Triple Therapy for Genotype 1 Treatment Experienced Patients

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Triple Therapy for Treatment-Experienced Patients

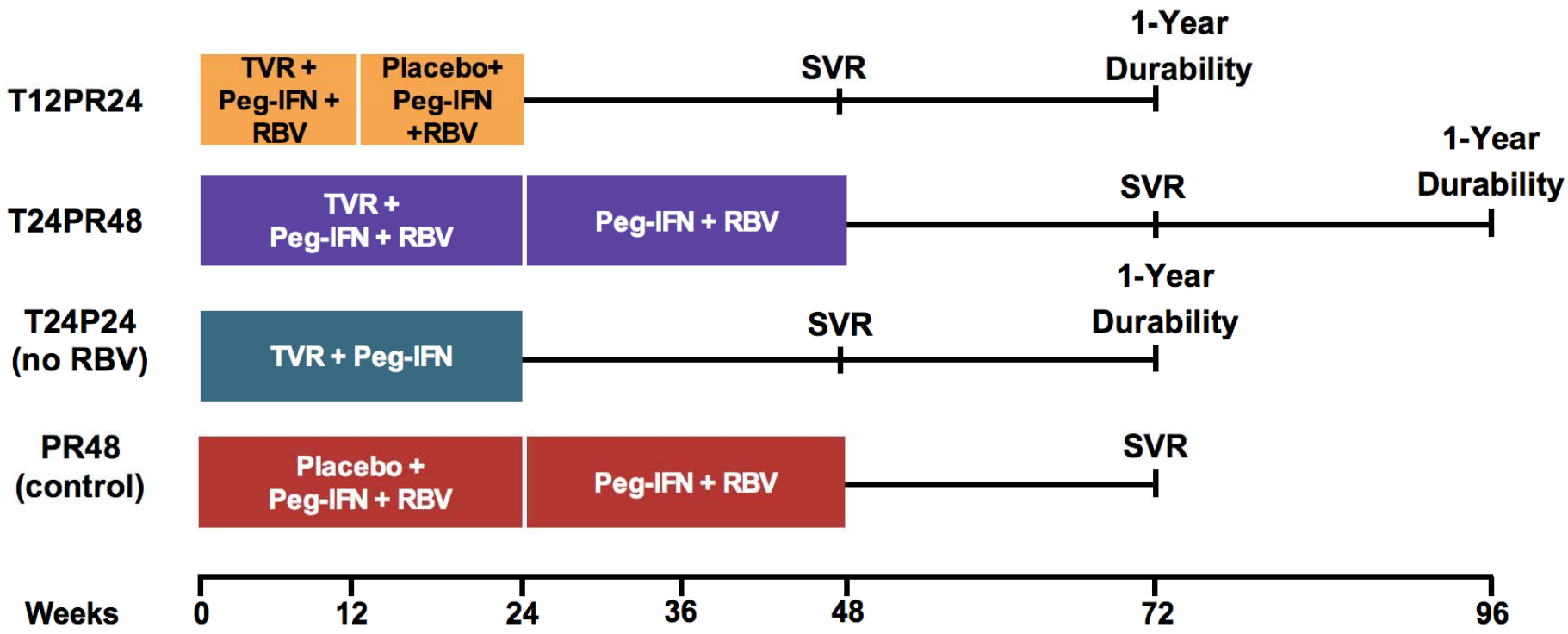
- Fast growing segment of patients
- Goal remains permanent viral eradication
- Limited, generally unsatisfactory response with currently available medications
  - "Those who cannot remember the past are doomed to repeat it" George Santayana 1905
- Triple therapy will offer an excellent therapeutic option for many patients
  - Telaprevir
  - Boceprevir

Definitions of Non-Sustained Response

- Differentiate Relapser from Partial responder from Null responder
  - Implications for subsequent treatment success, even for triple therapy combinations
  - Phase II and phase III studies of both protease inhibitors used different definitions and inclusion/exclusion criteria
    - General concepts apply, however

Telaprevir in Treatment Experienced Patients

PROVE3: Study Design



(P) Peg-IFN = pegylated interferon alfa-2a 180 µg/wk, subcutaneous injection;
(R) RBV = ribavirin 1,000 mg/day (body weight <75 kg) or 1,200 mg/day (body weight ≥75 kg);
(T) TVR = telaprevir 750 mg q8h (initial loading dose 1125 mg)

McHutchison JG et al, *N Engl J Med*. 2010;362(14):1292-1303

Telaprevir in Treatment Experienced Patients

PROVE3: Methods – Definition of Prior Peg-IFN + RBV Treatment Response

Nonresponders	Patients who never achieved undetectable HCV RNA after a course of Peginterferon and ribavirin of at least 12 weeks during or at the end of treatment period
Relapsers	Patients who achieved undetectable HCV RNA during treatment for at least 42 weeks but detectable HCV RNA levels observed during the follow-up period and did not achieve SVR
Breakthroughs	Patients who had undetectable HCV RNA during the treatment period, but detectable levels of HCV RNA before the end of treatment period

Eligibility and categorization of prior response was determined from medical records and prior HCV values

McHutchison JG et al, *N Engl J Med*. 2010;362(14):1292-1303

Telaprevir in Treatment Experienced Patients

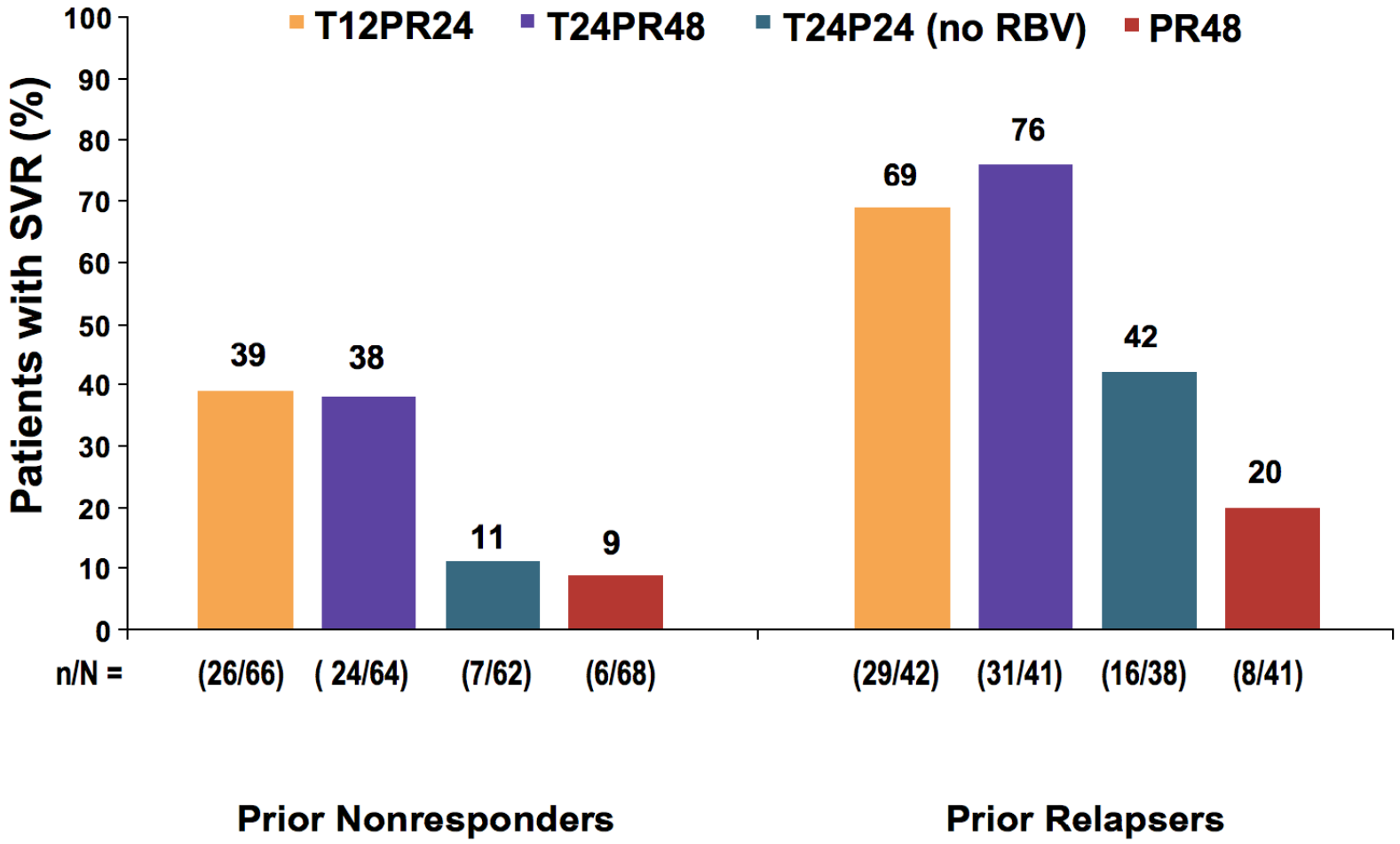
PROVE3: Stopping Rules

- Breakthrough from Week 4 through Week 24 of treatment
  - Increase in HCV RNA of >1 $\log_{10}$ as compared with nadir; or
  - HCV RNA level of >100 IU/mL after undetectability
- Nonresponse at Week 4
  - Control arm: <1 $\log_{10}$ HCV RNA decrease from baseline to Week 4
  - Telaprevir arms: HCV RNA levels ≥30 IU/mL
- Nonresponse at Week 12
  - All arms: ≤2 $\log_{10}$ reduction from baseline in HCV RNA by Week 12
- Week 24
  - Control (PR48) and T24PR48 arms: detectable HCV RNA by Week 24

McHutchison JG et al, *N Engl J Med*. 2010;362(14):1292-1303

Telaprevir in Treatment Experienced Patients

PROVE3: SVR Rates by Prior Response and Treatment Group



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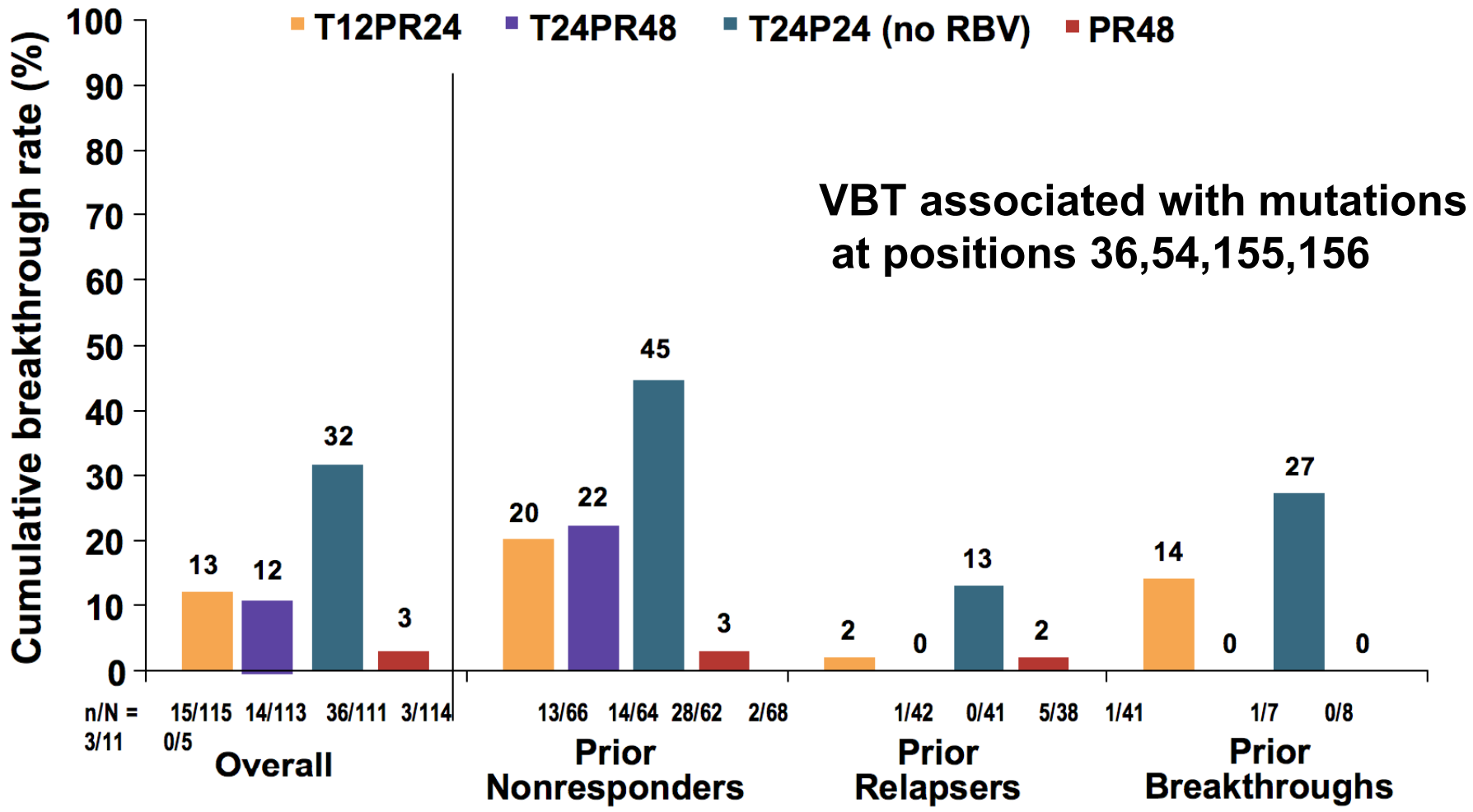
Telaprevir in Treatment Experienced Patients

PROVE3: Cumulative Viral Breakthrough Rate From Baseline Through Week 24 by Treatment Group



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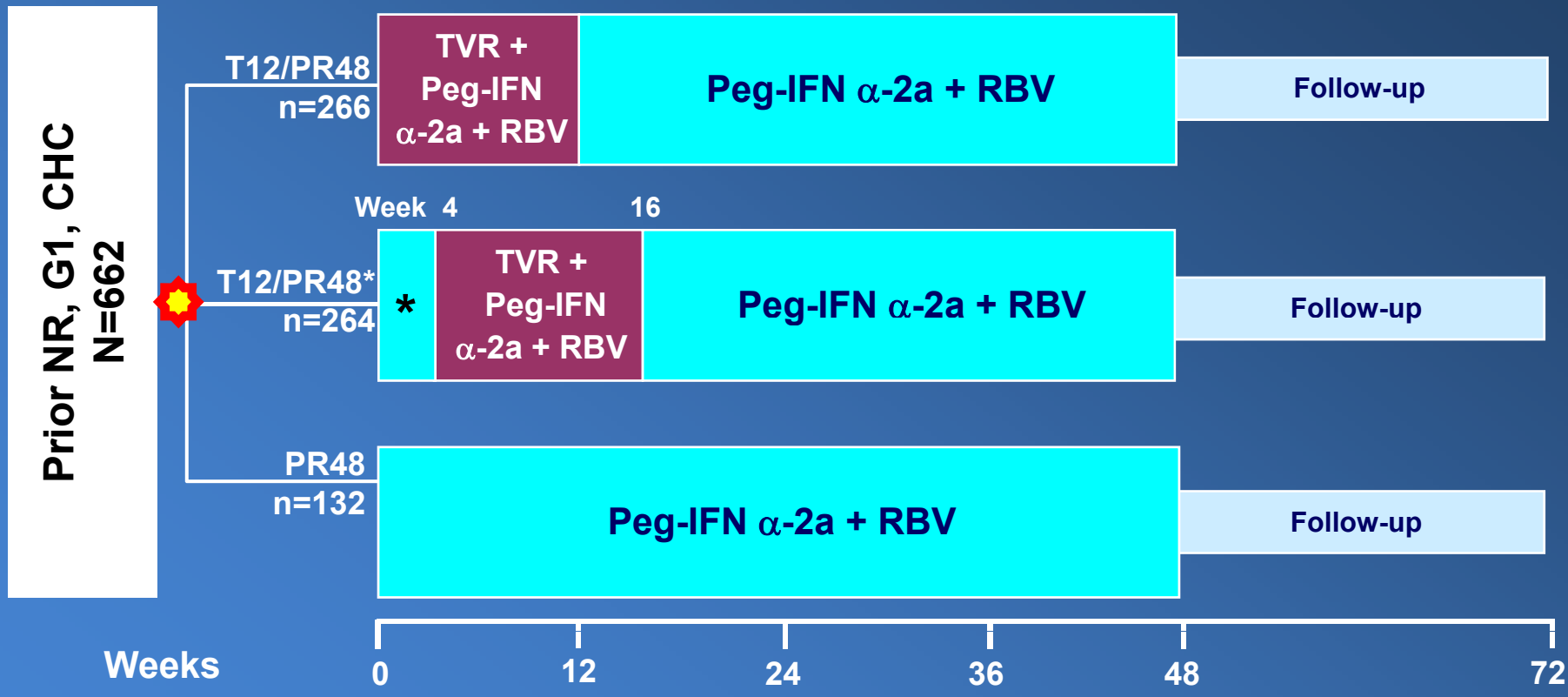
Telaprevir + Peg-IFN α-2a/RBV in Prior Nonresponders: REALIZE



Randomization 2:2:1 (two telaprevir arms and control PR48 arm, respectively)

NR = nonresponders (prior relapsers, 53%; prior partial responders, 19%; prior null responders, 28%)

* Includes a 4-week lead-in arm with Peg-IFN α-2a + RBV

T = telaprevir 750 mg q8h

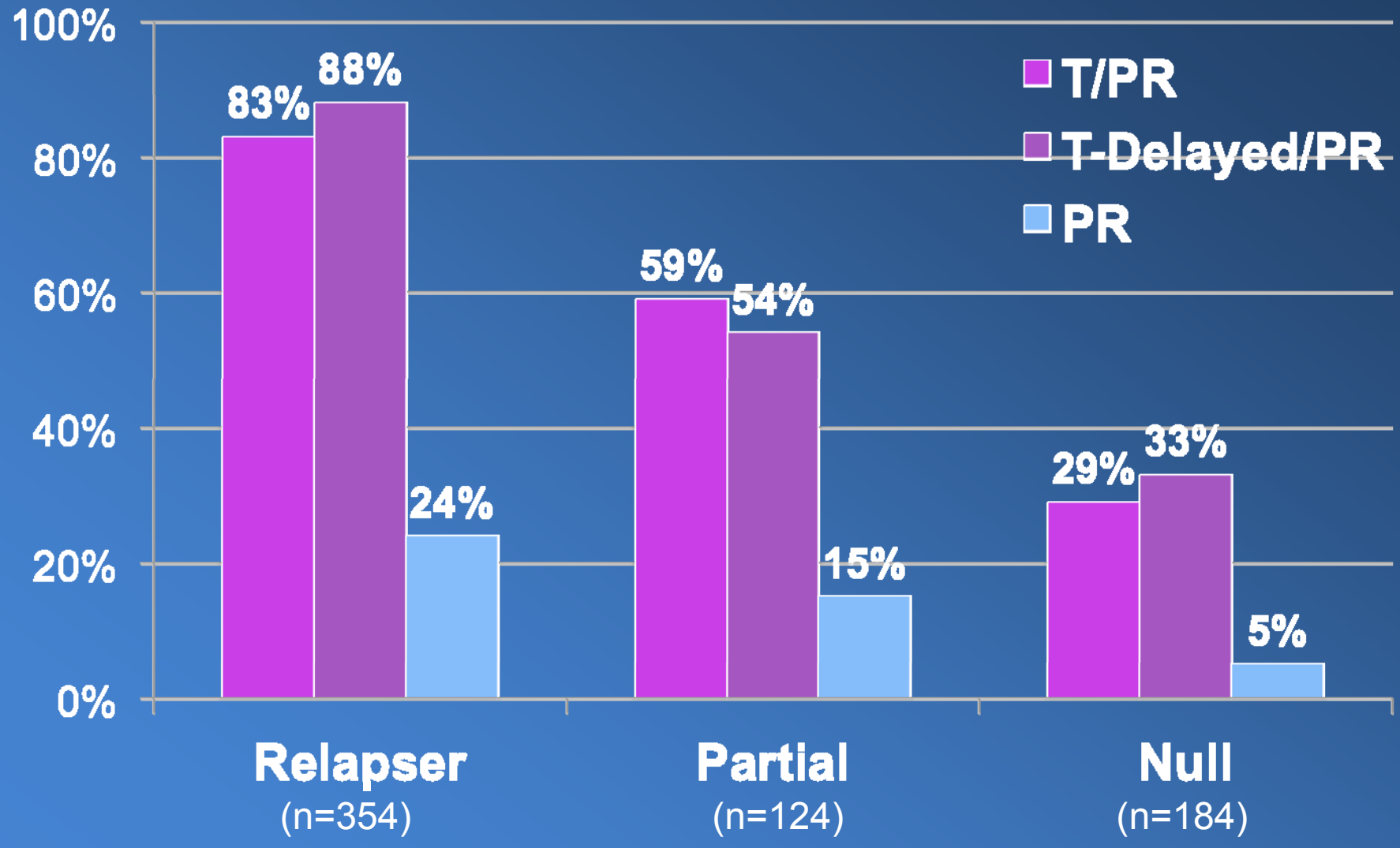
Vertex press release, September 7, 2010. Available at: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=505239

REALIZE: Definition of Prior Nonresponse

- Null responders: <2 $\log_{10}$ decline in HCV RNA at 12 weeks of prior Peg-IFN/RBV therapy
- Partial responders: ≥2 $\log_{10}$ decline in HCV RNA at week 12 of prior Peg-IFN/RBV therapy but not undetectable by week 24 of prior therapy
- Relapsers: undetectable HCV RNA at the completion of at least 42 weeks of prior Peg-IFN/RBV therapy but who relapsed after treatment ended (during follow-up)

Vertex press release, September 7th, 2010. Available at: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=505239

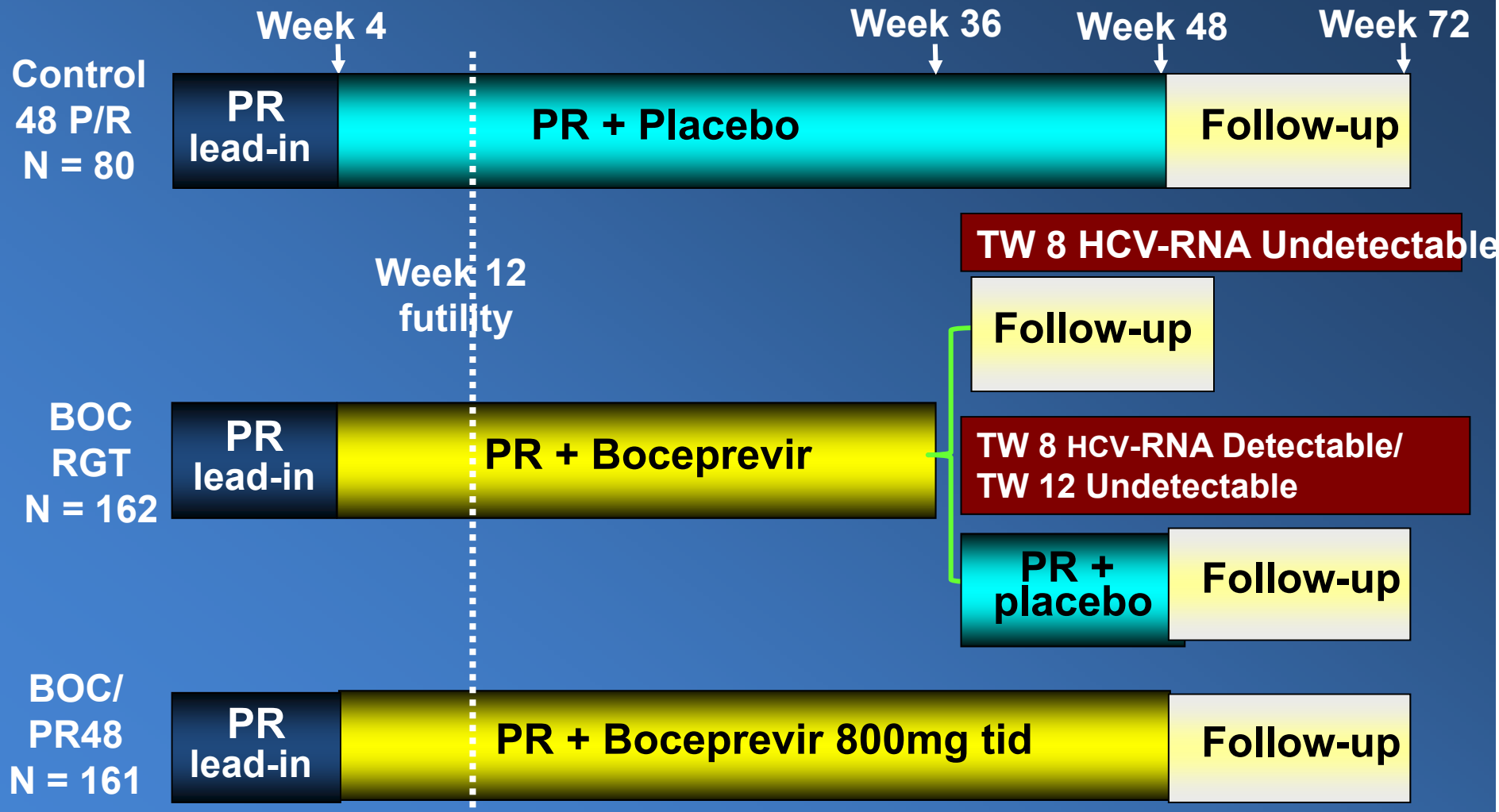
Telaprevir for Treatment Experienced Patients- SVR in REALIZE



T = telaprevir
PR = Peg-IFN α-2a + ribavirin

Vertex press release, September 7, 2010. Available at: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=505239

Boceprevir: RESPOND-2 Study Design



Patients with detectable HCV-RNA at week 12 were considered treatment failures.

Peginterferon (P) 1.5 µg/kg , plus Ribavirin (R) 600-1400 mg/day in a divided daily dose

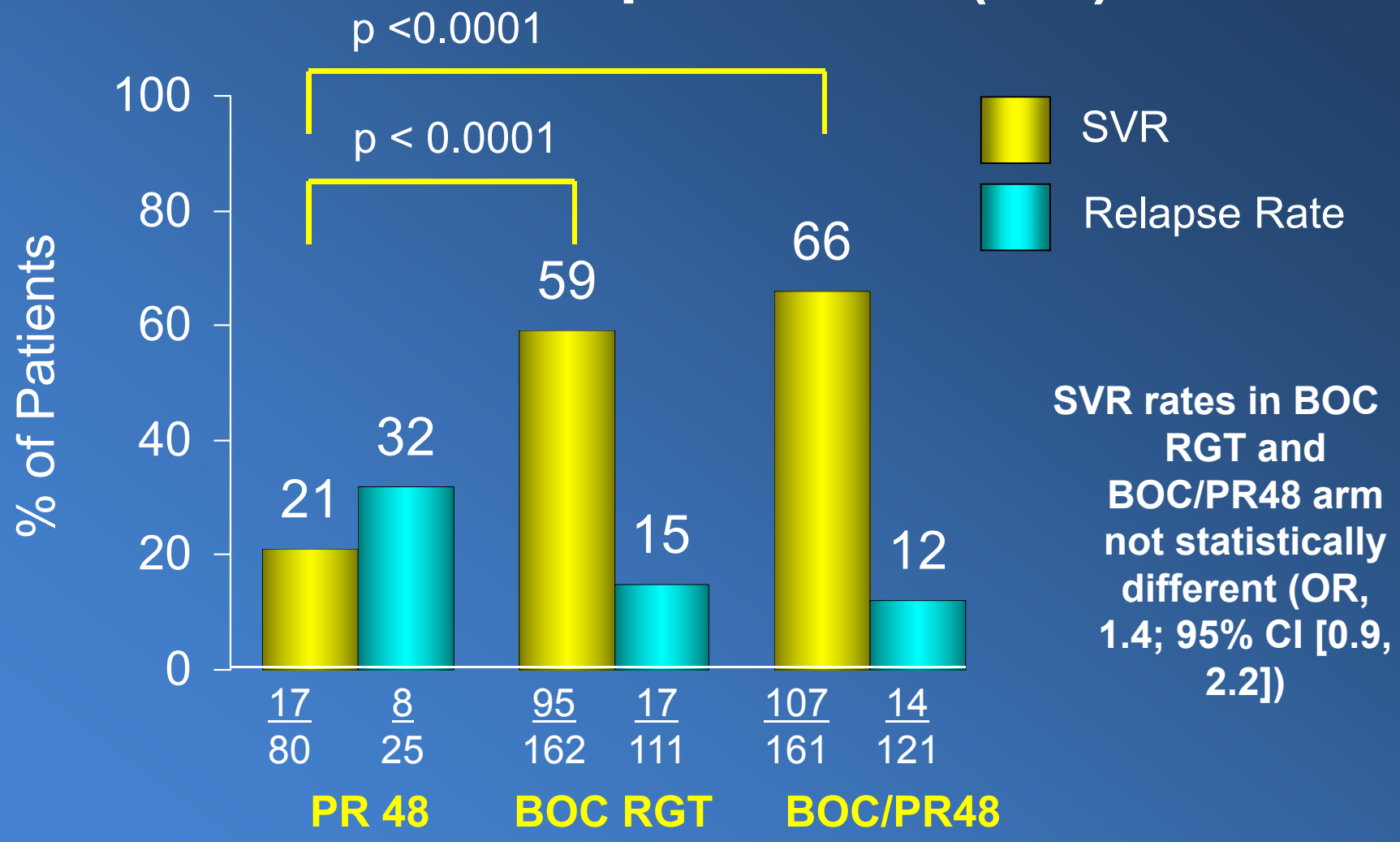
Bacon et al. Hepatology 2010; 52 (S1) [abstract 216]

Boceprevir RESPOND-2
Definition of prior nonresponse

- Nonresponder: ≥2 $\log_{10}$ decline in HCV RNA by week 12 of prior Peg-IFN/RBV therapy but with detectable HCV RNA throughout the course of therapy
  - Prior null-responders excluded
- Relapsers: undetectable HCV RNA at the end of prior Peg-IFN therapy without subsequent attainment of an SVR

Bacon BR, et al. Hepatology 2010; 52 (S1) [abstract 216]

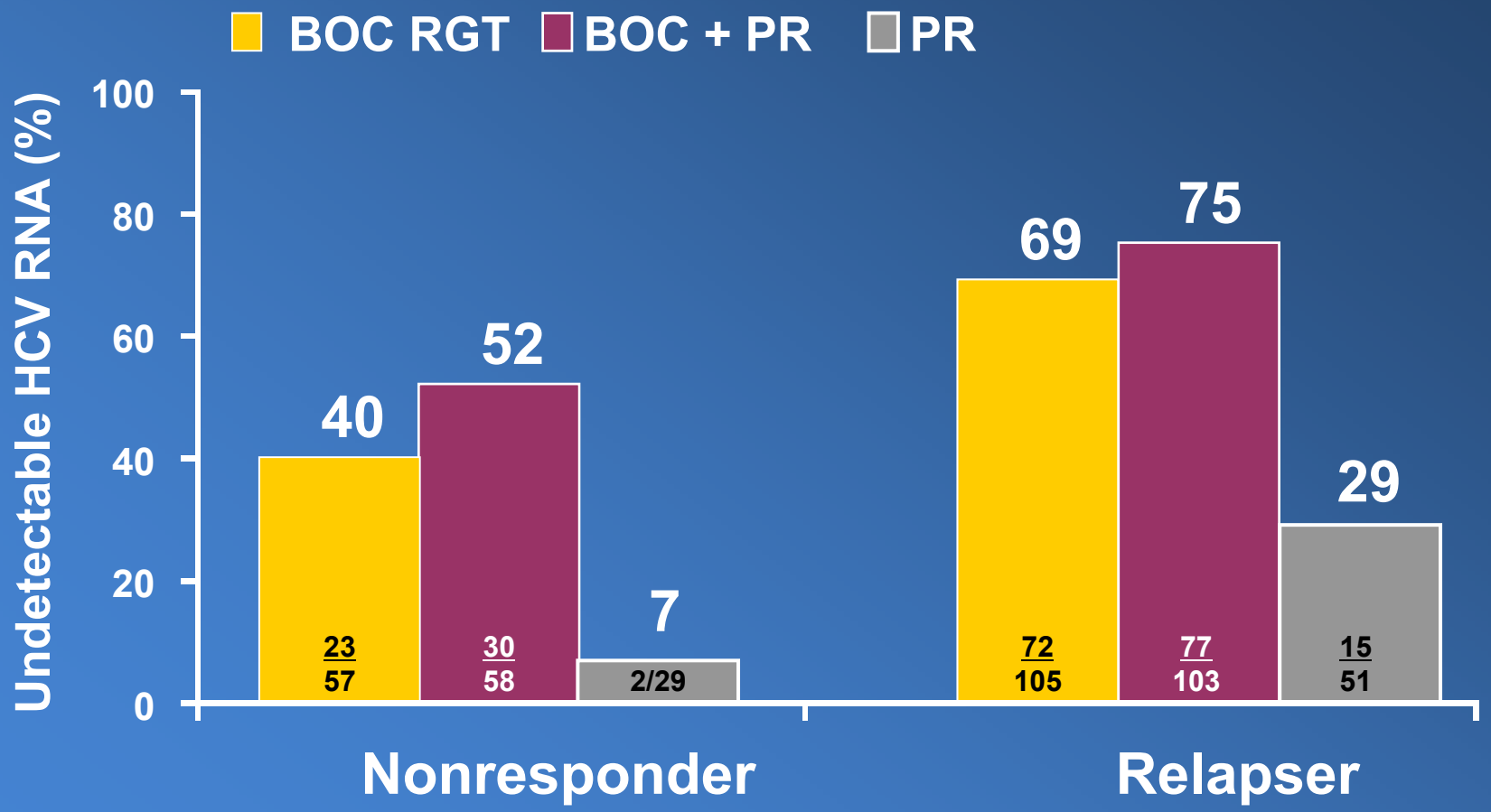
Boceprevir RESPOND-2
SVR and Relapse Rates (ITT)



SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])

12-week HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161), respectively.

RESPOND-2: SVR rates in prior nonresponders and relapsers to Peg-IFN/RBV



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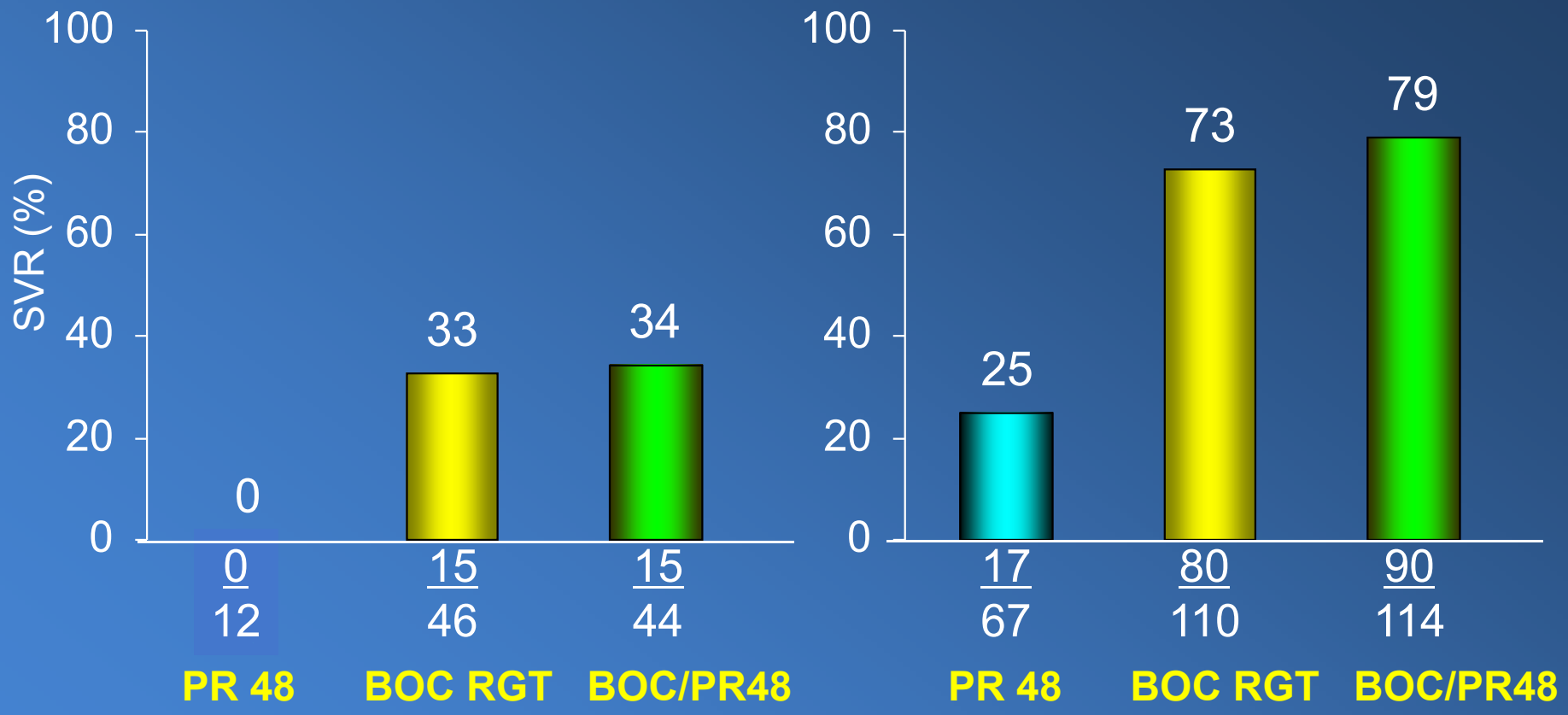
Boceprevir SPRINT-2
SVR by Week 4 PR Lead-In Response



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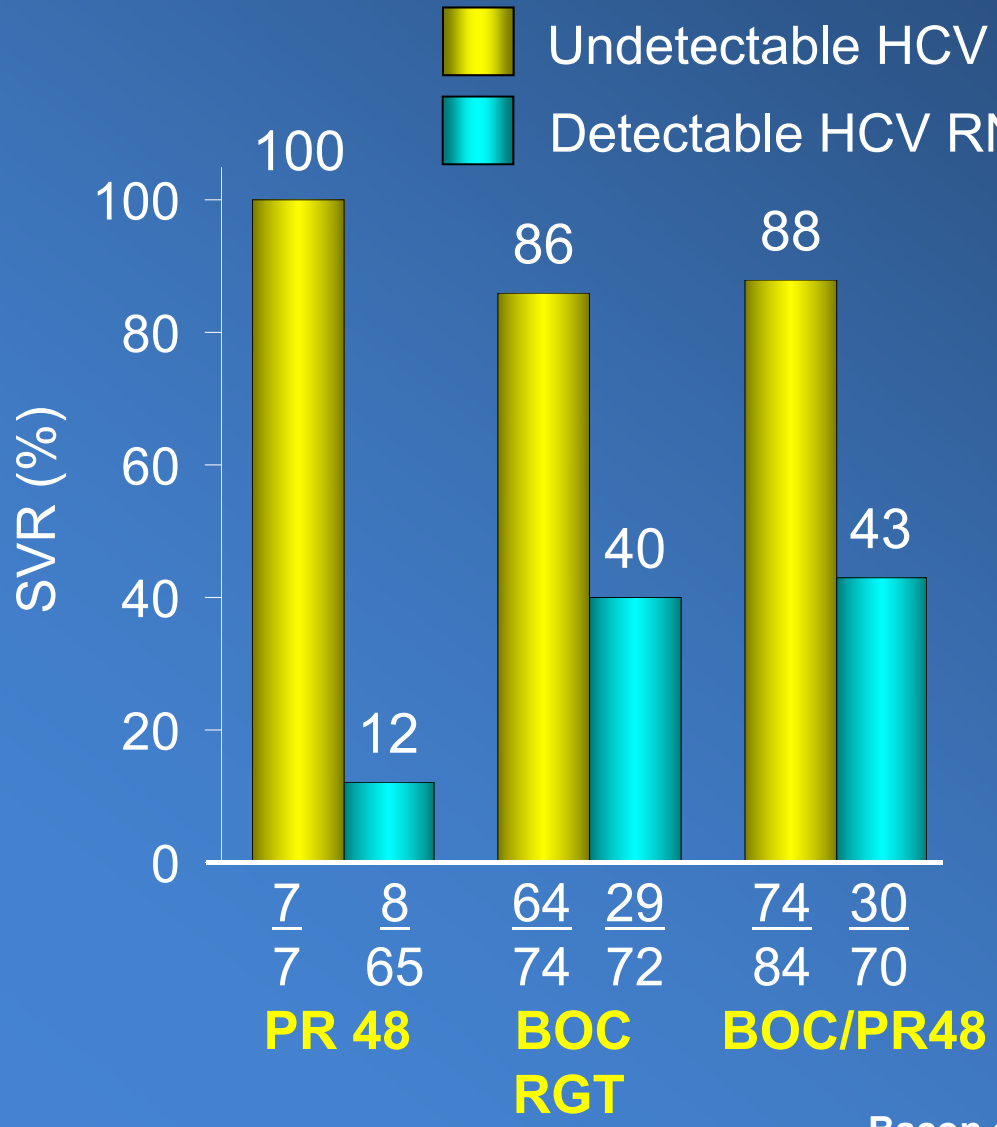
SVR by Week 8 HCV RNA Response
Intention to Treat Population

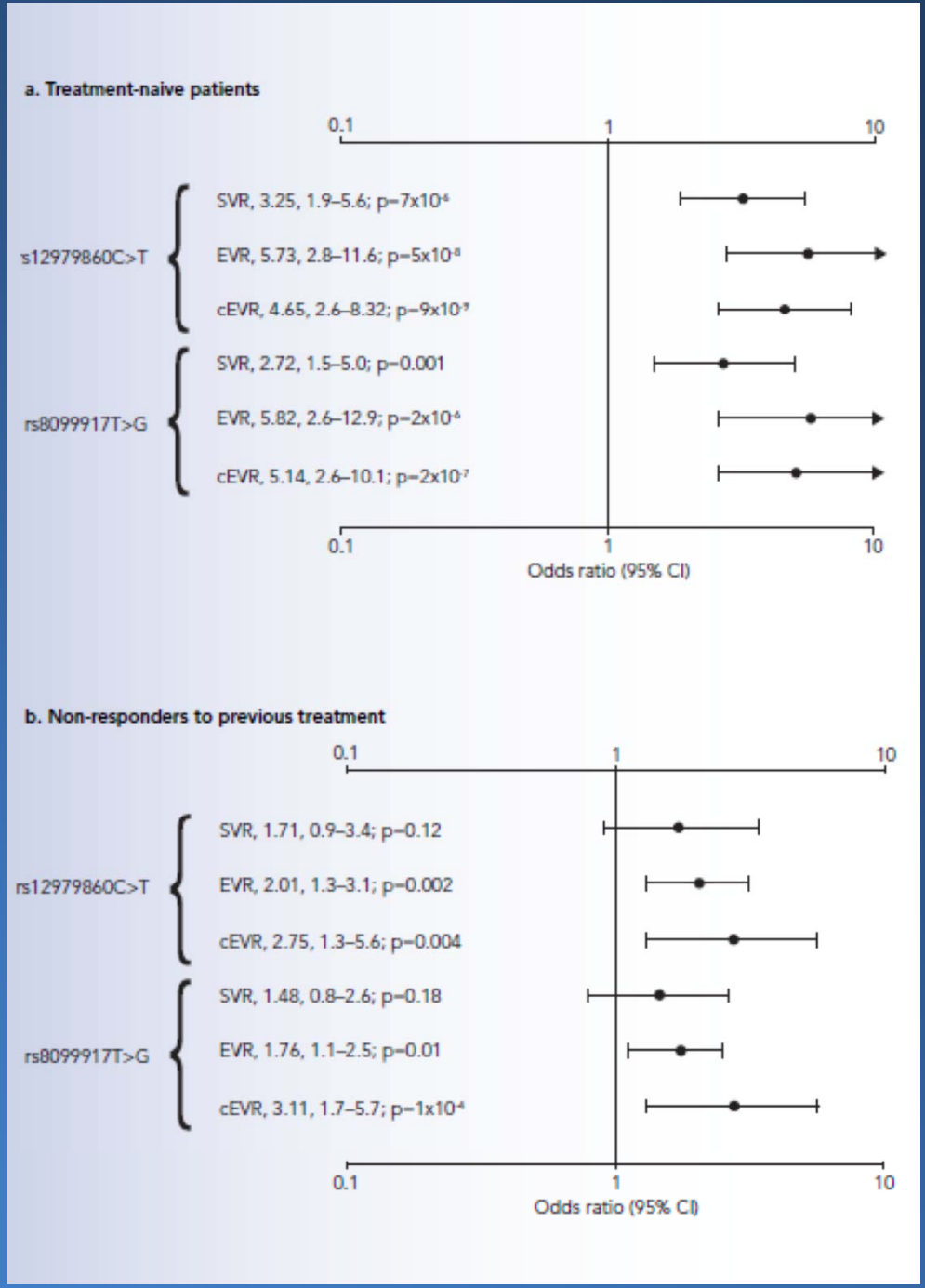


- 46% of patients in BOC RGT arm were eligible for shorter therapy (36 weeks)
- ~6 times as many patients on BOC regimens (46-52%) achieved undetectable HCV RNA at week 8 compared to control (9%)

Bacon et al. Hepatology 2010; 52 (S1) [abstract 216]

IL28B Genotypes in Naïve and Treatment-Experienced Patients

Impact of IL28B among non-responders is less than in treatment naïve patients suggesting that additional factors play a role



Asselah et al, AASLD 2010

Triple Therapy in Genotype 1 Treatment-Experienced Patients

- Telaprevir and Boceprevir will benefit many treatment-experienced patients
  - Subtle differences in study design, inclusion criteria, stopping criteria, RGT, make it impossible to compare across studies
- Common messages:
  - Ribavirin remains a critical component (“triple”)
  - Prior IFN response is predictive of outcome
    - Relapser > Partial Responder >Null responder
    - Virological breakthrough higher in non-responders
    - Early stopping rules are important to minimize resistance

Unanswered Questions

- What are the long-term clinical consequences of viral breakthrough and resistant mutations?
- Should null-responder patients be treated with triple therapy?
- Should some patients wait for quad therapy or combinations of other classes of drug?
- What factors will be most predictive so we can make informed decisions with our patients?