

DAA Drugs in Patients With Cirrhosis

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Ira M. Jacobson, M.D.

Vincent Astor Professor of Medicine

Chief, Division of Gastroenterology and Hepatology

Medical Director, Center for the Study of Hepatitis C

Weill Cornell Medical College

The Problem With Cirrhosis

Lower Efficacy; Safety Concerns

- Decreased “hepatic bioavailability” (does less drug get to the cell?)
- Impaired intracellular response to interferon, e.g. inadequate ISG expression or diminished downstream effector function?
- Impaired immunological contribution to response?
- Potential tolerability issues
 - Cytopenias
 - Infection
 - Decompensation

Potential Issues With DAAs

- Altered pK and/or liver accumulation
 - Potential for alterations in systemic or liver exposure with concomitant potential for toxicity
- *Hepatotoxicity concerns*
 - *Increased risk that it can occur*
 - *Increased “stakes” if it does occur*
- DDI profile could be different in cirrhotics

The Beginning of a New Era

What's Arrived in 2011 for Patients With Genotype 1

**SVR >70%
Genotype 1**

**Response-guided
therapy
(RGT)**

**Increased
side effects**

Resistance

**Drug-drug
interactions**

**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

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

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

Demographics and Baseline Characteristics

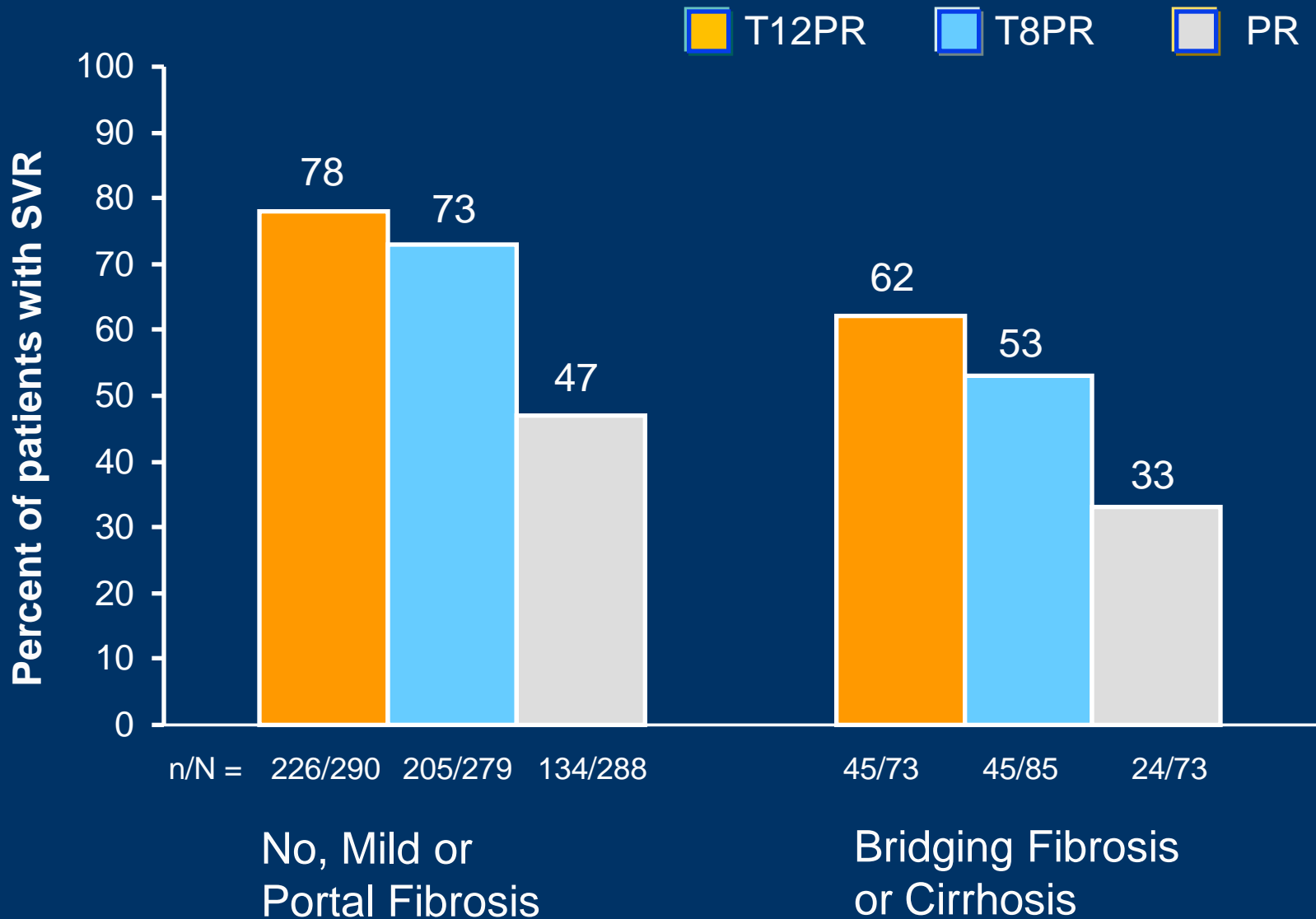
	T12PR N = 363	T8PR N = 364	PR N = 361
Gender, n (%)			
Male	214 (59)	211 (58)	211 (58)
Race†, n(%)			
Caucasian	325 (90)	315 (87)	318 (88)
Black/African American	26 (7)	40 (11)	28 (8)
Ethnicity, n (%)			
Hispanic/Latino	35 (10)	44 (12)	38 (11)
Age, median years (range)	49 (19-69)	49 (19-68)	49 (18-69)
BMI, median kg/m ² (range)	26 (18-47)	26 (17-46)	26 (17-48)
HCV RNA ≥ 800,000 IU/mL*, n (%)	281 (77)	279 (77)	279 (77)
HCV Genotype Subtype**, n (%)			
1a	213 (59)	210 (58)	208 (58)
1b	149 (41)	151 (41)	151 (42)
1, unknown	1 (<1)	3 (1)	2 (1)
Stage of fibrosis or cirrhosis, n (%)			
Bridging Fibrosis	52 (14)	59 (16)	52 (14)
Cirrhosis	21 (6)	26 (7)	21 (6)

†Race and ethnicity were self-reported

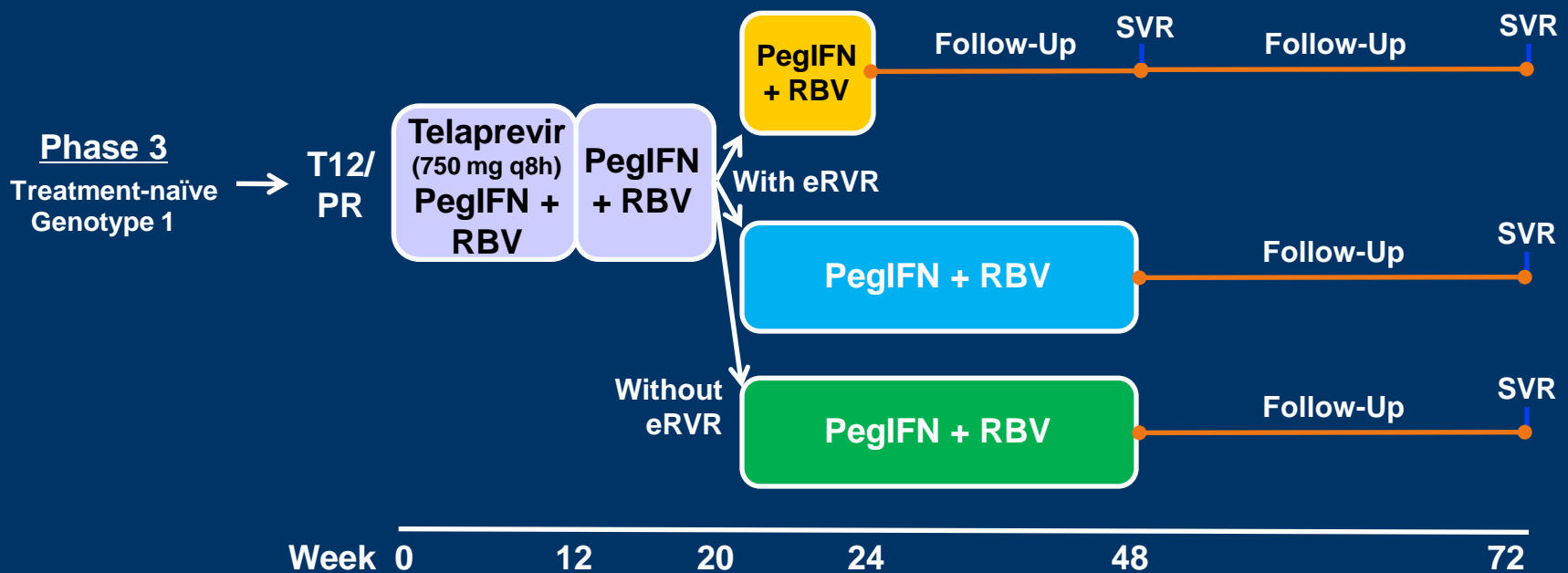
**5'NC InnoLipa assay

*Roche Taqman® v2 LLOQ of 25 IU/mL

ADVANCE: SVR Rates by Fibrosis Stage

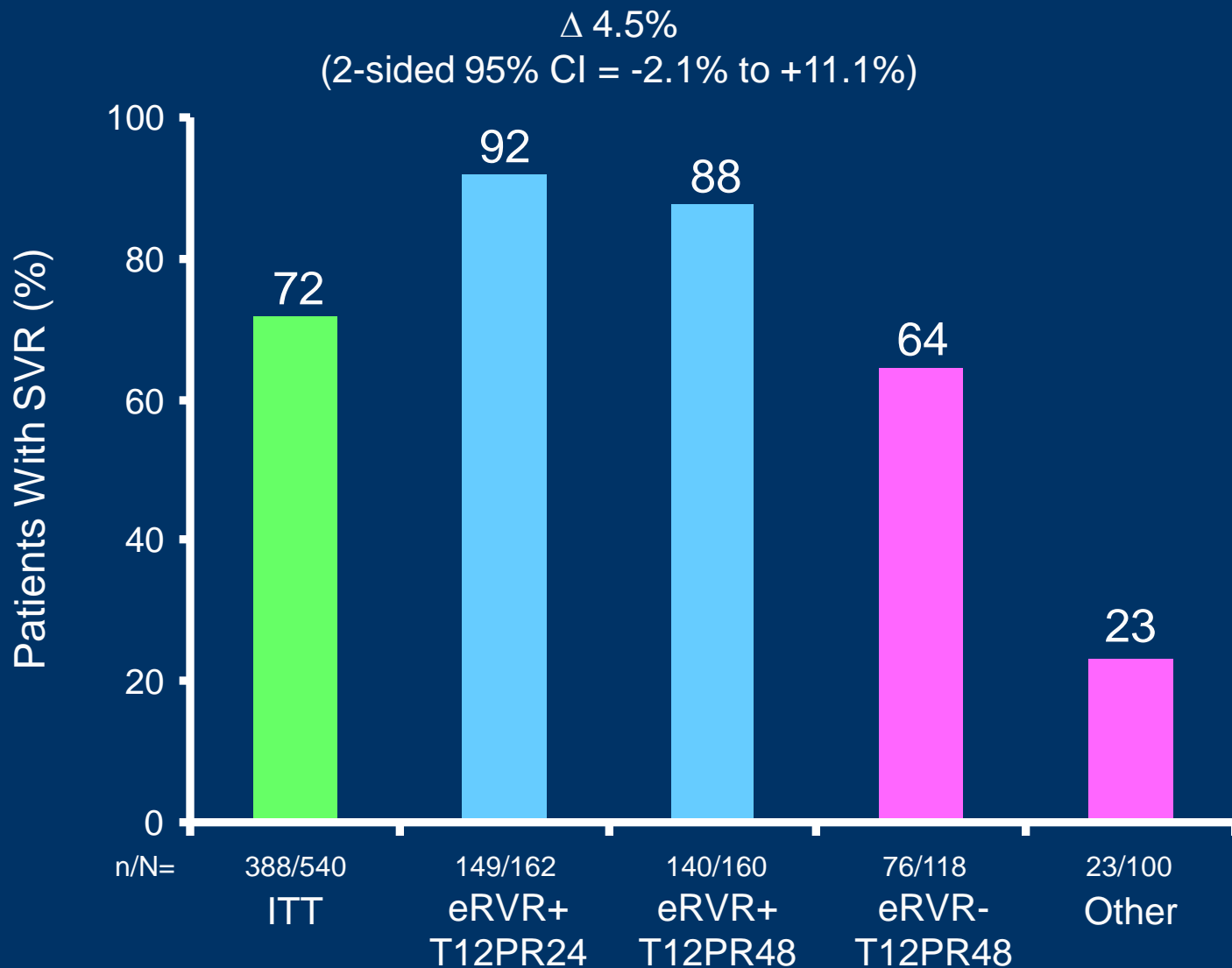


ILLUMINATE Study: Randomization of eRVR Patients to 24 Versus 48 Weeks

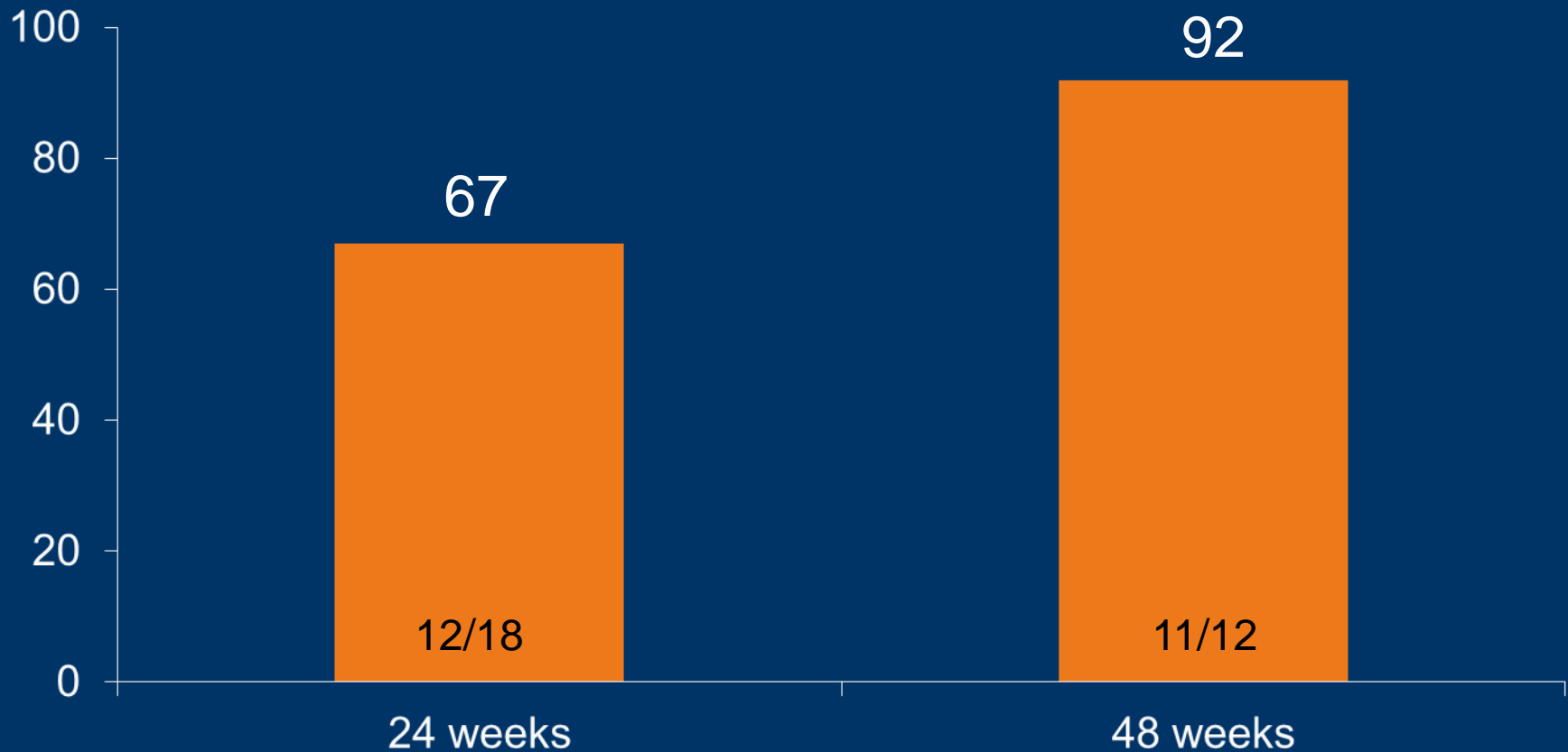


eRVR (extended rapid virologic response): HCV RNA <25 IU/mL at weeks 4 and week 20.

SVR Rates: ILLUMINATE



Effect of Shortening Therapy in Cirrhotics with eRVR: ILLUMINATE



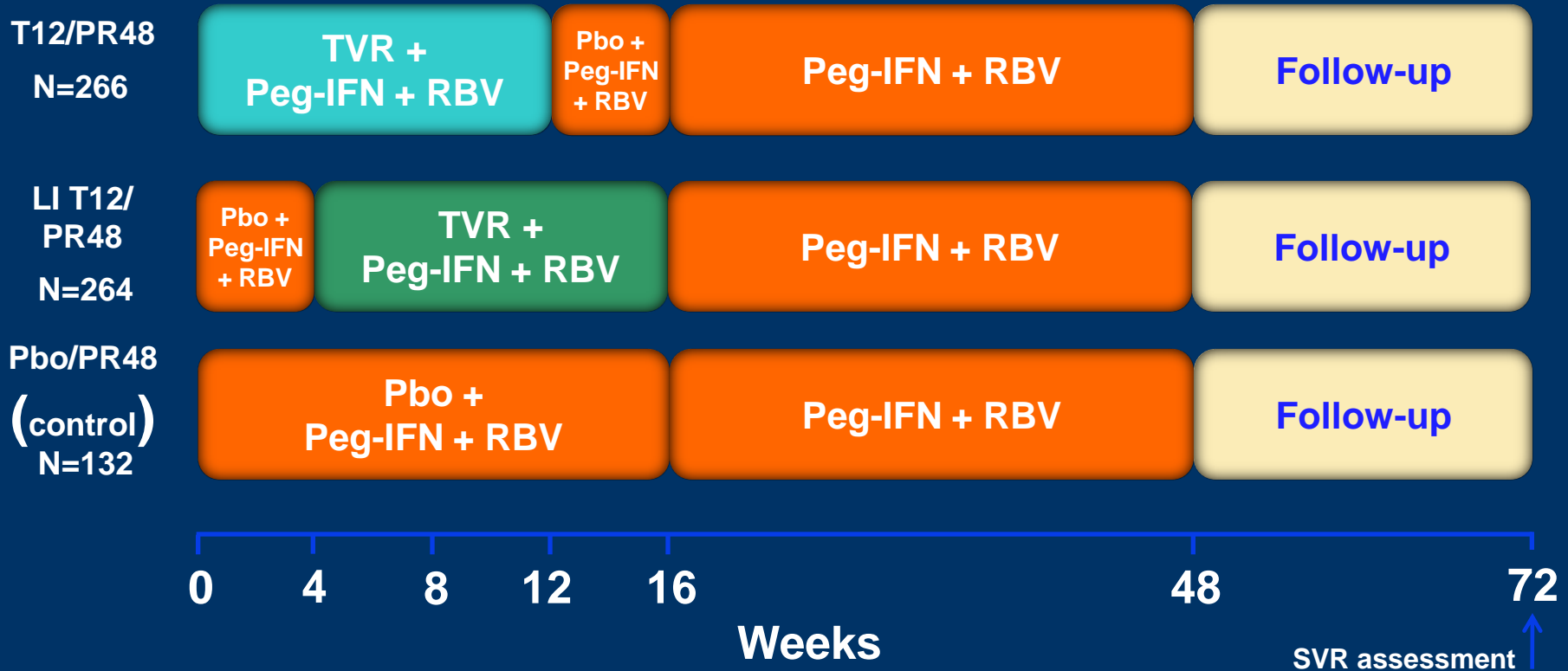
SVR Rates and Viral Resistance Profiles in Patients Treated With TVR: Effects of Fibrosis

- Comparison of SVR rates with T12PR in pooled ADVANCE / ILLUMINATE patients versus PR (ADVANCE)
 - F0–2 versus F3–4
 - In SVR failures, RVs evaluated
- RVs present in similar proportions of F0–2 and F3–4 who failed SVR
 - Low level 36% in F0–2, 41% in F3–4
 - High level 38% in F0–2, 44% in F3–4
 - Time to loss of RVs median 10 months

Liver fibrosis stage	Treatment	eRVR, n (%)	EOT, n (%)	SVR, n (%)	Relapse, n/N (%)	VF, n (%)
F0–F2	T12PR (n=681)	444 (65)	563 (83)	539 (79)	16/563 (3)	40 (6)
	PR (n=288)	25 (9)	183 (64)	140 (49)	42/183 (23)	78 (27)
F3–F4	T12PR (n=222)	121 (55)	158 (71)	144 (65)	11/158 (7)	28 (13)
	PR (n=73)	4 (5)	37 (51)	26 (36)	11/37 (30)	27 (37)

Comparable improvement with TVR in SVR (29-30%) above PR in advanced fibrosis/cirrhosis vs mild fibrosis, but absolute SVR remains lower than in those with mild fibrosis with higher rates of relapse/virologic failure. Of those who failed SVR, proportions of those with resistant variants were similar

REALIZE: Study Design (N=662)



Randomization was stratified by viral load and prior response. Stopping rules applied for TVR (Weeks 4, 6, and 8 for T12/PR48; Weeks 8, 10 and 12 for LI T12/PR48) and Peg-IFN/RBV (Weeks 12, 24, and 36 for T12/PR48; Weeks 16, 24 and 36 for LI T12/PR48)

Peg-IFN: Peg-IFN alfa-2a = 180µg/week; RBV = 1000–1200mg/day; TVR = 750mg every 8 hours

ClinicalTrials.gov identifier: NCT00703118

LI = lead-in; Pbo = placebo; TVR = telaprevir

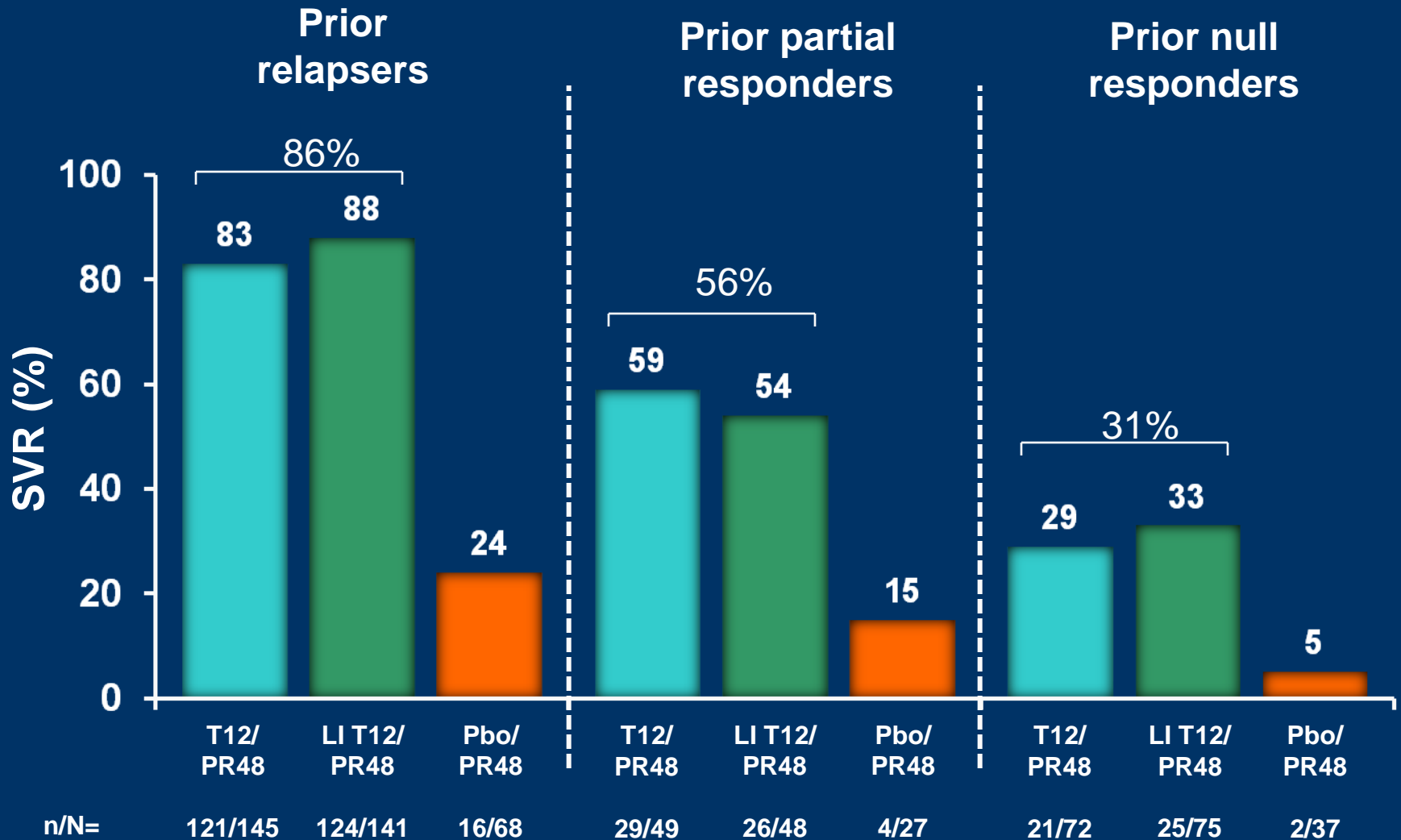
REALIZE: Baseline Characteristics

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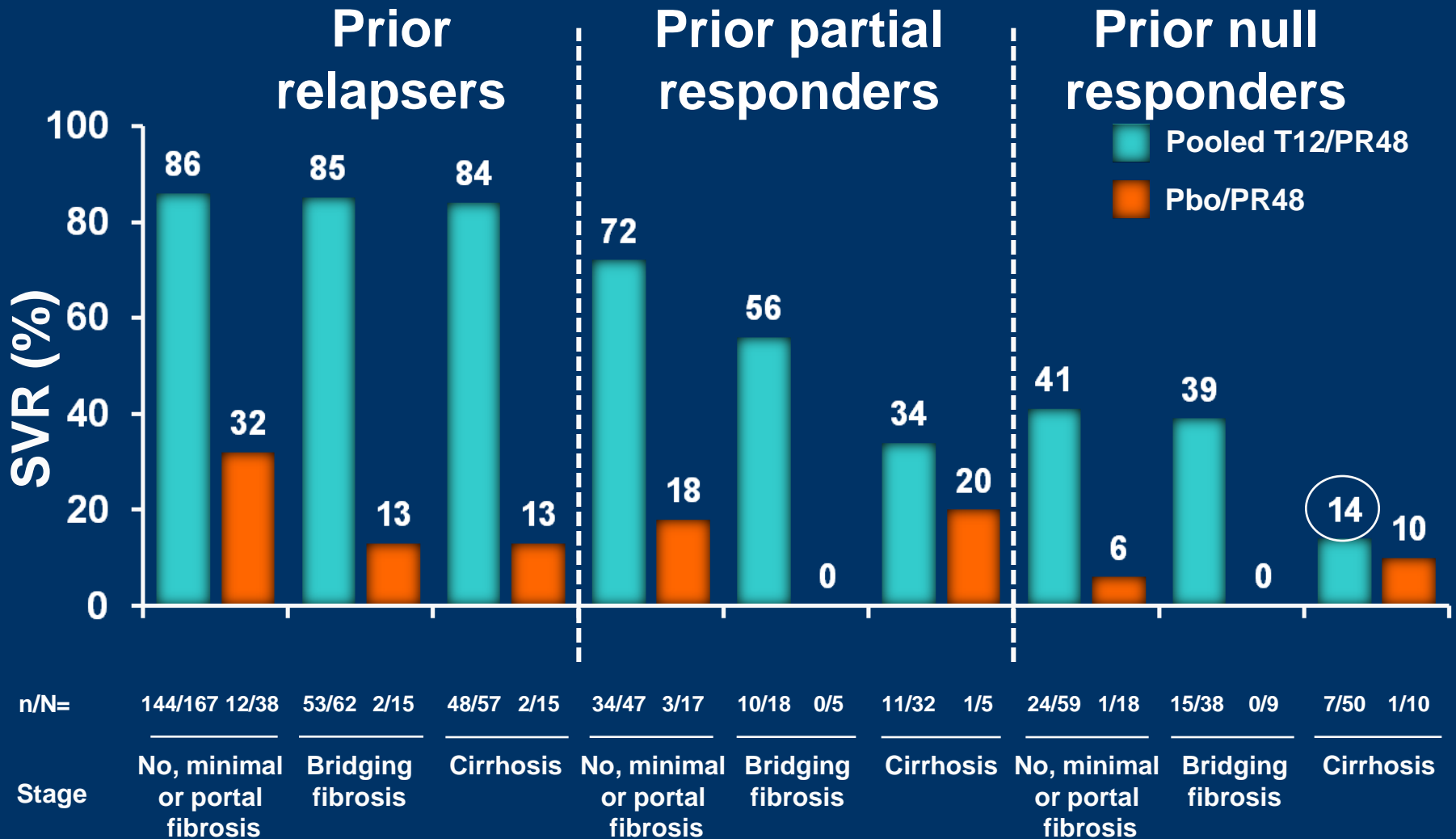
Characteristic	T12/PR48 (N=266)	LI T12/PR48 (N=264)	Pbo/PR48 (N=132)
Male, n (%)	183 (69)	189 (72)	88 (67)
Caucasian race, n (%)	246 (92)	252 (95)	117 (89)
Black race, n (%)	11 (4)	8 (3)	11 (8)
Years of age, median (range)	51 (23–69)	51 (24–70)	50 (21–69)
HCV RNA ≥800,000 IU/mL, n (%) [*]	238 (89)	234 (89)	114 (86)
Body mass index, mean (SD)	28 (5.0)	27 (4.8)	27 (4.6)
HCV genotype, n (%) [‡]			
1a	136/262 (52)	149/262 (57)	67/128 (52)
1b	126/262 (48)	113/262 (43)	61/128 (48)
Prior response, n (%)			
Null responder	72 (27)	75 (28)	37 (28)
Partial responder	49 (18)	48 (18)	27 (20)
Relapser	145 (55)	141 (54)	68 (52)
Bridging fibrosis, n (%) [§]	60 (23)	58 (22)	29 (22)
Cirrhosis, n (%) [§]	72 (27)	67 (25)	30 (23)

^{*}Determined using the HCV COBAS TaqMan[®] assay version 2.0; [‡]Determined by NS3 sequencing; [§]Defined by local pathologists

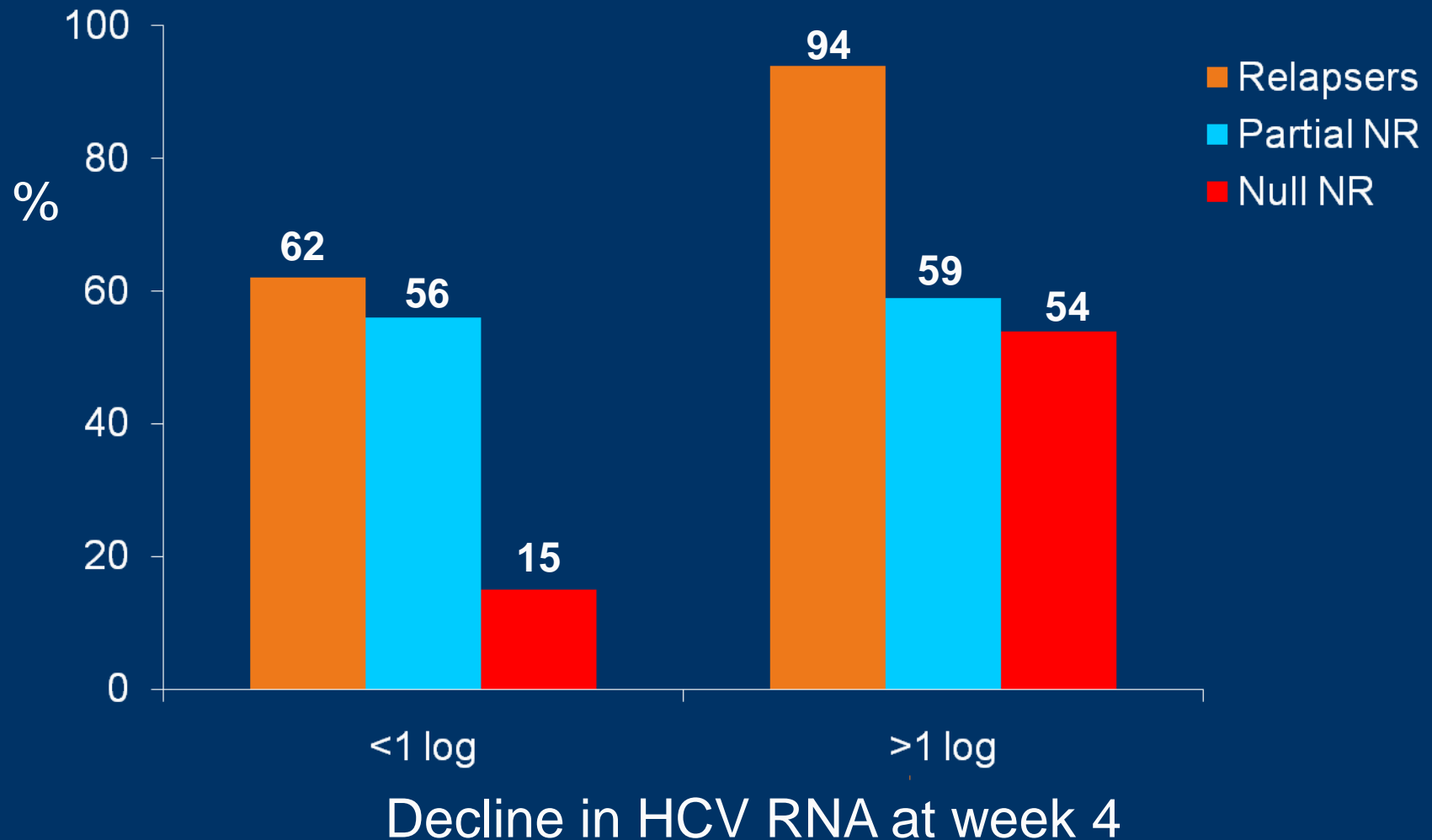
REALIZE: SVR in Prior Relapsers, Prior Partial Responders and Prior Null Responders



REALIZE: SVR by Baseline Fibrosis Stage and Prior Response



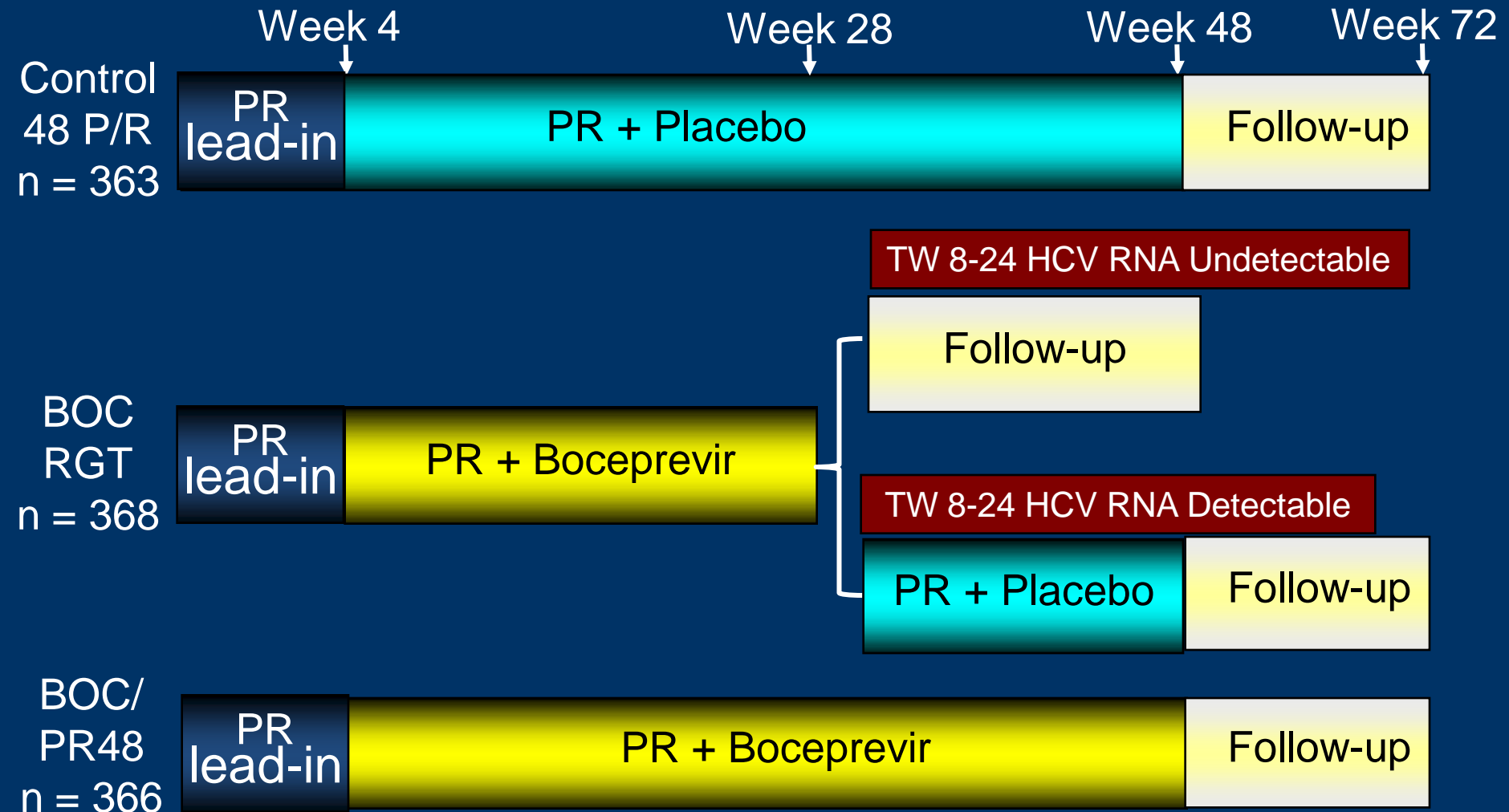
SVR by Response at Week 4 in Lead-In Arm of REALIZE: *HCV RNA at Week 4 in Nonresponders*



Impact of REALIZE Data on Management of Null Responder Cirrhotics

- Hesitation about treating in face of low chance of SVR
 - High chance of failure with resistance
 - Exclusion from clinical trials
- Use of lead-in by some clinicians to decide whether to proceed past PR phase

SPRINT-2: Boceprevir in G1 Naïve CHC



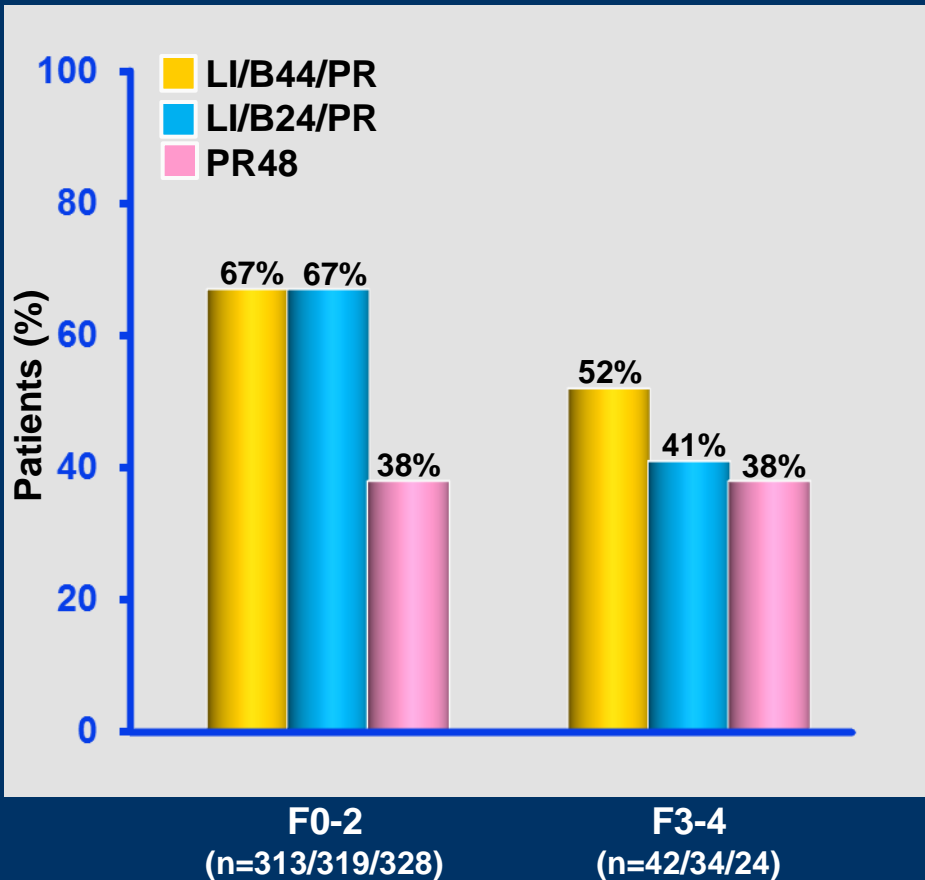
Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight-based dosing of 600-1400 mg/day in a divided daily dose
 Boceprevir dose of 800 mg thrice daily

SPRINT 2: Patient Population

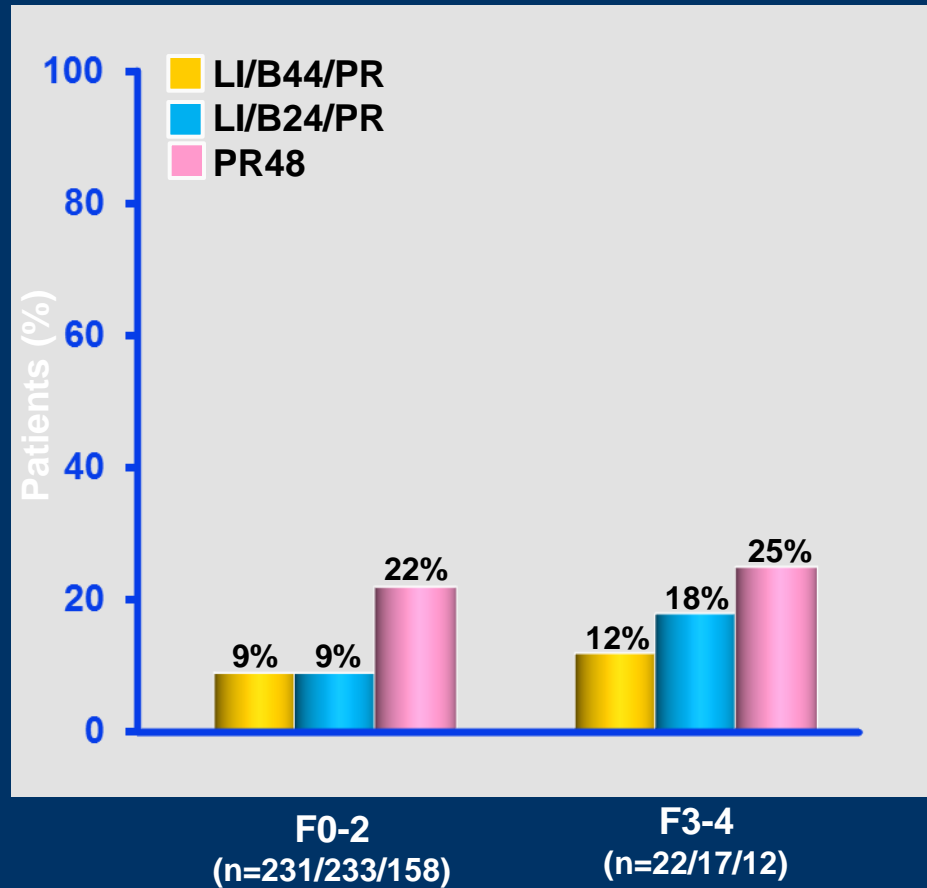
- 1,097 previously untreated (treatment-naïve) patients chronically infected with hepatitis C genotype 1
 - 2 separate cohorts
 - Cohort 1: 938 non-AA/Black patients
 - Cohort 2: 159 AA/Black patients (14.5%)
 - US and international sites
- 92% >400,000 IU/mL HCV RNA
- 9% biopsy-proven F3/4

SPRINT-2 Study: Advanced Liver Disease Subanalysis

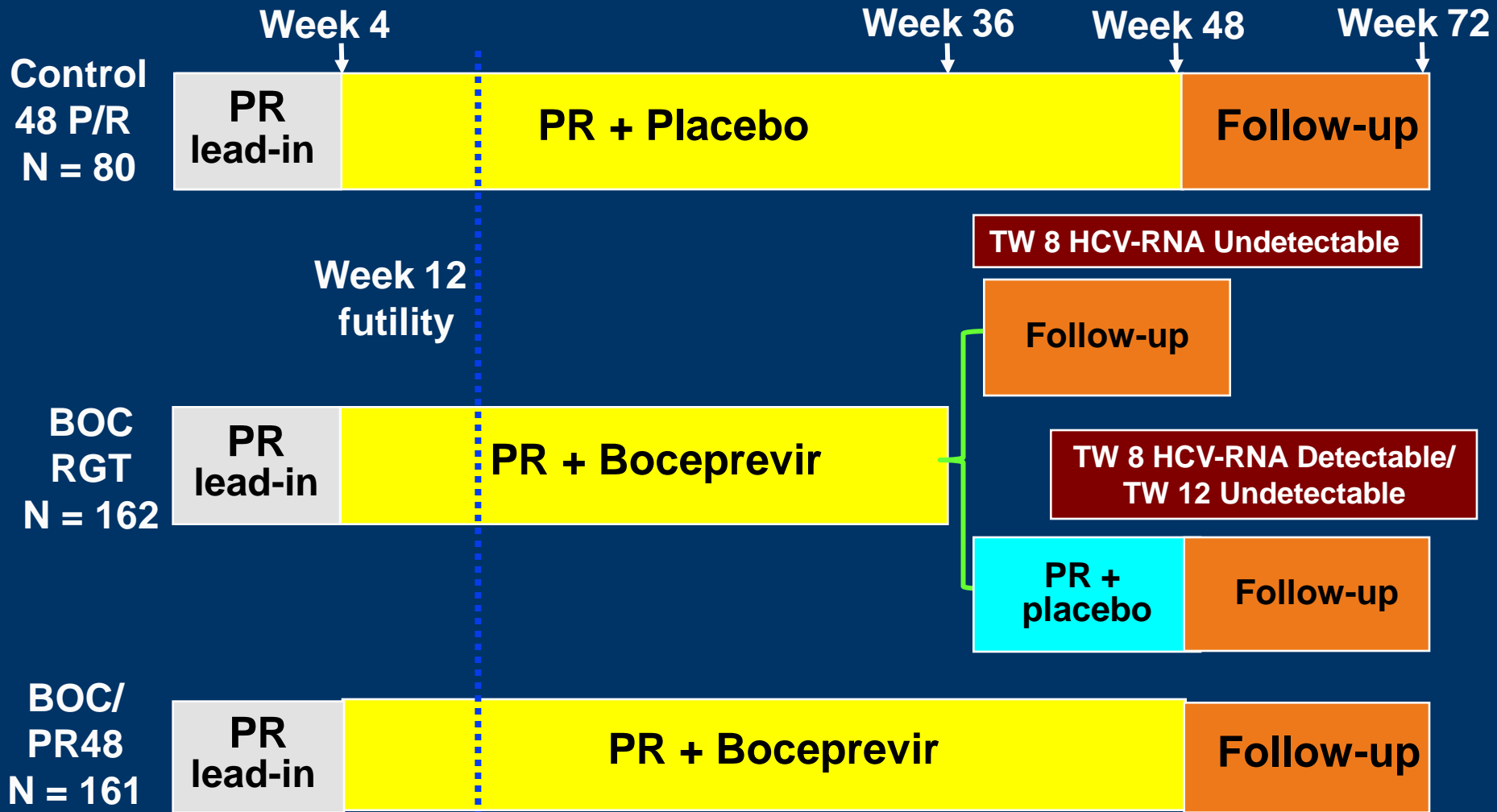
Sustained Virologic Response



Relapse



RESPOND 2: 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

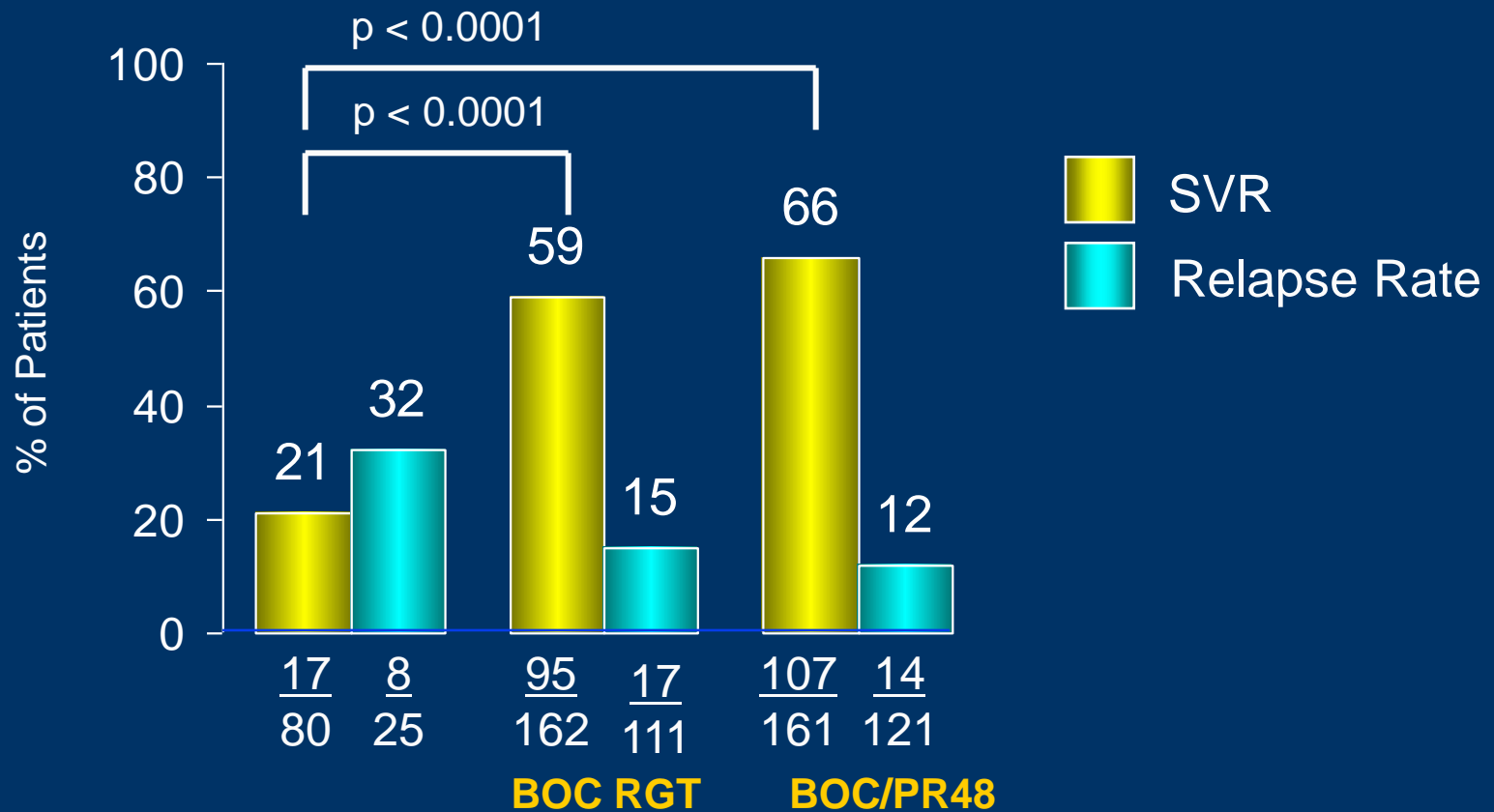
Boceprevir dose of 800 mg tid

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
Mean (SD) BMI	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

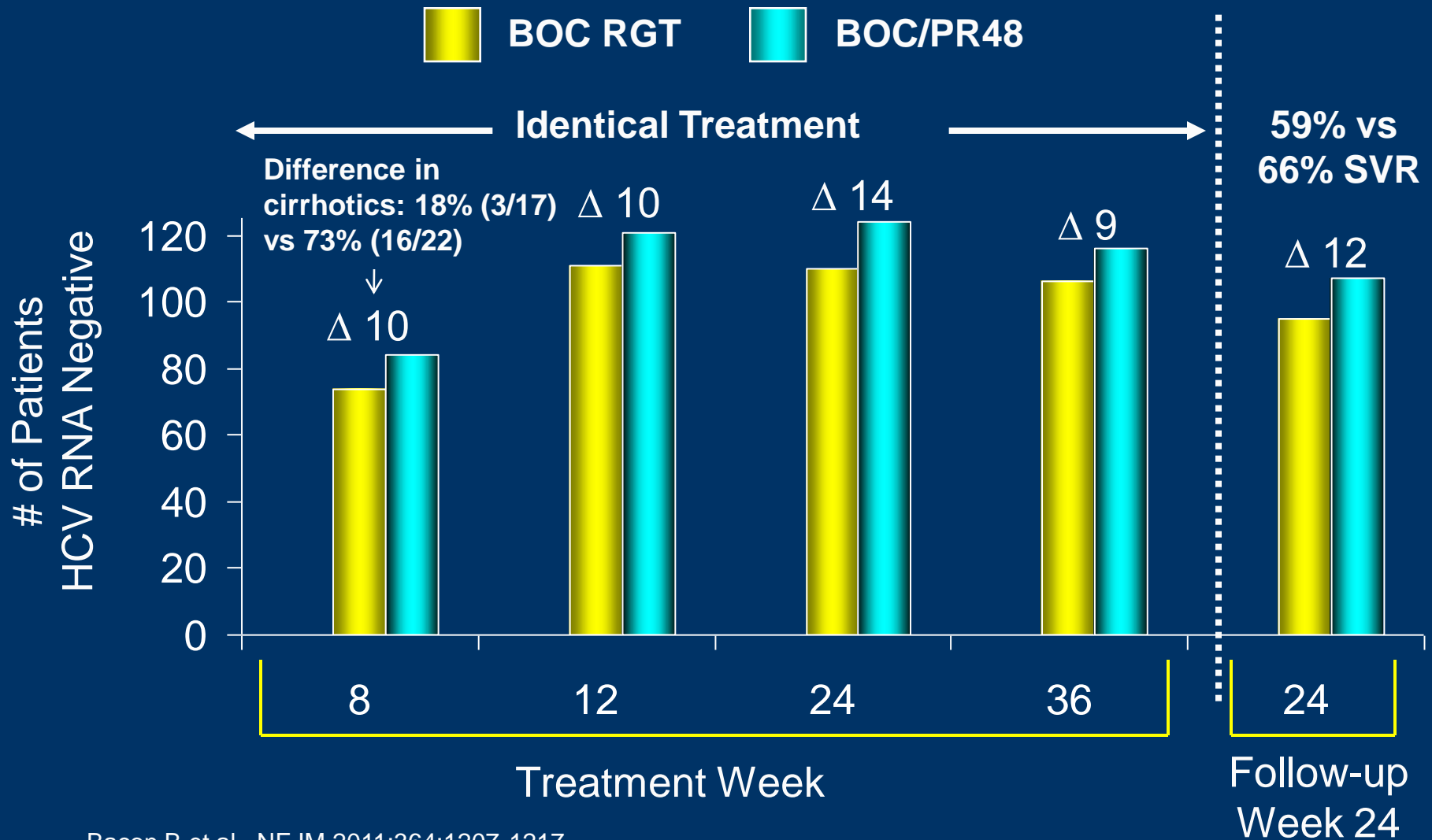
*Subtyping performed by NS5B sequencing

RESPOND-2 SVR and Relapse Rates Intention-to-Treat Population

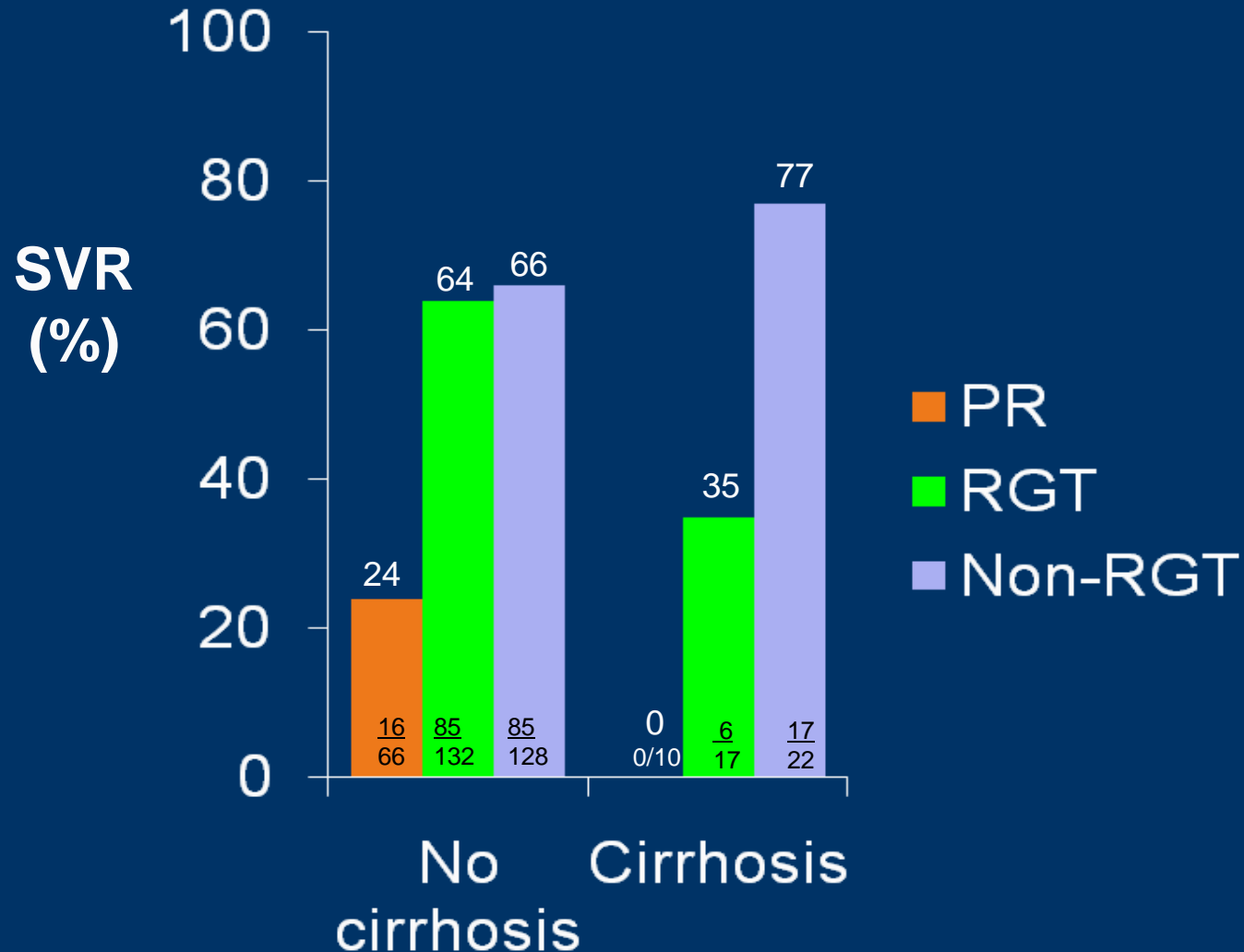


BOC RGT vs BOC/PR48

Is there a difference in response?



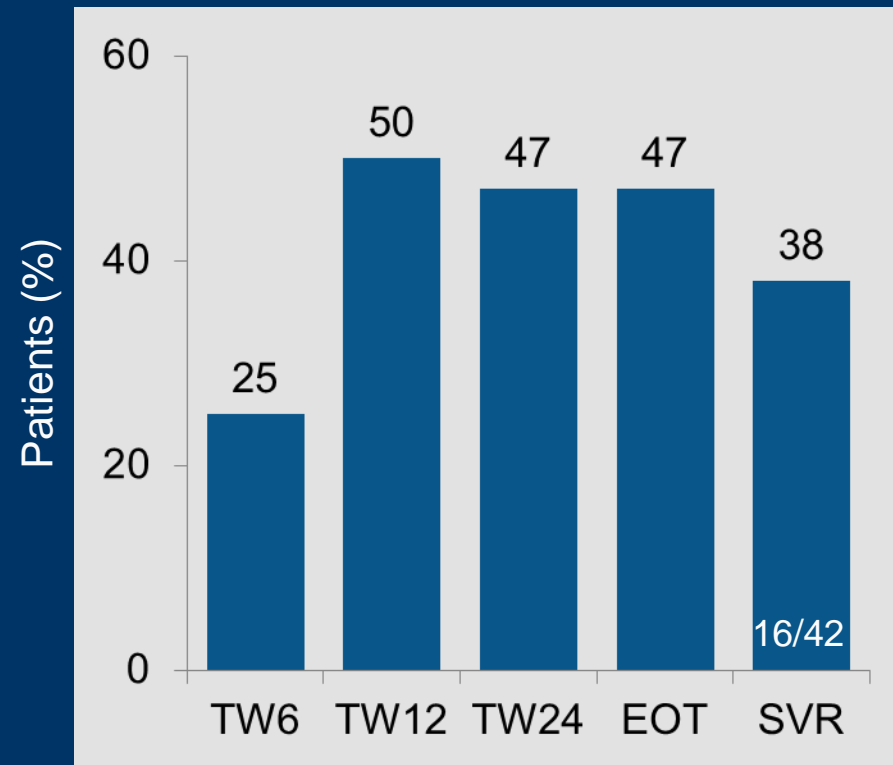
RESPOND-2: Impact of Cirrhosis on SVR



PROVIDE: Boceprevir in Null Responders

- Null responder SVR data with BOC have been lacking because these patients were excluded from RESPOND-2 (Phase III study)
- PROVIDE study: Treatment of non-SVR patients from SPRINT-2 and RESPOND-2 with open-label PR/BOC
- Present analysis: Prior null responders (n=37 from SPRINT-2, n=11 from RESPOND-2)
 - 8% had F3/4
 - 65% G1a, 35% G1b

Undetectable HCV RNA in prior null responders



Note: 3 patients d/c'ed during LI
2 others still on treatment,
1 in early f/u

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)
- *Leaves open the question of cirrhotic relapsers*

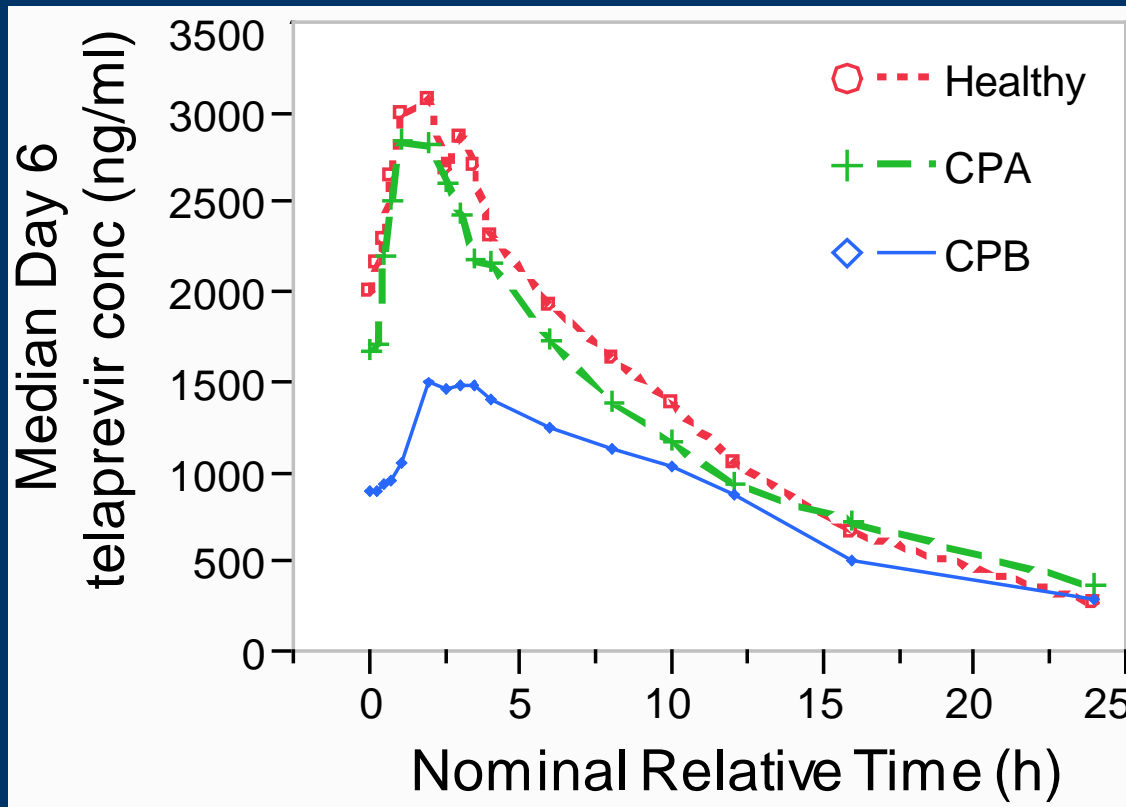
Response-Guided Therapy: Boceprevir

- 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/PR12)
 - Null responders
 - 48 weeks (PR4/PRB44)
-

Cirrhotics: 48 weeks (PR4/PRB44)

Selected pK Studies

Telaprevir Plasma Concentration – Time Profiles on Day 6 of TVR Dosing in Non-HCV Infected Patients



GLS Mean Ratio (90% CI)

CPA

C_{max} 0.90 (0.72, 1.10)

AUC_{8h} 0.85 (0.70, 1.02)

CPB

C_{max} 0.51 (0.41, 0.63)

AUC_{8h} 0.54 (0.43, 0.66)

Vertex data on file

TVR pK Study: Conclusions

- The effect of mild hepatic impairment on telaprevir PK was not clinically significant
 - No dose modification is required in Child-Pugh A patients¹
- Moderate hepatic impairment reduced the steady-state AUC of telaprevir by 46%
 - The appropriate dose of telaprevir in HCV-infected patients with moderate and severe hepatic impairment has not been determined; telaprevir is not recommended in these patients¹

pK of Boceprevir 400 mg (One Dose) in non-HCV Infected Cirrhotics by Child-Pugh (CP) Score

- Normal, CP5-6, CP7-9, CP10-12 patients
 - Single 400 mg dose
 - Mean AUC was 32% higher in CP7-9, 45% higher in CP10-12
 - C_{\max} 28-62% higher
-
- “No dose adjustment of VICTRELIS is required for patients with mild, moderate or severe hepatic impairment [see Clinical Pharmacology (12.3)]. Safety and efficacy of VICTRELIS have not been studied in patients with decompensated cirrhosis. See Package Inserts for peginterferon alfa for contraindication in hepatic decompensation” (from Victrelis Package Insert)

TMC435 Pharmacokinetics in Patients With Hepatic Impairment

- Healthy subjects and non-HCV subjects with moderate hepatic impairment (CP7-9) given TMC 150 mg for 7 d, and HCV patients with mild hepatic impairment treated for 28 days
- Steady state achieved by day 7

TMC435 Pharmacokinetics in Patients With Hepatic Impairment

- Median ratios between AUC_{24h} and C_{max} were 2.62 and 1.76 between moderate hepatic impairment and controls
- TMC435 parameters were similar between moderate impairment group at day 7 and mild impairment HCV group at day 28
- No relevant differences in unbound TMC435 between treatment groups
- No dose adjustment appears necessary with moderate hepatic impairment



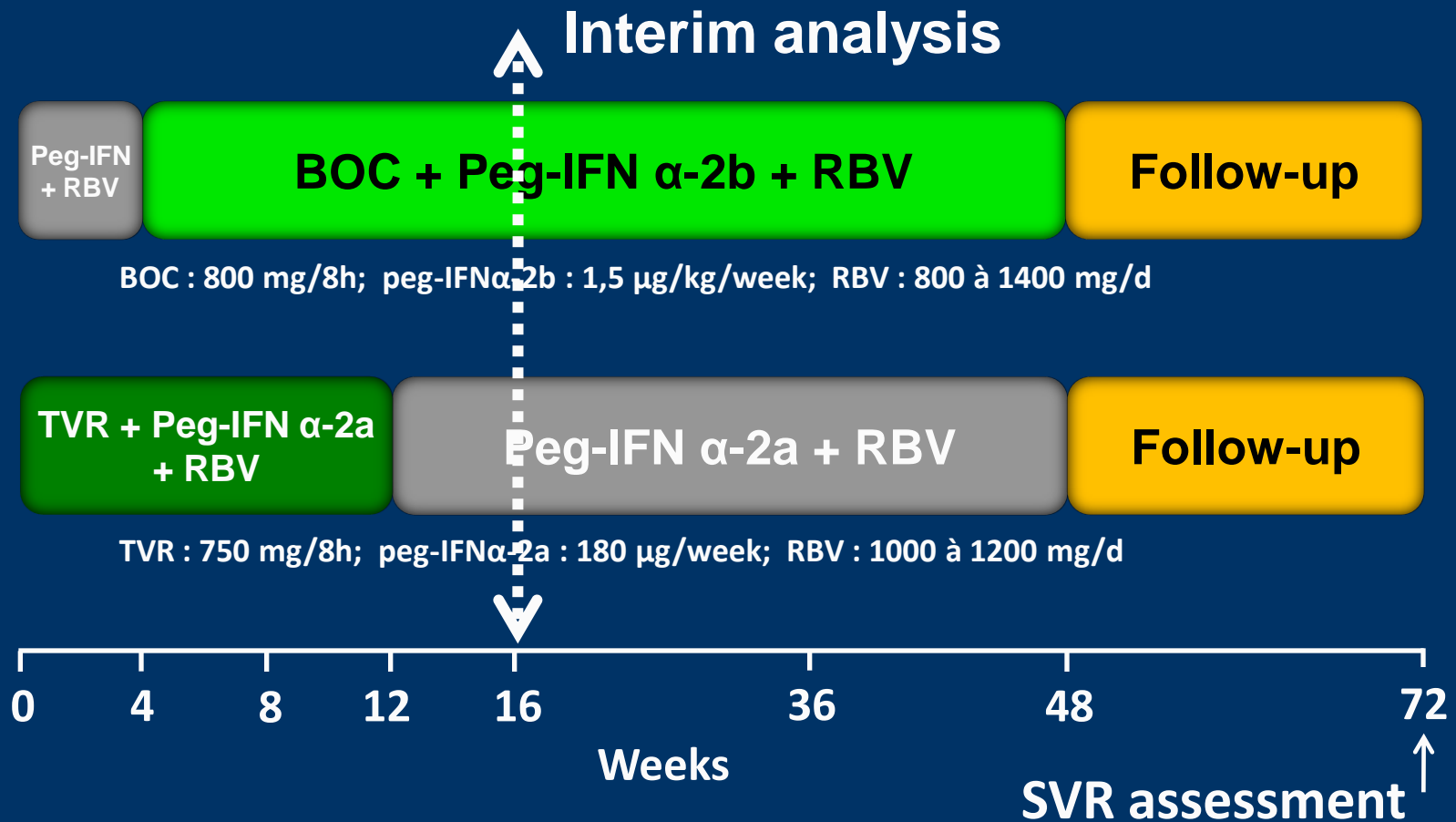
REAL-LIFE SAFETY OF TELAPREVIR OR BOCEPREVIR IN COMBINATION WITH PEGINTERFERON ALFA/RIBAVIRIN, IN CIRRHOTIC NON RESPONDERS. FIRST RESULTS OF THE FRENCH EARLY ACCESS PROGRAM (ANRS CO20-CUPIC)

C Hézode¹, C Dorival², F Zoulim³, V de Ledinghen⁴, T Poynard⁵, P Mathurin⁶, D Larrey⁷, M Bourlière⁸, S Pol⁹, P Cacoub⁵, PH Bernard¹⁰, D Lucidarme¹¹, Y Barthe², H Fontaine⁹, F Carrat², JP. Bronowicki¹² pour le groupe CUPIC (ANRS CO 20)

Hôpital Henri Mondor, Créteil¹, UMR-S 707, Paris², INSERM U871, Lyon³, Hôpital Haut-Lévêque, Pessac⁴, Hôpital de la Pitié-Salpêtrière, Paris⁵, Hôpital Claude Huriez, Lille⁶, Hôpital Saint-Eloi, Montpellier⁷, Fondation Hôpital Saint Joseph, Marseille⁸, Hôpital Cochin, Paris⁹, Hôpital Saint André, Bordeaux¹⁰, Hôpital Saint Philibert, Lomme¹¹, Hôpital de Brabois, Nancy¹²

Courtesy of Professor M Bourliere

CUPIC: Treatment Regimen



CUPIC: Telaprevir – Preliminary Safety Findings

Patients, n (%)	Telaprevir (n=176)
Serious AEs	90 (51)*
Discontinuation due to serious AE	21 (12)
Death	3 (1.7)
Rash	
Grade 3	12 (6.8)
SCAR	0
Infection (Grade 3/4)	6 (3.4)
Other AEs (Grade 3/4)	92 (52)
Anemia	
Grade 2 (8.0 – <10.0 g/dL)	58 (33)
Grade 3/4 (<8.0 g/dL)	23 (13)
EPO use	96 (55)
Transfusion	32 (18)
Neutropenia	
Grade 3 (500 – <1000/mm ³)	20 (11)
Grade 4 (<500/mm ³)	2 (1)
G-CSF use	5 (3)
Thrombopenia	
Grade 3 (25,000 – <50,000)	26 (15)
Grade 4 (<25,000)	12 (7)

*228serious AEs in 90 patients; SCAR: severe cutaneous adverse reaction; EPO: erythropoetin; G-CSF: granulocyte-colonystimulating factor

Courtesy of Professor M Bourliere

CUPIC: Boceprevir

Preliminary Safety Findings

Patients, n (%)	Boceprevir (n=134)
Serious AEs	39 (29)*
Discontinuation due to serious AE	8 (6)
Death	1(1)
Rash	
Grade 3	0
SCAR	0
Infection (Grade 3/4)	0
Other AEs (Grade 3/4)	43 (32)
Anemia	
Grade 2 (8.0 – <10.0 g/dL)	41 (31)
Grade 3/4 (<8.0 g/dL)	8 (6)
EPO use	70 (52)
Transfusion	8 (6)
Neutropenia	
Grade 3 (500 – <1000/mm ³)	10 (7)
Grade 4 (<500/mm ³)	5 (4)
G-CSF use	7 (5)
Thrombopenia	
Grade 3 (25,000 – <50,000)	8 (6)
Grade 4 (<25,000)	3 (2)

*86serious AEs in 39 patients; SCAR: severe cutaneous adverse reaction; EPO: erythropoietin; G-CSF: granulocyte-colony stimulating factor

A Largely Cirrhosis-Free Interregnum in DAA Combo Development

	<u>Cirrhosis</u>
PI/r + nuc \pm RBV	No
PI + non-nuc + RBV	No
Either of 2 nucs + RBV or together or monotherapy	10%
PI + nuc \pm RBV	Later cohort
PI/r + non-nuc + RBV	No
NS5A + nuc \pm RBV	No
PI + NS5A + non-nuc \pm RBV (or RBV alone)	No

This is expected to change soon

Conclusions

- **Compensated cirrhotics are strong candidates for PI-based therapy**
 - SVR rates proportionately increased above PR alone though still lower than noncirrhotics
 - Increment in side effects is acceptable
 - Most difficult decision to treat is in null responders to prior PR
 - Almost surely better things are coming but hard to withhold opportunity in cirrhotic who is declining
 - If fails, PI failure studies will likely start in next 1-2 years
- **Virtually no data in decompensated cirrhotics –**
 - Treat at your own (and patient's) risk
 - Platelet stimulating agents may have a limited role
- **We urgently need to study IFN free regimens in cirrhotics**