2013 6th PARIS HEPATITIS CONFERENCE

International Conference on the Management of Patients with Viral Hepatitis

*How to optimize current therapy of G1 patients*

# Predictors of response

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# HCV G1 treatment: predicting efficacy

- Predictors of HCV response to antivirals:
  - Host/virus/extrinsic factors linked *a priori* with outcome of therapy (pre-treatment predictors)
  - Factors evaluable during treatment (on-treatment predictors)
  - Predictors of treatment-related adverse outcomes
- Predictors should assist physician and patient in decision making concerning:
  - Whether to start and on which regimen
  - Whether to stop
  - Whether to modify the regimen

# HCV G1: determinants of efficacy of P/R

## Viral Factors :

- High viral load
- Viral kinetic under SOC
- NS5a & core mutations
- HCV Genotype 1a vs 1b(?)

## Disease-related factors:

- Cirrhosis
- Pattern of previous non-response
- Co-infection with HIV
- Organ transplant

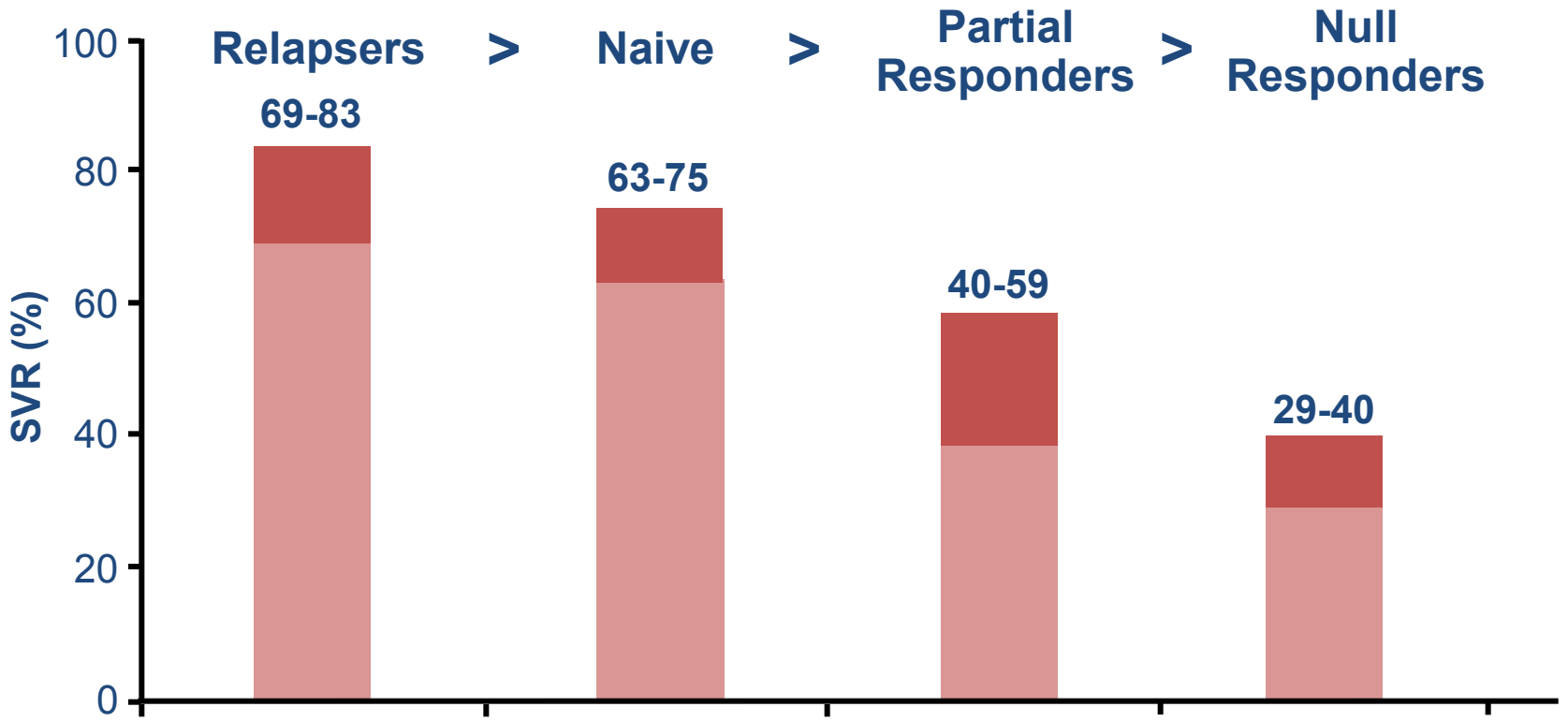
## Treatment-related factors:

- Low dose and short duration of Peg-IFN and ribavirin
- Low tolerability and AEs
- Low adherence

## Host factors :

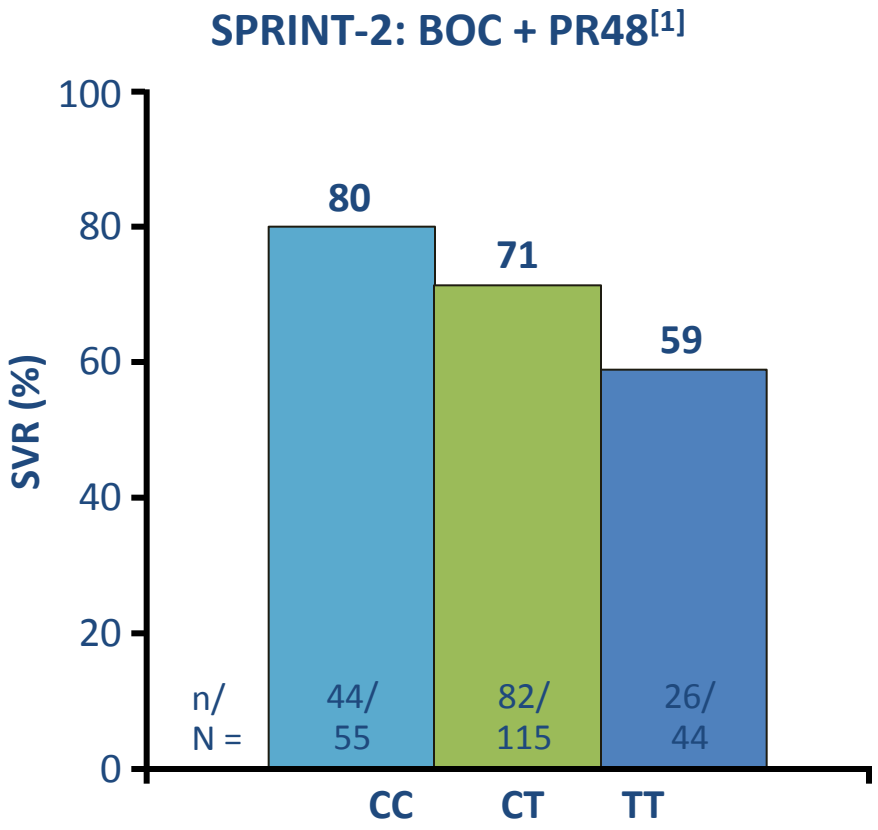
- IL28b polymorphism
- Male sex
- Age > 40 years
- overweight
- Insulin resistance
- Alcohol
- Ethnicity : AAs > caucasians> Asian

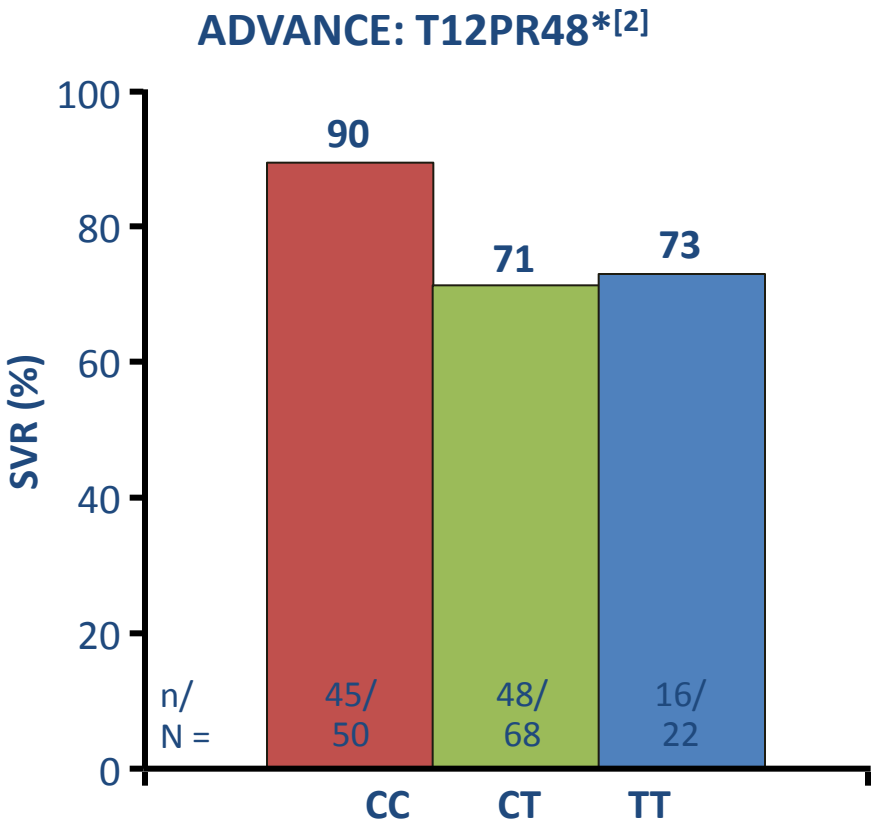
# HCV G1: SVR rates with P/R/ BOC or TVR according to treatment history




Poordad F, et al. N Engl J Med. 2011;364:1195-1206. Jacobson IM, et al. N Engl J Med. 2011;364: 2405-2416. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. Zeuzem S, et al. N Engl J Med. 2011;364: 2417-2428. Bronowicki JP, et al. EASL 2012. Abstract 11.

# SVR in naive HCV G1 patients according to IL28B genotype



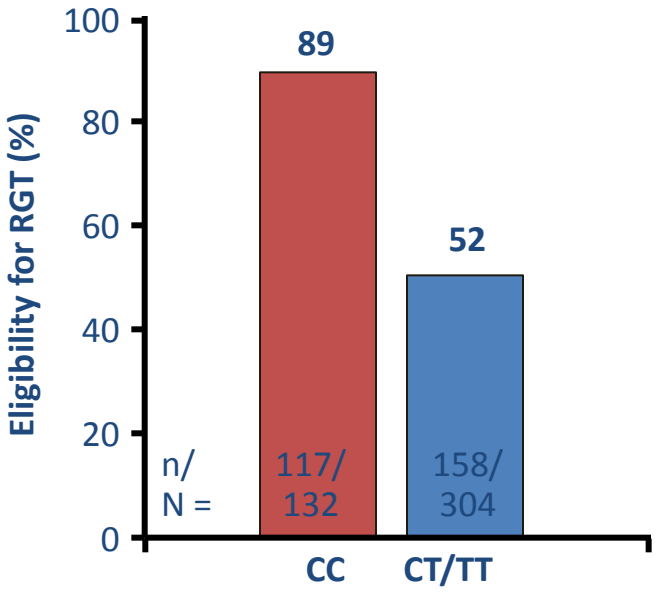




**IL28B* testing in ADVANCE was in whites only.

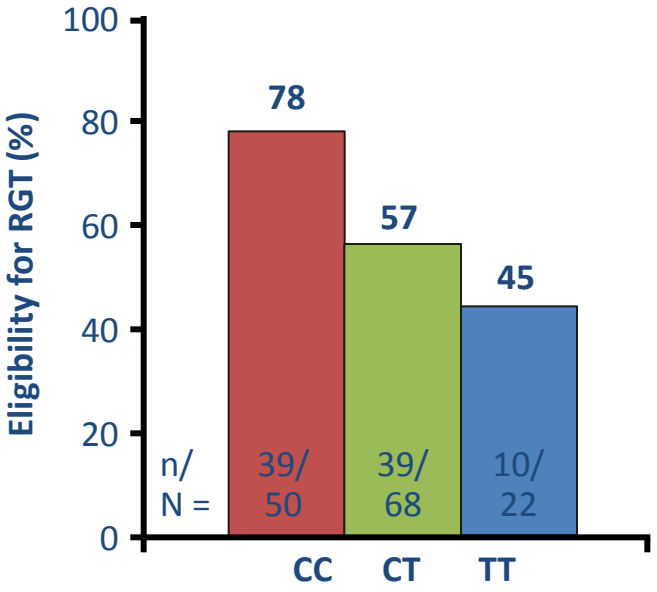
1. Poordad F, et al. Gastroenterology. 2012;143:608-618.
2. Jacobson IM, et al. EASL 2011. Abstract 1369.

# *IL28B* genotype as predictor of likelihood of shortened therapy

**SPRINT-2: BOC +**
PegIFN-α2b/RBV [1]




**ADVANCE: T12 +**
PegIFN-α2a/RBV *[2]



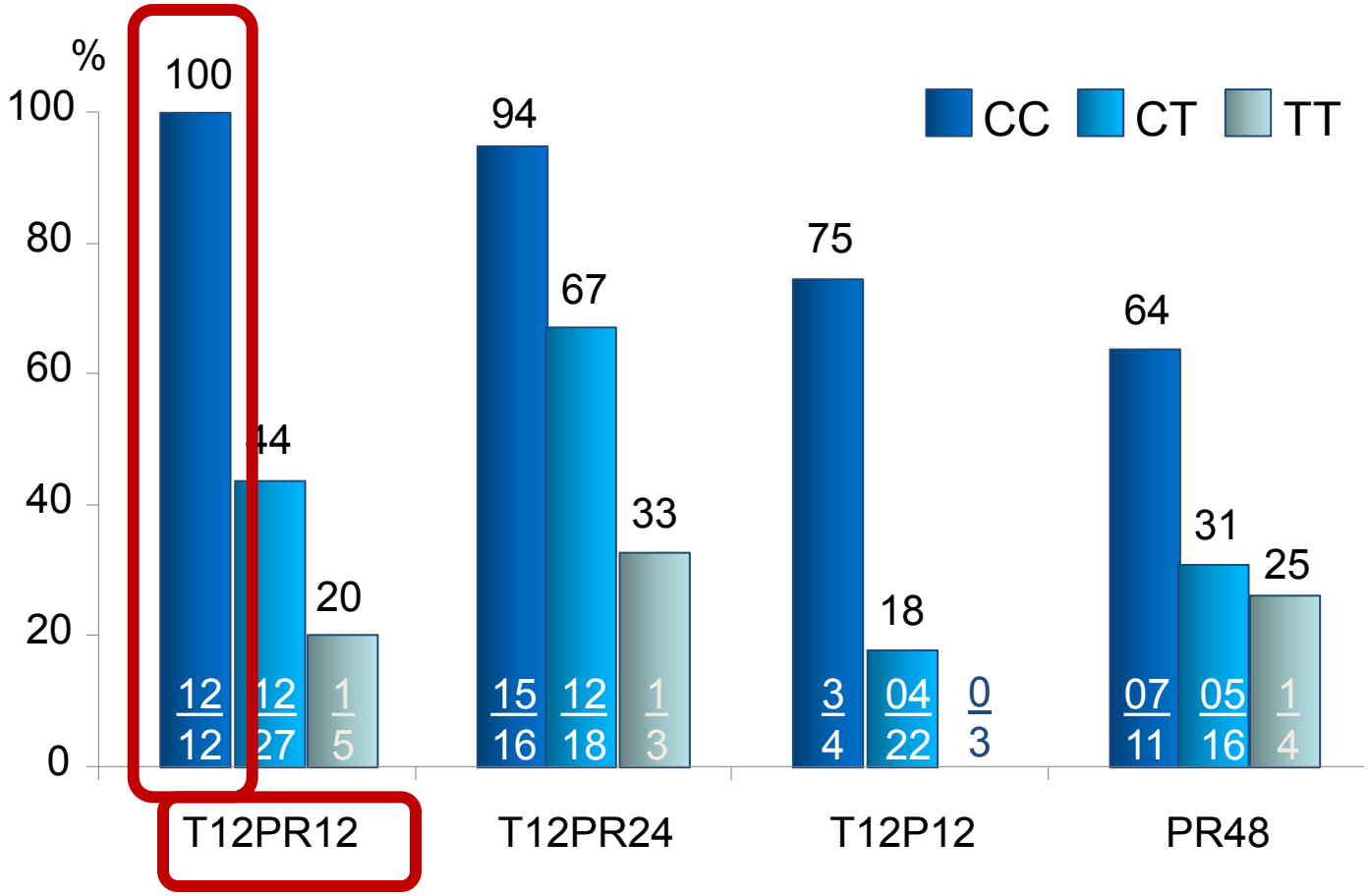

**IL28B* testing in ADVANCE was in whites only.

1. Poordad F, et al. Gastroenterology. 2012;143:608-618. 2. Jacobson IM, et al. EASL 2011. Abstract 1369.

# Can we shorten treatment duration in IL28B CC patients ? Lessons from PROVE2

141/171 French patients had IL28B genotype done retrospectively

SVR according to treatment arm and IL28B genotype




*Bronowicki JP, EASL 2012, Abs. 1094*

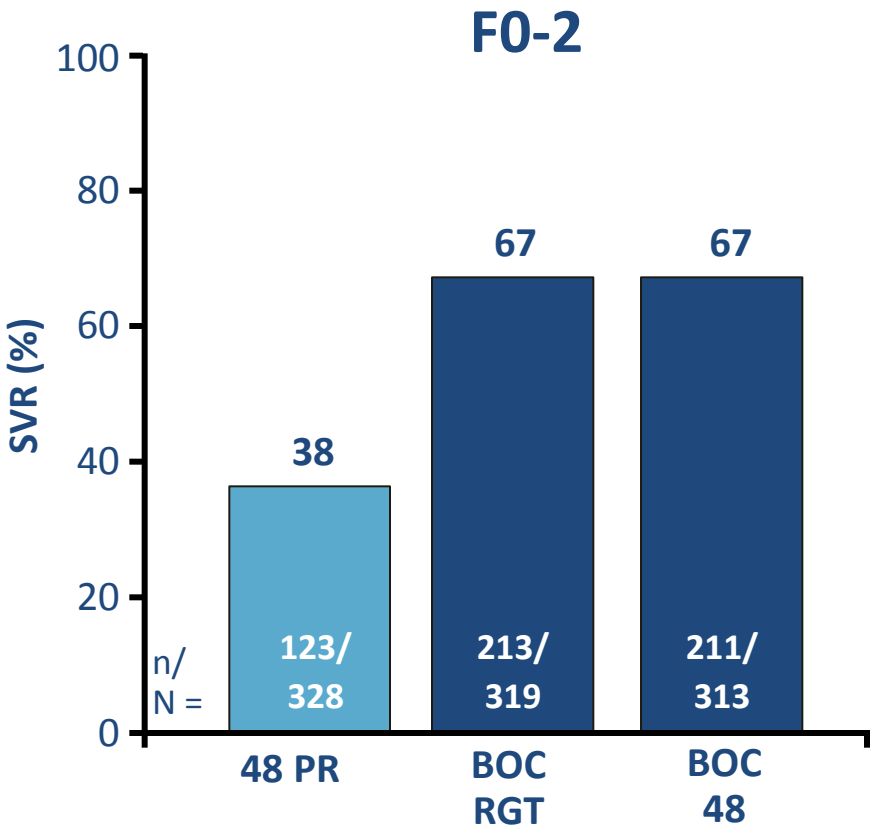
# *IL28B* genotype is not a predictor to exclude patients from triple therapy

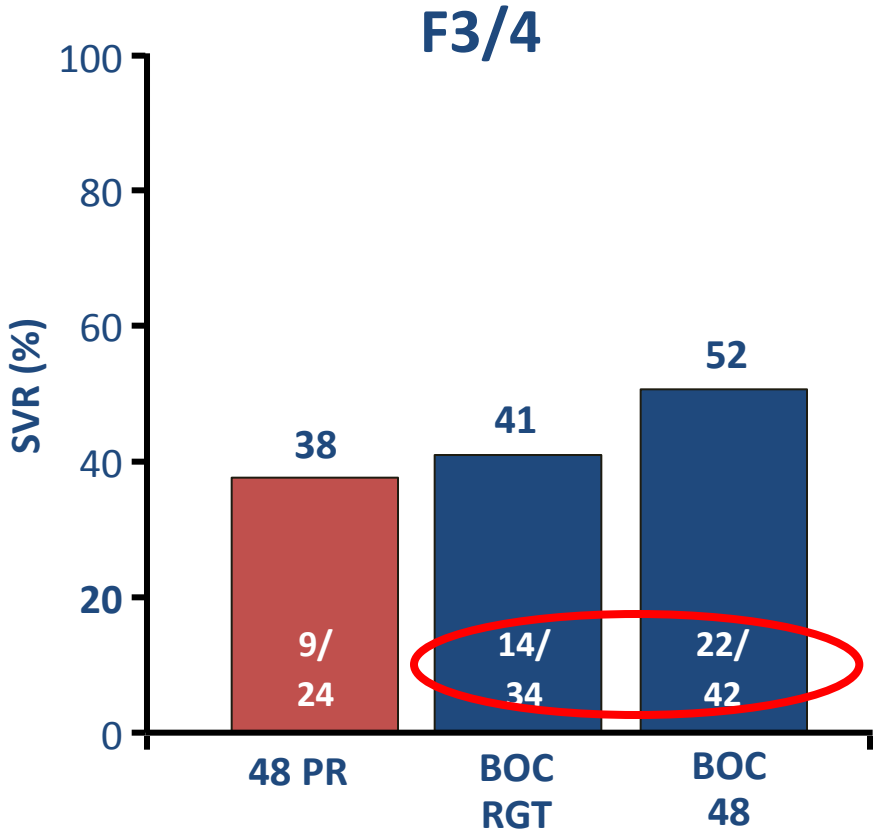
**_IL28B_ is a predictor of IFN sensitivity, but:**

- If patients have favorable CC genotype
  - Likelihood of SVR is high with pegIFN/RBV alone, but triple therapy may allow shorter therapy and, in one TVR study, higher SVR rates[1]
- If patients have unfavorable CT/TT genotype
  - Likelihood of SVR is higher with triple therapy than with pegIFN/RBV
    - 59% to 71% in SPRINT-2[2]
    - 71% to 73% in ADVANCE[1]
- Limited value of *IL28B* genotyping in treatment-experienced patients
  - Most have unfavorable TT or CT genotype
  - May be useful if pattern on non-response is unknown

1. Jacobson IM, et al. EASL 2011. Abstract 1369. 2. Poordad F, et al. Gastroenterology. 2012;143:608-618.

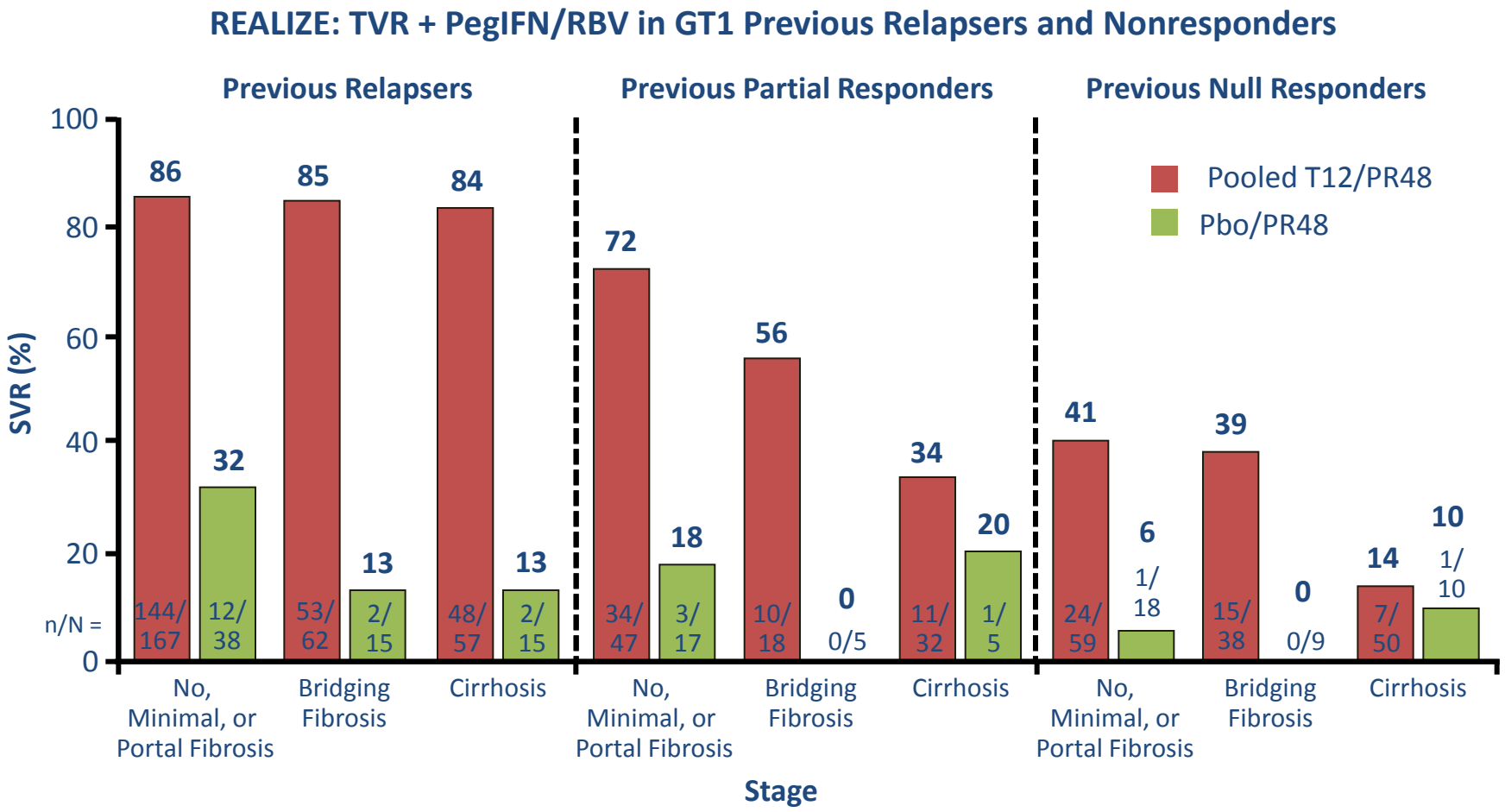
# SVR in naive HCV G1 patients according to stage of fibrosis (P/R/BOC)




Poordad F, et al. N Engl J Med. 2011;364:1195-1206.

# SVR in treatment-experienced HCV G1 patients according to stage of fibrosis (P/R/TPV)



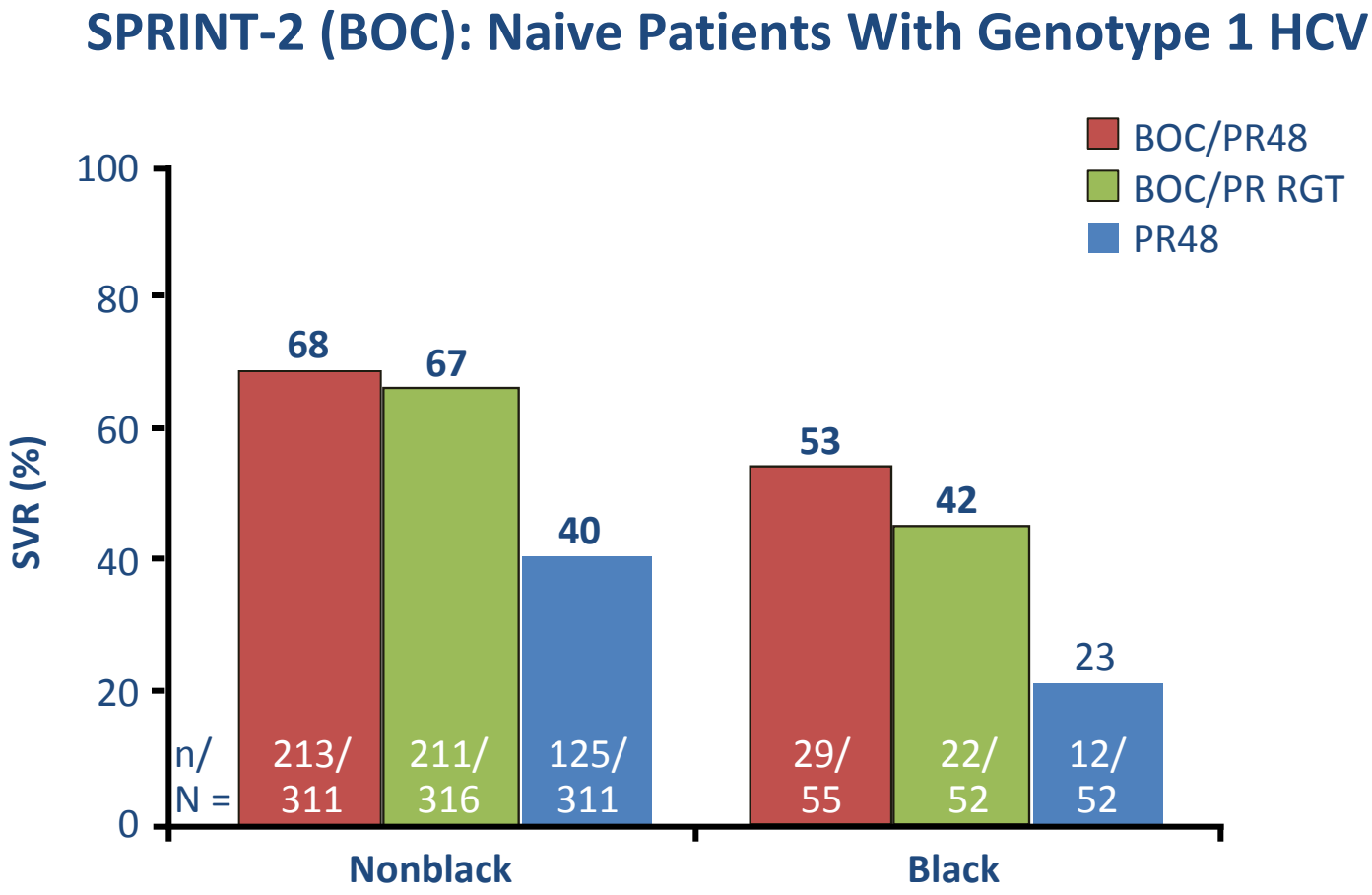

Zeuzem S, et al. EASL 2011. Abstract 5.

# HCV G1: SVR by stage of fibrosis on triple therapy

| Fibrosis Stage | SVR Rate (Phase III Trials), % |
|---|---|
| **Treatment-naive patients (TVR and BOC)[1,2]** | |
| Stage 0/1/2 | 67-78 |
| Stage 3/4 | 41-62 |
| **Treatment-experienced patients** | |
| Stage 0/1/2 (BOC)[3] | 66 |
| Stage 3/4 (BOC)[3] | 44 |
| Relapser (TVR)[4] | |
| ▪ No/minimal/portal | 86 |
| ▪ Bridging | 85 |
| ▪ Cirrhosis | 84 |
| Partial responder (TVR)[4] | |
| ▪ No/minimal/portal | 72 |
| ▪ Bridging | 56 |
| ▪ Cirrhosis | 34 |
| Null responder (TVR)[4] | |
| ▪ No/minimal/portal | 41 |
| ▪ Bridging | 39 |
| ▪ Cirrhosis | 14 |

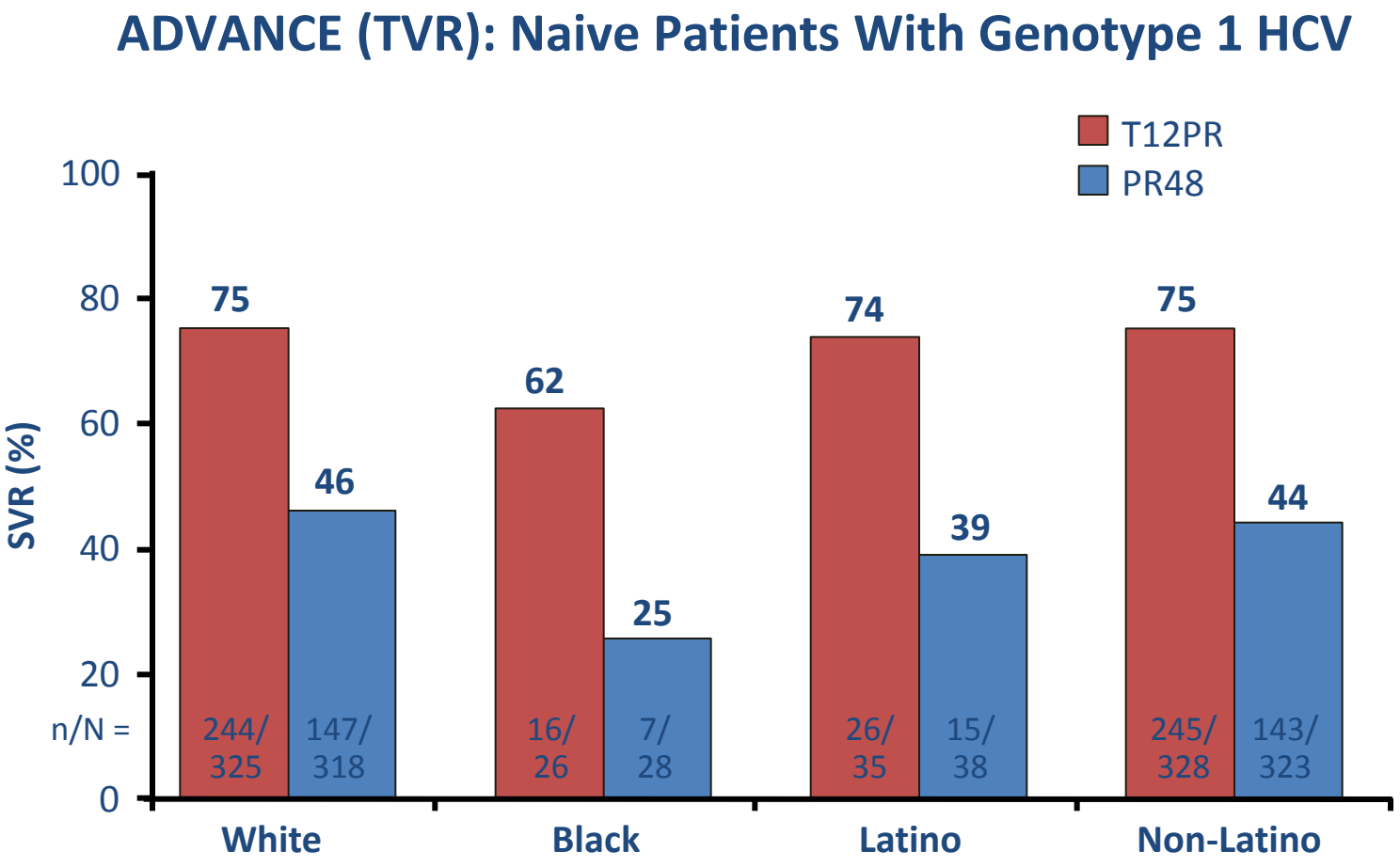
1. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 2. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
3. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 4. Zeuzem S, et al. EASL 2011. Abstract 5.

# HCV G1: SVR according to ethnicity



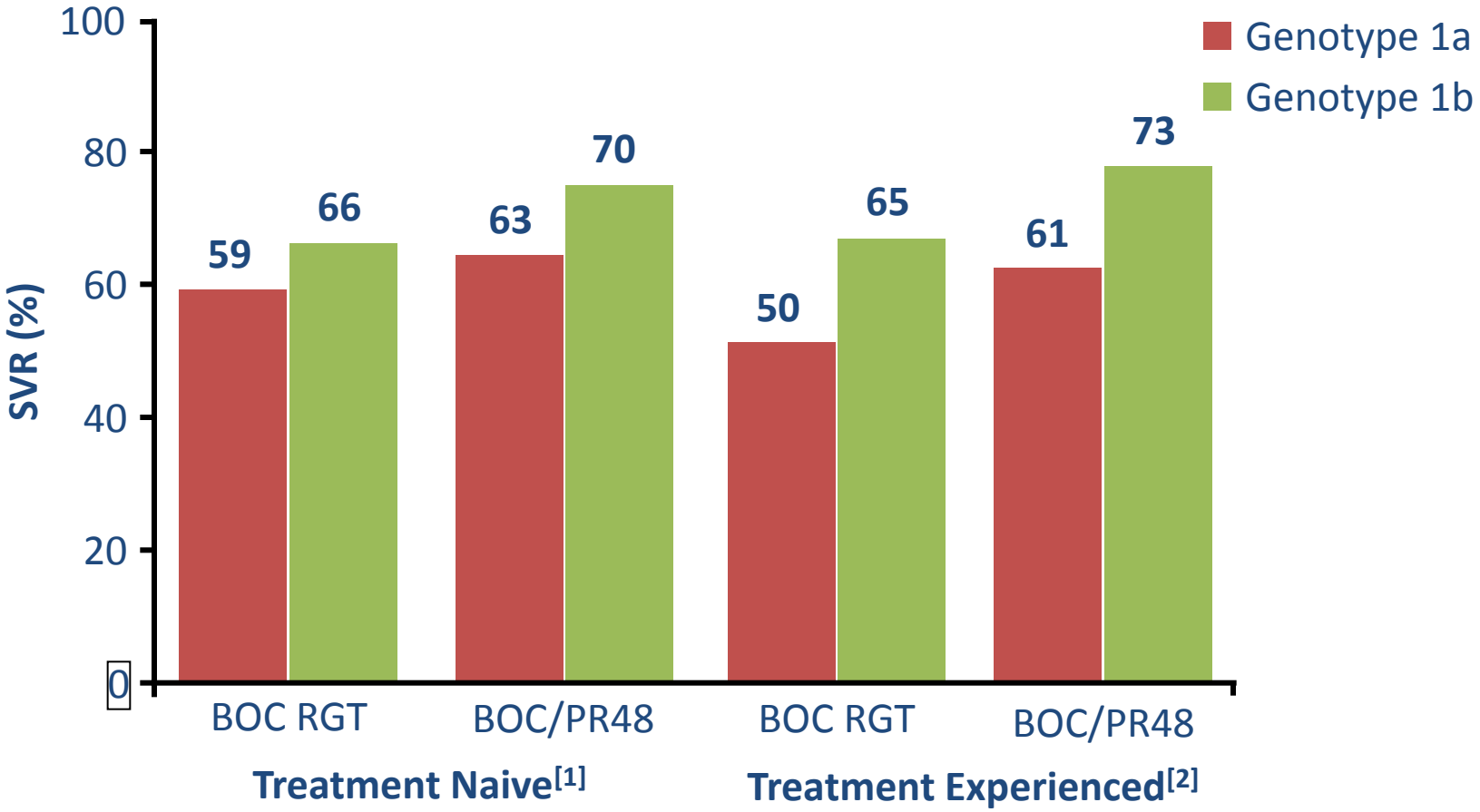

Poordad F, et al. N Engl J Med. 2011;364:1195-1206.

# HCV G1: SVR according to ethnicity




Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.

# Higher SVR Rates With BOC in Pts With HCV Genotype 1b vs 1a

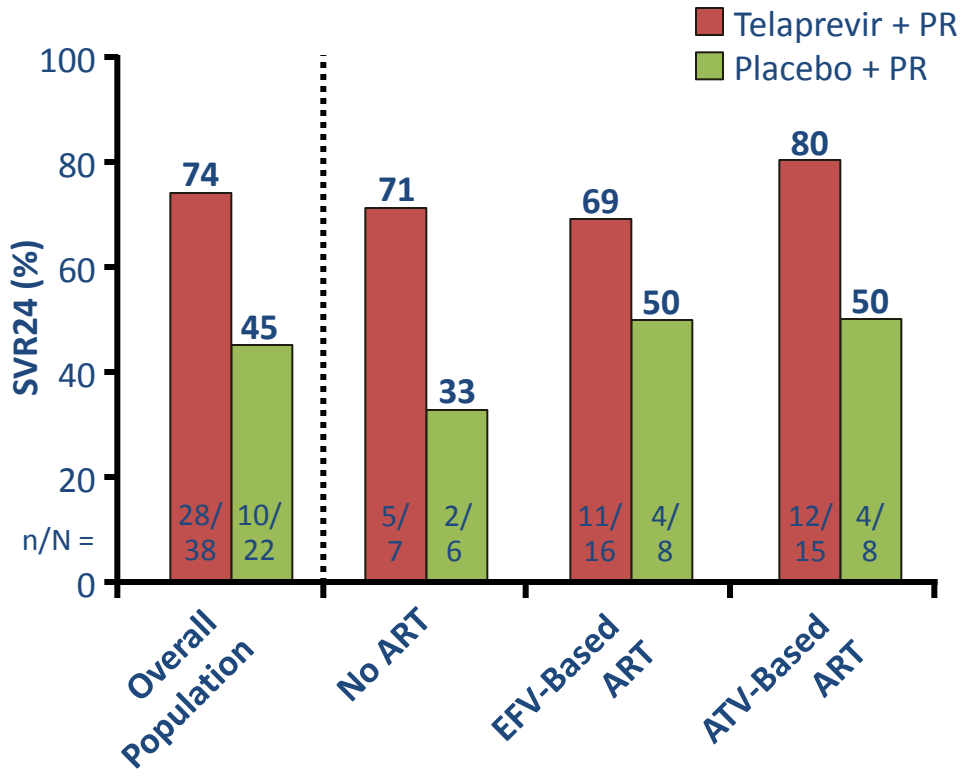




1. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

# Study 110: SVR24 With TVR + PegIFN/RBV in HCV GT1/HIV-Coinfected Patients

- Higher SVR24 rate with TVR-based therapy

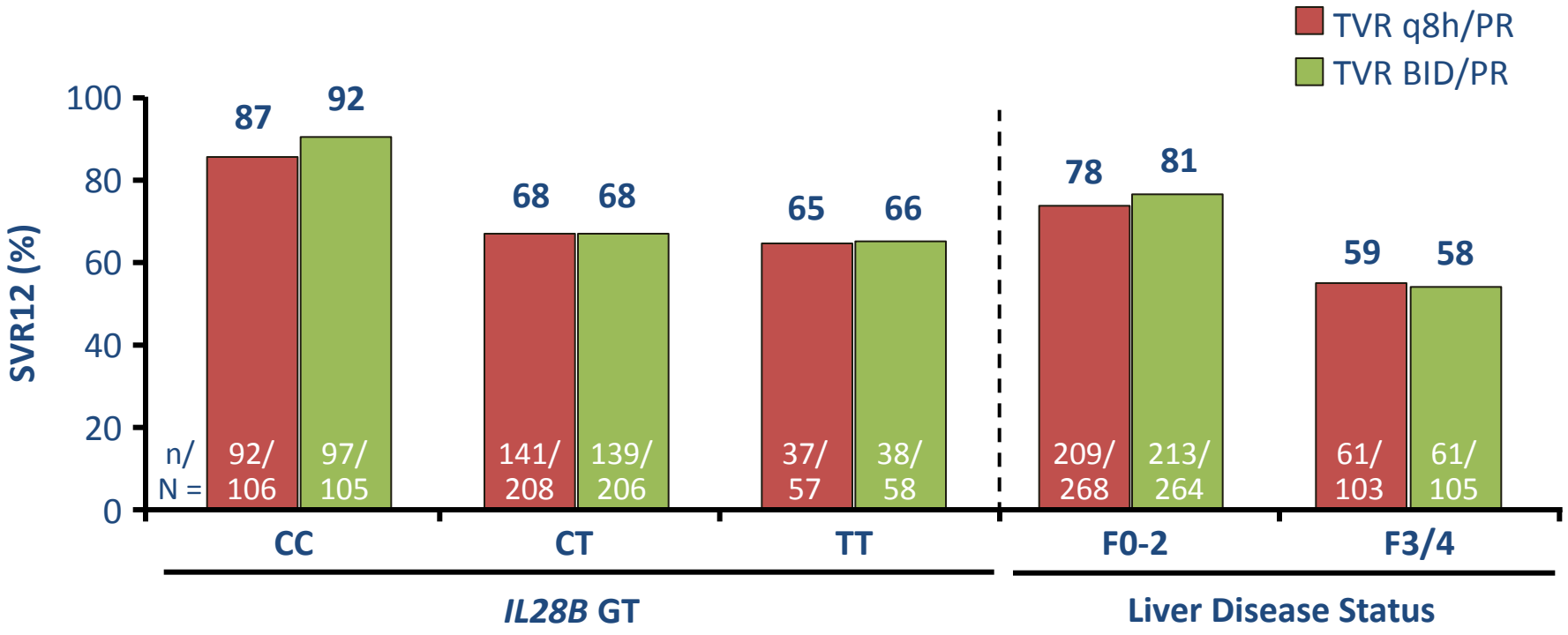



- No significant drug–drug interactions with TVR and ART
  - TVR plasma levels similar in patients with or without ART
  - EFV and ATV/RTV plasma levels similar in patients with or without TVR
- No HIV breakthroughs in patients using ART during HCV treatment
- Safety and tolerability similar to treatment in patients with HCV monoinfection

Sulkowski MS, et al. AASLD 2012. Abstract 54. Reproduced with permission.

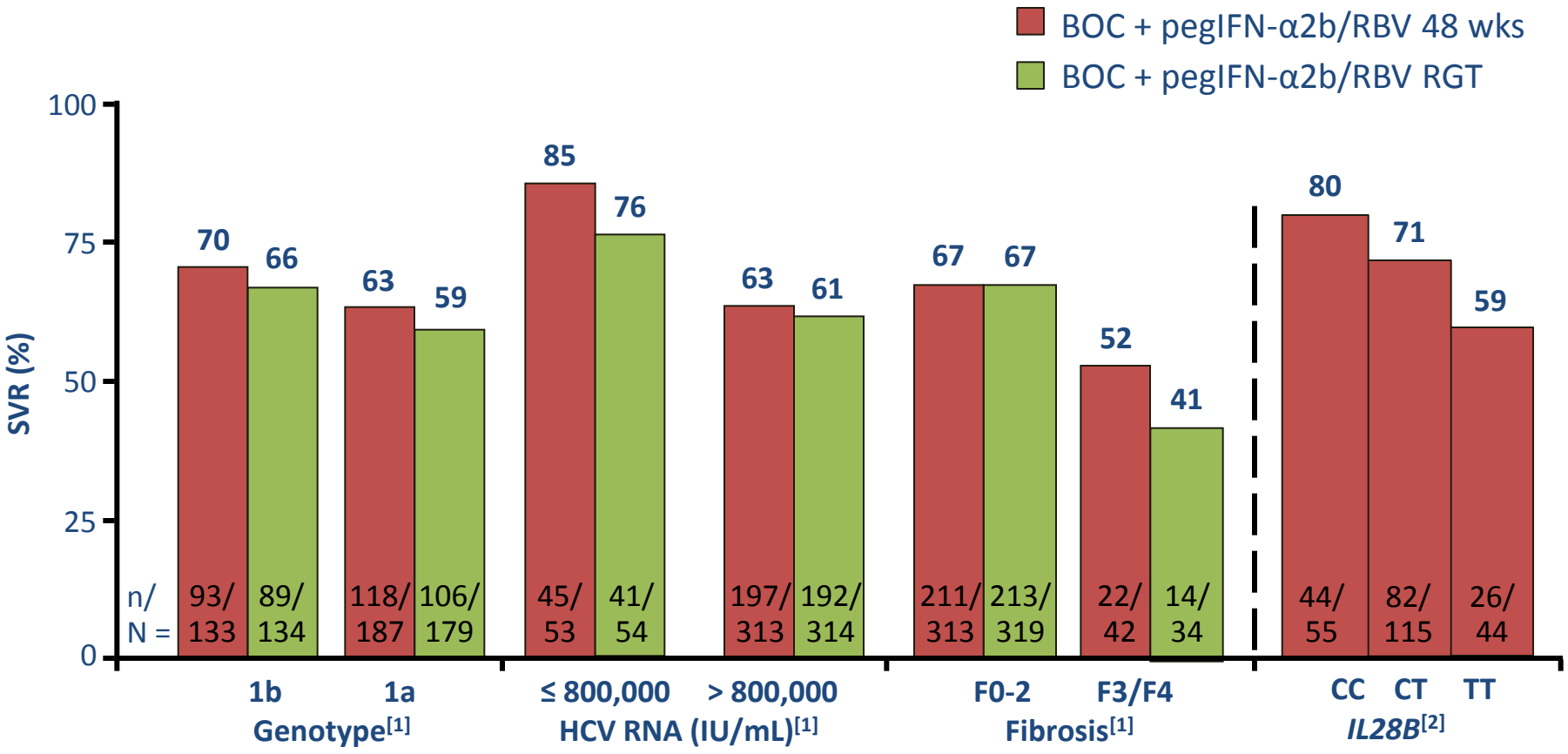
# OPTIMIZE: efficacy of TVR BID vs TID in HCV G1 patients according to predictors

Similar safety and tolerability profile in both treatment arms




Buti M, et al. AASLD 2012. Abstract LB-8.

# Pre-treatment predictors: influence on SVR in HCV G1 naives (SPRINT-2)

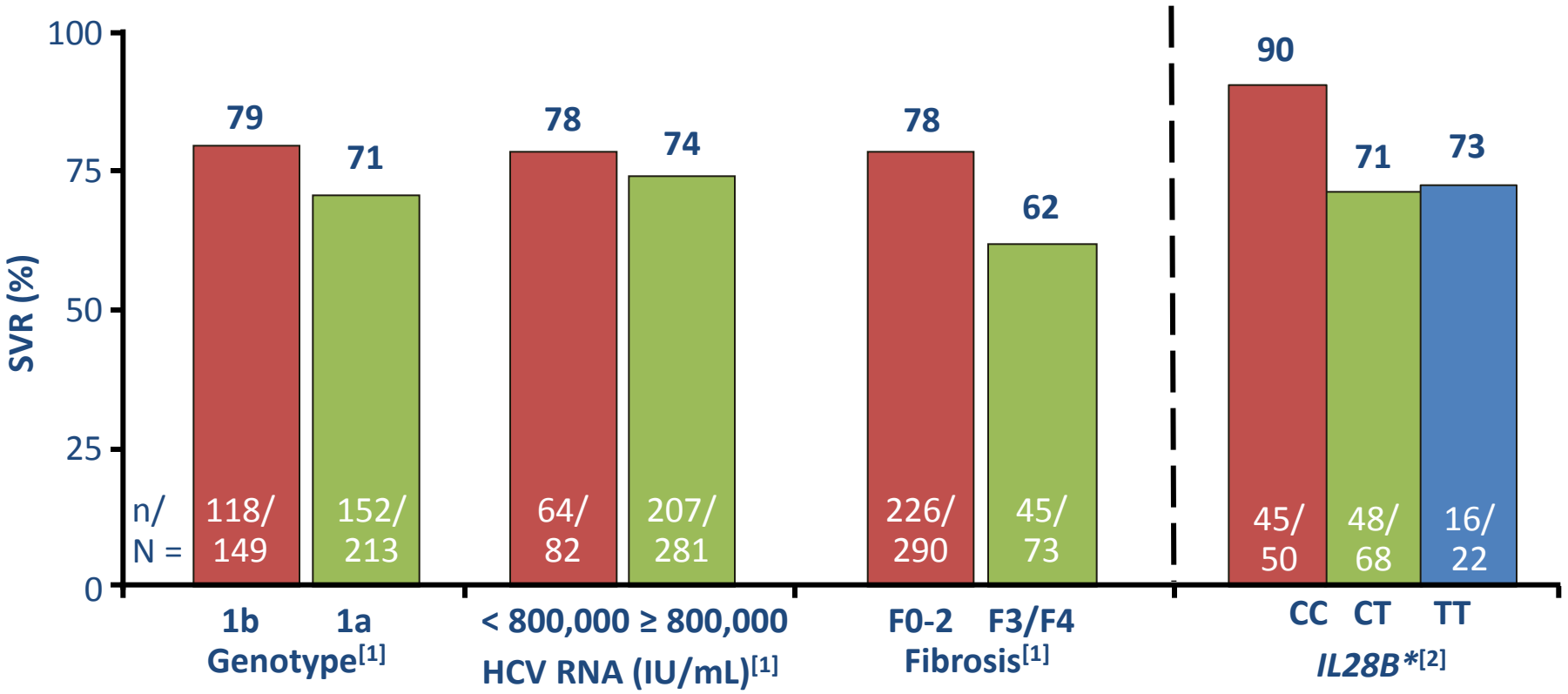




1. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
2. Poordad F, et al. Gastroenterology. 2012;143:608-618.

# Pre-treatment predictors: influence on SVR in HCV G1 naives (ADVANCE)

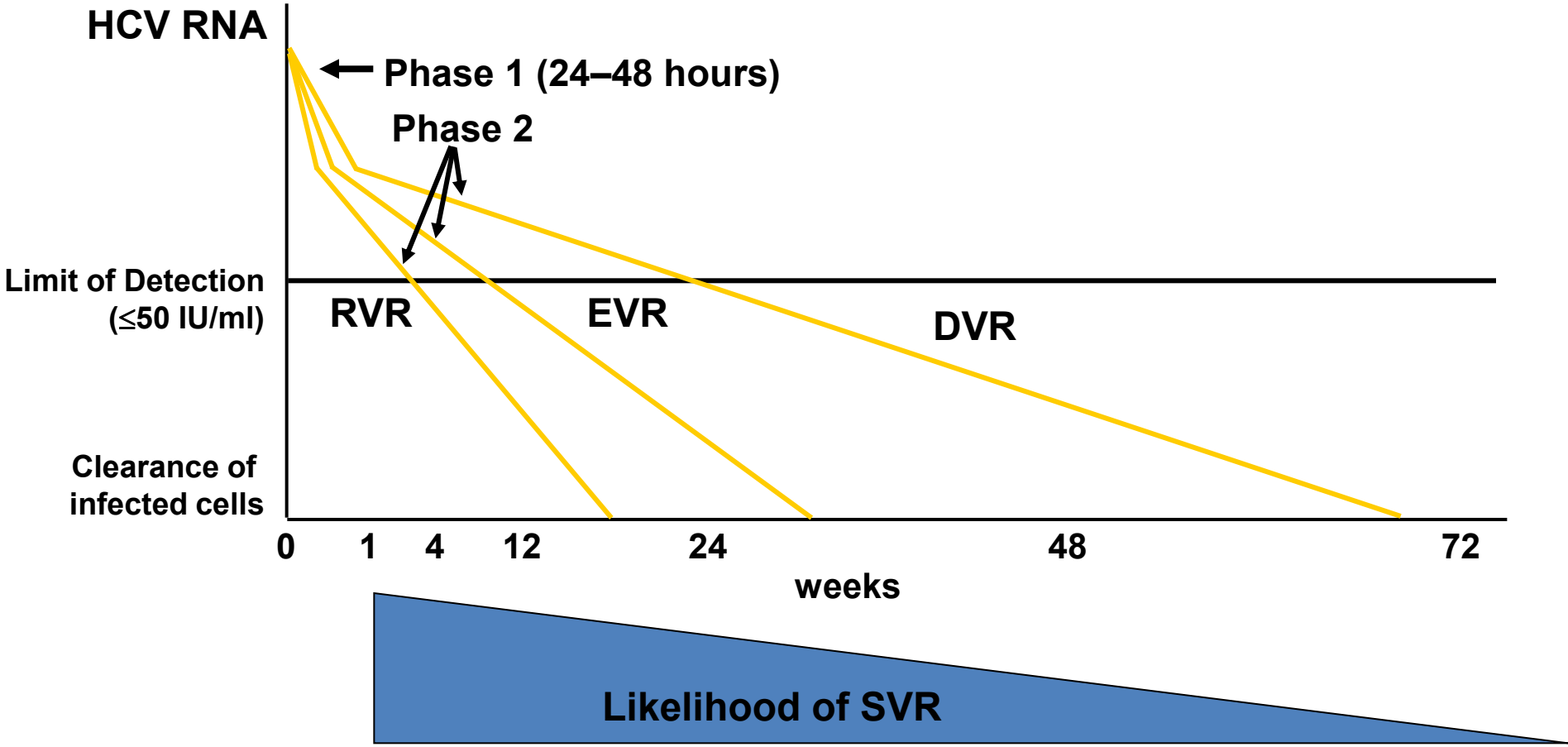
Data from TVR12 + pegIFN-α2a/RBV arm only




**IL28B* testing was in whites only.

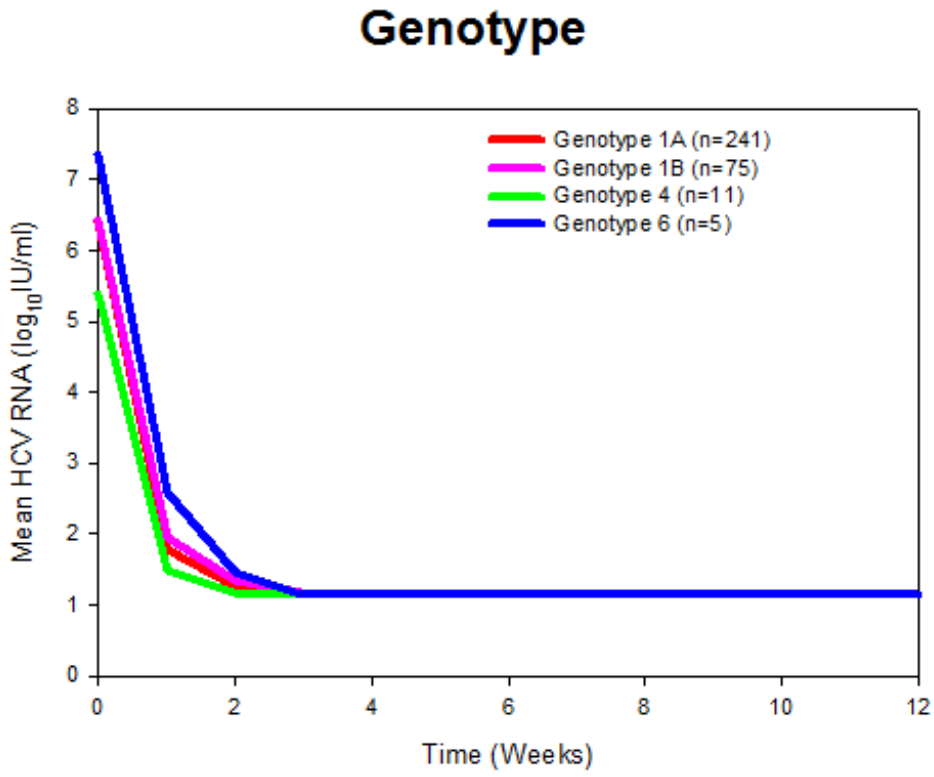
1. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 2. Jacobson IM, et al. EASL 2011. Abstract 1369.

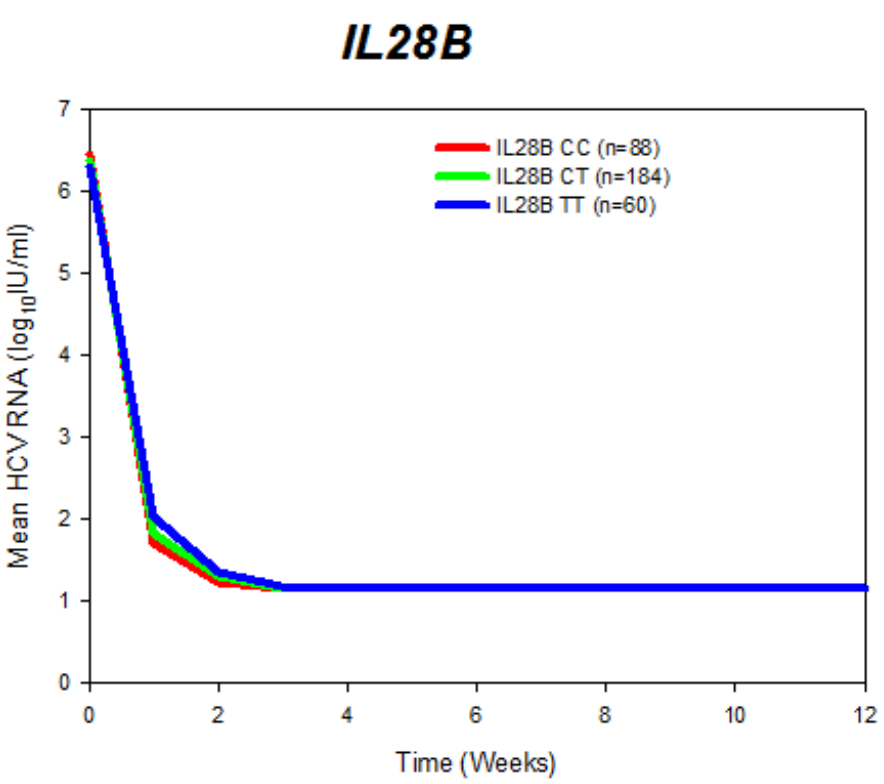
# Likelihood of SVR according to viral response in the first weeks of therapy




DVR, delayed virological response; EVR, early virological response; RVR, rapid virological response.

# Sofosbuvir plus RBV (ATOMIC study): Viral kinetics by HCV genotype and IL28b

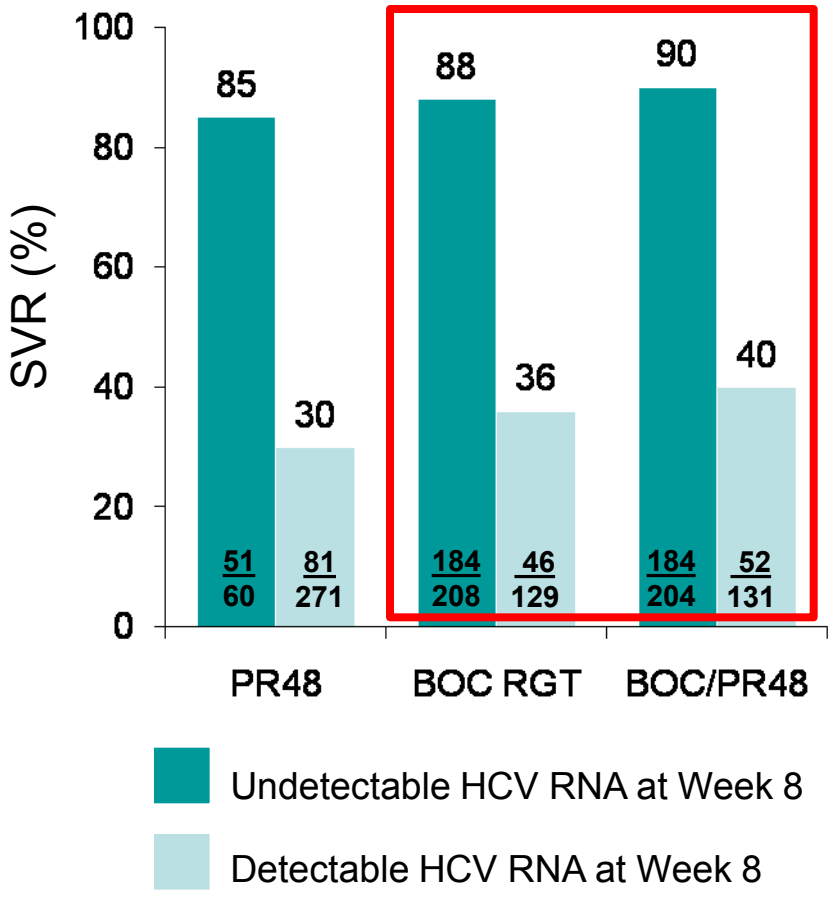


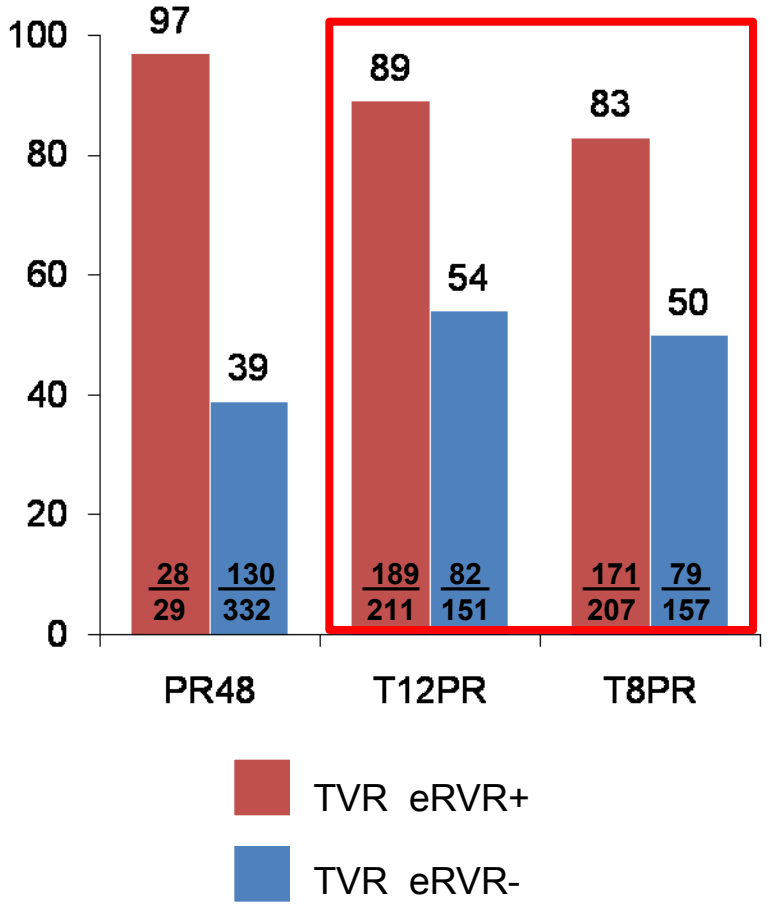




Similar viral dynamics regardless of genotype or *IL28B* status

Hassanein T, et al. AASLD 2012; Boston. #230.

# SVR for Early and Late Viral Responders With Boceprevir and Telaprevir



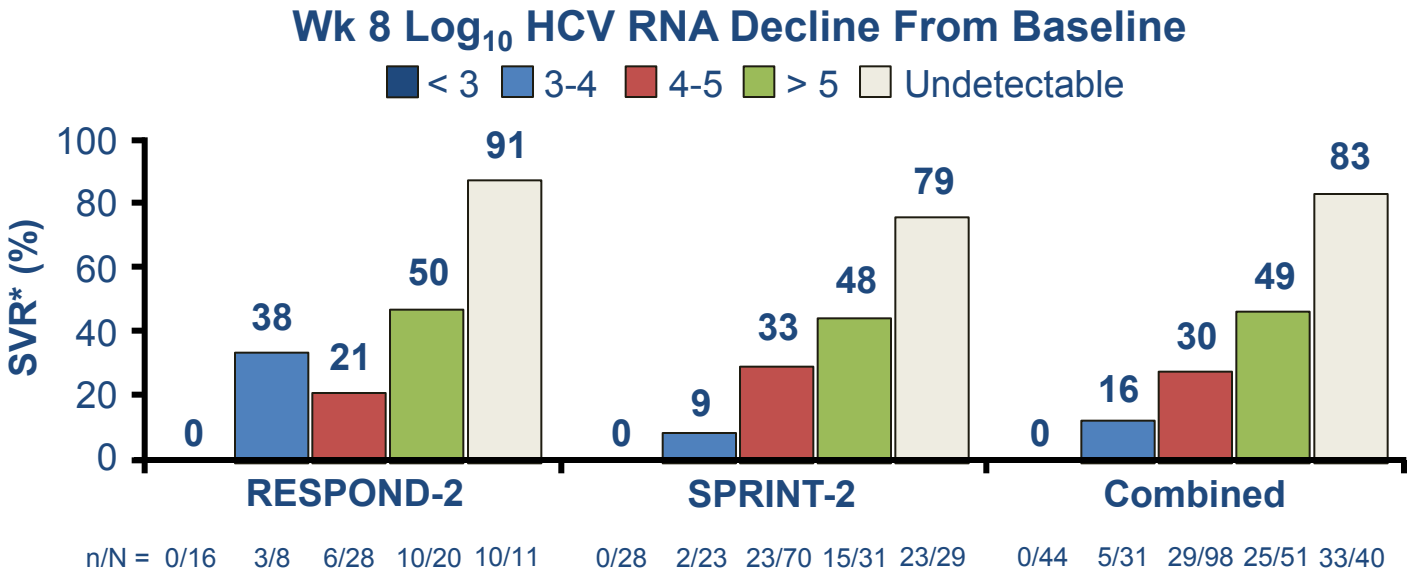




*Poordad F. N Engl J Med. 2011; 364:1195-1206.*

*Jacobson IM et al. Hepatology 2010;52(Suppl.):427A*

# Predictive Value of Wk 8 Response to BOC for SVR in Poorly IFN-Responsive Patients

- Poor IFN responsiveness: < 1 log HCV RNA decline by Wk 4 of PegIFN/RBV lead-in in BOC arms of phase III trials
- Among these patients, 0% with < 3 log decline in HCV RNA at Wk 8 of therapy achieved SVR

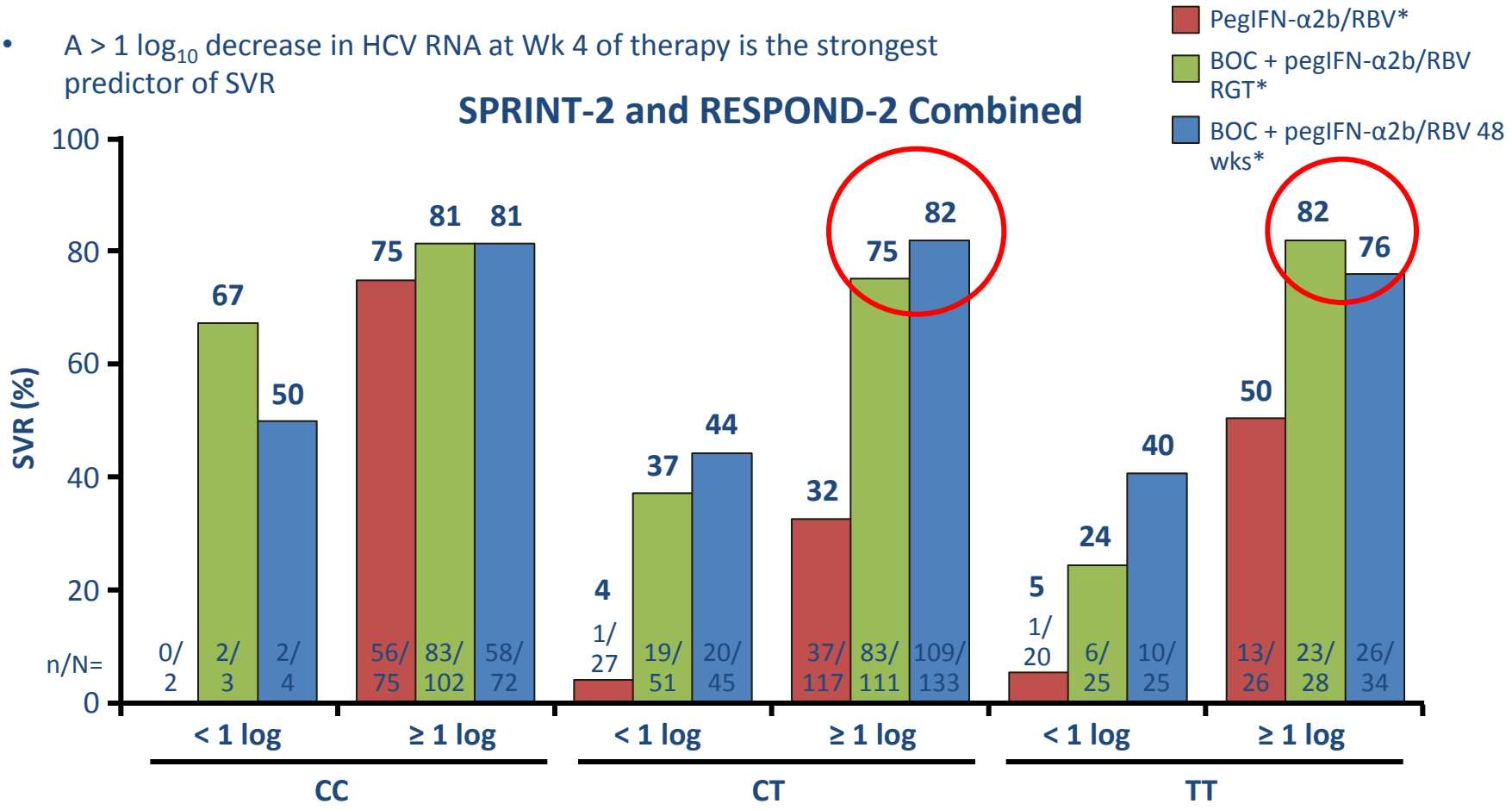



*BOC arms combined.

Poordad F, et al. Gastroenterology. 2012;143:608-618.

# Early response to P/R (Lead-in) defines likelihood of SVR of non-CC HCV G1 patients

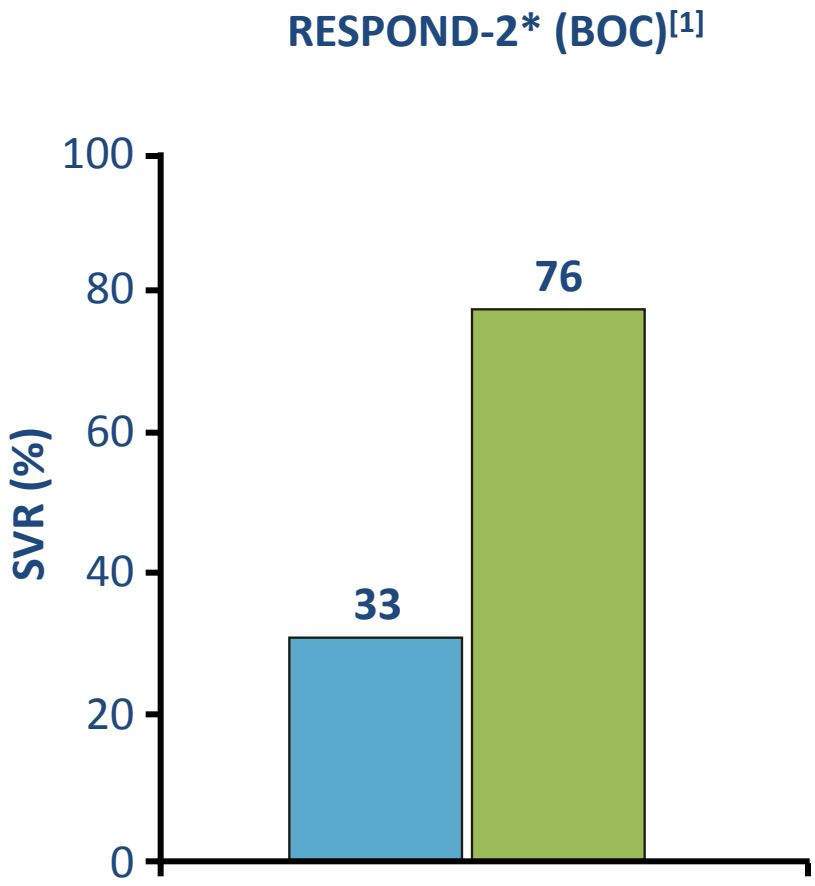
- A > 1 $\log_{10}$ decrease in HCV RNA at Wk 4 of therapy is the strongest predictor of SVR

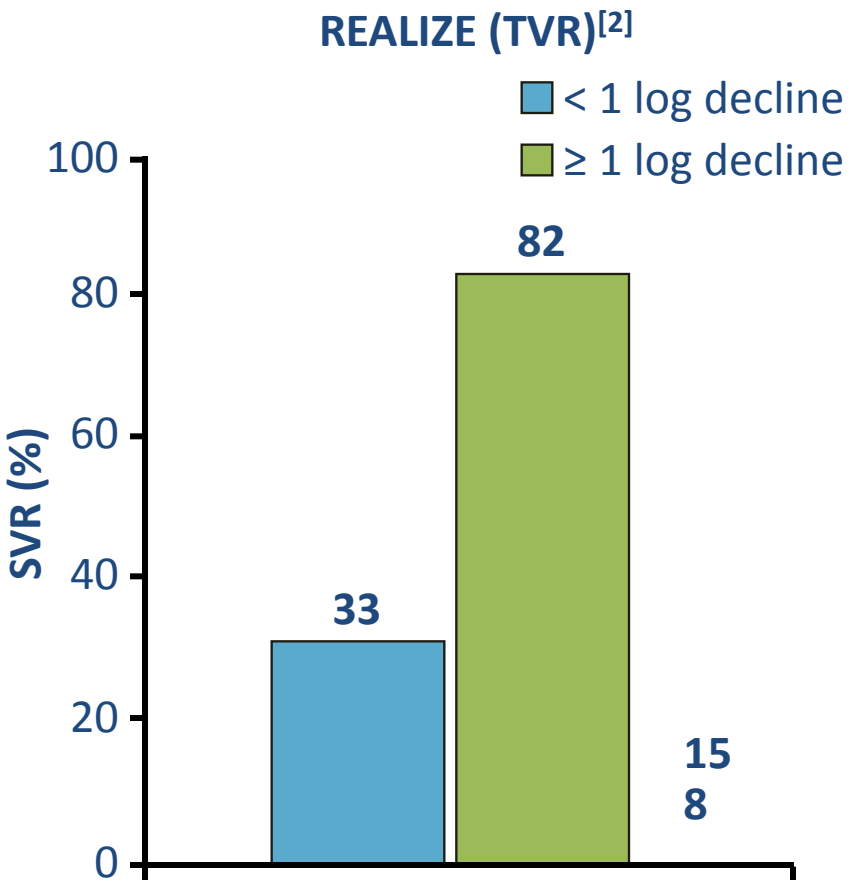



*BOC was administered with pegIFN-α2b in these trials.

Poordad F, et al. Gastroenterology. 2012;143:608-618.

# SVR by Response at Wk 4 in Lead-in Arms of Treatment-Experienced Trials

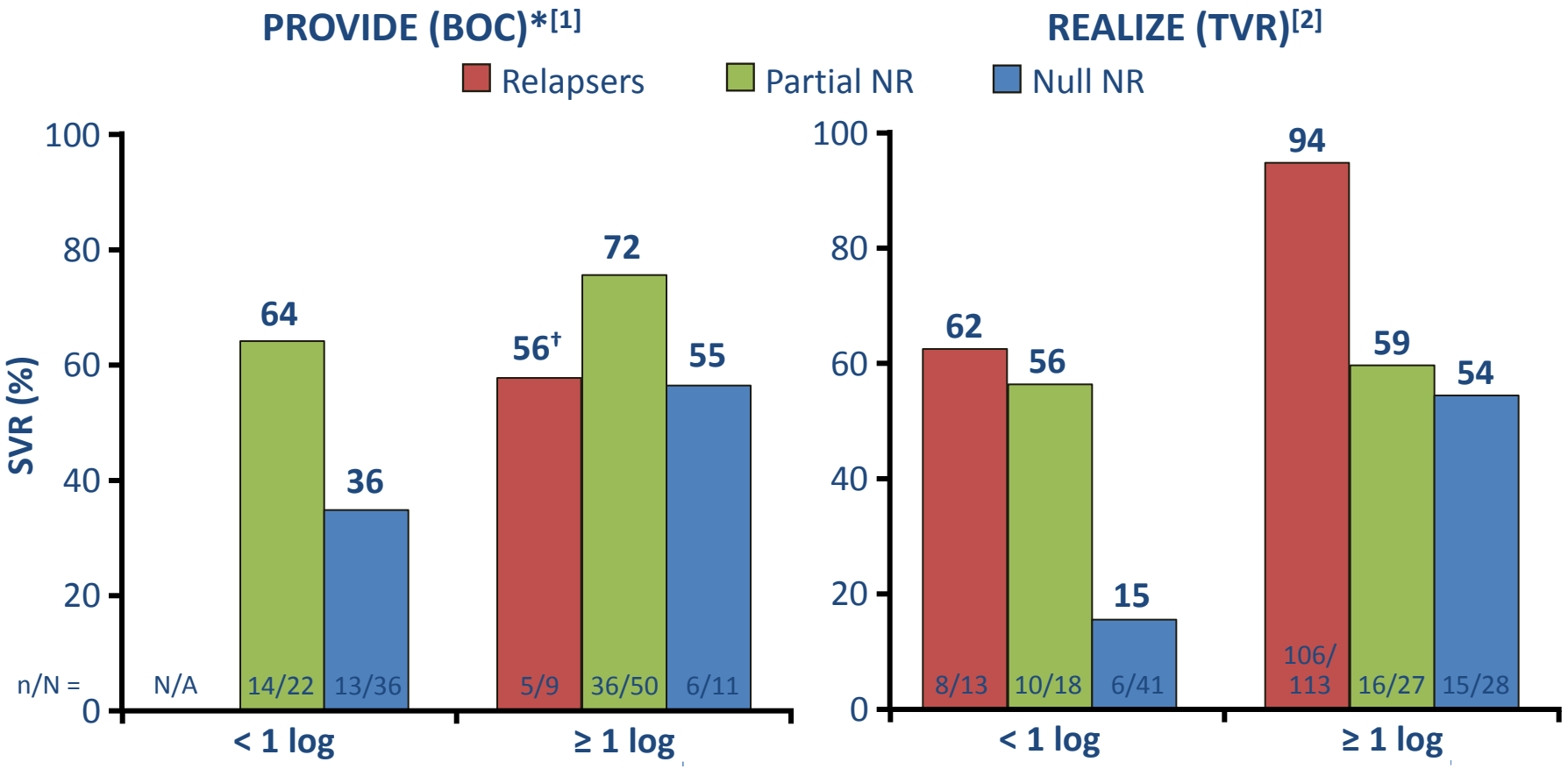



*Pooled data from RGT and fixed dose arms.

1. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 2. Foster G, et al. EASL 2011. Abstract 6.

# SVR by Response at Wk 4 in Lead-in Arms by Previous Response Category

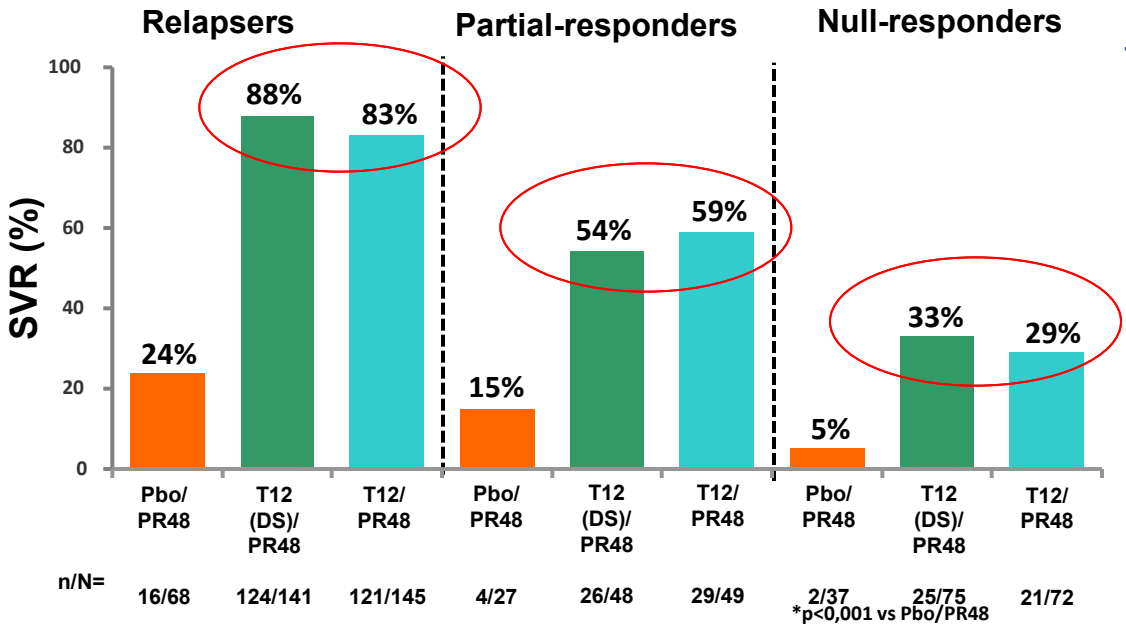


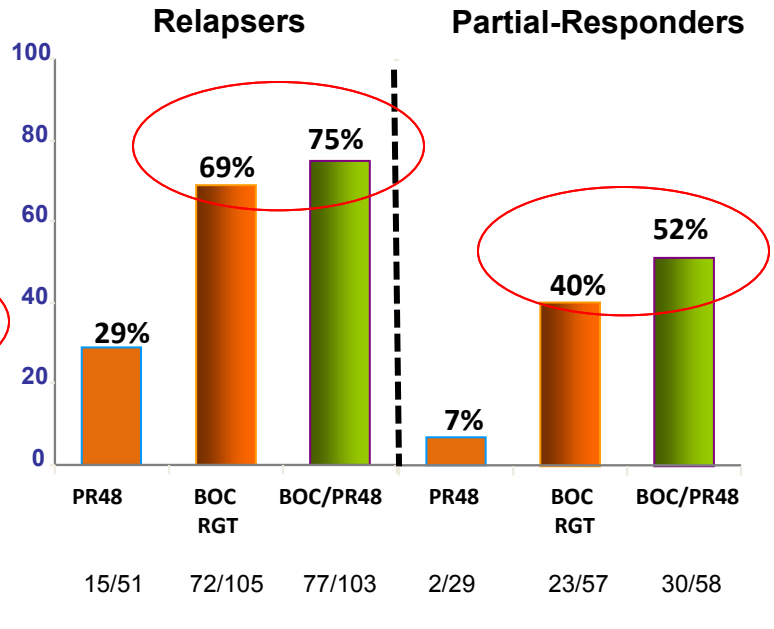

*Excludes 4 pts who dropped out during lead-in phase and 8 who were direct enrollers (ie, no pegIFN/RBV lead-in).
†40% of previous relapsers still receiving treatment.

1. Bronowicki JP, et al. EASL 2012. Abstract 11. 2. Foster G, et al. EASL 2011. Abstract 6.

# Predictive factors of SVR in treatment-experienced patients

- Previous treatment response
- Fibrosis stage
- Viral subtype (Realize) : SVR 59%  G 1a  vs 71% G 1b




*Zeuzem S. et al. N Engl J Med 2011;364:2417–28*

*Bacon BR. et al. N Engl J Med 2011; 364:1207-1217.*

# Response to lead-in is a predictor to exclude patients from triple therapy

4 wks of pegIFN/RBV lead-in before BOC (or TVR):

- Assess IFN responsiveness regardless of IL28b status
- Identifies rapid responders who may not need DAA
- Lowers HCV RNA burden
- Provides useful information regarding likelihood of SVR with addition of DAA
- Provides insight into tolerability of pegIFN/RBV backbone
- Elucidates hematologic response to pegIFN/RBV, especially in “marginal” patients; make needed dose adjustments before addition of DAA

# Multivariate analysis: baseline predictors of severe complications*

| Predictors | OR | 95%CI | p-value |
|---|---|---|---|
| **Prothrombin Time** (per unit decrease) | 1.03 | 1.01-1.06 | 0.038 |
| **Age** (per year increase) | 1.05 | 1.01-1.11 | 0.025 |
| **Platelet count** ≤100,000/ $mm^3$ | 3.19 | 1.32-7.73 | 0.0098 |
| **Albumin level** <35 g/L | 4.95 | 2.04-12.01 | 0.0004 |

* Death, severe infection and hepatic decompensation, n=32

Data by courtesy of Prof. J-P Bronowicki

# Multivariate analysis: predictors of anemia <8 g/dL or blood transfusion *

| Predictors | OR | 95%CI | p-value |
|---|---|---|---|
| Age<br>(per year increase) | 1.06 | 1.026-1.09 | 0.0003 |
| Gender<br>(Female) | 2.32 | 1.10-4.35 | 0.023 |
| No lead-in phase | 2.33 | 1.22-4.35 | 0.01 |
| Hemoglobin level<br>≤12 g/dL for female<br>≤13 g/dL for male | 5.85 | 2.83-12.08 | <0.0001 |

* n=71

Data by courtesy of Prof. J-P Bronowicki

# HEP3002 – interim analysis

**Design:** multicenter, open-label, early access program of telaprevir in combination with peginterferon-alfa and ribavirin.

**Inclusion:** Genotype 1, Severe fibrosis (F3) or compensated cirrhosis (F4)

**Recruitment:** **>**1900 patients recruited so far.
First 609 patients with data to Week 16 were included in the interim analysis.

**Guidelines for discontinuation of Telaprevir, Peg-IFN-alfa, and RBV treatment**

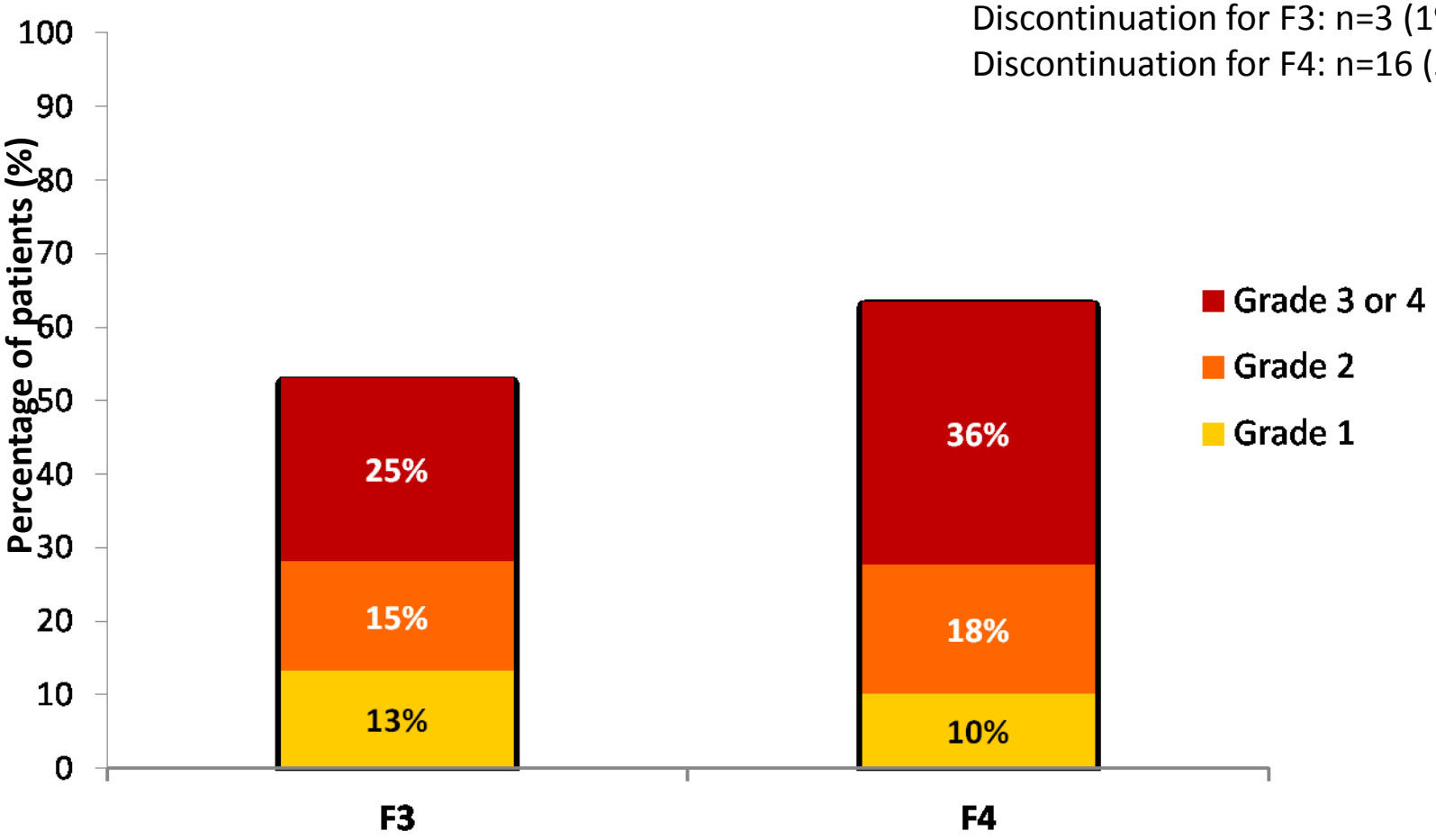
| Medicinal product(s) | HCV RNA >1,000 IU/mL at Week 4 of treatment[a] | HCV RNA >1,000 IU/mL at Week 12 of treatment[a] |
|---|---|---|
| Telaprevir | Permanently discontinue | Telaprevir treatment completed |
| Peg-IFN-alfa/RBV | Permanently discontinue | |

[a] Treatment with telaprevir, Peg-IFN-alfa, and RBV

Colombo M et al, late-breaker abstract, AASLD 2012

# Anaemia adverse events, by grade & cirrhosis at baseline (all cause). Overall phase

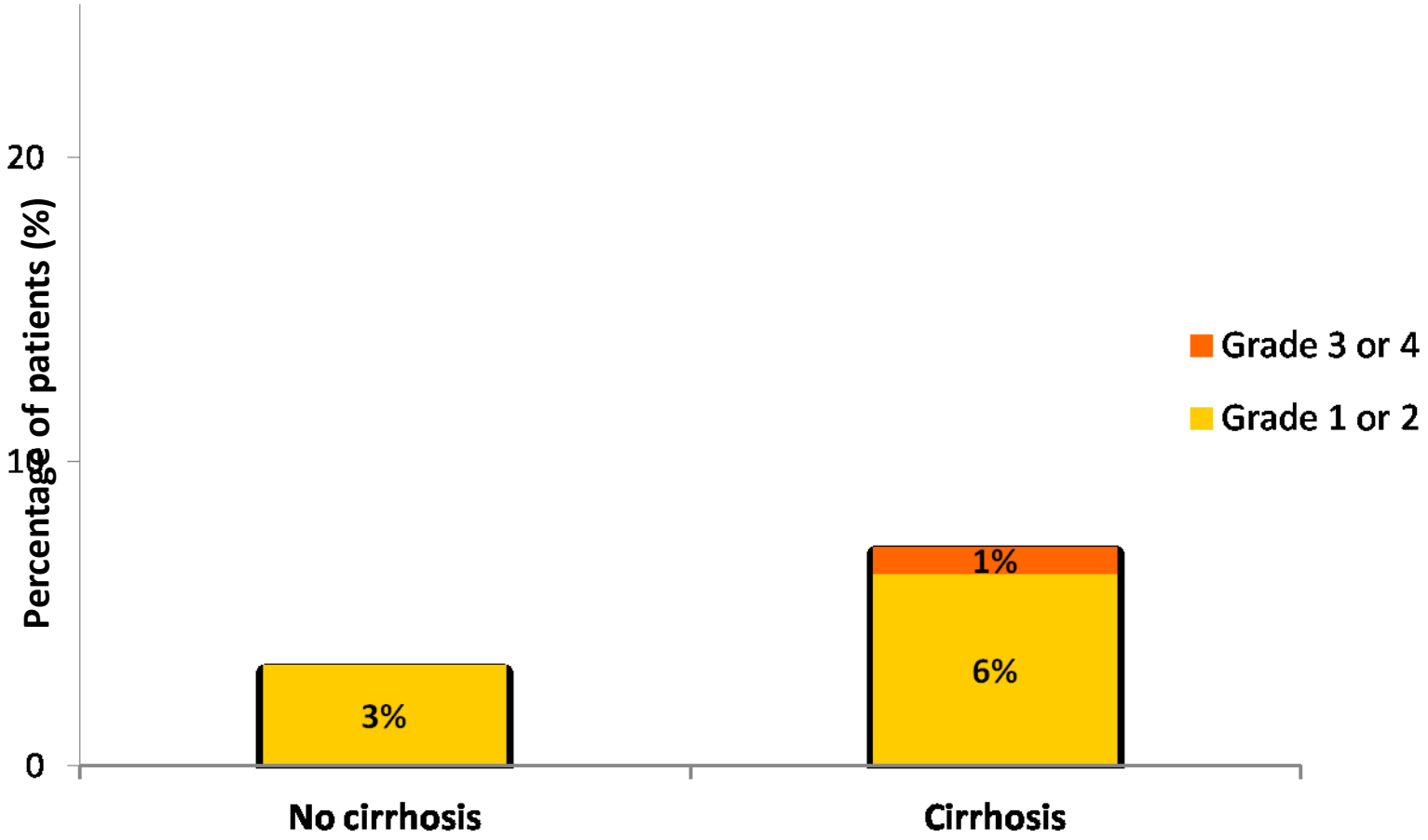
Discontinuation for F3: n=3 (1%)
Discontinuation for F4: n=16 (5%)




Analysis: 12th October 2012

Colombo M et al, late-breaker abstract, AASLD 2012

# Infections, by grade & cirrhosis at baseline (all cause). Overall phase




Analysis: 12th October 2012

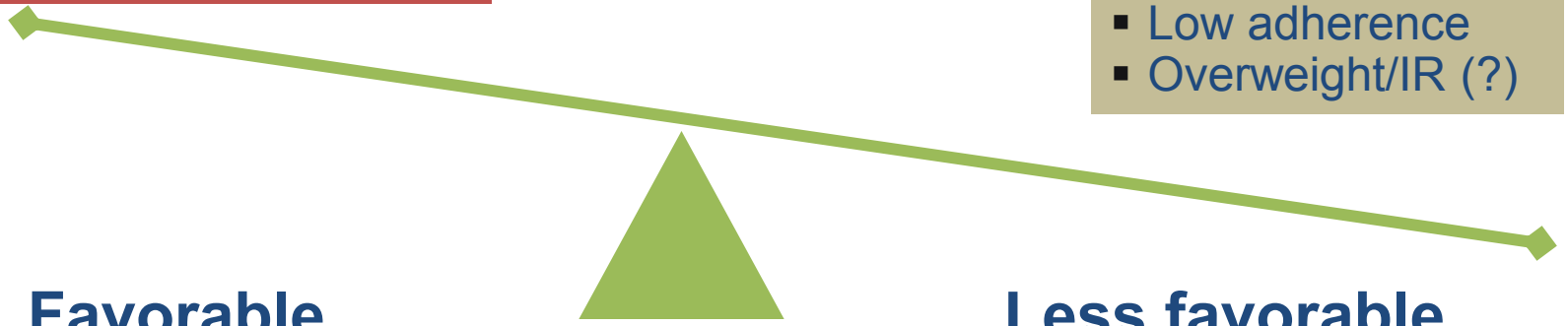
Table TSFAE01b

Colombo M et al, late-breaker abstract, AASLD 2012

# Which G1 patients are easy to cure with P/R/1st generation PI?

- Mild fibrosis
- Genotype 1b
- IFN responsive (eg, RVR/EVR or response to lead-in)
- Previous relapser
- *IL28B* CC
- Compliant
- Caucasian

- Cirrhosis
- Genotype 1a
- IFN nonresponsive
- *IL28B* TT
- African American
- Low adherence
- Overweight/IR (?)

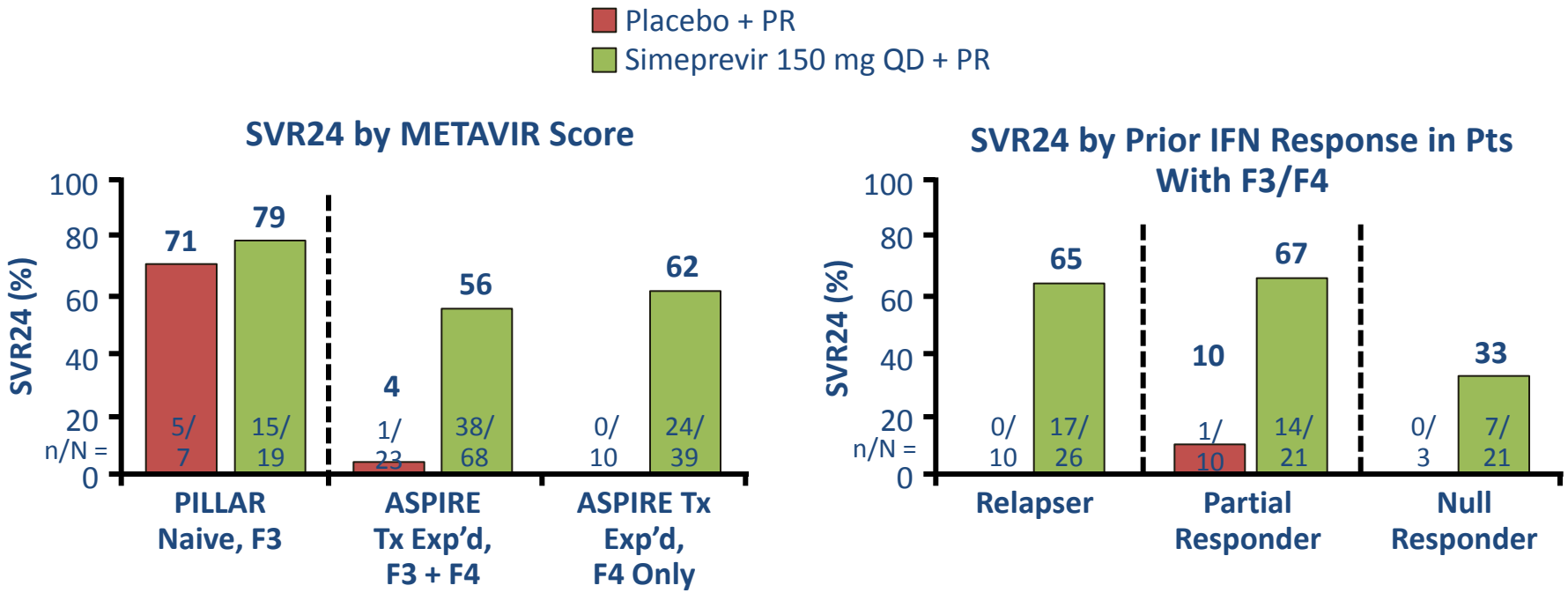


**Favorable predictive factors**

**Less favorable predictive factors**

# PILLAR/ASPIRE: Simeprevir + PegIFN/RBV in Pts With GT1 HCV, F3/4 Fibrosis

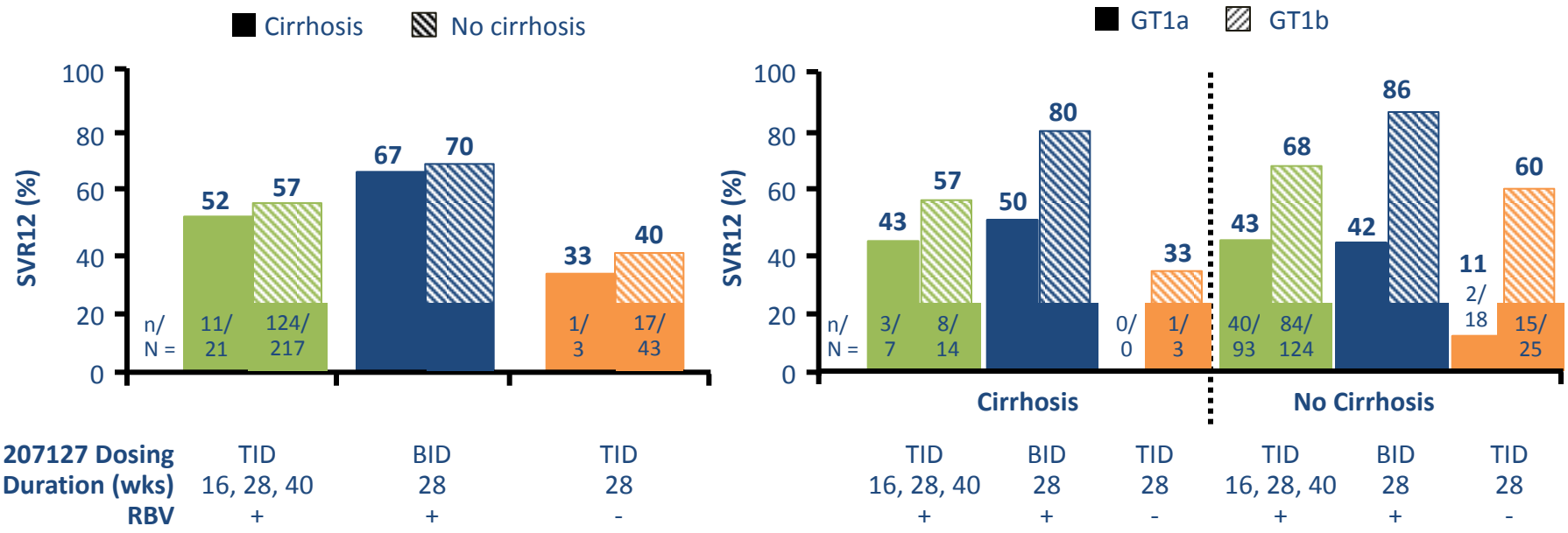
- Subanalysis of randomized, placebo-controlled phase IIb trials of simeprevir (protease inhibitor)
- Relatively high SVR24 rates in pts with advanced fibrosis
  - In ASPIRE, 4/13 (31%) F4 null responders achieved SVR24




Poordad F, et al. AASLD 2012. Abstract 83. Reproduced with permission.

# SOUND-C2 Subanalysis: Efficacy of Treatment in Patients With Cirrhosis

- Among 33 cirrhotic patients, outcomes with faldaprevir + BI 207217 + RBV similar to noncirrhotic patients
  - SVR12 rates higher in GT1b vs GT1a HCV
- Higher rate of discontinuations and SAEs with TID dosing

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