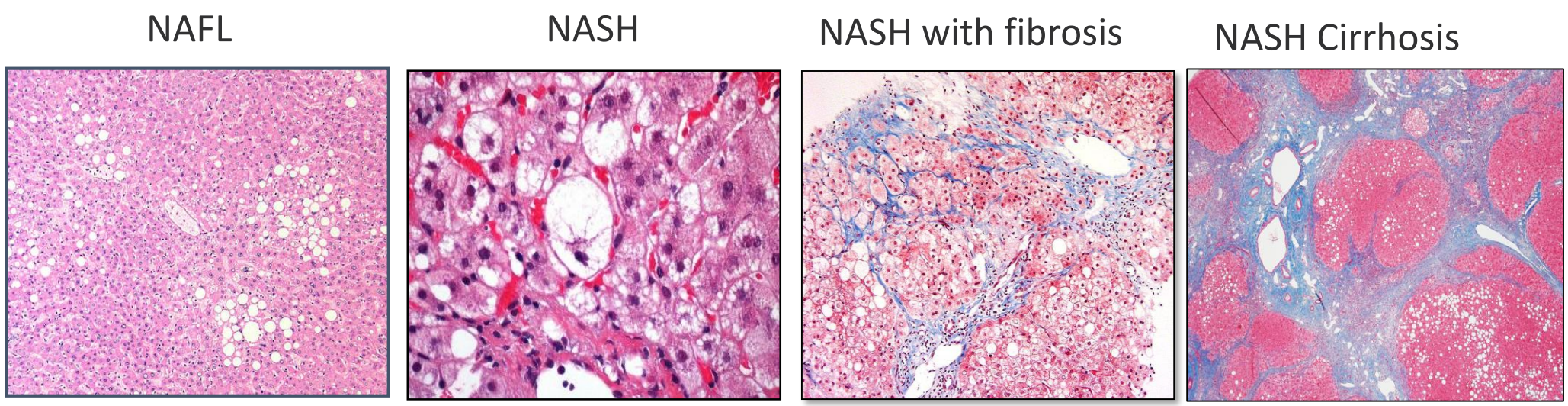
Future clinical trials for NASH



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Histology: courtesy David Kleiner, Elizabeth Brunt

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

ALL VIEW EXPRESSED ARE ENTIRELY MY OWN AND ARE NOT ENDORSED BY ANY OTHER PARTY

Drug Development score card for NASH

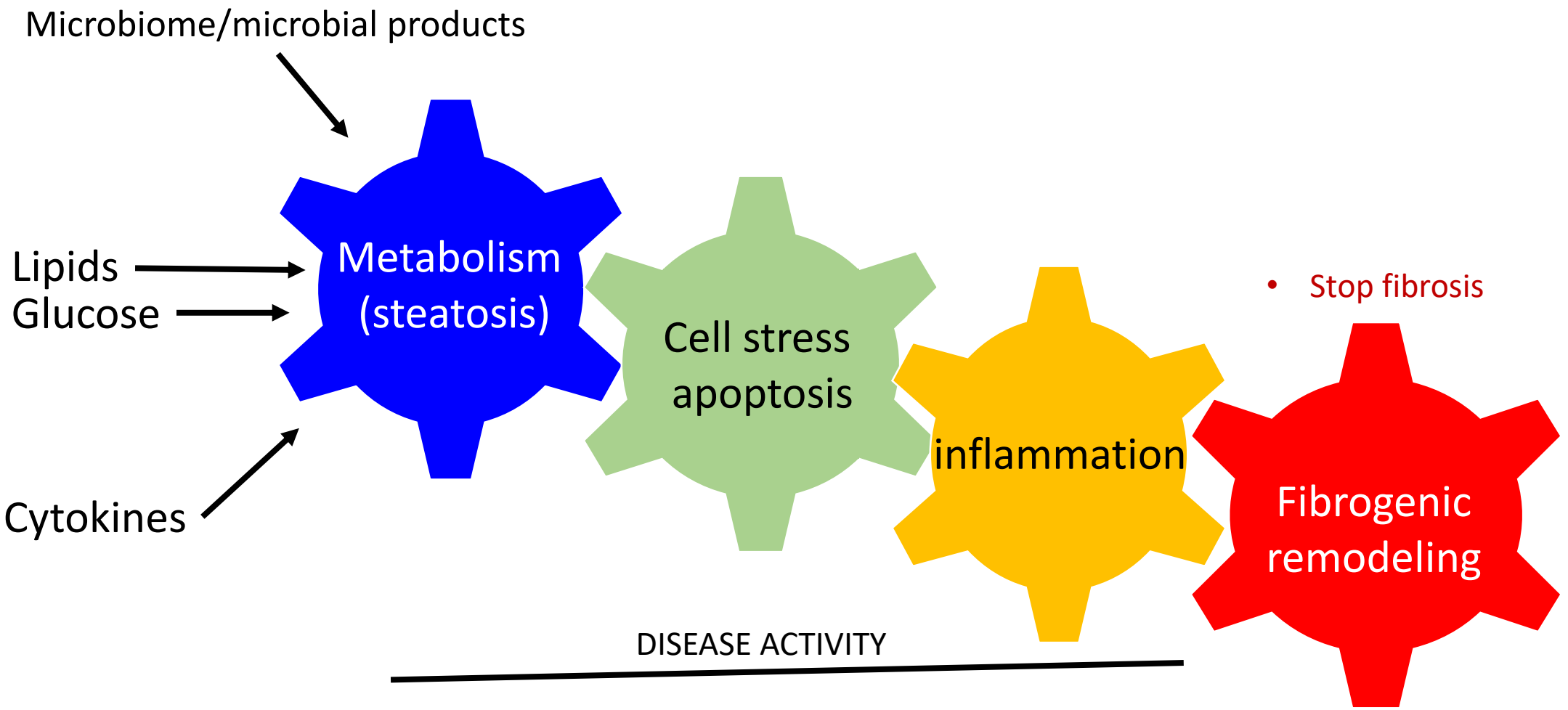
Positive Phase 2B/3 trials

- OCA- FLINT
- Elafibranor- GOLDEN
- Cenicrivaroc-CENTAUR
- Pioglitazone/vitamin E-PIVENS

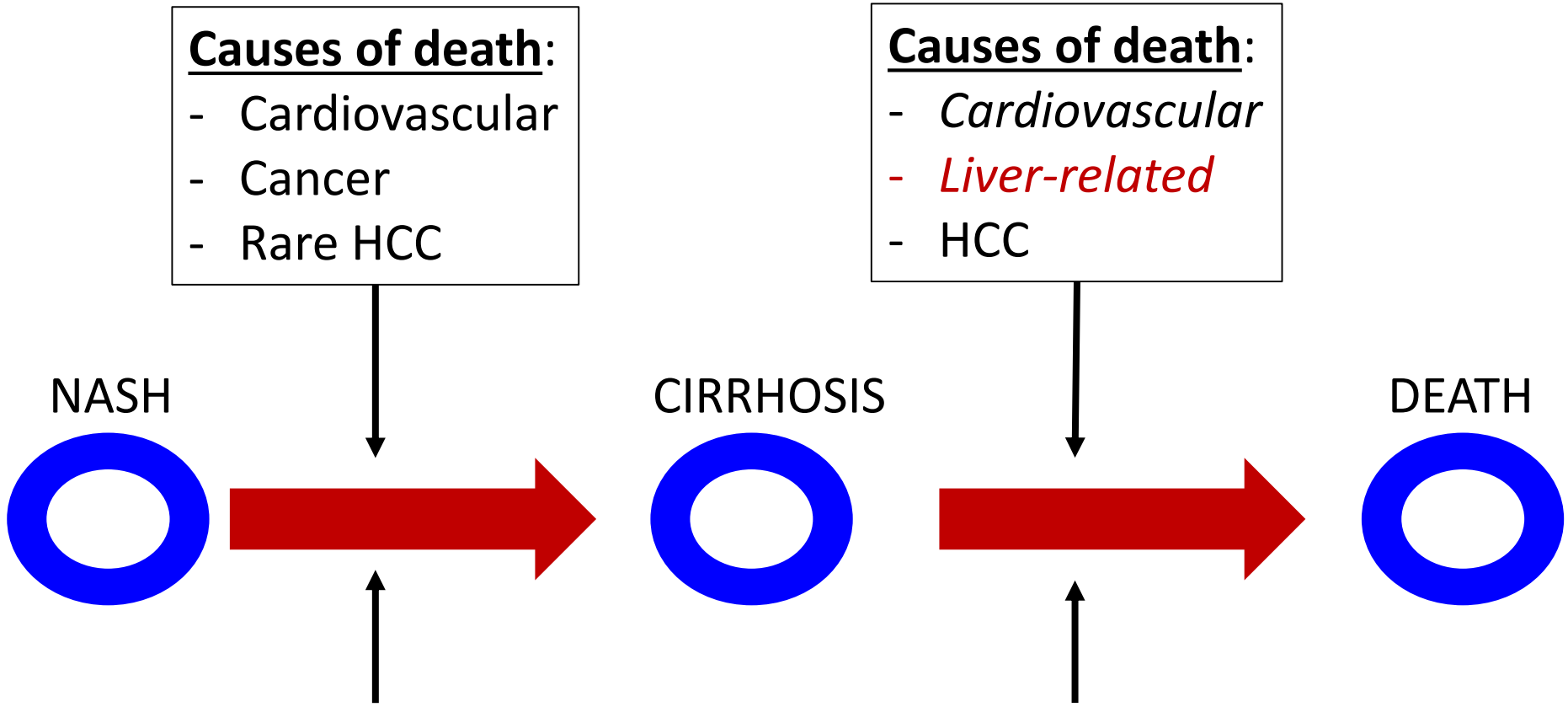
Negative Phase 2B/3 trials

- LOXL2- Simtuzimab
- ASK-1-Selonsirtib
- Caspases-Emricasan
- Galectin-
- TLR4- Naloxone
- 6-ethyl EPA- PUFA
- Bovine colostrum- Immuron

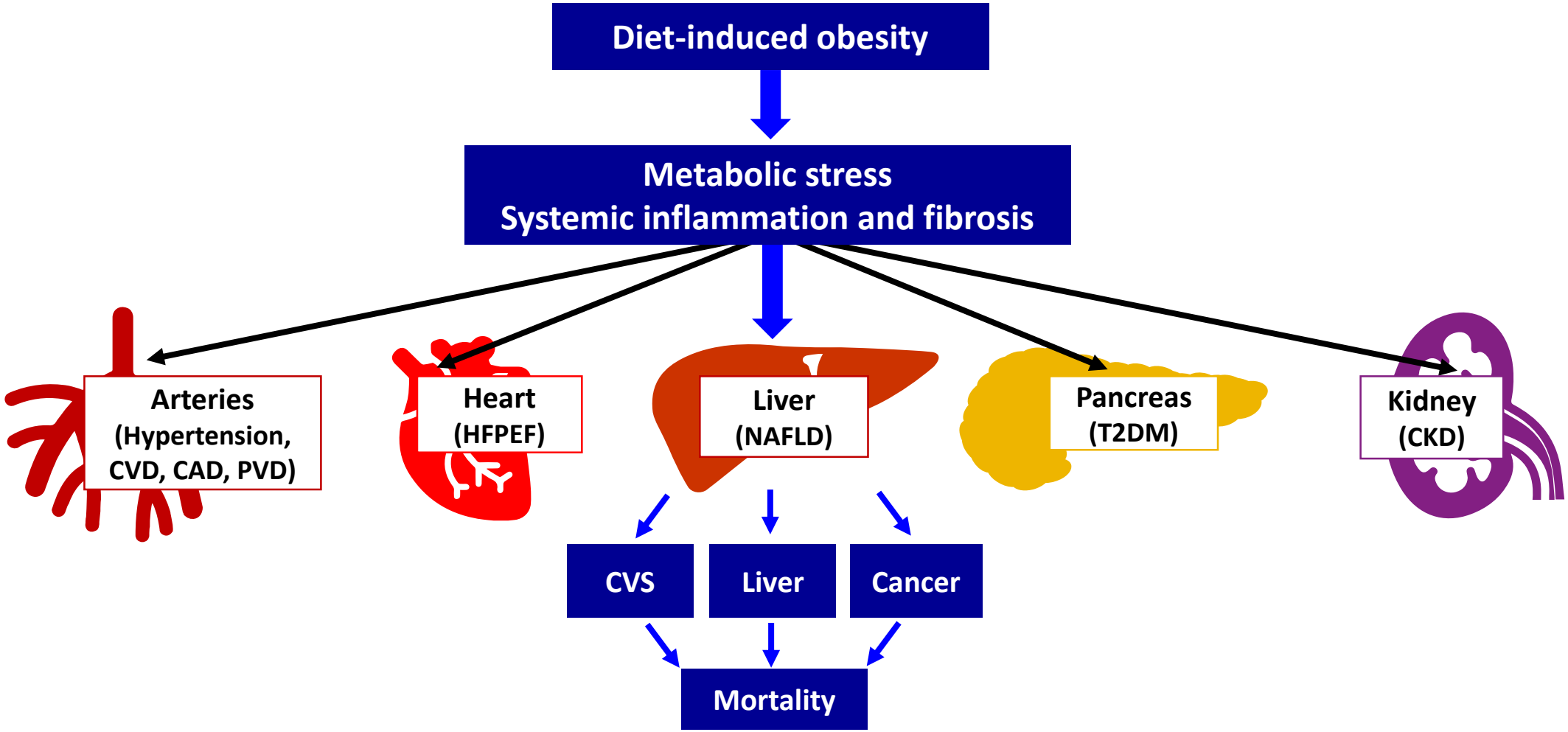
Clarity of objectives


Microbiome/microbial products
Lipids
Glucose
Cytokines
Metabolism (steatosis)
Cell stress apoptosis
inflammation
Fibrogenic remodeling
• Stop fibrosis
DISEASE ACTIVITY
• Improve systemic mileu
• Improve safe disposal
• Cytoprotection
• Inhibit cell death
• Anti-inflammatory

The development of cirrhosis is a key milestone in the course of cirrhosis



NAFLD is part of a multi-system disease with multiple competing risks to patient



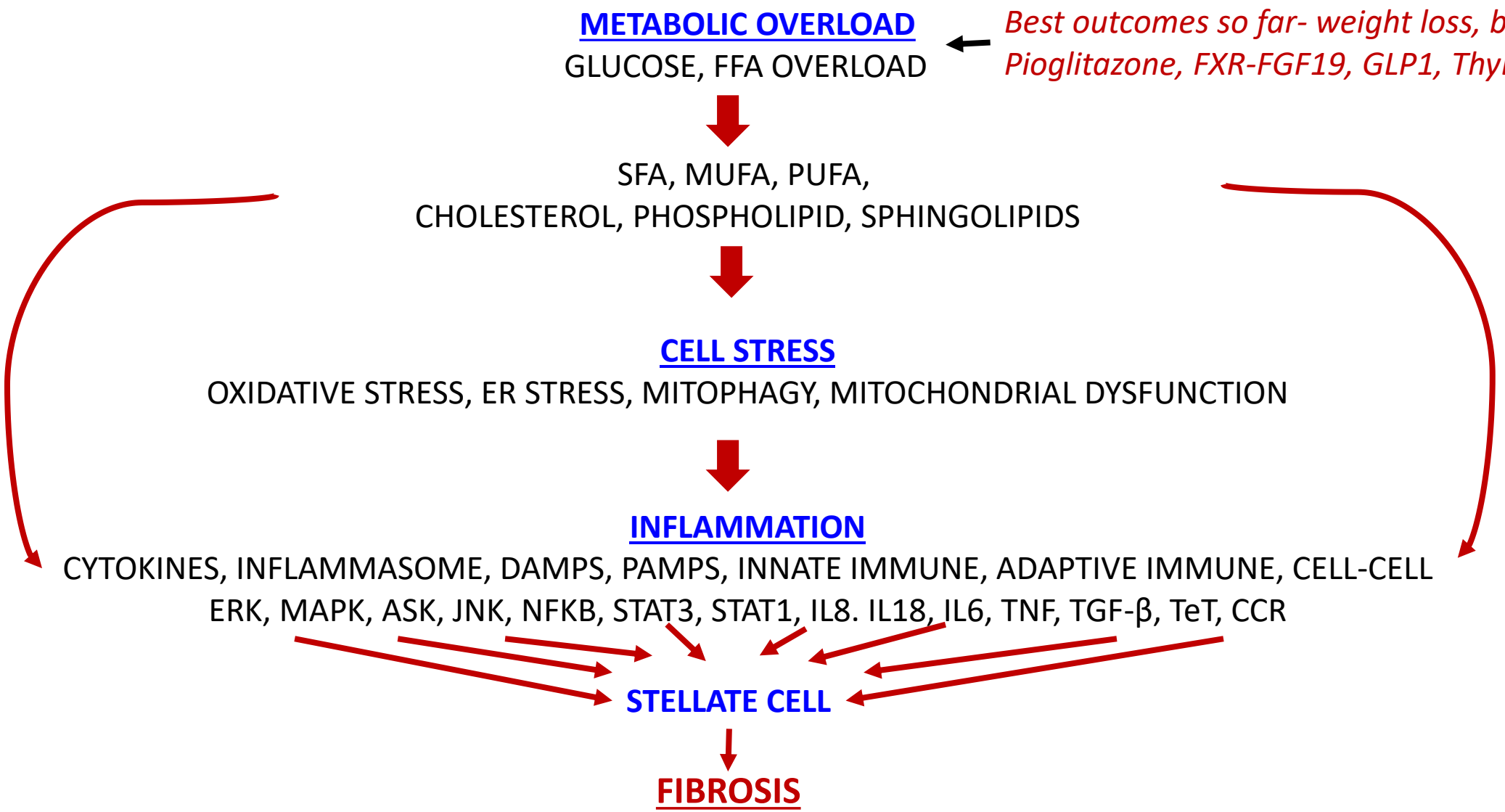
CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; CVS, cardiovascular system; HFPEF, heart failure with preserved ejection fraction; PVD, peripheral vascular disease; T2DM, type 2 diabetes mellitus.

Caveat # 1: Approval path should be considered in the context of use for intervention and mechanism of action

- Scenario A: MOA impacts root cause of disease- obesity, IR, metabolic inflexibility, systemic metabo-inflammation etc.
  - Extend what is currently being done for T2DM (A1C + cardiac) to include (cardiac, A1c, Liver, renal) endpoint as appropriate for MOA
- Scenario B: MOA affects liver disease activity with or without major systemic effects.
  - Pre-cirrhotic stages: Improve activity in short term and reduce progression to cirrhosis in long-term.
  - Cirrhotic stages: reduced progression to transplant consideration or clinical decompensation
- Scenario C: MOA affects fibrosis without major systemic effects.
  - Precirrhotic stages: prevent fibrosis progression to cirrhosis
  - Cirrhosis: reduce decompensation or reverse fibrosis and reduce decompensation

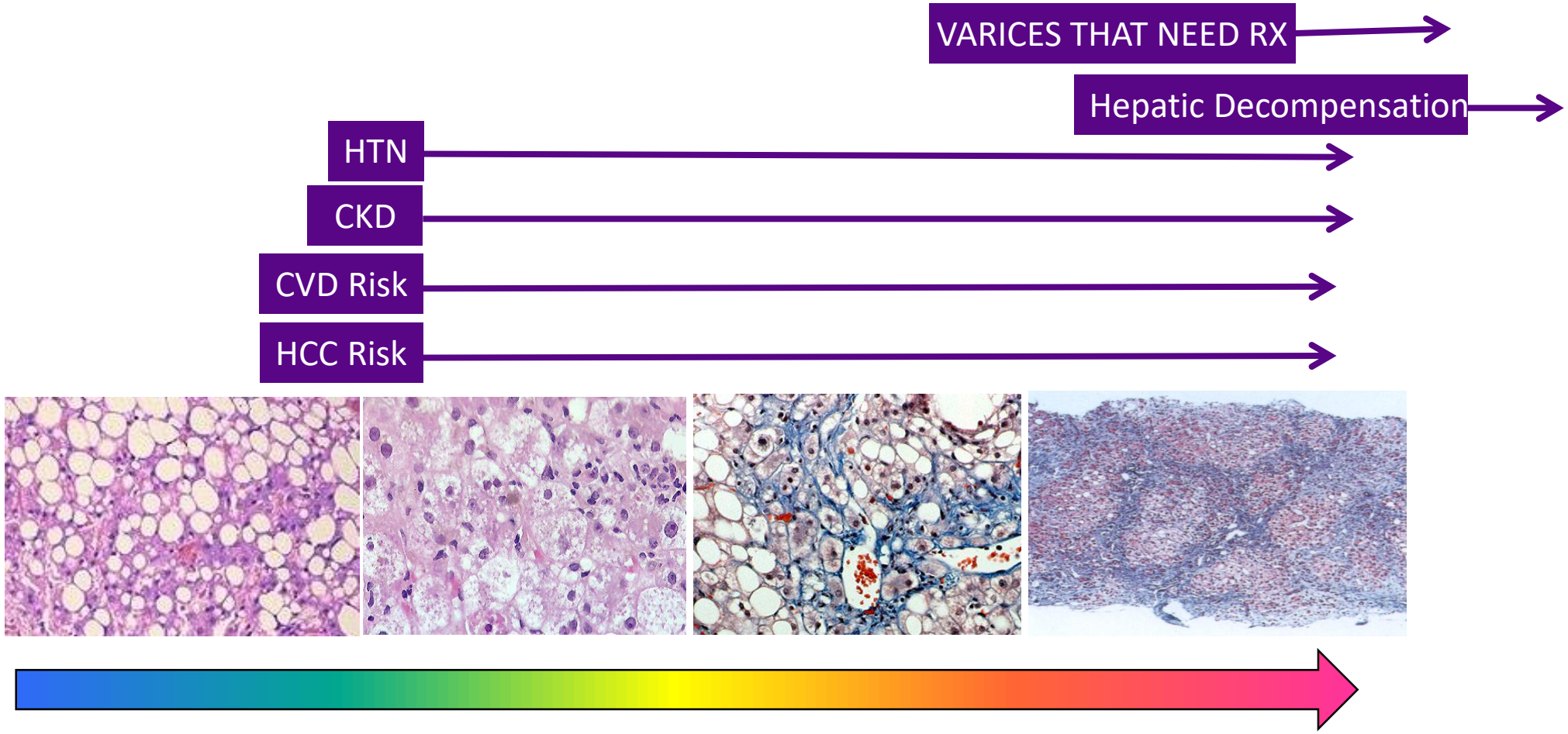
Right target

Caveat # 2: Choice of target should take in to consideration the redundancies in pathogenic pathways



Right population

Competing risks to patient welfare in NAFLD



Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; HCC, hepatocellular carcinoma.

Adapted from Mary Rinella

Scenario A: Systemic MOA with impact on multiple end-organs of interest

- Systemic risk factor profile- which features of Met S, severity status of individual end-organ disease- unmet need for holistic modeling of outcomes based on the patient not the organ.
- Liver disease profile-
  - NAFL, NASH with stage 0-1 fibrosis: MOA should focus on cardio-renal-metabolic outcomes.
  - NAFLD with stage 2-3 fibrosis: when prevention of cirrhosis is biologically plausible and supported by proof of concept/mechanism studies

It is time to dump the concept of NASH (vs NAFL) and consider NAFLD of certain activity level

- The Chronic Persistent Hepatitis vs Chronic Active Hepatitis Debate
  - long considered distinct clinical entities
  - Concept was that one was a mild less progressive disease and other was progressive and needed Rx
  - Was ultimately shown that both often present in same patient and that one could go in and out of it
- The Fatty liver vs NASH Debate
  - One considered to be mild and the other considered to be progressive and needing Rx
  - Both can be present in same patient
  - Patients flip in and out of these two states
  - Molecular mechanisms more different quantitatively rather than qualitatively

Caveat # 2: patient population considerations

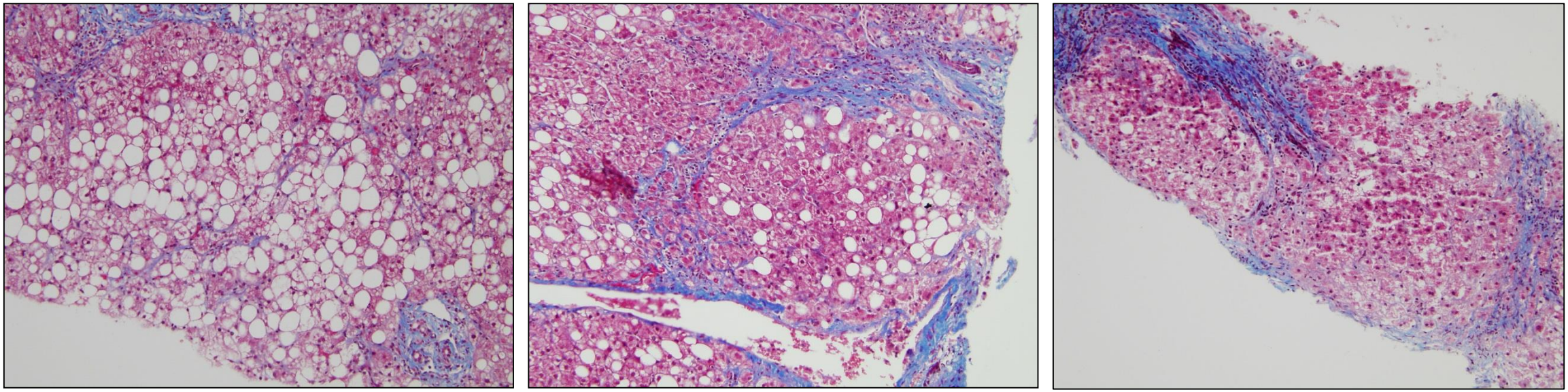
Scenario B: pre-cirrhotic populations And MOA is anti-disease activity

- Must have NAFLD with high activity scores (4 or higher) with components from fat, inflammation and ballooning
- Dump NASH as a requirement-
  - Gestalt Dx not quantifiable
  - Having fat, inflam and ballooning sets up for high spontaneous regression rates given intra- and inter-observer variance, influence of biopsy length etc

Scenario C: pre-cirrhotic populations and MOA is anti-fibrotic

- Stage 3: population is the key target population where prevention of cirrhosis is both feasible and will give greatest bang for the buck
- Stage 2: allows more patients to be included but dilutes the effect size massively increasing sample size to show reduced progression to cirrhosis and outcomes

Fibrosis progresses across a continuum not captured by current fibrosis staging systems

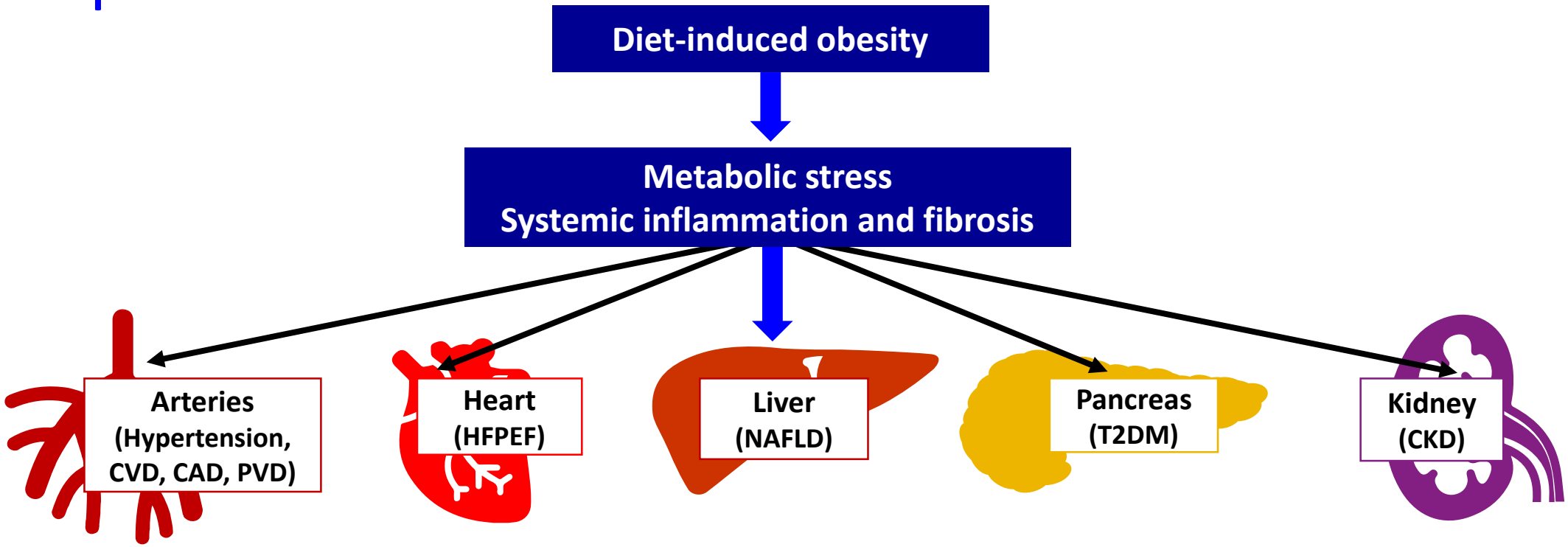


Considerations for regulatory agencies

- Dump histological assessment of stage 3 vs 4
- Consider use of digital methods such as CPA, 2-photon based methods to extend the dynamic scale of fibrosis.
- Consider combining stage 3 and compensated stage 4 (advanced fibrosis) when MOA is systemic with some anti-NASH activity- and endpoint is reduced progression to decompensation, alone or in combination. Also, applicable for drugs with primary anti-fibrotic MOA where quantitative reduction in collagen in short term and reduced outcomes in long term could be a development path.

Right endpoints

Scenario A: consider composite endpoint extending what has already been done for type 2 diabetes drug development



- CONSIDER USE OF ESTIMANDS
- USE ALTERNATE MODELS SUCH AS THOSE BASED ON DESIRABILITY FUNCTIONS

CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; CVS, cardiovascular system; HFPEF, heart failure with preserved ejection fraction; PVD, peripheral vascular disease; T2DM, type 2 diabetes mellitus.

Scenario B: it is time to push back and challenge traditional paradigm of anchoring disease assessment to histology

- Why:
  - numerous well known limitations of histological assessment
  - histology is only a surrogate especially when considering pre-cirrhotic stages
- Why not consider:
  - Reduction in markers of activity:
    - Liver injury- AST, ALT (greater reduction, proportion with normalization etc)
    - Reduction in liver fat- PDFF
    - Reduction of general measure of inflammation-fibrosis (cT1 or MRE)

Arguing to use alternate surrogates to assess disease activity- accumulation of fat, cellular injury/death and inflammation

	Anchor or Surrogate	Intra- and inter-observer error	Misclassification Rate for activity	Risk to patient	Ease of deployment	Patient preference
Liver histology	surrogate	High (> 15-20%)	Low to medium*	death	poor	low
Decreased AST/ALT	surrogate	< 10%	Low to medium	none	excellent	excellent
MRI-PDFF	surrogate	Low (< 2%)	Low for steatosis	low	good	good
2D MRE	surrogate	~ 15%	low to medium	low	good	good
cT1	surrogate	< 5%	Low to medium**	low	good	good

- In PIVENS and FLINT- asking the pathologists to re-read the biopsies led to 15-20% being misclassified
- ** need to consider confounding factors and work around them

Inter- and Intra-rater Agreement on Major Categories: how well-dressed is the emperor?

	Inter (adult)	Inter (ped)	Intra (adult)
Steatosis	0.79	0.64	0.83
Fibrosis	0.84	0.62	0.85
Lob. Inf.	0.45	0.28	0.60
Ballooning	0.56	0.22	0.66
Mallory's	0.58	0.69	0.64
Diagnosis	0.61	0.33	0.66

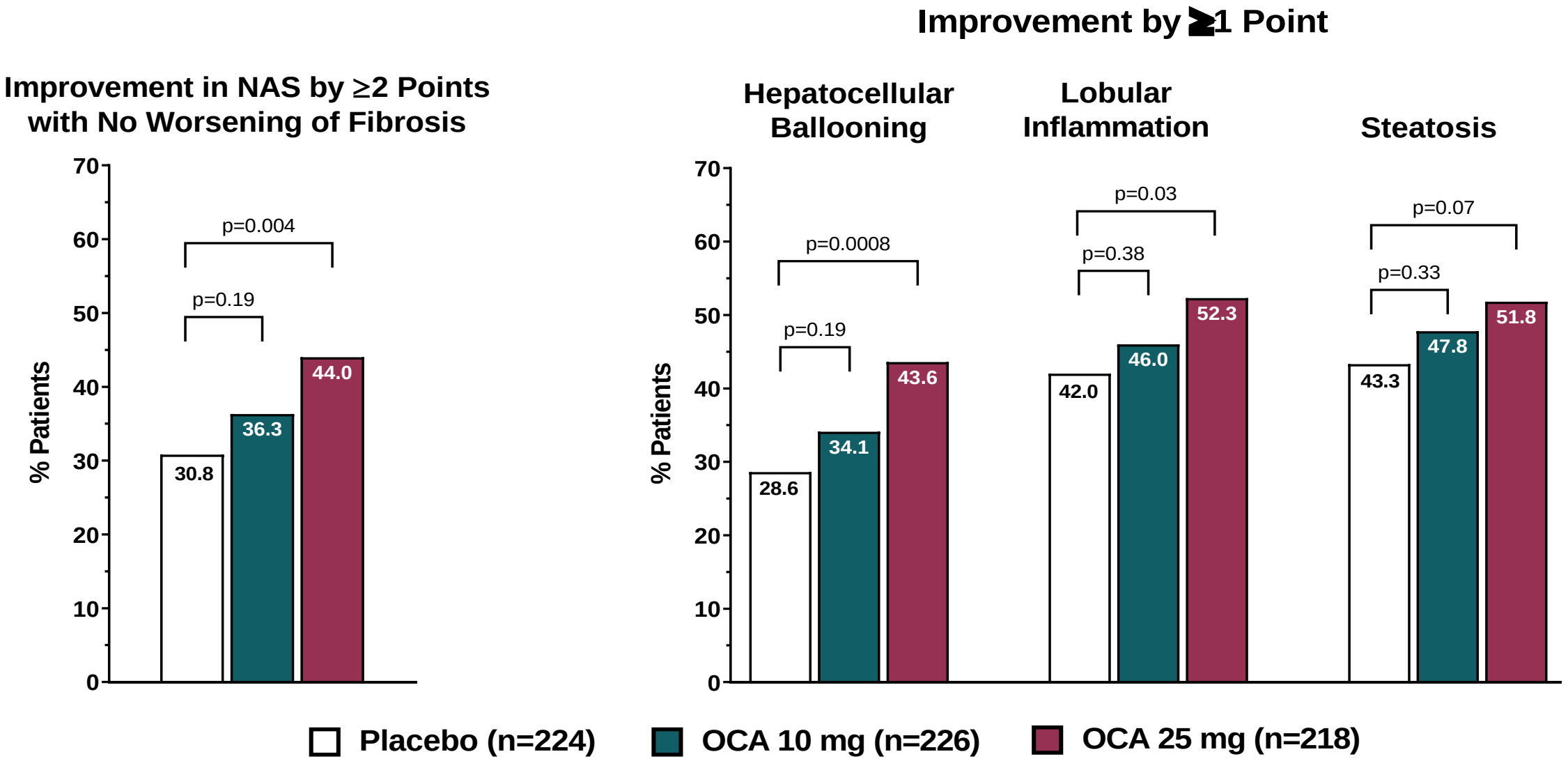
- Variable definitions
- Poor kappa for bal/inflame
- Gestalt not quantifiable

(All values are grouped, weighted Kappa values)

NASH CRN

Improvement in NAS ≥2 with No Worsening of Fibrosis and NAS Parameters ≥1

Per Protocol Population

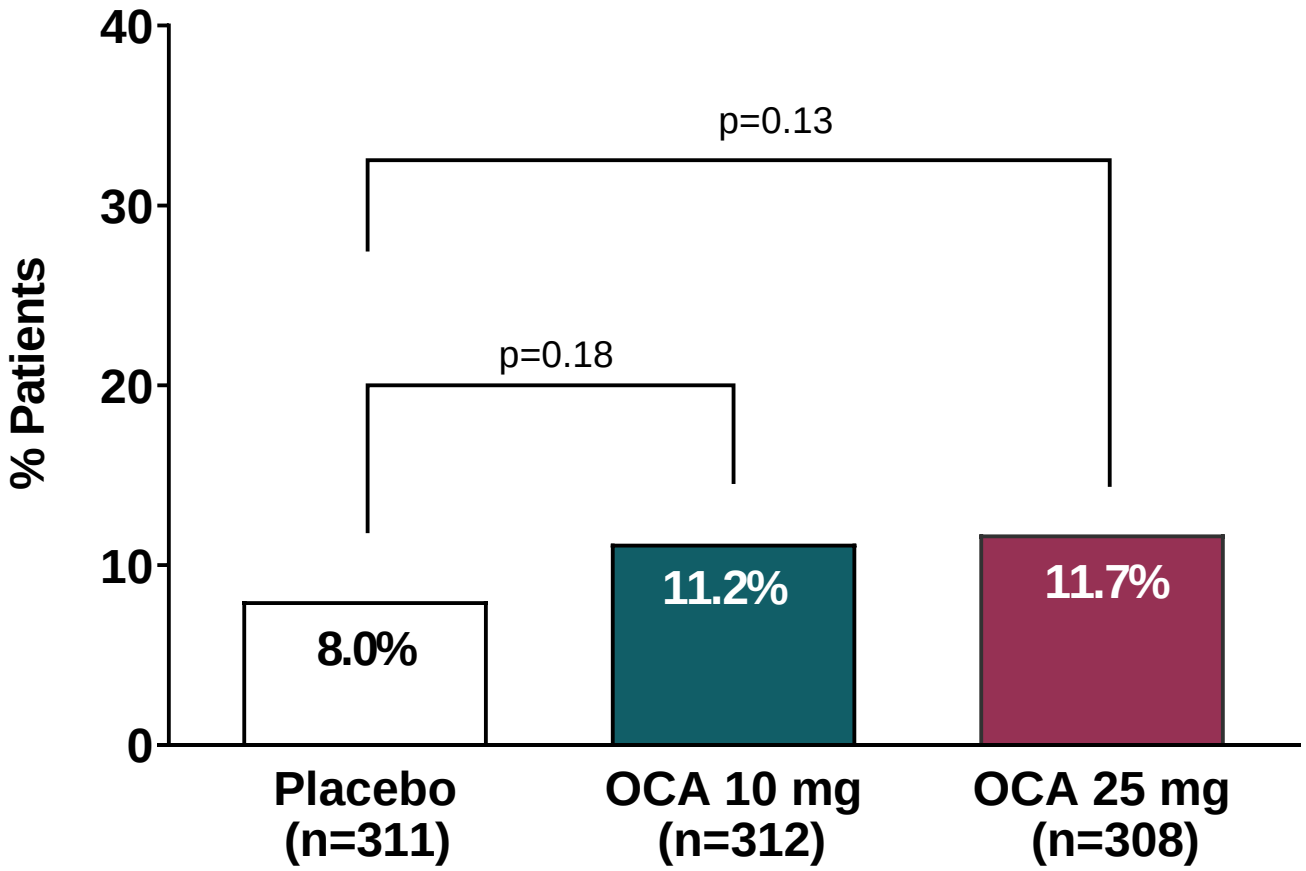


REGENERATE NASH FIBROSIS STUDY

P values are nominal.
Per protocol population (N=668).

NASH Resolution with No Worsening of Fibrosis

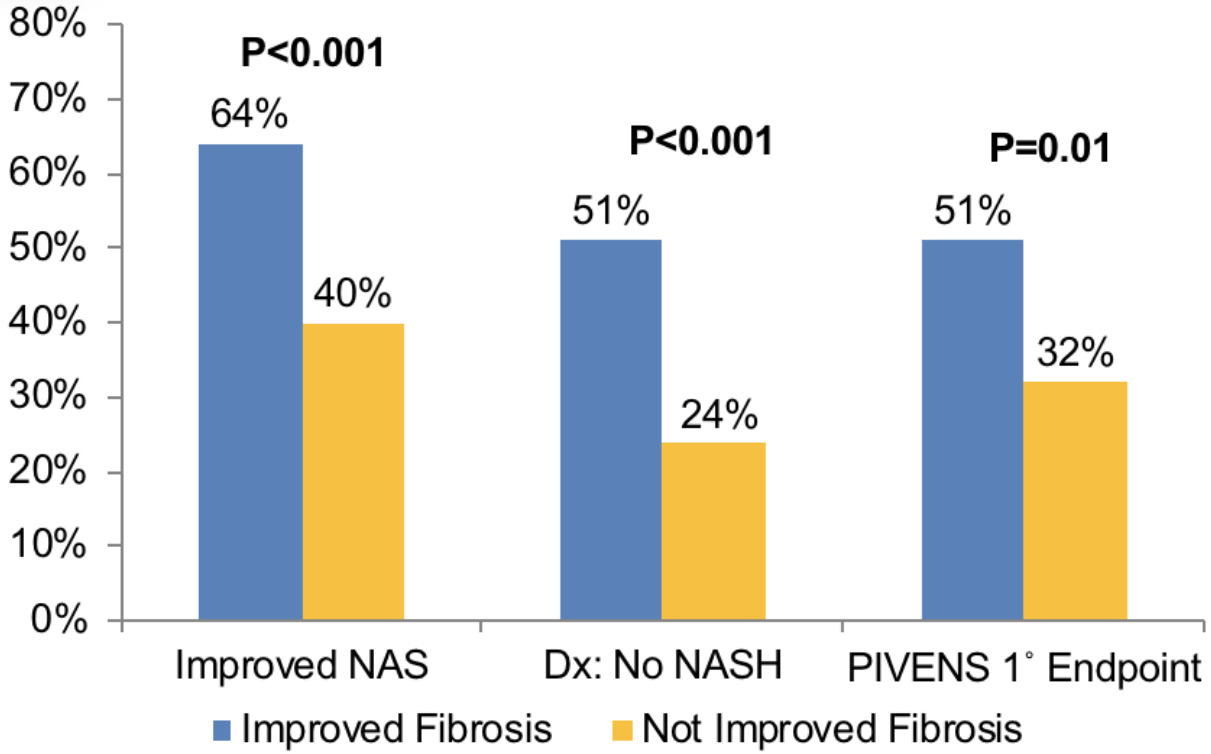
Additional Primary Endpoint: ITT Population, N=931

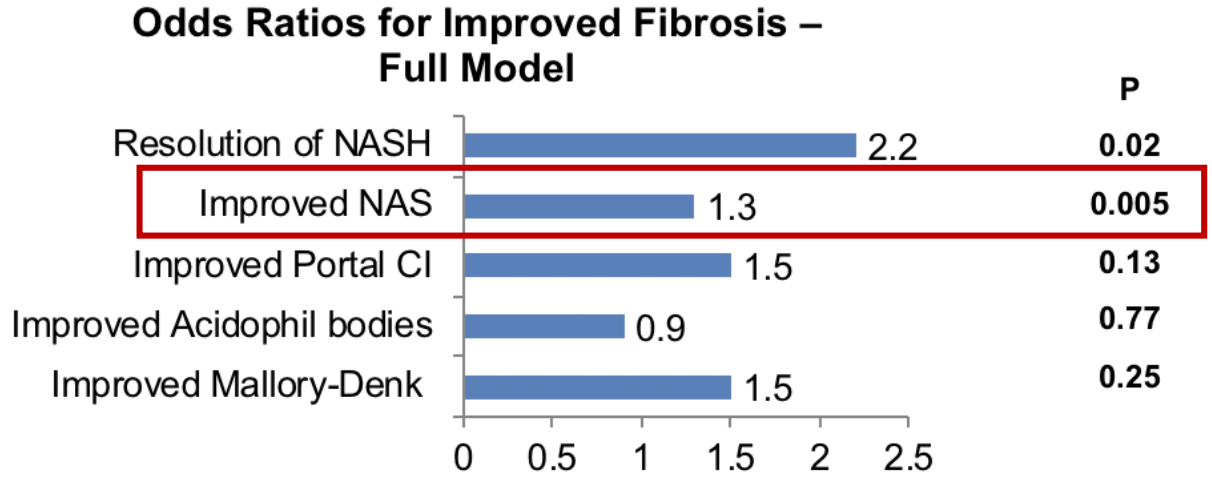


REGENERATE NASH FIBROSIS STUDY

Primary endpoint definition:
(i) overall pathologist assessment of “no steatohepatitis,” and (ii) hepatocellular ballooning = 0 and lobular inflammation = 0 or 1, and (iii) no increase in fibrosis stage from baseline.
Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 interim analysis.

For drugs with a “front end (metabolic-cell stress)”-targeted MOA, reducing disease activity is the key to reducing disease progression





Sanyal et al, N Engl J Med. 2010 May 6;362(18):1675-85.
Brunt et al. Hepatology. 2018 Dec 14. doi: 10.1002/hep.30418. [Epub ahead of print]

Caveat # 3: endpoint considerations

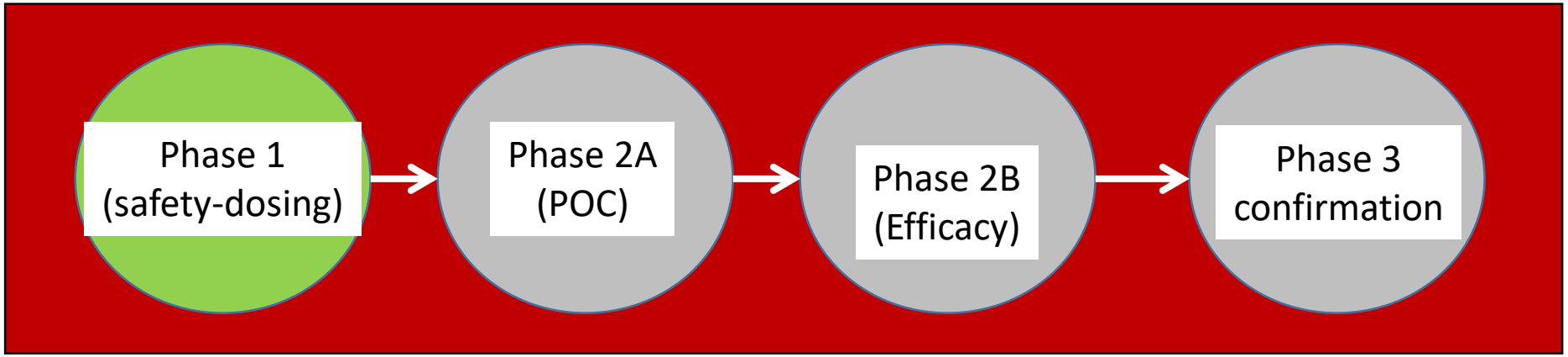
Scenario B: pre-cirrhotic populations And MOA is anti-disease activity

- Conditional approval based on extensive safety and composite of non-invasive markers
- Dump NASH resolution as a endpoint-
  - Gestalt Dx not quantifiable
  - Pathologists unable to discern ballooning zero in patient with residual fat
- Improvement in NAS should be re-considered- more reproducible
- Progression to cirrhosis should remain generally acceptable surrogate for approval

Scenario C: pre-cirrhotic and cirrhotic populations and MOA is anti-fibrotic

- Stage 3: reduced progression to cirrhosis rather than fibrosis regression is a more appropriate endpoint
- Stage 4:
  - Reduced fibrosis stage in short term
  - Reduced decompensation in long-term
  - Reduced MELD progression

Effective drug development must leverage disease biology, avoid traps associated with short-cut science and de-risk particularly for phase 3 programs



KEY ELEMENTS OF A SUCCESSFUL DEVELOPMENT PROGRAM

- Right target
- Right patient
- Right safety
- Right efficacy (demonstration of clinically meaningful benefit)

THANK YOU FOR YOUR ATTENTION