Therapeutic Approaches to Cirrhotic versus Pre-Cirrhotic NASH

Discovery on Target: NASH & Fibrosis

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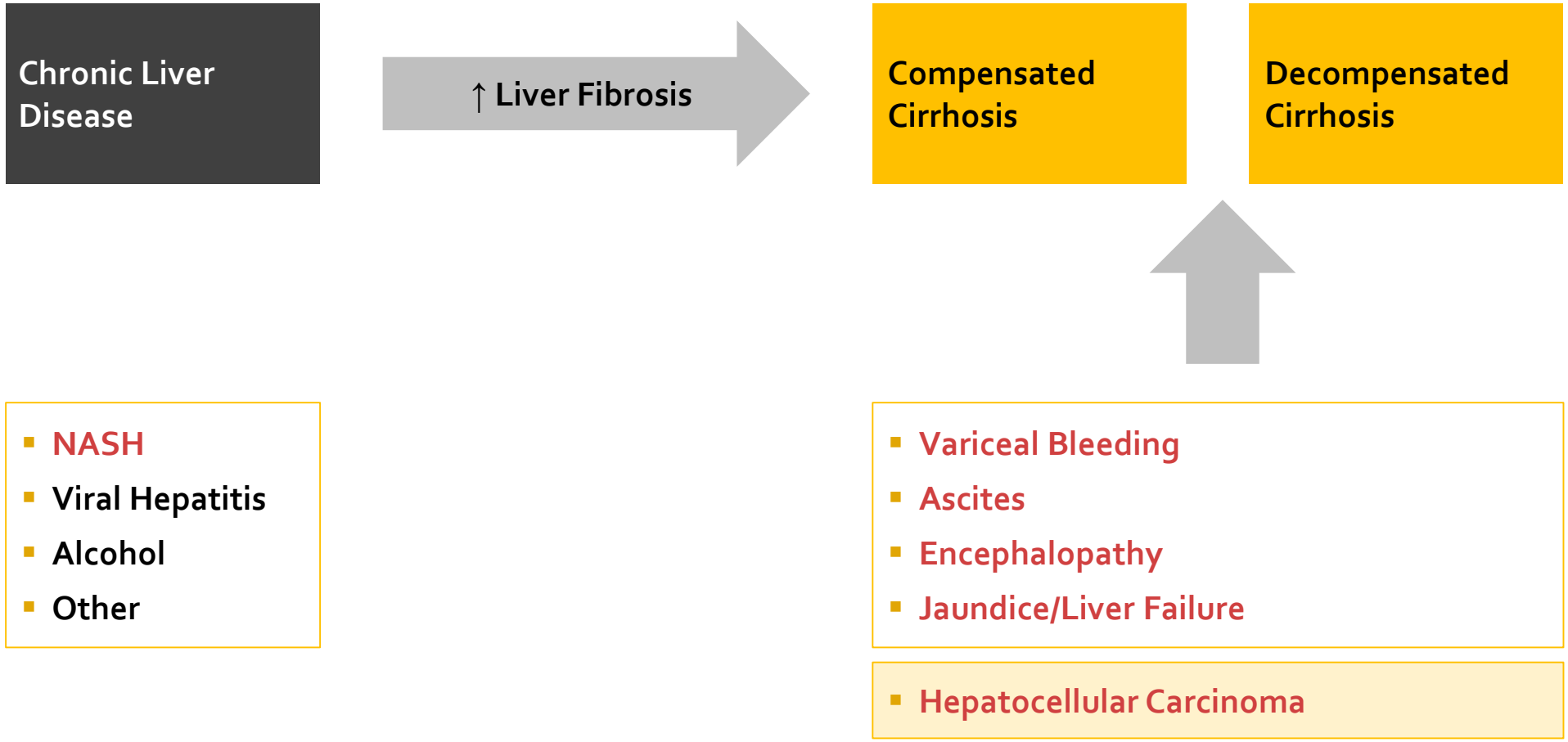
Chronic Liver Disease, Cirrhosis and its Progression



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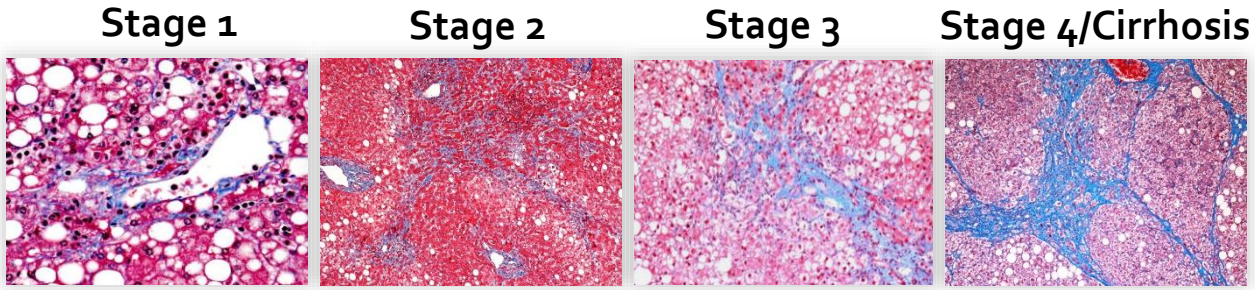
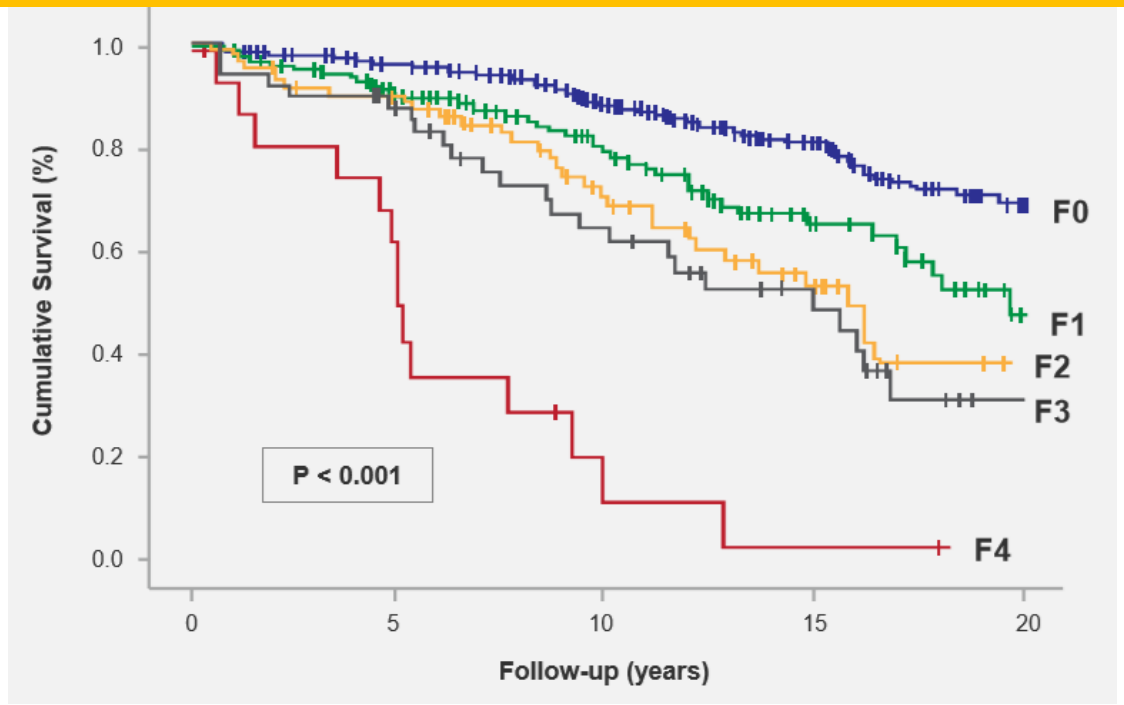
Fibrosis Stage Progression Associated with NASH



Survival Free of Liver Transplantation Based on Fibrosis Stage[1]



NASH and Fibrosis Stage

- Approximately one-third of patients with NASH will advance to Stage 3/4 fibrosis [2]
- An estimated 40% of NASH patients in the U.S. have a fibrosis stage of F2 or higher [3]
- NASH with advanced fibrosis carries the greatest risk of all-cause and liver-related mortality [2,4,5]

[1] Graphic taken from ICPT presentation May 2018 which re-graphs data from Angulo, et al. Gastroenterology 2015;149:389-397

[2] Caldwell, et al. Dig Dis 2010;28:162–168

[3] Estes, et al. Hepatology 2018;67:123-133

[4] Dulai, et al. Hepatology 2017;65:1557-1565

[5] Hagstrom, et al. J Hepatology 2017;67:1265-1273

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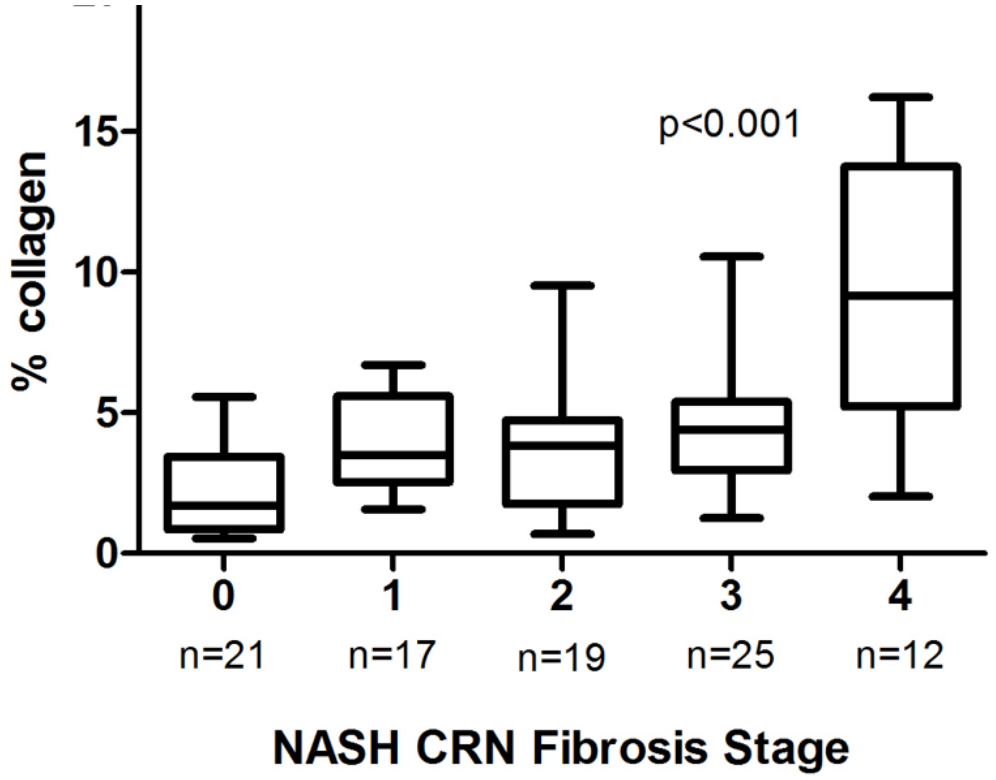
Percent Collagen in NASH Liver Biopsies per Stage of Fibrosis

Liver Biopsy Sirius Red Morphometry by Fibrosis Stage[1]



[1] Data from Goodman and Harrison

Collagen Accumulation in NASH

- The distribution of fibrosis in NASH is important in staging as well as the amount of collagen
- While there is an increase in the median percent collagen from stage 0 to 3, there is a great deal of overlap of values.
- In stage 4, or cirrhosis, there is a marked increase in the median amount of collagen and a very broad range.
- These and other published data show that progression of fibrosis after the development of cirrhosis is a critical element for development of complications of cirrhosis
- Better methods of quantifying fibrosis is required for early drug assessment

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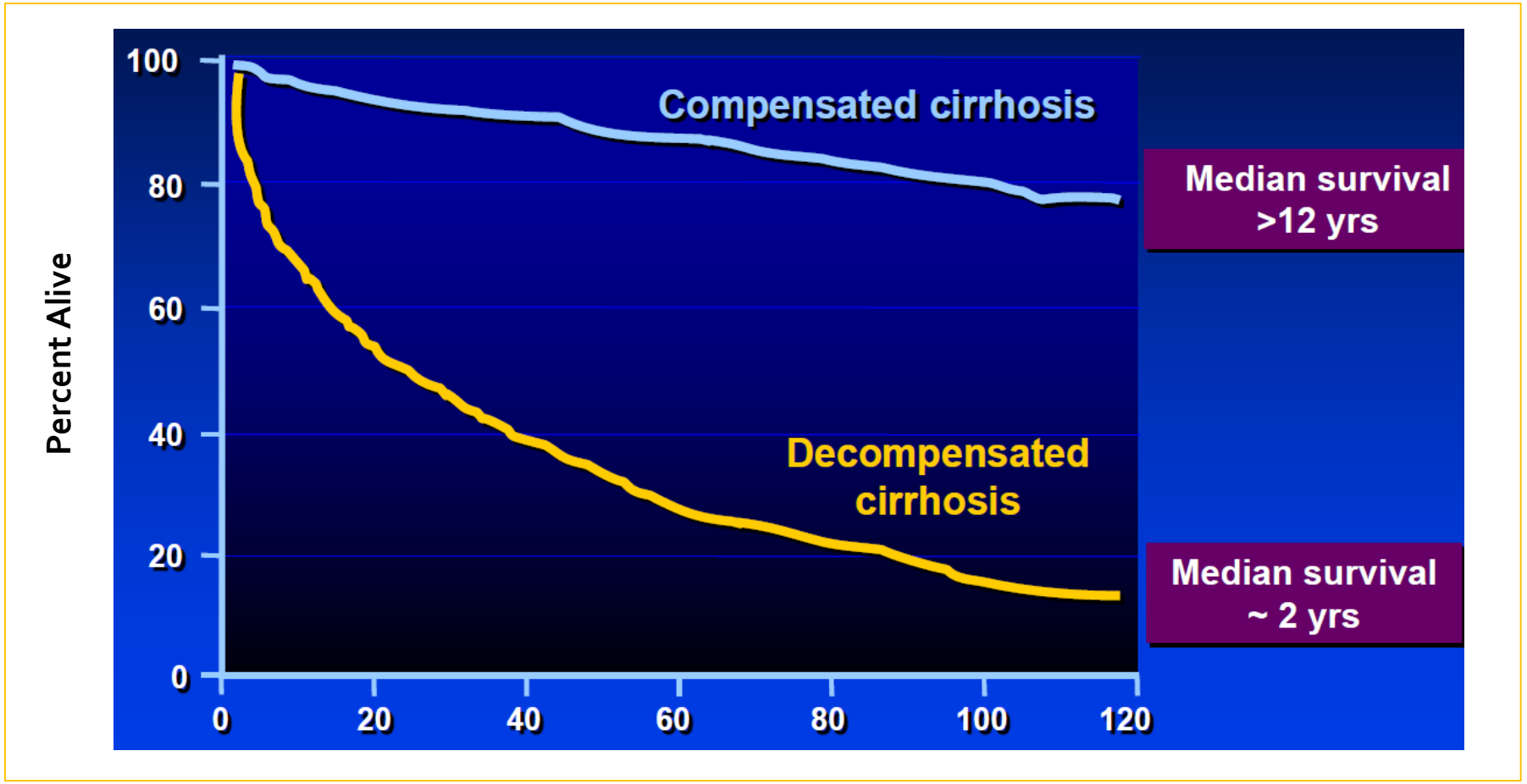
Survival Between Compensated and Decompensated Cirrhosis



D'Aminco et. Al., J Hepatol 2006;44:217 (Graphic borrowed from Dr. Guadalupe Garcia-Tso)

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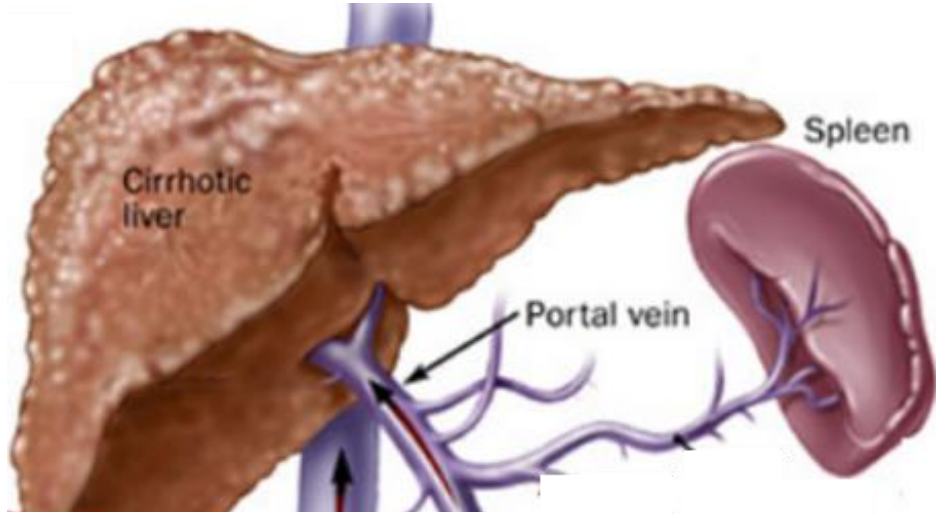
Portal Hypertension is a Major Driver of Decompensation

Increased pressure in the portal circulation is initiated by increased intrahepatic resistance to blood flow though the liver



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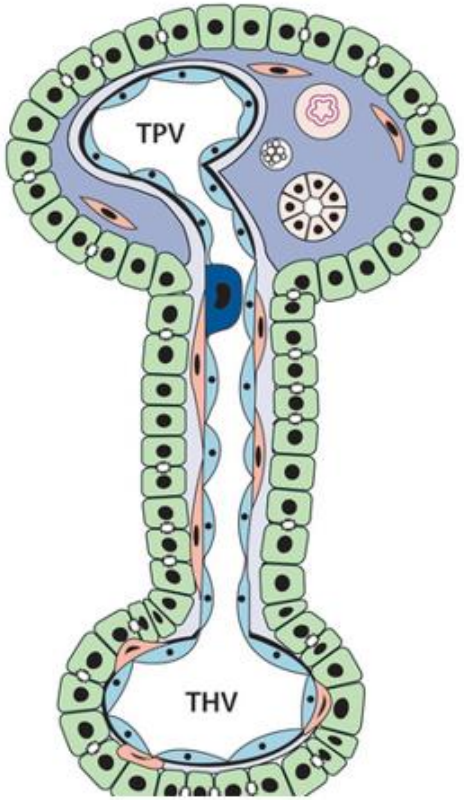
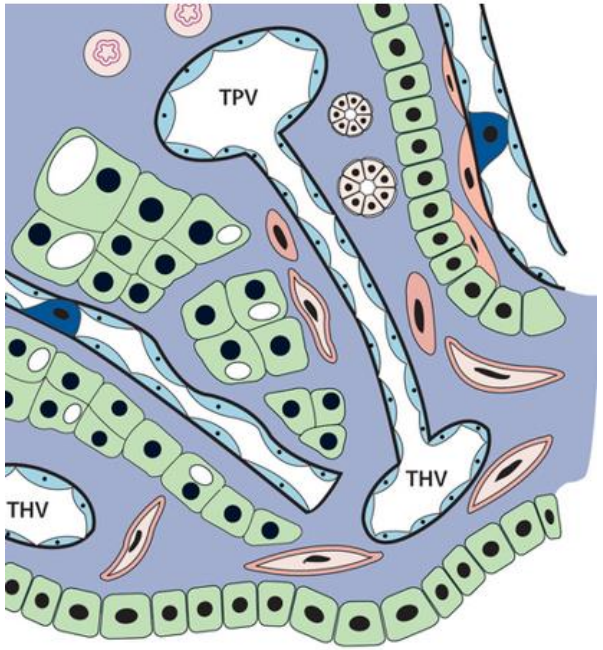
Multiple Contributors to Increased Intrahepatic Blood Flow Resistance in Cirrhosis

Normal Liver Acinar Unit



Distorted Architecture in Cirrhosis



- **Structural Components**
  - Scar tissue
  - Stellate cells
  - Regenerative nodules
  - Neoangiogenesis
  - Micro thrombosis
- **Non-Structural Components**
  - Nitric Oxide
  - Endothelin
  - Eiconsanoids
  - CO/others
  - "Endothelial Dysfunction"

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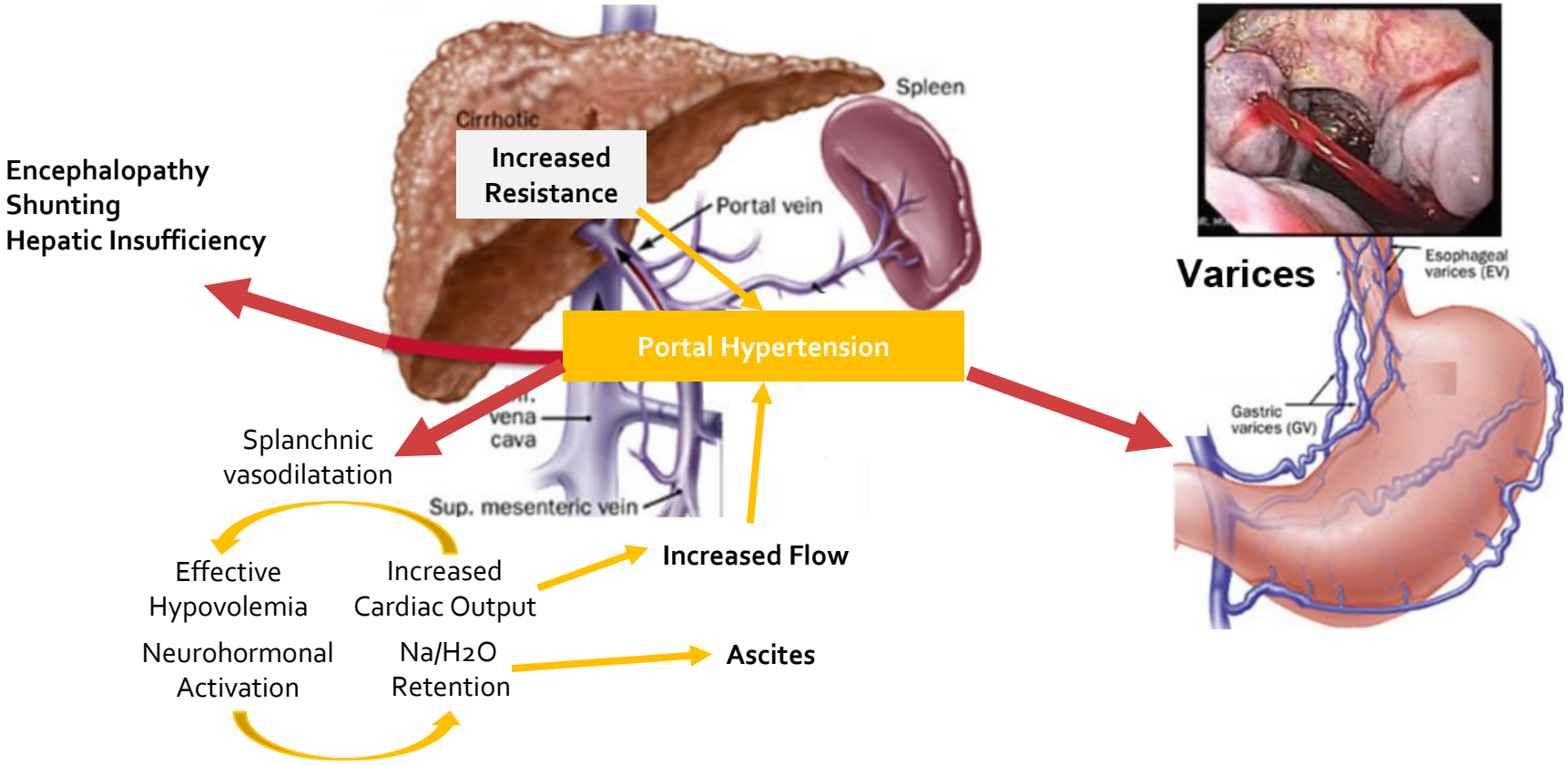
Cirrhosis Complications Center Around Increased Portal Vein Blood Pressure



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Portal Hypertension is the Main Driver of Decompensation

Portal Pressure (mmHg) ≥6 >10 >12

	Compensated Cirrhosis		Decompensated Cirrhosis	
	Stage 1	**Stage 2**	**Stage 3**	**Stage 4**
Varices	No	7% → Yes	Yes/No	Yes
Ascites	No	4.4% → No	→ Yes	Yes/No
Bleed	No	No	No	Yes
Mortality	1%	3%	20%	57%
Annual progression →				

D'Aminco et. Al., J Hepatol 2006;44:217

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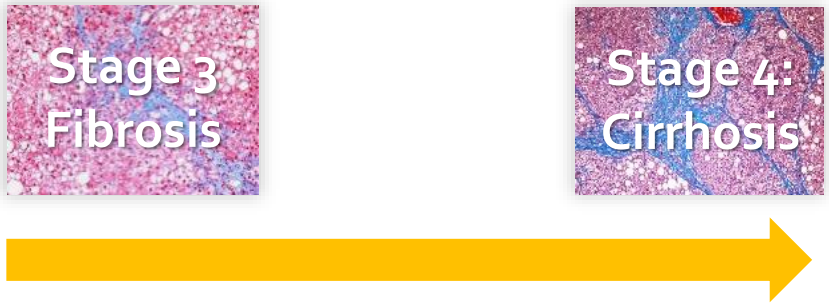
The Critical Cirrhosis Transition: Endpoints for Pre-Cirrhotic NASH



Pre-cirrhotic NASH Endpoints	
Surrogates for Accelerated Approval (agreement with Agencies as part of Phase 3 clinical trials)	**Clinical Outcomes for Full Approval**
Proportion of patients who achieve ≥ 1 stage improvement in fibrosis without worsening of NASH	Reduced time to cirrhosis complications, including the **progression to cirrhosis**
Proportion of patients who achieve NASH resolution without worsening of liver fibrosis	

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The Critical Cirrhosis Transition: Endpoints for NASH Cirrhosis

NASH Cirrhosis Endpoints	
Surrogates for Accelerated Approval (agreement with Agencies as part of Phase 3 clinical trials)	**Clinical Outcomes for Full Approval**
Proportion of patients who achieve ≥ 1 stage improvement in fibrosis without worsening of NASH	Reduced time to cirrhosis complications

The following are potential endpoints as there are no final phase 3 protocols

Reduction in HVPG (endpoints will need to define threshold and degree of reduction in specific populations TBD)	Reduced time to cirrhosis complications
Reduced time to development of esophageal varices in patients with no varices at baseline	Reduced time to cirrhosis complications

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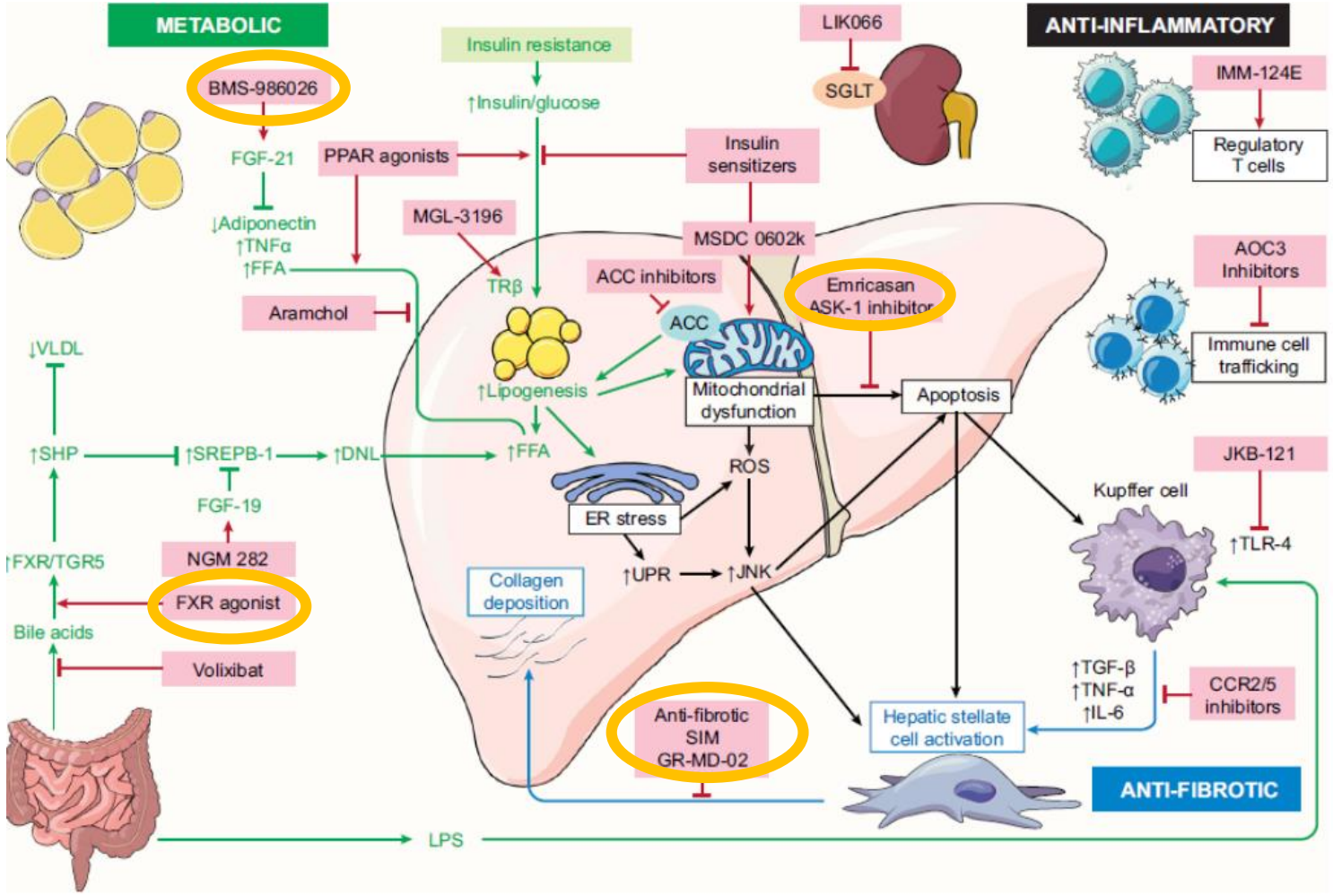
Targets for NASH Therapies



Konerman, et. al., J. Hepatology. 2018

Targets and drugs in current clinical trials for NASH cirrhosis

- **Inhibition of apoptosis pathway**
  - **Emricasan**
  - **Selonsertib**
- **Anti-fibrotic**
  - **GR-MD-02**
- **Metabolic regulator**
  - **BMS-986026 (FGF-21)**
- **FXR agonist**
  - **Obeticholic Acid**

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Phase 2/3 Clinical Trials in NASH Cirrhosis

NASH Cirrhosis Trial Supportive pre-cirrhotic NASH Fibrosis Trial

Drug (Company/Partner)	MOA/Route of Administration	Phase	Studies	Next Expected Data (estimate)
Selonsertib (Gilead)	ASK-1 inhib./oral	3 3 2	STELLAR-4: compensated cirrhosis STELLAR-3: NASH with F3 fibrosis ATLAS*: F3 and F4 patients	Q1 2019 Q2 2019 Q1 2020
Obeticholic acid (Intercept)	FXR Agonist/oral	3 3	REVERSE: compensated cirrhosis REGENERATE: NASH with F2/F3 fib	JUL 2020 H1 2019
GR-MD-02 (GALT)	Galectin-3 inhib./iv	3	Compensated cirrhosis w/o varices--Phase 3 start not yet announced	TBA
Emricasan (CNAT/Novartis)	Pan-caspase inhib./oral	2 2 2	ENCORE-PH (severe portal HTN) ENCORE-LF (decompensated cirrhosis) ENCORE-NF (NASH fibrosis)	Q4 2018 H2 2019 H1 2019
BMS-986036 (BMS)	PEG-FGF21/subcut	2	P2b multiple dose; compensated cirrhosis P2b multiple dose; stage 3 fibrosis	JAN 2020 JAN 2020

*** ATLAS study evaluates Selonsertib in combination with GS-0976 (ACC inhibitor) and GS-9674 (FXR agonist)**

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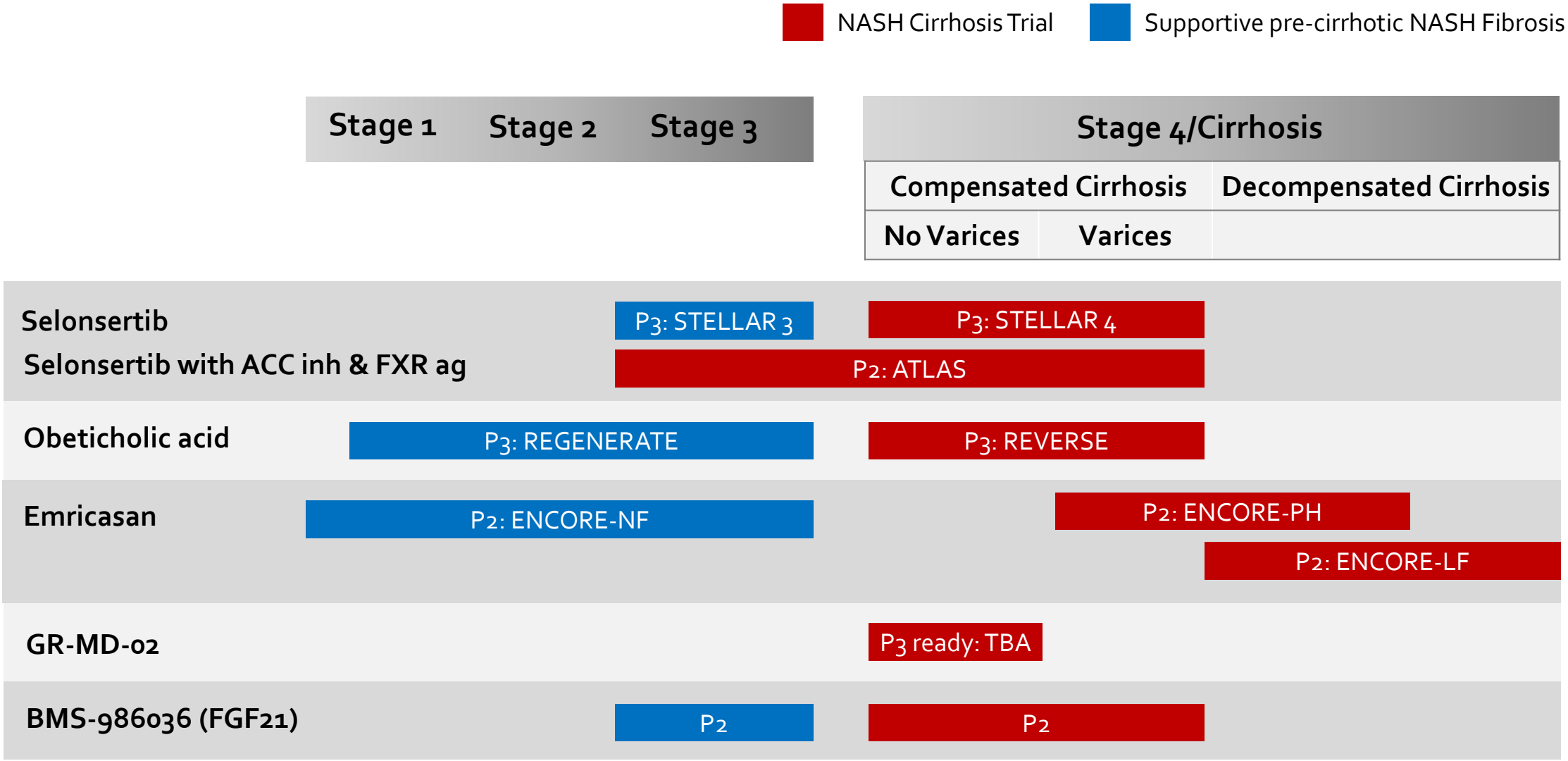
NASH Cirrhosis Clinical Trials Mapped to Patient Segment



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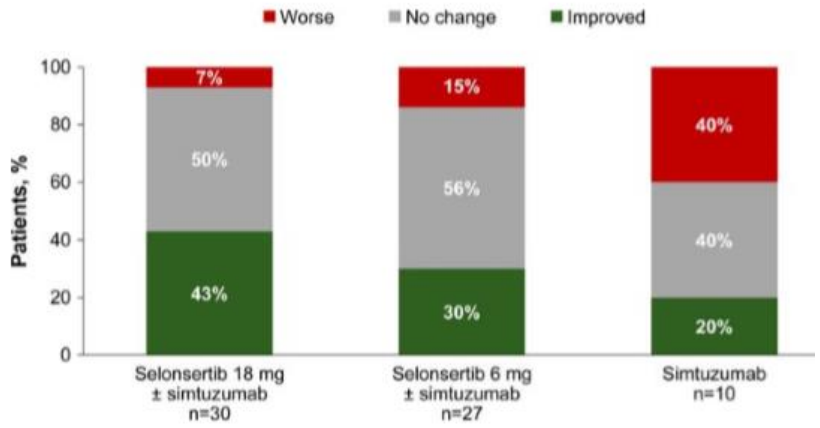
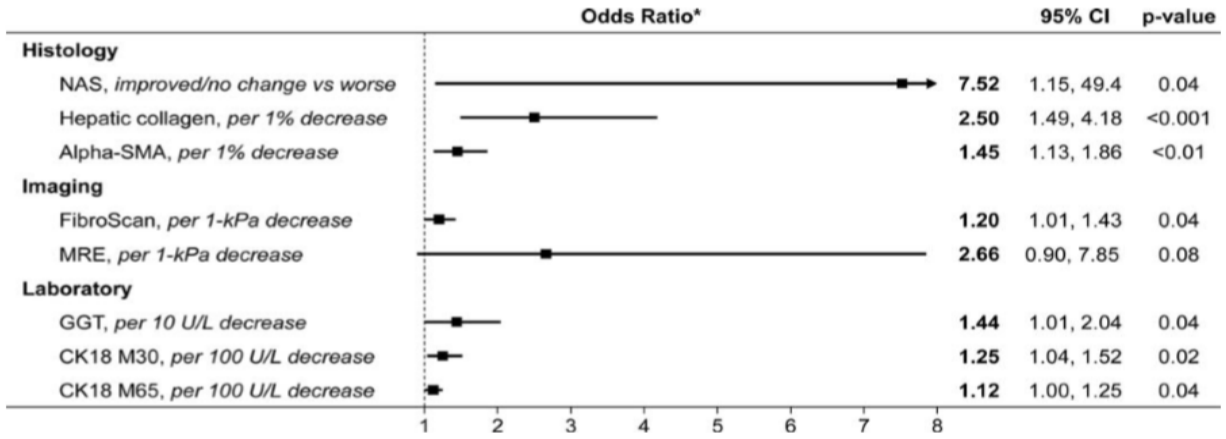
Selonsertib: Phase 2 Data Supporting Phase 3 Studies

Patients with NASH fibrosis (stage 2/3) showed improved histologic fibrosis staging from baseline to week 24



Histologic, imaging and laboratory factors were associated with fibrosis improvement seen on liver biopsy staging



Loomba, et. al., Hepatology 2018

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STELLAR-4: Selonsertib in Compensated NASH Cirrhosis

Phase 3 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 883 (actual)	▪ SEL 18 mg ▪ SEL 6 mg ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH cirrhosis (Stage 4 by NASH-CRN class) ▪ **Exclusion** › No history of decompensation › Child-Pugh score >7 › MELD >12	▪ Proportion of patients who achieve a ≥ 1 stage improvement in fibrosis without worsening of NASH [Week 48] ▪ Event-Free Survival as assessed by time to first clinical event [Week 240]

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STELLAR-3: Selonsertib in NASH with Bridging Fibrosis (stage 3)

Phase 3 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoint
▪ 808 (actual)	▪ SEL 18 mg ▪ SEL 6 mg ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH with bridging fibrosis (Stage 3 by NASH CRN classification) ▪ **Exclusion** › No history of decompensation › Child-Pugh score >6 › MELD >12	▪ Proportion of patients who achieve a ≥ 1 stage improvement in fibrosis without worsening of NASH [week 48] ▪ Event-Free Survival as assessed by time to first clinical event [Week 240]

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ATLAS: Selonsertib in Combination with GS-0976 (ACC inh) & GS-9674 (FXR ag)

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 350	▪ Seven groups covering active and placebo combinations with SEL	▪ **Inclusion** › Liver biopsy with NASH with bridging fibrosis (F_3) or cirrhosis (F_4) (NASH CRN class) › FibroScan + ELF, if no LBx ▪ **Exclusion** › No history of decompensation › Child-Pugh score >6 › MELD >12	▪ Safety: AEs and Lab Abnormalities ▪ Proportion of patients who achieve a ≥ 1 stage improvement in fibrosis without worsening of NASH [week 48]

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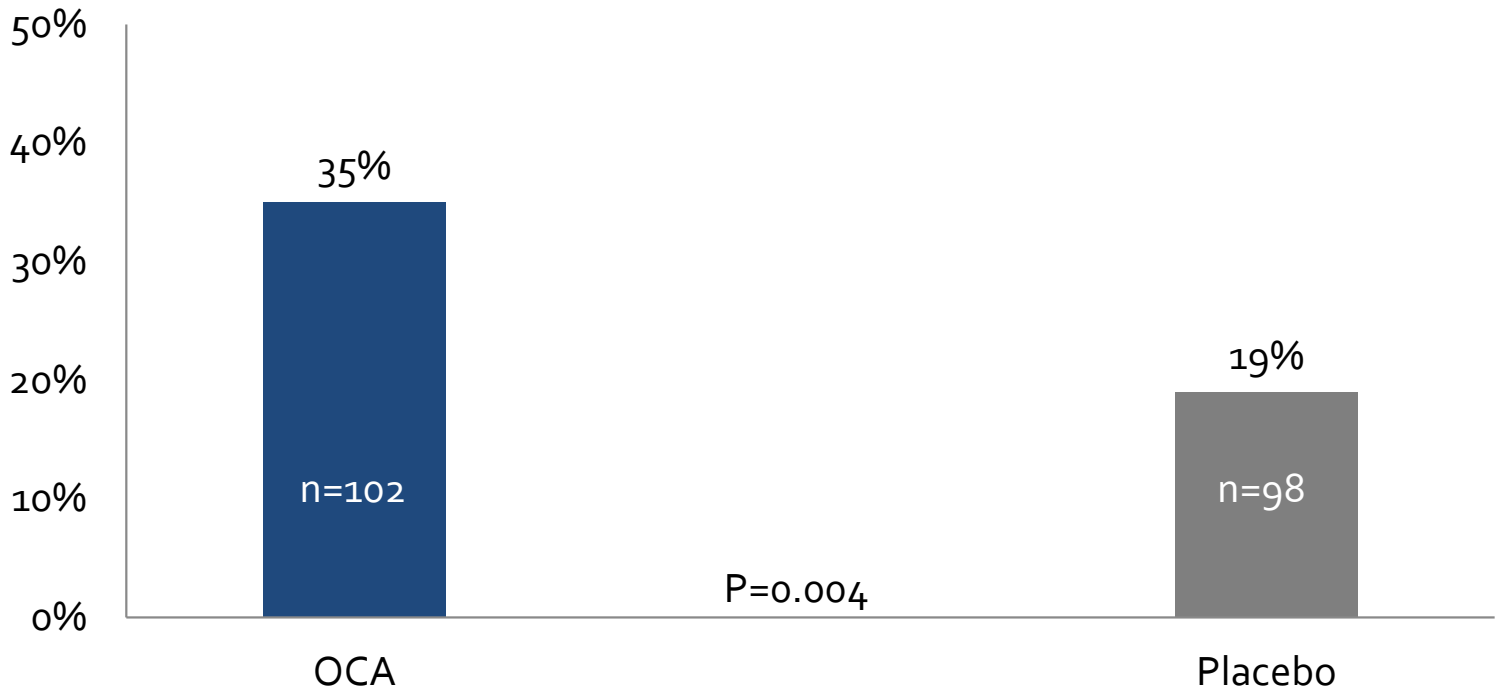
Obeticholic Acid: Phase 2 Data in NASH Fibrosis

Fibrosis stage improvement in Phase 2 FLINT trial (200 paired biopsies over 72 weeks)

≥ 1 Stage fibrosis improvement



Neuschwander-Tetri, et. al., Lancet 2015

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REVERSE: Obeticholic Acid in Compensated NASH Cirrhosis

Phase 3 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 540	▪ OCA 10 mg ▪ OCA 10-25 mg ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH cirrhosis (Stage 4 by NASH-CRN class) ▪ **Exclusion** › No history of decompensation › Child-Pugh score >7 › MELD >12	▪ Proportion of patients with ≥ 1 stage improvement in fibrosis without worsening of NASH [12 months]

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REGENERATE: Obeticholic Acid in NASH with F2/F3 Fibrosis

Phase 3 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ ~ 750 for interim (18 months) ▪ Additional ~1600 for outcomes	▪ OCA 25 mg ▪ OCA 10 mg ▪ Placebo	▪ **Inclusion** › Liver biopsy with fibrosis stage 2 or stage 3, or stage 1a or stage 1b if accompanied by ≥1 of obesity (BMI ≥30 kg/m2), type 2 diabetes, ALT >1.5× upper limit of normal (ULN). ▪ **Exclusion** › No history of decompensation › Child-Pugh score >6 › MELD >12	▪ Proportion of patients with ≥ 1 stage improvement in fibrosis without worsening of NASH **OR** ▪ Proportion of patients achieving NASH resolution without worsening of liver fibrosis [18 months] ▪ Event-Free Survival as assessed by time to first clinical event-includes progression to cirrhosis [~7 years]

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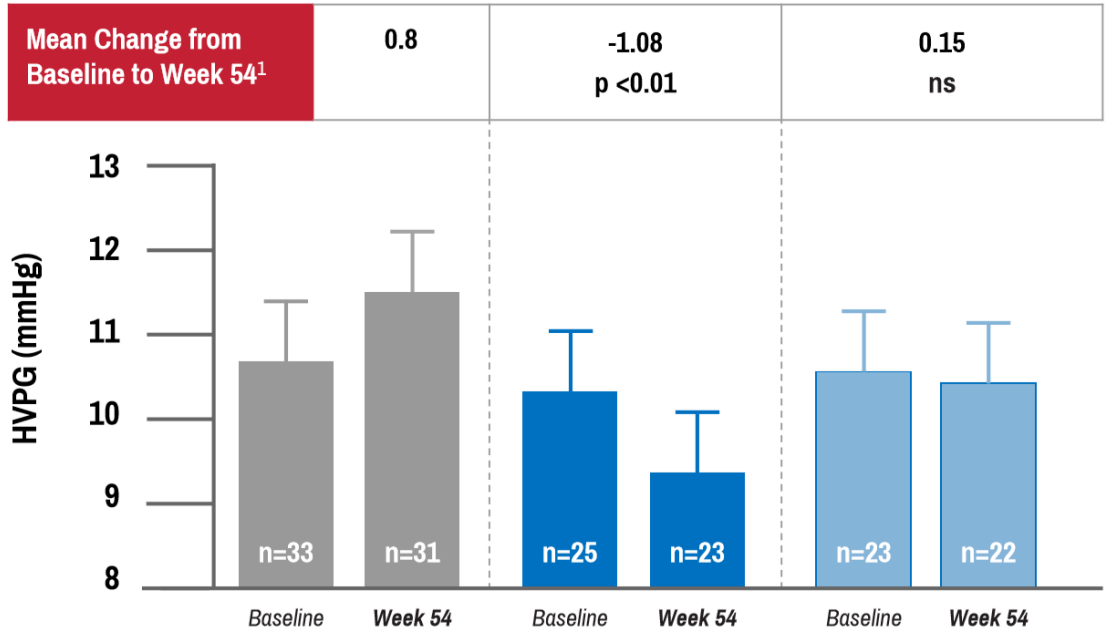
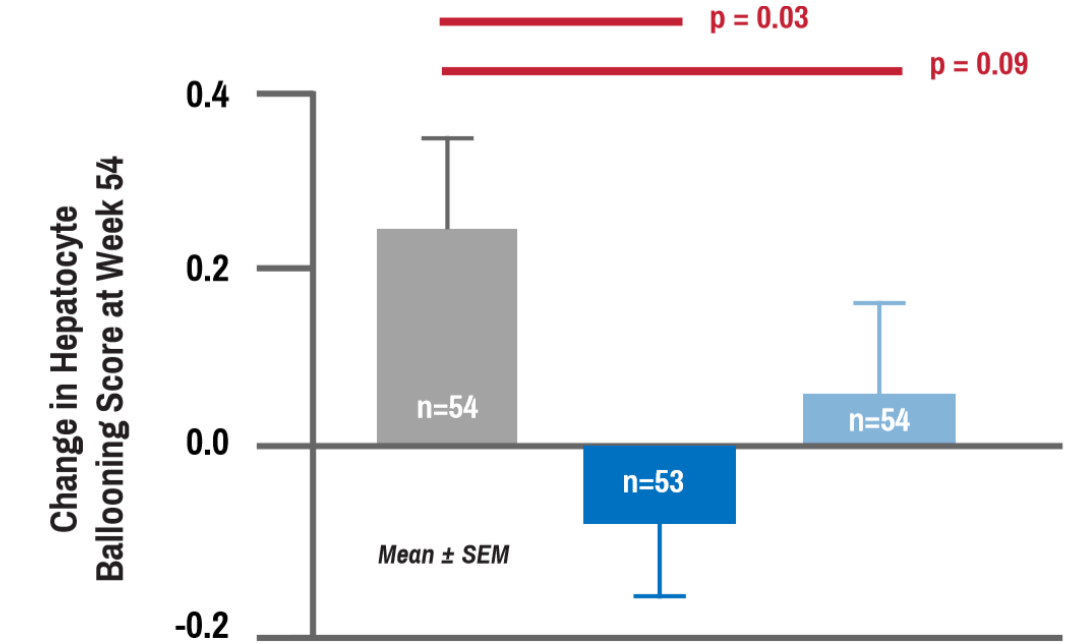
GR-MD-02: Phase 2b NASH Cirrhosis Study Results (NASH-CX)

Compensated Cirrhosis, No Varices (50% Total)[1]



Compensated Cirrhosis (Total Patients[1])



Disclosure: Presenter previously full time employee of GALT and continues to own equity in company. Figures taken from publicly disclosed July 2018 corporate presentation

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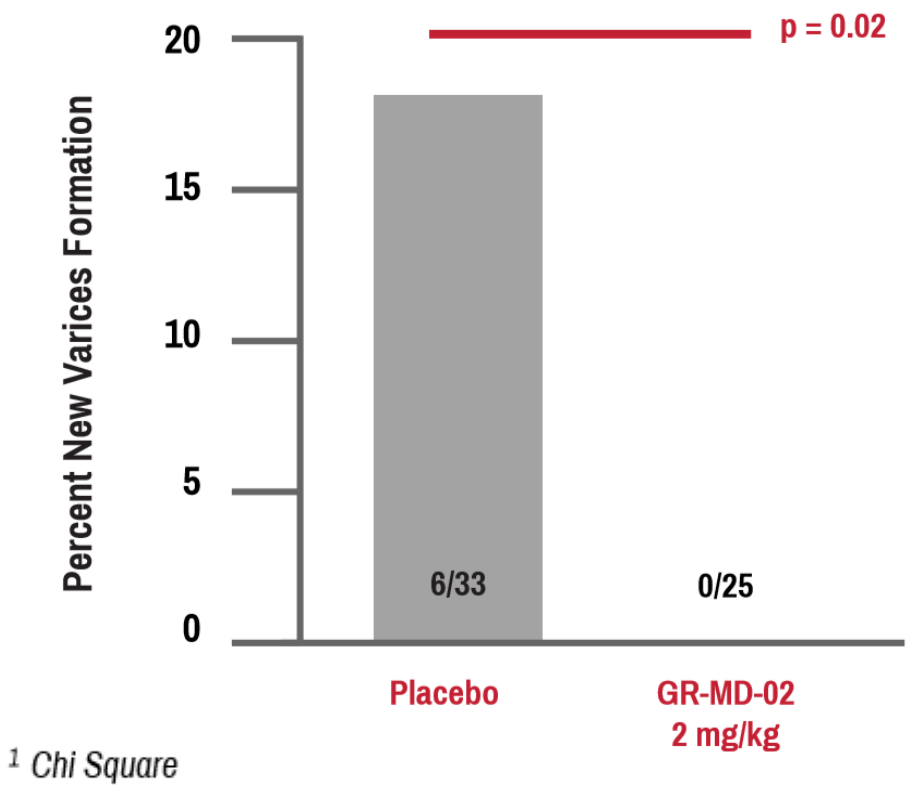
GR-MD-02: Phase 2b NASH Cirrhosis Study Results

Compensated Cirrhosis, No Varices (50% Total)[1]



[1] *Chi Square*

NASH-CX Study Conclusions

- **First clinical trial to show positive results in compensated cirrhosis without esophageal varices**
  - Clinically meaningful effect in reducing portal pressure in subgroup of patients
  - Improvement in liver cell death
  - Reduction in the development of new varices
- **Drug was safe and well tolerated**
- **Following meeting with FDA in May 2018, determined to be Phase 3-ready**
- **Proceeding with plans for a phase 3 clinical trial program**

Disclosure: Presenter previously full time employee of GALT and continues to own equity in company. Figures and text taken from publicly disclosed July 2018 corporate presentation

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Emricasan: Series of Phase 2a Studies Supported Additional Larger Phase 2 Studies in NASH Fibrosis and Cirrhosis

- NASH patients had reductions in ALT, suggesting reduced liver injury
- Patients with all etiology cirrhosis and severe portal hypertension had significant reductions in HVPG
  - Emricasan reduced number of circulating microparticles which may have vascular effects on portal pressure
- NASH cirrhosis patients with high MELD scores had improved MELD scores on emricasan

ENCORE-PH: Emricasan in NASH Cirrhosis and Severe Portal Hypertension

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 240	▪ EMR 50 mg ▪ EMR 25 mg ▪ EMR 5 mg ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH cirrhosis › HVPG ≥12 mmHg › Compensated or decompensated with 1 event ▪ **Exclusion** › Severe decompensation › Child-Pugh score ≥10	▪ Mean change in HVPG [Week 24] ▪ In this patient population with HVPG ≥12 mmHg, changes in HVPG may be an acceptable surrogate endpoint

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ENCORE-LF: Emricasan in Decompensated NASH Cirrhosis

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 210	▪ EMR 25 mg ▪ EMR 5 mg ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH cirrhosis › History of variceal hemorrhage or moderate ascites › MELD ≥12 and ≤20 › Albumin ≥12 g/dL › Serum creatine ≤1.5 mg/dL ▪ **Exclusion** › Severe decompensation › Child-Pugh score ≥10	▪ Event-free survival on composite clinical endpoint [final treatment; at least 48 weeks to a max of 120 weeks]

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ENCORE-NF: Emricasan in NASH Fibrosis

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 330	▪ EMR 50 mg ▪ EMR 5 mg ▪ Placebo	▪ **Inclusion** › Liver biopsy definitive NASH › NAS ≥4 with 1 in each component › Fibrosis stage 1, 2, or 3 ▪ **Exclusion** › Severe decompensation › Child-Pugh score ≥10	▪ Proportion of patients with ≥ 1 stage improvement in fibrosis without worsening of NASH [week 72]

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BMS-986036 (FGF-21) in Compensated NASH Cirrhosis

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 100	▪ 3 dose levels ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH cirrhosis (Stage 4 by NASH-CRN class) ▪ **Exclusion** › No history of decompensation › No hepatocellular carcinoma	▪ Proportion of patients who achieve a ≥ 1 stage improvement in fibrosis without worsening of NASH [Week 48] ▪ Change in NASH-CRN fibrosis score [Week 48] ▪ Change in NAFLD Activity Score [Week 48]

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BMS-986036 (FGF-21) in NASH with Bridging Fibrosis (stage 3)

Phase 2 Study

# patients	Groups	Inclusion/Exclusion Criteria	Primary Endpoints
▪ 160	▪ 3 dose levels ▪ Placebo	▪ **Inclusion** › Liver biopsy with NASH with bridging fibrosis (Stage 3 by NASH CRN classification) › NASH with a score of at least 1 for steatosis, lobular inflammation, and ballooning ▪ **Exclusion** › No history of decompensation › No hepatocellular carcinoma	▪ Proportion of patients who achieve a ≥ 1 stage improvement in fibrosis without worsening of NASH [week 24] ▪ Proportion of patients who achieve NASH improvement with no worsening of fibrosis [week 24] ▪ Change in NAFLD Activity Score [Week 24]

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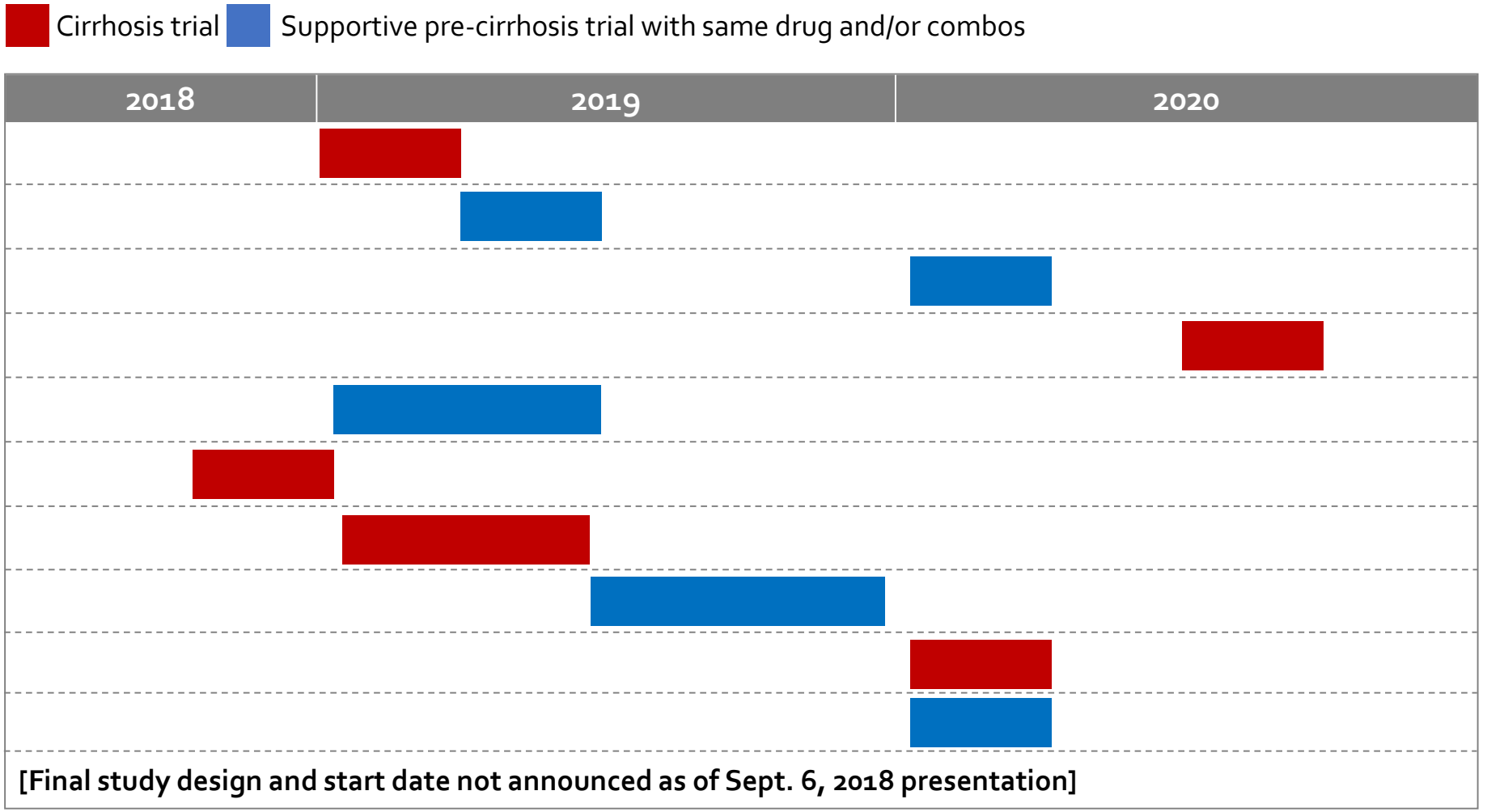
Estimated Data Milestones for NASH Cirrhosis Trials*



*** Based on clinicaltrial.gov postings plus company guidance when available; when a specific month was designated, the milestone is indicated over the ensuing one quarter**

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Thank You!

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