

## Treatment Naïve

# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial

Manns M, et al. Lancet. 2014;384:414-26.

# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1

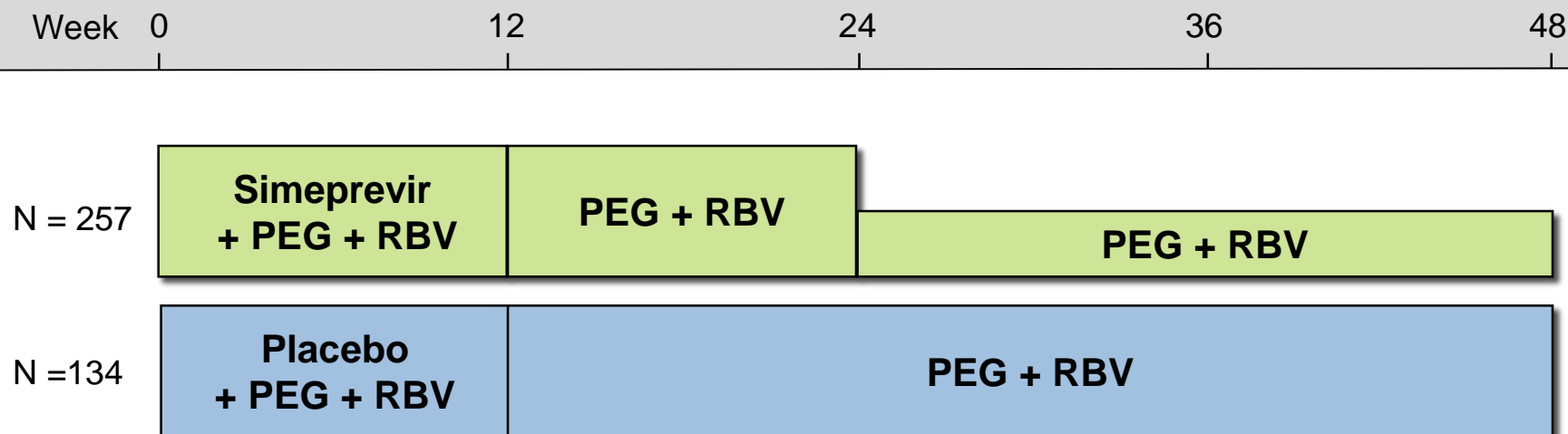
## QUEST-2 Trial: Background

### QUEST-2 Trial: Features

- **Design:** Randomized, double-blind, placebo-controlled, phase 3 trial of simeprevir + PEG + RBV versus PEG + RBV in HCV GT1
- **Setting:** Multicenter at 76 sites in 14 countries
- **Entry Criteria**
  - Treatment-naïve, chronic HCV mono-infection
  - HCV Genotypes 1a or 1b
- **Patient Characteristics**
  - N = 391
  - HCV Subtype: 1a (41%); 1b (58%); other (<1%)
  - IL28B Genotype: 30% CC
  - Age and Sex: median age 46; 55% male
  - Race: 92% white
  - Liver disease: 14% with F3; 6% with F4
- **Primary end-points:** Efficacy (SVR12) and safety

# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1

## QUEST-2 Trial: Design



### Study Notes

- Randomized 2:1, stratified on IL28B and HCV subtype
- 63% in each arm randomized to receive PEG alfa-2a or PEG alfa-2b; remainder assigned PEG alfa-2a
- Response-guided therapy (RGT): In simeprevir study arm, patients with HCV RNA <25 IU/ml at week 4 (undetectable or detectable) and <25 IU/ml at week 12 (undetectable) stopped treatment after 24 weeks

### Drug Dosing

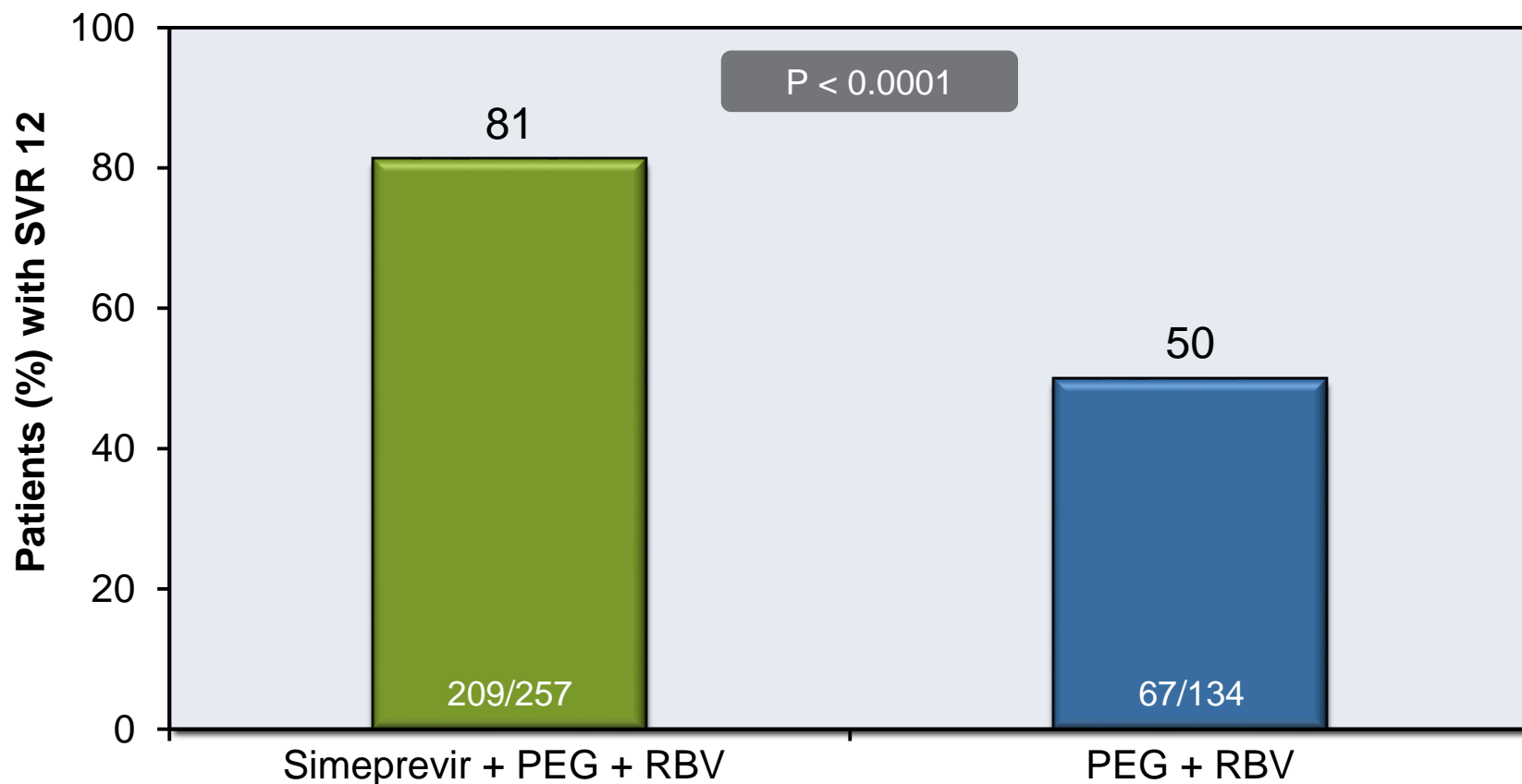
Simeprevir: 150 mg once daily

Peginterferon alfa-2a (PEG): 180 mcg/week OR Peginterferon alfa-2b: 1.5 mcg/kg/week

Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

## QUEST 2: Proportion of Patients with SVR12

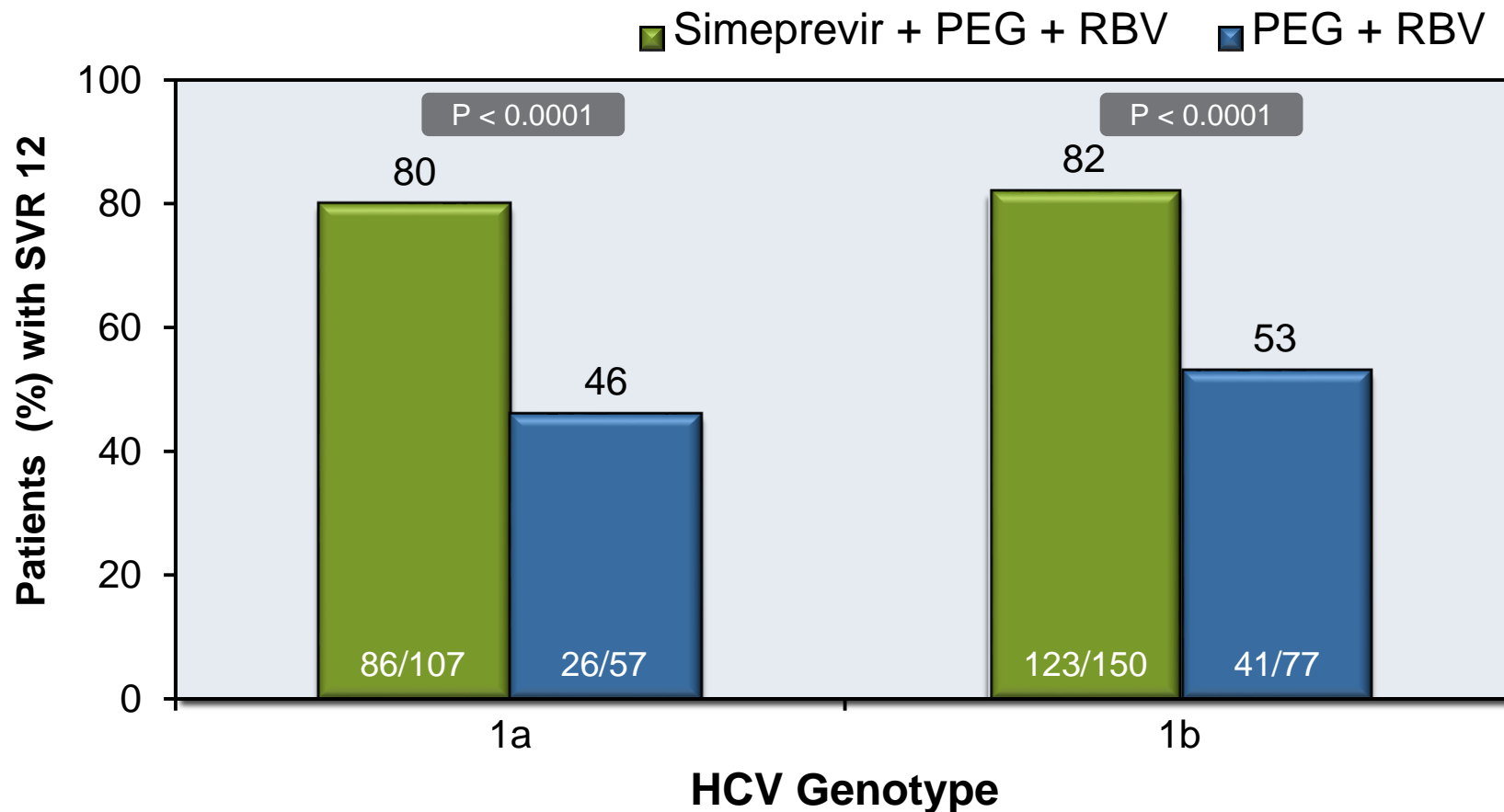


Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Manns M, et al. *Lancet*. 2014;384:414-26.

# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

## QUEST 2: SVR12 by HCV Genotype 1 Subtype

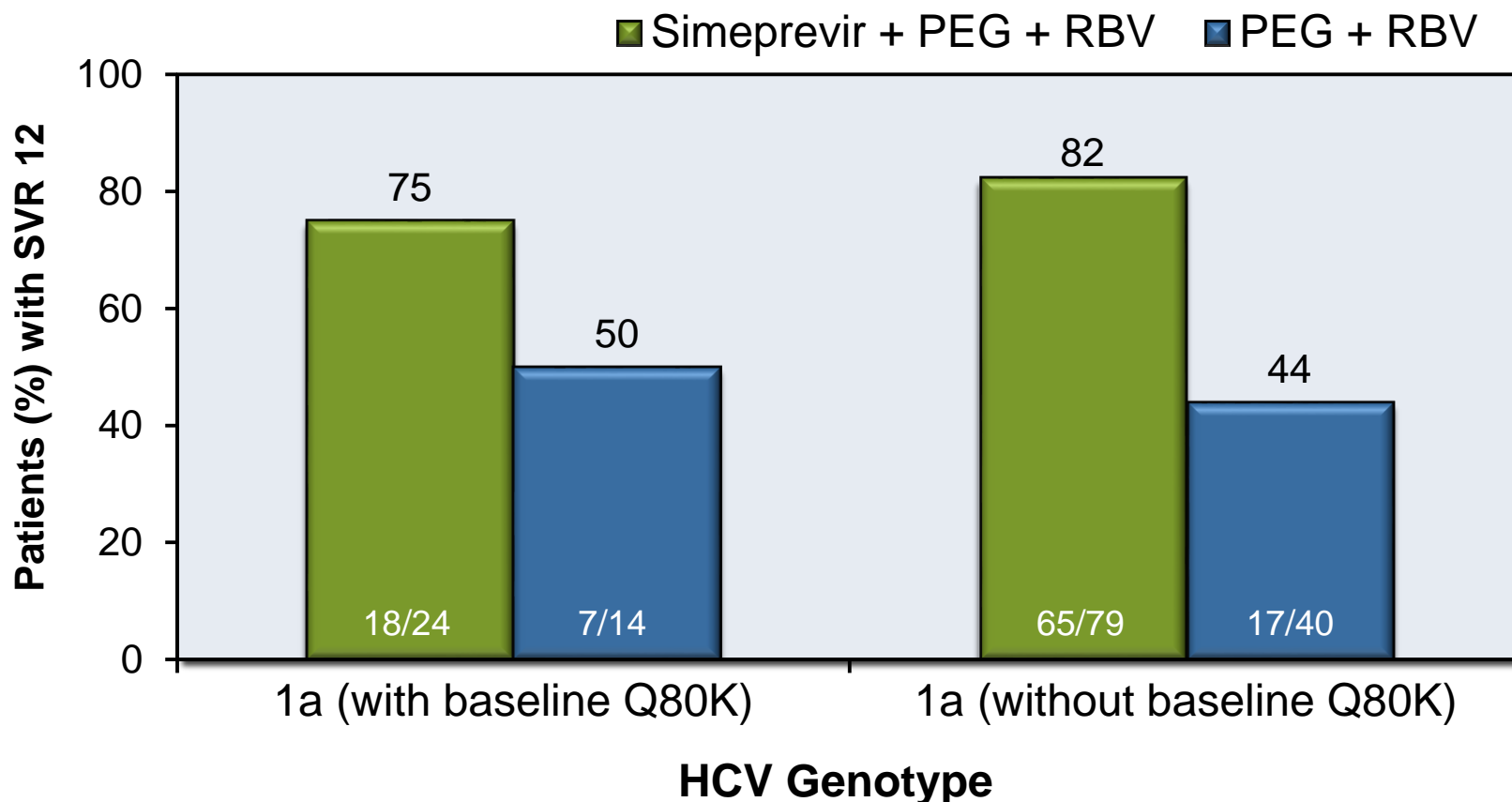


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# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

## QUEST 2: SVR12 for HCV 1a by Baseline Q80K Status



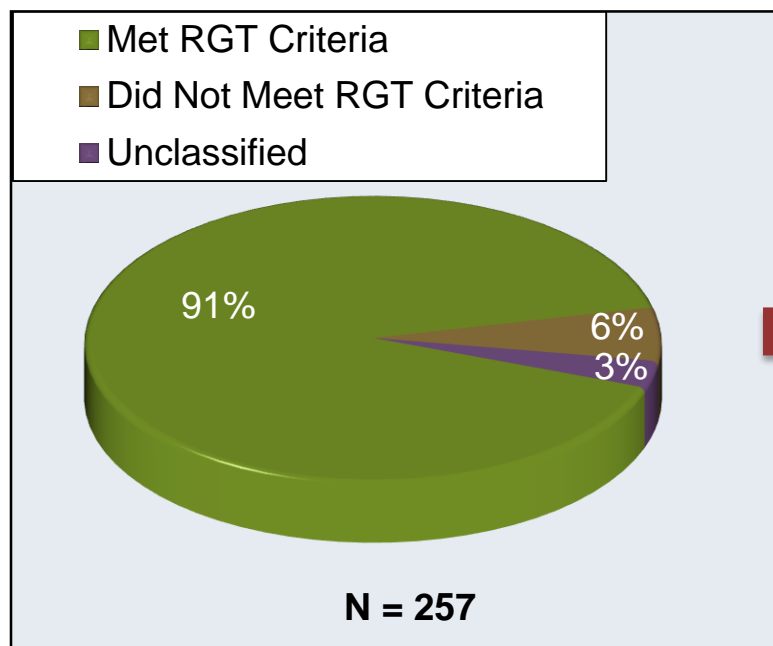
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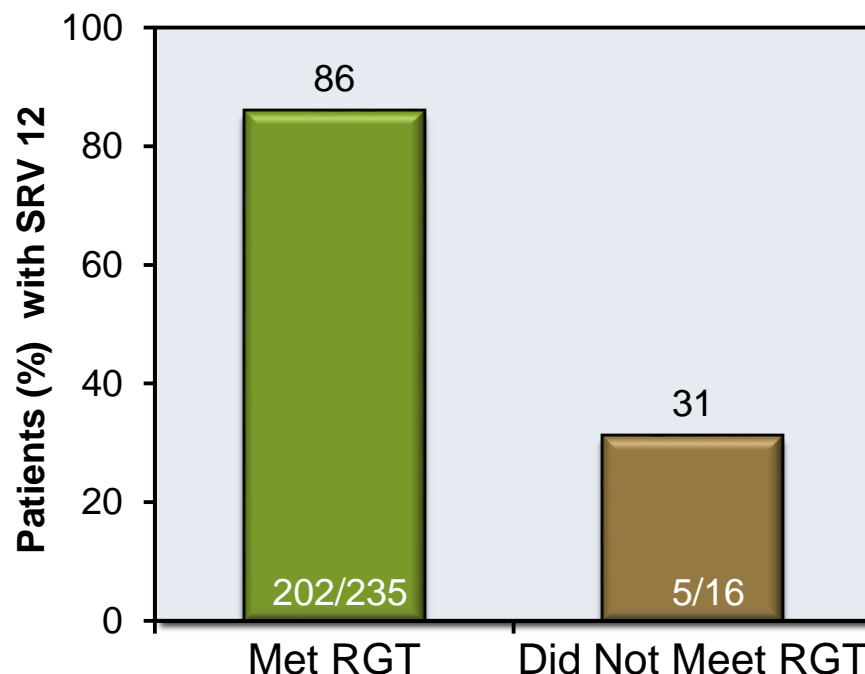
# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

## QUEST 2: SVR12 Response in Simeprevir Arm Based on RGT Criteria

### Patients (%) who Met RGT Criteria



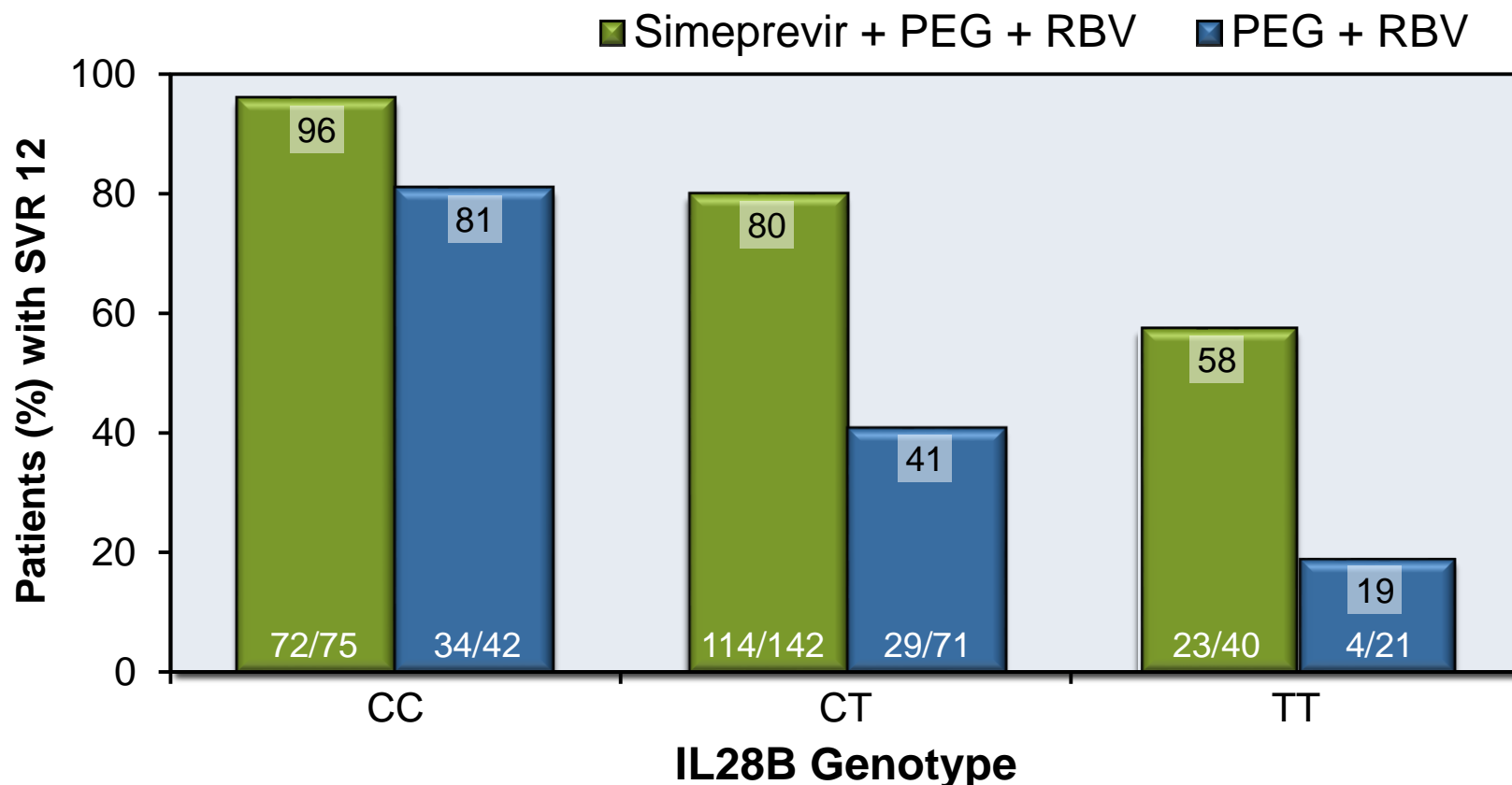
### SVR 12 Based on Meeting RGT



RGT= response-guided therapy: in simeprevir study arm, patients with HCV RNA<25 IU/ml at week 4 (undetectable or detectable) and <25 IU/ml at week 12 (undetectable) stopped treatment after 24 weeks

# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

## QUEST 2: SVR12 by Host *IL28B* Genotype



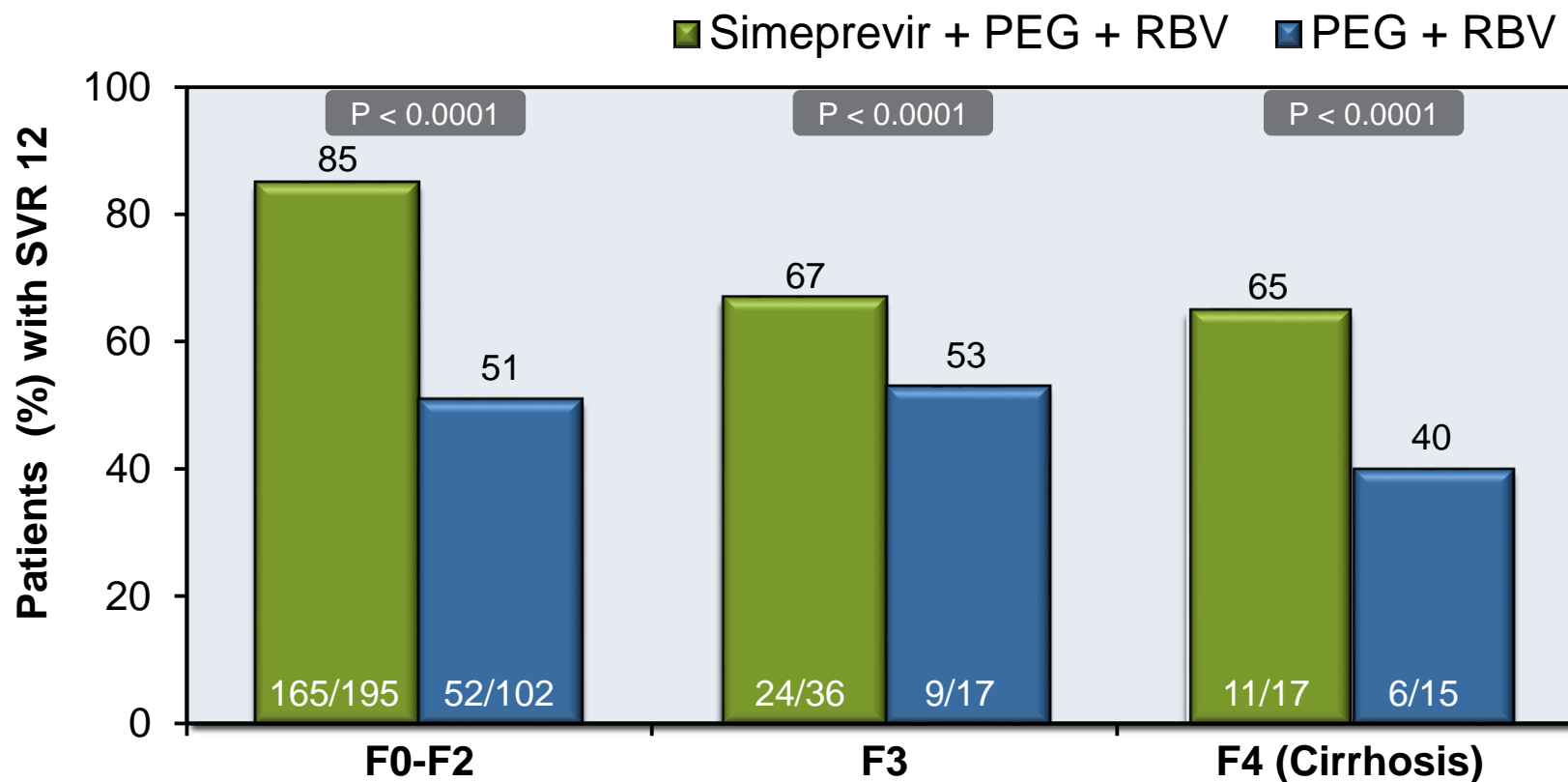
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# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

## QUEST 2: SVR12 by Liver Fibrosis (Metavir Score)

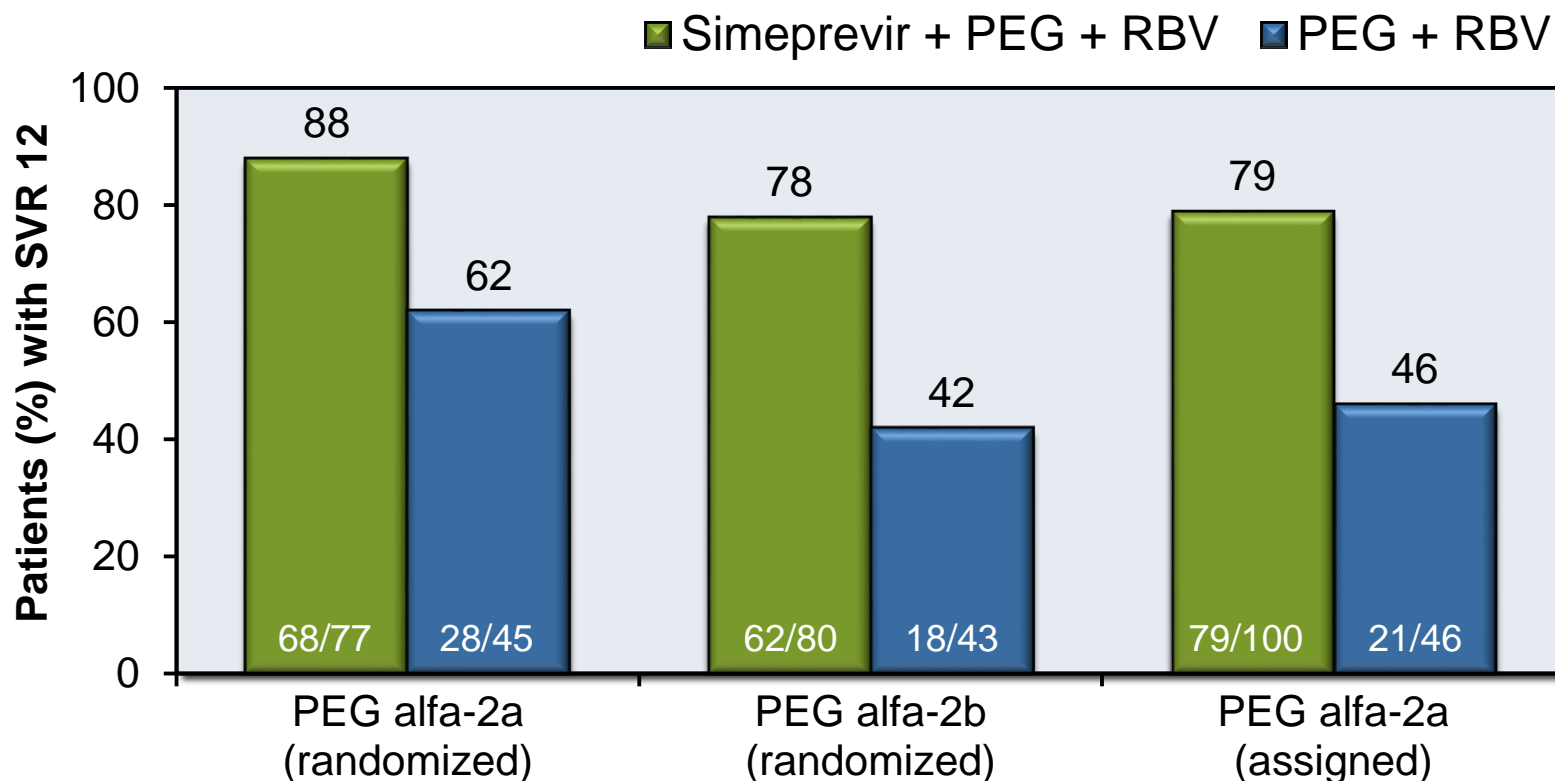


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# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

## SVR12 by Type of Peginterferon

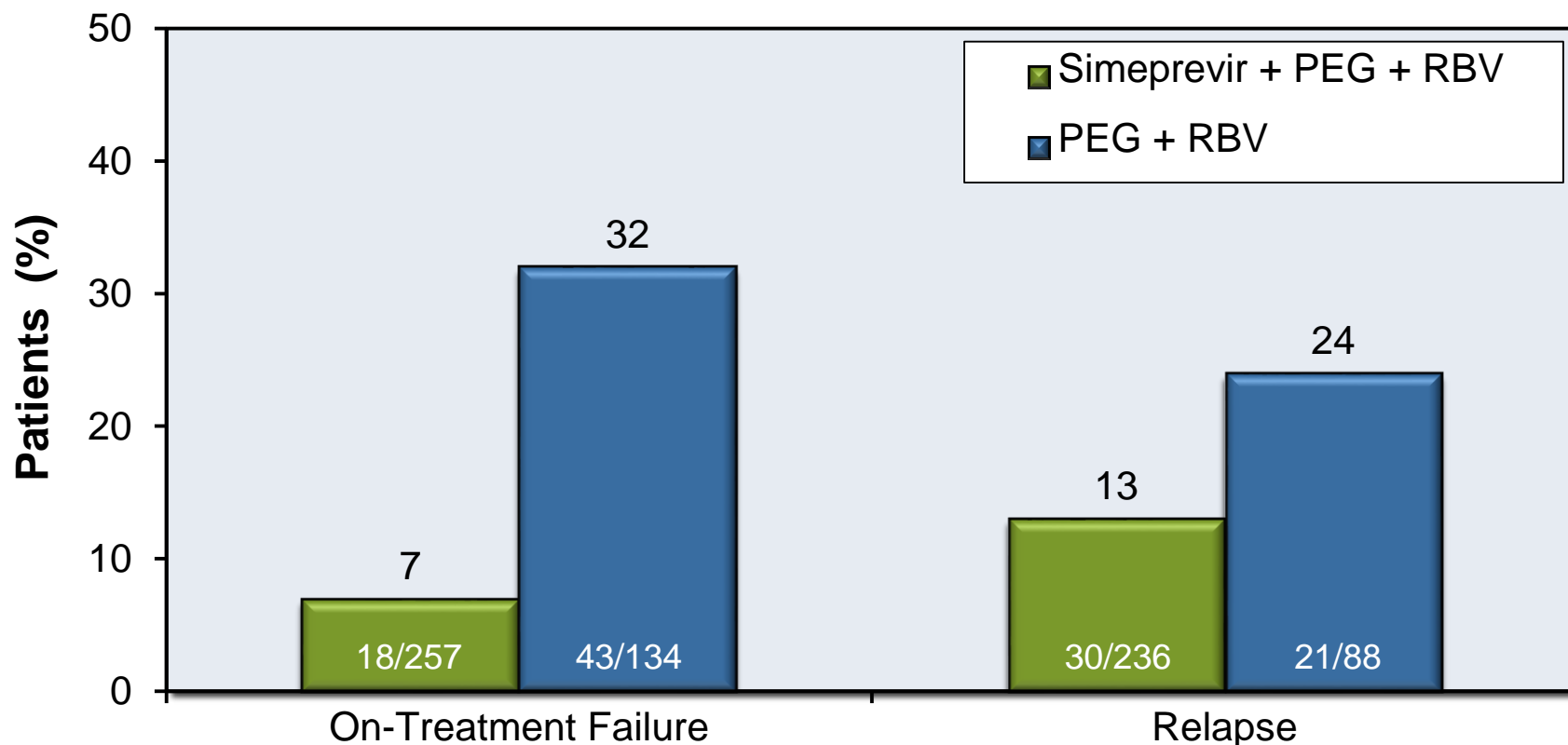


Type of PEG: 63% of patients randomized to receive PEG alfa-2a versus alfa-2b; remainder assigned PEG alfa-2a  
Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1

## QUEST-2 Trial: Results

### QUEST 2: Patients Who Had On-Treatment Failure or Relapse



Abbreviations: PEG = Peginterferon; RBV = Ribavirin

On-Treatment Failure: Detectable HCV RNA at end of treatment.

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## QUEST-2 Trial: Adverse Effects

QUEST 2: Event	Simeprevir + PEG/RBV (n=257)	Placebo + PEG/RBV (n=134)
Discontinuation (due to adverse event)	<1%	<1%
Grade 3 adverse event	27%	31%
Grade 4 adverse event	6%	4%
Headache	39%	37%
Fatigue	37%	42%
Pyrexia	31%	40%
Influenza-like illness	26%	26%
Rash (any type)	27%	20%
Pruritus	26%	27%
Photosensitivity reactions	4%	<1%
Anemia	21%	28%
Neutropenia	21%	27%

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# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

## QUEST 2: Emergent Resistance in Patients who Failed to Achieve SVR12

- Among simeprevir-treated patients who failed to achieve SVR12, emergent mutations in NS3 protease domain detected in 98%
- Genotype 1A: Most common mutation = R155K alone or in combination with mutations at codons 80 and/or 168
- Genotype 1B: Most common mutation = D168V and Q80R + D168E

# Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Conclusions

**Interpretation:** “Addition of simeprevir to either peginterferon alfa 2a or peginterferon alfa 2b plus ribavirin improved

SVR in treatment-naïve patients with HCV genotype 1 infection, without worsening the known adverse events associated with peginterferon alfa plus ribavirin.”

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*Hepatitis C Online* and *Hepatitis Web Study* projects.

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<http://depts.washington.edu/hepstudy/>

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