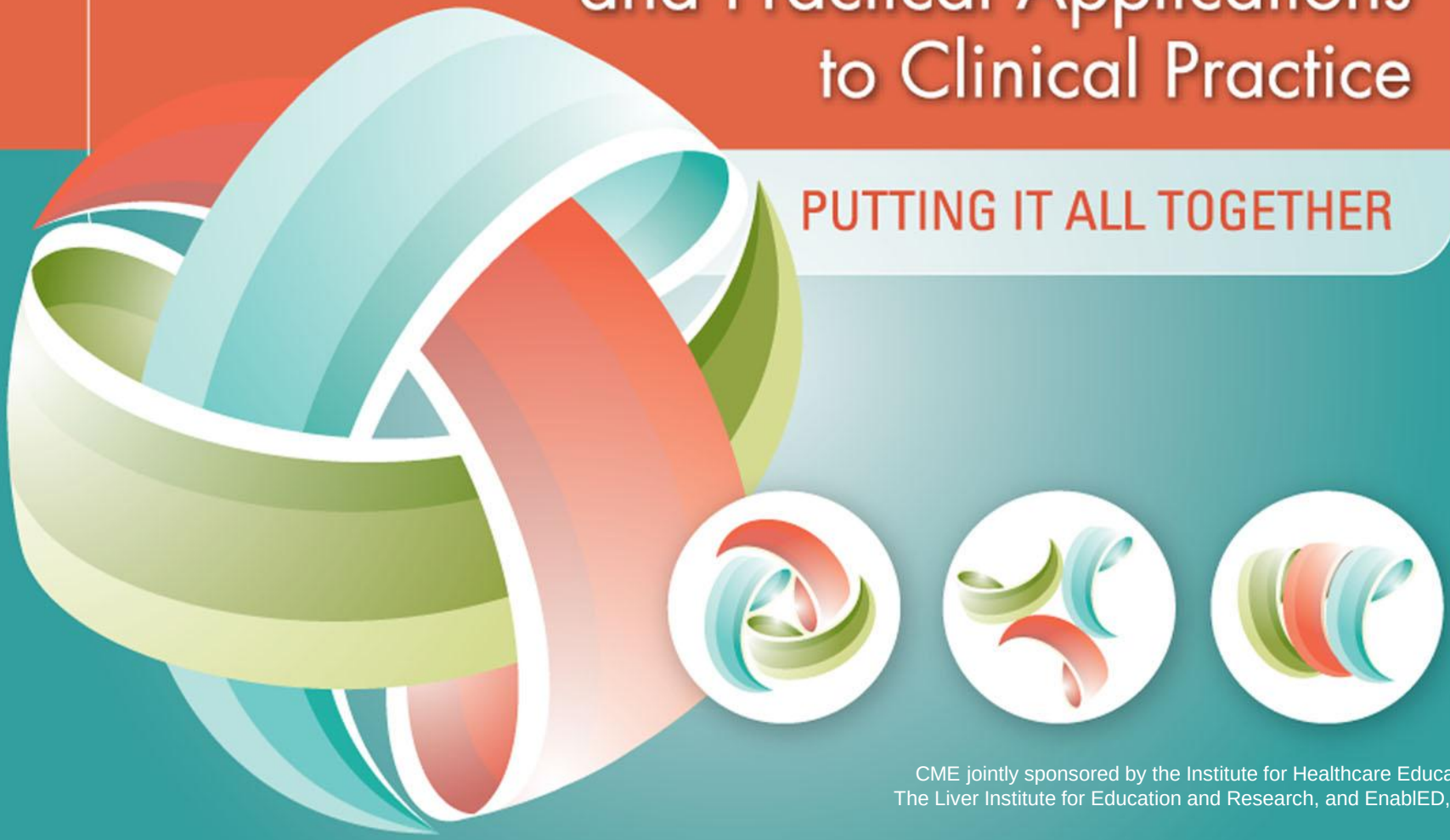
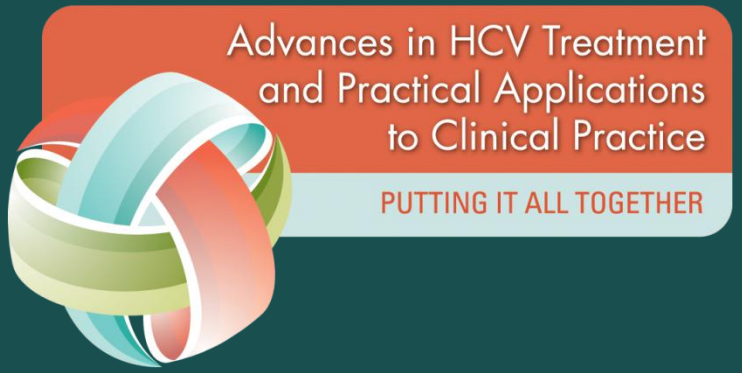
Advances in HCV Treatment and Practical Applications to Clinical Practice

PUTTING IT ALL TOGETHER



CME jointly sponsored by the Institute for Healthcare Education, The Liver Institute for Education and Research, and EnablED, LLC



Case:
Predictors of Response

Case: Predictors of Response

- 35-year-old mother of 3 young children
- HCV genotype 1b, viral load 350,000 IU/L
- Transmission date and mechanism unknown
- No previous treatment
- Transaminases normal for 3 years
- Recent TEG showed fibrosis stage of F0–F1 (4.3 kPa)
- No extrahepatic symptoms, no other relevant diseases

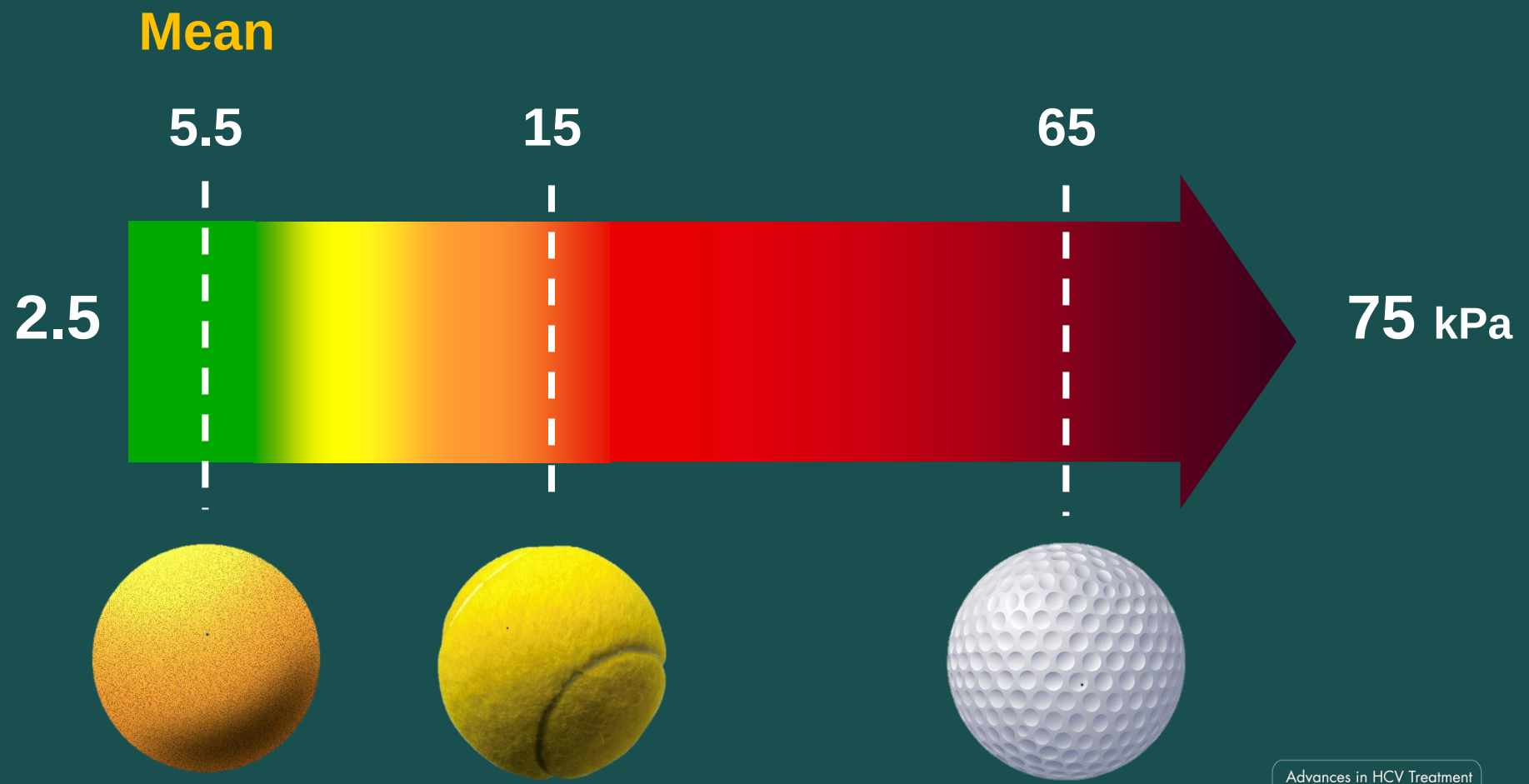
TEG = transient elastography.

The Patient with Mild Disease

- Liver biomarker panel score 0.19
- No alcohol, no psychiatric history
- Physical examination normal
- Body mass index 24.5 kg/m^2
- *IL-28b* genotype CC
- Hemoglobin 13.5 g/dL

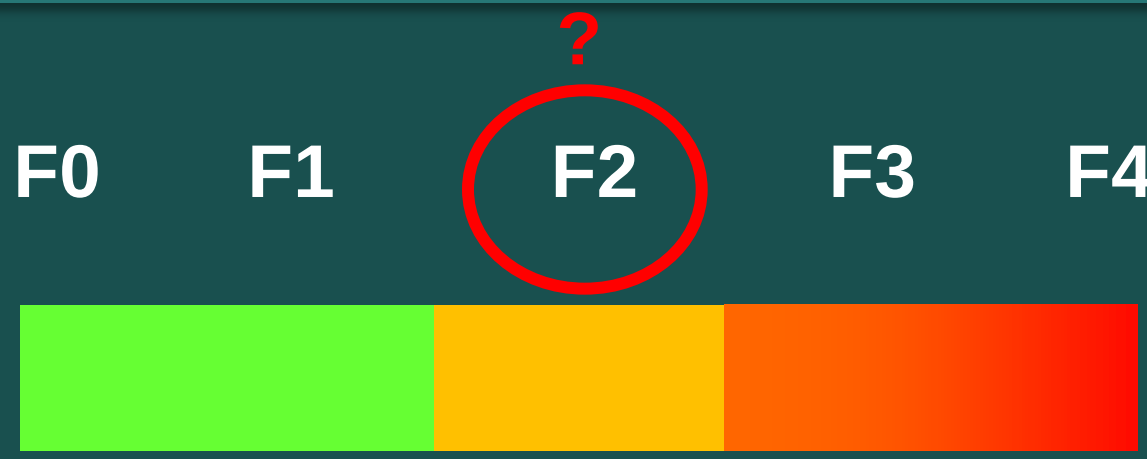
"Doctor, do I need a liver biopsy?"
"Doctor, what are my chances of success?"

Measuring Liver Stiffness



Roulot D, et al. J Hepatol 2008;48(4):606-13; Castéra L, et al. J Hepatol 2008;48:835-47.

Is Diagnosing Significant Fibrosis Still Important in the Era of DAAs ?



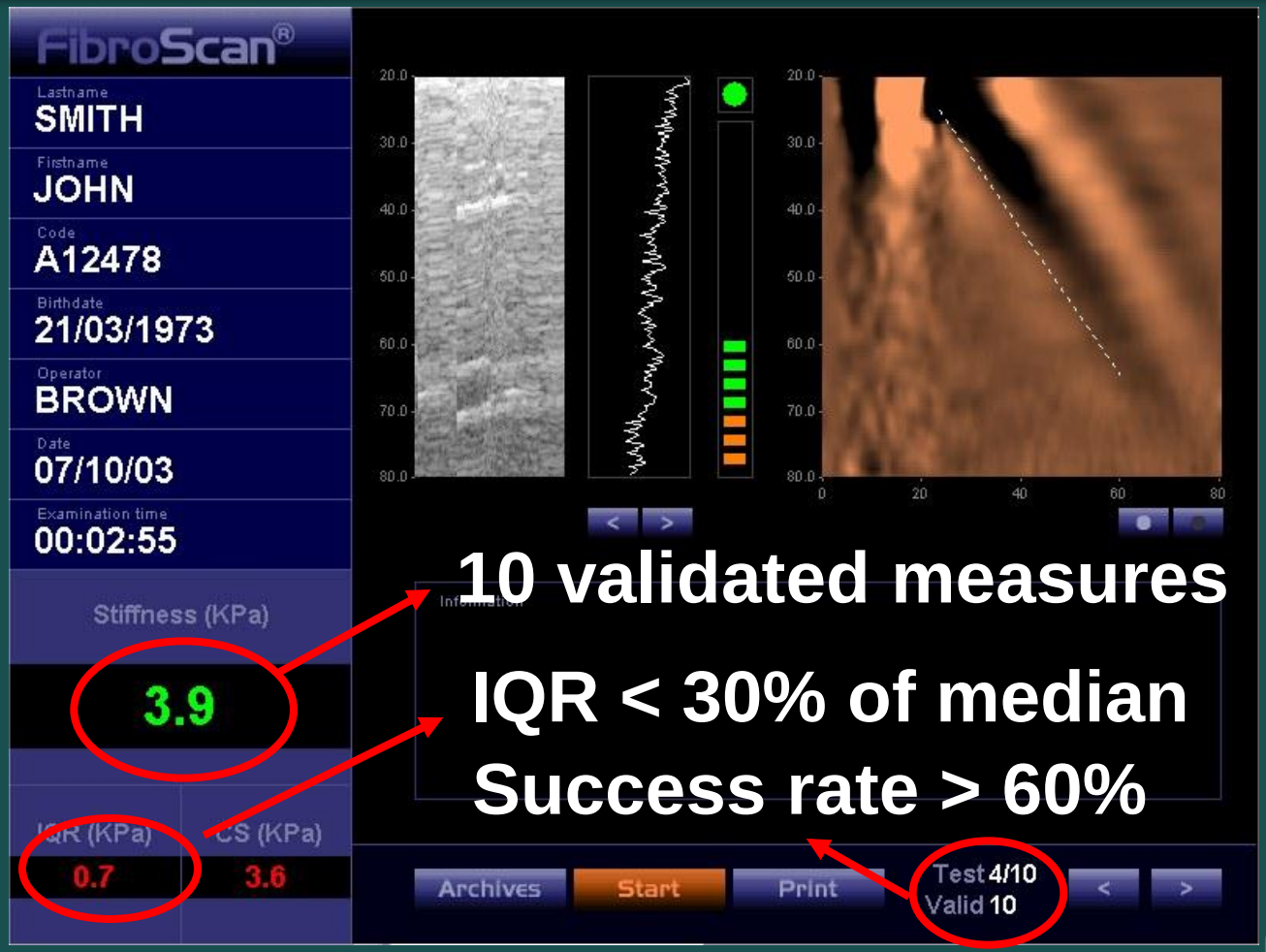
Indication for antiviral treatment

Boceprevir

Telaprevir

DAAs = direct-acting antivirals.

Interpreting Transient Elastography Results: Manufacturer's Recommendations



IQR = interquartile range.

Castéra L, et al. J Hepatol 2008;48:835-47,

Applicability of TEG

Failure 3.1%

Unreliable 15.8%

Valid shot (VS) = 0

Obesity

SR < 60%
8.1%

VS < 10
3.1%

IQR/LSM > 30%
9.2%

Operator experience

TEG not applicable in 20% of cases

N=13,669 examinations

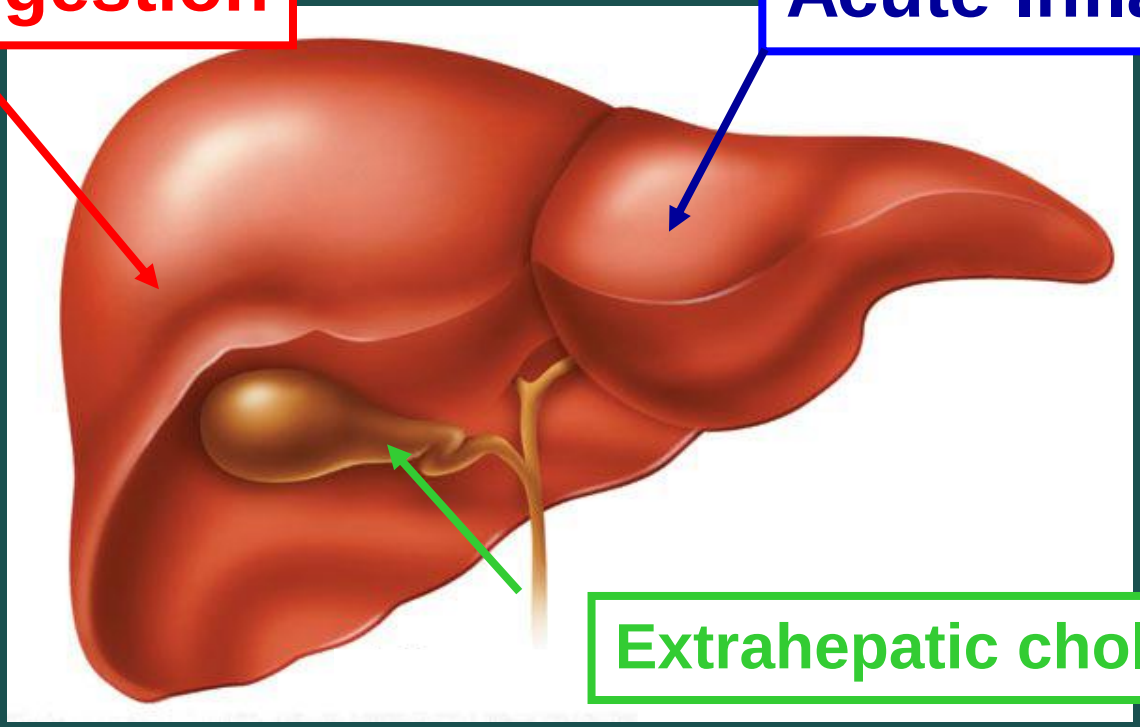
Castéra L, et al. Hepatology 2010;51:828-35.

SR = success rate; LSM = least squares mean.

Confounding Factors for Liver Stiffness

Liver congestion

Acute Inflammation



Extrahepatic cholestasis

Millonig G, et al. J Hepatol 2009;52(2):206-10; Coco B, et al. J Viral Hepat 2007;14(5):360-9; Arena U, et al. Hepatology 2008;47(2):380-4; Sagir A, et al. Hepatology. 2008;47(2):592-5; Millonig G, et al. Hepatology 2008;48(5):1718-23.

Treatment-Naïve Patients Without Comorbid Conditions

Use as first-line assessment

Serum markers

+

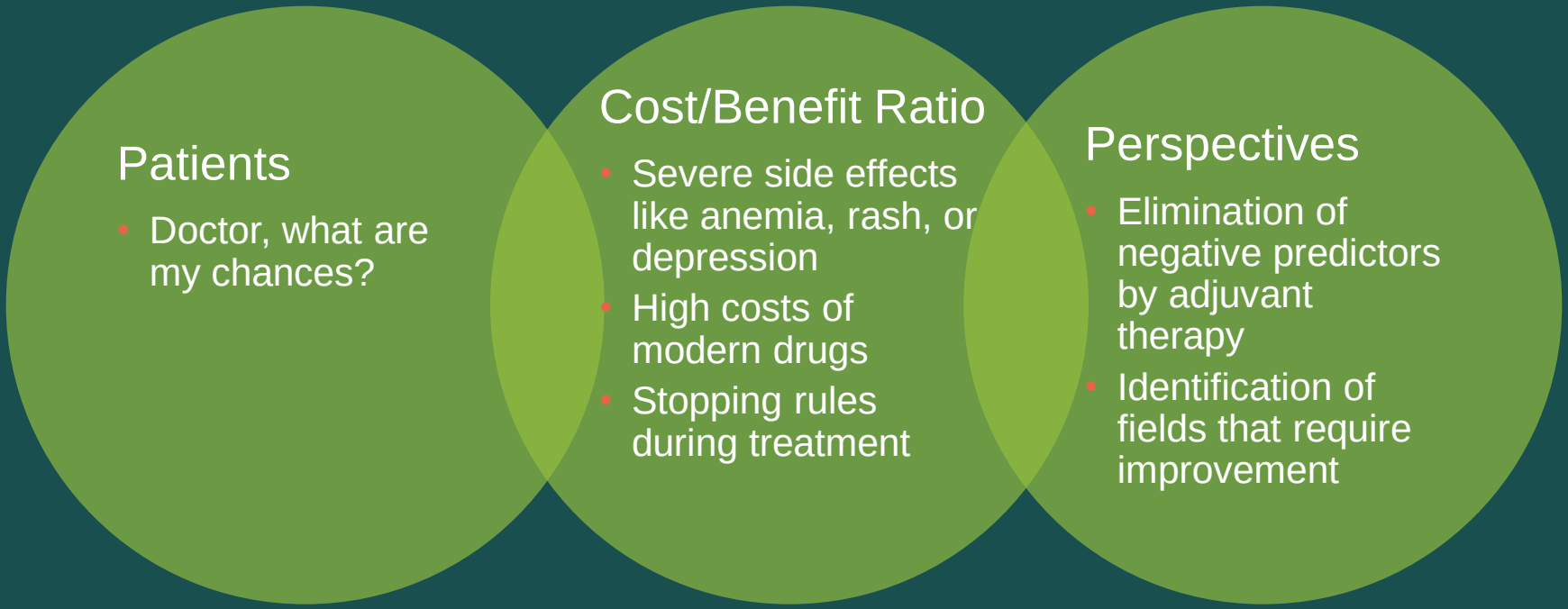
Transient elastography

Haute Autorité de Santé, 2008; EASL Clinical Practice Guidelines.
J Hepatol 2011;55(2):245-64.

No Biopsy Indicated for Our Patient

- Noninvasive tests can be used as first-line assessments when crude evaluation of fibrosis is needed
- Main limitation of transient elastography is limited applicability in obese patients
- Combining transient elastography with serum biomarkers increases diagnostic accuracy, especially when they agree

Introduction: Why do We Need Predictive Factors?



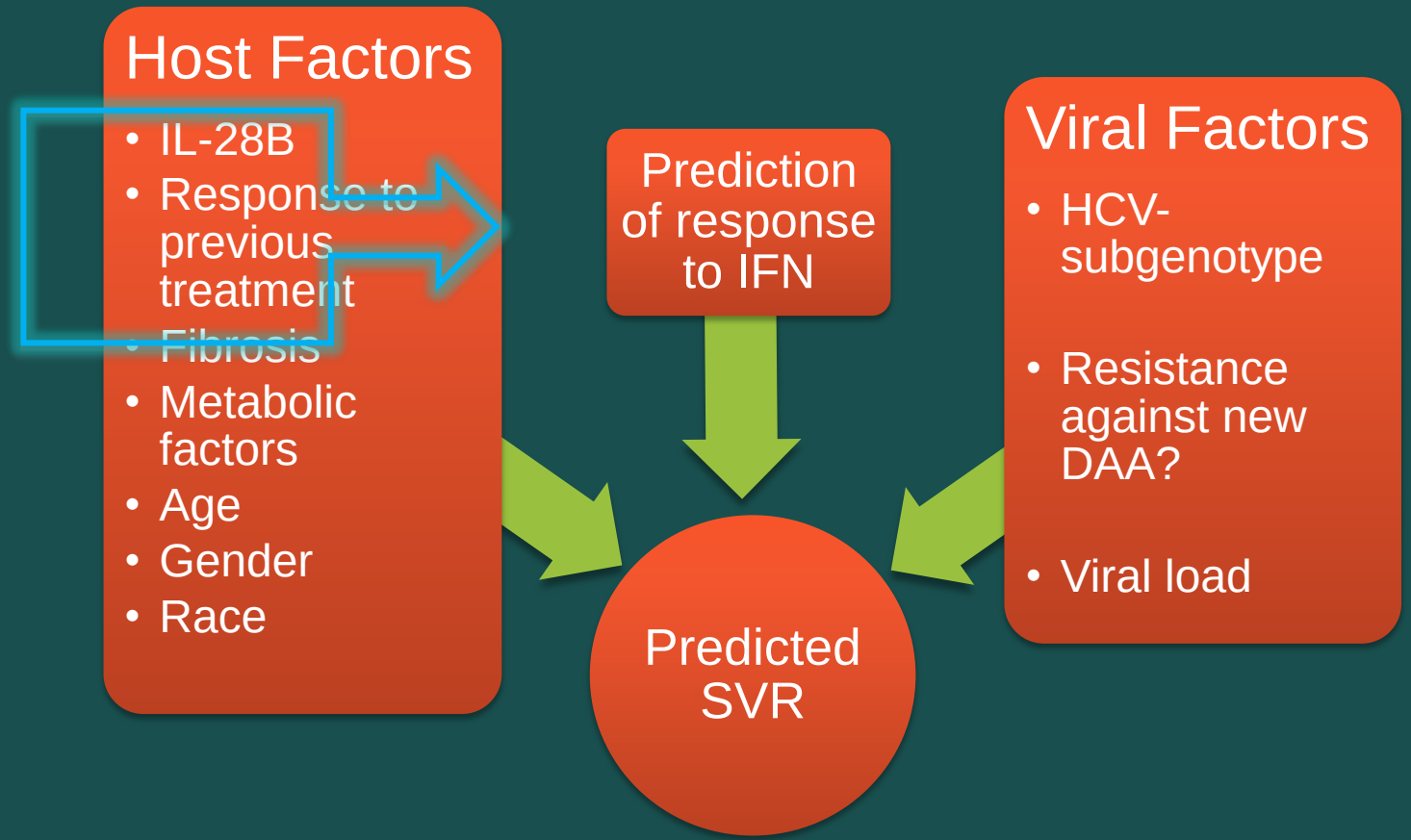
Different Predictive Factors: Past and Present Treatment

Pre-treatment

- Host factors
- Viral factors

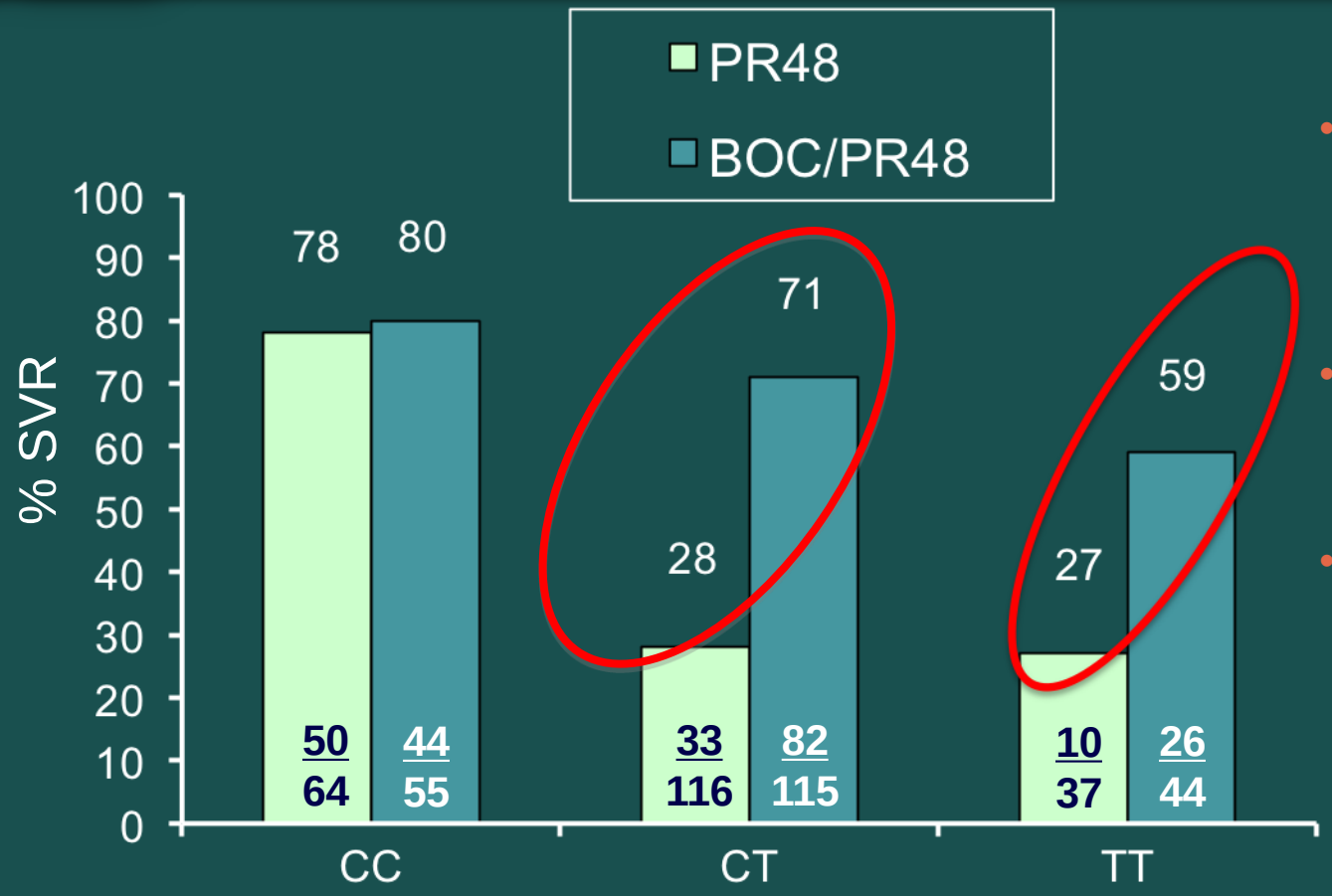
On-treatment

Pretreatment: PEG-Interferon with Ribavirin



PEG = pegylated; IFN = interferon; SVR = sustained virologic response.

SVR and *IL-28B* Polymorphisms

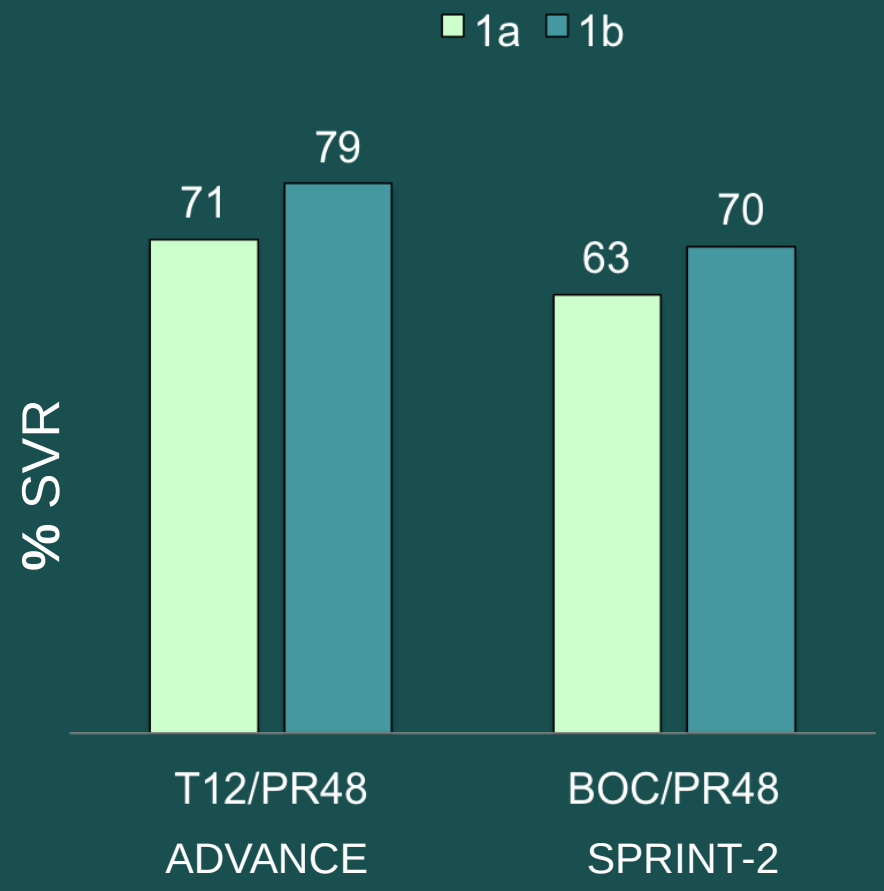


- *IL-28B* still important but less relevance for SVR with current triple therapy
- Highly predictive for response to IFN/ribavirin
- Valid predictor, especially for lead-in phase and shorter treatment duration

PR48 = PEG-IFN with ribavirin x 48 wks; BOC = boceprevir.

Poordad F, et al. EASL 2011 Abstract.

HCV Genotype 1: Relevance of Subtype

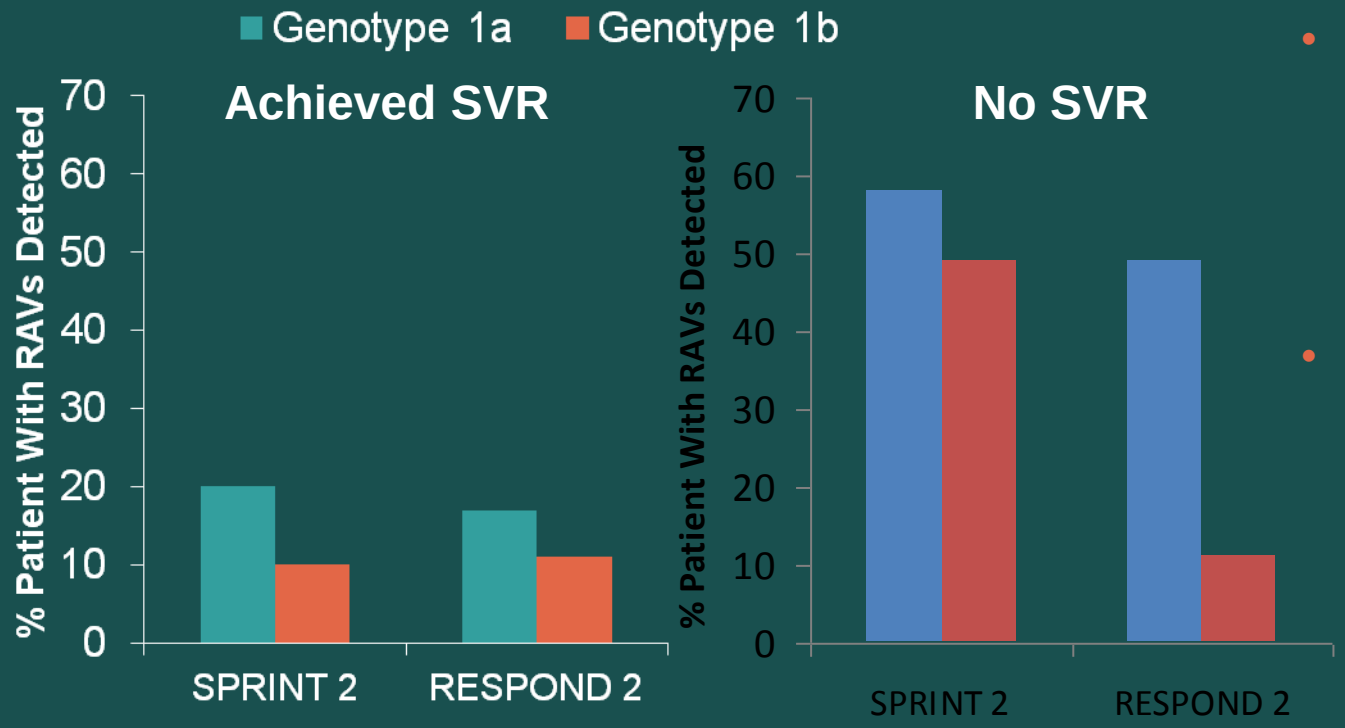


- Subtype still matters in triple therapy that includes a protease inhibitor (PI)
- Genotype 1a is associated with a lower rate of SVR after triple therapy with a PI

T12 = telaprevir x 12 wks.

Kwo PY. Liver Int 2012;32(Suppl 1):39-43.

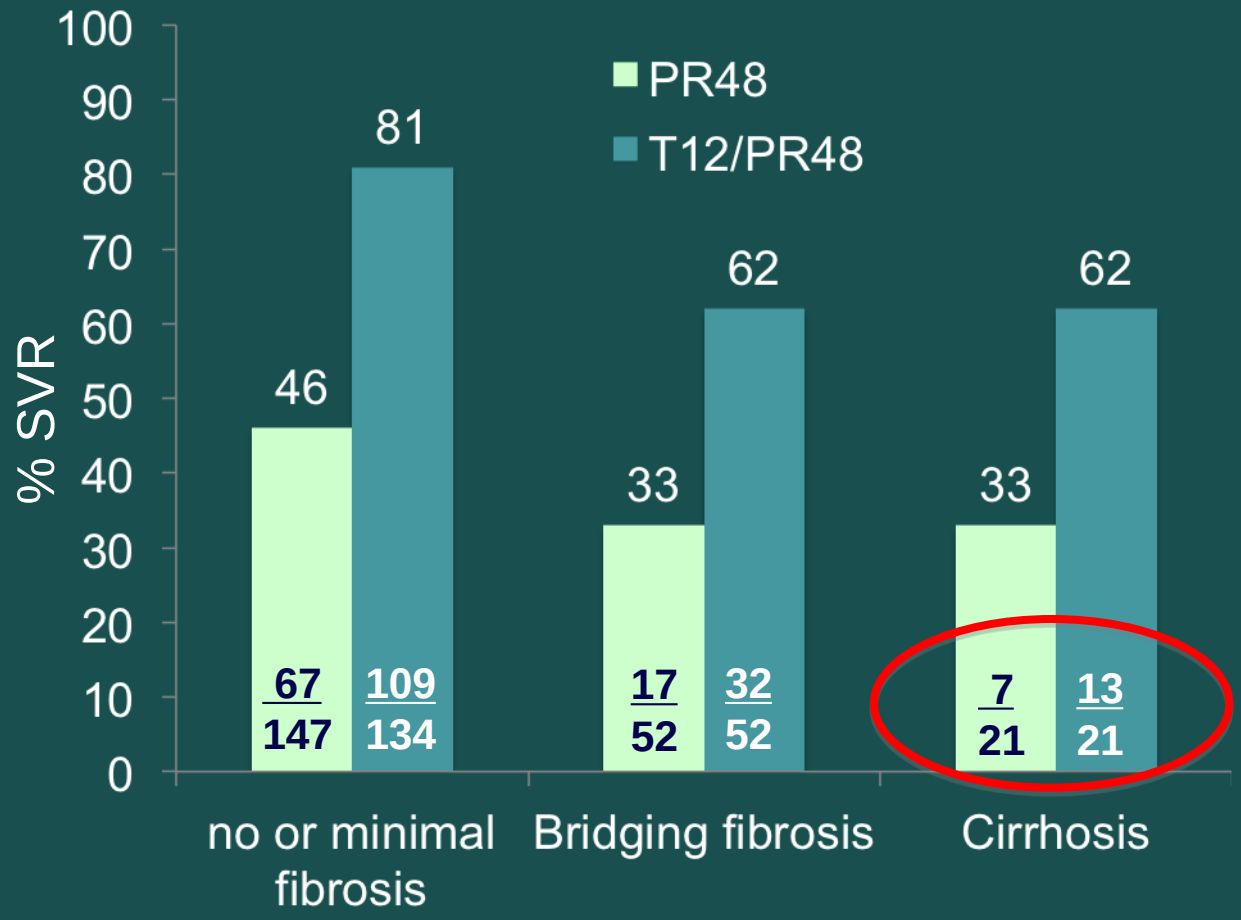
Incidence of Resistance-Associated Variants (RAVs) Might Explain Differences in SVR



- Genetic differences might be responsible for higher incidence of RAVs in genotype 1a versus 1b
- Increased incidence of RAVs might be linked to lower rate of SVR

Brass CA, et al. EASL 2011 Abstract.

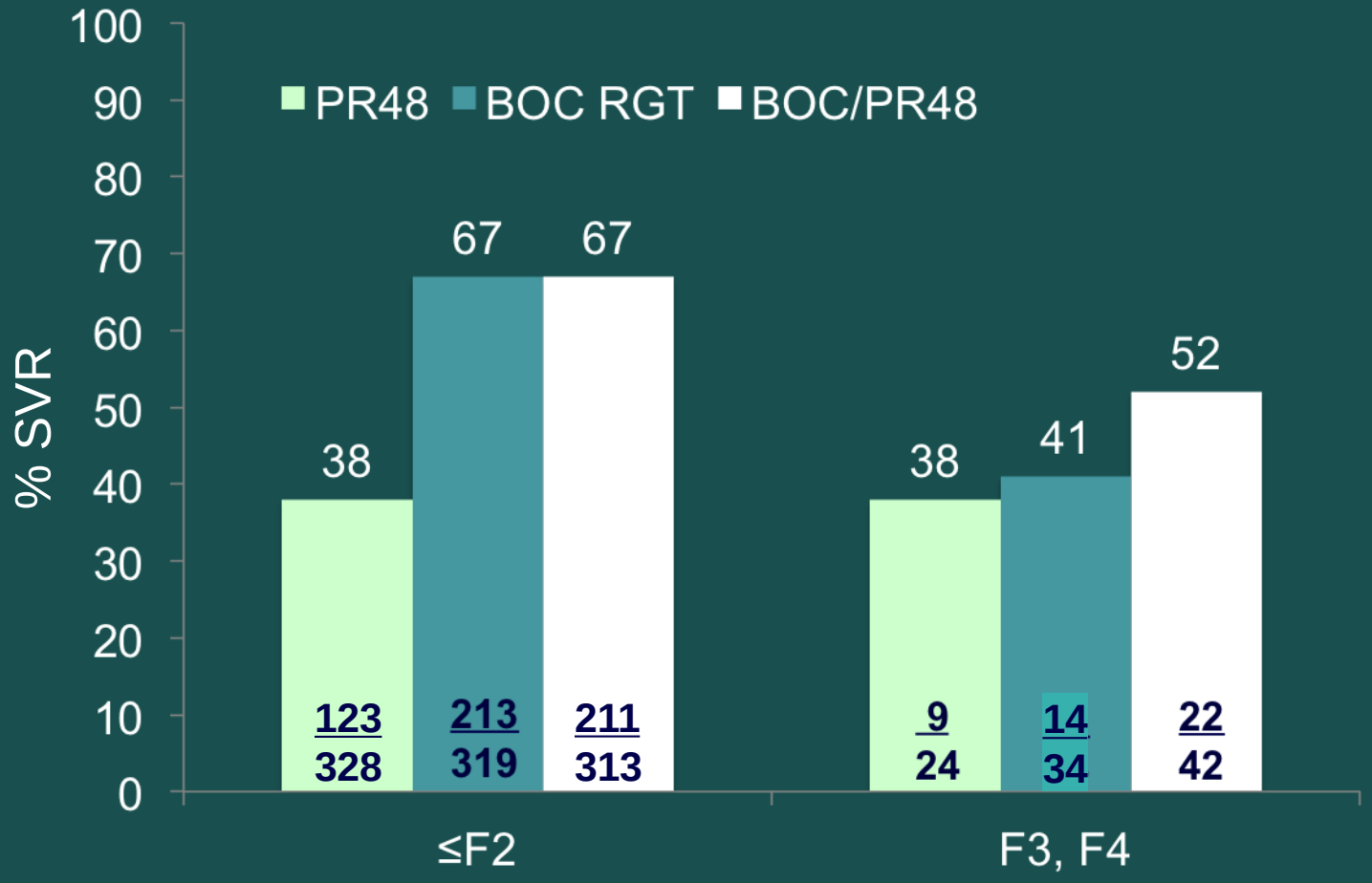
Fibrosis and SVR in HCV Genotype 1: Telaprevir



- Stage of liver fibrosis is an important predictive factor
- Small numbers of patients with cirrhosis in Phase III studies of boceprevir and telaprevir

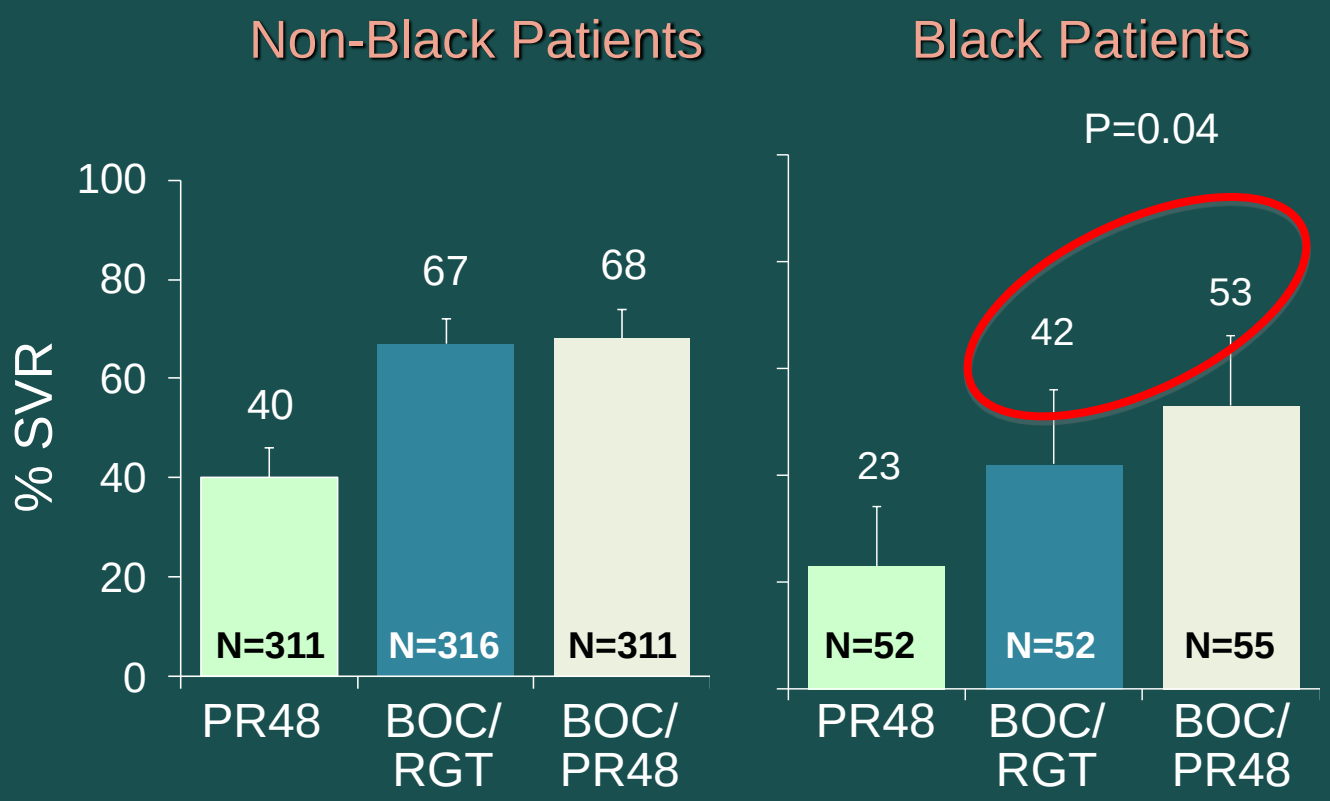
Jacobson IM, et al. N Engl J Med 2011;364(25):2405-16.

Fibrosis and SVR in HCV Genotype 1: Boceprevir



Poordad F, et al. N Engl J Med 2011;364(13):1195-206.

The Effect of Race on SVR



- Consider longer treatment duration in therapy-naïve black patients?

Poordad F, et al. N Engl J Med 2011;364(13):1195-206.

Practical Application of Predictive Factors

Patients with Poor Outcome: Characteristics of a Difficult-to-Treat Patient

- Previous null response to IFN
- Cirrhosis
- HCV genotype 1a
- *IL-28B* CT or TT
- High viral load
- Over 40 years old
- Diabetes
- Obesity

Asselah T, et al. Liver Int 2010;30(9):1259-69.

Different Predictive Factors: Past and Present Treatment

Pretreatment

- Host factors
- Viral factors

During treatment

Different Predictive Factors: Past and Present Treatment

Pretreatment

- Host factors
- Viral factors

During treatment

- Lead-in phase
- Rapid viral response
- Adherence
- Anemia

Predictive Factors During Treatment

- Lead-in
- Rapid virologic response
- Adherence
- Anemia

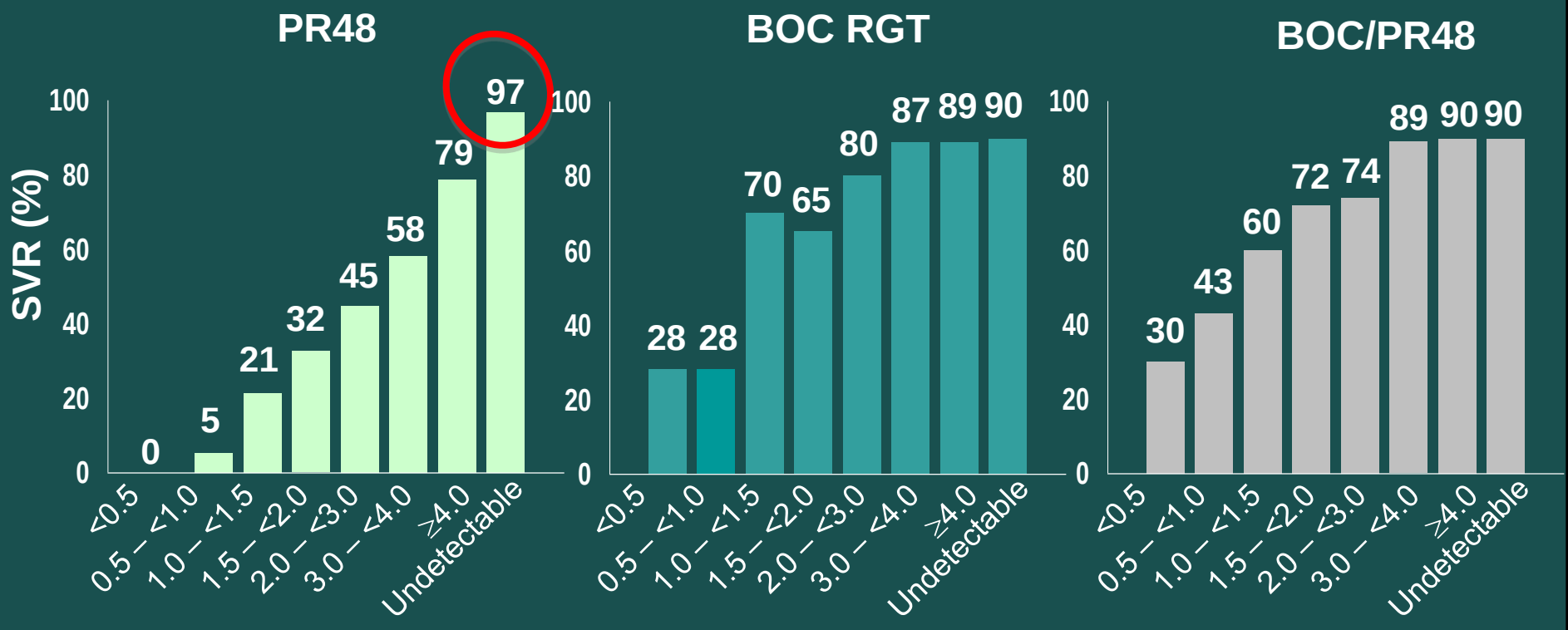
Lead-In Phase

- Real-time response to PEG-IFN and ribavirin before the addition of a PI
- Standard regimen for triple therapy with boceprevir
- Also can be considered in triple therapy with telaprevir under certain circumstances (off-label)

Zeuzem S, et al. N Engl J Med 2011;364:2417-28.

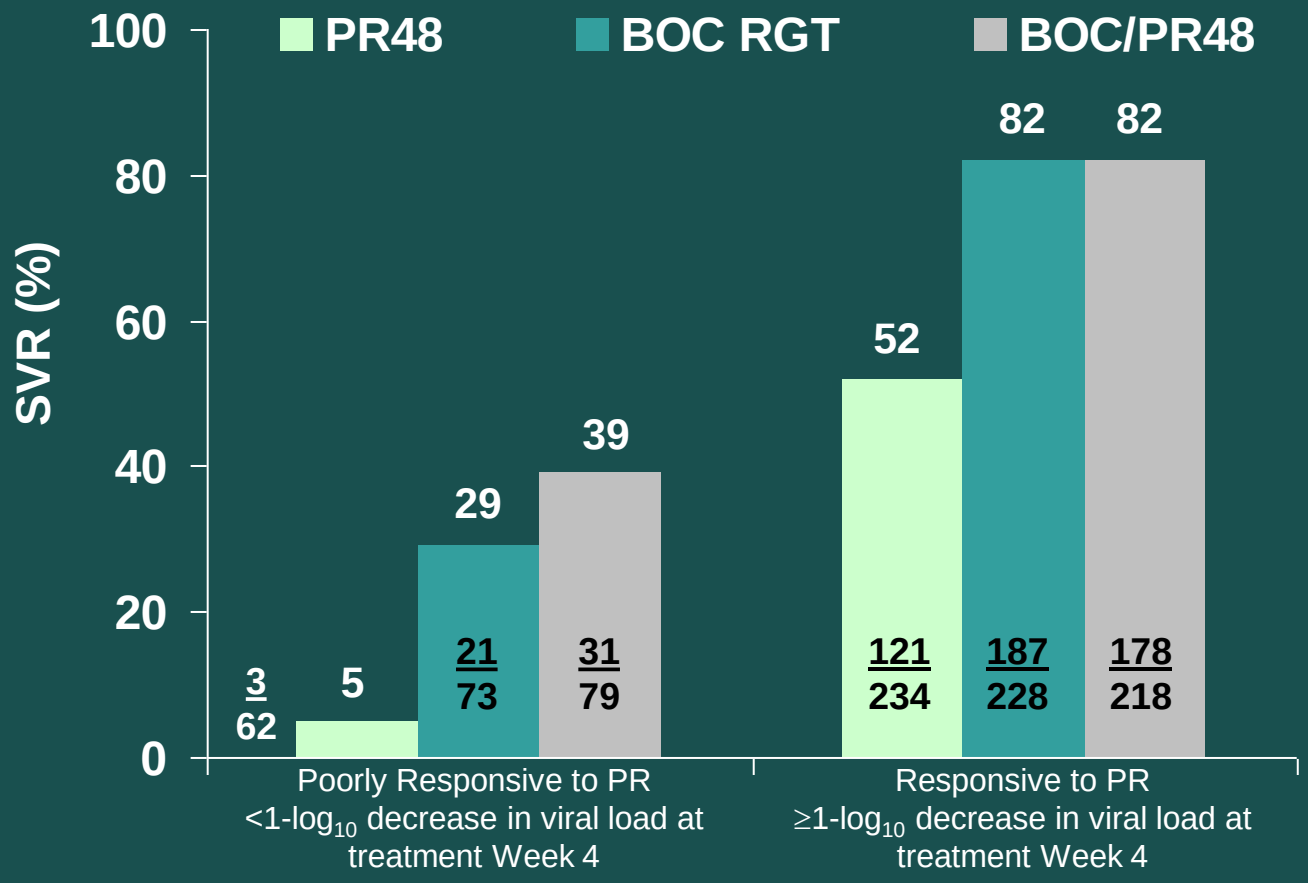
Response to PR After Lead-In Is Highly Predictive for SVR

SPRINT-2 and RESPOND-2, Treatment-Naïve, Cohort 1 (non-black patients)



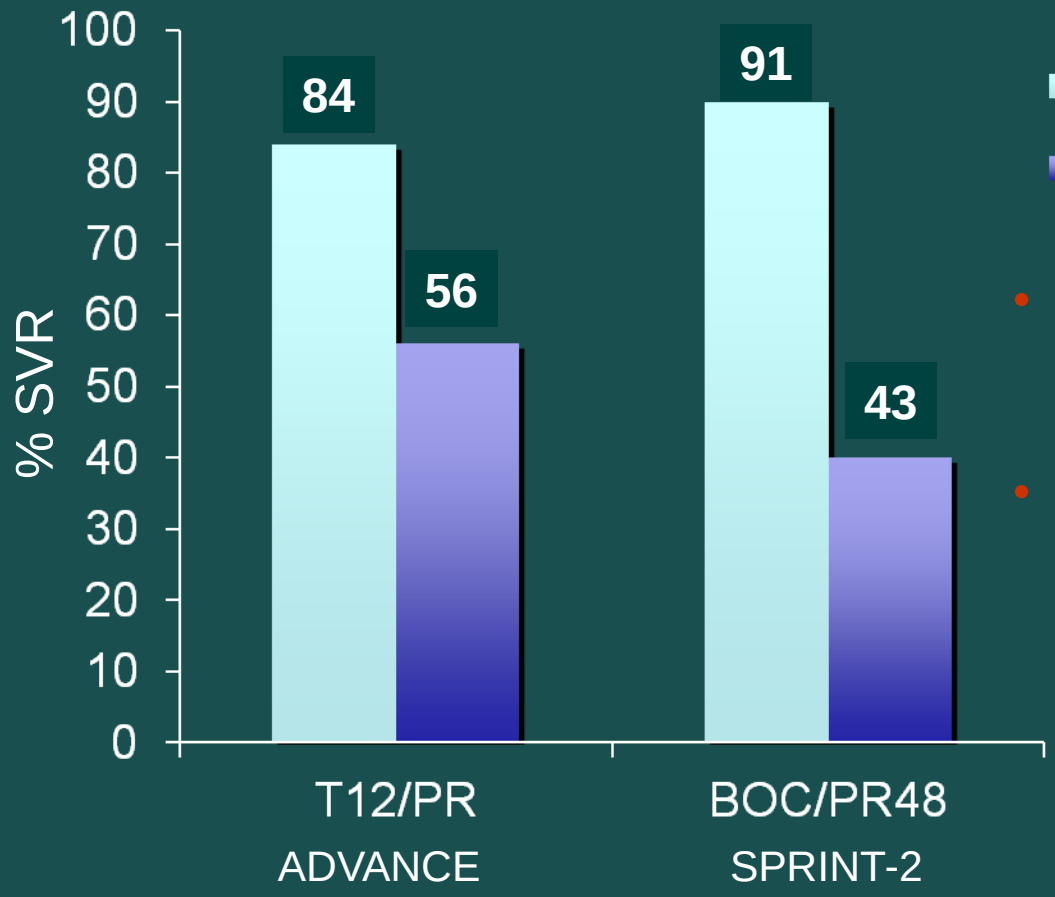
VierlingJM, et al. EASL 2011 Abstract.

Boceprevir: SVR and Lead-In Response



Poordad F, et al. N Engl J Med 2011;364(13):1195-206.

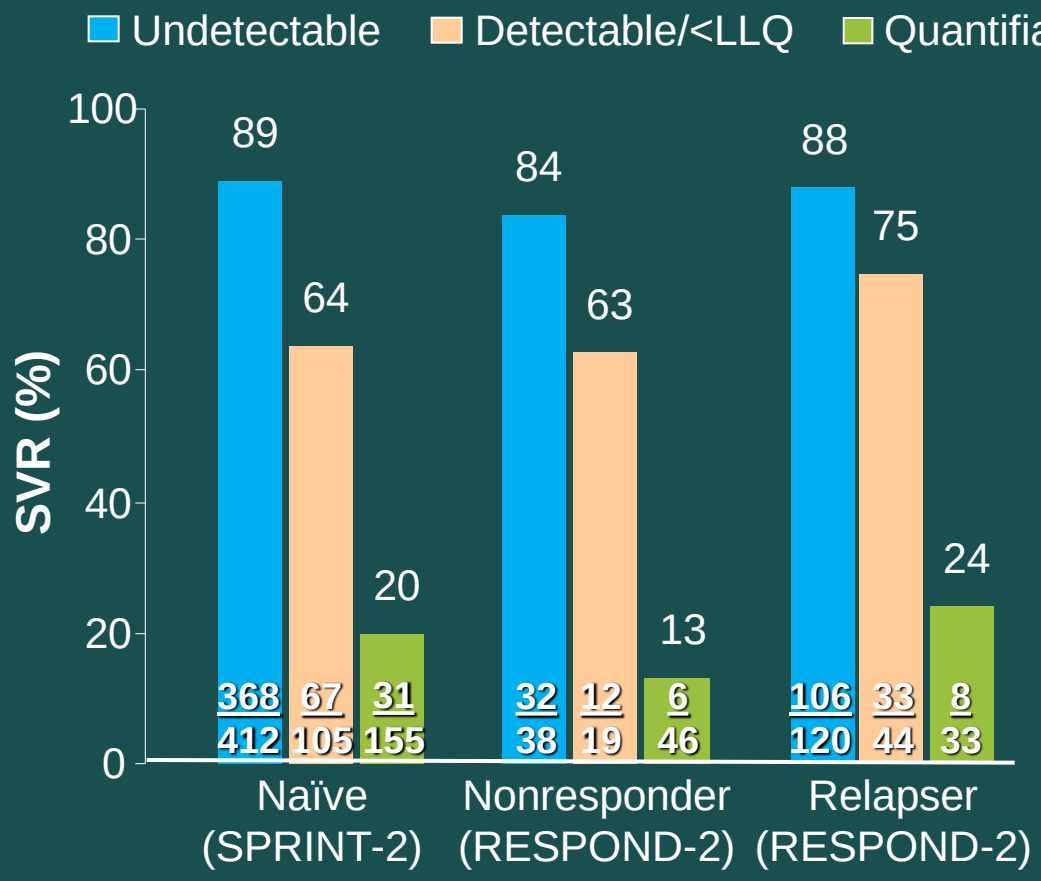
Rapid Viral Response (RVR) as a Predictor of SVR



- ADVANCE: RVR = HCV undetectable at treatment Week 4
- SPRINT-2: RVR = HCV undetectable at Treatment Week 8

Jacobson IM, et al. N Engl J Med 2011;364(25):2405-16;
Poordad F, et al. N Engl J Med 2011;364(13):1195-206.

Response at Week 8 as a Predictive Factor for SVR, by Prior Response to PR



- Prior response not highly predictive for SVR after assessment of Week 8 response

Lawitz E, et al. AASLD 2011 Abstract.

Conclusions and Discussion

- On-treatment response to PEG-IFN/ribavirin lead-in treatment and RVR are stronger predictors of SVR than any single pretreatment variable
- Direct correlation between decrease in HCV RNA after 4-week lead-in and SVR rate

Conclusions and Discussion

- Patients with <1-$\log_{10}$ decrease in HCV RNA after PR lead-in who have other negative predictors (e.g., cirrhosis) have poor outcome
  - Risk/benefit ratio!
  - Discontinuation might be considered
  - "Wait and see" strategy? Better treatment options to come?
- Conversely, patients with undetectable HCV RNA after lead-in may not benefit from treatment with a protease inhibitor, in terms of SVR, given the high SVR rate with PR alone