A CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

THE 46TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

A Continuing Medical Education Internet Symposium

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

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Updates on Current Status of HCV Therapy

K. Rajender Reddy, MD

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Philadelphia, Pennsylvania

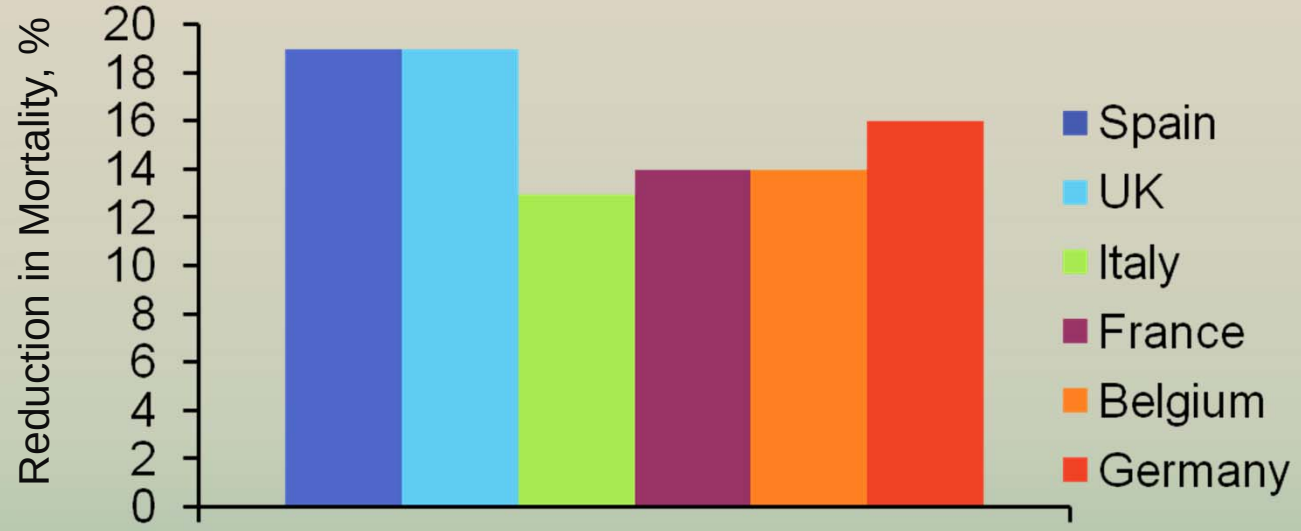
HCV in Europe: Impact of Treatment on Future HCV-related Morbidity and Mortality

- Data from France, Belgium, Germany, Italy, Spain and UK in 2010
- 33% of patients were HCV-RNA negative (ranging 31% in Italy to 42% in France), 20% after successful treatment
- 49% were aware of their infection
- Cirrhosis 15% (31% decompensation)
- HCC 5%

Deuffic-Burban S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 122.

HCV in Europe: Impact of Treatment on Future HCV-related Morbidity and Mortality

- Current treatment paradigm will reduce HCV mortality by 13% until 2025
- Cirrhosis incidence will also be reduced by 21% until 2025
- If all naïve patients and 70% of NR are treated with PI, HCV mortality would be reduced by an additional 15%



Deuffic-Burban S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 122.

Extension for Community Health Outcomes (ECHO): Objectives

- Train primary care clinicians in rural areas and prisons to treat hepatitis C in rural New Mexico
- Show that such care is as safe and effective as in a university clinic
- Show that Project ECHO improves access to hepatitis C care for minorities

Arora S, et al. 46th EASL, Berlin, Germany, March 30-April 3, 2011; Abst. 402.

ECHO: Method

- Use Technology (telemedicine and internet) to leverage scarce healthcare resources
- Disease Management Model focused on improving outcomes by reducing variation in processes of care and sharing “best practices”
- Case based learning: Co-management of patients with UNMHSC specialists
- HIPAA compliant centralized database to monitor outcomes

Arora S, et al. 46th EASL, Berlin, Germany, March 30-April 3, 2011; Abst. 402.

ECHO: Participants

- Study sites
  - Intervention (ECHO)
    - Community-based clinics: 16
    - New Mexico Department of Corrections: 5
  - Control: University of New Mexico Liver Clinic
- Subjects meeting inclusion/exclusion criteria
  - Community cases seen by primary care physicians
  - Consecutive University patients

Arora S, et al. 46th EASL, Berlin, Germany, March 30-April 3, 2011; Abst. 402.

ECHO: Patient Characteristics

- 407 hepatitis C patients met inclusion and exclusion criteria
  - Age: 43.0 ± 10.0 years
  - Men: 63.3%
  - Minority: 65.2%
  - Genotype 1: 57.0%
  - Log_{10} viral load: 5.89 ± 0.95

Arora S, et al. 46th EASL, Berlin, Germany, March 30-April 3, 2011; Abst. 402.

ECHO: Treatment Outcomes

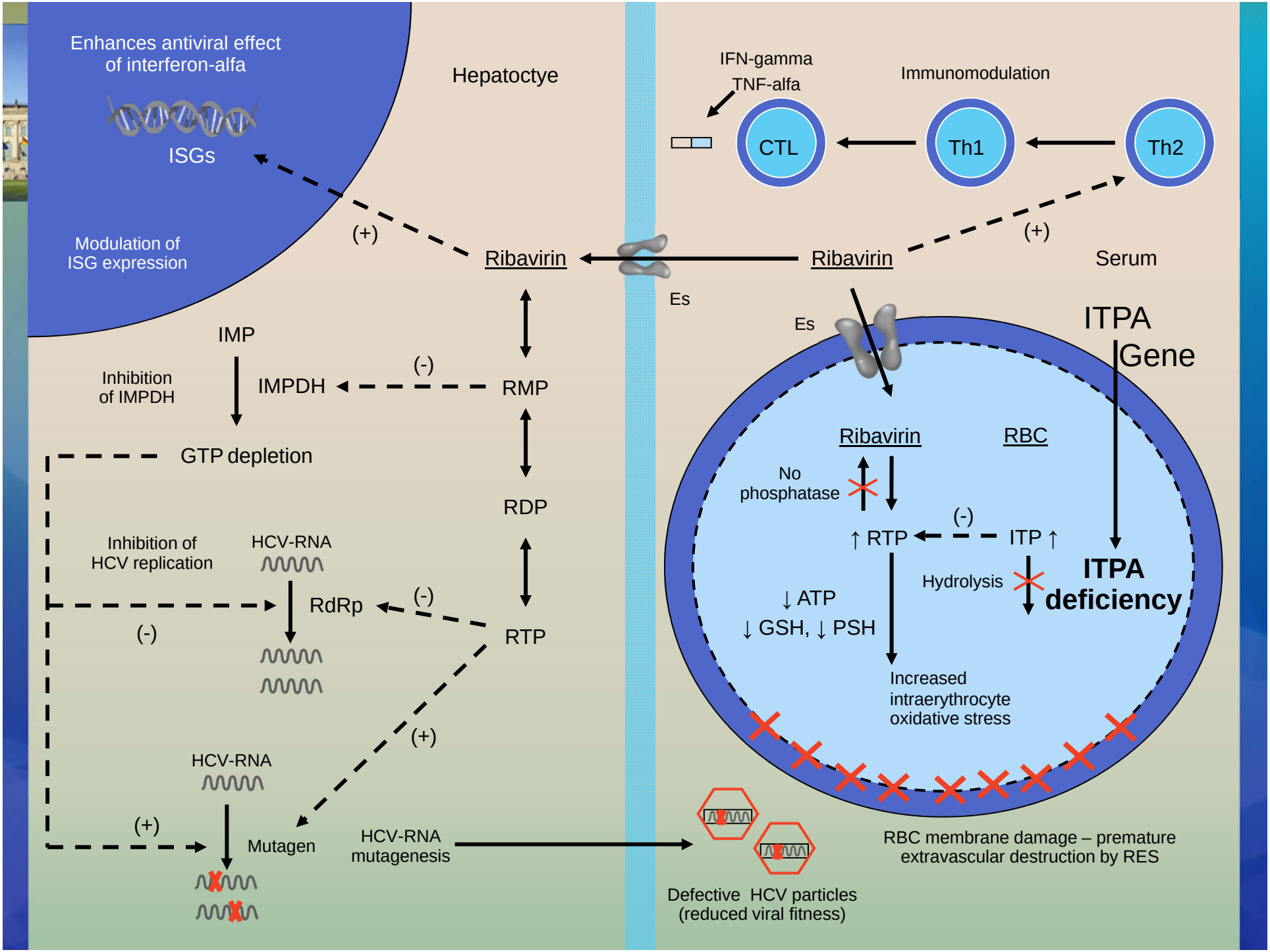
Outcome	ECHO	UNMH	*P*-value
	N=261	N=146	
Minority	68%	49%	*P*<0.01
SVR (Cure) Genotype 1/4	50%	46%	NS
SVR (Cure) Genotype 2/3	70%	71%	NS

Arora S, et al. 46th EASL, Berlin, Germany, March 30-April 3, 2011; Abst. 402.

ECHO: Conclusions

- Rural primary care clinicians deliver hepatitis C care through Project ECHO that is as safe and effective as that given in a university clinic
- Project ECHO improves access to hepatitis C care for New Mexico minorities

Arora S, et al. 46th EASL, Berlin, Germany, March 30-April 3, 2011; Abst. 402.


Enhances antiviral effect of interferon-alfa
ISGs
Modulation of ISG expression
Hepatoctye
IFN-gamma
TNF-alfa
Immunomodulation
CTL
Th1
Th2
(+)
Ribavirin
Ribavirin
Serum
Es
Es
ITPA Gene
IMP
Inhibition of IMPDH
IMPDH
(-)
RMP
GTP depletion
RDP
Ribavirin
RBC
No phosphatase
(-)
↑ RTP
ITP ↑
Hydrolysis
ITPA deficiency
↓ ATP
↓ GSH, ↓ PSH
Increased intraerythrocyte oxidative stress
Inhibition of HCV replication
HCV-RNA
RdRp
(-)
(-)
RTP
(+)
HCV-RNA
(+)
Mutagen
HCV-RNA mutagenesis
RBC membrane damage – premature extravascular destruction by RES
Defective HCV particles (reduced viral fitness)

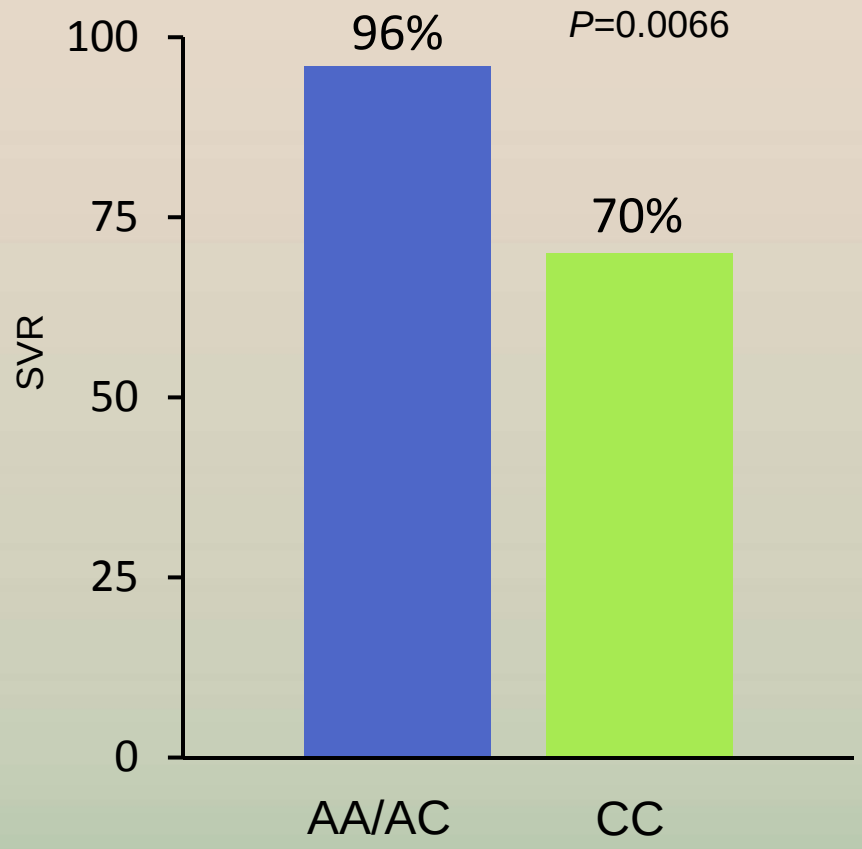
ITPA Gene Variant Protects Against Anemia and Improves Viral Clearance by PEG-IFN/RBV

- Multicenter, retrospective cross-sectional study of chronic HCV treated with PegIFN/RBV from 4 centers in Japan (N=474)
- 3 SNPs within or adjacent to ITPA gene were genotyped (rs6051702, rs7270101, rs1127354)
- A functional SNP, rs1127354 was strongly associated with a protection against anemia
  - Only 1/129 (0.8%) patients with variant A developed severe anemia

Sakamoto N, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 469.

ITPA Gene Variant Protects Against Anemia and Improves Viral Clearance by PegIFN/RBV

- In patients who were treated with 24-week PegIFN/RBV regimen
  - Excluding HCV genotype 1b and high viral load
- Patients with ITPA minor variant A achieved higher SVR than those with major variant CC



Sakamoto N, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 469.

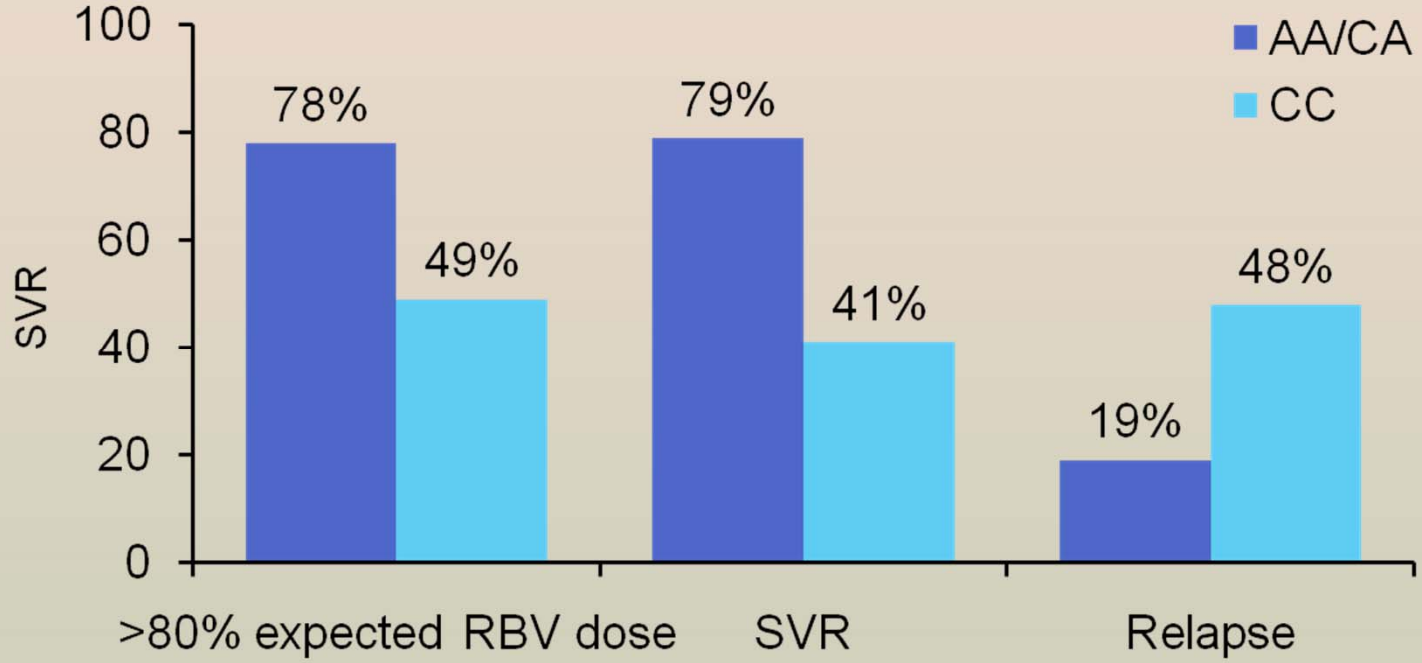
ITPA Gene Variant and Response to Therapy: Genotype 1b

- Retrospective analysis of chronic HCV genotype 1b treated with PegIFN/RBV in Japan (N=355)
- SNP of the ITPA gene (rs1127354) and IL28B gene (rs8099917) were genotyped
- Frequency of ITPA minor allele A was 0.16
- Incidence of anemia was less in the patients with AA/CA than CC genotype:

	Hemoglobin Reduction >3.0 g/dL	
Genotype	Week 4	Through Week 48
AA/CA	0%	39%
CC	42%	75%

Kurosaki M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 441.

ITPA Gene Variant and Response to Therapy: Genotype 1b



- AA/CA genotypes were associated with lower incidence of relapse and higher rate of SVR in a subset of Japanese patients with the favorable IL28B genotype

Kurosaki M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 441.

Effect of Fluvastatin in HCV Treated with PegIFN/RBV

- Double-blinded, placebo-controlled, RCT at single center in Romania
- Chronic HCV patients randomized to fluvastatin 20 mg QD or placebo (total of 72 weeks) in additional to 48-week PegIFN/RBV (N=209)

Georgescu EF, et al. 46th EASL; Berlin, Germany; March 30-April 3; Abst. 10.

Potential Enhancement of Virological Response by Fluvastatin in HCV Treated with PEG-IFN/RBV

Viral responses in all patients

	Fluvastatin	Placebo	*P* value	Δ
EVR (n=144)	76.0%	61.9%	0.041	+15.1%
SVR (n=118)	63.5%	49.5%	0.05	+14.0%

Viral responses in patient without metabolic syndrome(50/209)

	Fluvastatin	Placebo	*P* value	Δ
EVR	85.4%	71.4%	0.034	+14.0%
SVR	74.4%	58.4%	0.049	+16.0%

Georgescu EF, et al. 46th EASL; Berlin, Germany; March 30-April 3; Abst. 10.

SVR among HCV G1 Patients with Elevated LDL Treated with Intensified PEG-IFN Regimen

- Retrospective analysis from PROGRESS study
- Evaluated HCV genotype 1, VL ≥400,000 IU/mL and BW ≥85 kg (N=537)
- Randomized (1:1:2:2) to 48 wks of 180 µg PEG-IFN α-2a plus RBV either at a dose of 1200 or 1400/1600 mg/day, or 12 wks of 360 µg PEG-IFN α-2a followed by an additional 36 wks of 180 µg plus RBV either at a dose of 1200 or 1400/1600 mg/day
- LDL cut-point =100 mg/dL

Harrison SA, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 238.

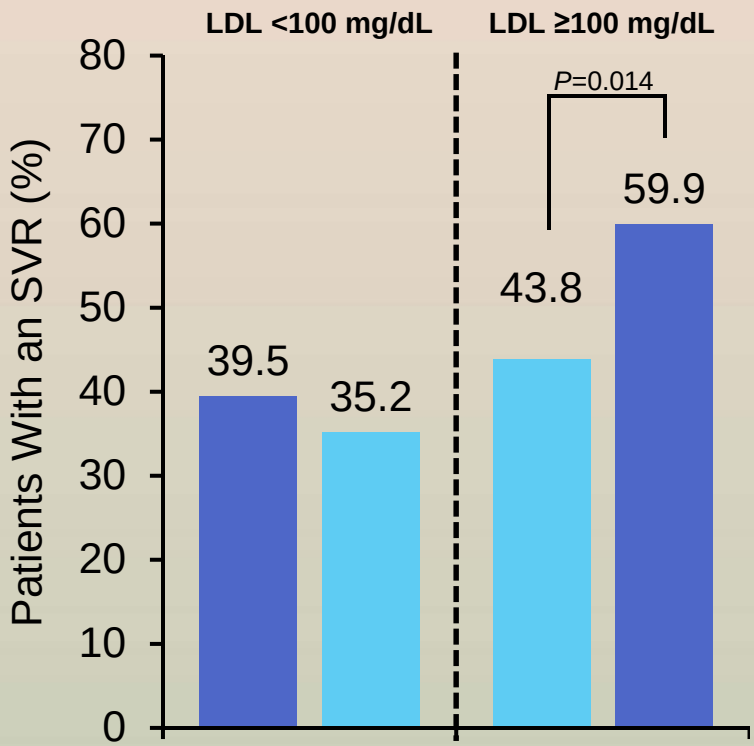
SVR among HCV G1 Patients with Elevated LDL Treated with Intensified PEG-IFN Regimen

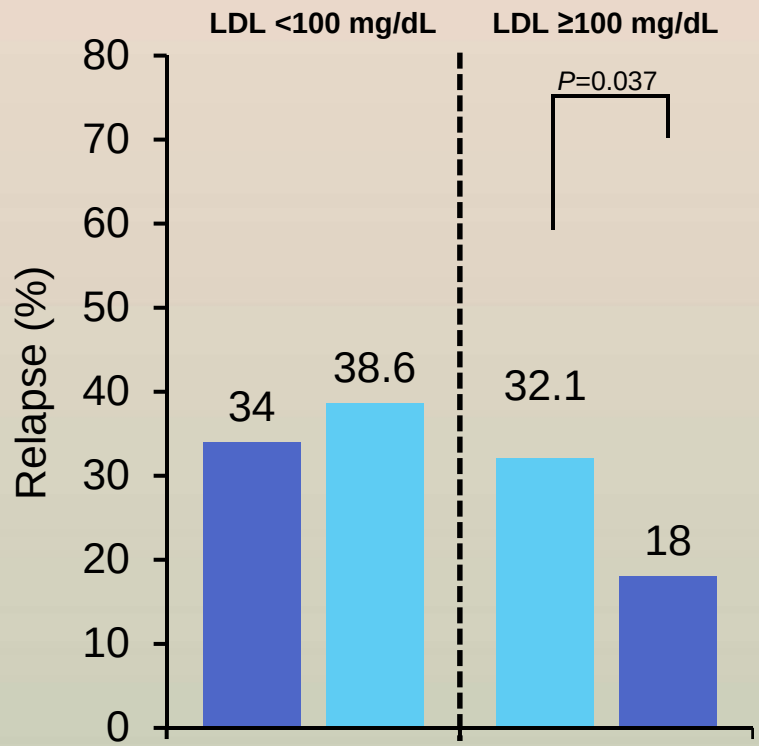
- Intensified dosing of PEG-IFNα-2a increases SVR rates among patients with elevated LDL

Parameter	OR (95% CI)	*P*-value
Age ≤40 vs. >40 years	2.30 (1.51-3.49)	<0.0001
HCV RNA <800,000 vs. ≥800,000 IU/mL	2.05 (1.22-3.44)	0.0063
Genotype 1b vs. 1a	1.99 (1.32-2.99)	0.0010
Steatosis score <5% vs. ≥5%	1.82 (1.18-2.81)	0.0070
RBV (pts with LDL <100 mg/dL) 1600/1400 vs. 1200 mg	0.66 (0.39-1.13)	0.1273
RBV (pts with LDL ≥100 mg/dL) 1600/1400 vs. 1200 mg	1.33 (0.79-2.23)	0.2816
PeglFN α-2a (pts with LDL <100 mg/dL) 360/180 vs. 180 µg	0.70 (0.40-1.24)	0.2214
PeglFN α-2a (pts with LDL ≥100 mg/dL) 360/180 vs. 180 µg	2.16 (1.25-3.73)	0.0060

Harrison SA, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 431.

SVR rates are higher among HCV G1 patients with elevated LDL levels when treated with intensified PEG-IFN regimen



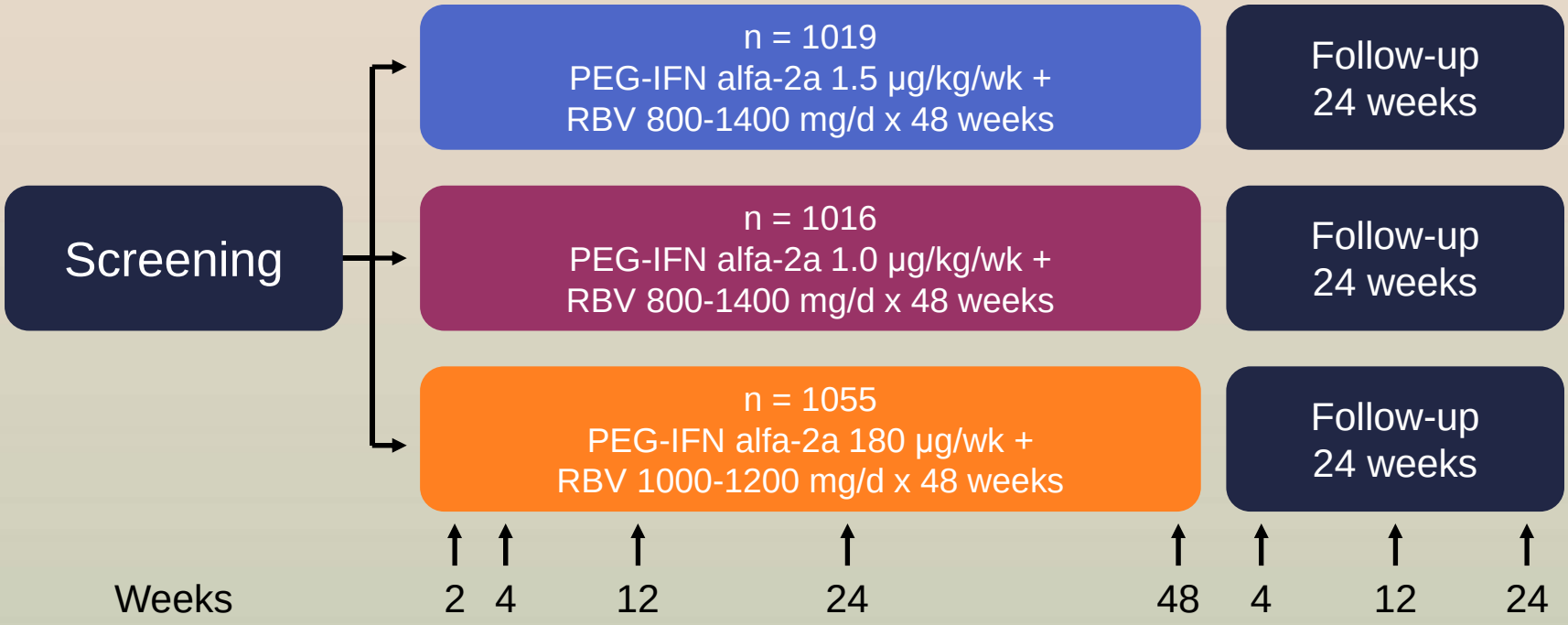


PEGINF alfa-2a (40KD) 180 µg/week + ribavirin (Groups A+B)

PEGINF alfa-2a (40KD) 360/180 µg/week + ribavirin (Groups C+D)

Harrison SA, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 431.

Infections during PEG-IFN/RBV Use Associated with Magnitude of Decline in Lymphocyte Count



- While on Rx, 36% had infections (of any grade) and 19% had moderate to life-threatening infections

Melia M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 478.

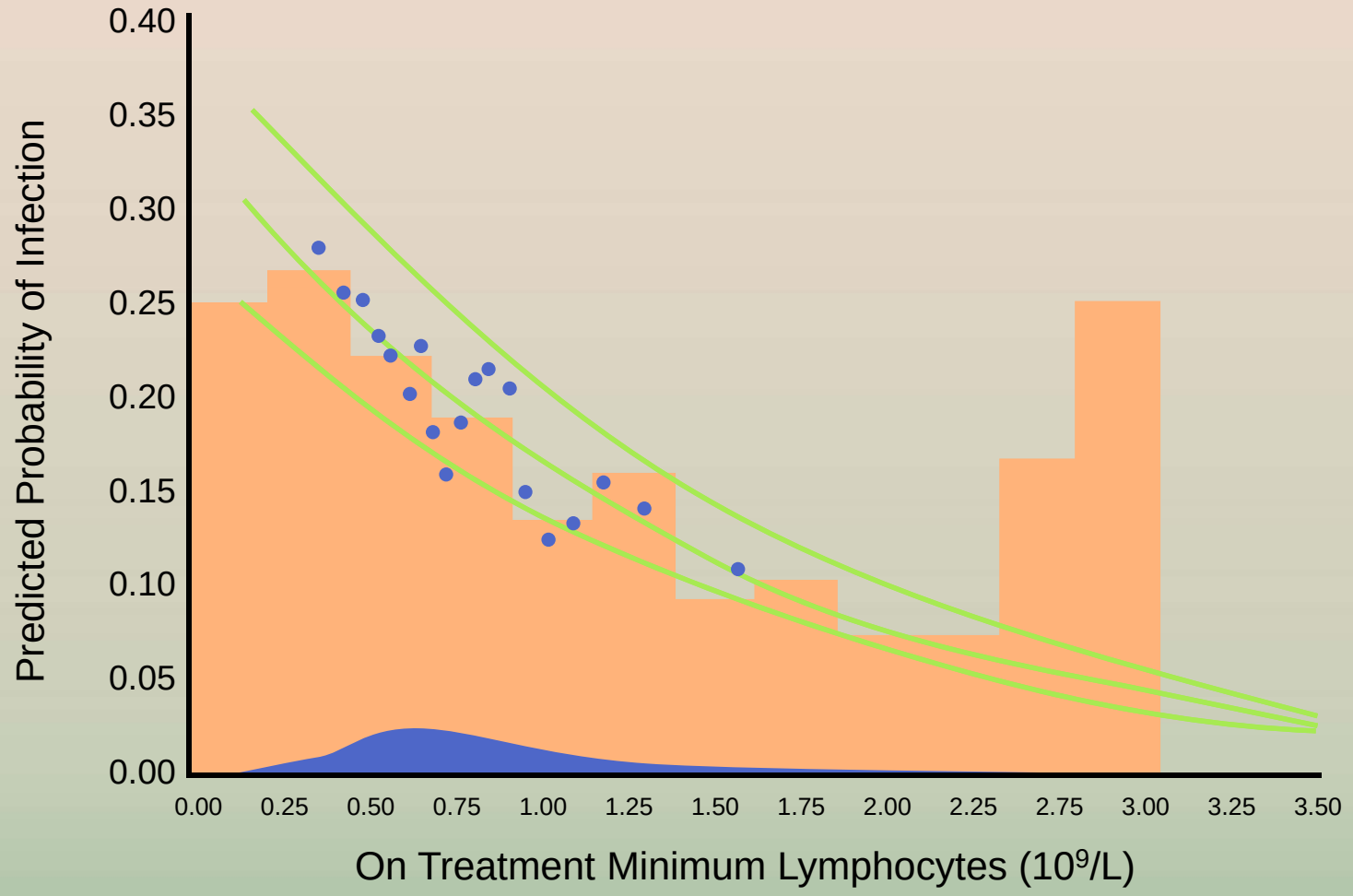
Infections during PEG-IFN/RBV Use Associated with Magnitude of Decline in Lymphocyte Count

- Multivariate analysis: predictors for moderate to life threatening infections

Factors	Odds ratio	*P* value
PegIFN α-2b vs. α-2a	0.84	0.37
Gender (female vs. male)	1.61	<0.001
METAVIR score (F0/1/2 vs. F3/4)	1.17	0.22
Baseline HCV-RNA	1.00	0.32
Age	0.99	0.10
Minimum on-Rx neutrophils	1.00	0.98
Minimum on-Rx lymphocytes	0.48	<0.001
Minimum on-Rx hemoglobin	0.96	0.25

Melia M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 478.

Infections during PEG-IFN/RBV Use Associated with Magnitude of Decline in Lymphocyte Count



Melia M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 478.

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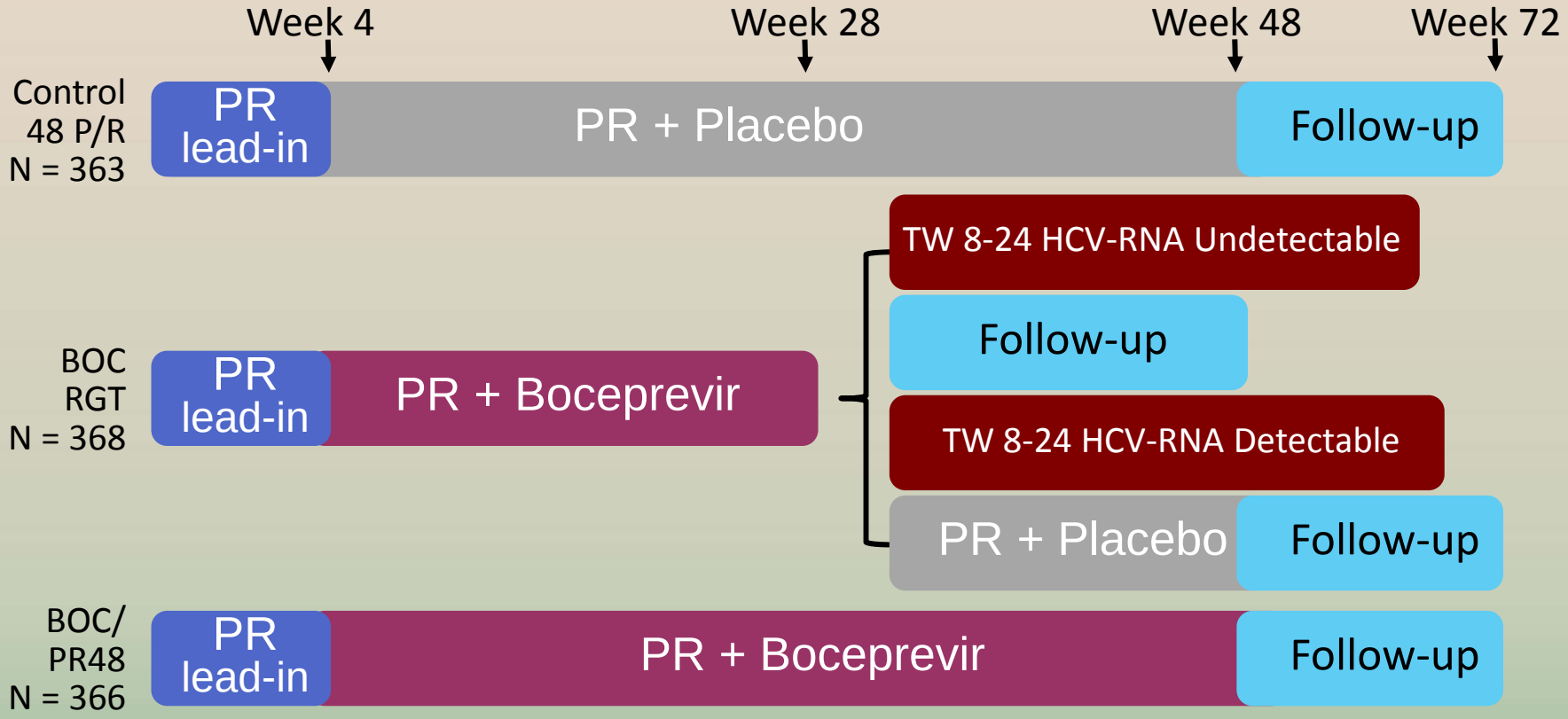
Boceprevir Studies

Fred Poordad, MD

Chief, Hepatology
Cedars-Sinai Medical Center
Associate Professor of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California

SPRINT-2: Study Design

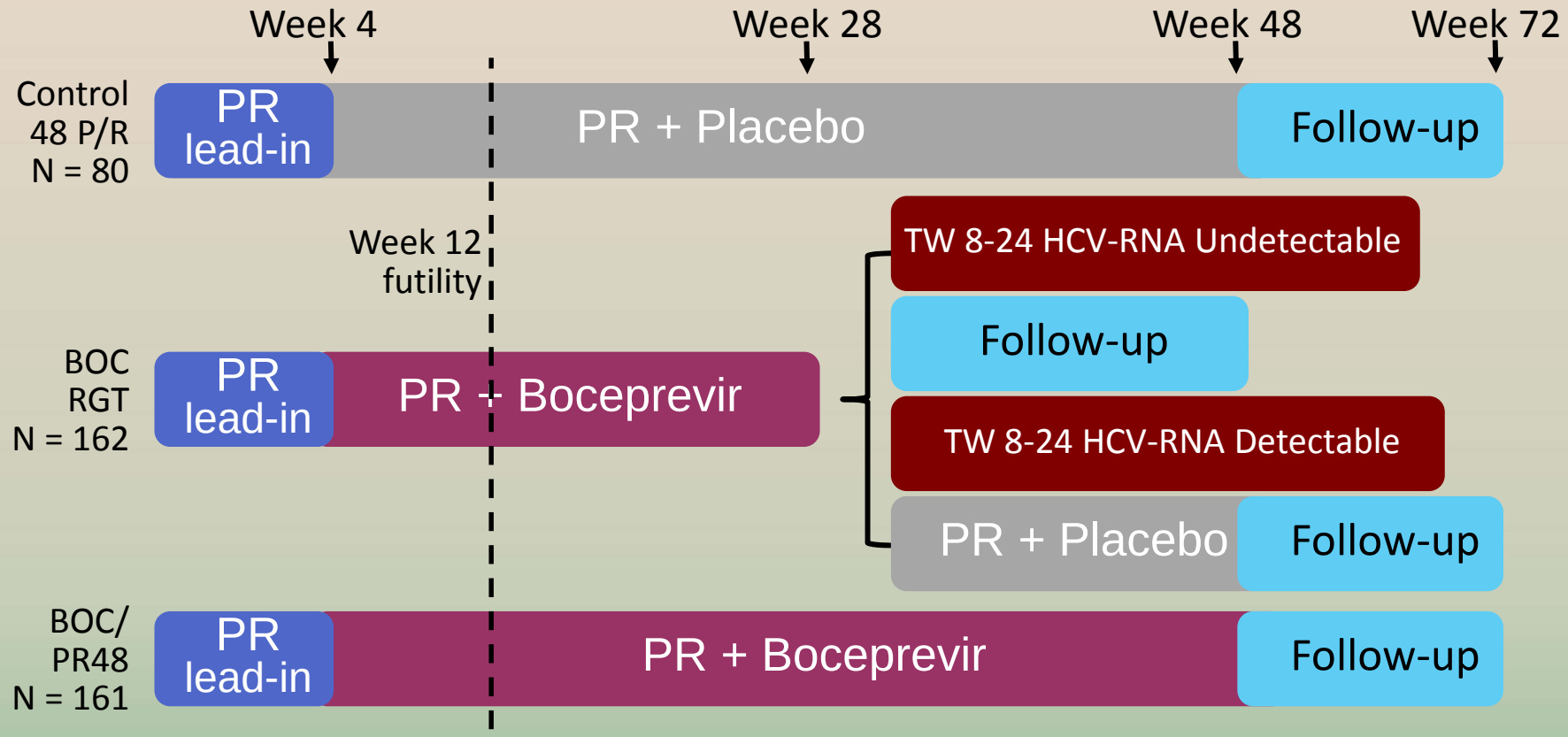
Study to compare safety/efficacy of two treatment strategies with boceprevir added to peginterferon/ribavirin (PR) versus PR alone in treatment naïve HCV genotype 1 patients



Poordad F, et al. 61st AASLD; Boston, MA; October 29 – November 2, 2010; Abst. LB-4.

RESPOND-2: Study Design

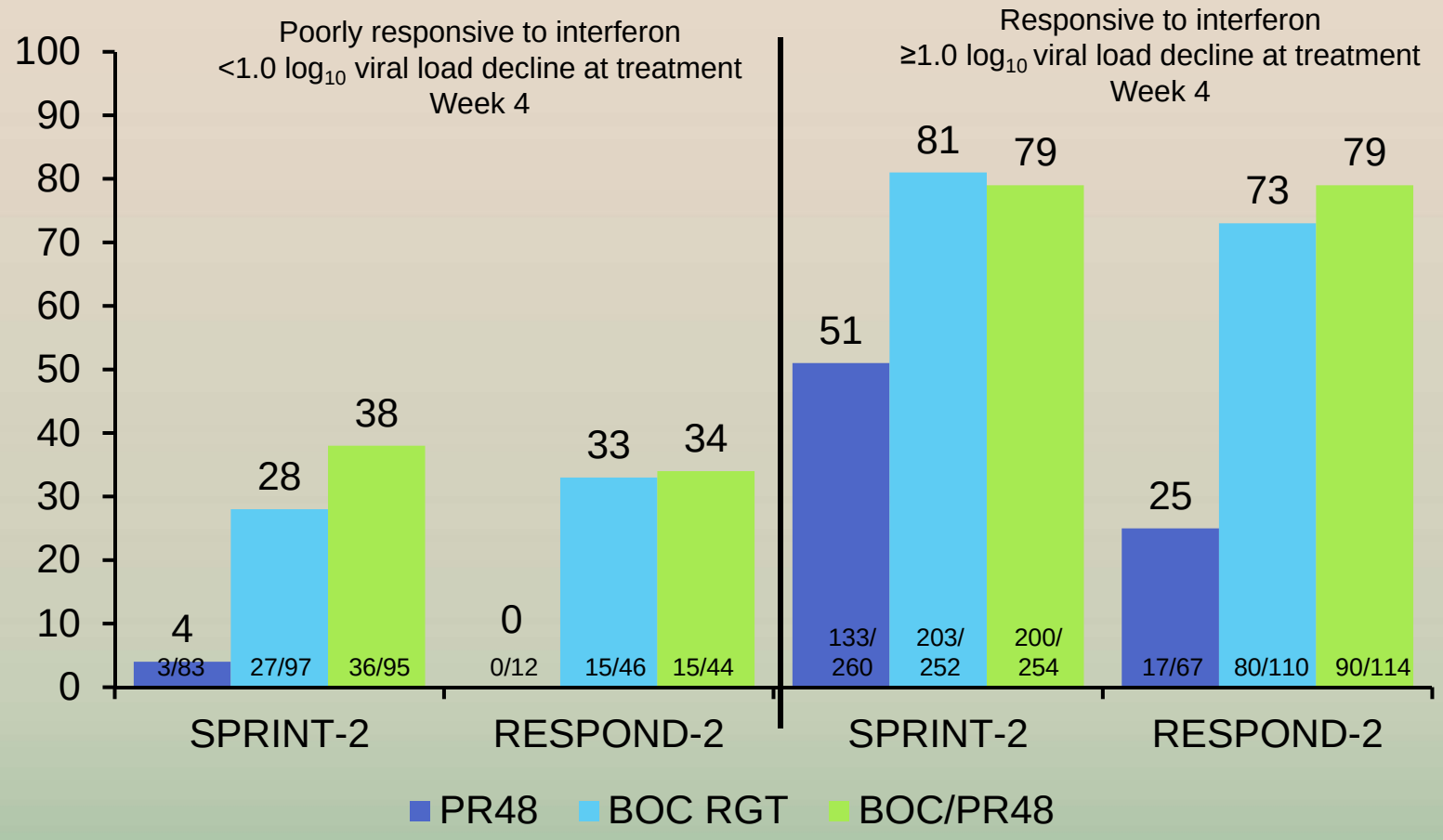
Study to assess safety/efficacy of BOC plus PegIFN (P) and RBV (R) in re-treatment of previous non-responders (NRs) and relapsers to P/R therapy



Bacon B, et al. 61st AASLD; Boston, MA; October 29 – November 2, 2010; Abst. 216.

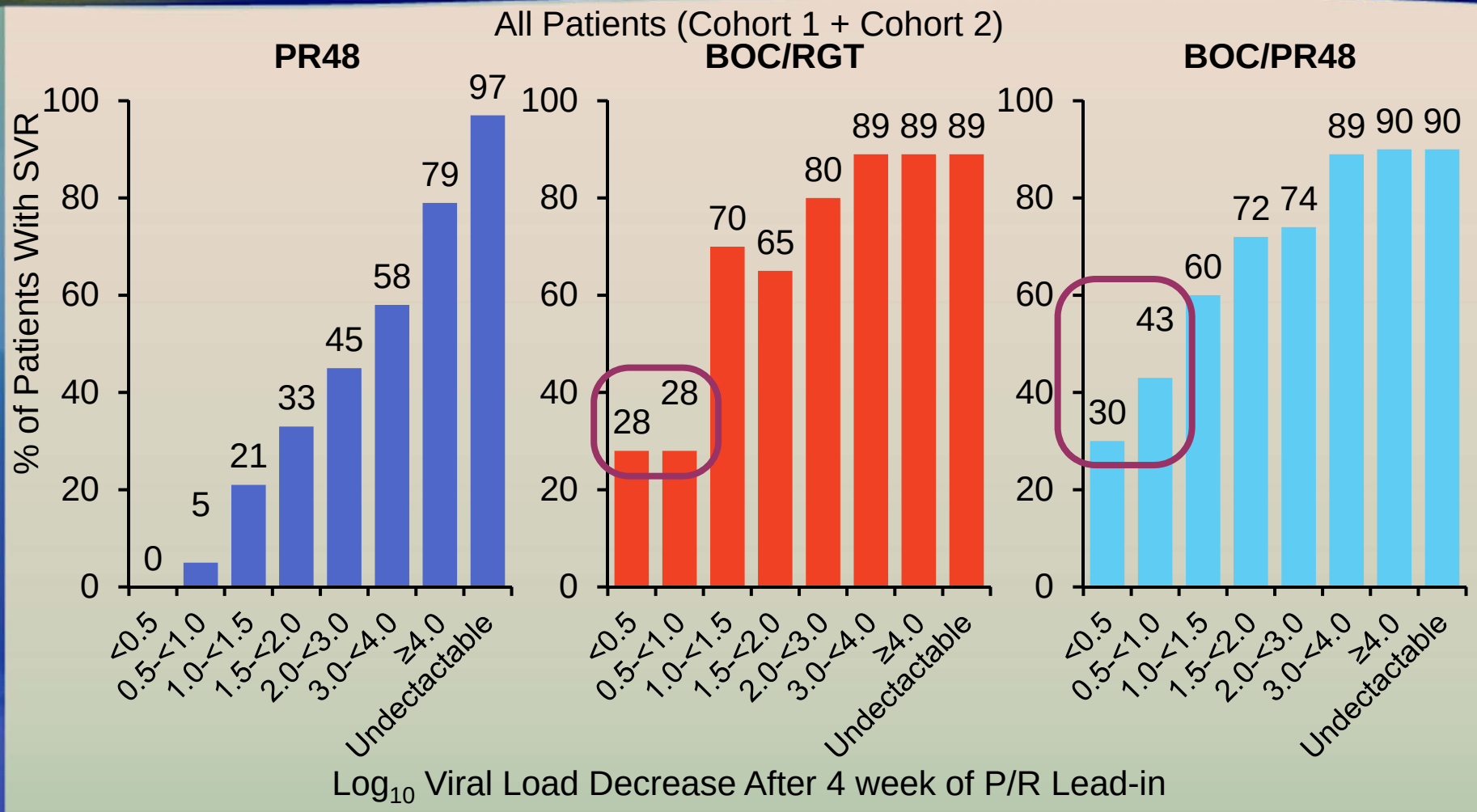
SPRINT-2 and RESPOND-2: Evaluation of Predictive Value of PegIFN/RBV 4-week Lead-in Therapy

Relationships Between Week 4 Lead-in And SVR



Vierling JM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 481.

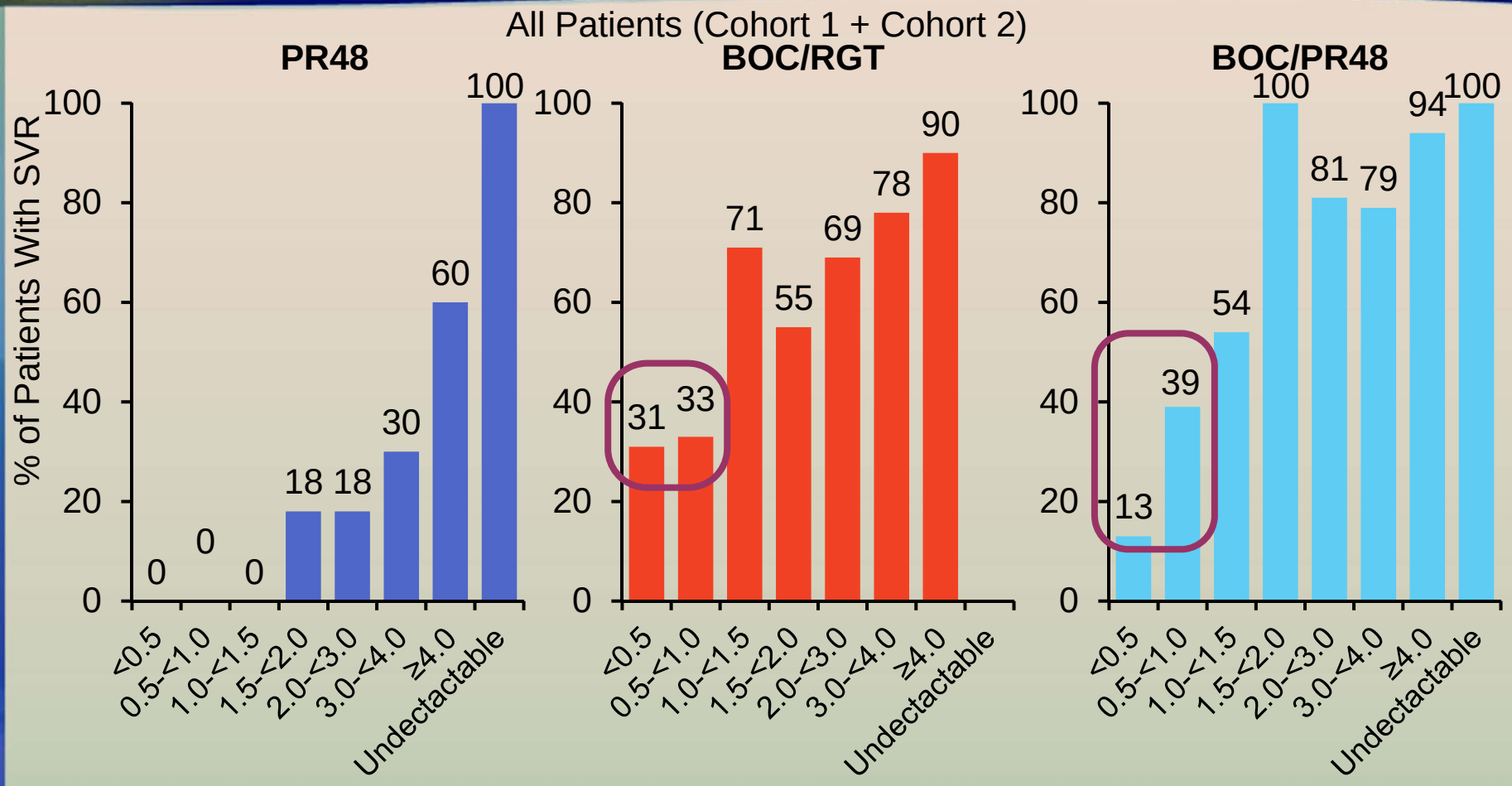
SPRINT-2: SVR Based on Early Interferon Response



- In SPRINT-2, the degree of real-time interferon responsiveness at week 4 correlated with SVR

Vierling JM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 481.

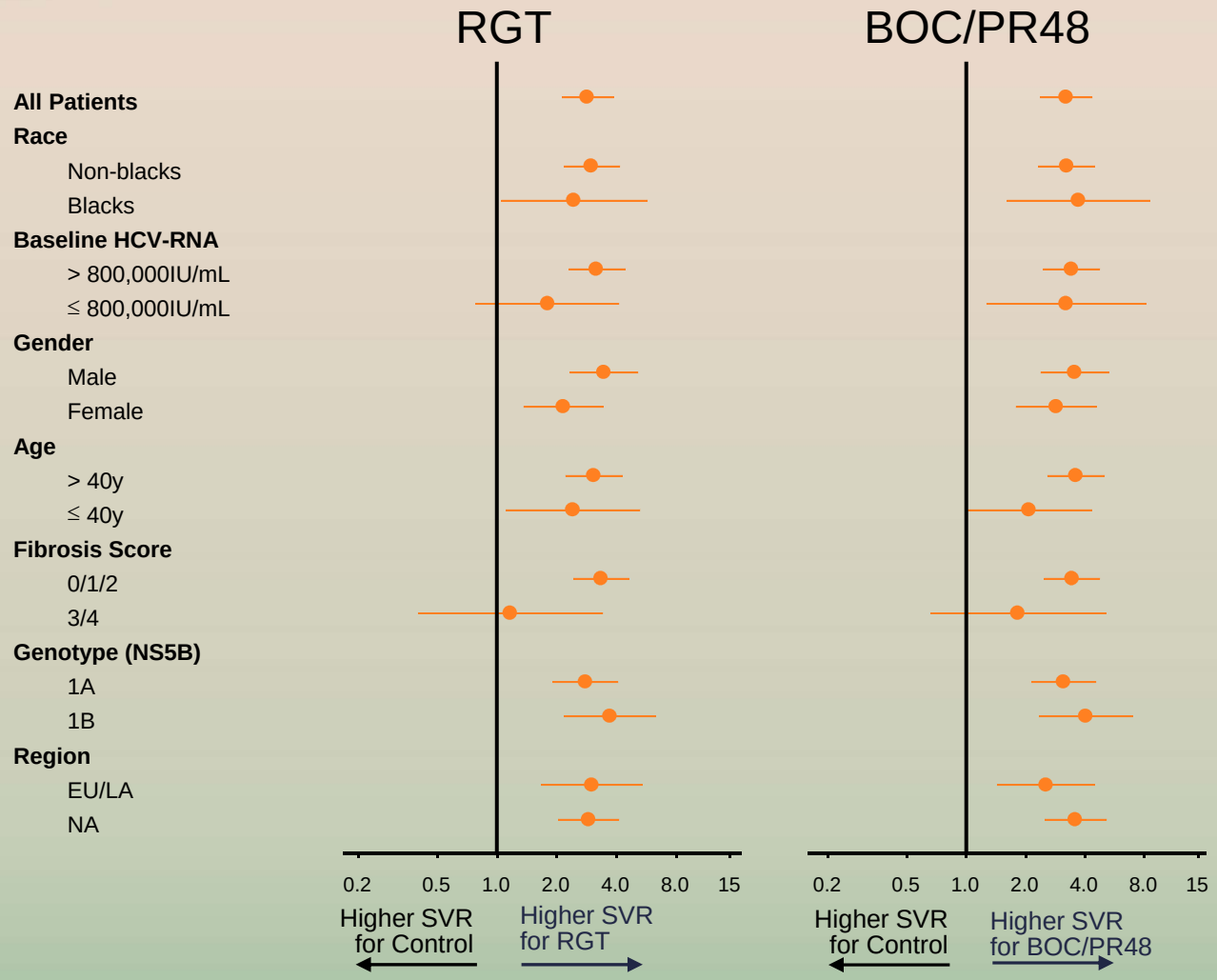
RESPOND-2: SVR Based on Early Interferon Response



- For those in BOC/PR48 and BOC/RGT arms with a <1.0 log_{10} week 4 HCV-RNA decline, 33%-34% attained SVR compared with no patients attaining SVR in the P/R control arm
- For the 6% of patients who attained undetectable HCV-RNA at week 4 in any of the treatment arms, >90% achieved SVR

Vierling JM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 481.

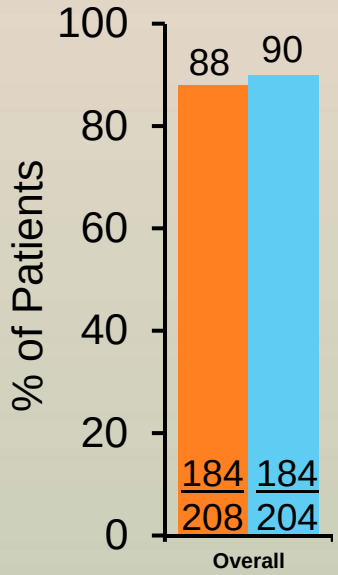
SPRINT-2 Sub-Group Analysis SVR for RGT, BOC/PR48 vs. Control



Reddy KM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 466.

SPRINT-2 and RESPOND-2: Effect of RGT with BOC + PegIFN/RBV on Treatment Duration

SPRINT-2: SVR in Early Responders (Undetectable HCV-RNA at Treatment Week 8), Overall Population



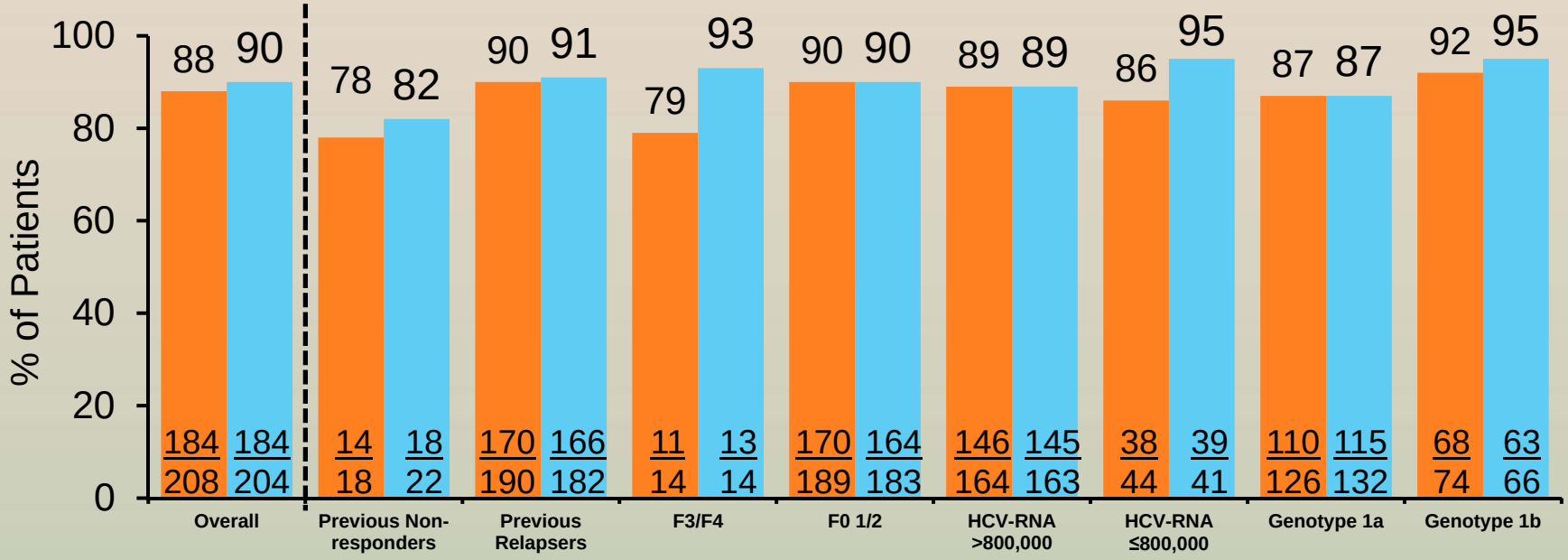
- SVR in the overall population of early responders was 88% and 90% in BOC RGT and BOC/PR48

Manns MP, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 448.

BOC RGT BOC/PR48

Results

SPRINT-2: SVR in Early Responders (Undetectable HCV-RNA at Treatment Week 8), Overall Population and by Key Baseline Characteristics



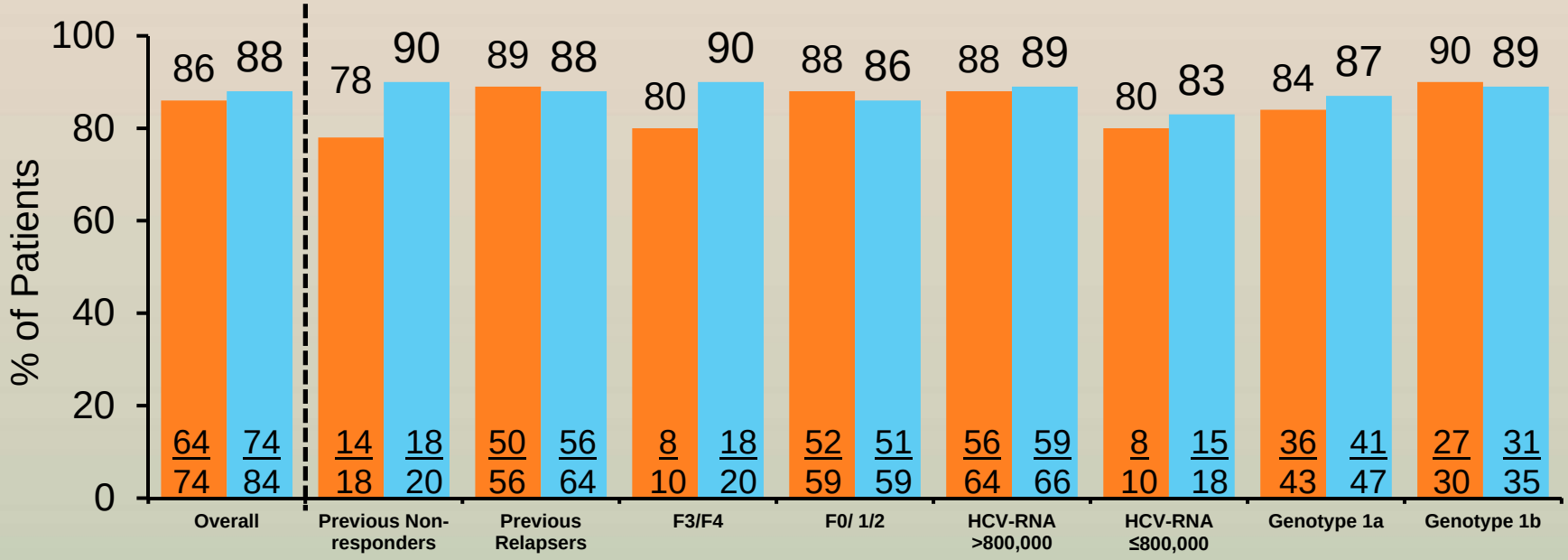
- SVR in subgroups was similar in both the BOC RGT and BOC/PR48 arms with the exception of advanced fibrosis (F3/F4, <15 patients per group)

Manns MP, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 448.

BOC RGT BOC/PR48

Results

RESPOND-2: SVR in Early Responders (Undetectable HCV-RNA at Treatment Week 8) by Baseline Characteristics

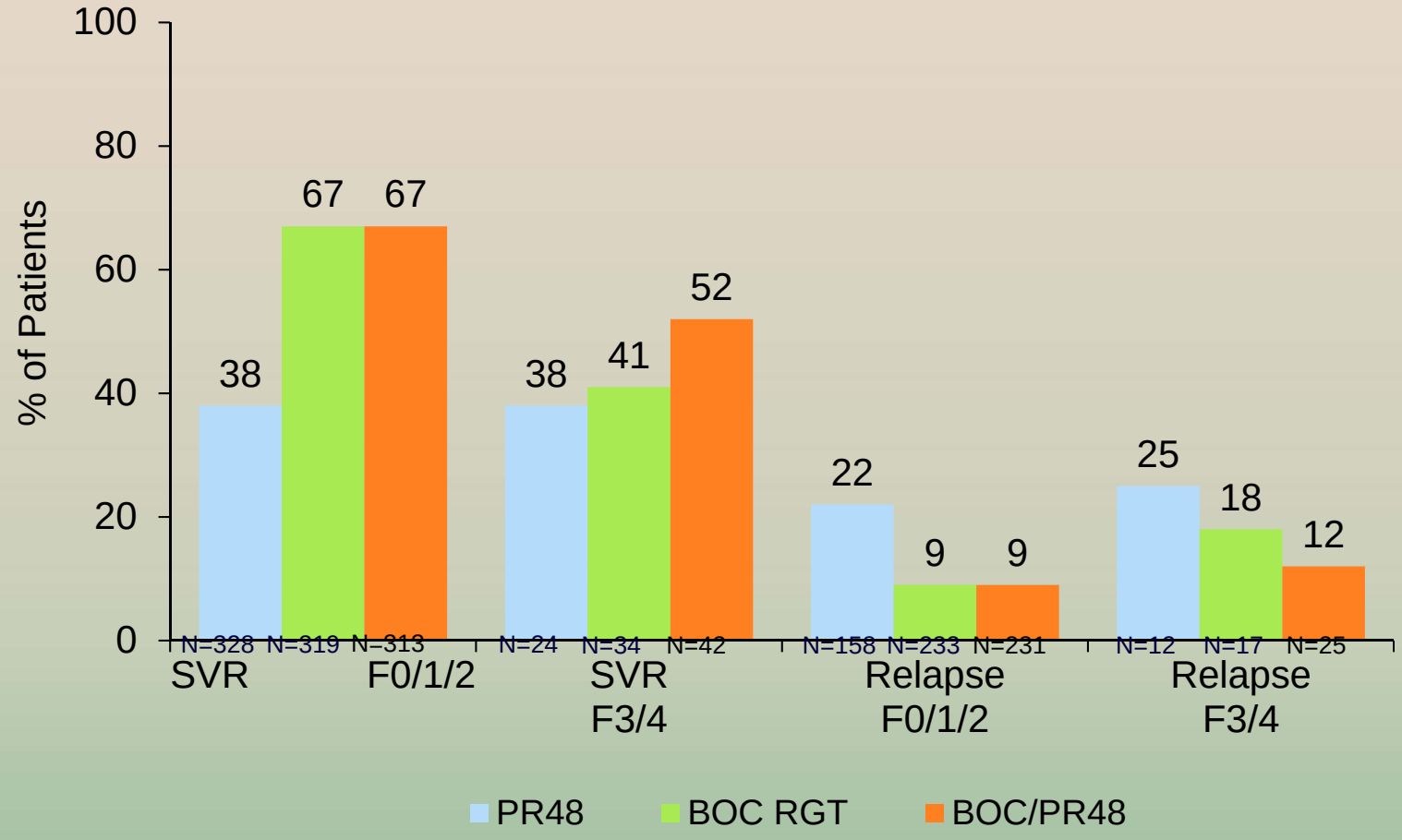


- 46% of patients had undetectable HCV RNA at week 8 (early responders) and 86% achieved SVR with a total treatment duration of 36 weeks

Manns MP, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011: Abst. 448.

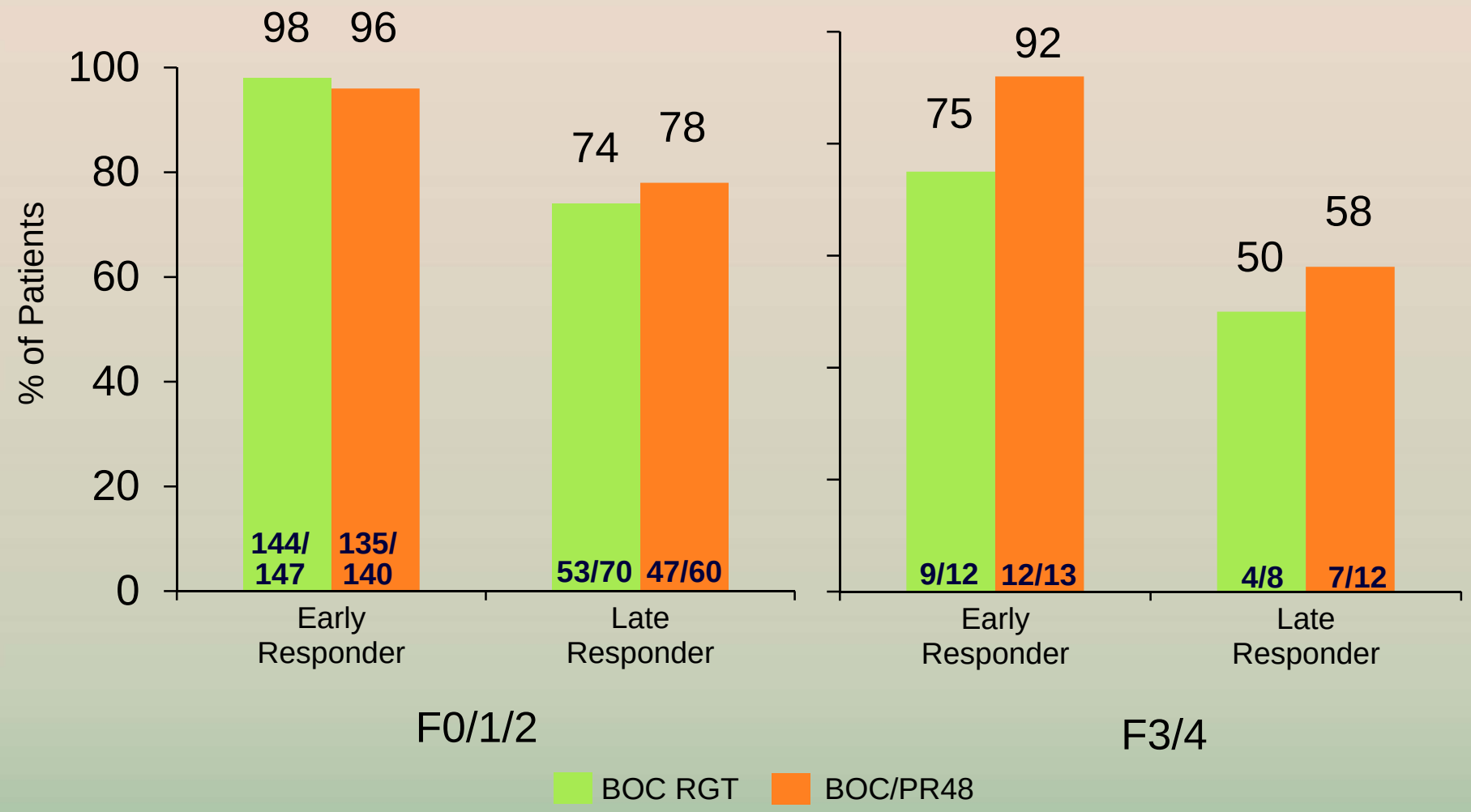
SPRINT-2
SVR and Relapse Rate by Fibrosis Score

SPRINT-2 and RESPOND-2: BOC + PegIFN/RBV in HCV GT 1 with Advanced Fibrosis/Cirrhosis



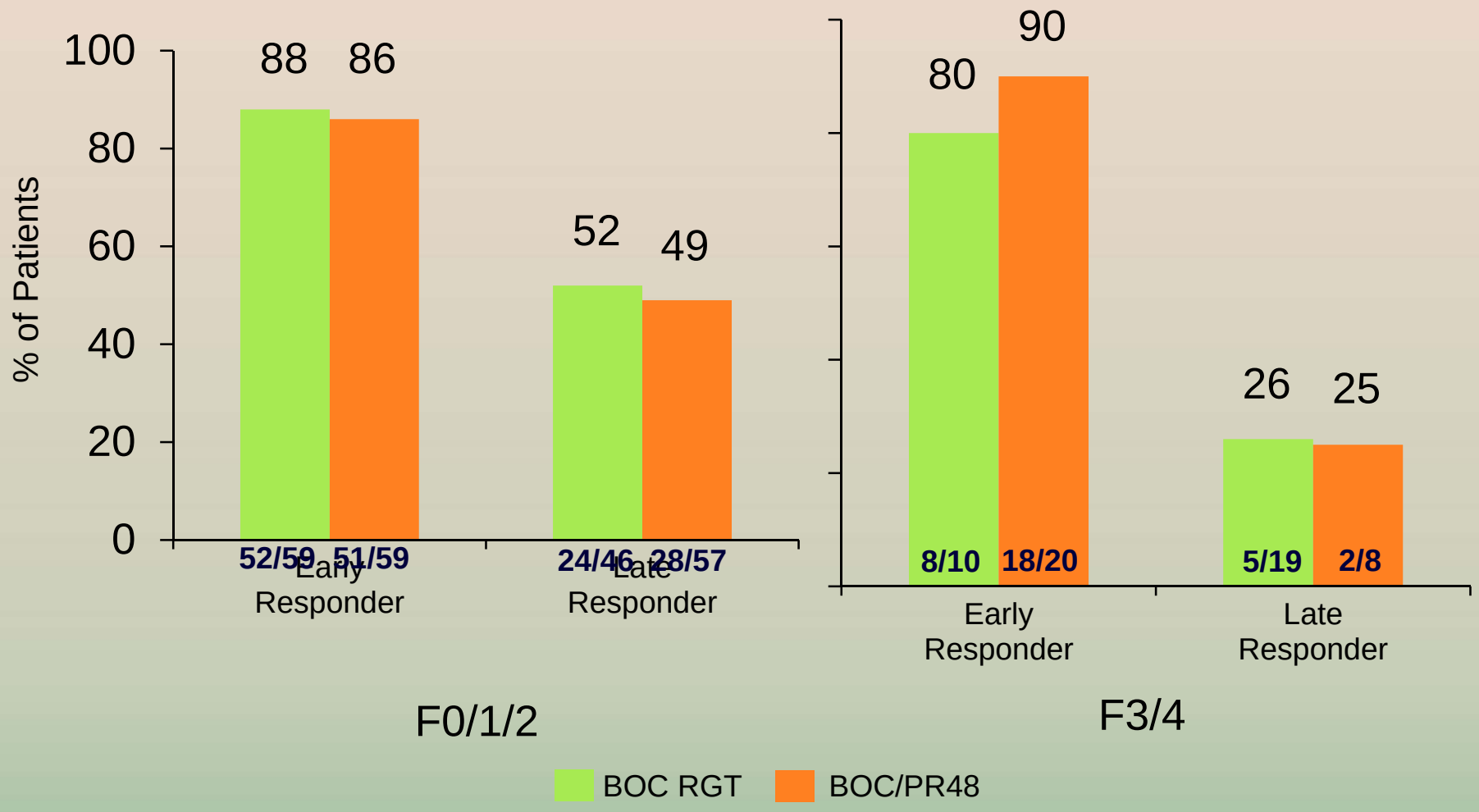
Bruno S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 7.

SPRINT-2: SVR in Early (Week 8 HCV-RNA-negative) and Late (Week 8 HCV-RNA-positive) Responders by Fibrosis Score



Bruno S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 7.

RESPOND-2SVR: SVR in Early (Week 8 HCV-RNA-negative) and Late (Week 8 HCV-RNA-positive) Responders by Fibrosis Score



Bruno S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 7.

SPRINT-2 and RESPOND-2: Adverse Events

Most Common Treatment-Related AEs (incidence ≥ 20% in any arm) and Other Events of Interest

AE	P/R N=547 %	BOC/PR N=1548 %
Fatigue	57	57
Headache	43	44
Nausea	40	45
Insomnia	31	32
Pyrexia	31	31
Anemia	29	49
Chills	29	33
Rash/skin eruption	27	30
Alopecia	25	26
Influenza-like illness	25	22
Myalgia	24	23
Pruritus	23	21
Decreased appetite	23	25
Irritability	22	23
Depression	20	20
Diarrhea	18	23
Neutropenia	18	23
Dysguesia	15	37
Other events of interest		
Rash	17	16
Anorectal discomfort	1	1
Hemorrhoids	3	4
Total bilirubin (mg/dL)		
2.60 to 5.09 x ULN (WHO grade 2)	2	1
5.10 to 10.0 x ULN (WHO grade 3)	0	0
>10.0 x ULN (WHO grade 4)	0	0

Manns MP, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 449.

Anemia Associated with Increased SVR

Adverse Event of Anemia (Hb <10 g/dL) and Nadir Hemoglobin by Modified WHO Grade During the Treatment Phase

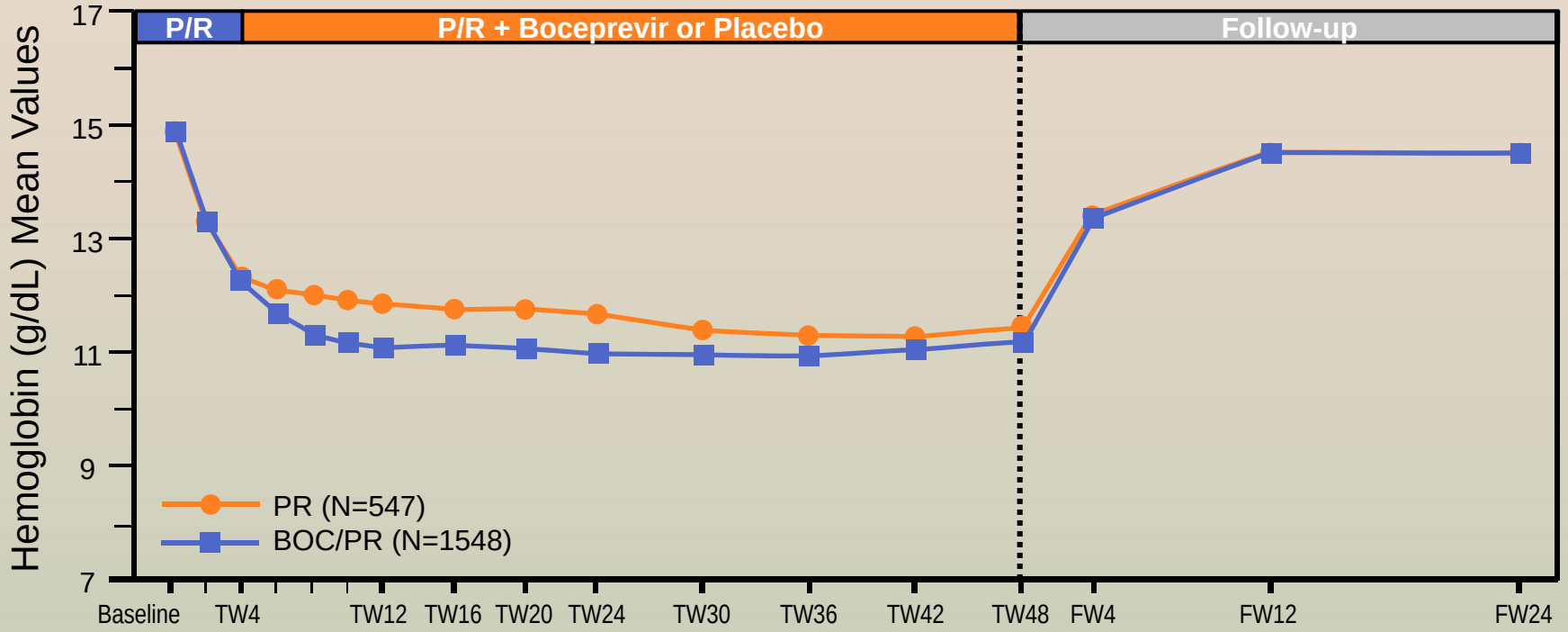
		Previously Untreated (SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
		PR48 N=358	BOC/PR N=728	PR48 N=80	BOC/PR N=322
Anemia		n (%)	n (%)	n (%)	n (%)
Hb <10 g/dl		109 (30)	366 (50)	20 (25)	158 (49)
HB <8.5		15 (4)	53 (7)	1 (1)	31 (10)
By WHO grade					
Hb (g/dL)	WHO Grade	n (%)	n (%)	n (%)	n (%)
≥11	0	161 (45)	171 (23)	44 (55)	82 (25)
9.5 to <11.0	1	130 (36)	313 (43)	26 (33)	139 (43)
8.0 to <9.5	2	61 (17)	222 (30)	9 (11)	83 (26)
6.5 to <8.0	3	6 (2)	19 (3)	1 (1)	17 (5)
<6.5	4	0	3 (<1)	0	1 (<1)

- Anemia (Hb <10 g/dL) occurred more often in the BOC (49-50%) arms than the control arms (25-30%)

Sulkowski M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst.. 476.

Results

Mean Hb Concentration Over Time By Treatment Arm
(includes phase 2 study of previously untreated patients)



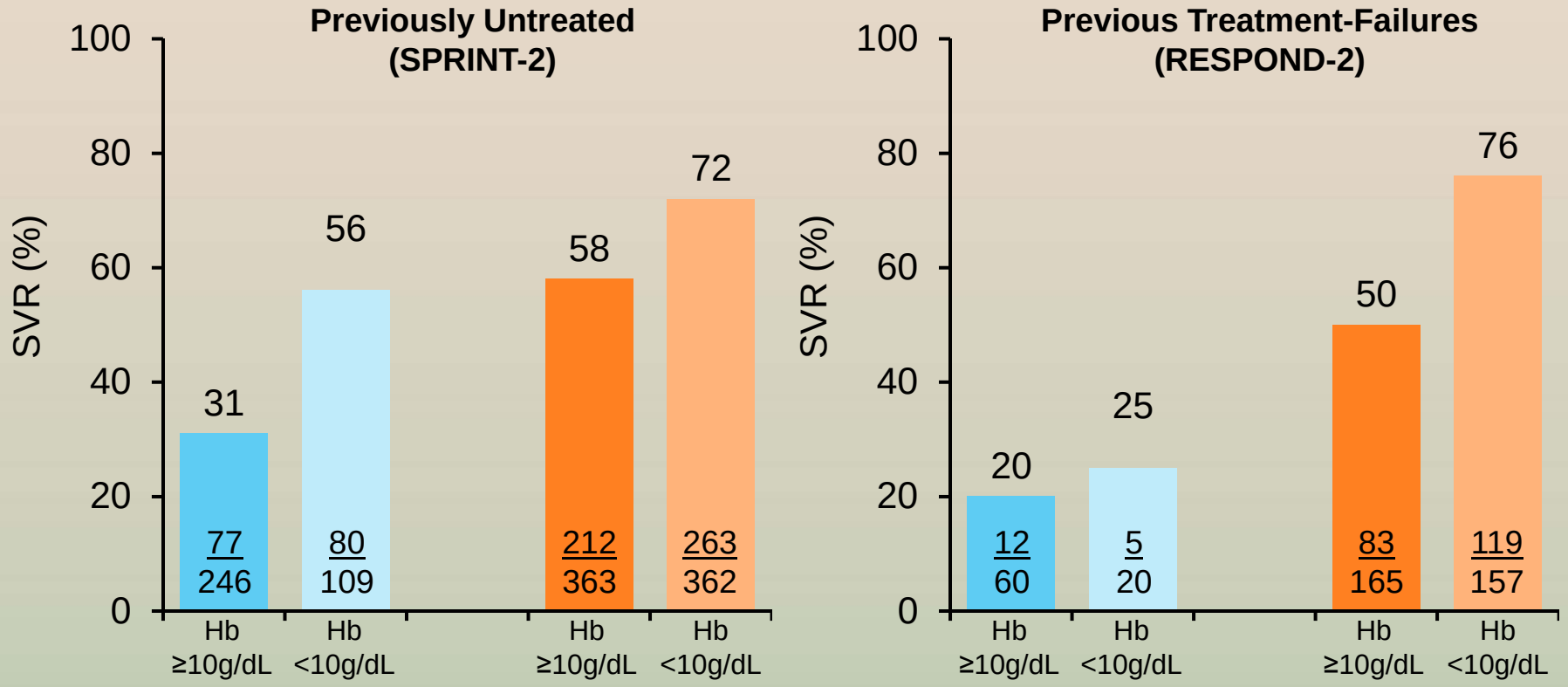
- In both studies, Hb levels returned to baseline post-therapy in the control (PR48) and experimental (BOC/PR) arms
- The pattern of mean Hb concentration over time was similar in the BOC/PR arms and the PR48 control arms

The x-axis numbers are not to scale.

Sulkowski M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 476.

Results

SVR by Absence/Presence of Anemia



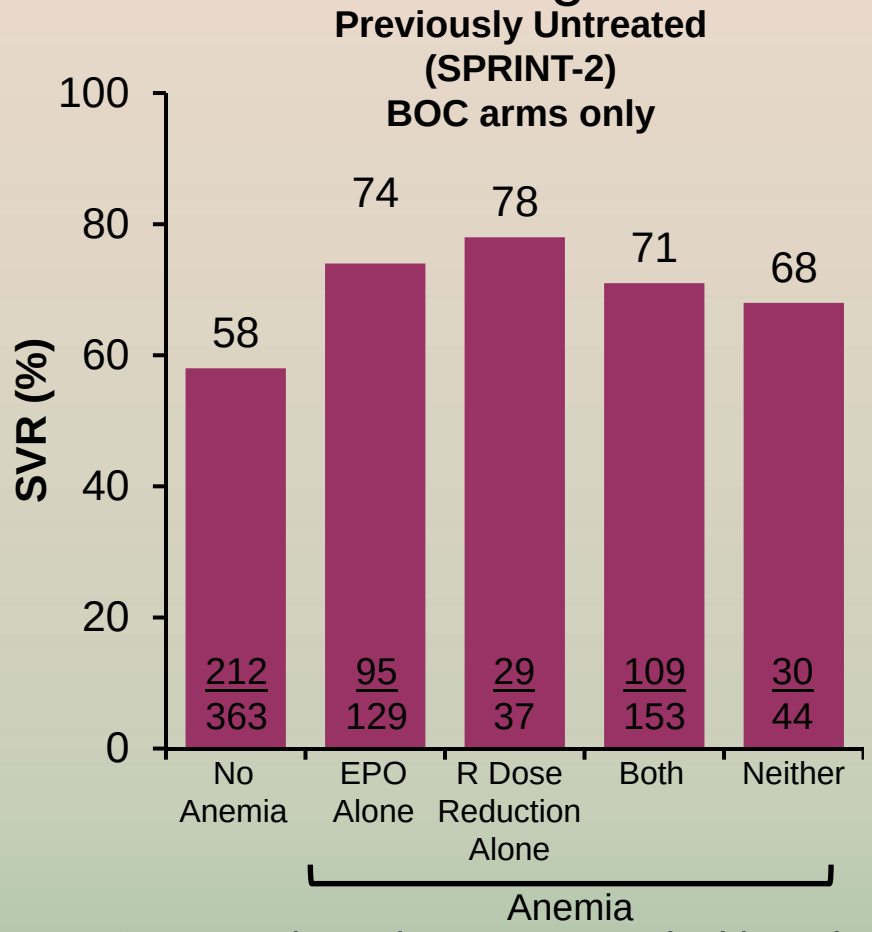
- Anemia on treatment was identified as a significant factor for attaining SVR (*P*<0.001)

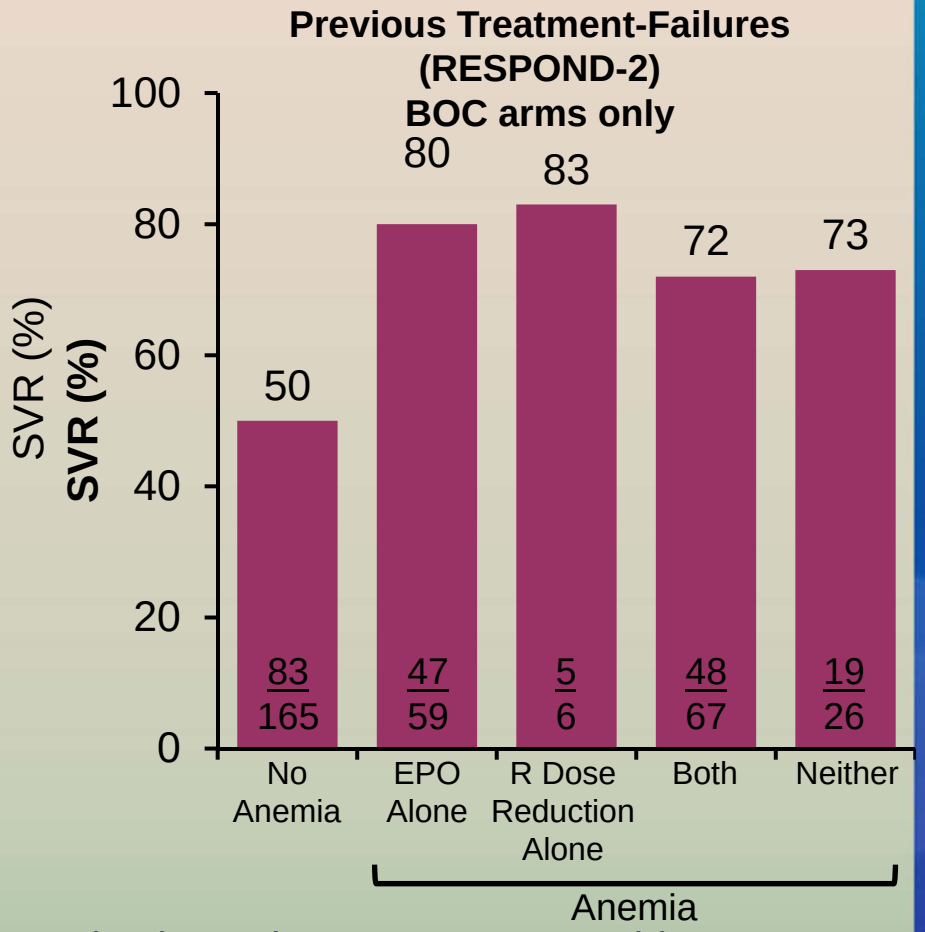
PR48 Control BOC/PR

Sulkowski M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 476.

Results

SVR According to EPO Use and R Dose Reduction





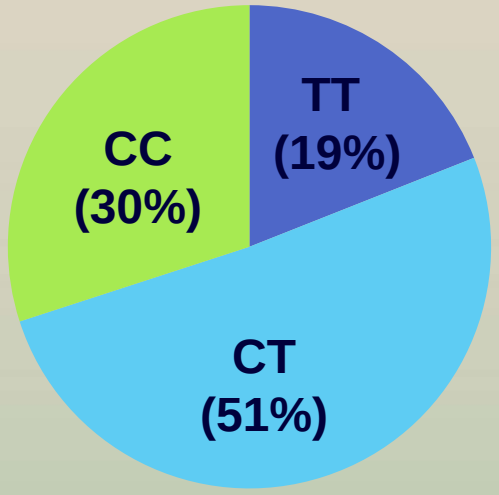
- SVR rate in patients managed with R dose reductions alone were comparable to those in patients managed with EPO, with or without R dose reduction

Sulkowski M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 476.

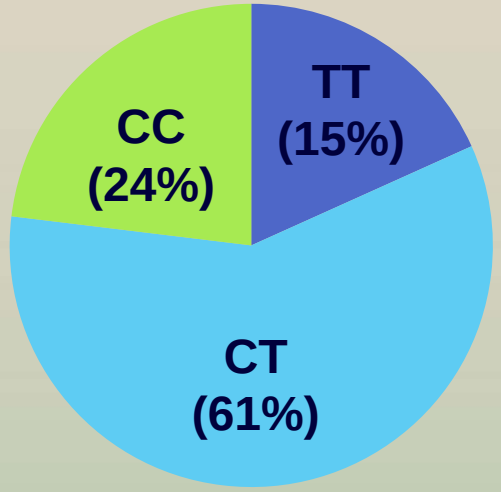
Distribution of IL-28B Polymorphisms

SPRINT-2 and RESPOND-2: Assessment of Effect of IL28B Polymorphism on Virologic Response

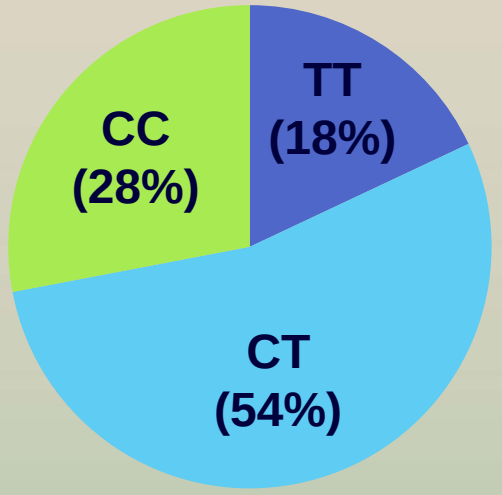
- IL28B polymorphisms assessed with DNA Sanger Sequencing
  - rs12979860/rs12980275/rs8103143
- Patients analyzed were consented prospectively and received at least one dose of BOC or placebo (63%)



SPRINT 2
62% (653/1048)



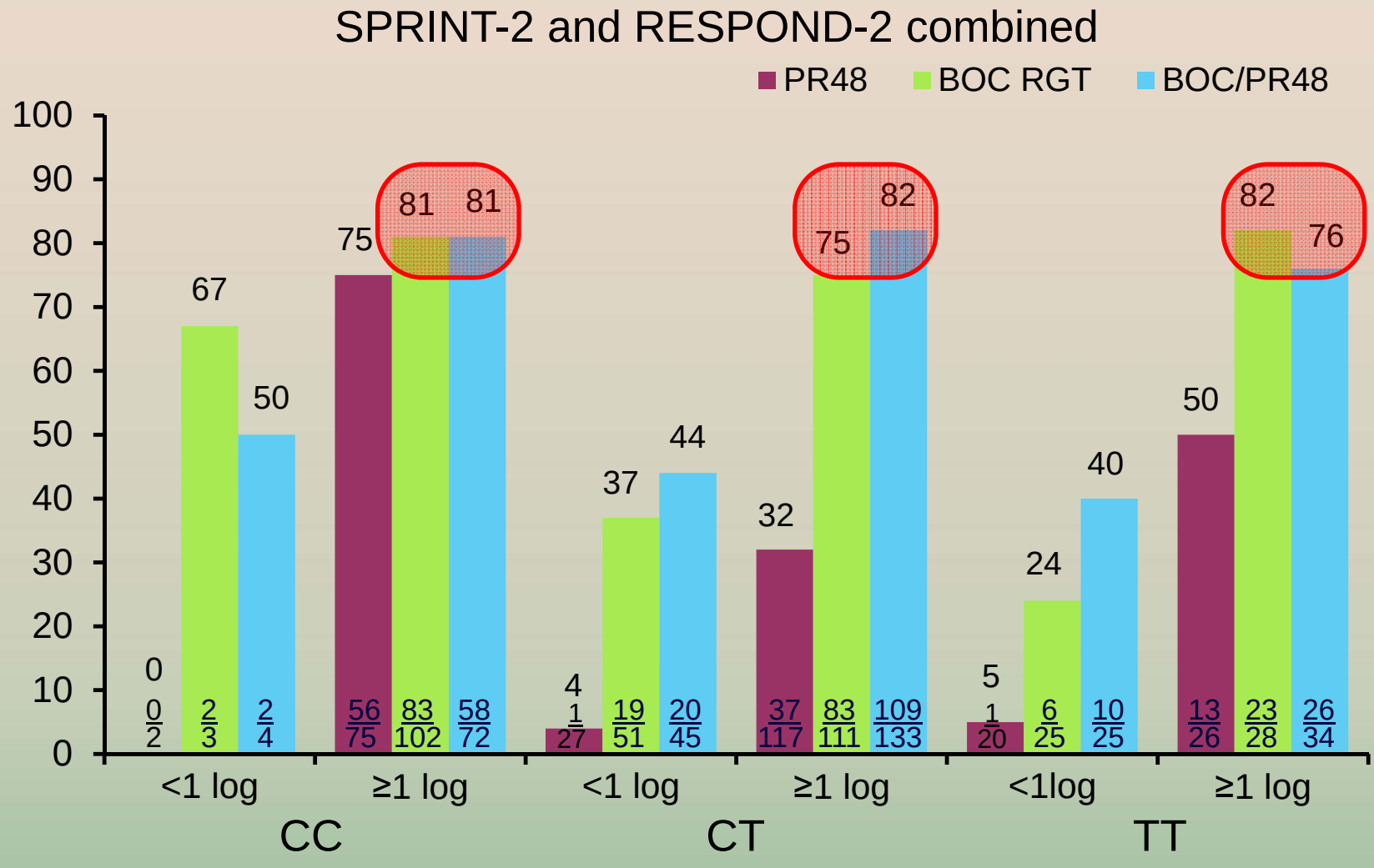
RESPOND 2
66% (259/394)



Total
63% (912/1442)

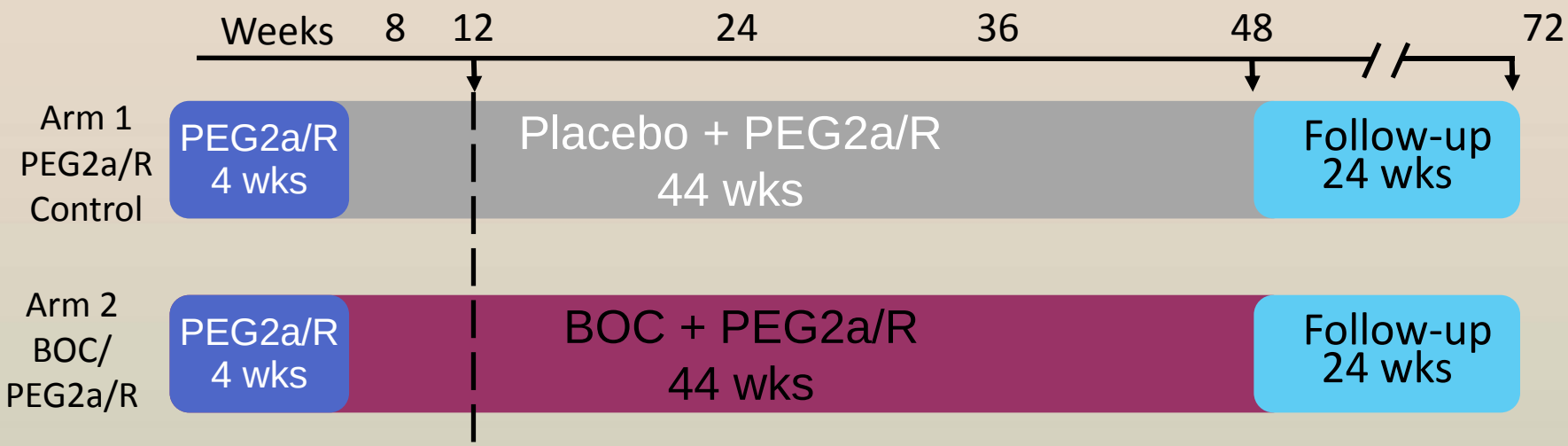
Poordad F, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 12.

Early Interferon Response (Lead-In) Further Defines Likelihood of Success for Non-CC Patients



Poordad F, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 12.

Assessment of Virologic Response in HCV GT 1 Previous Non-responders and Relapsers to BOC + PegIFN/RBV



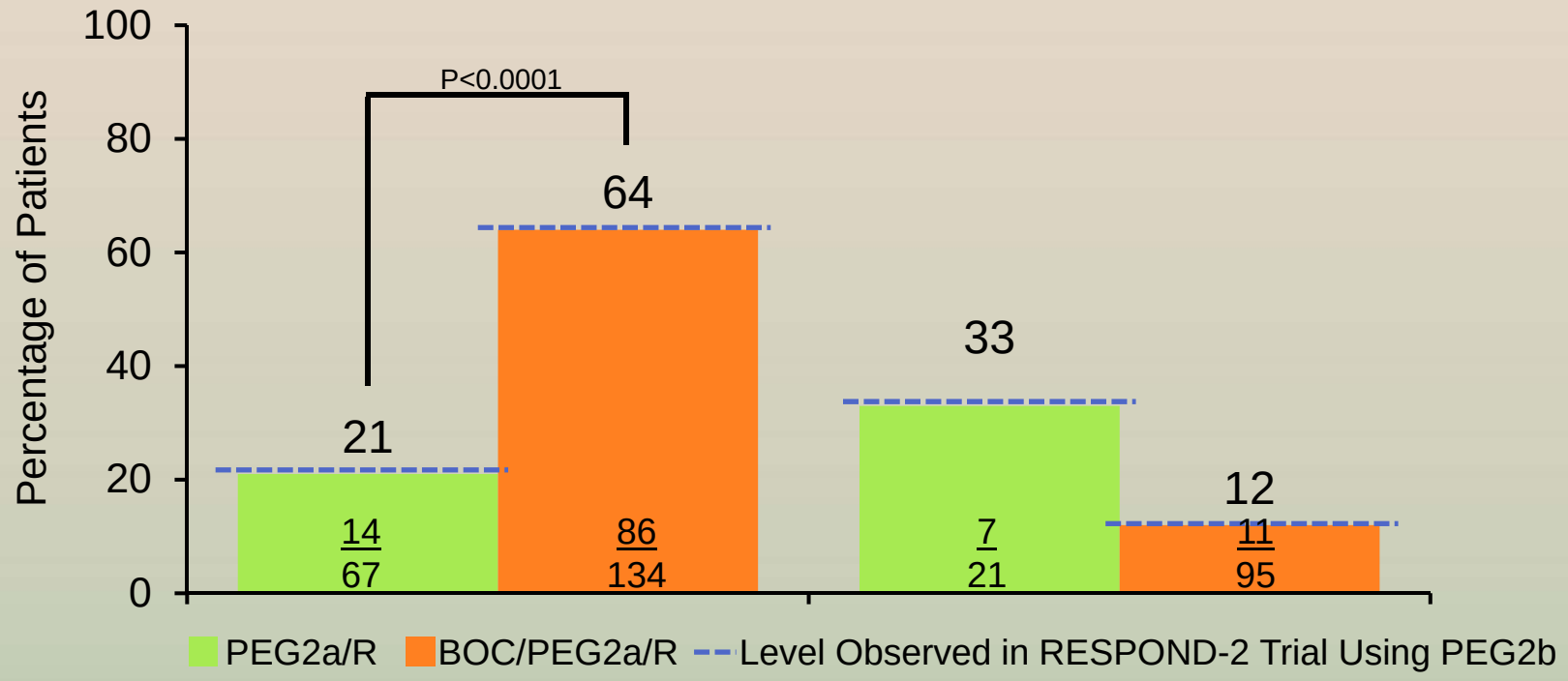
Stopping Rule:

Patients with detectable HCV-RNA at week 12 were discontinued from treatment for futility. Peginterferon alfa-2a (PEG2a) administered subcutaneously at 180 µg once weekly, plus ribavirin (R) using weight-based dosing of 1000-1200 mg/day in a divided daily dose. BOC administered 800 mg TID

Flamm S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1366.

Results

Sustained Virologic Response (SVR) and Relapse Rates for Randomized Patients Who Received at Least One Dose of Any Study Drug

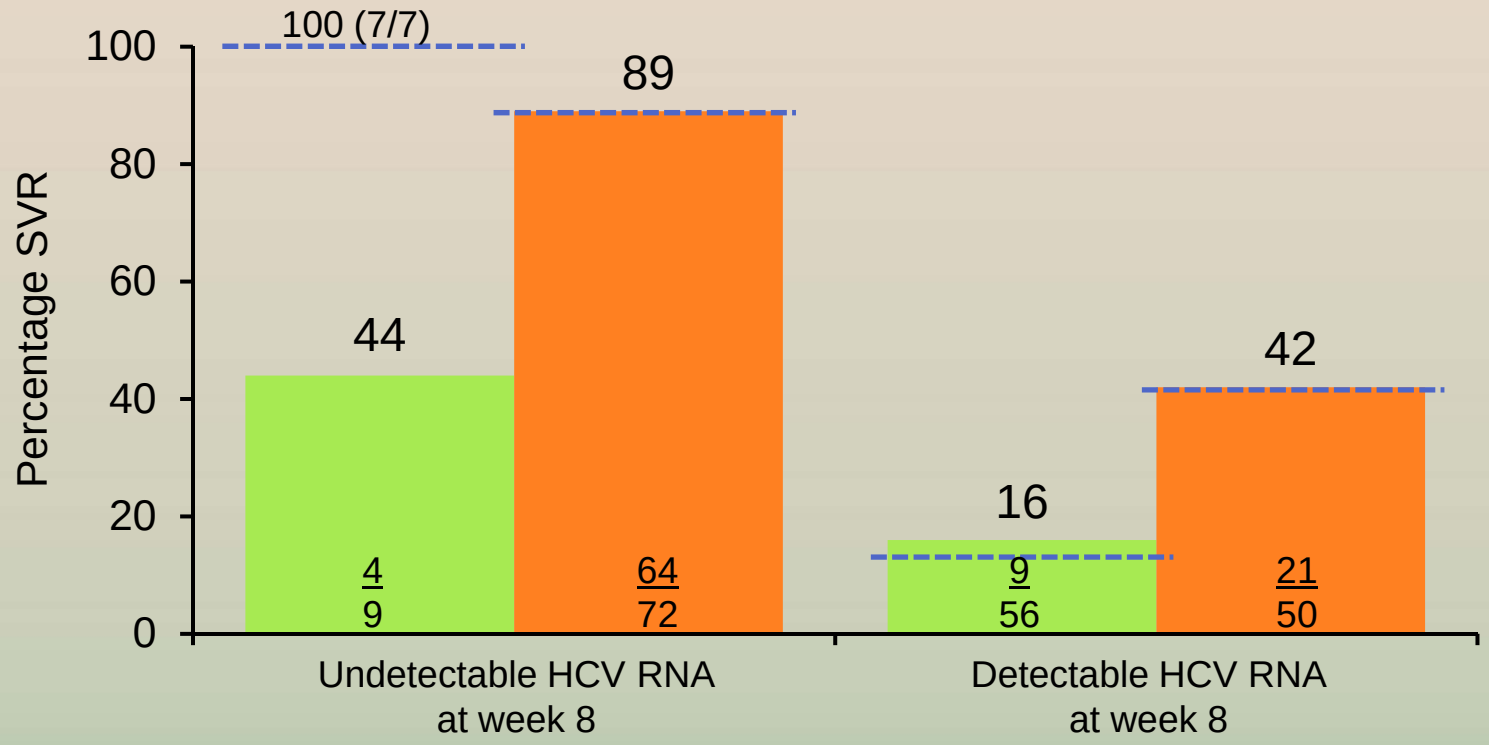


- Significantly more patients achieved SVR in the BOC treatment arm than in the PEG2a/R arm

Flamm S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1366.

Results

Sustained Virologic Response (SVR) by Early Response to Treatment (ie, Undetectable HCV RNA By Treatment Week 8)



- Early response (undetectable HCV RNA at week 8) was associated with high SVR

Flamm S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1366.

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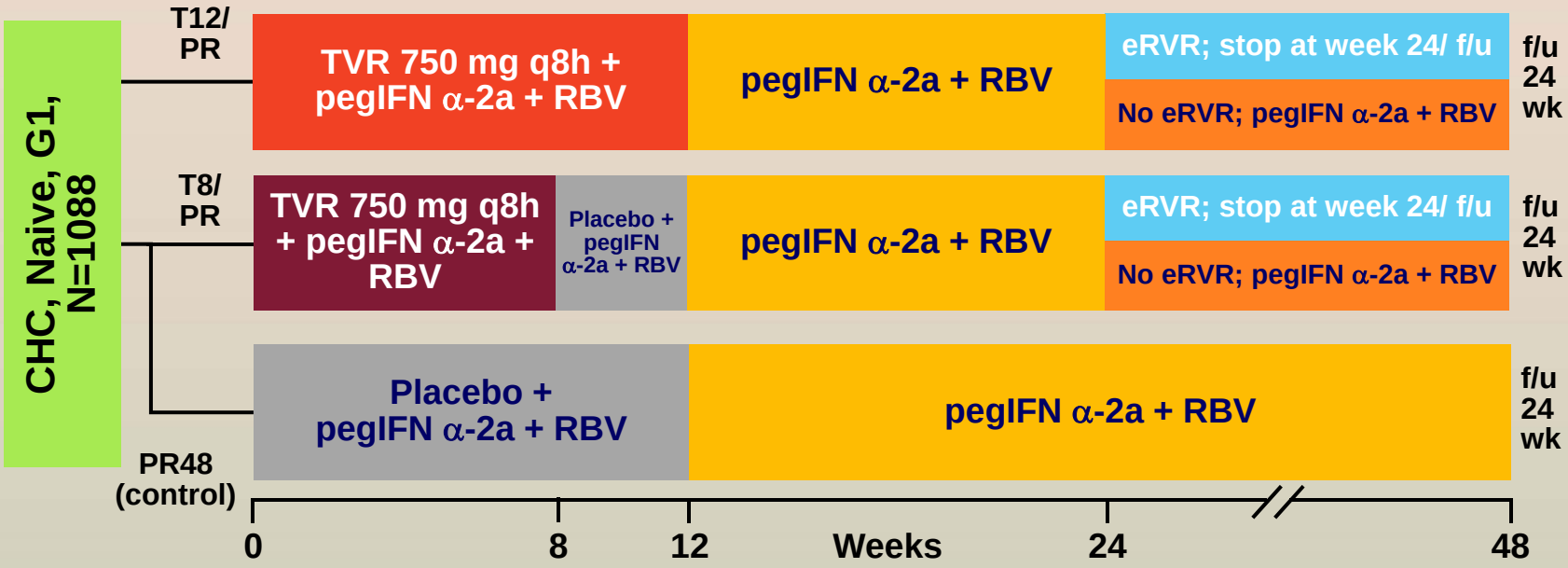
Telaprevir Studies

Mark Sulkowski, MD

Associate Professor of Medicine and Medical Director,
Viral Hepatitis Center,
Johns Hopkins University School of Medicine
Baltimore, Maryland

ADVANCE Study Design: Telaprevir + PegIFN/RBV in G1 Treatment-naïve Patients

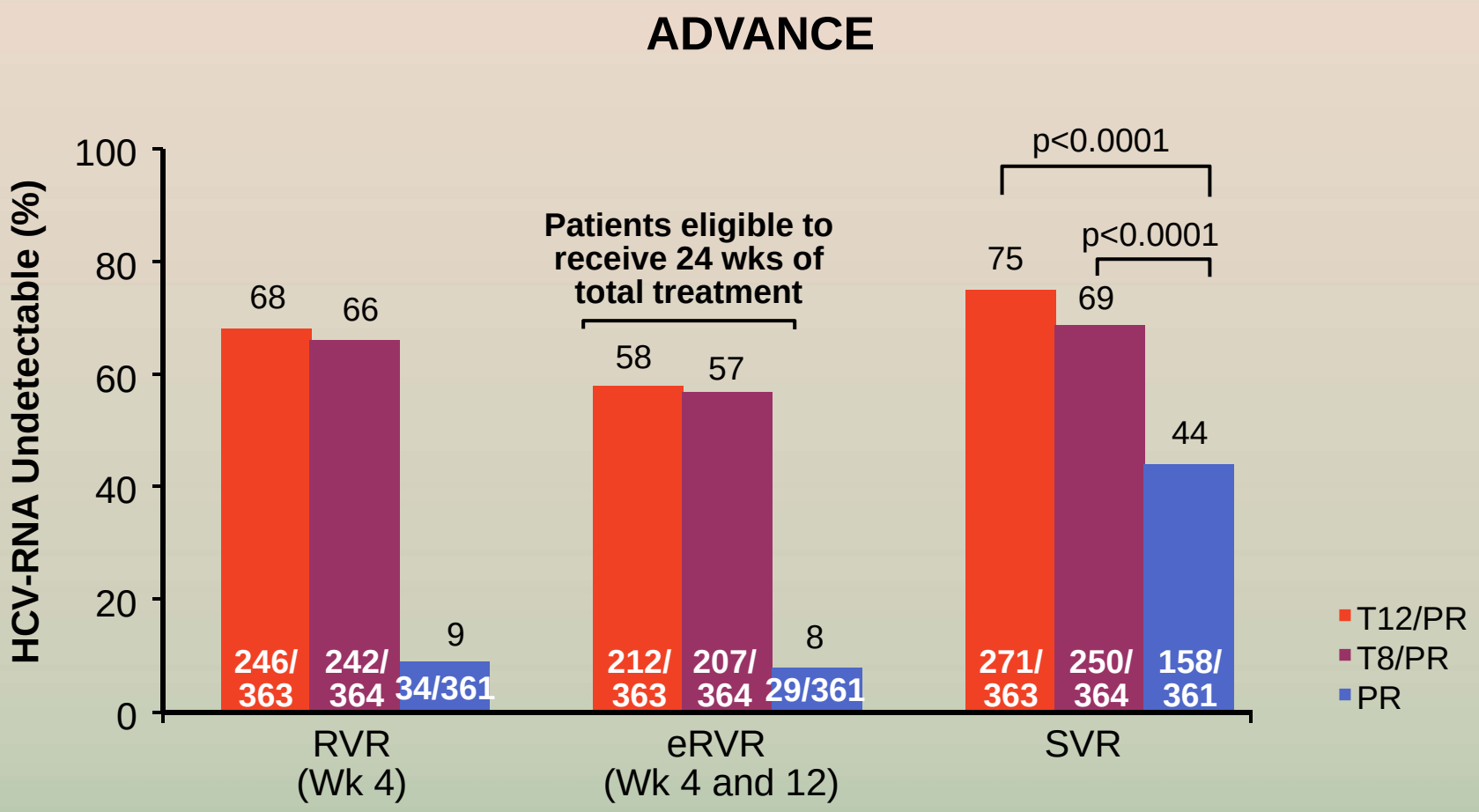


- Treatment duration for telaprevir arms:
  - Patients with eRVR (undetectable HCV-RNA at Week 4 and Week 12): receive 24 weeks of therapy
  - Patients without eRVR continue on PegIFN and RBV for a total of 48 weeks

G=genotype; CHC=chronic hepatitis C; TVR=telaprevir; eRVR=extended rapid virological response; f/u=follow-up

Jacobson IM, et al. Hepatology 2010;52(Suppl 1):Abst. 211.

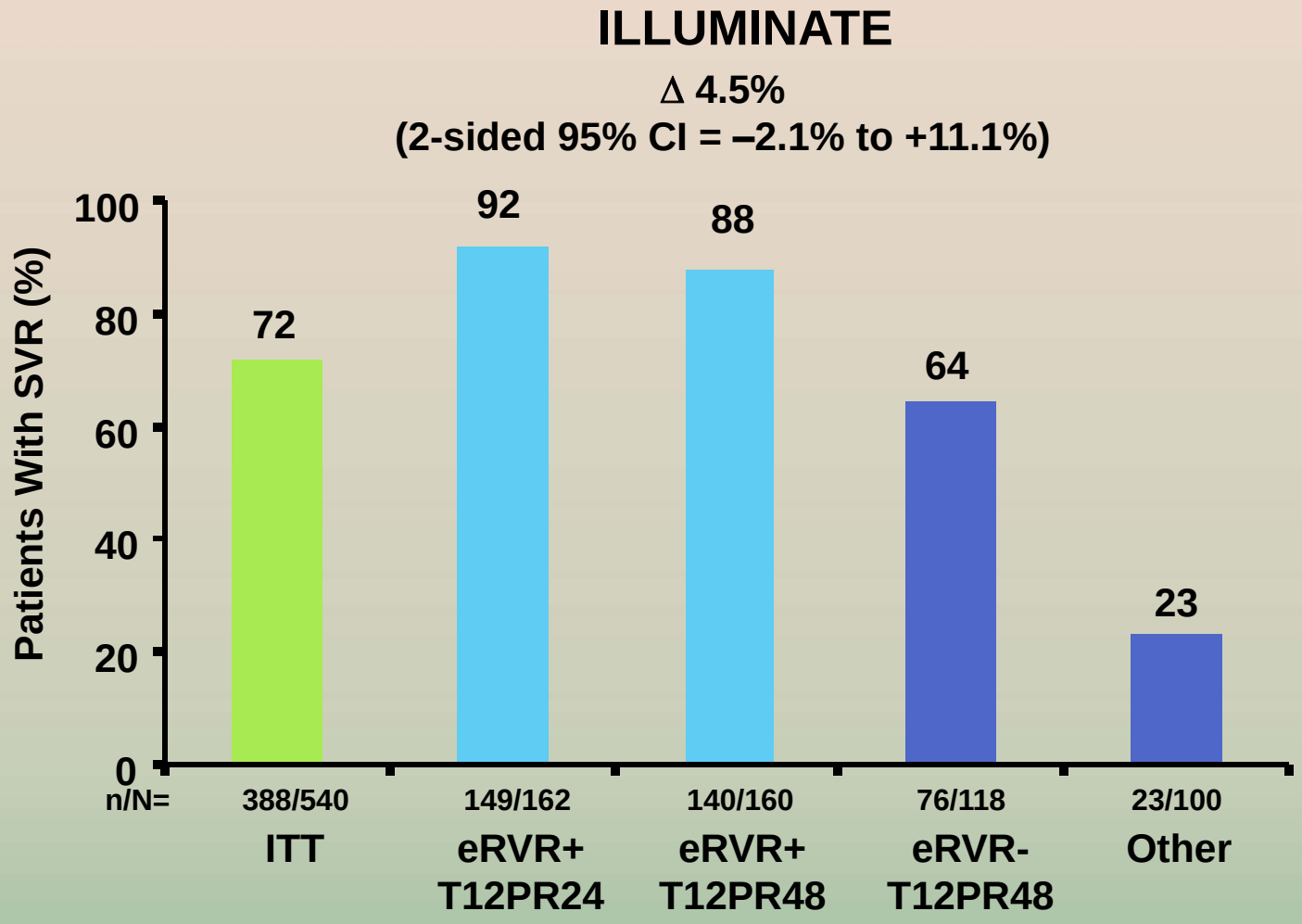
Higher RVR and SVR Rates with Telaprevir + PegIFN/RBV Versus PegIFN/RBV Alone



RVR=rapid virological response

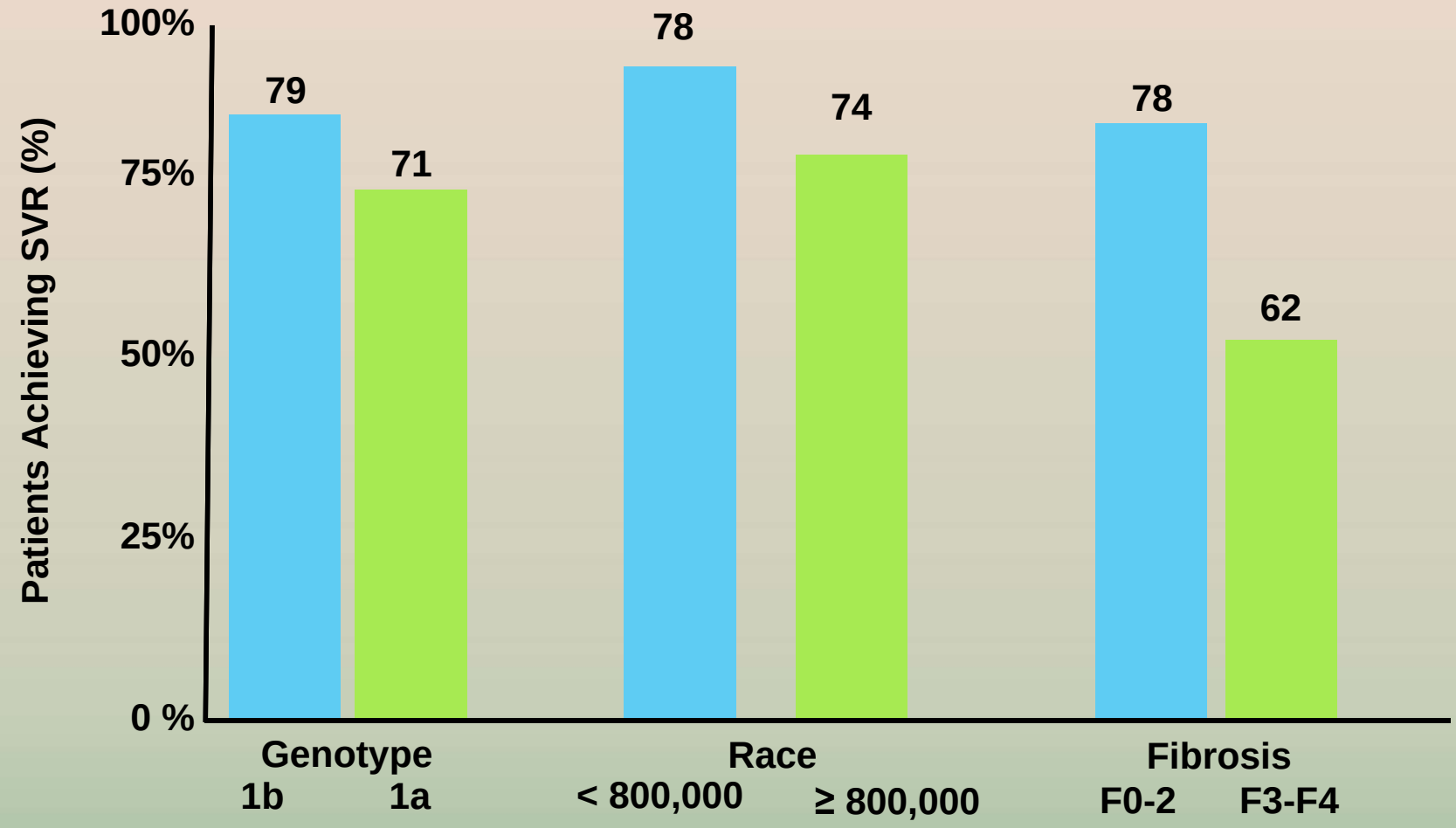
Jacobson IM, et al. Hepatology 2010;52(Suppl 1):Abst. 211.

SVR Rates in All Treatment Groups



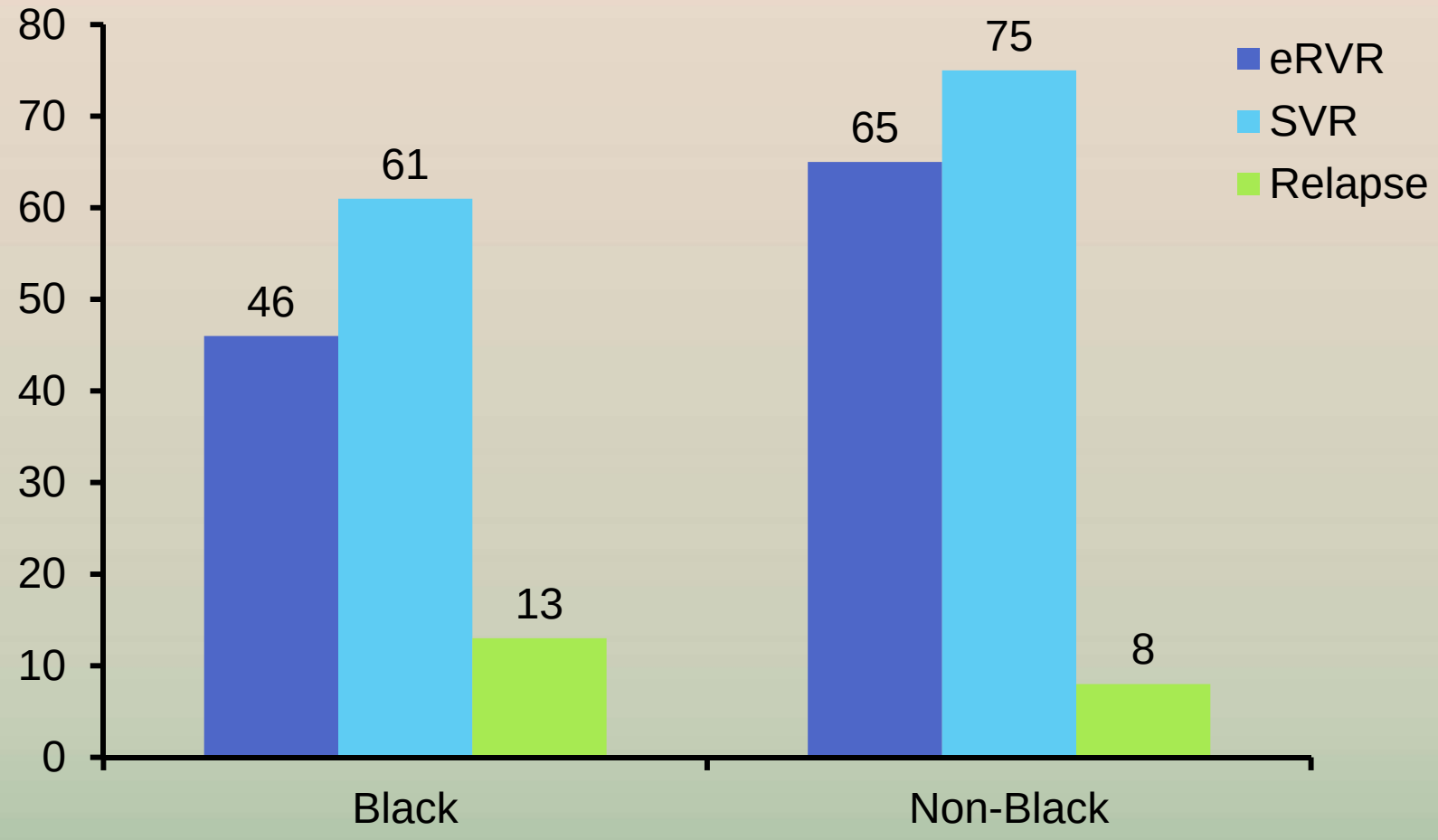
Sherman KE, et al. Hepatology 2010;52(Suppl 1):Abst. LB-2.

ADVANCE: Influence of Patient and Virus Factors on SVR with Telaprevir + PegIFN/RBV



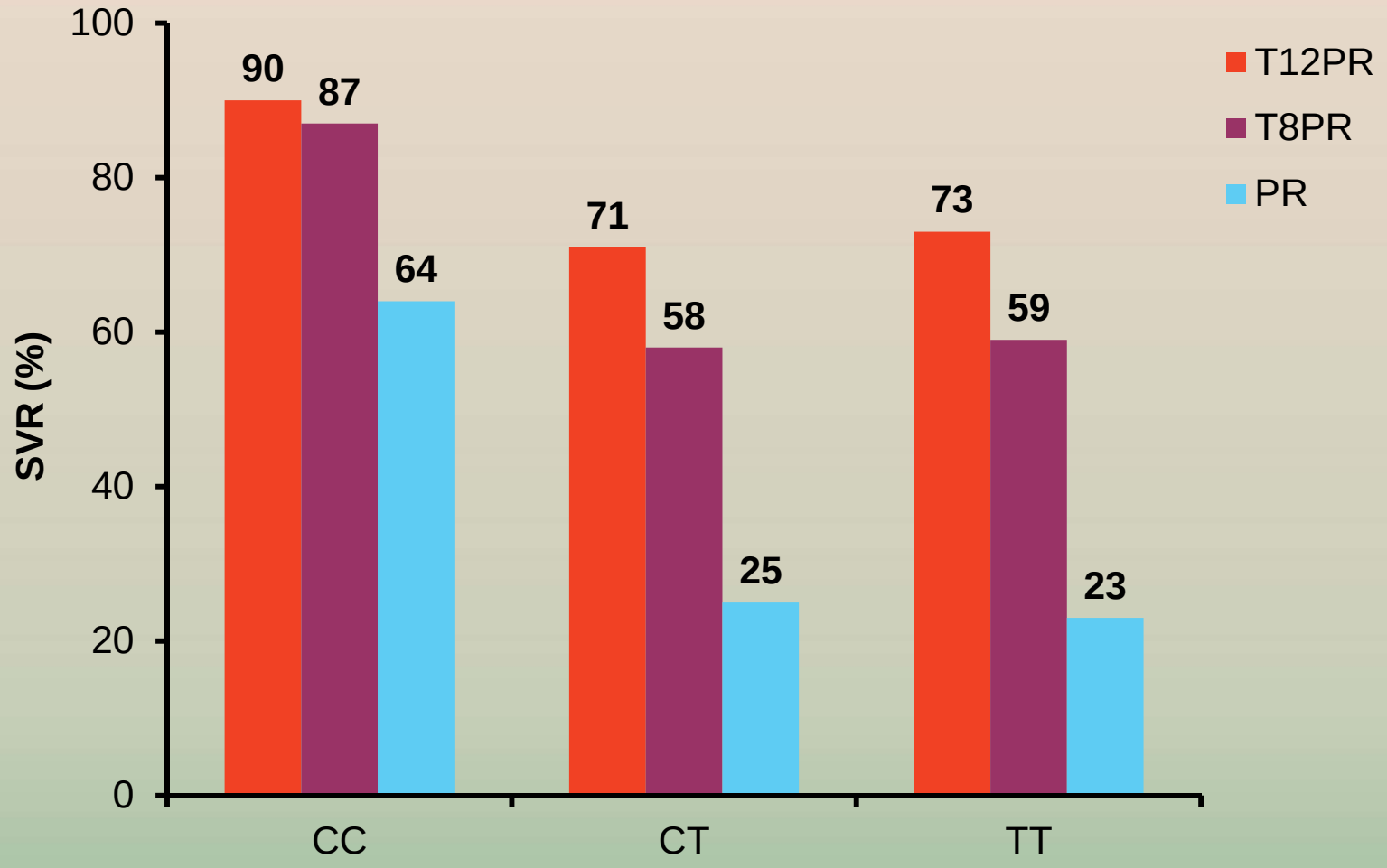
Marcellin P, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 451;
Dusheiko GM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 415.

ADVANCE/ILLUMINATE: Viral Response According to Race/ethnicity



Dusheiko GM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 415.

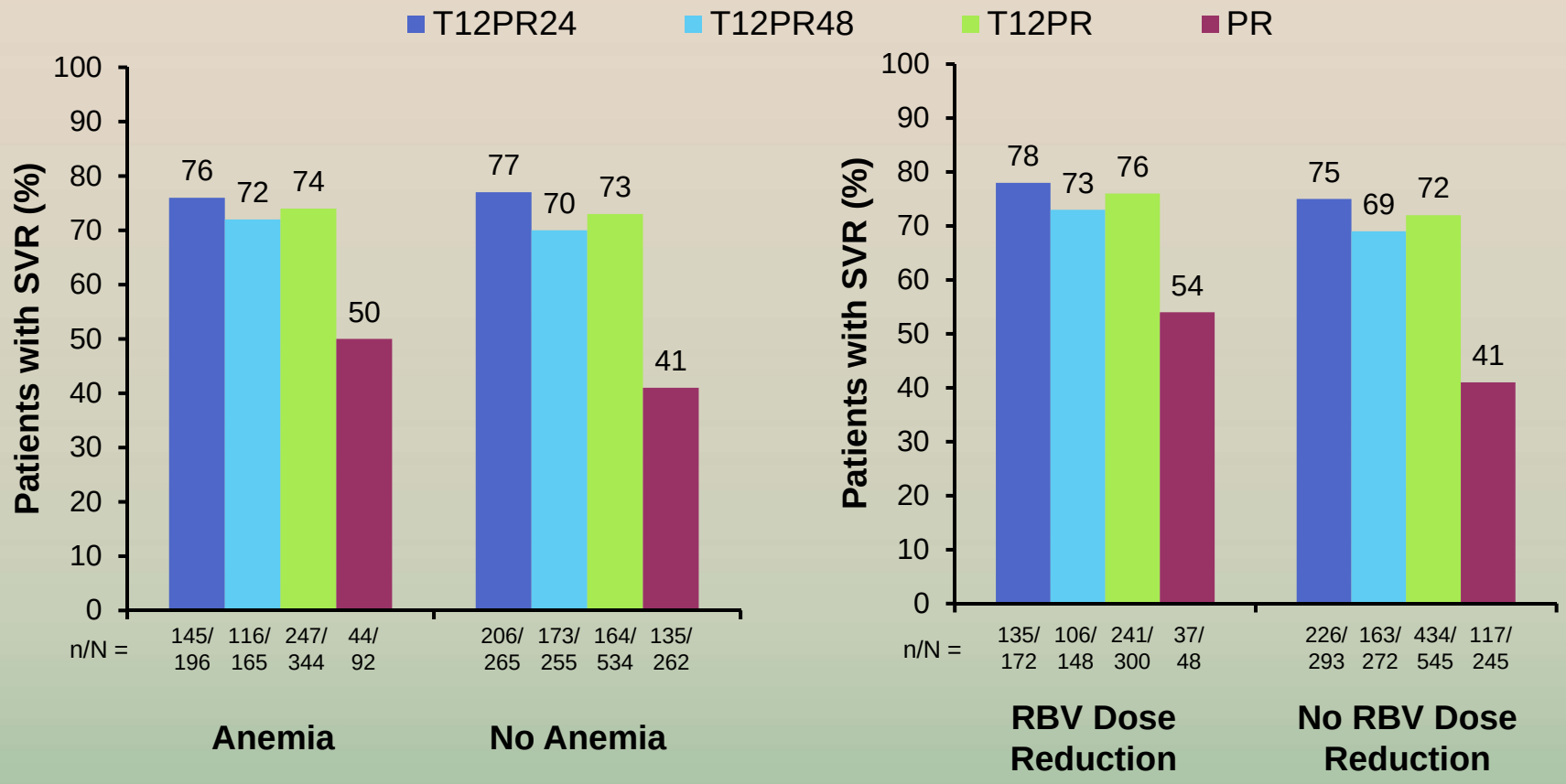
ADVANCE: SVR According to IL28B Genotype – Telaprevir



Jacobson IM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1369.

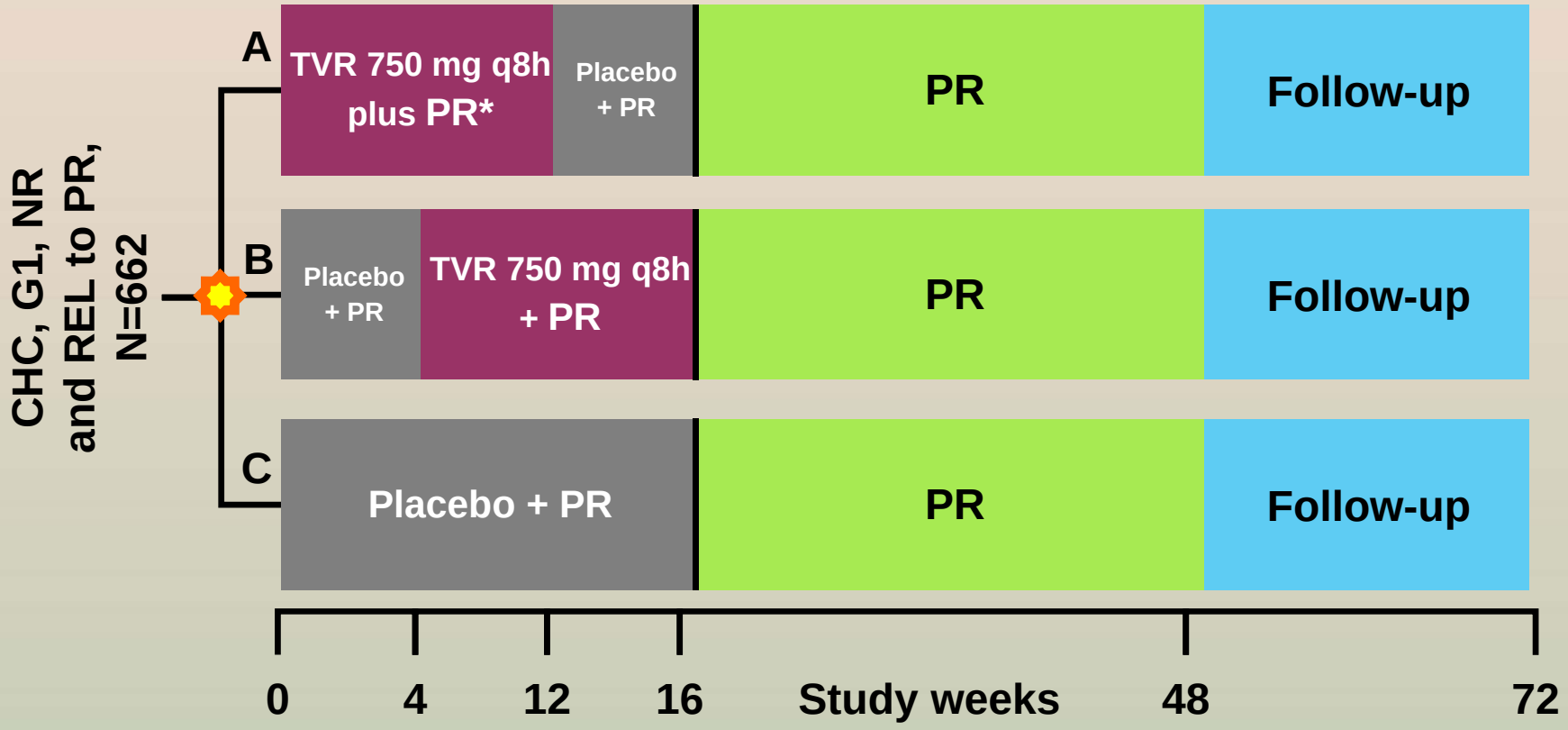
ADVANCE/ILLUMINATE: SVR According to Anemia and RDV Dose Reduction

- Patients who achieved sustained viral response according to anemia and by Ribavirin dose reduction due to an AE



Jacobson IM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 1369.

REALIZE Study: TVR + PR in G1 Non-responders and Relapsers to PR – Phase III



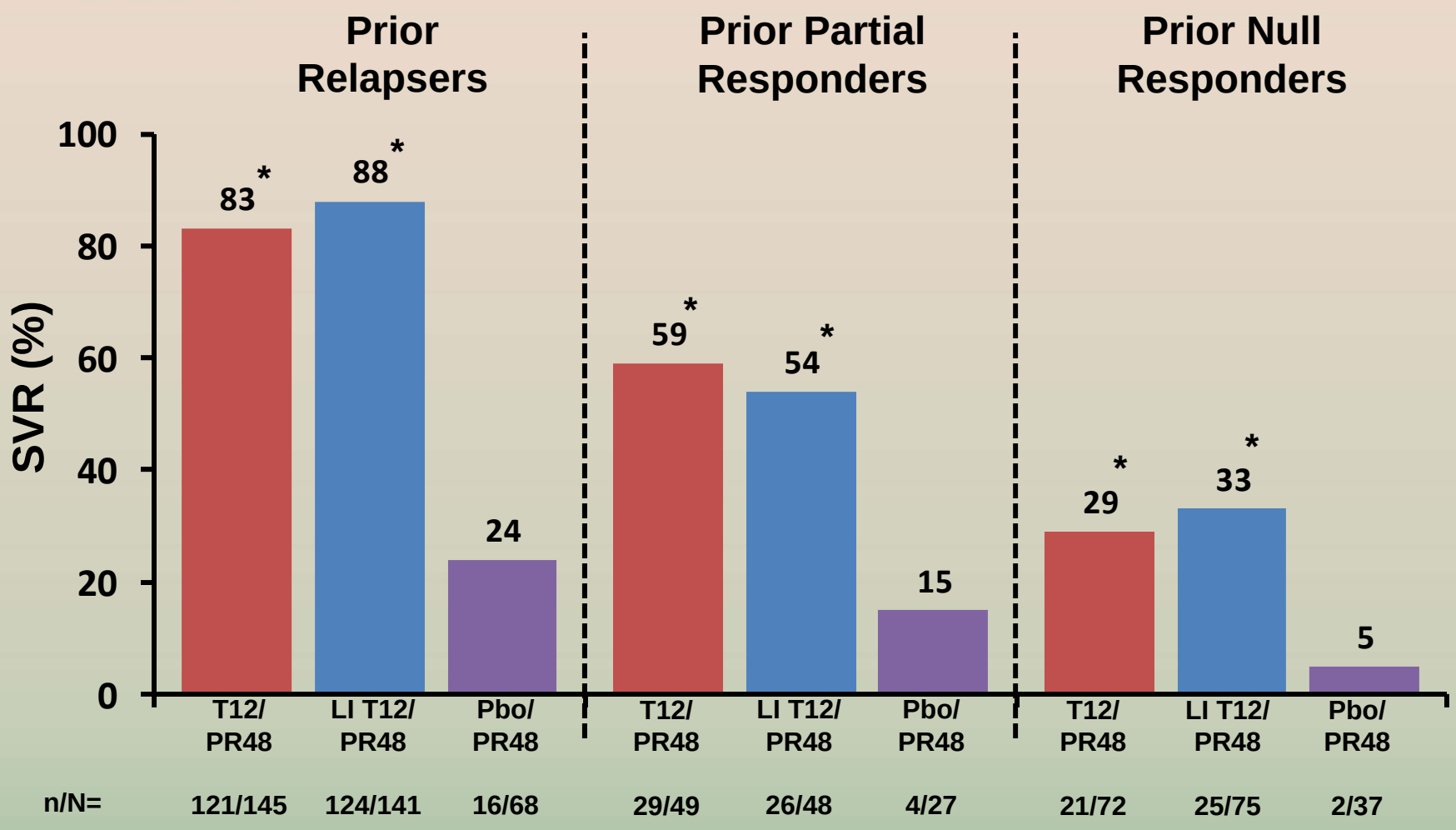
Randomisation (2:2:1, stratified by viral load and type of prior response)

CHC = chronic hepatitis C; G1 = genotype 1; NR = Null responders (<2 log10 drop at week 12 of prior therapy); PR = partial responders (≥2 log10 drop at week 12 but never HCV RNA negative by week 24); REL = relapsers

* Peg-IFN alfa-2a 180 µg, RBV 1000/1200 mg/d

Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.

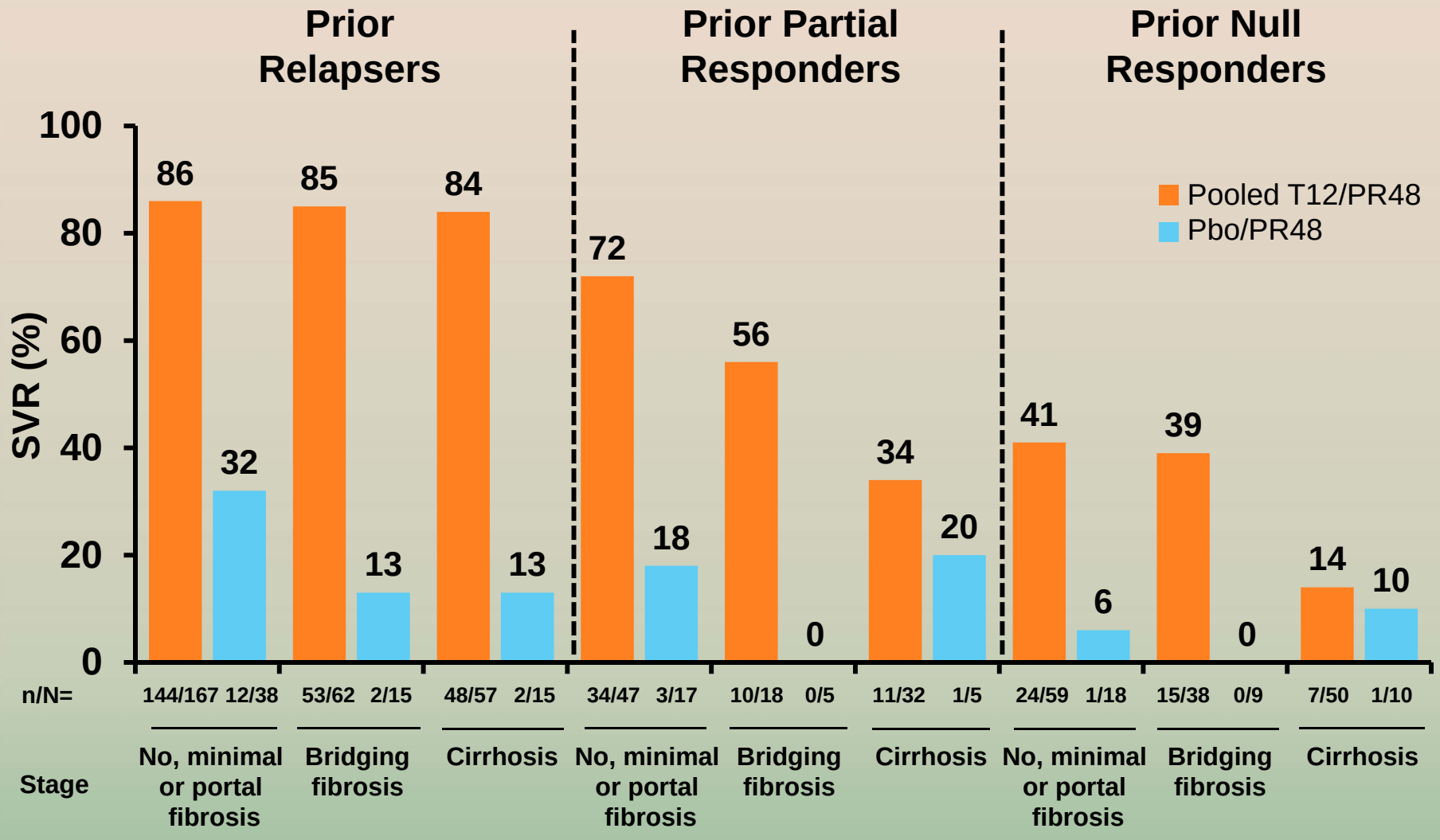
REALIZE: SVR in Prior Relapsers, Prior Partial Responders and Prior Null Responders



*P<0.001 vs. Pbo/PR48

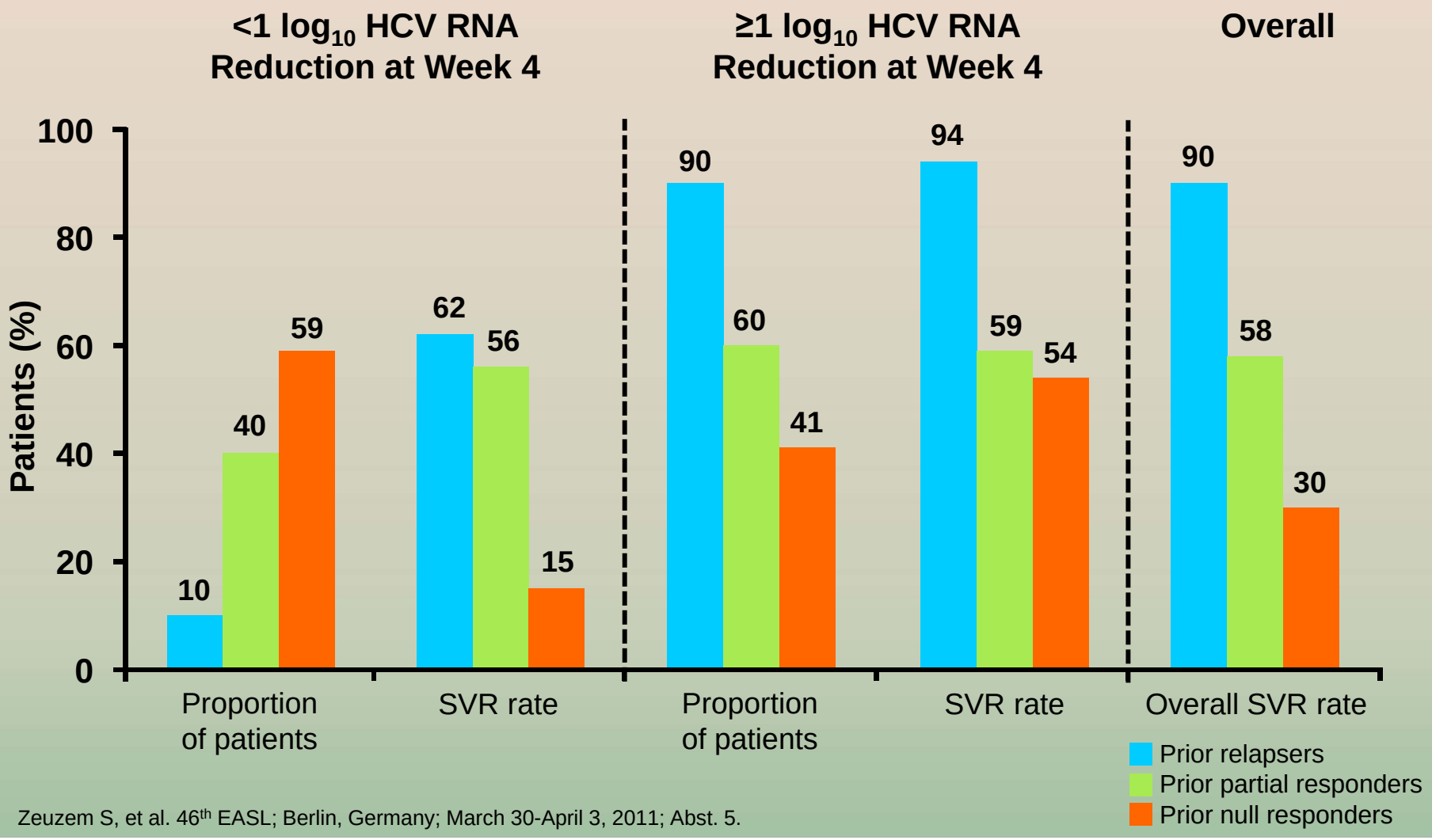
Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.

REALIZE: SVR by Baseline Fibrosis Stage and Prior Response



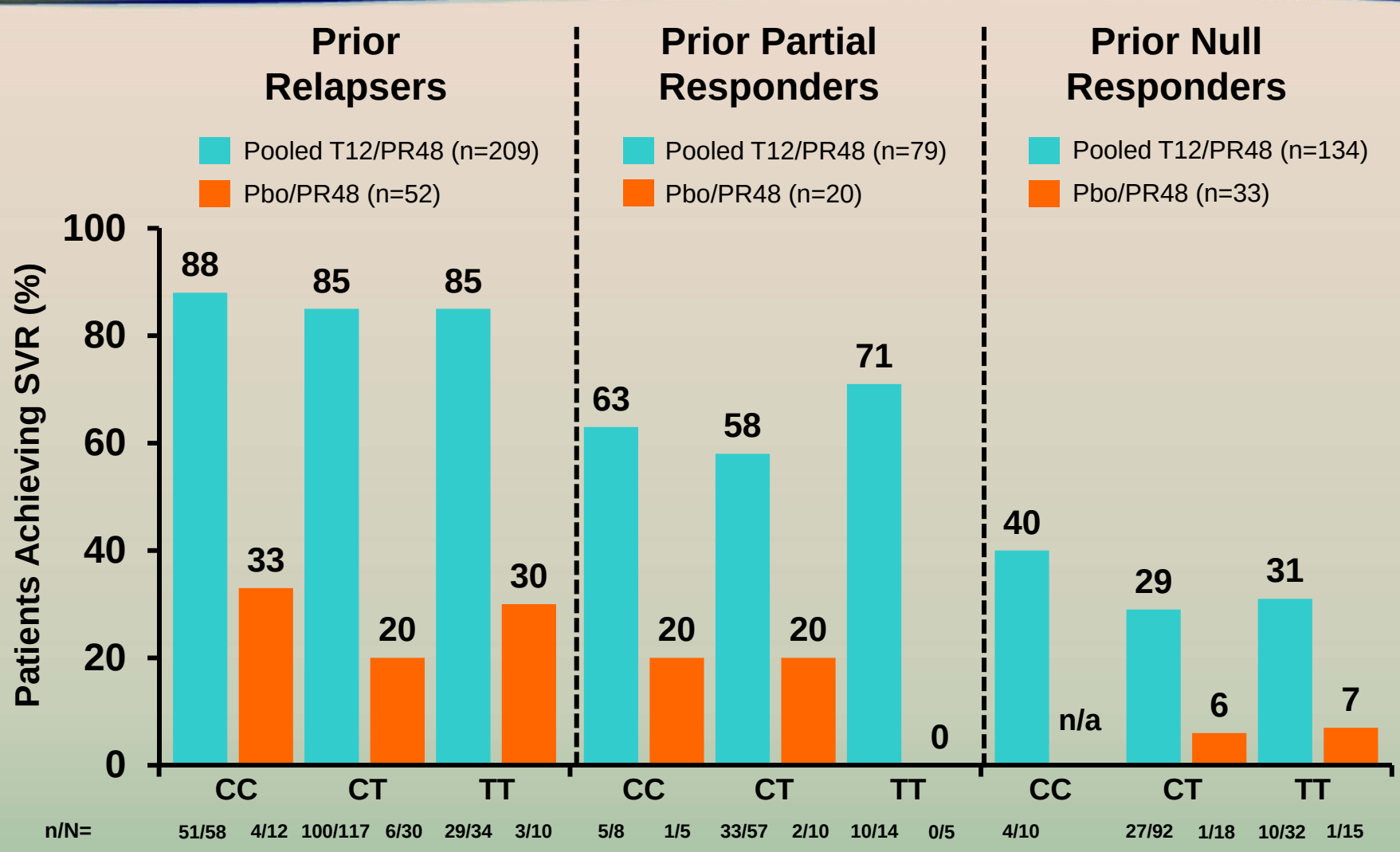
Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.

REALIZE: SVR by Prior Response Category and Week 4 Response to PegIFN/RBV Lead-in



Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.

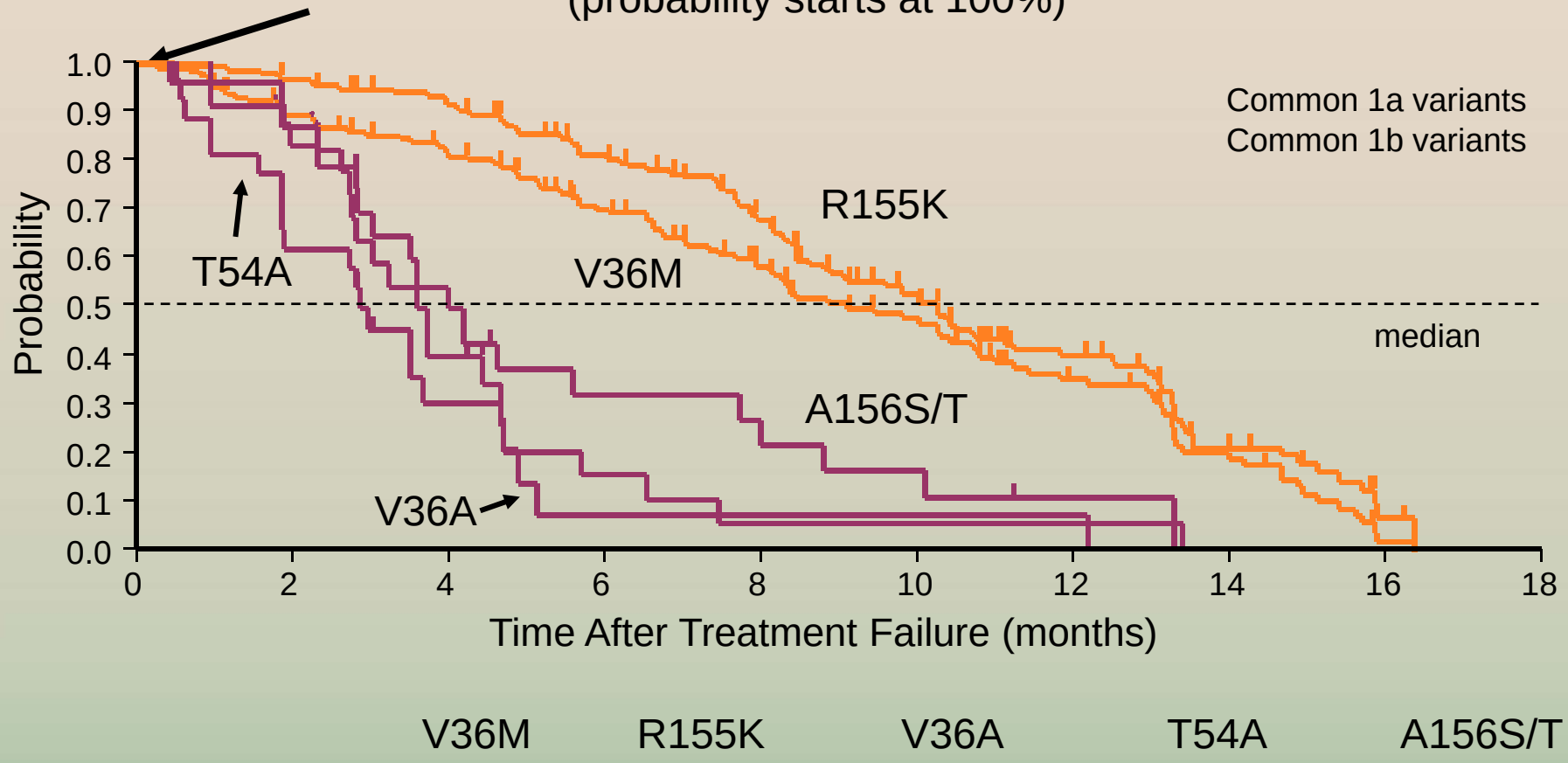
SVR Rates by IL28B Genotype and Prior Response



Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.

Loss of Resistance by NS3 Position

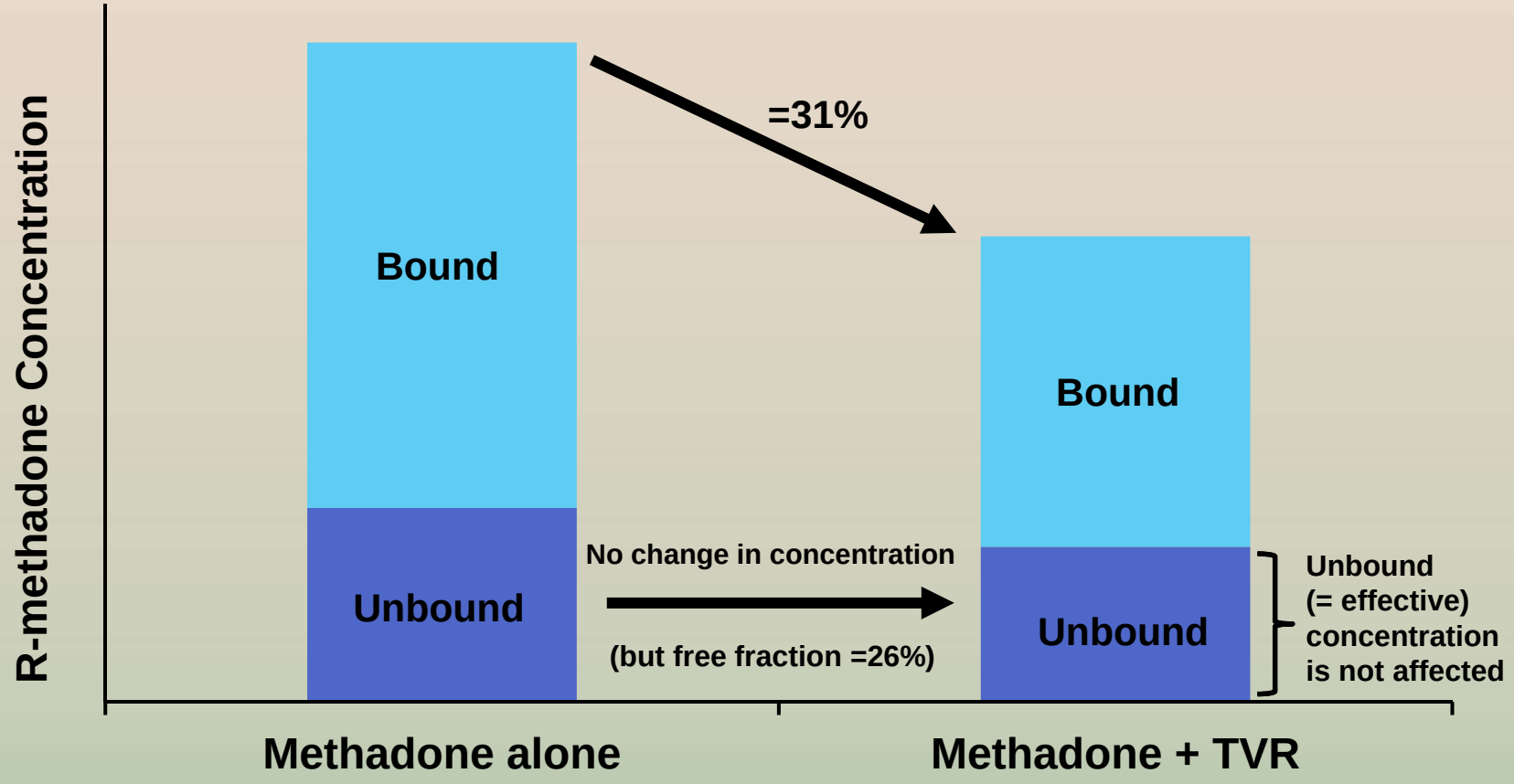
Analysis includes only patients with follow-up data and resistant variant(s)
(probability starts at 100%)



Hash marks indicate censored observations

Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.

Absolute Unbound Concentration of R-methadone Was Not Affected by TVR Co-administration



Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 5.

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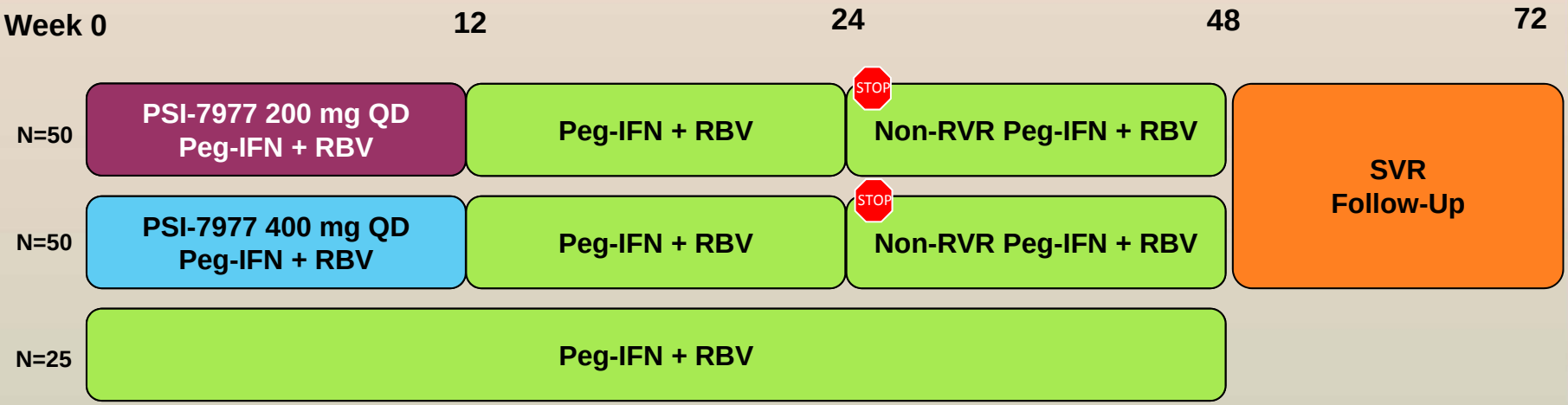
Novel Therapies and Strategies

Nezam H. Afdhal, MD

Associate Professor of Medicine,
Harvard School of Medicine
Chief of Hepatology, Director of Liver Center,
Beth Israel Deaconess Medical Center
Boston, Massachusetts

PROTON: PSI-7977 + PegIFN/RBV (Phase IIb)

HCV GT1[1]



HCV GT2/GT3[2]

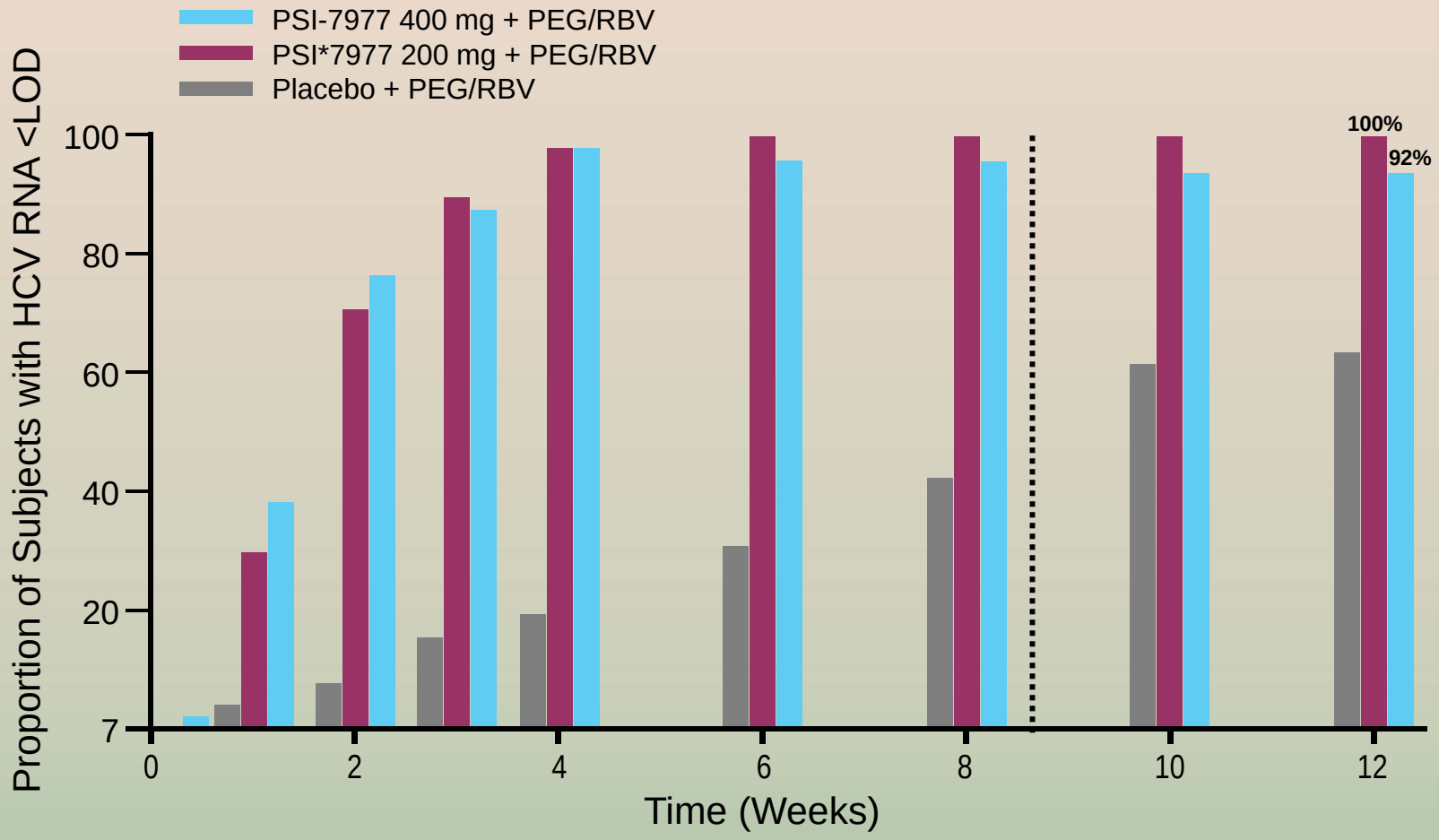
1. Nelson , et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1372.
2. Lalezari J, et al. ibid; Abst. 61.

PROTON: HCV GT 2/GT 3 Results

	Week 2	Week 4 RVR	Week 12 cEVR/EOT	SVR12
n (evaluable)	24	24	24	24
HCV RNA <LOD	21	24	24	24
% Response	88%	100%	100%	100%
Lost to follow-up	1	1	1	1
% Response (ITT)	84%	96%	96%	96%

Lalezari J, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 61.

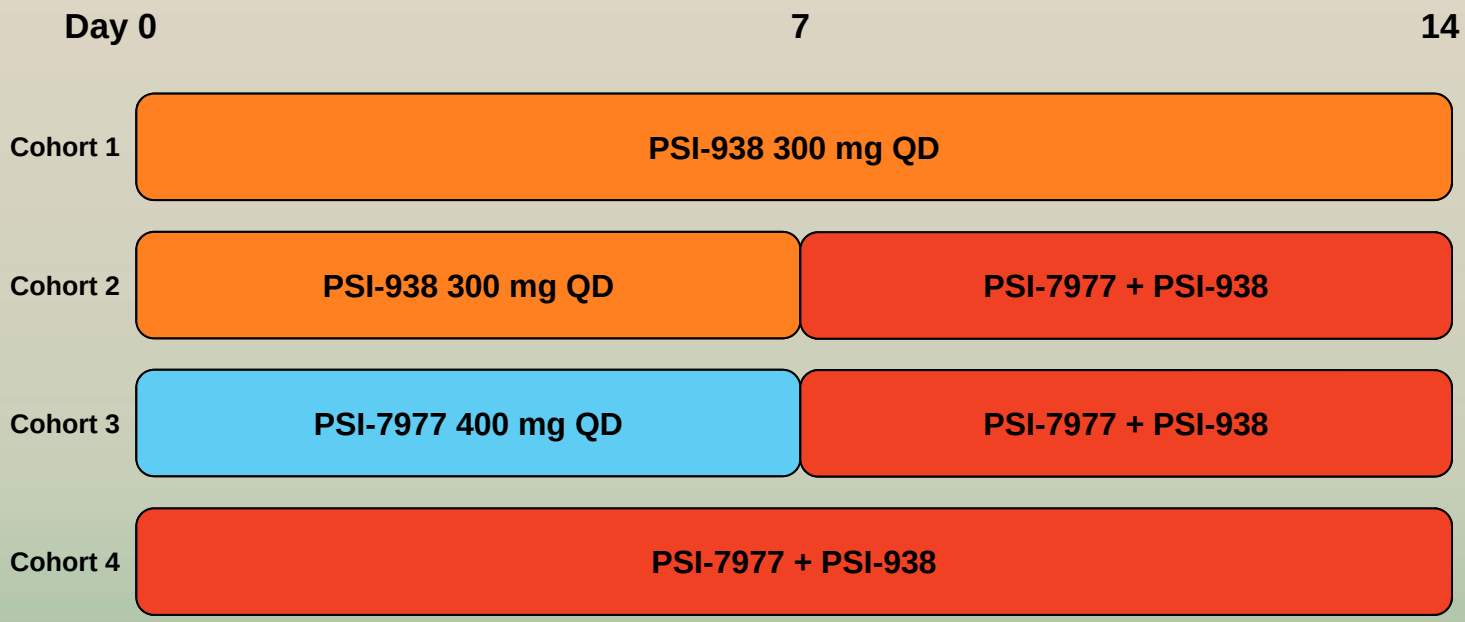
PROTON: HCV GT 1 Results



Nelson DR, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1372.

Nuclear: PSI-7977 and PSI-938

- 40 HCV GT 1, treatment-naïve subjects
  - 8 active and 2 placebo per cohort
- HCV RNA >50,000 IU/mL, no evidence of cirrhosis



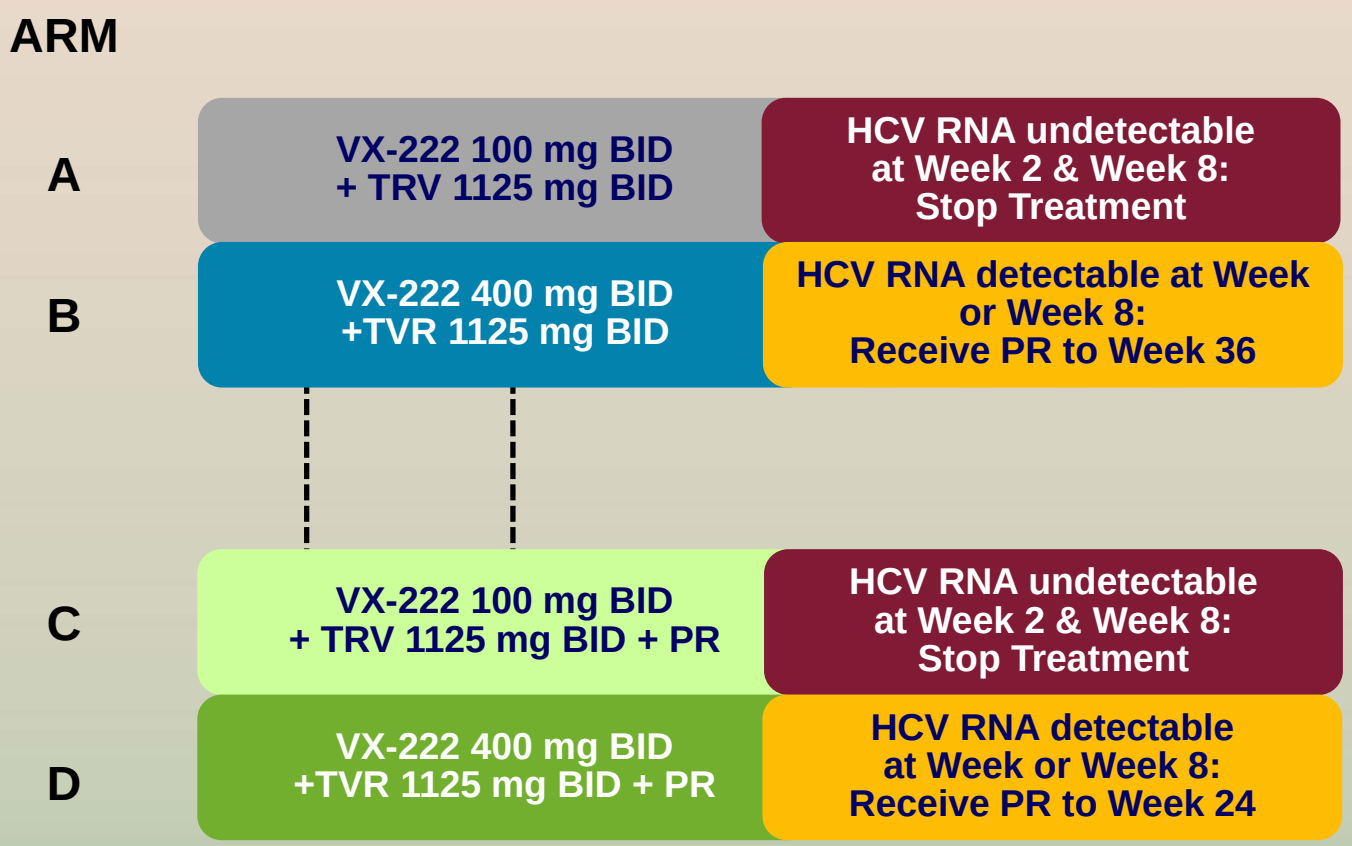
Lawitz E, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1370.

Nuclear: Antiviral Activity

Median (Q1,Q3) HCV RNA Change from Baseline and Number of Subjects with HCV RNA <15 IU/mL (LOD) by Cohort			
	Median HCV RNA Change (log_{10} IU/mL) [Q1,Q3]		
Arm	Day 7	Day 14	Total < 15 IU/mL
PSI-938	-4.5 (-4.3,-4.7)	-5.2 (-4.8,-5.8)	4/8 (50%)
PSI-938/PSI-7977 + PSI-938	-4.6 (-4.2,-5.0)	-5.2 (-4.8,-5.5)	8/8 (100%)
PSI-7977/PSI-938 + PSI-7977	-4.7 (-4.3,-4.8)	-5.0 (-4.6,-5.4)	7/8 (88%)
PSI-7977 + PSI-938	-4.4 (-4.2,-4.8)	-5.0 (-4.7,-5.3)	7/8 (88%)

Lawitz E, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1370.

ZENITH: VX-222 + TVR ± PR or RBV



Di Besceglie AM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1363.

ZENITH: Results

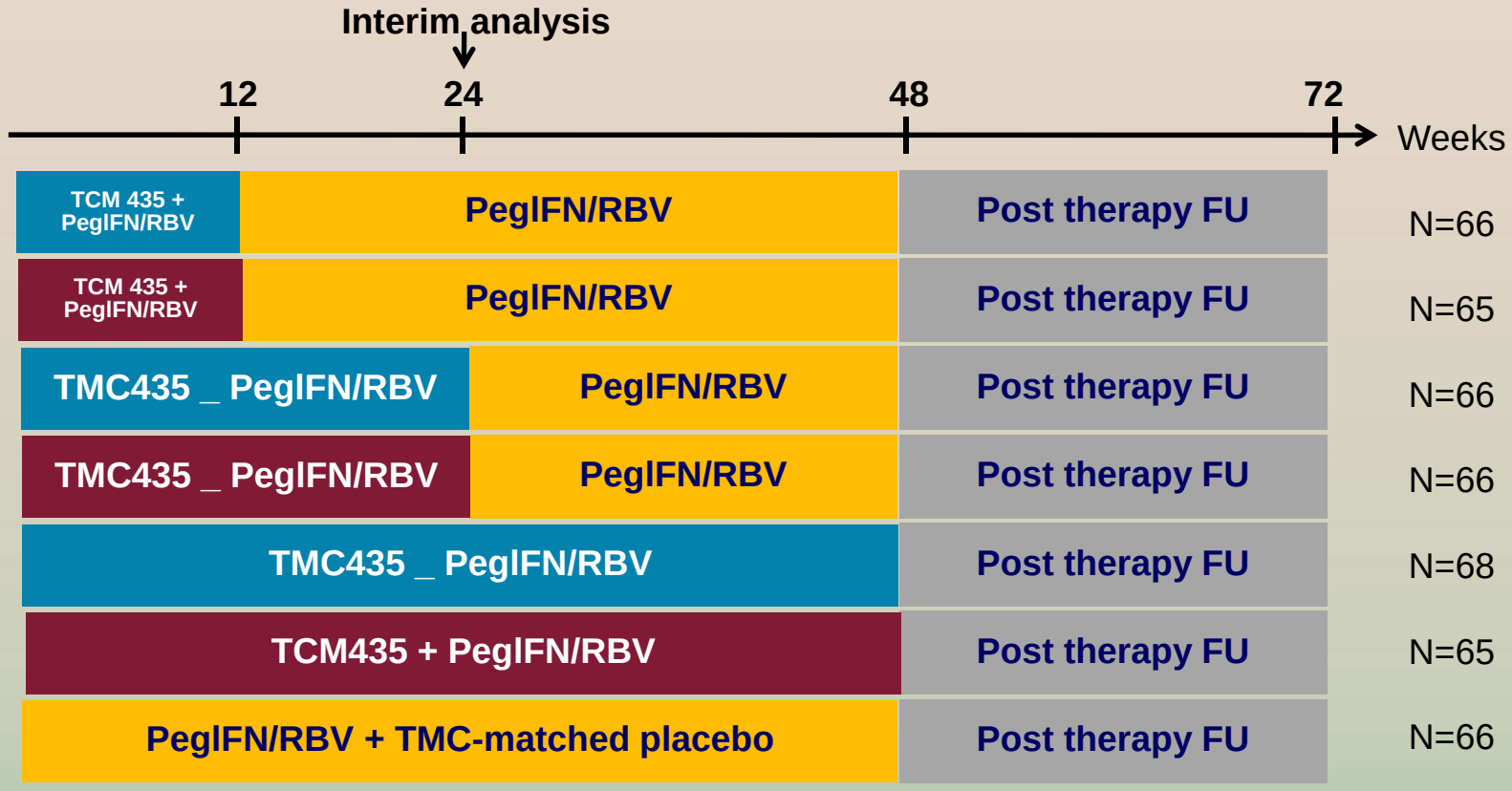
n%		A (N=18)	B (N=29)	C (N=29)	D (N-30)
Week 2	HCV RNA Undetectable†	4 (22)	7 (24)	11 (38)	17 (57)
	RCV RNA <LLOQ‡	12 (67)	19 (66)	27 (93)	26 (87)
Week 4 (RVR)	HCV RNA Undetectable†	3 (17)	17 (59)	25 (86)	26 (87)
	RCV RNA <LLOQ‡	4 (22)	25 (86)	28 (97)	29 (97)
Weeks 2 and 8	HCV RNA Undetectable†	0	4 (14)	11 (38)	15 (50)
	RCV RNA <LLOQ‡	0	11 (38)	25 (86)	24 (80)
Week 12 (cEVR)	HCV RNA Undetectable†	0	7 (24)	24 (83)	27 (90)
	RCV RNA <LLOQ‡	0	7 (24)	24 (83)	27 (90)
Viral breakthrough	Total	3 (17)	9 (31)	0	0

† HCV RNA was evaluated using the TaqMan assay version 2.0 (LLOQ 25 IU/mL)
‡HCV RNA <LLOQ: HCV RNA below limit of quantification (25 (IU/mL), detectable or undectable

Di Besceglie AM, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1363.

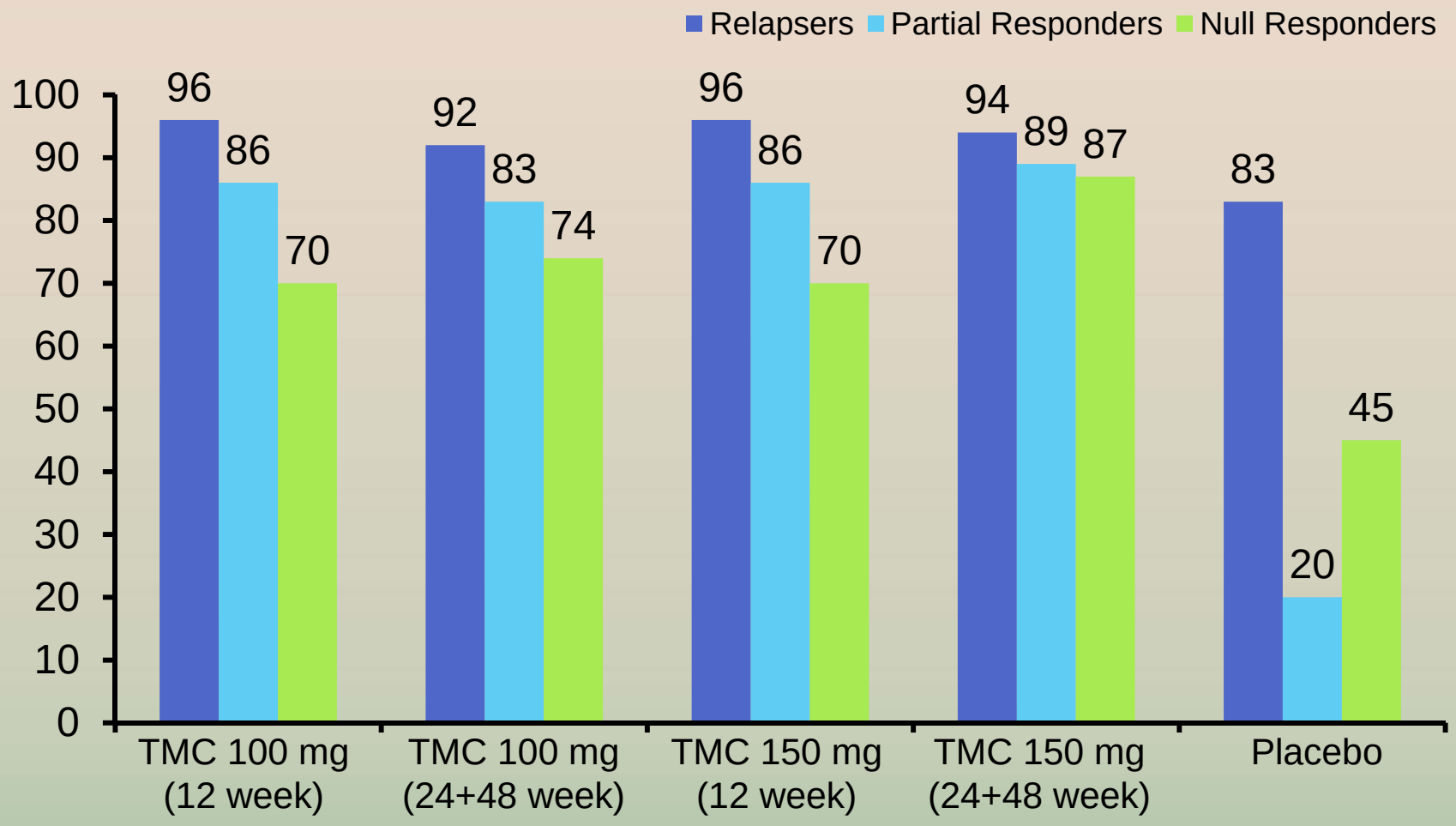
ASPIRE: TMC435 + PegIFN/RBV

Study of TMC435 in patients with HCV GT1 who have previously failed PegIFN/RBV



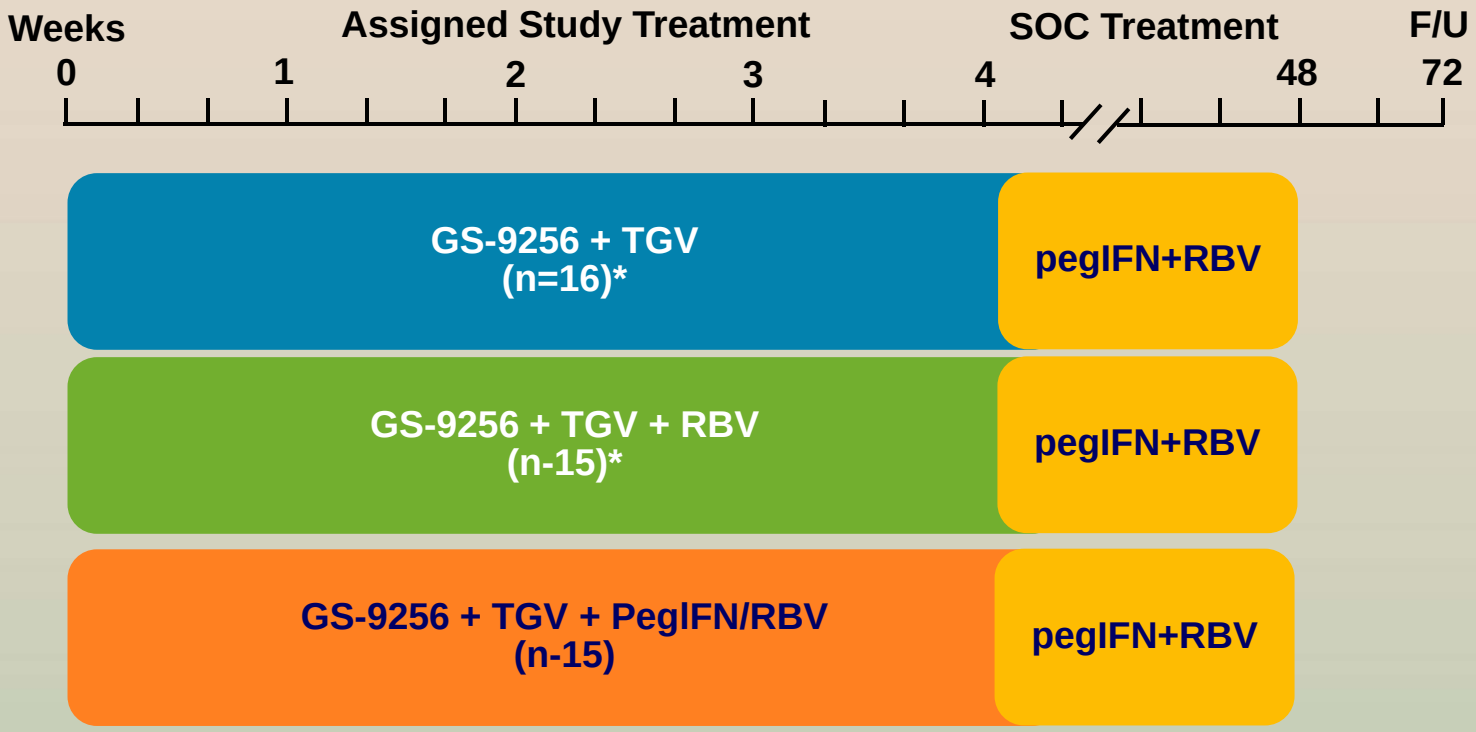
Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1376.

ASPIRE: Observed Virologic Responses at Week 24



Zeuzem S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1376.

Tegobuvir (GS-9190) + GS-9256 ± PegIFN/RBV or RBV

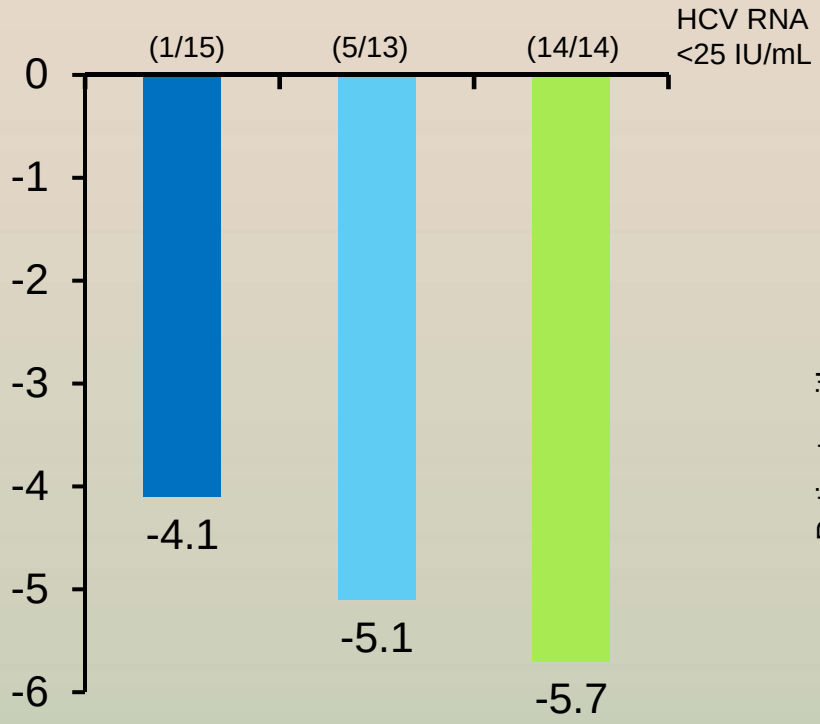


* Early initiation of PegIFN/RBV SOC if poor response/breakthrough

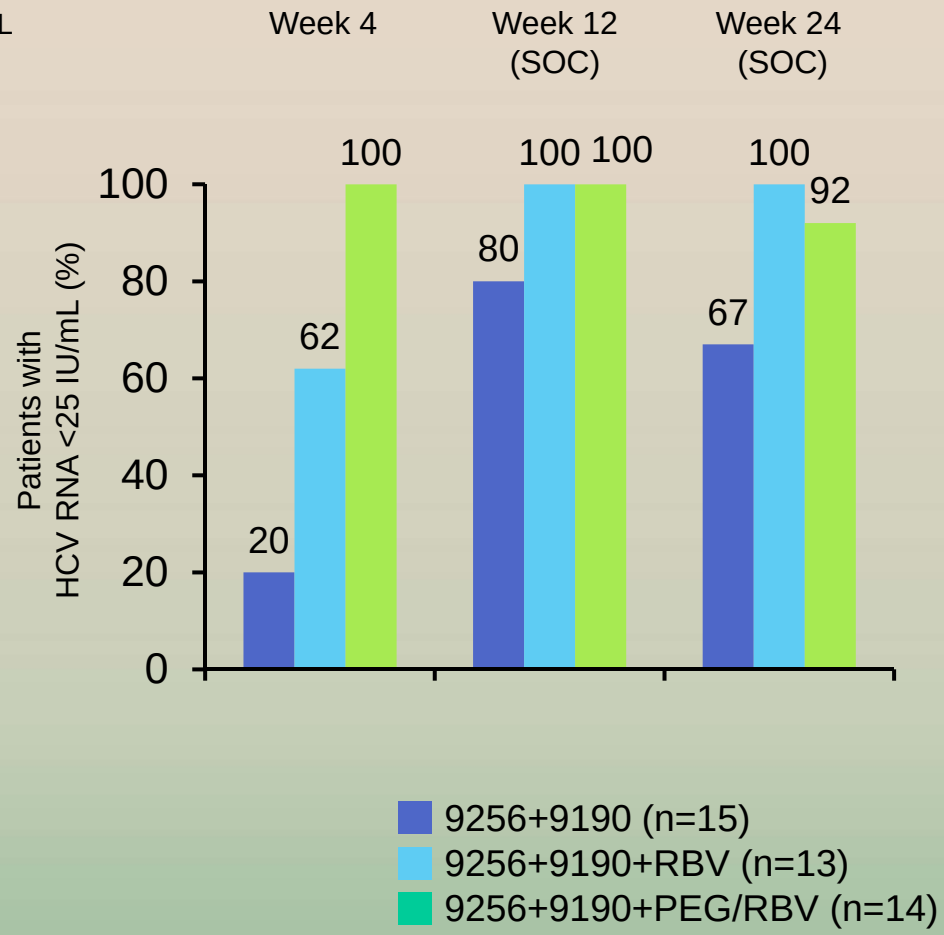
Foster G, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 425.

TGV + GS-9256 ± PegIFN/RBV or RBV: Results

Median HCV RNA Change from Baseline



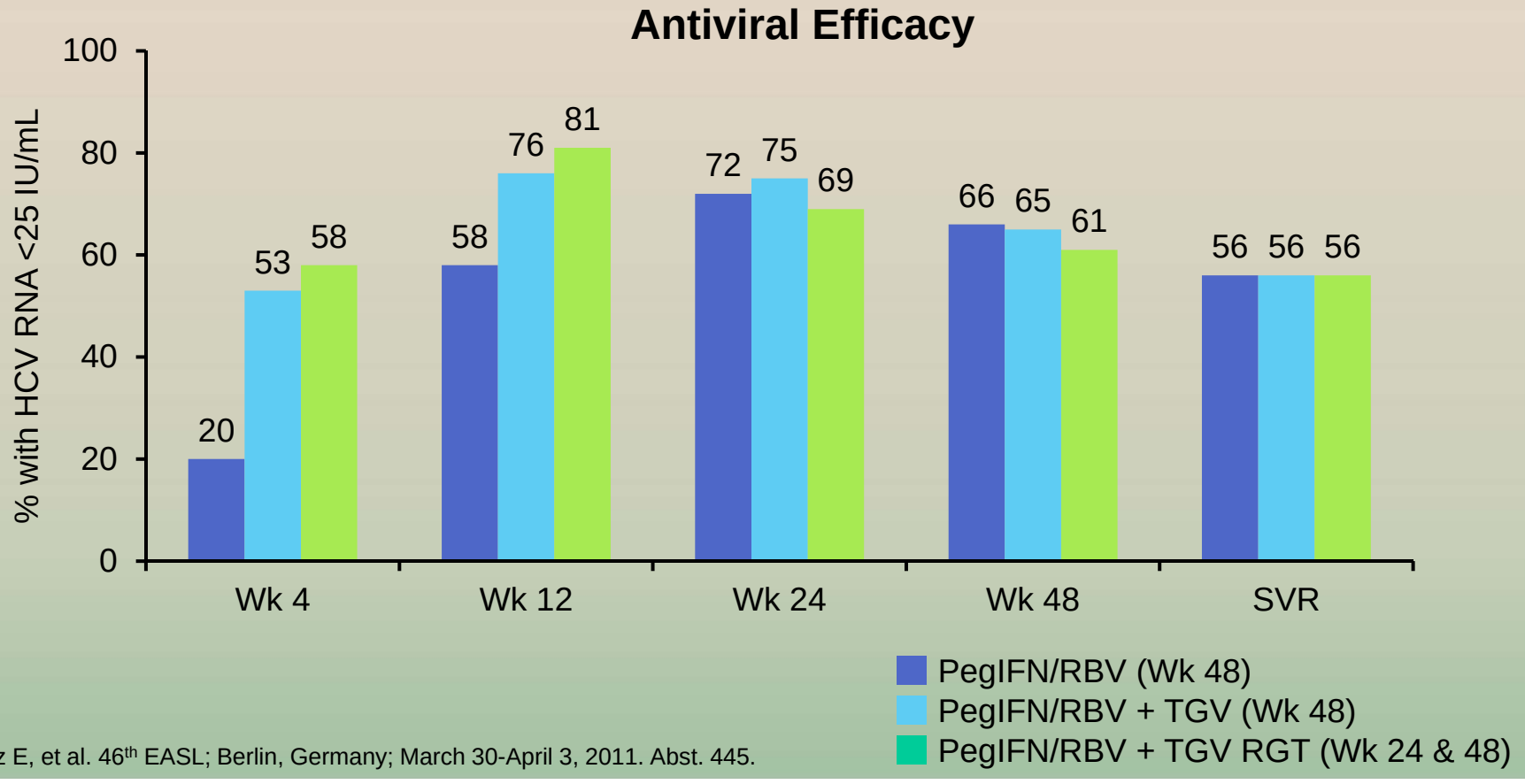
Virologic Response over Time



Foster G, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 425.

Tegobuvir (GS-9190) for HCV GT 1

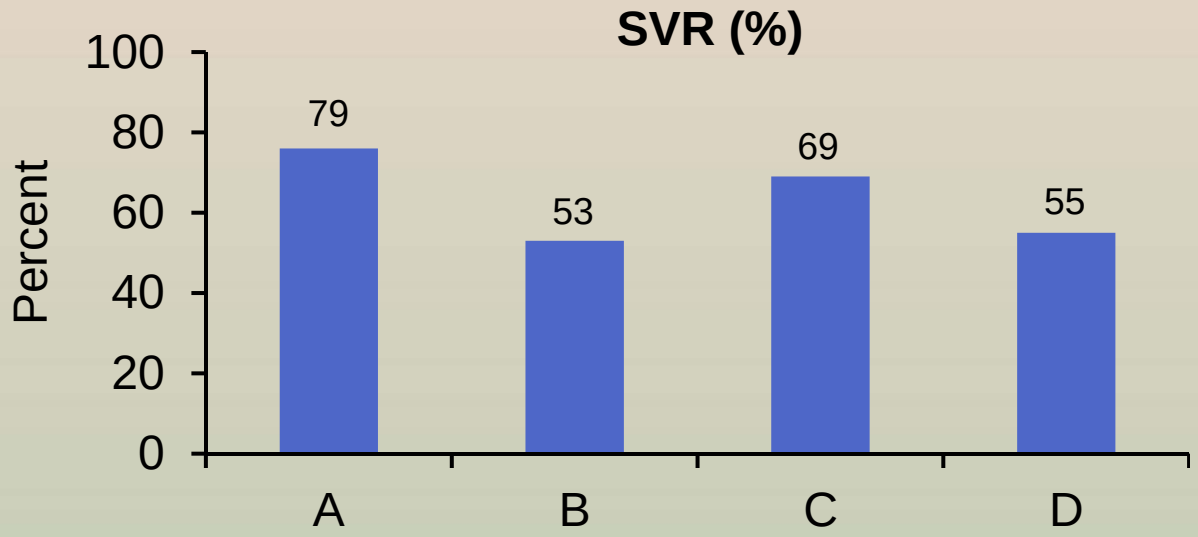
24-48 weeks treatment with TGV + PegIFN/RBV vs. 48 weeks PegIFN/RBV alone for HCV GT 1



Lawitz E, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 445.

Alisporovir (DEB025) + PegIFN/RBV in HCV GT 1, Treatment-naïve Patients

- Four arms (N=288)
  - DEB025 + PegIFN/RBV (48wks)
  - DEB025 + PegIFN/RBV (24wks)
  - DEB025 + PegIFN/RBV RGT by RVR (24 vs. 48 wks)
  - PegIFN/RBV



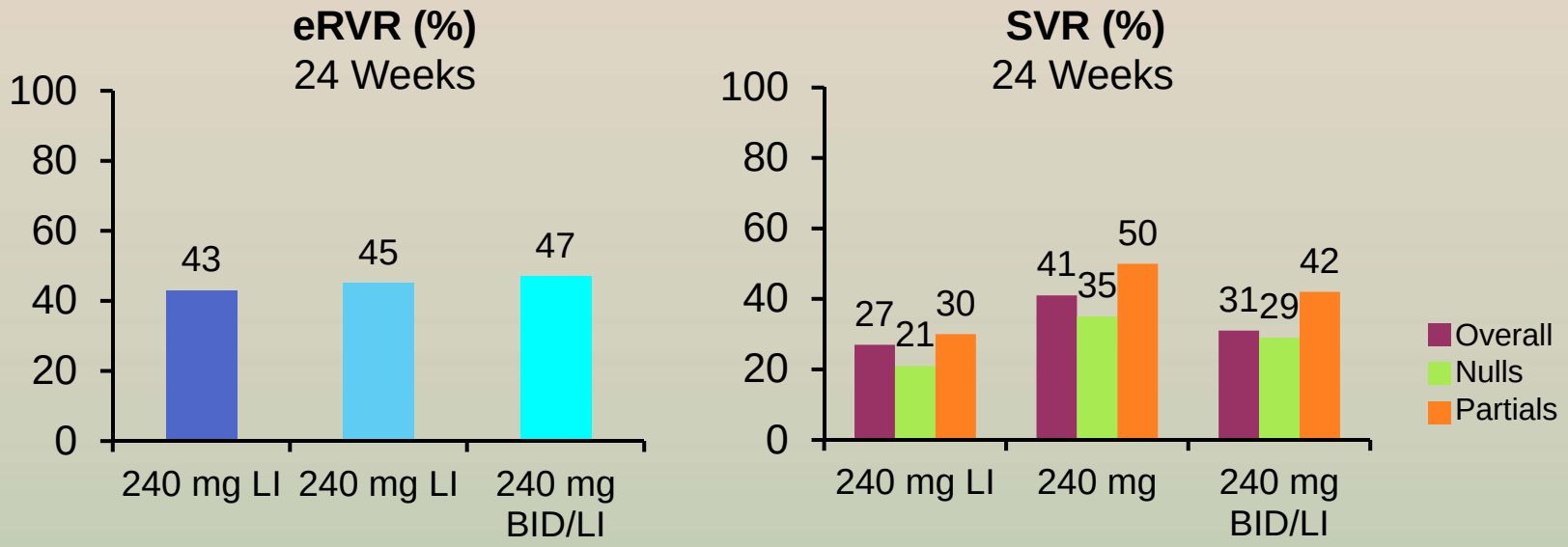
- Hyperbilirubinemia in 4.2% of DEB025 pts, reversible, no ALT elevations
- Jaundice in 10%
- Bilirubin elevation mixed attributed to transporter effect

Flisiak R, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 4.

SILENC-2: BI201335 with PegIFN/RBV in G1 Nonresponders

Nonresponders (N=290) with 2:1:1 randomization

*	BI120335 240 mg qd/PR	PR	1**
	BI201335 240 mg qd/PR	PR	2
*	BI201335 240 mg bid qd/PR	PR	3



Adverse Events higher in arm 3 and jaundice and rash most common

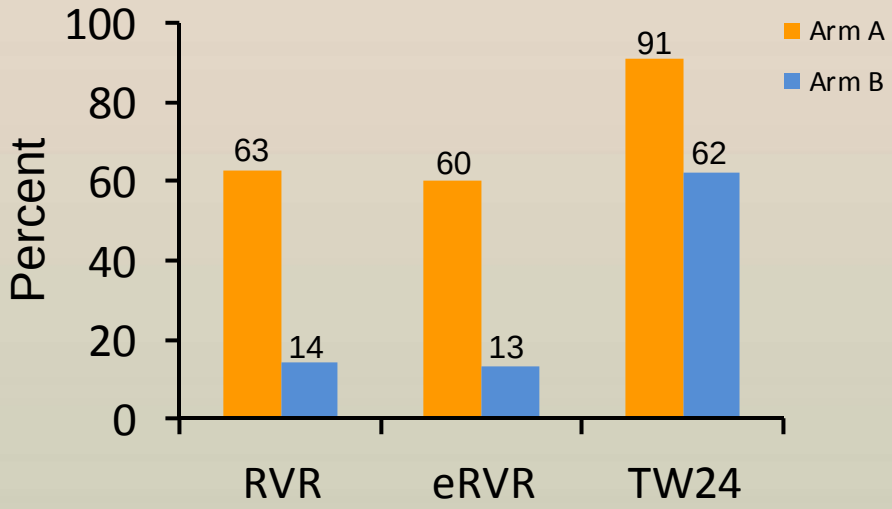
*3-day PR lead-in
**eRVR 24 vs 48 wks

Sulkowski M, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 66

Meracitabine (RG7128) RGT Combined with PEG IFN/RBV in HCV GT 1/4, Treatment-naive

- Study arms (all MCB 1000 mg BID):
  - RGT:
    - MCB/PR 24 wks if eRVR
    - MCB/PR 24 wks then PR 24 wks if no eRVR (n=81)
  - PegIFN/RBV 48 weeks (n-85)
- No significant AE or resistance issues

RVR, eRVR, TW24

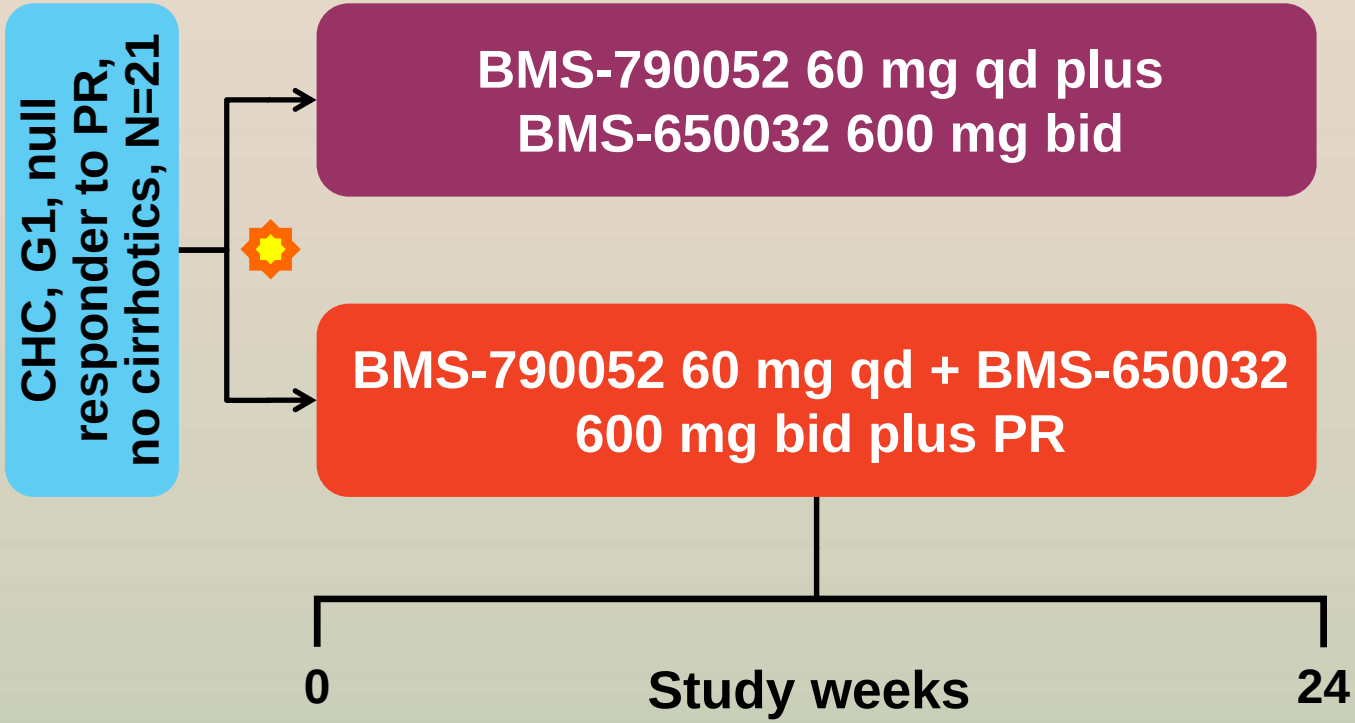


SVR12 in Arm A patients with eRVR

SVR	Relapse
76% (37/49)	24%(12/49)

Pockros P, et al, 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1359.

BMS-790052 (NS5A inhibitor) + BMS-650032 (PI) ± PR in null responders: phase IIa study



Randomisation

Null response defined as <2 log10 decline in HCV RNA following 12 weeks of treatment with PR

Lok A, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1356.

BMS-790052 + BMS-650032 ± PR in null responders: results

n (%)	Dual therapy (N=11)	Quadruple therapy (N=10)
HCV RNA <10 IU/mL at week 4	7 (63.6%)	6 (60%)
SVR24	4 (36.4%)	10 (100%)
Viral breakthrough	6	0
Relapse	1	0

- 19/21 had *IL28B* genotypes CT or TT
- Safety:
  - Diarrhoea was the most common AE (71.4%) (mainly mild-moderate)
  - 6 patients experienced ALT >3x ULN, all had total bilirubin <2x ULN
  - 6 patients (all receiving PR) experienced Grade 3/4 neutropenia
  - No SAEs/discontinuations due to Aes
  - All genotype 1B patients had SVR

Lok A, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011. Abst. 1356.

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