Liver Forum 21 Meeting
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Reporting on ACLF
Early Drug Development Webinar

Richard Moreau, MD
European Foundation for the Study of Chronic Liver Failure (EF CLIF), Barcelona, Spain
& INSERM, Paris, France

I have no disclosure

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- Dean Hum
- Meghan Rakowski
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- LF Sponsors

Webinar Held on June 24, 2026

- Convened by the Liver Forum-ACLF Steering Committee
- Jacqueline O'Leary (Dallas VA Medical Center) & Pejvack Motlagh (GENFIT): **Why ACLF drug development is unique?**
- Cornelius Engelmann (Charité (Universitätsmedizin Berlin), Thomas Berg, (Leipzig University Medical Center) & Dominique Thabut (AP-HP Sorbonne Université): **Challenges in recruitment and assessment in early phase studies in ACLF.**
- Scott Berry (Berry Consultants): **Phase 1 oncology trials.**
- Alexia Iasonos (Memorial Sloan Kettering Cancer Center): **Utilizing randomization, backfill and expansion cohorts to gain greater understanding in phase 1 trials.**

Novel therapies to be used on top of standard of care are needed to improve transplant-free survival of ACLF

Why is ACLF Early Drug Development Challenging?

- Heterogeneity of ACLF:
  - Precipitants: bacterial, fungal infections; alcohol-related hepatitis; GI hemorrhage; HBV flare; absent in 30%
  - Presence of one or more organ system failures (liver, kidney, brain, circulation, respiration)
  - Dynamicity during first days
  - Risk of death w/o liver transplantation by 28 days increases with the number of failing organs (20% to ~100%)
- Pathophysiology: Poorly understood
- Impaired liver and kidney functions, liver bypass through portosystemic shunts: necessity of testing pharmacokinetic and safety in phase 1/2a studies.

Lessons from the First Trials in ACLF

- GRAFT (Phase 2, G-CSF vs SOC): primary end point: 90-day transplant-free survival; early termination because conditional power analysis low probability of detecting a survival benefit.*
- DHELIVER (Phase 2, stem cell therapy vs SOC): primary end point: overall survival by 90 days; slow recruitment; early termination (sponsor decision).
- CONFIRM (Phase 3, terlipressin for HRS): Positive for the primary end point “verified HRS reversal”. Death was not the primary end point.
- None of these trials developed biomarkers.

*GRAFT: Engelmann et al. J Hepatol 2021;75:1346-54.

Why Oncology?

- Cancer:
  - Patients are too sick to wait
  - Early trials go directly to patients, not healthy volunteers
  - Disease heterogeneity is high, requiring biomarker-driven patient selection
  - Urgent to quickly identify active agents.
- ACLF: similar drug development challenge

Lessons from Oncology

- Oncology conducts first-in-human studies directly in “nonresponders” allowing joint efficacy-toxicity assessment in a single phase 1/2a “adaptive” trial.
- 3 different designs:
  - “Classical” 3 + 3
  - Continual Reassessment Method (CRM)
  - Backfilling included in Bayesian Optimal INterval (BOIN) design; allows trials generating robust data packages required by FDA across multiple doses simultaneously, saving time and protecting patients.

Next steps

- Writing a manuscript on challenges in ACLF early drug development and potential solutions:
    - Includes master protocols: adaptive platform, basket & umbrella trials.
- Pursue multidisciplinary discussions through the Liver Forum.