



# Treatment-Naive Patient With HCV Infection: Improving the Odds of Achieving a Sustained Virologic Response

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# Educational Objectives

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- ◆ Identify pretreatment factors predictive of response to HCV therapy
- ◆ Assess the impact of viral kinetics and treatment duration on achieving an SVR
- ◆ Individualize HCV therapy based on pretreatment risk factors and on-treatment responses

# Patient NS: History

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- ◆ 44-year-old Hispanic male recently referred for chronic hepatitis C virus (HCV) infection
- ◆ Liver biopsy in 2007 showed stage 2 disease, HCV genotype 1 with HCV-RNA 650,000 IU/mL
- ◆ No medical comorbidities
- ◆ Exam negative, weight = 110 kg, BMI = 33

# Question 1

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What is the optimal dose of ribavirin and duration of therapy that will maximize his likelihood of achieving an SVR?

- A. Ribavirin 1200 mg/day for 72 weeks
- B. Ribavirin 1400 mg/day for 72 weeks
- C. Ribavirin 1200 mg/day for 24 weeks
- D. Ribavirin at 15 mg/kg/day for 36 weeks
- E. None of the above

# Answer to Question 1

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- ◆ Answer is E
  - Data suggest that increased ribavirin in heavier patients may increase the likelihood of sustained virologic response. However, the optimal duration of therapy can only be determined based upon the change in HCV-RNA observed at key time points during therapy

# Factors Associated With SVR

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## Pretreatment or Fixed

- ◆ Genotype
- ◆ HCV-RNA level
- ◆ Histology
- ◆ Race
- ◆ HIV coinfection
- ◆ Steatosis
- ◆ Body weight
- ◆ Adherence

## Dynamic Factors

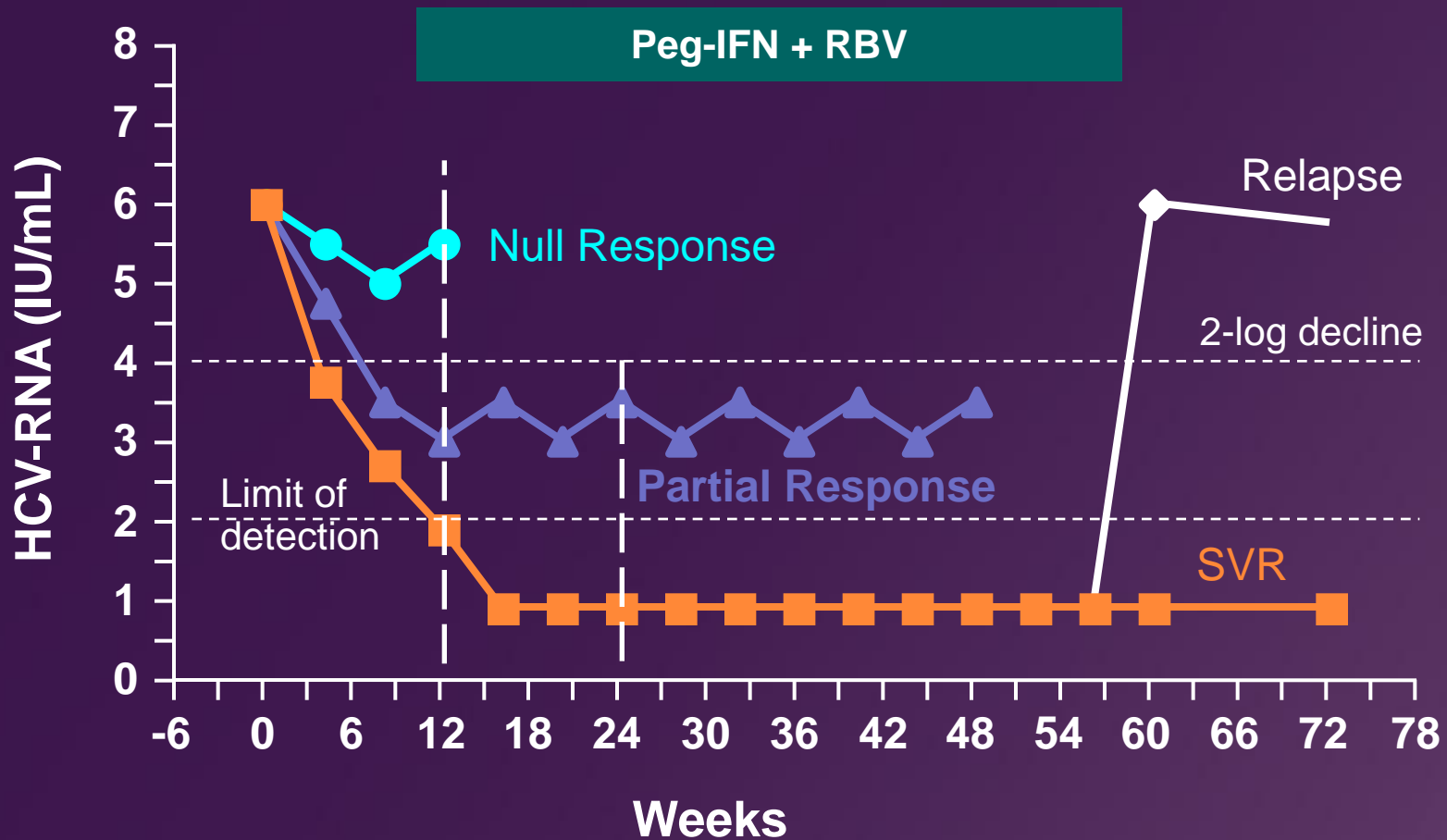
- ◆ Rapid virologic response (RVR)
- ◆ Early virologic response (EVR)
  - Partial
  - Complete

# Maximizing Therapeutic Response

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- ◆ Importance of adequate ribavirin dosing
- ◆ Importance of adherence
- ◆ On-treatment response as a predictor of sustained virologic response (SVR)
- ◆ Extending duration of therapy for slow virologic responders
- ◆ Shortening therapy in rapid virologic responders

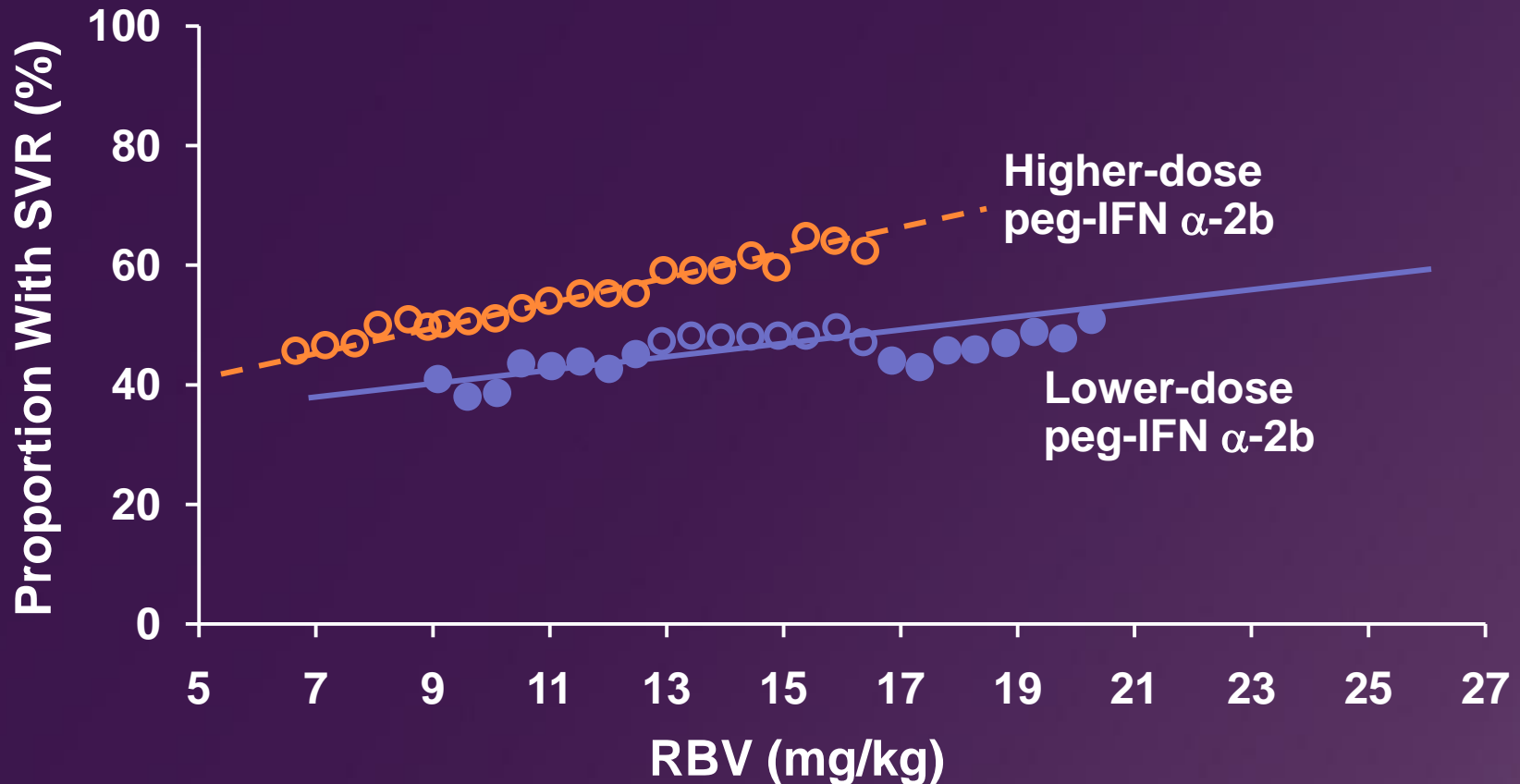
# Patterns of Response to Peginterferon and Ribavirin



Peg-IFN = pegylated interferon; RBV = ribavirin.

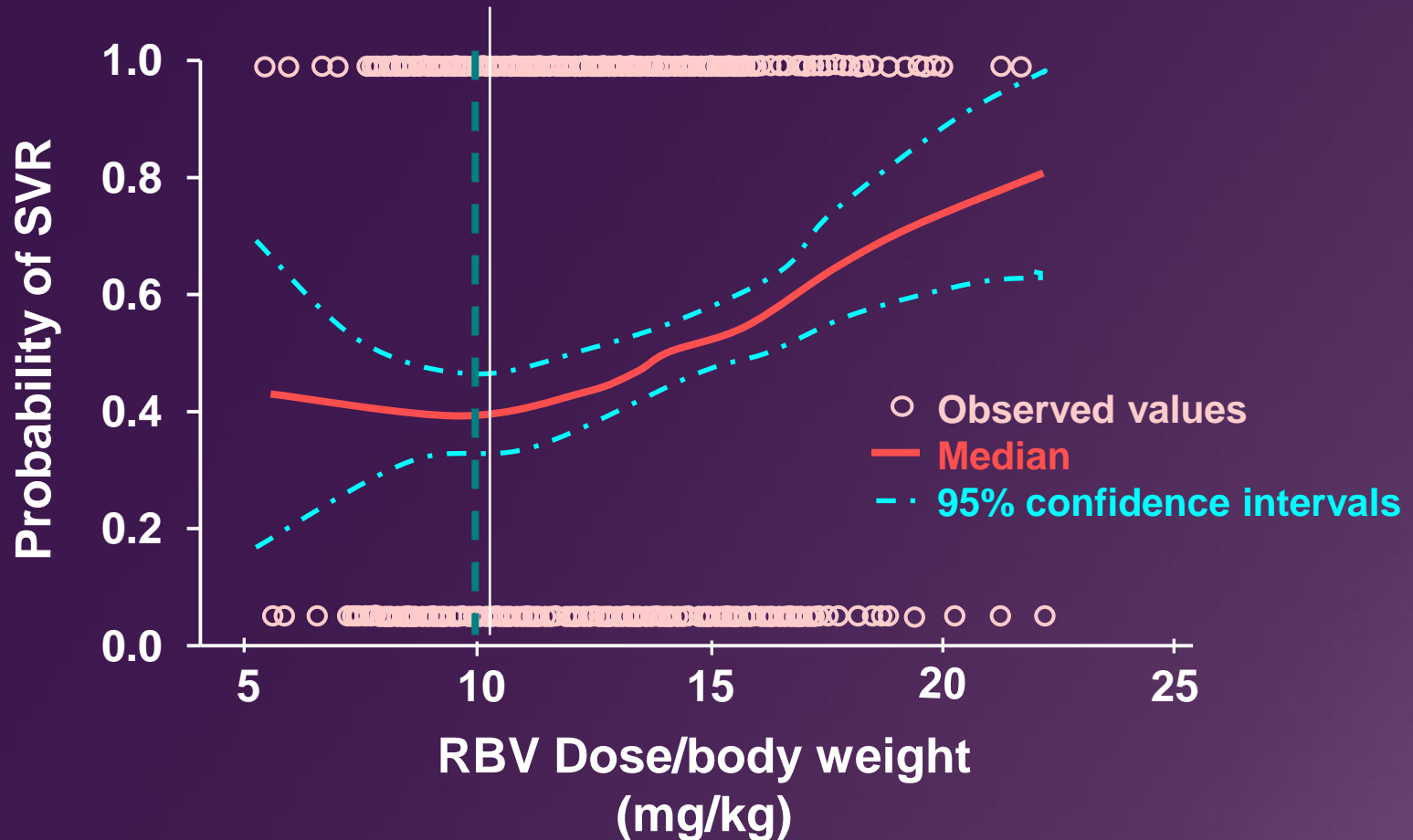
Shiffman ML. *Curr Gastroenterol Rep.* 2006;8:46-52 with kind permission of Current Medicine Group, LLC.

# Optimizing RBV With Peg-IFN

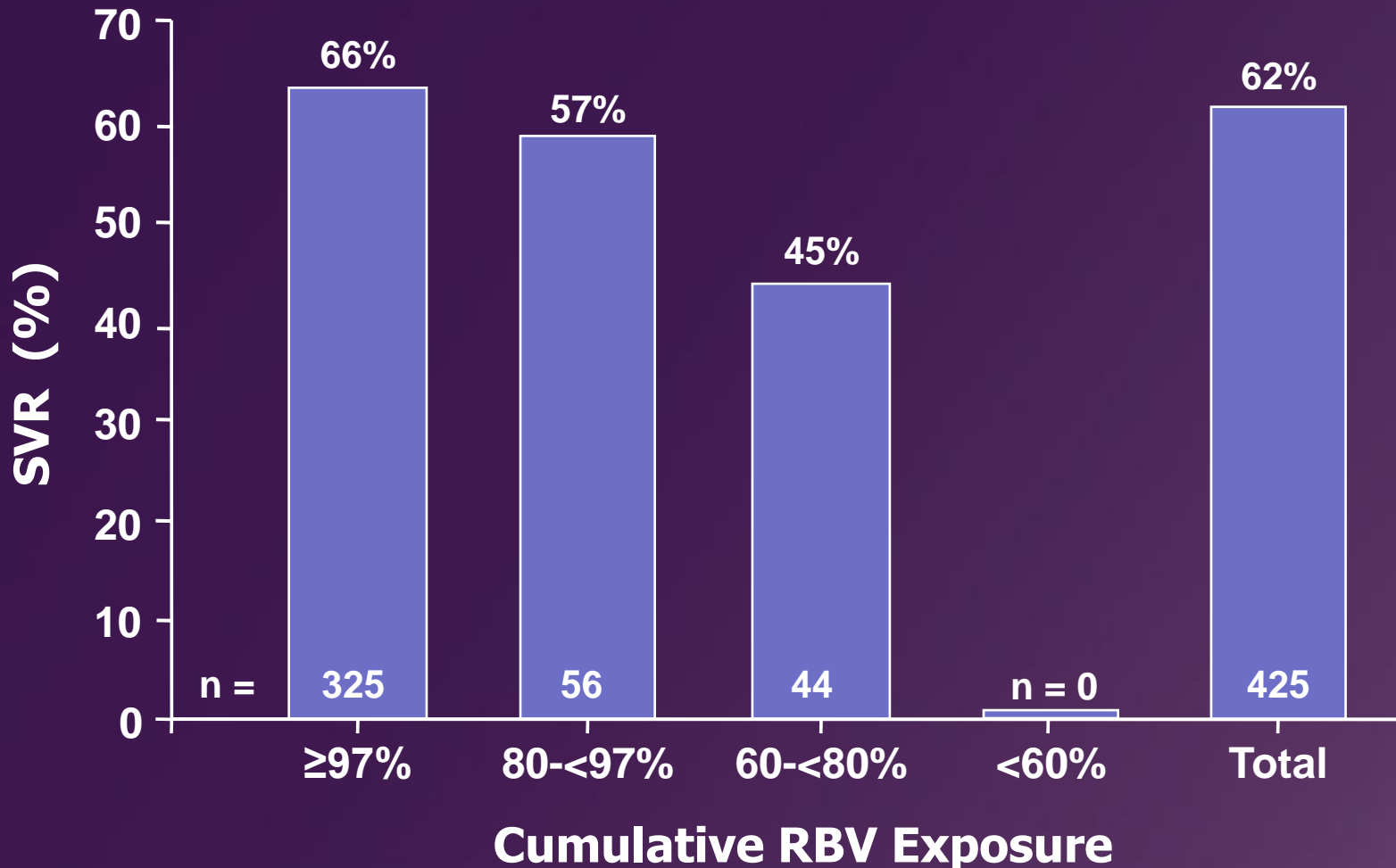


- ◆ SVR rate was higher in all groups when RBV dose was  $>10.6$  mg/kg body weight (or  $>800$  mg/day for a 75 kg person)

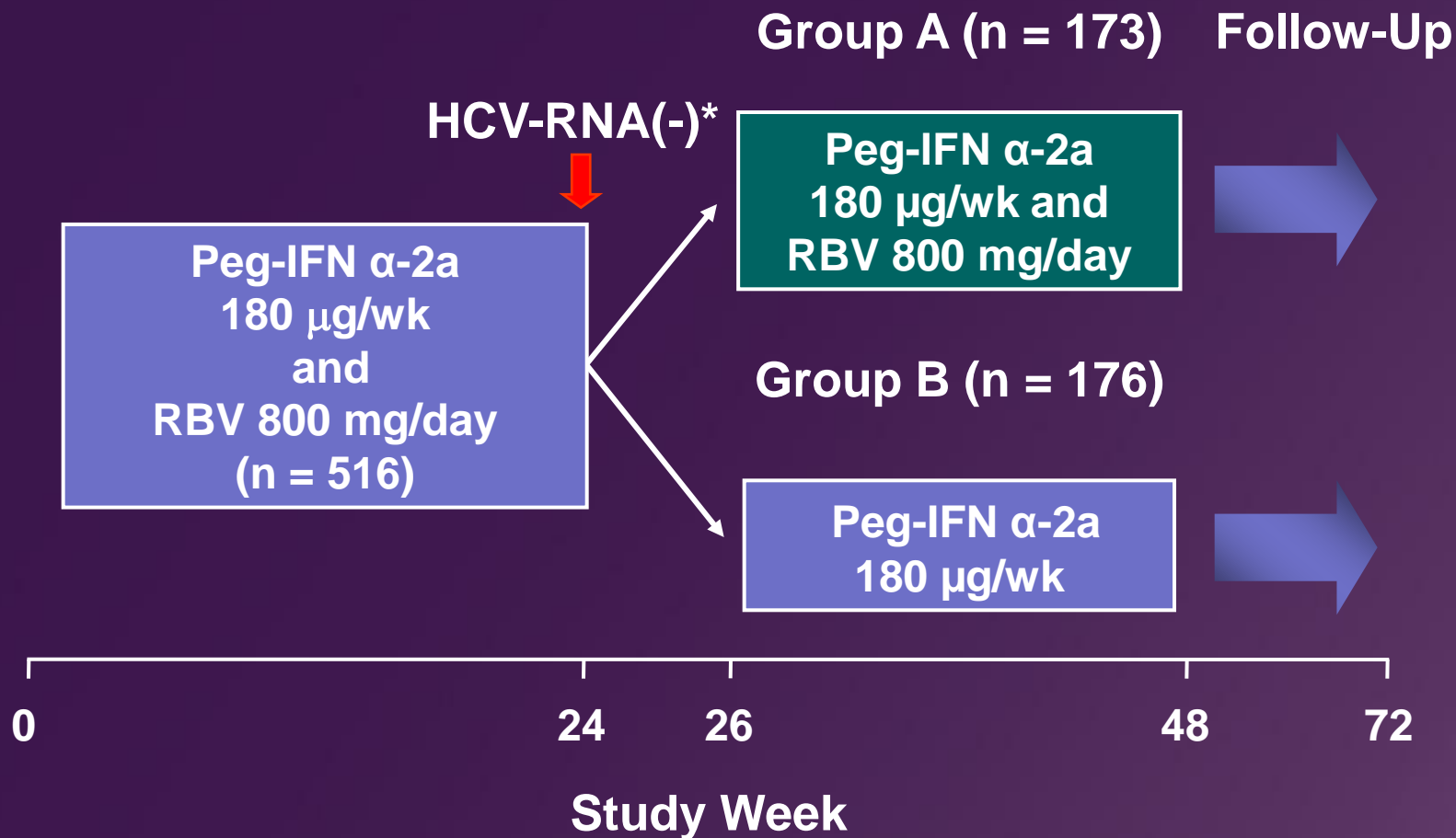
# Peg-IFN $\alpha$ -2a and RBV: Predicting SVR in Patients With Genotype 1



# Influence of Cumulative RBV Exposure: SVR in Genotype 1 in Weeks 1-12

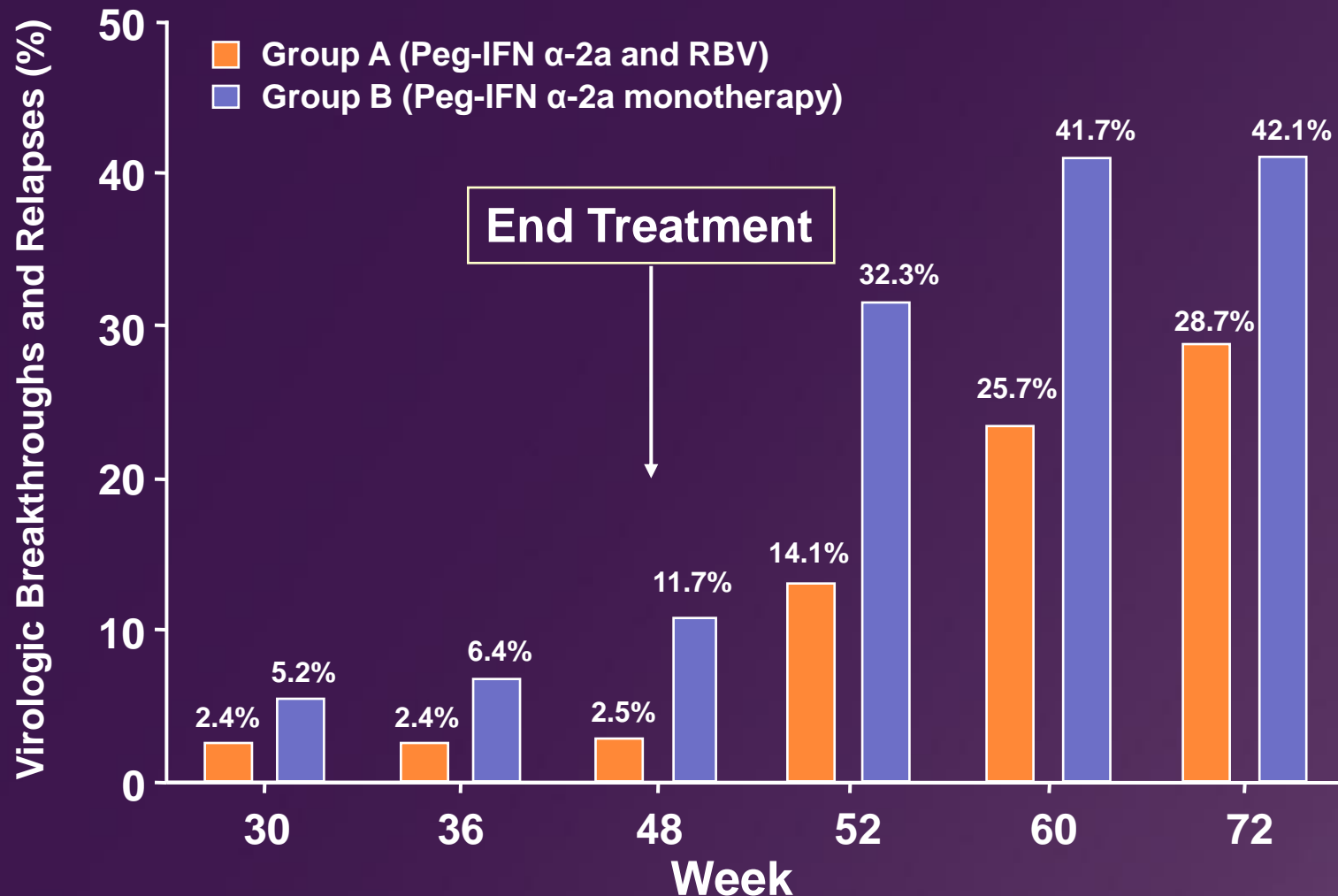


# Discontinuing RBV: Effect in Patients With Genotype 1 Responding to Therapy



\*HCV-RNA negative defined as HCV-RNA <50 IU/L.  
Bronowicki JP et al. *Gastroenterology*. 2006;131:1040-1048.

# Effect of Discontinuing RBV in Patients Responding to Therapy: Virologic Breakthroughs and Relapses



Reprinted from *Gastroenterology*, 131 Bronowicki JP et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. Copyright 2006, with permission from Elsevier.

## Patient NS (cont)

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- ◆ The patient is started on peg-IFN and ribavirin 1400 mg/day (~13 mg/kg/day)
- ◆ At week 4, HCV-RNA is 400,000 IU/mL
- ◆ At week 12, HCV-RNA is 8000 IU/mL
- ◆ At week 20, HCV-RNA is undetectable

## Question 2

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How would you characterize this patient's virologic response?

- A. He had a rapid virologic response because virus level dropped more than 3 logs by week 12
- B. He had a rapid virologic response defined as undetectable HCV-RNA by week 12
- C. He would be characterized as having a slow virologic response because he cleared virus only after week 12
- D. He had a complete early virologic response

# Answer to Question 2

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- ◆ The answer is C
- ◆ This patient experienced a slow virologic response, clearing virus only between weeks 12 and 20
  - Rapid virologic response is defined as undetectable viremia at week 4. Patients who achieve RVR have the greatest chance of cure
  - Patients with a slow virologic response who relapse may benefit from an extended course of therapy

# Maximizing Therapeutic Response

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- ◆ Importance of adequate ribavirin dosing
- ◆ Importance of adherence
- ◆ On-treatment response as a predictor of SVR
- ◆ Extending duration of therapy for slow virologic responders
- ◆ Shortening therapy in rapid virologic responders

# HCV Therapy: Is it rational for all patients to be treated the same?

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- ◆ Individualizing treatment based on patient characteristics
- ◆ Tailoring therapy to individual response
  - Importance of RVR
  - Extending duration of therapy to prevent relapse
  - Shortening duration of therapy to minimize adverse events

# Factors Associated With SVR

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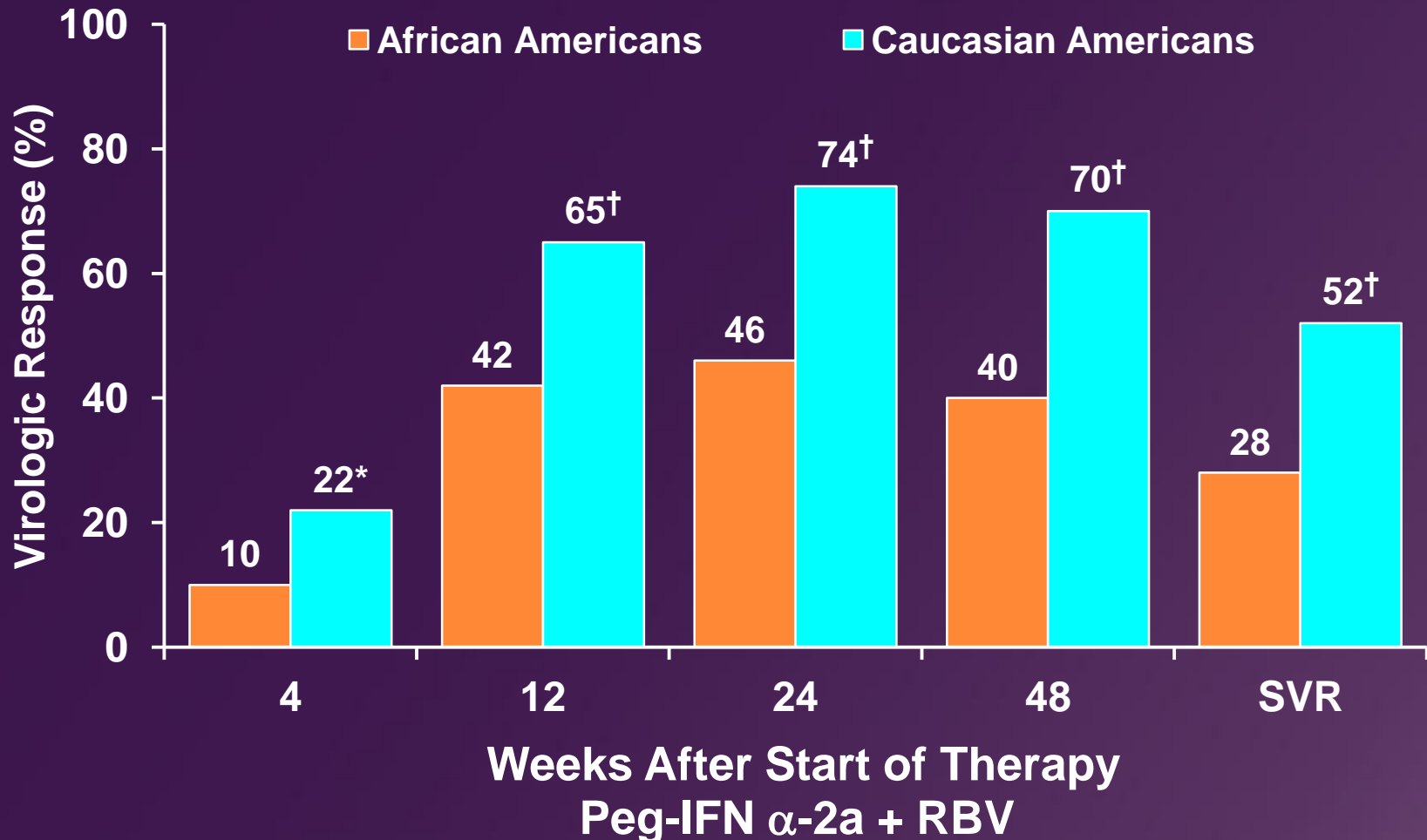
## Pretreatment or Fixed

- ◆ Genotype
- ◆ HCV-RNA level
- ◆ Histology
- ◆ Race
- ◆ HIV coinfection
- ◆ Steatosis
- ◆ Body weight
- ◆ Adherence

## Dynamic Factors

- ◆ Rapid virologic response
- ◆ Early virologic response
  - Partial
  - Complete

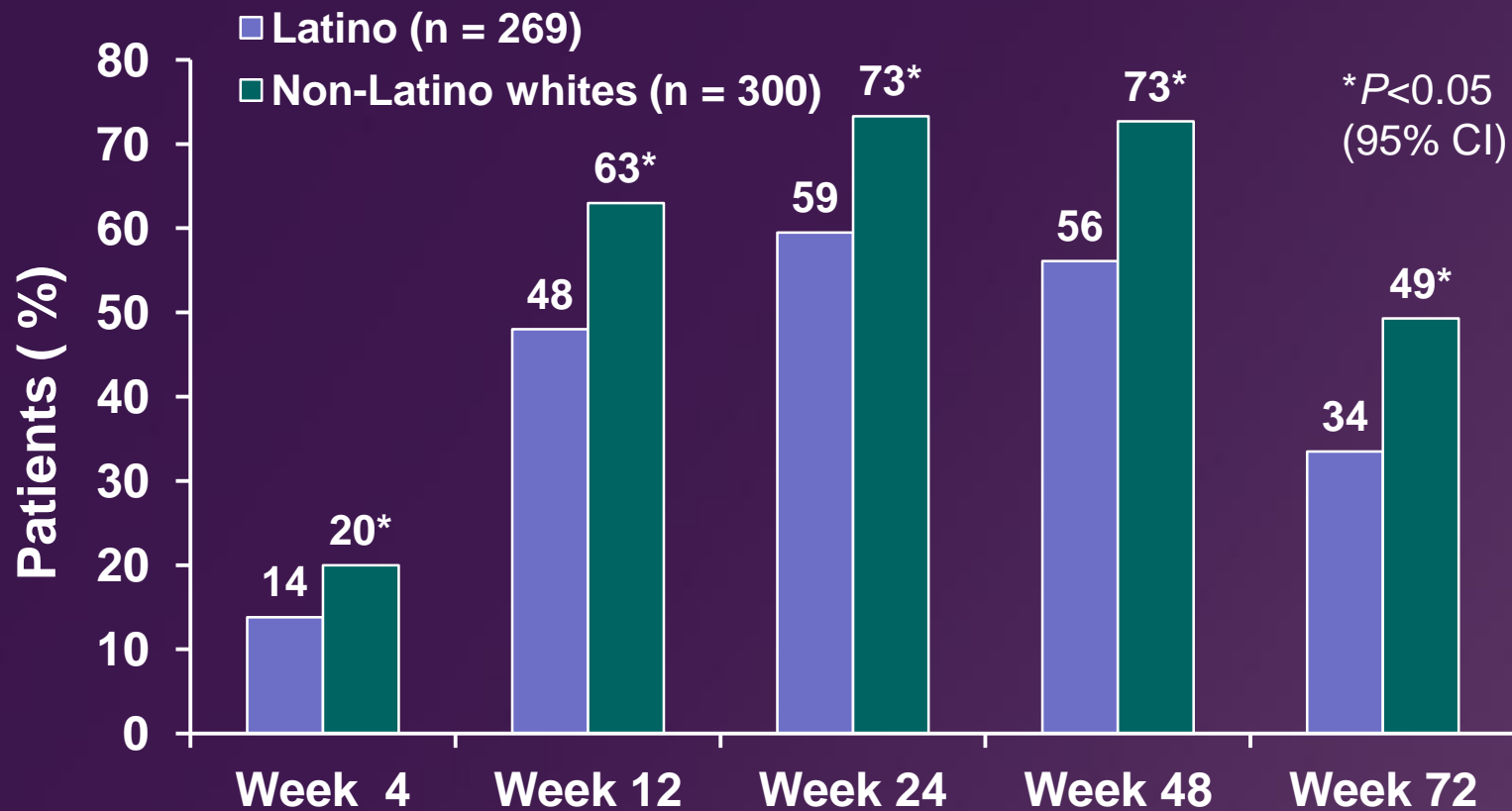
# VIRAHEP-C: Virologic Response and Race



\* $P < 0.01$ ; † $P < 0.0001$ .

Conjeevaram HS et al. *Gastroenterology*. 2006;131:470-477.

# The LATINO Study: Virologic Response Rates



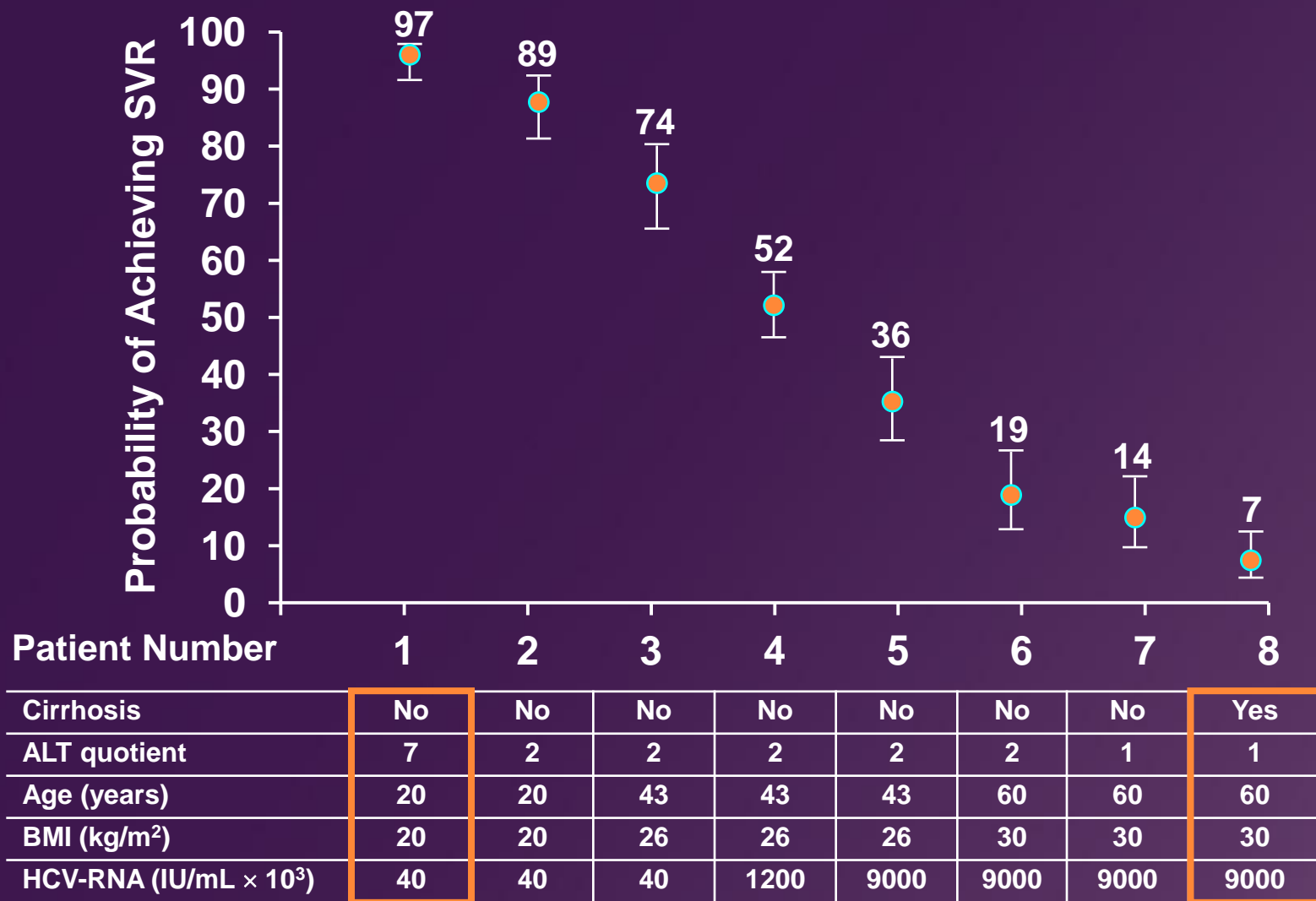
SVR was higher in the non-Latino whites group than in the Latino group (49% vs 34%;  $P < 0.0001$ )

# Prediction of SVR

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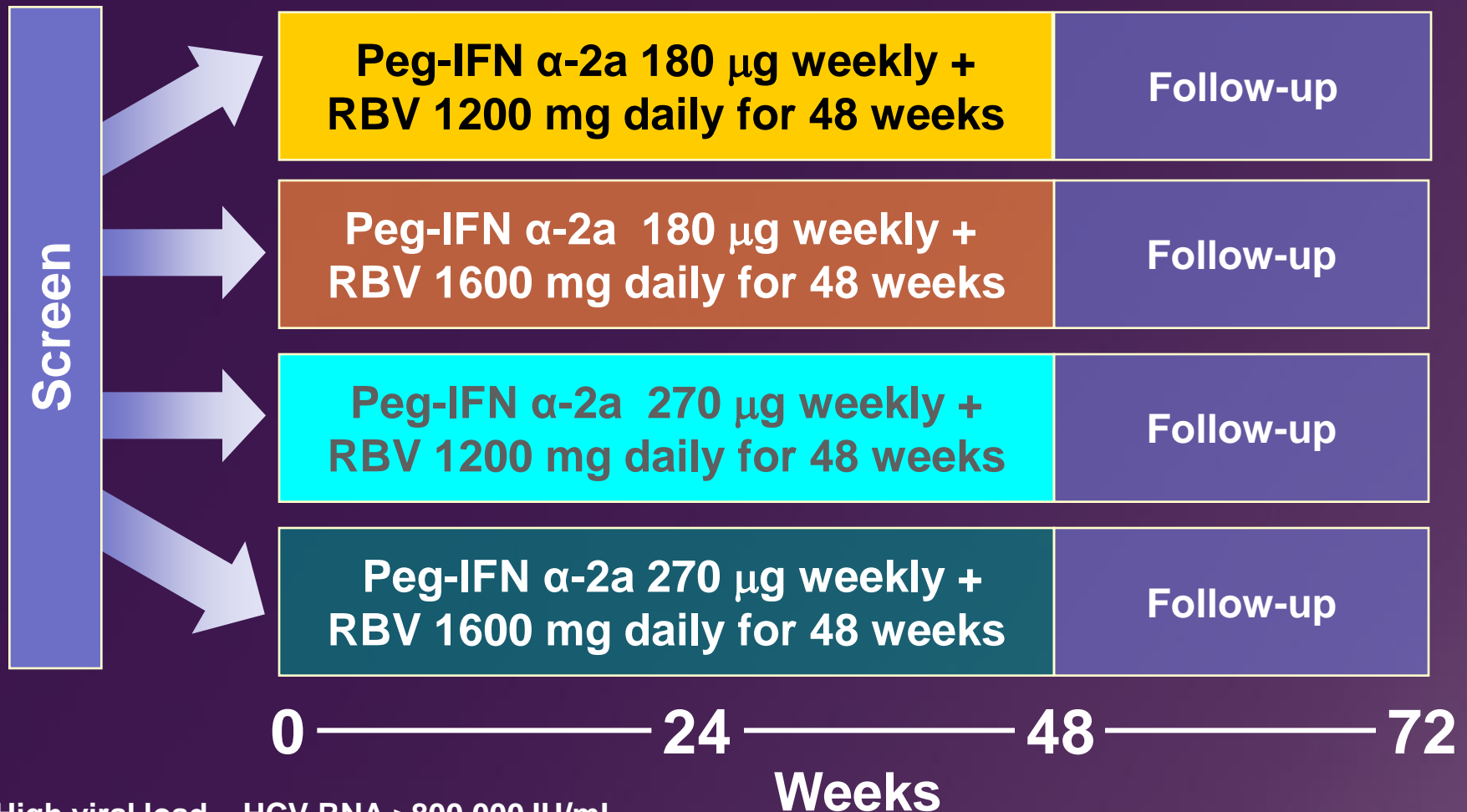
- ◆ Likelihood of SVR depends on interactions of multiple factors
- ◆ Can individual probabilities of SVR be estimated?
- ◆ Data from 2 registration trials of peg-IFN  $\alpha$ -2a + RBV were used to identify significant factors related to SVR
- ◆ Modeling was used to vary important baseline characteristics

# Probability of SVR: Interactions of Multiple Factors



# Intensive Regimen in Patients With Genotype 1 >85 kg + High Viral Load: Study Design

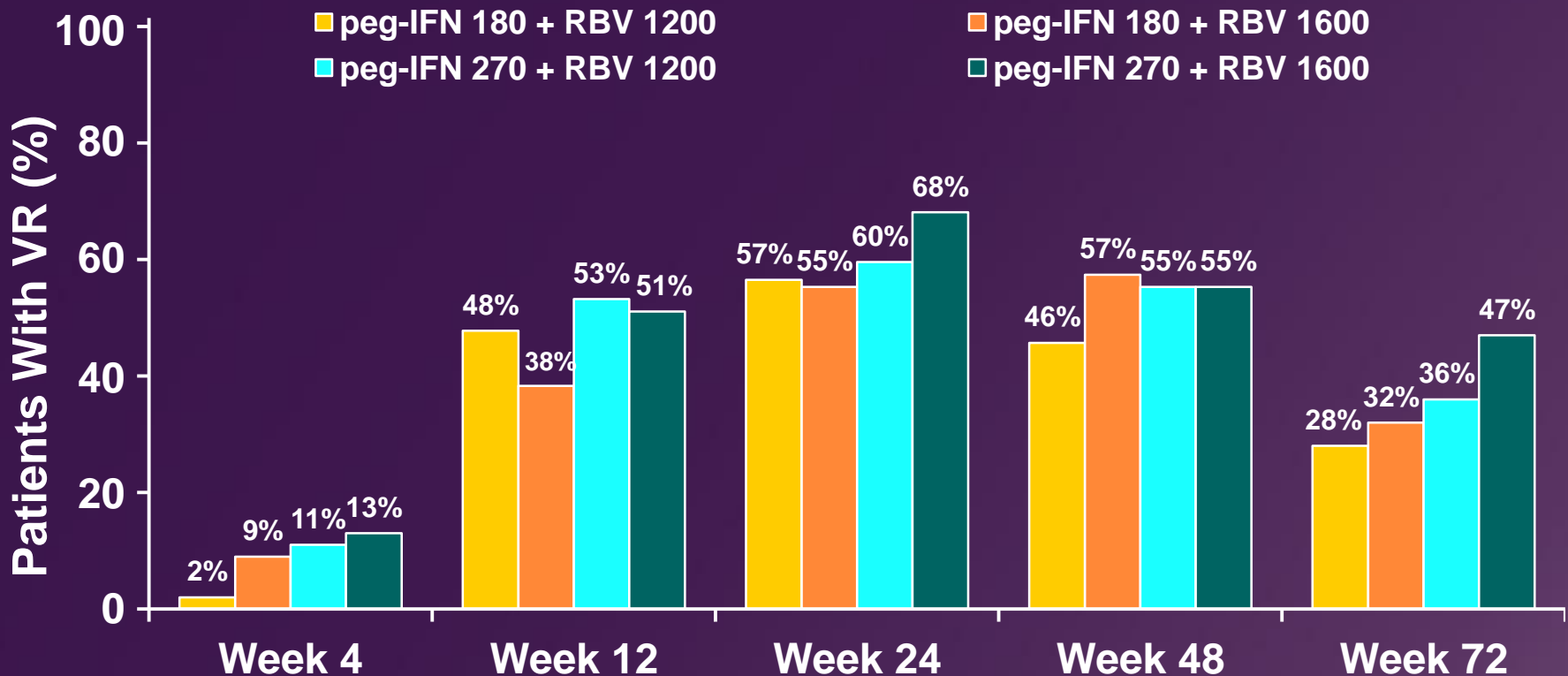
N = 188



High viral load = HCV-RNA >800,000 IU/mL

Fried MW et al. *Hepatology*. 2008;48:1033-1043. Permission requested.

# Intensive Regimen: Treatment-Resistant Characteristics and Virologic Response Over Time



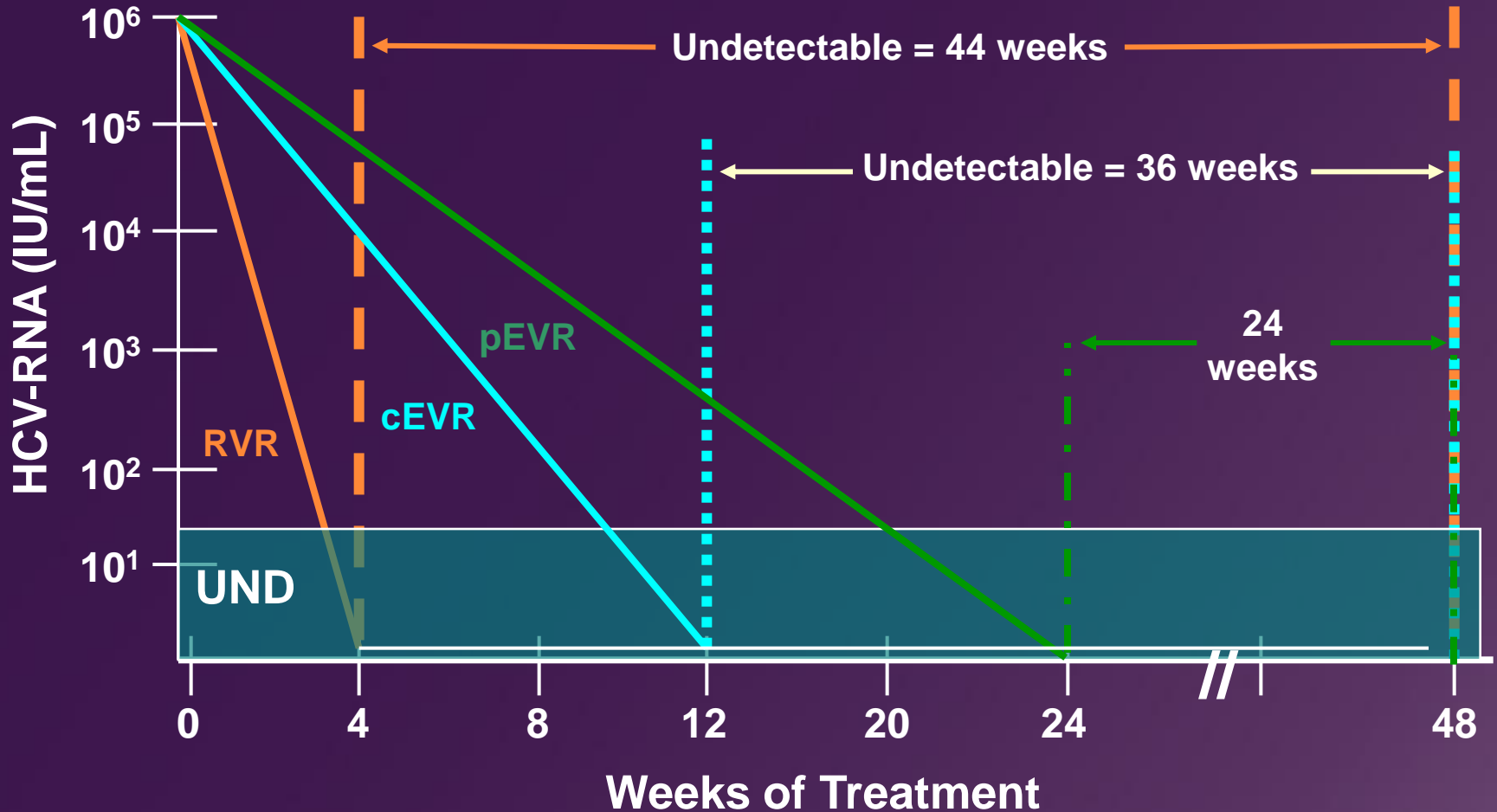
All treated; VR = HCV-RNA <50 copies/mL; Missing = Failure.  
Fried MW et al. *Hepatology*. 2008;48:1033-1043.

# Definitions of On-Treatment Response

Response		Definition
RVR		HCV-RNA negative (<50 IU/mL) at week 4
EVR	Complete EVR	HCV-RNA positive at week 4 but negative at week 12
	Partial EVR	HCV-RNA positive at week 4 and 12 but $\geq 2 \log_{10}$ drop from baseline at week 12
Non-EVR		$< 2 \log_{10}$ drop from baseline at week 12

RVR = rapid virologic response; EVR = early virologic response.

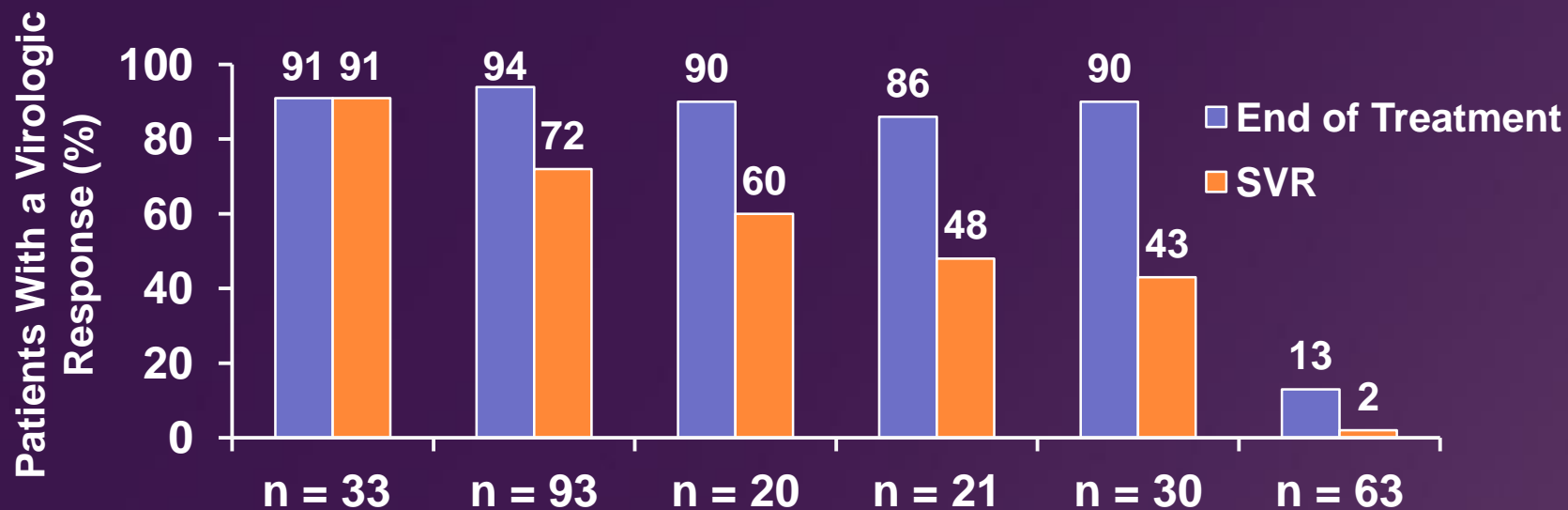
# Rate of HCV-RNA Clearance



UND = undetectable.

Courtesy of Michael W. Fried, MD.

# Predicting SVR: Viral Kinetics and Outcomes in Patients Treated With Peg-IFN $\alpha$ -2a + RBV

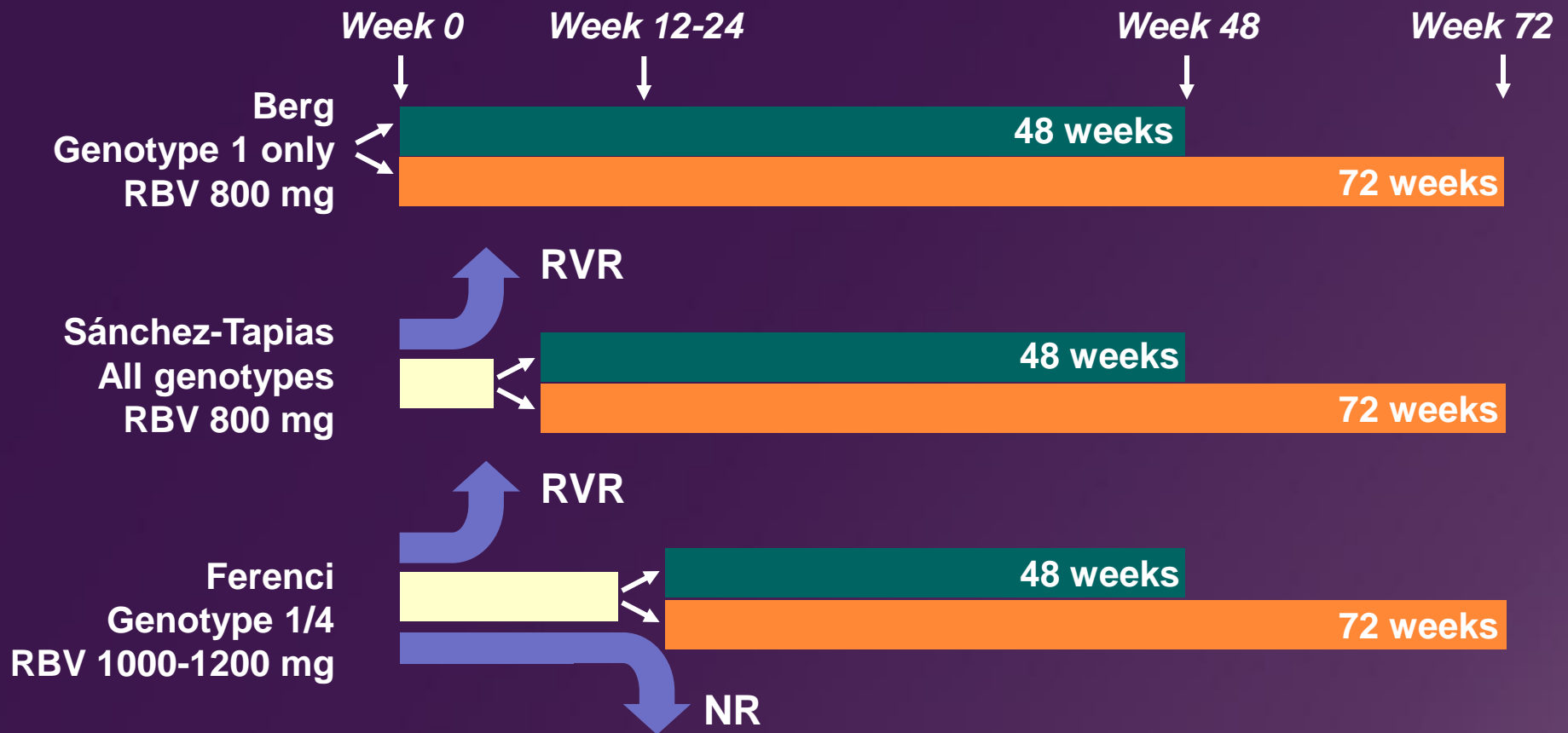


HCV-RNA Status						
Week 4	Negative	>2 Log <sub>10</sub>	<2 Log <sub>10</sub>	>2 Log <sub>10</sub>	<2 Log <sub>10</sub>	Any
Week 12	Negative	Negative	Negative	>2 Log <sub>10</sub>	>2 Log <sub>10</sub>	Any
Week 24	Negative	Negative	Negative	Negative	Negative	Positive
	<b>RVR</b>		<b>cEVR</b>		<b>pEVR</b>	

SVR = sustained virologic response.

Ferenci P et al. *J Hepatol.* 2005;43:425-433. Permission requested.

# Extending Therapy: Prospective Study Designs

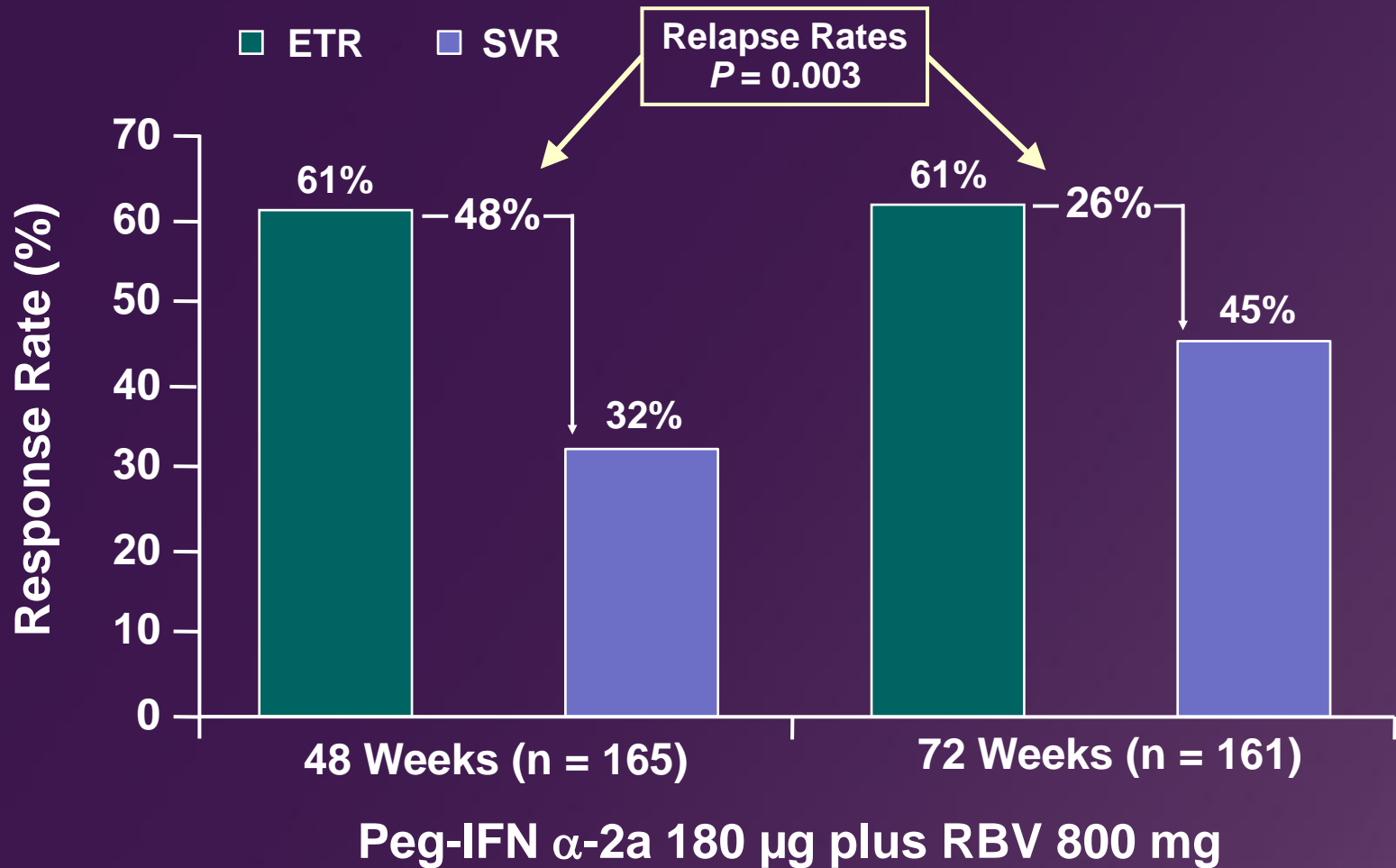


Berg T et al. *Gastroenterology*. 2006;130:1086-1097.

Sanchez-Tapias JM et al. *Gastroenterology*. 2006;131:451-460.

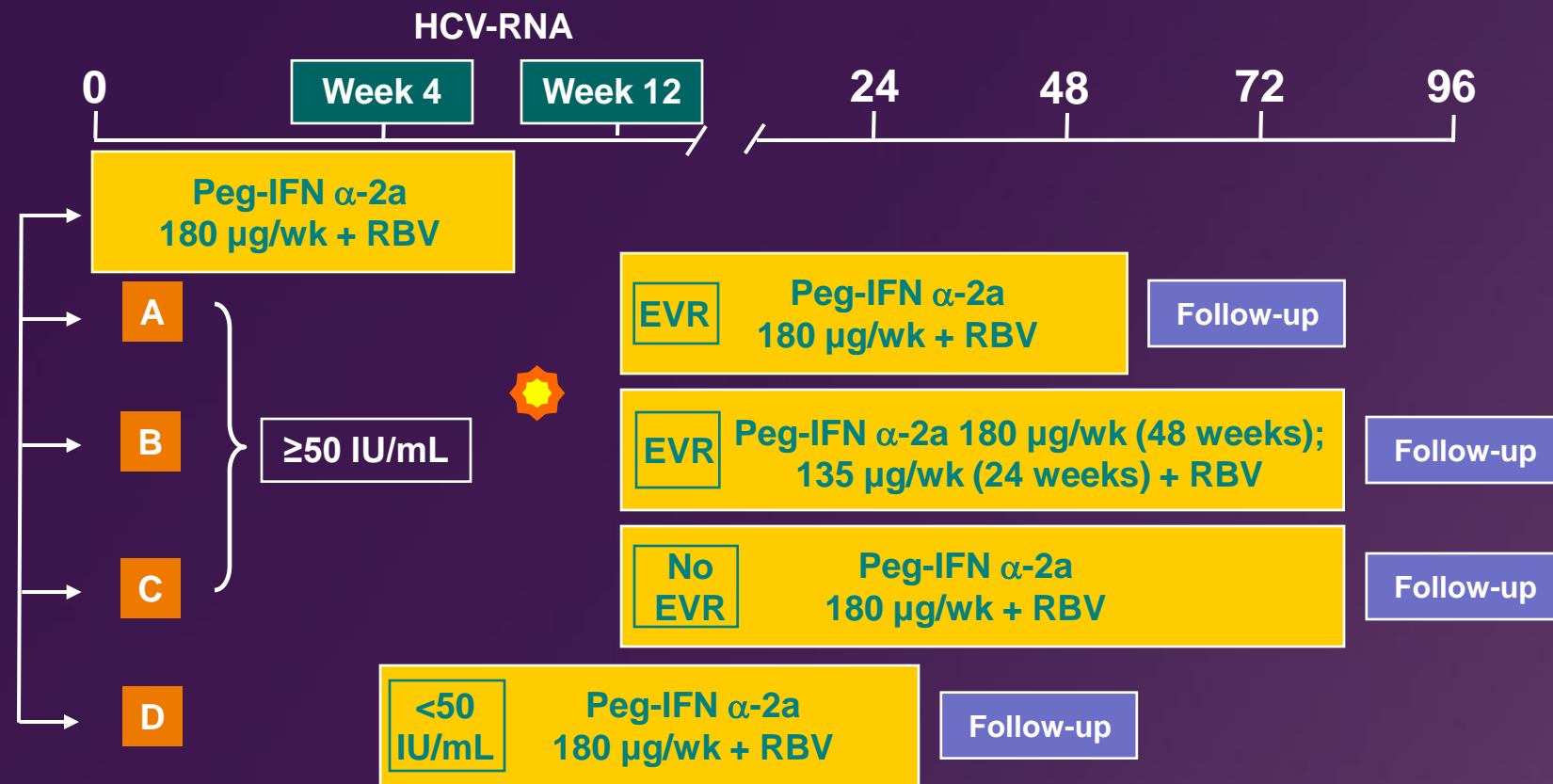
Ferenci P et al. 57th AASLD 2006. Abstract 390.

# Patients Without RVR at Week 4: ETR vs SVR (ITT)



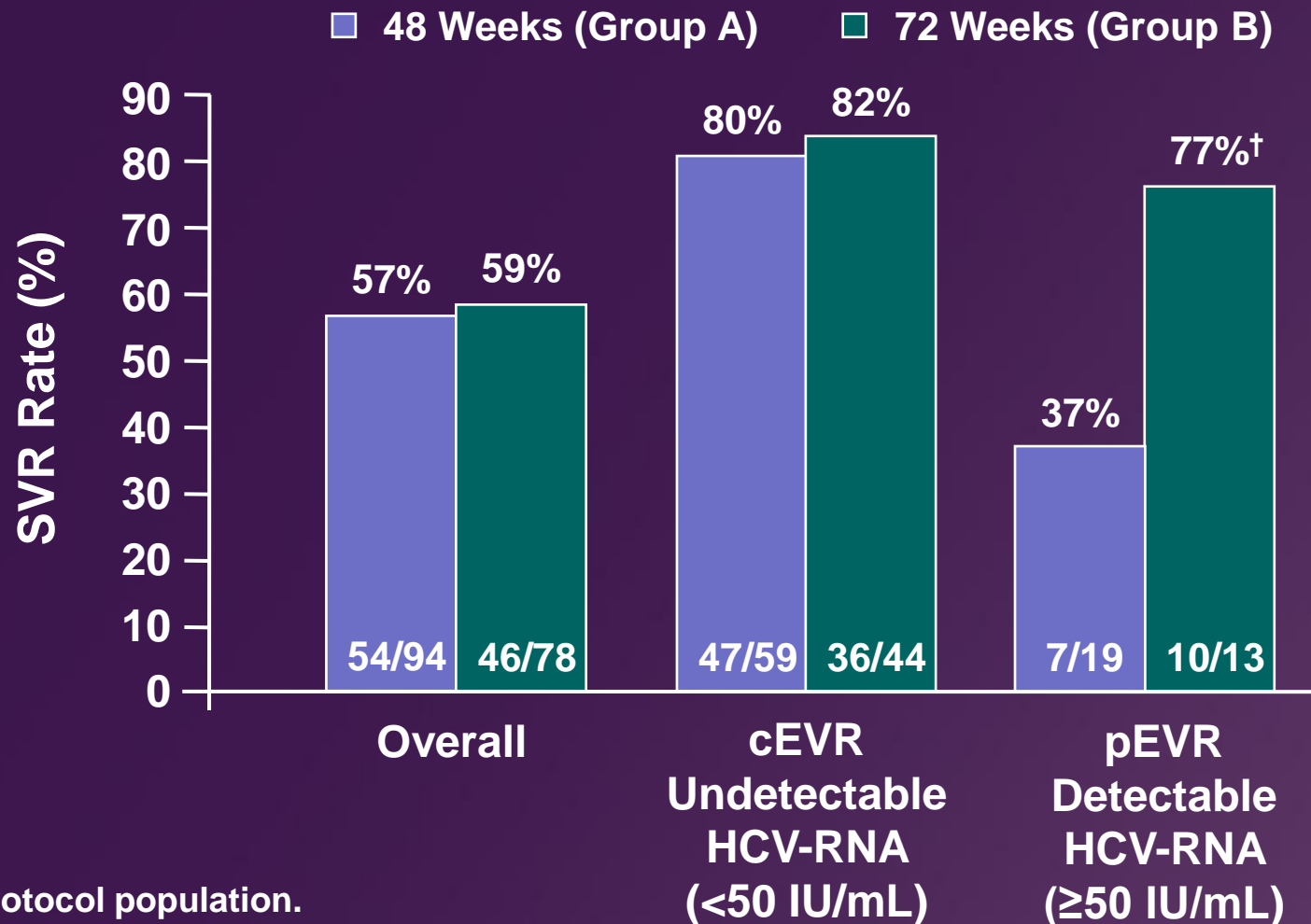
ETR = end of treatment response; ITT = intention to treat.  
Sanchez-Tapias JM et al. *Gastroenterology*. 2006;131:451-460.

# Peg-IFN $\alpha$ -2a + RBV Dosing by Virologic Response: Study Design



★ Randomization to Group A or B in patients with unquantifiable HCV-RNA or  $\geq 2 \log_{10}$  drop in HCV-RNA at week 12; RBV = ribavirin 1000/1200 mg/day.

# Extended Duration of Therapy: SVR in Patients Without RVR Who Achieved Complete or Partial EVR\*

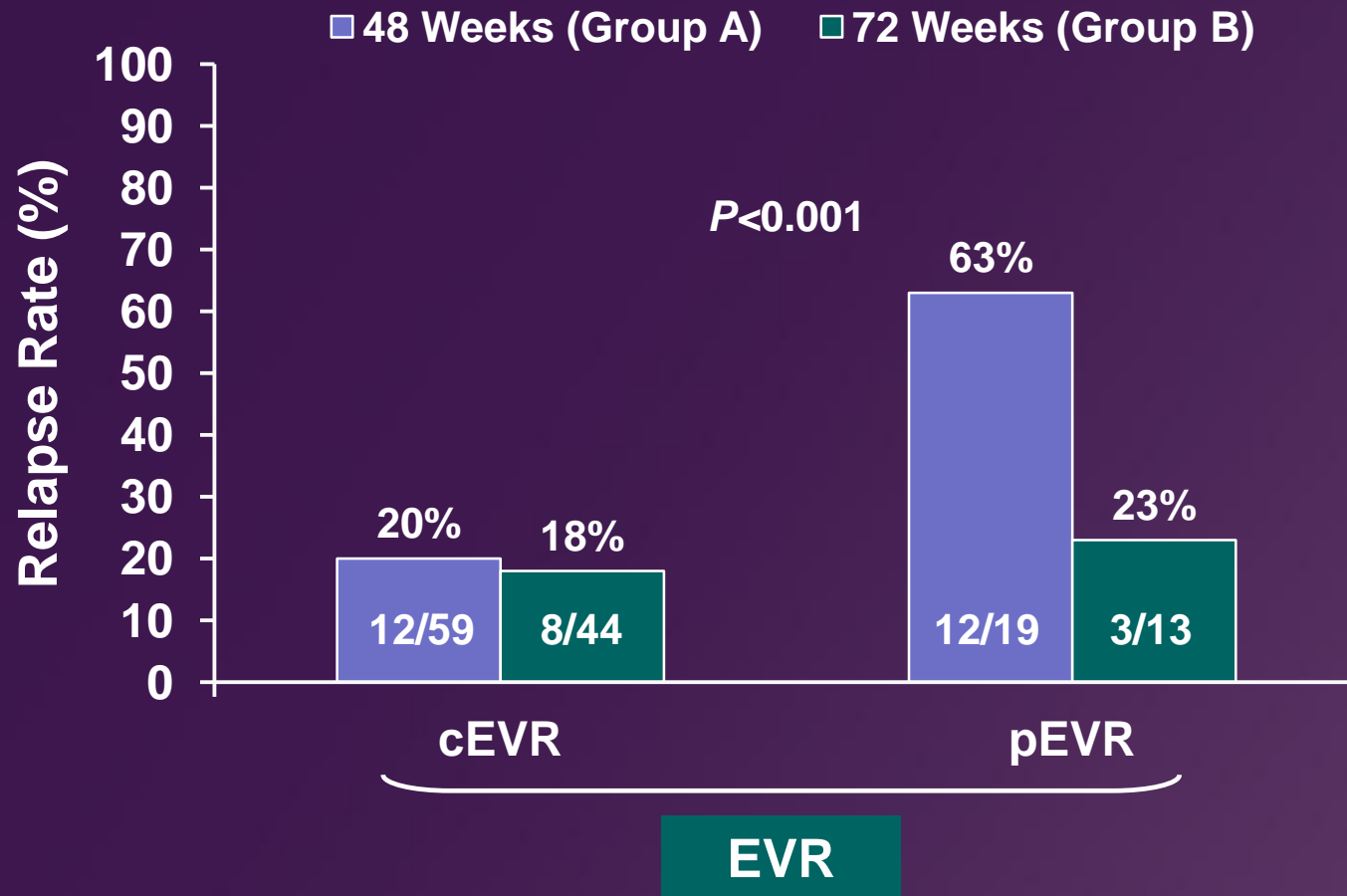


\*Per protocol population.

† $P < 0.001$ .

Ferenci P et al. 57th AASLD 2006. Abstract 390.

# Extended Duration of Therapy: Relapse Rates in Patients With cEVR or pEVR

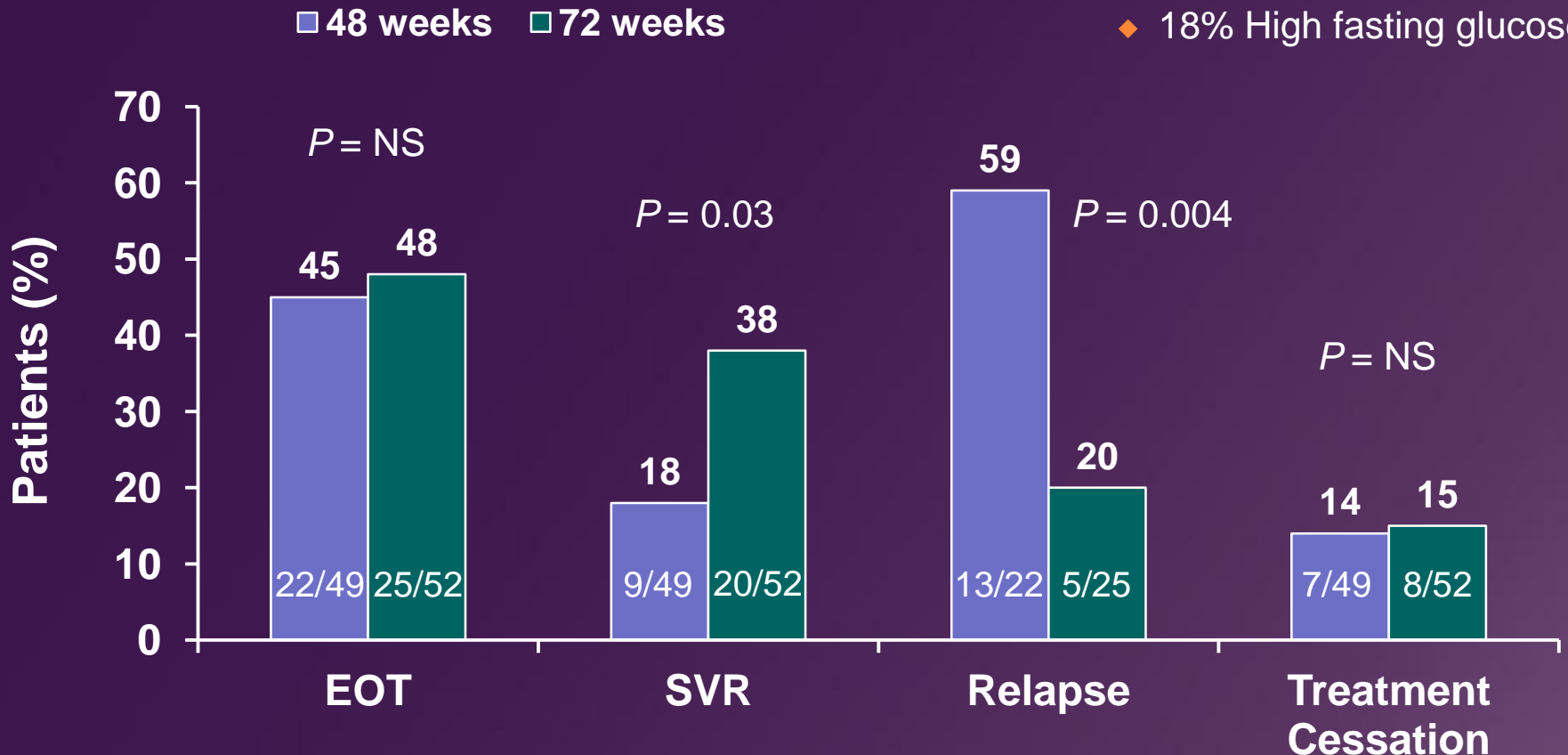


All available data from 126 patients with an EVR who maintained an end-of-treatment (EOT) response. Ferenci P et al. 57<sup>th</sup> AASLD 2006. Abstract 390.

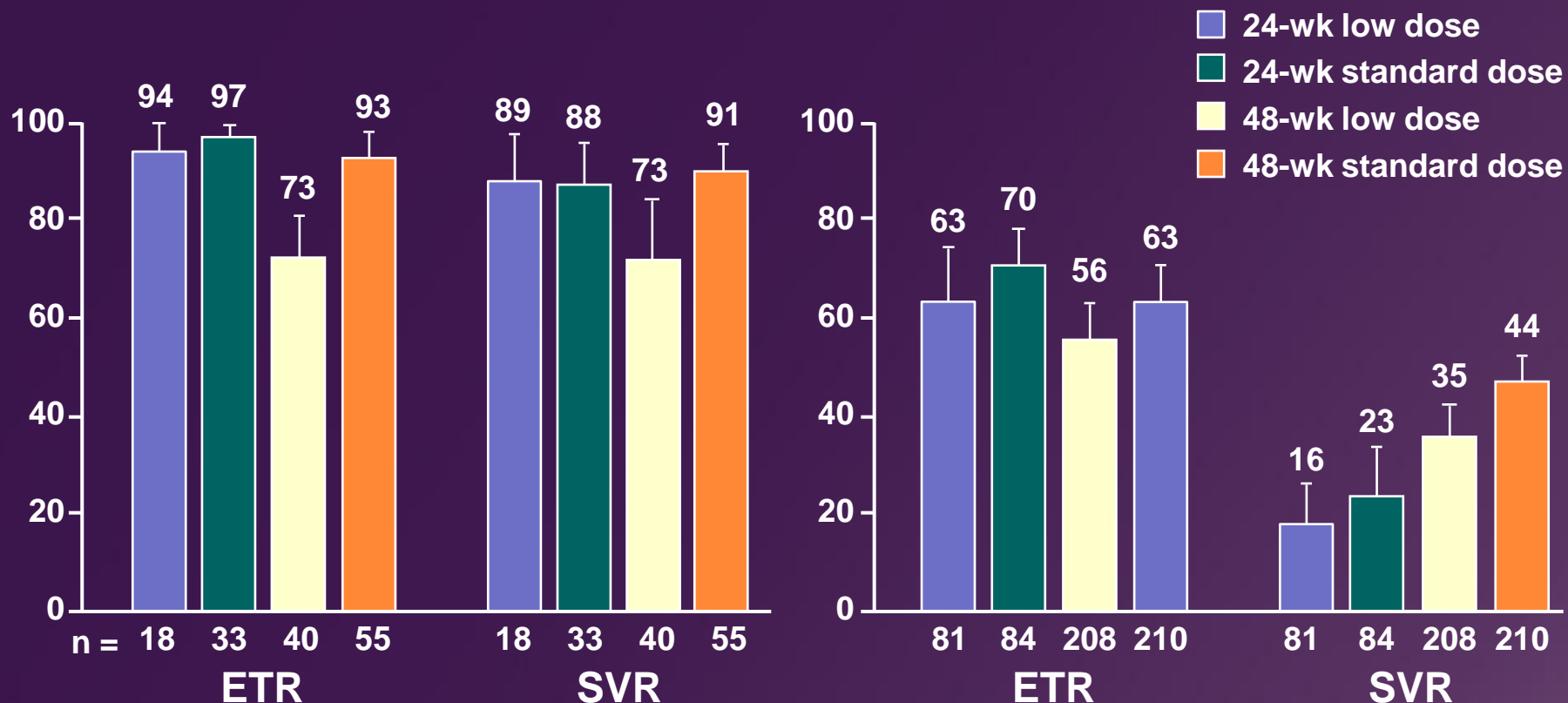
# Improved SVR Rates With 72 Weeks of Treatment in Patients With Genotype 1 and Partial EVR

- ◆ Peg-IFN  $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 800-1400 mg/d
- ◆ HCV-RNA (+) at week 12 (n = 101 slow responders)

- ◆ 48% African American
- ◆ 78% High viral load
- ◆ 26% F3/4 fibrosis
- ◆ 34% BMI  $\geq$ 30 kg/m<sup>2</sup>
- ◆ 18% High fasting glucose



# Response to Peg-IFN $\alpha$ -2a + RBV in Patients With Genotype 1 With or Without RVR at Week 4



Patients With an RVR at Week 4

Patients Without an RVR at Week 4

Low dose = RBV 800 mg/d; standard dose = RBV 1000 mg/d for <75 kg or 1200 mg/d for  $\geq$  75 kg.  
 Jensen DM et al. *Hepatology*. 2006;43:954-960. Permission requested.

# Virologic Response Rates With Standard Doses

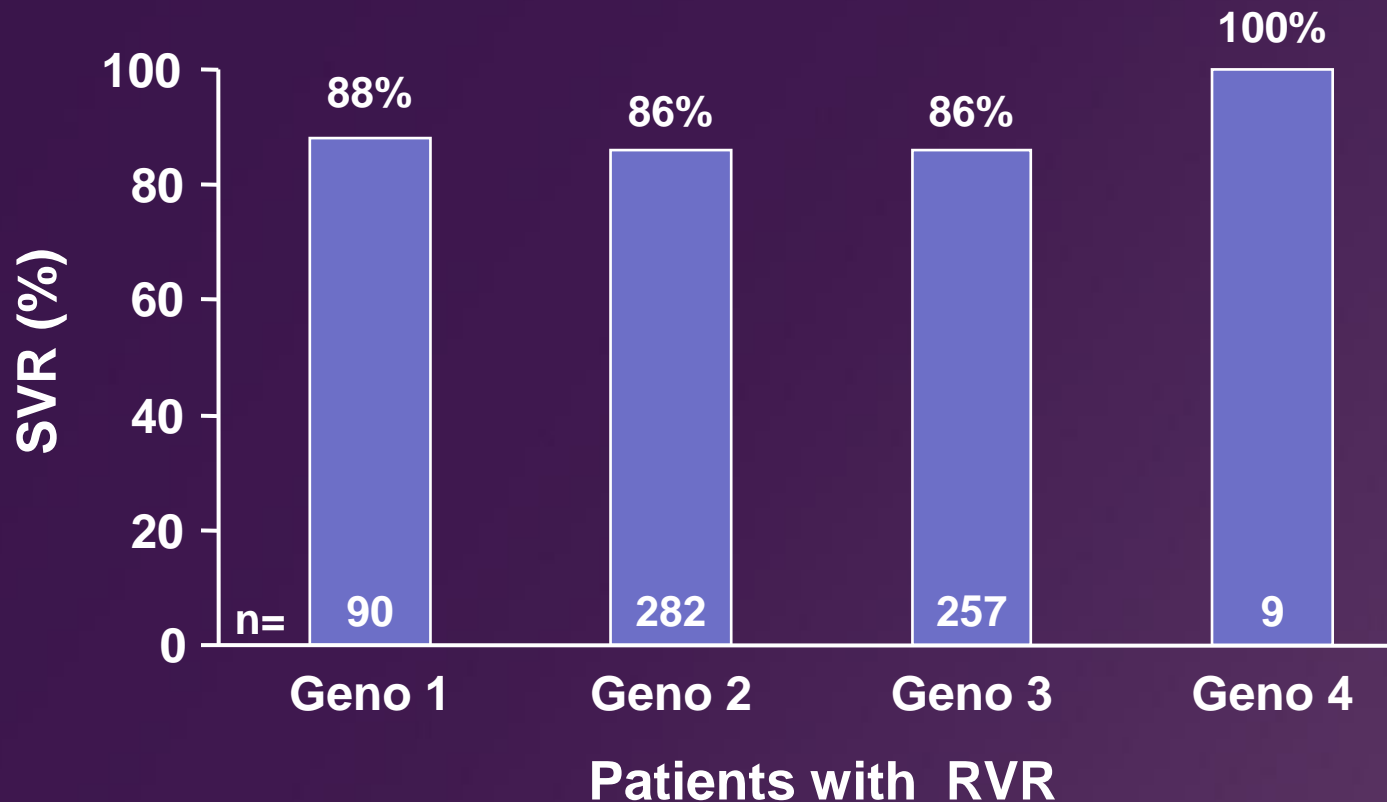
	Genotype 1 (n = 569)	Genotype 2 (n = 395)	Genotype 3 (n = 426)	Genotype 4 (n = 24)
RVR	16%	71%	60%	38%
cEVR	42%	24%	29%	46%
pEVR	20%	1%	3%	8%
SVR	49%	77%	68%	79%

RVR = HCV-RNA negative (<50 IU/mL) at week 4.

cEVR = HCV-RNA positive at week 4 but negative at week 12.

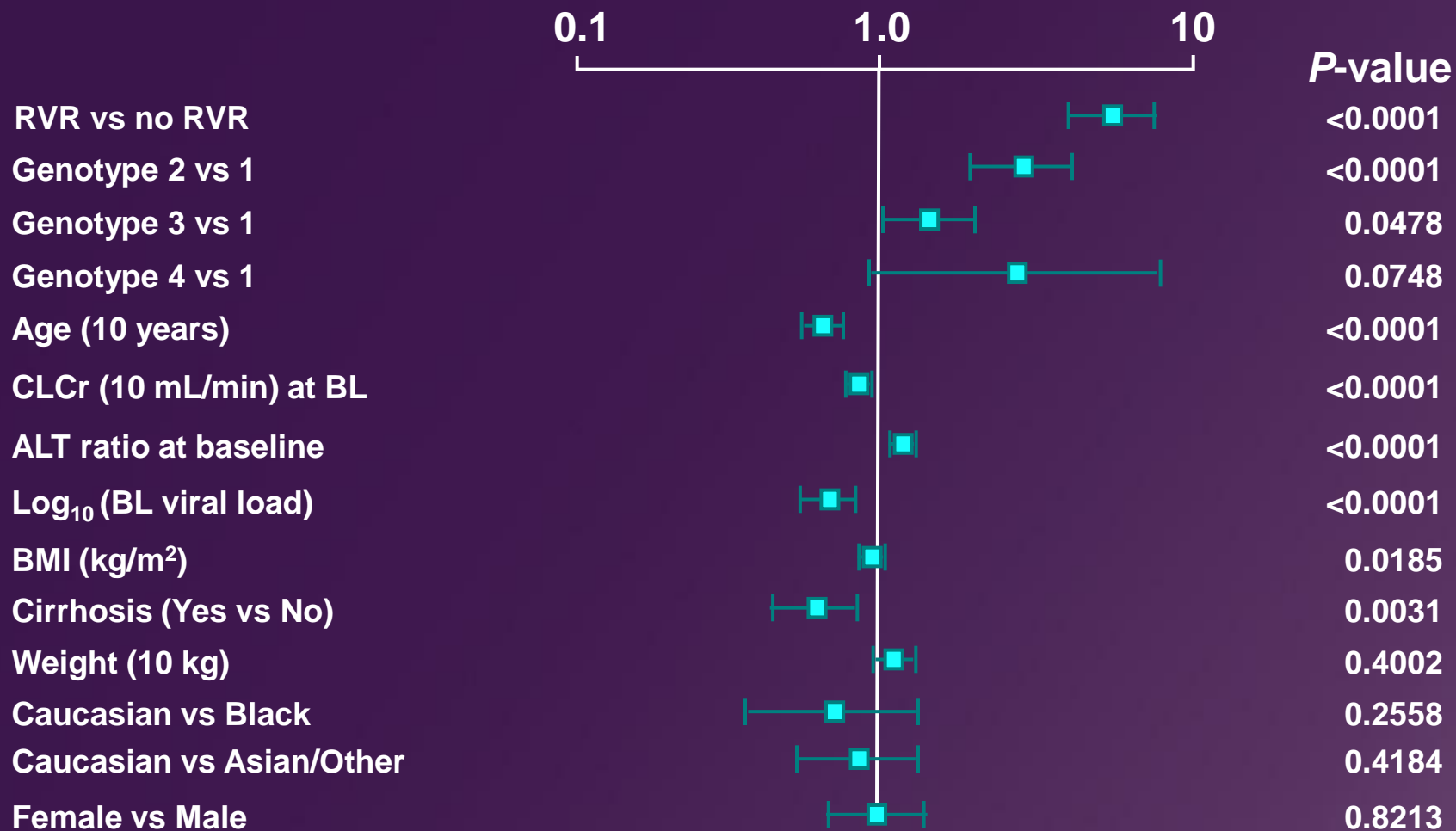
pEVR = HCV-RNA positive at week 4 and 12 but  $\geq 2 \log_{10}$  drop from baseline at week 12.

# Patients With RVR Achieved Similar SVR Across Genotypes



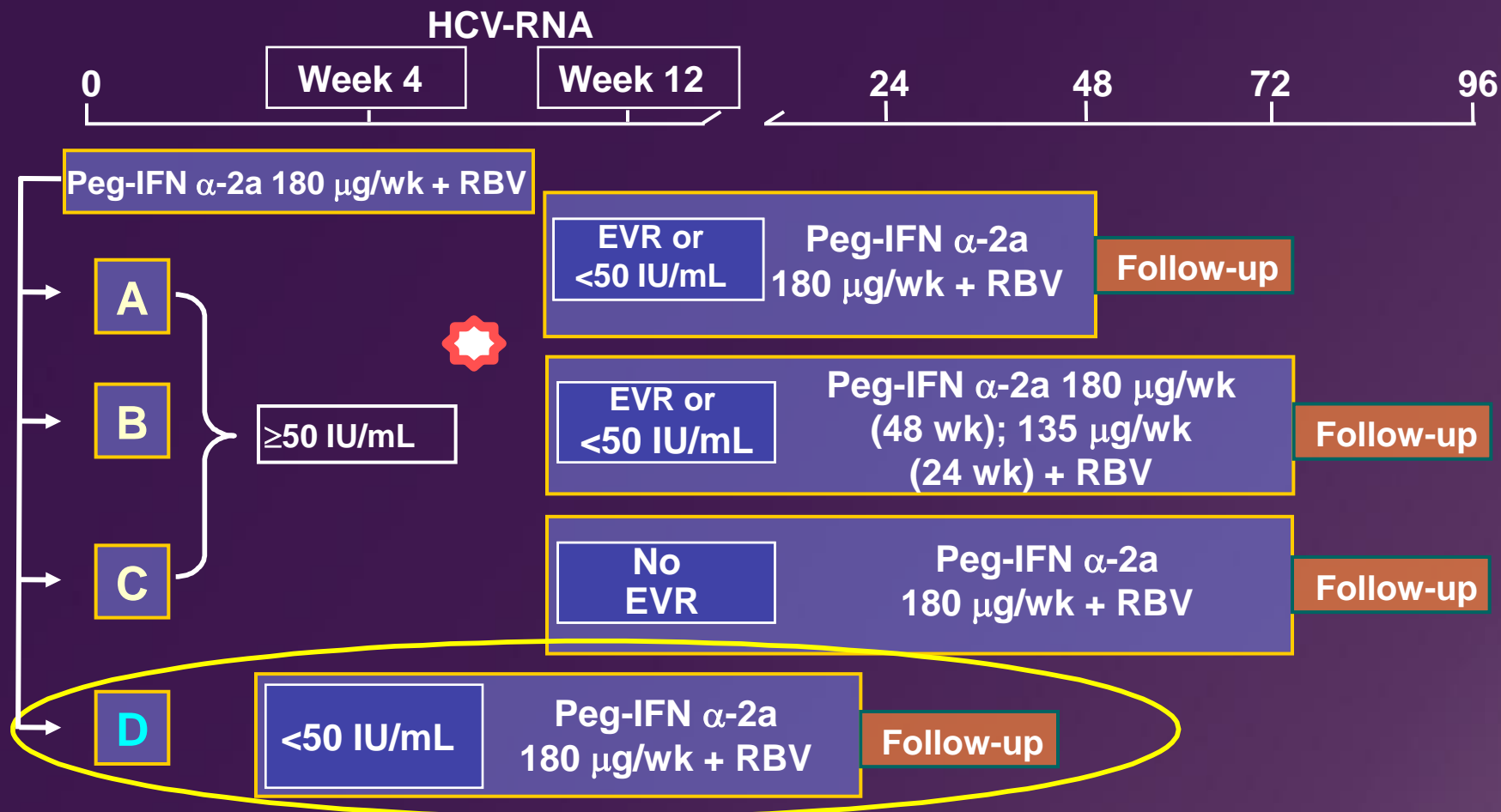
RVR = HCV-RNA negative (<50 IU/mL) at week 4; genotypes 1 and 4, patients were treated for 48 weeks; genotypes 2 and 3, patients were treated for 24 weeks.

# Multiple Logistic Regression Model for Prediction of SVR\*



\*Adjusted for other baseline factors.  
Fried MW et al. 43rd EASL 2008.

# Peg-IFN $\alpha$ -2a + RBV in HCV Genotype 1/4 With RVR: Study Design

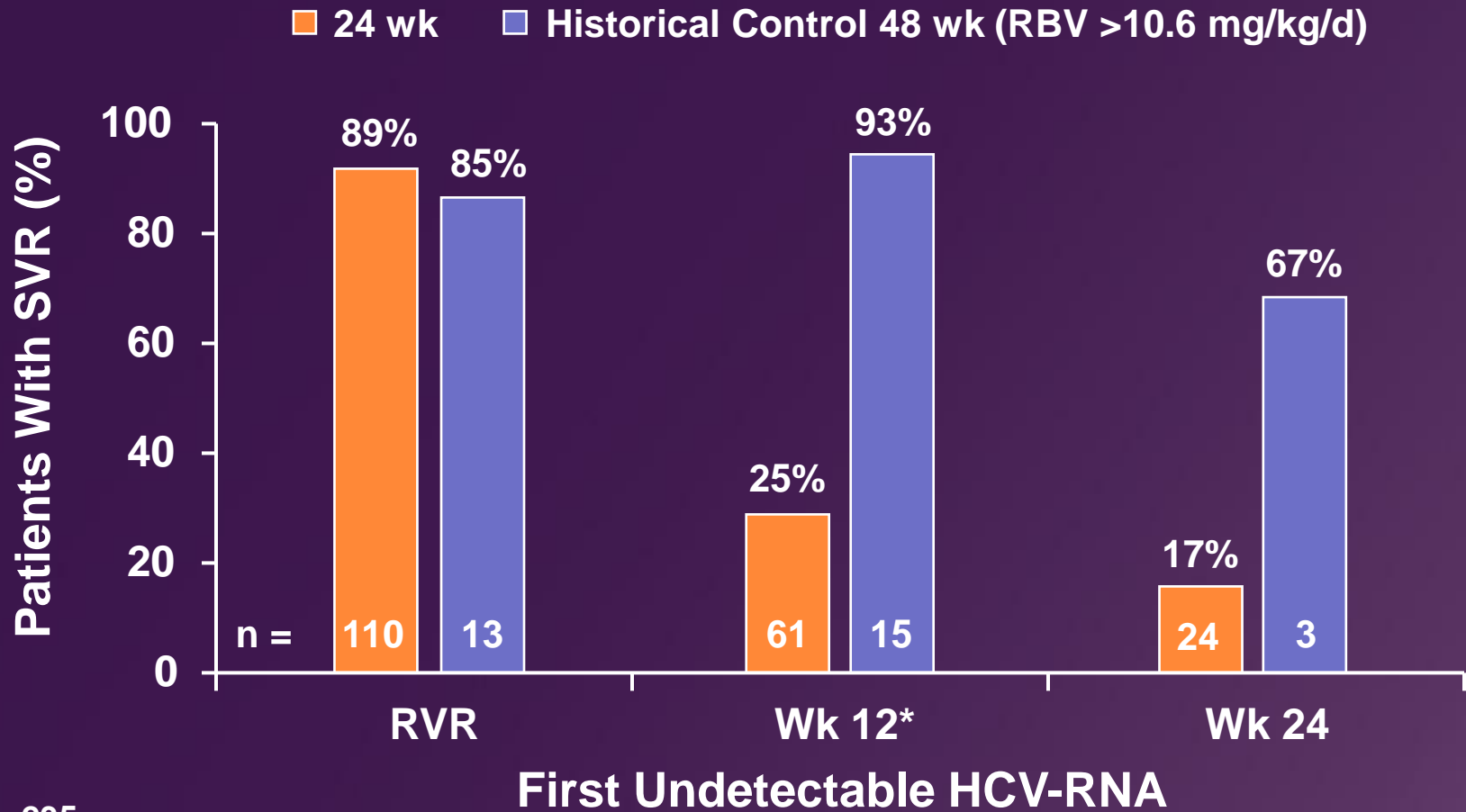


★ Randomization to Group A or B with week 12 HCV-RNA level <600 IU/mL.  
 RBV = ribavirin 1000/1200 mg/day.

# SVR in Genotype 1/4 Patients With RVR Who Completed 24 Weeks of Therapy

	Genotype 1, n/N (%; 95% CI)	Genotype 4, n/N (%; 95% CI)	All patients, n/N (%; 95%CI)
Overall	89/113 (78.8; 70.1–85.9)	26/30 (86.7; 69.3–96.2)	115/143 (80.4; 72.9–86.6)
HCV-RNA level ≤400,000 IU/mL	52/64 (81.3; 69.5–89.9)	9/10 (90)	61/74 (86.5; 76.5–93.3)
HCV-RNA level 400,000–800,000 IU	25/31 (80.6; 62.5–92.5)	12/14 (85.7; 57.2–98.2)	37/45 (82.2; 67.9–92.0)
HCV-RNA level >800,000 IU	12/18 (66.7; 41.0–86.6)	5/6 (83.3; 35.9–99.6)	17/24 (70.8; 48.9–87.4)
METAVIR F0-2	74/93 (79.6; 70.0–87.2)	23/26 (88.5; 69.8–97.6)	97/119 (81.5; 74.3–88.0)
METAVIR F3-4	15/20 (75; 50.9–91.3)	3/4 (75)	18/24 (75.0; 53.3–90.2)

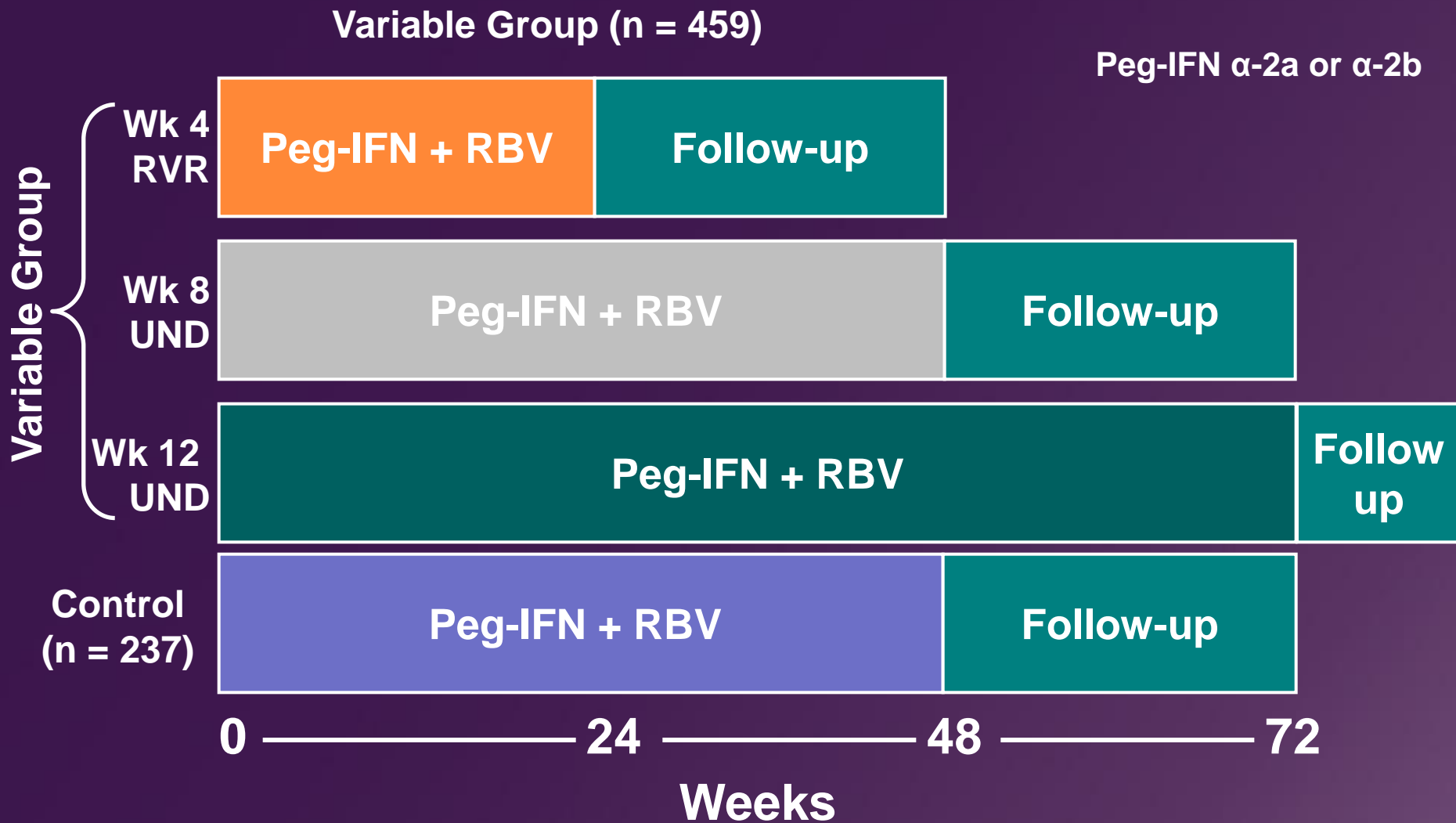
# Individualizing HCV Treatment in Patients With Genotype 1, HCV-RNA <600,000 IU/mL



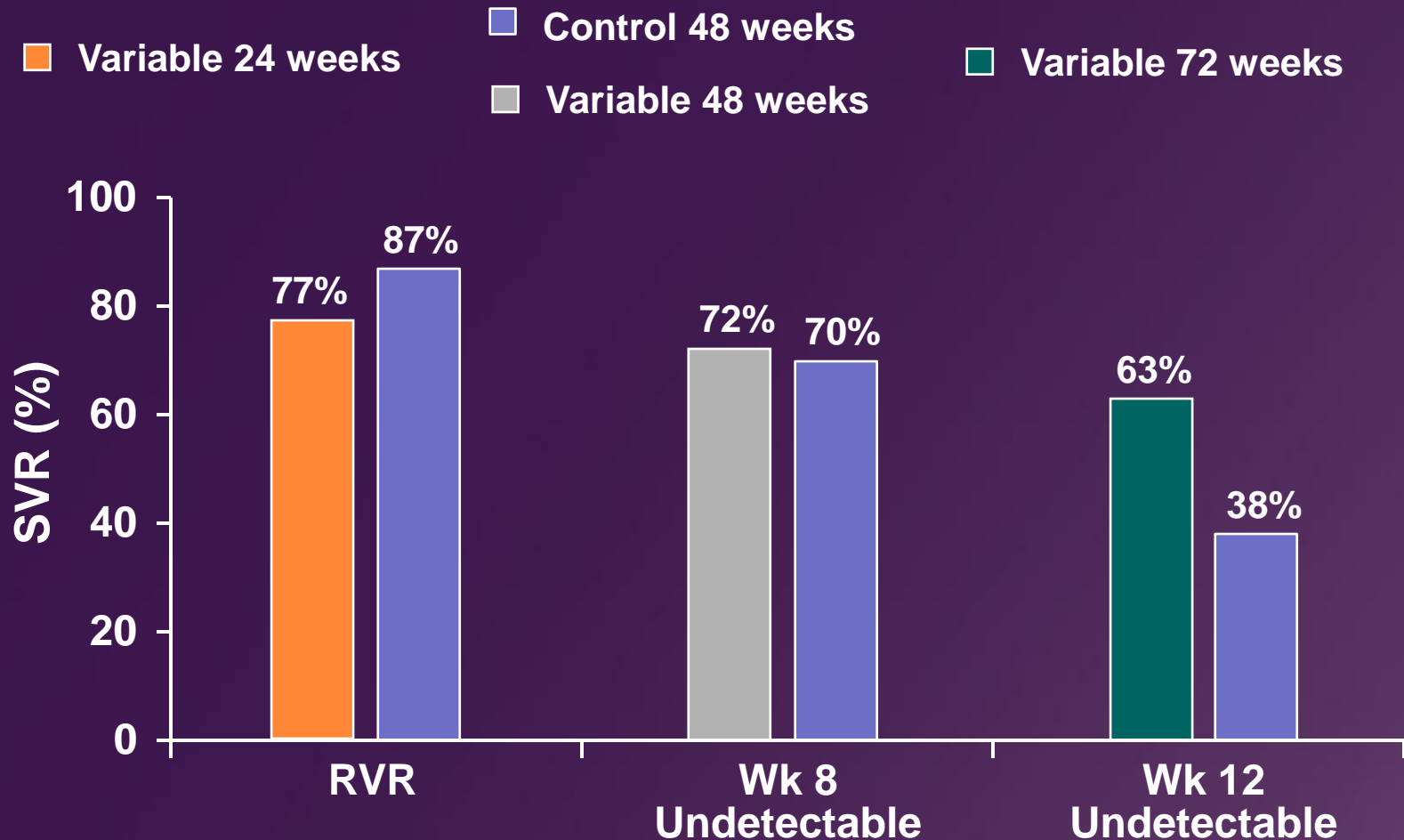
N = 235

\*Wk 12 undetectable relapse = 75%.  
Peg-IFN  $\alpha$ -2b + RBV 800-1400 mg/day  
Zeuzem S et al. *J Hepatol.* 2006;44:97-103.

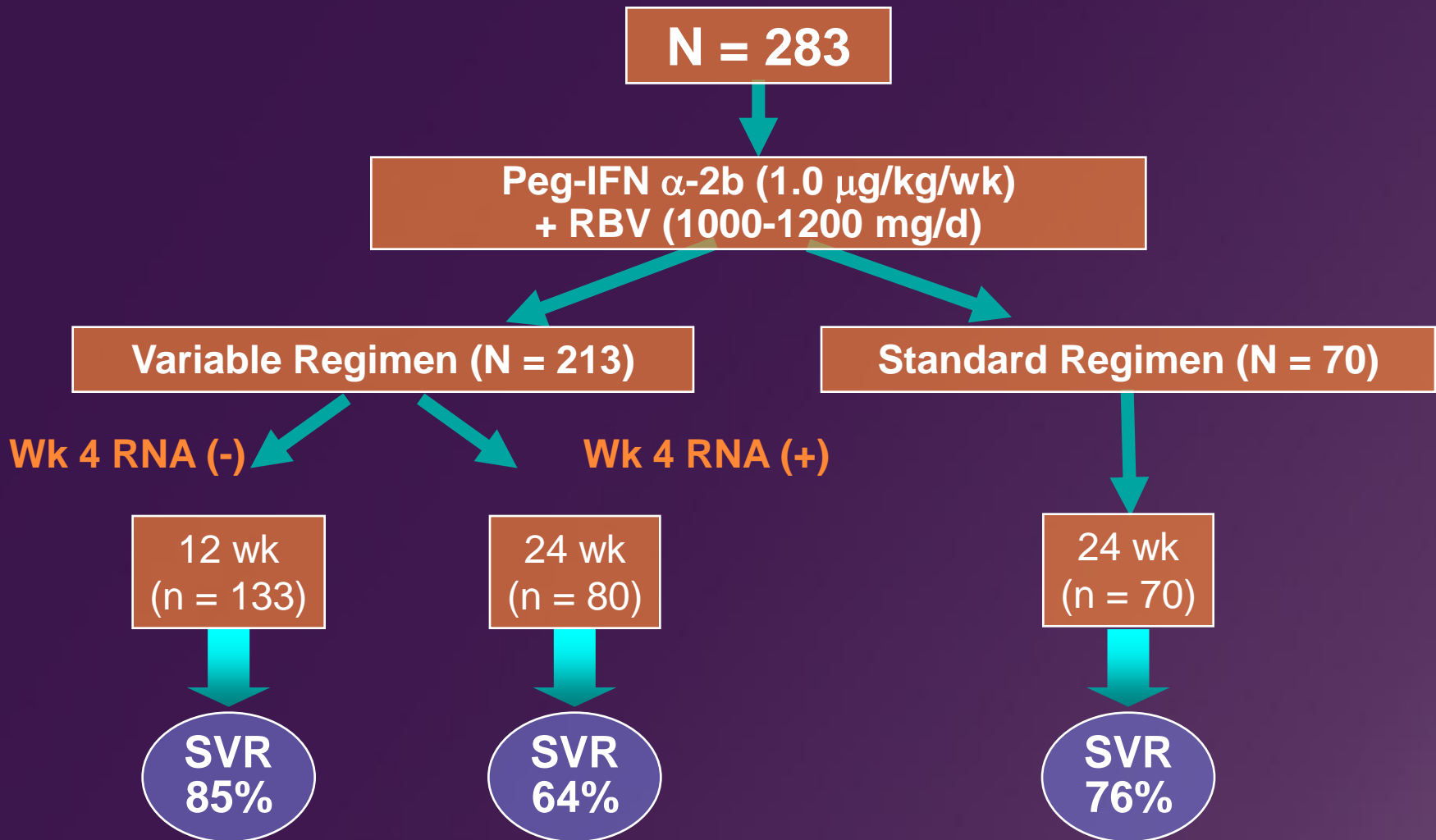
# Individualized HCV Treatment in Patients With Genotype 1



# Individualized Therapy: Time to First Undetectable HCV-RNA and SVR

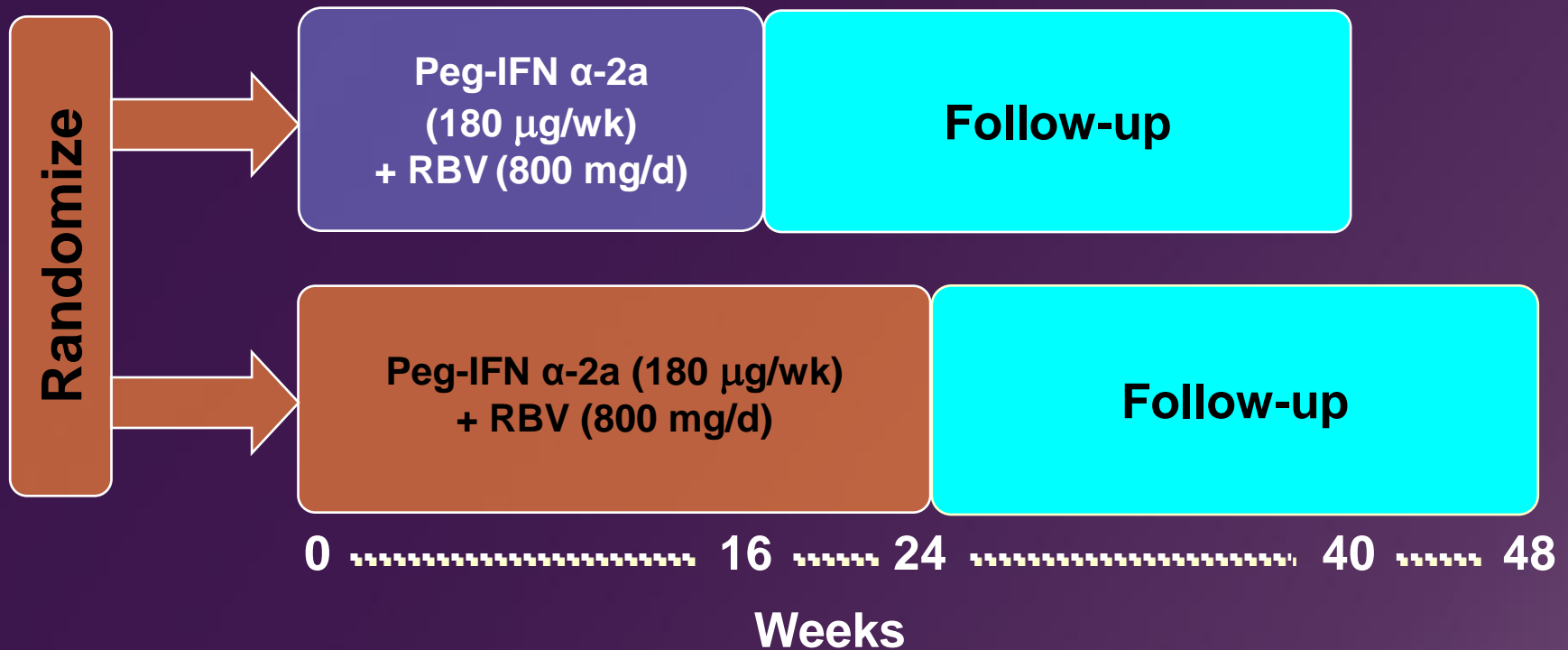


# Shorter Treatment for Genotypes 2 and 3: 12 vs 24 Weeks

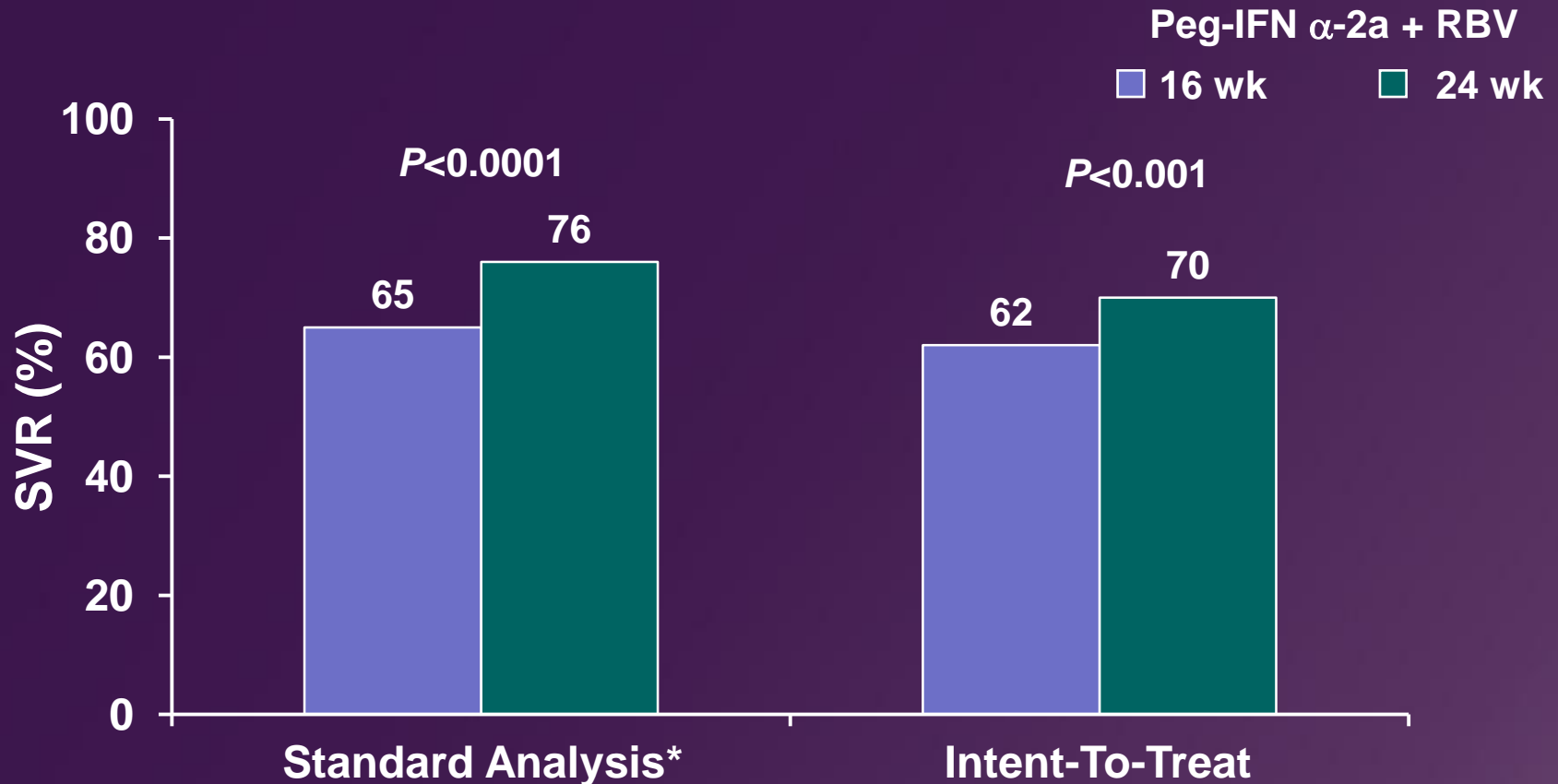


# ACCELERATE: Study Design

Randomized (1:1), open-label study; 132 centers; N = 1469; genotypes 2/3

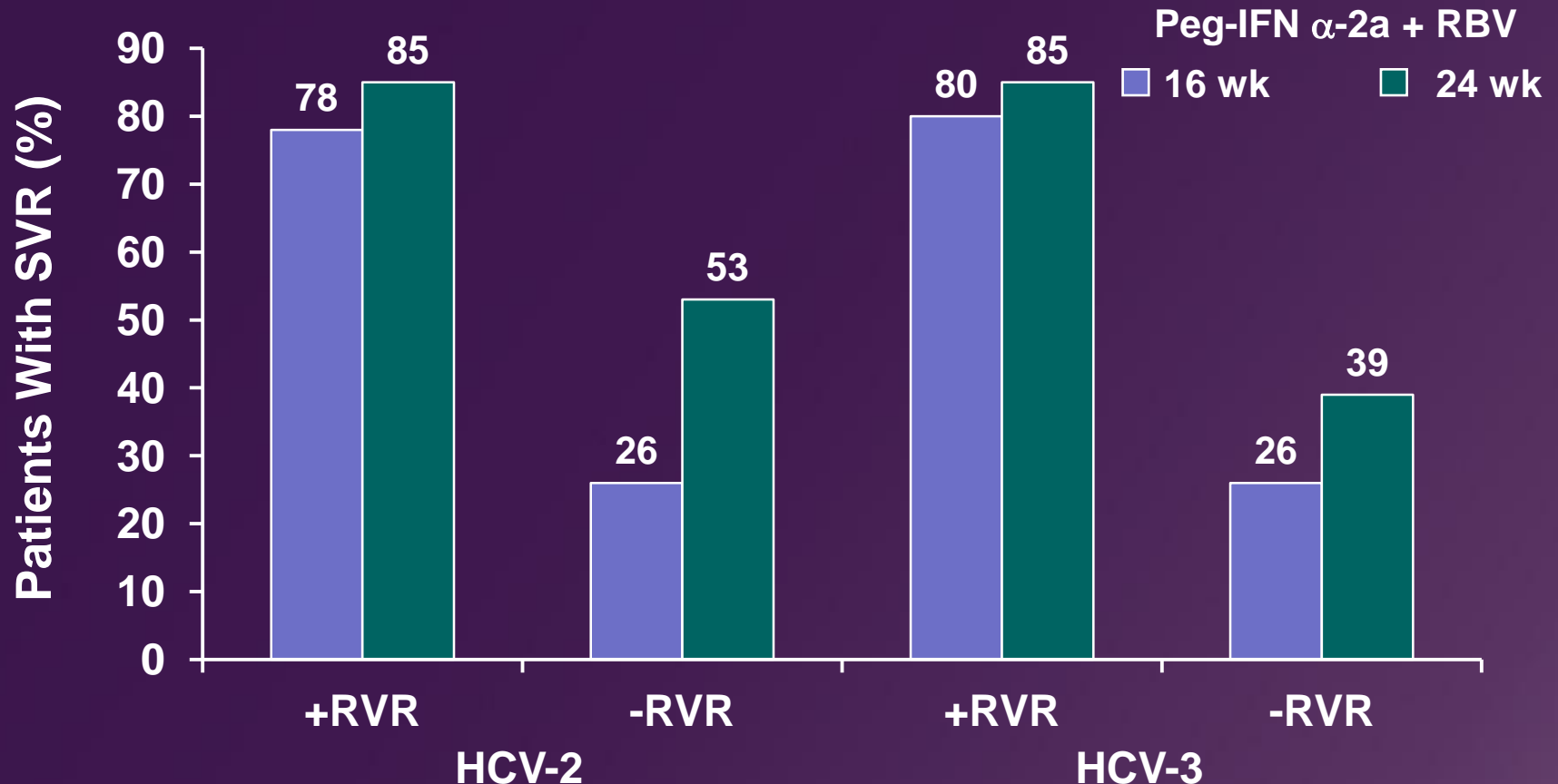


# ACCELERATE: Primary End Point (SVR)



\*Standard population analysis is primary efficacy analysis.  
SVR = HCV-RNA  $< 50$  IU/mL at 24 weeks after treatment.

# ACCELERATE: SVR in Patients With and Without an RVR



Overall: 24 vs 16 weeks  
+RVR : 85% vs 79%,  $P = 0.02$   
-RVR : 45% vs 26%

RVR = rapid virologic response.  
Shiffman ML et al. *N Engl J Med.* 2007;357:124-134 .

## Question 3

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What is the optimal duration of therapy for this patient?

- A. 48 weeks, but with a higher dose of ribavirin (>1600 mg/day)
- B. 24 weeks because he cleared HCV-RNA at week 20
- C. 72 weeks because he was a slow virologic responder
- D. 48 weeks because he had undetectable viremia at week 24

# Answer to Question 3

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- ◆ Choice C is a reasonable answer
  - Patient NS was a slow virologic responder, only clearing HCV-RNA between weeks 12 and 20
  - Data presented suggest that extending the duration of treatment will decrease the likelihood of relapse
  - RBV dose increase may also be considered because this patient is overweight
  - Shortening duration of therapy may also be feasible in select patients (RVR with low level of pretreatment viremia)

# Conclusion

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- ◆ Optimizing ribavirin dosing remains important to maximizing SVR
- ◆ Adherence throughout the treatment course is important
- ◆ RVR is highly predictive of SVR
- ◆ EVR remains a good negative predictor of response
- ◆ Tailoring duration of therapy to virologic response should be considered for some patients (risk of relapse may be slightly higher)

# Additional Slides

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# HALT-C: Effect of Peg-IFN and RBV Dose Reductions During Weeks 1-20

Ribavirin dose	Peginterferon alfa-2a dose				
	98%-100%	81%-97%	61%-80%	0%-60%	Total
98%-100%	17% (56/334)	16% (11/68)	9% (4/47)	7% (3/46)	15% (74/495)
81%-97%	22% (14/65)	15% (7/48)	15% (4/26)	10% (2/21)	17% (27/160)
61%-80%	19% (11/57)	14% (5/36)	19% (5/27)	0% (0/23)	15% (21/143)
≤ 60%	21% (6/28)	0% (0/11)	0% (0/11)	6% (1/16)	11% (7/66)
Ribavirin stopped	4% (1/26)	0% (0/12)	6% (1/17)	0% (0/17)	3% (2/72)
Total	17% (88/510)	13% (23/175)	11% (14/128)	5% (6/123)	14% (131/936)

- ◆ Values are the percentage and proportion of patients with SVR
- ◆ Full dose RBV: Decline in SVR when peg-IFN dose decreased
- ◆ Full dose peg-IFN: No effect on SVR when RBV as low as 60%
- ◆ Stopping RBV: Virtually no chance of SVR

# HALT-C: Effect of Peg-IFN and RBV Dose Reductions During Weeks 20-48

Ribavirin dose	Peginterferon alfa-2a dose				
	98%-100%	81%-97%	61%-80%	<60%	Total
98%-100%	56% (41/73)	38% (3/8)	64% (7/11)	83% (5/6)	57% (56/98)
81%-97%	35% (8/23)	50% (12/24)	67% (8/12)	38% (5/13)	46% (33/72)
61%-80%	50% (6/12)	55% (6/11)	42% (5/12)	0% (0/8)	40% (17/43)
≤ 60%	33% (6/18)	44% (4/9)	63% (5/8)	50% (3/6)	44% (18/41)
Ribavirin stopped	60% (3/5)	0% (0/1)	0% (0/3)	29% (2/7)	31% (5/16)
Total	49% (64/131)	47% (25/53)	54% (25/46)	38% (15/39)	48% (129/269)

- ◆ Values are the percentage and proportion of patients with SVR
- ◆ Full dose RBV: No change in SVR with decreased peg-IFN
- ◆ Full dose peg-IFN: No change in SVR
  - ALL PREVIOUS NONRESPONDERS
  - Small number in many groups

Shiffman ML et al. *Gastroenterology*. 2007;132:103-112.

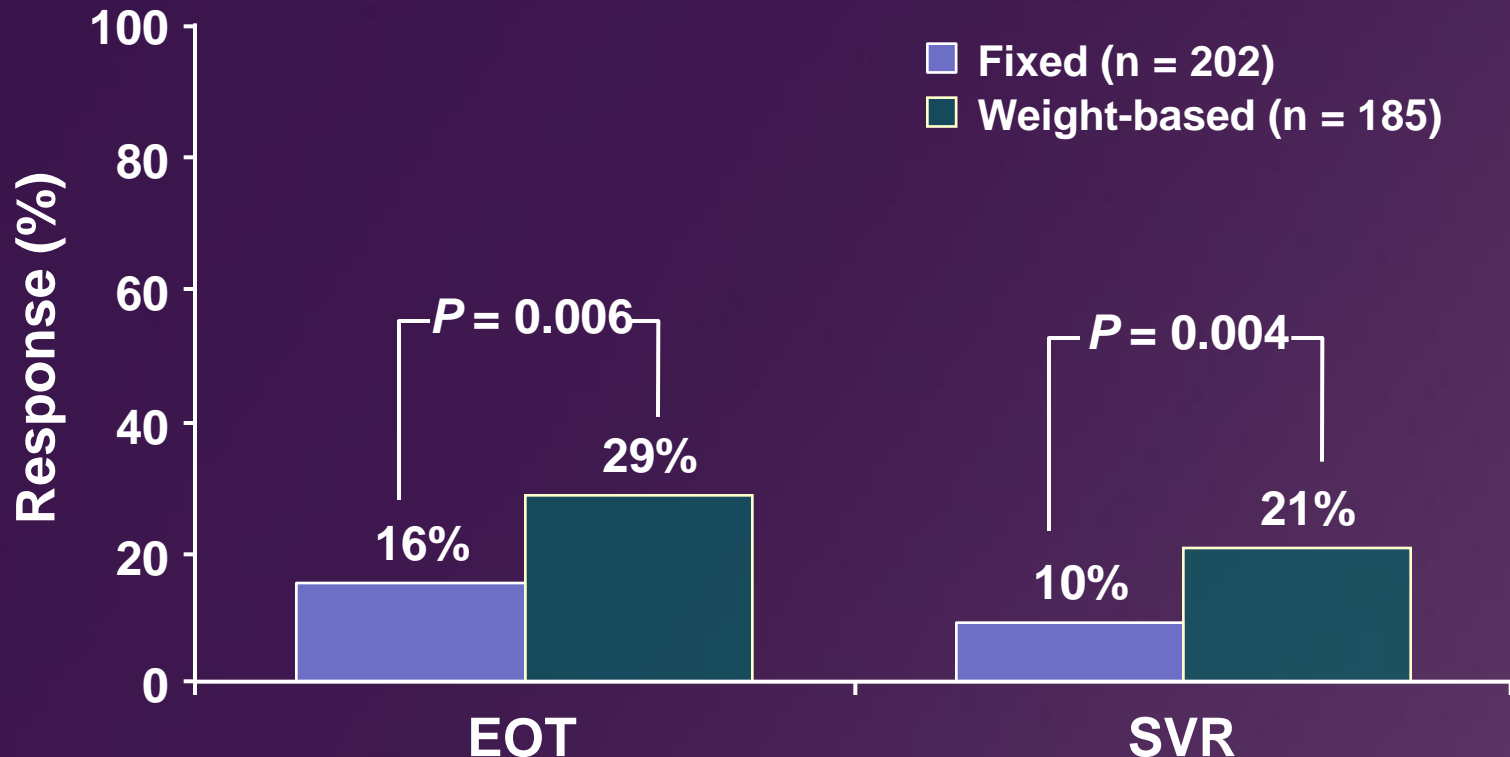
# The LATINO Study

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- ◆ Prospective, open-label, nonrandomized study
- ◆ Objective: to compare the virologic response of peg-IFN  $\alpha$ -2a + RBV in treatment-naive Latino and non-Latino white patients with HCV genotype 1
- ◆ Results:
  - SVR rate was higher in non-Latino white patients than in Latino patients (49% vs 34%;  $P < 0.0001$ )
  - Tolerability was similar in both populations
  - Discontinuation from the study due to AEs was less common for Latino than for Caucasian patients but more Latinos than Caucasians withdrew for non-safety reasons—primarily, insufficient response

# WIN-R Trial: Peg-IFN + Weight-Based RBV vs Peg-IFN + Fixed-Dose RBV in African Americans >65 kg With Genotype 1

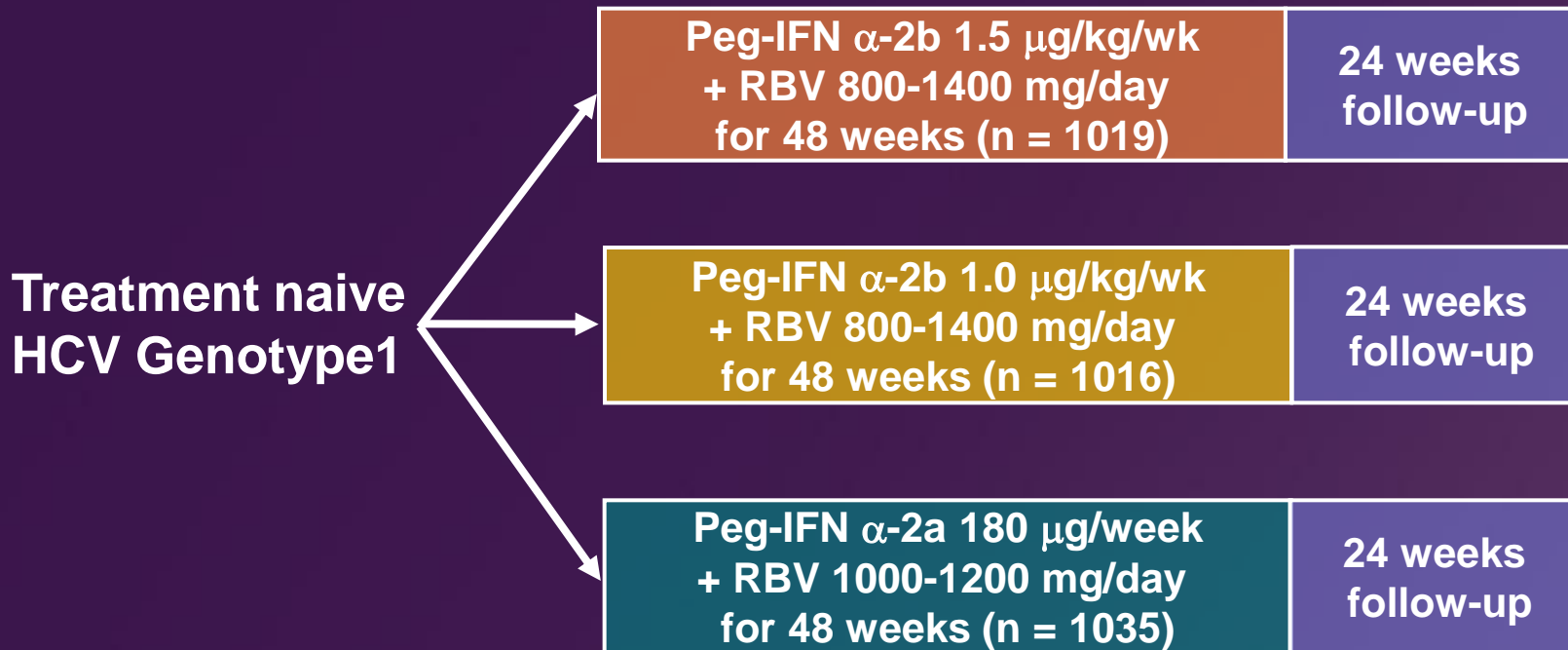
Peg-IFN  $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 800 mg/d vs 800-1400 mg/d



Fixed dose = Peg-IFN  $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 800 mg/d x 48 weeks.

Weight-based dose = Peg-IFN  $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 800-1400 mg/day, depending on weight, x 48 weeks.

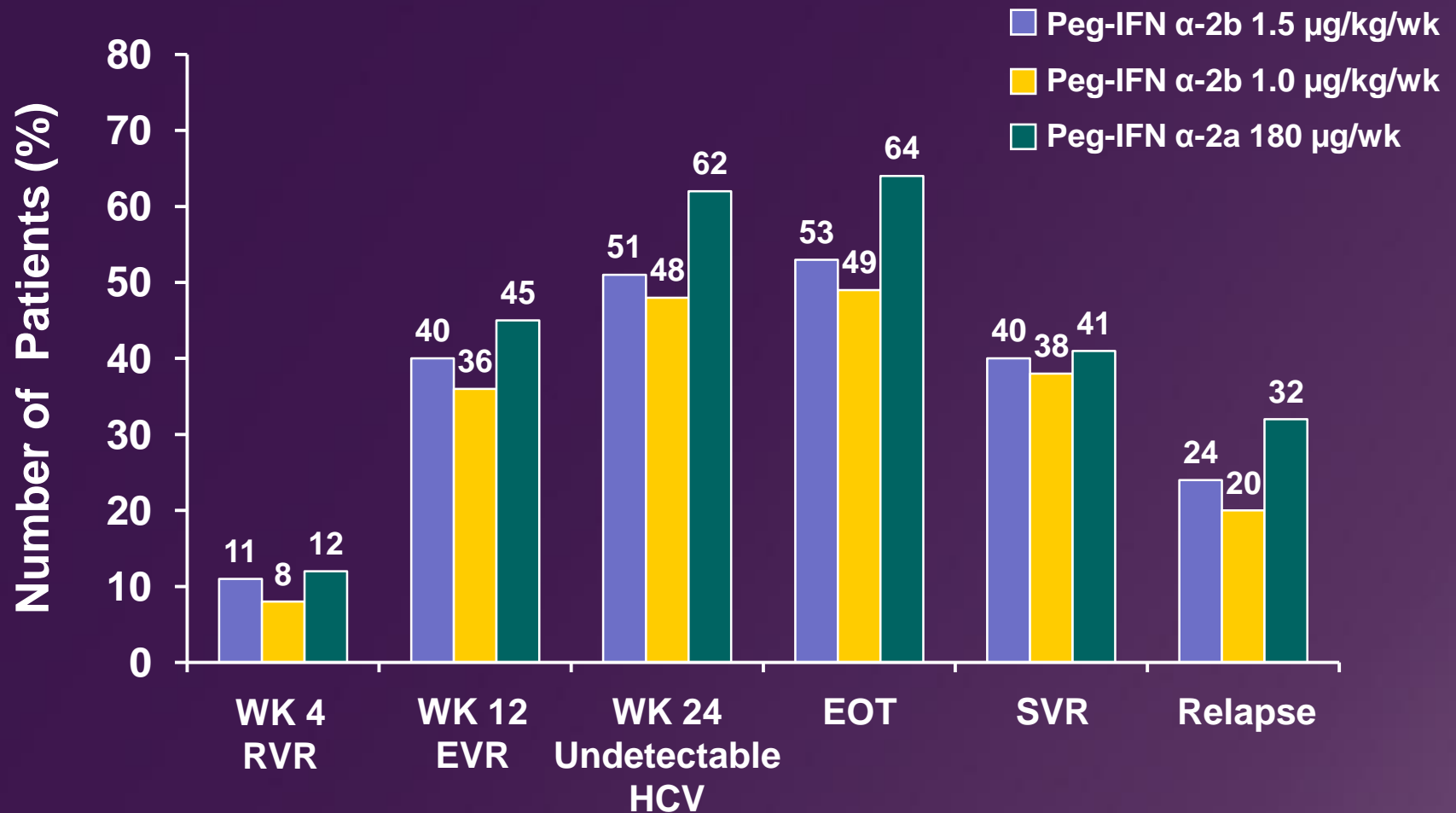
# Individualized Dosing Efficacy vs Flat Dosing to Assess Optimal Pegylated Interferon Therapy: IDEAL Study



- ◆ Similar baseline characteristics in all arms
- ◆ RBV dose adjustment for adverse events
  - Peg-IFN  $\alpha$ -2b arms: 2-step dose reduction
    - Decrease by 200 mg or 400 mg\*; decrease by additional 200 mg if necessary
  - Peg-IFN  $\alpha$ -2a arm: decrease to 600 mg

\*Depending on original dose.

# IDEAL Study: Results



# IDEAL Study: Adverse Events

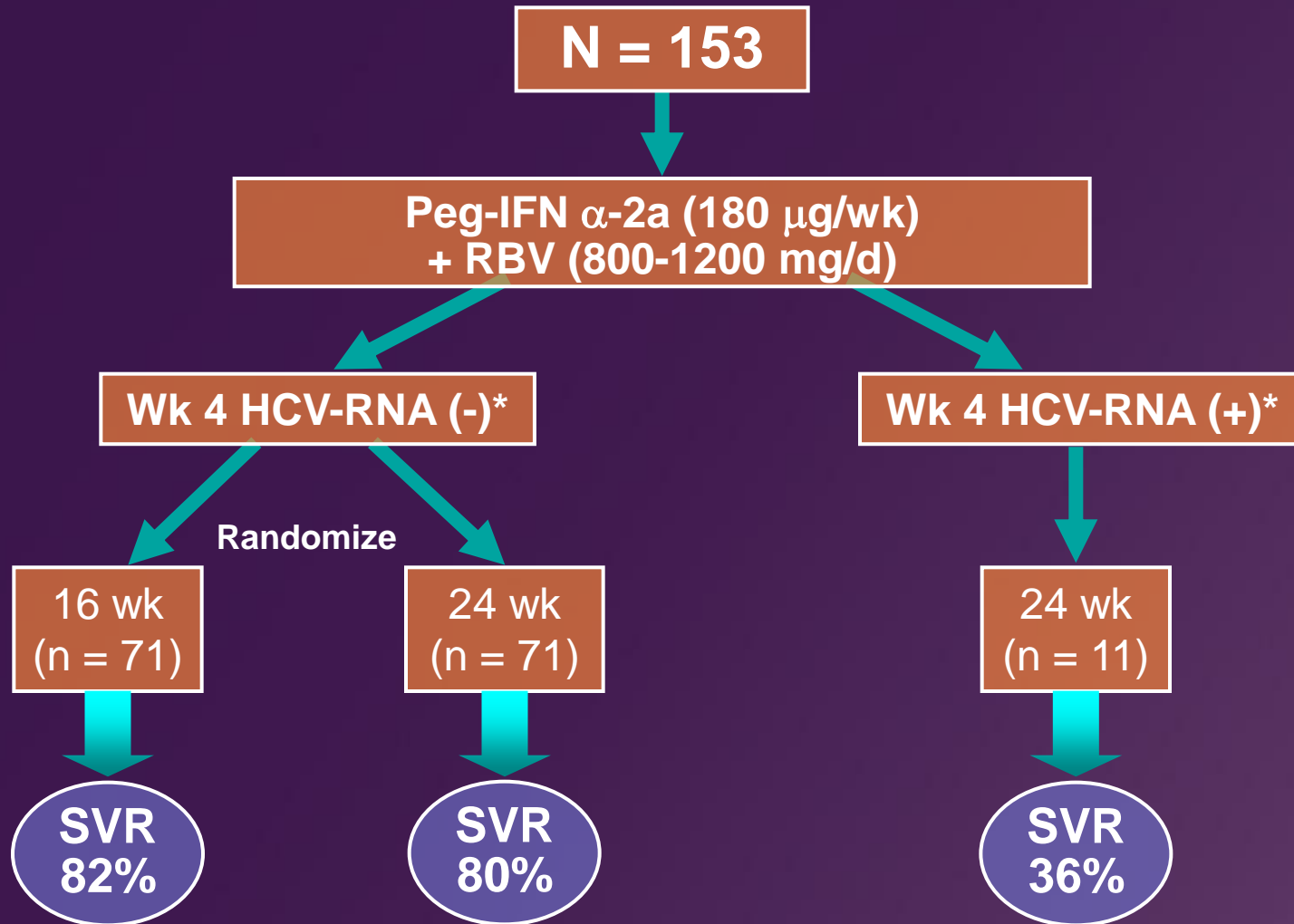
	Peg-IFN $\alpha$ -2b 1.5 $\mu$ g/kg/wk + RBV 800-1400 mg/day (n = 1019)	Peg-IFN $\alpha$ -2b 1.0 $\mu$ g/kg/wk + RBV 800-1400 mg/day (n = 1016)	Peg-IFN $\alpha$ -2a 180 $\mu$ g/week + RBV 1000-1200 mg/day (n = 1035)
<b>Deaths (n)</b>			
◆ All	5	1	6
◆ Treatment related	1	0	1
<b>Serious AEs (%)</b>			
◆ All	9%	9%	12%
◆ Treatment related	4%	4%	4%
<b>Discontinuations due to AE (%)</b>	13%	10%	13%
<b>Dose modification due to AE (%)</b>	43%	33%	43%

# HCV Genotypes 2 and 3: Duration of Treatment

Study	Von Wagner M et al	Dalgard O et al	Mangia A et al	Shiffman ML et al
<b>N</b>	153	122	283	1469
<b>Treatment</b>	Peg-IFN $\alpha$ -2a (180 $\mu$ g/wk) + RBV (800-1200 mg/d)	Peg-IFN $\alpha$ -2b (1.5 $\mu$ g/kg/wk) + RBV (800-1400 mg/d)	Peg-IFN $\alpha$ -2b (1.0 $\mu$ g/kg/wk) + RBV (1000-1200 mg/d)	Peg-IFN $\alpha$ -2a (180 $\mu$ g/wk) + RBV (800 mg/d)
<b>Duration</b>	16 vs 24 wk	14 vs 24 wk	12 vs 24 wk	16 vs 24 wk
<b>Results</b>	Similar SVR at 16 (82%) and 24 wk (80%) in patients who were HCV-RNA (-) at wk 4	SVR = 86% at 14 wk vs 93% at 24 wk in patients who were HCV-RNA (-) at wk 4; noninferiority not established	SVR = 85% at 12 wk in patients who were HCV-RNA (-) at wk 4	<ul style="list-style-type: none"> <li>◆ SVR in 16 wk vs 24 wk = 62% vs 70% (<math>P &lt; 0.001</math>)</li> <li>◆ SVR = 79% at 16 wk vs 85% at 24 wk (<math>P = 0.02</math>) in patients who were HCV-RNA (-) at wk 4</li> </ul>

Von Wagner M et al. *Gastroenterology*. 2005;129:522-527; Dalgard O et al. *Hepatology*. 2008;47:35-42; Mangia A et al. *N Engl J Med*. 2005;352:2609-2617; Shiffman ML et al. *N Engl J Med*. 2007;357:124-134<sub>59</sub>

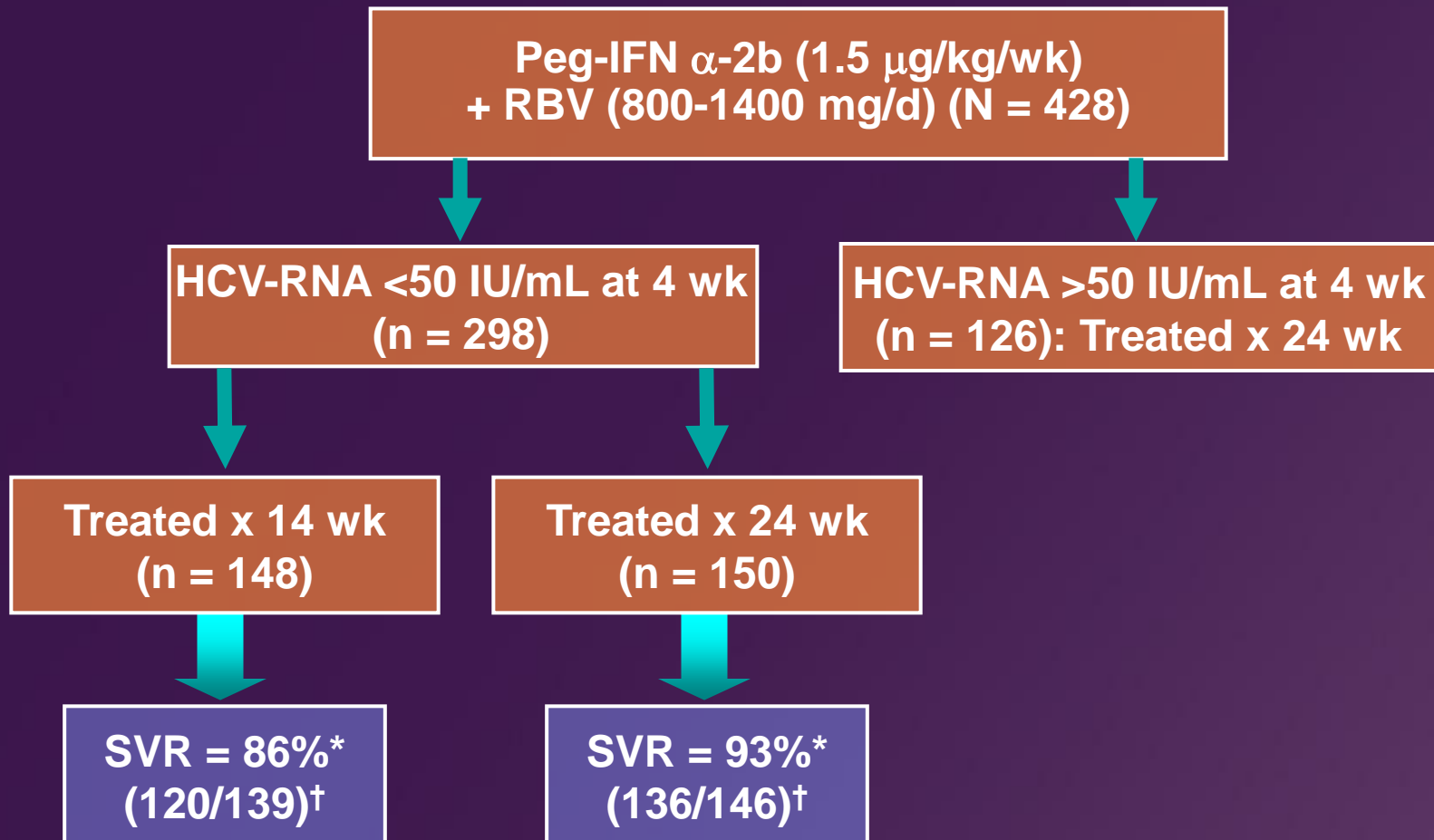
# Shorter Treatment for Genotypes 2 and 3: 16 vs 24 Weeks



\*HCV was assessed after 4 weeks with a lower limit of detection of 600 IU/mL.

Von Wagner M et al. *Gastroenterology*. 2005;129:522-527.

# Shorter Treatment for Genotypes 2 and 3: 14 vs 24 Weeks



\*Noninferiority not established.

†Patients with an HCV-RNA test 24 weeks after the end of treatment.

Dalgard O et al. *Hepatology*. 2008;47:35-42.