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Chairs:
Pietro Lampertico
and **Heiner Wedemeyer**

Delta *cure*

5th International Meeting



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Histologic improvement and reduction in necroinflammation with lonafarnib-based therapy in chronic hepatitis delta: phase 3 D-LIVR trial

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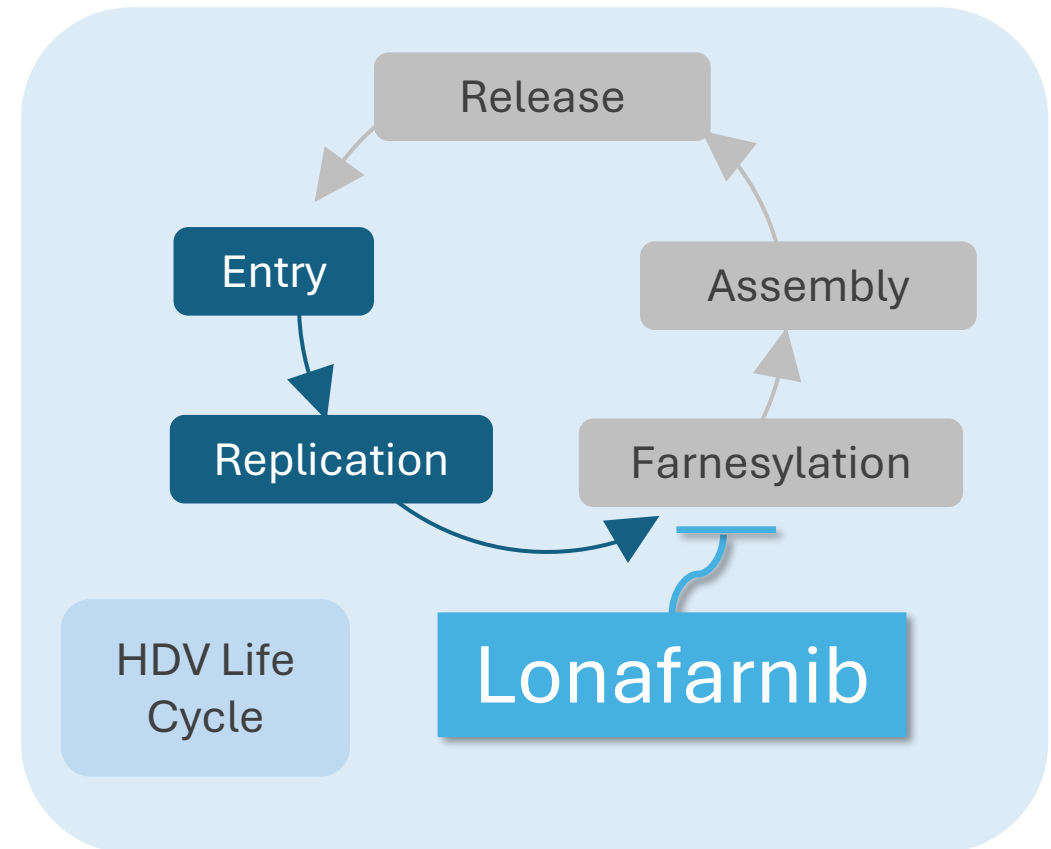
Lonafarnib inhibits critical step in HDV virion assembly

Targeting intracellular host-mediated step in viral life cycle inhibits release of infective particles

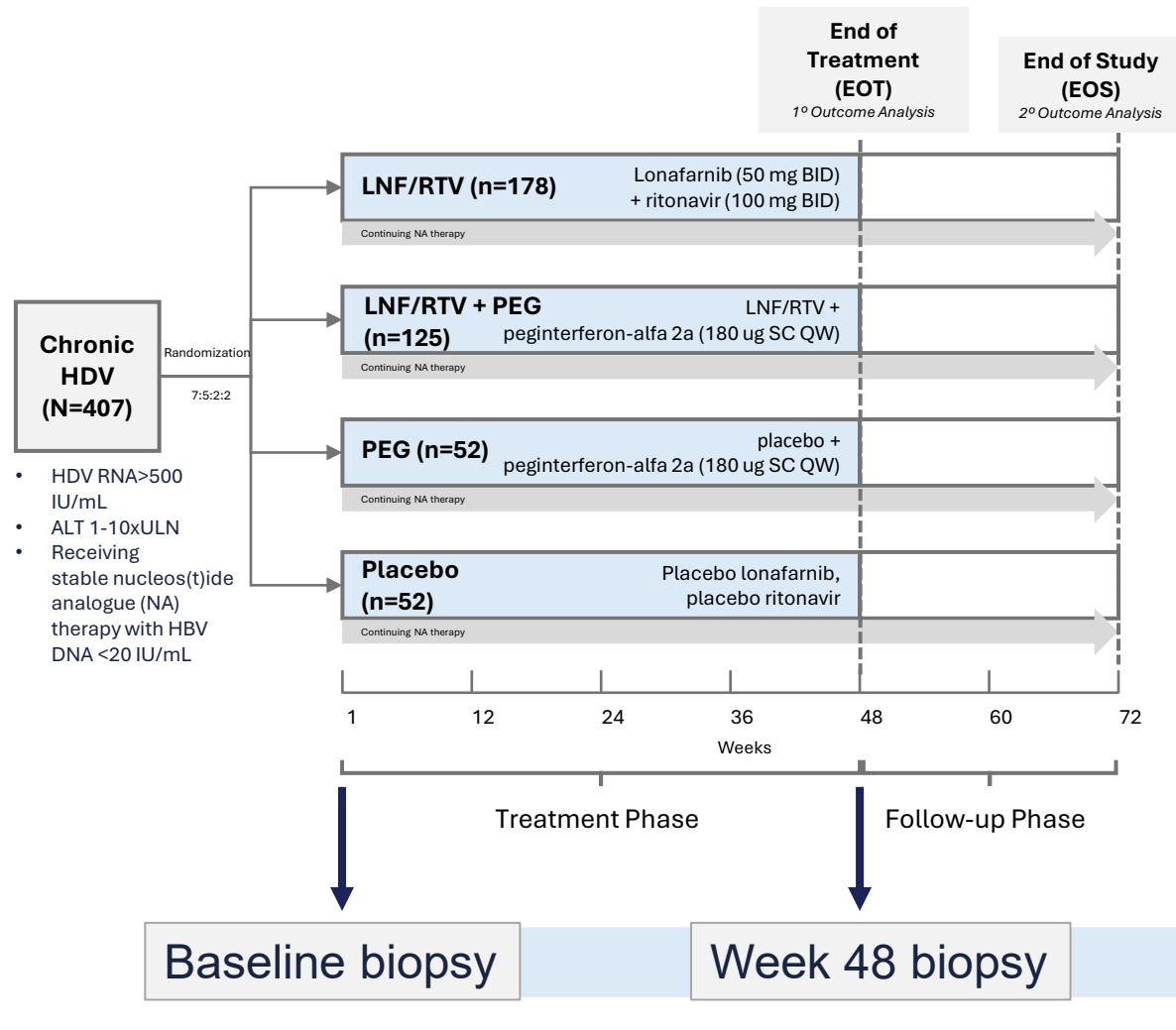
By inhibiting farnesyltransferase, lonafarnib (LNF) disrupts HDV virion assembly in infected hepatocytes and promotes immune modulation.

LNF is the only late-stage oral agent under development for HDV.

LNF pharmacokinetically boosted with ritonavir (LNF/RTV) has been tested in a 48-week oral treatment course either as monotherapy or in combination with peginterferon alfa-2a (PEG).



The positive ph3 D-LIVR study included a large biopsy population



Histology assessment is key to D-LIVR study design

Both LNF/RTV and LNF/RTV+PEG achieved the primary endpoint of composite virologic and biochemical response at Week 48 of treatment and 24 weeks after treatment cessation.

The study also included a histologic improvement endpoint

Direct assessment of liver tissue health through collection of paired biopsies is key to distinguishing true antiviral efficacy from fluctuations in biomarkers.

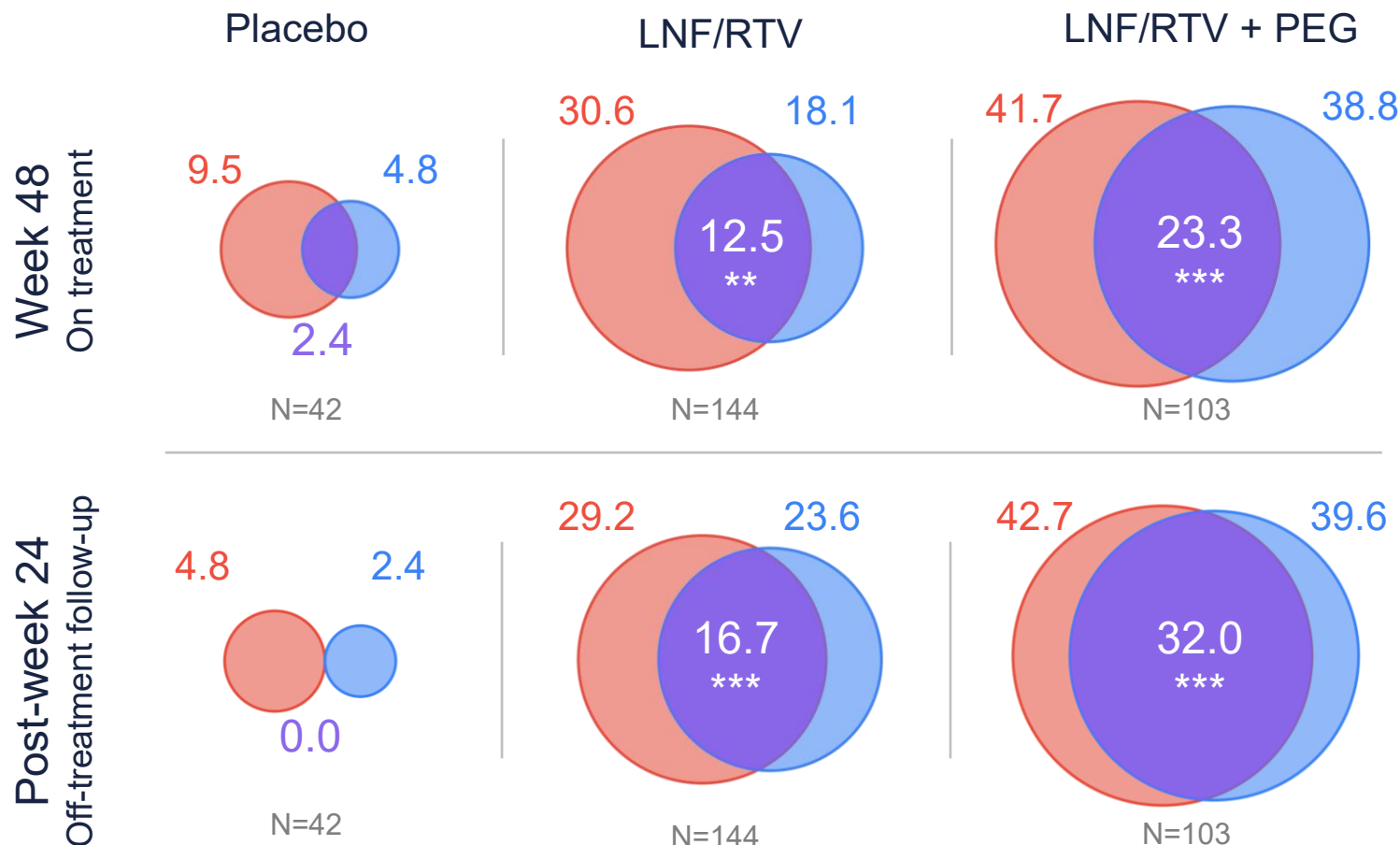
LNF treatments achieve composite endpoint at 48 weeks on treatment and after 24-week follow-up

- Composite Responders (%)**
(ALT normalization AND ≥ 2 log₁₀ reduction in HDV RNA)
- Biochemical responders (%)**
(ALT Normalization)
- Virologic Responders (%)**
(≥ 2 log₁₀ reduction in HDV RNA)

Lonafarnib treatment achieves significant composite response

Significant proportions of patients treated with LNF/RTV both with and without PEG treatment achieved composite virologic and biochemical response at 48 weeks of treatment.

The effect of LNF/RTV $\pm$ PEG treatment was still apparent after 24 weeks of off-treatment follow-up.



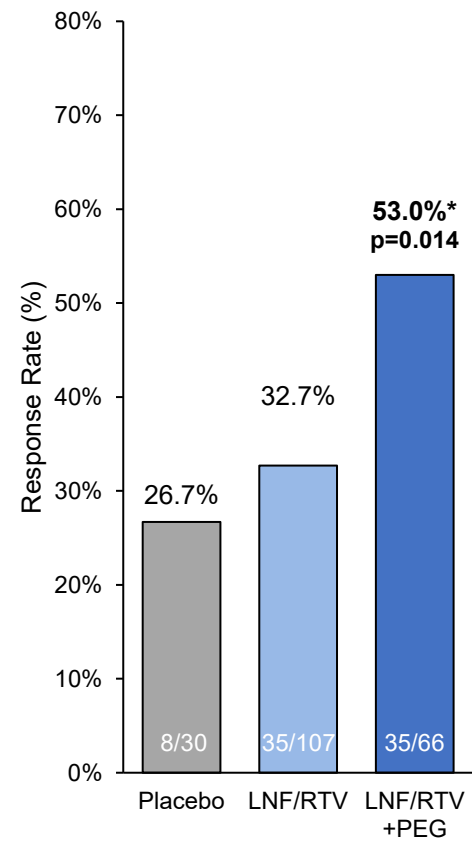
*** $p < 0.0001$, ** $p < 0.01$

Per protocol analysis includes the Completer population (all participants with a Week 48 visit) and carries forward EOS data from Post Week 20 data in cases of missing Post Week 24 data. Week 48 composite response comparing LNF/RTV and LNF/RTV + PEG against placebo was the primary prespecified endpoint for the D-LIVR trial with Bonferroni adjustments to α of 0.03 to LNF/RTV vs Placebo and 0.02 to LNF/RTV + PEG vs Placebo.

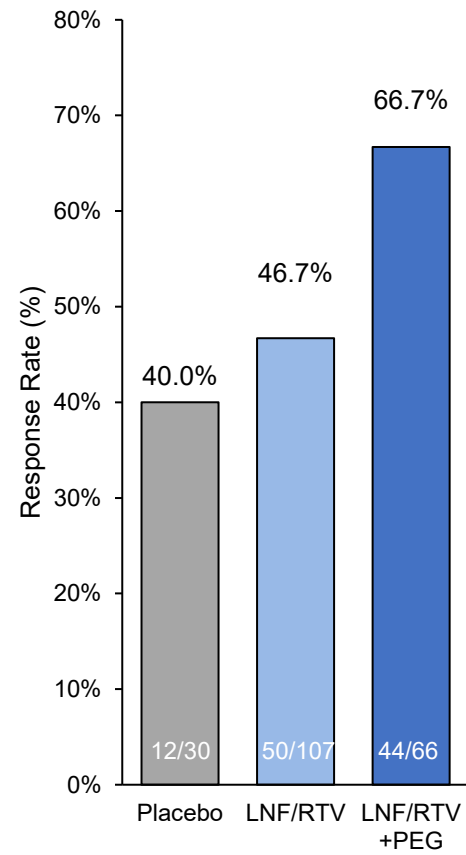
Post-week 24 comparisons were a pre-specified secondary endpoint comparing LNF therapies against placebo with an α of 0.05 for each.

LNF-based therapy improves histologic response

Histologic Response
≥2 pt improvement in Ishak
HAI without fibrosis
worsening



≥1 point improvement in
Ishak HAI



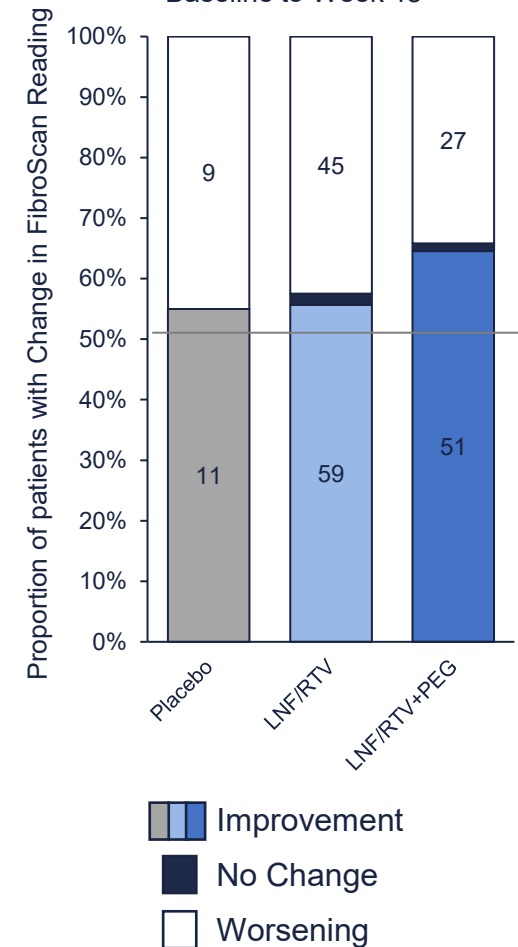
**LNF-based therapy
improves histology above
background HBV therapy**

Histology effects were assessed in a
large paired biopsy population.
N=229 with evaluable paired biopsies.

This effect is above the background
histology benefits all patients experienced
due to background HBV NA therapy, as
most patients initiated NA therapy within 1
year of study start.

Histologic response pattern is confirmed by
less-rigorous Ishak threshold and post-hoc
analysis of change in FibroScan readings
between baseline and Week 48

Change in FibroScan
Baseline to Week 48

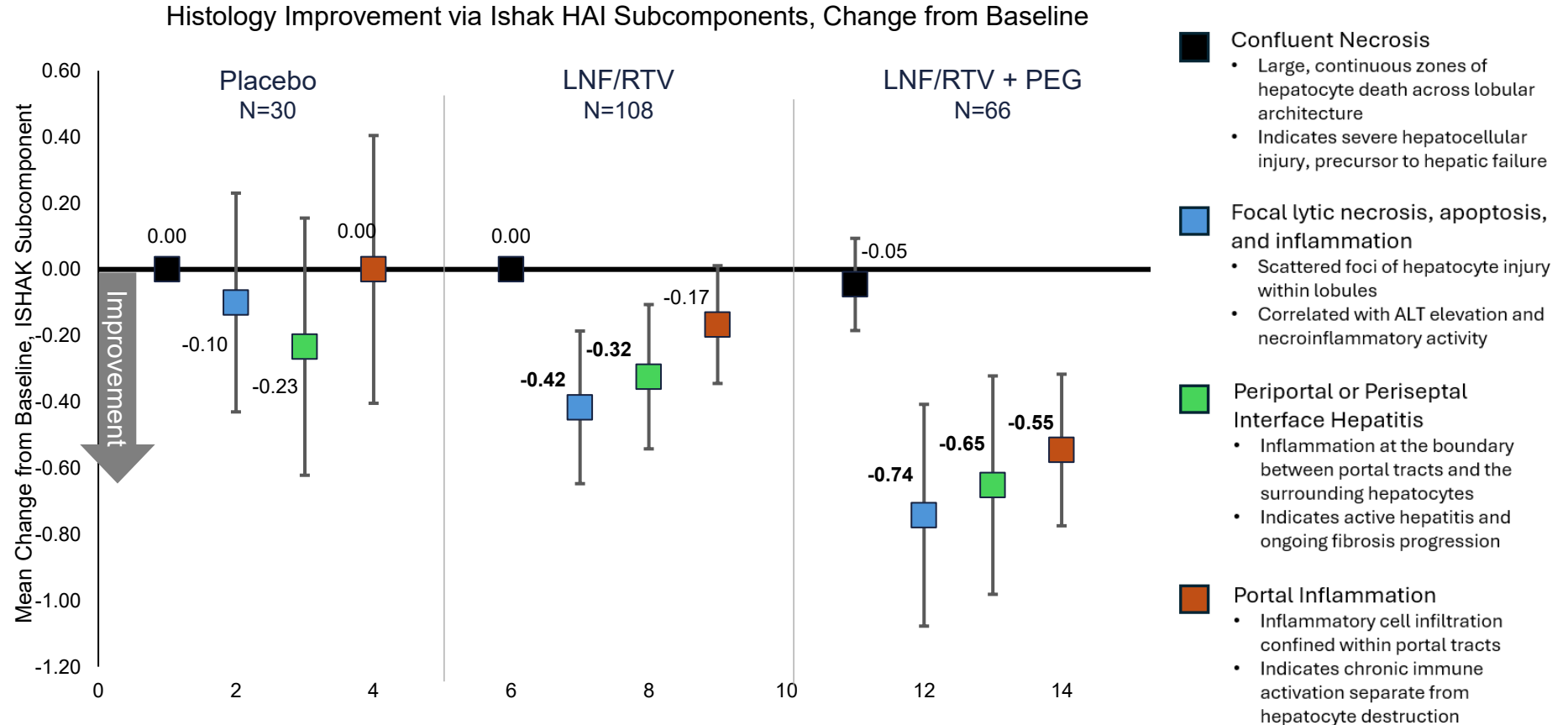


Analysis of Ishak subcomponents to characterize histology

Inflammatory subdomains are the most strongly affected by LNF

The most dramatic treatment effects are seen in inflammatory subdomains, particularly in reduction of focal hepatocyte necrosis, apoptosis, and inflammation

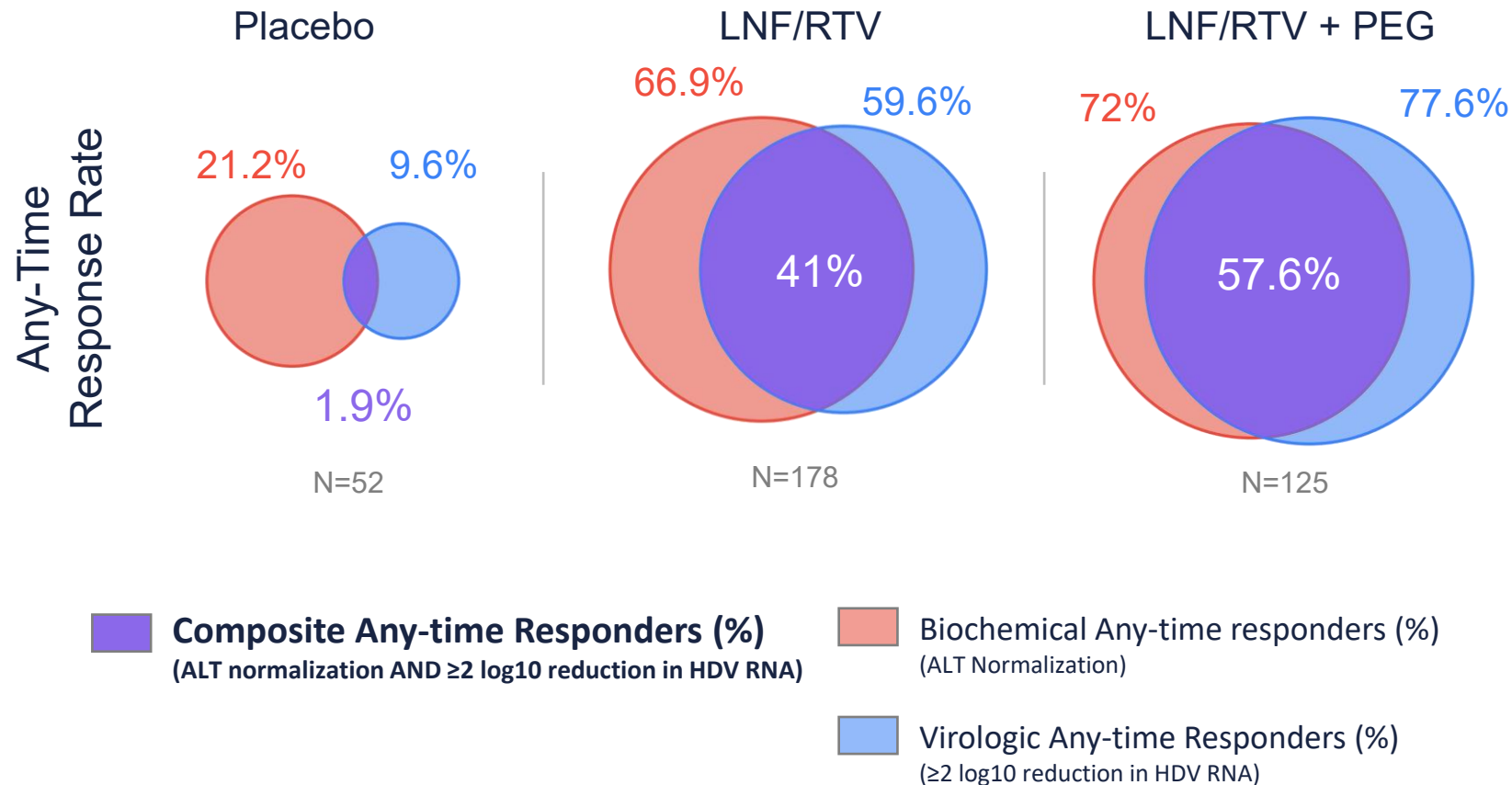
Large confluent necrosis was not affected by any treatment



Mean change from baseline in Ishak score among distinct Ishak subcomponents. Squares indicate mean change from baseline and error bars indicate 95% confidence intervals. Subcomponents whose 95% CIs do not cross the axis (bold data labels) can be considered to be nominally significantly changed compared to their own baseline. The Ishak subcomponents are represented as follows: black squares: confluent necrosis, blue squares: focal lytic necrosis, apoptosis, and inflammation, green squares: periportal or periseptal interface hepatitis, red squares: portal inflammation.

Abbreviations: LNF: Isonafarnib, PEG: pegylated interferon alfa-2a, RTV: ritonavir

Any-Time Response Analysis



LNF-based therapies promote composite response at times outside the primary endpoint

To assess the breadth of treatment response, including response outside the Week 48 timepoint, **we assessed the achievement of virologic and biochemical composite response at any time during the study.**

These “Any-time” responders represent a large proportion of the treated population, including more than 50% of the combination treatment arm.

Widespread any-time response may indicate a broader treatment response to LNF-based therapies than is captured at the Week 48 timepoint

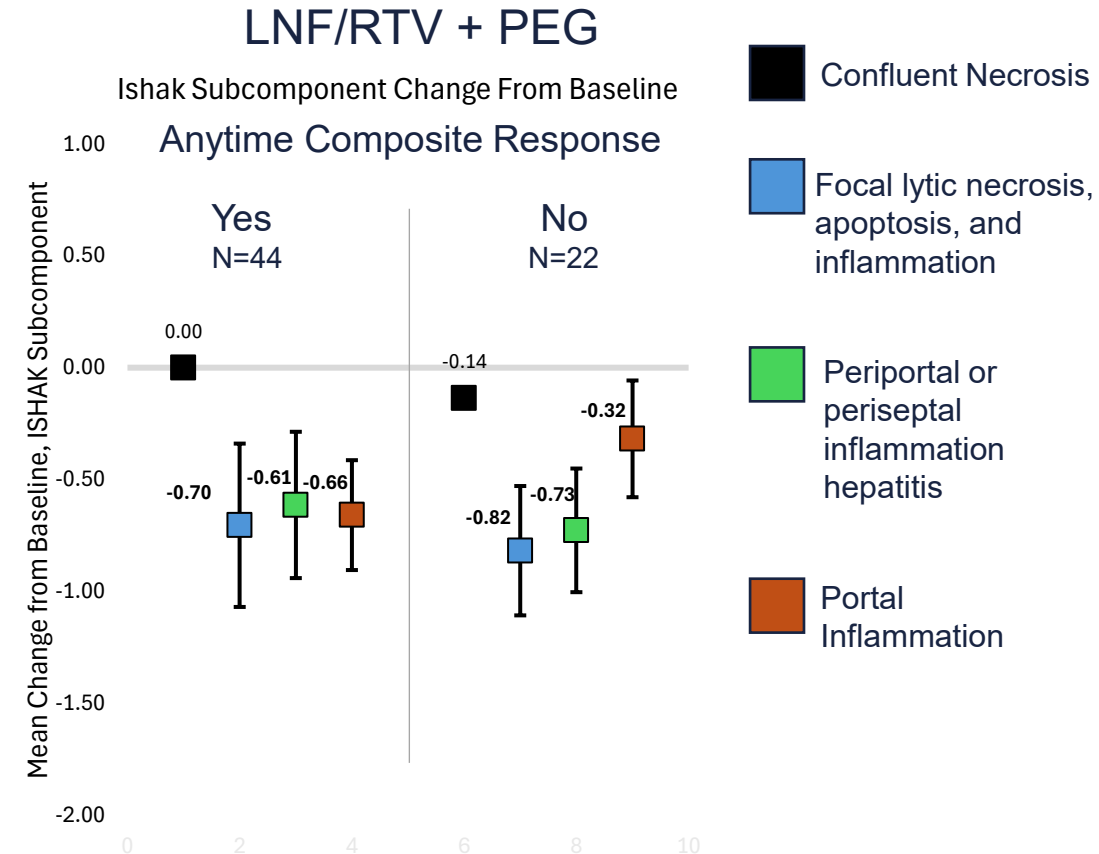
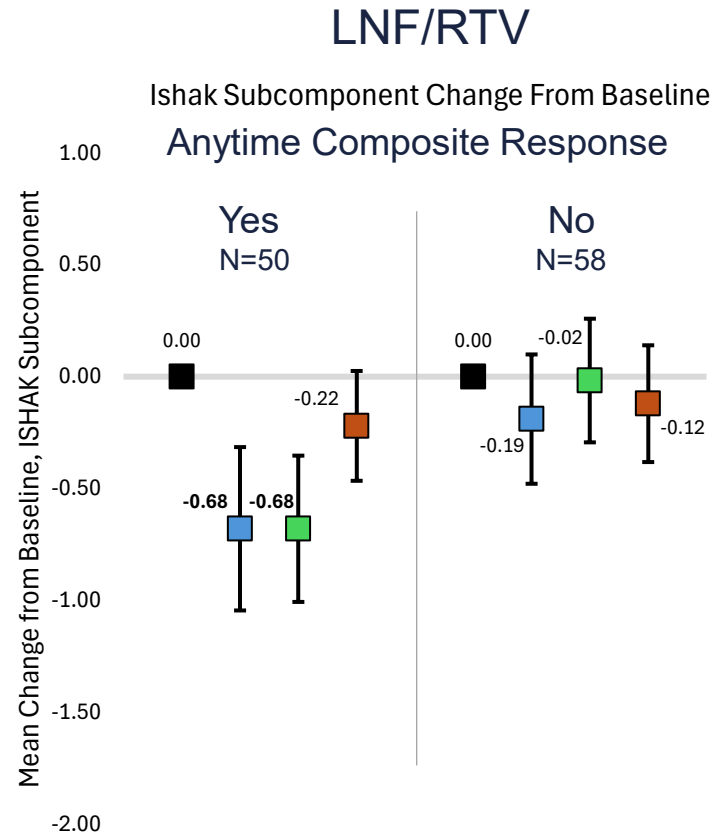
In a post hoc time-to-response analysis, the first occurrence at which patients met the prespecified composite, virologic, and biochemical response criteria was evaluated, with such patients classified as “any-time responders.” This analysis applied the same responder definitions as the primary analysis but extended the evaluation window beyond the single assessment at Week 48 or end of treatment.

Ishak Subcomponents by Any-time Response

Ishak subdomain improvement is associated with any-time response

In the LNF/RTV monotherapy group, composite any-time responders had improved Ishak subdomains, while any-time non-responders did not.

This association supports the meaningfulness of the any-time composite response as related to histology improvement.



Mean change from baseline in ISHAK score among distinct ISHAK subcomponents stratified by any-time composite response. Anytime responders defined as patients who achieved composite response at any time during the study, regardless of status at EOT. Composite response defined as ≥ 2 log₁₀ IU/mL decrease in HDV RNA and ALT normalization. Abbreviations: LNF: lonafarnib, PEG: pegylated interferon alfa-2a, RTV: ritonavir

Summary

- Lonafernib-based therapies were effective in the large ph3 D-LIVR study
- LNF/RTV+PEG statistically improved liver histologic response after only 48 weeks of treatment, and LNF/RTV treatment produced directional improvement
- Analysis of the Ishak subdomains reveals improvement in necroinflammatory subdomains compared to baseline in both LNF-based treatment regimens
- Ishak subdomain improvement was associated with achievement of composite virologic and biochemical treatment response at any time during the study
- **Hard histologic endpoint improvements in the D-LIVR study support continued development of LNF-based therapies**

Thank you to all the investigators and participants who took part in the D-LIVR study, particularly those who contributed biopsy samples

