What have we learned from the Lonafarnib and pegIFN lambda trials?

Tarik Asselah
Professor of Medicine
Hepatology, INSERM UMR 1149,
Hôpital Beaujon, Clichy, France.

Disclosures

- Thanks Ohad Etzion for helpful discussion
- Employee of Paris Public University Hospitals (AP-HP, Beaujon's Hospital) and University of Paris.
- Principal investigator for research grants: Funds paid to Hospital (AP-HP)
- Consultant, expert and speaker for: Abbvie, Bristol-Myers Squibb, Gilead, GSK, Janssen, Merck Sharp Dohme, MYR Pharmaceuticals, Roche.
- Grants from: ANR, CNRS , INSERM , University of Paris, ANRS.


DIOR
PRADA
PRADA
PRADA
PRADA
Fratelli Prada
Santoni


14

What have we learned from the Lonafarnib and pegIFN lambda trials?

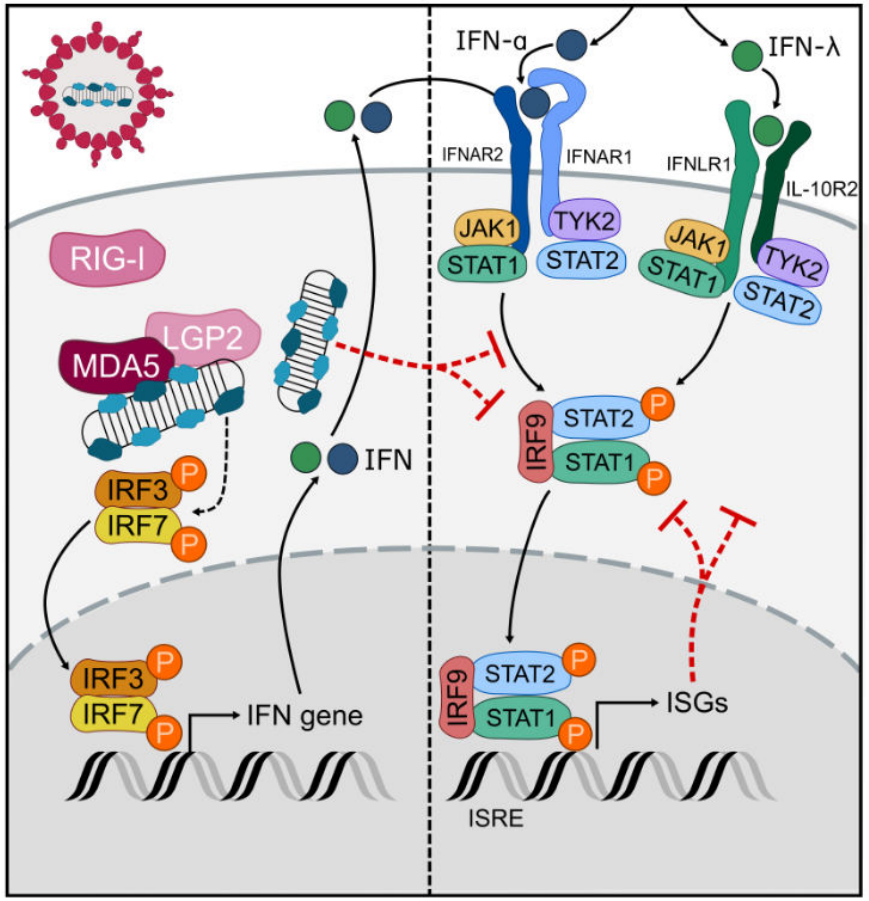
pegIFN lambda

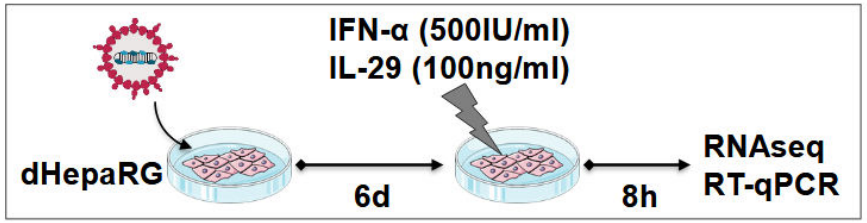
1. Mode of Action
2. Results
3. Lessons learned

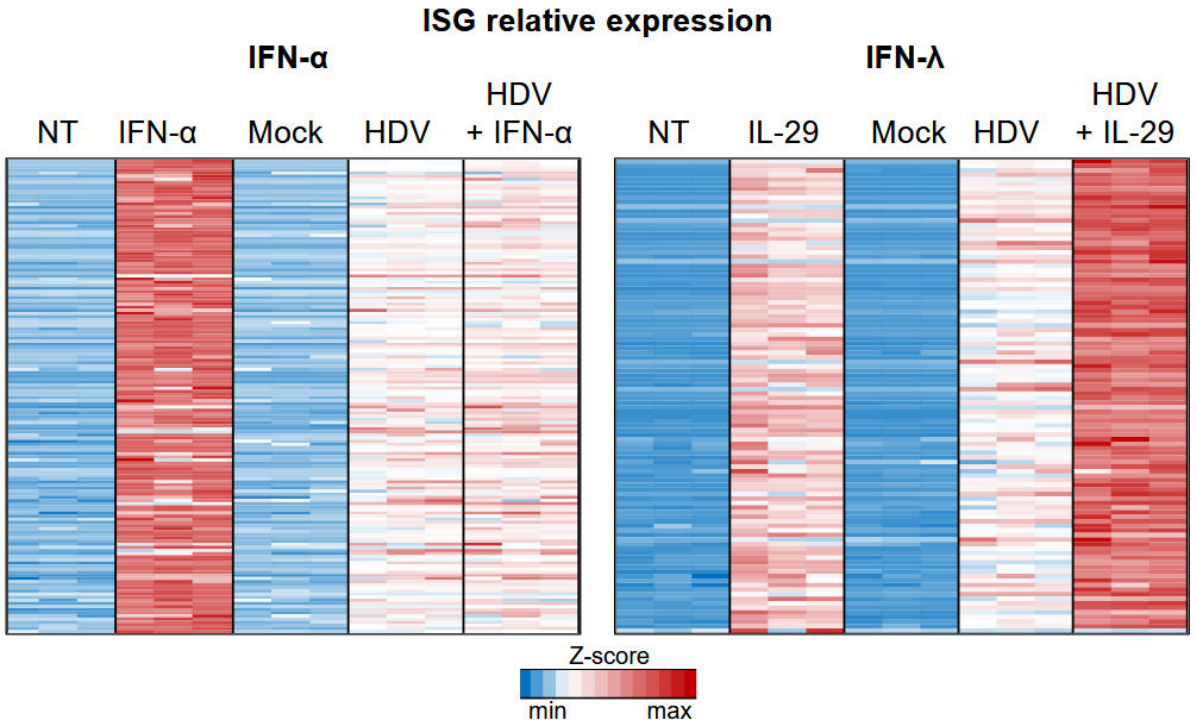
Lonafarnib

1. Mode of Action
2. Results
3. Lessons learned

pegIFN lambda: Mode of Action







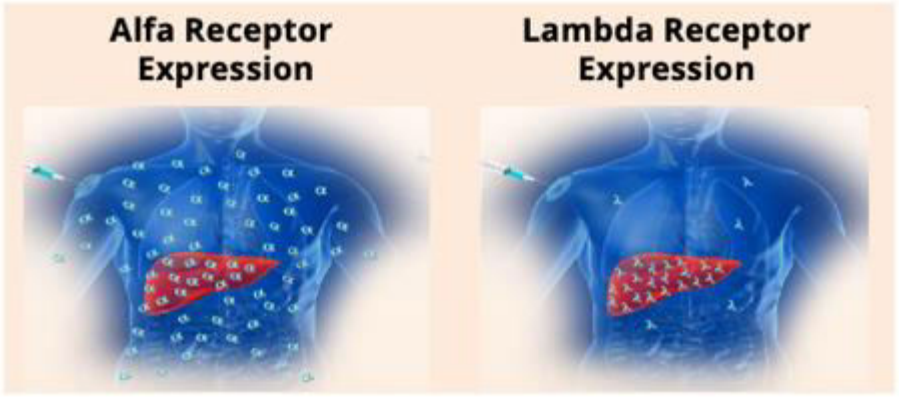
- HDV infection induces a **refractoriness specific to IFN-α, but not IFN-λ (IL-29) treatment**
- **IFN-λ is a stronger inducer of the antiviral immune response** than IFN-α in HDV-infected cells

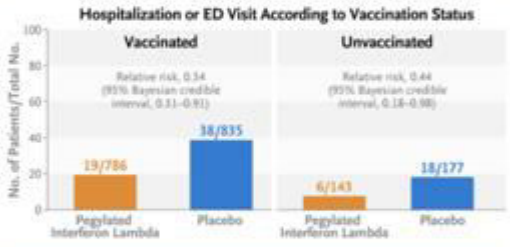
Eber et al., Poster N°23

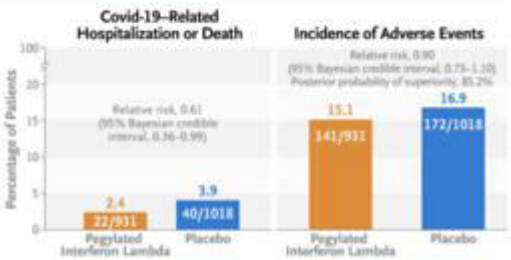
Delta Cure 3rd International Meeting 2024

pegIFN lambda

- A novel first-in-class Type III IFN
- Less of the typical IFN Alfa-related side effects[1]
- > 3,000 patients in 17 clinical trials (HCV/ HBV)
- Single dose reduces hospitalization rates by 50% in Covid-19 infected patients[2]







1. Chan, HLY et al, J Hepatology 2016; 2. Reis G et al. N Engl J Med. 2023

What have we learned from the Lonafarnib and pegIFN lambda trials?

pegIFN lambda

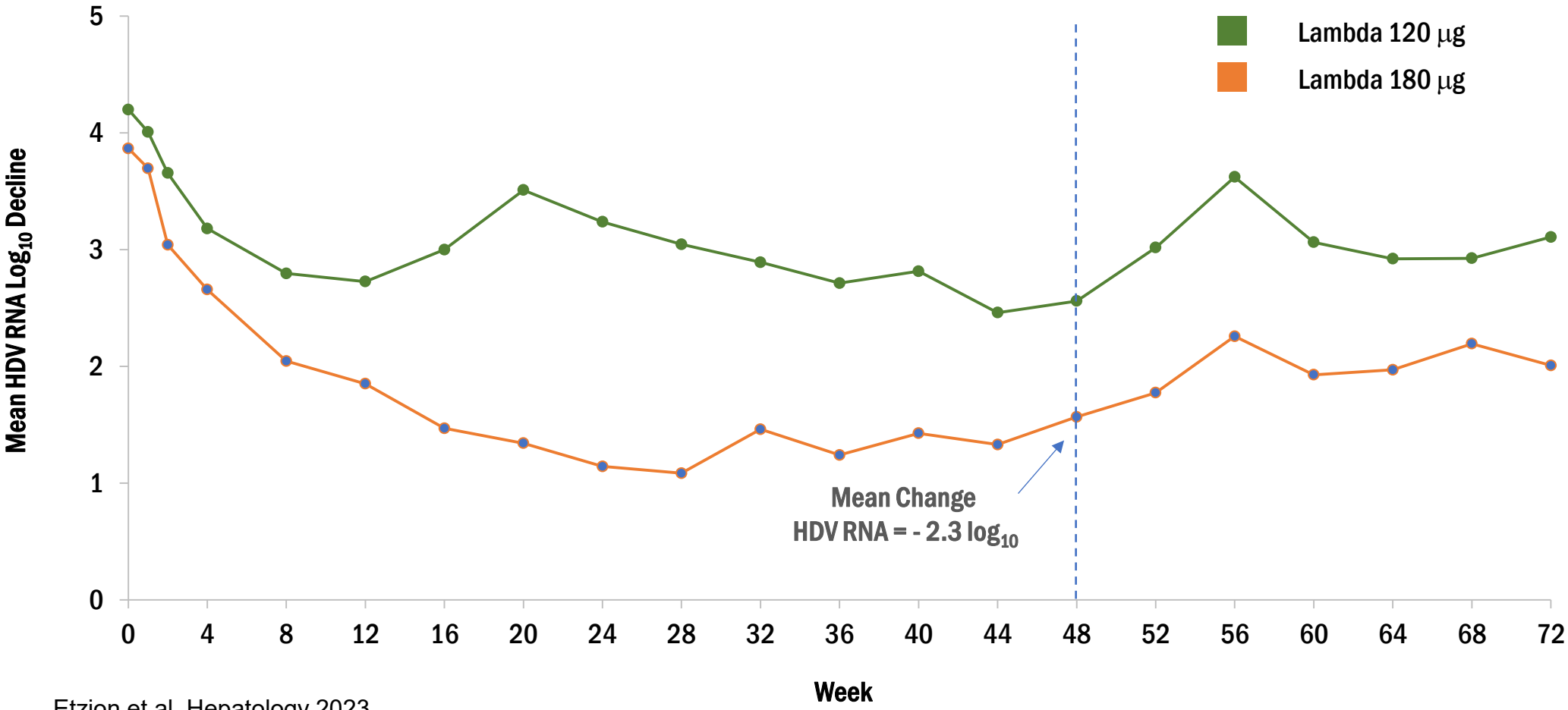
1. Mode of Action
2. **Results**
3. Lessons learned

Lonafarnib

1. Mode of Action
2. Results
3. Lessons learned

HDV-RNA reduction with IFN-LAMBDA

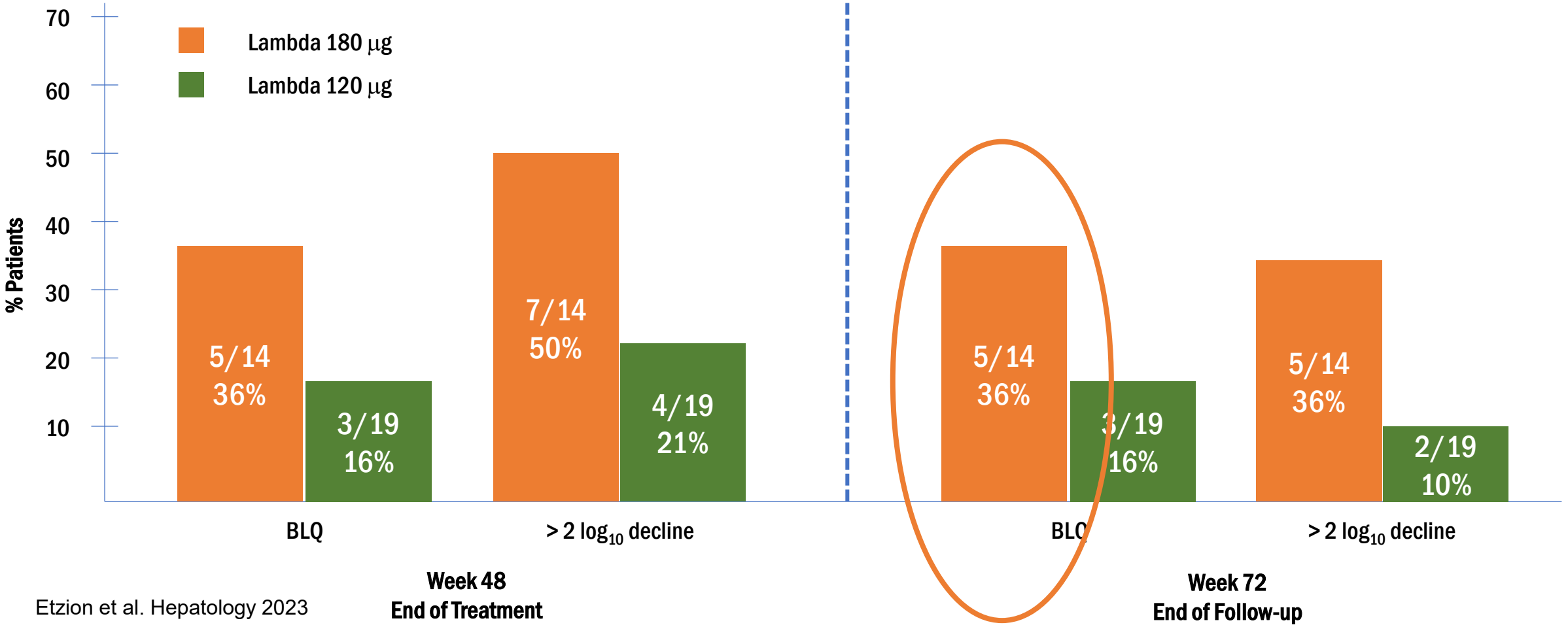
Lambda 180 μg Comparable to Historical Alfa 180 μg



Etzion et al. Hepatology 2023

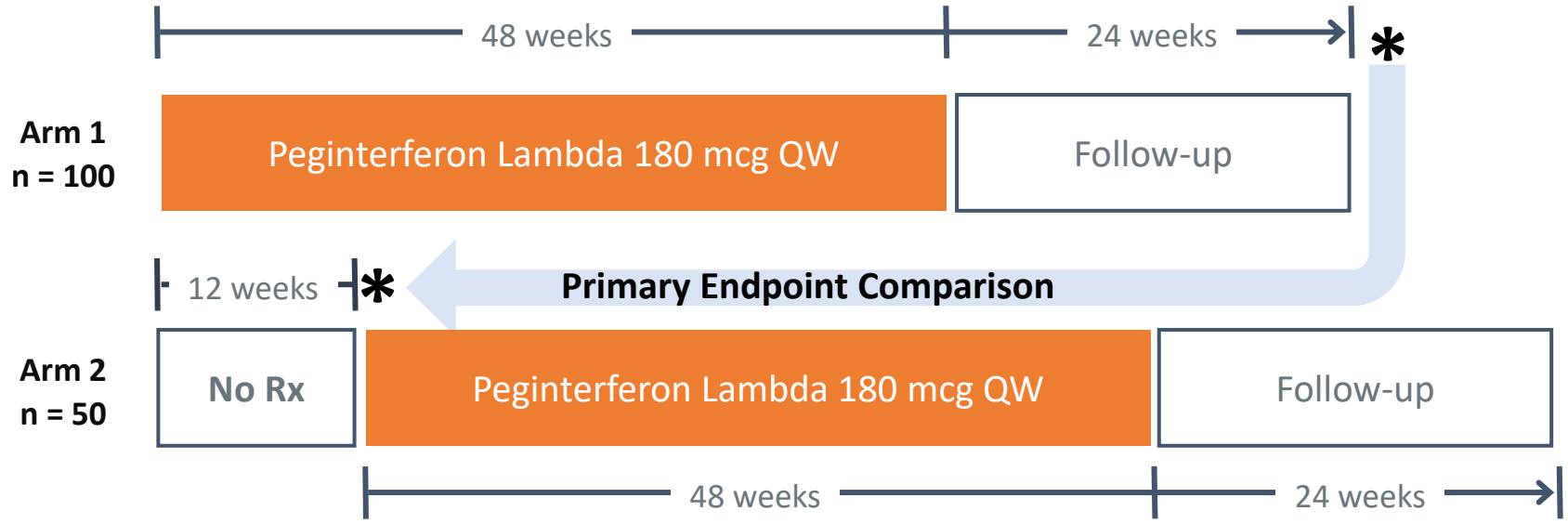
Durable Virologic Response (DVR)

DVR = 36% BLQ at 24 Weeks Post-Treatment with Lambda 180 μg



Etzion et al. Hepatology 2023

PEGINTERFERON LAMBDA PHASE 3 STUDY OF HDV



***Primary Endpoint:** DVR (Arm 1) versus HDV RNA BLQ After 12 Weeks No TRx (Arm 2)

DVR (Durable Virologic Response) = Below the Limit of Quantification (BLQ) at 24 Weeks Post-Treatment

DATA SUMMARY

Patient Disposition	
Randomized (Arm 1/2)	157 (104/53)
Dosed (Arm 1/2)	141 (103/38)
Completed Study	4
METAVIR F3	48 (30.6%)
METAVIR F4	48 (30.6%)
Baseline F4 and platelets<150,000	24 (15.3%)

Rx Discontinuations and SAEs	
Discontinued	22 (15.6%)
Hepatobiliary TEAEs	18 (12.8%)
Withdrew Consent	4 (2.5%)
Hy's Law Cases	24 (17%)
Jaundice Cases	3 (2.1%)
Ascites*	4 (2.8%)

*All cases occurred between W4-W12 and in patients with F3/4

Multivariate Logistic Regression for Development of Hy's Law and/or Jaundice/Ascites

Procedure	Variable	P-value
backward	GGT	0.0041
	PLAT	0.0082
forward	GGT	0.0041
	PLAT	0.0082
stepwise	GGT	0.0041
	PLAT	0.0082

PegIFN lambda: Lessons learned

- Lambda exerts anti viral activity against HDV through mechanisms that are not identical to IFN-Alfa
- Patients with low baseline viral load and a monophasic kinetic response respond more favorably to Lambda
- Lambda is highly tolerable but is associated with increased incidences of jaundice and/or ALT flares
- Hepatobiliary TEAEs associated with several cases of decompensation led to premature termination of LIMT-2 Phase 3 Clinical Trial
- Lambda Limit 2 terminated prematuraly for safety concerns (how to rescue)
    - Review carefully safety: related to patients severity or DILI
    - Independent expert panel to meticulously reviewed the data
    - Large data base for safety for IFN Lambda

What have we learned from the Lonafarnib and pegIFN lambda trials?

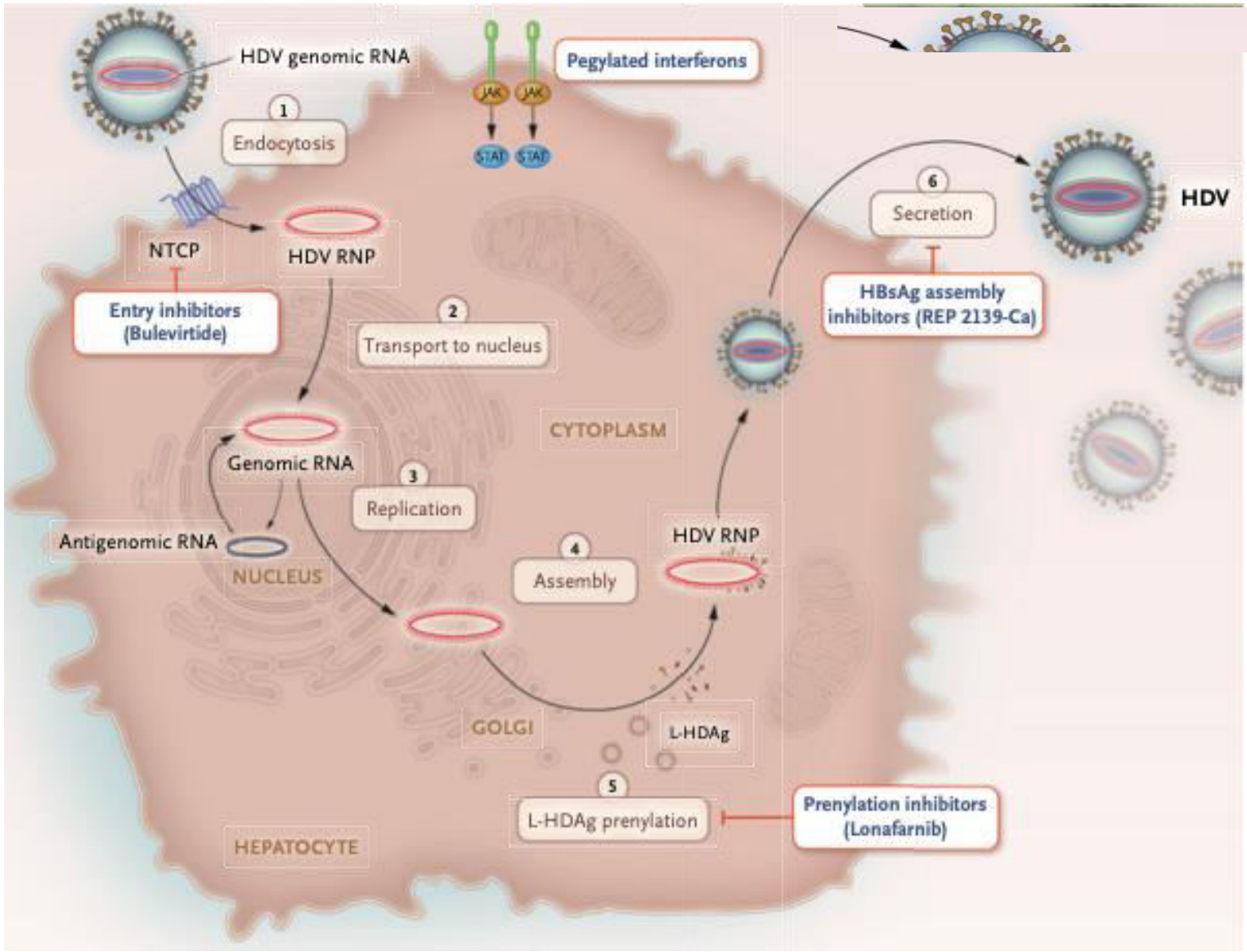
pegIFN lambda

1. Mode of Action
2. Results
3. Lessons learned

Lonafarnib

1. **Mode of Action**
2. **Results**
3. Lessons learned

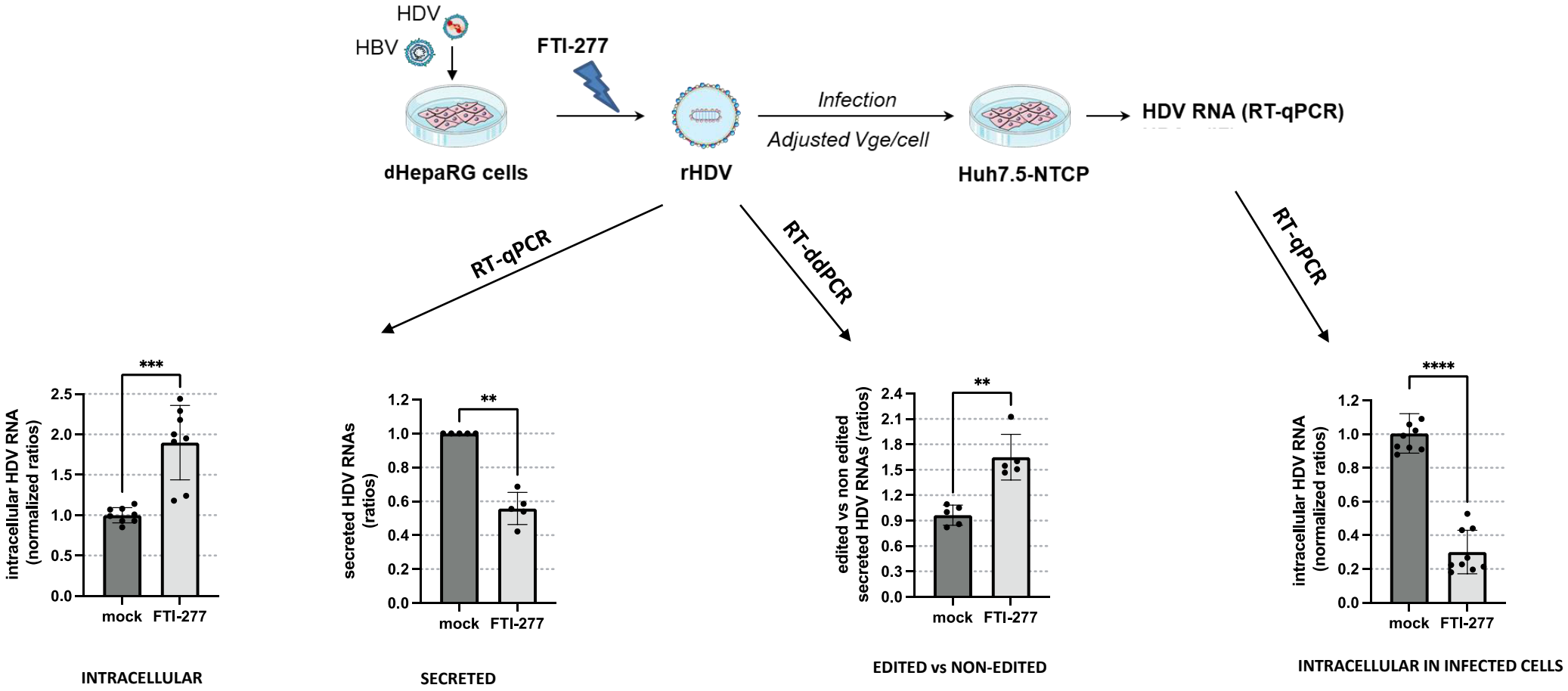
HDV replication cycle and targets for drug development



1. Endocytosis: HDV binds to NTCP,
2. Transport to the nucleus.
3. Replication of HDV genomic RNA into the HDV antigenome in the nucleus.
4. Assembly of the neosynthetized HDV ribonucleoprotein (RNP) in cytoplasm.
5. Farnesylation of the C terminal in L-HDAg;
6. Secretion

Asselah & Rizzetto; N Engl J Med. 2023; 389 (1):58-70.

Lonafarnib: Mode of action

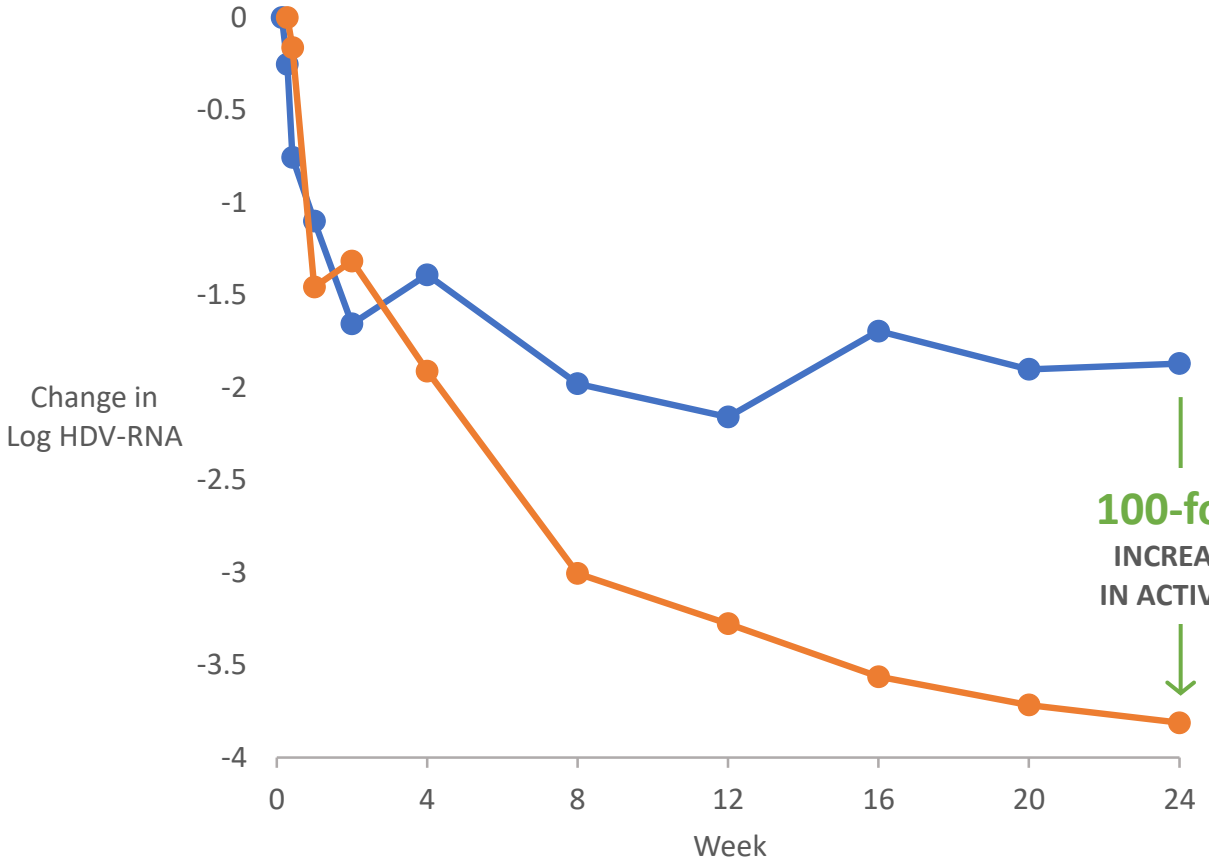


- Farnesyl transferase inhibitors including lonafarnib and FTI-277 **induce an accumulation of intracallular HDV RNA and inhibits HDV secretion**
- Lonafarnib and FTI-277 treatment modulate the ratio between **edited and non-edited HDV genome** that are secreted, leading to a **decrease in the infectivity of HDV viral particles**

Verrier et al., Antiviral Res 2022
Bac, Lucifora et al., Antiviral Res 2023

Lonafarnib Phase 2 Data

TWO LONAFARNIB-BASED REGIMENS IDENTIFIED FOR REGISTRATION



LNF 50 mg BID + RTV (N=12)

LNF 50 mg BID + RTV + PEG IFN-alfa-2a (N=4)

COMPOSITE ENDPOINT

≥ 2 log Decline HDV-RNA + ALT Normalization

29%

63%

Tarik Asselah – HDV-2022-19/25

*Yurdaydin et al, J Hepatology **2018**, Phase 2 LOWR 2 Study, Abstract #PS-161*

Lonafarnib Phase 3 Data

D-LIVR Phase 3 Clinical trial

Objective

To evaluate the safety, tolerability, and efficacy of LNF boosted with RTV with or without pegIFN Alfa for treatment of chronic HDV infection compared to placebo

Primary Endpoint at Week 48

≥ 2 log decline in HDV RNA
+
Normalization of ALT

Secondary Endpoint at Week 48

No worsening in fibrosis
+
≥ 2-point in Ishak HAI Score

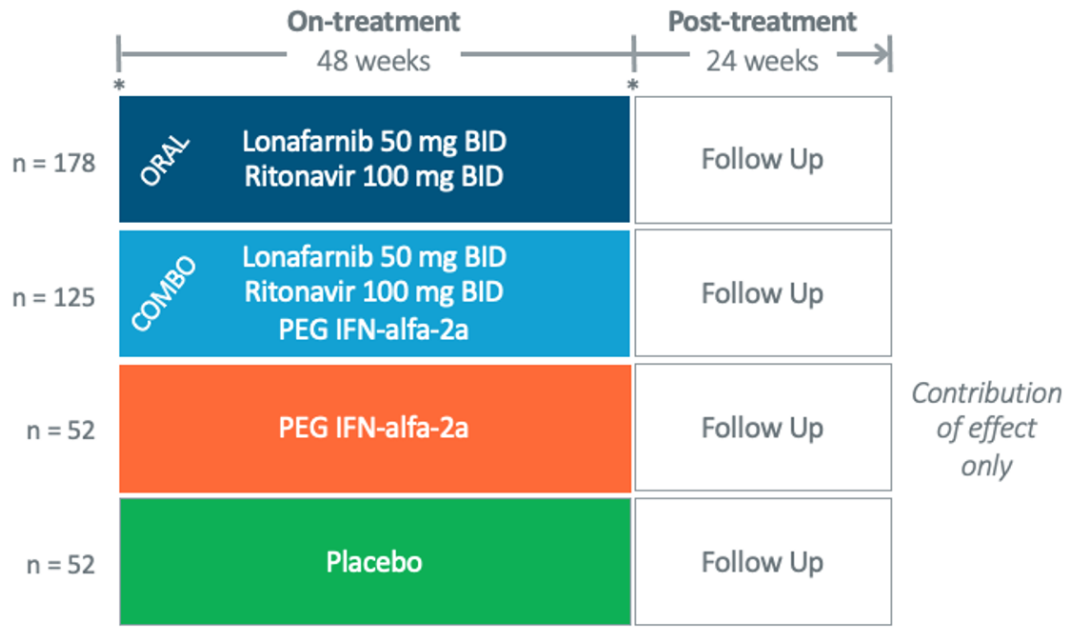
Key Inclusion criteria

CHD with compensated liver disease

HDV RNA > 500 IU/mL

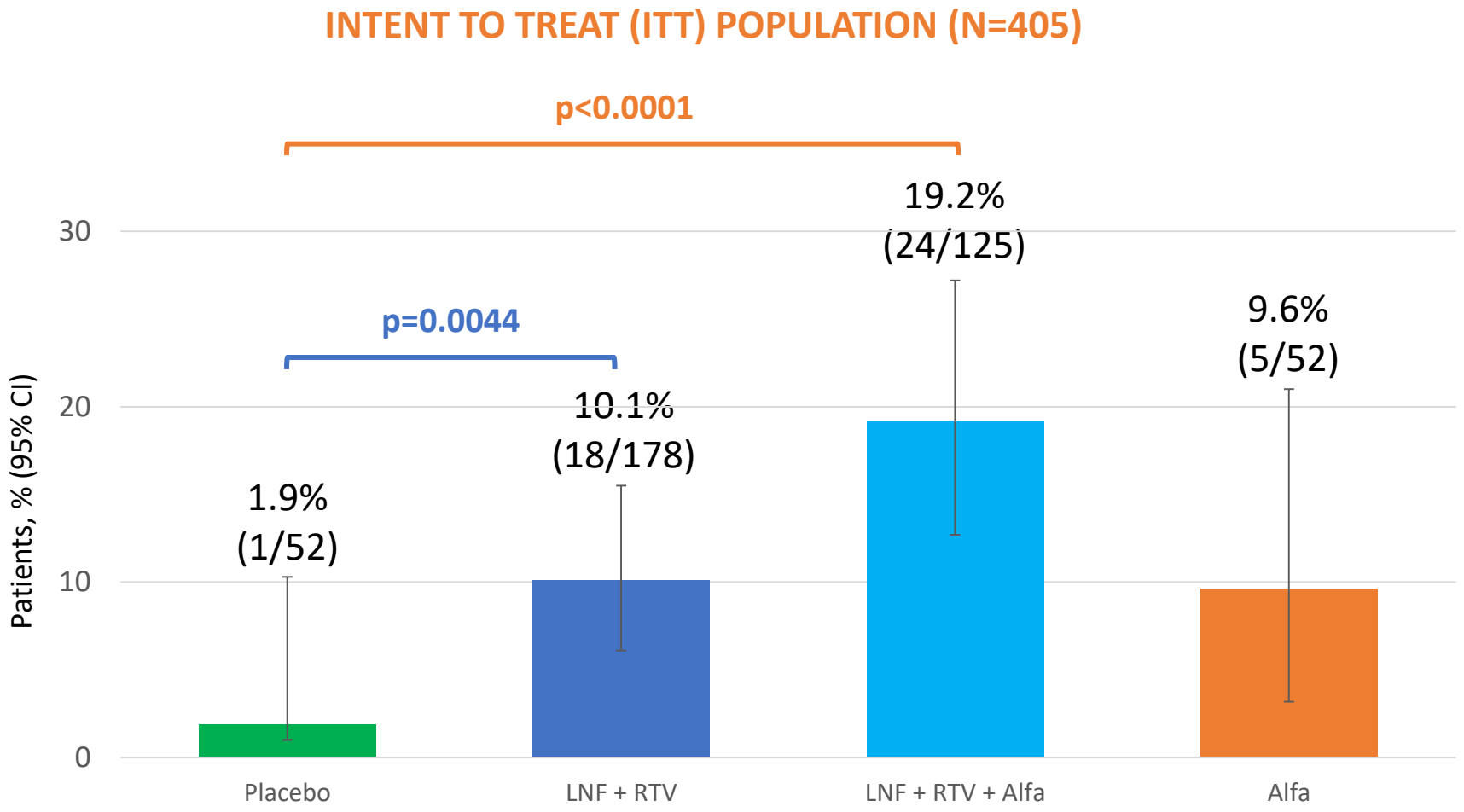
ALT > 1.3X < 10X ULN

HBV DNA < 20 IU/mL



Etzion & Hamid et al. EASL 2023

Primary Endpoint: Composite Response at Week 48

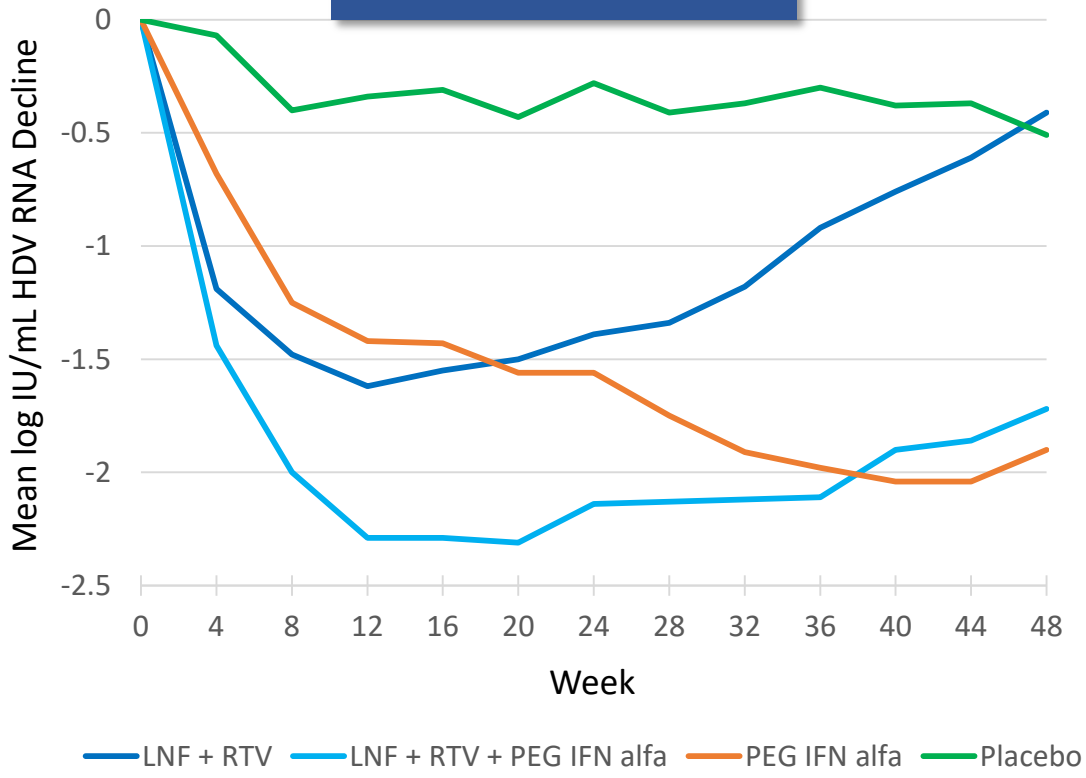


Etzion & Hamid et al. EASL 2023

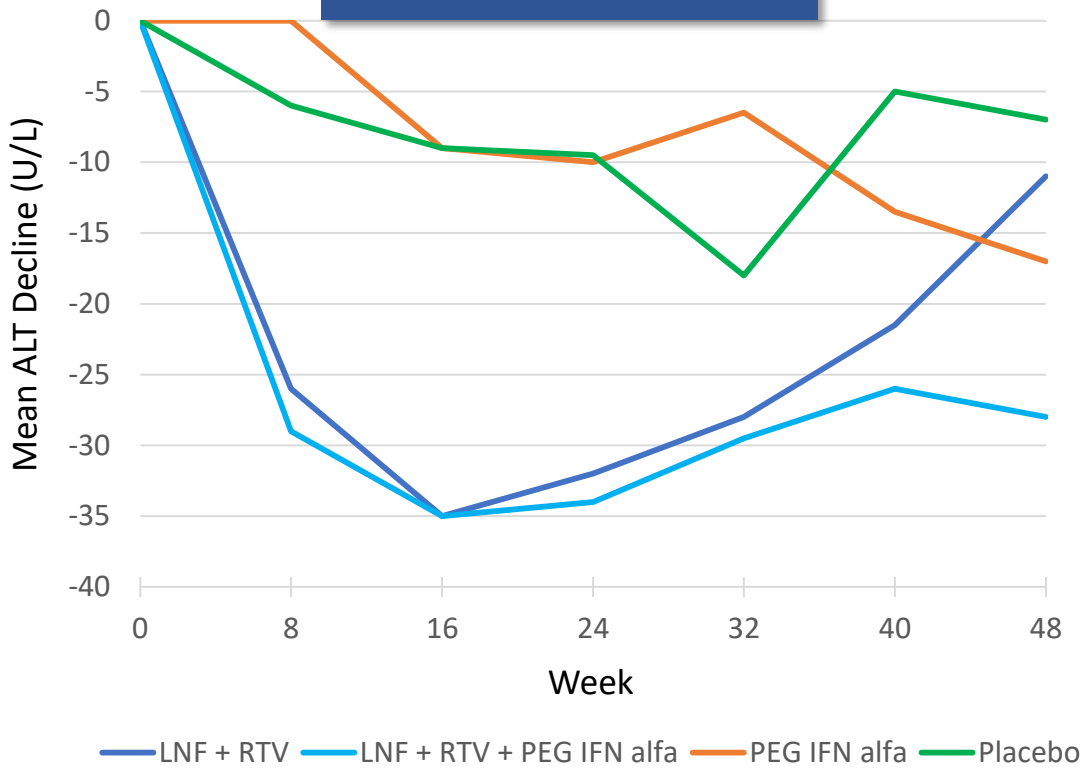
Mean HDV RNA and ALT Decline Through End of Treatment

INTENT TO TREAT (ITT) POPULATION (N=405)

Virological Response:
HDV RNA Decline



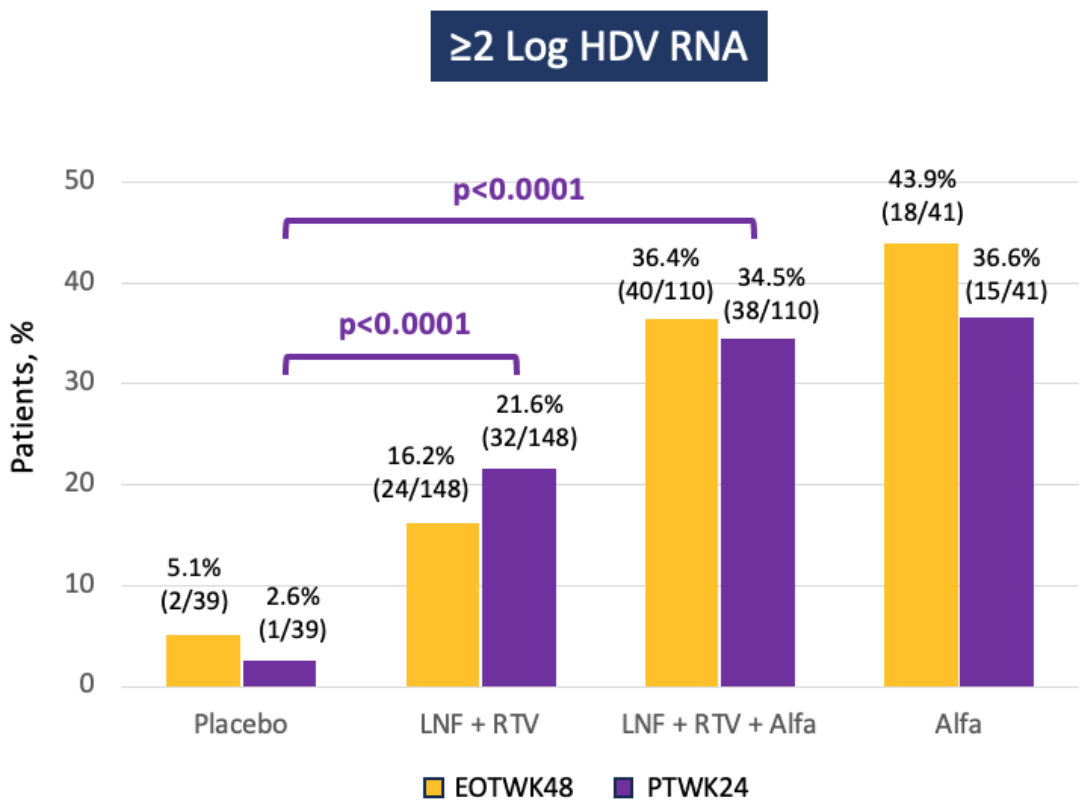
Biochemical Response:
ALT Decline

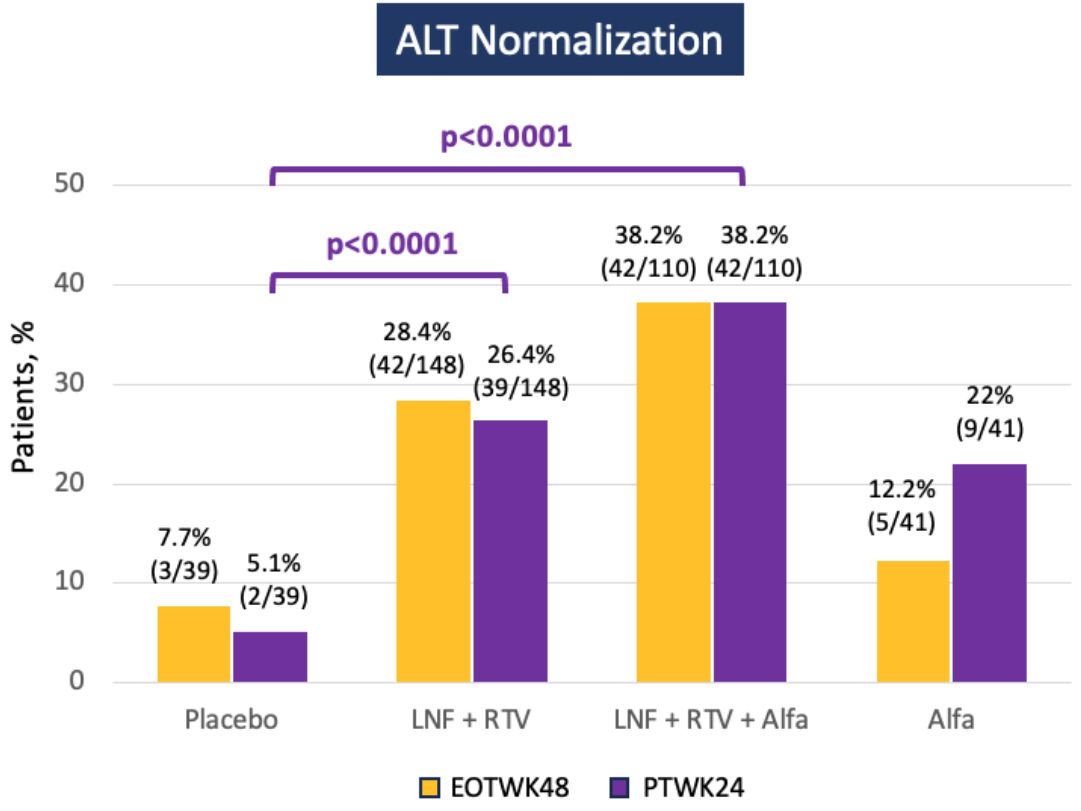


Etzion & Hamid et al. EASL 2023

End of Study Results: Virological & Biochemical Components

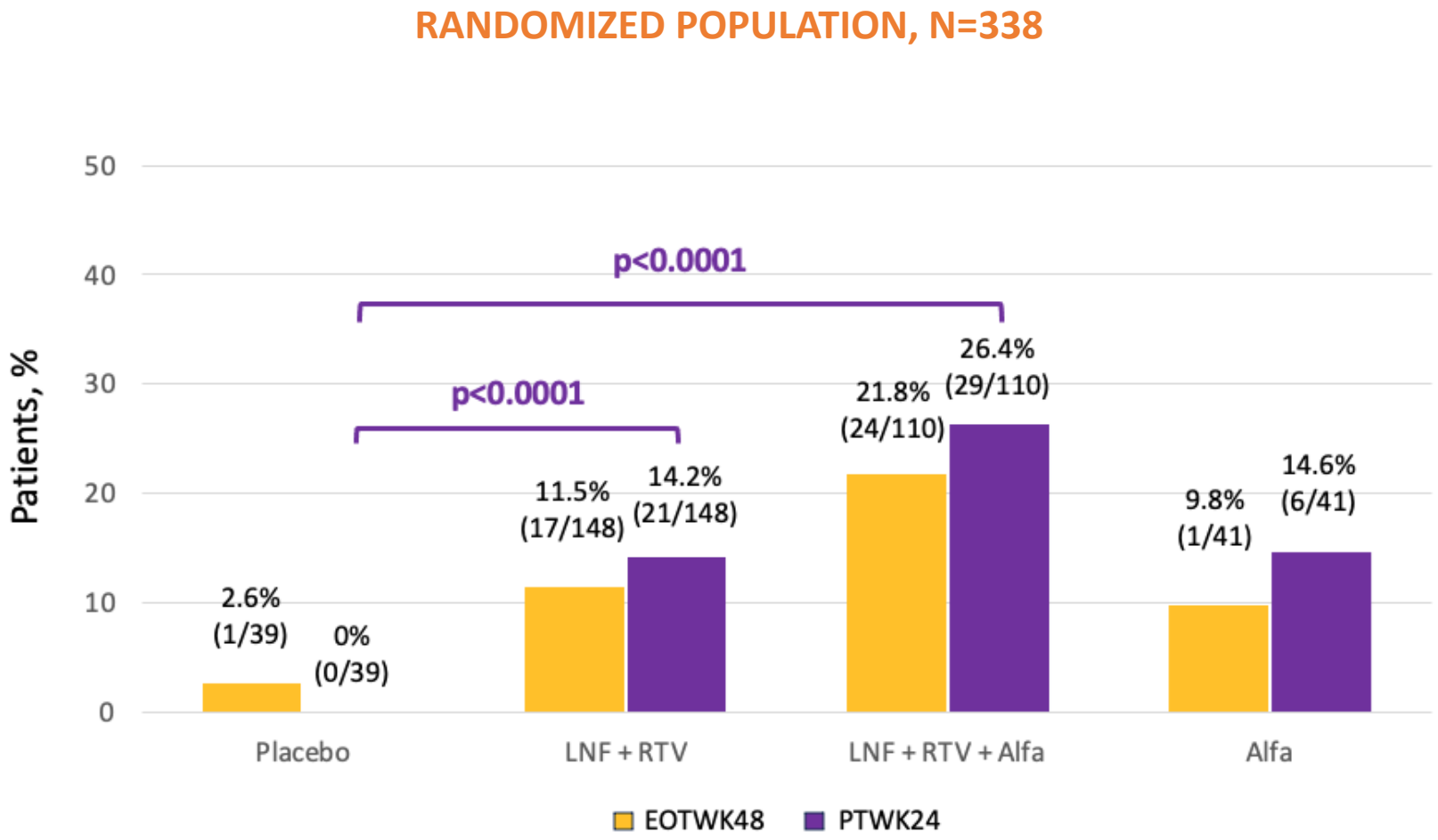
RANDOMIZED POPULATION, N=338





Etzion & Hamid et al. EASL 2023

End of Study Results: Composite Endpoint



Etzion & Hamid et al. EASL 2023

Lonafarnib: Lessons learned, how to go forward 1/2

1. **D-LIVER**

- Well performed study
- Largest study on HDV
- High retention rate
- Few baseline features are associated with EOT response
- Off-treatment responses are the major driver of durable response

Lonafarnib: Lessons learned, how to go forward 2/2

2. Why Considering Lonafarnib

- Viral response in a proportion of patients
- Oral drug
- Finite duration of treatment
- ALT flare after the end of treatment (immune response ?)

3. How to move forward

- Review the all data
- Predictors of response
- Need for long-term data
- Combine with other drugs

FAILURE is SUCCESS in PROGRESS

- Albert Einstein