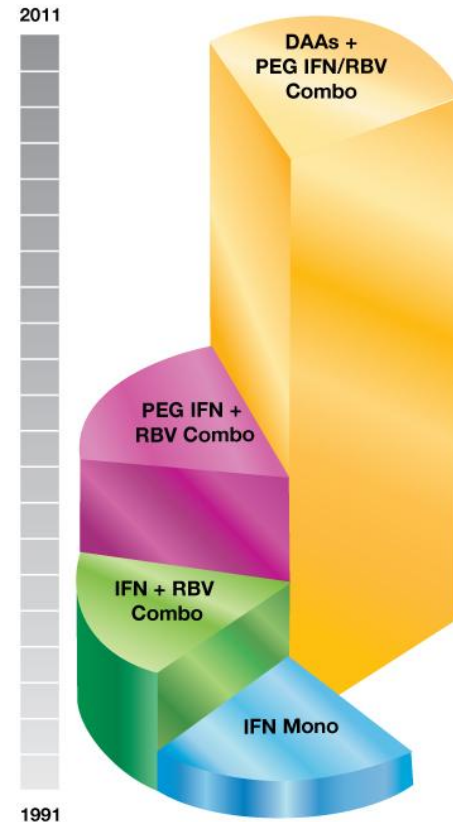



Paradigm Shift in HCV Standard of Care Treatment: DAAs

*A CME/CE
Satellite Symposium*



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DAA—A New Standard of Care in the Treatment of HCV

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Overview

**Treatment-Naive Data
and Regimens**

**Treatment-Experienced Data
and Regimens**

Futility Rules

Adverse Effects

2011 New Standard of Care for HCV Genotype 1

- Boceprevir or Telaprevir in combination with PEG IFN/RBV
- Adults with compensated liver disease, including cirrhosis
 - Treatment-naive
 - Failed previous interferon-based therapy
- *Must not be used as monotherapy*

Overview

**Treatment-Naive Data
and Regimens**

**Treatment-Experienced Data
and Regimens**

Futility Rules

Adverse Effects

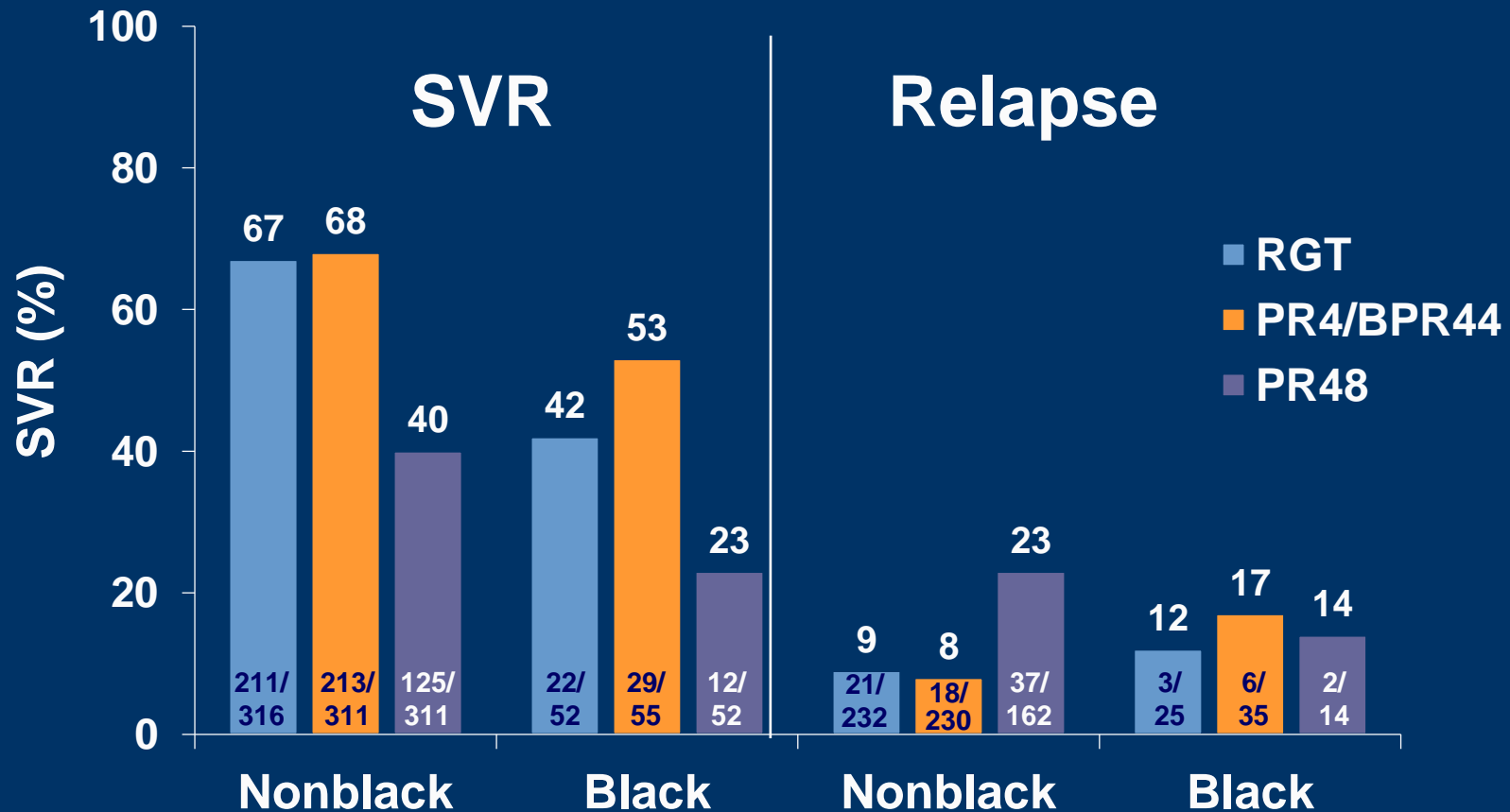
Boceprevir—RGT in Treatment-Naive Patients with No Cirrhosis

PEG IFN/RBV for 4 weeks,
followed by boceprevir 800 mg TID + PEG IFN/RBV

HCV RNA		Recommendation
TW8	TW24	
Undetectable	Undetectable	Administer all 3 drugs through TW28
Detectable	Undetectable	Administer all 3 drugs through TW36, then administer PEG IFN/RBV through TW48

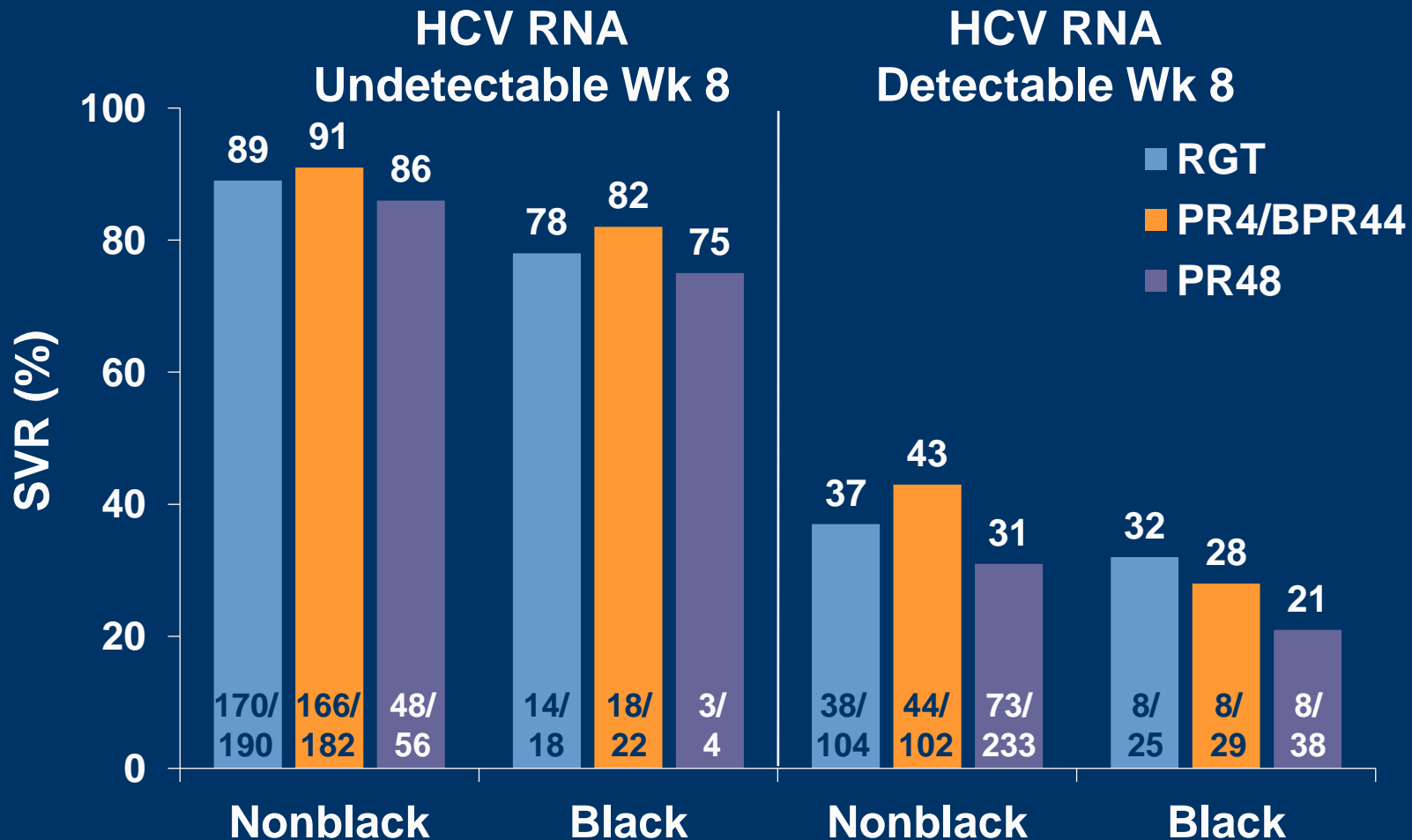
Abbreviations: RGT, response-guided therapy; TW, treatment week.
Victrelis [package insert]. Whitehouse Station, NJ: Schering Corporation; 2011.

SPRINT-2—BOC/PR: Overall SVR and Relapse Rate by Cohort and Treatment Arm



Abbreviations: RGT, response-guided therapy; SVR, sustained virologic response.
 Nonblack N = 938; black N = 159.
 Poordad F, et al. *N Engl J Med.* 2011;364:1195-1206.

SPRINT-2—BOC/PR: SVR According to HCV RNA Response at Week 8



Boceprevir—Treatment-Naive Non-RGT Regimens

Poor Interferon Responsiveness¹

Consideration should be given to extending treatment for treatment-naive patients with poor interferon responsiveness (< 0.5 or 1-log drop²) at week 4: 4 weeks of P/R followed by 44 weeks of B + P/R

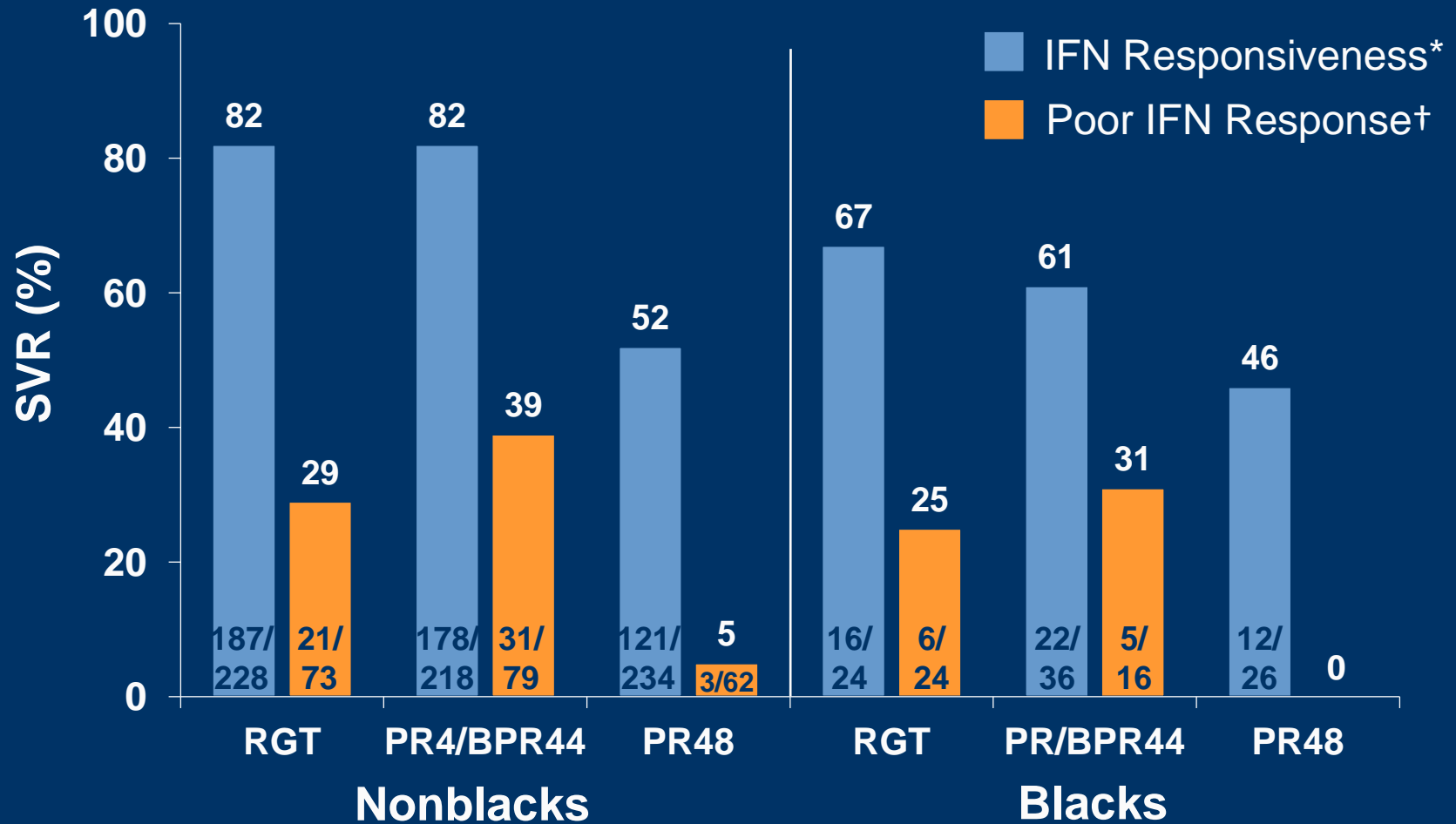
Compensated Cirrhosis¹

4 weeks of P/R followed by 44 weeks of B + P/R

1. Victrelis [package insert]. Whitehouse Station, NJ: Schering Corporation; 2011.

2. Poordad F, et al. *N Engl J Med*. 2011;364:1195-1206.

SPRINT-2—BOC/PR: SVR Based on Week 4 Lead-In Response

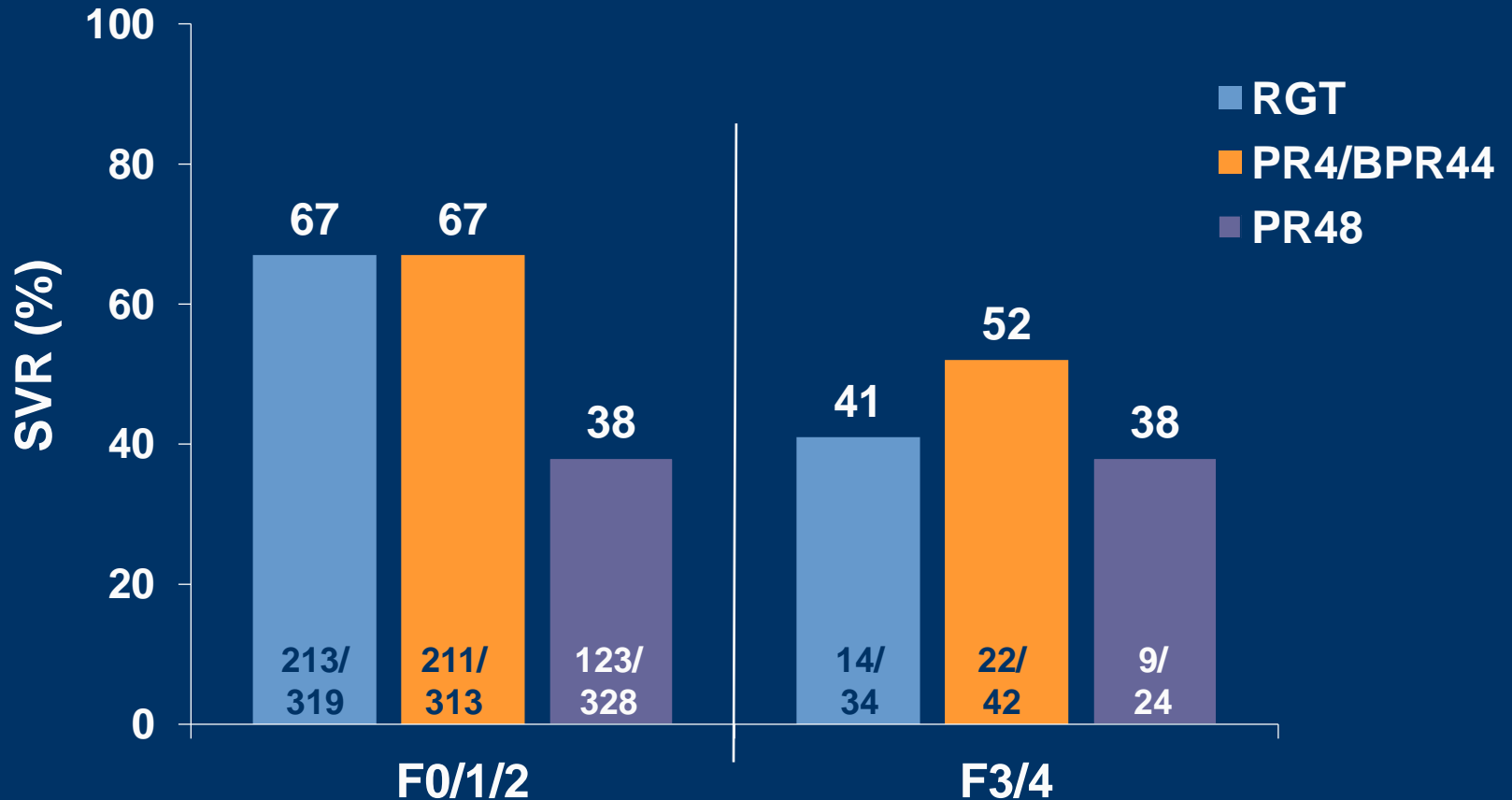


*Undetectable or ≥ 1 -log decline.

† < 1 -log decline.

Poordad F, et al. *N Engl J Med.* 2011;364:1195-1206.

SPRINT-2—BOC/PR: SVR in Advanced Fibrosis/Cirrhosis

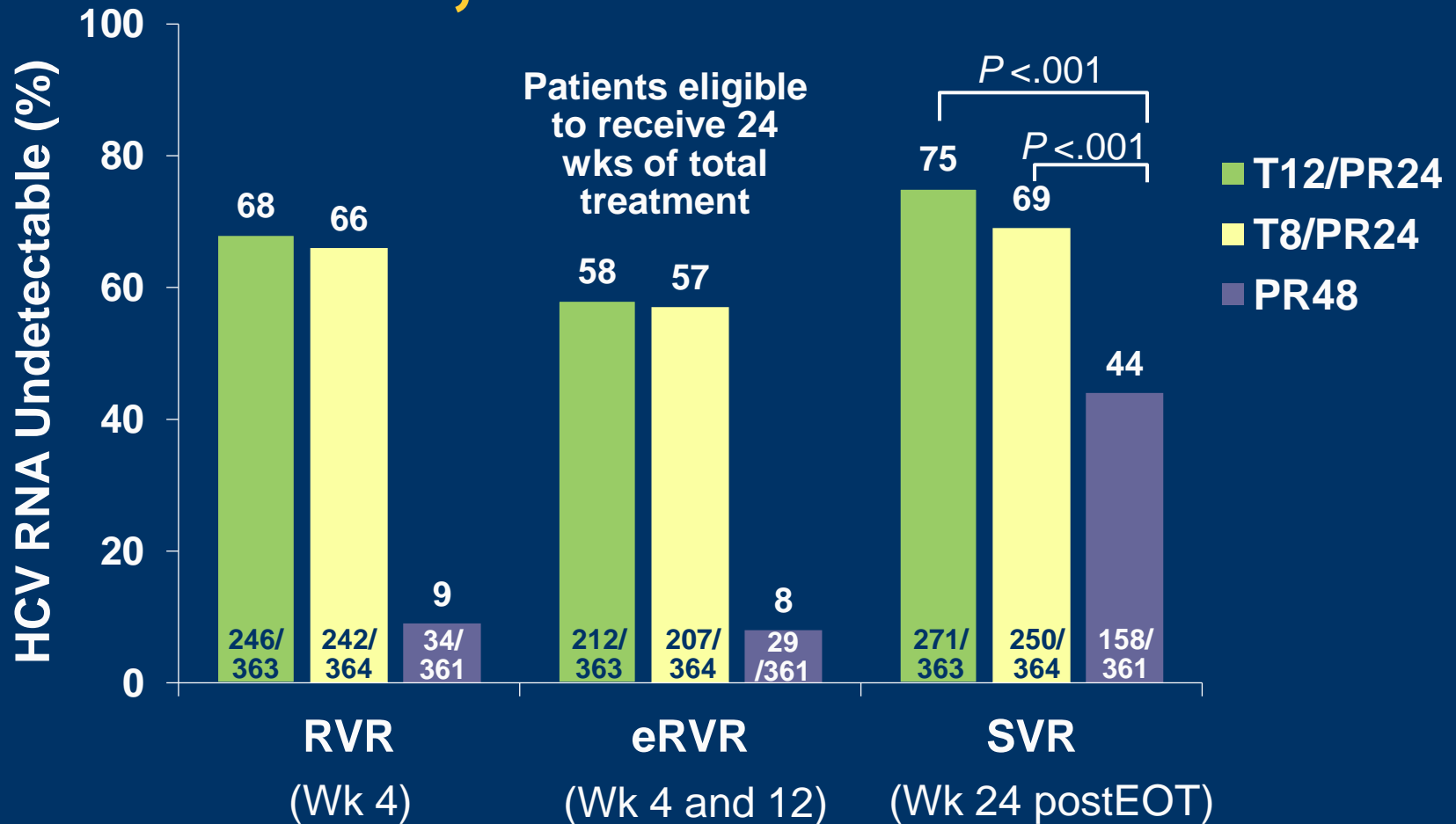


Telaprevir—RGT in Treatment-Naive Patients

Telaprevir 750 mg TID, PEG IFN, and RBV
starting on day 1

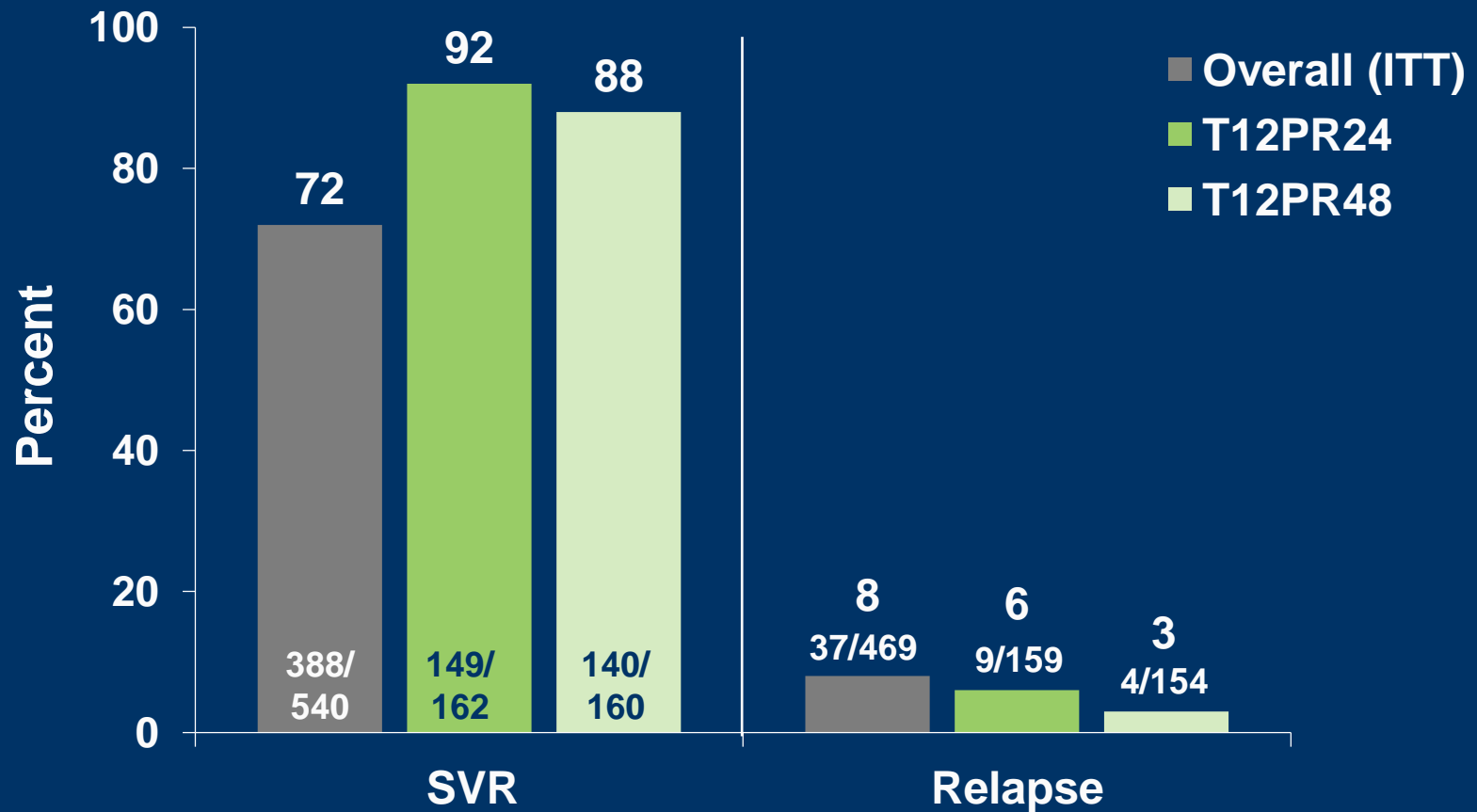
HCV RNA	Recommendation
Undetectable at TW4 and TW12	Administer all 3 drugs through TW12, then administer PEG IFN/RBV through TW24
Detectable (≤ 1000 IU/mL) at TW4 and/or TW12	Administer all 3 drugs through TW12, then administer PEG IFN/RBV through TW48

ADVANCE—TVR/PR: Overall RVR, eRVR, and SVR Rates



Abbreviations: EOT, end of treatment; eRVR, extended rapid virologic response; P, peginterferon; R, ribavirin; RVR, rapid virologic response; SVR, sustained virologic response; T, telaprevir.
 Jacobson IM, et al. *N Engl J Med*. 2011;364:2405-2416.

ILLUMINATE—TVR/PR: SVR and Relapse Rates



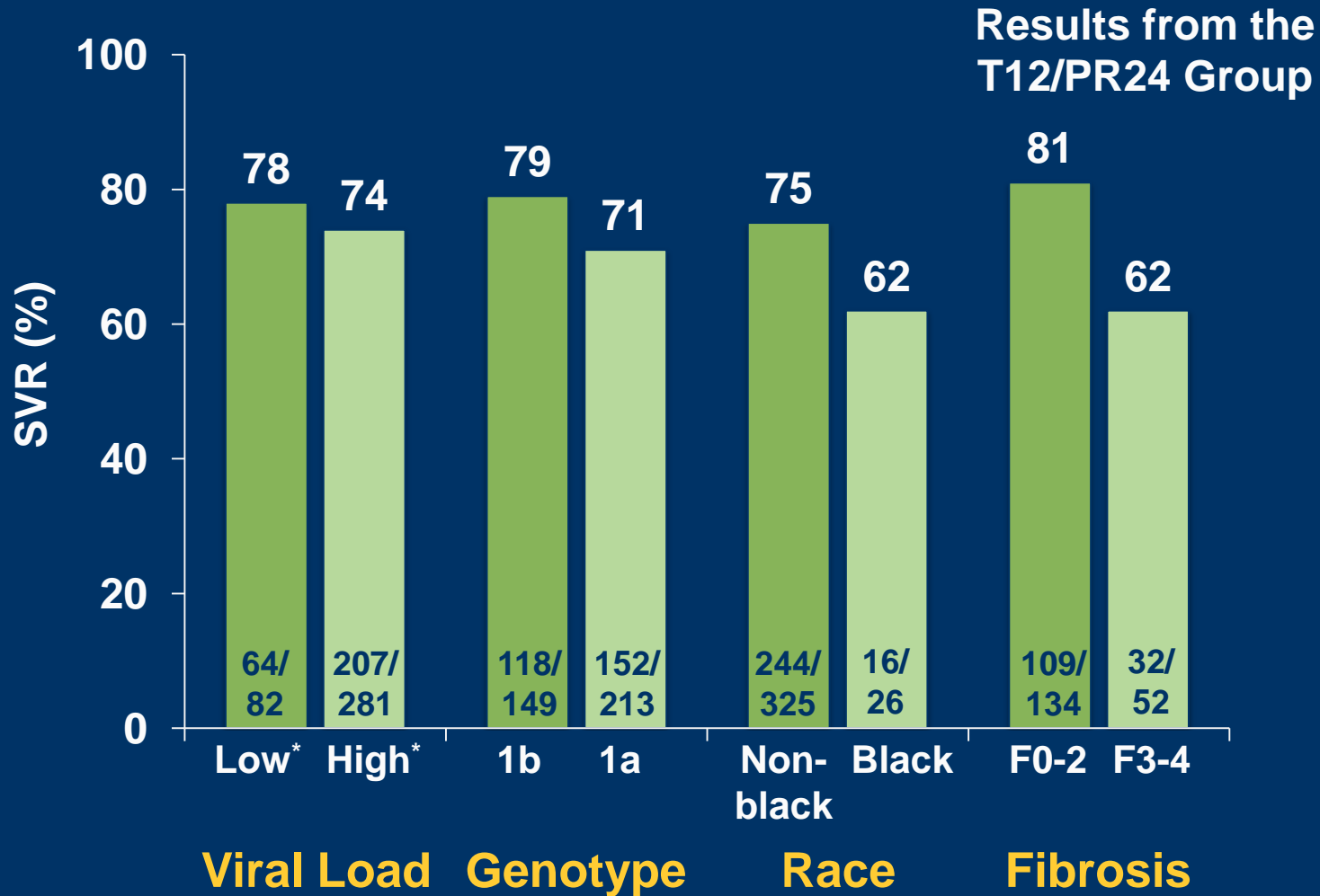
Abbreviations: ITT, intent-to-treat; SVR, sustained virologic response.
Sherman KE, et al. *N Engl J Med.* 2011;365:1014-1024.

Telaprevir—Treatment-Naive NonRGT Regimens

Compensated Cirrhosis

Treatment-naive patients with cirrhosis and undetectable HCV RNA at weeks 4 and 12 may benefit from continuing PEG IFN/RBV through week 48

ADVANCE—TVR/PR: Impact of Host and Viral Factors



* <800,000 IU/mL vs ≥800,000 IU/mL.

Jacobson IM, et al. *N Engl J Med.* 2011;364:2405-2416.

Overview

Treatment-Naive Data
and Regimens

Treatment-Experienced Data
and Regimens

Futility Rules

Adverse Effects

Treatment-Experienced Patients are Heterogeneous

- **Prior relapsers¹**
 - Undetectable HCV RNA at the end of therapy but detectable during follow-up
- **Prior partial responders¹**
 - ≥ 2 -log drop HCV RNA at week 12 but never undetectable
- **Prior null responders**
 - < 2 -log drop HCV RNA at week 12^{2,3}
 - Included in telaprevir trials²
 - Excluded from boceprevir trials; Interferon responsiveness assessed with 4 week lead-in³

1. Ghany MG, et al. *Hepatology*. 2009;49:1335-1374. 2. Zeuzem S, et al. *N Engl J Med*. 2011;364:2417-2428. 3. Bacon BR, et al. *N Engl J Med*. 2011;364:1207-1217.

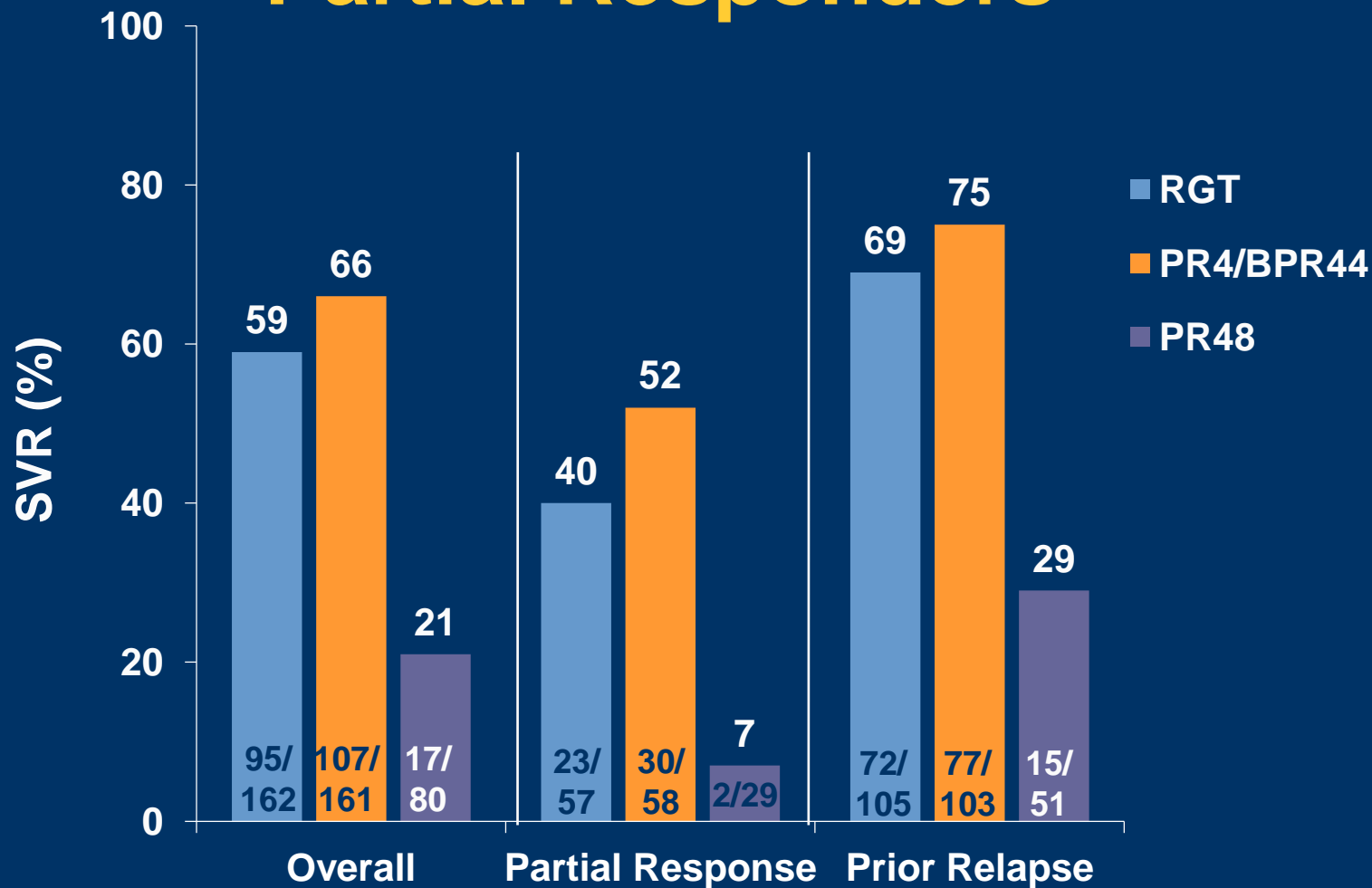
Boceprevir—RGT in Prior Partial Responders or Relapsers Without Cirrhosis

PEG IFN/RBV for 4 weeks,
followed by boceprevir 800 mg TID + PEG IFN/RBV

HCV RNA		Recommendation
TW8	TW24	
Undetectable	Undetectable	Complete 3-medicine regimen at TW36
Detectable	Undetectable	Continue all 3 medicines through TW36, then administer PEG IFN/RBV through TW48

Abbreviations: RGT, response-guided therapy; TW, treatment week.
Victrelis [package insert]. Whitehouse Station, NJ: Schering Corporation; 2011.

RESPOND-2—BOC/PR: Relapsers and Partial Responders



Abbreviations: B, boceprevir 800 mg TID; P, PEG IFN α -2b 1.5 μ g/kg/wk; R, ribavirin 600–1400 mg/d; RGT, response-guided therapy; Bacon BR, et al. *N Engl J Med.* 2011;364:1207-1217.

Boceprevir—Treatment-Experienced Non-RGT Regimens

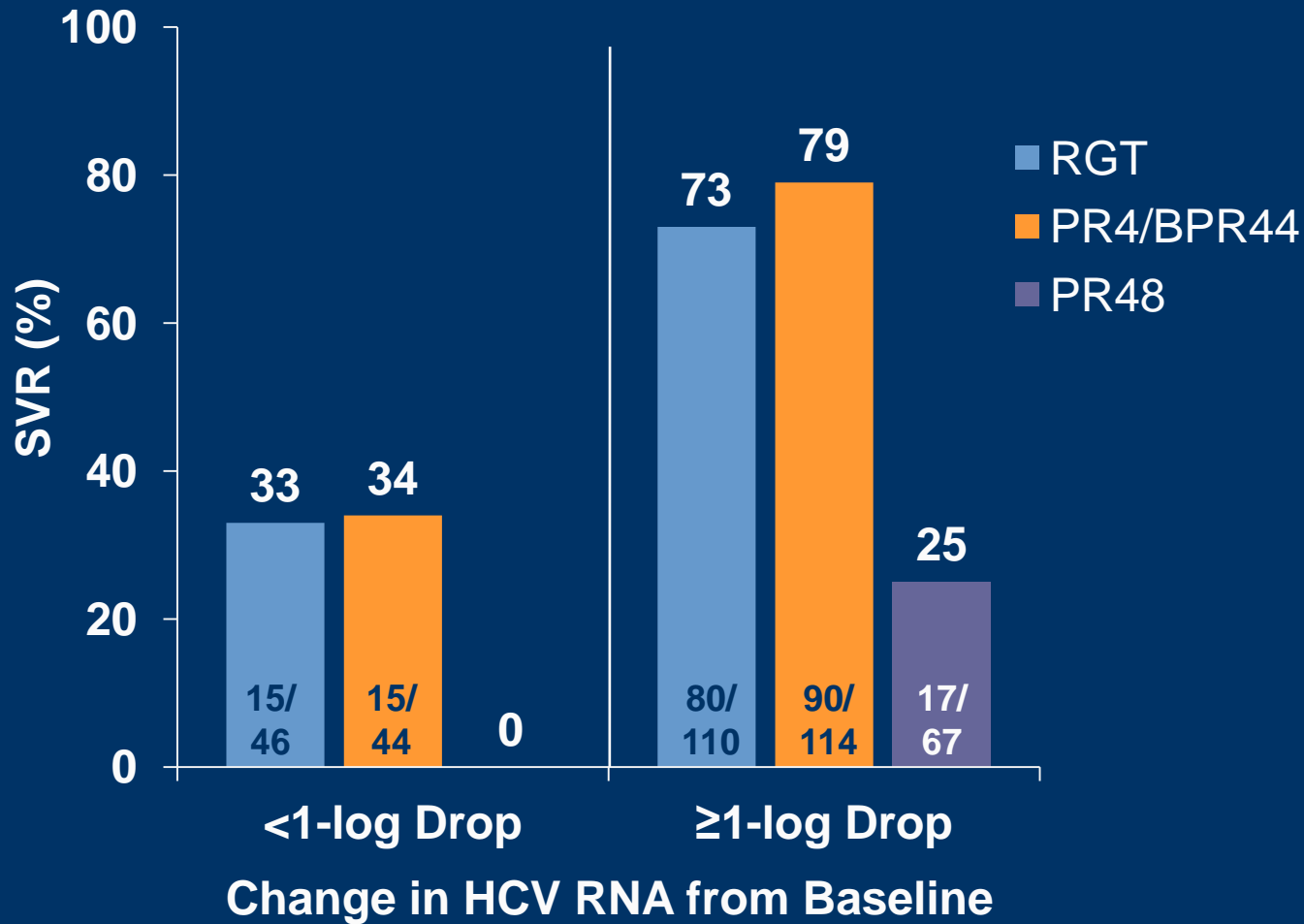
Compensated Cirrhosis

4 weeks of P/R followed by 44 weeks of B + P/R

Null Responders

4 weeks of P/R followed by 44 weeks of B + P/R

RESPOND-2—BOC/PR: SVR by Week 4 Lead-In Response to Peginterferon/Ribavirin



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

With permission from Bacon BR, et al. *N Engl J Med*. 2011;364:1207-1217.

Telaprevir—RGT in Prior Relapsers

Telaprevir 750 mg TID, PEG IFN, and RBV
starting on day 1

HCV RNA	Recommendation
Undetectable at TW4 and TW12	Administer all 3 drugs through TW12, then administer PEG IFN/RBV through TW24
Detectable (≤ 1000 IU/mL) at TW4 and/or TW12	Administer all 3 drugs through TW12, then administer PEG IFN/RBV through TW48

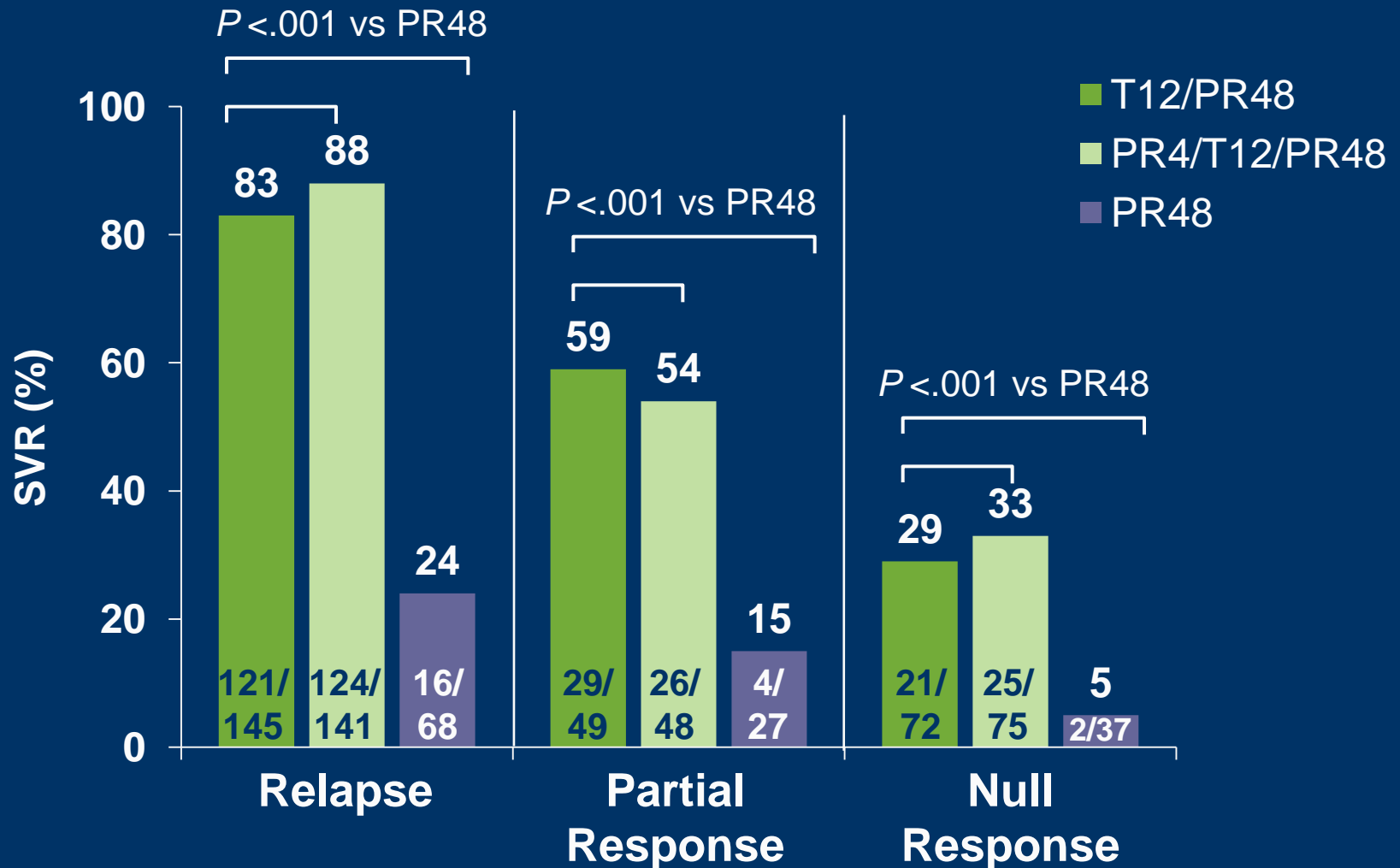
Telaprevir—Non-RGT in Prior Partial or Null Responders

Telaprevir 750 mg TID, PEG IFN, and RBV
starting on day 1

Recommendation

Administer all 3 drugs through TW12,
then administer
PEG IFN/RBV through TW48

REALIZE—SVR by Prior Response



Abbreviations: P, peginterferon α -2a 180 μ g/wk; R, ribavirin 1000–1200 mg/d; T, telaprevir 750 mg q8h. Zeuzem S, et al. *N Engl J Med*. 2011;364:2417-2448.

Overview

Treatment-Naive Data
and Regimens

Treatment-Experienced Data
and Regimens

Futility Rules

Adverse Effects

Boceprevir—Futility (Stopping) Rules



Week 12 HCV RNA \geq 100 IU/mL

OR

Week 24 HCV RNA confirmed detectable

Telaprevir—Futility (Stopping) Rules



Week 4 and/or Week 12 HCV RNA >1000 IU/mL

OR

Week 24 HCV RNA confirmed detectable

HCV RNA Assays—“Not Detected” Is Required for Shortened Therapy

- Below lower limit of quantification (LLOQ) but still “detectable” is *not* sufficient to shorten therapy—ie, patient should continue for 48 weeks

Overview

**Treatment-Naive Data
and Regimens**

**Treatment-Experienced Data
and Regimens**

Futility Rules

Adverse Effects



Boceprevir Triple Therapy— Adverse Effects

Pooled Data from Treatment-Naive Population
(SPRINT-1, SPRINT-2)

Adverse Effect	Boceprevir + PEG IFN/RBV (n = 1225)	PEG IFN/RBV (n = 467)
Anemia*	50%	30%
Neutropenia	25%	19%
Dysgeusia	35%	16%

*Anemia was managed with erythropoiesis-stimulating agents, with or without RBV dose reduction (boceprevir + PEG IFN/RBV, 43%; PEG IFN/RBV, 24%).

Telaprevir Triple Therapy— Adverse Effects

Pooled Data from Treatment-Naive and -Experienced Populations (ADVANCE, ILLUMINATE, REALIZE)

Adverse Effect	Telaprevir + PEG IFN/RBV (n = 1797)	PEG IFN/RBV (n = 493)
Rash	56%	34%
Anemia*	36%	17%
Anorectal Effects	29%	7%

*Anemia was managed with RBV dose reduction; ESA not permitted. (Telaprevir + PEG IFN/RBV, 32%; PEG IFN/RBV, 12%).

Telaprevir—Rash Summary from Pooled Safety Database

- **Rash was primarily eczematous**
 - Mild to moderate in most
 - Severe rash in 4%
 - May occur at any time during telaprevir exposure
- **Led to discontinuation of telaprevir in 6%**
 - Serious skin reaction in <1%, including Stevens-Johnson Syndrome or DRESS
- **Treat with oral antihistamines and/or topical corticosteroids**
 - Systemic steroids are not recommended

Conclusion

- **New standard of care for HCV genotype 1 infection**
 - Higher SVR rates observed across all patient groups including “difficult to treat” with peginterferon/ribavirin
- **Response-guided therapy allows for shorter duration of therapy for patients with rapid virologic response**
- **Regimen complexity related to TID dosing and additional adverse effects**
 - Patient education and adherence is critical

New and Evolving Perspectives: What the New Data Tell Us

Robert G. Gish, MD

Medical Director

**Center for Hepatobiliary Disease and Abdominal
Transplantation**

Chief of Hepatology

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University of California San Diego

San Diego, California

AASLD 2011

- **What do we know now that we didn't know when phase III registration trials were published?**
 - **March 2011: phase III boceprevir trials (SPRINT-2 and RESPOND-2) published**
 - **June 2011: phase III telaprevir trials (ADVANCE and REALIZE) published**
- **More than 40 abstracts and posters on boceprevir and telaprevir scheduled at AASLD 2011**



Boceprevir

Telaprevir

Boceprevir—SVR Predictors in Poor IFN Responders

- Post-hoc analysis of phase III data
- Incidence of poor interferon (IFN) response (<1-log drop HCV RNA at week 4)
 - SPRINT-2 (treatment-naive) 20%–25%
 - RESPOND-2 (treatment-experienced) 15%–28%
- Sustained virologic response (SVR) in poor IFN responders
 - Boceprevir triple therapy 28%–34%
 - PR control 0%–4%
- Baseline characteristics and treatment week 8 response were evaluated in poor IFN responders who achieved SVR vs those patients who did not achieve SVR

Boceprevir—Predictive Value of Genotype and Fibrosis Level in Poor IFN Responders

Conclusions

- Predictive value of HCV genotype-1b versus -1a subtypes was variable, depending on whether patients were treatment-naïve or -experienced
- Fibrosis level (F3–4 vs F0–2) was strongly associated with nonresponse
- HCV RNA decline at treatment week 8 also predictive in this patient group
 - <3-log drop HCV RNA at week 8 had a 100% negative predictive value

Boceprevir—Stopping Rule Analysis of SPRINT-2 AND RESPOND-2

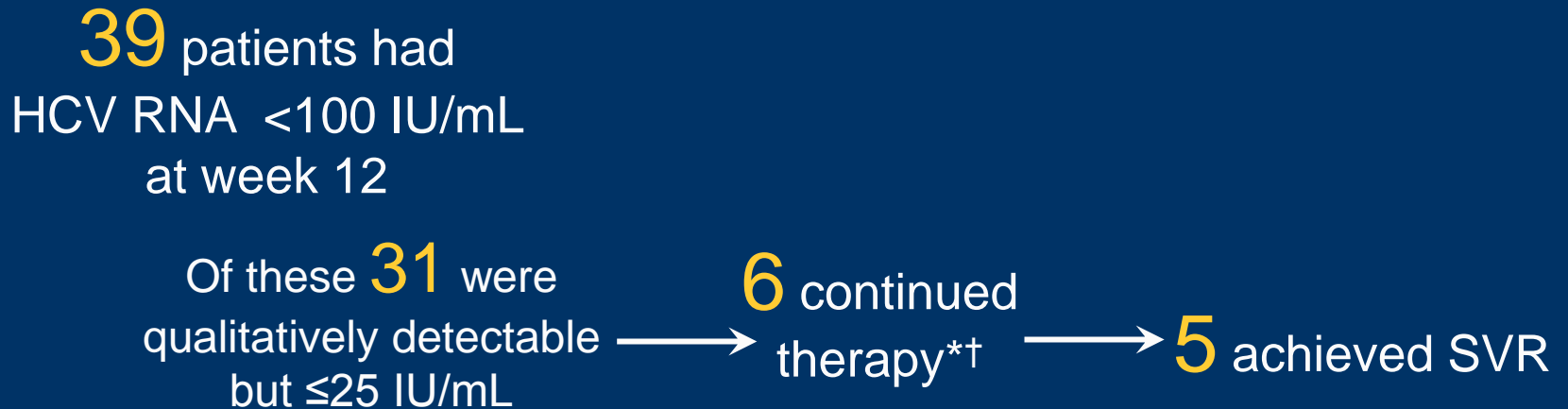
- **Treatment-naive patients**
 - **SVR: Associated with HCV RNA detectable but <100 IU/mL at week 12**
 - **No SVR: Associated with HCV RNA \geq 100 IU/mL at week 12**
- **Treatment-experienced patients**
 - **Some patients with HCV RNA detectable but \leq 25 IU/mL at week 12 achieve SVR**
- **Current stopping rules for both patient groups from product information**
 - **HCV RNA \geq 100 IU/mL at week 12 and detectable at week 24**

SPRINT-2 and RESPOND-2—Patients with HCV RNA <100 IU/mL and ≤25 IU/mL at Week 12

SPRINT-2

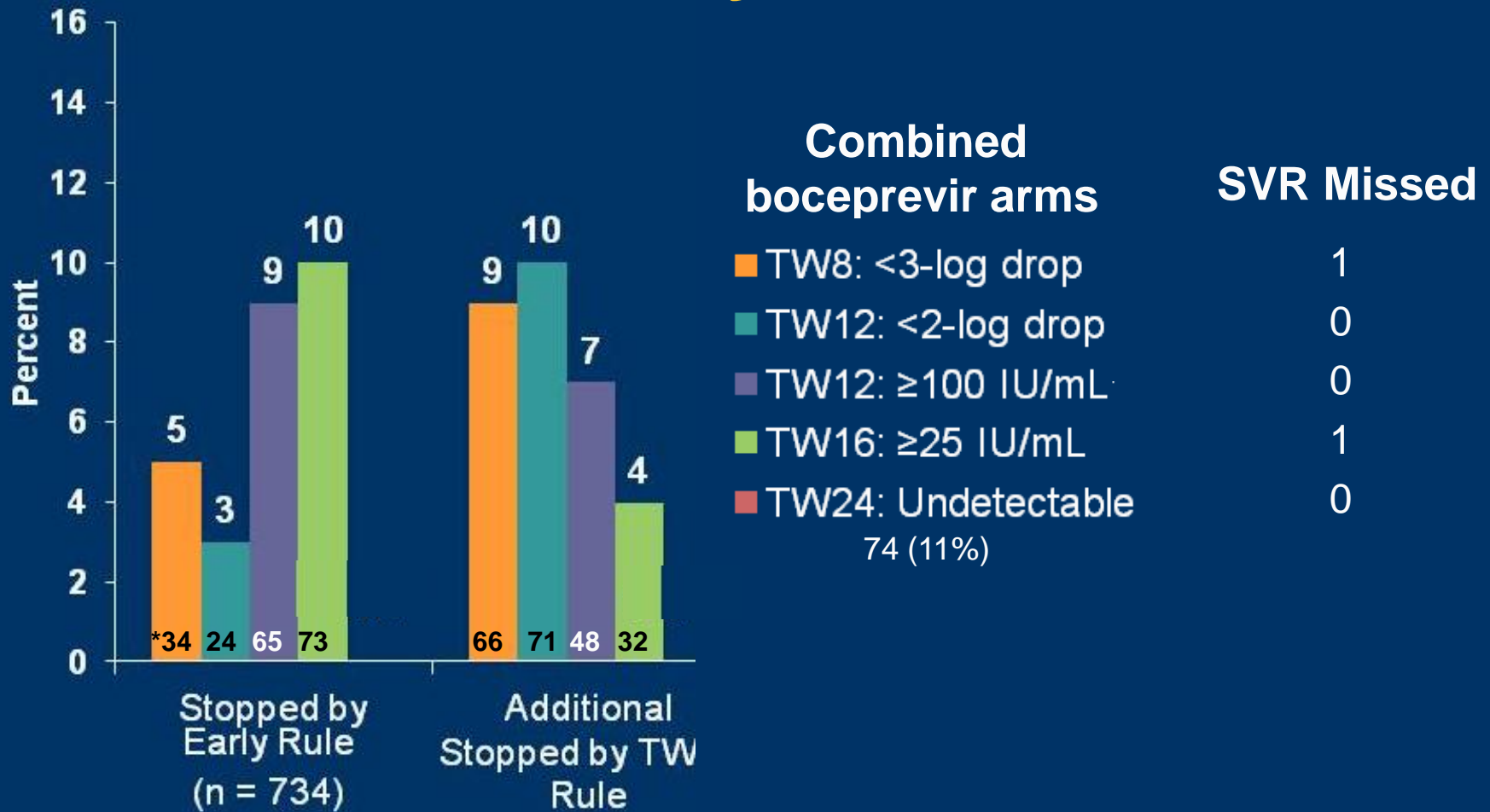


RESPOND-2



*Written communication, Dr. Ira M. Jacobson; †Protocol deviations.
Jacobson IM, et al. *Hepatology*. 2011;54:Abstract 954.

SPRINT-2—Analysis of Considered Futility Rules



* (N=)
Jacobson IM, et al. *Hepatology*. 2011;54:Abstract 954.

SPRINT-2 and RESPOND-2— Stopping Rule Analysis

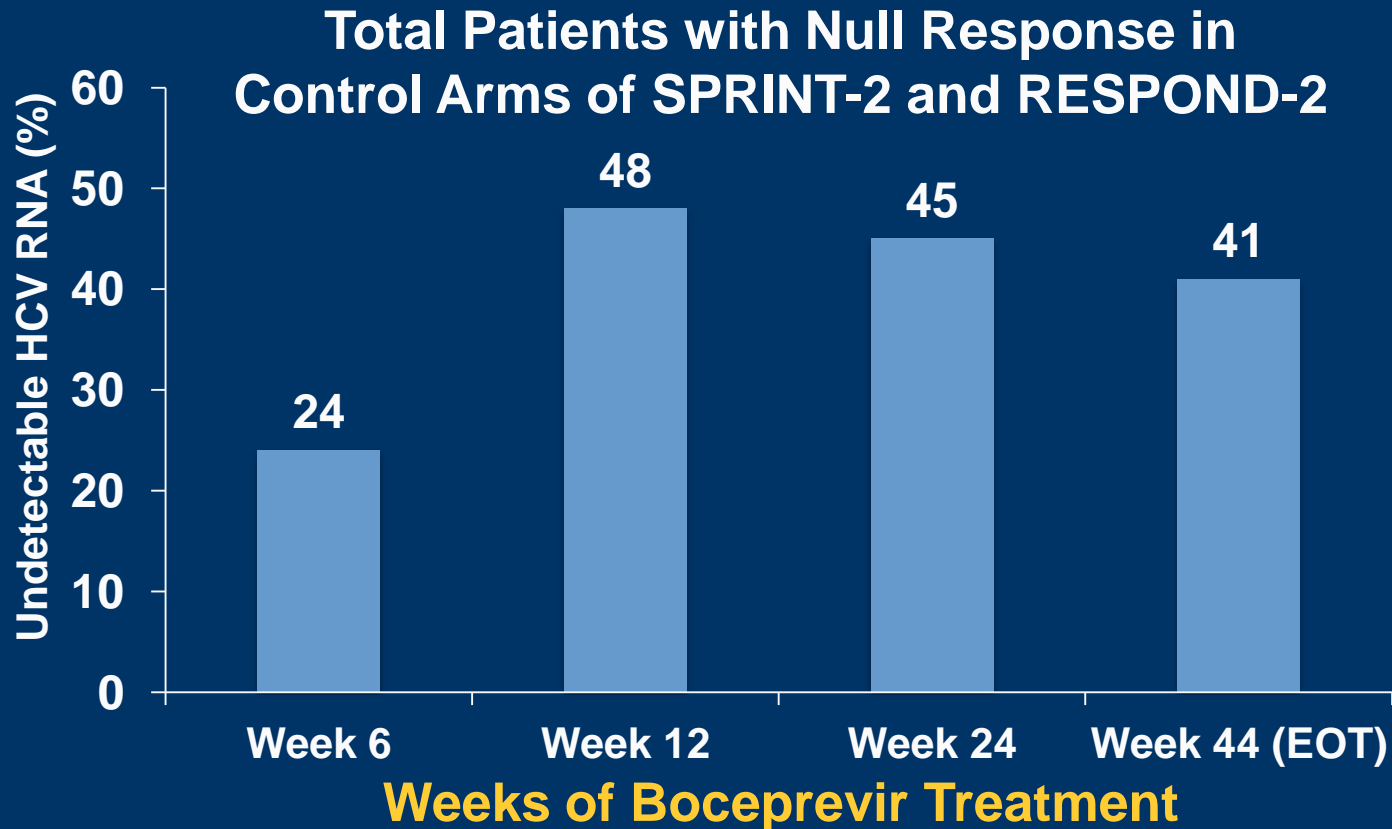
Conclusions

- **Overall, stopping rules are robust with few, if any, patients missed who could reach SVR**
- **Stopping rules are harmonized between treatment naive and treatment experienced patients**

PROVIDE—Efficacy of Boceprevir in Null Responders

- Rollover prospective study of null responders from control arms of SPRINT-2 and RESPOND-2
 - Null response = <2 -log HCV RNA drop at week 12 of PEG IFN/RBV alone
 - 46 patients enrolled
- Boceprevir + PEG IFN/RBV given for up to 44 weeks
 - Lead-in repeated if >2 weeks elapsed since previous treatment

PROVIDE—Prior Null Responders with Undetectable HCV RNA



Rate of undetectable HCV RNA at end of treatment is comparable to rate in poor IFN responders; relapse rate in this historical group was 19%

Concomitant Medication Use with Boceprevir

- Patients who received concomitant CYP3A4/5 substrates, inhibitors, and/or inducers in phase II and III trials were evaluated for adverse effects
- Boceprevir is metabolized by
 - Aldo-ketoreductase – primary
 - CYP3A4/5
- Boceprevir strongly inhibits CYP3A4/5
 - May increase levels of coadministered drugs that are metabolized by CYP, most importantly 3A4/5

Adverse Effects in Patients Treated with Boceprevir and Concomitant Medications

Drug	Observations
Antidepressants*	Adverse effects (AEs) similar to overall population
Azole antifungals	Dysgeusia: boceprevir 43% vs control 37% Paresthesia: boceprevir 13% vs control 4%
Macrolide antibiotics	Anemia: boceprevir 68% vs control 49%
Methadone	No dose reduction for psychiatric AEs or recurrence of intravenous drug use
Oral contraceptives	Anemia: boceprevir 67% vs control 48% Gastroesophageal reflux: boceprevir 11% vs control 6%

*Most commonly used concomitant medications of interest.
Poordad F, et al. *Hepatology*. 2011;54:Abstract 937.

Boceprevir

Telaprevir



REALIZE—TVR/PR: SVR Predictors with Telaprevir in Treatment-Experienced Patients

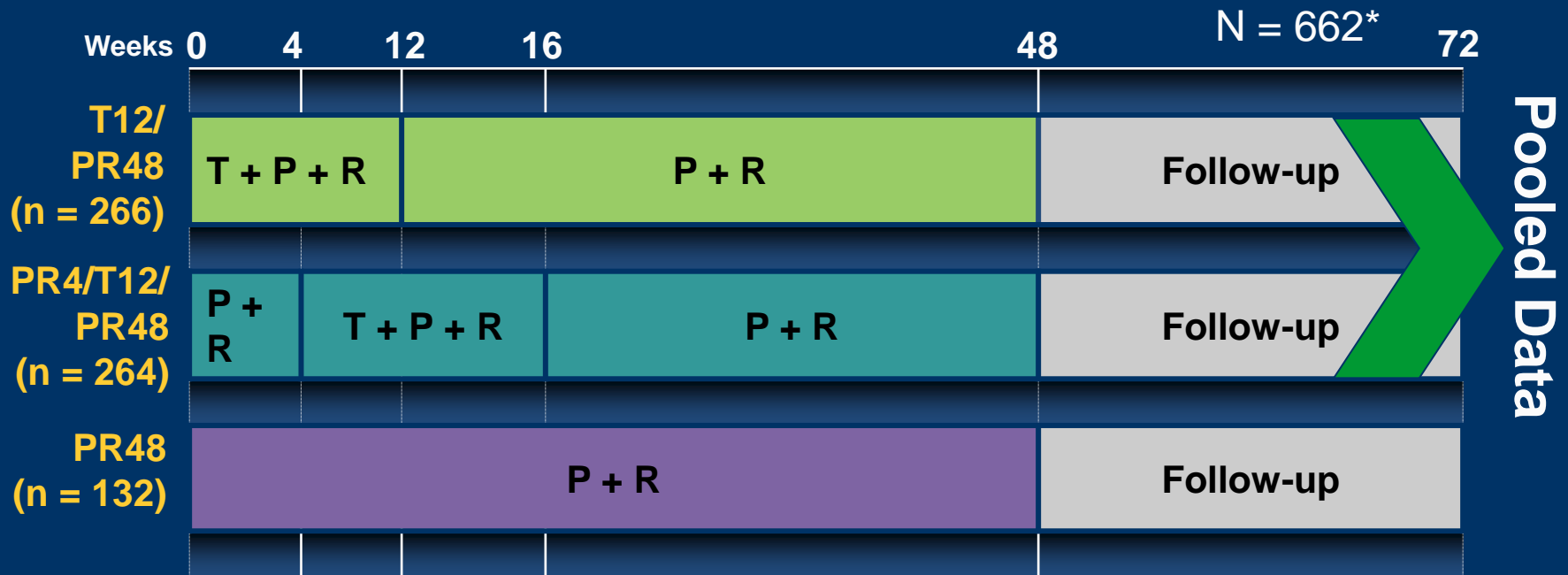
- **Post-hoc analysis of patients with prior treatment failure**
- **Multiple logistic regression analyses to assess impact of baseline host and viral factors**
- **Data available for 578/662 randomized patients**

REALIZE—TVR/PR: SVR Predictors with Telaprevir in Treatment-Experienced Patients

Factor	Observations
eRVR	Strongest predictor of SVR (OR = 7.8)
Prior on-treatment virologic response	Significant predictor overall in patients receiving telaprevir or control (OR 2.81)
Baseline higher LDL	Significant predictor overall in patients receiving telaprevir or control (OR 2.13)
Higher fibrosis stage	Impact greatest in patients receiving telaprevir who were prior nonresponders (OR = .60) and relapsers (OR = .41)
Baseline HCV RNA level	Not predictive of SVR in patients receiving telaprevir

Abbreviations: eRVR, extended rapid virologic response; LDL, low-density lipoprotein.
Berg T, et al. *Hepatology*. 2011;54:Abstract 32.

REALIZE—TVR/PR: Impact of Anemia and RBV Dose Reduction on SVR in Telaprevir Triple Therapy



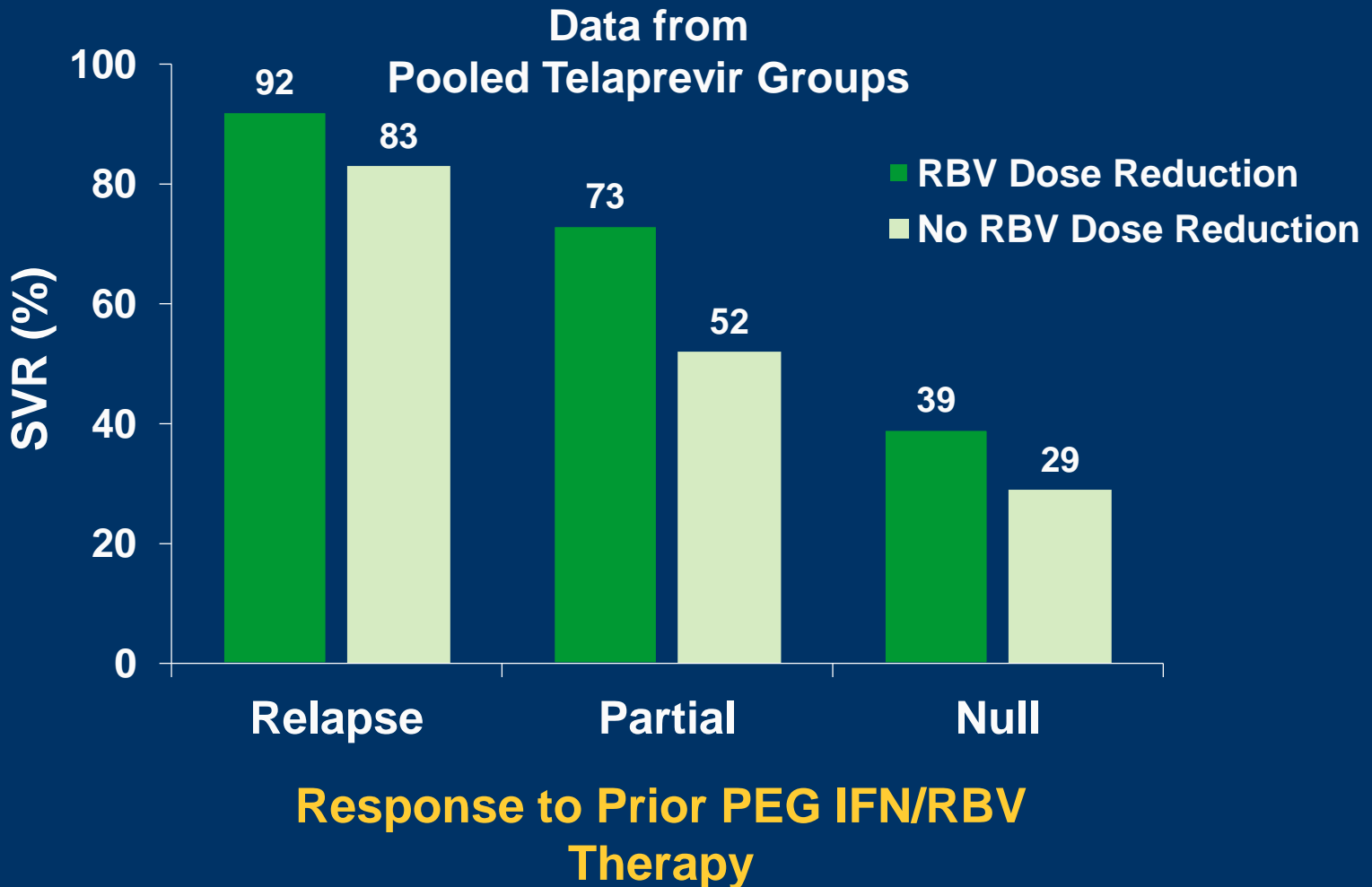
- No erythropoiesis-stimulating agents allowed
- Data pooled from 2 telaprevir arms

*Including null responders, partial responders, and relapsers randomized and stratified by HCV RNA prior response.

Abbreviations: P, peginterferon α -2a 180 μ g/wk; R, ribavirin 1000–1200 mg/d; T, telaprevir 750 mg q8h.

Roberts SK, et al. *Hepatology*. 2011;54:Abstract 1368.

REALIZE—TVR/PR: Impact of RBV Dose Reduction on SVR



REALIZE—TVR/PR: Impact of Anemia on SVR

- Anemia with ribavirin dose reduction does not appear to be a significant predictor of lower SVR with telaprevir triple therapy in previously treated patients
- Factors significantly associated with anemia on telaprevir triple therapy include
 - Older age, lower body mass index, and lower baseline hemoglobin ($P < .0001$)
 - More advanced fibrosis ($P = .0369$)

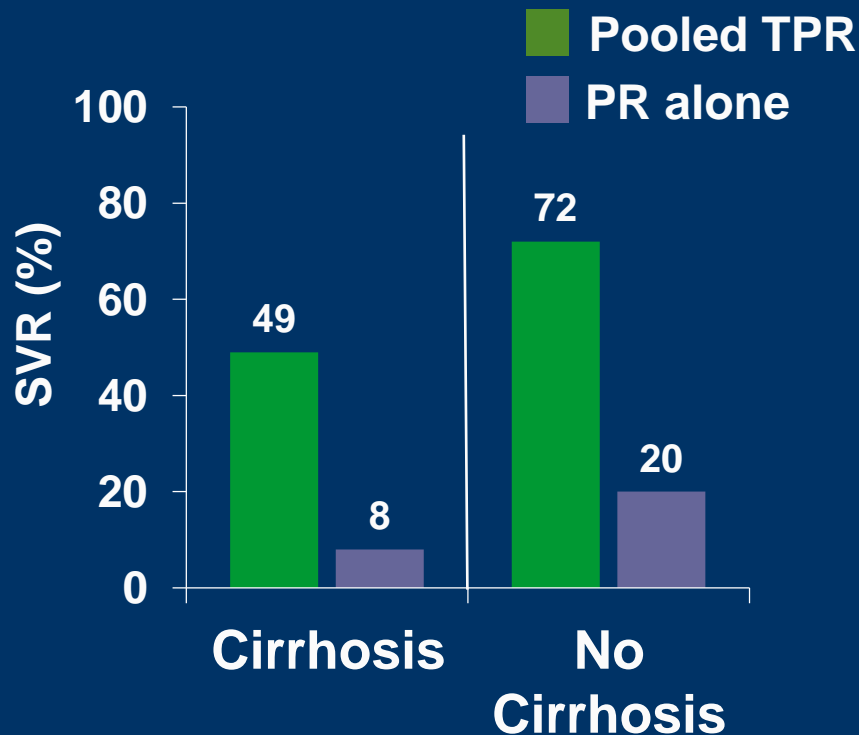
REALIZE—TVR/PR: Subanalysis of Patients with Cirrhosis on Telaprevir Triple Therapy

Patient Demographics

Patient Group	Prior Response n (%)			Male
	Null	Partial	Relapser	
Cirrhosis (n = 143)	51 (36)	29 (20)	63 (44)	104 (73)
No cirrhosis (n = 435)	113 (26)	79 (18)	243 (56)	294 (68)

- Mean age: Cirrhotics 54 years; noncirrhotics 50 years
- Mean log viral load: Cirrhotics 6.57; noncirrhotics 6.56

REALIZE—TVR/PR: Efficacy in Patients with Cirrhosis



Univariate Predictors of SVR with Telaprevir Triple Therapy in Patients with Cirrhosis

High baseline LDL

High baseline ALT or AST*

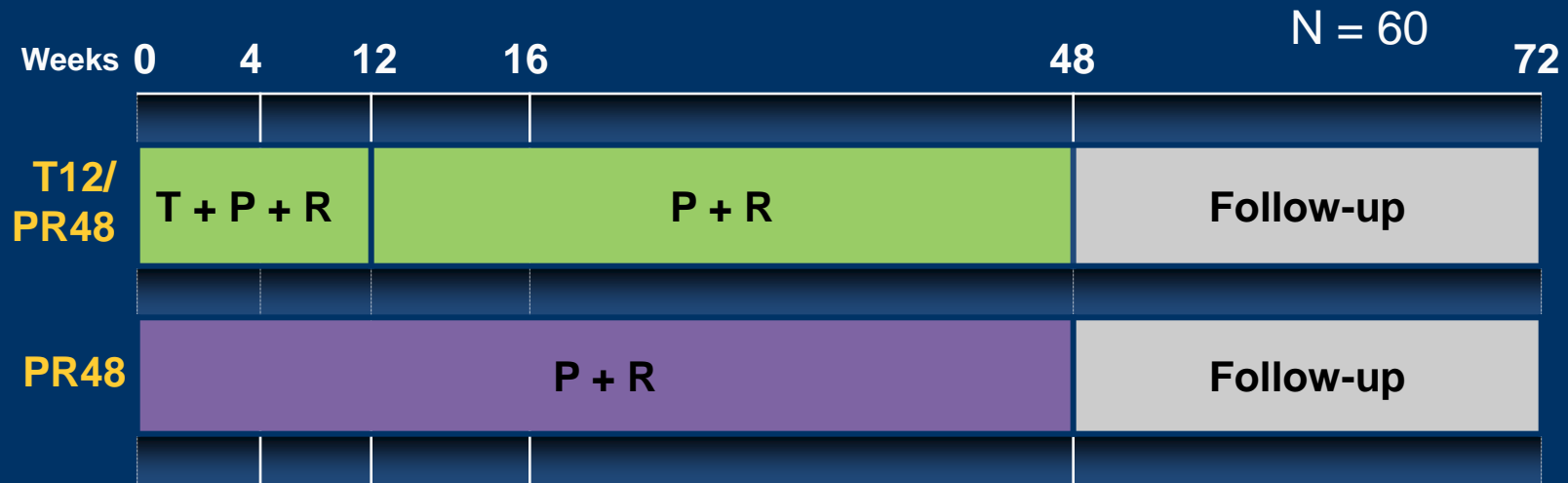
Prior PR response*

In patients failing telaprevir triple therapy, the presence or level of telaprevir resistance was not associated with fibrosis stage.

*Multivariate predictors also.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low-density lipoprotein; P, peginterferon; R, ribavirin; T, telaprevir. Pol S, et al. *Hepatology*. 2011;54:Abstract 31.

Telaprevir Triple Therapy In HCV/HIV-Coinfected Patients Treatment-Naive for HCV



- **2-part trial¹**
 - **Part A: No concurrent antiretroviral therapy (ART)**
 - **Part B: stable on efavirenz- or atazanavir/ritonavir-based regimen**
- **Telaprevir dose = 750 mg q8h; 1125 q8h with efavirenz**
- **Primary outcomes: Adverse effects and HCV RNA at wk 12²**

Abbreviations: P, peginterferon α -2a 180 μ g/wk; R, ribavirin 1000–1200 mg/d; T, telaprevir 750 mg q8h.

1. Sherman KE, et al. *Hepatology*. 2011;54:Abstract LB-8. 2. ClinicalTrials.gov. NCT00983853. Accessed 10/10/11 at: www.clinicaltrials.gov/ct2/show/NCT00983853.

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

Part/Regimen	n	Wk 12 Undetectable (%)		Wk 24 Undetectable (%)	
		T12PR48	PR48	T12PR48	PR48
A – No ART	13	86	33	86	33
B – EFV regimen	24	88	25	75	50
B – ATV/r regimen	23	73	38	67	75

- AEs $\geq 10\%$ 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%)

Abbreviations: ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; EFV, efavirenz; P, peginterferon; R, ribavirin; T, telaprevir.

Sherman KE, et al. *Hepatology*. 2011;54:Abstract LB-8.

Conclusion—Boceprevir

- **HCV RNA decline at week 8 and HCV fibrosis level predict response in poor IFN responders**
 - **Predictive value of genotype subtype was variable depending on whether patients were treatment-naive or -experienced**
- **Stopping rules for boceprevir are robust**
- **In response to boceprevir triple therapy, approximately one third of prior null responders achieve SVR**
- **Adverse effects of concomitant medications during boceprevir triple therapy appear to be modest and manageable**

Conclusion—Telaprevir

- eRVR remains the strongest predictor of success or failure with telaprevir triple therapy
- In HIV/HCV-coinfected patients, treatment with triple therapy results in substantial response rates at week 12 and 24 with modest adverse effects and drug-drug interactions
- Anemia and ribavirin dose reduction do not appear to affect SVR rates with telaprevir triple therapy in treatment-experienced patients
- 49% SVR in treatment-experienced patients with compensated cirrhosis is favorable and encourages clinicians to utilize telaprevir triple therapy in this patient group

Putting DAAs into Practice: Case-Based Discussion with Patient Videos

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Vincent Astor Professor of Medicine

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**Medical Director of the Center for the Study
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Weill Medical College of Cornell University

New York, New York

Case 1—Mr. L

Treatment-Naive Patient

- 42-year-old black male
 - Supervisor
- HCV genotype 1a infection
 - Has risk factors dating back 20 years
- Presents with his spouse, 33-year-old professional
- Stage 2 fibrosis

Case 1—Discussion Point 1

Would you order an *IL28B* test?
If so, what is your rationale?

Case 1—Discussion Point 2

This patient is started on boceprevir and has undetectable HCV RNA at week eight.

Would you apply response-guided therapy (RGT)?

Case 1—Conclusion

- **Black patients have a large proportionate increase in SVR with PI-based therapy relative to PEG IFN/RBV**
 - SVR rates remain lower than other groups
 - Are eligible for response guided therapy
 - Potential total duration 24 wks with telaprevir, 28 wks with boceprevir
- **Clinicians vary regarding use of *IL28B* with PI-based therapy**
 - Enables “fine tuning” of discussion with patient
 - Less determinative of whether to treat than with PEG IFN/RBV therapy

Case 2—Mr. C

Cirrhotic Relapser

- 62-year-old white male, active executive who often flies for his job
- Genotype 1
- Cirrhotic
- Prior relapser to PEG IFN/RBV
 - Experienced anemia with prior treatment (9.8 g/dL)
- Patient had been following HCV research and made an appointment as soon as the new direct-acting antivirals (DAAs) were approved
- Started on telaprevir
 - Undetectable at 4 weeks
- Patient returned for appointment at 8 weeks

Case 2—Discussion Point 1

How long would you treat a cirrhotic HCV relapser who has a rapid virologic response?

Case 2—Discussion Point 2

The patient's hemoglobin level
at week 8 = 8.6 g/dL

In light of this patient's hemoglobin level, rapid virologic response, and remaining 4 weeks of telaprevir therapy, how should his anemia be addressed?

Case 2—Conclusion

- Relapsers have very high SVR rates with PI-based therapy
- Cirrhosis impacts minimally on SVR in prior relapsers
- Telaprevir label implies cirrhotic relapsers eligible for RGT; 48 weeks recommended for all cirrhotics with boceprevir
 - Individual judgments may differ among clinicians
- RBV dose reductions are first intervention of choice for anemia in most patients (no proven impact on SVR)
 - Erythropoiesis-stimulating agents can be used on a selective basis

Case 3—Ms. H

Partial Responder

- **58-year-old Hispanic female high school teacher**
- **Genotype 1a**
- **Partial responder to prior PEG IFN/RBV therapy**
 - Baseline HCV RNA 4.5 million IU/mL
 - Week 12: 18,000 IU/mL; week 24: 6500 IU/m
 - Moderate pruritic rash; hemoglobin 10.1 g/dL
- **Metavir F2 with focal bridging fibrosis**
- **Started on PEG IFN/RBV for 4 weeks, then boceprevir added**
 - HCV RNA 70 IU/mL at week 8
 - Hemoglobin drops from 13.2 g/dL to 8.8 g/dL at week 8
 - Develops mild rash and moderate depression
- **Presents for 12-week visit**

Case 3—Discussion Point 1

What would you tell this patient about the anticipated duration of therapy?

Case 3—Discussion Point 2

How would you address this patient's anemia and depression?

Case 3—Conclusion

- **Prior nonresponders not eligible for RGT with either boceprevir or telaprevir**
 - **Boceprevir: 4 weeks PEG IFN/RBV lead-in + 32 weeks triple + 12 weeks PEG IFN/RBV for partials**
 - **4 + 44 for cirrhotics**
 - **4 + 44 for nulls**
 - **Telaprevir: 12 weeks triple + 36 weeks PEG IFN/RBV for partials and nulls**
- **Consider drug-drug interactions when choosing antidepressants**
- **Individualize decisions on whether to d/c or switch statins**

Case 4—Mr. S

Null Responder

- **68-year-old white male, recently retired mechanic**
 - Acquired infection likely with drug use at 18 years old, otherwise healthy
 - Genotype 1b
- **Null response to prior PEG IFN/RBV**
 - Tolerated prior treatment well
- **Prior liver biopsy – established nodule formation: stage 4 (cirrhosis)**
- **Albumin 3.6 g/dL, platelets 94,000 mm³**

Case 4—Discussion Point 1

What is this patient's chance of SVR with PI-based therapy?

What would you advise this patient to do?

Case 4—Discussion Point 2

The decision is made to treat with telaprevir triple therapy

Would you use a lead-in regimen?

Case 4—Conclusion

- **Prior null responders have lower chances of SVR with PI-based therapy than others**
 - **Chance of emergent resistance is higher**
- **Overall optimism prevails regarding long-term impact of resistance but should be discussed with patients**
- **Lead-in standard with boceprevir; may provide useful information about likelihood of SVR with telaprevir in null responders (although not labeled for use)**
- **Early indications that “quad regimens” may be highly effective in null responders**
- **Unclear if IFN responsiveness will affect response to IFN-free combination regimens**

Conclusion: HCV—Present and Future

David R. Nelson, MD

Professor of Medicine

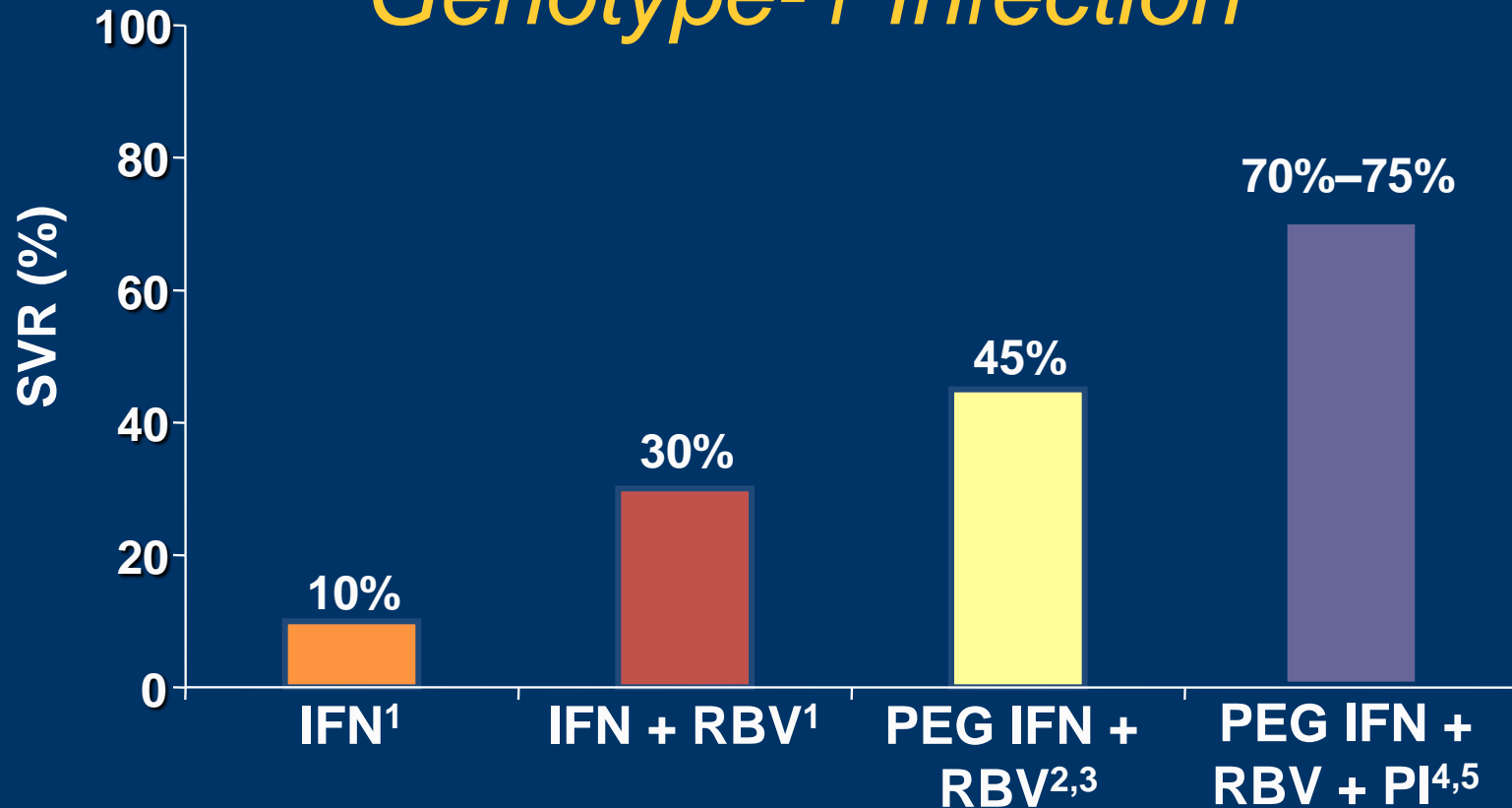
Associate Dean for Clinical Research

University of Florida College of Medicine

Gainesville, Florida

The New Standard of Care

SVR in Treatment-Naive HCV Genotype-1 Infection

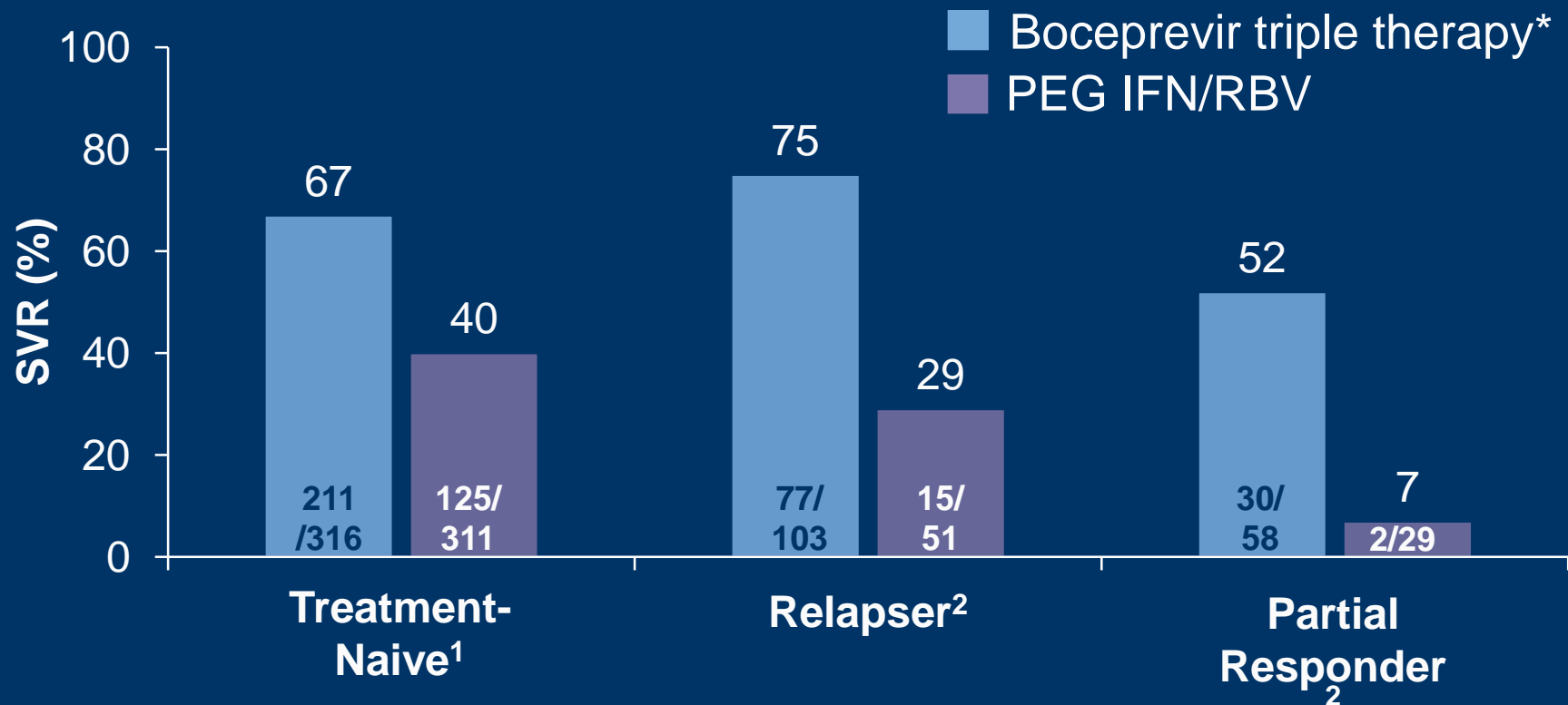


Abbreviations: IFN, interferon; PEG IFN, peginterferon; PI, protease inhibitor; RBV, ribavirin.

1. McHutchison JG, et al. *Semin Liver Dis.* 1999;19:57-65. 2. Manns MP, et al. *Lancet.* 2001;358:958-965. 3. Fried MW, et al. *N Engl J Med.* 2002;347:975-982. 4. Jacobson IM, et al. *N Engl J Med.* 2011;364:2405-2416. 5. Poordad F, et al. *N Engl J Med.* 2011;364:1195-1206. Graphic courtesy of Dr. David R. Nelson.

Boceprevir—Improved SVR for All Genotype 1 Patients

SPRINT-2¹ and RESPOND-2² Phase III Trials

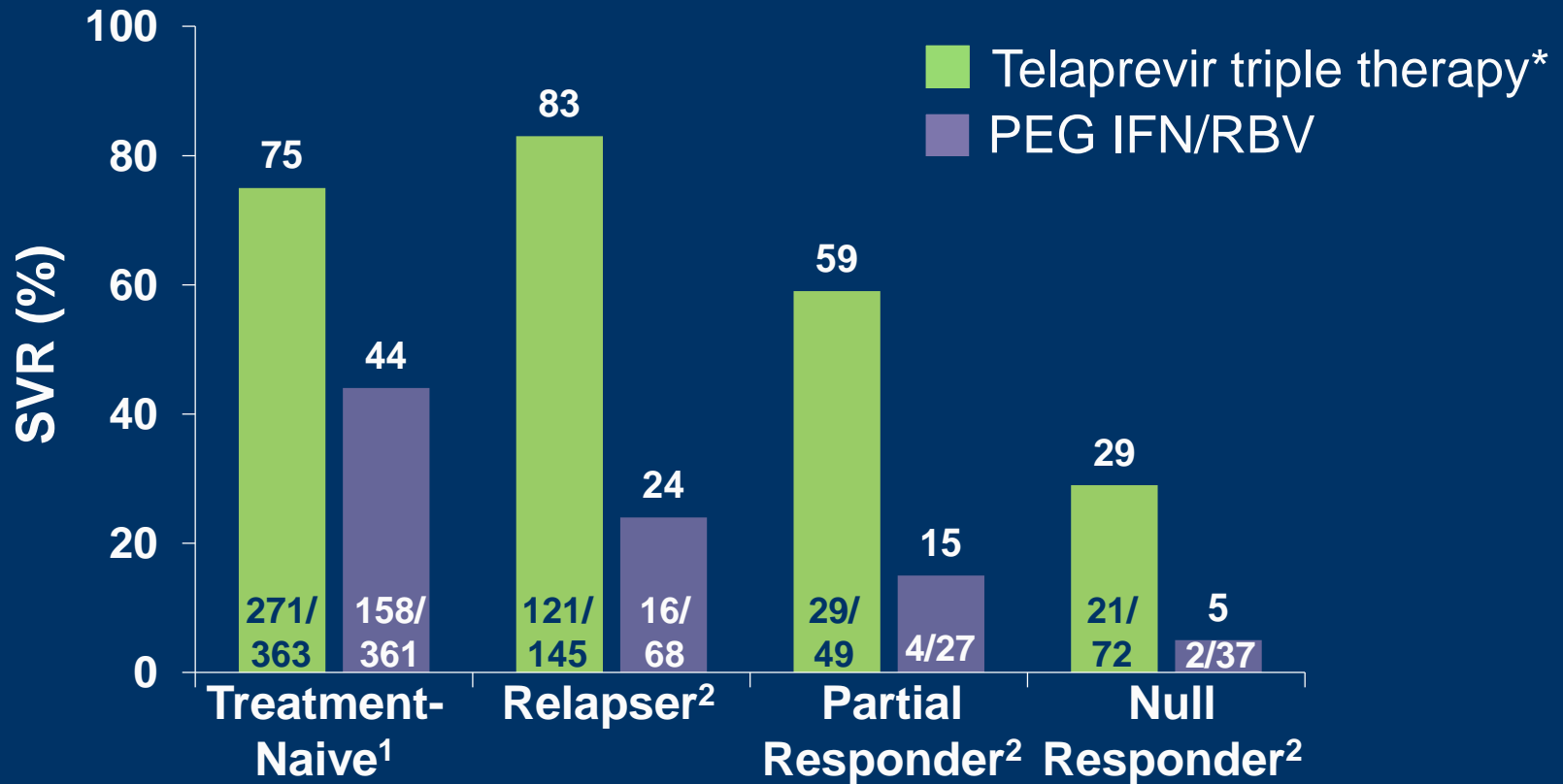


*Based on RGT arm in SPRINT-2 and PR4/BPR44 arm in RESPOND-2.

1. Poordad F, et al. *N Engl J Med.* 2011;364:1195-1206. 2. Bacon BR, et al. *N Engl J Med.* 2011;364:1207-1217. Graphic courtesy of Dr. David R. Nelson.

Telaprevir—Improved SVR for All Genotype-1 Patients

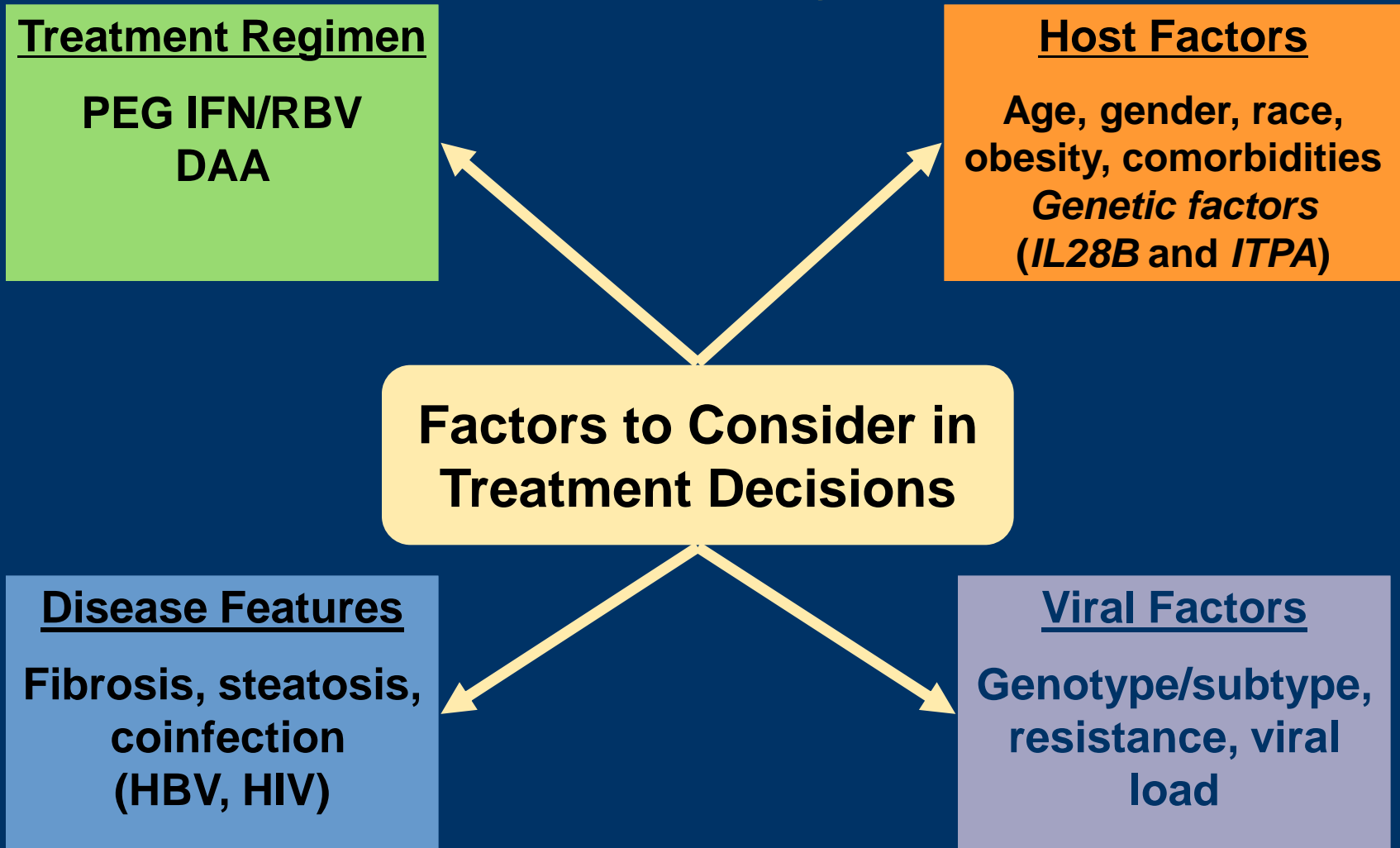
ADVANCE¹ and REALIZE² Phase III Trials



*Based on T12/PR24 arm in ADVANCE and T12PR48 arm in REALIZE.

1. Jacobson IM, et al. *N Engl J Med.* 2011;364:2405-2416. 2. Zeuzem S, et al. *N Engl J Med.* 2011;364:2417-2428.

Identifying Candidates For Triple Therapy



Anti-HCV Treatment Decisions for Protease Inhibitors

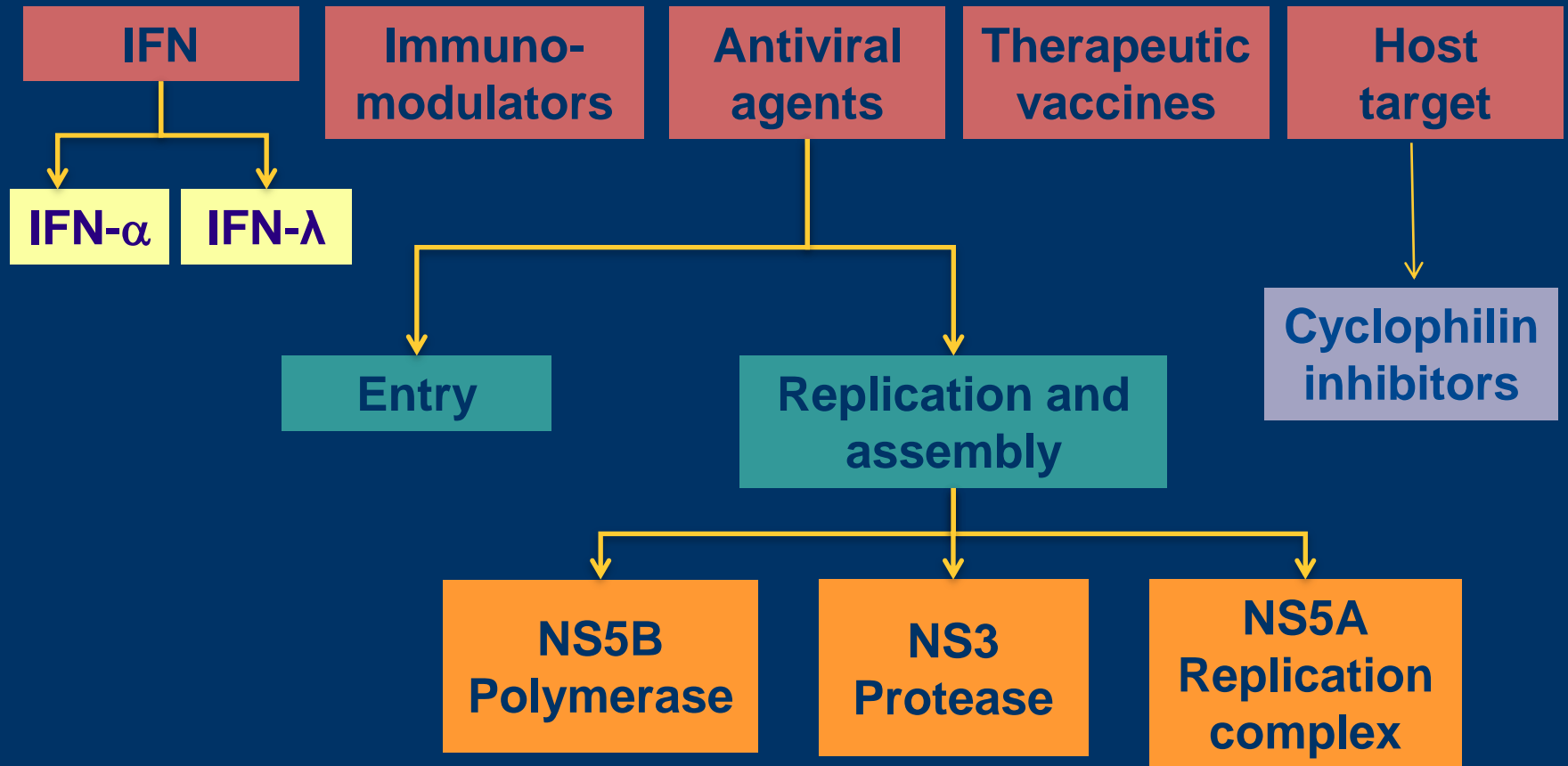
PROs

- Protease inhibitors substantially increase chance of SVR across all genotype-1 patient groups
- Protease inhibitors shorten duration of therapy in many
- Successful treatment improves morbidity and mortality

CONs

- Suboptimal response rates in many populations
- Complicated regimens, challenging adverse events, and drug-drug interactions
- Risk of resistance if therapy fails: impact on future options?

Antiviral Targets and Approaches for the Future



IFN-Free Regimens—AASLD 2011

- **BMS-790052 (NS5A) + BMS-650032 (PI)¹**
 - 24 weeks treatment in genotype 1b null responders
 - SVR12 = (9/10) 90%
- **BI-201335 (PI) + BI-207127 (NNI) + RBV²**
 - Up to 40 weeks treatment in naive, genotype 1a/1b patients
 - cEVR at week 12: PI + NNI + RBV = 76%; PI + NNI = 57%

Abbreviations: NNI, non-nucleoside NS5B inhibitor; PI, protease inhibitor; RBV, ribavirin.

1. Chayama K, et al. *Hepatology*. 2011;54:Abstract LB-4.

2. Zeuzem S, et al. *Hepatology*. 2011;54:Abstract LB-15.

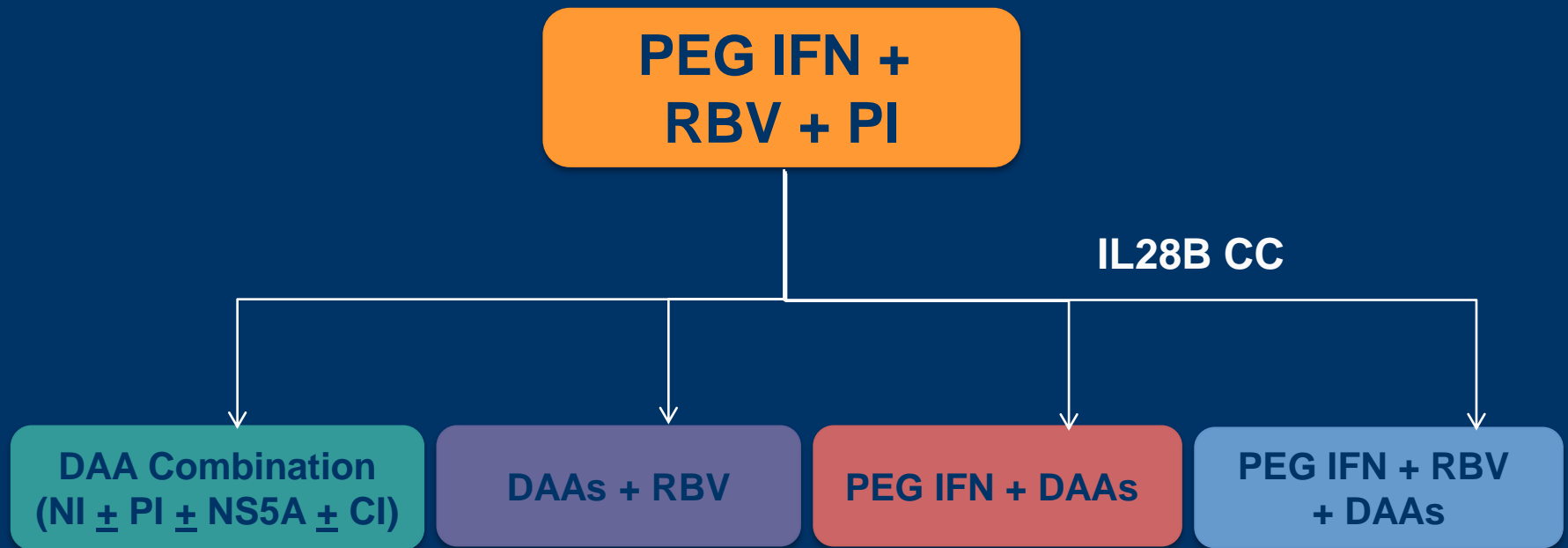
IFN-Free Regimens—AASLD 2011

- **Alisporivir (cyclophilin inhibitor)¹**
 - Alisporivir monotherapy + RBV in genotype-2 and -3 naive patients
 - 33% alisporivir mono and 48%–51% alisporivir + RBV on-treatment viral response (HCV <25 IU by week 6)
- **Miravirsen (antisense oligo targeting miR-122)²**
 - Given sq weekly to genotype-1 naive patients
 - Week 10 decline in HCV RNA: mean 2.2 log

1. Pawlotsky J, et al. *Hepatology*. 2011;54:Abstract LB-11.

2. Janssen HL, et al. *Hepatology*. 2011;54:Abstract LB-6.

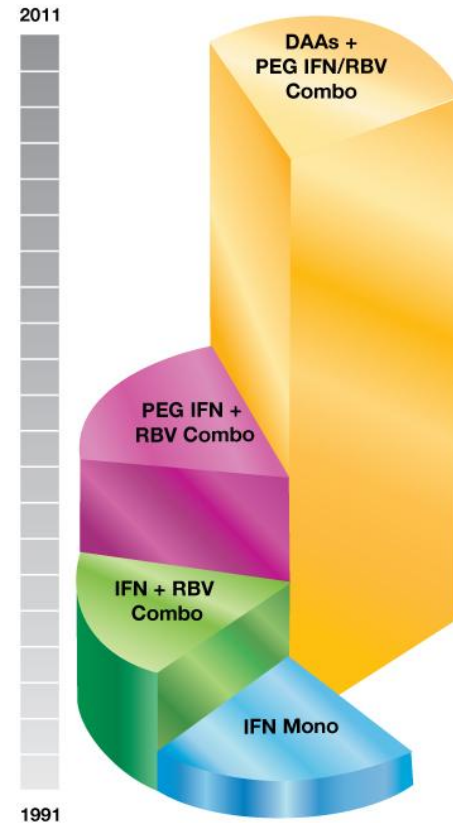
Towards a Future of Personalized Medicine




Abbreviations: CI, cyclophilin inhibitor; DAA, direct-acting antiviral; NI, nucleoside inhibitor; PEG IFN, peginterferon; PI, protease inhibitor; RBV, ribavirin. Graphic courtesy of Dr. David R. Nelson.

Paradigm Shift in HCV Standard of Care Treatment: DAAs

*A CME/CE
Satellite Symposium*



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