THE FORUM
For Collaborative Research℠

Overview: Trials in Patients with Cirrhosis

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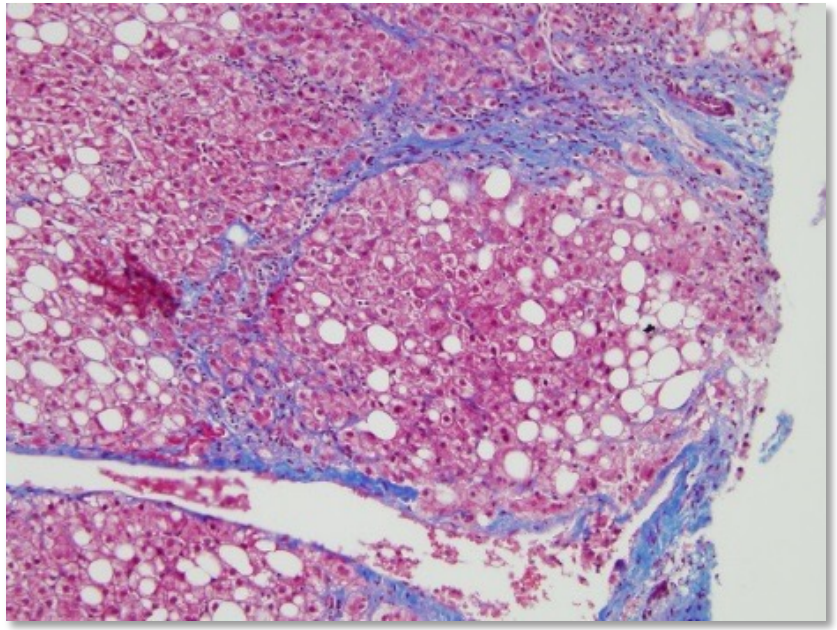
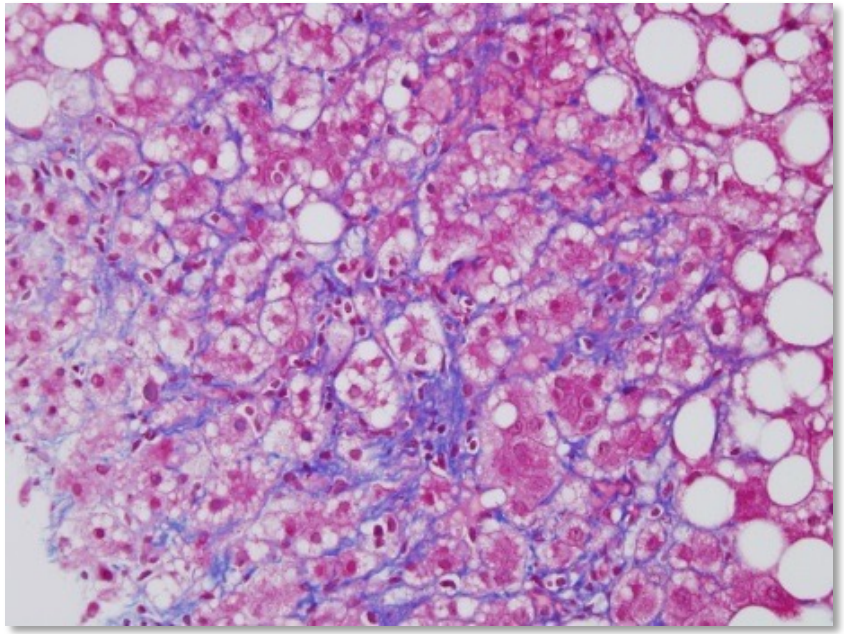
Clinical Trials Landscape-cirrhotic NASH





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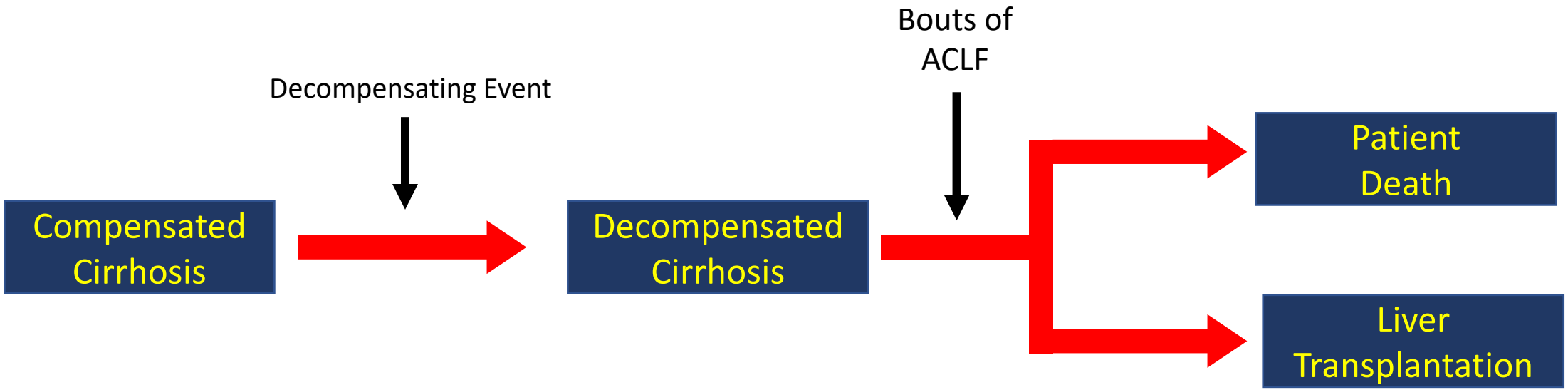
Conflicts of Interest

- Dr. Sanyal is President of Sanyal Biotechnologies
- Stock options for Genfit, Tiziana, Indalo, Durect, Exhalenz, Galmed
- Consultant- Gilead, Intercept*, Allergan*, Lilly, Novo Nordisk, Astra Zeneca-Medimmune*, Novartis, Pfizer, Genentech*, Merck, Bristol Myers*, Boehringer Ingelhiem*, Immuron*, Echosense, GE, OWL*, Birdrock, Tern, Sundise, RedX*, IFMO, Lipocine*, Innovate*, Zydus*, AMRA, Hemoshear,
- Grant support: Bristol Myers, Intercept, Gilead, Allergan, Merck, Echosense, Novartis, Boehringer Ingelhiem

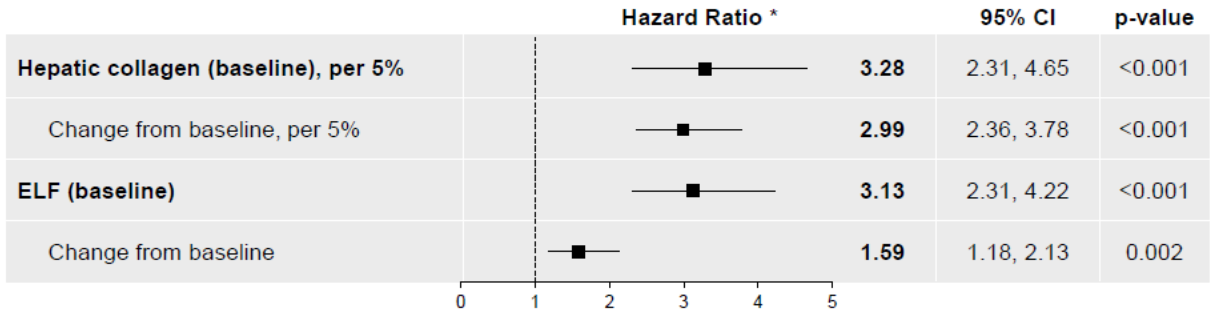
* *no financial remuneration in last 24 months*

Natural History of Cirrhosis



Fibrogenesis as the target

- Heterogeneity in study population:

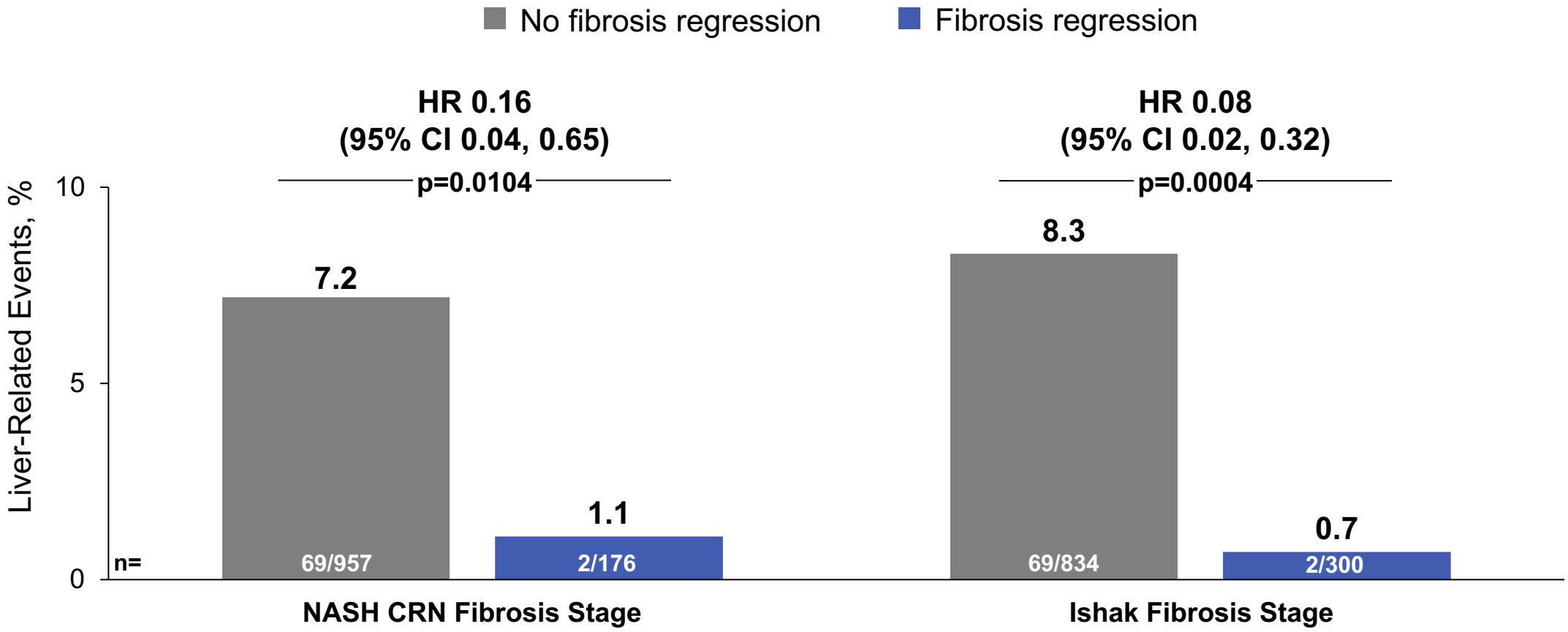


α-SMA	Hazard ratio (95% CI)	P value
PROGRESSION (per 5%) Baseline Change from baseline	 1.19 (1.04-1.36) 1.15 (1.01-1.31)	 0.01 0.03
REGRESSION Baseline Change from baseline	 0.247 (0.1-0.55) 0.28 (0.13-0.59)	 <0.001 <0.001

- Duration of trial
- Quality of prior studies

Sanyal et al, Hepatology, 2019, 70:1913-1927

Fibrosis Regression is Associated with Reduction in Events in Patients with Cirrhosis

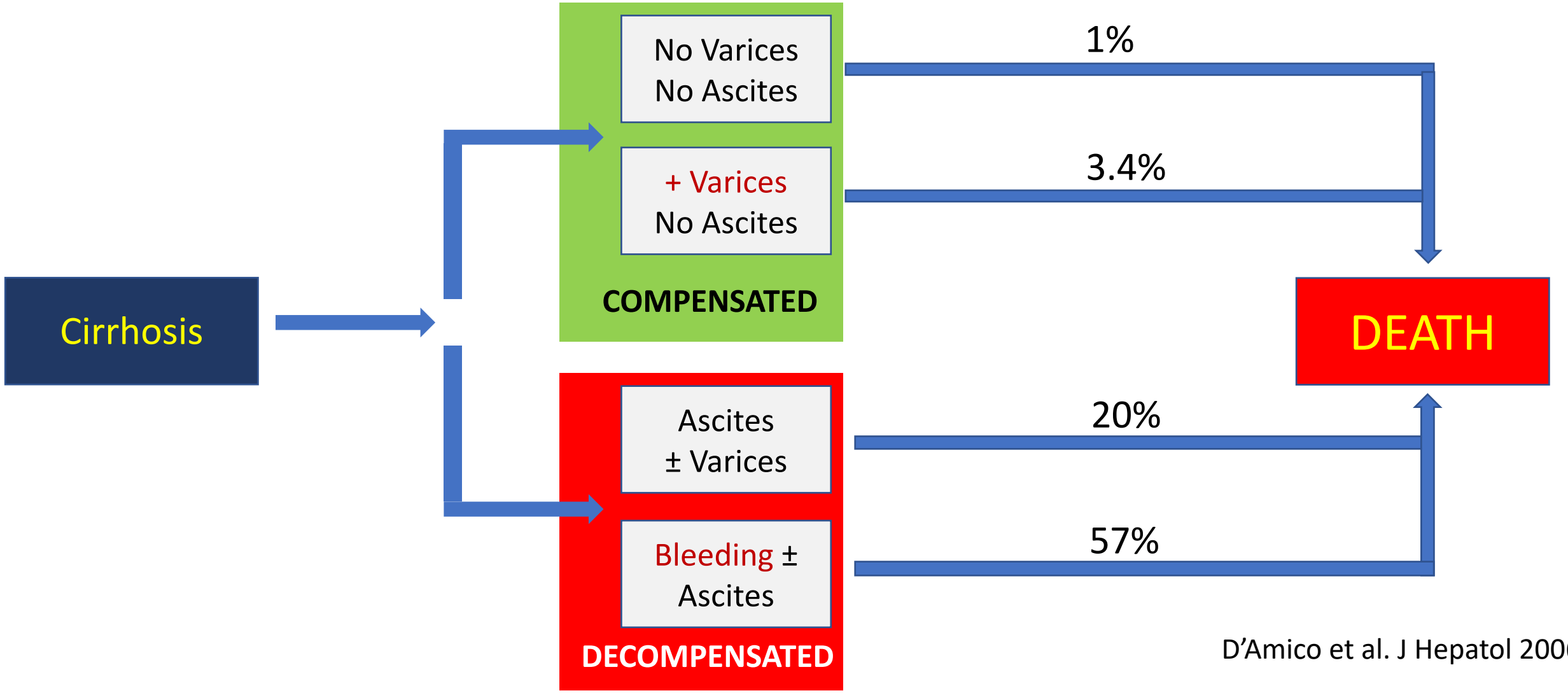


- Cirrhosis regression observed in 16% (176/1135) of patients over 48 weeks

HR, hazard ratio. p-values by Fisher's exact test.

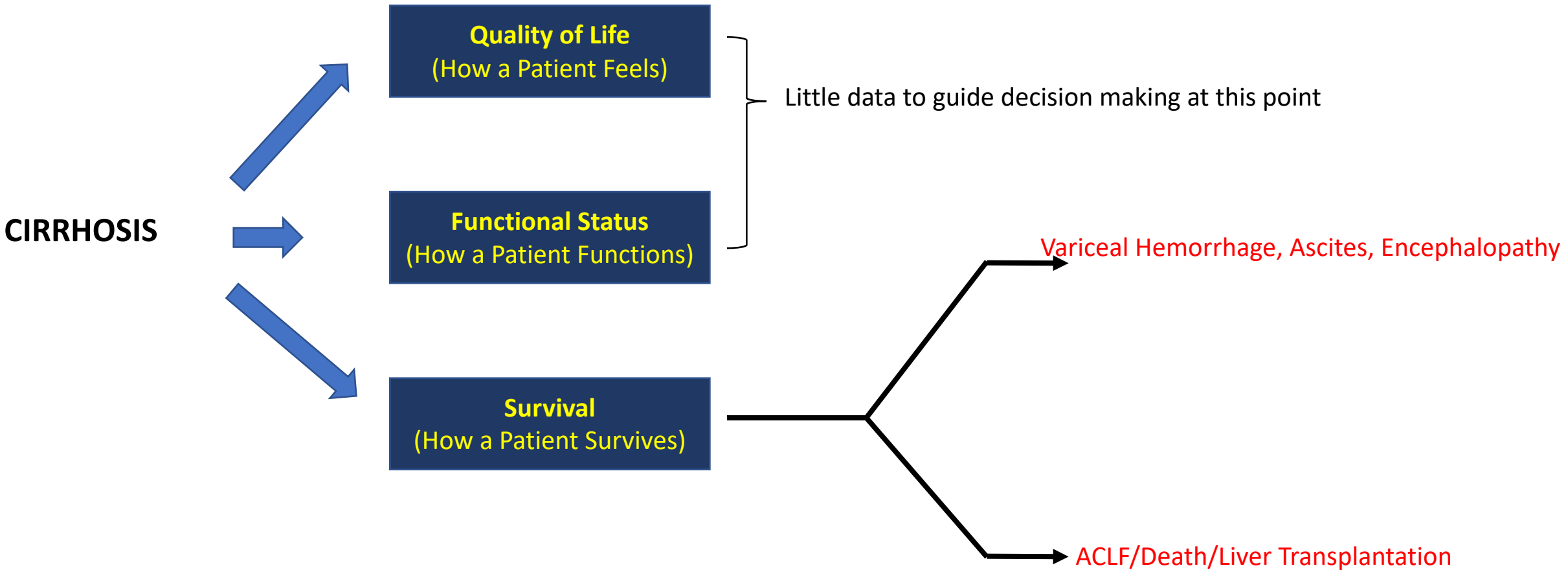
Sanyal et al, Hepatology, 2021

Impact of Portal HTN on Mortality



D'Amico et al. J Hepatol 2006

Potential Clinical Endpoints in NASH Cirrhosis



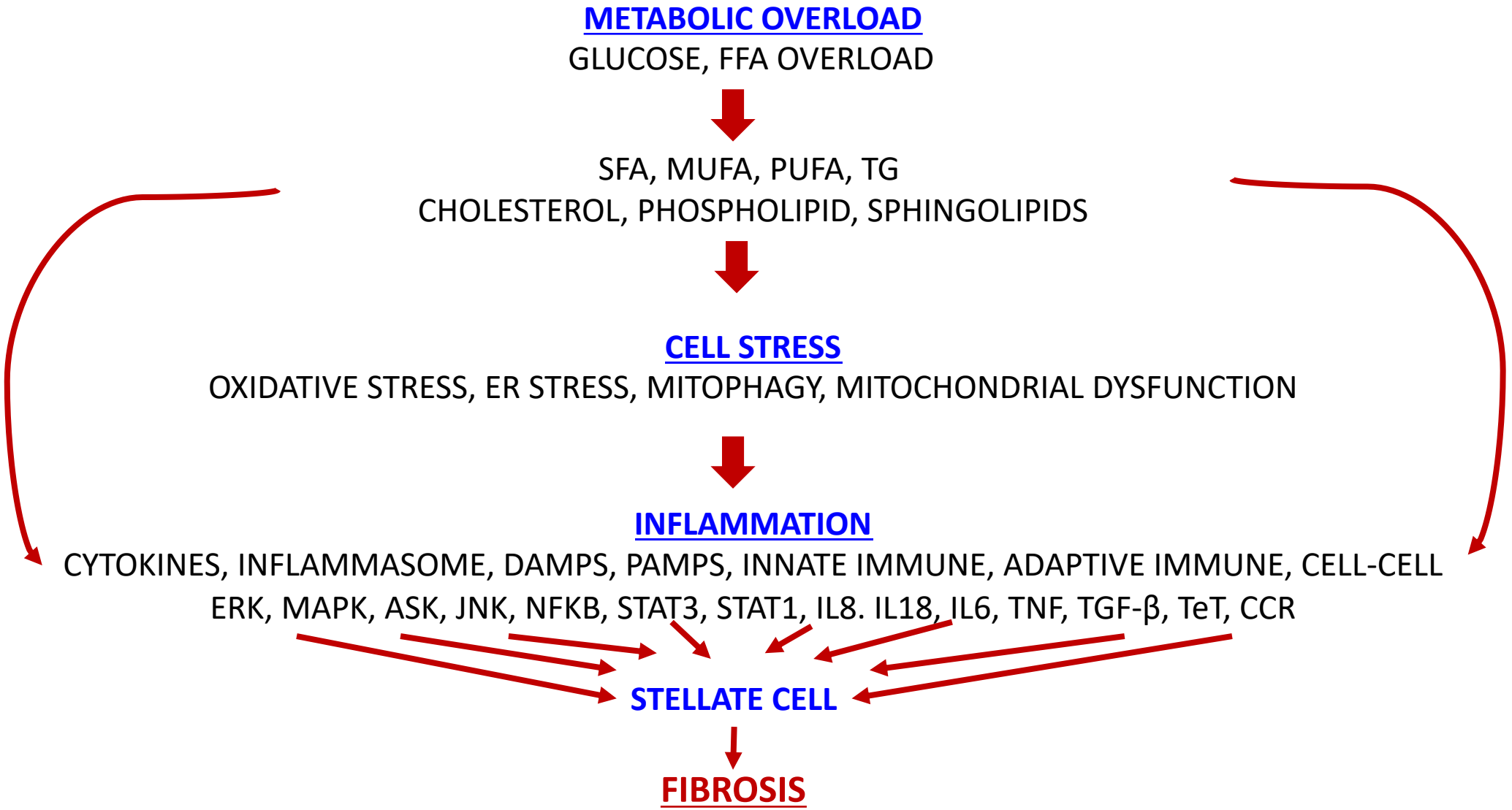
Current landscape

The past and the present

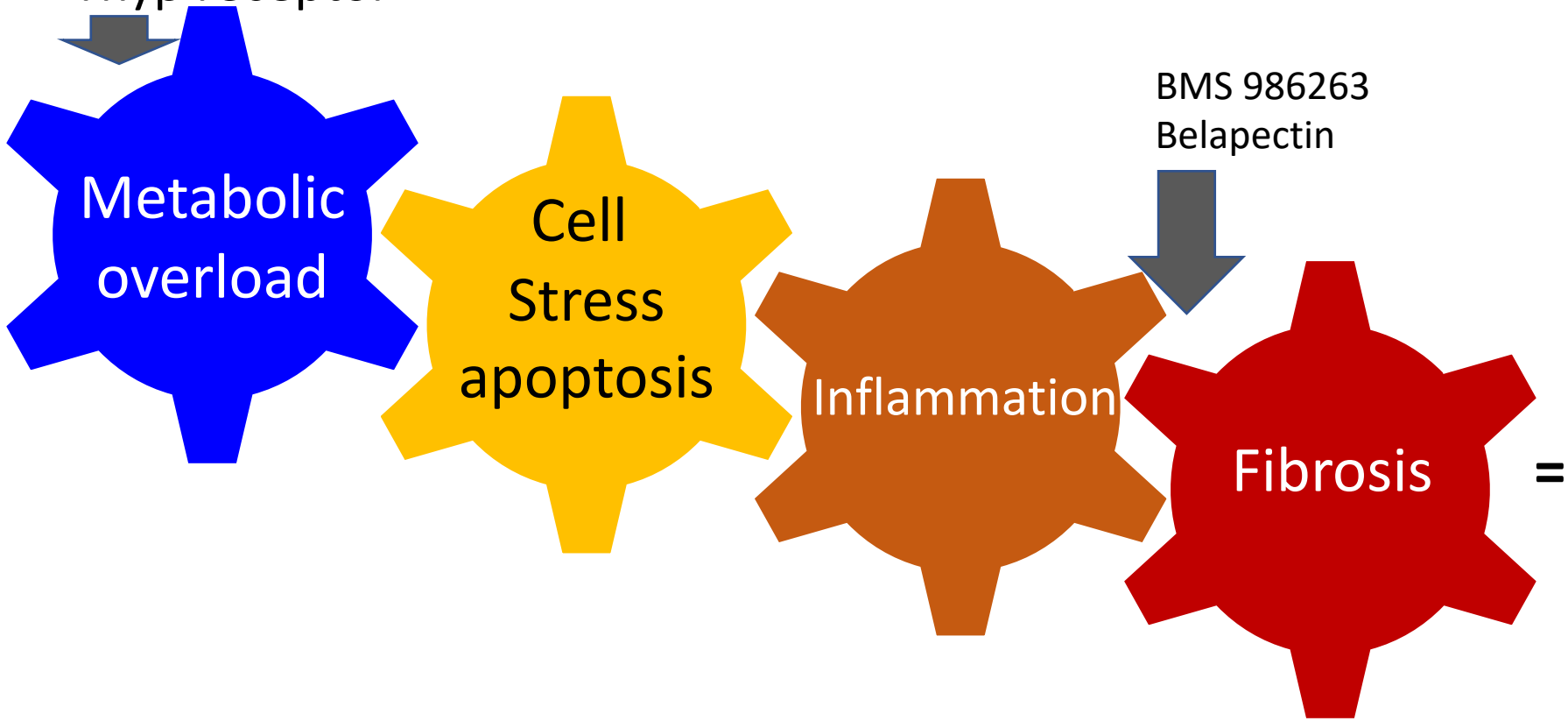
NASH cirrhosis trials have consistently failed so far

- Simtuzimab
- Selonsirtib
- Belapectin
- Emricasan
- Falcon-2
- Semaglutide

Redundancy of downstream pathways requires more careful target identification when anti-inflammatory or anti-fibrotic strategies are used



PPARs
FXR/FGF19
GLP-1 axis
FABAC, ACCi
FGF21
Thyβ receptor



BMS 986263
Belapectin

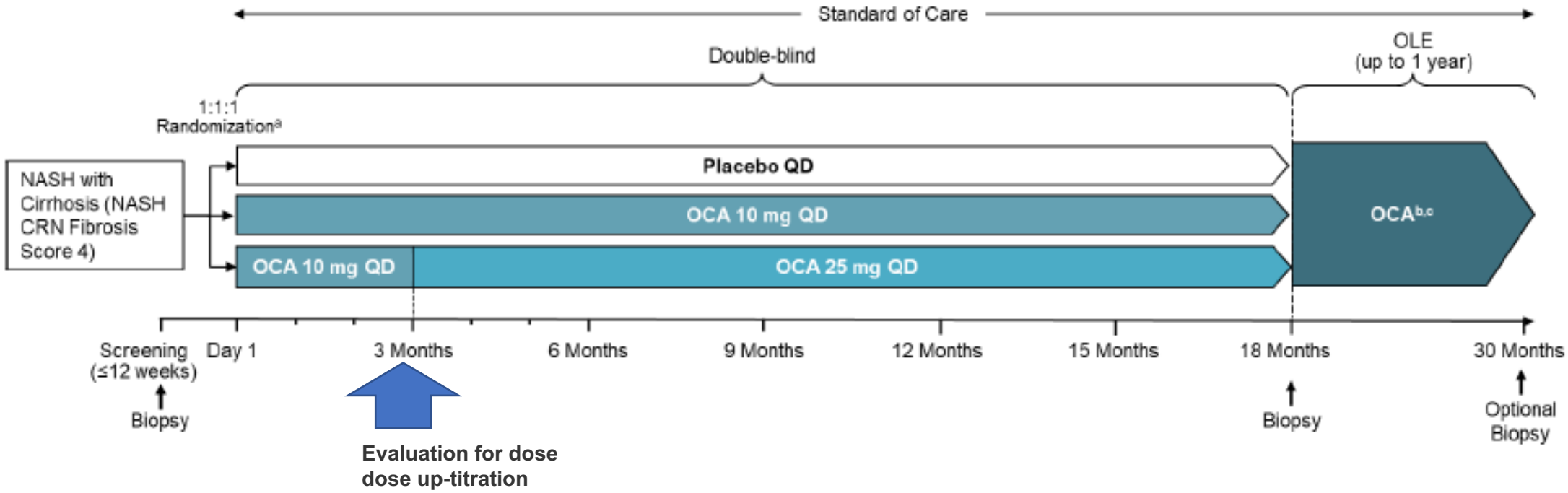
= CIRRHOSIS

Adapted from Friedman et al, Nature Med 2018

747-304: The REVERSE Study

A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Obeticholic Acid in Subjects with Compensated Cirrhosis due to Nonalcoholic Steatohepatitis

Study Design Diagram



CP = Child-Pugh; CRN = clinical research network; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; OLE = open-label extension; QD = once daily.

[a] Subjects who meet the entry requirements will be randomized in a 1:1:1 ratio to one of the three treatment arms: once daily dosing of OCA 10 mg, OCA 10 mg → 25 mg (i.e., OCA 10 mg with uptitration to OCA 25 mg at Month 3), or placebo, in conjunction with the standard of care.

[b] All subjects will receive OCA upon entry into the OLE: Subjects who received placebo during the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg titration.

747-304: The REVERSE Study – Uptitration Criteria

- **Uptitration criteria have been designed to ensure that only subjects with evidence of adequate functional hepatic reserve will be exposed to the higher OCA dose (25 mg).**
- Subjects may only be uptitrated at Month 3 (DB or OLE phase) if, in addition to no safety or tolerability concerns, they meet laboratory criteria at both baseline and all visits up to and including Month 3.
  - total bilirubin ≤1.2 mg/dL
  - serum albumin ≥3.5 g/dL
  - INR <1.5
  - platelet count >100,000/mm^3
- Uptitrated subjects must continue to meet the criteria throughout the study to stay on the uptitrated dose
  - if at any time a subject exceeds these thresholds (including upon retesting), they will be downtitrated to the lower OCA dose (10 mg).
  - once a subject is downtitrated, there is no rechallenge – the subject remains on the downtitrated dose for the remainder of the study

REVERSE-baseline data (ITT population shown with permission)

Demographic	N=919
Age, years, mean (SD); range	60 (9); 29–78
Female, n (%)	605 (66)
White, n (%)	798 (87)
Hispanic or Latino, n (%)	151 (16)
BMI, kg/m^2, mean (SD)	35 (7)
Type 2 diabetes mellitus, n (%)	713 (78)
Age at NASH diagnosis, years, mean (range)	60 (22-77)
Duration of NASH, years, mean (SD)	3.6 (4.7)
Current or former smoker, n (%)	362 (40)

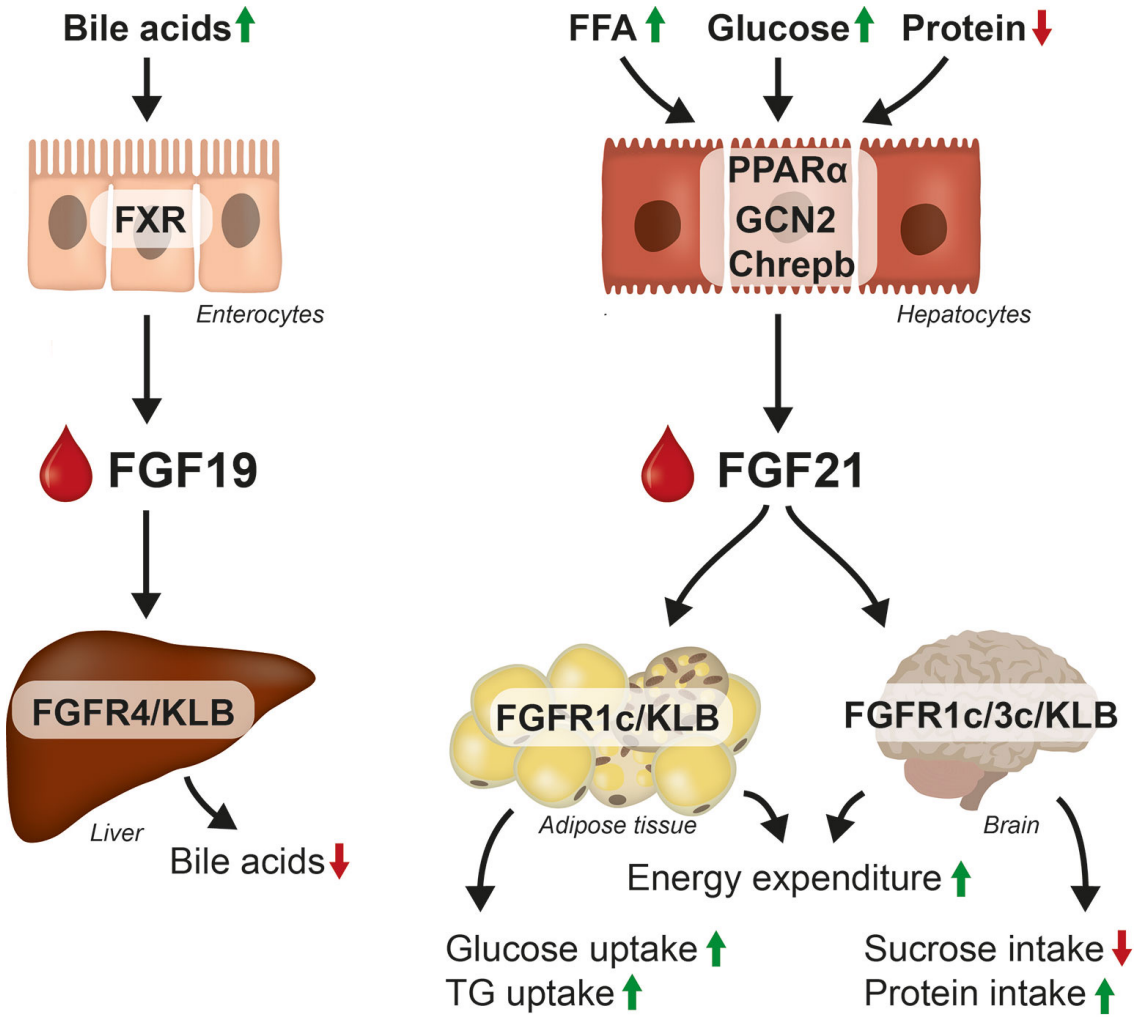
Demographic	N=919
Country	
Australia, n (%)	22 (2%)
Canada, n (%)	34 (4%)
Germany, n (%)	25 (3%)
Spain, n (%)	20 (2%)
France, n (%)	48 (5%)
United Kingdom, n (%)	32 (3%)
Hungary, n (%)	8 (1%)
New Zealand, n (%)	10 (1%)
Poland, n (%)	20 (2%)
Ukraine, n (%)	3 (<1%)
United States, n (%)	697 (76%)

BMI, body mass index; ITT, intent-to-treat; NASH, nonalcoholic steatohepatitis; SD, standard deviation.

Outcomes in REVERSE

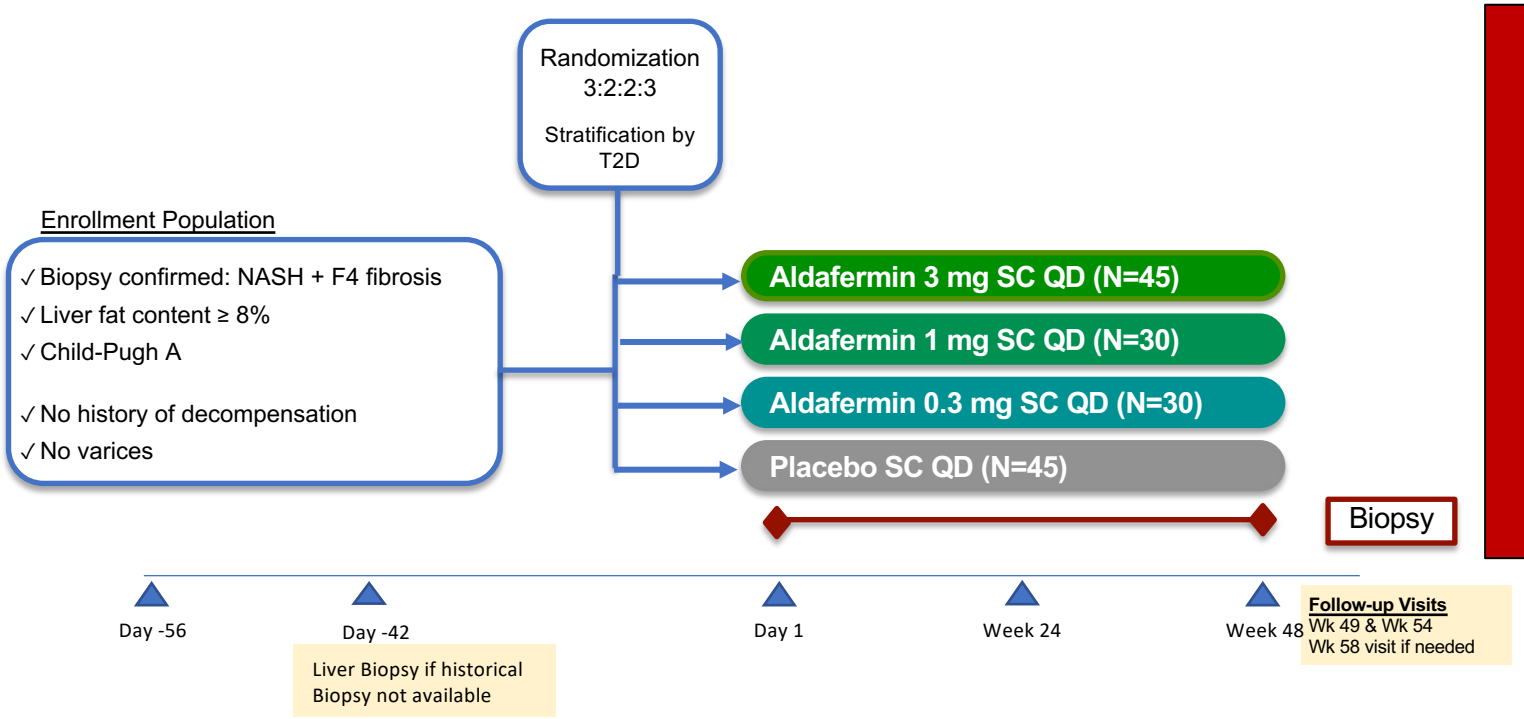
- Efficacy:
  - fibrosis regression by 1 stage or more: 9.9 (placebo) vs 11.3 (10 mg OCA) vs 11.9% (25 mg OCA)
- Safety:
  - TEAS balanced across arms
  - Pruritus: 31% (placebo) vs 41% (OCA 10 mg) vs 57% (OCA 25 mg)
  - Gallbladder events: 0.6% (placebo) vs 1% (OCA 10 mg) vs 1% (OCA 25 mg)

FGF 21 and 19: basic physiology



Henrikkson et al, Frontiers Endocrinol, Dec 2020

Alpine 4 is an ongoing trial in NASH-cirrhosis



Primary end point

Liver Fibrosis ≥ 1 Stage

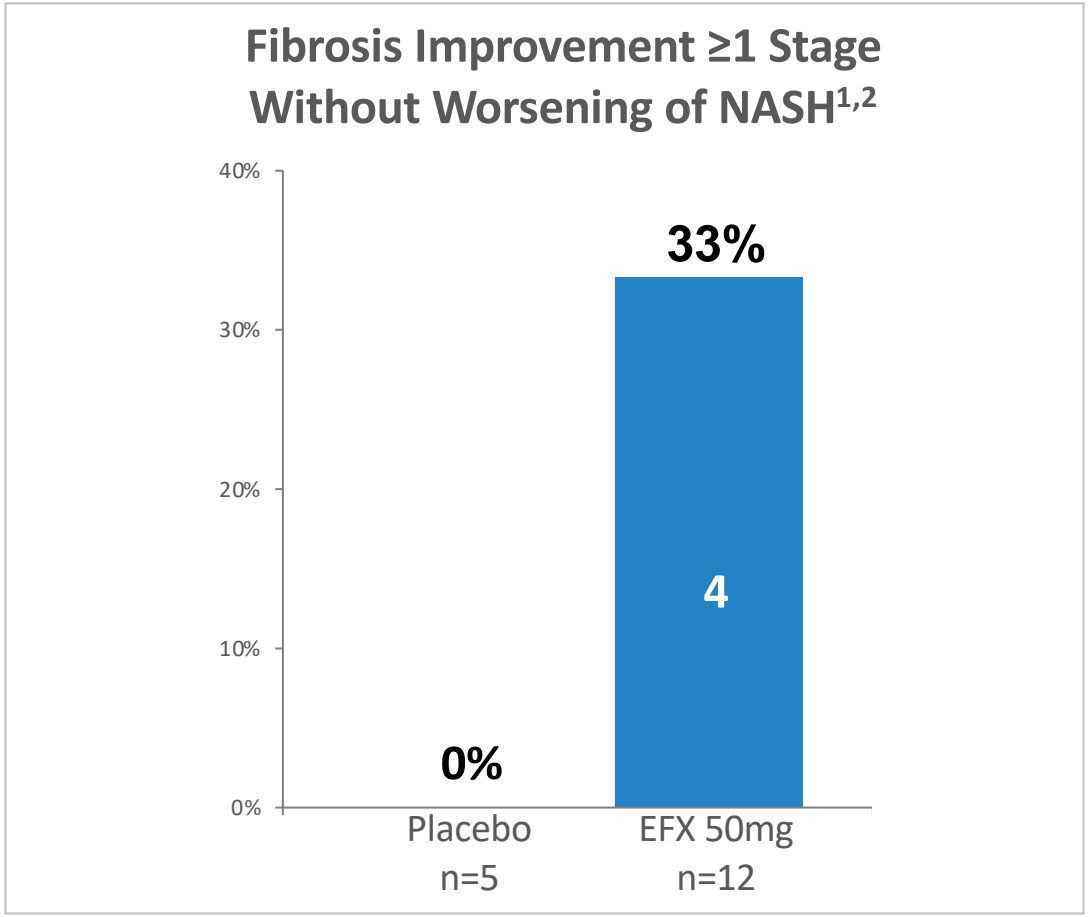
+

No worsening of Steatohepatitis

(no increase in NAS for ballooning, inflammation, or steatosis)

Clinical trials.gov

FIBROSIS IMPROVEMENT IN CIRRHOTIC NASH PATIENTS AFTER 16 WEEKS



[1] No increase in NAS for ballooning, inflammation, or steatosis

[2] Study not powered to assess statistical significance of changes in histological endpoints

Biopsy Reading

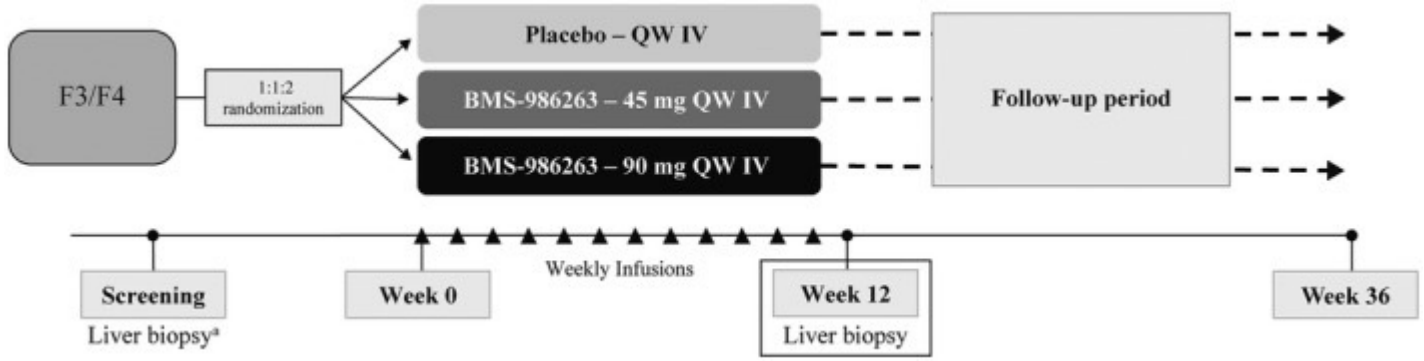
- All baseline and end-of-treatment biopsies were read by a single NASH-CRN pathologist
- All biopsies were read blinded to both treatment assignment and patient
- Baseline biopsies were read independently of end-of-treatment biopsies, in random fashion and not paired

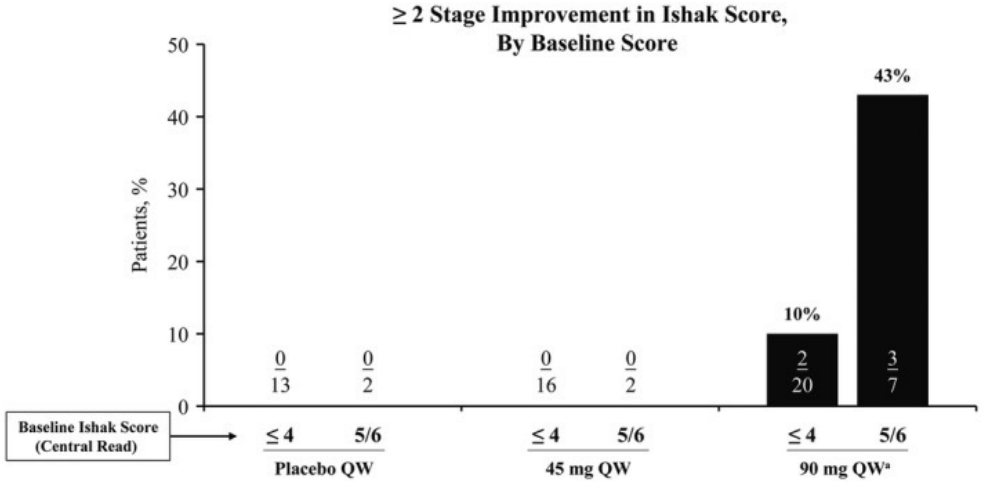
Source Data: Liver Biopsy Analysis Set (all subjects confirmed by central reader as F4 at baseline with Week 16 liver biopsy results)

Harrison et al, ILC 2021

BMS 986263 (siRNA to HSP47 directed to stellate cells via nanoparticles)

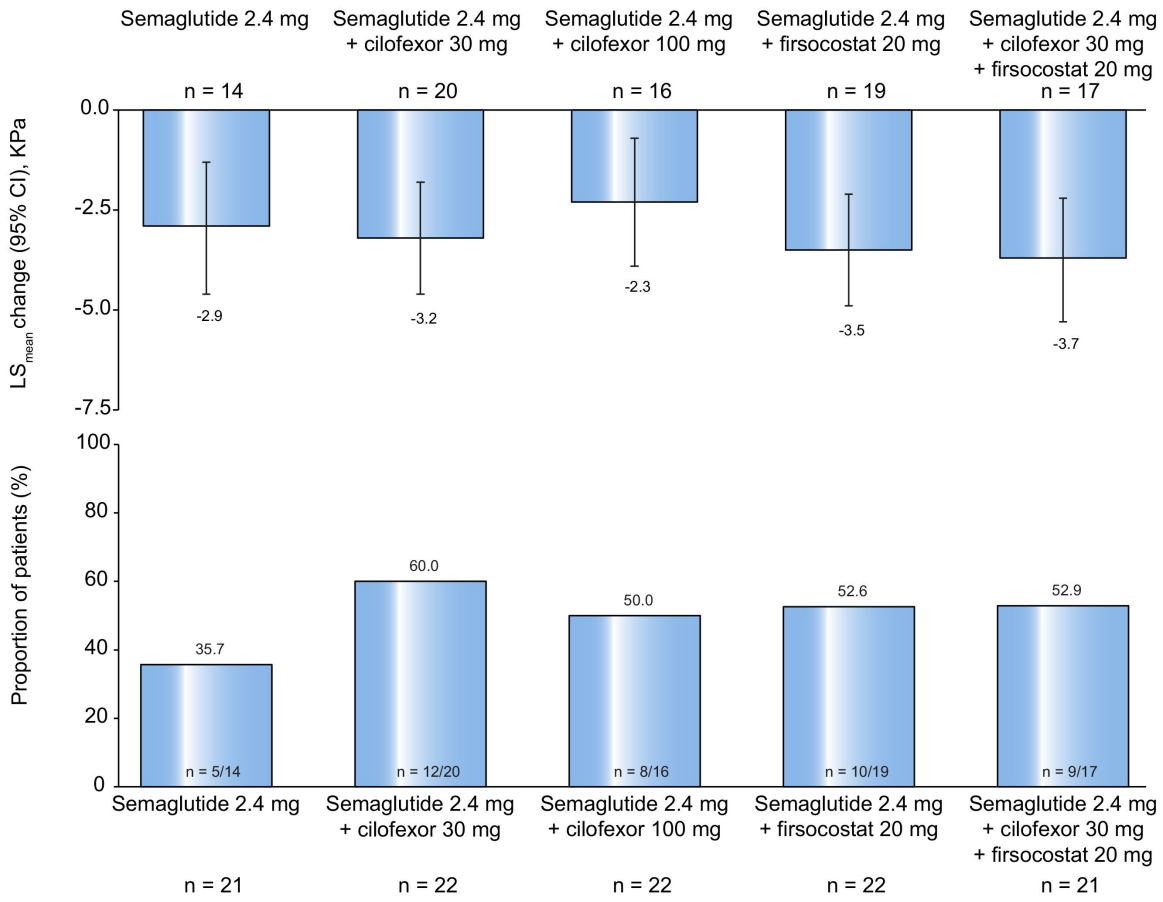
Study population: HCV post SVR





Lawitz et al, Hepatology. 2022 Apr; 75(4): 912–923.

Combination therapy: semaglutide + cilofexor + fircostat- phase 2A trial



NCT04971785

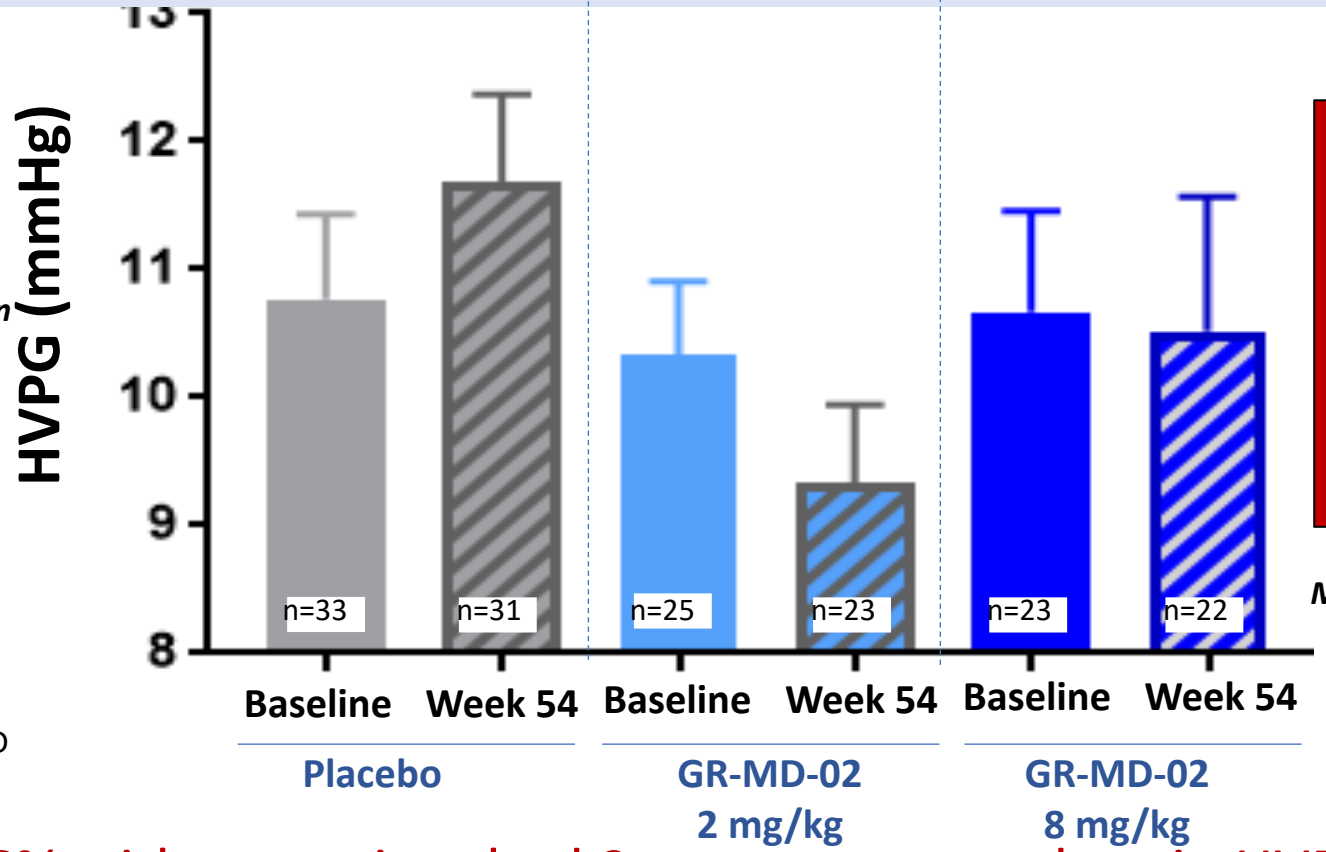
- N=440 compensated cirrhosis
- Parallel assignment
- Sema (0.24-2.4 mg/week + fixed dose Cilofexor/fircostat alone or in combination
- Primary outcome: % with ≥1 stage fibrosis improvement

Alkhoury et al, J Hepatol 2022, 77:607-618

NASH Cirrhosis Without Varices at Baseline (50% of total population)

Statistically significant effect of 2 mg/kg dose on absolute change in HVPG

Mean Change From Baseline to Week 54[1]	**0.8**	**-1.08** **p < 0.01** **p = 0.01**	**0.15** **p = 0.36** **p = 0.17**	**(Absolute Change)** **(Percent Change)**



Overall mean baseline HVPG=10.6 mmHg (No significant difference between groups at baseline-ANOVA)

Mean ± SEM

NCT04365868 (NAVIGATE)
- Phase 2B/3
- Belapectin 2-4 mg/kg IV q2 weekly vs placebo
- Proportion of patients who develop new esophageal varices

[1]ITT with LOCF, ANCOVA with LSD

43 vs 16% without varices had 2 mm or greater drop in HVPG (p< 0.03)

Looking to the future

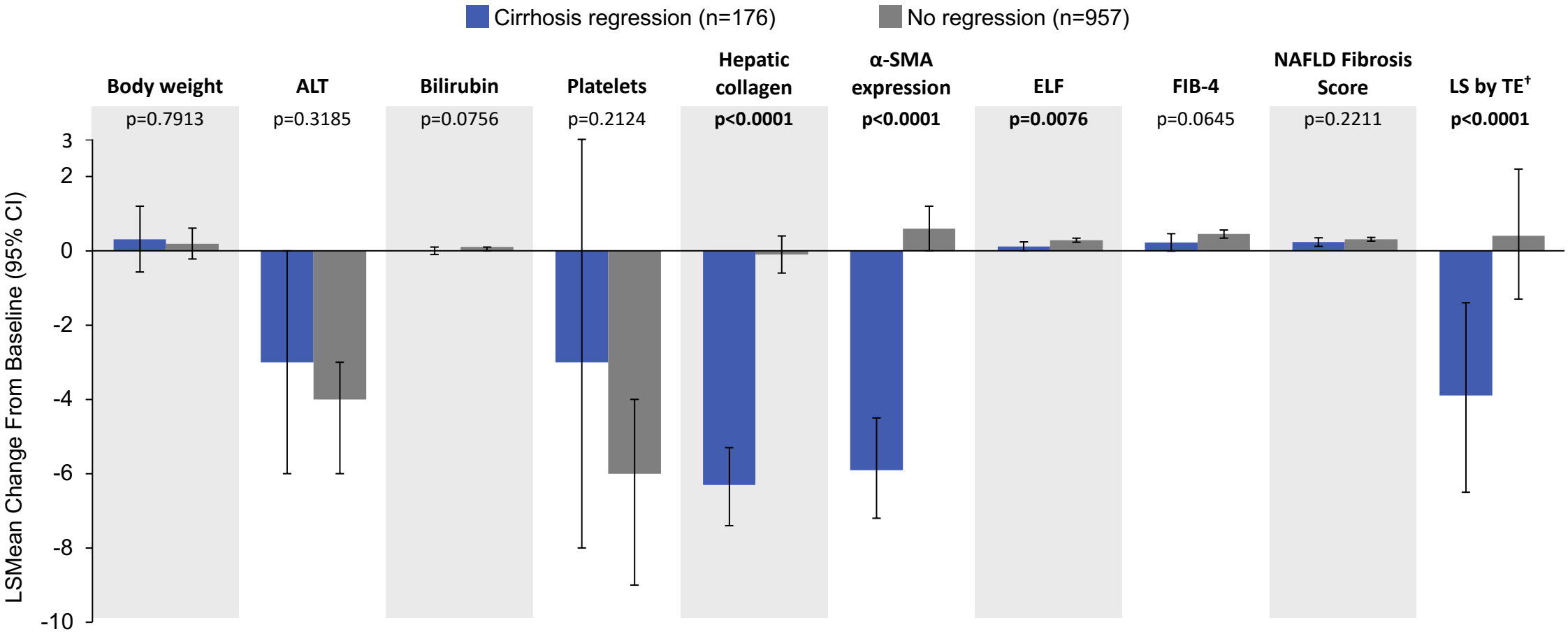
Improved population segmenting

	Strata linked to risk of outcomes		
VCTE (LSM kp)	14-20	21-25	>25
2D-MRE (kp)	4.7-6.48	> 6.48	
Liver cT1 (ms)	825-909	> 909	
ELF	<9.8	9.8-11.3	> 11.3

Additional tools:
- Histoindex SNOF score
- Path AI MLScore
- Spleen cT1
- PROC3/CTx etc.
- HepQuant
- Liver Frailty Index

NITs can be leveraged to assess treatment response

Change from Baseline*



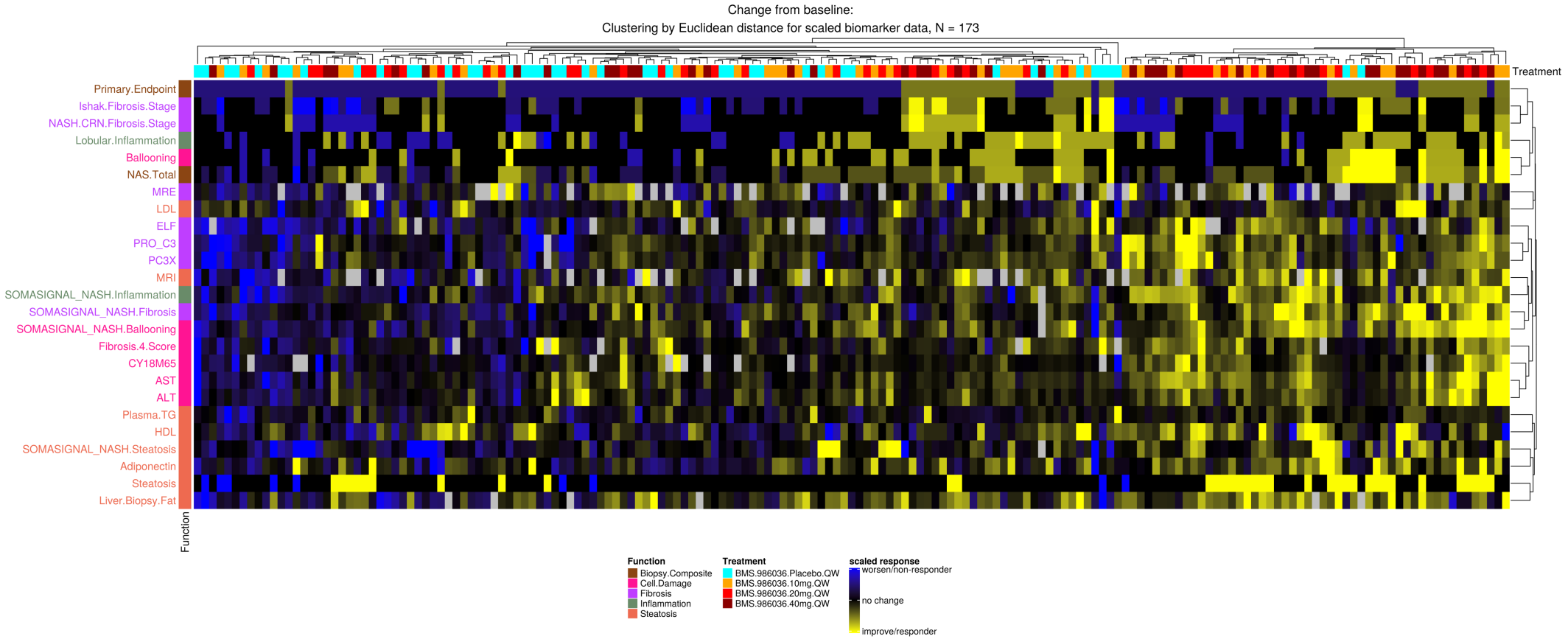
- Patients with cirrhosis regression had greater reductions in hepatic collagen and α-SMA expression, ELF, and LS by TE

LSMeans and p-values by ANCOVA with adjustment for baseline value and study. * Change from baseline up to clinical event.
† Available in 40 patients in SIM study and 694 patients in STELLAR-4.

Sanyal et al, 2019, 70:607-618

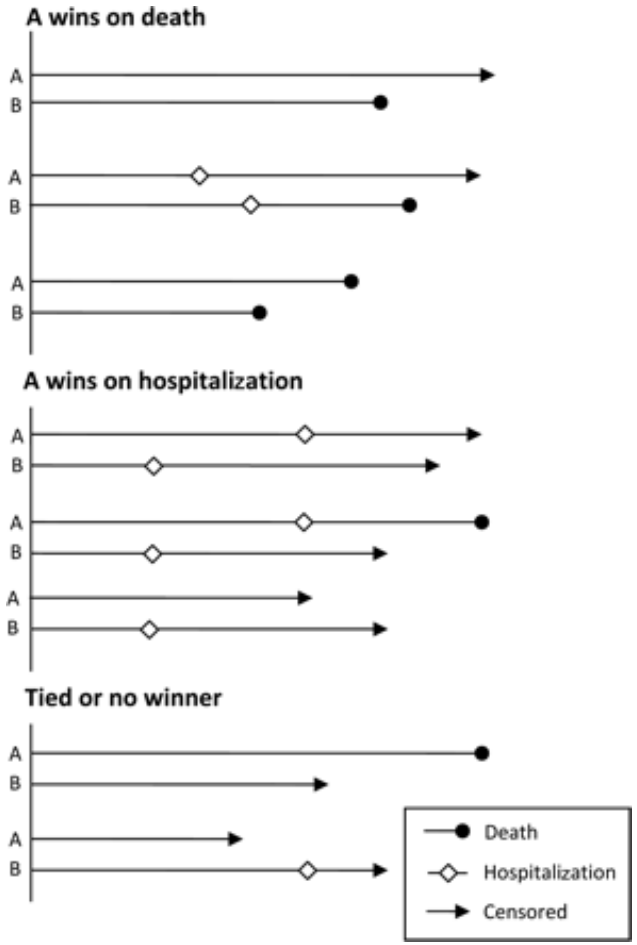
Holistic assessment of outcomes integrating histology and NIT data

Data from Falcon trials



Sanyal et al, AASLD 2021

Innovations in endpoint construction and analysis



$$N_b + N_d = N_w$$
$$N_b + N_d = N_w$$
$$z = (p_w - 0.5)/[p_w(1-p_w)/(N_w + N_L)]$$

European Heart Journal, Volume 33, Issue 2, January 2012, Pages 176–182, https://doi.org/10.1093/eurheartj/ehr352

Summary

- Development of effective therapy for patients with cirrhosis due to NASH is a public health priority
- Current development pathways are suboptimal:
  - need for biopsy for enrollment is a barrier to drug development for this population
  - do not consider competing threats
  - do not consider patterns of histological fibrosis regression
  - do not consider NITs as even reasonable surrogates
  - outcomes in compensated cirrhosis take a long time
- There needs to be innovation in design and endpoint construction to capture clinically meaningful benefit in this population or a reasonable surrogate thereof.

THANK YOU FOR YOUR ATTENTION

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