CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

# Advances in Chronic Hepatitis C Management and Treatment

*REPORTING FROM*

## THE 62ND AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES ANNUAL MEETING

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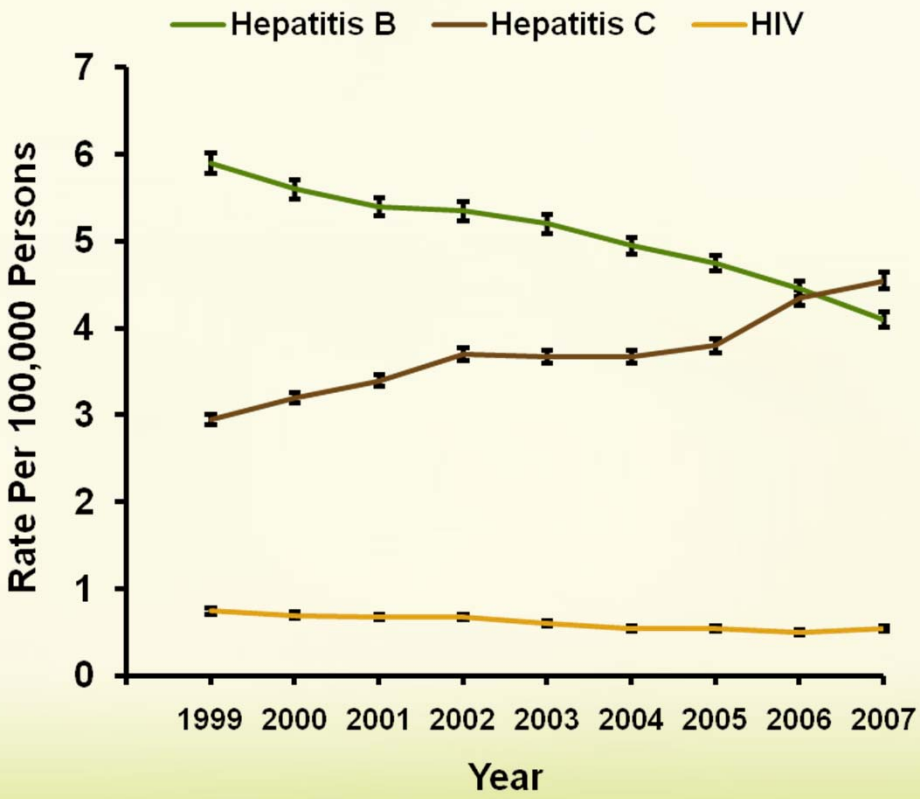
# Updates on Current Status of HCV Therapy

**K. Rajender Reddy, MD**
**Professor of Medicine, Professor of Medicine in Surgery,**
**Director of Hepatology**
**Medical Director of Liver Transplantation**
**University of Pennsylvania**
**Philadelphia, Pennsylvania**

# Growing Burden of Mortality Associated with Viral Hepatitis in the US (1999-2007)

- National multiple-cause mortality data 1999-2007
- 73 % of HCV and 59 % of HBV-related deaths in persons aged 45-64
- Co-morbidities associated with increased odds ratio of mortality
  - Chronic Liver Disease (32.1;HCV and 34.4;HBV)
  - co-infection with other hepatitis virus (29.9;HCV and 31.5;HBV)
  - Alcohol related (4.6;HCV and 3.7;HBV)
  - HIV co-infection (1.8;HCV and 4.0;HBV)

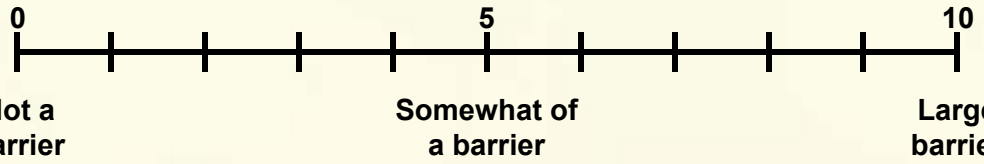
**Mortality rates of HBV, HCV, and HIV; United States 1999-2007**




Holmberg SD , et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 243

# Global Barriers to HCV Therapy

- International survey study of HCV treatment providers
- Study developed by the International Conquer C Coalition (I-C3)
  - Panel of HCV experts from around the world
  - Committee and study support provided by Merck
- 1400 physicians identified in 8 global regions:
  - United States
  - Canada
  - Latin America
  - Western Europe
  - Central/Eastern Europe
  - Nordic
  - Asia/Pacific
  - Middle East/Africa
- Physicians required to treat a minimum of 5 HCV patients / month
- Physicians asked to rate 31 potential barriers divided into patient, provider, government, and payer categories
- Each barrier rated on a 10-point Likert scale:

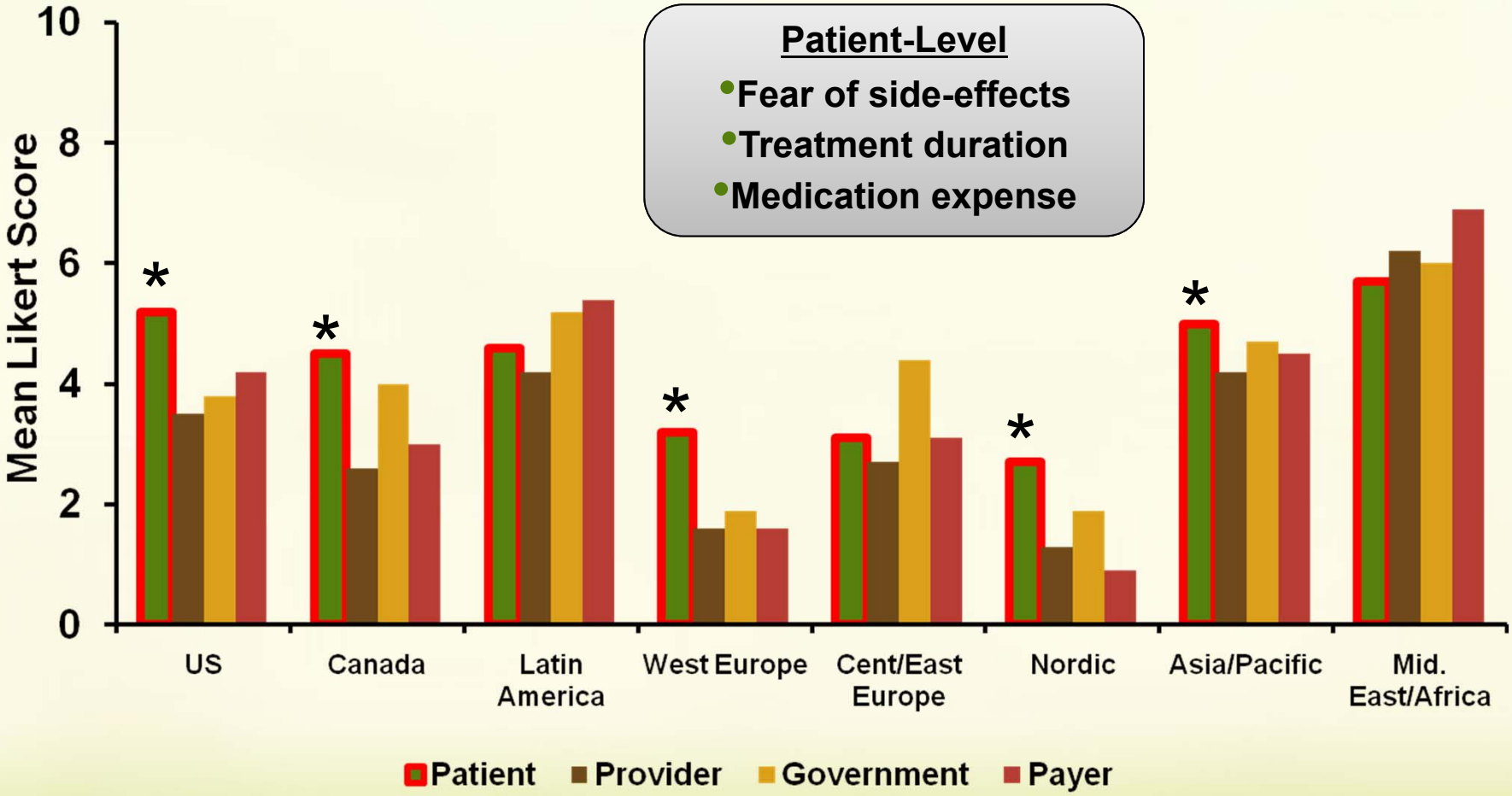



  - Additional questions addressing physician demographics, practice characteristics, and knowledge of HCV treatment principles
  - Survey administered by phone interview or online by a professional survey company*

*Volk, 2010

McGowan CE, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 101.

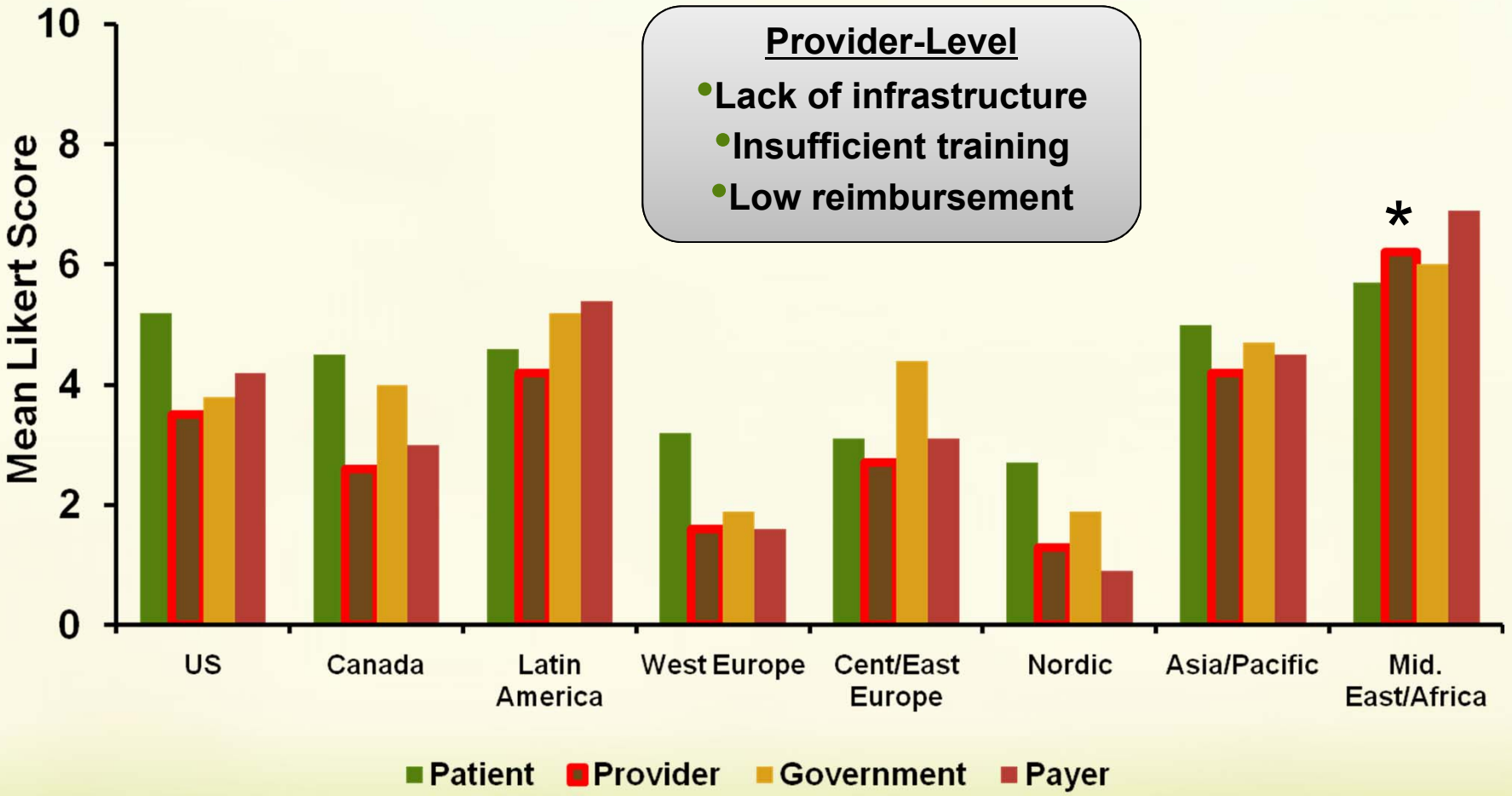
# Regional Barriers by Category




*Highest rated barrier category

McGowan CE, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 101.

# Regional Barriers by Category

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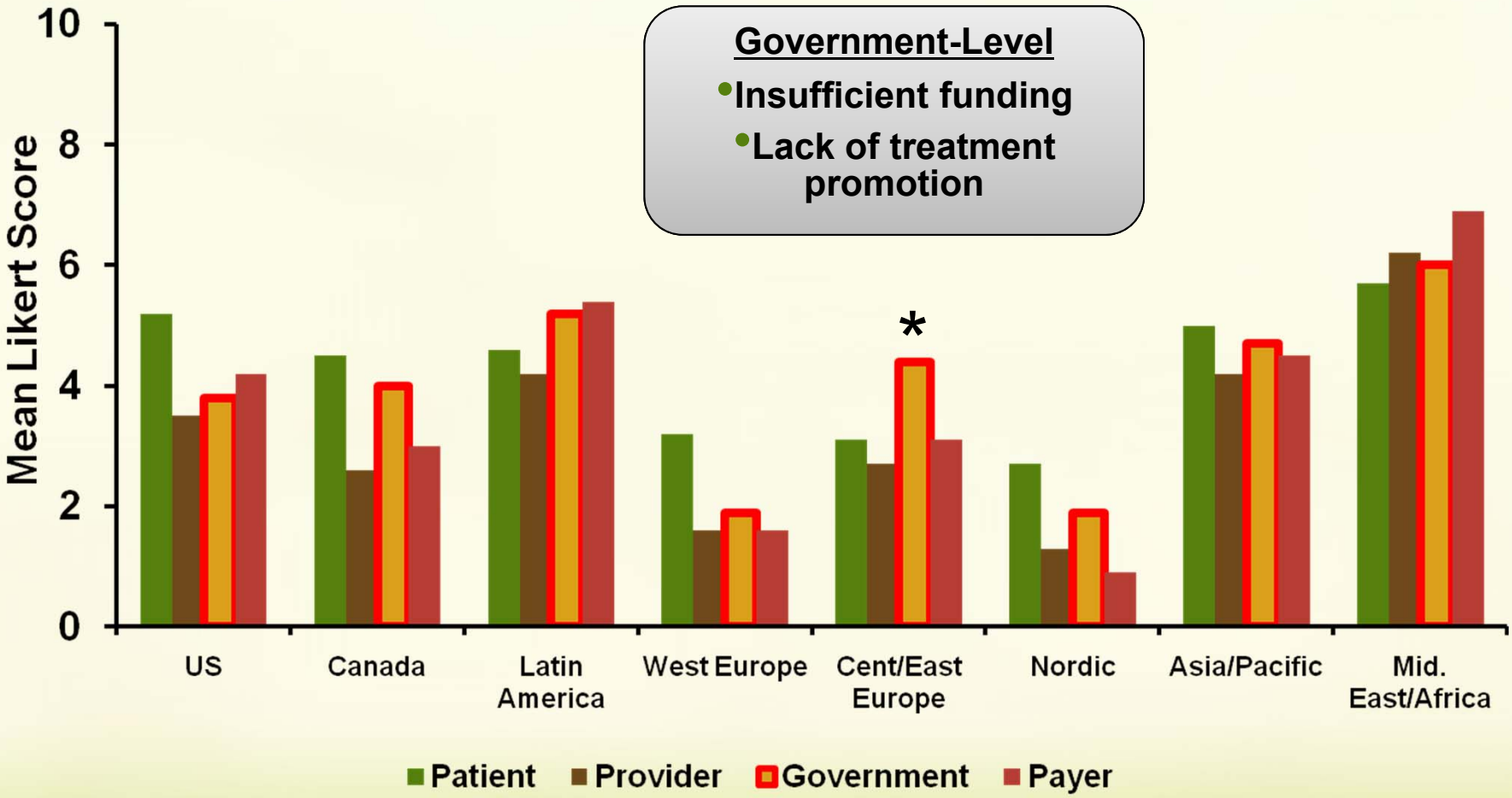
McGowan CE, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 101.

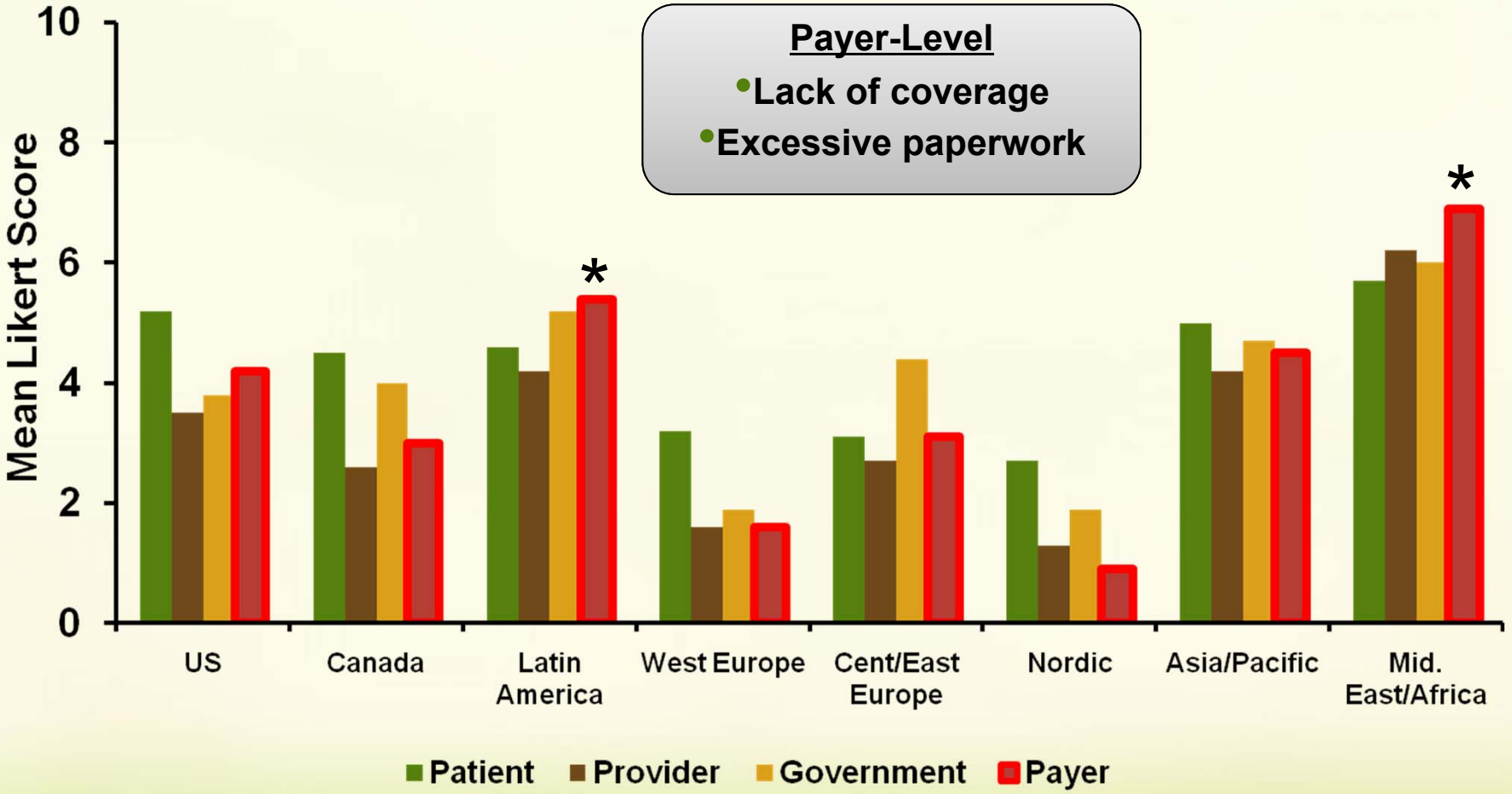
# Regional Barriers by Category




*Highest rated barrier category

McGowan CE, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 101.

# Regional Barriers by Category




*Highest rated barrier category

McGowan CE, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 101.

# Global Barriers to HCV Therapy: Summary

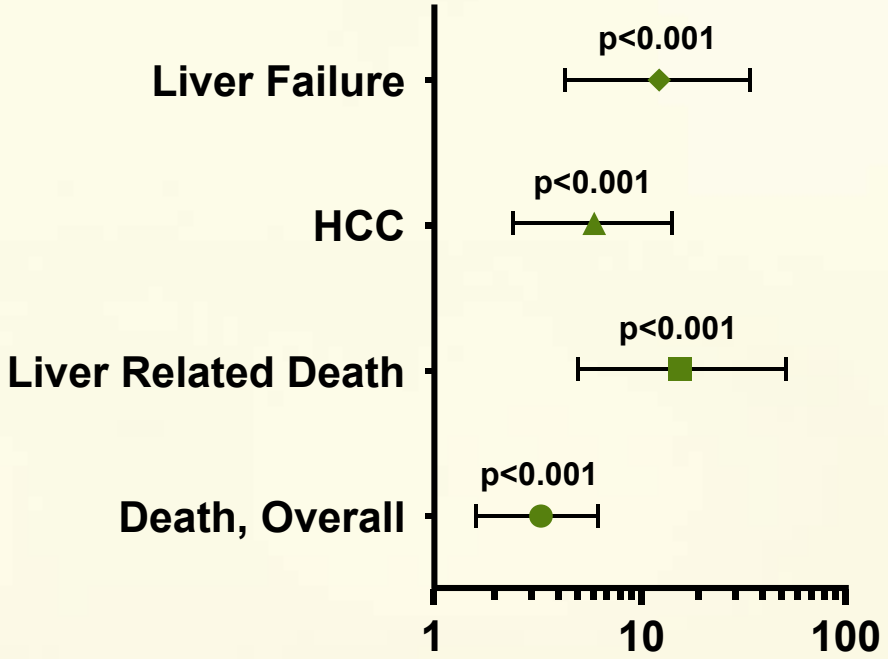
- Perceived treatment barriers vary significantly by global region
- Barriers are least prominent in Nordic and Western European countries and most prominent in Middle East and African countries
- Patient-level factors are most frequently cited and include fear of side effects, treatment duration, and expense
- The perception of barriers is significantly associated with physician experience and knowledge level

McGowan CE, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 101.

# Sustained Virologic Response Improves Overall Survival in Chronic HCV with Advanced Fibrosis

- 5 large centers from Europe and Canada
- 1990-2003, advanced fibrosis. Treated with interferon based regimens
- 529 patients followed for 20.2 years (median follow up 7.7 years)
- 191 ( 36.1%) achieved SVR

**Hazard Ration of NR vs. SVR**

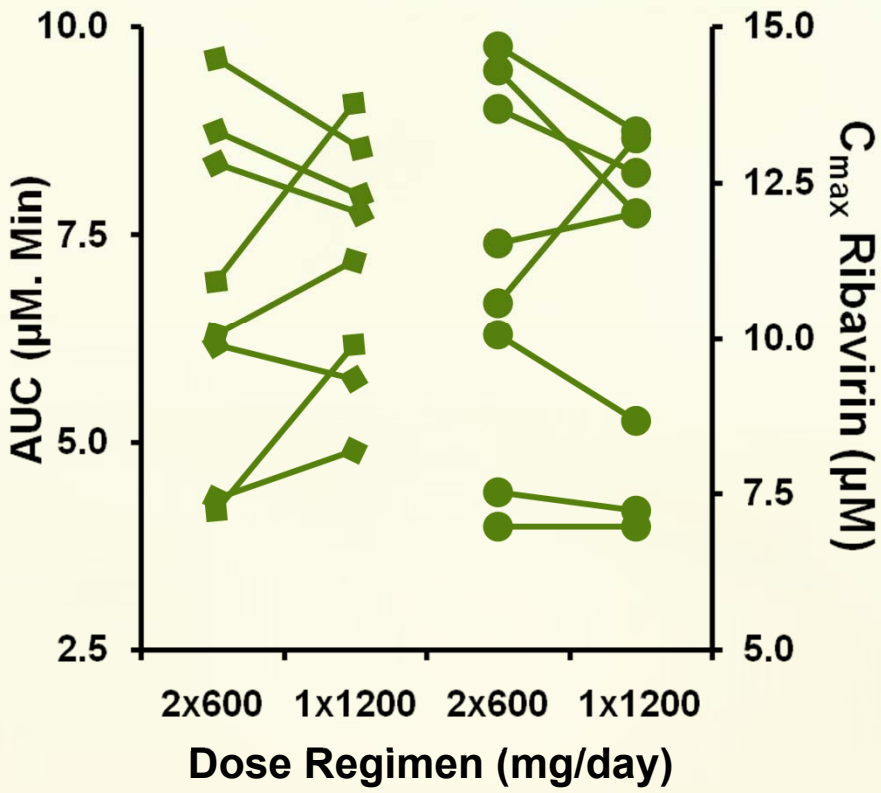



*Hazard Ratio's are adjusted for age, gender, center, fibrosis score, diabetes mellitus, heavy alcohol use treatment period.

Van der Meer AJ, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 165.

# Pharmacokinetics of Once Daily Compared with Twice Daily Regimen of Ribavirin

- Aim: Compare once daily ribavirin ( 1200 mg a day) with twice daily ( 600 mg a day) ribavirin
- 10 chronic HCV genotype 1 patients enrolled; also received PEG-IFN alfa-2a
- Cross over design after 12 weeks
- Hematologic profile and side effect profile recorded
- Conclusion: Single dose regimen pharmacokinetically comparable to twice daily regimen; no increase in adverse events




Balk J, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 1356.

# ENABLE 1: Eltrombopag as Adjunct to HCV Therapy

- Chronic HCV-baseline platelets < 75,000/µL
- Part 1-open label eltrombopag oral eltrombopag 25 mg/day escalated to 100 mg/day until platelets ≥ 90,000/µL
- Part-2 Patients randomized( 2:1) to eltrombopag or placebo

  - 715 patients, 78 % bridging fibrosis or cirrhosis, median platelets 59,000/µL
- Patients treated with PEG-IFN alfa 2a and RBV
- Primary end-point was SVR

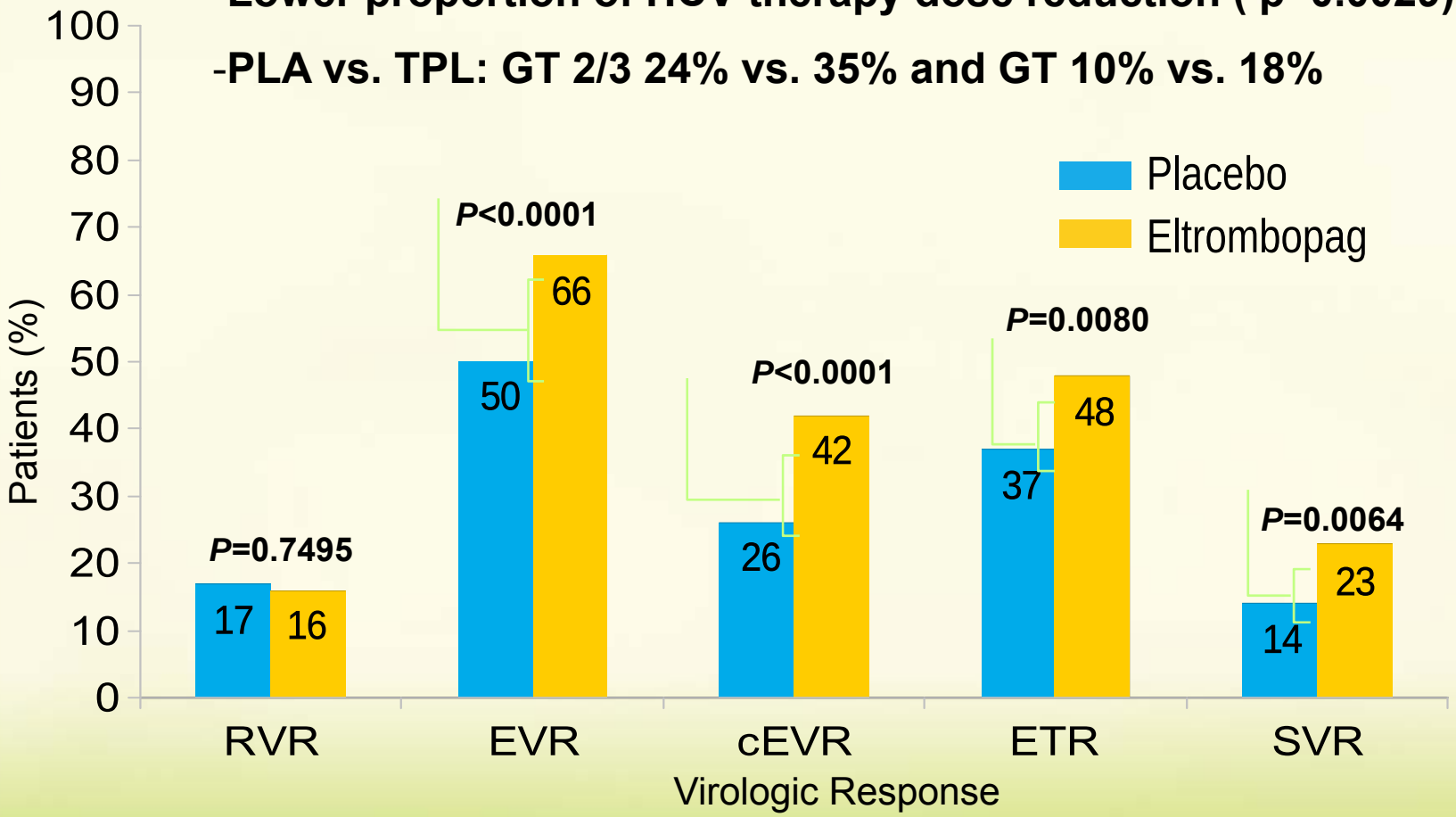
Afdhal N, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. LB-3.

# ENABLE 1: Final Results

-Longer interval to first HCV therapy dose reduction ( p=<0.0001)

-Lower proportion of HCV therapy dose reduction ( p=0.0029)

-PLA vs. TPL: GT 2/3 24% vs. 35% and GT 10% vs. 18%




Afdhal N, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. LB-3.

# Silymarin for Hepatitis C

- Silymarin is an extract of milk thistle widely used as a botanical treatment for liver disorders
  - A mixture of flavonolignans, with silibinin constituting approximately 50%
- Participants were randomized to receive silymarin (SM) or placebo for 24 weeks
  - 700 mg three times daily (5 capsules of SM tid)
  - 420 mg three times daily (3 caps of SM + 2 caps PLA tid)
  - Placebo (5 capsules of placebo tid)
- Primary outcomes after 24 weeks of treatment:
  - Serum ALT < 45 IU (approximate ULN)
  - OR Serum ALT decline of at least 50% to < 65 IU (approximately 1.5X ULN)

Fried MW et al CE, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 228

# Silymarin for Hepatitis C
# Analysis of Primary and Secondary Endpoints

| Endpoint | Placebo (n=52) | Silymarin 420 mg (n=50) | Silymarin 700mg (n=52) | p-value |
|---|---|---|---|---|
| **ALT ≤ 45 IU** | 1 (1.9%) | 2 (4%) | 2 (4%) | 0.8 |
| **Serum ALT decline of at least 50% to < 65 IU** | 2 (3.8%) | 1 (2%) | 2 (3.8%) | 0.8 |
| **Either of the Above** | 2 (3.8%) | 2 (4%) | 2 (3.8%) | 1.0 |
| **Change in HCV RNA ($log_{10}$ IU)** | 0.07 | -0.03 | 0.04 | 0.54 |

Fried MW et al CE, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 228

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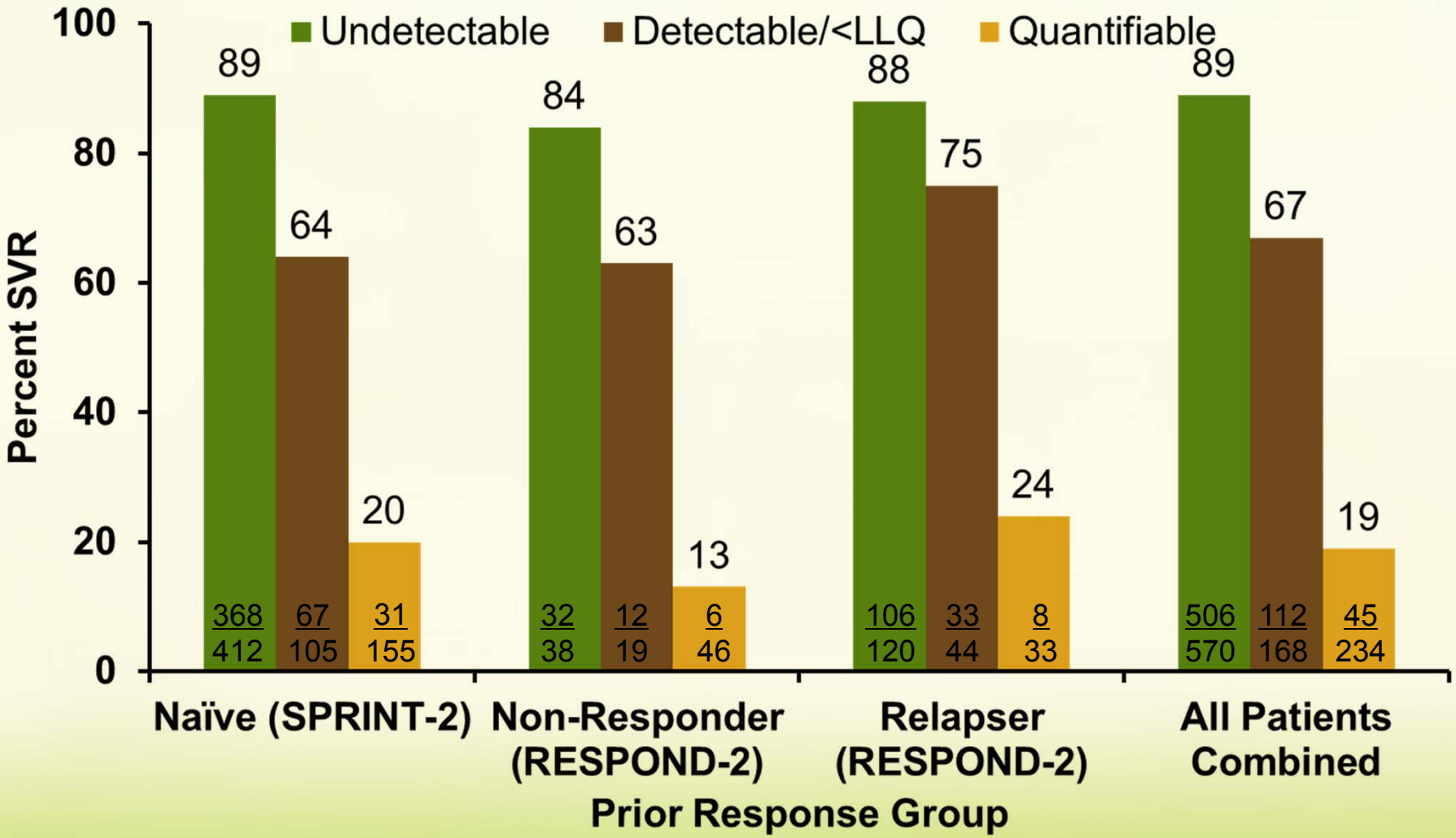
# Boceprevir Studies

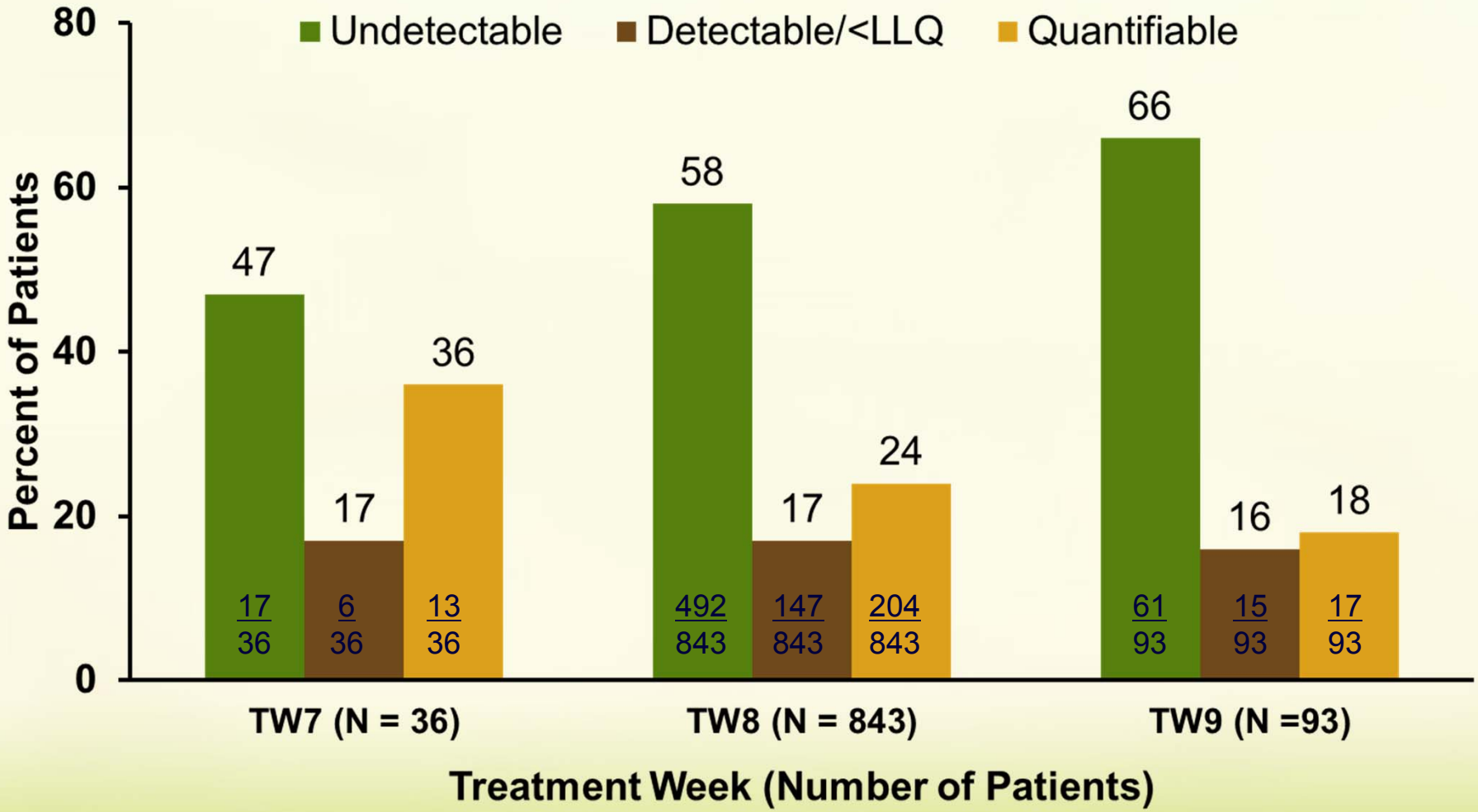
**Fred Poordad, MD**
**Chief, Hepatology**
**Cedars-Sinai Medical Center**
**Associate Professor of Medicine**
**David Geffen School of Medicine at UCLA**
**Los Angeles, California**

# SPRINT-2 and RESPOND-2: SVR by TW8 Response Category and Prior Response Group



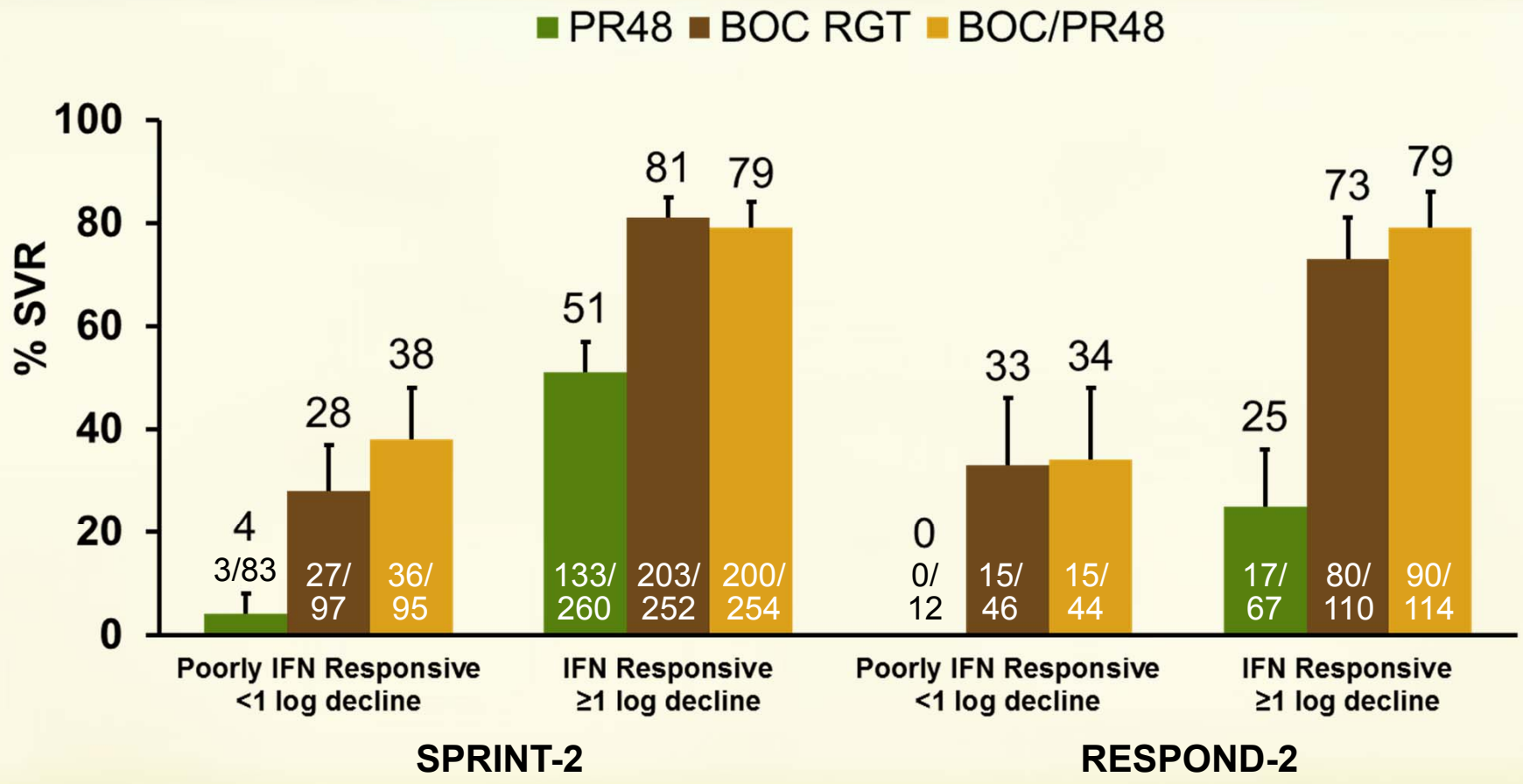

Lawitz E, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 167.

# SPRINT-2 and RESPOND-2: Timing of TW8 HCV RNA Testing Impacts Percent of Patients With Undetectable Virus




Lawitz E, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 167.

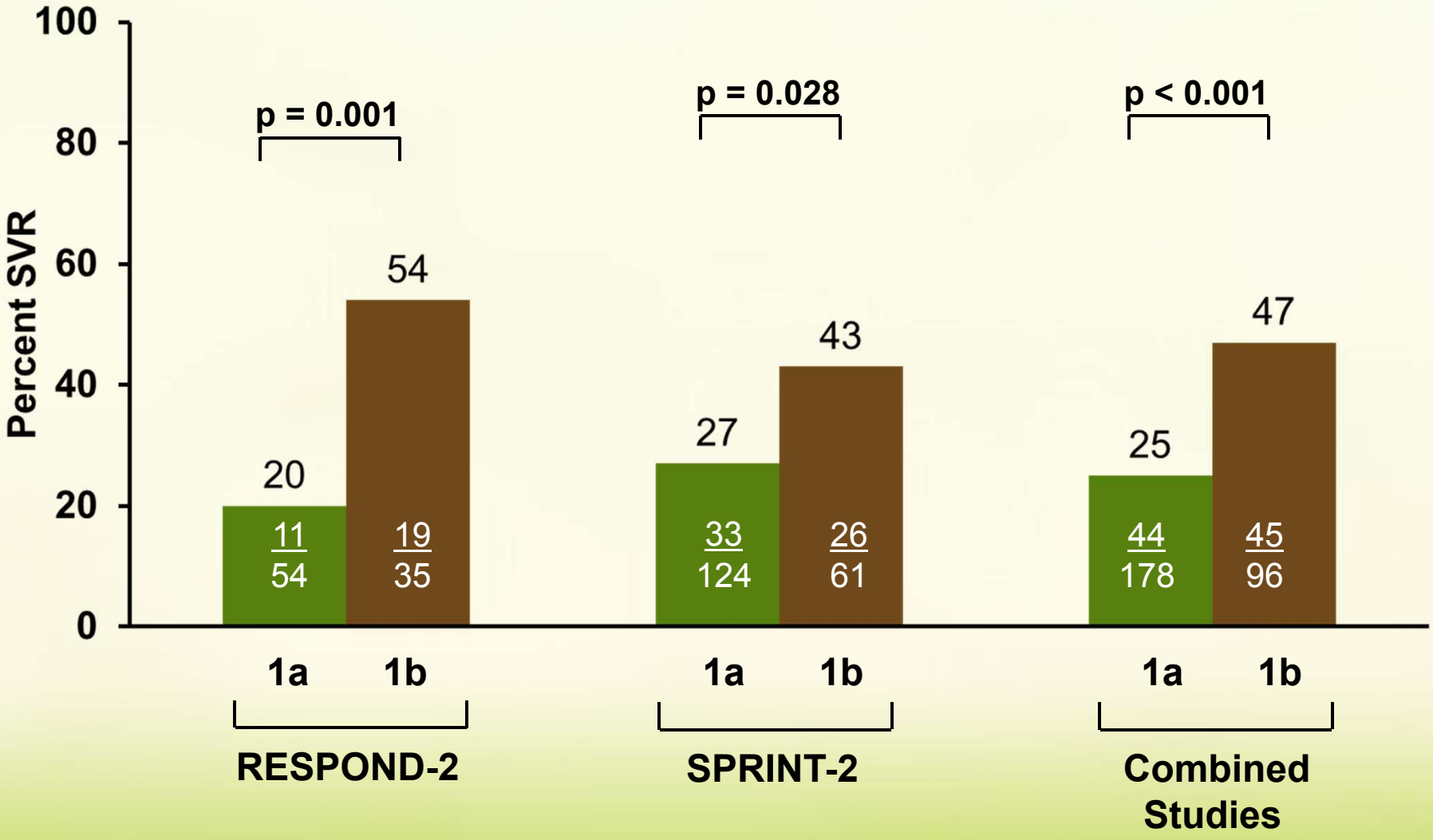
# SPRINT-2 and RESPOND-2: SVR by TW4 Response




SVR=sustained virologic response; TW=treatment week; IFN=interferon; PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/peginterferon α-2b + ribavirin 48 weeks.

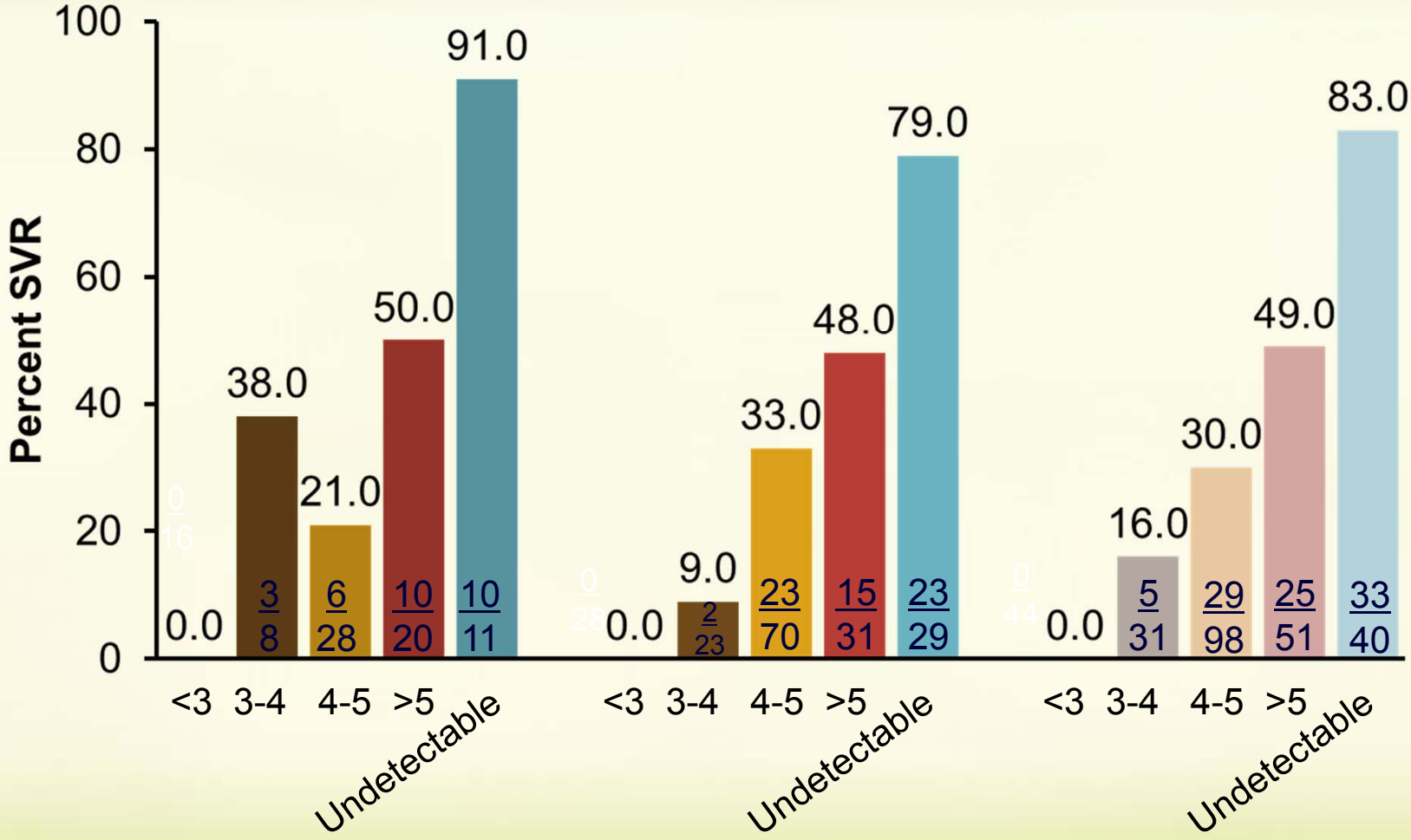
Bacon B, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 33.

# SPRINT-2 and RESPOND-2: HCV G1 Subtype as a Predictor of SVR in Patients with Poor IFN Response (BOC Arms Combined)



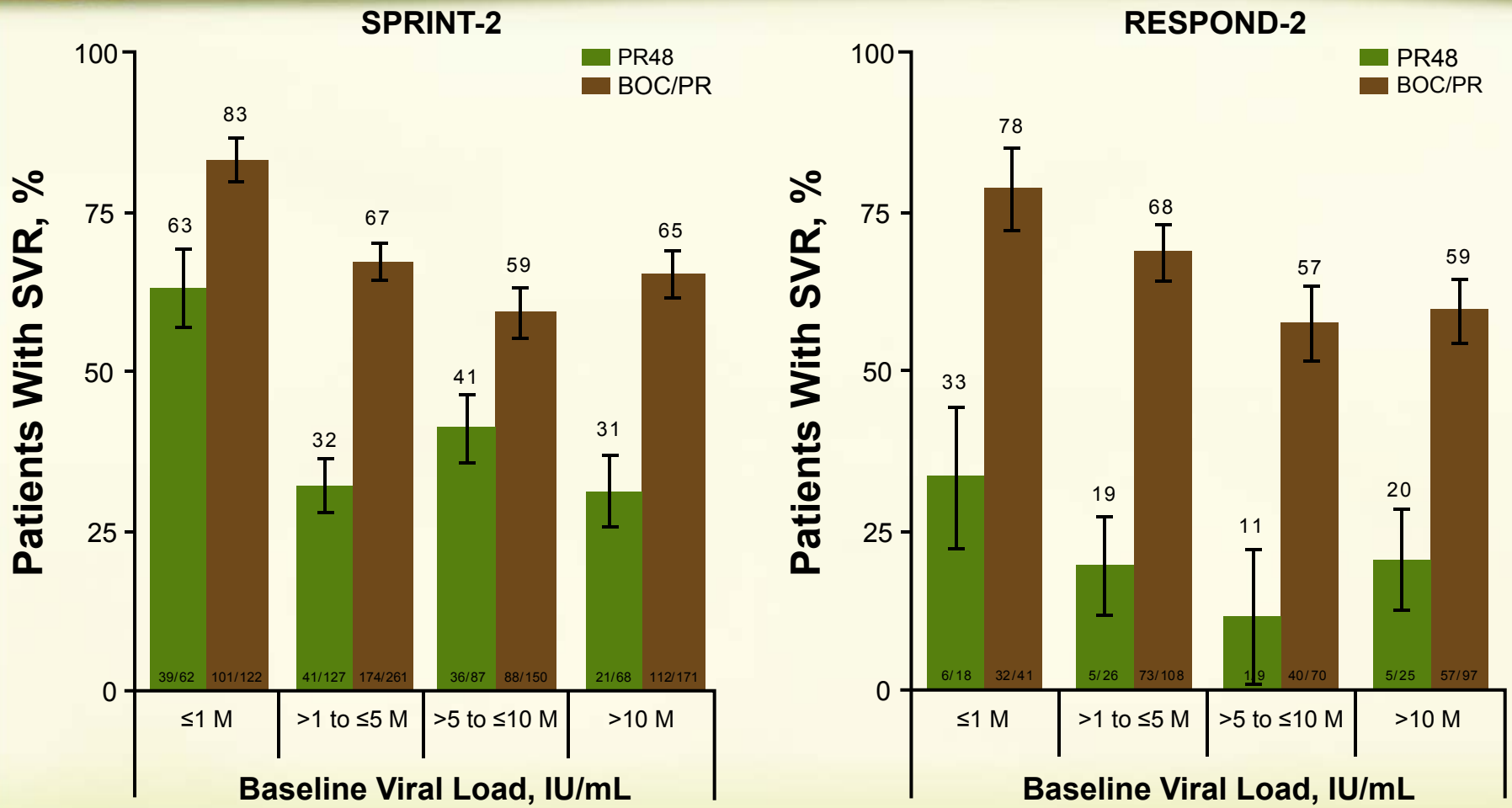

Bacon B, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 33.

# SPRINT-2 and RESPOND-2: SVR in Poor IFN Responders Based on TW8 Response (Log Decline in VL Compared to BL VL) (BOC Arms Combined)




Bacon B, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 33.

# SPRINT-2 and RESPOND-2: SVR rates according to baseline VL categories.




BOC/PR, boceprevir + PR-treated patients (arms 2 and 3); PR48, PR-treated patients (arm 1); SVR, sustained virologic response.

Gordon SC, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 961

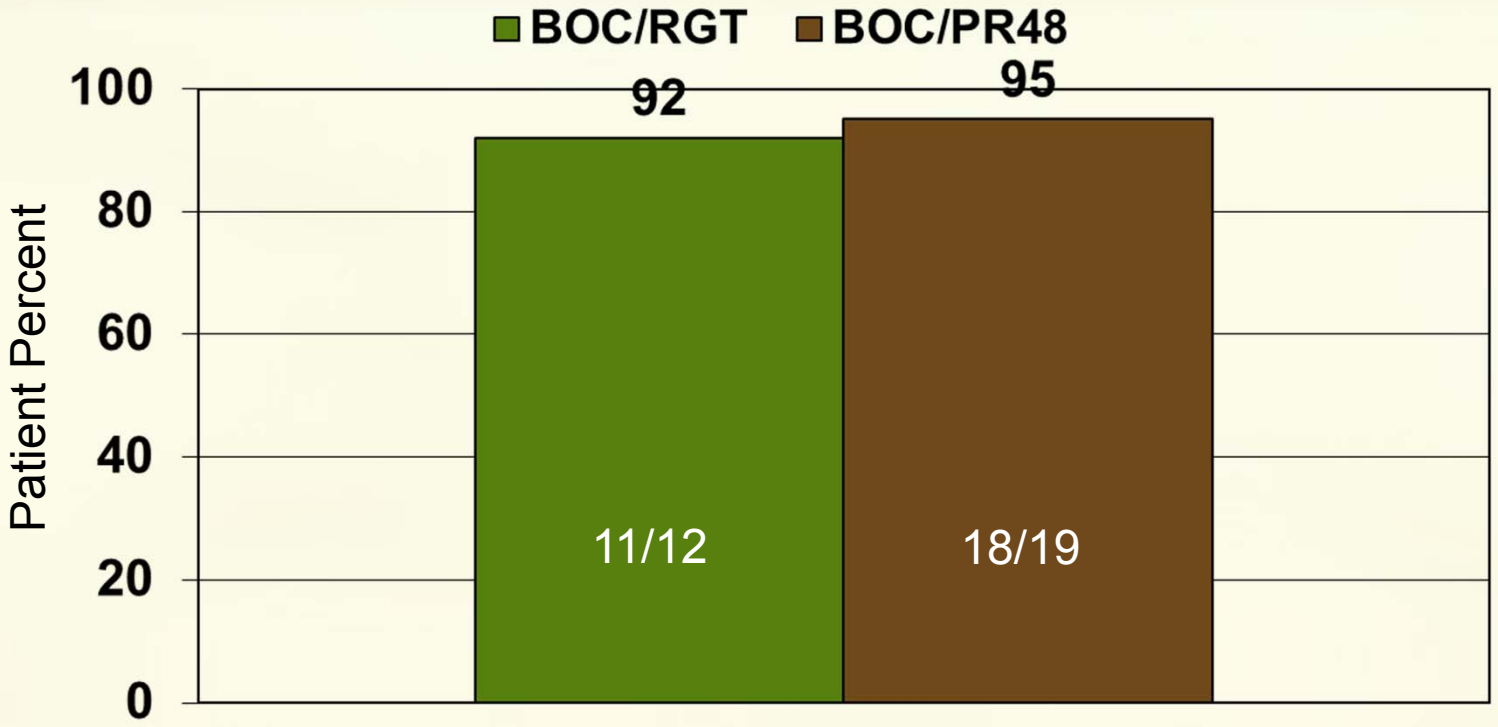
# Impact of TW12 Stopping Rules: SPRINT-2

| Stopping Rule | Stopped by TW12 Rule (N= 734) | Additional Stopped by TW24 Rule | Total Stopped | SVR Missed Using TW12 Rule |
|---|---|---|---|---|
| **>LLD, 9.3 IU/mL** | 144 (20%) | 20 | 164 (22%) | 21 |
| **>LLQ, 25 IU/mL** | 83 (11%) | 41 | 124 (17%) | 5 |
| **≥50 IU/mL** | 78 (11%) | 43 | 121 (16%) | 4 |
| **≥100 IU/mL** | 65 (9%) | 49 | 114 (16%) | 0 |
| **≥1000 IU/mL** | 43 (6%) | 61 | 104 (14%) | 0 |
| **<2 log decline** | 24 (3%) | 71 | 95 (13%) | 0 |
| **<3 log decline** | 34 (5%) | 66 | 100 (14%) | 0 |

- >100 IU/mL rule prevents any missed SVRs and maximizes the number of patients who can stop for futility
  - Actual stopping rule included in product labeling

Jacobson I, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 954.

# SPRINT-2: SVR in Non-Cirrhotic Black Early Responders*



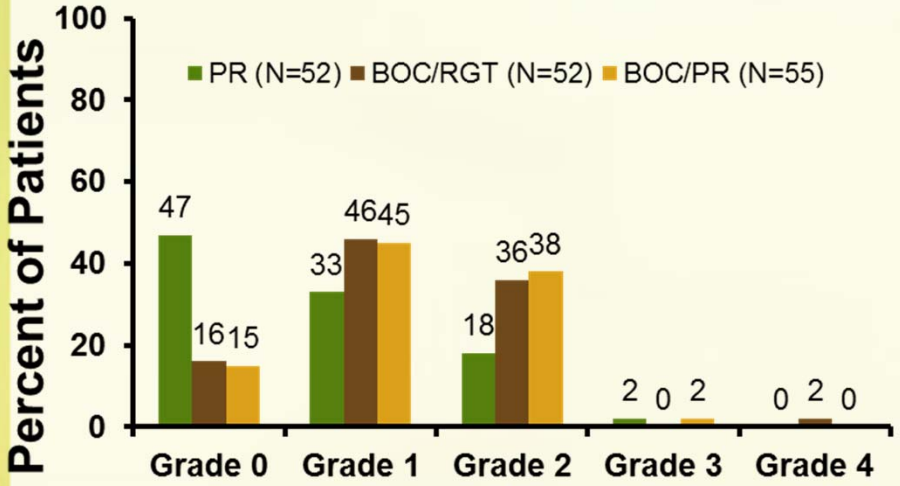

*HCV-RNA undetectable TW8 through TW24 and received at least 28 weeks of therapy

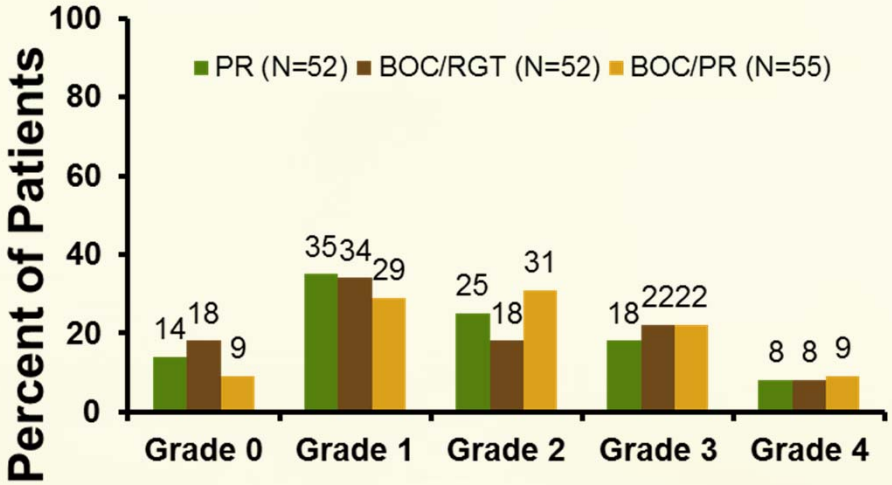
Black patients without cirrhosis who were early responders (HCV-RNA undetectable weeks 8-24) had SVR rates of 92-95%, similar to the non-black patients in SPRINT-2 (96-97%)

Black patients overall who were early responders (HCV-RNA undetectable weeks 8-24) had SVR rates of 87% (BOC/RGT) to 95% (BOC/PR48)

McCone J, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 981.

# SPRINT-2: Nadir Hemoglobin and Neutrophils in Black Patients




| | | | | | |
|---|---|---|---|---|---|
| PR n= | 24 | 17 | 9 | 1 | 0 |
| RGT n= | 8 | 23 | 18 | 0 | 1 |
| BOC/PR n= | 8 | 25 | 21 | 1 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| | 7 | 18 | 13 | 9 | 4 |
| | 9 | 17 | 9 | 11 | 4 |
| | 5 | 16 | 17 | 12 | 5 |

## Hemoglobin (g/dL)

Grade 0 ≥ 11.0
Grade 1 = 9.5 to < 11.0
Grade 2 = 8.0 to < 9.5
Grade 3 = 6.5 to < 8.0
Grade 4 < 6.5

## Neutrophils

Grade 0 > 1500/mm$^3$
Grade 1 = 1000 to 1500/mm$^3$
Grade 2 = 750 to <1000/mm$^3$
Grade 3 = 500 to < 750/mm$^3$
Grade 4 < 500/mm$^3$

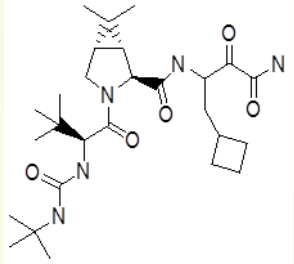
- Rates of grade 3/4 anemia and neutropenia were similar between BOC and PR arms

McCone J, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 981.

# Mechanism of BOC clearance

Excreted (11%)*

**Boceprevir**



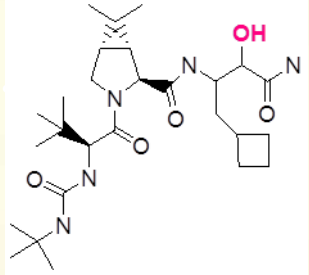
**CYP3A4/5**

**Oxidative products**
**- +O, +2O**
**- Cleavage**

**AKR-C** ⇅ **CYP3A**

Excreted (50%)*

Excreted (22%)*




**4 diastereomers**

**CYP3A**

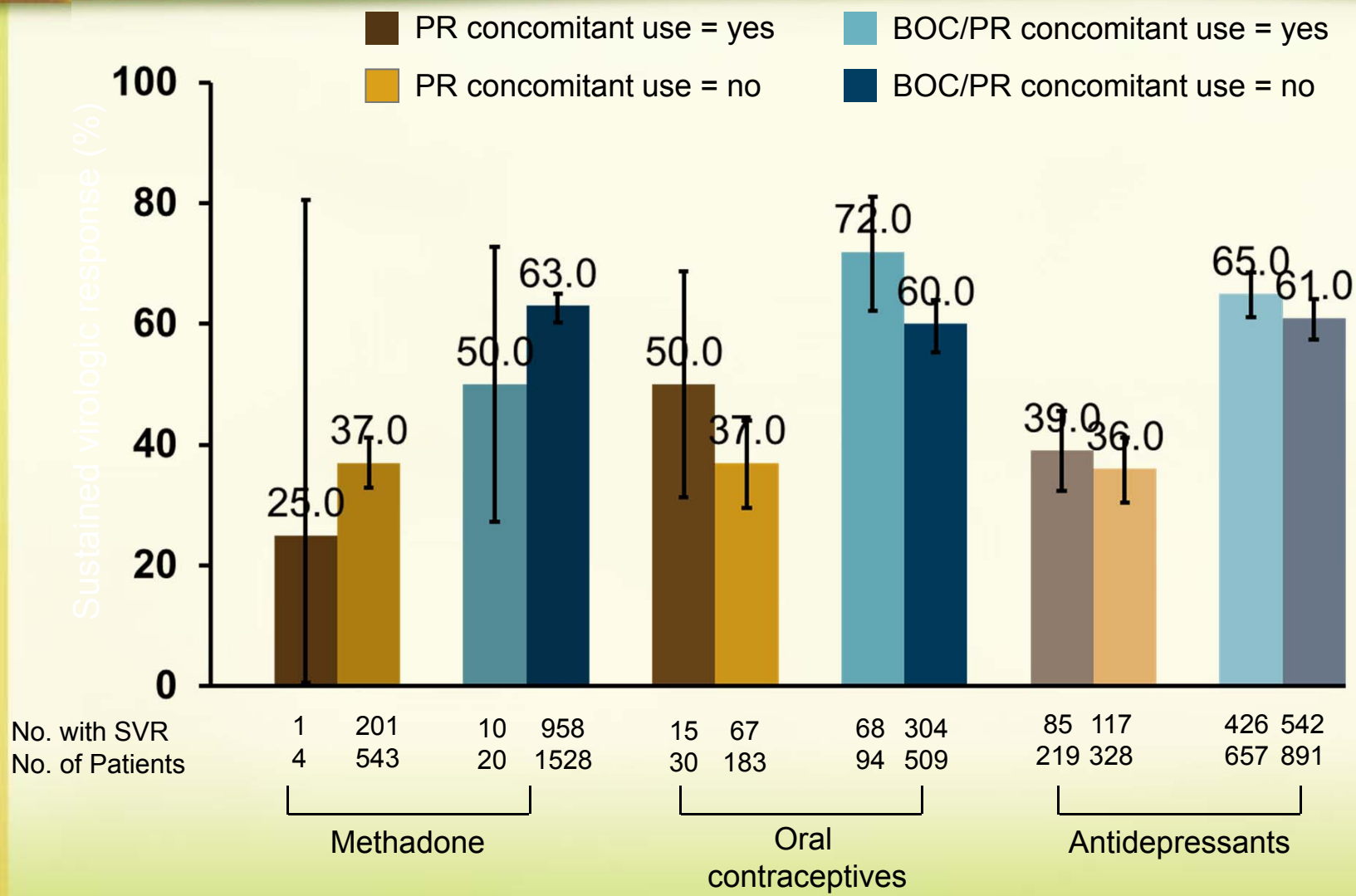
**Oxidation + Reduction**

Numerous products

*From human $^{14}$C-ADME study.

Poordad F, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 937.

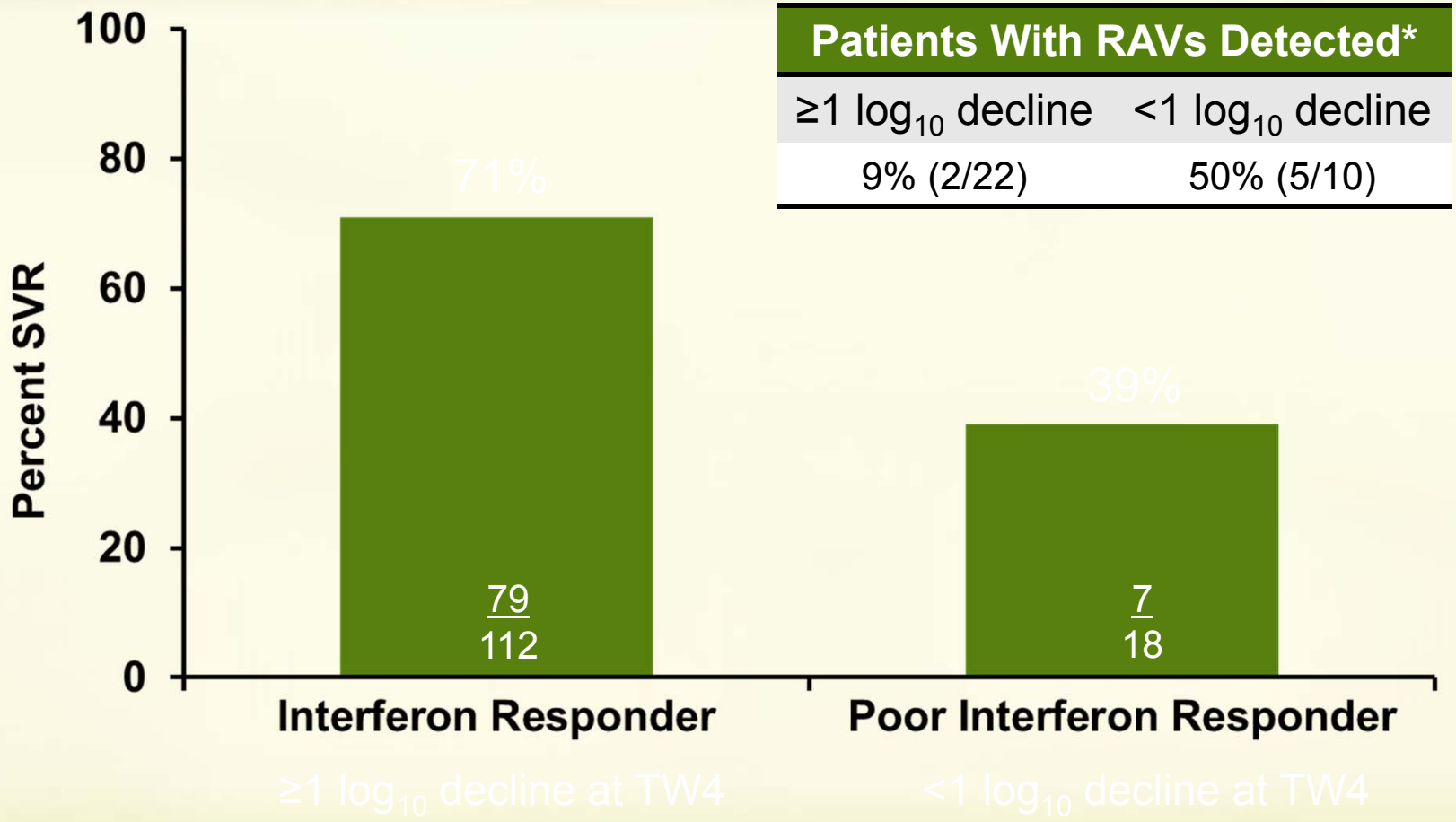
# SVR by Concomitant Medication Use




Poordad F, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 937.

# Patients With Poor Interferon Response and Fail Treatment Are More Likely to Have RAVs

| Patients With RAVs Detected* | |
|---|---|
| ≥1 $\log_{10}$ decline | <1 $\log_{10}$ decline |
| 9% (2/22) | 50% (5/10) |

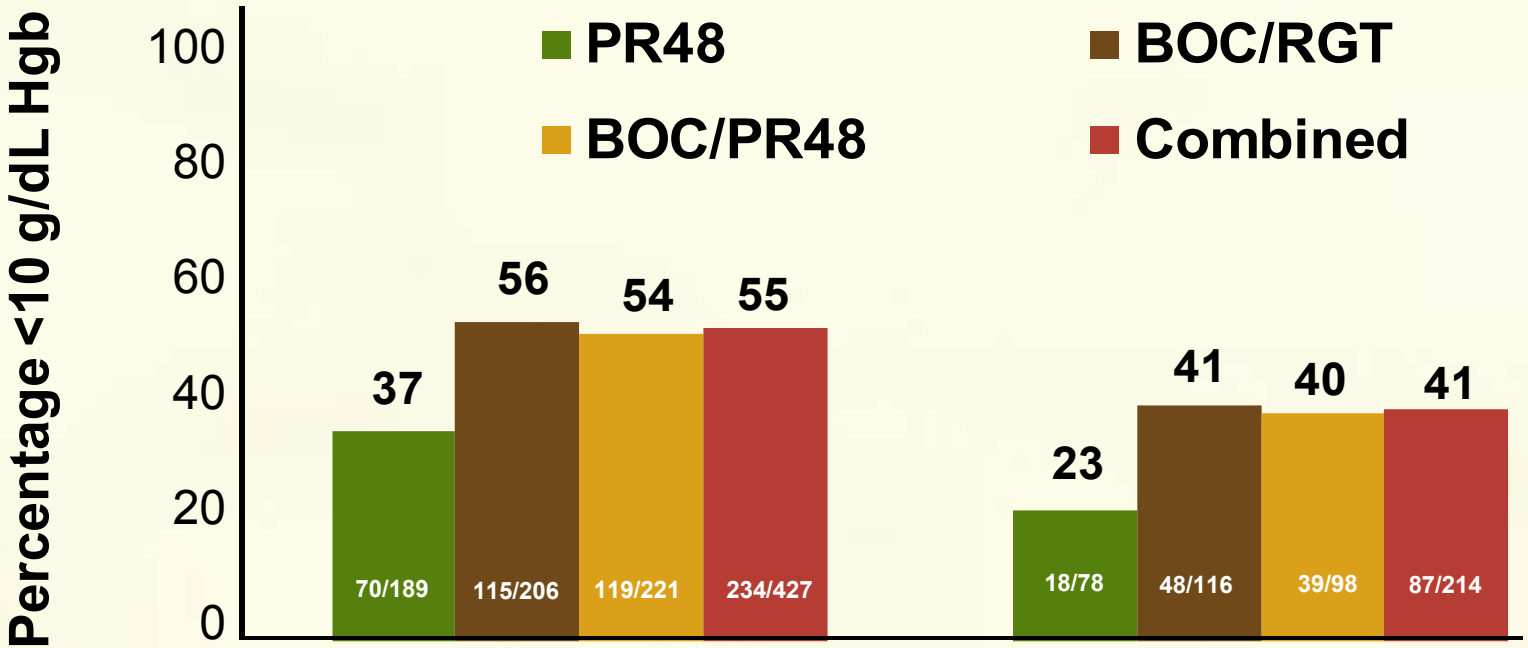



*Expressed as a percentage of patients with sequence data.

RAVs resistance associated variants; TW, treatment week; VL, viral load.

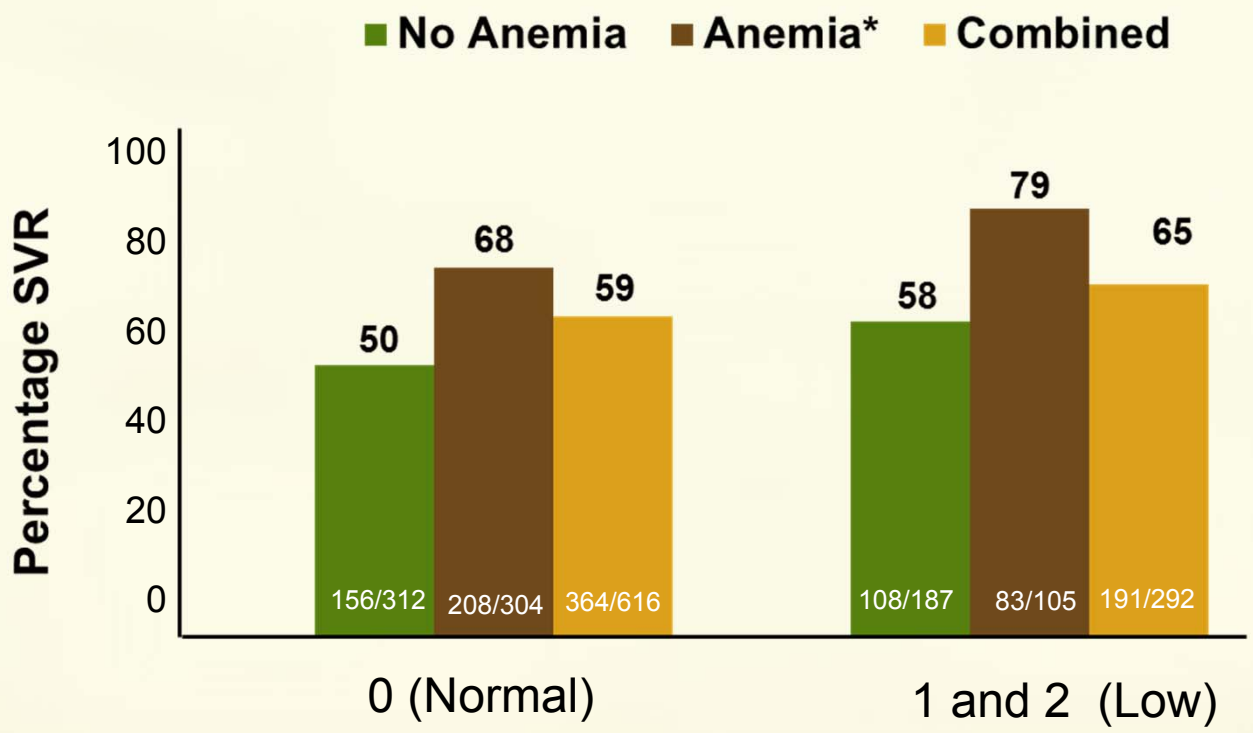
Howe J, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 168.

# Fewer Patients with Low ITPA Activity Experience Anemia While On Treatment




Sulkowski M, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 934.

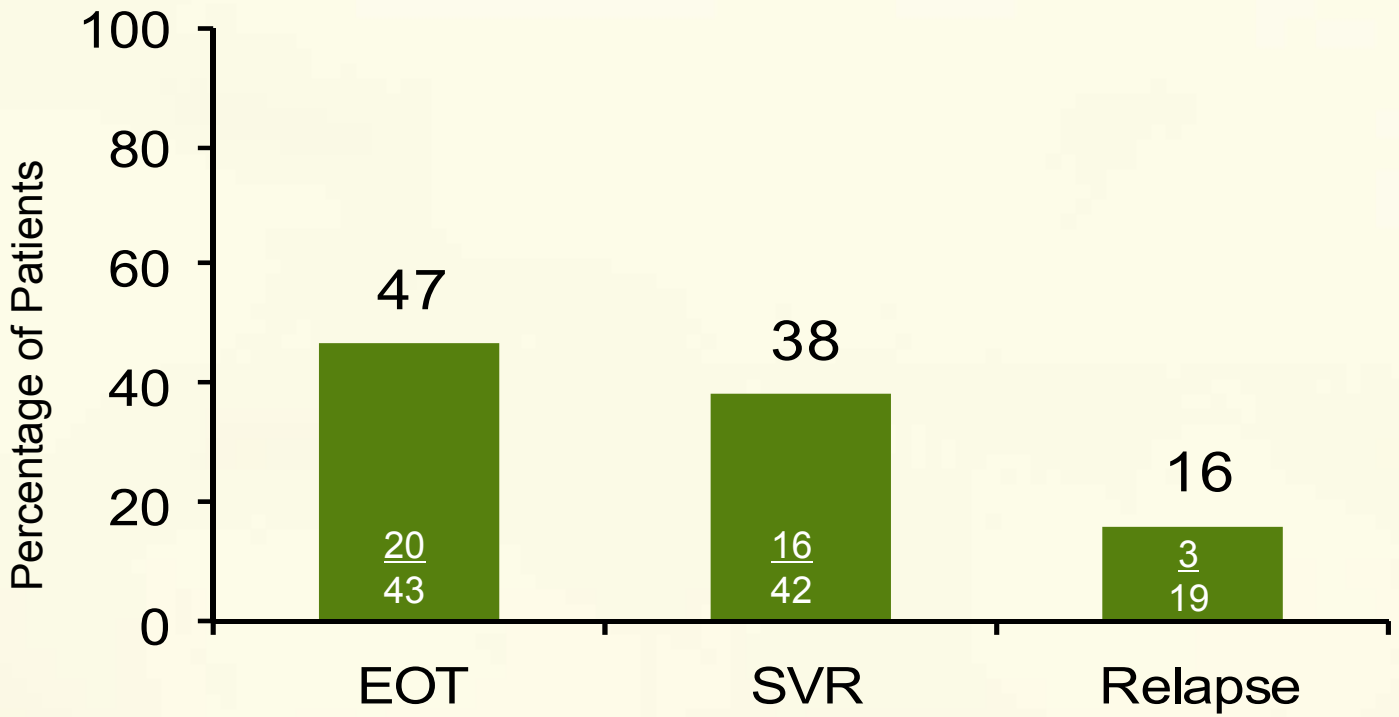
# Numerically Higher SVR Rates Observed in Patients with Low ITPA Activity




* Anemia defined as <10 g/dL

Sulkowski M, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 934.

# PROVIDE Study: Responses in Prior Null Responders*




*Of 48 prior Null Responders from SPRINT-2 and RESPOND-2, 3 discontinued during the 4-week lead-in phase, 2 are ongoing treatment (1 entering TW3, 1 entering TW18 of BOC/PR) and 1 is in follow-up phase

EOT = end of treatment.
SVR = sustained virologic response
Relapse = an undetectable HCV RNA level at EOT, but with a detectable HCV RNA level during the follow-up period

Vierling J, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 931.

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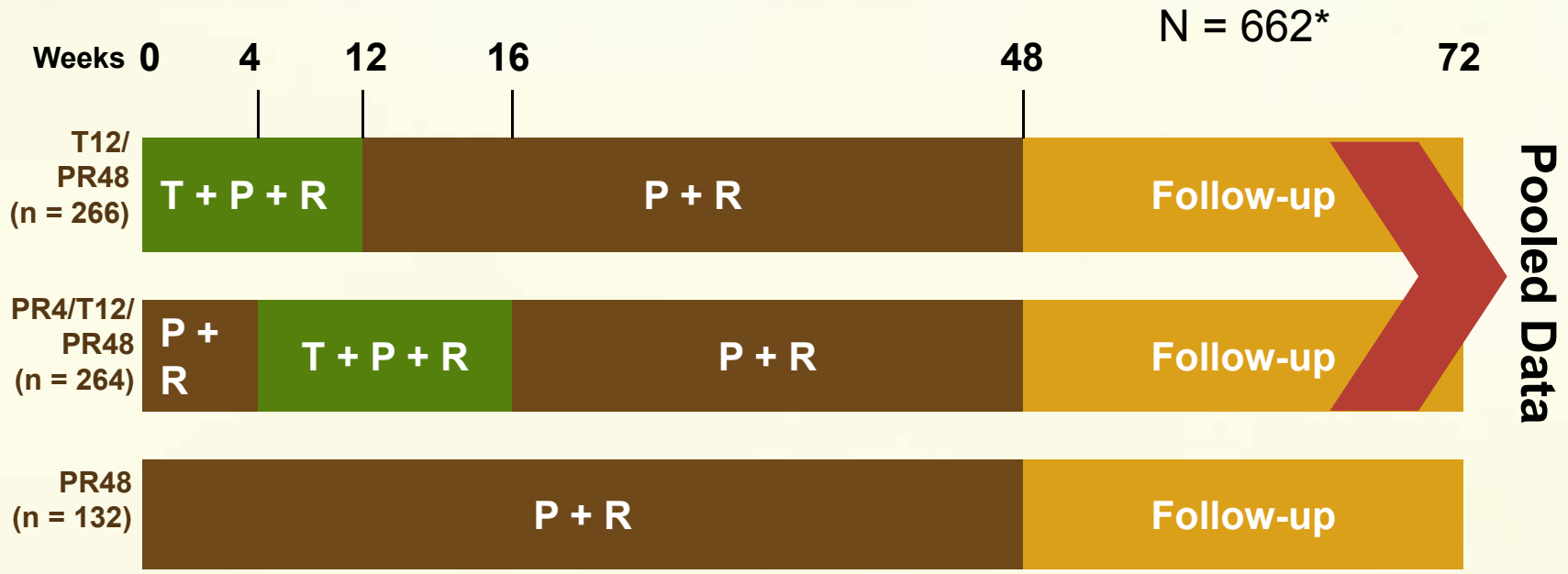
# Telaprevir Studies

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

# REALIZE: Sub-analysis of SVR according to baseline and on-treatment factors

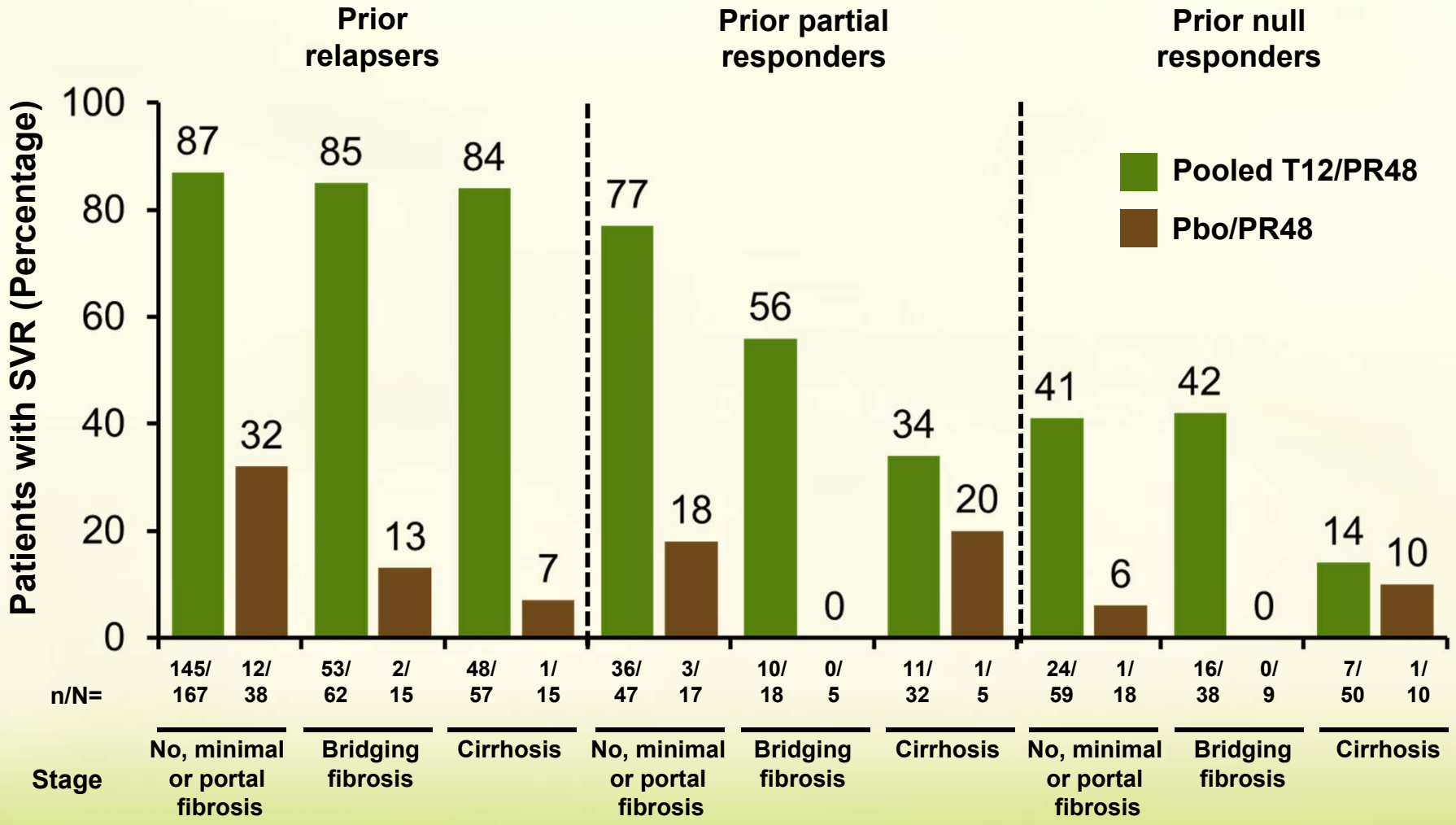



- No erythropoiesis-stimulating agents allowed
- Data pooled from 2 telaprevir arms

*Including null responders, partial responder, and relapsers randomized and stratified by HCV RNA prior response. Abbreviations: P, peginterferon □-2a 180 µg/wk; R, ribavirin 1000–1200 mg/d;T, telaprevir 750 mg q8h.

Roberts SK, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 1368.

# REALIZE: SVR by Baseline Fibrosis Stage and Prior Response




Roberts SK, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 1368.

# REALIZE: Reasons for not Achieving an SVR in TVR-treated Patients

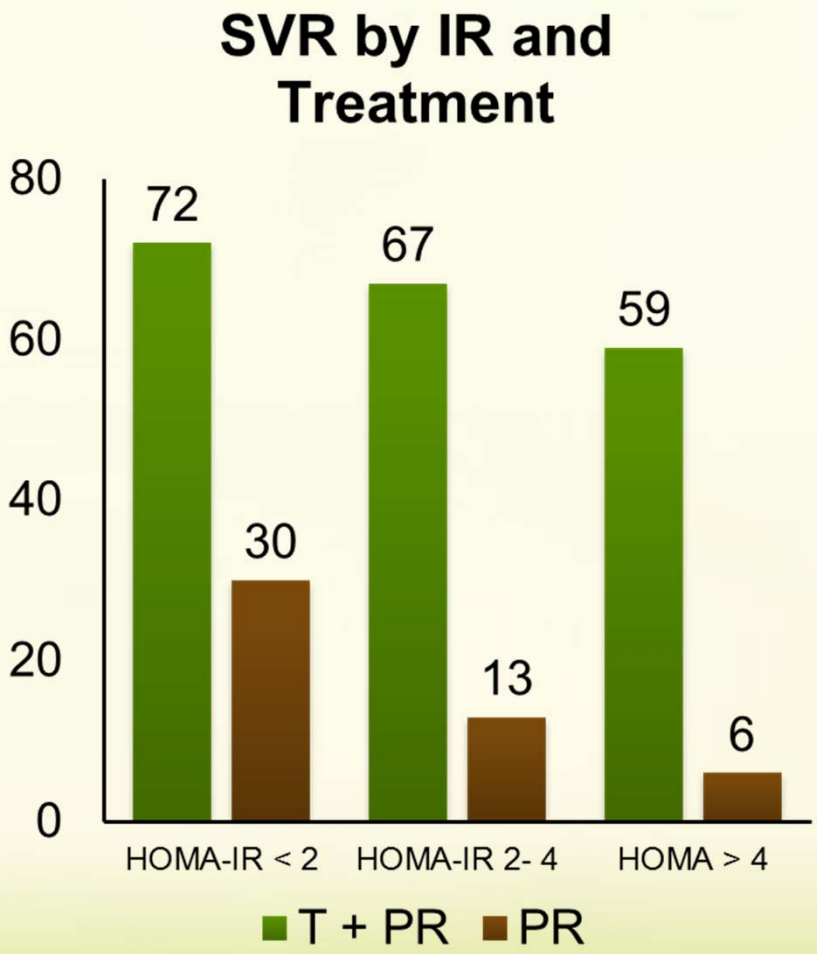
| Category, n (percentage) | Cirrhotics (F4) N=139 | Non-cirrhotics (F0–3) N=391 |
|---|---|---|
| **Patients without SVR** | 73 (53) | 107 (27) |
| **On-treatment virologic failure*** | 44 (32) | 52 (13) |
| **Prior relapsers** | 1 (1) | 2 (1) |
| **Prior partial and null responders** | 43 (31) | 50 (13) |
| **Relapse‡** | 17 (12) | 20 (5) |
| **Prior relapsers** | 3 (2) | 5 (1) |
| **Prior partial and null responders** | 14 (10) | 15 (4) |
| **Other§** | 12 (9) | 35 (9) |
| **Prior relapsers** | 5 (4) | 24 (6) |
| **Prior partial and null responders** | 7 (5) | 11 (3) |

*Includes patients with viral breakthrough and/or patients who discontinued due to a virologic stopping rule
‡Relapse rate calculated relative to total number of patients
§Includes patients with detectable HCV RNA at the end of treatment (for reasons other than virologic stopping rules) without viral breakthrough, or who had undetectable HCV RNA at the end of treatment but were subsequently lost to follow up before Week 72

Roberts SK, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 1368.

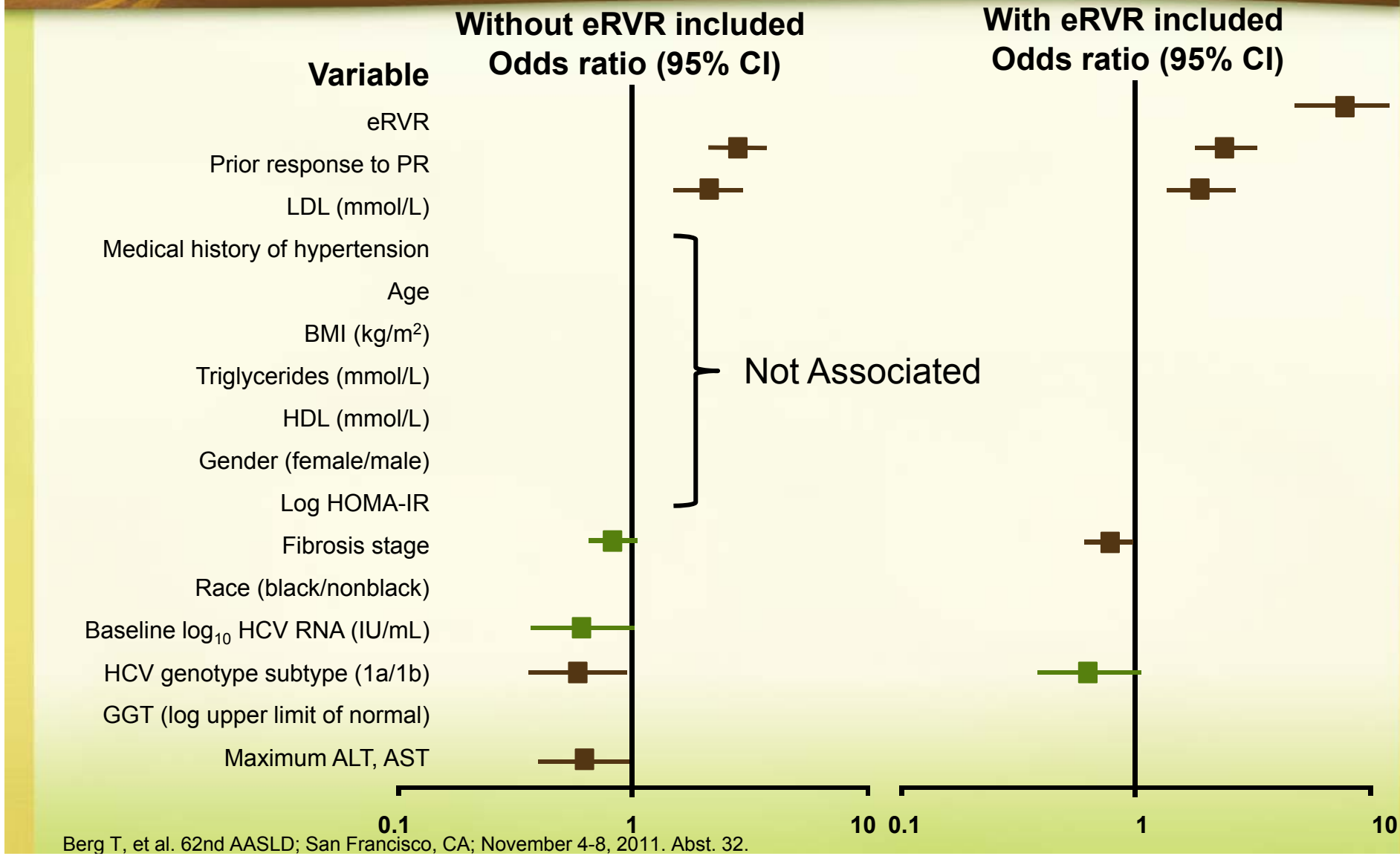
# REALIZE: Insulin resistance was not an independent determinant of SVR

- 578 patients with HOMA-IR at baseline
  - Cirrhosis, 25%
  - Mean BMI, 27 kg/m2
  - Median HOMA-IR, 2.6 (IQR 1.7 – 4.3)
  - HOMA-IR > 4, 28.5%
- With Telaprevir +PR, insulin resistance was not independently associated with SVR



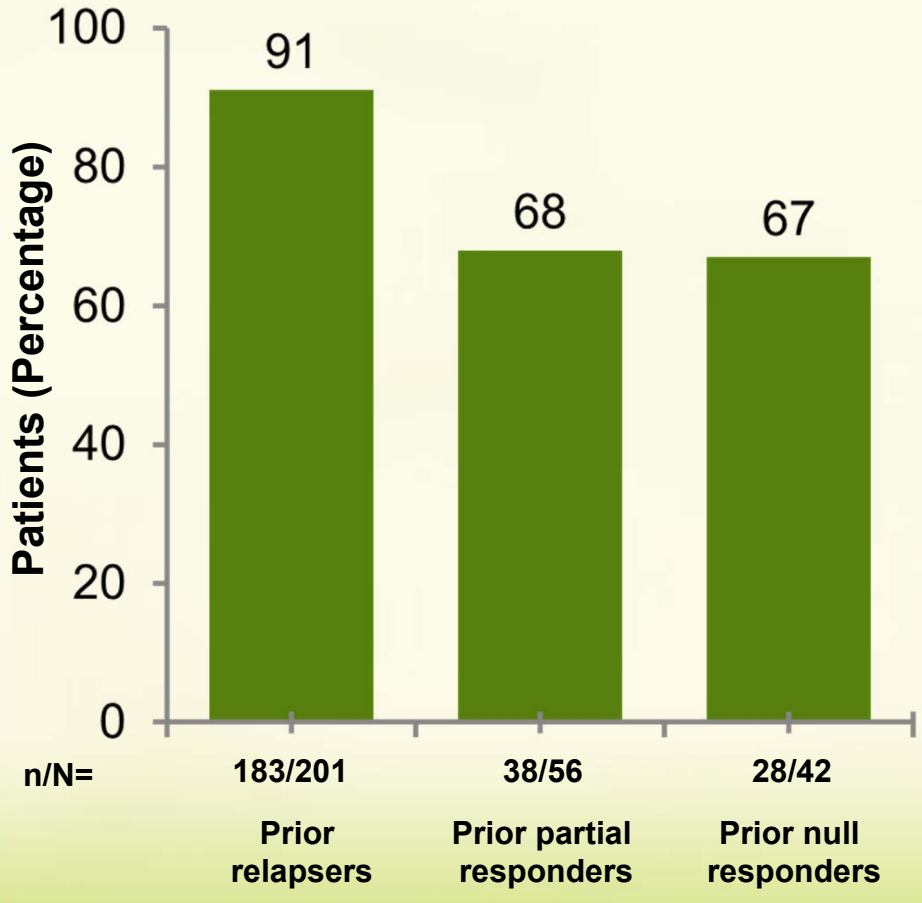

Younossi ZM, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 1369.

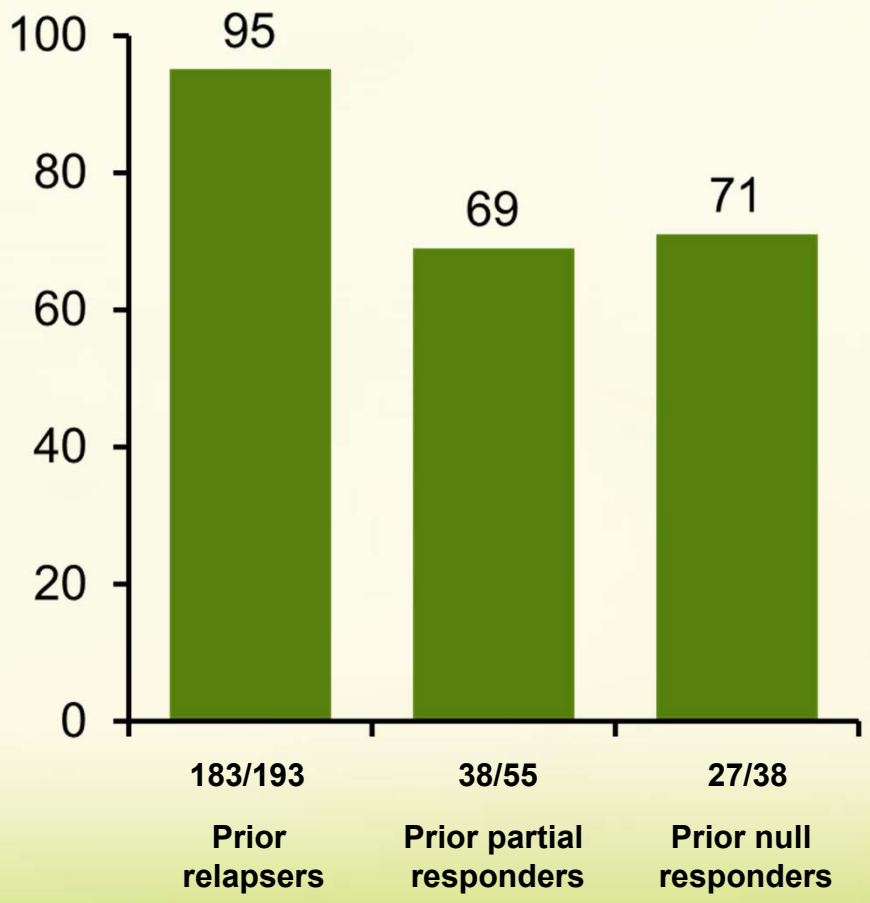
# REALIZE: Multivariate Analysis of Baseline Factors and eRVR Status as Predictors of SVR, MLR Analysis Subset




Berg T, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 32.

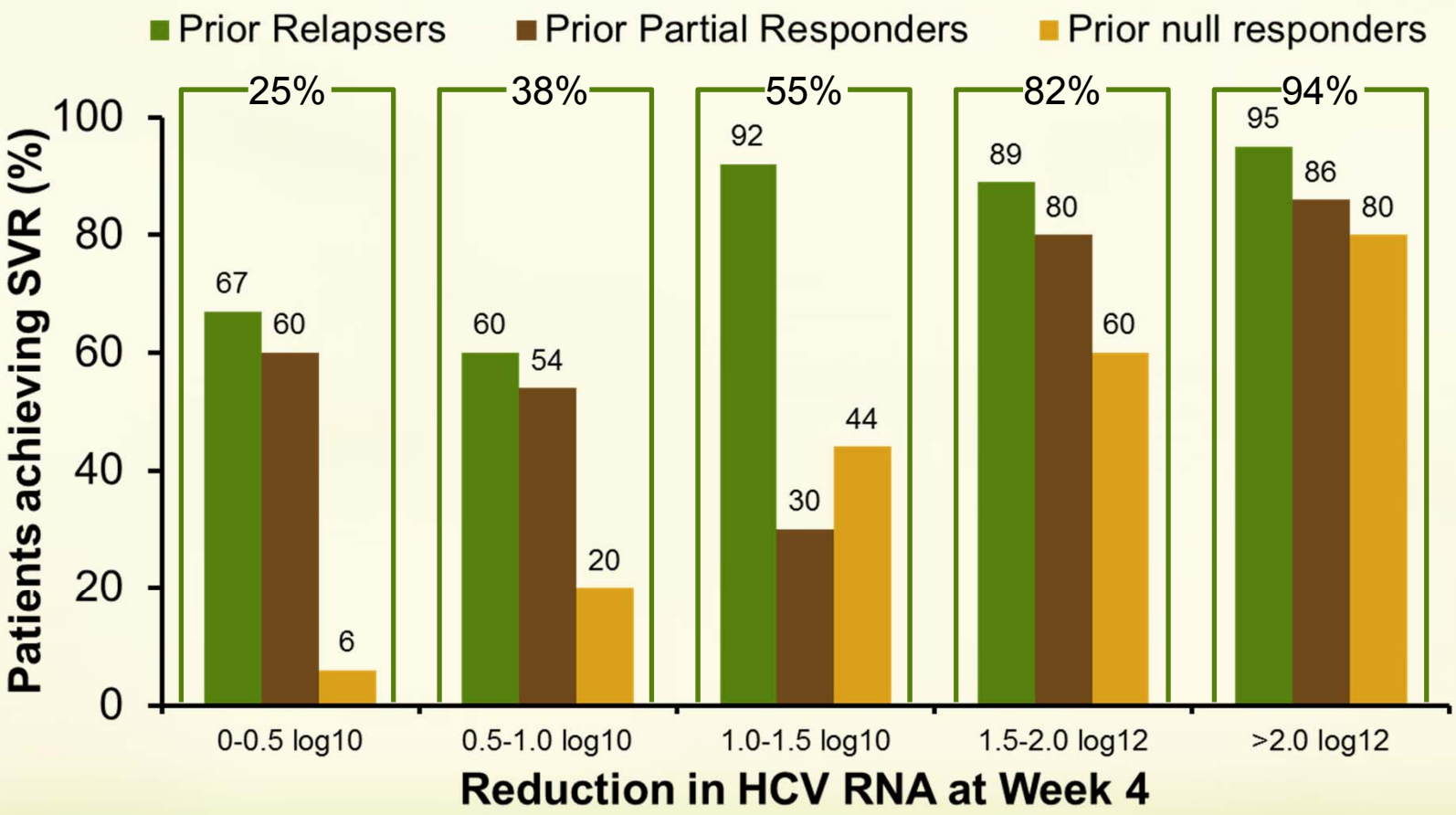
# REALIZE: SVR among TVR-treated Patients with RVR and eRVR, according to Previous Response




Berg T, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 32.

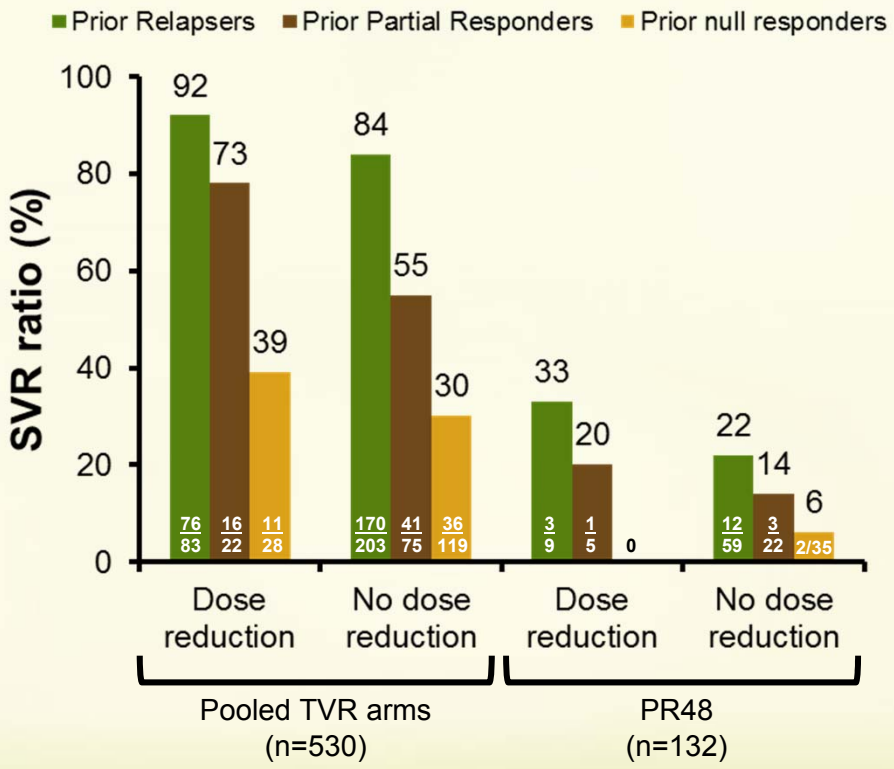
# REALIZE: SVR rate according to prior response and change in HCV RNA after 4 week lead-in




Berg T, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 32.

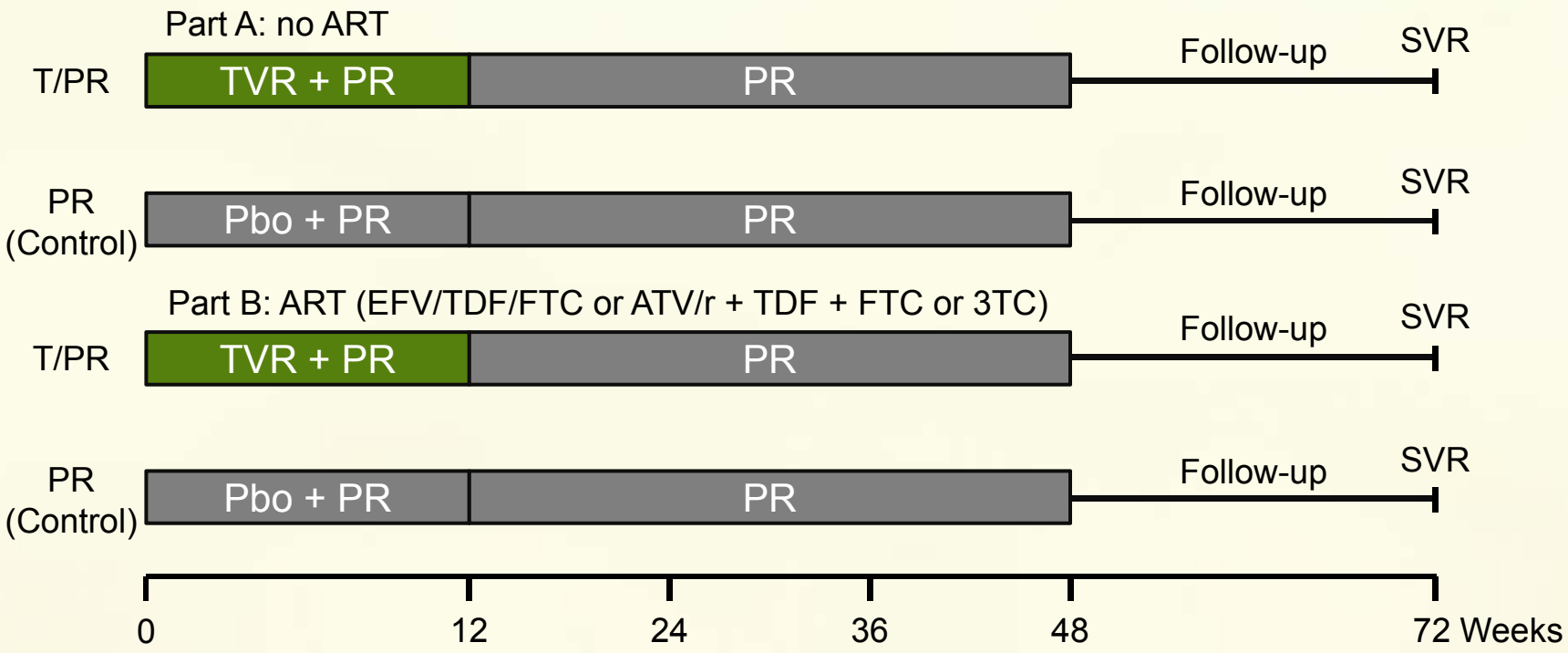
# REALIZE: Impact of anemia/RBV dose reduction on SVR

- Hb <10 g/d occurred in 219/530 (41%) TVR patients and 29/132 (22%) PR48
  - older age, lower BMI, lower Hb, more advanced fibrosis
- RBV was reduced due to anemia in 25% of TVR patients and 12% of PR48 patients
  - No effect on SVR




Roberts SK, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 1368.

# Telaprevir Triple Therapy in HCV-HIV Coinfection—24-Wk Interim Analysis

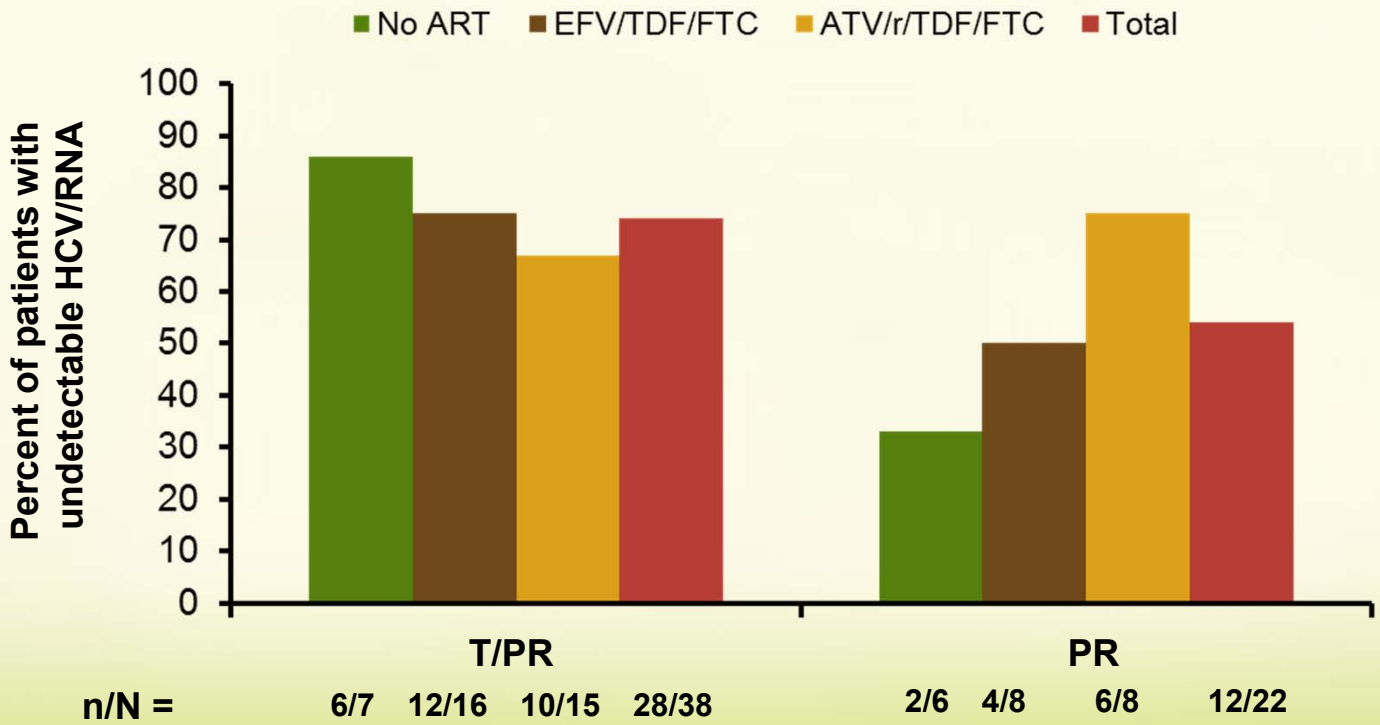



(EFV)=efavirenz; (TDF)=tenofovir; (FTC)=emtricitabine; (ATV/r)=ritonavir-boosted atazanavir; (3TC)=lamivudine; (T) TVR=telaprevir 750 mg q8h or 1125 mg q8h (with EFV); Pbo=Placebo; (P) Peg-IFN=peginterferon alfa-2a (40 kD) 180 µg/wk; (R) RBV=ribavirin 800 mg/day or weight-based (1000 mg/day if weight <75 kg, 1200 mg/day if weight ≥75 kg; France, Germany). Roche COBAS TaqMan HCV test v2.0, LLOQ of 25 IU/mL, LOD of 10 IU/mL

Sherman KE, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. LB-9.

# Proportion of Patients with Undetectable HCV RNA at Week 24

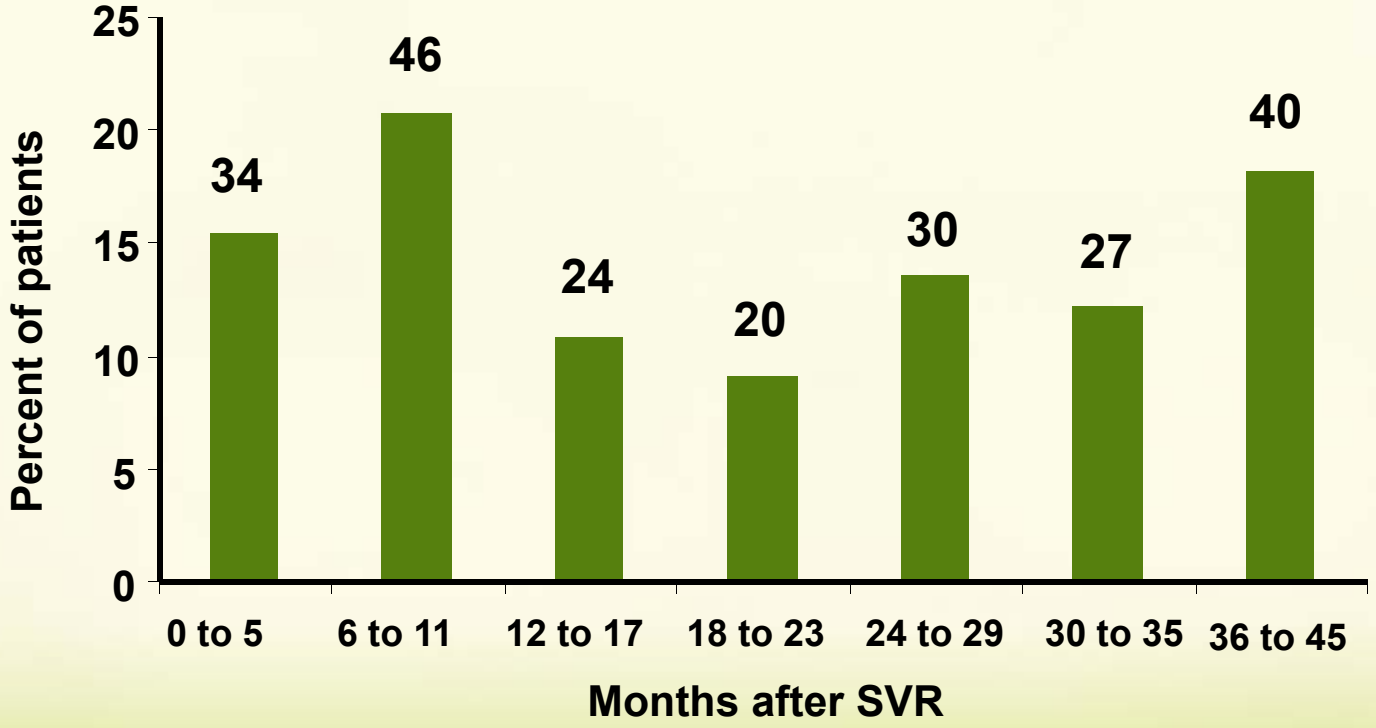
- AEs ≥10% more frequent in T/PR vs PR include:
  - Abdominal pain, vomiting, nausea, pyrexia, dizziness, depression, and pruritis
- Bilirubin AEs more frequent with ATV/r (27% vs 0%)




Sherman KE, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. LB-9.

# EXTEND: SVR after TVR-based Therapy was Durable > 99%

- Median time to follow-up: 21 months after SVR (range 4-44)
- One previously described patient experienced late relapse in parent study 48 weeks after prematurely discontinuing treatment after 10 weeks[1]




Viral load was determined by Roche Taqman® v2 LLOQ of 25 IU/mL

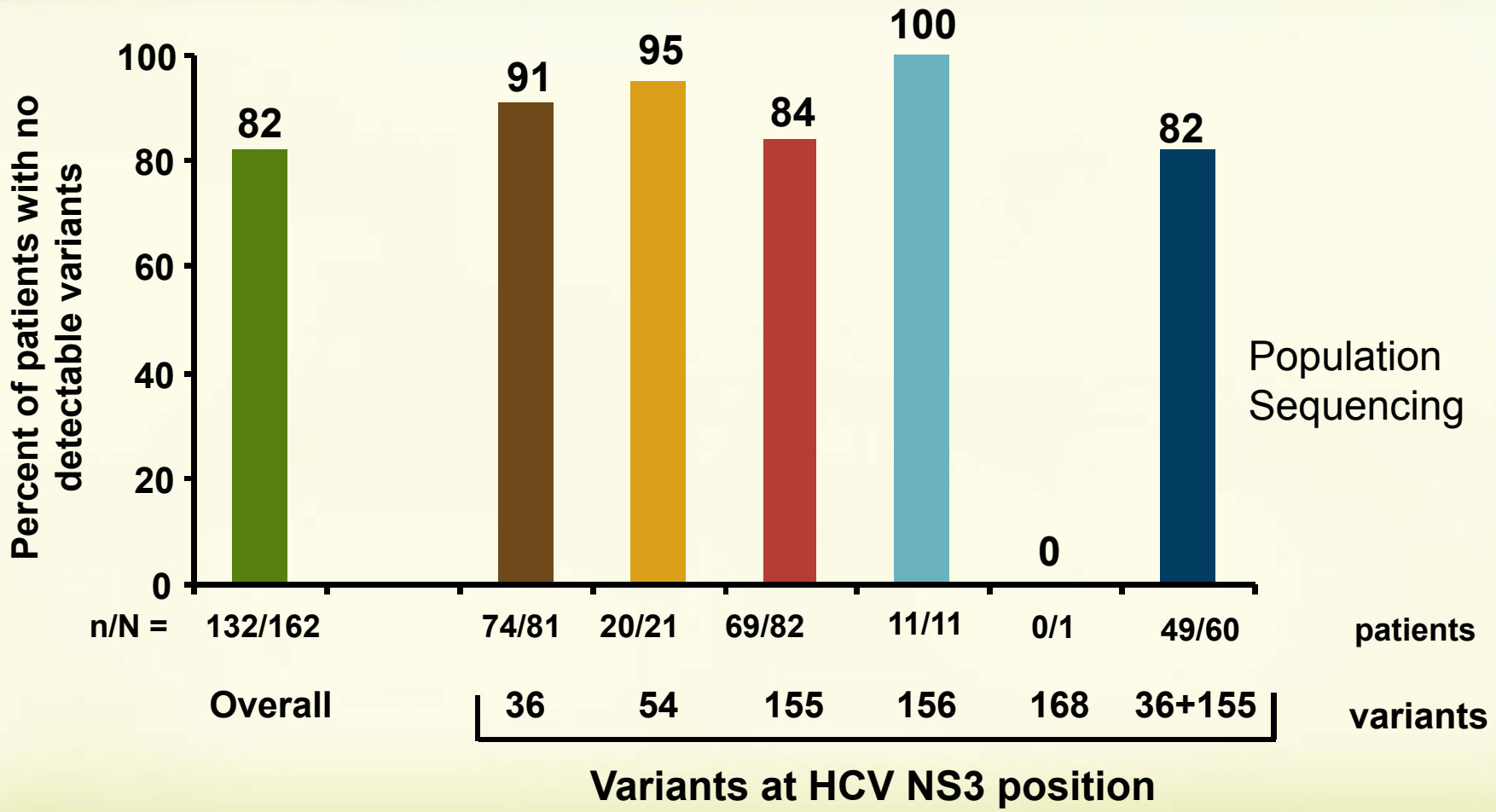
Marcellin P, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 2015.

# EXTEND: Liver-related Clinical Events

- SVR patient population (n=223)
  - No clinical events
- Non-SVR patient population (n=185)
  - 2 patients developed HCC (1 had liver transplant)
  - 1 patient developed hepatic encephalopathy
  - 1 patient had liver decompensation

Marcellin P, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 2015.

# EXTEND: 82% of Patients Do Not Have Detectable Resistant Variants by Last Visit




**Median follow-up time from treatment-failure: 29 months (range 7-49)**

Variant categories are not mutually exclusive

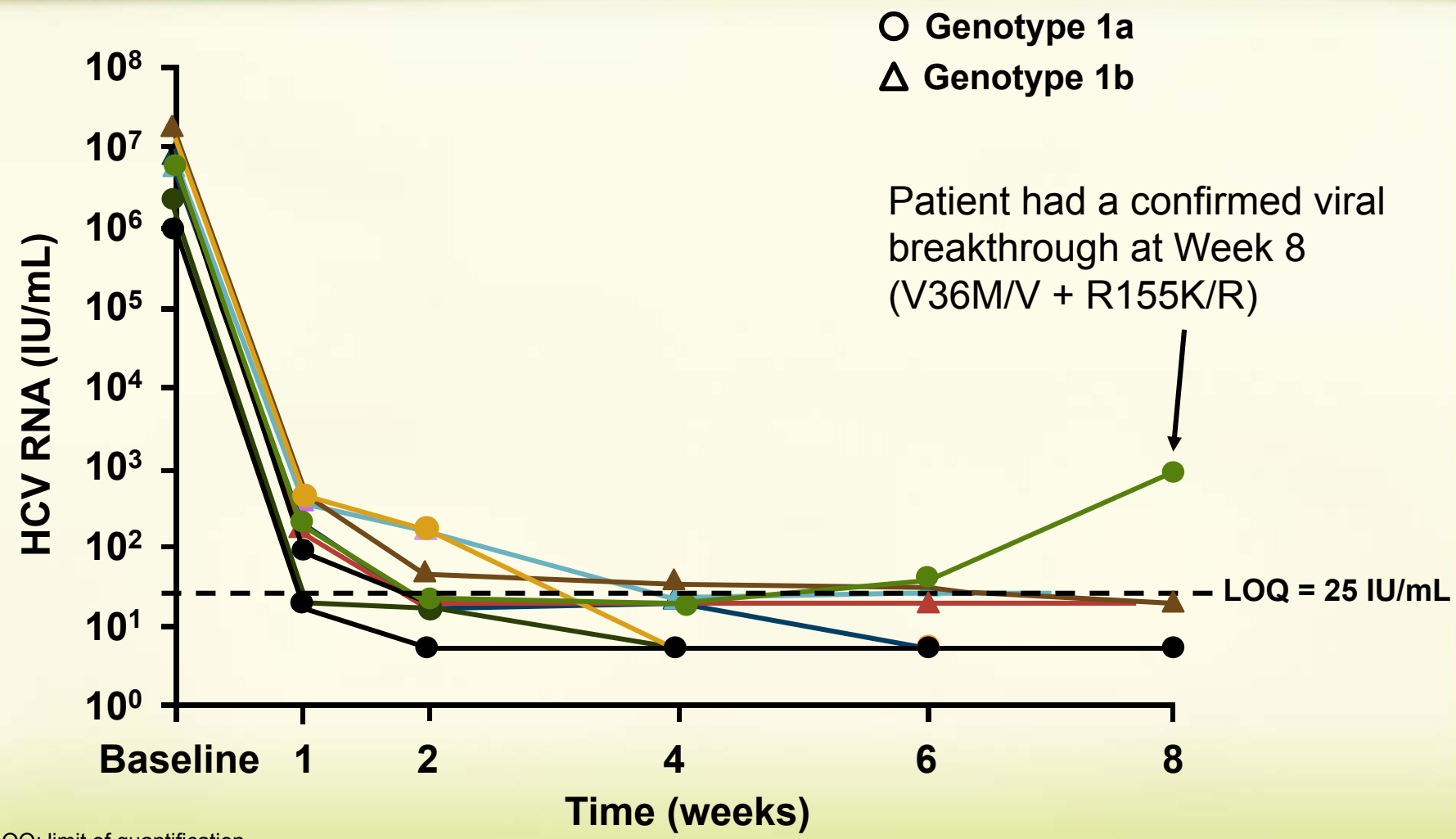
Marcellin P, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 2015.

# C219: Retreatment with TVR+PR after short exposure to TVR in phase 1 studies

- 9 patients previously treated with TVR
  - Genotype 1A, (n = 6)
  - Prior PR failure (n=6)
  - Resistance previously detected (n =8)
    - V36A/M+R155K/T/G (n=6)
    - A156T/V (n=1)
    - V36A+T54A (n=1)
- Retreated with PegIFN/RBV + TVR 750 mg PO TID
  - Absence of TVR-resistant Variants at Baseline by Illumina® deep sequencing data (~ 1%)

Bartels DJ, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 1328.

# C219: HCV RNA Values over Time (Week 8 Interim Analysis, TVR-exposed)




LOQ: limit of quantification

HCV RNA values below LOQ are imputed with an arbitrary value: 17.5 for <25 IU/mL detectable and 5 for <25 IU/mL undetectable

Bartels DJ, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 1328.

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

# Advances in Chronic Hepatitis C Management and Treatment

*REPORTING FROM*

## THE 62ND AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES ANNUAL MEETING

(This coverage is not sanctioned by the conference organizers and is not an official part of the conference proceedings.)

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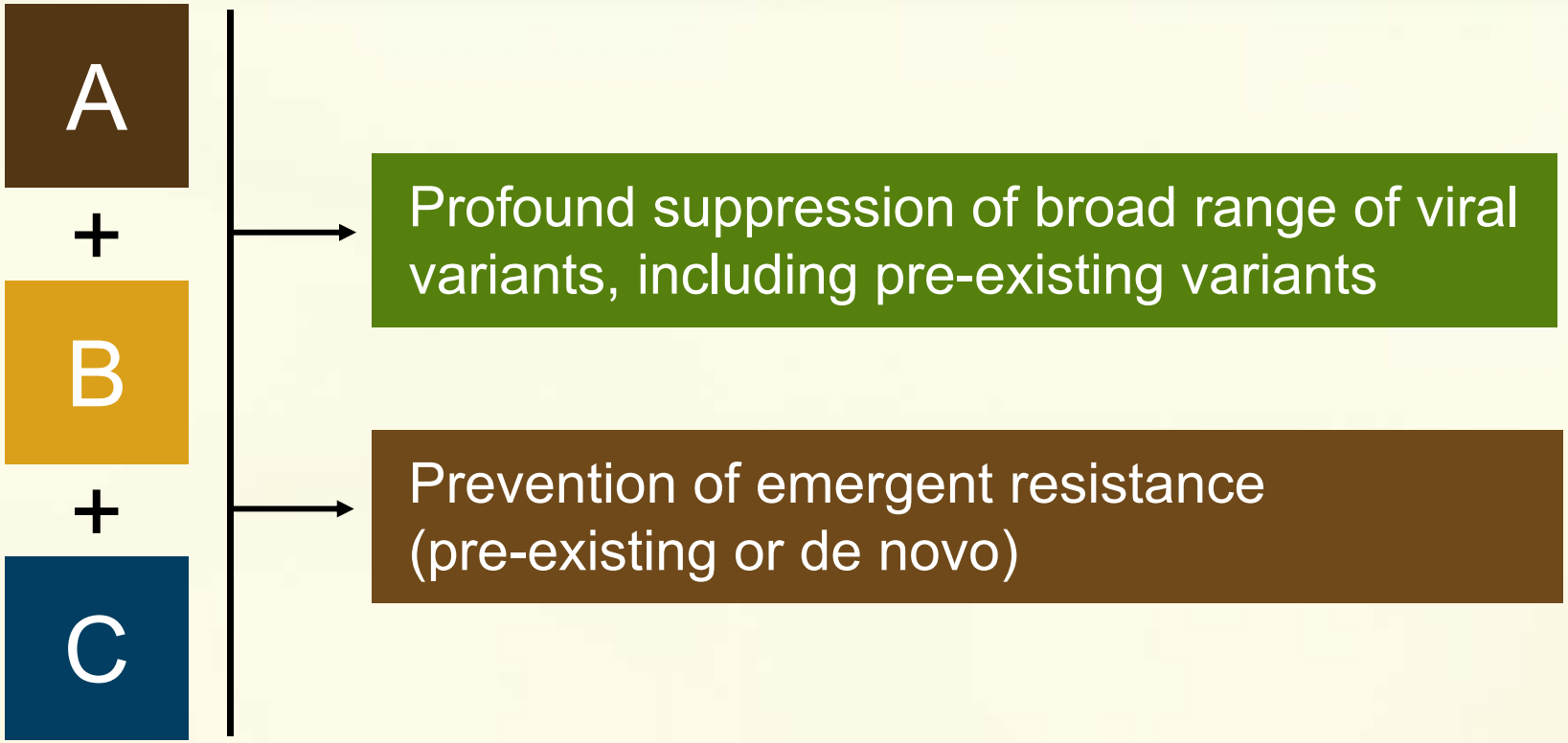
# Novel Therapies and Strategies

Nezam H. Afdhal, MD
Director of Hepatology
Beth Israel Deaconess Medical Center
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

# The Goal of Combination Regimens




- Different drugs may contribute variably to each of these goals. Not all components have to be DAA

# HCV Pipeline by Mechanism of Action and Stage of Development

| Mechanism | Direct-acting antiviral agents | | | | Host-targeting agents | | | |
|---|---|---|---|---|---|---|---|---|
| | Inhibitor of polyprotein processing | Inhibitor of HCV replication | | | Anti-apoptotic agent | Antiviral agent | Immunomodulatory agent | Inhibitor of virus fusion with host cell |
| **Target** | NS3 or NS3/NS4A protease | NS5A | NS5B polymerase | | Caspases | Cyclophilins | Interferons | Viral entry |
| | | | Nucleoside analogue | Non-nucleoside inhibitor | | | | |
| **Recently approved** | Telepravir (Vertex)<br>Boceprevir (Merck) | None | None | None | None | None | None | None |
| **Phase III** | TMC435 (Tibotec and Medivir)<br>BI201335 (Boehringer Ingelheim) | None | None | None | None | Alisporivir (DEB025: Novartis) | None | None |
| **Phase II** | ACH-1625 (Achillion)<br>BMS-650032 (Bristol-Myers Squibb)<br>BMS-791325 (Bristol-Myers Squibb)<br>Danoprevir (RG7227 ; Roche)<br>GS-9256 (Gilead)<br>GS-9451 (Gilead)<br>ABT-450/r (Abbott and Enanta)<br>Vaniprevir (MK-7009 ; Merck) | ABT-267 (Abbot)<br>BMS-790052 (Bristol-Myers Squibb)<br>GS-5885 (Gilead) | IDX184 (Idenix)<br>Mericitabine (RG7128; Roche)<br>PSI-7977 and PSI-7851 (Pharmasset)<br>RG7128 (Roche and Pharmasset) | ABT-333 (Abbott)<br>ABT-072 (Abbott)<br>ANA598 (Anadys)<br>BBI207127 (Boehringer Ingelheim)<br>Filibuvir (Pfizer)<br>IDX375 (Idenix)<br>Tegobuvir (GS-9190; Gilead)<br>VCH-916 (Vertex)<br>VX-222 (Vertex) | IDN-6556 (Idun/Conatus) | NIM811 (Novartis)<br>SCY-635 (Scynexis) | PEGylated interferon-λ (Bristol-Myers Squibb) | None |
| **Phase I** | GSK2336805 (GlaxoSmithKline)<br>IDX320 (Idenix)<br>MK-5172 (Merck)<br>VX-985 (Vertex) | AZD7295 (AstraZeneca)<br>PPI-461 (Presidio) | GS-6620 (Gilead)<br>INX-08189 (Inhibitex)<br>PSI-938 (Pharmasset) | GSK2485852 (GlaxoSmithKline)<br>VX-759 (VCH-759; Vertex)<br>GS-9669 (Gilead) | None | None | GS-9620 (Gilead) | ITX-5061 (iTherX) |
| **Preclinical** | ACH-1095 (Achillion)<br>ACH-2684 (Achillion)<br>AVL-192 (Avila)<br>GNS-227 (GenoScience Pharma) | ACH-2928 (Achillion)<br>BMS-766 (Bristol-Myers Squibb)<br>EDP-239 (Enanta)<br>IDX380 and IDX719 (Idenix)<br>PPI-437, PPI-668, PPI-883 and PPI-1301 (Presido) | PSI-661 (Pharmasset) | BILB 1941 (Boehringer Ingelheim) | None | None | None | ITX4520 (iTherX) PRO 206 (discontinued; Progenics)<br>REP 9C (REPLICor)<br>SP-30 (Samaritan) |

*Only represents a sample of agents in development for HCV

Schlutter J. Nature. 2011;474(7350):S5-S7. 

# Challenges as HCV Therapy Evolves to Incorporate DAA Agents

**Baseline predictors of response**
- Who to treat
- Tailored therapies
- Tailored duration

**New viral kinetic rules with new therapies**
- Positive predictive values
- Negative predictive values
- Tailored duration

**Resistance issues**
- Impact of baseline variants
- Persistence of resistant variants
- Cross resistance within classes
- Impact of dosing/adherence

**Markers of complete viral eradication**

**Additional toxicities**

**Cost**

# PILLAR Study: TMC435 + PEG-IFN + RBV in Treatment-Naïve G1 Patients

**Phase 2b, randomized, double-blind study in treatment-naïve, HCV G1, TMC435 (QD oral HCV NS3/4A PI) + PEG-IFN α-2a/RBV (P/R)**

| Response, n/N (%) | TMC435 12W P/R RGT | TMC435 24W P/R RGT | TMC435 12W P/R RGT | TMC435 24W P/R RGT | Placebo/P/R 48W |
|---|---|---|---|---|---|
| | 75 mg | | 150 mg | | |
| | N=78 | N=75 | N=77 | N=79 | N=77 |
| **RVR[1]** | 59/78 (75.6) | 51/75 (68.0) | 58/77 (75.3) | 59/79 (74.7) | 4/77 (5.2) |
| **EOT[2]** | 72/78 (92.3) | 73/75 (97.3) | 71/77 (92.2) | 74/79 (93.7) | 61/77 (79.2) |
| **SVR24[3]** | 64/78 (82.1)* | 56/75 (74.7) | 62/77 (80.5)* | 68/79 (86.1)** | 50/77 (64.9) |
| **SVR W72[4]** | 63/78 (80.8)* | 53/75 (70.7) | 60/77 (77.9)* | 67/79 (84.8)** | 50/77 (64.9) |
| **Viral relapse** | 8/72 (11.1) | 14/72 (19.4) | 6/69 (8.7) | 6/75 (8.0) | 11/62 (17.7) |

HCV RNA <25 IU/mL undetectable at [1]Week 4 (rapid virologic response);[2]End of treatment; [3]24 weeks after planned end of treatment; [4]Week 72 *$P$<0.05, **$P$<0.005, significant difference vs control (closed testing procedure), other SVR differences not significant

Fried M, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. LB-5.

# ATLAS Study: SVR24 Rates with Response-guided Danoprevir + PEG-IFN + RBV

- Treatment-naive HCV G1 patients

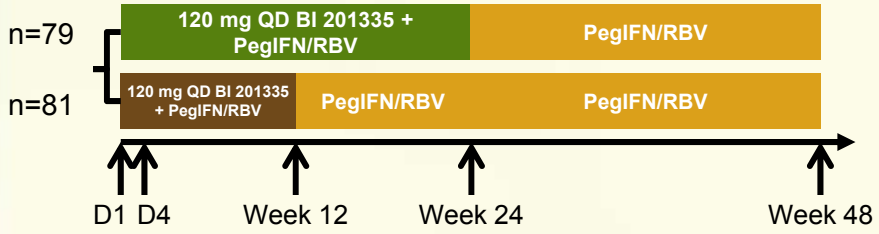
| N (%) | DNV 300 mg q8h + PR (n=72) | DNV 600 mg q12 + PR (n=72) | DNV 900 mg q12h + PR (n=50)* | PBO + PR (n=31) |
|---|---|---|---|---|
| **Overall SVR24** | 49 (68%) | 60 (83%) | 38 (76%) | 13 (43%) |
| **eRVR** | 47 (65%) | 57 (79%) | 9 (18%) | N/A |
| **SVR24 in eRVR Patients** | 41/47 (87%) | 54/57 (95%) | 8/9 (89%) | N/A |

*900mg dose DNV was D/C early due to 3 case of reversible grade 4 ALT elevations; only 8 of 50 patients in 900mg arm received the full 12 weeks of DNV Tx
DNV=danoprevir

Terrault N, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 79.

# SILEN-C3: Treatment for 12 or 24 weeks with BI201335 combined with peg-INFα-2a + RBV in treatment-naive patients with chronic G1 HCV

- Phase 2b; n=159; naïve, geno 1




  - Geno 1b 46%/53%
  - No IL28B data obtained
- AEs: GI disorders 57% and 48%
  - Jaundice: 3.8% and 5.1% (indirect hyperbilirubinemia)
  - Rash/photosensitivity: 28% and 25%
  - eRVR in 71% (12 wk) and 82% (24 wk)
- SVR 63% (12 wk) vs 71.8% (24 wk)
  - Early viral clearance (<8 wks) achieved SVR of 79% and 87%
  - If undetectable at >8 wks SVR of 0%
    - Breakthroughs higher in 12 wk arm 10% vs 4%

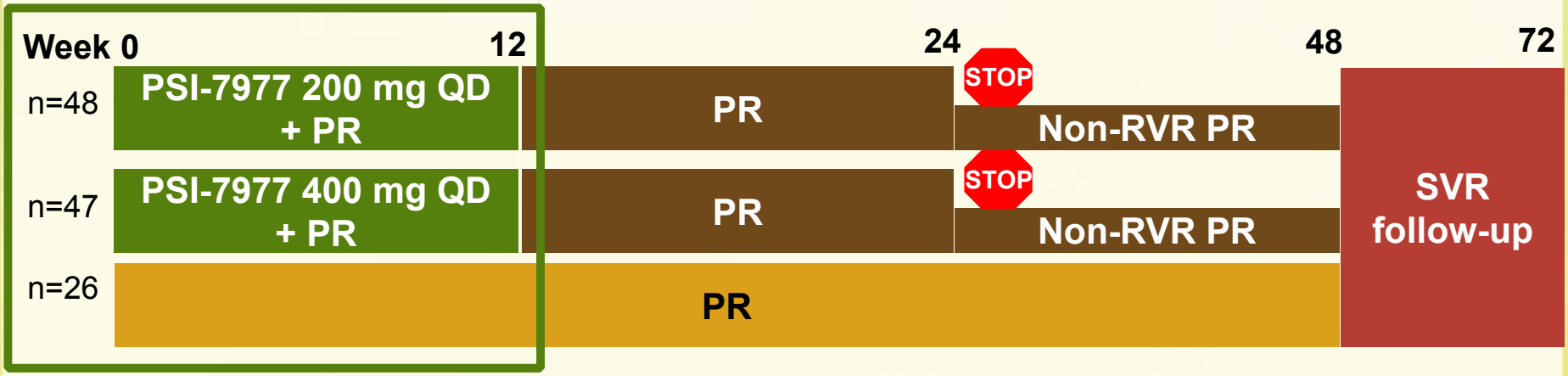
| Time to 1st undetectable VL | 12 wks BI201335 (n=81) | | 24 wks BI201335 (n=78) | |
|---|---|---|---|---|
| | N (%) | SVR, % | N (%) | SVR, % |
| **Wk 2** | 17 (21.0) | 100 | 25 (32.1) | 92.0 |
| **Wk 4** | 31 (38.3) | 77.4 | 32 (41.0) | 87.5 |
| **Wk 8** | 16 (19.8) | 62.5 | 11 (14.1) | 45.5 |
| **>Wk 8** | 3 (3.7) | 0 | 3 (3.8) | 0 |
| **Never undetectable** | 14 (17.3) | 0 | 7 (9.0) | 0 |

- Daily dosed PI with comparable efficacy and safety profile to current PIs. Confirms that earlier the patients become negative on PI-based therapy, the more likely to achieve SVR.
- Is toxicity an issue with many options in class?

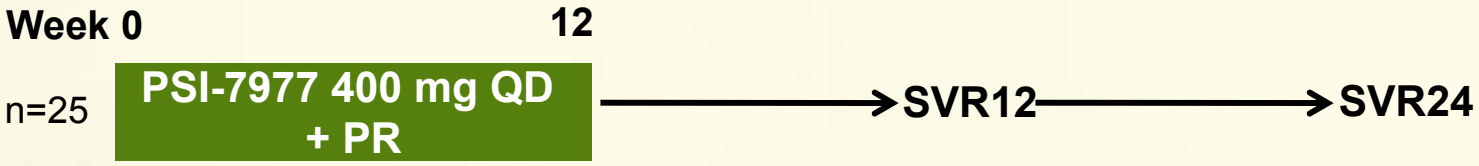
Dieterich D, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 36.

# PROTON: Once Daily PSI-7977 + PEG-IFN + RBV in HCV Treatment-Naïve Patients with G1 or G2/G3

## HCV G1 (N=121 treatment-naïve patients)




## HCV G2/G3 (N=25 treatment-naïve patients)

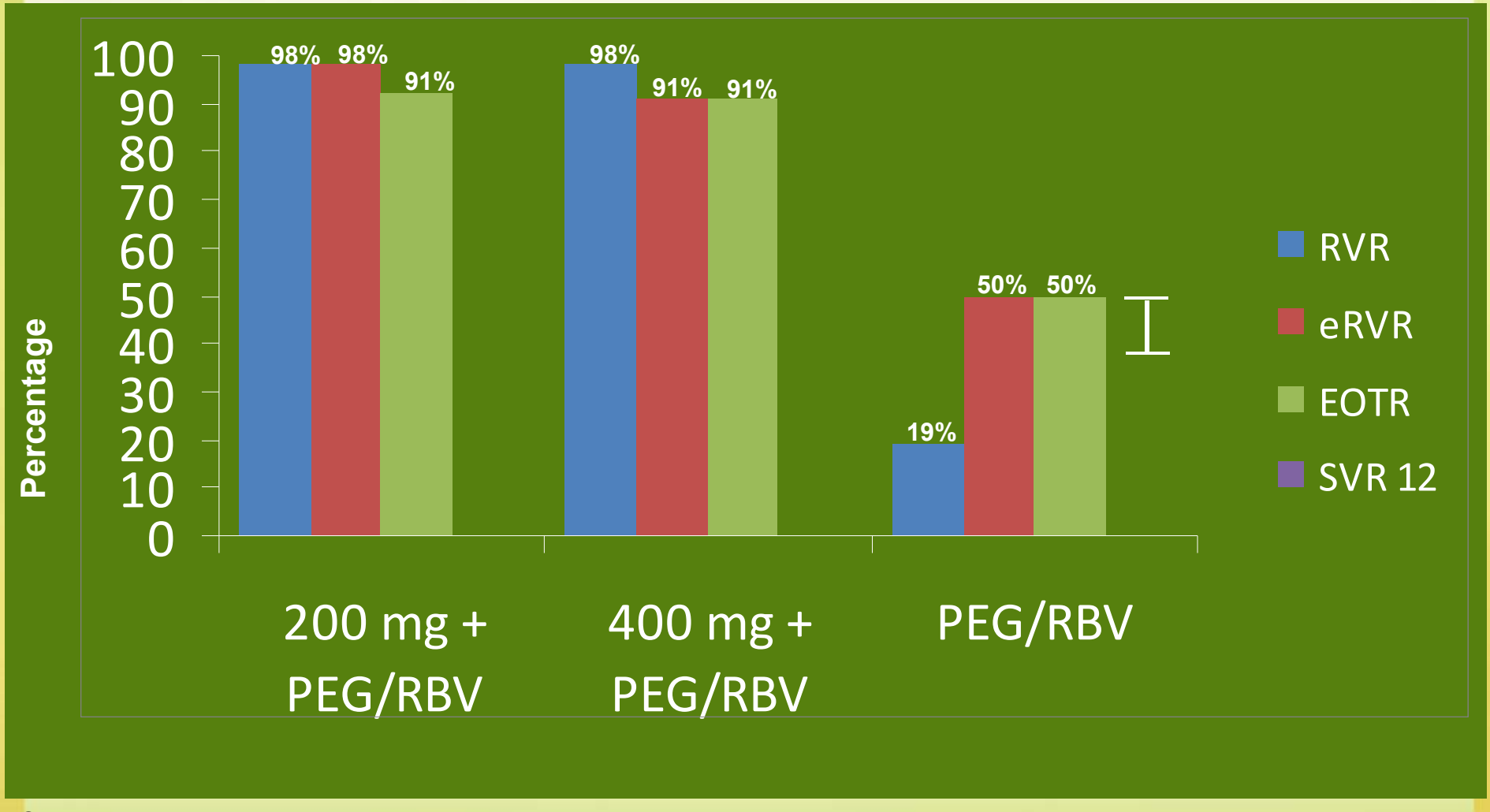




Nelson DR, et al. Poster presented at: EASL: The International Liver Congress 2011; March 30-April 3, 2011; Berlin, Germany. Poster LB1372.
Lalezari J, et al. Presented at: EASL: The International Liver Congress 2011; March 30-April 3, 2011; Berlin, Germany. Oral Presentation 61.

Lawitz E, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 225.

# PROTON RESULTS: PSI-7977 200 mg and 400 mg Cohorts >91% EOTR (through wk 24)



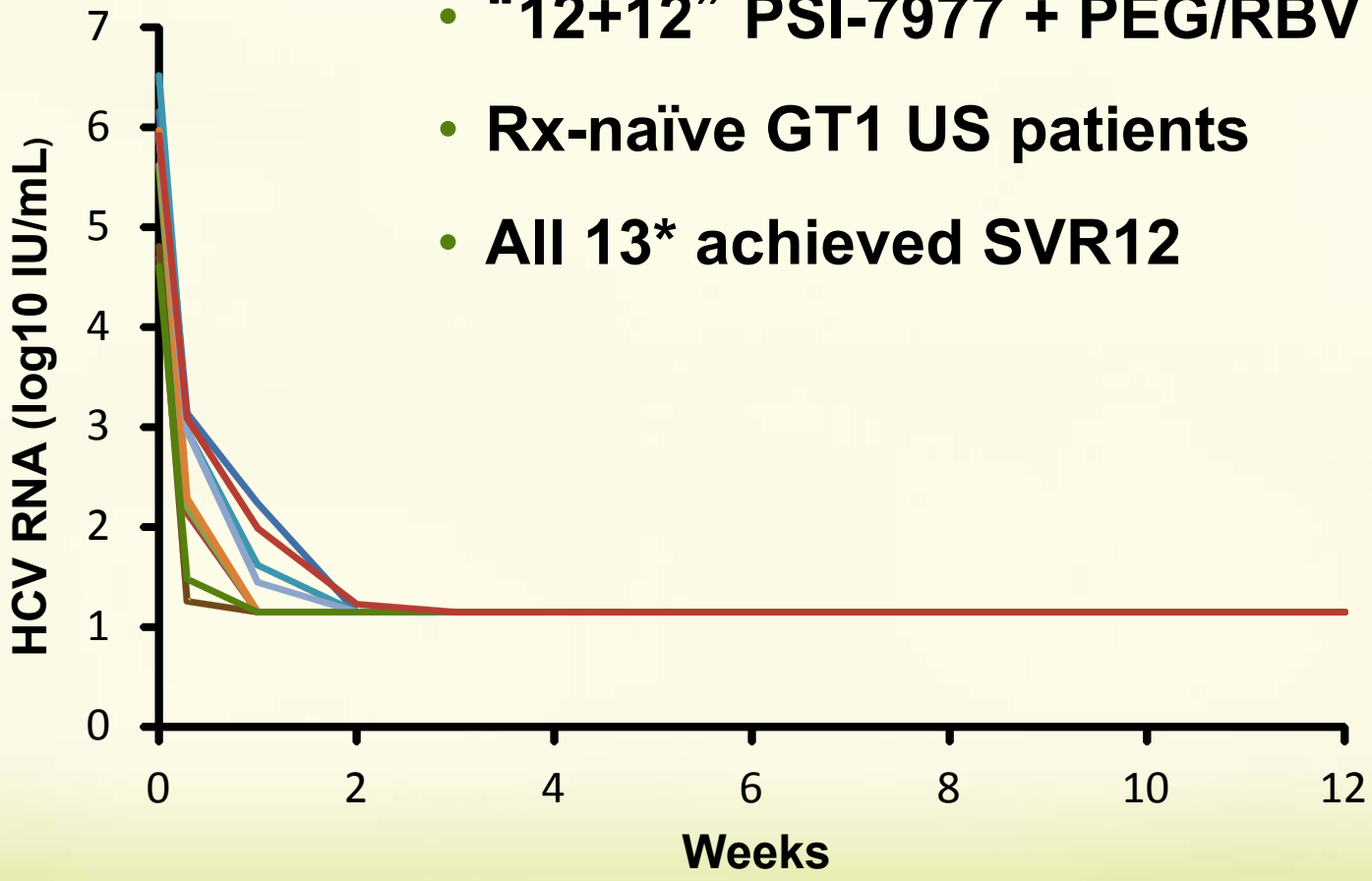

LOD= 15 IU/mL

** 2/26 data pending

Lawitz E, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 225.

# PROTON Results: Consistent Antiviral Response In Subjects With Genetic Predictors Of Non-response To IFN (IL28B T/T)

- "12+12" PSI-7977 + PEG/RBV
- Rx-naïve GT1 US patients
- All 13* achieved SVR12

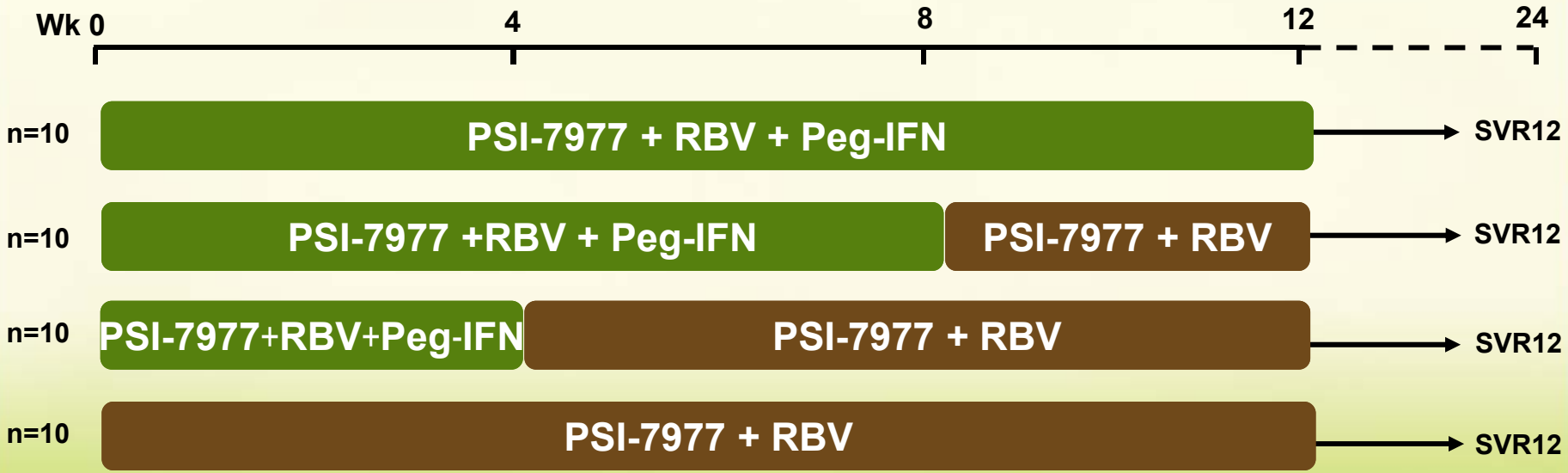



* 10 subjects with IL28 T/T allele randomized to the 400 mg group and 3 randomized to the 200 mg group

Lawitz E, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 225.

# PSI-7977 ELECTRON: Study Design for HCV GT2/3

- Treatment-naïve, non-cirrhotic, age ≥18 years
- HCV RNA >50,000 IU/mL
- Allowed concurrent methadone use
- Stratified by HCV genotype and IL28B genotype
- Randomized 1:1:1:1 into IFN-sparing or IFN-free




Gane EJ, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 34.

# PSI-7977 ELECTRON Results

| Time Wk | PSI-7977 RBV 12 weeks PEG | | PSI-7977 RBV 8 weeks PEG | | PSI-7977 RBV 4 weeks PEG | | PSI-7977 RBV NO PEG | |
|---|---|---|---|---|---|---|---|---|
| | n=11 | %<LOD | n=10 | %<LOD | n=9 | %<LOD | n=10 | %<LOD |

Gane EJ, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 34.

# PSI-7977 ELECTRON
# IFN-free PSI-7977/RBV ➡ 100% RVR

| Time Wk | PSI-7977 RBV 12 weeks PEG | | PSI-7977 RBV 8 weeks PEG | | PSI-7977 RBV 4 weeks PEG | | PSI-7977 RBV NO PEG | |
|---|---|---|---|---|---|---|---|---|
| | n | %<LOD | n | %<LOD | n | %<LOD | n | %<LOD |
| **2** | 9/11 | 82 | 7/8 | 88 | 8/9 | 89 | 8/10 | 80 |
| **4** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |

Gane EJ, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011. Abst. 34.

# PSI-7977 ELECTRON
# IFN-free PSI-7977/RBV ➡ 100% EOTR

| Time Wk | PSI-7977 RBV 12 weeks PEG | | PSI-7977 RBV 8 weeks PEG | | PSI-7977 RBV 4 weeks PEG | | PSI-7977 RBV NO PEG | |
|---|---|---|---|---|---|---|---|---|
| | n | %<LOD | n | %<LOD | n | %<LOD | n | %<LOD |
| **2** | 9/11 | 82 | 7/8 | 88 | 8/9 | 89 | 8/10 | 80 |
| **4** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **8** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **12** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |

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# PSI-7977 ELECTRON
# IFN-free PSI-7977/RBV ➡ 100% SVR12

| Time Wk | PSI-7977 RBV 12 weeks PEG | | PSI-7977 RBV 8 weeks PEG | | PSI-7977 RBV 4 weeks PEG | | PSI-7977 RBV NO PEG | |
|---|---|---|---|---|---|---|---|---|
| | n | %<LOD | n | %<LOD | n | %<LOD | n | %<LOD |
| **2** | 9/11 | 82 | 7/8 | 88 | 8/9 | 89 | 8/10 | 80 |
| **4** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **8** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **12** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **SVR4** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **SVR8** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **SVR12** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |

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# PSI-7977 ELECTRON
## 100% concordance of SVR12 with SVR24

| Time Wk | PSI-7977 RBV 12 weeks PEG | | PSI-7977 RBV 8 weeks PEG | | PSI-7977 RBV 4 weeks PEG | | PSI-7977 RBV NO PEG | |
|---|---|---|---|---|---|---|---|---|
| | n | %<LOD | n | %<LOD | n | %<LOD | n | %<LOD |
| **2** | 9/11 | 82 | 7/8 | 88 | 8/9 | 89 | 8/10 | 80 |
| **4** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **8** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **12** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **SVR4** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **SVR8** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **SVR12** | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |
| **SVR24** | 6/6 | 100 | 5/5 | 100 | 5/5 | 100 | 4/4 | 100 |

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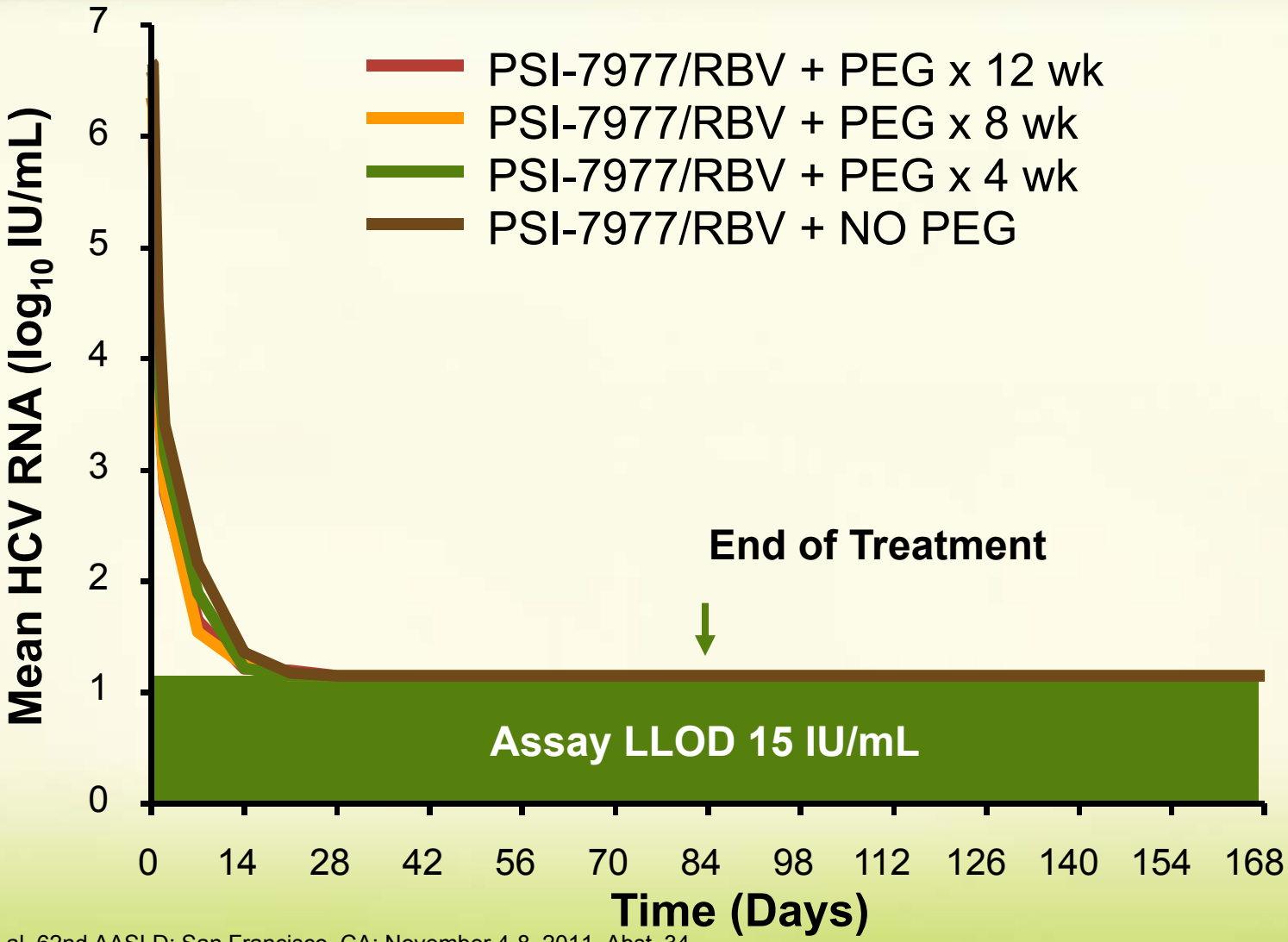
# PSI-7977 ELECTRON

## Rapid Viral Suppression with or without IFN

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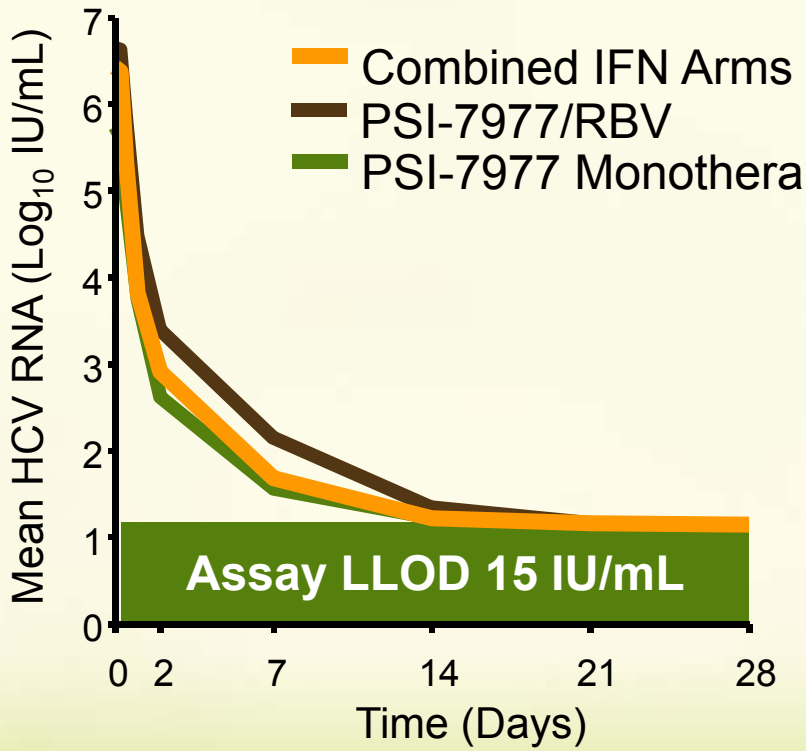
# PSI-7977 ELECTRON
# What is the role of Ribavirin?

- PSI-7977 monotherapy arm (n=10) was added




- No on-treatment viral breakthroughs or resistance
- 6/10 subjects achieved SVR4
- Further studies of PSI-7977 monotherapy in progress
- PSI-7977/RBV for 12 weeks being advanced in IFN-free Phase 3 program

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# PSI-7977 ELECTRON
## Significant improvements in safety and tolerability with IFN-free PSI-7977/RBV

| | PSI-7977 RBV 12 wks PEG n=11 | PSI-7977 RBV 8 wks PEG n=10 | PSI-7977 RBV 4 wks PEG n=9 | PSI-7977 RBV NO PEG n=10 |
|---|---|---|---|---|
| **SAE** | 0 | 0 | 0 | 0 |
| **>1 AE: n (%)** | 8 (72) | 5 (50) | 6 (67) | 4 (40) |
| **Headache** | 2 (18) | 2 (20) | 1 (11) | 1 (10) |
| **Fatigue** | - | 1 (10) | 1 (11) | 1 (10) |
| **Depression** | 3 (27) | - | - | - |
| **Insomnia** | 1 (9) | - | 2 (22) | - |
| **Anxiety** | 1 (9) | - | 1 (11) | - |
| **Irritability** | 2 (18) | - | - | - |
| **Myalgia** | 1 (9) | - | - | 1 (10) |
| **Upper RTI** | 1 (9) | - | 1 (11) | - |

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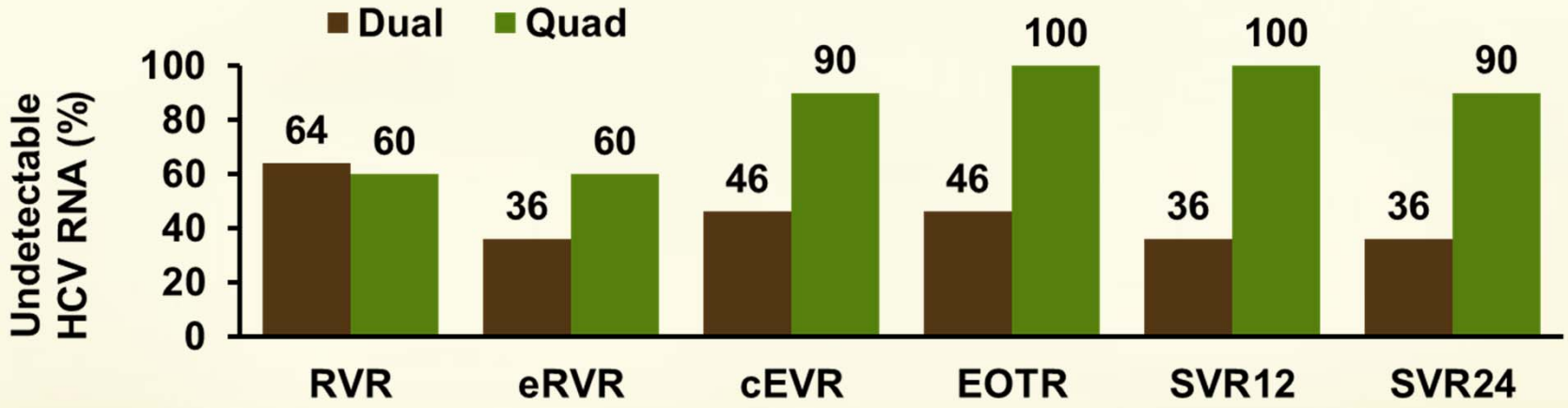
# Dual Oral vs Quad Therapy: BMS-790052 + BMS-650032 ± PR

| | | |
|---|---|---|
| Group A | BMS-790052 (60 mg QD) + BMS-650032 (600 mg BID) (n=11) | Follow-up x 48 weeks |
| Group B | BMS-790052 (60 mg QD) + BMS-650032 (600 mg BID) + PR (n=10) | Follow-up x 48 weeks |

24-week treatment

Post treatment: Week 24: SVR24




Phase 2a study; N=21; 19 with CT/TT *IL28B* genotype.
BMS-790052=NS5A replication complex inhibitor; BMS-650032=NS3 PI

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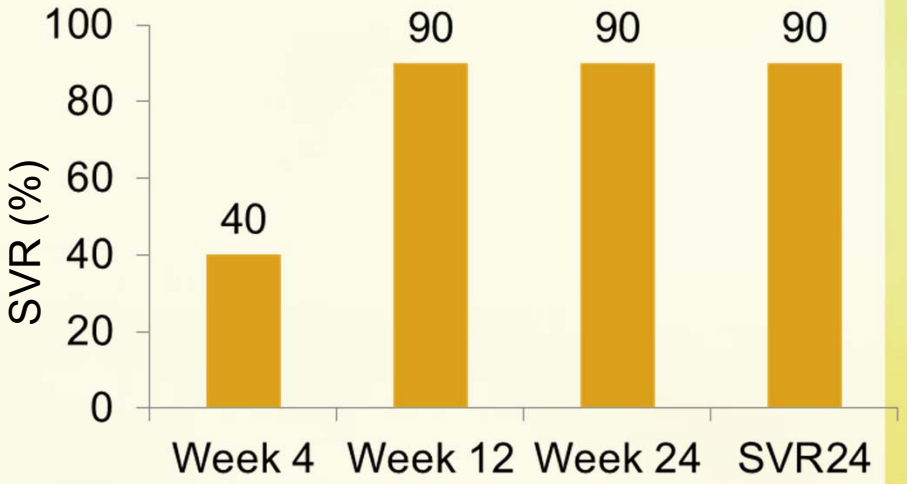
# Dual oral combination therapy with the NS5A inhibitor BMS-790052 and the NS3 PI BMS-650032 achieved 90% SVR24 in HCV G1b-infected null responders

- Present study: dual therapy in 10 G1b null responders, non-cirrhotic
- Treated for 24 weeks
- Dose of BMS 650032 reduced from 600mg bid to 200mg bid secondary to ALT elevations
- No viral breakthrough and no effect of pre Existing viral mutants
- 2 SAE's: 1 hyperbilirubineia, 1 pyrexia




Very important confirmation of high SVR in G1b patients with IFN-free regimen despite history of null response to PR. Need for high resistance barrier component of IFN-free regimens may be subtype-dependent (less in G1b than G1a).
New names: Daclatasavir (NS5A), Asunaprevir (PI)

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# What's In the Future? – IFN Free?

Polymerase Backbone

- Highest Resistance Barrier
- Pan-genotypic

- Second Generation PI / NS5A / NNI / RBV
- Cyclophilin inhibitor
- 3- or 4-drug regimens

- SVR?

# HCV — The Revolution Has Begun

- Antiviral activity in all HCV genotypes
- No selection of resistance
- All-oral combination regimen
- Short treatment duration
- QD (or BID) dosing
- Excellent safety and tolerability

**Applicable in difficult-to-treat populations:**

- Transplant
- Coinfection
- End-stage renal disease, etc.

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*REPORTING FROM*

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