

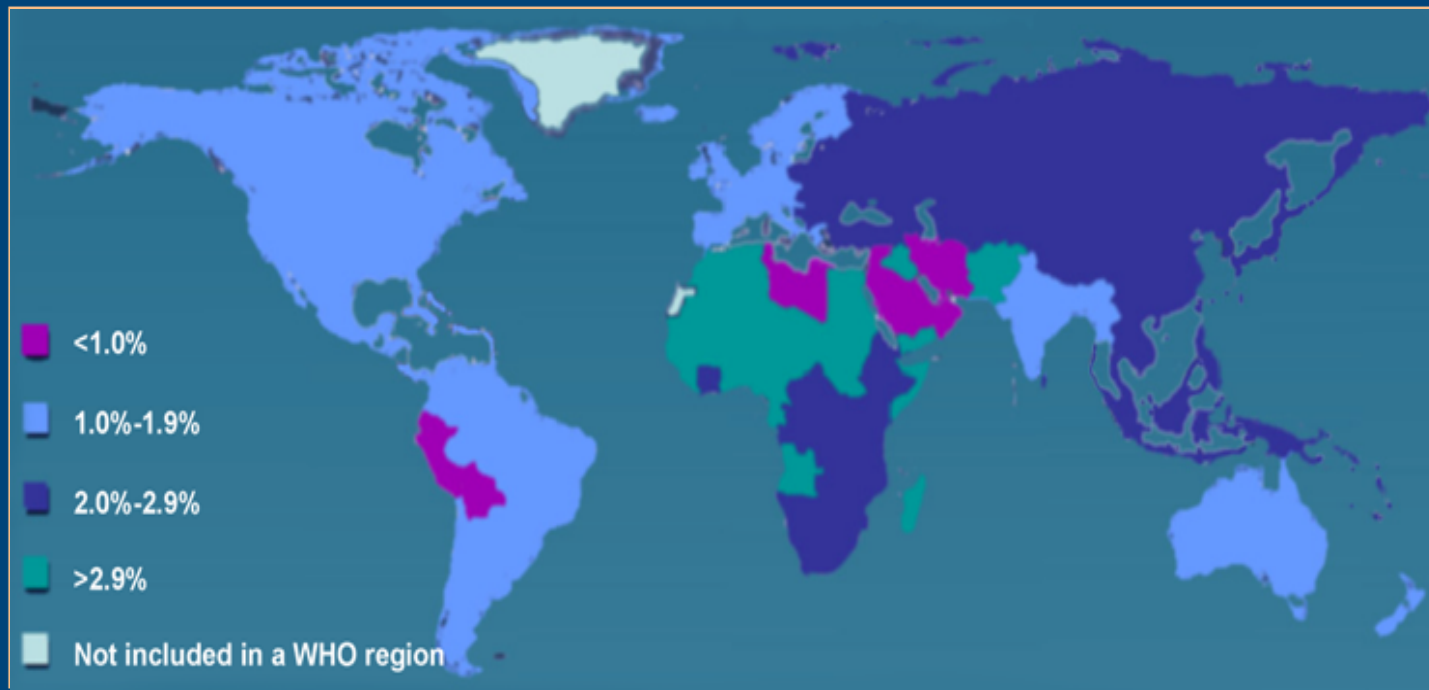
Direct-Acting Antivirals: The New Era of Hepatitis C Treatment

*NATAP Program
June 25, 2011*

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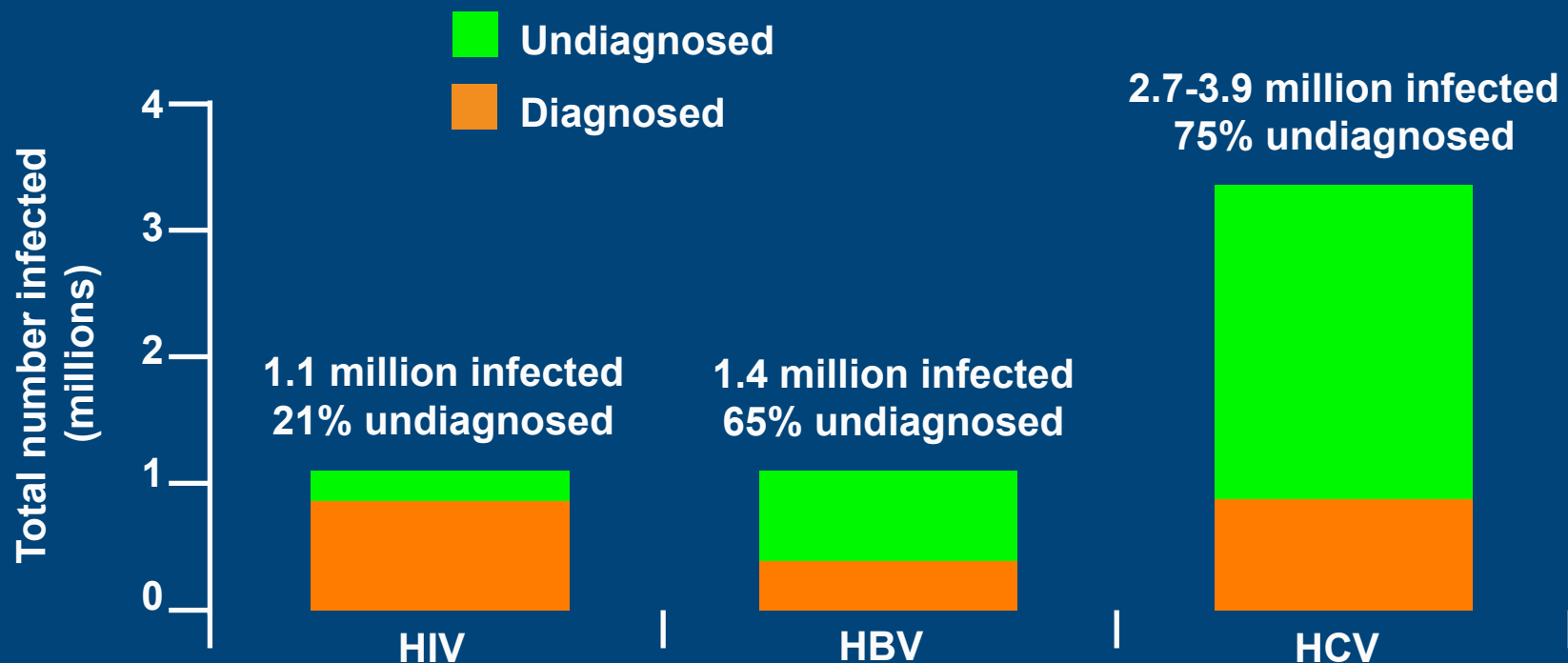
Hepatitis C Is a Global Disease

- ~ 170 million people currently infected
- 3 to 4 million people newly infected annually
- 75% of cases in US are Genotype 1

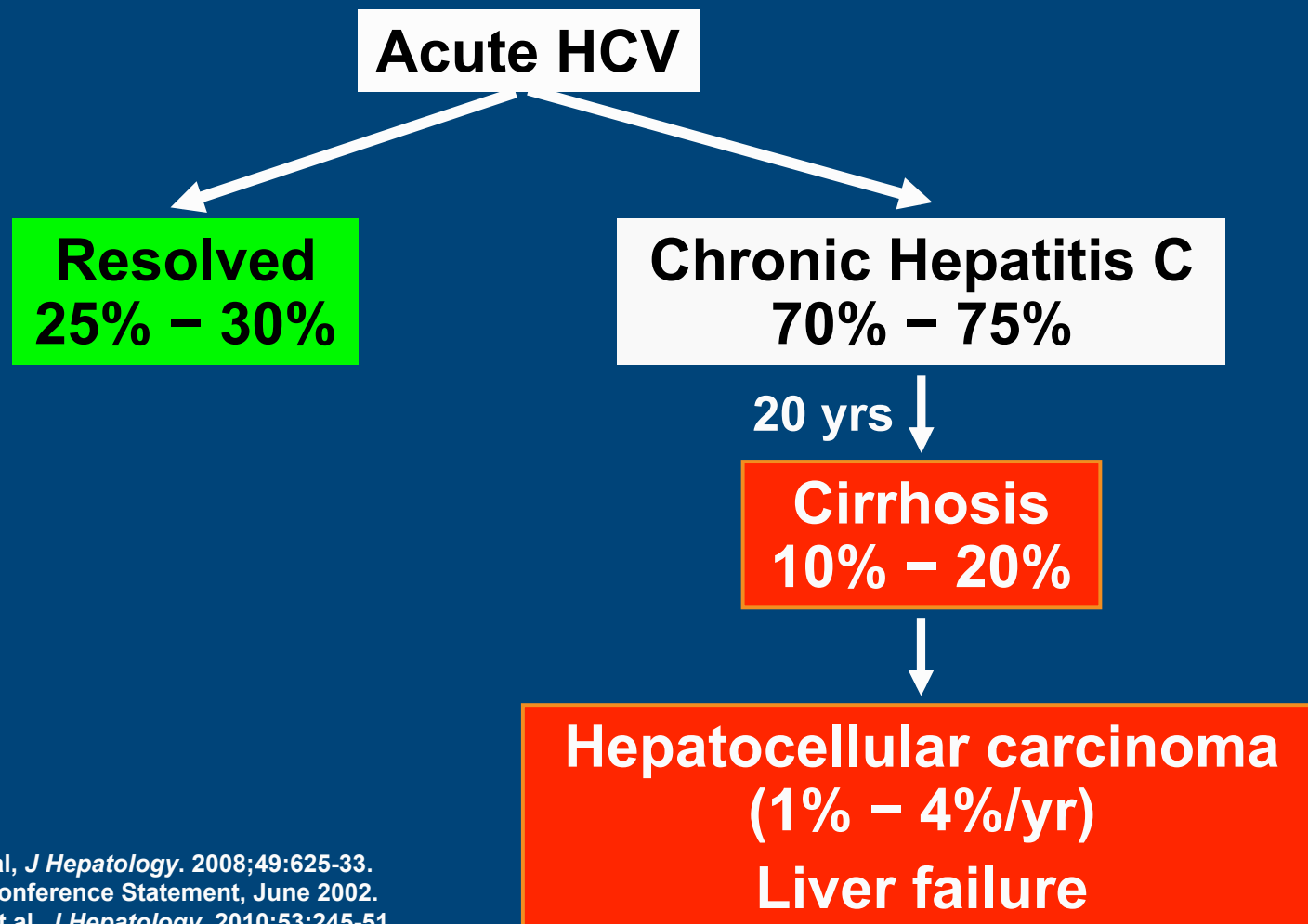


In the US, Prevalence of HCV Higher Than HIV or HBV

Number of infected individuals vs
number aware they are infected (diagnosed)



Natural History of HCV Infection



Santantonio T et al, *J Hepatology*. 2008;49:625-33.
NIH Consensus Conference Statement, June 2002.
John-Baptiste A et al, *J Hepatology*. 2010;53:245-51.
Seeff LB, *Liver International*. 2009;29(suppl 1):89-99.

Hepatitis C—Not Just a Liver Disease

- Other diseases associated with HCV
 - Diabetes
 - B cell proliferative disorders
 - Essential mixed cryoglobulinemia
 - Non-Hodgkin's lymphoma
 - Depression and cognitive disorders
 - Arthritis
 - Sjogren's syndrome

Current HCV Treatment

- Goal = SVR
 - Considered virologic cure
- Peg-IFN/RBV is the current therapy for HCV
 - Genotype 1
 - 40% – 52% of patients achieve SVR^{a-f}
 - Duration of therapy 48 weeks^{a-f}
 - Low success rates with retreatment in nonresponders and relapsers (10% – 25%)^{g-i}
- Peg-IFN/RBV has known toxicities^{a-i}
 - Rationale for response-guided therapy with potential to shorten therapy

^a Pegasys [package insert]. Nutley, NJ: Hoffmann-La Roche Inc.; 2011. ^b Copegus [package insert]. Nutley, NJ: Hoffmann-La Roche Inc.; 2010.

^c Hadziyannis SJ, et al. *Ann Intern Med.* 2004;140:346-355. ^d Fried MW, et al. *NEJM.* 2002;347:975-982. ^e Manns MP, et al. *Lancet.* 2001;358:958-965.

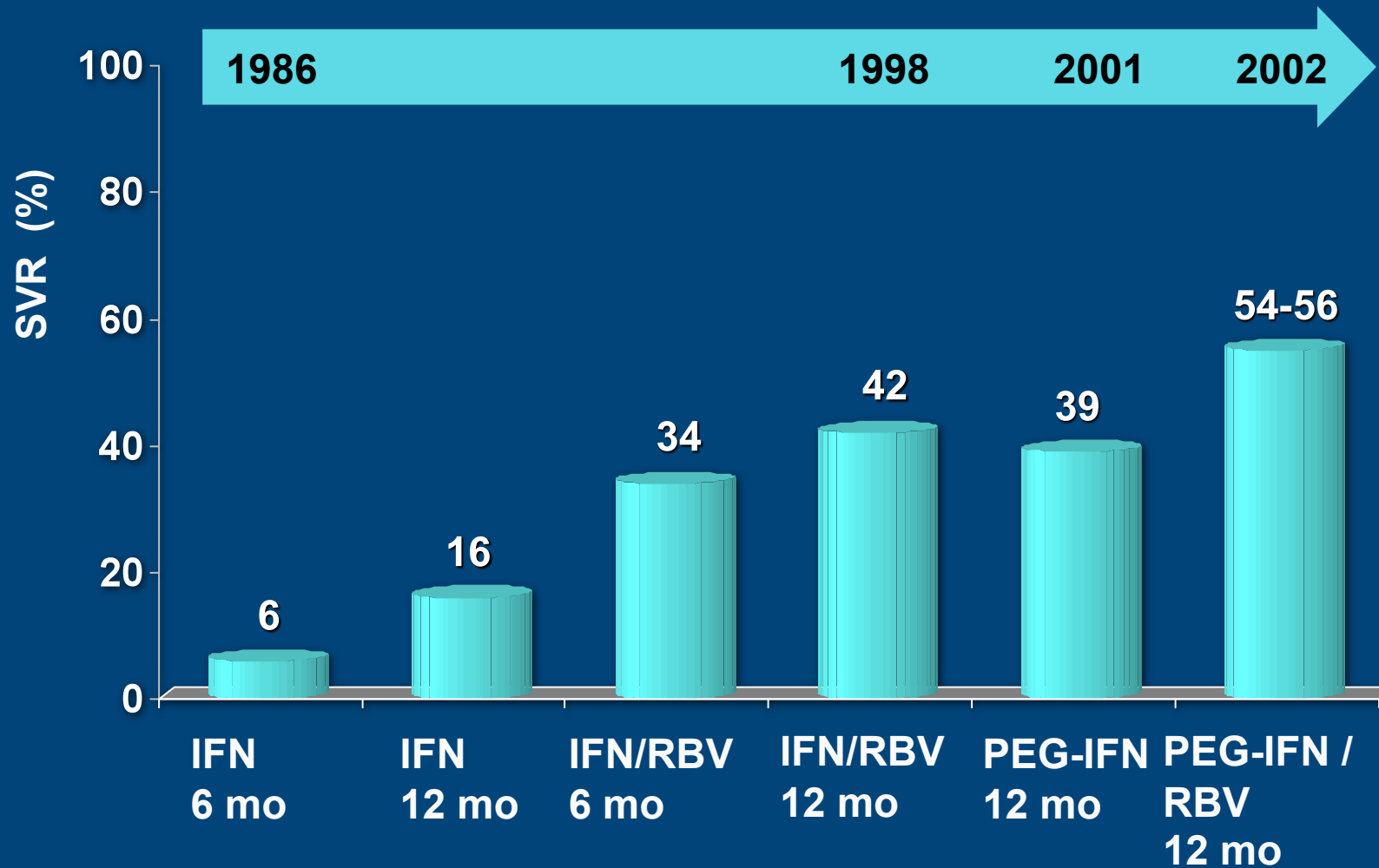
^f McHutchinson JG, et al. *NEJM.* 2009;361:58-593. ^g Bacon BR, et al. *Hepatology.* 2009;49:1838-1846. ^h Jensen DM, et al. *Ann Intern Med.*

2009;150:528-540. ⁱ Poynard T, et al. *Gastroenterology.* 2009;136:1618-1628.

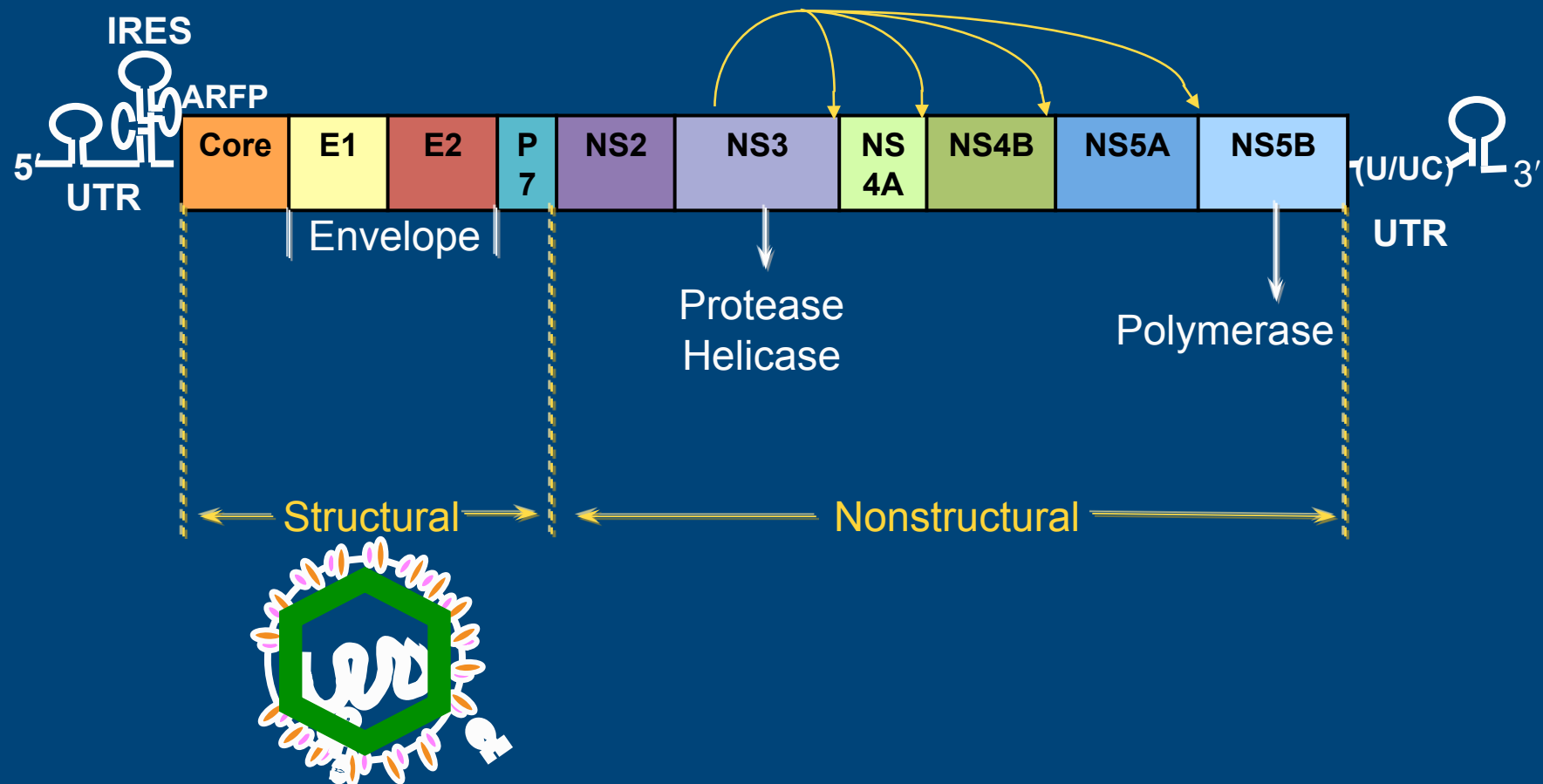
Common Factors That May Lead to Lower SVR with Peg-IFN/RBV

- Genotype 1
- High HCV RNA levels
- Cirrhosis/bridging fibrosis
- Age $\geq$ 40 years
- Heavy body weight
- Insulin resistance
- African American and Latino ethnicity
- Genetic polymorphisms (IL28B)
- HIV coinfection

The Evolution of HCV Therapy

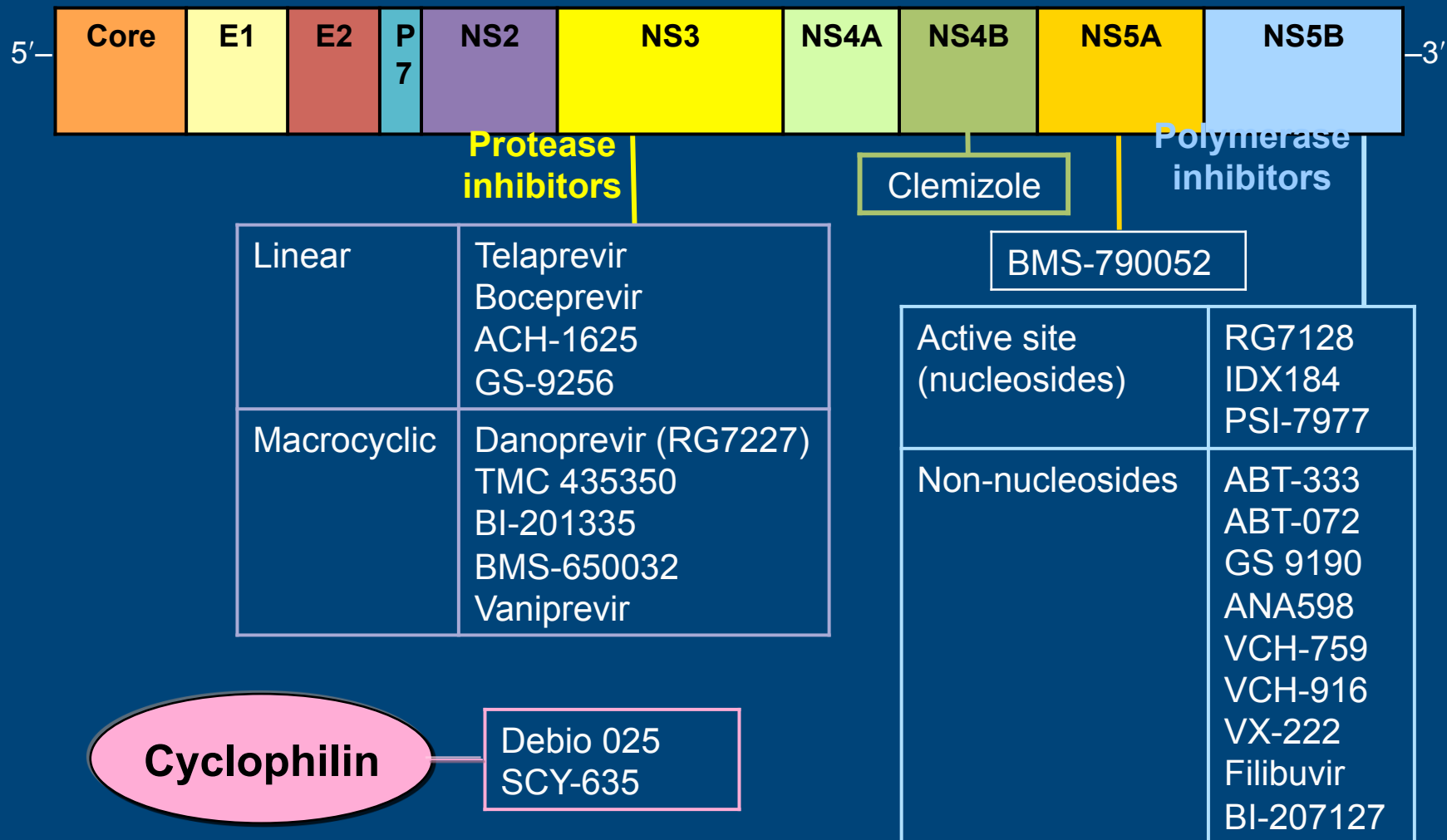


Hepatitis C Virus Genome



Abbreviations: ARFP, alternate reading frame protein; IRES, internal ribosome entry site; UTR, untranslated region.
Glenn JS. *Clin Liver Dis.* 2005;9:353-369.

Targets for New Hepatitis C Drugs



Not all-inclusive

The Beginning of a New Era

What's Coming in 2011 for Patients With Genotype 1

**SVR >70%
Genotype 1**

**Response-
guided
therapy
(RGT)**

**Increased
side effects**

Resistance

**April 27-28, 2011: FDA Advisory Panel voted 18-0 for
approval of boceprevir and telaprevir**

Boceprevir approved by FDA May 13, 2011

Telaprevir approved May 23, 2011

Phase 3 Trials of Telaprevir and Boceprevir

Telaprevir

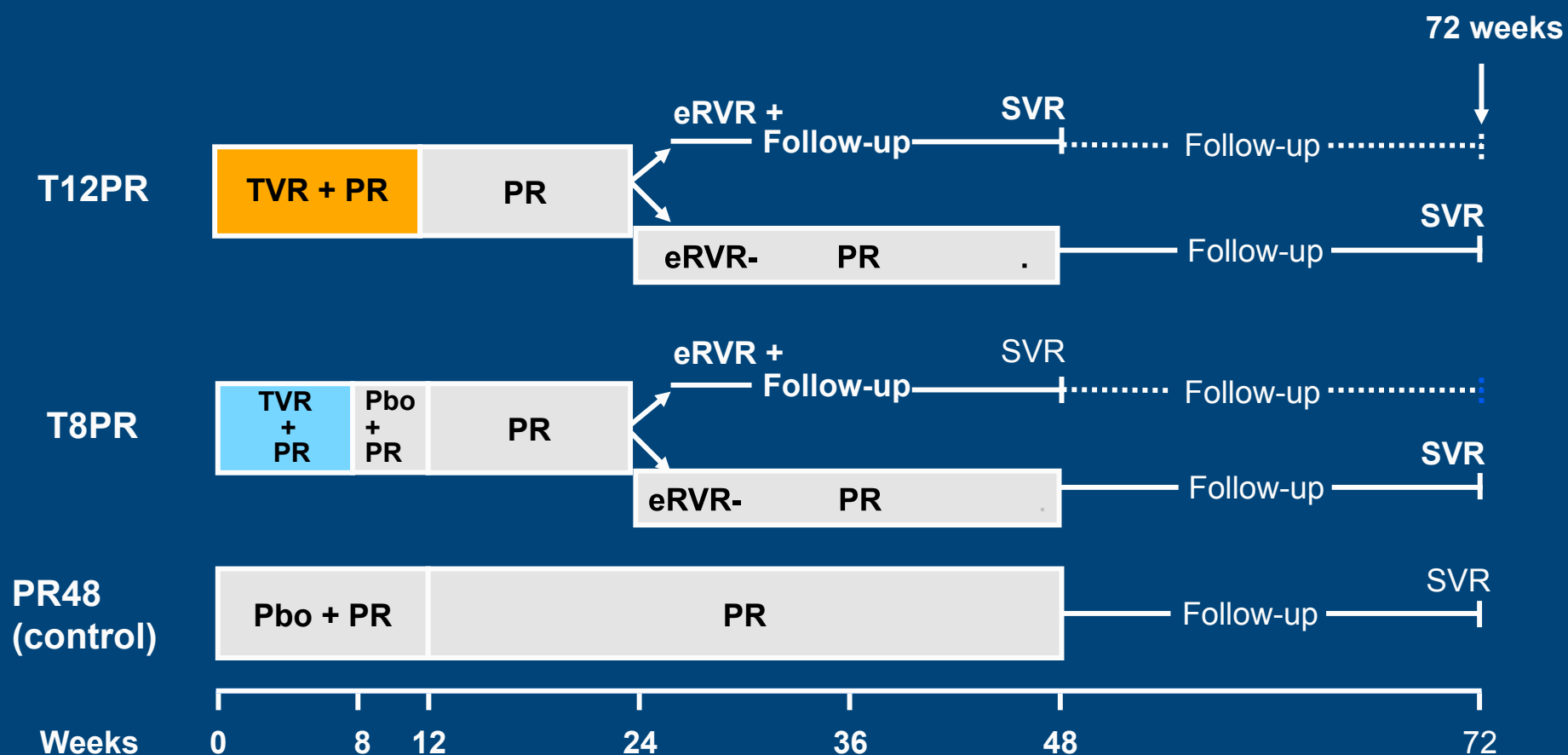
- Naïve
 - ADVANCE
 - ILLUMINATE
- Experienced
 - REALIZE

Boceprevir

- Naïve
 - SPRINT-2
- Experienced
 - RESPOND-2

ADVANCE: Treatment Naïve G1

Randomized, Double-Blind, Placebo-Controlled for Telaprevir



eRVR = HCV RNA undetectable at week 4 and week 12 (Taqman v2.0)

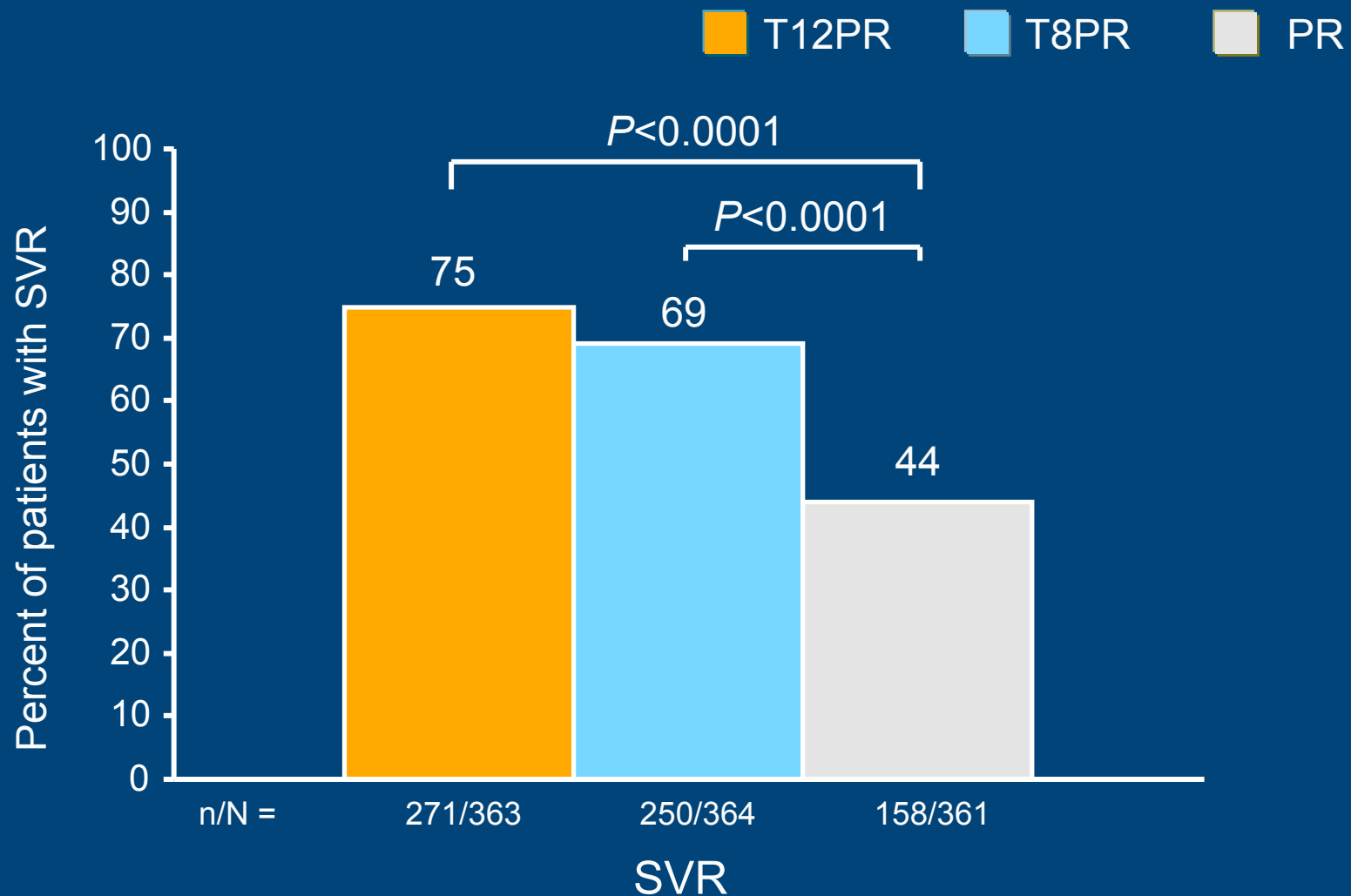
(T) TVR = telaprevir 750 mg q8h; Pbo = Placebo; (P) Peg-IFN = pegylated interferon alfa-2a (40 kD) 180 µg/wk;
(R) RBV = ribavirin 1,000 or 1,200 mg/da

ADVANCE: Stopping Rules

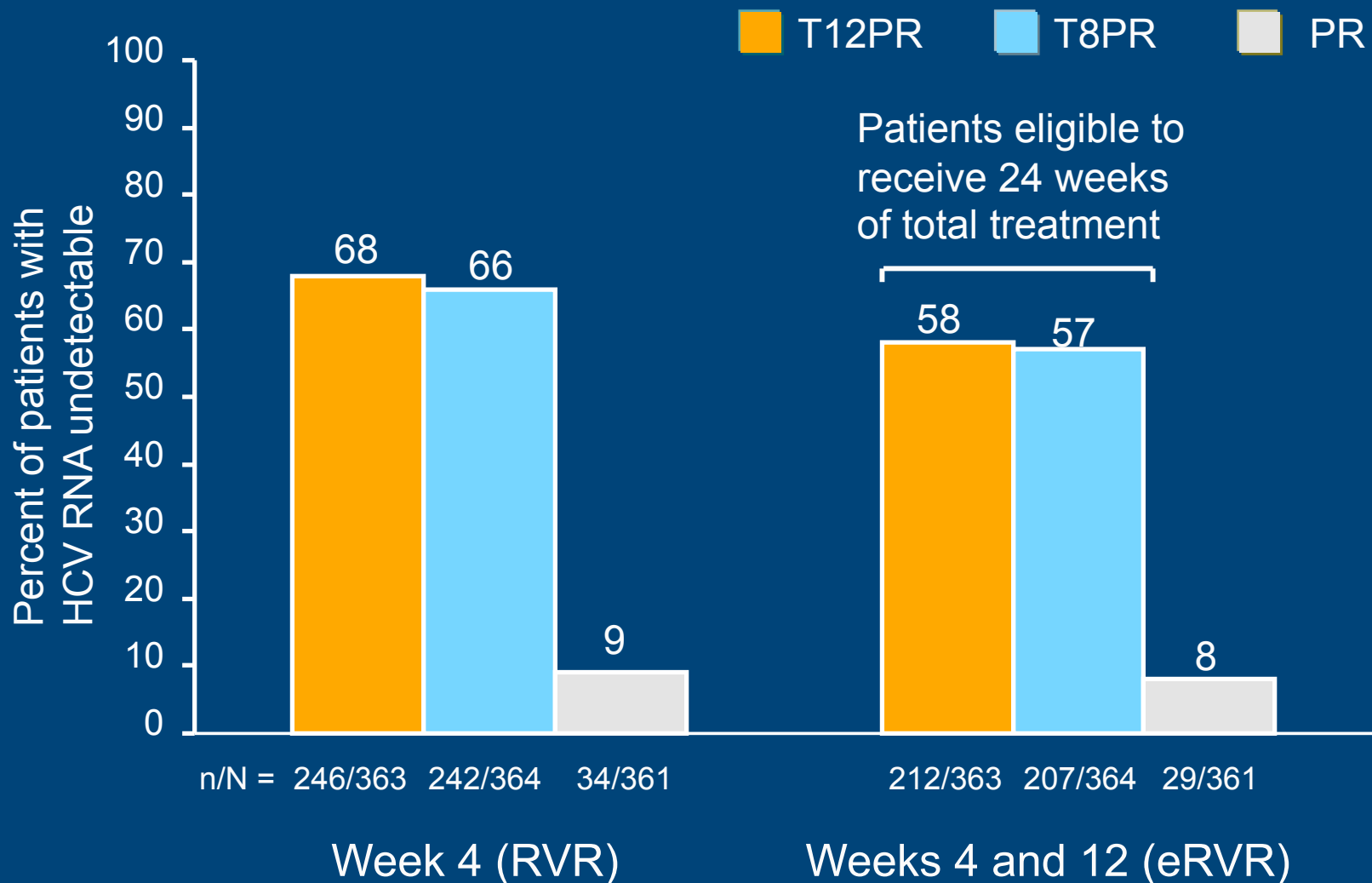
- Stopping rules are important to avoid treatment in the face of futility
- With DAA drugs, also important in prevention of resistance

Timepoint	Criteria for Stopping	Action
Week 4*	HCV RNA >1000 IU/mL	Discontinue TVR, continue PR
Week 12	HCV RNA <2 log ₁₀ decline	Discontinue all treatment
Week 24-40	HCV RNA detectable	Discontinue all treatment

ADVANCE: SVR Rates

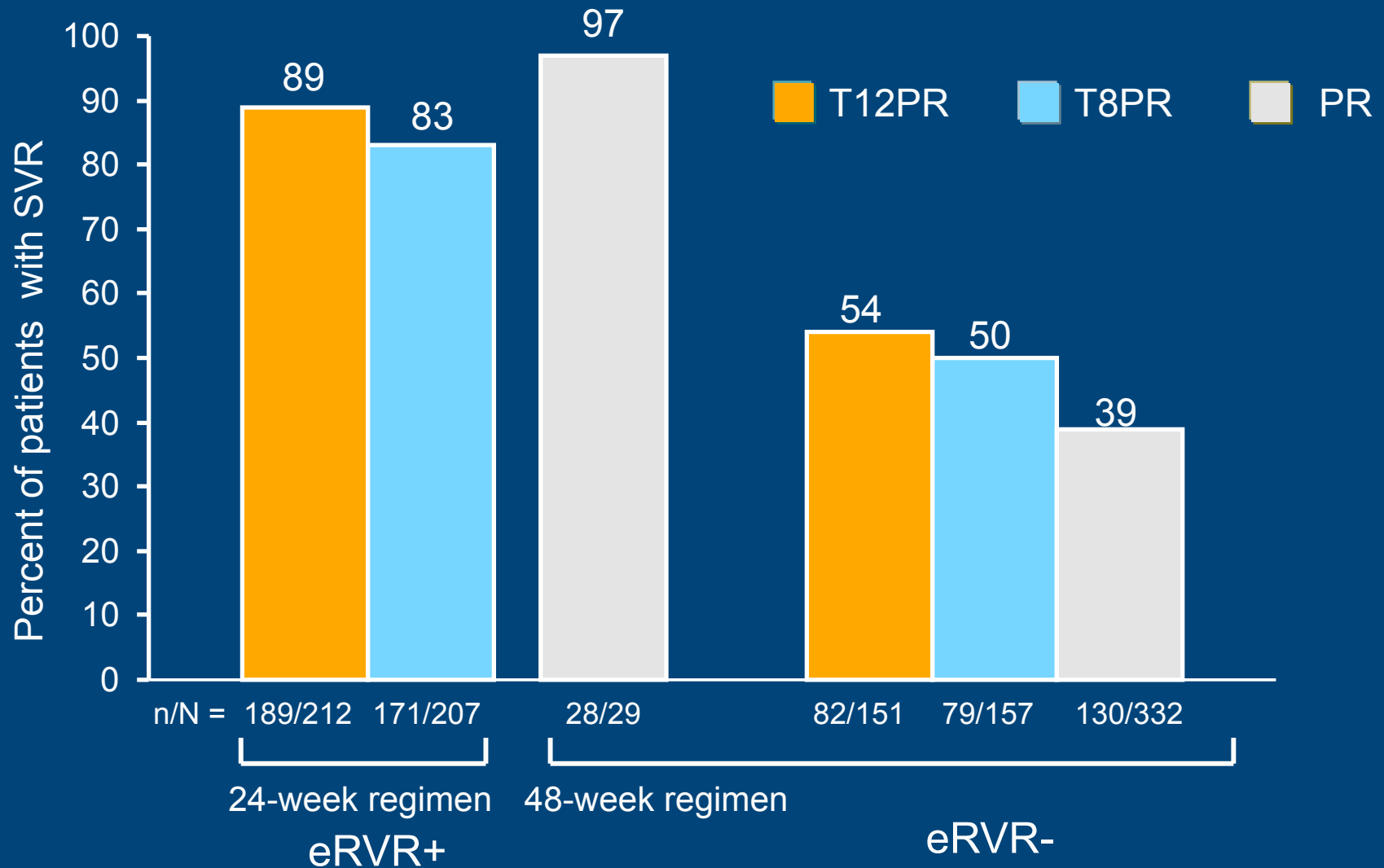


ADVANCE: RVR and eRVR Rates

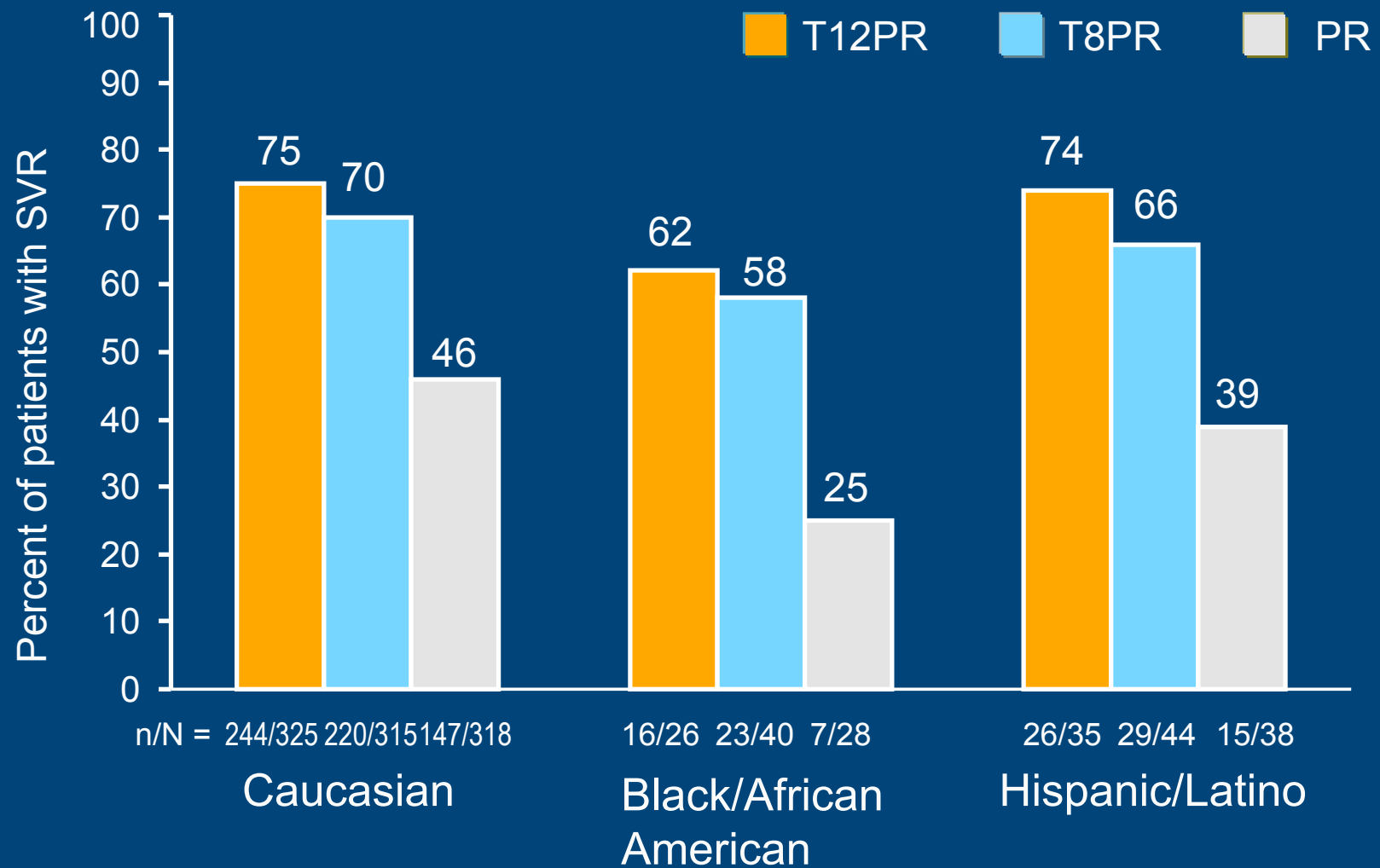


Jacobson IM, et al. *Hepatology*. 2010;52(suppl 1):112A. Abstract 211.

ADVANCE: SVR Rates by eRVR Status



ADVANCE: SVR Rates by Race or Ethnicity



ADVANCE: Most Common Adverse Events

% of Patients with	T12PR N=363	T8PR N=364	PR (control) N=361
Any Adverse Event*	99	99	98
Fatigue	57	58	57
Pruritus	50	45	36
Headache	41	43	39
Nausea	43	40	31
Rash	37	35	24
Anemia	37	39	19
Insomnia	32	32	31
Diarrhea	28	32	22
Influenza-like illness	28	29	28
Pyrexia	26	30	24

Shaded areas: 10% or greater incidence in either TVR groups vs control

Rash Events During Telaprevir/ Placebo Phase

% of Patients with	T12PR N=363	T8PR N=364	PR (control) N=361
Rash events	56	53	37
Severe rash events	6	3	1
Discontinuation of telaprevir/ placebo only due to rash events	7	5	1
Discontinuation of all study drugs due to rash events	1.4	0.5	0

- Rash was primarily eczematous and resolved upon cessation of therapy
- Severe/worsening moderate rash was managed by sequentially discontinuing telaprevir, followed by ribavirin and, if indicated, peginterferon for continued progression
- Anorectal symptoms in ~29% with telaprevir

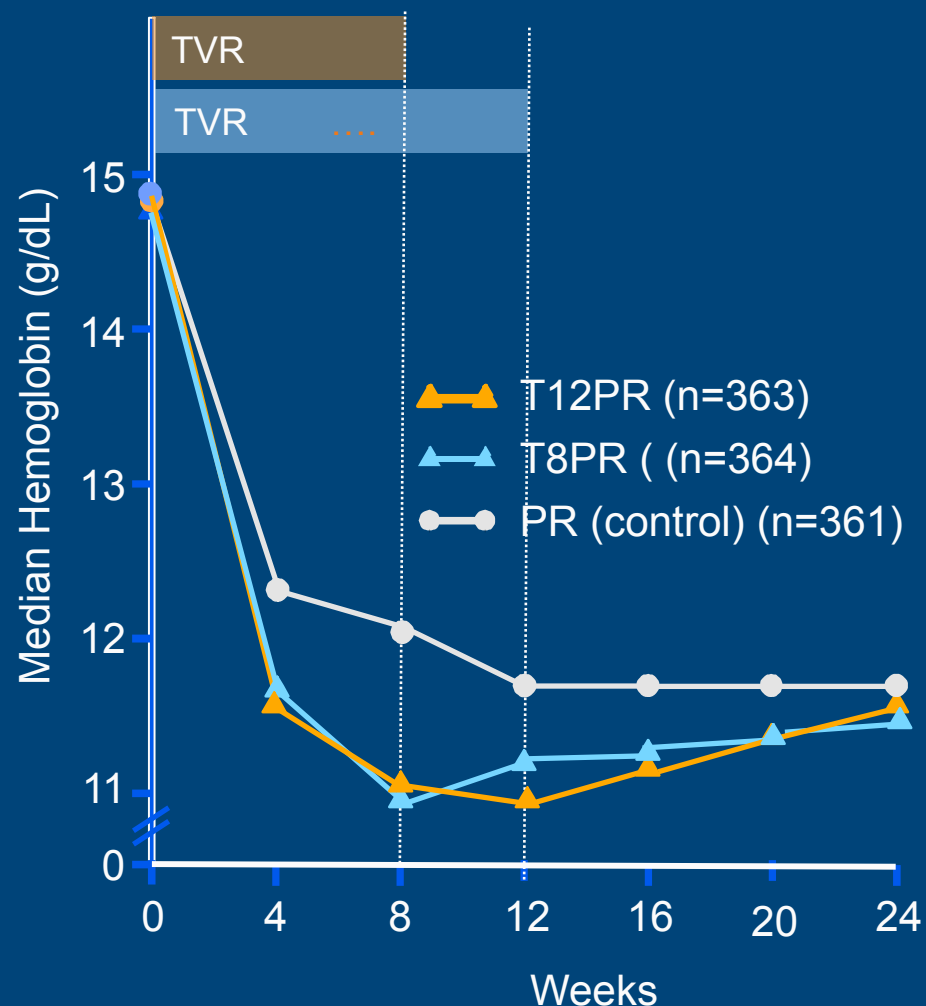
Nadir Hemoglobin, Discontinuation for Anemia, and Median Hemoglobin Levels

Hemoglobin nadir during TVR/Pbo Phase

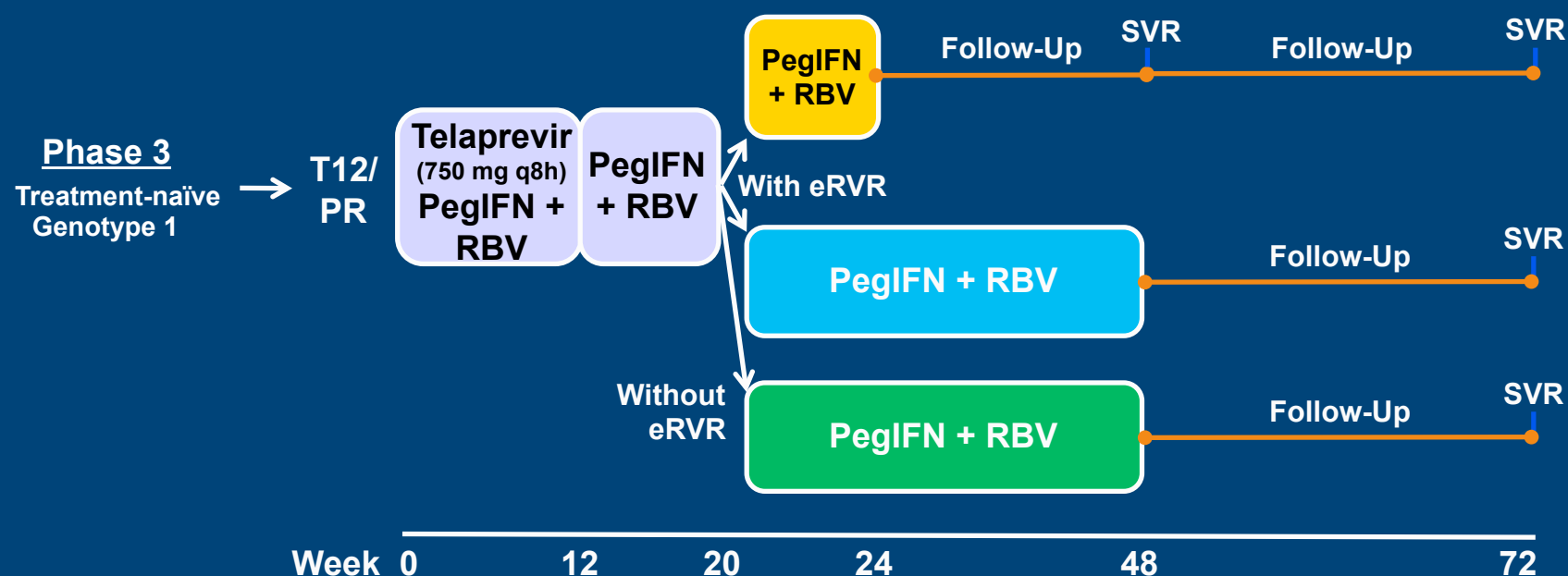
% of Patients with	T12PR N=363	T8PR N=364	PR N=361
Hemoglobin <10 g/dL	36	40	14
Hemoglobin <8.5 g/dL	9	9	2

- Per protocol, anemia was to be managed with RBV dose modifications and ESAs were not allowed
- 1%, 3% and 1% of patients in T12PR, T8PR and PR, respectively discontinued all drugs due to anemia events
- 4%, 2% and 0% of patients in T12PR, T8PR and PR, respectively discontinued telaprevir/placebo only

Median Hemoglobin



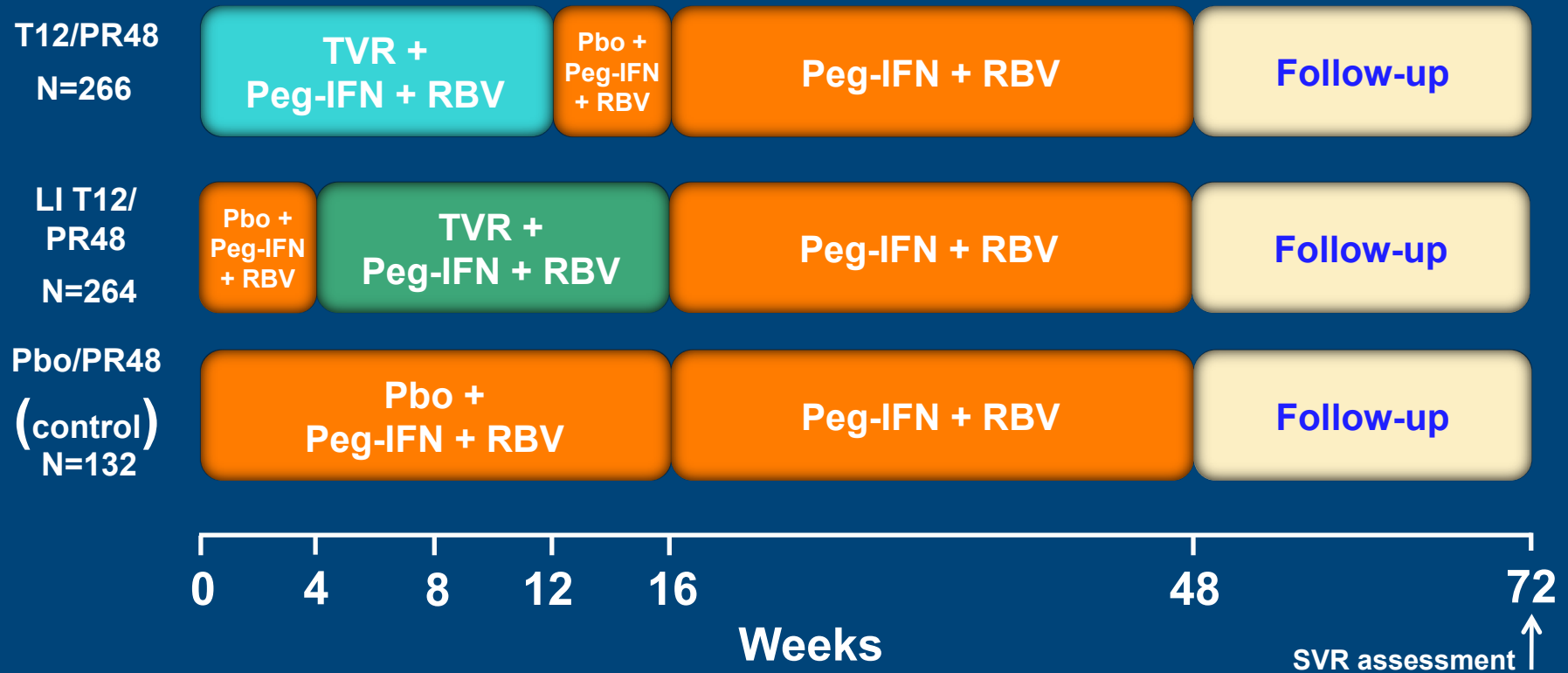
ILLUMINATE Study: 24 vs 48 Weeks After eRVR With Telaprevir



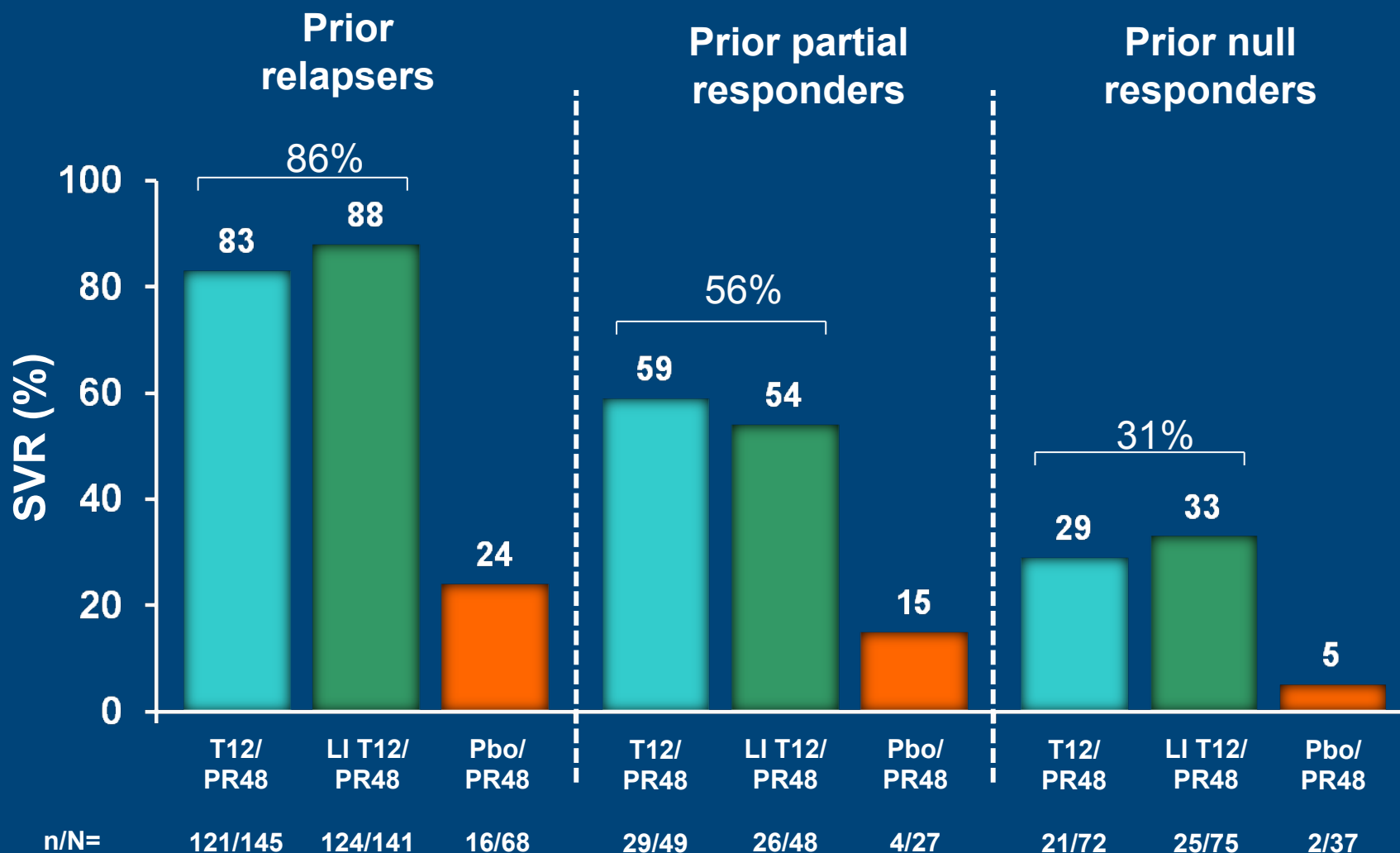
eRVR (extended rapid virologic response): HCV RNA <25 IU/mL at weeks 4 and week 20.

Sherman KE, et al. *Hepatology*. 2010;52(suppl 1):106A. Abstract LB2.

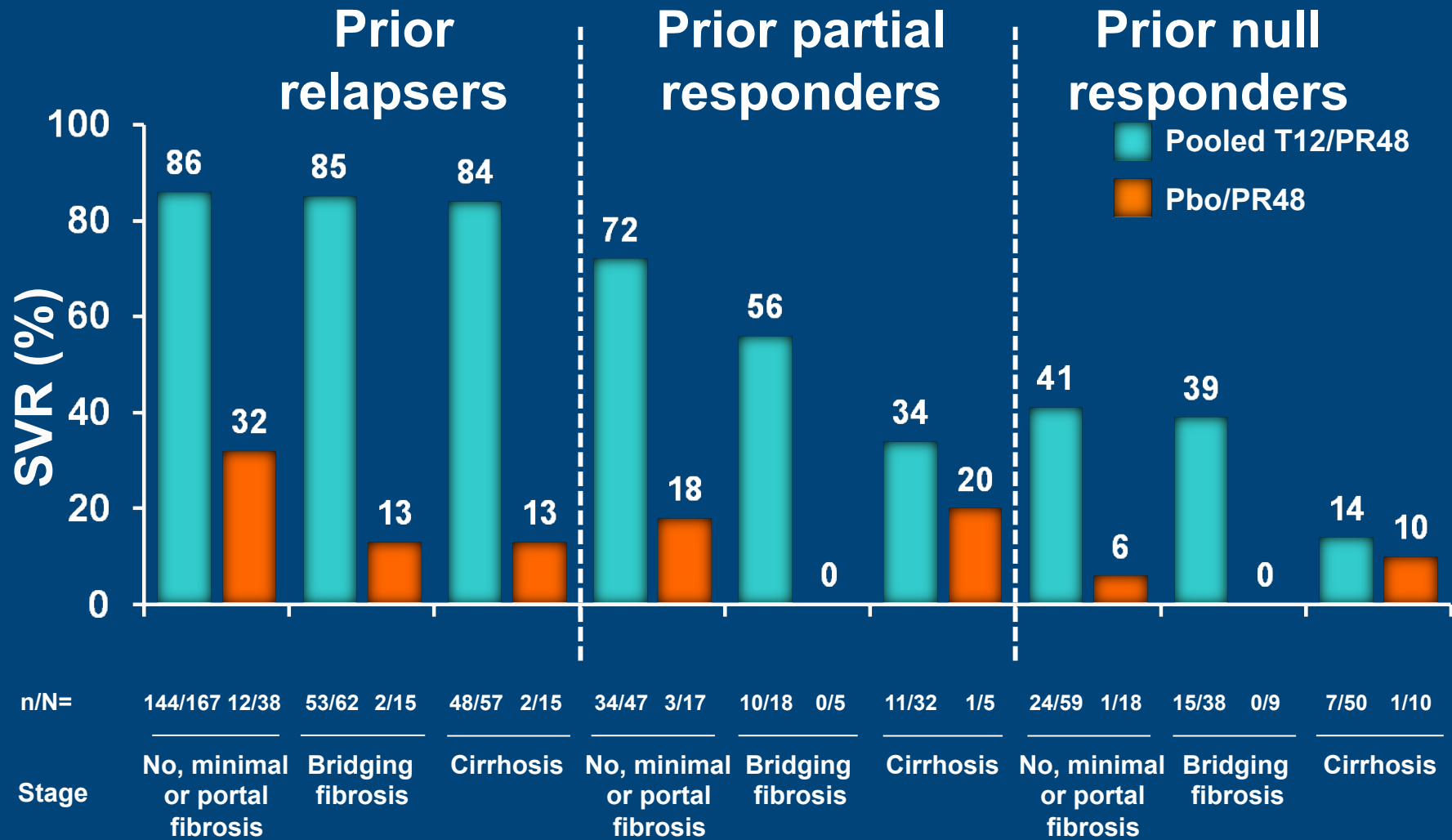
REALIZE: Study Design (N=662)



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

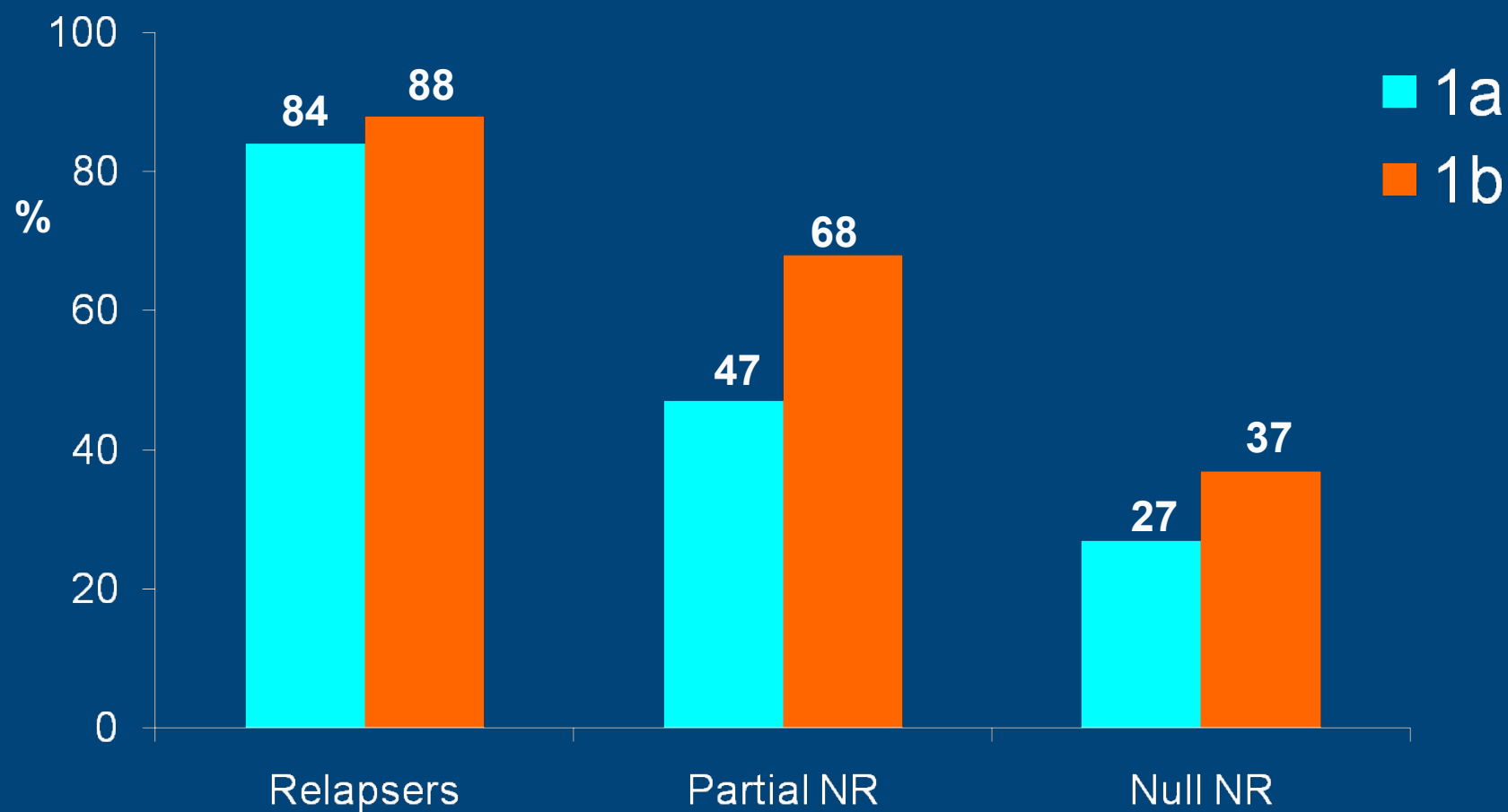


REALIZE: SVR by Baseline Fibrosis Stage and Prior Response

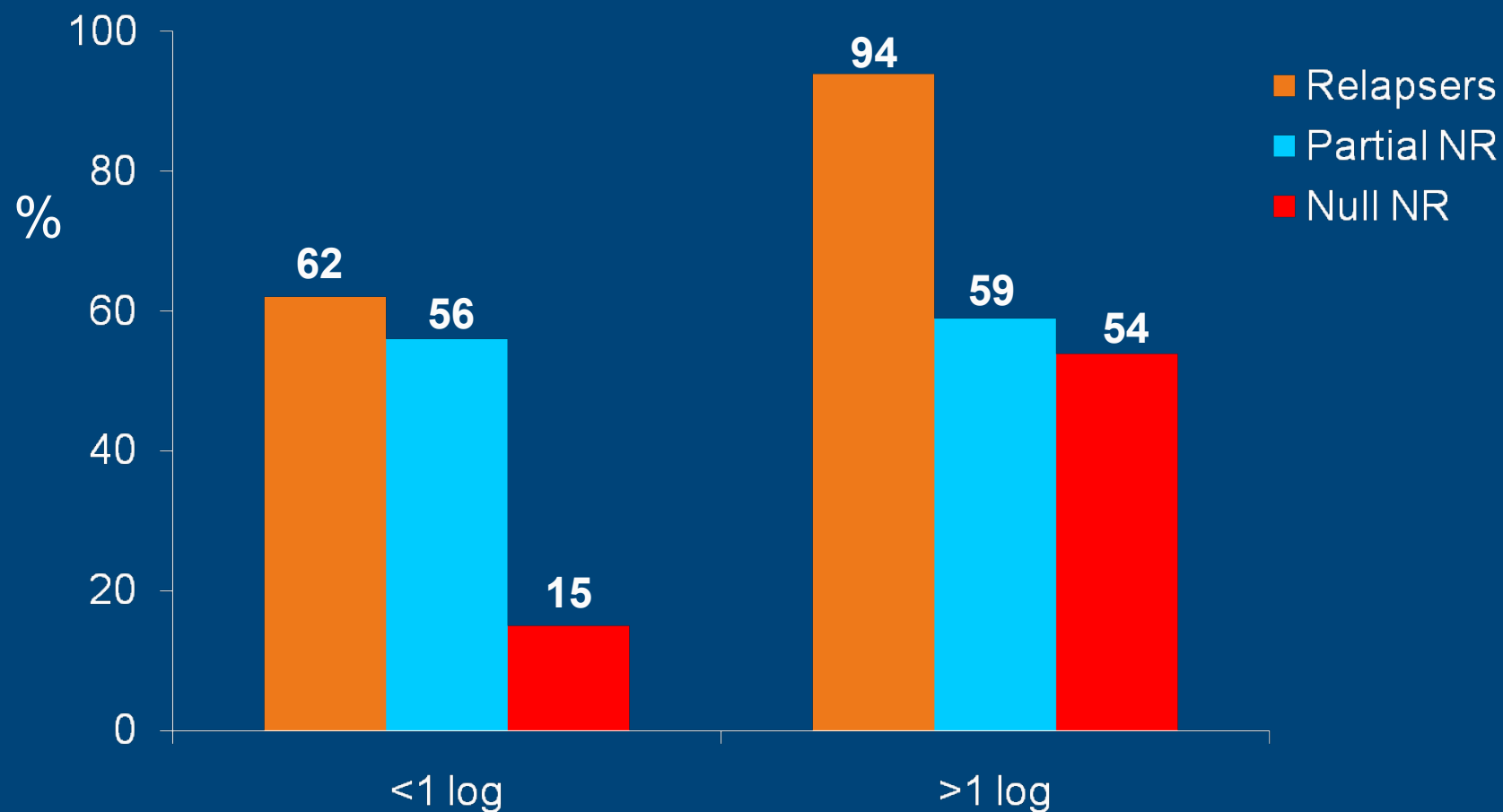


SVR by Subtype in REALIZE

Higher SVR Rates in Genotype 1b

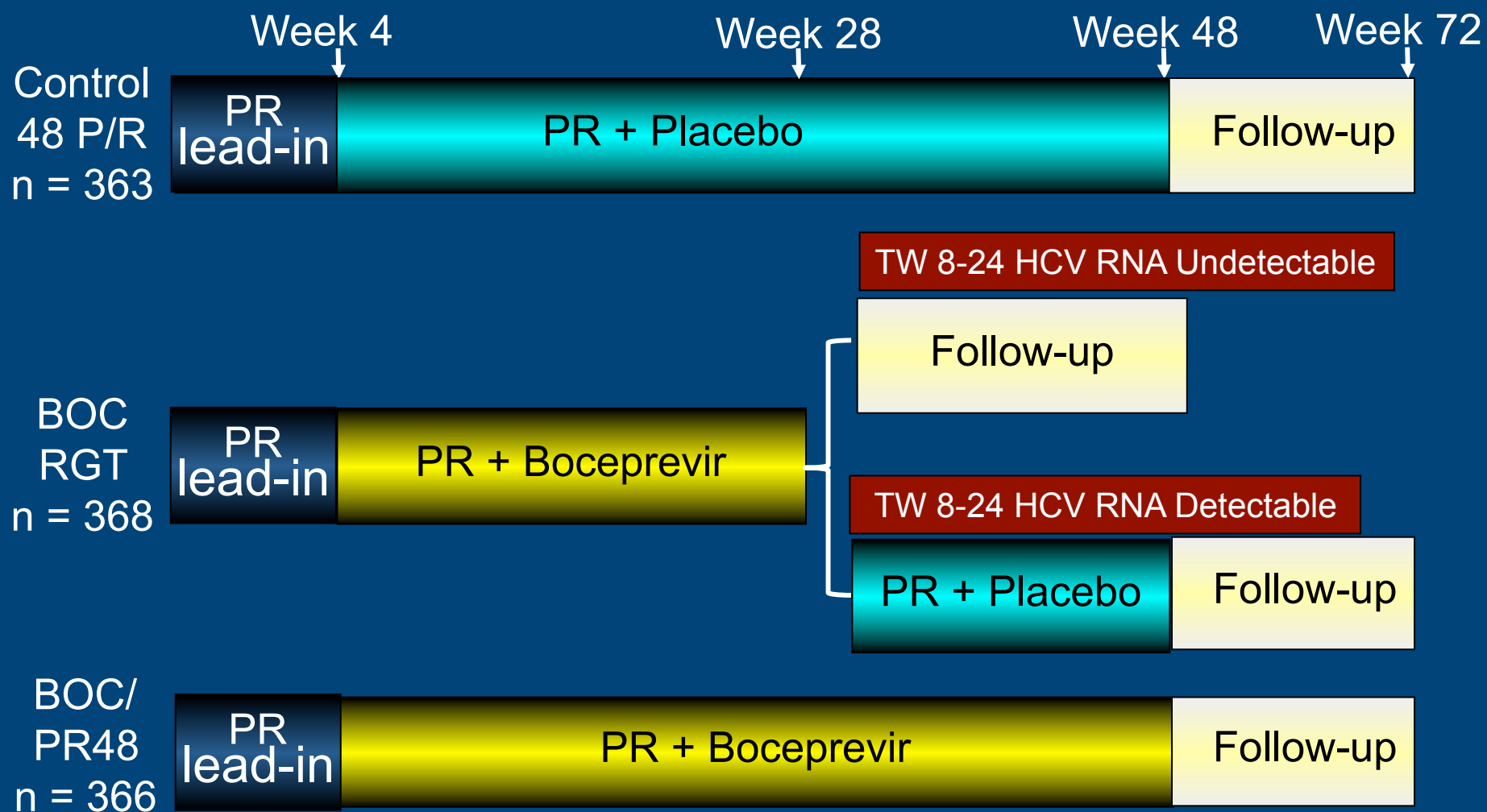


SVR by Response at Week 4 in Lead-In Arm of REALIZE: *HCV RNA at Week 4 in Nonresponders*



Decline in HCV RNA at week 4

SPRINT-2: Boceprevir in G1 Naïve CHC

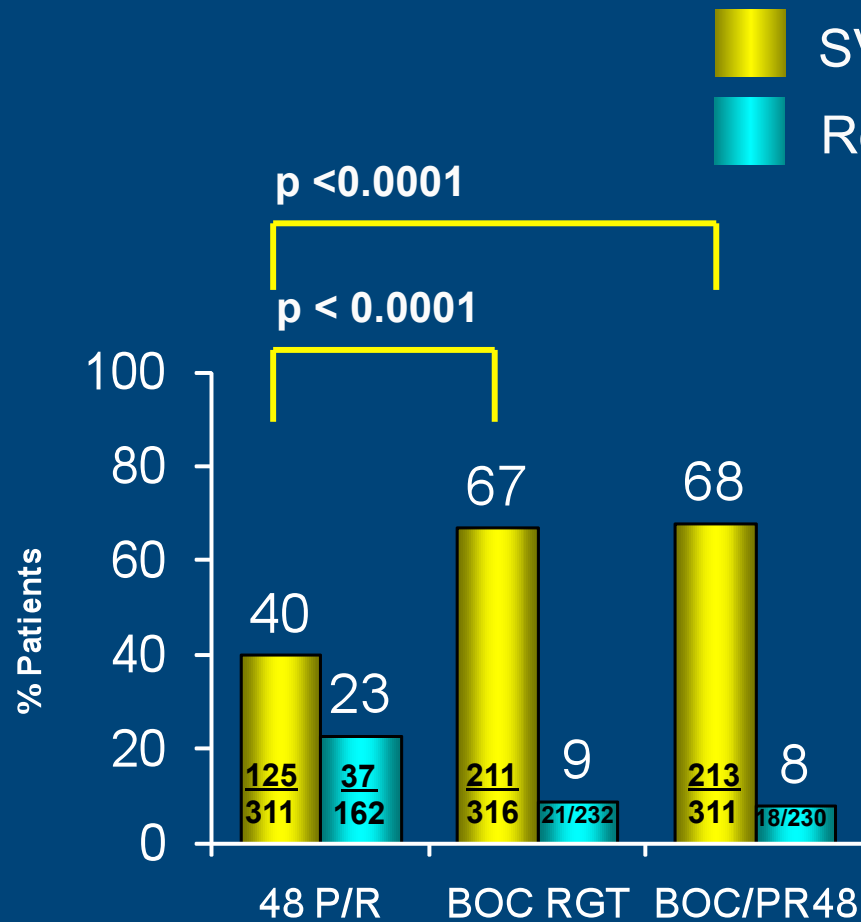


Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight-based dosing of 600-1400 mg/day in a divided daily dose

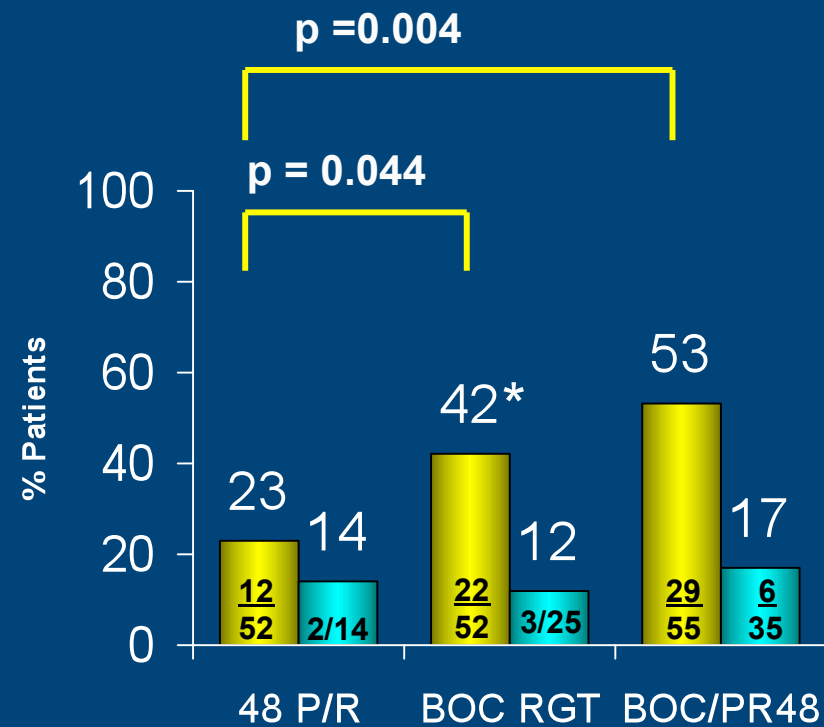
Boceprevir dose of 800 mg thrice daily

Poordad F et al. NEJM 2011;364:1195-1206

SPRINT-2: SVR and Relapse Rates (ITT)



Non-Black Patients

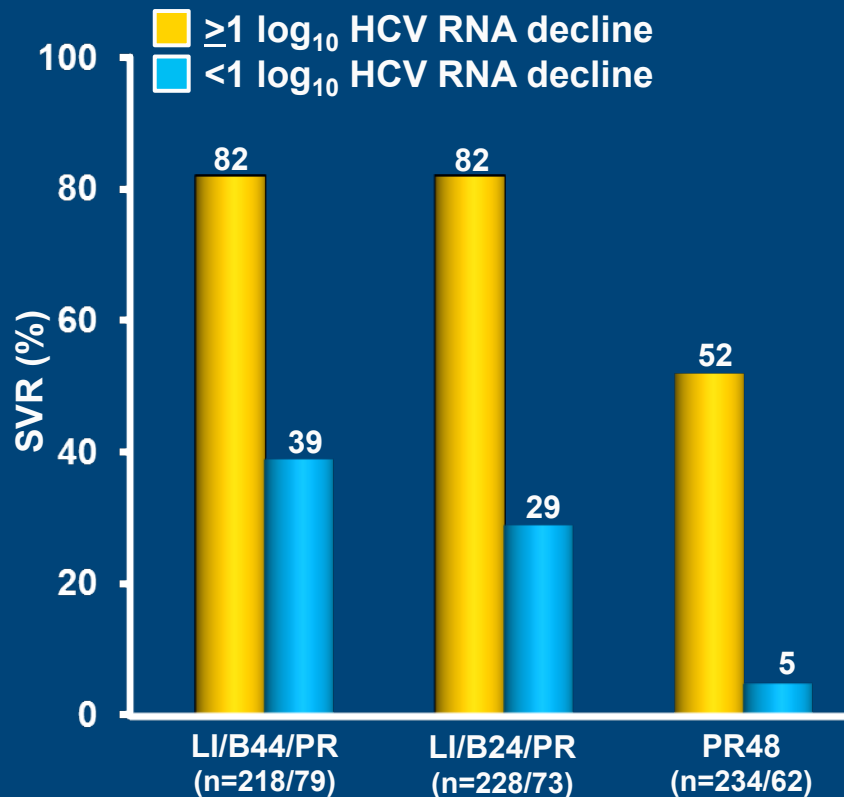


Black Patients

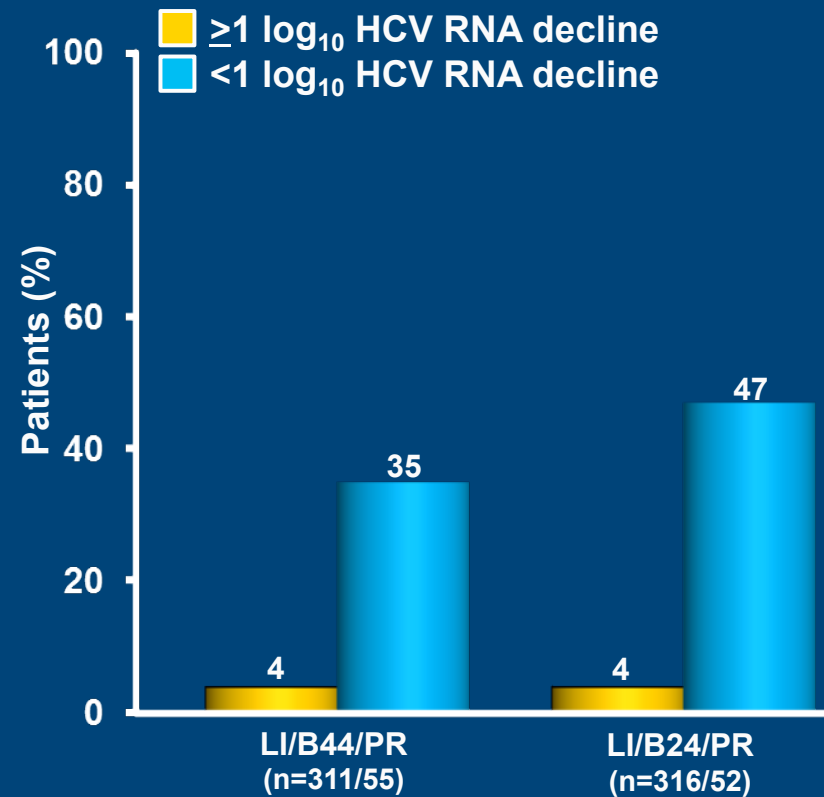
*(mITT in 47% vs 53%)

SPRINT-2 Study Outcomes Based on Week 4 Lead-In (Nonblack Patients)

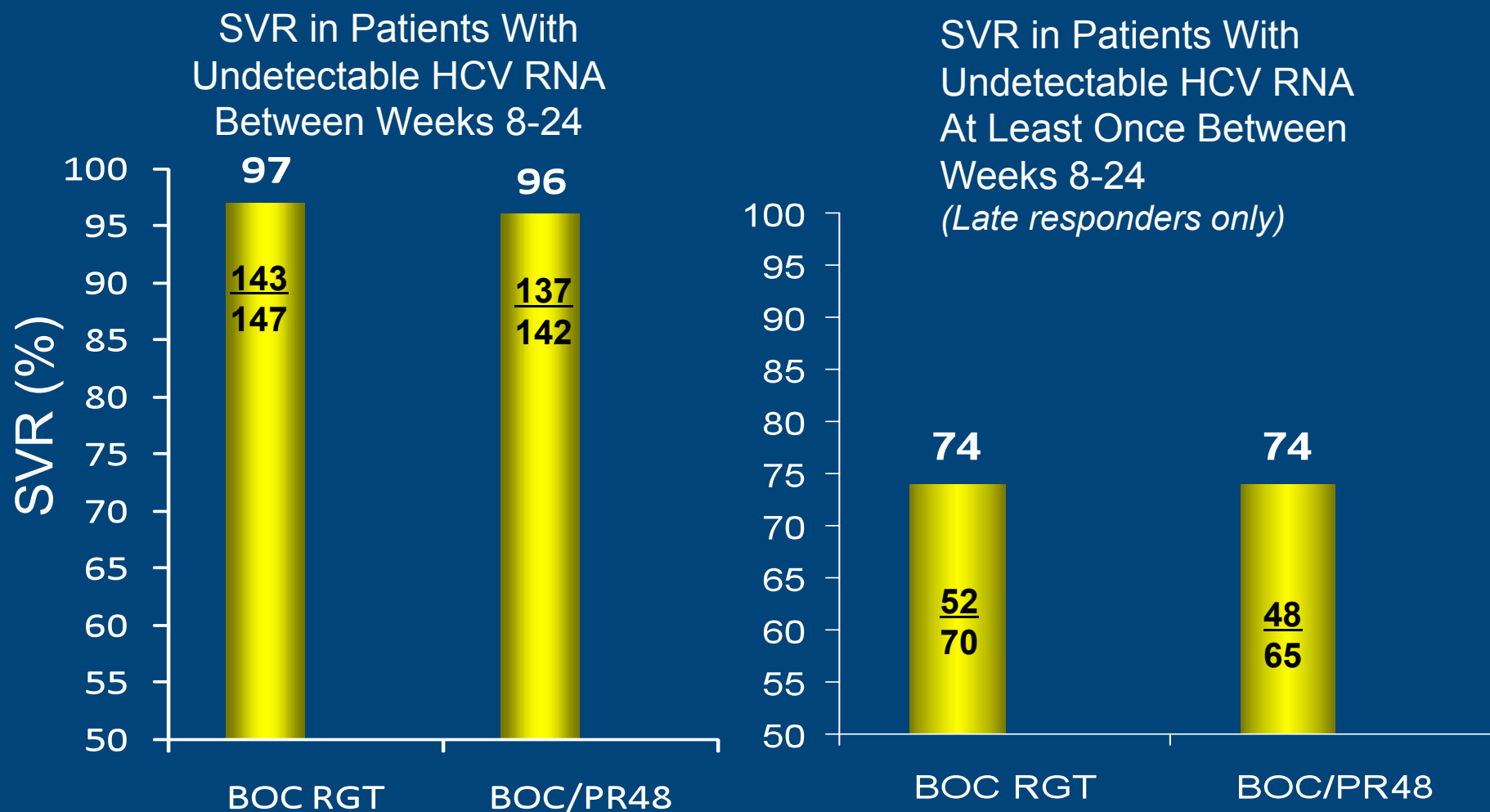
SVR and HCV RNA at wk 4



Resistant variants



SPRINT-2: SVR By Response Pattern (Non-Black)



Combined cohorts:

- 44% of all patients (both cohorts) eligible for shortened treatment
- In FDA briefing document, late responders had SVR in 66% (RGT) vs 75% (48 wks)

SPRINT-2: Most Common Treatment-Related Adverse Events

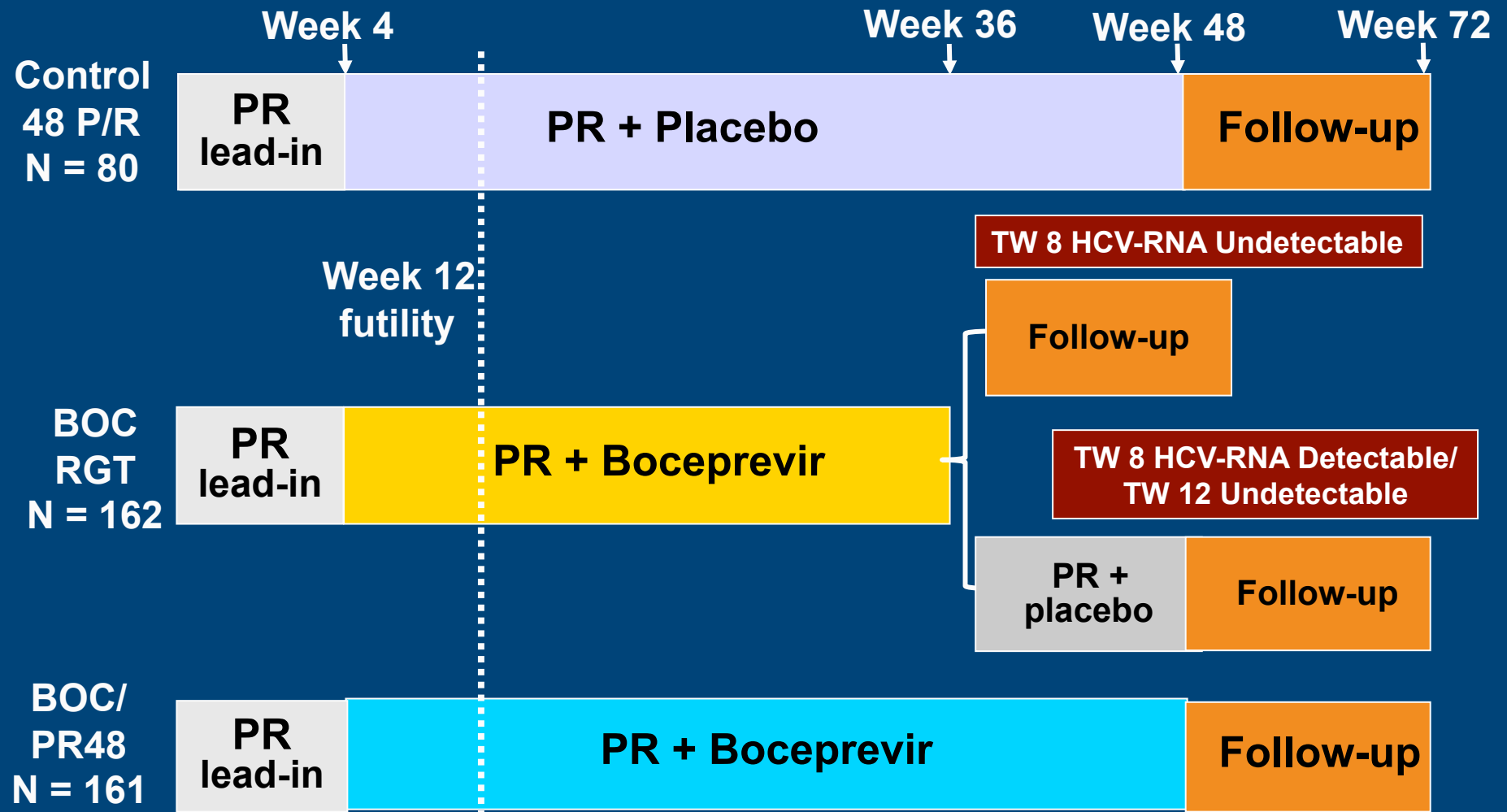
Adverse Event	Arm 1 (PR48) n = 363 (%)	Arm 2 (BOC RGT) n = 368 (%)	Arm 3 (BOC/PR48) n = 366 (%)
Fatigue	59	52	57
Headache	42	45	43
Nausea	40	46	42
Anemia	29	49	49
Dysgeusia	18	37	43
Chills	28	36	33
Pyrexia	32	33	30
Insomnia	32	31	32
Alopecia	27	20	28
Decreased appetite	25	26	24
Pruritis	26	23	25
Neutropenia	21	25	25
Influenza-like illness	25	23	22
Myalgia	26	21	24
Rash	22	24	23
Irritability	24	22	22
Depression	21	23	19
Diarrhea	19	19	23
Dry skin	18	18	22
Dyspnea	16	18	22
Dizziness	15	21	17

*Reported in >20% of patients in any treatment arm and listed by decreasing overall frequency
 *Reported in >20% of patients in any treatment arm and listed by decreasing overall frequency

SPRINT-2: Safety Profile Over Entire Course of Therapy

	48 PR n = 363	BOC RGT n = 368	BOC/PR48 n = 366
Median treatment duration, days	203	197	335
Deaths	n = 4	n = 1	n = 1
Serious AEs	9%	11%	12%
Discontinued due to AEs	16%	12%	16%
Dose modification due to AEs	26%	40%	35%
Hematologic parameters			
Hemoglobin (<10 to 8.5 g/dL / <8.5 g/dL)	26% / 4%	45% / 5%	41% / 9%
Discontinuation due to anemia	1%	2%	2%
Dose reductions due to anemia	13%	20%	21%
Erythropoietin use	24%	43%	43%
Mean (median) days of use	121 (109)	94 (85)	156 (149)
Neutrophil count (<750 to 500/mm³ / <500/mm³)	14% / 4%	24% / 6%	25% / 8%

RESPOND 2: G1 Relapsers & Partial Responders



HCV-RNA measured by the Cobas TaqMan assay (Roche).

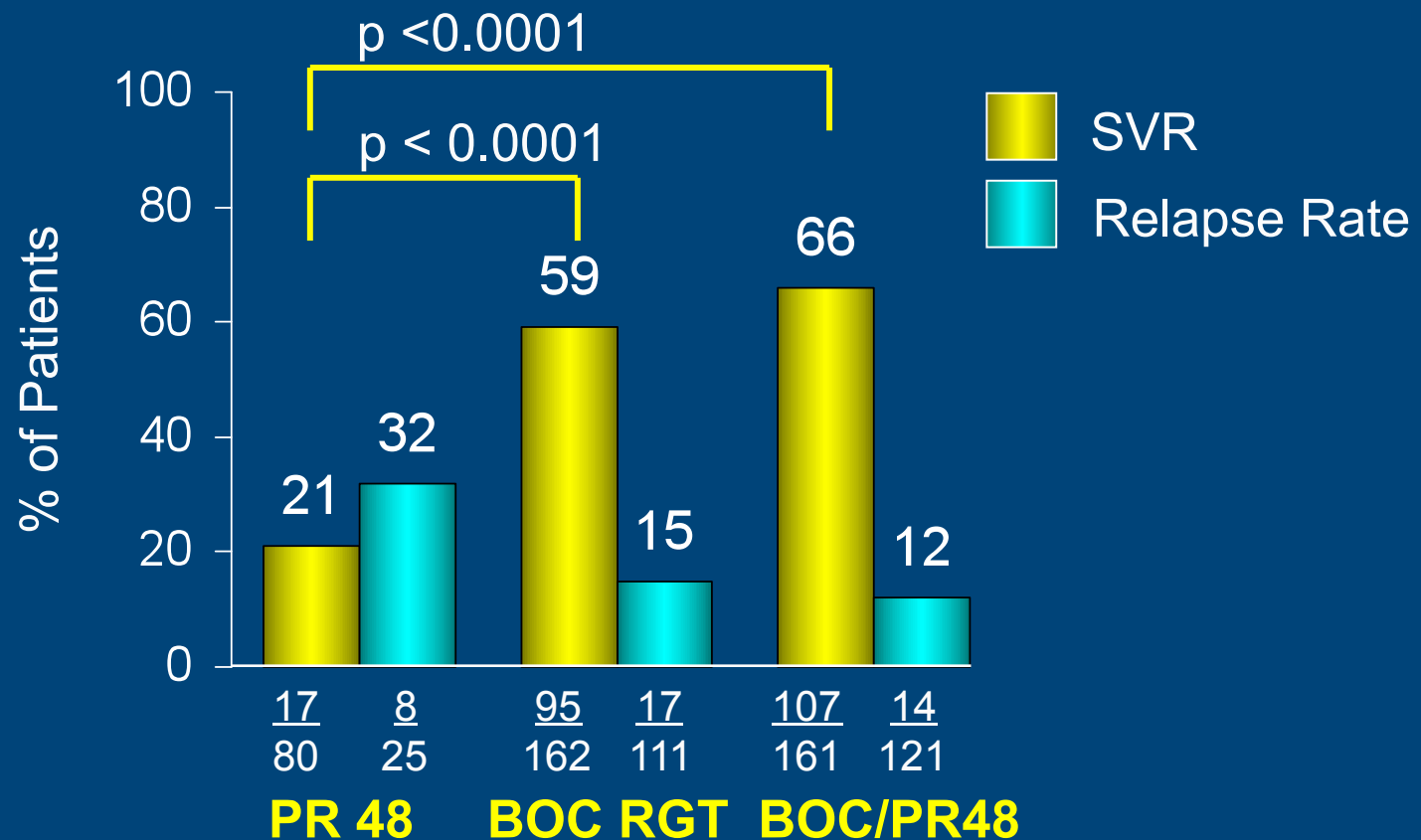
Peginterferon alfa-2b (P) administered subcutaneously at 1.5 µg/kg once weekly, plus Ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose

Boceprevir dose of 800 mg tid

Bacon BR et al, NEJM 2011;364:1207-12

RESPOND-2 SVR and Relapse Rates

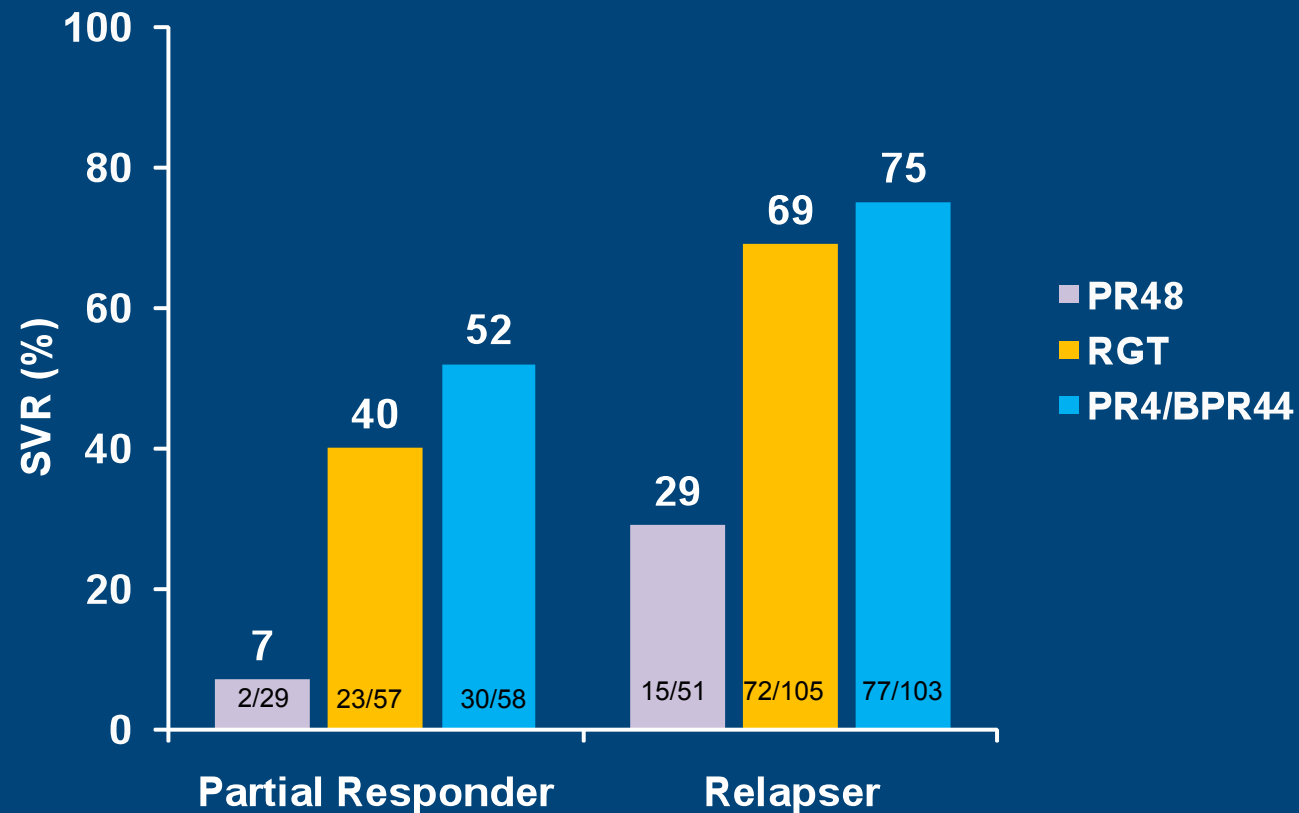
Intention to Treat Population



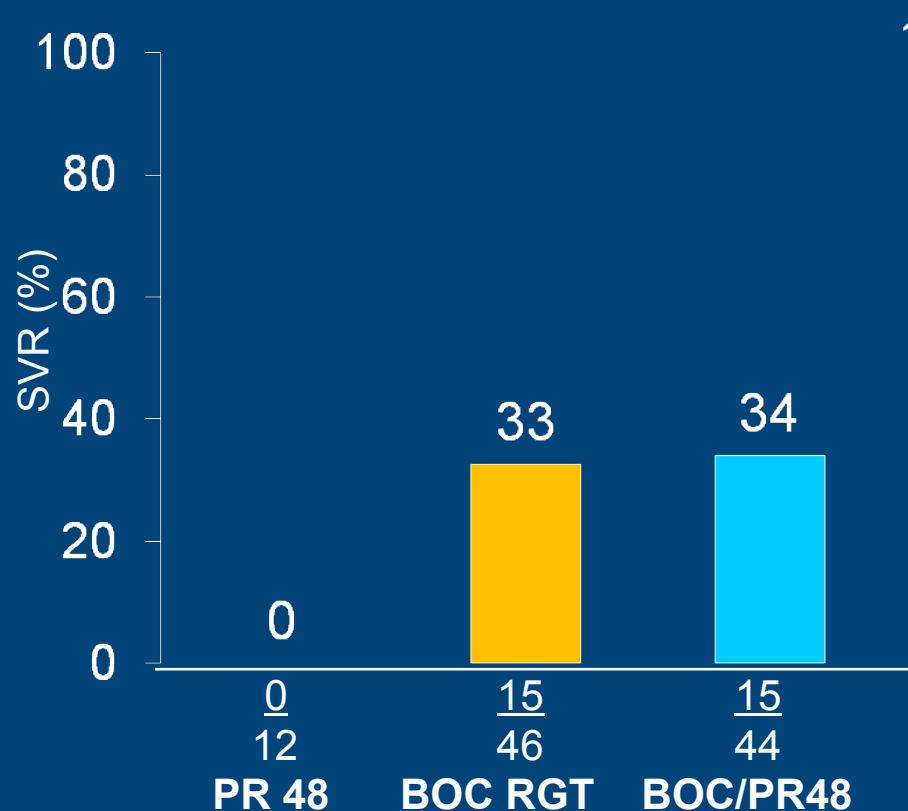
- SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])
- Difference in on-treatment response may have contributed to numerical differences

RESPOND-2—SVR by Prior Response

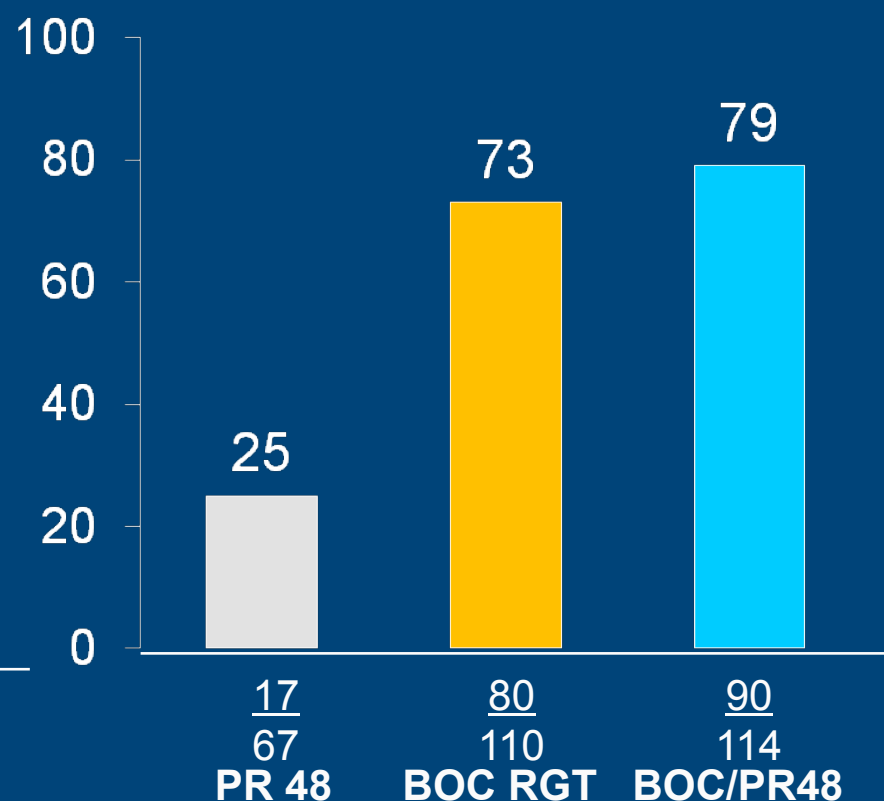
B, boceprevir 800 mg TID; P,
P, PEG IFN α -2b 1.5 μ g/kg/wk;
R, ribavirin 600–1400 mg/d;
RGT, response-guided therapy;



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



Poorly Responsive to IFN
<1 log₁₀ viral load decline at
treatment week 4



Responsive to IFN
≥1 log₁₀ viral load decline at
treatment week 4

What Will Resistance to DAAs Mean in Hepatitis C?

RESISTANCE

(V36, T54, R155, A156)

resistance

- Majority of PI treatment failure pts are left with resistant variants
- Some HCV variants are “fit” and can persist in the long term
- Theoretical impact on future regimens that incorporate PI's

- HCV doesn't appear to be archived
- Encouraging data re: clearance of variants from BOC + TVR studies
- Diverse pipeline decreases concern

- Patients need to understand resistance at appropriate level (which means doctors must, too)
- No group of patients should be categorically denied treatment on basis of resistance fears but it must be discussed with patients
- Null responder cirrhotics: most urgent need, lowest SVR rates, highest risk of resistance

Stopping Rules for Telaprevir

Treatment Naïve & Experienced

Week 4

**HCV RNA
>1000 IU/ml**

**Stop all
therapy**

Week 12

**HCV RNA
>1000 IU/ml**

**Stop
all therapy**

Week 24

**HCV RNA
detectable**

**Stop
all therapy**

Stopping Rules for Boceprevir

Treatment Naïve & Experienced

Week 12

**HCV RNA
≥100 IU/ml**

Stop all therapy

Week 24

**HCV RNA
detectable**

Stop all therapy

Response-Guided Therapy: Telaprevir

- **Naives, relapsers**
 - eRVR+
 - 24 weeks (TPR12/PR12)
 - eRVR-
 - 48 weeks (TPR12/PR36)
- **Nonresponders (Partial and null)**
 - 48 weeks (TPR12/PR36)

“Treatment-naïve patients with cirrhosis and eRVR may benefit from additional 36 weeks of PR” (package insert)

Response-Guided Therapy: Boceprevir

- Naives
 - HCV RNA undetectable at weeks 8, 24
 - 28 weeks (PR4/BPR24)
 - HCV detectable at week 8, undetectable week 24
 - 48 weeks (PR4/BPR32/PR12)
- Relapsers, partial responders
 - HCV RNA undetectable weeks 8, 24
 - 36 weeks (PR4/BPR32)
 - HCV RNA detectable week 8, undetectable week 24
 - 48 weeks (PR4/BPR32/PR44)
- Null responders
 - 48 weeks (PR4/PRB44)

NOTE: Cirrhotics should be treated for 48 weeks (PR4/PRB44) (NO RGT)

Management of Adverse Events With Protease Inhibitors

- Anemia
 - Occurs with both drugs, mean increment in hemoglobin decline ~ 1.0-1.5 gm/dl
 - Mechanism not clear
 - Duration of incremental anemia depends on time of drug administration, i.e. longer with boceprevir
 - Reassuring that RBV dose reduction does not seem to affect SVR with either basis
 - Await additional data from ongoing trial of epo vs RBV dose reduction
 - Epo can be used on individualized basis

Rash

- Most telaprevir rashes are eczematous clinically and histologically
- Difficult to distinguish from ribavirin-related rash, but if severe much more likely related to telaprevir
- Most telaprevir rashes (>90%) are *not* severe
- For severe rash, d/c telaprevir and observe, then d/c RBV $\pm$ PEG IFN as needed
- Antihistamines and topical steroids were used in trials but efficacy unknown
- Studies on treatment of rash are needed

Pharmacology and Drug-Drug Interactions: Be Familiar With the Information in the Label

Telaprevir

- Metabolized by cytochrome CYP3A4 (strong inhibitor) and substrate of P-glycoprotein
- Can increase exposure to other drugs metabolized by CYP3A4
- Other drugs that induce CYP3A4 can decrease exposure to TVR
- DDI studies have included methadone, escitalopram, OC, esomeprazole, HIV drugs, atorvastatin, midazolam, digoxin, cyclosporin, tacrolimus, rifampin

Boceprevir

- Metabolized principally by aldoketo-reductase (AKR) enzymes and partially by CYP3A4 (potent inhibitor); substrate of P-glycoprotein
- Can increase exposure to other drugs metabolized by CYP3A4
- Other drugs that induce CYP3A4 can decrease exposure to BOC
- DDI studies have included midazolam, OC (drospirinone/ethinyl estradiol), ibuprofen, diflusal, ketoconazole

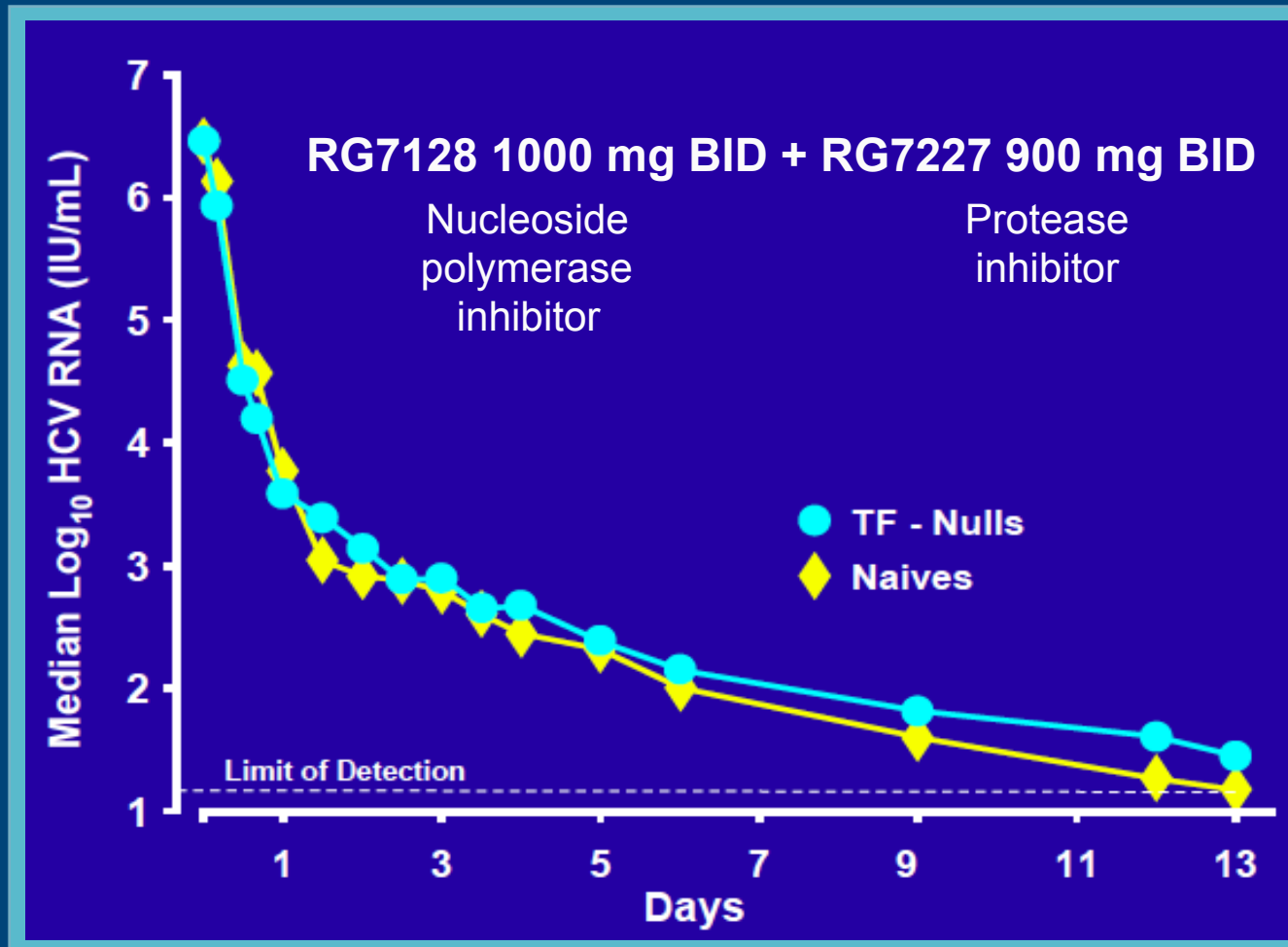
Contraindicated Drugs Common to Telaprevir and Boceprevir

- Rifampin
- Alfuzosin
- Ergot derivatives
- Cisapride
- St. John's wort
- Lovastatin, simvastatin (atorvastatin-telaprevir)
- Sildenafil or tadalafil for PA hypertension
- Oral midazolam, triazolam
- Drospirinone (boceprevir)

Package inserts

A Glimpse Into the Future of HCV Therapy

Nucleoside (RG7128) + Protease Inhibitor(RG7227) G1 Interferon-Naive and Null Responders



Profound viral suppression, no breakthroughs

The Study That “Stole the Show”: EASL 2011

NS5A + Protease Inhibitor + Peg IFN/RBV in Null Responders

BMS-790052 (60 mg QD) + BMS-650032 (600 mg BID) (n=11)	Follow-up
BMS-790052 + BMS-650032 + PEG IFN/RBV (n=10)	Follow-up

24-week
treatment

Post treatment:
Week 24: SVR24

- SVR
 - Dual: 36% (4/11, including 2/2 G1b, 2/9 G1a)
 - Quad: 100% (10/10)
- Proof of concept for curability of HCV without IFN
- Major potential for quad therapy in null responders (and others)

The Future Is Coming Faster Than We Thought

- Many protease, polymerase, NS5A, and host-factor inhibitors are being studied with PEG IFN/RBV
- Combinations of antivirals are being studied at a pace unanticipated until recently: from IFN-free to quad
- Proof of concept for SVR without IFN is finally available – should accelerate development of IFN-free DAA-based regimens
- A robust IFN-free dual therapy should contain at least one drug with a high barrier to resistance
- Ribavirin may continue to be an important adjunct
- Quad regimens may be the “way to go” for nonresponders

The Ten Commandments of Protease Inhibitor (PI) Therapy



Courtesy of Dr Ira Jacobson

I. You shall
not use PI
monotherapy.

II. You shall not try to replace ribavirin
with a PI, nor shall you
use two PI's together.

III. You shall emphasize the importance
of adherence to your patients.

IV. You shall understand when to apply
response-guided therapy.

V. You shall understand the principles of
viral resistance, and be able to discuss
them with patients at an understandable
level.

VI. You shall be aware of “stopping rules” that warrant discontinuation of therapy at specific time points for insufficient viral response.

VII. You shall monitor for virologic breakthrough, and stop the PI if it occurs.

VIII. You shall understand the differences in outcomes between genotype 1a and 1b.

IX. You shall be aware of potential drug-drug interactions.

X. You shall be aware of, and know how to manage, the toxicities of PIs that you choose.