Validation of a Machine Learning-Based Approach (DELTA Liver Fibrosis Score) for the Assessment of Histologic Response in Patients With Advanced Fibrosis Due to NASH

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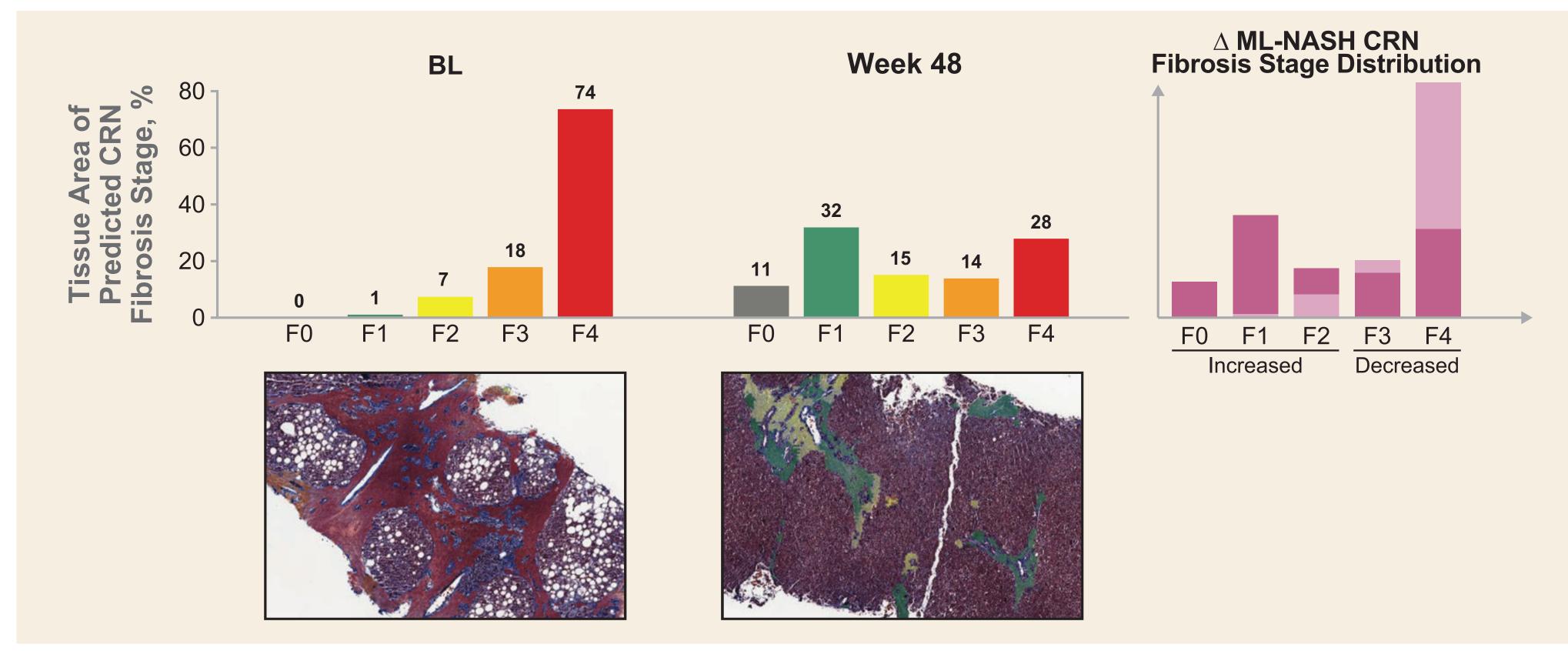Foster City, CA 94404
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Introduction

- Fibrosis, as assessed by liver biopsy, is the primary determinant of disease progression in patients with nonalcoholic steatohepatitis (NASH)[1,2]
- Liver biopsy plays an integral role in the diagnosis and monitoring of disease progression, both in routine clinical practice and clinical trials
- Human pathologist staging of fibrosis is limited by intra- and inter-reader variability[3-6]
- Machine learning (ML) approaches to interpretation of liver histology may enable more reliable and quantitative assessment of both traditional and novel histologic features, with potential prognostic relevance in NASH[7-9]

Objectives

- To develop and validate an ML-based approach for the evaluation of antifibrotic response in clinical trials of therapies for NASH
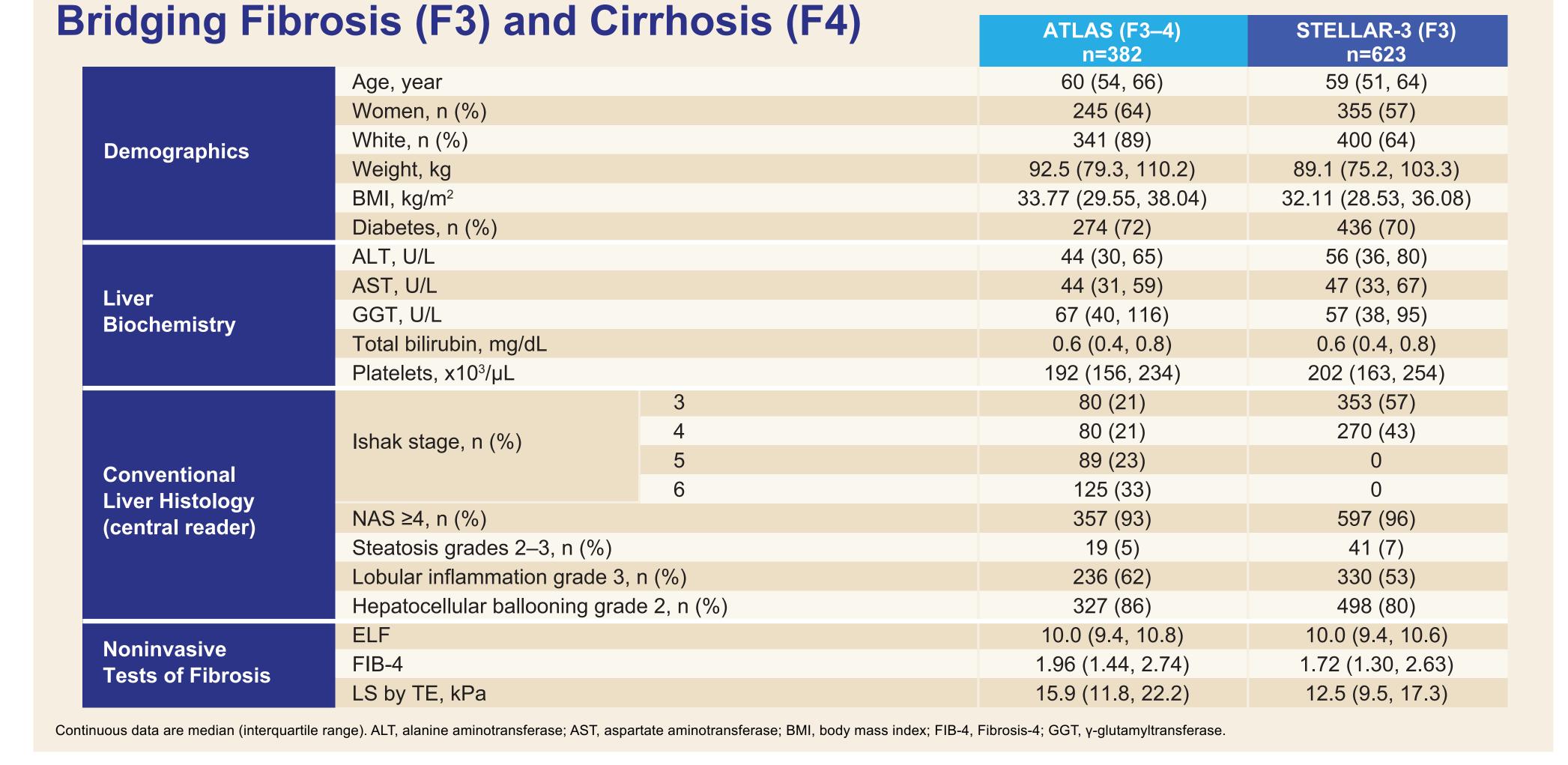
Methods

- Study population:
  - Adults with bridging fibrosis (NASH Clinical Research Network [CRN] F3) or compensated cirrhosis (F4) due to NASH (Nonalcoholic Fatty Liver Disease Activity Score [NAS] ≥3) enrolled in the Phase 2b, placebo-controlled ATLAS trial (NCT03449446), exploring combinations of selonsertib, cilofexor (CILO), and firsocosat (FIR) over 48 weeks
  - Adults with F3 fibrosis enrolled in the Phase 3 STELLAR-3 trial of selonsertib (NCT03053050), which was discontinued after 48 weeks due to lack of efficacy[10]
- Conventional liver histology:
  - Central pathologist review of liver biopsies at baseline (BL) and Week 48
  - Fibrosis staged according to NASH CRN and Ishak classifications
- ML assessment of liver histology and development of the DELTA (Deep Learning Treatment Assessment) Liver Fibrosis Score (PathAI, Inc., Boston, MA)[7,9]:
  - For quantification of fibrosis on images of trichrome (TC)–stained biopsies, an "end-to-end" model was trained using slide-level central pathologist scores to recognize unique patterns and proportions of fibrotic regions associated with each stage
  - DELTA, which reflects the 1st Wasserstein distance between the distributions of fibrotic patterns at BL and Week 48 multiplied by the overall shift in mean between time points, was used to evaluate antifibrotic treatment response
  - DELTA was calculated using biopsy images of NASH subjects with F3–4 fibrosis treated with CILO 30 mg and FIR 20 mg daily (n=78) or placebo (n=39) in ATLAS, and in subjects with F3 fibrosis in STELLAR-3 (n=605)
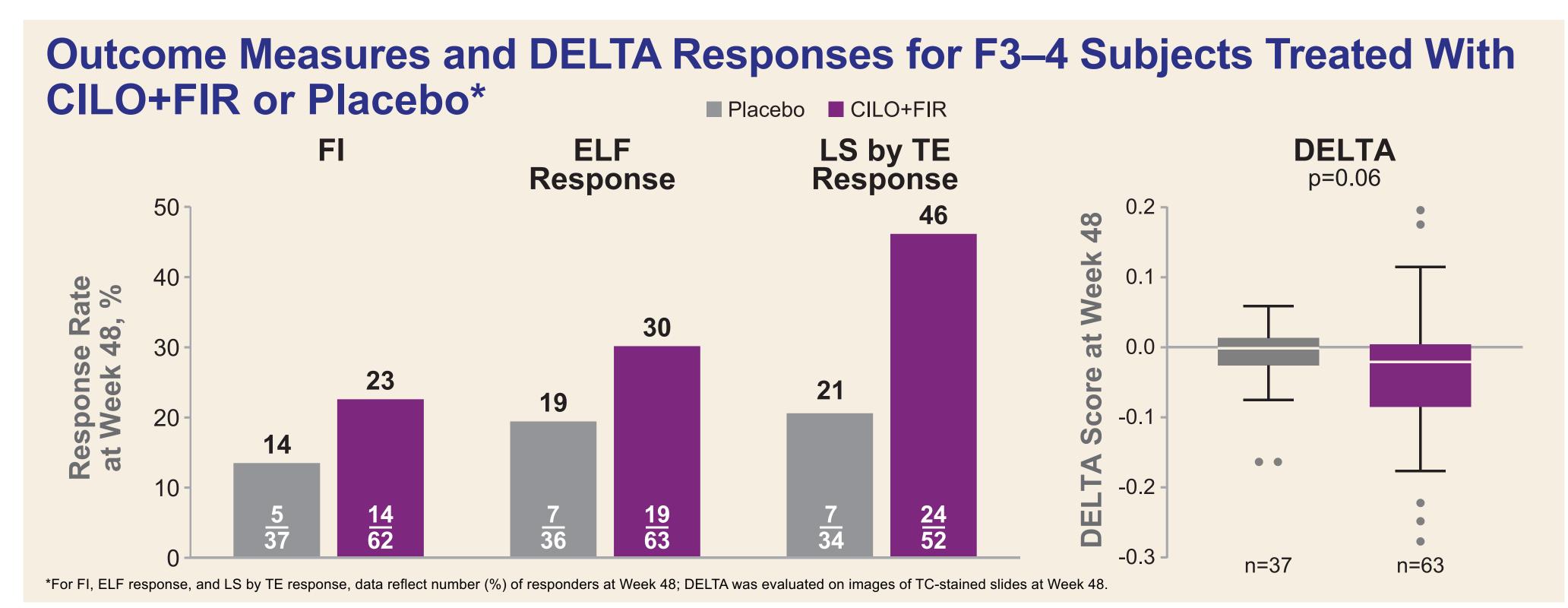

- Outcome measures:
  - ATLAS subjects only: ≥1-stage fibrosis improvement (FI) at Week 48 based on central reader, Enhanced Liver Fibrosis test (ELF™; Siemens Healthcare GmbH, Erlangen, Germany) response (≥0.5-unit decrease), and liver stiffness (LS) by transient elastography (TE) response (>25% decrease)[2,10]
  - ATLAS and STELLAR-3 subjects: histologic progression to cirrhosis on Week-48 biopsy in subjects with F3 at BL based on central reader or adjudication-confirmed, liver-related clinical events (ie, ascites, Grade ≥2 hepatic encephalopathy, gastrointestinal bleeding due to portal hypertension, liver transplantation, qualification for transplantation [Model for End-Stage Liver Disease ≥15], and death)
- Statistical analyses: associations between DELTA and outcome measures evaluated using Wilcoxon rank-sum tests
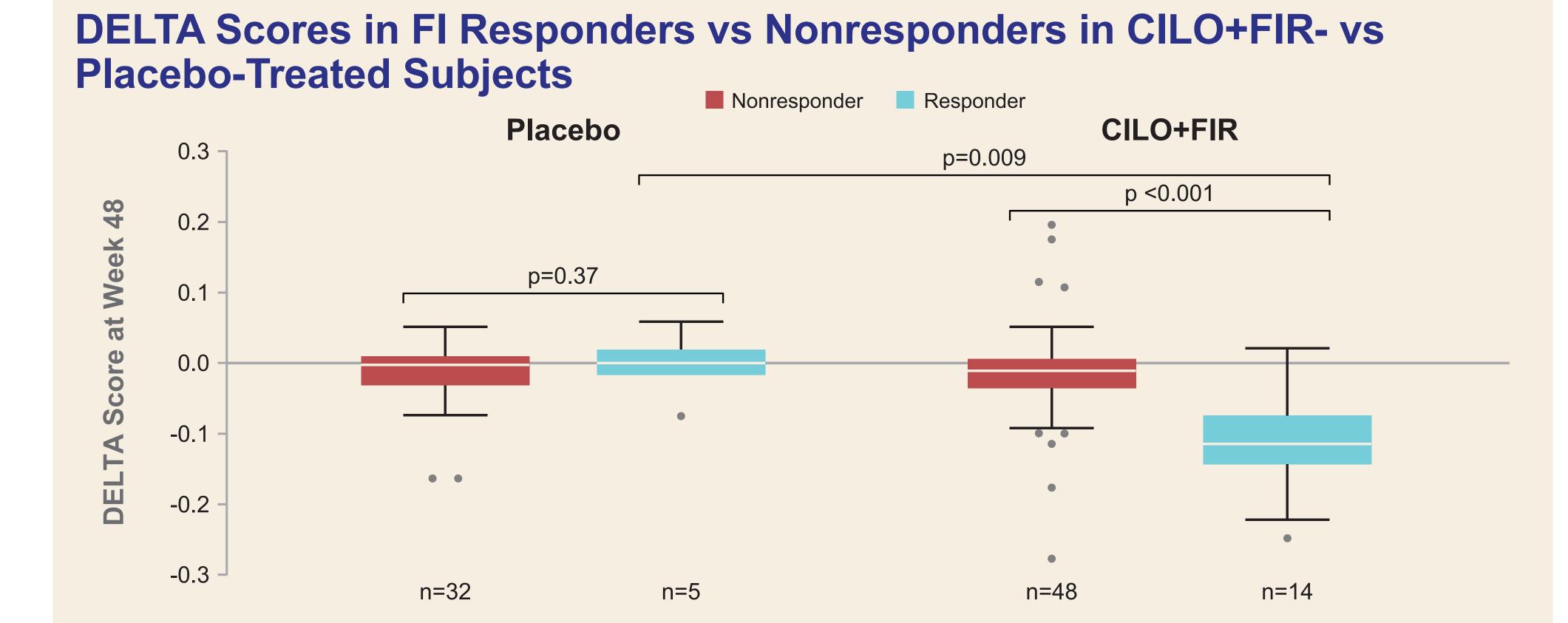
Results

Baseline Demographics and Clinical Characteristics of Subjects With Bridging Fibrosis (F3) and Cirrhosis (F4)

		ATLAS (F3–4) n=382	STELLAR-3 (F3) n=623
Demographics	Age, year	60 (54, 66)	59 (51, 64)
	Women, n (%)	245 (64)	355 (57)
	White, n (%)	341 (89)	400 (64)
	Weight, kg	92.5 (79.3, 110.2)	89.1 (75.2, 103.3)
	BMI, kg/m²	33.77 (29.55, 38.04)	32.11 (28.53, 36.08)
	Diabetes, n (%)	274 (72)	436 (70)
Liver Biochemistry	ALT, U/L	44 (30, 65)	56 (36, 80)
	AST, U/L	44 (31, 59)	47 (33, 67)
	GGT, U/L	67 (40, 116)	57 (38, 95)
	Total bilirubin, mg/dL	0.6 (0.4, 0.8)	0.6 (0.4, 0.8)
	Platelets, x10³/μL	192 (156, 234)	202 (163, 254)
Conventional Liver Histology (central reader)	Ishak stage, n (%) — 3	80 (21)	353 (57)
	4	80 (21)	270 (43)
	5	89 (23)	0
	6	125 (33)	0
	NAS ≥4, n (%)	357 (93)	597 (96)
	Steatosis grades 2–3, n (%)	19 (5)	41 (7)
	Lobular inflammation grade 3, n (%)	236 (62)	330 (53)
	Hepatocellular ballooning grade 2, n (%)	327 (86)	498 (80)
Noninvasive Tests of Fibrosis	ELF	10.0 (9.4, 10.8)	10.0 (9.4, 10.6)
	FIB-4	1.96 (1.44, 2.74)	1.72 (1.30, 2.63)
	LS by TE, kPa	15.9 (11.8, 22.2)	12.5 (9.5, 17.3)

Continuous data are median (interquartile range). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4; GGT, γ-glutamyltransferase.

- Within studies, treatment groups were well balanced for baseline demographics and clinical characteristics

Outcome Measures and DELTA Responses for F3–4 Subjects Treated With CILO+FIR or Placebo*

*For FI, ELF response, and LS by TE response, data reflect number (%) of responders at Week 48; DELTA was evaluated on images of TC-stained slides at Week 48.
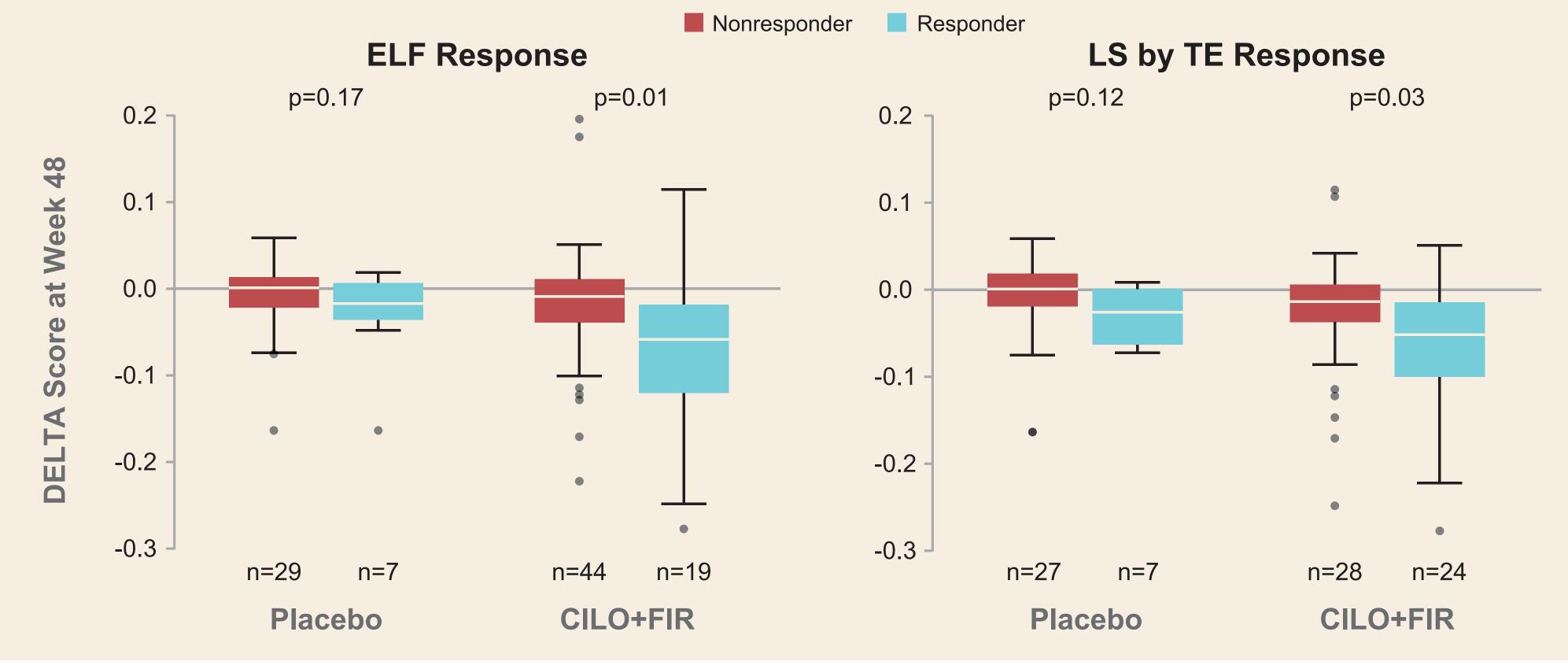
- In F3–4 subjects compared with placebo, treatment with CILO+FIR led to higher rates of FI, ELF response, and LS by TE response at Week 48
- At Week 48, median DELTA was lower in CILO+FIR- vs placebo-treated subjects (-0.02 vs 0.00; p=0.06)

DELTA Scores in FI Responders vs Nonresponders in CILO+FIR- vs Placebo-Treated Subjects
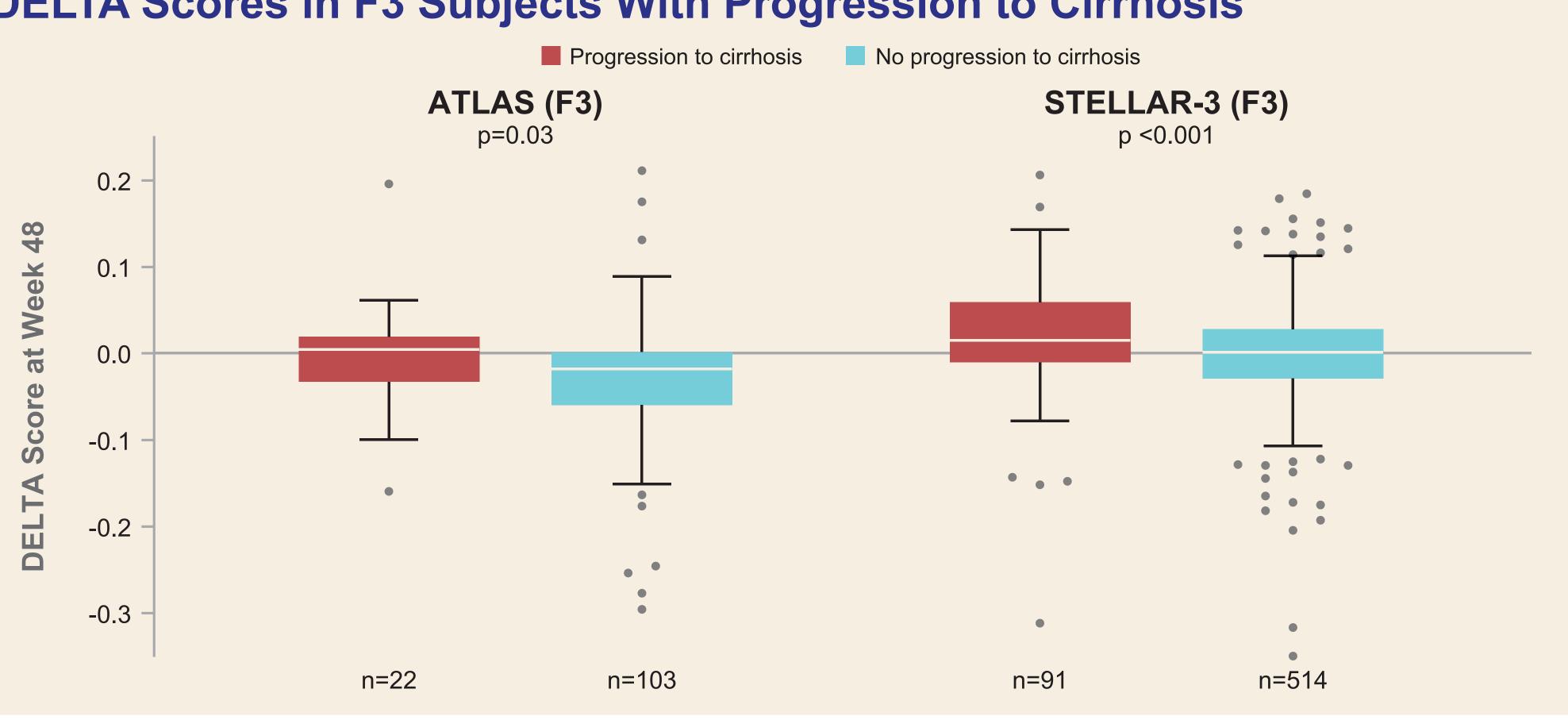

- Subjects treated with CILO+FIR who achieved FI at Week 48 had significantly lower DELTA than those on placebo (p <0.001), whereas no difference in DELTA was observed in placebo FI responders vs nonresponders (p=0.37)
- Among F3–4 subjects with FI at Week 48, those treated with CILO+FIR had significantly lower DELTA than those on placebo (p=0.009)

DELTA Scores in ELF and LS by TE Responders vs Nonresponders in CILO+FIR- vs Placebo-Treated Subjects

- Compared with nonresponders at Week 48, a significantly lower DELTA was observed in CILO+FIR-treated subjects who achieved an ELF response (p=0.01) and LS by TE response (p=0.03)
- No differences in DELTA in ELF and LS by TE responders vs nonresponders were observed in placebo-treated subjects (p=0.17 vs p=0.12) at Week 48

DELTA Scores in F3 Subjects With Progression to Cirrhosis

- In both ATLAS and STELLAR-3, F3 subjects with progression to cirrhosis at Week 48 had higher DELTA vs nonprogressors

Conclusions

- In patients from the ATLAS and STELLAR trials with advanced fibrosis (F3–4) due to NASH, an ML-based evaluation of antifibrotic effects (DELTA Liver Fibrosis Score) may offer a more sensitive, specific, and reliable measure of treatment effects than manual assessment
- Greater improvements in DELTA were observed in subjects from the STELLAR and ATLAS trials treated with CILO+FIR who were considered treatment responders, as determined based on FI by a central reader or by noninvasive tests including ELF and LS by TE
- These data support the utility of ML-based assessment of liver histology for evaluation of antifibrotic treatment effect in future NASH clinical trials

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