3rd Paris NASH Symposium

French-US Meetings

July 6 & 7, 2017

Institut Pasteur - Paris

Organized by

Arun Sanyal & Lawrence Serfaty

Virginia Commonwealth University School of Medicine, Richmond, Virginia, US
Hôpital Saint-Antoine, APHP, Inserm, Université Pierre & Marie Curie, Paris, France

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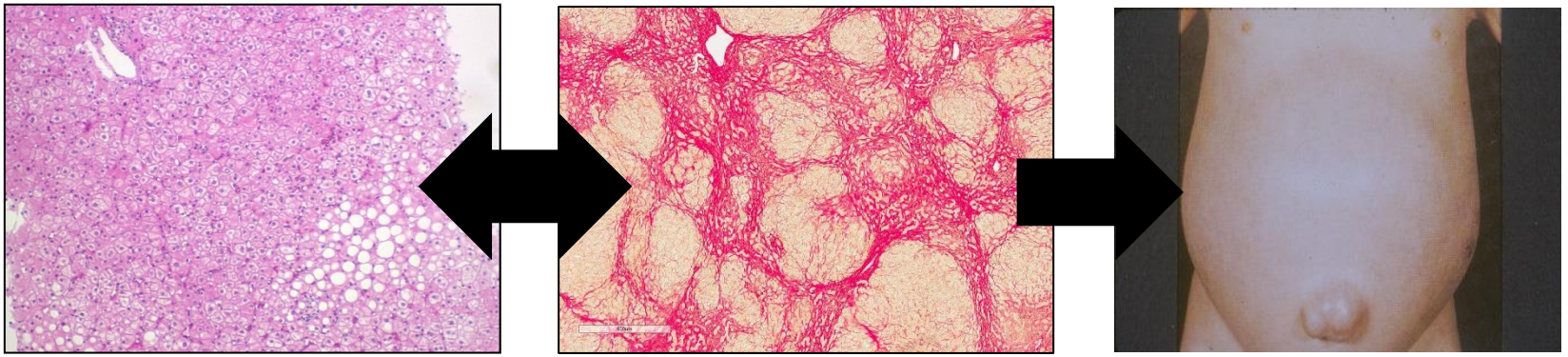
FORUM for Collaborative Research

Prospective evaluation of disease evolution in NAFLD



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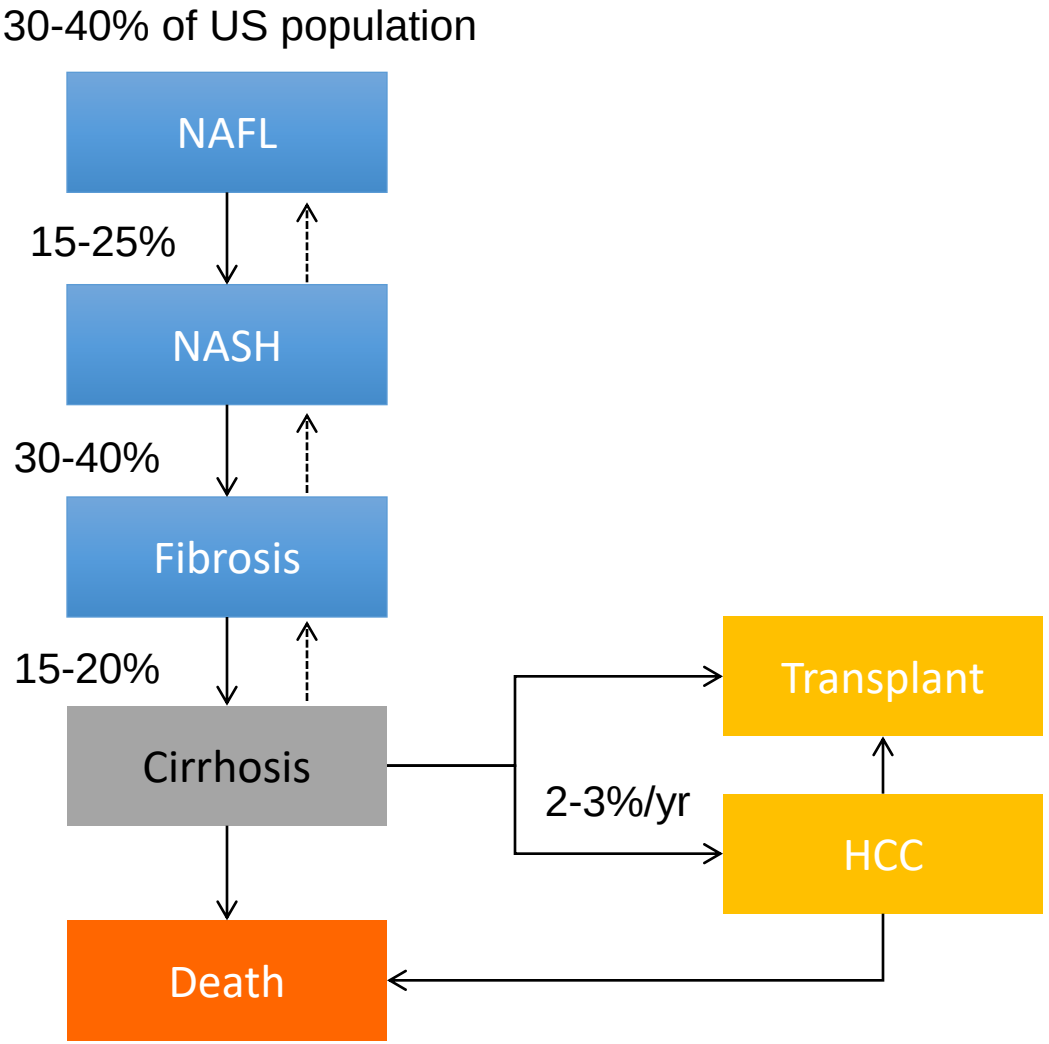
Conflicts of Interest

- President, Sanyal Biotechnologies
- Stock options: Genfit, Akarna, Tiziana, Indalo, Durect, Exhalenz, Hemoshear
- Advisor with compensation: Lilly, Pfizer, Novartis, Ardelyx, Salix, Hemoshear
- Advisor without compensation: Galectin, Intercept, Merck, Bristol Myers, Immuron, Gilead, Chemomab, Affimmune, Protalix, Nitto Denko, Novo Nordisk, Cirius, Boehringer Ingelhiem
- Grants to institution: Gilead, Tobira, Allergan, Merck, Bristol Myers, Astra Zeneca, Immuron, Intercept, Novo Nordisk, Shire, Boehringer Ingelhiem, Cirius

Epidemiology of NAFLD



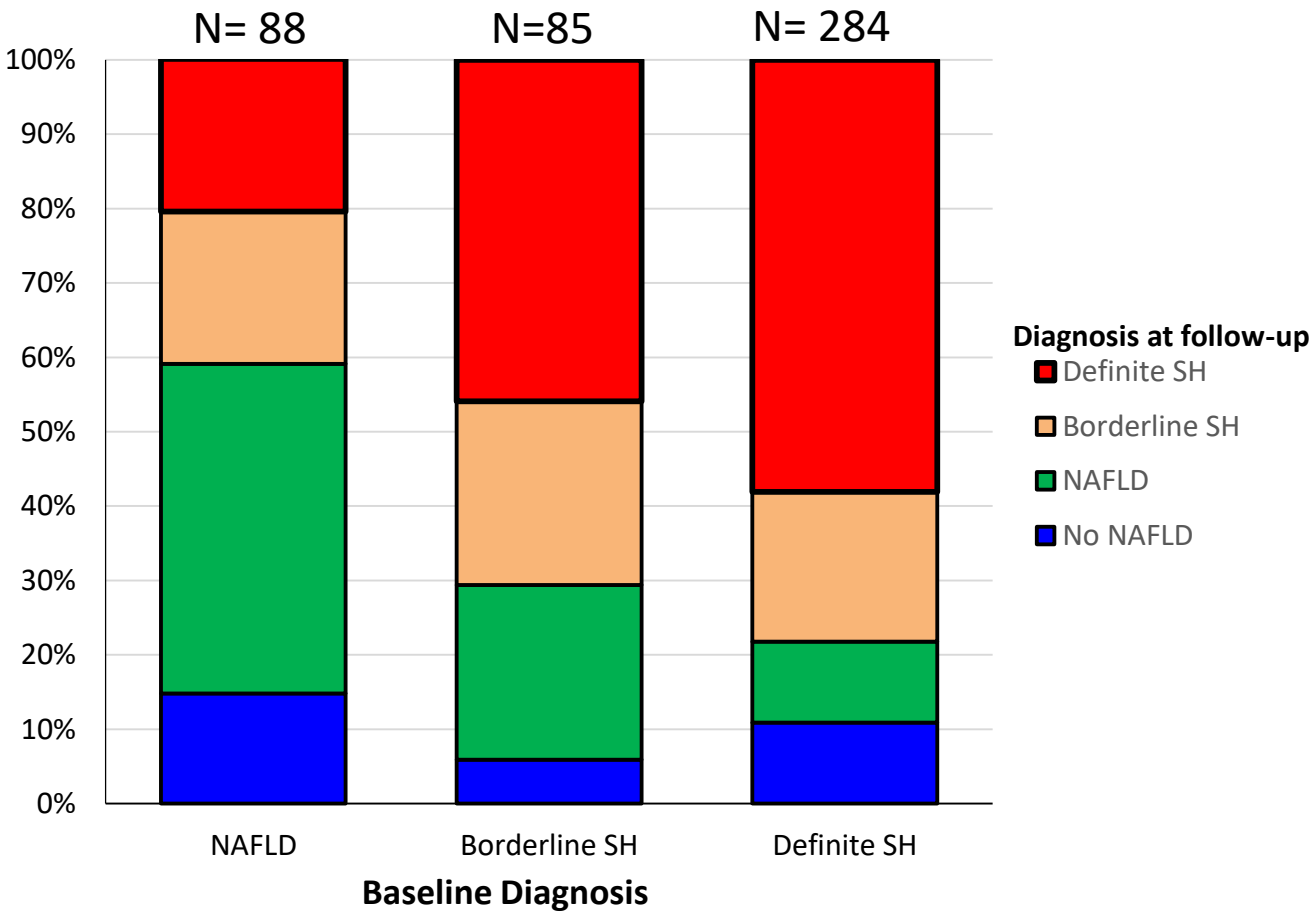
Spengler EK, et al. *Mayo Clin Proc.* 2015;90(9):1233-1246.

Status of current literature

- Largely retrospective
- Some of the most cited papers are severely flawed methodlogically
- Impact:
  - misguided clinical trial strategies
  - increased sample size requirement to account for noise in natural history assessment

What is the evolution of NAFLD phenotype over time without specific intervention?

NAFLD phenotype changes bi-directionally over time



- NAFL progressed to borderline or definite NASH in 41% of cases
- Borderline SH is more likely to progress than regress (46% vs 29%)
- Definite SH regressed to borderline (20%), NAFL (11%) or normal (11%)

Kleiner et al, AASLD 2016

Weight gain and rise in liver enzymes are related to progression from NAFL to NASH

Variable	Odds ratio	95% CI	p
ALT change (per 10 U/L)	2.2	1.1 – 4.1	0.02
AST change (per 10 U/L)	3.5	1.2 – 10.4	0.03
Alk Phos change (per 10 U/L)	1.3	0.8 – 2.1	0.25
Insulin change (per 10 µU/mL)	1.5	0.8 – 2.7	0.23
Weight change (per 1 kg)	1.7	1.1 – 2.5	0.01
NAS	0.9	0.4 – 1.9	0.72
MetS	2.0	0.5 – 8.5	0.35

Analysis based on subjects with NAFL (n=34, 12 progressors) within subset with entire metadata available (n=197)

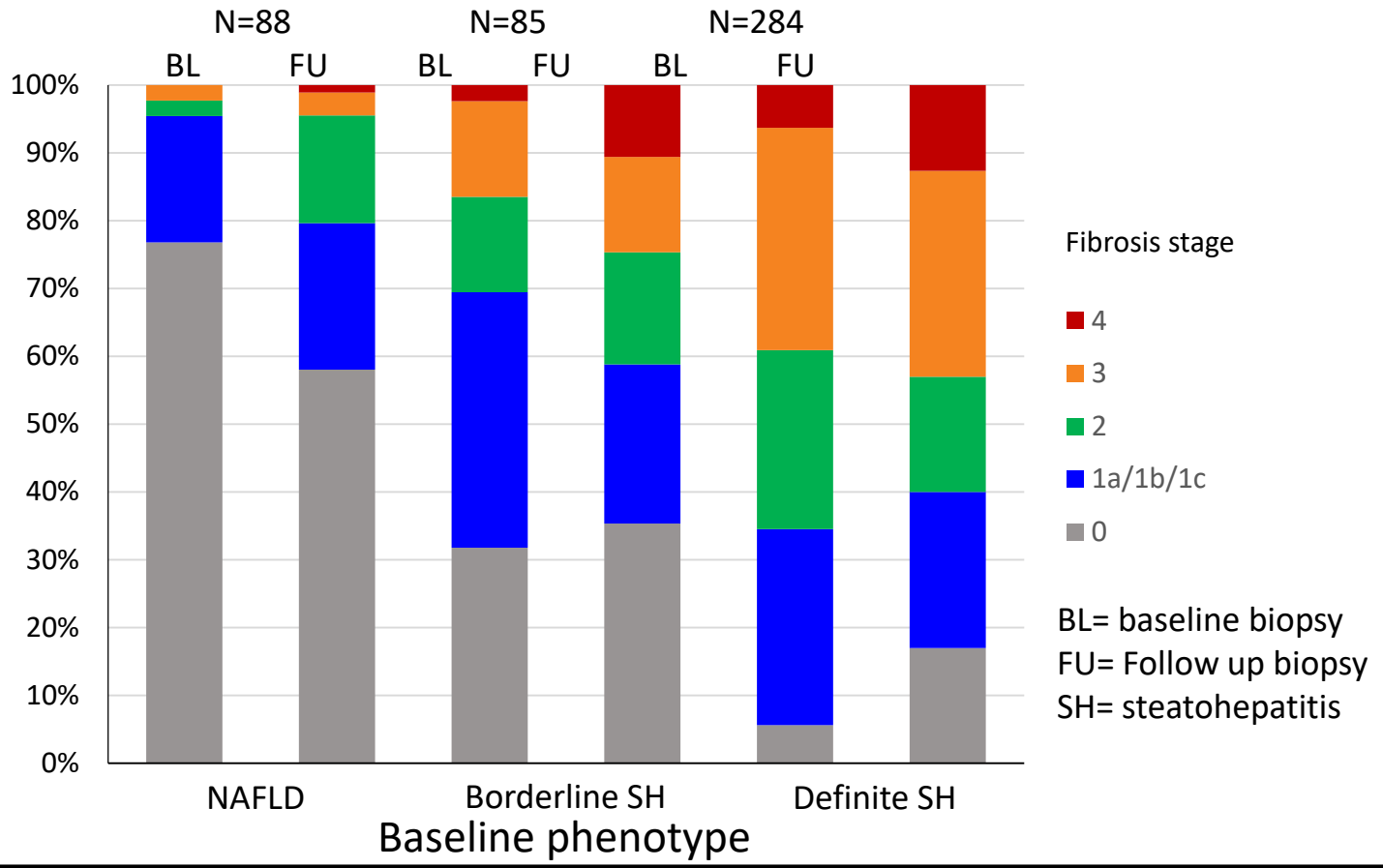
Weight loss is associated with resolution of NAFLD

Variable	Odds ratio	95% CI	p
ALT change (per 10 U/L)	0.9	0.9 – 1.0	0.11
AST change (per 10 U/L)	0.9	0.9 – 1.0	0.12
Alk Phos change (per 10 U/L)	1.0	0.8 – 1.3	0.98
Insulin change (per 10 µU/mL)	0.9	0.8 – 1.1	0.43
Weight change (per 1 kg)	0.9	0.8 – 0.9	<0.001
NAS	0.7	0.5 – 1.0	0.04
Met S	0.7	0.3 – 1.9	0.49

Analysis based on subjects with complete resolution (n=19) within subset with entire metadata available (n=197)

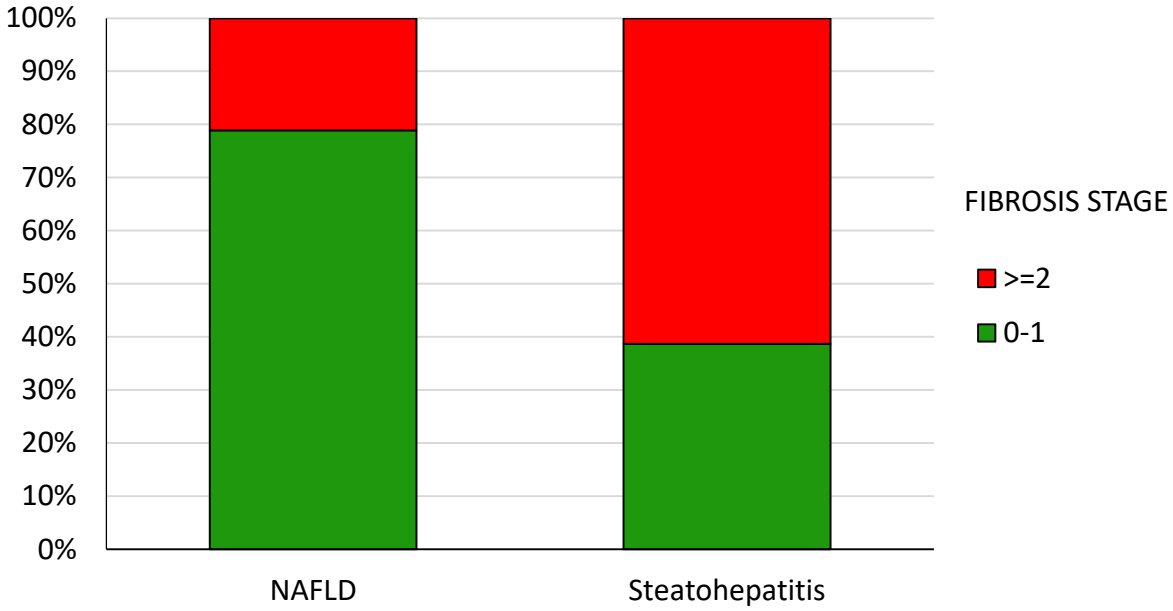
What about fibrosis evolution?

Evolution of fibrosis in various NAFLD phenotypes



- At baseline- 23% of NAFL had some fibrosis
- 42% of NAFL subjects had fibrosis ≥ stage 1 by Bx 2
- Similar proportion of those with borderline and definite NASH progressed to cirrhosis

Steatofibrosis is related to progression to NASH from NAFL

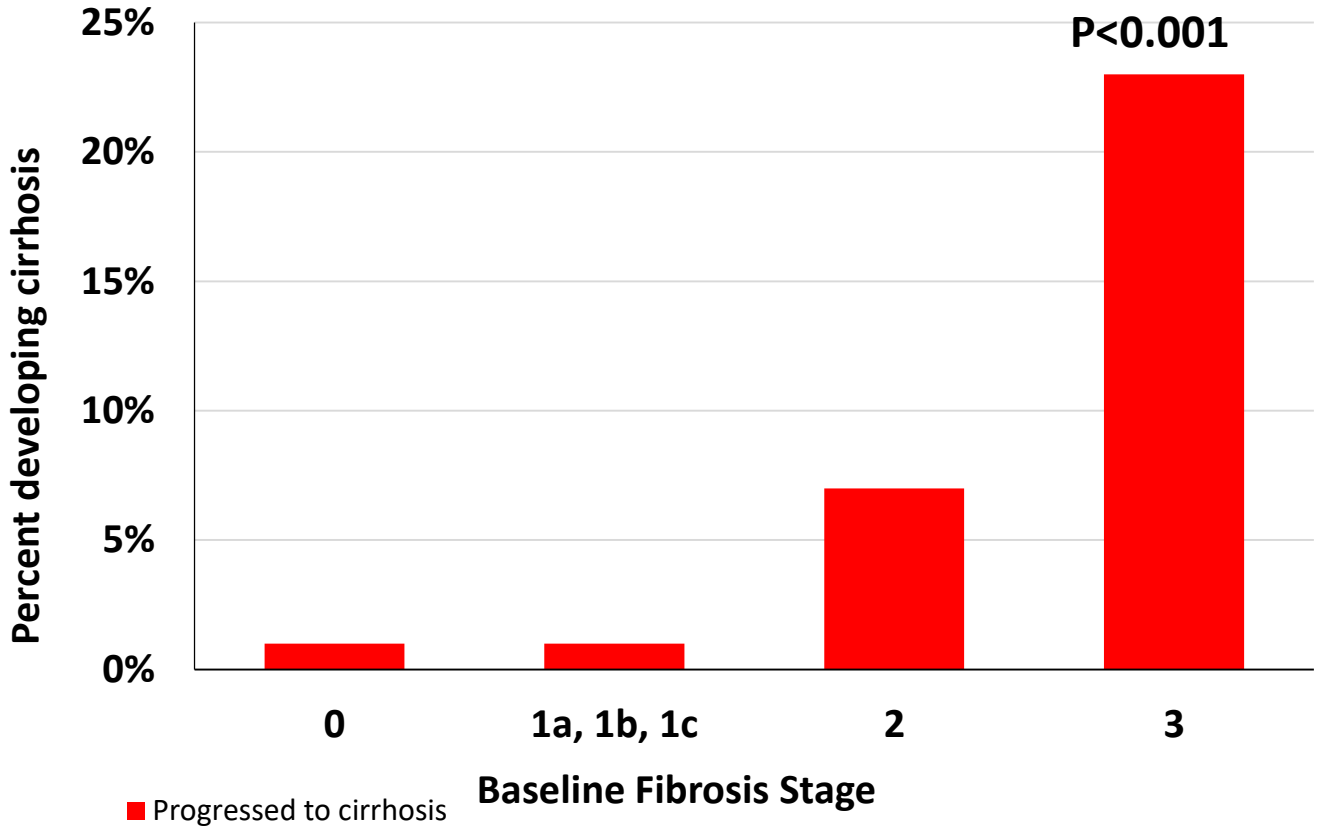


Histologic phenotype on BX #2

	Odds ratio for fibrosis progression	95% CI	P*
NAFLD progression	9.0	3.1 – 25.9	<0.001
Years between Lbx	1.1	0.9 – 1.3	0.46

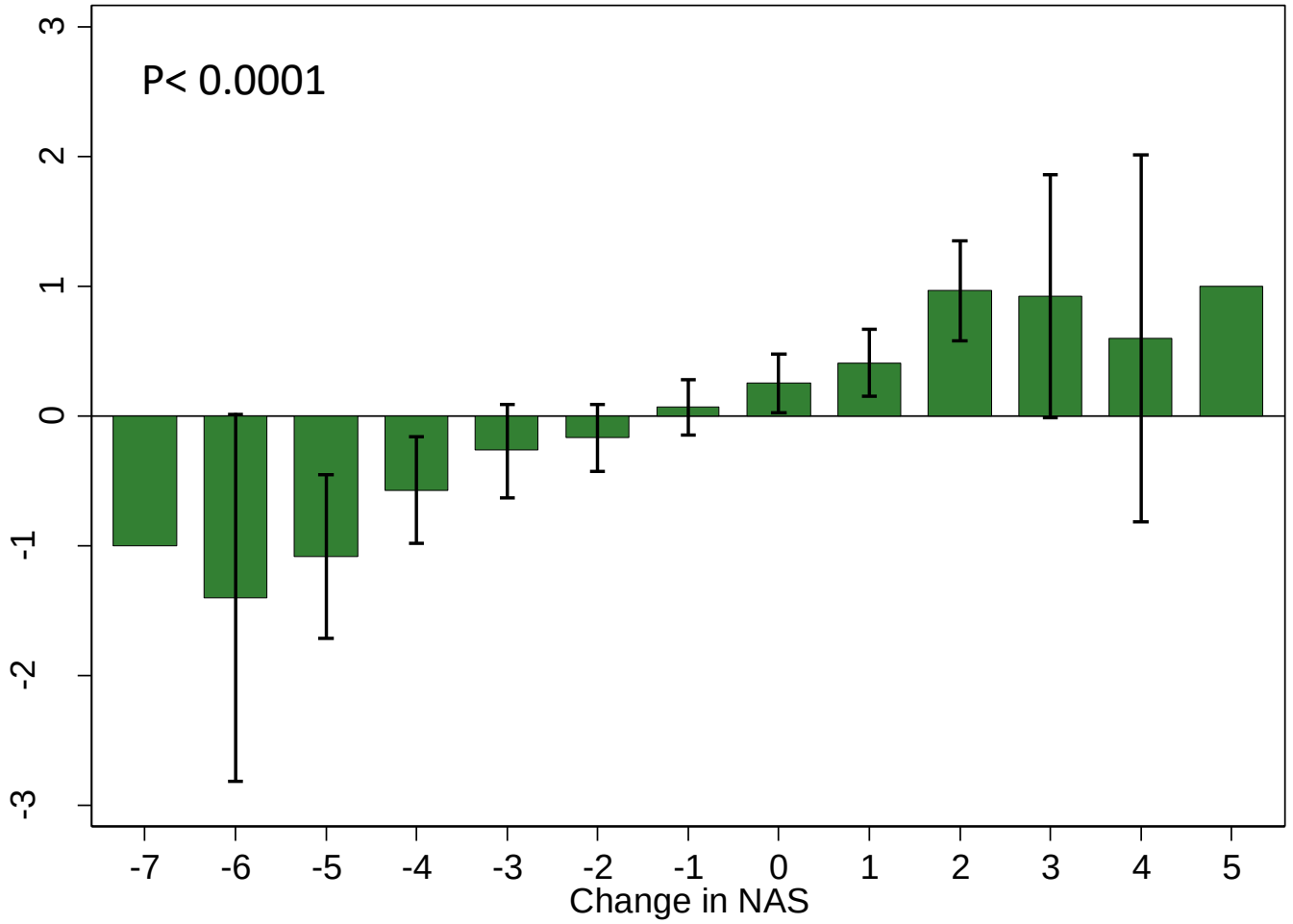
*NAFLD progression x years between bx interaction P=0.77; Mean years between Lbx=4.9±2.8
Total N=86; N=29 with fibrosis progression≥1 stage in those with NAFLD on first biopsy; N=36 with NAFLD progression

Progression to cirrhosis is not a linear function of baseline fibrosis stage

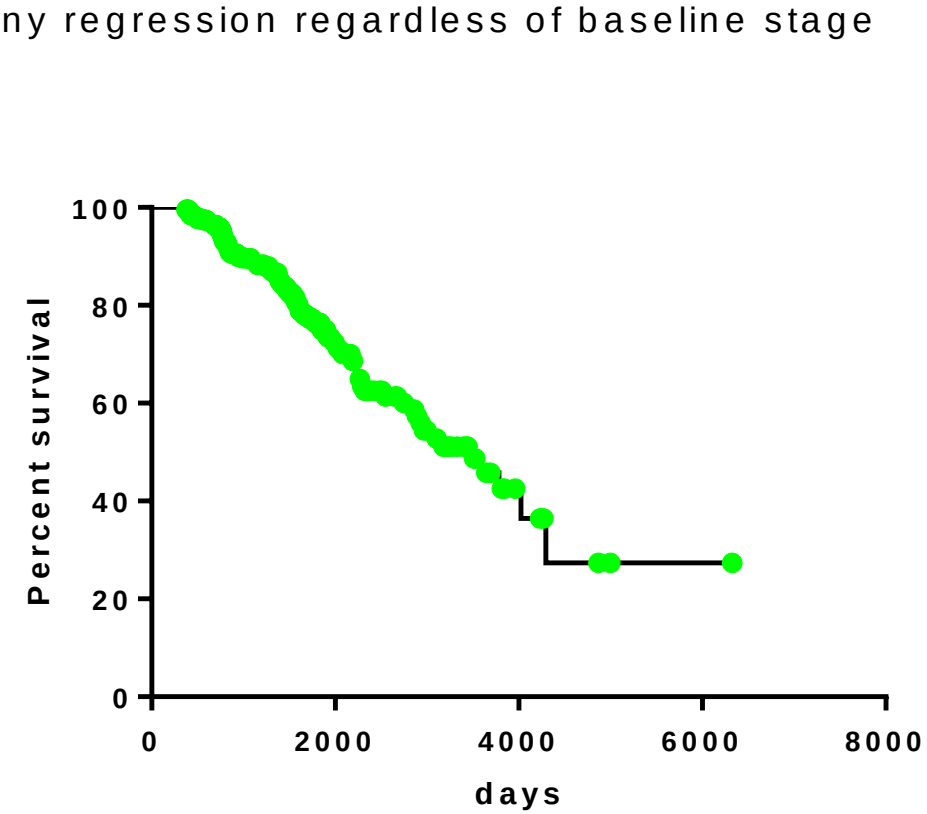


N=434 with baseline fibrosis stage 0-3; N=33 progressed to cirrhosis

Changes in disease activity are closely linked to changes in disease stage



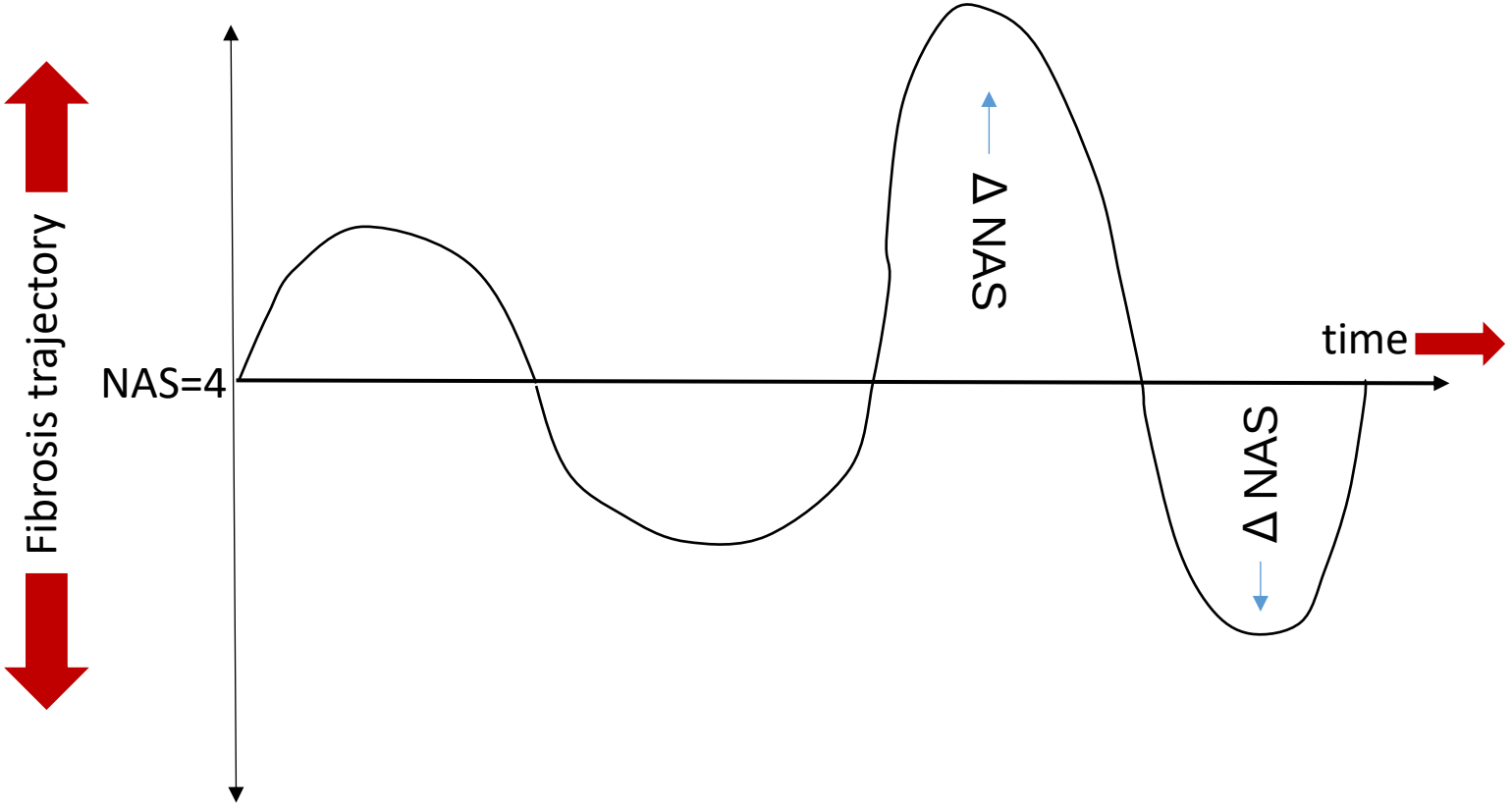
Fibrosis regression occurs frequently even without specific therapeutic intervention



Liver enzymes, hyperinsulinemia, portal inflammation and change in NAS and baseline fibrosis stage predict fibrosis evolution

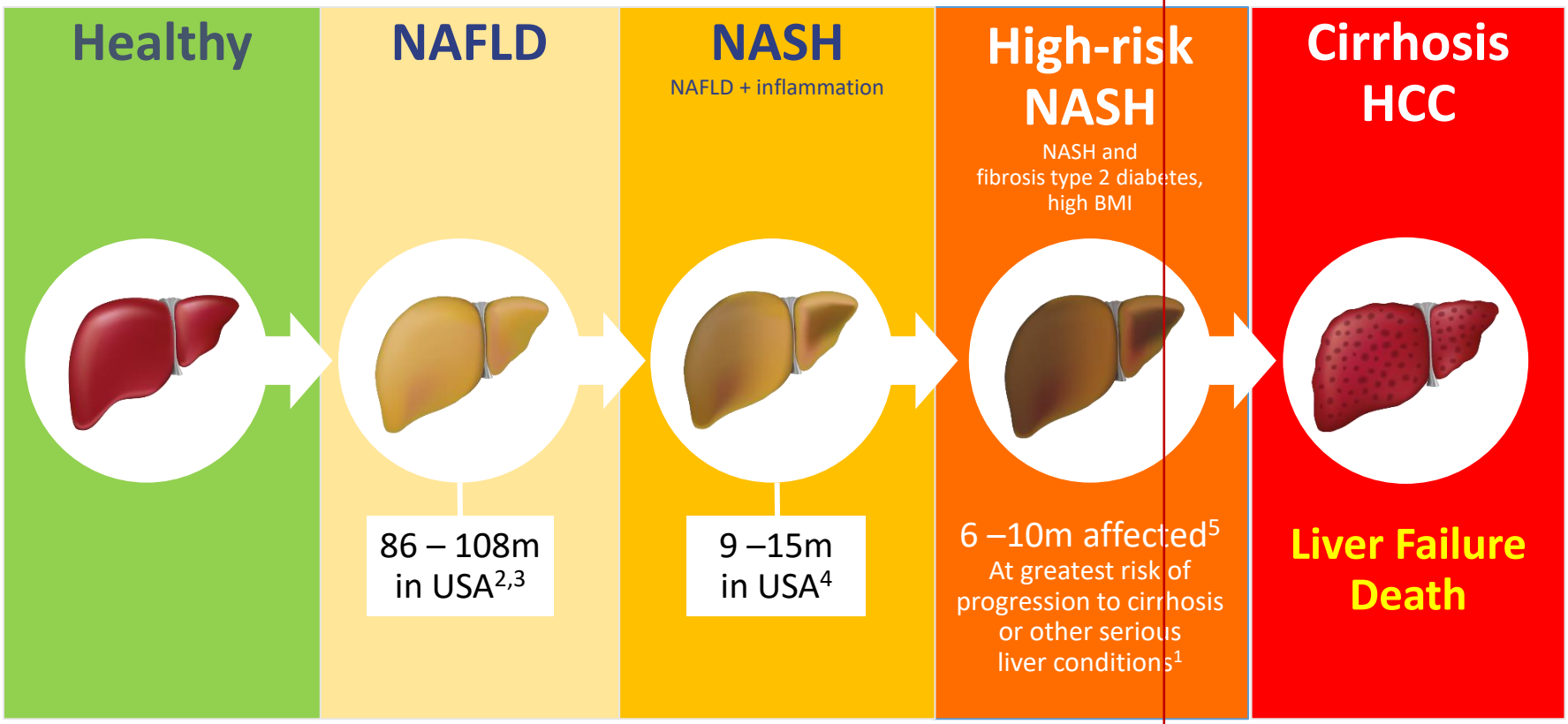
Variable	Odds ratio	95% CI	p
Baseline ALT (per 10 U/L)	0.9	0.8 – 1.0	0.02
Baseline AST (per 10 U/L)	1.4	1.2 – 1.6	<0.001
Change in AST (per 10 U/L)	1.2	1.0 – 1.3	0.003
Baseline insulin (per 10 µU/mL)	1.1	1.0 – 1.2	0.04
Baseline NAS	1.8	1.3 – 2.4	<0.001
Change in NAS	1.7	1.4 – 2.0	<0.001
Baseline steatosis grade <33% (ref.) 33-66% >66%	 1.0 0.4 0.5	 0.2 – 0.7 0.2 – 1.2	0.02
Baseline portal inflammation None (ref.) Mild More than mild	 1.0 1.9 6.0	 0.9 – 4.2 2.2 – 16.5	0.001
Baseline fibrosis stage	0.3	0.2 – 0.4	<0.001

A model for disease development

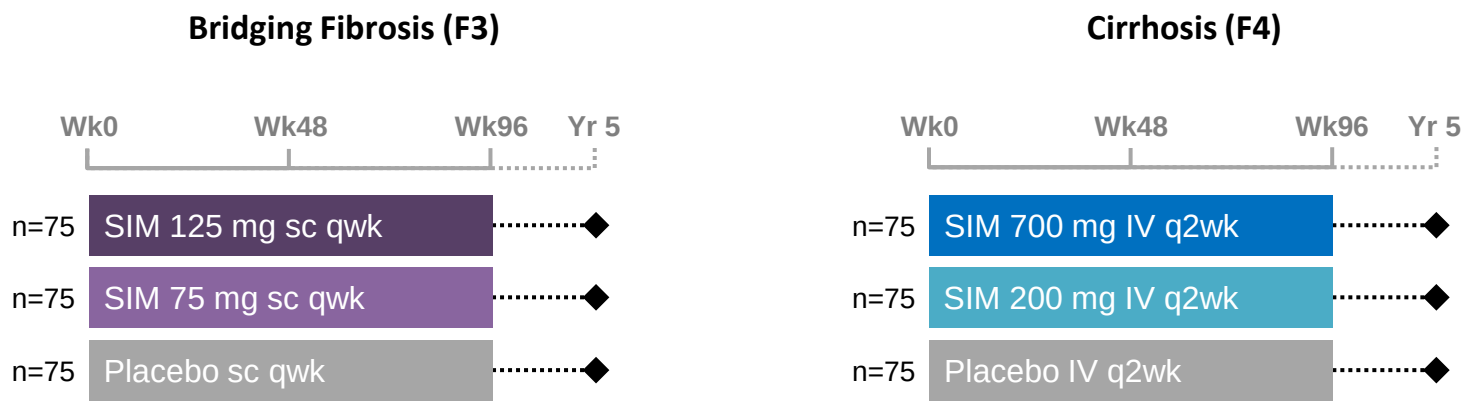


Sanyal AJ. unpublished

Defining the course of NASH with advanced fibrosis



Study Designs

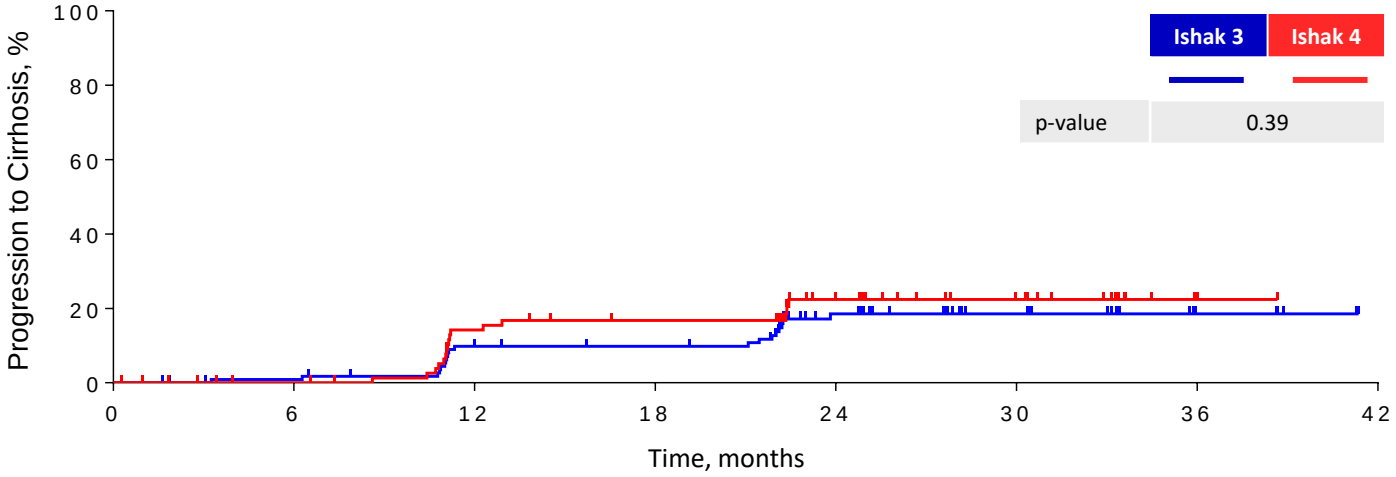


- Key inclusion criteria
  - Histologically confirmed NASH with bridging fibrosis (F3) or compensated cirrhosis (F4)
- Randomization stratified by diabetes and HVPG ≥10 mmHg (F4 only)
- **Studies terminated at Week 96 due to lack of efficacy**
  - **Treatment groups pooled for analysis**

HVPG, hepatic venous pressure gradient.
Sanyal A, Harrison S, et al. EASL 2017, abstr GS-004.

Sanyal et al, EASL 2017

Progression to cirrhosis from bridging fibrosis: results from the Gilead 105 trial



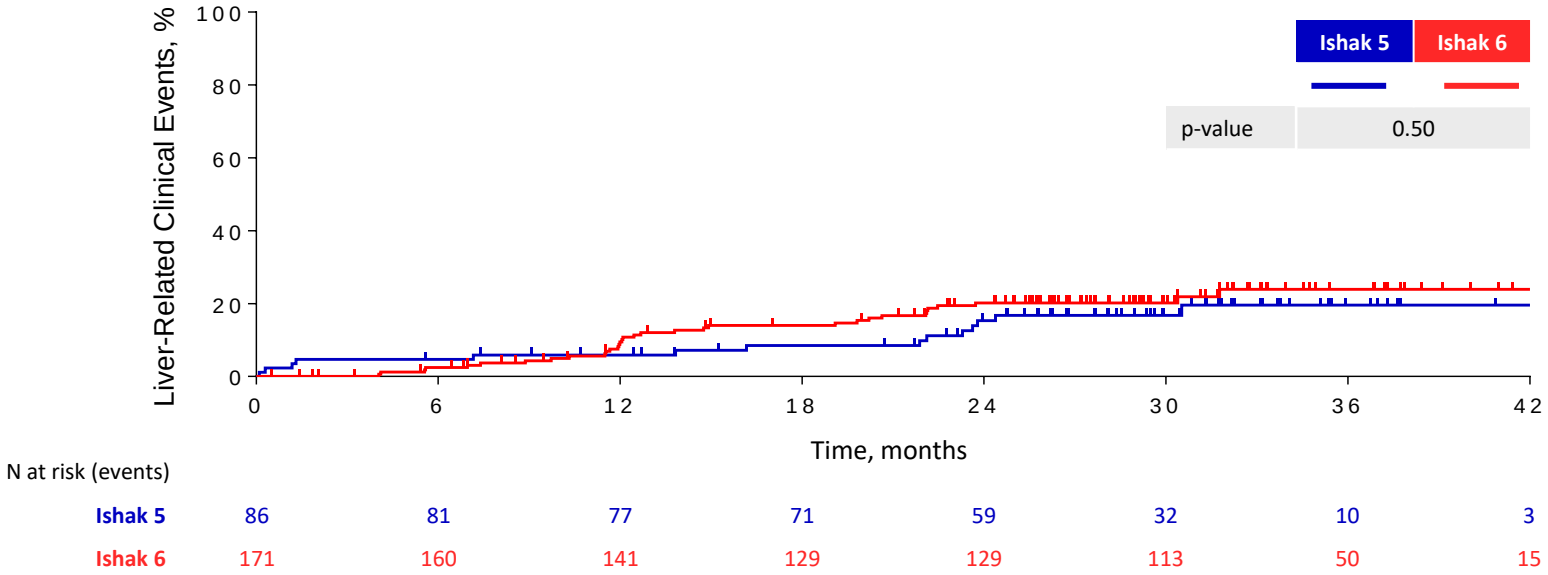
N at risk

Ishak 3	124	119	99	97	58	27	5	0
Ishak 4	93	86	66	60	35	21	2	0

- Median follow-up 24.9 months (range, 0.3–41.4)
- 47 patients (21.5%) progressed to cirrhosis
  - 89% (n=42) histologic progression
  - 11% (n=5) clinical events

Sanyal et al, EASL 2017

Liver-Related Clinical Events in those with NASH-cirrhosis: results from Gilead 106 trial

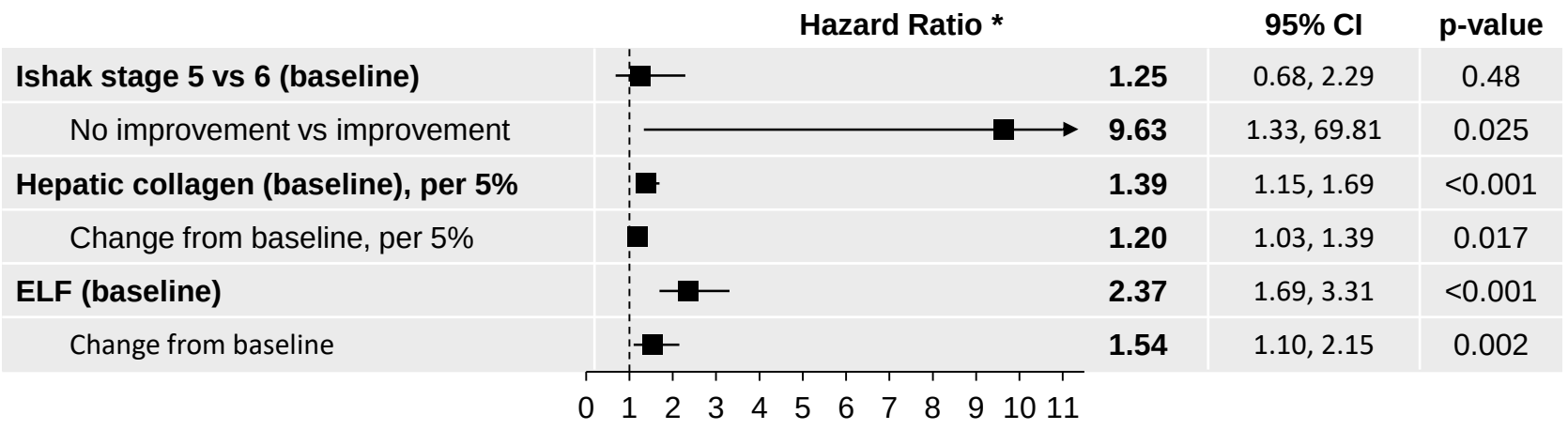


- Median follow-up 26.7 months (range, 0.1–42.3)
- 49 patients (19.0%) had an event *
  - Ascites (n=19)
  - Encephalopathy (n=13)
  - Variceal hemorrhage (n=6)
  - Newly-diagnosed varices (n=4)
  - ≥2-point increase in Child-Pugh score and/or MELD ≥15 (n=6)
  - Death (n=1)

* Only first event per patient included.

Sanyal et al, EASL 2017

Impact of Fibrosis on Clinical Events



- Increased risk of clinical events with:
  - Higher baseline hepatic collagen content and ELF
  - Worsening of fibrosis (by Ishak stage, collagen content, ELF)

Sanyal et al, EASL 2017

* Separate multivariate models run with baseline and change from baseline for each variable.

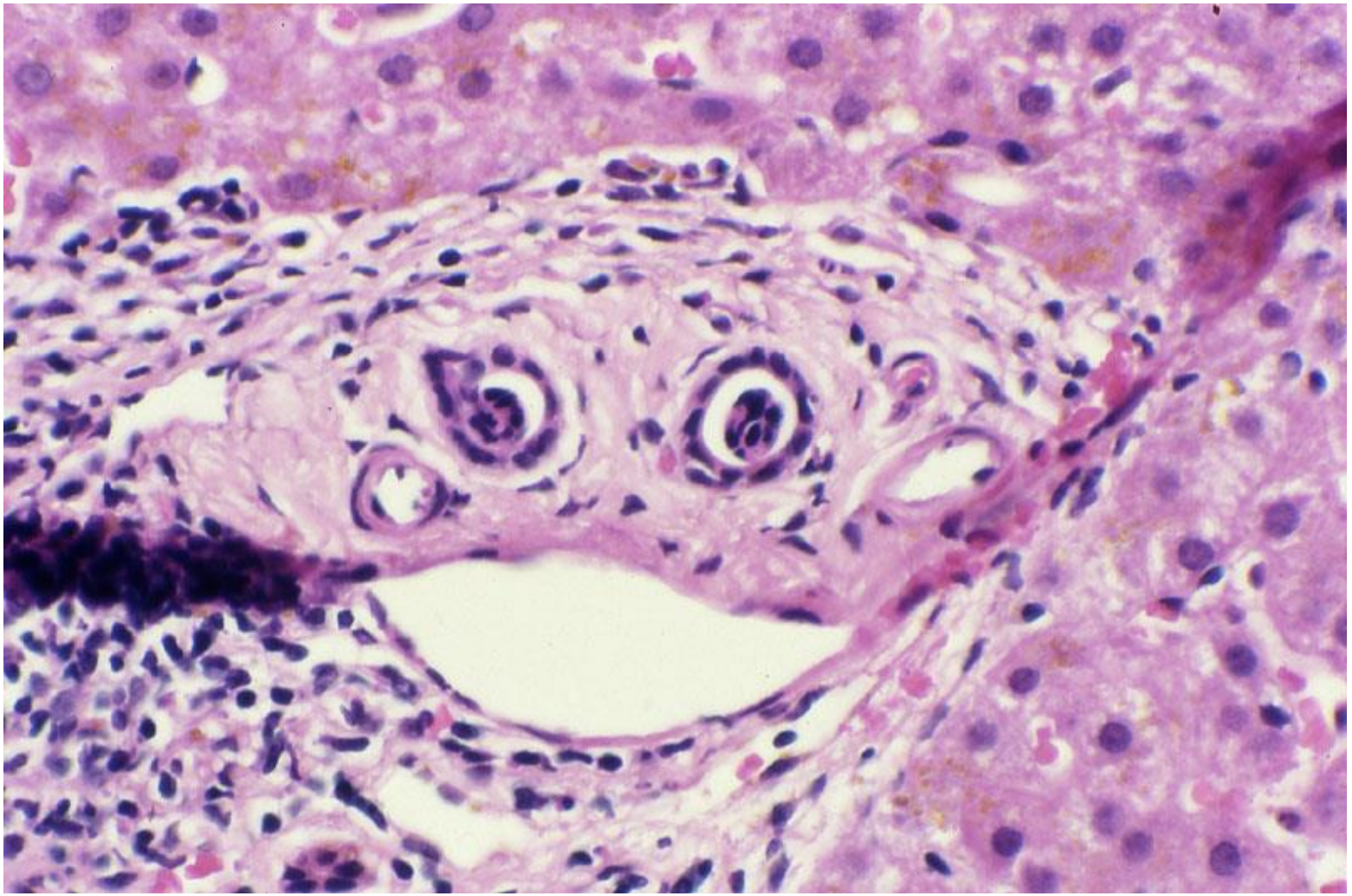
Summary

- NAFLD phenotype can move bi-directionally over time
- Development of fibrosis in those with NAFL is linked to development of NASH
- Fibrosis can progress or regress spontaneously
- Weight changes, changes in liver enzymes, severity of insulin resistance, portal inflammation and changes in NAFLD activity scores are key predictors of disease progression or regression

Acknowledgements

- NIDDK NASH CRN
  - Clinical investigators
  - Pathology committee
  - Data coordinating center
- Gilead
  - Investigators especially Zach Goodman
  - Rob Myers, Mani Subramaniam
- Patients who provided their tissue

Thank You



Courtesy- Dr. David Kleiner

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