2015 8th PARIS HEPATITIS CONFERENCE

12 & 13 January 2015

PARIS - Palais des Congrès

## How to optimize current therapy for GT1 patients

# Shortened therapy with IFNa-based therapy

**Thomas Berg**

**Sektion Hepatologie**

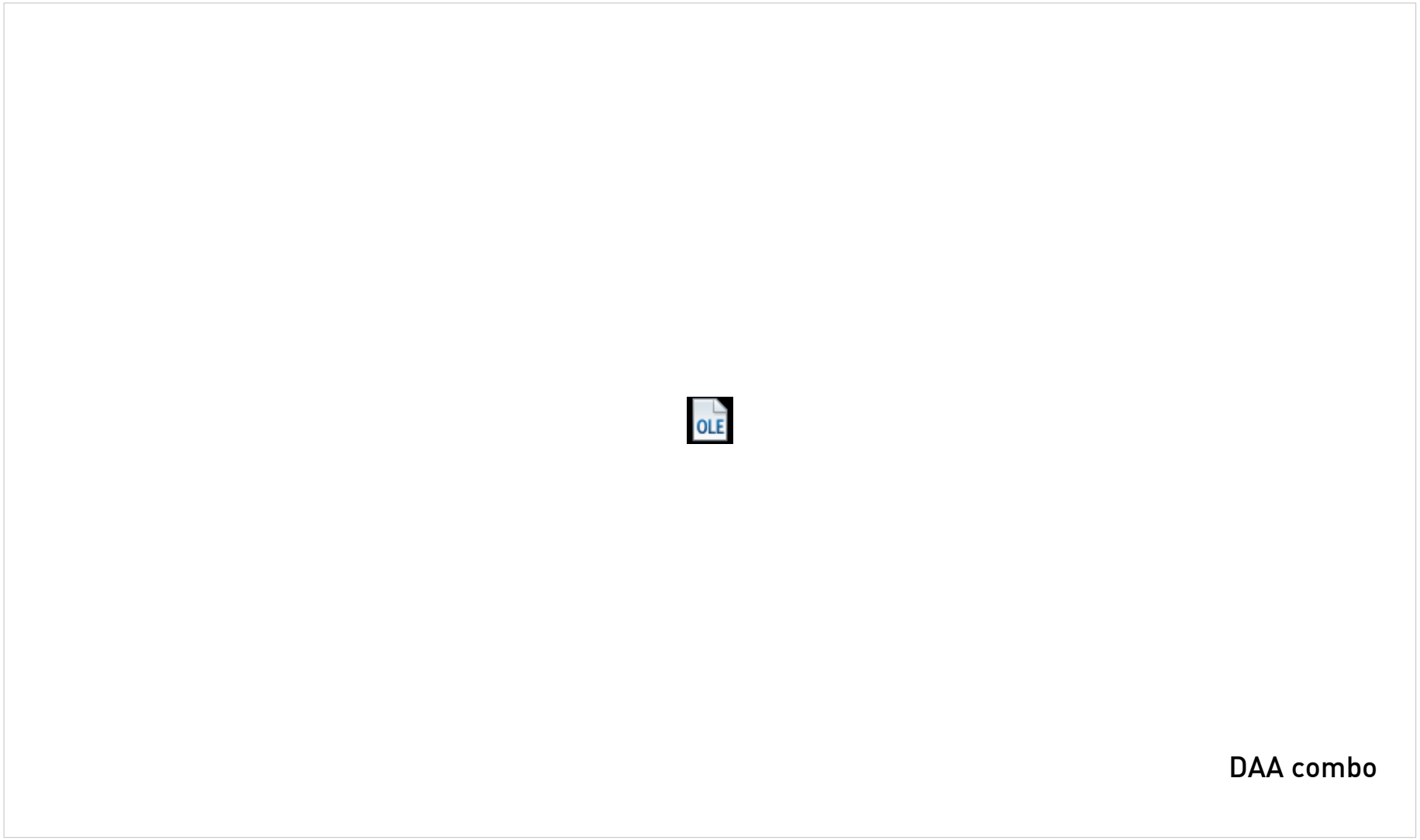
**Klinik und Poliklinik für Gastroenterologie und Rheumatologie**

**Leber- und Studienzentrum am Checkpoint, Berlin**

# Shortened therapy with IFNa-based therapy

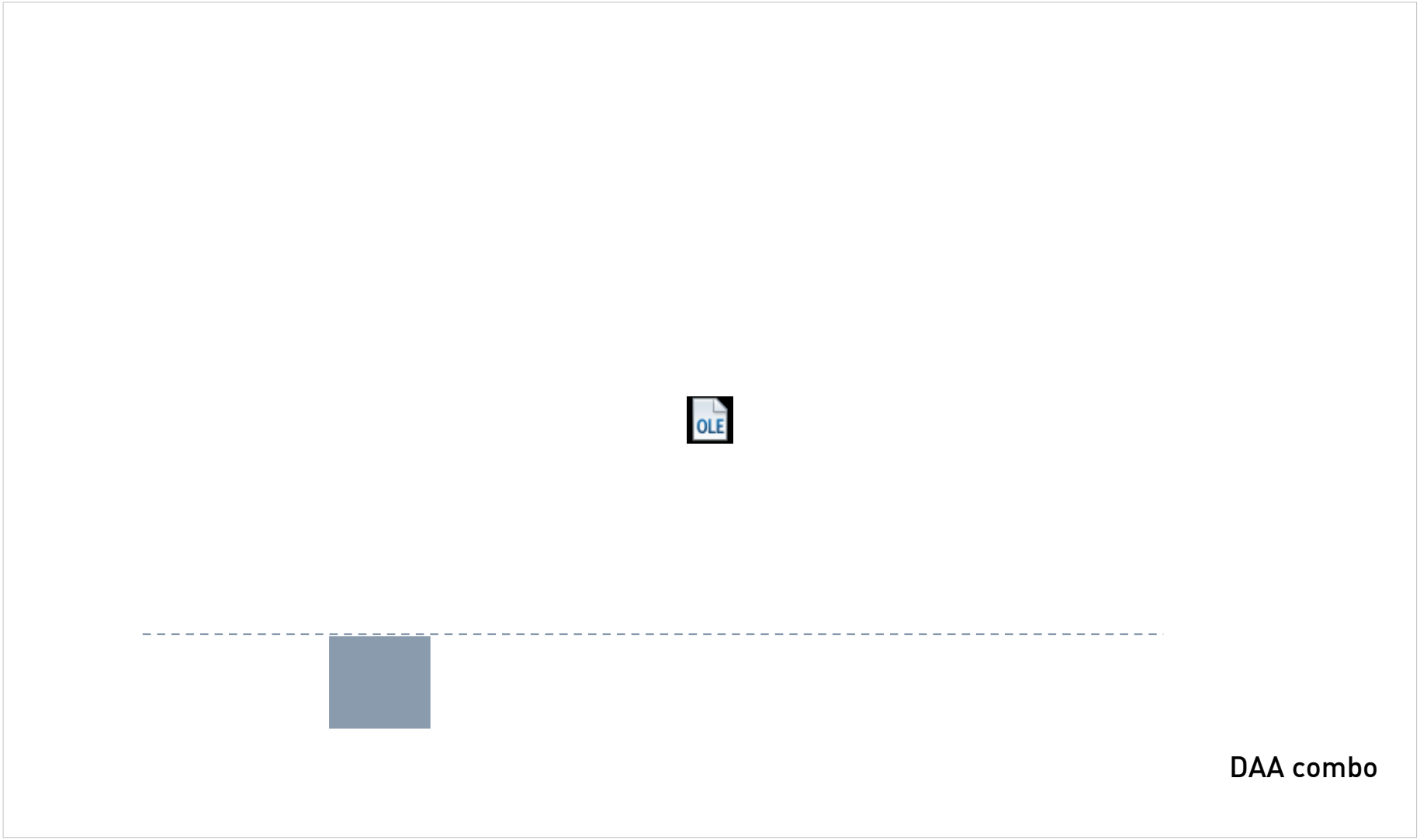
- The concept
  - Treatment individualisation
- Shortening PegIFNa/RBV dual combination therapy
  - Preconditions - in whom can tx be shortened
  - The effect of adding DAA
    - Low-barrier to resistance drugs (protease inhibitors)
    - High-barrier to resistance drugs (nucleosidic polymerase inhibitors)

# Observed cure rates in HCV-infected patients in relation to the effectiveness of the antiviral regimen



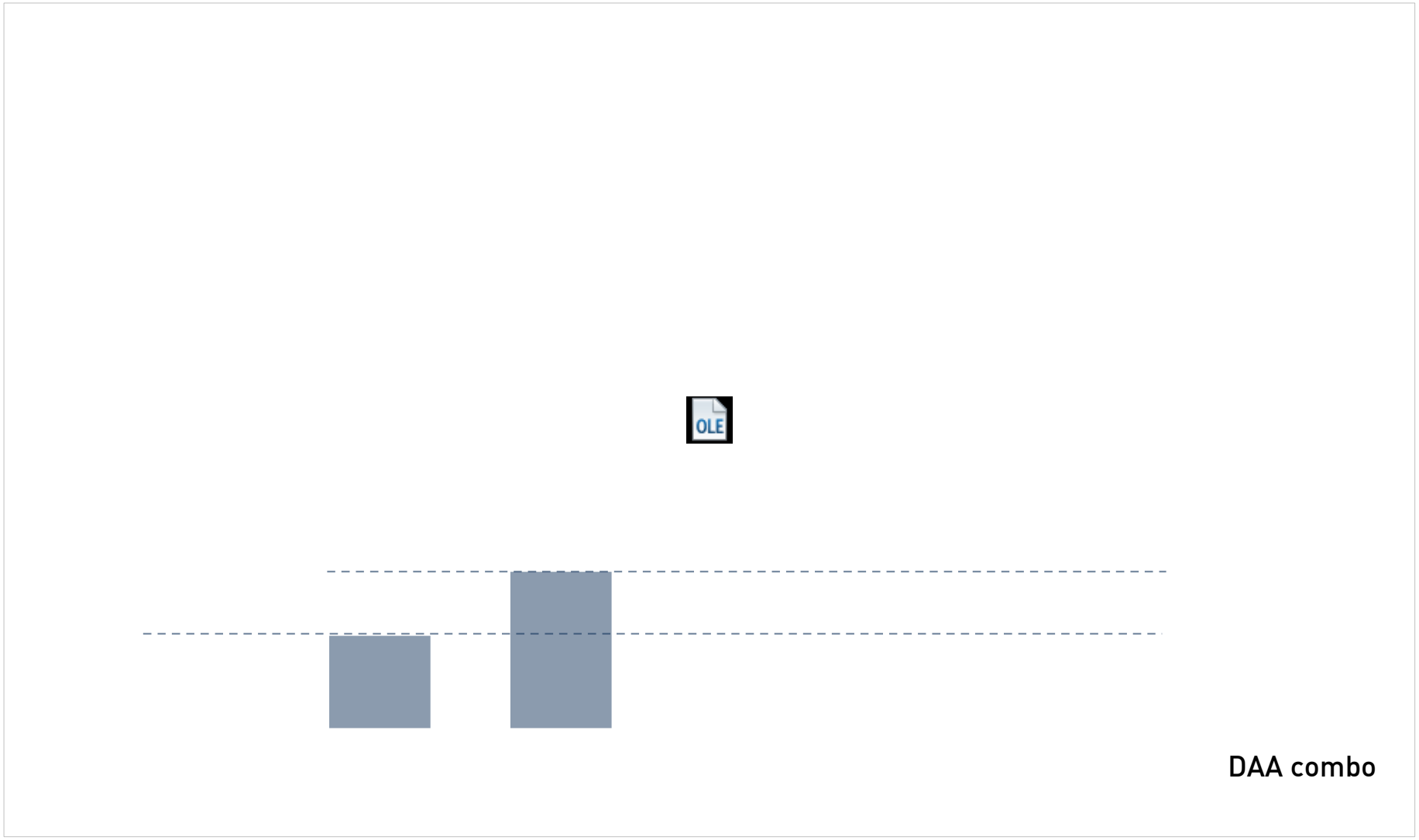

PI = protease inhibitor, NUC = nucleosidic polymerase inhibitor, DAA = direct acting antiviral drugs

# Observed cure rates in HCV-infected patients in relation to the effectiveness of the antiviral regimen



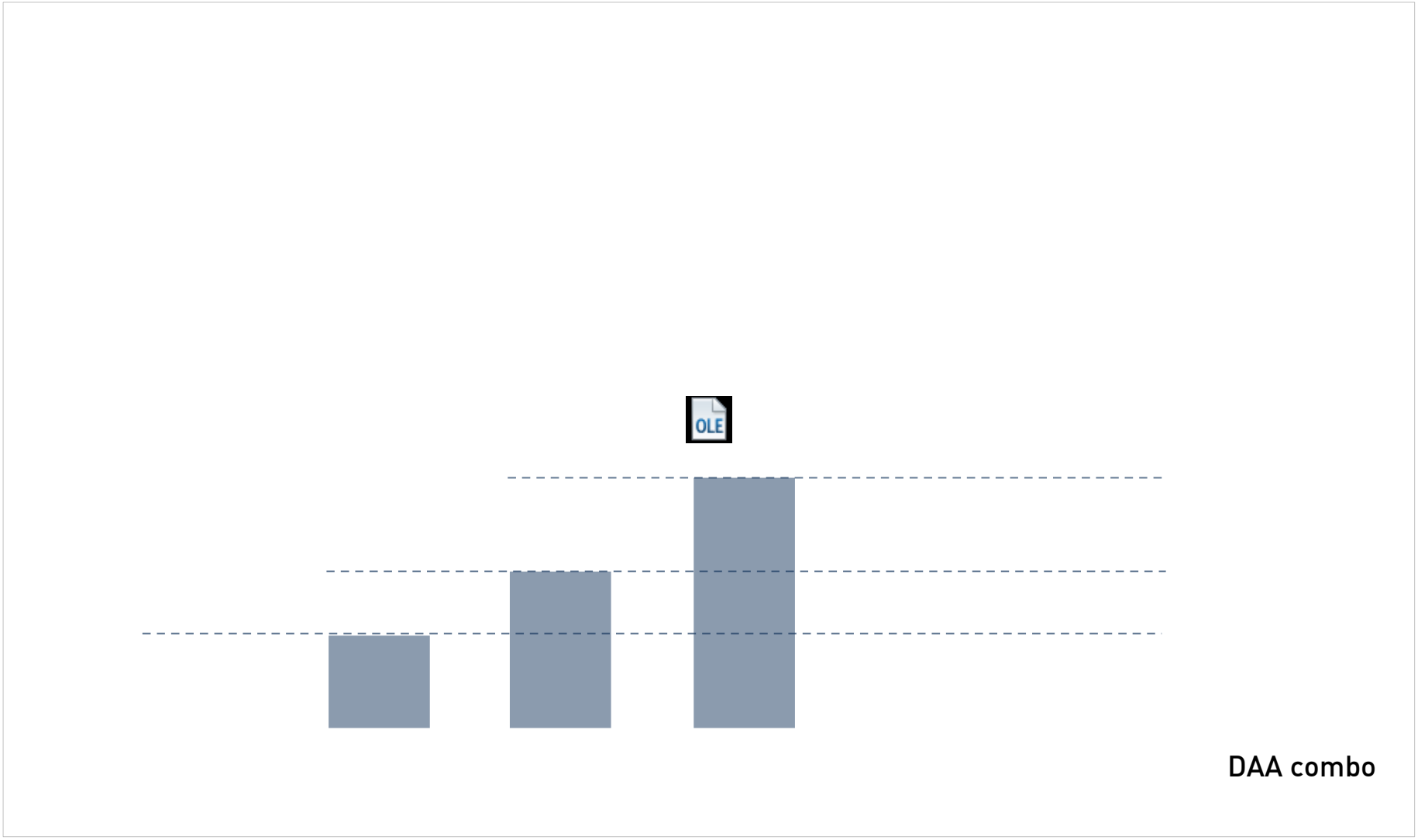

PI = protease inhibitor, NUC = nucleosidic polymerase inhibitor, DAA = direct acting antiviral drugs

# Observed cure rates in HCV-infected patients in relation to the effectiveness of the antiviral regimen



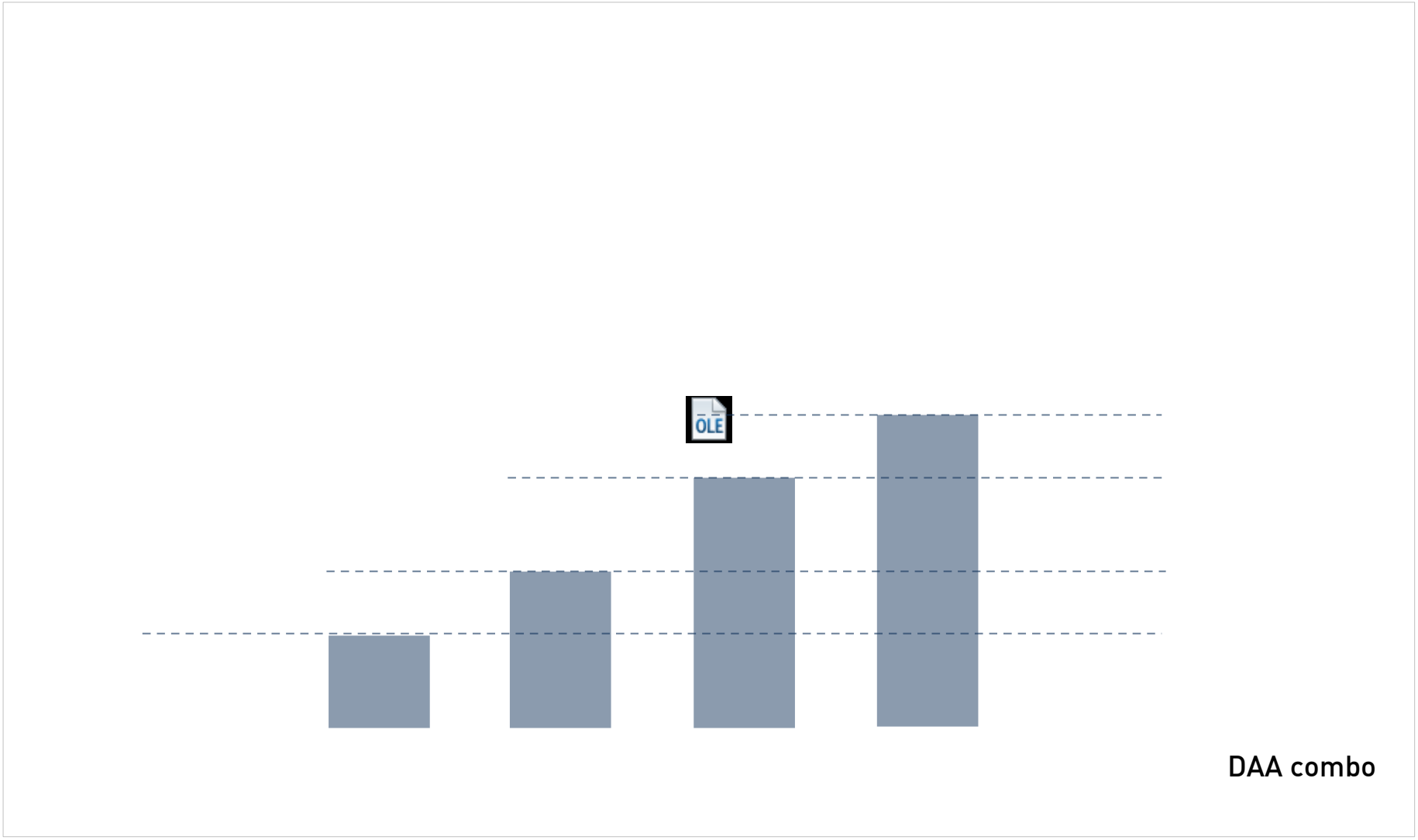

PI = protease inhibitor, NUC = nucleosidic polymerase inhibitor, DAA = direct acting antiviral drugs

# Observed cure rates in HCV-infected patients in relation to the effectiveness of the antiviral regimen



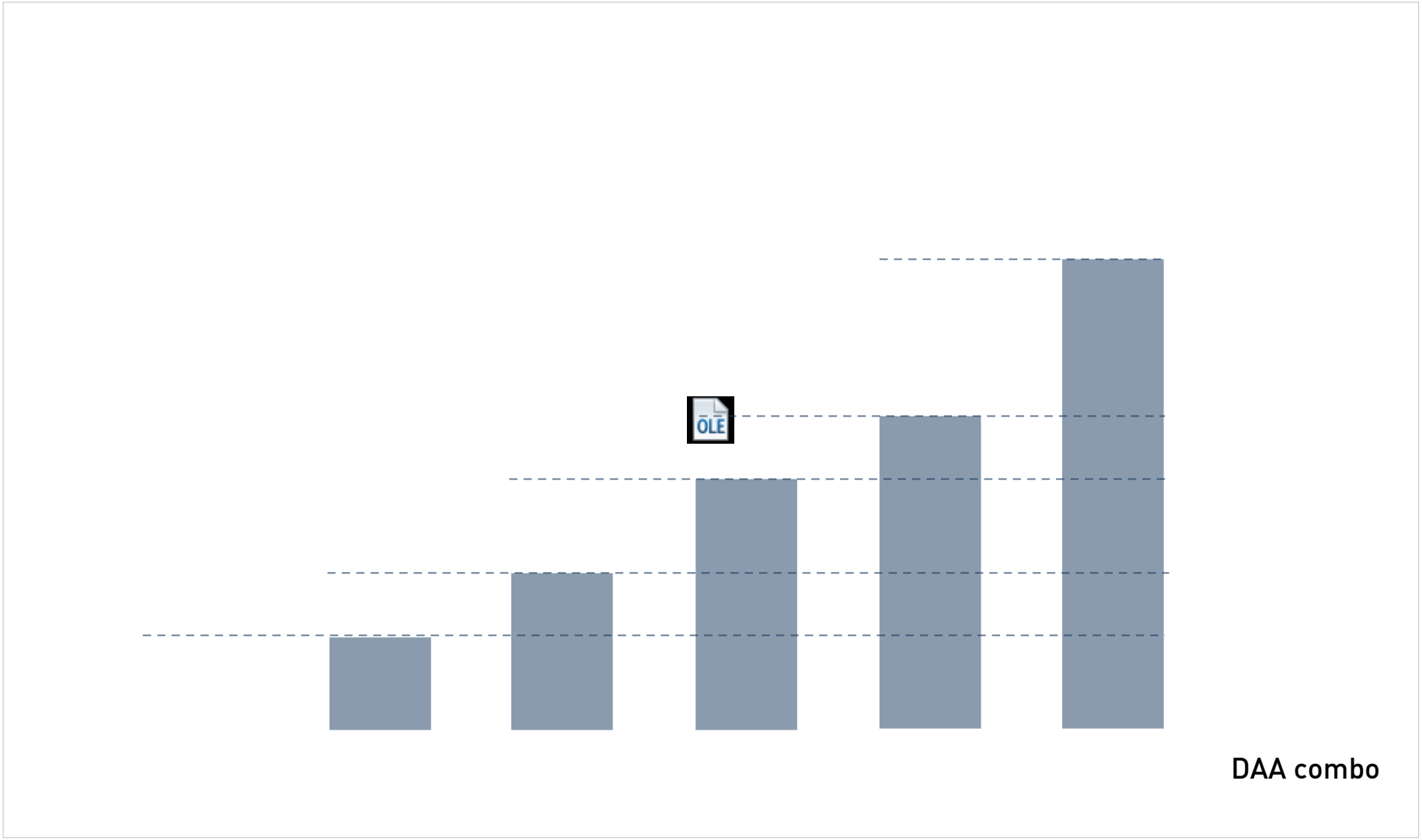

PI = protease inhibitor, NUC = nucleosidic polymerase inhibitor, DAA = direct acting antiviral drugs

# Observed cure rates in HCV-infected patients in relation to the effectiveness of the antiviral regimen




PI = protease inhibitor, NUC = nucleosidic polymerase inhibitor, DAA = direct acting antiviral drugs

# Observed cure rates in HCV-infected patients in relation to the effectiveness of the antiviral regimen




PI = protease inhibitor, NUC = nucleosidic polymerase inhibitor, DAA = direct acting antiviral drugs

# Individual likelihood of response

## Virologic factors

HCV genotype
level of replication
mutational pattern
(ISDR)
(HCV genetic mutations)

## Host factors

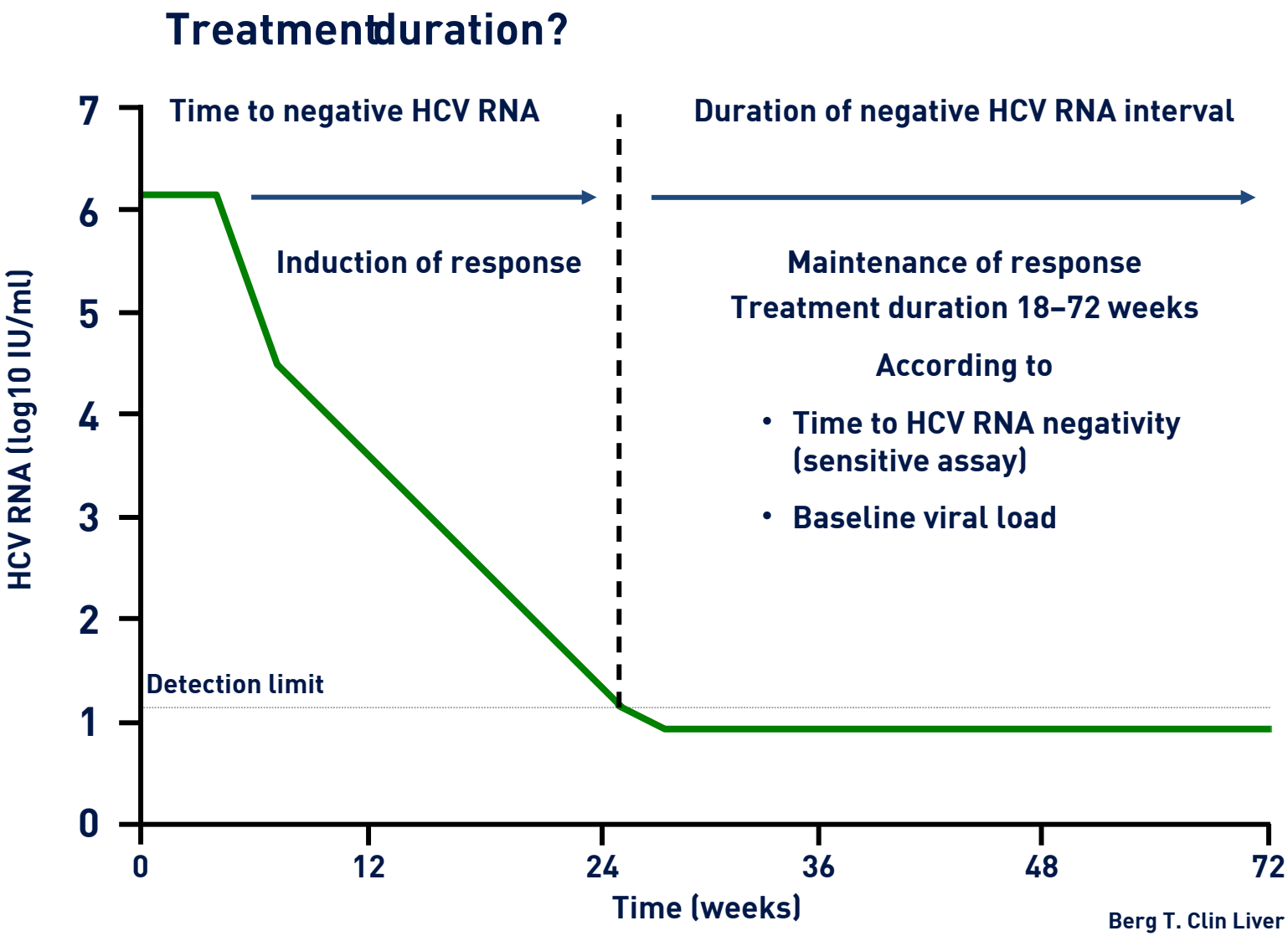
age
gender
stage of fibrosis
insulin resistance/steatosis
cholesterol/LDL levels
ALT levels
GGT levels
genetic polymorphisms

## Early viral kinetics

## Summarising the individual likelihood of response

Berg T. Clin Liver Dis 2008; 12: 507

# Concept of response-guided therapy (RGT)




Berg T. Clin Liver Dis 2008; 12: 507

Berg T et al. Hepatology 2009:50:369; Sarrazin C et al. Gastroenterology 2011;141:1656

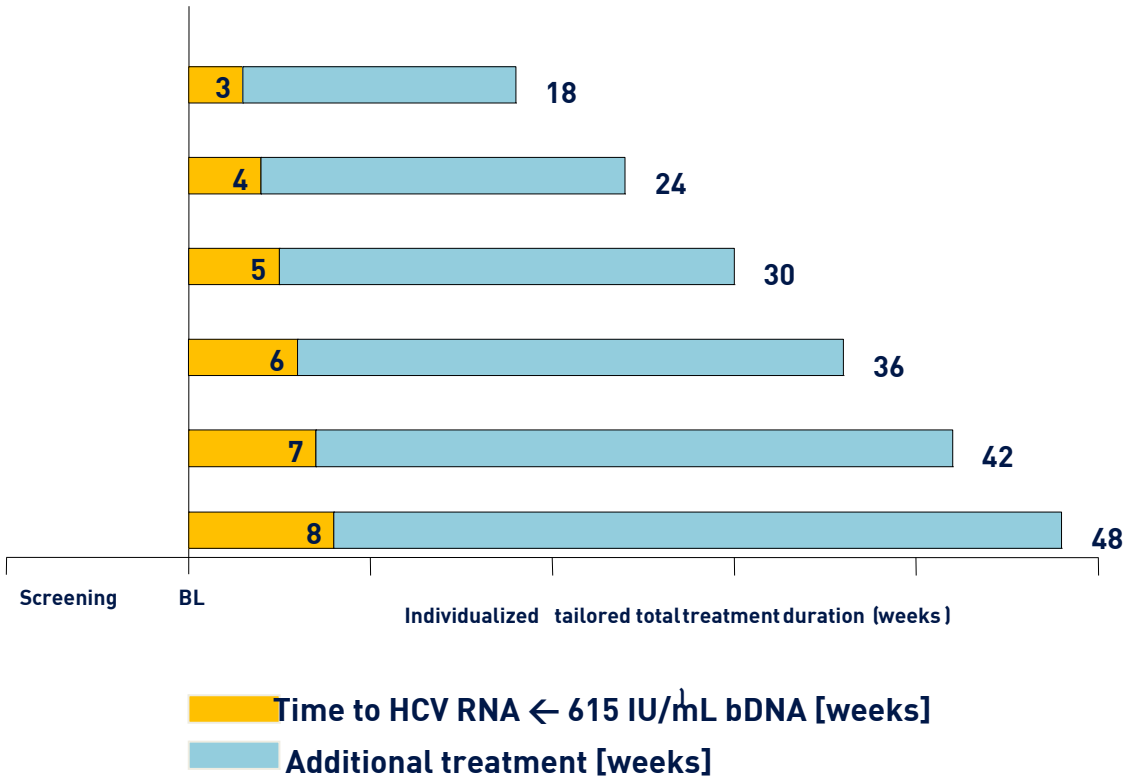
# Individualization of Treatment Duration
# INDIV-1 Study

## PEG-IFN alfa 2b / Ribavirin, naive HCV type 1, n=433

randomized,
controlled study

**A**
n=225
PEG-IFNa-2b 1.5 µg/kg
+ Ribavirin 800-1400 mg/da
for 48 weeks

**B**
n=208
PEG-IFNa-2b 1.5 µg/kg/
+ Ribavirin 800-1400 mg/da
for 18-48 weeks




Berg T et al. *Hepatology* 2009; 50: 369-377.

# INDIV-1 Study - Summary

- **HCV RNA Assay:**

**Definition of virologic response by highly sensitive assay (TMA ←10IU/ml instead of bDNA ←615 IU/ml)**

- **Baseline viral load:**

**Shortening of treatment duration is possible if RVR and low baseline viral load (←800.000 IU/ml)**

**High baseline viral load (HCV-RNA ↗ 800.000 IU/ml): general higher relapse rates**

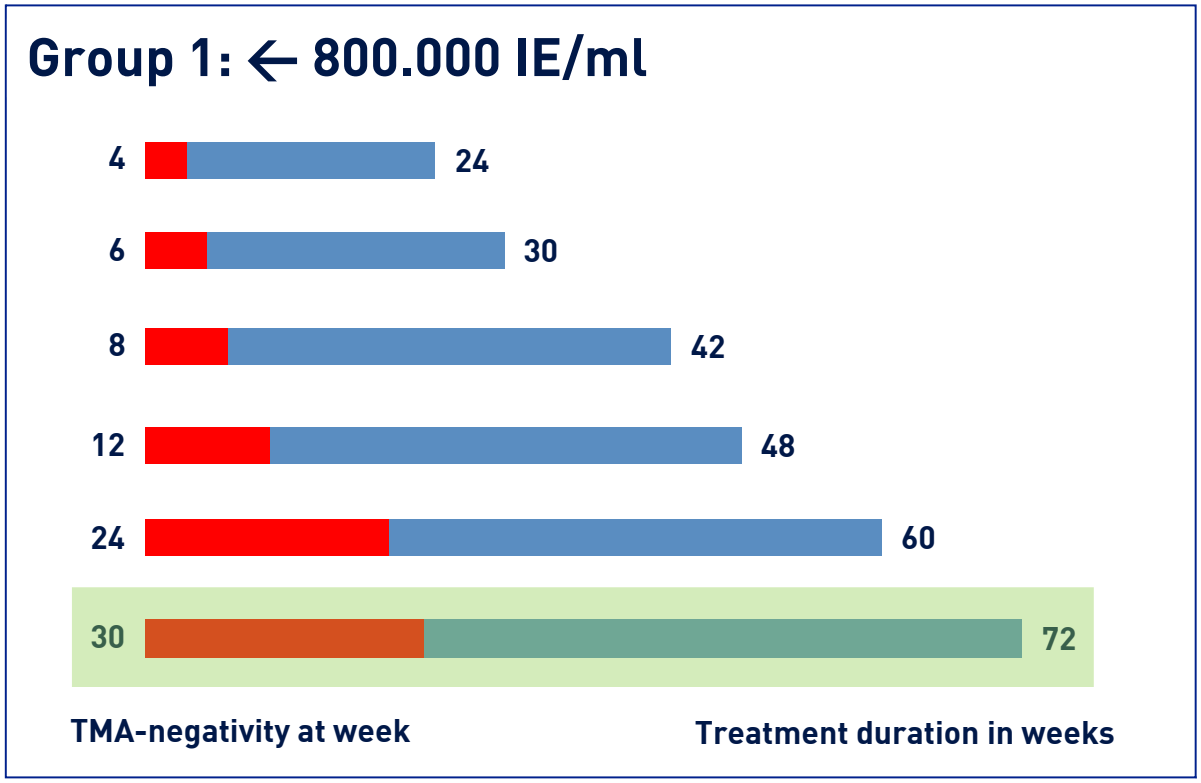
- **Prolongation of treatment duration:**

**HCV-RNA negative after week 12 was associated with high relapse-Rates (35%)**

Berg T et al. *Hepatology* 2009; 50: 369-377.

# INDIV-2 Study
## Study design (prospective multi center study)

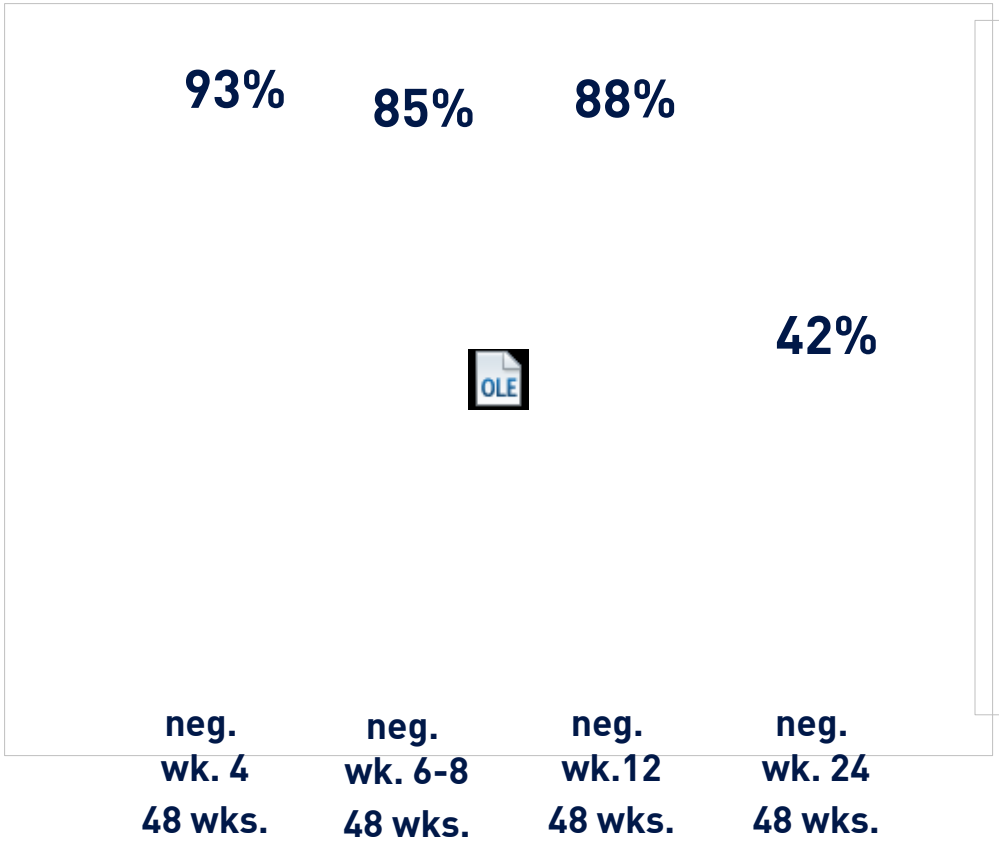
### PEG-IFN-α2b 1,5µg / Ribavirin 800-1400mg, treatment naïve, HCV Genotype 1, n = 398



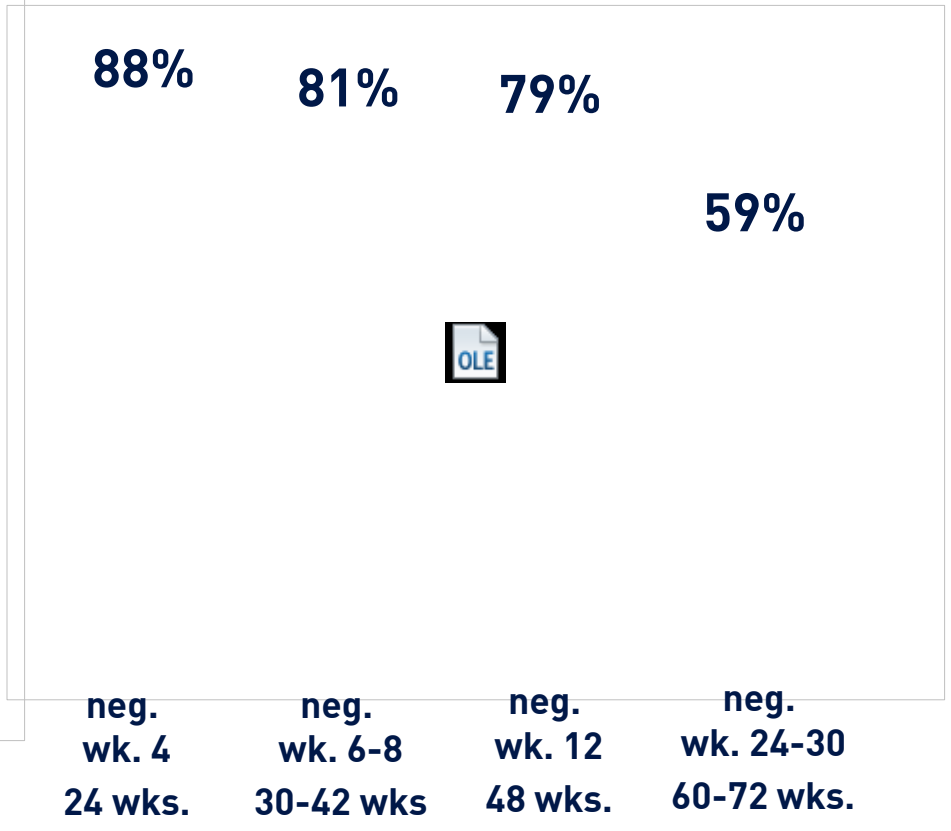

Sarrazin C et al. Gastroenterology 2011;141:1656

# Comparison of SVR from INDIV-2 vs. Control

## Patients with low baseline viral load




Control group (SOC 48 wks)
Low baseline viral load (LVL)
←800.000 IU/ml

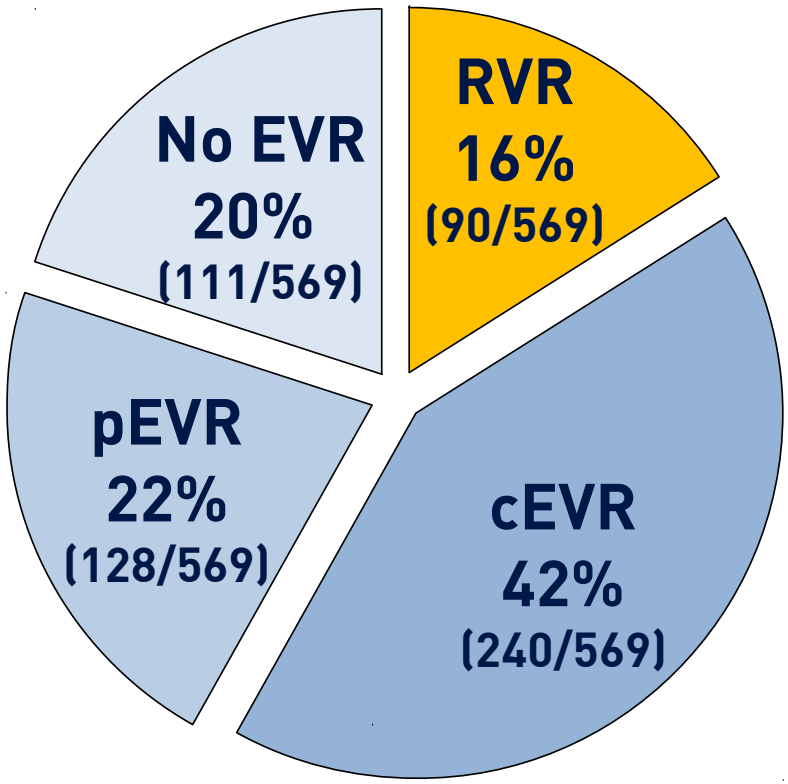



INDIV-2
Low baseline viral load (LVL)
←800.000 IU/ml

Sarrazin C et al. Gastroenterology 2011;141:1656

# On-treatment response rates on dual therapy

**PEG-IFNa-2a 180 μg/wk plus Ribavirin 1000/1200 mg/day for 48 weeks; n=569**



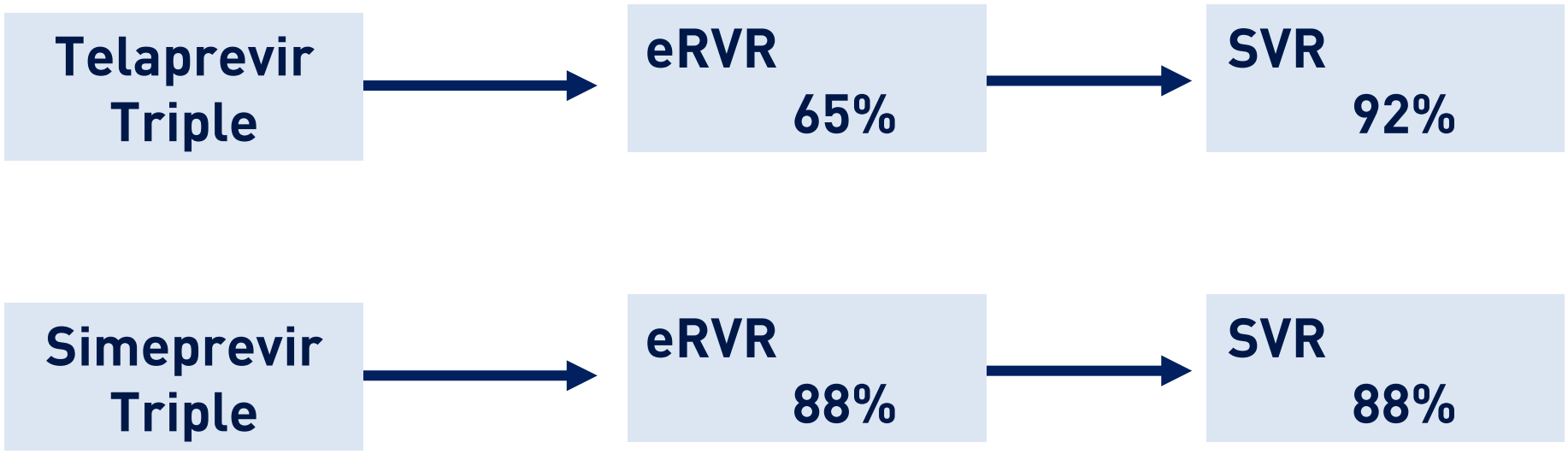

RVR = rapid virologic response at week 4
cEVR = complete virologic response at week 12
pEVR = partial virologic response with → 2 log decline at week 12

Marcellin P et al. AASLD 2007; Abstract 1308

**Increasing RVR rates by adding a DAA**

**increasing the number of patients who can be cured by a shortened 24 week regimen**

## Response-guided concept of first and second generation PI triple regimen in HCV type 1 treatment naive (Phase III studies)



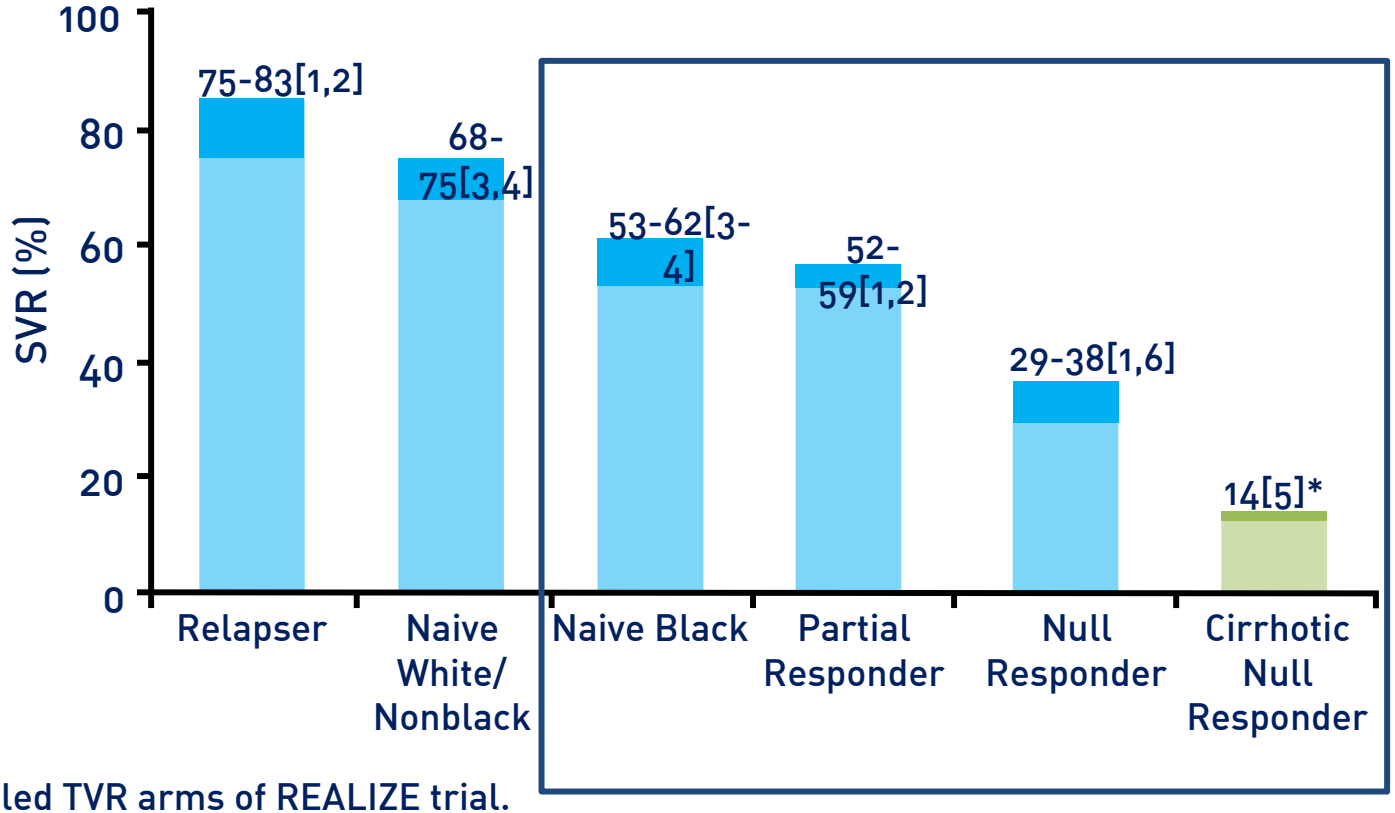

**24 weeks treatment duration in most patients**

PI = protease inhibitor
eRVR = extended rapid virologig response week 4 and 12

ILLUMINATE: Sherman KE et al. N Engl J Med 2011; 365: 1014
QUEST-1: Jacobson I et al. Lancet 2014; 384:403
QUEST-2: Manns M et al. Lancet 2014; 384:414

# Susceptibility to PegIFNa/RBV is key in low barrier to resistance DAA triple regimen

# IFNa-based triple therapy with low barrier to resistance DAA – Efficacy depends on IFNa responsiveness



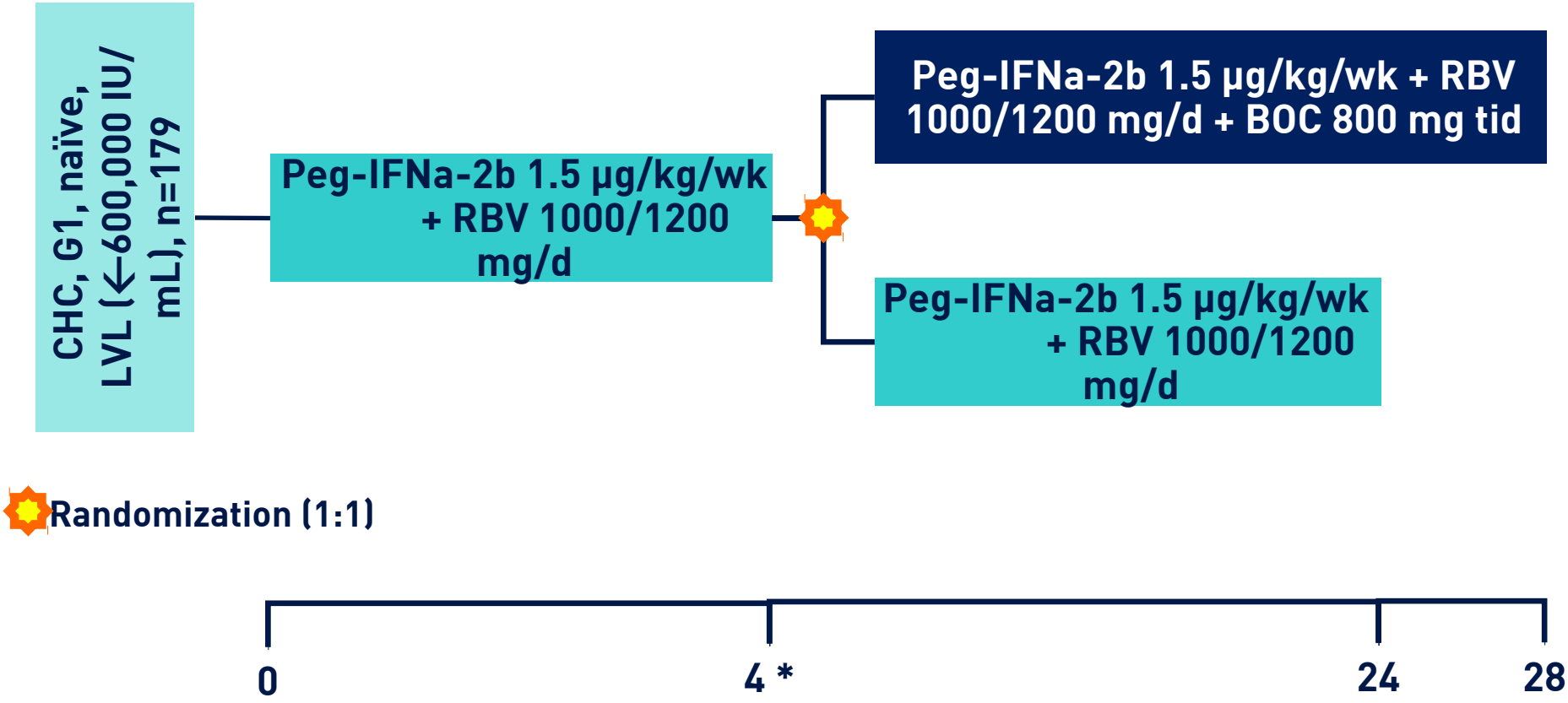

*Pooled TVR arms of REALIZE trial.

1. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.
3. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 4. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
5. Zeuzem S, et al. EASL 2011. Abstract 5. 6. Vierling JM, et al. AASLD 2011. Abstract 931.

# Do we need DAA add-on in RVR patients

# the “lead in concept”

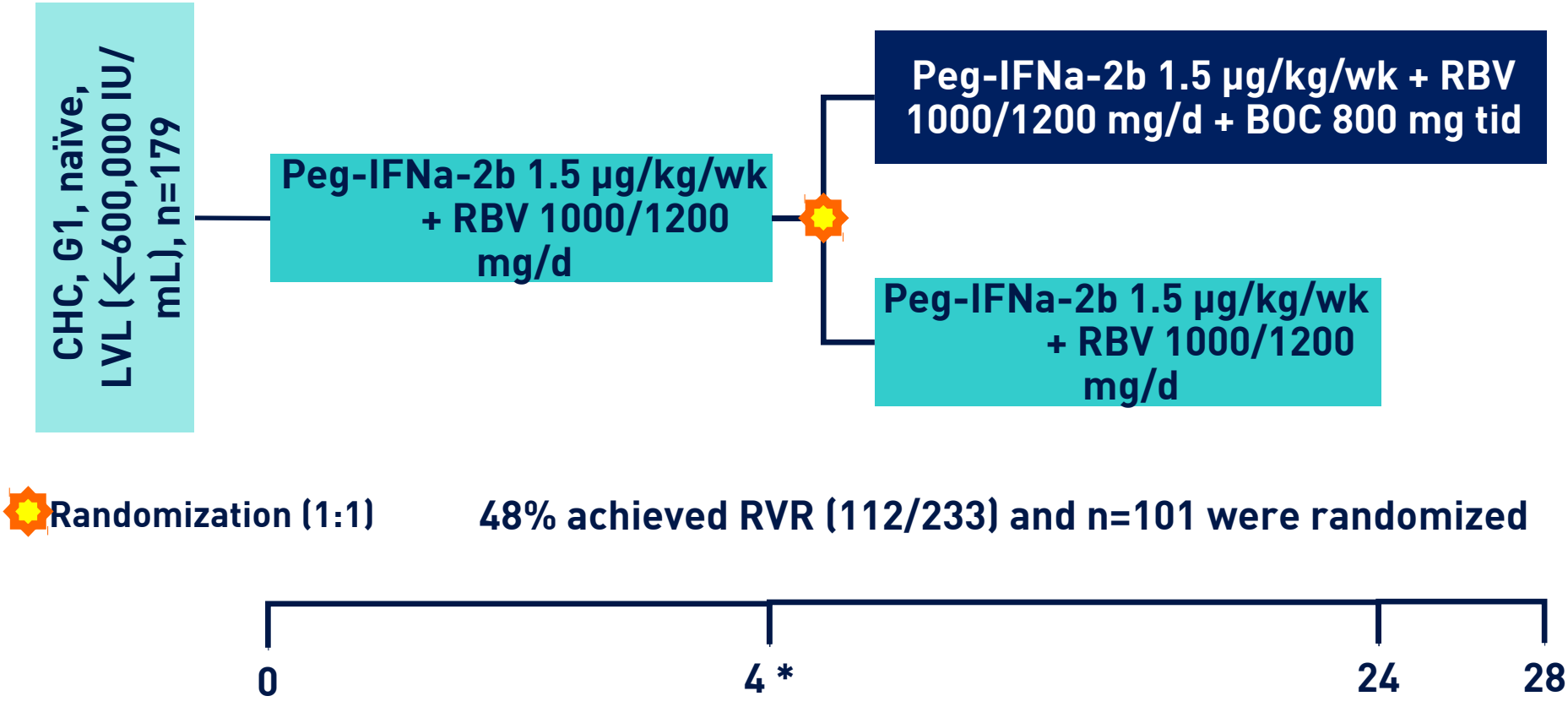
# Peg-IFNa-2b + RBV ± Boceprevir in HCV type 1 naïve patients with LVL and RVR




* Patients with RVR were randomized

Pearlman BL et al. Hepatology 2014; 59: 59

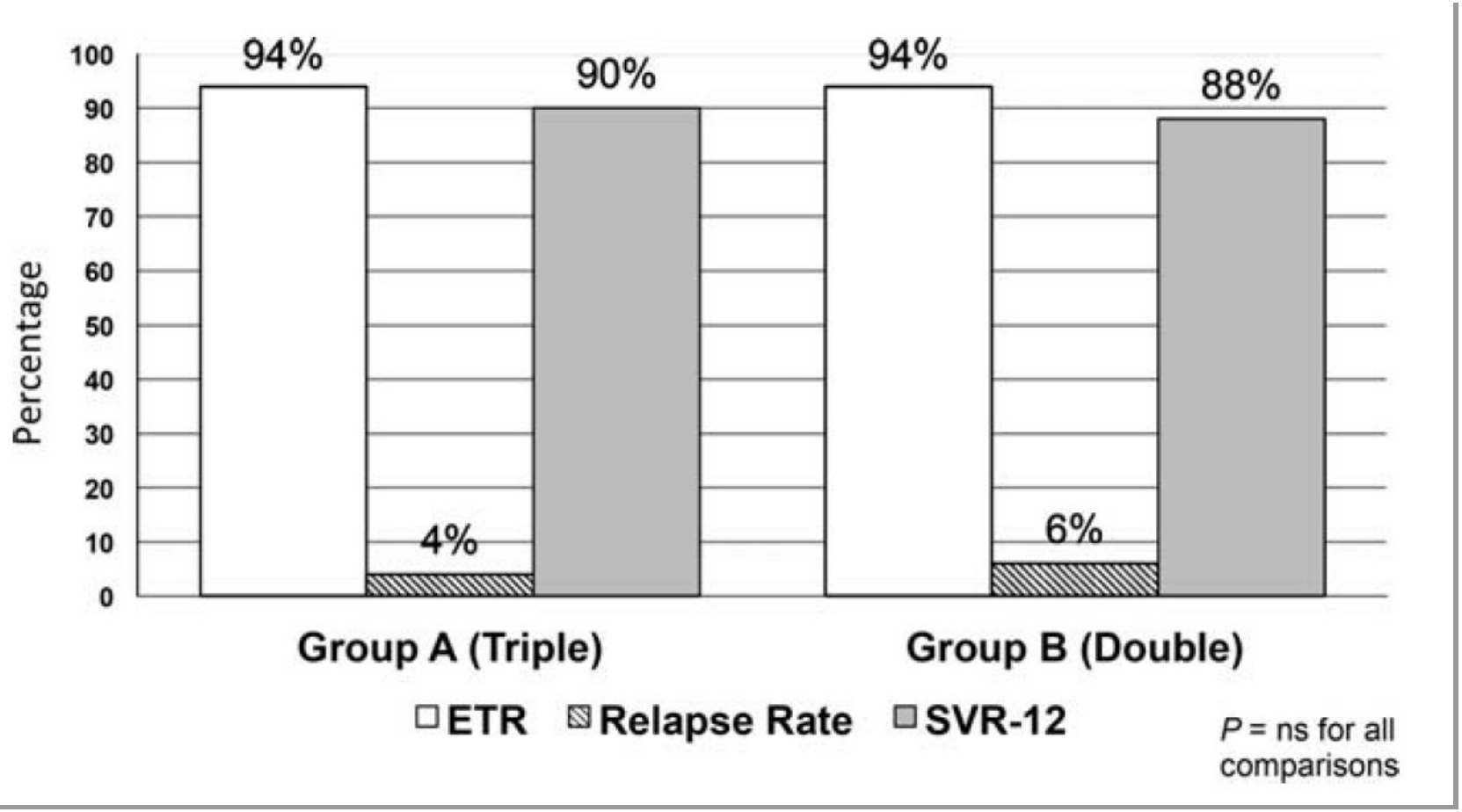
# Peg-IFNa-2b + RBV ± Boceprevir in HCV type 1 naïve patients with LVL and RVR




* Patients with RVR were randomized

Pearlman BL et al. Hepatology 2014; 59: 59

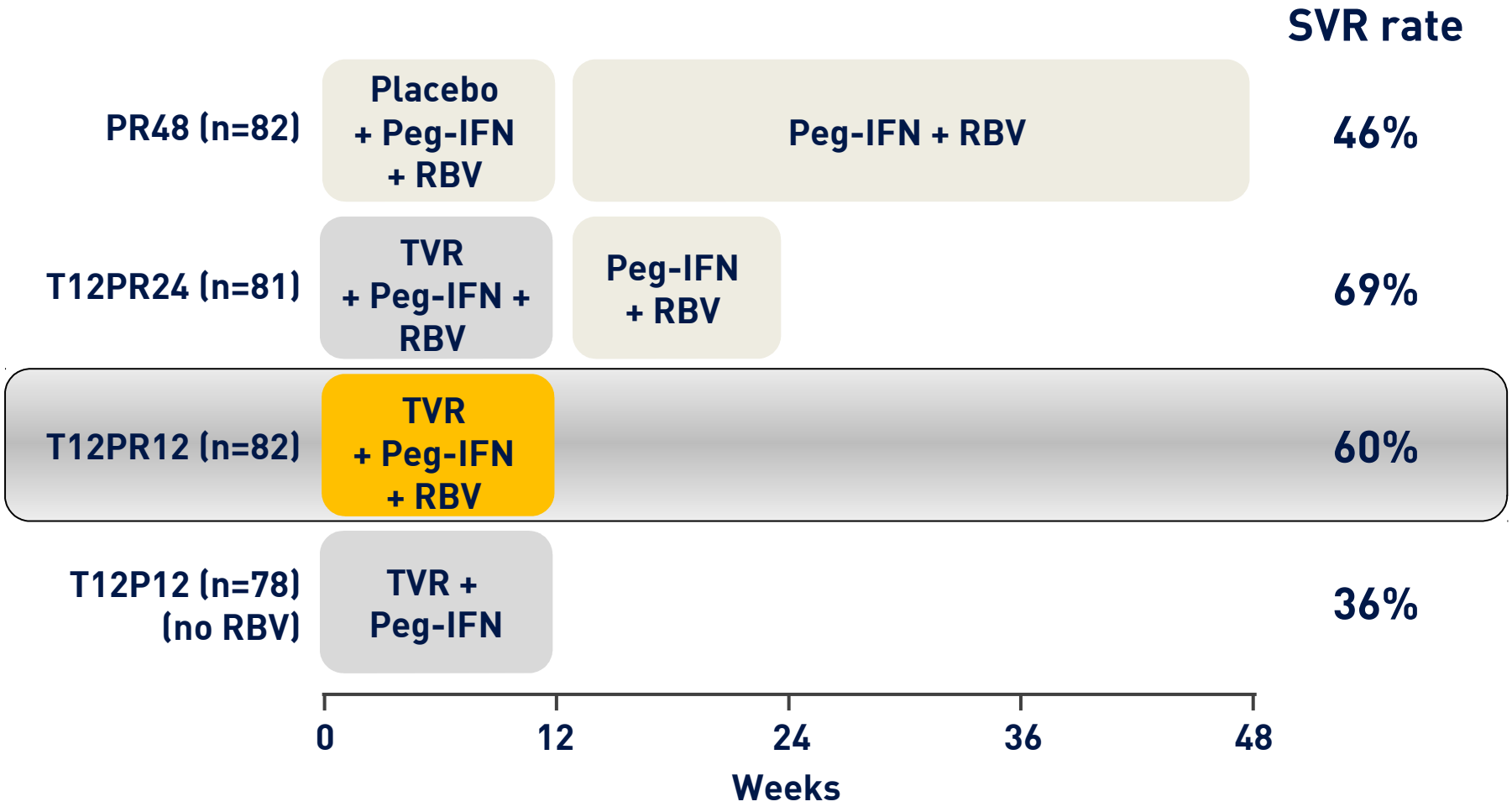
# Rapid virologic response to Peg-IFNa/RBV obviates a protease inhibitor




Pearlman BL et al. Hepatology 2014; 59: 59

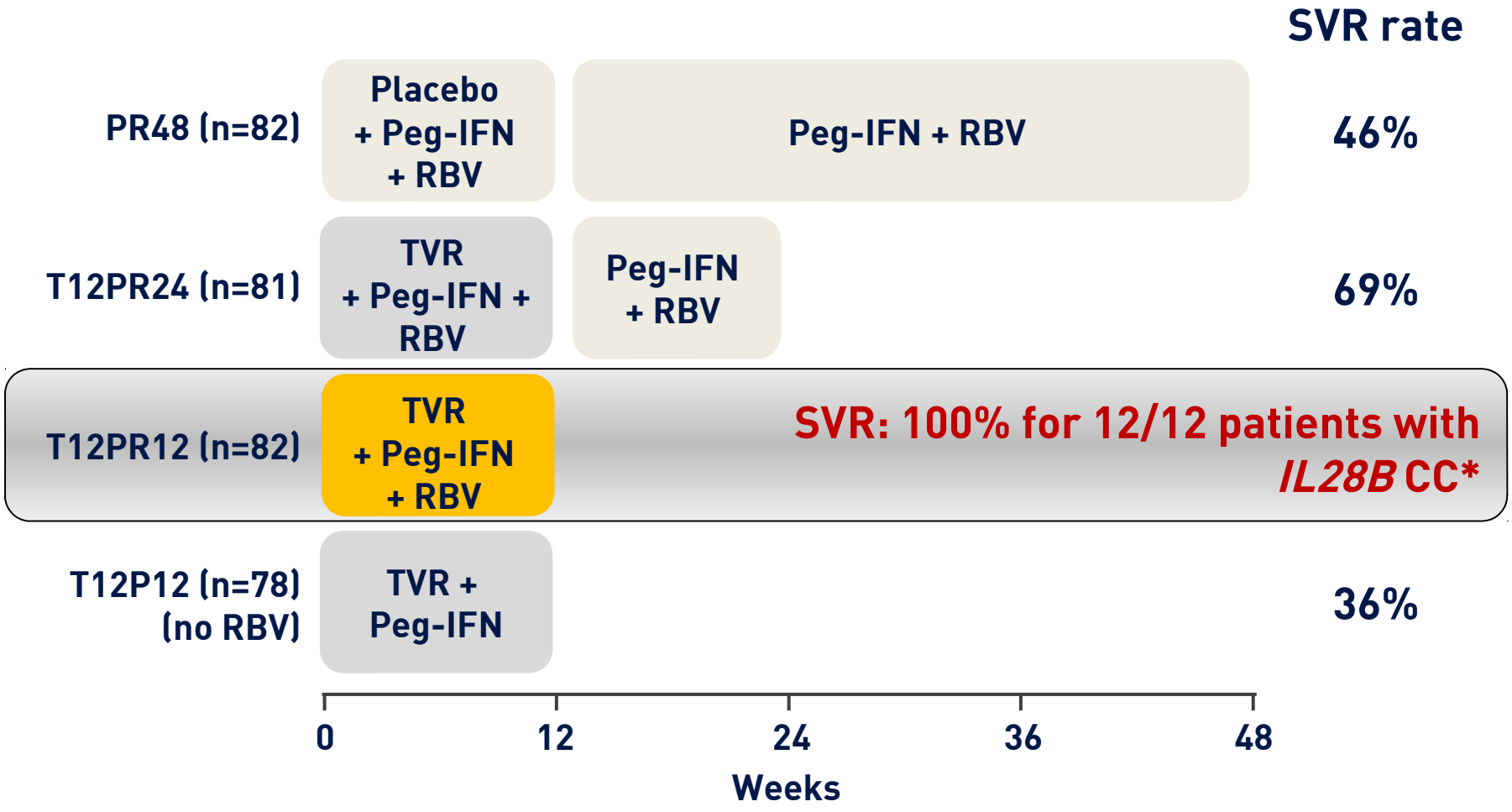
**Can we shorten DAA triple in patients with favourable IFN response predictors (high interferon susceptibility)?**

# PROVE2: SVR Rates after a 12 weeks TVR Triple regimen




Hézode C et al. N Engl J Med 2009;360:1839–50

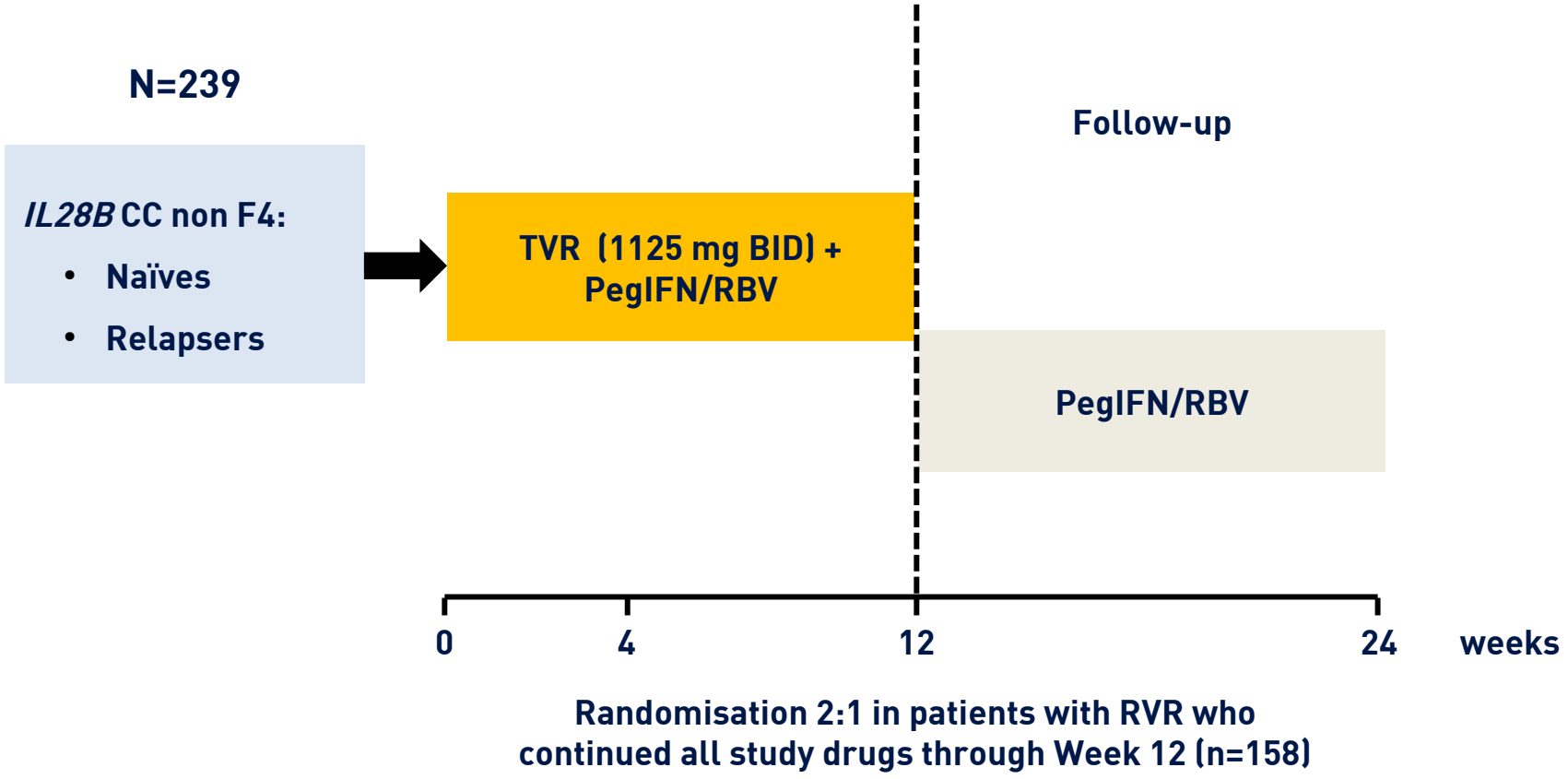
# PROVE2: 12 weeks TVR triple: IL28B (IFNL3) makes the difference




*Bronowicki J-P et al, EASL 2012, poster (1094

Hézode C et al. N Engl J Med 2009;360:1839–50

# CONCISE Study:
# 12-week telaprevir (TVR) triple

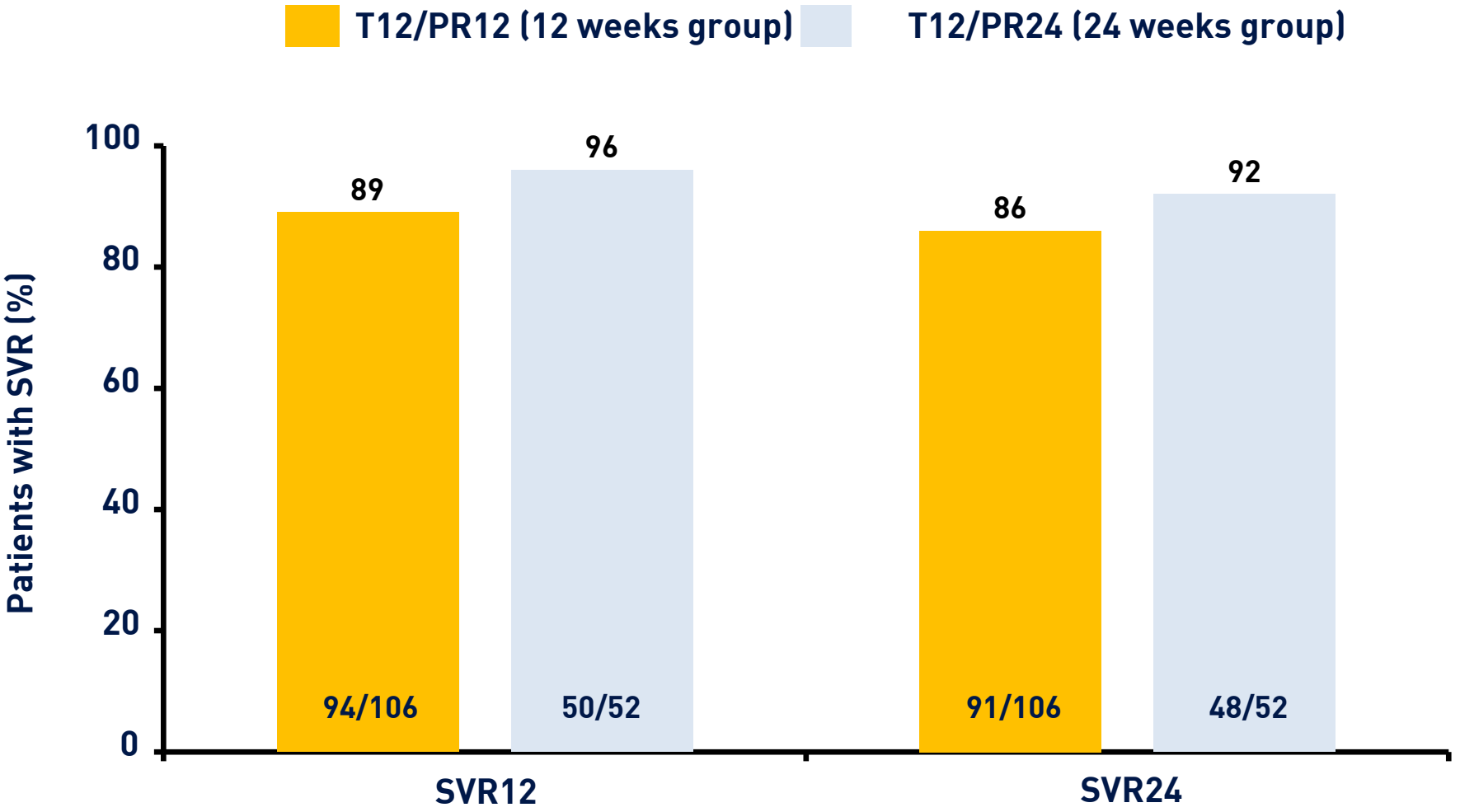



Randomisation 2:1 in patients with RVR who continued all study drugs through Week 12 (n=158)

*239 patients were followed for 16 or more weeks; N=158 were randomized at Week 12, respectively: 106 in T12/PR12 and 52 in T12/PR24 arms
RVR: Week 4 HCV RNA ←25 IU/mL, target not detected
PR: Peg-IFN alfa-2a (180 µg/week) and ribavirin (1000–1200 mg/day)

Nelson DR, et al. HepDART2013. Poster 118

# CONCISE: SVR12 and SVR24 by treatment duration for randomised patients – final results

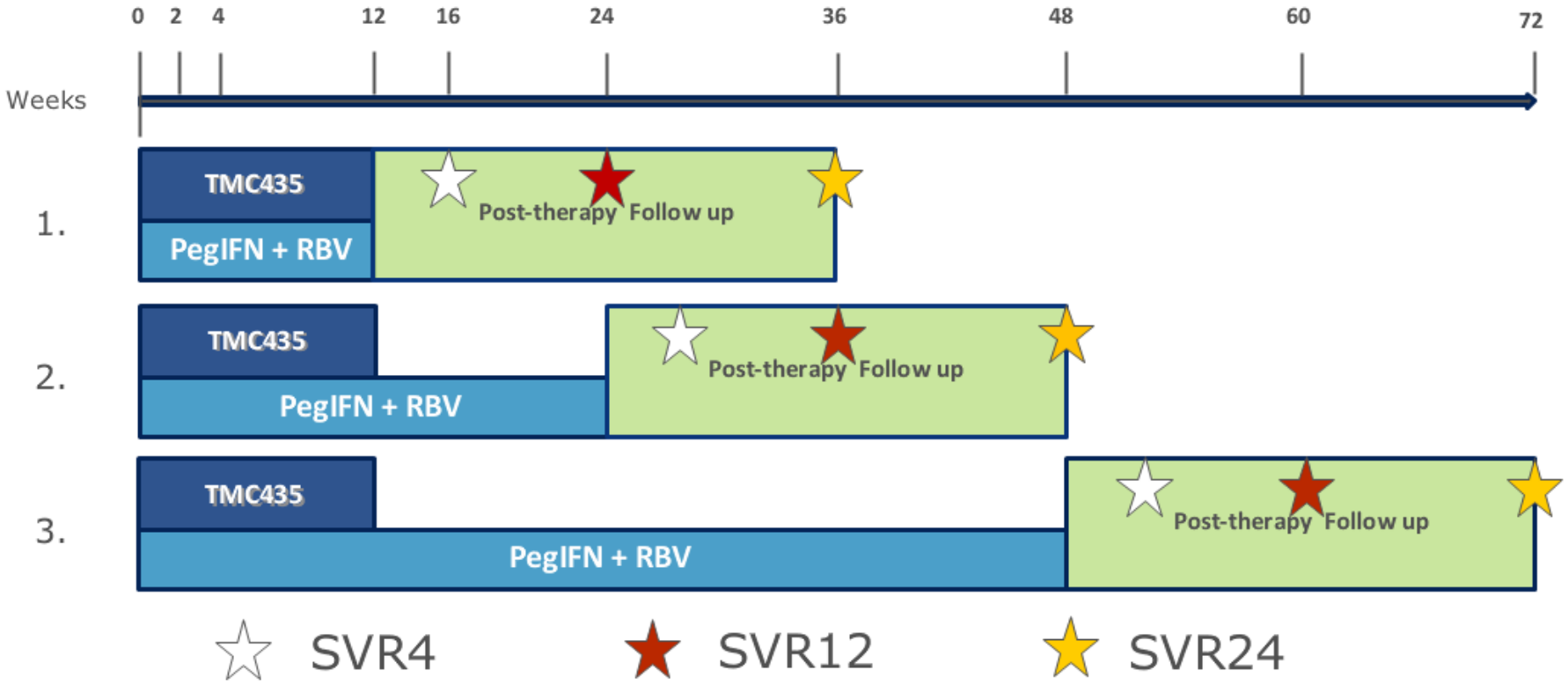



HCV RNA was measured using the Roche COBAS® TaqMan® HCV RNA Assay (v2.0), LLOQ=25 IU/mL HCV RNA values ←LLOQ were reported as either HCV RNA not detected or ←25 IU/mL detected.
SVR12: SVR at 12 weeks after end of planned treatment;
SVR24: SVR at 24 weeks after end of planned treatment

Nelson DR, et al. HepDART2013. Poster 118

# Is week 4 the optimal time point to tailor treatment duration in DAA based triple regimen?

# 12 weeks simeprevir triple in HCV type 1 and 4 naive TMC435HPC3014 study design

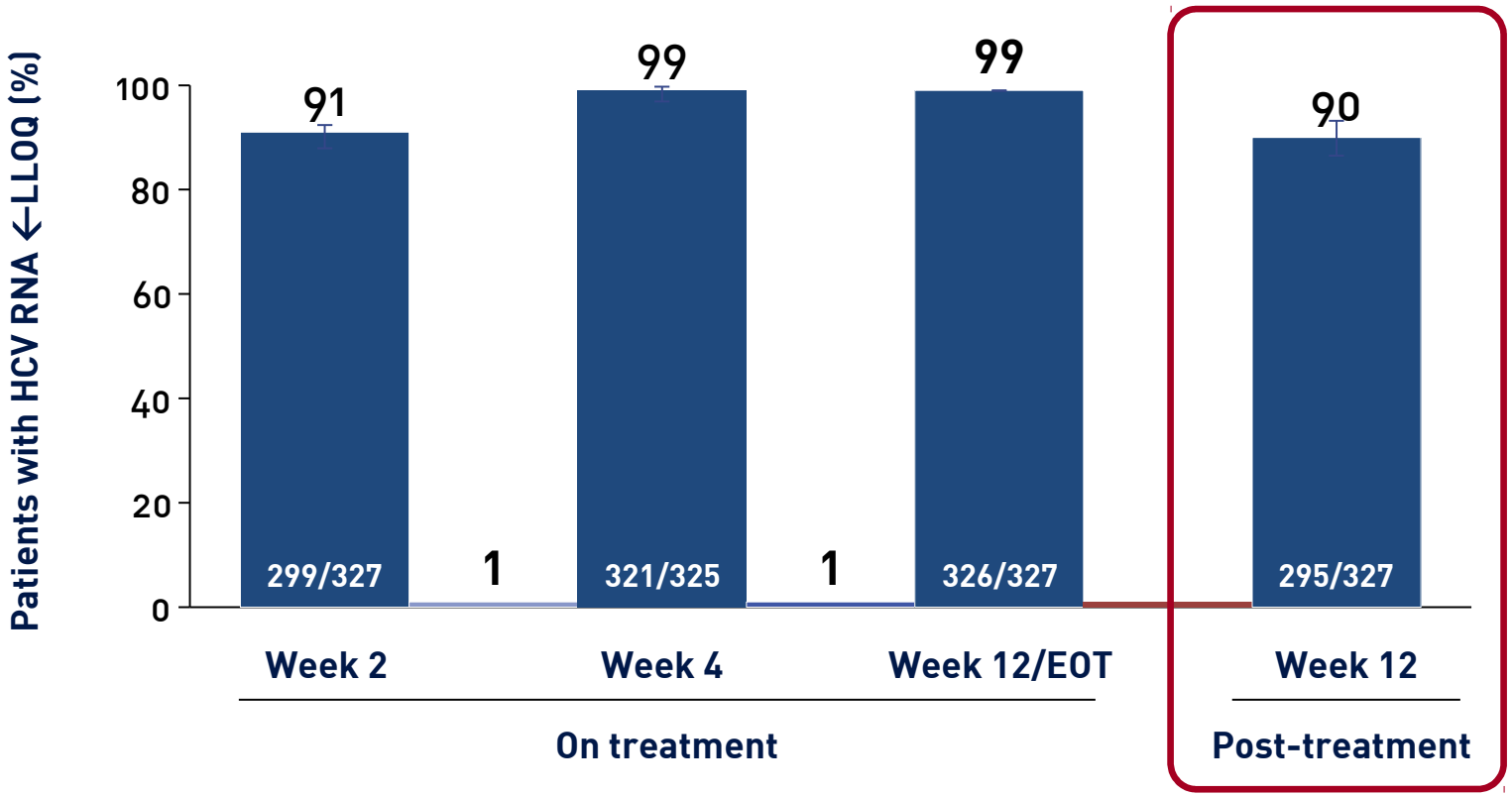



1. Stop at week 12 if HCV RNA ← 25 IU/mL at W2 and undetectable at week 4 and 8
2. If any of the above criteria not met, extension of PegIFN+RBV
3. Second extension until week 48 possible for subjects with HCV RNA ← 25 detectable at week 4 (investigator discretion)

*ClinicalTrials.gov*

# Shortening treatment duration by using high-barrier to resistance drugs (NUC polymerase inhibitor)

# Sofosbuvir plus PegFNa/RBV for 12 weeks (Neutrino Study) Virologic Response Rates

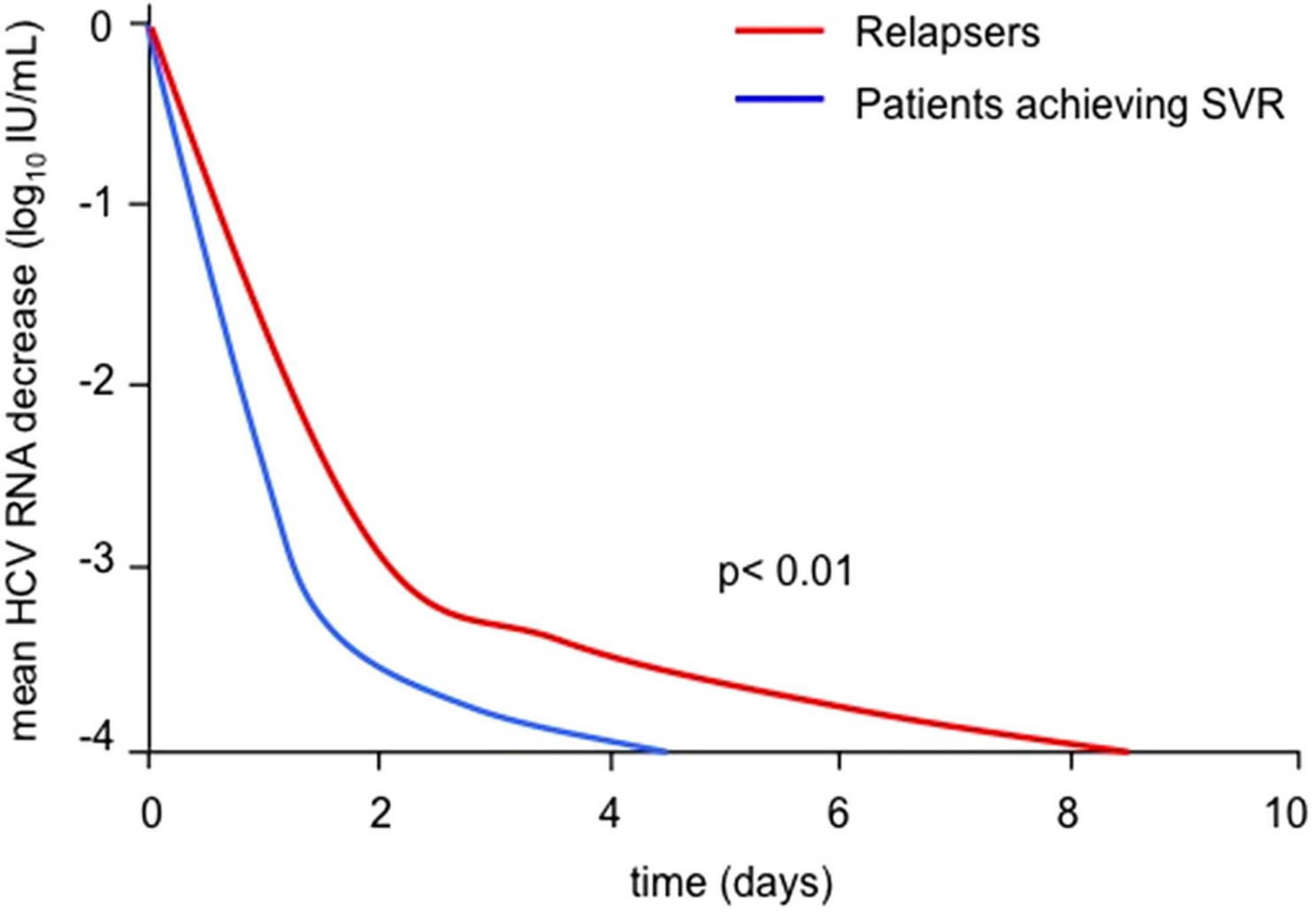



- Relapse accounted for all virologic failures

Error bars represent 95% confidence intervals.

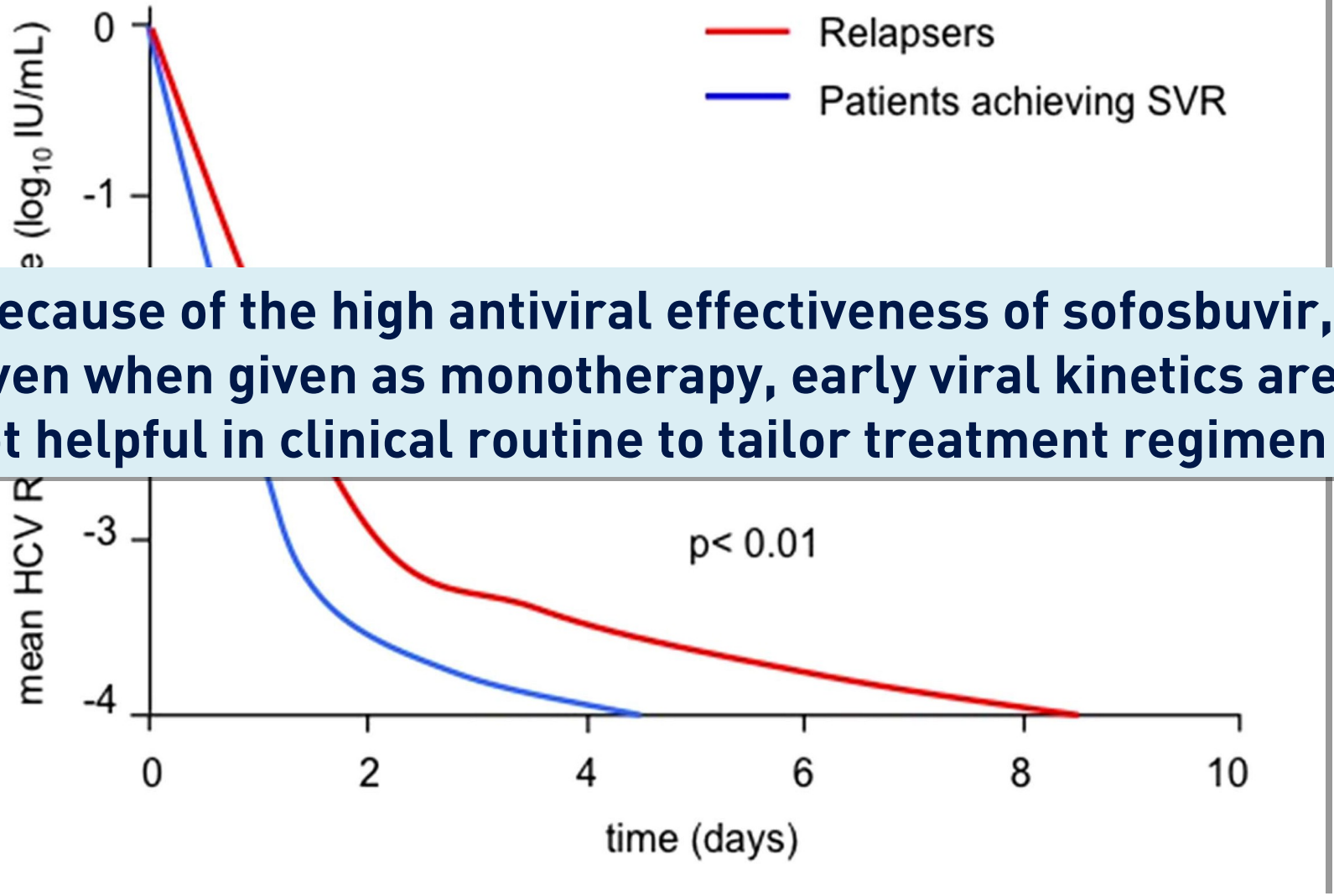
Lawitz E et al. N Engl J Med 2013; 368: 1878

# Early viral kinetics during sofosbuvir + ribavirin comparing patients with SVR and relapse




NIH SPARE: Osinusi A et al. CROI 2013 Atlanta (Abstract

# Early viral kinetics during sofosbuvir + ribavirin comparing patients with SVR and relapse

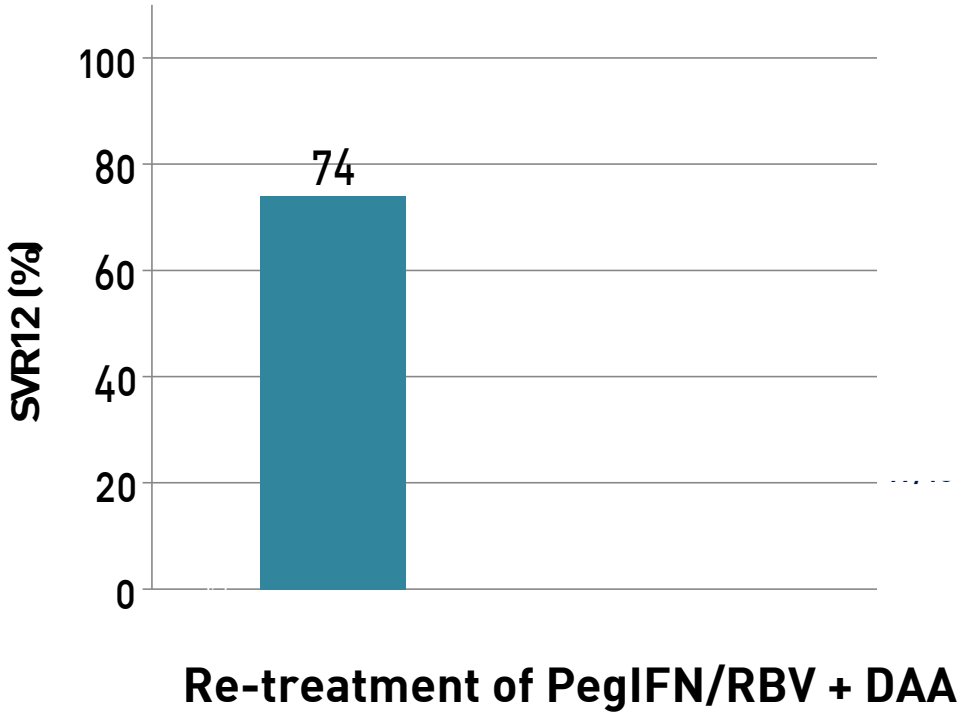



**Because of the high antiviral effectiveness of sofosbuvir, even when given as monotherapy, early viral kinetics are not helpful in clinical routine to tailor treatment regimen**

NIH SPARE: Osinusi A et al. CROI 2013 Atlanta (Abstract

# Sofosbuvir triple in patients with prior treatment failure (interim analysis)

**HCV type 1, failure to PegIFNa/RBV + DAA → re-treatment with SOF-Triple for 12 weeks**




Pol S et al., EASL 2014, #055

# Summary and conclusions

- Shortening PegIFNa/RBV to ↖ 24 weeks is feasible in a small subgroup of patients with RVR and favorable baseline response predictors (i.e. low baseline viral load, no cirrhosis, treatment naïve)
- These patients achieve cure rates comparable to DAA based regimen
- Adding a low barrier to resistance DAA (PI) increases the proportion of patients who will be cured with a 24 week regimen
- Shortening PI triple to 12 weeks is only recommended for very rapid responders (week 2) with high PegIFN/RBV susceptibility (favorable baseline

# Summary and conclusions

- A 12 week triple regimen represents the standard of care when using high barrier to resistance DAA (i.e. sofosbuvir)
- Shortening PegIFN/RBV-based treatment duration is not recommended for patients with low PegIFNa/RBV susceptibility (i.e. treatment failures with partial or null response)
- The results should be interpreted in the context of recent findings showing cure rates of → 90% in patients with easy to treat characteristics after