Validating pre-identified morphological baseline features for predicting fibrosis progression in MAESTRO-NASH

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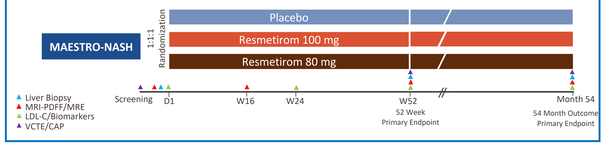
Background

- Resmetirom is an oral liver-directed THR-β selective agonist
- It is FDA-approved in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis)[1]
- MAESTRO-NASH is an ongoing 54-month randomized, double-blind, placebo-controlled Phase 3 trial (Figure 1) evaluating the efficacy & safety 80 mg or 100 mg resmetirom daily in adults with biopsy-confirmed NASH (NCT03900429).
  - At week 52, both primary endpoints were met at both clinical doses Fibrosis Improvement[2]
  - Month 54 measures clinical outcomes including histologic conversion to cirrhosis
- Fibrosis staging remains the pinnacle predictor of clinical outcomes in MASH clinical trials.
- Liver histology using ordinal fibrosis staging may limit the ability to visualize dynamic fibrosis features throughout the liver lobule
- Non-invasive tests (NITs) are currently explored to predict progression to cirrhosis and decompensated cirrhosis, but they have yet to replace biopsies.

Figure 1. MAESTRO-NASH trial design



- Study objective: To use qFibrosis, an AI-driven fibrosis assessment tool, to validate whether specific pre-identified fibrotic features can predict fibrosis progression in MAESTRO-NASH, a 54-month phase 3 trial which achieved NASH resolution and fibrosis reduction.

Methods

- qFibrosis, an AI-driven fibrosis assessment tool that utilizes laser driven (SHG) collagen detection on unstained biopsy slides was used.
- Patient data were assessed with qFibrosis and corresponding selected NITs:
  - VCTE
  - AST
  - MRE
  - MRE
  - GGT
  - PRO-C3
  - Platelets
- 30 fibrosis features previously identified from SteatoSITE were used.
- 6 fibrosis features (5 from portal tract region, 1 from zone 2) were chosen for exploration with clinical data and subsequent validation.

Statistical Analysis

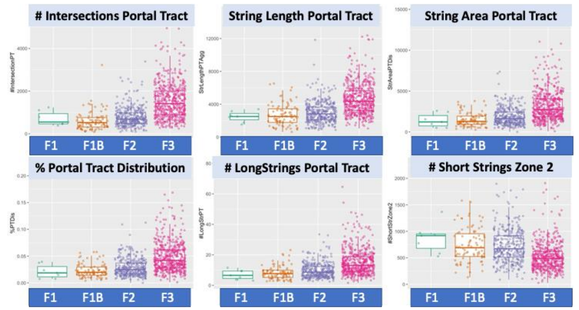
- Univariate analyses and a random forest model with baseline fibrosis stage. as the outcome were used to identify the fibrosis features used in the analysis.
- Spearman correlation analysis of fibrosis features against pathologist scores was carried out.

Sample Numbers

- Based on sample availability at baseline, 845 patients had qFibrosis assessment and corresponding selected NITs (except for MRE, for which only 495 patients had available baseline samples).

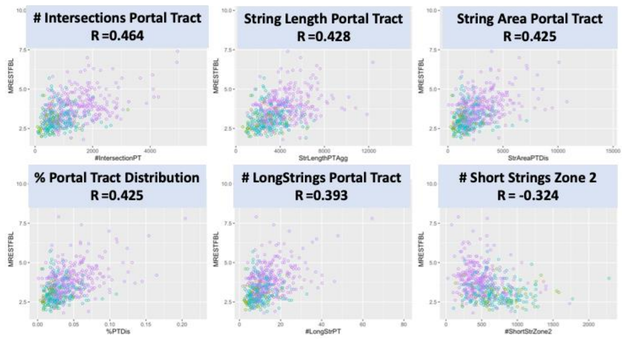
Results

Figure 1: Spearman correlation of pathologist baseline fibrosis stages with 6 qFibrosis features.



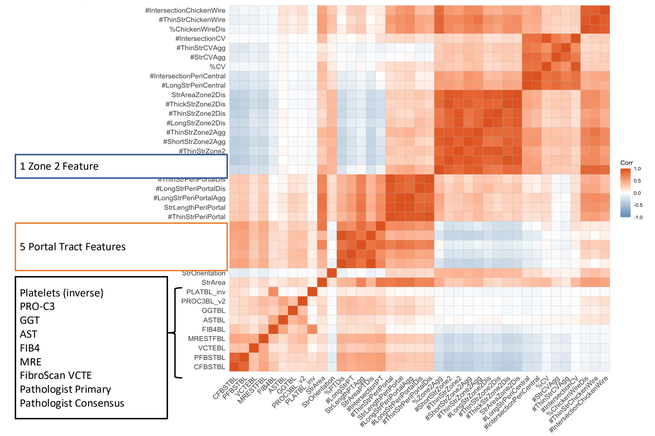
- The baseline values of 6 qFibrosis features are aligned with pathologist baseline fibrosis stage scores.
- The 6 features are:
  - **#IntersectionPT:** Number of intersections of all strings for portal tract fibrosis per unit tissue area
  - **StrLengthPTAgg:** Length of aggregated for portal tract fibrosis per unit tissue area
  - **StrAreaPTDis:** Area of distributed for portal tract fibrosis per unit tissue area
  - **%PTDis:** Percentage of distributed collagen for portal tract fibrosis in tissue area
  - **#LongStrPT:** Number of long strings for portal tract fibrosis per unit tissue area
  - **#ShortStrZone2:** Number of short strings for zone 2 fibrosis per unit tissue area
- Short Strings in Zone 2 is associated with a negative correlation.

Figure 2: Spearman correlation of baseline MRE with 6 qFibrosis features. Purple= Pathologist-staged F3; Turquoise=Pathologist-staged F2.



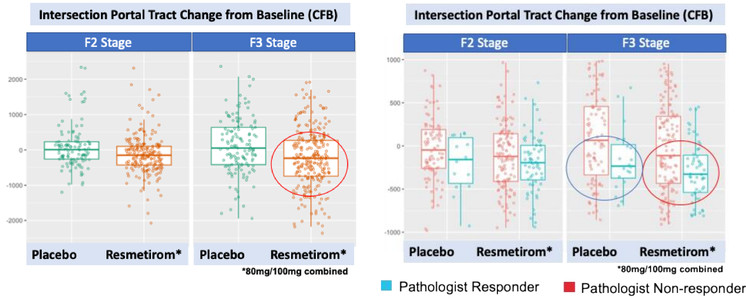
- Baseline MRE and VCTE correlations with the 6 features closely matched with pathologist baseline scores, suggesting that they are nuanced markers of fibrosis progression
  - MRE, 0.393 to 0.464
  - VCTE, 0.233 to 0.342 (plot not shown)
- The correlations of the zone 2 fibrosis feature with MRE and VCTE are –0.324 and –0.255, respectively
- Of the NITs, MRE scored the highest correlations with baseline qFibrosis features, with VCTE also showing a good correlation (plot not shown for VCTE).

Figure 3: Spearman correlation heatmap of 845 patients with qFibrosis assessment with selected NITs and pathologist baseline fibrosis stages.



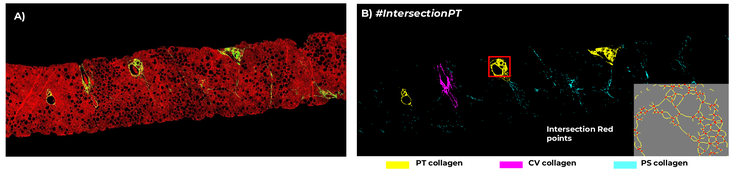
- NITs showed modest correlation with pathologist scores, the highest being
  - MRE, 0.489
  - VCTE, 0.309
- Quantitative readouts of the selected fibrosis features from baseline samples also showed weak to modest correlations with the NITs, ranging from 0.05 to 0.46
  - The zone 2 feature (number of short strings) demonstrated a negative correlation, which ranged from –0.07 to –0.324
  - Other features showed positive correlations

Figure 4: Week 52 change from baseline for qFibrosis progression feature. The number of intersections of all strings for portal tract fibrosis per unit tissue area is presented here for the qFibrosis feature.



- Marked reductions in qFibrosis progression features occurred in the resmetirom F3 population, concordant with fibrosis responders according to pathologist staging.

Figure 5: (A) SHG/TPEF image of a baseline biopsy showing the (Bottom) morphological feature of intersections of all strings for portal tract fibrosis.



Conclusions

- **MRE followed by FibroScan showed strong correlations with the 6 qFibrosis features at baseline.**
- **The identification of negatively correlating features reveals the complexity of fibrosis progression markers, emphasizing the need for a composite NIT approach that integrates both positively and negatively correlating fibrosis features.**
- **Across the 6 fibrosis features, the Week 52 data indicate that resmetirom treatment at 80 mg and 100 mg shows more frequent improvement in fibrosis compared with placebo across consensus baseline fibrosis stages F1b, 2, and 3.**
- **Resmetirom treatment relative to placebo, particularly in F3, reduced qFibrosis features, showing potential in benefiting patients with MASH with advanced liver fibrosis by reversing fibrosis and preventing progression to more advanced liver disease**
- **Confirmation of clinical relevance will require further analyses of Month 54 biopsies and subsequent clinical outcomes**

References

1. REZDIFFRA (resmetirom) approved product labeling. Madrigal Pharmaceuticals, West Conshohocken, PA (3/2024).
2. Harrison SA et al. Lancet 2019; 394(10210): 212-2014. Harrison SA, et al. N Engl J Med. 2024;390(6):497-509. doi:10.1056/NEJMoa2309000

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