Communications: Advisory Committee or Review Pan

Mack C. Mitchell – Amygdala Neuroscience: Stock Shareholder; Pfizer: Stock Shareholder; Johnson & Johnson: Stock Shareholder

Craig J McClain – NIH: Grant/Research Support; VAMC: Employment; Nestle: Advisory Committee or Review Panel; Durect: Consulting; Amgen: Consulting; Diapharma: Advisory Committee or Review Panel; Discus: Advisory Committee or Review Panel; Gilead: Grant/Research Support; Allergan: Grant/Research Support; Target NASH: Grant/Research Support; Intercept: Grant/

Srinivasan Dasarathy – National Institutes of health: Grant/Research Support

The following people have nothing to disclose: Arthur J. McCullough, Laura Nagy, Svetlana Radaeva

Disclosure information not available at the time of publication: Aimee Kroll-Desrosiers, Bruce Barton

LB-2

Nivolumab in Patients with Child-Pugh B Advanced Hepatocellular Carcinoma (aHCC) in the CheckMate-040 Study

Dr. Masatoshi Kudo[1], Dr. Ana M Matilla[2], Dr. Armando Santoro[3], Dr. Ignacio Melero[4], Dr. Antonio Cubillo Gracian[5], Dr. Mirelis Rivera Acosta[6], Dr. Su Pin Choo[7], Dr. Anthony El-Khoueiry[8], Dr. Ryoko Kuromatsu[9], Dr. Bassel El Rayes[10], Dr. Kazushi Numata[11], Dr. Yoshito Itoh[12], Dr. Francesco Di Costanzo[13], Dr. Oxana Crysler[14], Dr. Maria Reig[15], Yun Shen[16], Jaclyn Neely[17], Christine Dela Cruz[17], Carlos Baccan[17] and Dr. Bruno Sangro[18], (1)Kinki University, (2)Hepatology, H.G.U. Gregorio Marañón, (3)Department of Medical Oncology and Hematology, Humanitas Research Hospital, (4)Immunology and Immunotherapy Service, Clinica Universidad De Navarra, (5)Medical Oncology, Hospital of Madrid, (6)Department of Medicine, Fundacion De Investgacion, (7)Gastrointestinal Cancer Service, National Cancer Center Singapore, (8) Norris Comprehensive Cancer Center, University of Southern California, (9)Department of Medicine, Kurume University Hospital, (10)Clinical Research of the Department of Hematology and Medical Oncology, Emory University Winship Center, (11)Gastroenterological Center, Yokohama City University Medical Center, (12)Division of Gastroenterology and Hepatology, Kyoto Prefectural University, (13)Department of Medical Oncology, Azienda Ospedaliero Universitaria Careggi, (14)Medical Oncology, University of Michgan Rogel Cancer Center, (15)Barcelona Clinic Liver Cancer (BCLC) Group. Liver Unit, Hospital Clínic, Idibaps, Ciberehd, University of Barcelona, Spain, (16)Biostatistics, Bristol-Myers Squibb, (17)Clinical Research, Bristol-Myers Squibb, (18)Liver Unit, Clinica Universidad De Navarra

Background: Many patients (pts) with HCC have Child-Pugh B liver function status and tend to have a poorer prognosis (Greten et al *British J Cancer* 2005), but are often excluded from aHCC trials. Lack of novel treatments and the unclear benefit of sorafenib (SOR) in pts with Child-Pugh B result in a high unmet need for this patient population (Federico et al *Oncol Lett* 2015, Da Fonseca et al *Mol Clin Oncol* 2015). The PD-1 inhibitor nivolumab (NIVO) is approved in the US, Canada, and elsewhere for SOR-treated pts with Child-Pugh A aHCC based on results from dose-escalation and -expansion phases of CheckMate-040 (NCT01658878) (El-Khoueiry et al *Lancet* 2017). Here we report data from the Child-Pugh B cohort of CheckMate-040, the first prospective study of immunotherapy in pts with Child-Pugh B aHCC. **Methods:** SOR-naïve (n=25) or -experienced (n=24) pts with Child-Pugh B (B7–B8) aHCC received NIVO 240 mg IV for 30 min Q2W (flat dose) until unacceptable toxicity or disease progression. Primary endpoints were objective response rate (ORR) (investigator assessed [INV], using RECIST v1.1) and duration of response (DOR). Safety analysis was performed on all treated pts using NCI CTCAE v4.0. Data from cohorts 1 and 2, in which almost all pts had Child-Pugh A status, are presented for comparison. **Results:** Among 49 analyzed pts,