SAT-214

Using machine learning models to predict baseline fibrosis stage in patients from phase 3 resmetirom trials (MAESTRO-NAFLD and MAESTRO-NASH)

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Background and Aims: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed NASH/MASH and fibrosis (F1B-F3 and exploratory F1). MAESTRO-NAFLD-1 (NCT04197479) is a completed, randomized, placebo-controlled trial Phase 3 trial evaluating resmetirom safety and its effects on biomarkers in patients with NASH without a biopsy confirmation. 180 patients with well-compensated NASH cirrhosis were enrolled in an open label arm of MAESTRO-NAFLD-1. 1813 patients had baseline or historic biopsy spanning stage F0-F4 with multiple non-invasive biomarker and imaging measures of NASH with fibrosis.

Method: Adults with ≥3 metabolic risk factors were screened. Pts with FibroScan VCTE, liver stiffness ≥8.5 kPa, MRI-PDFF ≥8%, biopsy-confirmed F1B-F3 NASH, NAS ≥4, were eligible for MAESTRO-NASH. MAESTRO-NAFLD-1 included pts with non-invasive measures of NASH (MRI-PDFF ≥8%, Fibroscan VCTE ≥5.5) or well-compensated NASH cirrhosis. Machine learning models evaluated the relative importance of patients' intrinsic characteristics and screening/baseline biomarkers. The Random Forrest (RF) model was selected due to its predictive performance. The Full model (FM) included 36 possible explanatory variables, and the lean model (LM) had 21 predictors more likely to be used in clinical practice. LM was based on 1765 patients with non-missing data compared to 607 pts in FM. Among the potential predictors assessed were demographic characteristics, T2DM, liver tests, MRI-PDFF, MRE, Fibroscan CAP and VCTE, FAST, MAST, FIB-4, Pro-C3, ELF, M30, thyroid hormones, SHBG, and liver and spleen volumeS.

Results: Baseline characteristics excluding the population with liver biopsies included: 207=F0, 271=F1a or c, 156=F1b (designated F2-equivalent), 395=F2, 605=F3, 131=F4 (Cirrhotic). The RF model was used to classify patients: F0/F1A/F1C (Early) vs. F1B/F2/F3 (At-risk) vs. F4, a 3-class model. AUC and classification error rates were assessed in repeated cross-validation. The variables that most impacted classification (FM) included: MRE, Fibroscan VCTE, MRI-PDFF, MAST, SHBG and Platelet count; for LM: Fibroscan VCTE, FIB-4, Pro-C3, FAST, GGT, Platelets, AST and Fibroscan CAP. In the FM, mean (SD) AUROC for F0/1A/1C vs Rest=0.804 (0.055); F1B/F2/F3=0.776 (0.047); F4 vs Rest=0.930 (0.031). In the LM AUROC for F0/1A/1C vs Rest=0.854 (0.017); F1B/F2/F3=0.815 (0.018); F4 vs Rest=0.89 (0.028)
Conclusion: In a population selected for high baseline metabolic risk factors, liver stiffness and liver fat, both FM and LM were able to accurately identify early NASH pts versus those with more significant fibrosis. FM and LM accurately discriminated F4 (cirrhosis) from all others. LM, based on commonly collected biomarkers and lab tests, performed as well as FM.