EF CLIF
EUROPEAN FOUNDATION FOR THE STUDY OF CHRONIC LIVER FAILURE

20 October 2023

The 5th DECISION General Assembly highlights the commitment and collaborative effort of all partners in the Consortium

Members of the DECISION Consortium meet in Padova, Italy, to discuss recent research results in preparation of several manuscripts shedding some new light on the pathophysiology of acute decompensation of cirrhosis and development of acute-on-chronic liver failure (ACLF) – a syndrome associated with high short-term mortality. After three years of intensive work, the upcoming COMBAT trial will use newly identified biomarkers to predict disease progression and test safety and effectiveness of a combinatorial drug therapy.

PADOVA—The DECISION General Assembly was held on 18–20 October 2023 and run in a hybrid format from Padova, Italy. This annual meeting is meant to bring together members of partner institutions to review project progress and help researchers to put their results into perspective, sharing their findings contributes to add clarity to the studies carried out within the project and set the direction to achieve expected project outcomes.

On day 1, in an extraordinary investigator meeting before the official start of the 5th DECISION General Assembly, **Paolo Caraceni** (University of Bologna, Italy) described the objectives, design, methodology, statistical considerations and logistic aspects related to the COMBAT trial – a clinical trial that will evaluate safety and effectiveness of the most promising drug combination identified through data-driven and pre-clinical studies carried out within DECISION. **Cristina Sánchez-Garrido** (Head of the Data Management Center at EF CLIF, Spain) introduced the features on the newly designed electronic case report form that will be used to collect data from patients participating in the clinical study.

Later, Coordinator of DECISION **Pierre-Emmanuel Rautou** (Inserm–Université Paris Cité, France), for and on behalf of EF CLIF, welcomed all members of the Consortium attending the General Assembly both in person and online, and introduced **Paolo Angeli** (University of Padova, Italy) who delighted the audience with a keynote lecture on the natural history of decompensation of cirrhosis.

On day 2, **Estefania Huergo Iglesias** (Navarrabiomed, Spain) presented results on epigenetic signatures of circulating immune cells in patients with acute decompensation of cirrhosis in the PREDICT cohort. The epigenetic signatures identified are the basis of a new prognostic model to be developed that will be validated in the ACLARA cohort. **Richard Moreau** (Inserm–Université Paris Cité, France; EF CLIF, Spain) presented an update on whole-blood transcriptomics. RNA-sequencing identified distinct patient clusters based on gene expression characteristics at hospital admission. Moreau showed differentially expressed genes and differentially expressed blood transcription modules across clusters that were associated with development of ACLF and poor patient outcomes. **Sara Palomino** (Navarrabiomed, Spain) and **Theresa Wirtz** (University Hospital Aachen, Germany) used single-cell transcriptomic approaches to understand the pathophysiological characteristics of peripheral immune cells in patients with acute decompensation of cirrhosis at single cell level. They evaluated the relevance of peripheral immune cell differentially expressed genes for risk stratification and prognosis with the aim to identify novel diagnostic and therapeutic targets during the course of acute decompensation of cirrhosis and ACLF. Their results were validated in the PREDICT and ACLARA cohorts. **Christian Trautwein** (University Hospital

Aachen, Germany) presented the results of a study that analyzed microRNAs in selected groups of patients within PREDICT and ACLARA. **Cristina López-Vicario** (Fundació Clínic per a la Recerca Biomèdica, Spain) looked at plasma inflammatory proteins and lipid mediators to identify new biomarkers of bacterial infections, development of ACLF and mortality at 90 days in a selected group of patients with acute decompensation of cirrhosis from the PREDICT cohort. **Shantha Valainathan** (Inserm–Université Paris Cité, France) used proteomic profiling approaches to identify large extracellular vesicle proteins associated with acute decompensation of cirrhosis and development of ACLF in a group of patients from the PREDICT and MICRO-SPY cohorts. Validation of selected extracellular vesicle protein biomarkers was carried out in a large number of samples from the PREDICT and ACLARA cohorts. Valainathan showed that plasma-derived large extracellular vesicles convey distinct protein signatures that reflect several pathophysiological processes of acute decompensation of cirrhosis and are associated with patient outcomes.

In the afternoon, **Sabine Klein** (University Hospital Münster, Germany) presented results on the characterization of liver injury induced by short- and long-term exposure to hepatotoxic chemical agents and consumption of a western-style diet in rats. Under these conditions, rats developed single or multiorgan system failure mimicking human chronic liver disease and ACLF. **Paolo Caraceni** (University of Bologna, Italy) presented an update on the status of the COMBAT trial protocol, regulatory approval and submission to the EU Clinical Trials Information System. With all logistics aspects regarding labeling and distribution of drugs solved and the electronic case report form set up and ready for use, Caraceni announced that the clinical trial will be initiated within the first quarter of 2024.

Next, **Tamara Breitinger** (Concentris GmbH, Germany) presented social media engagement indicators with a focus on DECISION Master Classes views. Master Classes are 1 h instructional videos by subject matter experts within the Consortium that review current knowledge and trends within a relevant topic of interest particularly addressed to participating early career researchers as part of the DECISION training program. The session ended with a Master Class on health economics trends and the economic burden of liver diseases by **Isabelle Durand-Zaleski** (Assistance Publique Hôpitaux de Paris, France).

On day 3, **Sara Palomino** presented results on a newly developed unsupervised clustering framework for stratification of patient with acute decompensation of cirrhosis. In a nutshell, she used data-driven methods to classify heterogenous mixed patient groups into homogenous patient groups based on clinical and laboratory data within the PREDICT and ACLARA cohorts. Palomino also showed that this computer model was robust and able to predict risk of developing ACLF and short-term mortality. **David Gomez-Cabrero** (Navarrabiomed, Spain) put results on data-driven models for stratification of patients with acute decompensation of cirrhosis and uniomics studies previously presented into perspective for future integrative, multiomics studies with the aim to develop a biomarker-based prognostic test and test for prediction of response to treatment. Next, **Hermann Mucke** (HM Pharma Consultancy, Austria), on behalf of all members of the Scientific and Ethical Advisory Board, shared his insights on the work presented throughout this three-day event. He acknowledged the mechanism-agnostic approach of DECISION in the collaborative effort to develop patient stratification models based on omics data.

In the final wrap-up and closing session, Rautou highlighted main results and papers to be submitted in the following months, reviewed key aspects of the COMBAT trial and briefly discussed next steps in the DECISION project. He thanked and congratulated each and everyone for the great work and feedback received.

This study received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 847949.

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About DECISION

Decompensated cirrhosis is an advanced form of cirrhosis of the liver associated with development of ascites, hepatic encephalopathy, gastrointestinal hemorrhage, and progression to acute-on-chronic liver failure (ACLF). Despite multiple treatments, mortality in patients with decompensated cirrhosis remains high. The EU-funded DECISION project aims to understand the pathophysiology of decompensated cirrhosis leading to ACLF and to decrease patient mortality. This project will integrate results of high-throughput multiomic profiling with comprehensive clinical data from 2200 fully characterized patients with available standardized biological samples. DECISION will help to identify novel combinatorial therapies to prevent high mortality for patients with decompensated cirrhosis. Combinatorial therapies will be optimized in novel animal models and the best combinations will be tested in patients at high-risk of progressing to ACLF in a phase II clinical trial.

About the COMBAT trial

The primary objective of the COMBAT trial – A novel combinatorial therapy with albumin and enoxaparin in patients with decompensated cirrhosis at high-risk of poor outcome – is to determine if a combinatorial therapy based on the administration of human albumin and enoxaparin is safe and effective in patients with decompensated cirrhosis discharged from the hospital.

ClinicalTrials.gov Identifier: NCT05895136

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