Triple therapy: who and how?

treatment-experienced patients

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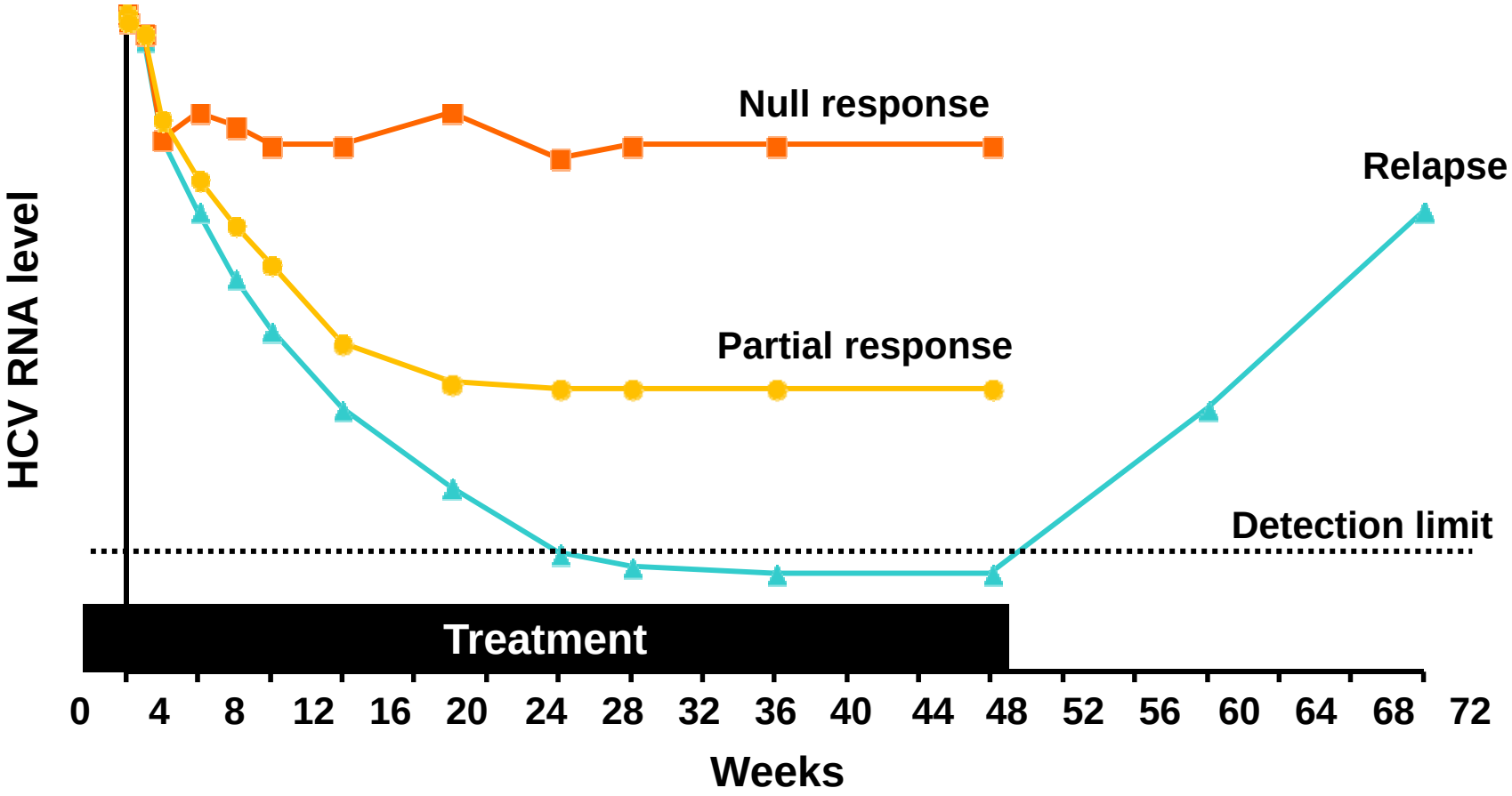
Paris, 17 January 2011

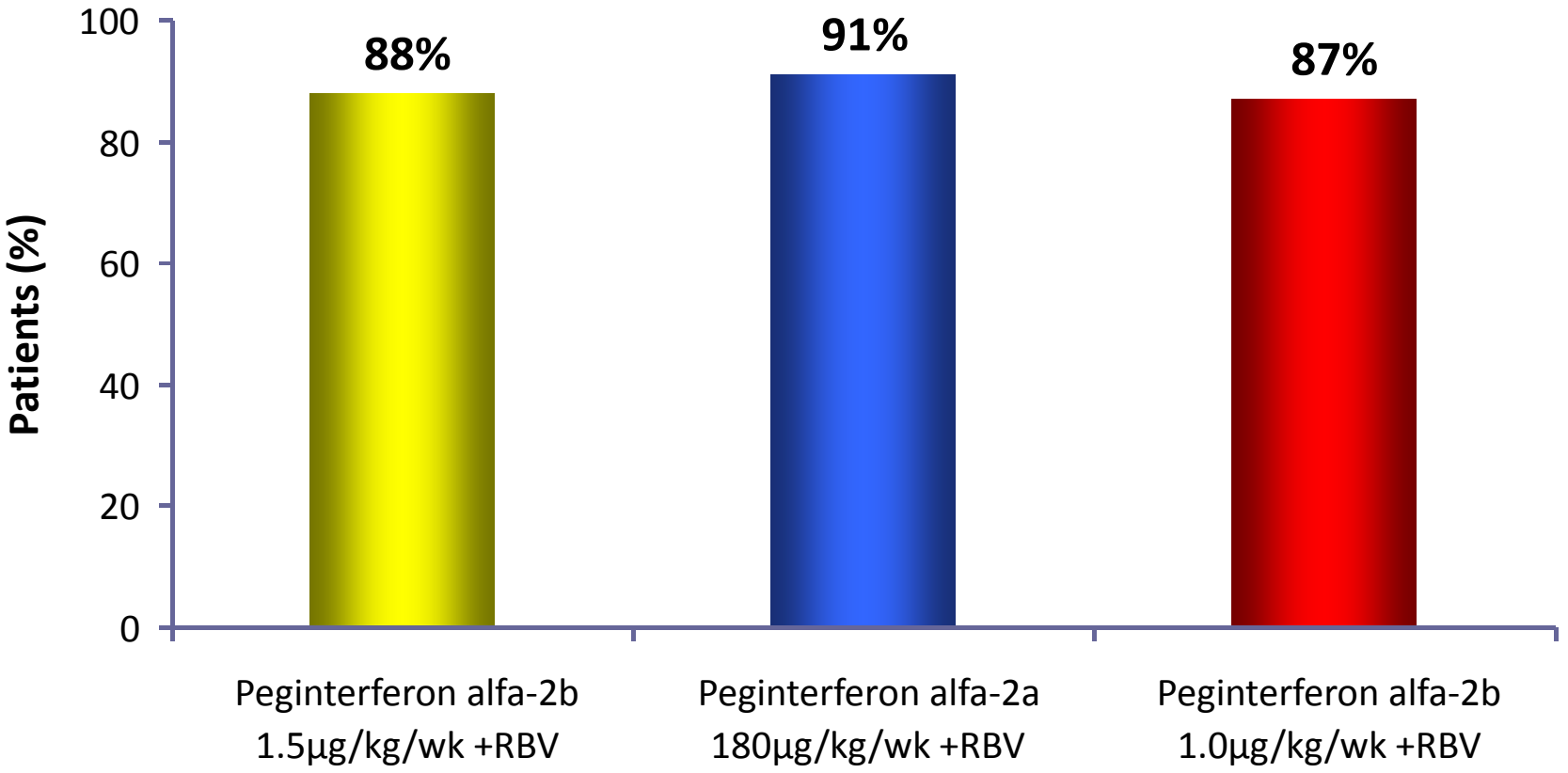
Virological Response Patterns With Peg-IFN/RBV: Treatment Failure



PR 4 week Lead-In as a predictor of response?

- Lead-in allows real time assessment of patient's interferon responsiveness vs. historic response
- Viral load decline of <1 $\log_{10}$ after 4 weeks of PR is significantly correlated to a <2 $\log_{10}$ decline after 12 weeks of treatment ?

IDEAL: Concordance between Week 4 and Week 12 as the Definition for Null Response



Poordad F, et al. AASLD 2010

IDEAL: Concordance between Week 4 and Week 12 as the Definition for Null Response

		Week 12 response	
	Week 4 response	**Null***	**Non-Null**
Peginterferon alfa-2b 1.5µg/kg/wk +RBV (n=900)	**<1 log_{10} decline**	150	56 **(27.2%)**
	≥1 log_{10} decline	55	639
Peginterferon alfa-2a 180µg/kg/wk +RBV (n=945)	**<1 log_{10} decline**	148	65 **(30.5%)**
	≥1 log_{10} decline	22	710
Peginterferon alfa-2b 1.0µg/kg/wk +RBV (n=932)	**<1 log_{10} decline**	235	51 **(17.8%)**
	≥1 log_{10} decline	69	577

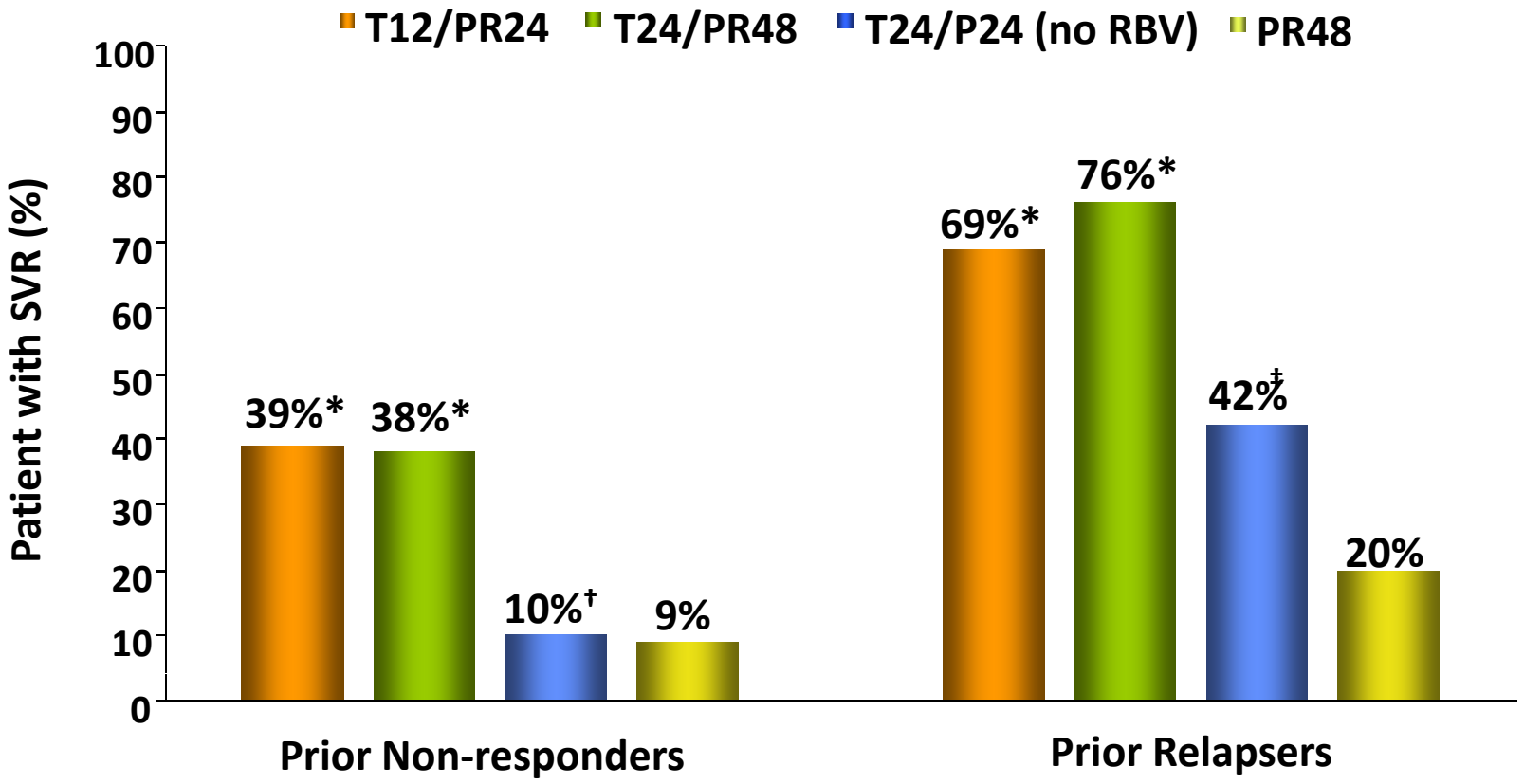
172/705 (24.4%) patients had <1 log_{10} decline at W4 and ≥2 log_{10} decline at W12

*< 2 log10 decrease from baseline

Poordad F, et al. AASLD 2010

TELAPREVIR

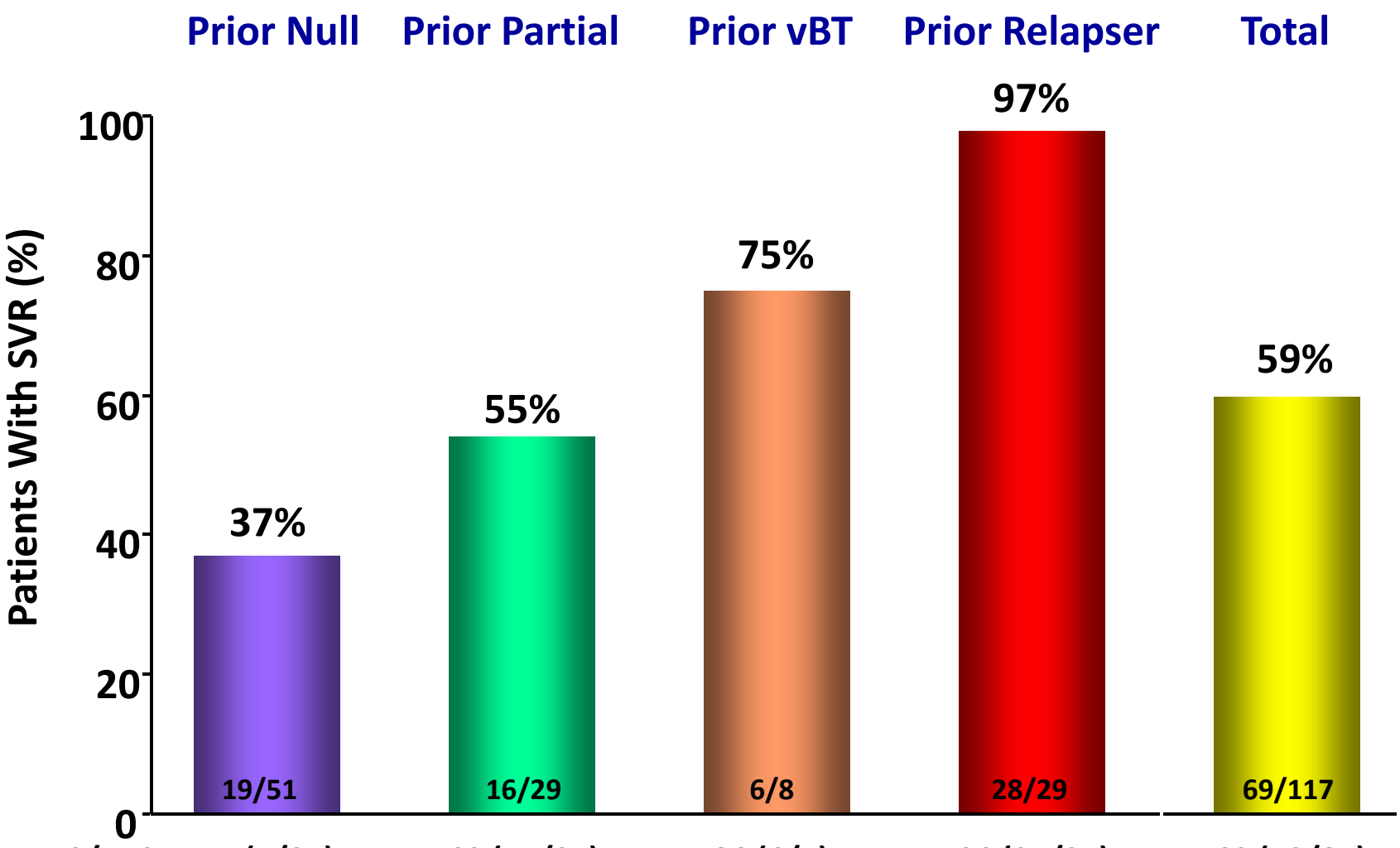
PROVE3: SVR by Prior Response and Treatment Group (ITT)



P value shown is versus PR48 control group; *$P<0.001$; †$P=0.471$; ‡$P=0.029$

McHutchison JG, et al. N Engl J Med 2010;362:1292–303

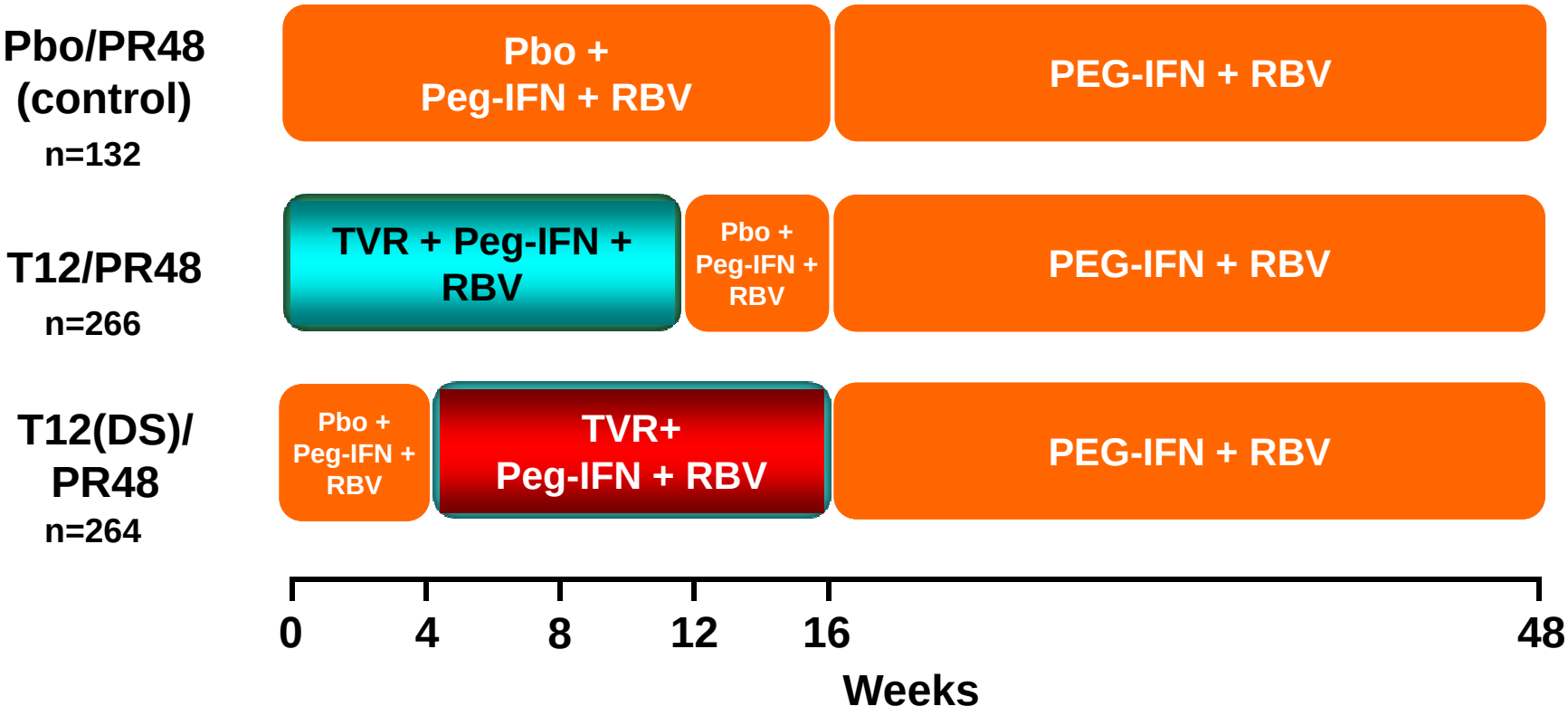
107 Rollover trial: SVR Rates



	Prior Null	Prior Partial	Prior vBT	Prior Relapser	Total
T12/PR24:	17 (4/24)	60 (15/25)	86 (6/7)	96 (24/25)	60 (49/81)
T12/PR48:	56 (15/27)	0 (0/3)	0 (0/1)	100 (3/3)	53 (18/34)
Unassigned:	-	100 (1/1)	-	100 (1/1)	100 (2/2)

Berg, et al. J Hepatol 2010;52:S2

REALIZE: Study Design



*Randomization stratified by viral load and prior response; stopping rules applied for TVR (Week 4, 6, and 8) and Peg-IFN/RBV (Week 12, 24, and 36)

P = Peg-IFN alfa-2a 180µg/week; Pbo = placebo
R = RBV 1000–1200mg/day; T = TVR 750mg every 8 hours

ClinicalTrials.gov identifier: NCT00703118

Press release, 7 September 2010

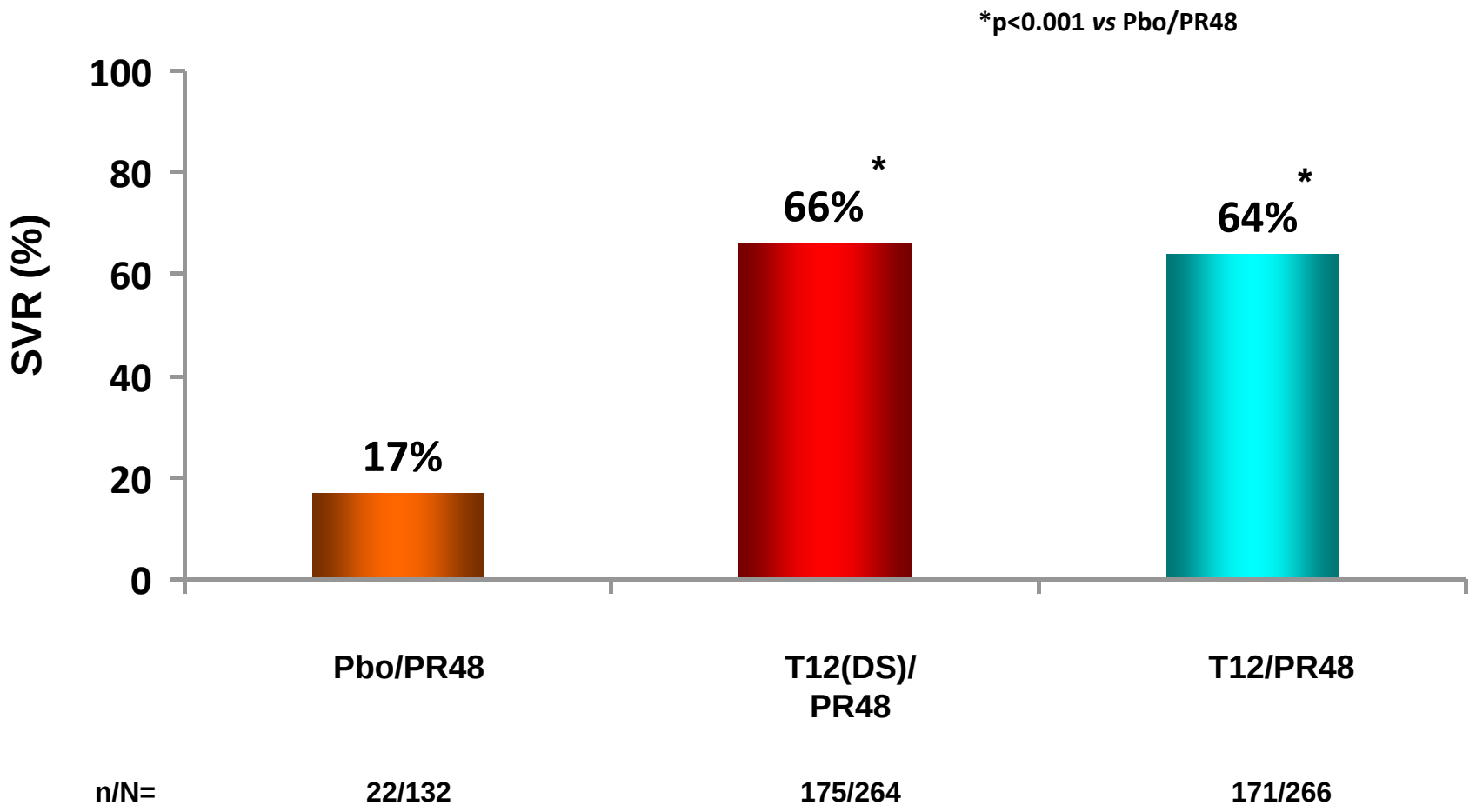
REALIZE: Baseline Characteristics

Characteristic	Pbo/PR48 (n=132)	T12(DS)/PR48 (n=264)	T12/PR48 (n=266)
HCV RNA ≥800,000 IU/mL, n (%)*	114 (86)	234 (89)	238 (89)
HCV genotype, n (%)†			
1a	59 (45)	120 (46)	118 (44)
1b	59 (45)	115 (44)	121 (45)
1c/unknown	14 (11)	28 (11)	27 (10)
Prior response, n (%)			
Null responder	37 (28)	75 (28)	72 (27)
Partial responder	27 (20)	48 (18)	49 (18)
Relapser	68 (52)	141 (53)	145 (55)
Bridging fibrosis, n (%)	29 (22)	58 (22)	60 (23)
Cirrhosis, n (%)	30 (23)	67 (25)	72 (27)

*Determined using the COBAS TaqMan HCV assay; †Determined by the Trugene method

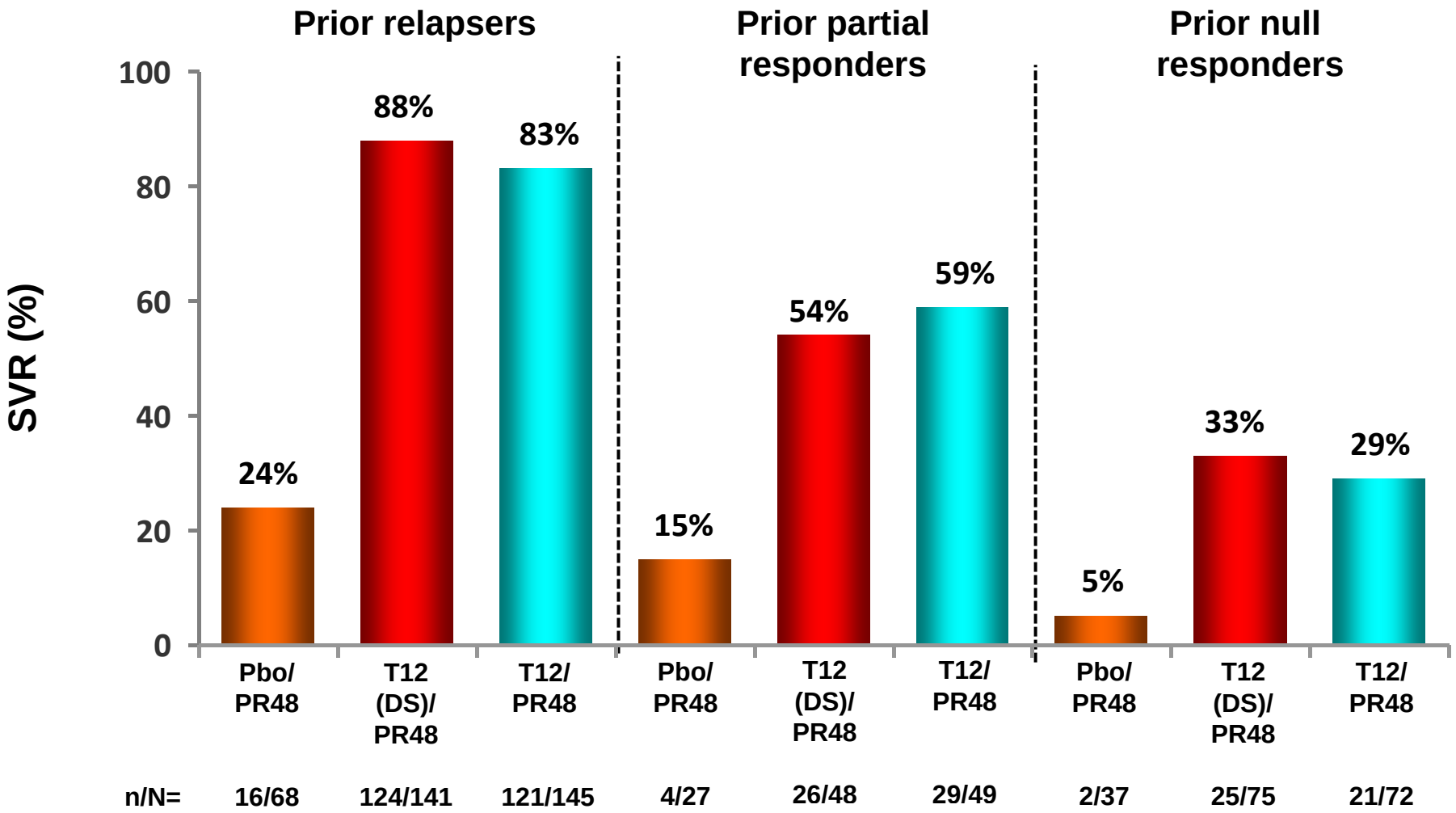
Press release, 7 September 2010

REALIZE: Overall SVR Rate



Press release, 7 September 2010

REALIZE: SVR in Prior Partial Responders, Null Responders and Relapsers



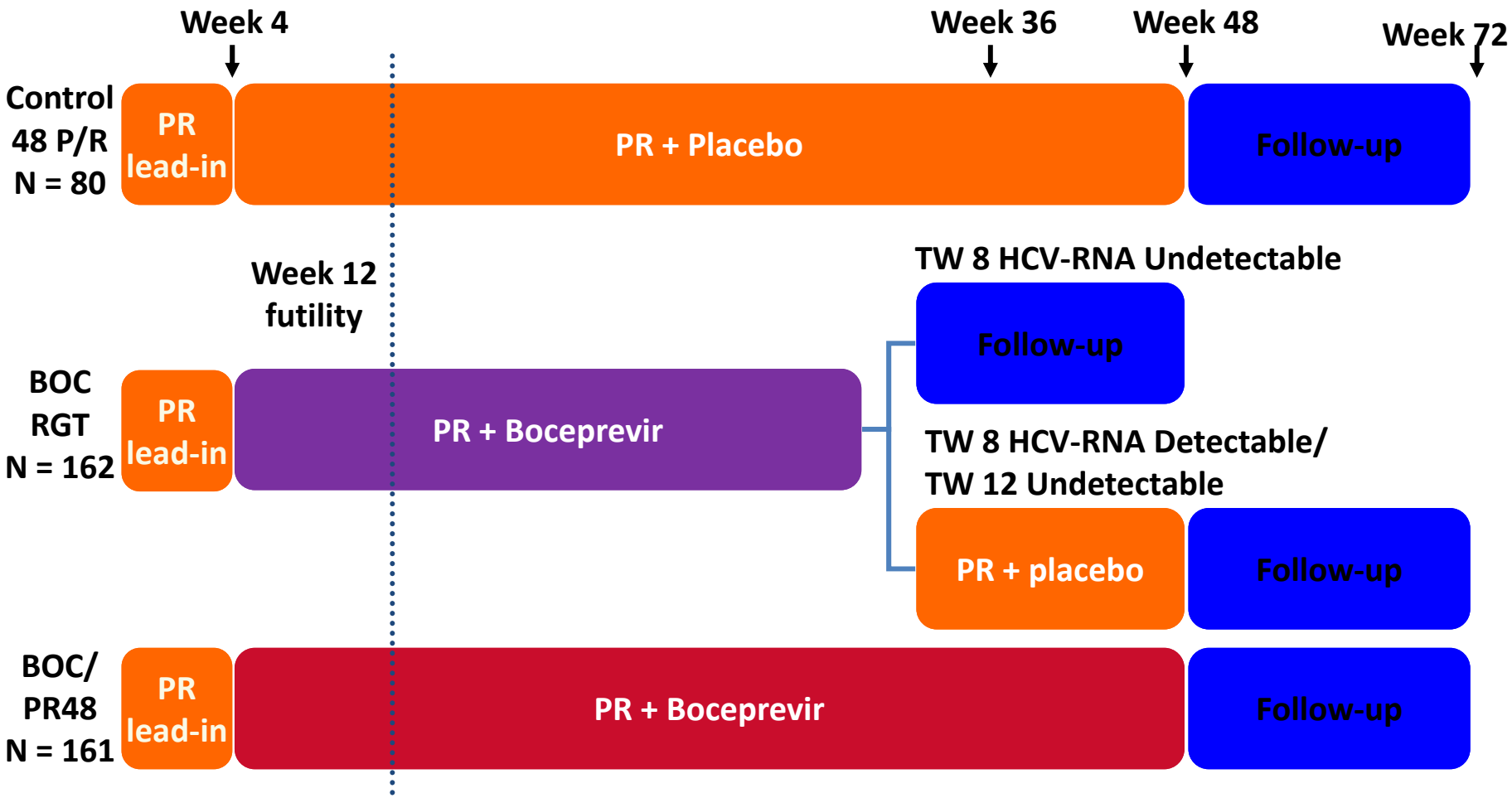
Press release, 7 September 2010

REALIZE: Summary

- **TVR/Peg-IFN/RBV was significantly superior to Peg-IFN/RBV in all prior treatment-experienced populations including null- (31%) and partial-responders (57%), and relapsers (86%)**
- **A lead-in/delayed start strategy did not improve SVR rates with a telaprevir regimen**
- **This data supports a T12/PR48 regimen for all types of previously treated patients, including prior null responders**

BOCEPREVIR

RESPOND-2: Study Design



HCV-RNA measured by the Cobas TaqMan assay (Roche). Patients with detectable HCV-RNA (LLD=9.3 IU/mL) at week 12 were considered treatment failures.

Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly; plus Ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose; Boceprevir dose of 800 mg thrice daily

Bacon R, et al. AASLD 2010

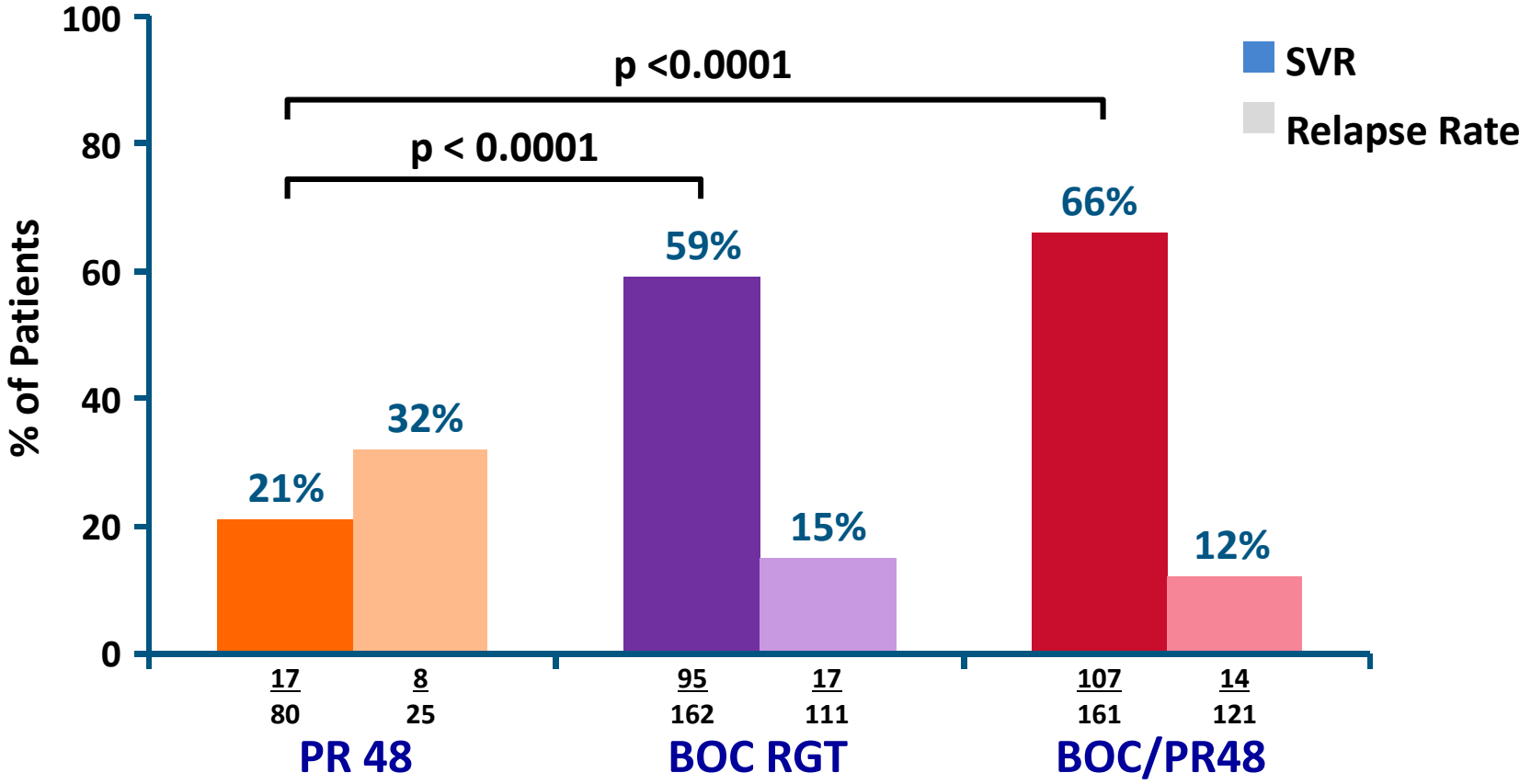
RESPOND-2: Baseline Characteristics

	Arm 1: 48 P/R N = 80	Arm 2: BOC RGT N = 162	Arm 3: BOC/PR48 N = 161
Mean age (years)	52.9	52.9	52.3
Male (%)	73	60	70
Black (%)	15	11	12
Region (%)			
North America	64	71	75
Europe	36	28	26
Latin America	0	1	0
BMI – mean (SD)	28 (4)	29 (5)	28 (5)
HCV subtype (%)*			
1a	48	46	48
1b	45	46	42
HCV RNA level >800,000 IU/mL (%)	81	91	88
METAVIR F3/F4 (%)	19	20	19
Non-responder (%)	36	35	36
Relapser (%)	64	65	64

*Subtyping performed by NS5B sequencing (Virco, Mechelen, Belgium)

Bacon R, et al. AASLD 2010

RESPOND-2: SVR and Relapse Rates
Intention to treat population



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

Bacon R, et al. AASLD 2010

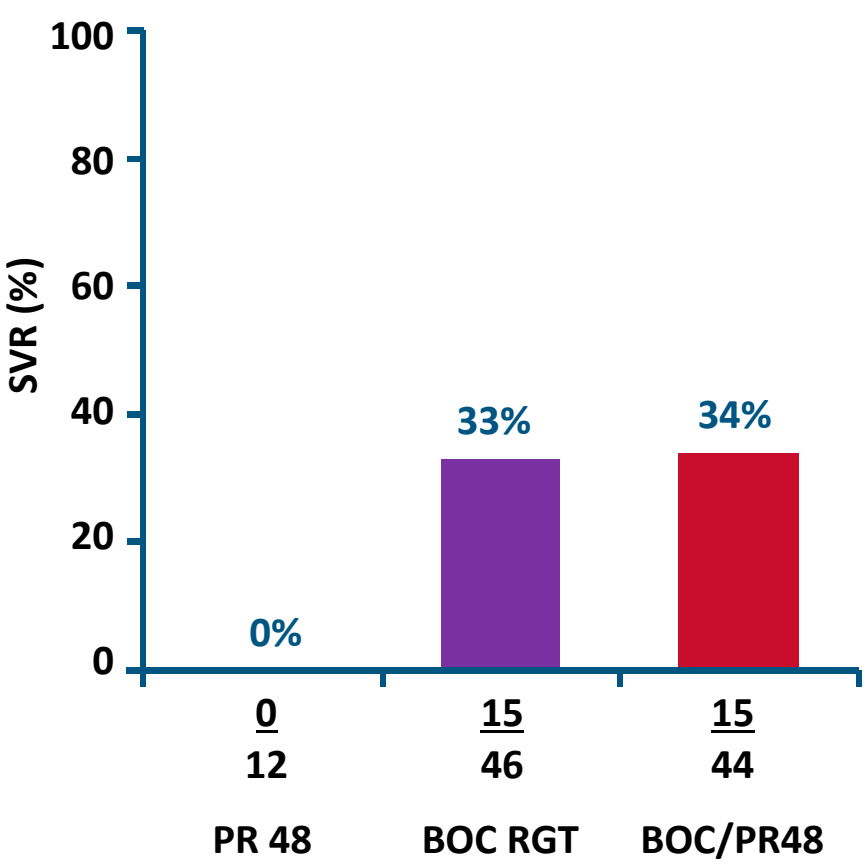
RESPOND-2: SVR by Historical Response Non-responders and Relapsers*

	Arm 1: 48 P/R N = 80	Arm 2: BOC RGT N = 162	Arm 3: BOC/PR48 N = 161
Partial-responder – n/n (%)	**2/29 (6.9%)**	**23/57 (40.4%)**	**30/58 (51.7%)**
Relapser – n/n (%)	**15/51 (29.4%)**	**72/105 (68.6%)**	**77/103 (74.8%)**

*Non-responders had a decrease in plasma HCV-RNA of at least 2-$\log_{10}$ by week 12 of prior therapy but with detectable HCV-RNA throughout the course of therapy. Relapsers had undetectable HCV-RNA at end of prior therapy without subsequent attainment of a sustained virologic response

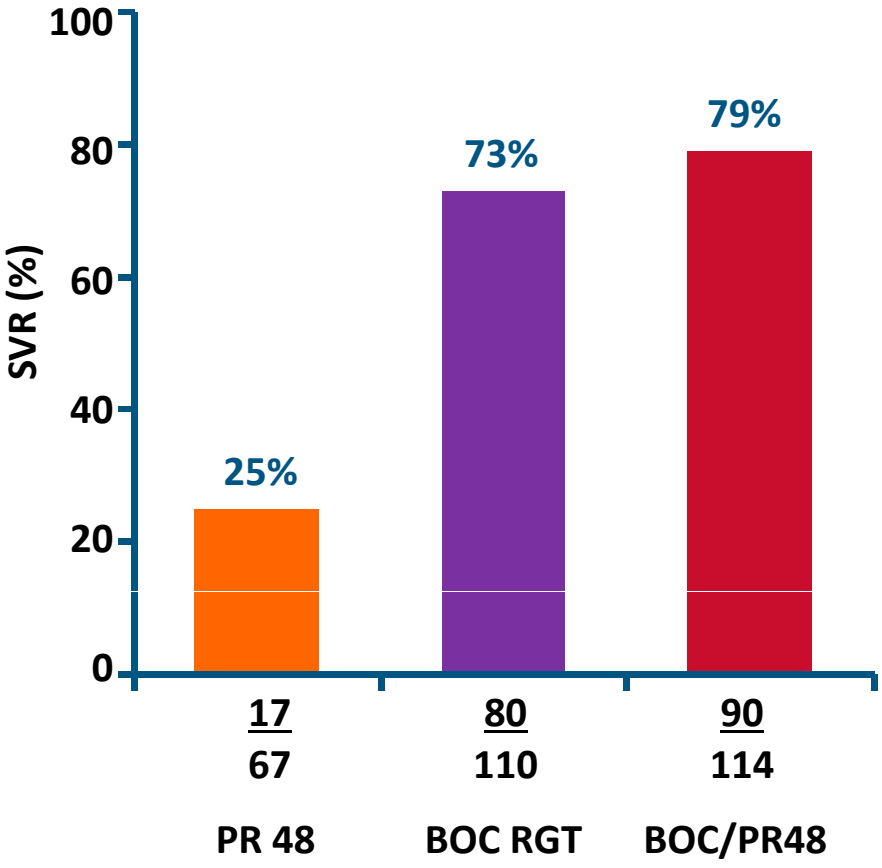
Bacon R, et al. AASLD 2010

RESPOND-2: SVR by Week 4
PR Lead-In Response



Poorly Responsive to IFN

<1 log_{10} viral load decline at treatment week 4

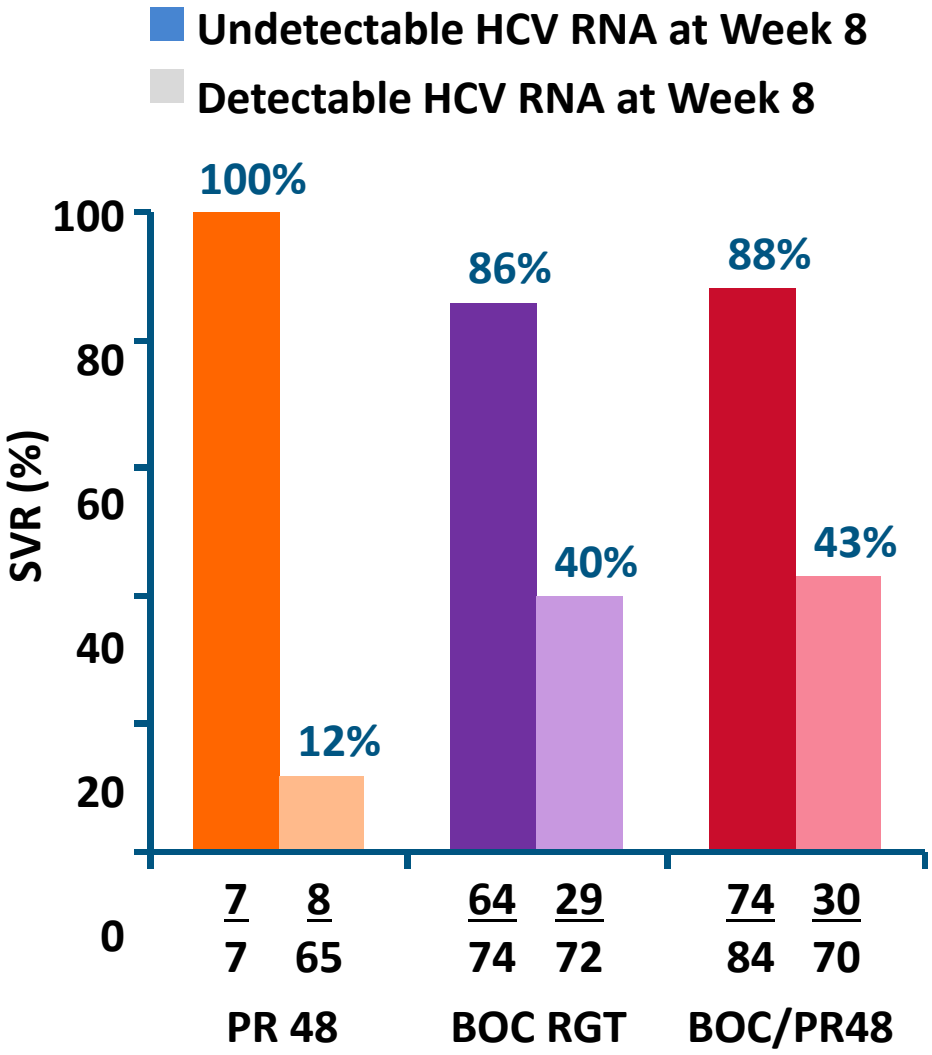


Responsive to IFN

≥1 log_{10} viral load decline at treatment week 4

Bacon R, et al. AASLD 2010

RESPOND-2: SVR by Week 8 HCV RNA Response (ITT)



- 46% of patients in BOC RGT arm were eligible for shorter therapy

Bacon R, et al. AASLD 2010

RESPOND-2: Summary

- **Boceprevir added to PR significantly increased SVR compared to PR control can be used to treat patients with all categories of interferon responsiveness**

- **RGT and BOC/PR 48 were equally effective for treatment failure patients PR lead-in allows for real time assessment of patient's interferon responsiveness**

- **Poorly Responsive: 33-34% achieved SVR *vs* 0% in control**

  Responsive: 73-79% achieved SVR *vs* 26% in control

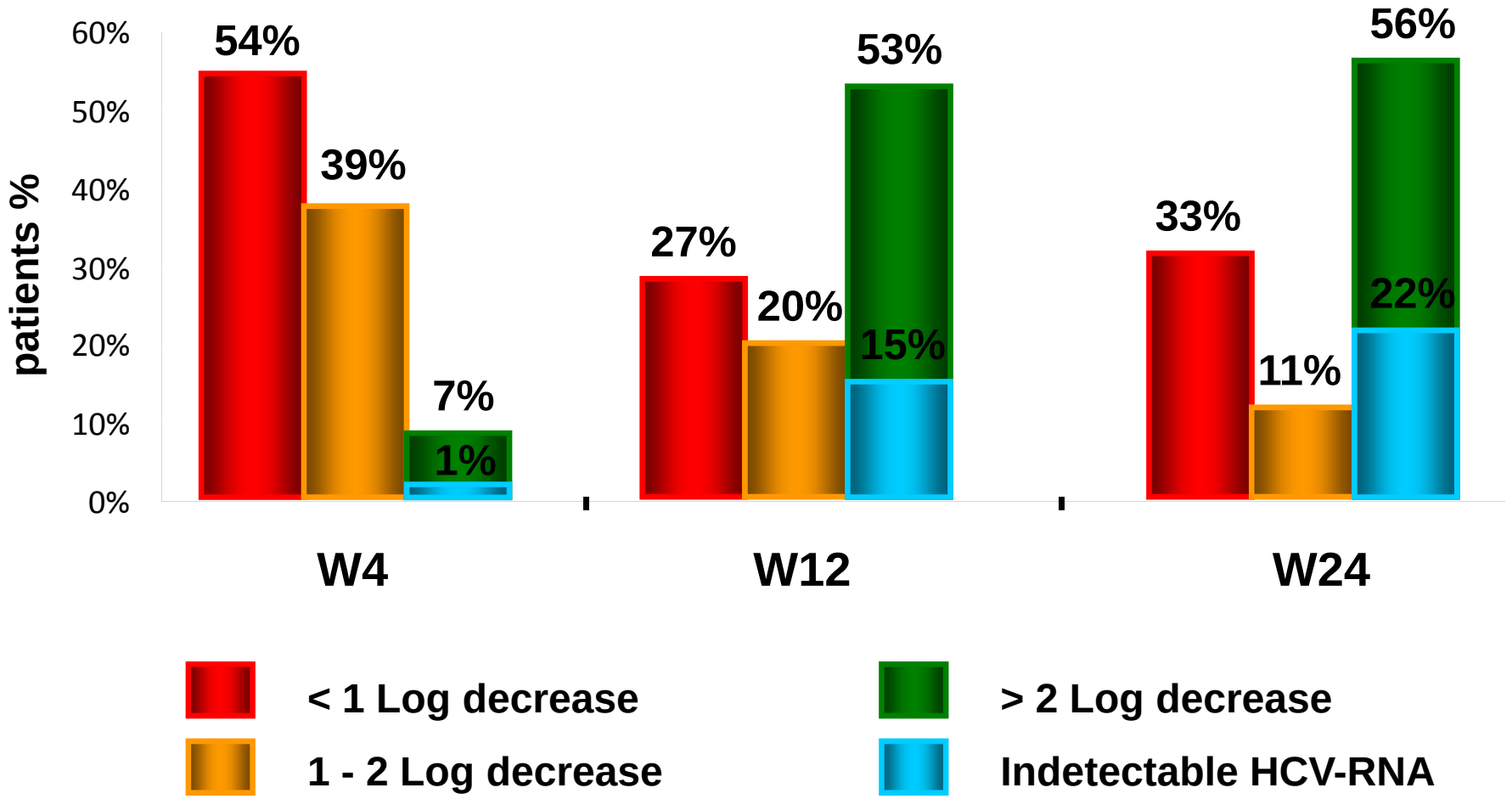
Bacon R, et al. AASLD 2010

How can we prevent treatment failure with triple combination therapy ?

Today treatment failure prevention

- **Prediction of probability to achieve SVR (“lead-in”, baseline characteristics)**
- **Offer alternative therapeutic options to non-responders to Peg-IFN and RBV (new trials)**

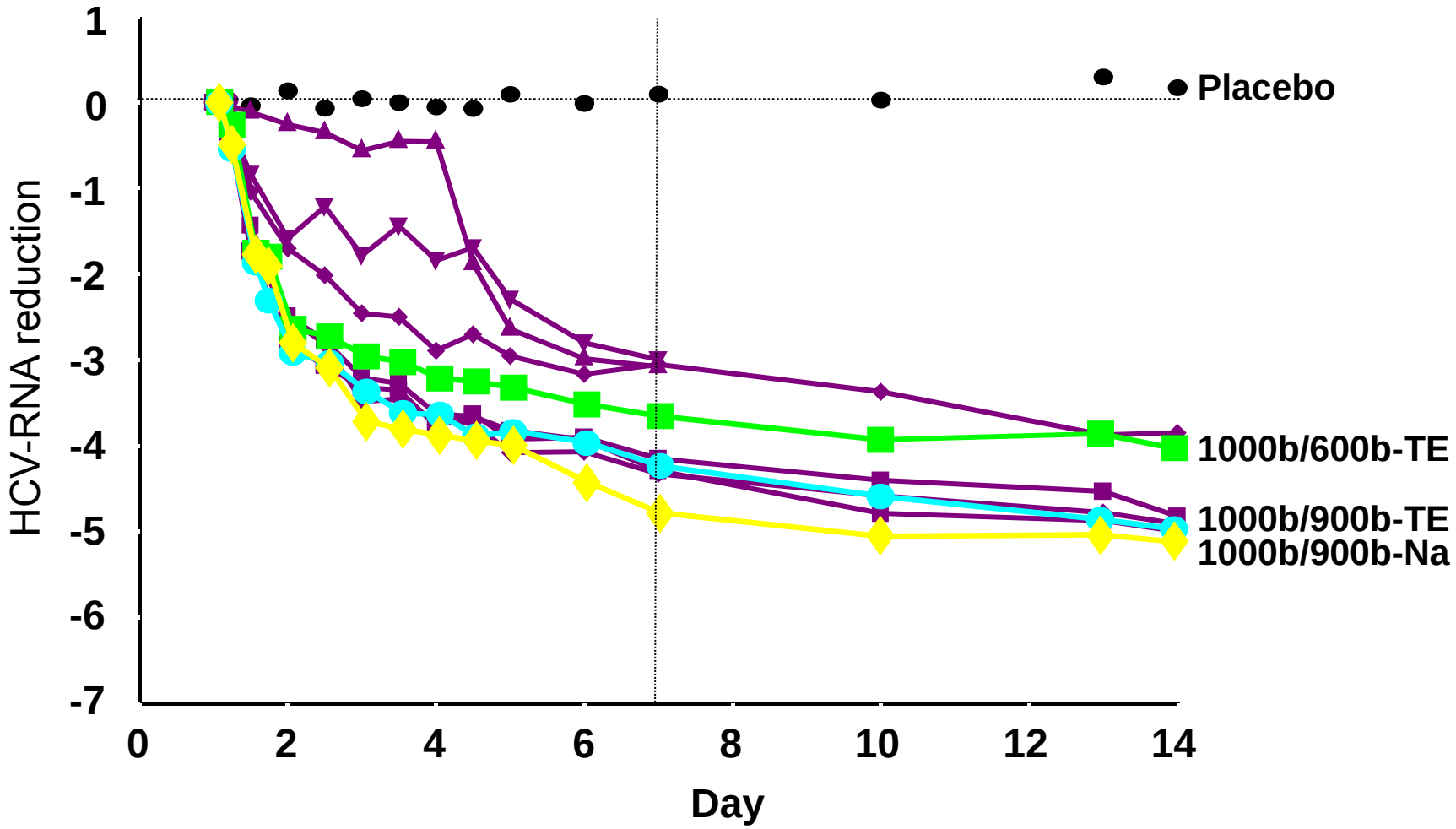
SYREN Trial: Virological Responses at week 4, week 12, week 24



Hézode C et al; AASLD 2010

Combinaison R7128/R7227

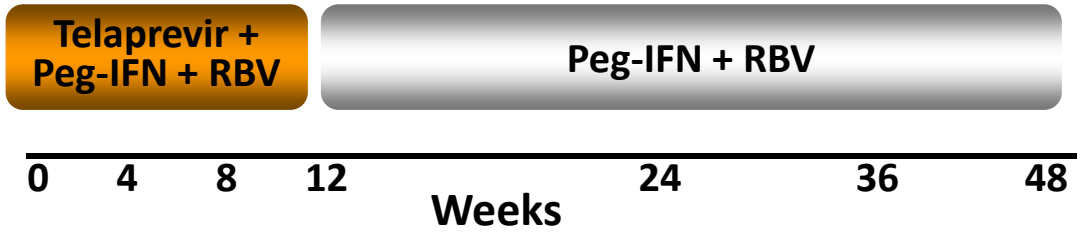
INFORM Trial



Gane EJ et al, Lancet 2010;376:1467-75

Conclusions: Treatment experienced Patients

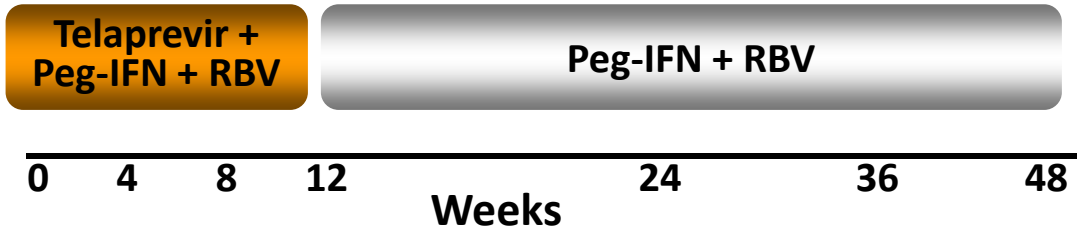
Telaprevir



SVR:
Relapsers: 86%
Partial responders: 57%
Null responders: 31%

Conclusions: Treatment experienced Patients

Telaprevir



SVR:
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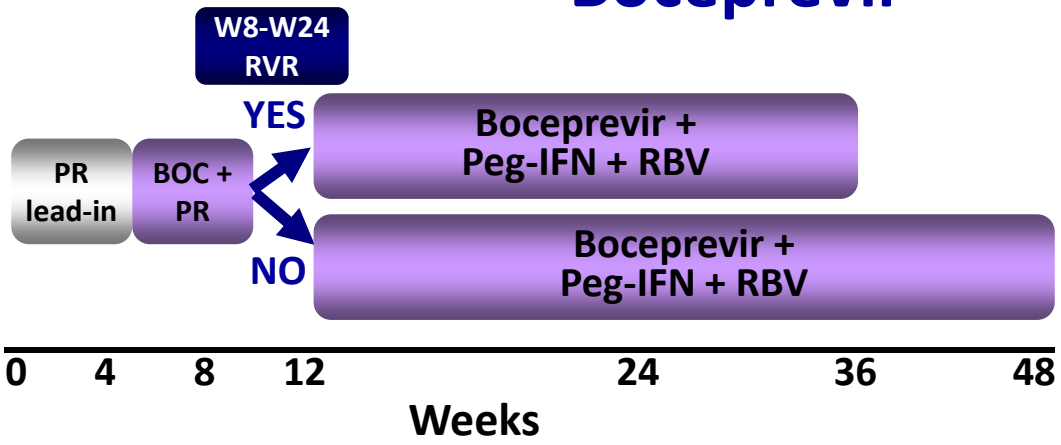
Boceprevir*



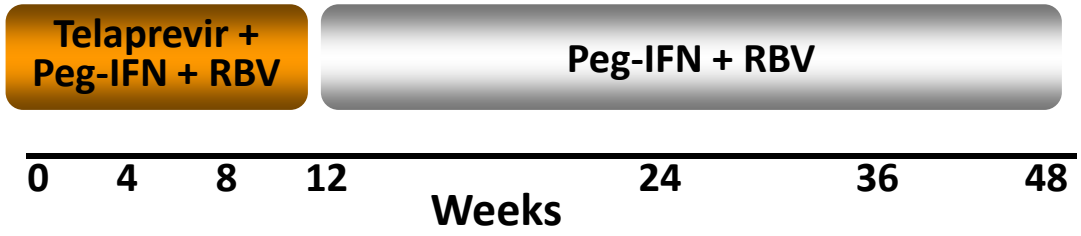
Short duration (36W): 46%*
SVR: 86%

SVR: 43%

**** Data only in prior relapsers or partial responders***

Conclusions: Treatment experienced Patients

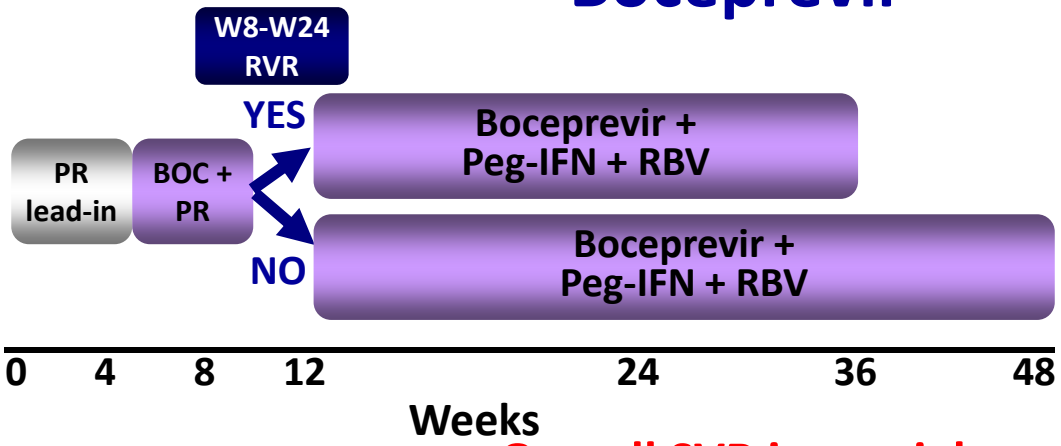
Telaprevir



SVR:
Relapsers: 86%
Partial responders: 57%
Null responders: 31%

Overall SVR in partial responders + relapsers: 77% *vs* 21%

Boceprevir*



Short duration (36W): 46%*
SVR: 86%

SVR: 43%

Overall SVR in partial responders + relapsers: 66% *vs* 21%

**** Data only in prior relapsers or partial responders***