Disease Assessment Strategies to Accelerate Drug Development

https://forumresearch.org/liver-forum/liver-forum-meetings/1744-liver-forum-12

April 22-23 Meeting Theme
“Show us the data”

Roadmap

- Improving the reference standard
- Opportunities & challenges
- Diagnostic COU
- Prognostic COU
- Predictive/monitoring COU

Liver Biopsy Reads: Statistical Issues

Amrik Shah

Karma Statistics, LLC

Underestimation of Treatment Effect Size

- Reading Error always dilutes Treatment Effect size
  - only ”accurately read” slides contribute to effect size
- From published/observed kappas,

  Fibrosis sensitivity of 0.7 is reasonable

  Example: NASH trial setting focusing on Fibrosis endpoint

  Endpoint is binary, BUT “improve”, “stable” and “worsen” buckets must be considered when assessing impact of reading error

Key Takeaway Learnings

- Endpoint based on Biopsy Reads has severe limitations and not appropriate for assessing drug efficacy.

- Impact of reading error CANNOT be overcome by increasing sample size

  -Doubling sample size still yields same % Delta

- If forced to stick with Biopsy Reads, the dilution of effect size MUST be considered for Benefit-Risk assessment.

  - Dilution may range from 30% - 60%

Digital Pathology with AI analyses of tissue slides is already used in clinical practice and trials: recent examples

➢ **Prostate Cancer diagnosis**	- Paige Prostate AI software - Paige (FDA approved) - Galen Prostate AI software – Ibex (approved in EU)
➢ **Breast Cancer diagnosis**	- Galen Breast Solution AI model – Ibex (approved in EU)
➢ **Detection of Breast Cancer metastases in lymph nodes**	- Paige Breast Lymph Node, AI digital tool *Paige - Press Release 2022*
➢ **PD-L1 tumour expression**	- Digital quantification with AI tool, BMS/PathAI, *AACR June 22-24 2020, Poster 2017*
➢ **Cardiac Allograft rejection**	- Diagnosis and grading in of endomyocardial biopsies *J Lipkova, T Chen et al. Nature Medicine 2022:28;575–582*

A Meta-Analytic Summary of NIT Applications in NASH Development

Liver Forum 'Disease Assessment Strategies to Accelerate Drug Development '
Washington DC, USA, April 2022

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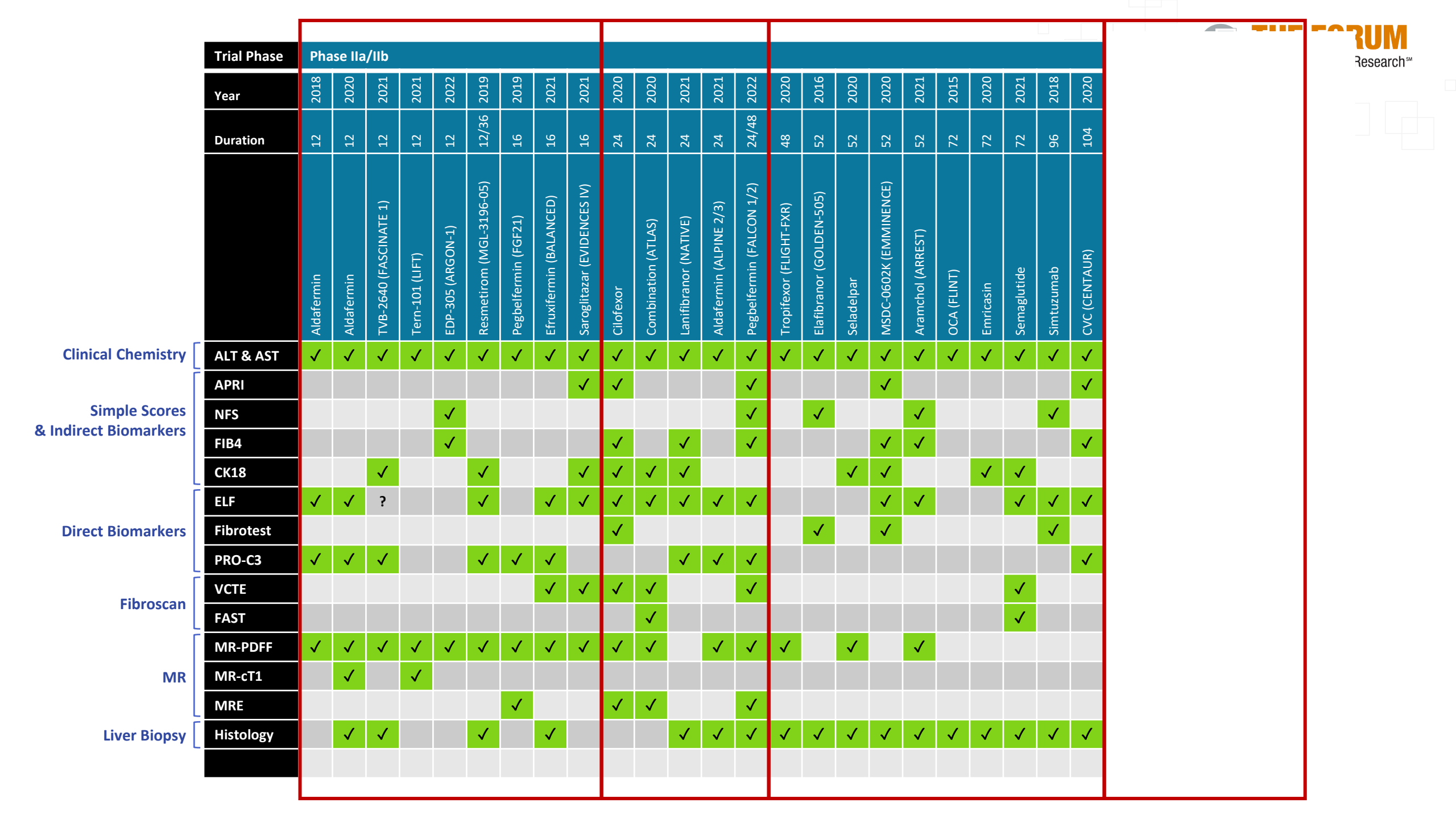
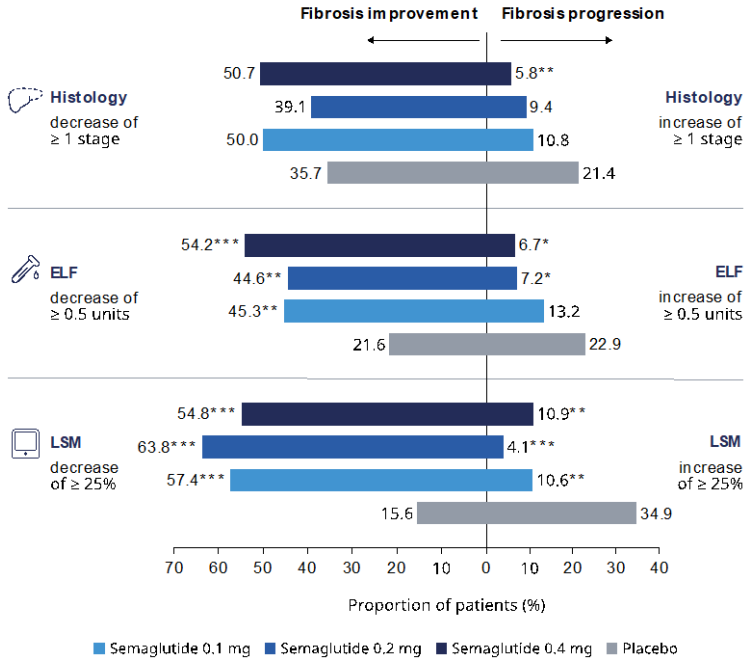
Newcastle University

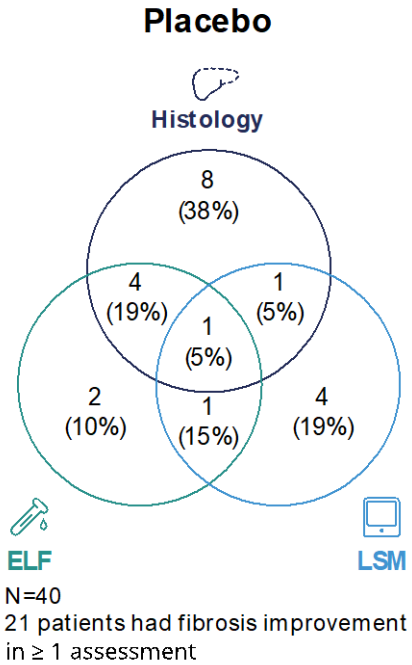

Trial Phase
Phase IIa/IIb
Year
Duration
Aldafermin 2018 12
Aldafermin 2020 12
TVB-2640 (FASCINATE 1) 2021 12
Tern-101 (LIFT) 2021 12
EDP-305 (ARGON-1) 2022 12
Resmetirom (MGL-3196-05) 2019 12/36
Pegbelfermin (FGF21) 2019 16
Efruxifermin (BALANCED) 2021 16
Saroglitazar (EVIDENCES IV) 2021 16
Cilofexor 2020 24
Combination (ATLAS) 2020 24
Lanifibranor (NATIVE) 2021 24
Aldafermin (ALPINE 2/3) 2021 24
Pegbelfermin (FALCON 1/2) 2022 24/48
Tropifexor (FLIGHT-FXR) 2020 48
Elafibranor (GOLDEN-505) 2016 52
Seladelpar 2020 52
MSDC-0602K (EMMINENCE) 2020 52
Aramchol (ARREST) 2021 52
OCA (FLINT) 2015 72
Emricasin 2020 72
Semaglutide 2021 72
Simtuzumab 2018 96
CVC (CENTAUR) 2020 104
Clinical Chemistry
ALT & AST
Simple Scores & Indirect Biomarkers
APRI
NFS
FIB4
CK18
Direct Biomarkers
ELF
Fibrotest
PRO-C3
Fibroscan
VCTE
FAST
MR
MR-PDFF
MR-cT1
MRE
Liver Biopsy
Histology
?

Wholistic Assessment of Biomarker Response

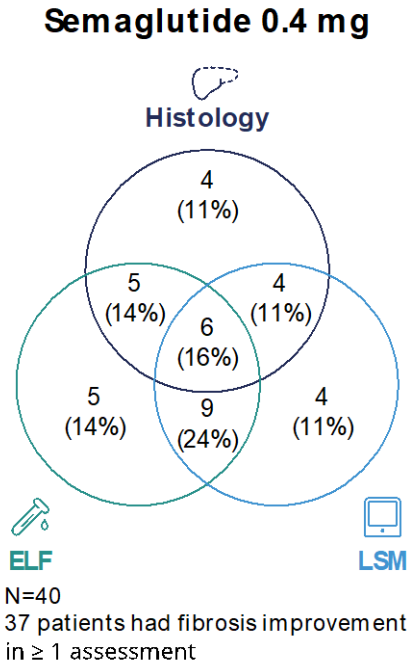
Overview of bi-directional NIT changes per study arms



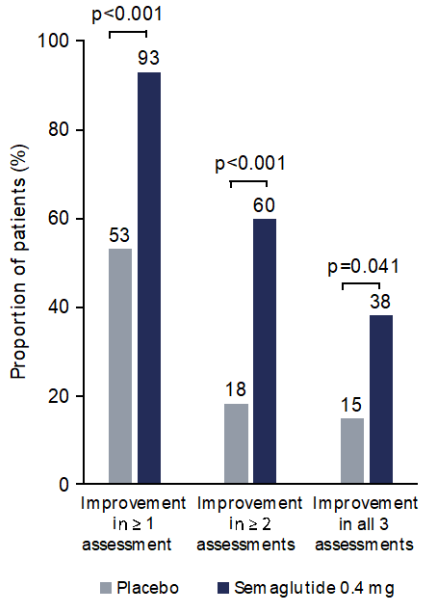
Assessment of consistency of NIT change at the *per patient* level



N=40
21 patients had fibrosis improvement in ≥ 1 assessment



N=40
37 patients had fibrosis improvement in ≥ 1 assessment



1. Anstee et al, Fibrosis response assessed by enhanced liver fibrosis and FibroScan liver stiffness measurement in patients with non-alcoholic steatohepatitis treated with subcutaneous semaglutide. EASL 2021.

Conclusions

A range of tractable biomarkers are available to support drug development in NASH.

When considering the use of biomarkers in drug development, it is essential to consider the specific **Context of Use** (and population/setting) that is being addressed.

There remains a need for more sensitive and specific, independently validated and qualified biomarkers for use in NAFLD drug development.

Progress to date:

1. **Diagnostic CoU:** LITMUS and NIMBLE are bringing clarity and objectivity to biomarker performance – still room for innovation to identify better biomarkers.
2. **Pharmacodynamic/Response CoU:** remains an area where there is a lack of consistency but the RCTs to date have helped generate important data to support biomarker utility.
   We are now better placed to build consensus and *standardise NIT selection* and the *consistency of NIT reporting* as study endpoints to support NASH drug development.
3. **Surrogacy potential:** It is notable that there is an expanding dataset to demonstrate that fibrosis biomarkers have prognostic value and change with progression/regression of disease, potentially with greater inter-test consistency than histology.

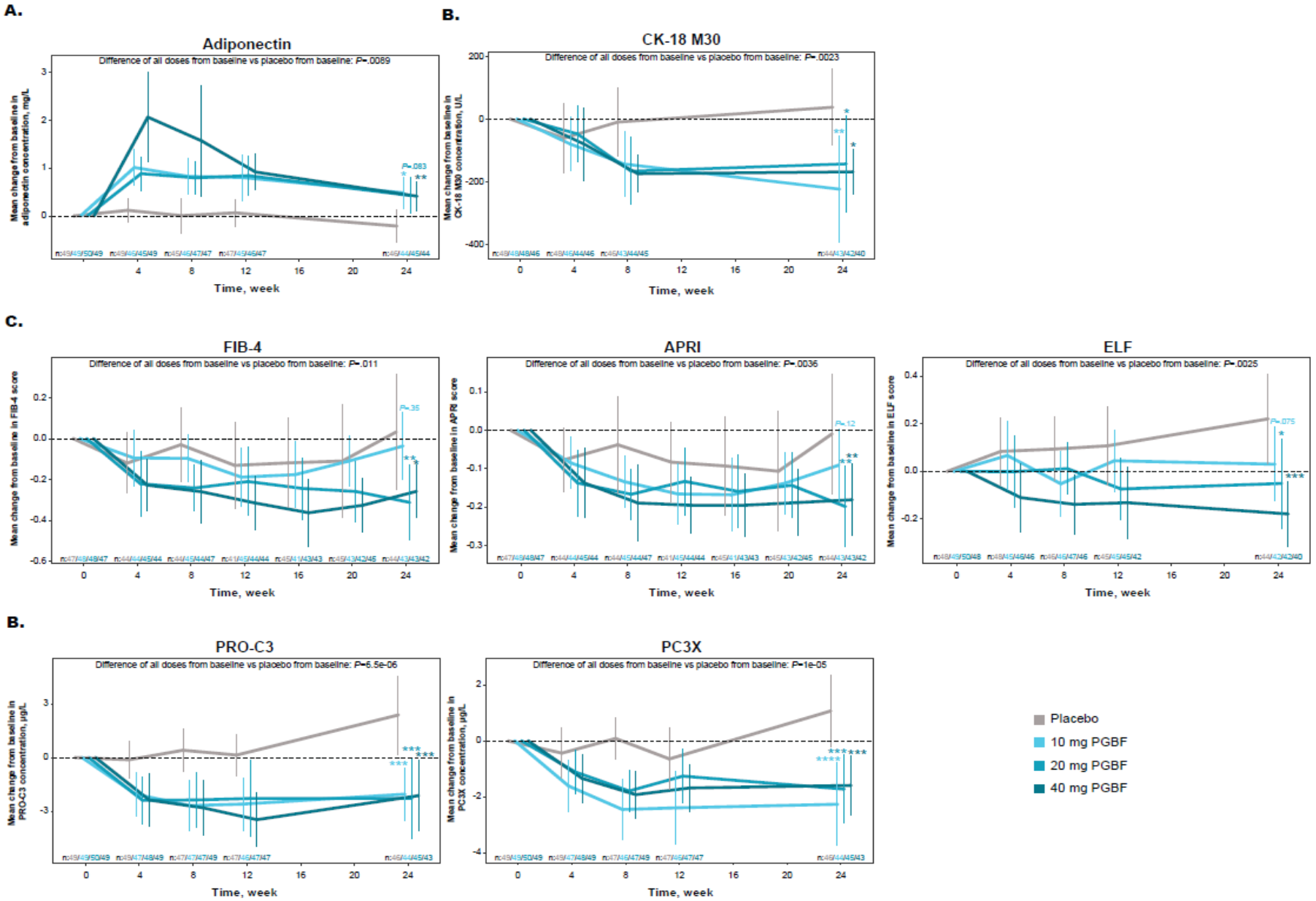
Liver forum 12
Effects of pegbelfermin on NIT's for NASH in a Phase 2b study: Falcon-1

April 23rd 2022

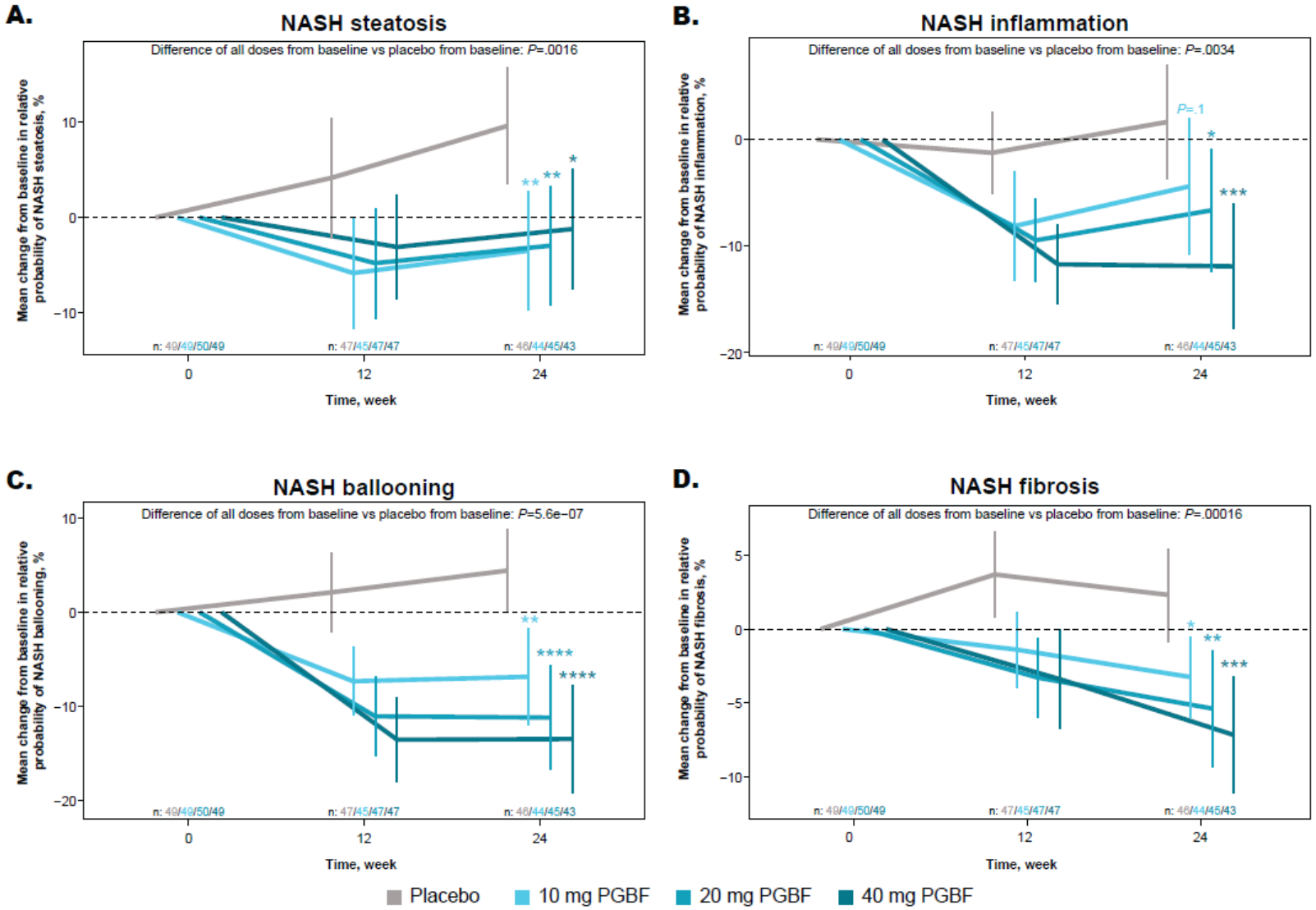
Anne Minnich

Bristol Myers Squibb™

PGBF modulates blood biomarkers of liver injury and fibrosis

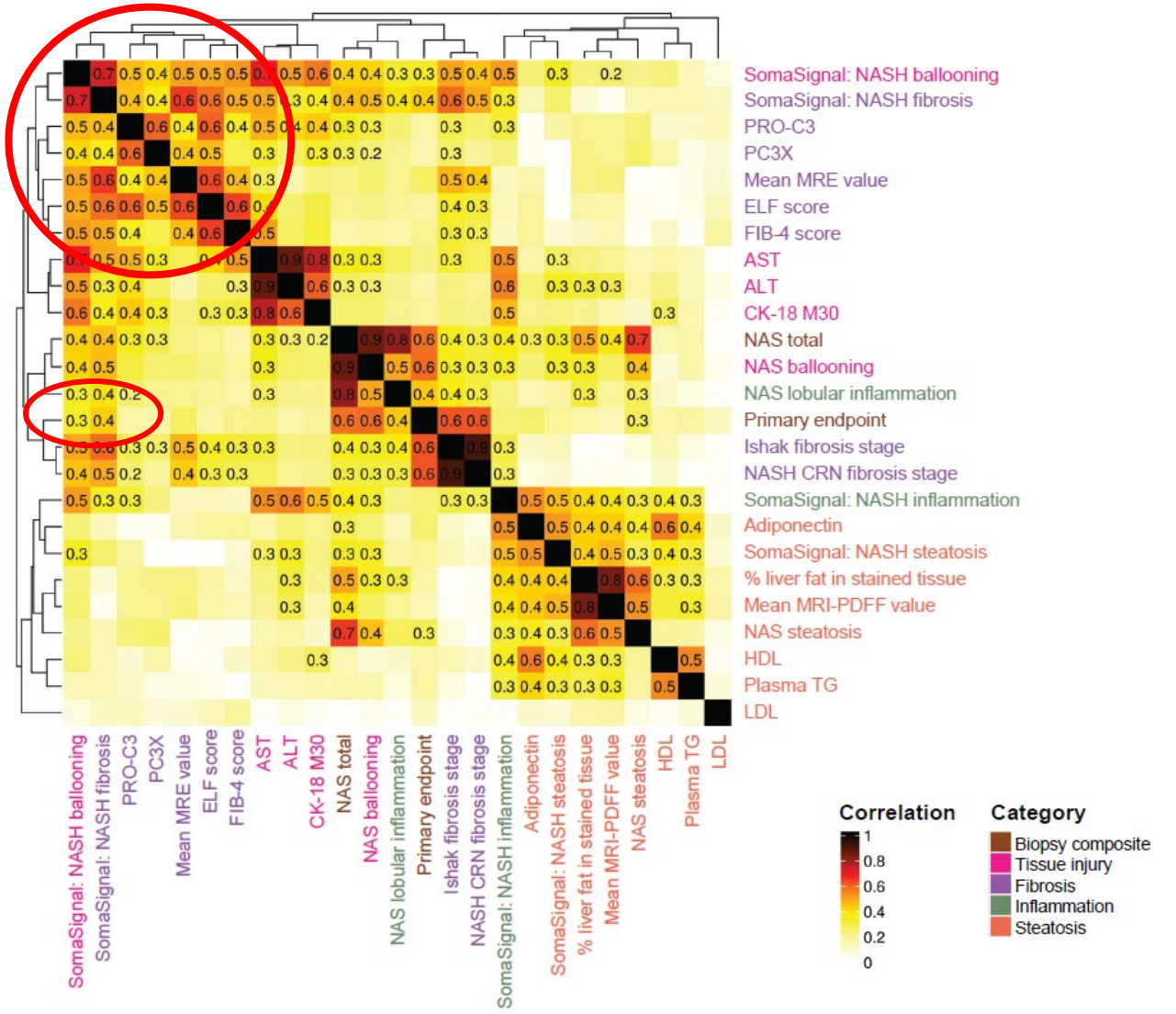


Somasignal NASH bundle



Clustering of correlation coefficients for biomarkers and histological assessments

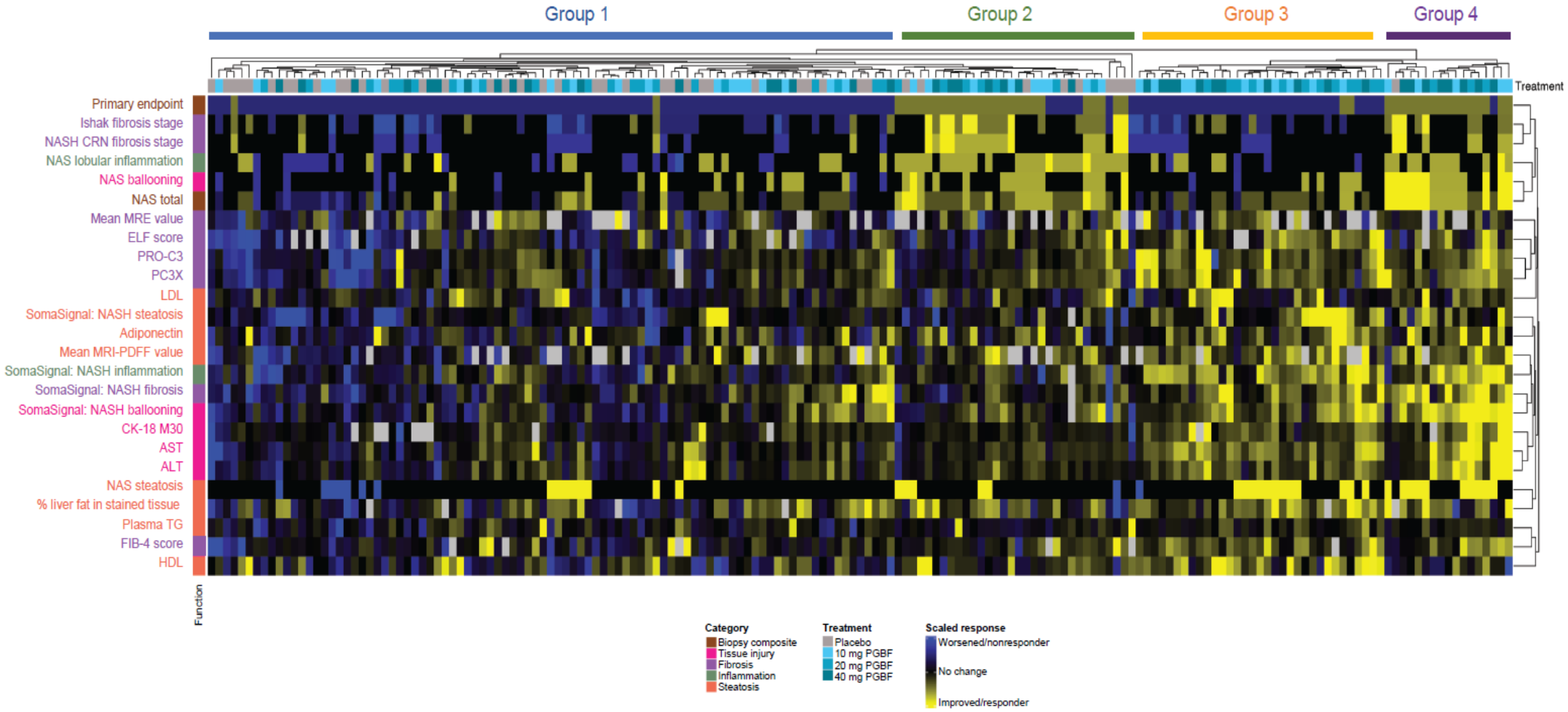
Pairwise week 24 correlation



Fibrosis NIT's cluster well together but not with the primary endpoint

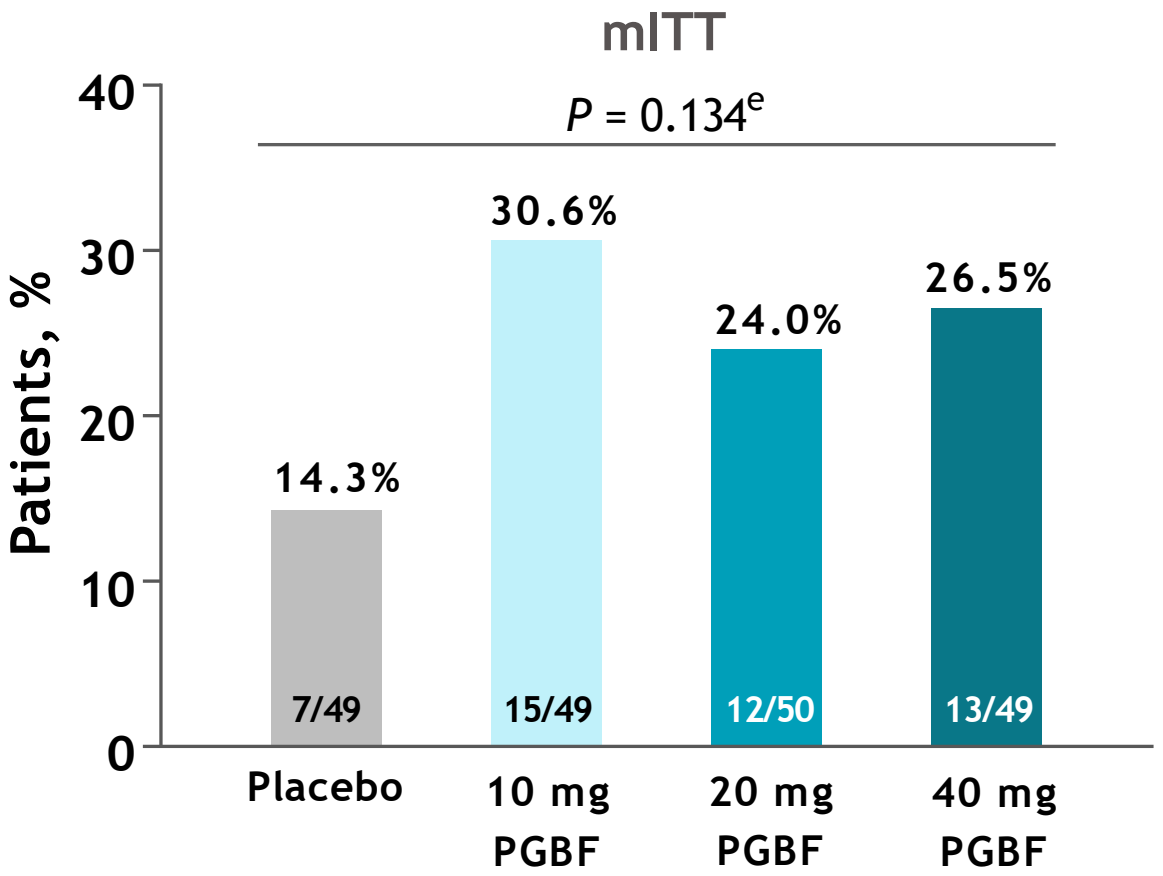
Soma-NASH = only NIT to cluster with primary endpoint

Concordance analysis between primary endpoint and week 24 biomarker responses



Primary Endpoint

At Week 24: ≥ 1 stage improvement in fibrosis[a] without worsening of NASH[b] **OR**
NASH improvement[c] without worsening of fibrosis[d]



[a]Improvement of fibrosis = ≥ 1 stage decrease in NASH CRN fibrosis score; [b]Worsening of NASH = increase in NAS by ≥ 1 point; [c]NASH improvement = ≥ 2 point decrease in NAS with contribution from > 1 NAS component; [d]Worsening of fibrosis = ≥ 1 stage increase in NASH CRN fibrosis score; [e]Cochran-Armitage trend test across proportions of responders in the treatment groups at a 1-sided 0.05 level of significance provided at least 80% power if 160 patients were randomized 1:1:1:1. mITT, modified intent-to-treat; NASH, nonalcoholic steatohepatitis; PGBF, pegbelfermin.

Next steps

- Today's Session 2
- Ongoing, iterative discussions (plenary)
- Working Group (focused)
  - Compile/synthesize data for each COU
  - Present the case