INNOVATIONS IN CLINICAL TRIAL DESIGN FOR NASH

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Conflicts of Interest

• Dr. Sanyal is President of Sanyal Biotechnologies
• Stock options for Genfit, Tiziana, Indalo, Durect, Exhalenz, Galmed
• Grant support: Bristol Myers, Intercept, Gilead, Allergan, Merck, Echosense, Novartis, Boehringer Ingelhiem

* no financial remuneration in last 24 months
Global Pipeline for NASH

Failed drugs
- UDCA
- PUFA
- Fibrates
- Rosiglitazone
- LOXL2 mAB
- Selonsirtib
- Emricasan
- TLR4 antagonist
- Bovine Colostrum

Wong et al., Biostatistics 2018
<table>
<thead>
<tr>
<th>STRENGTHS</th>
<th>WEAKNESSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Path to approval is clear</td>
<td>• Does not provide value proposition</td>
</tr>
<tr>
<td>• Target enriched disease</td>
<td>• No drug shown to prevent OR reverse cirrhosis</td>
</tr>
<tr>
<td>• Reconsider populations/endpoints</td>
<td>• Ignores hierarchies of outcomes</td>
</tr>
<tr>
<td>• Design innovations:</td>
<td></td>
</tr>
<tr>
<td>- Master protocols</td>
<td></td>
</tr>
<tr>
<td>• New knowledge re systemic nature of disease process</td>
<td></td>
</tr>
<tr>
<td>• Competing risks for outcomes</td>
<td></td>
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<tr>
<td>• No reliable way to keep patients on placebo for long periods</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>OPPORTUNITIES</th>
<th>THREATS</th>
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<tbody>
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</table>
Targeting a relevant target
Therapeutic targets for NASH

- Metabolism (steatosis)
- Cell stress apoptosis
- Inflammation
- Fibrogenic remodeling

CIRRHOSIS
Caveat # 1: Choice of target should take into consideration the redundancies in pathogenic pathways

**METABOLIC OVERLOAD**
GLUCOSE, FFA OVERLOAD

- SFA, MUFA, PUFA,
- CHOLESTEROL, PHOSPHOLIPID, SPHINGOLIPIDS

**CELL STRESS**
OXIDATIVE STRESS, ER STRESS, MITOPHAGY, MITOCHONDRIAL DYSFUNCTION

**INFLAMMATION**
CYTOKINES, INFLAMMASOME, DAMPS, PAMPS, INNATE IMMUNE, ADAPTIVE IMMUNE, CELL-CELL ERK, MAPK, ASK, JNK, NFKB, STAT3, STAT1, IL8, IL18, IL6, TNF, TGF-β, TeT, CCR

**FIBROSIS**

Best outcomes so far - weight loss, bariatrics
Pioglitazone, FXR-FGF19, GLP1, ThyBR

**STELLATE CELL**
Caveat # 2: NAFLD is part of a multi-system disease with multiple competing risks to patient-need to target multiple end organs

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.
Targeting the right population and pairing with study design
Sources of excess clinical outcomes in NAFLD and where interventions will have greatest impact

Closest to cirrhosis
And most likely to benefit from prevention
Of progression

Closest to liver-related
Mortality

Cardiovascular, CKD and all-cause cancer outcomes

Liver decompensation
Challenges in NASH trials

• Background therapy will increasingly include GLP-1 agonists and SGLT2 inhibitors

• Increasing number of approved drugs for obesity
  • Lorcanerin- (Merck)
  • Hydrgels- (Gelesis)

• How to keep patients on placebo in post subpart-H?
The use of master-protocols may accelerate drug development

<table>
<thead>
<tr>
<th>Types of master protocols</th>
<th>What they do</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbrella</td>
<td>Test multiple drugs in the context of a homogeneous population with a single disease</td>
</tr>
<tr>
<td>Basket</td>
<td>Test single drug in multiple populations</td>
</tr>
<tr>
<td>Platform</td>
<td>To study multiple therapies for a single disease in a sequential perpetual manner</td>
</tr>
</tbody>
</table>

Design and analysis of a clinical trial using previous trials as historical control

“Bayesian hierarchical model, providing a sample from the posterior predictive distribution of the outcome estimand of a new trial, which, along with the standard error of the estimate, can be used to calculate the probability that the estimate exceeds a threshold. We then calculate criteria for statistical significance as a function of the standard error of the new trial and calculate sample size as a function of difference to be detected”

Schonfeld and Finkelstein, Clinical Trials, 2019
A prospective analysis of non-hepatic outcomes in NASH

<table>
<thead>
<tr>
<th></th>
<th>Cirrhosis (n=159)</th>
<th>No Cirrhosis (n=1539)</th>
<th>R.R.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td># events</td>
<td>Rate/1000 py</td>
<td># events</td>
</tr>
<tr>
<td>Death</td>
<td>13</td>
<td>18.7</td>
<td>31</td>
</tr>
<tr>
<td>CAD event</td>
<td>5</td>
<td>8.7</td>
<td>54</td>
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<tr>
<td>CVD</td>
<td>6</td>
<td>9.1</td>
<td>24</td>
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<tr>
<td>eGFR &lt; 60 ml/min</td>
<td>24</td>
<td>42.3</td>
<td>143</td>
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</table>

Sanyal et al, AASLD 2019
A prospective analysis of liver outcomes in NASH

<table>
<thead>
<tr>
<th>Condition</th>
<th># events</th>
<th>Rate/1000 py</th>
<th># events</th>
<th>Rate/1000 py</th>
<th>R.R.</th>
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</thead>
<tbody>
<tr>
<td>Death</td>
<td>13</td>
<td>18.7</td>
<td>31</td>
<td>4.4</td>
<td>4.3</td>
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<tr>
<td>HCC</td>
<td>2</td>
<td>2.9</td>
<td>8</td>
<td>1.1</td>
<td>2.7</td>
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<tr>
<td>Variceal bleed</td>
<td>5</td>
<td>7.5</td>
<td>1</td>
<td>0.1</td>
<td>54.4</td>
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<tr>
<td>Ascites</td>
<td>15</td>
<td>23.5</td>
<td>11</td>
<td>1.6</td>
<td>14.8</td>
</tr>
<tr>
<td>HE</td>
<td>16</td>
<td>23.5</td>
<td>11</td>
<td>1.6</td>
<td>16.1</td>
</tr>
<tr>
<td>MELD ≥ 15</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>2.9</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Sanyal et al, AASLD 2019
Alternate drug development paradigm # 1- for MOA targeting root cause

**STUDY A LARGE POPULATION WITH NAFLD**
- Population defined non-invasively
- Composite outcome measure:
  - All cause mortality
  - Liver outcomes
  - Progression to cirrhosis
  - Progression to CKD
  - MACE

**CHALLENGES**
- What to do with heterogeneous response
- Label implications
- Applicable for drugs targeting root cause

**Goals:** reduced outcomes
Alternate drug development paradigm # 2

Goals: reduced outcomes

LIVER TARGETED APPROACH
- NAFLD- f3/f4 COMPENSATED vs those with advanced liver stiffness
- Composite outcome
  - All cause mortality
  - Ascites
  - HE
  - Varices requiring treatment
  - MELD 15

CHALLENGES
- What to do with heterogeneous response
- Long time to outcomes

NAFL → NASH → NASH + F3/4 → OUTCOMES
Clinical trials for NASH-cirrhosis pose specific challenges

Many patients also have:
- Diastolic dysfunction
- Lower eGFR
- Prolonged QTc
- T2DM
- Peripheral neuropathy
Phase 2 paradigm for NASH F3/F4 trials for drugs with MOA targeting root cause

• Stratify by eGFR
• Stratify by LSM or histology

• Endpoints:
  • Primary (weight loss)
  • Secondary:
    • liver stiffness, histology, HVPG, varices, ascites, HE,
    • eGFR
    • Cardiac MRI based assessment of function
    • PRO
    • resource utilization

This approach will allow you to assess if your drug benefits any patients and how to design phase 3 trial
Phase 2 development paradigm for NASH F3/4 with anti-inflammatory, anti-fibrotic MOA

- Study populations F3/compensated F4
- Endpoints:
  - Liver stiffness vs histology
  - Static biomarkers- ELF, PROC3
  - Proteolytic signatures (novel potentially important approach)
- Secondary endpoints:
  - Liver outcomes
  - Stabilization of myocardial dysfunction
  - Stabilization of eGFR
Endpoint assessment
Changes in disease activity are closely linked to changes in disease stage.

Kleiner Sanyal et al, In press 2019
Reduction in NAS is strongly linked to fibrosis regression.


NAS correlates with changes in fibrosis

Data from Conatus phase 2B trial
Additional points to consider

• Heirarchical care and outcomes- hierarchical mixed logistic regression. (see Munoz Venturelli et al...J Am Heart Assoc. 2019 Jul 2; 8(13): e0126400
• Estimands
• Finkelstein-Schonfeld approach of comparisons of all pairs of ordered outcomes.
The special case of children with NASH
Bayesian design using adult data to augment pediatric trials.

- a hierarchical model for which the efficacy parameter from the adult trial and that of the pediatric trial are considered to be draws from a normal distribution

In summary, back to basics

• Right target(s)
• Right population
• Right endpoints
• Right design
THANK YOU FOR YOUR ATTENTION