Combination Therapy in Cirrhotic NASH

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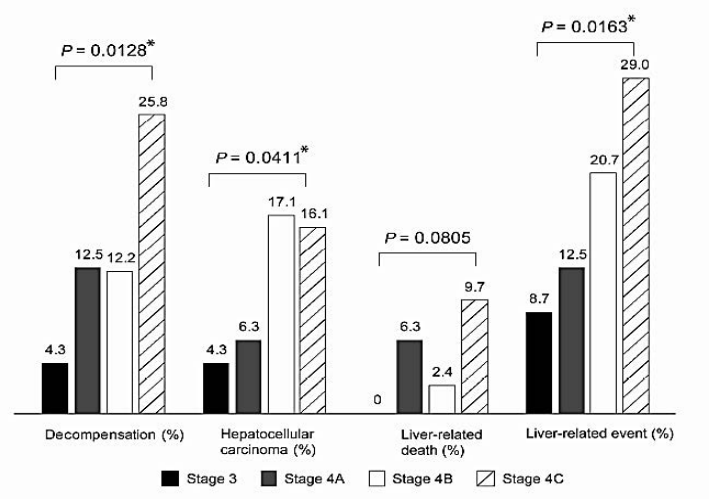
Disclosures

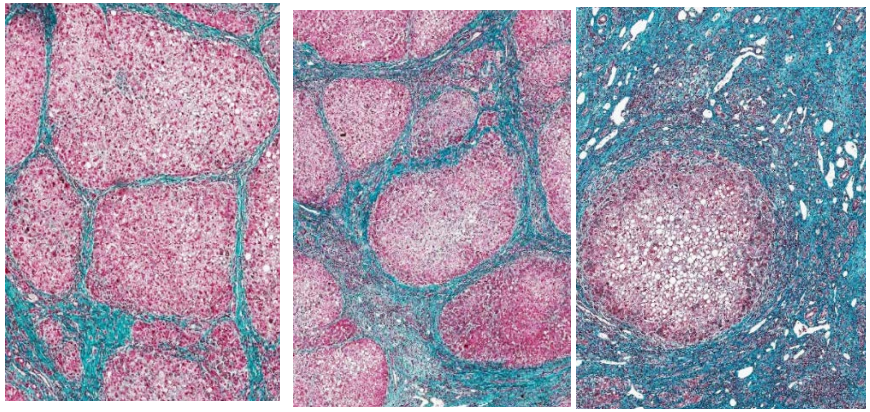
- Research Grants/Contracts: Galectin, Intercept, Genfit, Janssen*, Shire, Conatus, Zydus
- Consulting: Astra Zeneca/MedImmune
- * includes IP

Combination Therapy: NASH Cirrhosis

- Defining cirrhosis
- Targeting disease activity and fibrosis
- Safety in more advanced liver disease
- Monitoring combinations over [a long] time
- Endpoints – combining practical and meaningful

Cirrhotic NAFLD: spectrum within a spectrum





4a 4b 4c

	F1-F3		F4 (Cirrhosis)	
Histological				
Clinical	*Non-cirrhotic*	*Compensated*	*Compensated*	*Decompensated*
Symptoms	None	None (no varices)	None (varices present)	Ascites, VH, Encephalopathy
Sub-stage	-	Stage 1	Stage 2	Stages 3 and 4
Hemodynamic (HVPG, mmHg)	>6		>10	>12

courtesy P. Bedossa

Garcia-Tsao G, et al. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology 2010; 51: 1445–9

SU Kim, et al. The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. J Hepatol 2012

Compensated cirrhosis

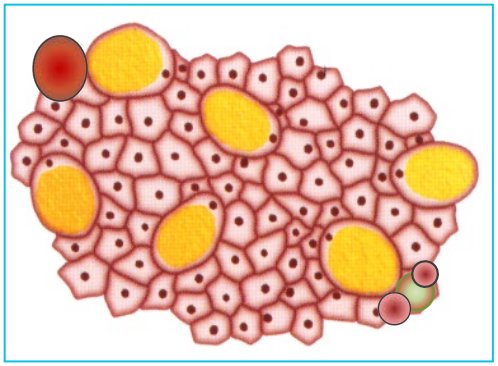
Minimal portal hypertension (MPH)

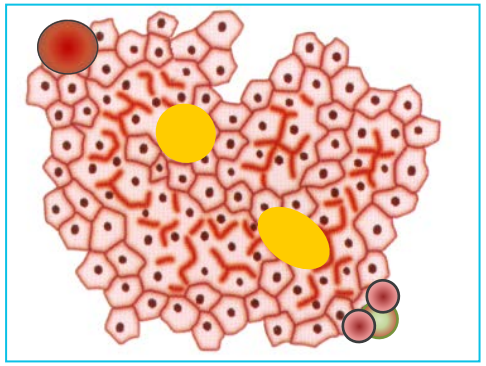
- 5mmHg < HVPG < 10mmHg
- Very low risk of decompensation
- Less liver fibrosis
- Increased intrahepatic resistance
- Treatment of underlying mechanism = may *prevent* CSPH

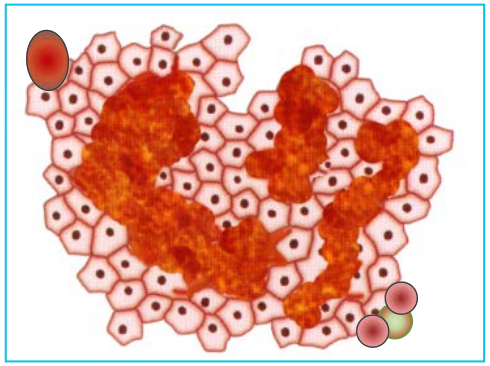
Clinically significant portal hypertension (CSPH)

- HVPG ≥ 10 mmHg
- 4 times higher risk of decompensation
- More fibrosis
- Increased splanchnic blood flow
- Treatment may decrease *time* to decompensation but risk still exists

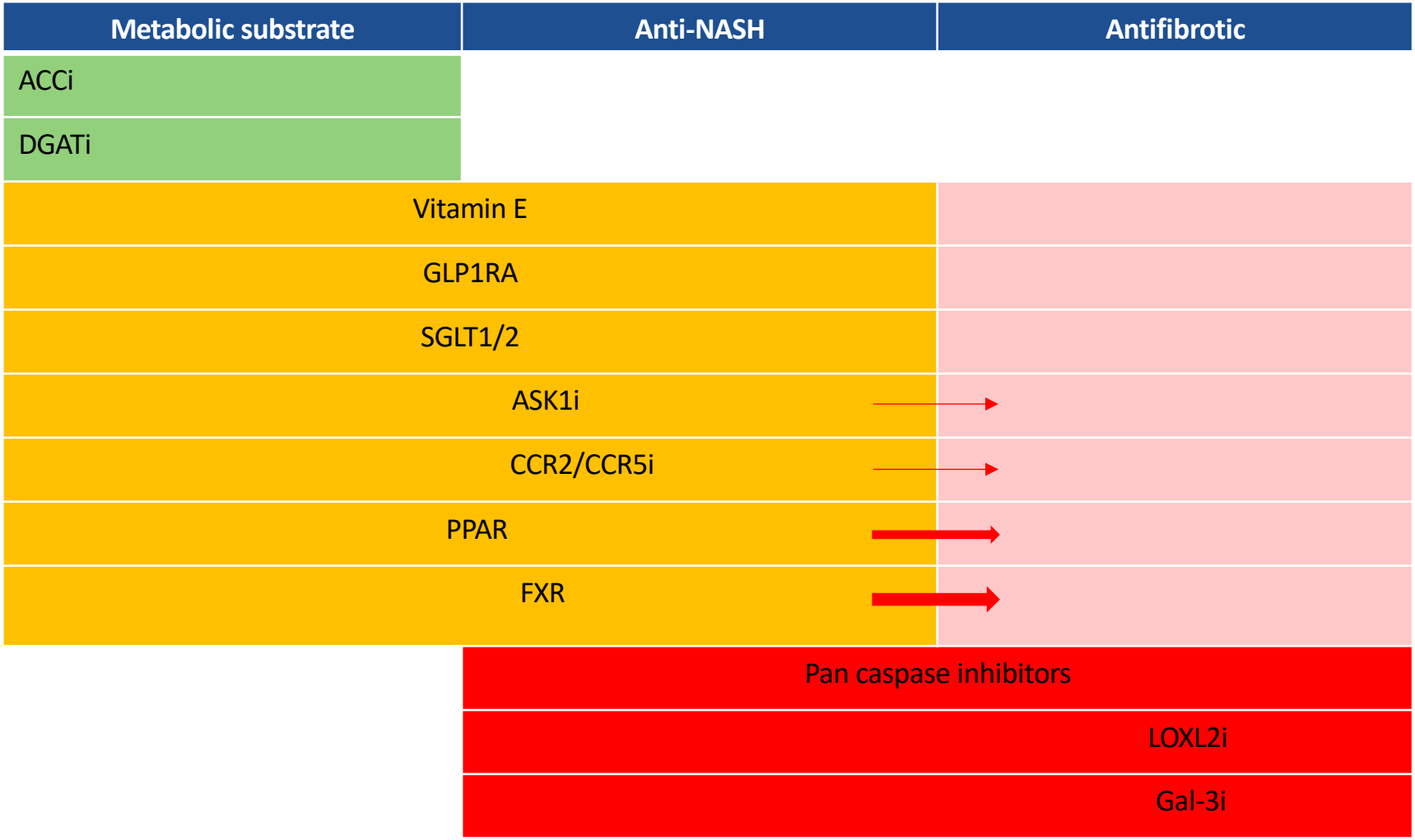
Combos in NASH Cirrhosis





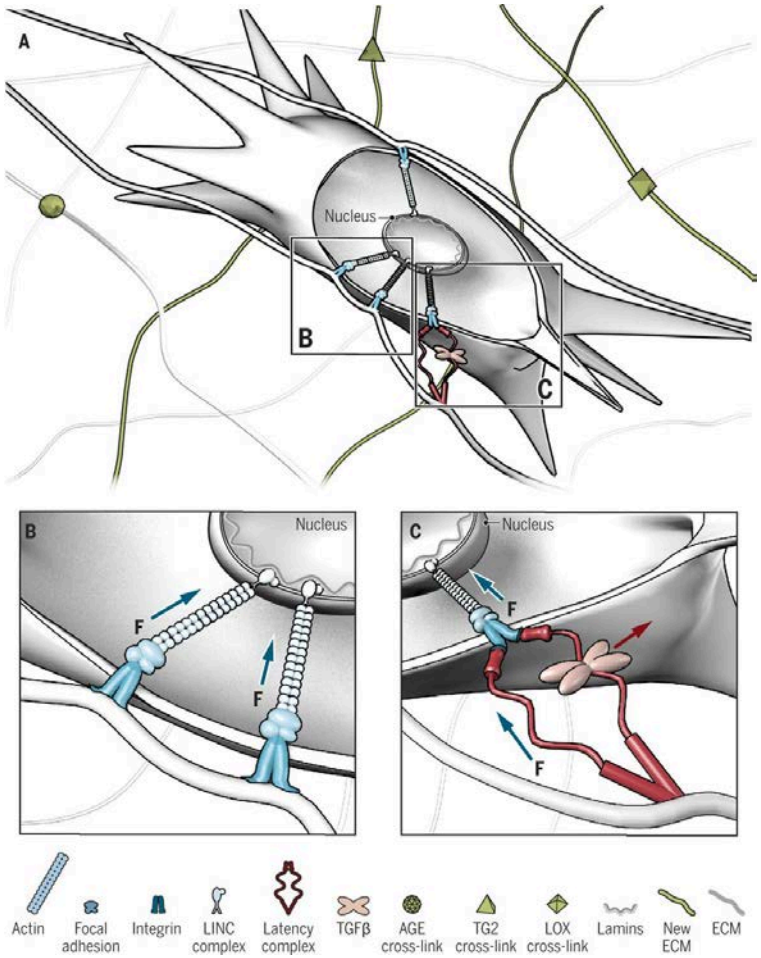


R E V E R S I B I L I T Y


Metabolic substrate
Anti-NASH
Antifibrotic
ACCi
DGATi
Vitamin E
GLP1RA
SGLT1/2
ASK1i
CCR2/CCR5i
PPAR
FXR
Pan caspase inhibitors
LOXL2i
Gal-3i

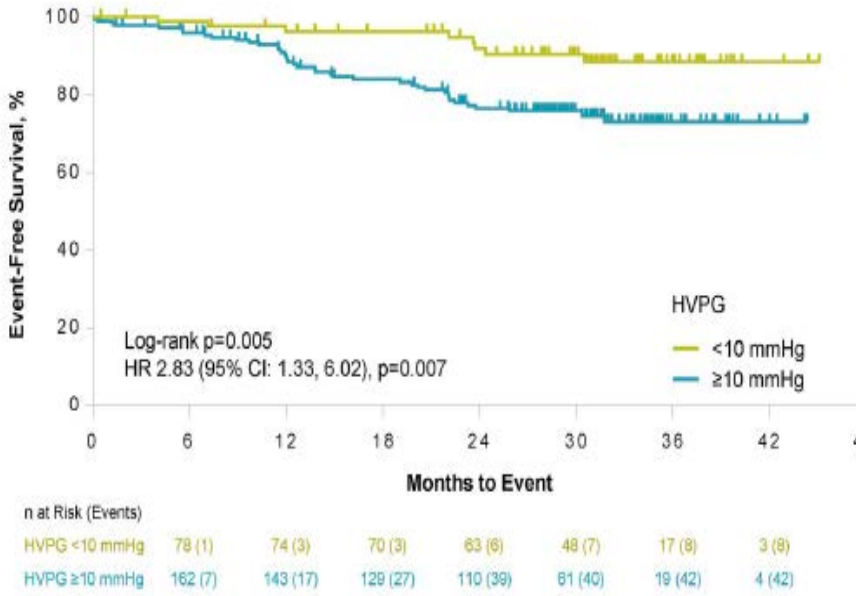
Rationale for Simtuzumab

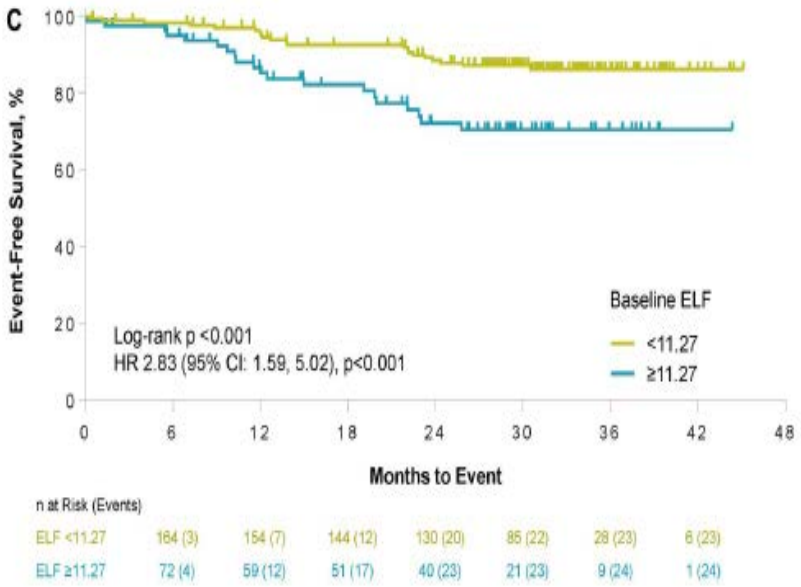
- Lysyl oxidase - like 2 is a secreted, copper dependent amino oxidase
- LOXL2 contributes to fibrogenesis by cross-linking collagen and elastin
- In murine models, LOXL2 stabilizes fibrotic matrix
  - Inhibition shown to decrease liver fibrosis
- Simtuzumab = monoclonal antibody directed at LOXL2



Marsha C. Lampi and Cynthia A. Reinhart-King Sci Transl Med 2018;10:eaao0475

Liver Related Clinical Events in Cirrhosis





Median follow up 30.1 mos (range, 0.1-45.1)
Events: ascites, encephalopathy, varices (new), EVH, CPT ≥2 point increase and/or MELD ≥15, death

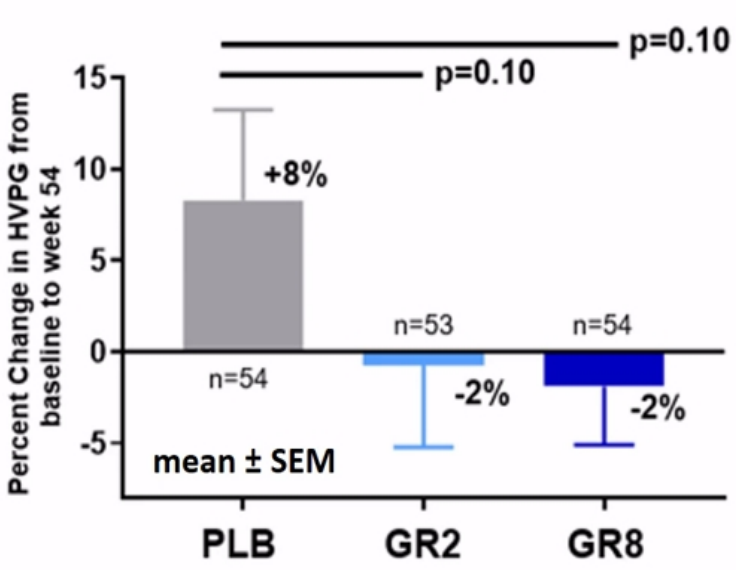
Sanyal, *Hepatology* 2019.

Rationale for GR-MD-02 (Galectin)

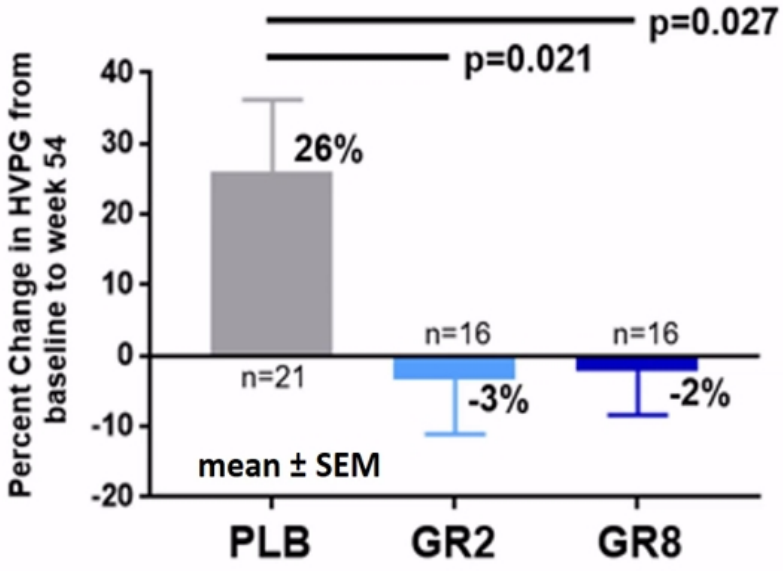
- Gal-3 is a lectin protein, binds galactose residues on glycoproteins
  - Increased in NASH, liver fibrosis, cirrhosis
  - Preclinical knockout models: resistant to development of NASH, fibrosis
- GR-MD-02 = complex carbohydrate drug
  - Inhibits gal-3
  - Improves histopathology of NASH and reverses fibrosis in animal models
  - Phase 1 studies demonstrated safety, tolerability in NASH with advanced fibrosis

HVPG Primary Endpoint (Pre-Specified Analyses)

Total Patient Population



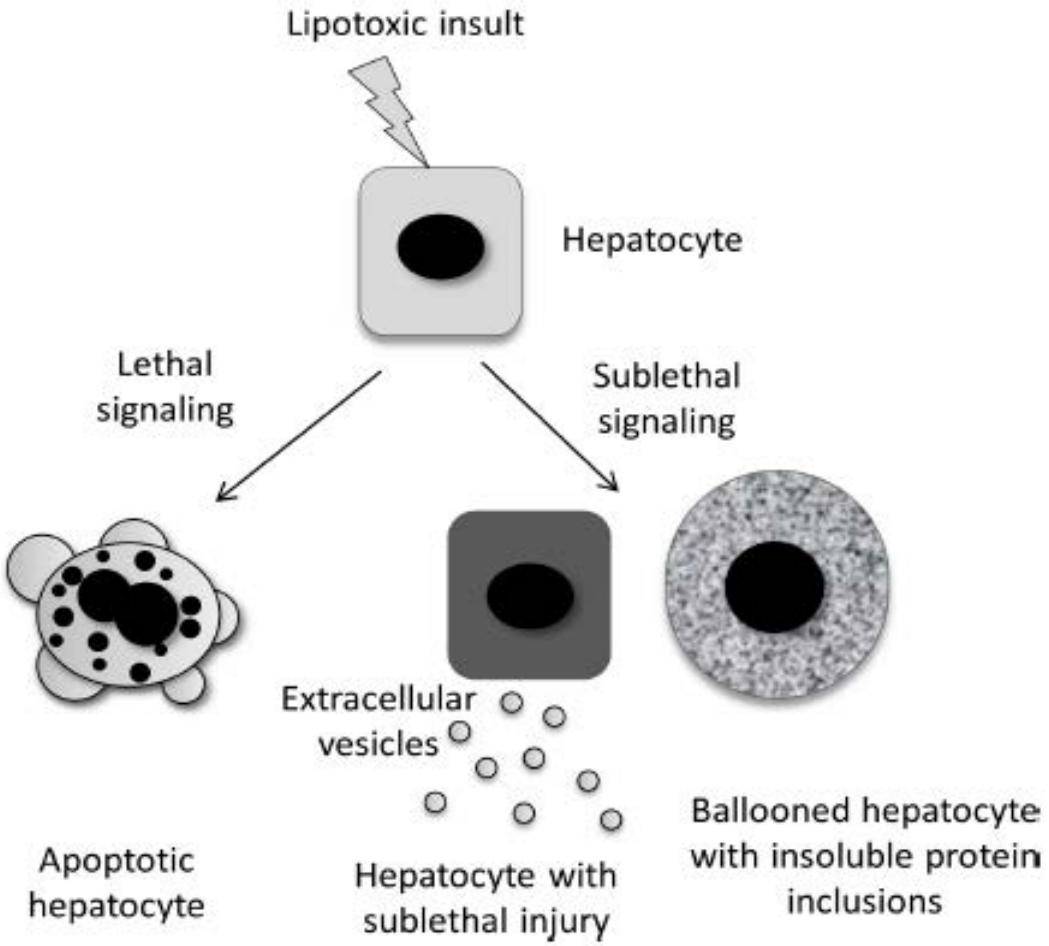
Mild Portal Hypertension



ITT with LOCF (last observation carried forward); ANOVA with LSD (least squared difference)

Emricasan: Rationale

- Caspase-mediated apoptosis has been observed with chronic liver disease (viral, metabolic)
- Accumulation of apoptotic cells and subcellular fragments like microvesicles contain biologically active particles
- Caspase cleaves cytokeratin-18 (CK-18)
  - Cleaved CK18 (cCK18) is a biomarker associated with inflammation in different etiologies of chronic liver disease (HCV, NAFLD, NASH)
- Inhibition of caspase activity may decrease apoptosis and associated microparticles



Ibrahim et al. *Gut*, Jan 2018

- NASH cirrhosis and baseline HVPG ≥12 mmHg
- Randomized vs placebo (5, 25, 50mg)
- N=263
- Primary endpoint HVPG at 24w
- Result: Failed to meet primary endpoint

Mean change from baseline at Wk 24	Emricasan 5 mg N=65	Emricasan 25 mg N=65	Emricasan 50 mg N=66	Placebo N=67
HVPG (Overall)	-0.6; p=0.96	-0.8; p=0.79	-1.0; p=0.65	-0.4
HVPG (compensated, HVPG ≥16 mmHg)	-1.6; p=0.01	-1.7; p<0.01	-1.5; p=0.02	+0.5

Garcia-Tsao EASL/ILC LB 2019

Safety in Cirrhosis

Metabolism altered with more advanced fibrosis and decompensation

Study population	CYP 450 enzyme	Child-Pugh scores	Change in activity
50 explanted cirrhotic livers[28]	CYP1A2	B/C	Reduced activity at Child-Pugh class C
Controls and liver failure patients[53]	CYP1A2	A/B/C	Reduced activity at Child-Pugh class C
50 explanted cirrhotic livers[28]	CYP2C9	B/C	Reduced activity at Child-Pugh class C
Controls and liver failure patients[53]	CYP2C19	A/B/C	Reduced activity at Child-Pugh class A, B, and C
Controls and liver failure patients[53]	CYP2D6	A/B/C	Reduced activity at Child-Pugh class B and C
In vitro liver tissue[50]	CYP3A	Noncholestatic cirrhosis	Reduced activity at Child-Pugh class B and C
		Cholestatic cirrhosis	No difference at any Child-Pugh class

CYP2D6 also expressed in adipose (Human Protein Atlas)

Doligalski et al. *Gastroenterology and Hepatology* 2012.

Safety – Combos with Caution

- ACCi - increased circulating TG + FXR agonist → increased LDL = increased atherogenesis
- Vitamin E + immunomodulators = carcinogenesis (long term follow-up)
- Malignancy concerns with advanced fibrosis
- Potentiation of off-target effects with potent antifibrotic combos

Endpoints in Cirrhosis (Compensated)

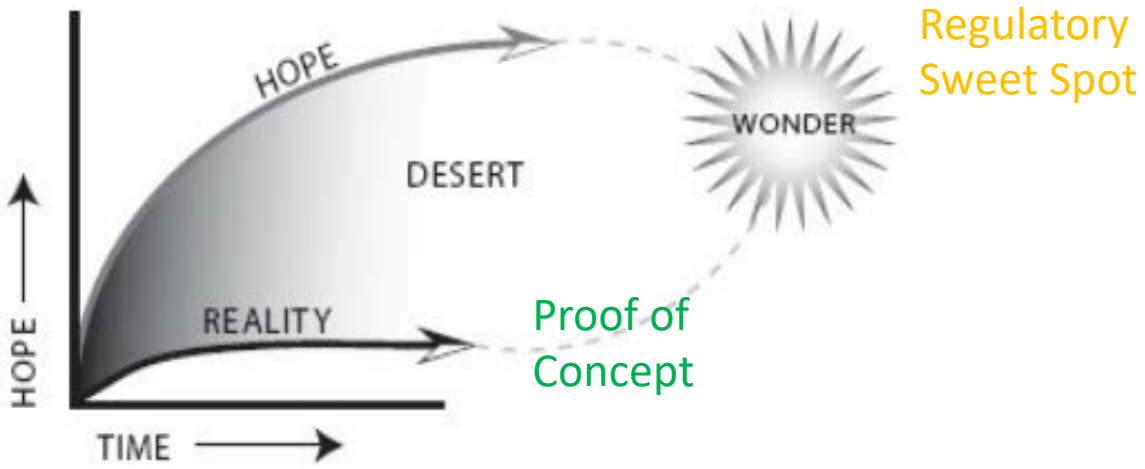
Proof of Concept

- Improvement in disease activity (NAS)
- No worsening of fibrosis
- No worsening of HVPG

Meaningful Benefit

- Reversal of fibrosis
  - >1 stage improvement in fibrosis
- Time to progression to CSPH
- Time to liver related clinical events

Meaningful benefit



Adapted from Paul Miller, NavPress 2009.