V. Di Marco[1] and RESIST-HCV (Rete Sicilia Selezione Terapia – HCV).
[1]RESIST-HCV and Palermo; [2]RESIST-HCV, Messina; [3]RESIST-HCV, Catania; [4]RESIST-HCV, Siracusa; [5]RESIST-HCV, Agrigento; [6]RESIST-HCV, Modica; [7]RESIST-HCV, Comiso; [8]RESIST-HCV, Enna; [9]RESIST-HCV, Castelvetrano; [10]RESIST-HCV, Trapani; [11]RESIST-HCV, Messina, Italy
E-mail: giuseppe.cabibbo78@gmail.com

Background and Aims: Direct-acting antivirals (DAAs) therapy induces the clearance of hepatitis C virus (HCV) in the majority of patients with chronic liver disease. The risk developing hepatocellular carcinoma (HCC) decreases after Sustained Virological Response (SVR). However, the risk of HCC occurrence during and after DAA based treatment and the clinical pattern is still debated. With this aim we analysed the on-going dataset from RESIST-HCV, which includes all HCV patients who started DAAs treatment in 22 Centres of Sicily.
Methods: Between March 2015 and October 2016, 10,123 patients with HCV chronic liver disease were included in the RESIST-HCV and 5130 started the treatment. Each physician established DAA regimen and use of RBV. Patients performed surveillance of HCC as indicate by guidelines before and after treatment. We evaluated the HCC occurrence in 3447 patients who concluded DAA treatment. The primary endpoints of this analysis were the time to HCC occurrence from start of DAA and the pattern of HCC at the diagnosis.
Results: Patients had a mean age of 64.3 years, 58% were males and 47% were naïve to antiviral therapy. The diagnosis of chronic hepatitis was performed in 764 patients (22.2%), while 2363 patients (68.6%) had Child-Pugh A cirrhosis and 320 patients (9.2%) had Child-Pugh B cirrhosis. Diabetes was present in 802 patients (23%). The Ribavirin was associated to DAA regimes in 1577 patients (45.7%), 2197 patients (63.7%) received a 12 weeks DAA regimen and 1250 patients (36.3%) received a 24 weeks regimen. During the observation (mean 34.2 weeks, range 8–72) 55 patients developed HCC with an overall rate of 1.44%. The occurrence of HCC was 0.13%, 1.69% and 4.37% in chronic hepatitis, Child-Pugh A cirrhosis and Child-Pugh B cirrhosis, respectively ($p < 0.001$). At the time of HCC diagnosis 49 patients (89.1%) meet Milan criteria and 6 patients (10.9%) were Milan-out. The evaluation of SVR was available in 2001 patients. By intention to treat analysis, 1752 patients (87.5%) achieved a SVR and 249 (12.5%) patients remained HCV-RNA positive. The rate of HCC occurrence was 1.48% (26/1752) in patients who achieved SVR and 4.0% (10/249) in patients who maintained HCV viremia ($p = 0.0089$).
Conclusions: The occurrence of 'de novo' HCC in patients treated with DAAs was similar to that observed in historical cohorts of patients who obtained SVR after interferon-based therapy. Patients with virological response to DAA and who achieved SVR had a lower risk to develop HCC than patients who maintained HCV viremia.

Hepatitis B and D: Emerging treatment options

PS-039
A phase 2 dose-escalation study of lonafarnib plus ritonavir in patients with chronic hepatitis D: final results from the Lonafarnib with ritonavir in HDV-4 (LOWR HDV-4) study

H. Wedemeyer[1], K. Port[1], K. Deterding[1], A. Wranke[1], J. Kirschner[1], B. Bruno, B. Martins[2], J.S. Glenn[3], M. Kornberg[1], M.P. Manns[1].
[1]Hannover University Medical School, Hannover, Germany; [2]Eiger BioPharmaceuticals; [3]Stanford University School of Medicine, Palo Alto, United States
E-mail: eduardo.b.martins@green.oxon.org

Background and Aims: Globally 15–20 million people are co-infected with hepatitis delta (HDV) and hepatitis B (HBV) viruses. Lonafarnib (LNF) is an oral prenylation inhibitor (PI) that has been shown to reduce levels of HDV RNA in a dose-dependent manner. Prenylation inhibitors are associated with gastrointestinal (GI) adverse effects (AE) at higher doses, but a slow step-wise increase in dose has been shown to be well-tolerated in a pediatric population. LOWR HDV-4 is an open-label, dose-escalation study of LNF + ritonavir (RTV) in patients with HDV to investigate if rapid step-wise increases in LNF dose can allow more patients to achieve higher doses.
Methods: Inclusion criteria: positive HDV RNA by qPCR, ALT < 10 × ULN, compensated liver disease, platelets > 90.000/µL. All patients were started on LNF/RTV (50 mg/100 mg bid). If well tolerated, LNF could be increased to 75 mg bid after a minimum of 4 wks, and next to 100 mg bid after a minimum of 2 weeks since the last escalation. RTV was maintained at 100 mg bid. Treatment was administered for 24 wks, followed by 24 wks of treatment-free follow-up (FU). HDV RNA (Robogene 2.0, LLOQ 14 IU/mL) and ALT were assessed at each visit.
Results: 15 patients (11 male) were enrolled. At baseline (BL), mean HDV RNA was 4.60 ± 1.05 $\log_{10}$ IU/mL; mean ALT 118 IU/mL (54–362 IU/mL), mean Fibroscan 14.6 kPA (3.6–35.3 kPA). 12 patients were on a HBV nucleos(t)ide (NUC) at BL, and 3 added a NUC during treatment in response to increasing HBV DNA associated with HDV RNA decline. A dose-escalation to LNF 100 mg bid + RTV was possible in 10 patients (66%), 5 of which remained at this dose until EOT. 13/15 patients completed 24 weeks of therapy. At EOT, mean HDV RNA decline from BL was -1.58 ± 1.38 $\log_{10}$ IU/mL; one patient became PCR-negative and one patient had HDV RNA < LLOQ. ALT normalized in 53% of patients. In FU visits to date, one patient remains <LLOQ at wk 8 of FU; 5 patients had post-treatment ALT flares with normal liver function. AE were mostly grade 1–2 intermittent diarrhea; 4 patients had grade 3 AE (2 diarrhea; 1 asthenia, 1 weight loss). There was 1 SAE (traumatic jaw fracture, unrelated to LNF).
Conclusions: LNF therapy leads to HDV RNA decline in all patients, a proportion may achieve HDV RNA suppression which can be sustained beyond therapy. Individualized LNF dose-escalation is a possible strategy to overcome GI adverse effects allowing longer durations of this all-oral treatment regimen. Final end of study data will be presented.

PS-040
Pharmacokinetics, safety and antiviral activity of CMX157, a novel prodrug of tenofovir, administered as ascending multiple doses to healthy volunteers and Hepatitis B virus-infected subjects

T. Tanwandee[1], S. Chatsiricharoenkul[2], S. Thongsawat[3], W. Sukeepaisarnjaroen[4], P. Tangkijvanich[5], P. Komolmit[6], A. Avihingsanon[7], T. Piratvisuth[8], P. Sunthi[9], T. Mahasanprasert[9], T. Matkovits[10], M. Conover[11], J. Cobb[10], C. Canizares[11], J. Sullivan-Bolyai[12]. *[1]Division of Gastroenterology; [2]Department of Pharmacology, Siriraj Hospital, Bangkok; [3]Division of Gastroenterology, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai; [4]Division of Gastroenterology and Hepatology, Srinagarind Hospital, Khon Kaen; [5]Hepatitis and Liver Cancer Unit; [6]Division of Gastroenterology, King Chulalongkorn Hospital; [7]Department of HBV Research, HIV Netherlands Australia Thailand Research Collaboration, Bangkok; [8]Division of Gastroenterology and Hepatology, Songklanagarind Hospital, Songkla; [9]Clinical Operations, Aclires Bangkok, Ltd., Bangkok, Thailand; [10]Drug Development; [11]Clinical Operations; [12]Medical, ContraVir Pharmaceuticals Inc., Edison, United States*
E-mail: jgreytok@contravir.com

Background and Aims: CMX157 is a novel prodrug of the acyclic nucleotide phosphonate tenofovir (TFV). By converting TFV into a lipid moiety, there is an increase in oral bioavailability, targeted cellular uptake through natural lipid absorption pathways and cellular conversion of CMX157 into TFV di-phosphate. A single dose rat study of 20 mg/kg CMX157 demonstrated 86% first pass liver extraction. This experiment along with preclinical safety, ADME, and early toxicology results lead to the development of a clinical program. The present, multiple dose, studies were designed