Treatment Naïve

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

Jacobson IM, et al. Lancet. 2014;384:403-13.

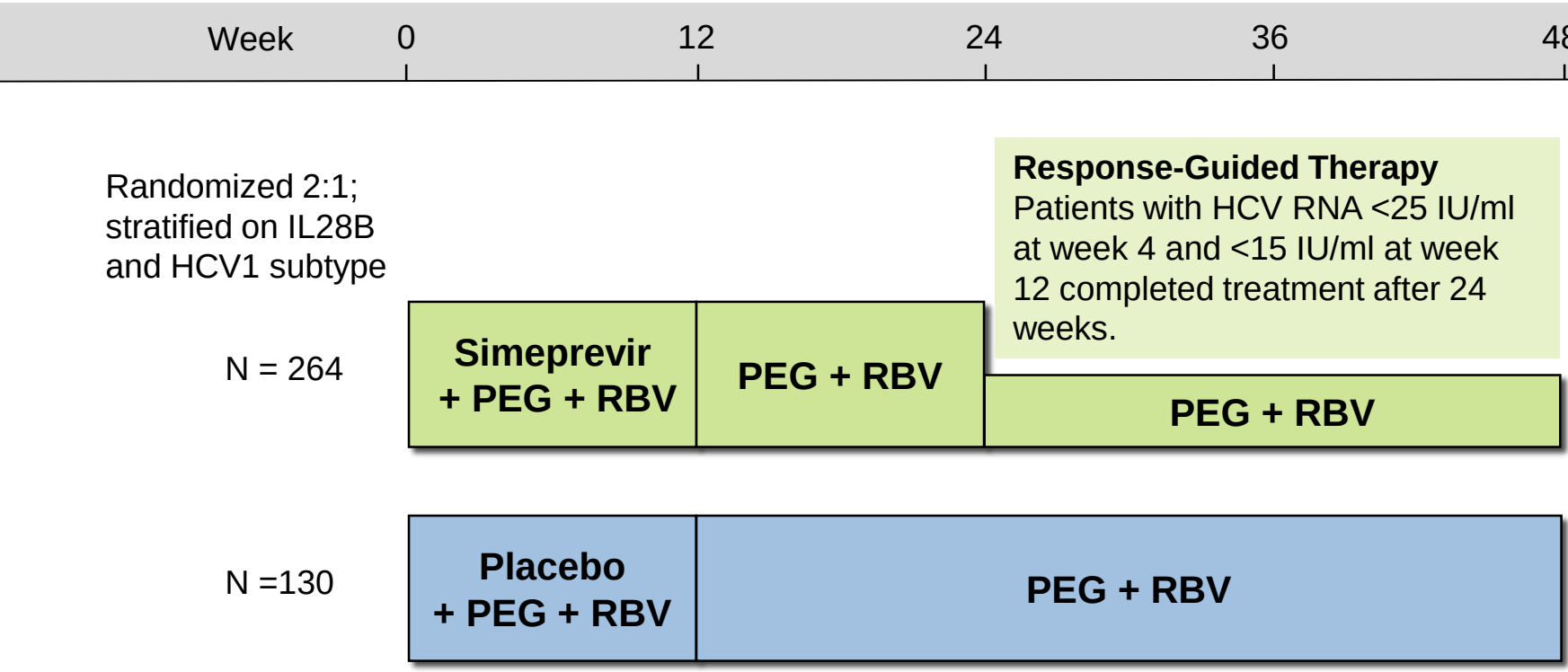
Simeprevir + PEG + Ribavirin for Treatment-Naïve HCV GT1 QUEST-1 Trial

QUEST-1 Trial: Features

- **Design**: Randomized, double-blind, placebo-controlled, phase 3 trial with simeprevir + PEG + RBV versus PEG + RBV in treatment-naïve GT 1
- **Setting**: Multicenter at 71 sites in 13 countries
- **Entry Criteria**
  - Treatment-naïve, chronic HCV monoinfection
  - HCV Genotype 1 (1a or 1b)
- **Patient Characteristics**
  - N = 394
  - HCV Genotype: 1a (56%); 1b (44%)
  - IL28B Genotype: 71% non-CC
  - Age: median age 48
  - Sex: 56% male
  - Race: 89% white, 8% black
  - Liver disease: F3 = 18%; F4 = 12%
- **Primary end-points**: Efficacy (SVR12) and safety

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Design



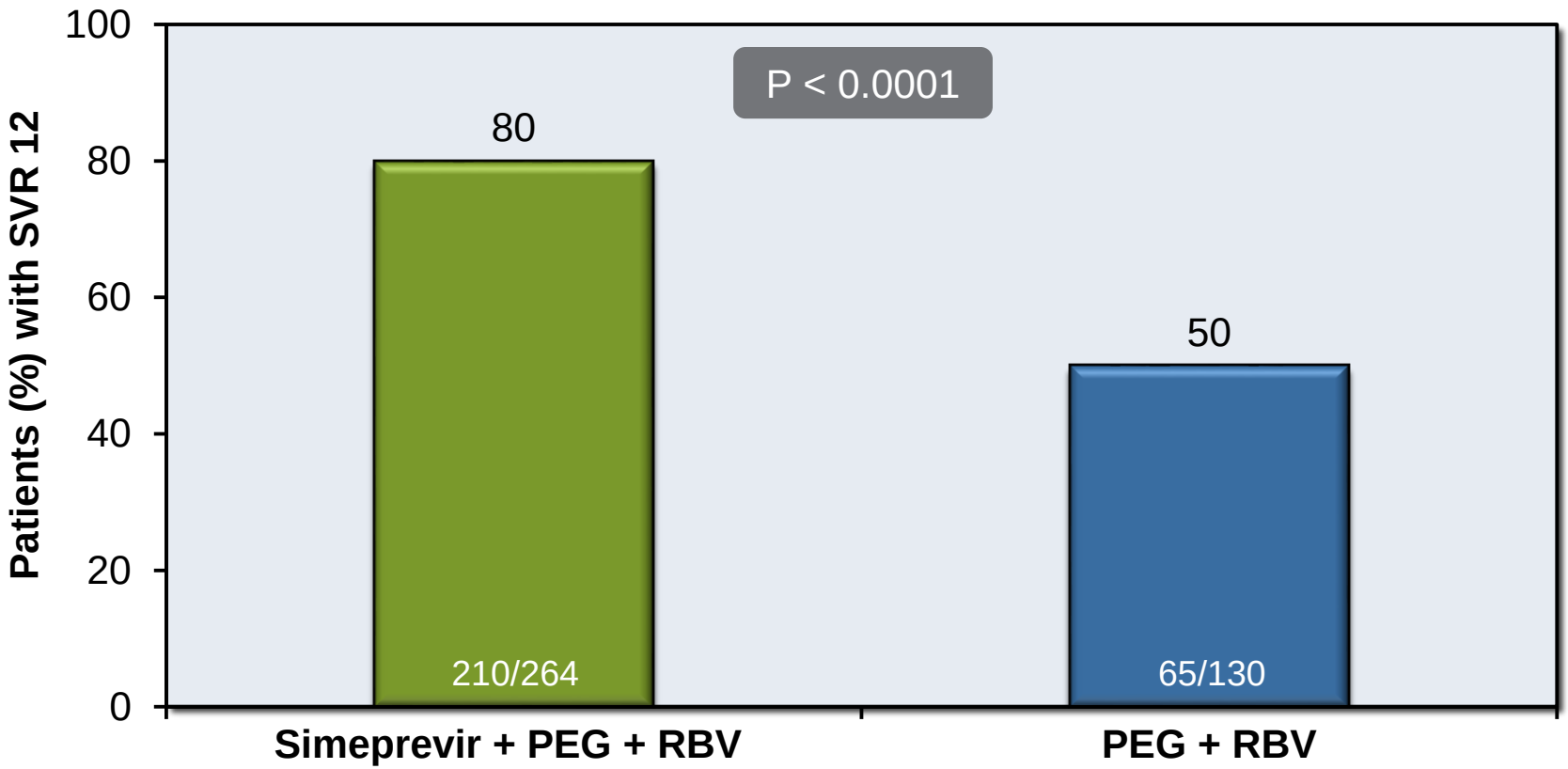
Response-Guided Therapy
Patients with HCV RNA <25 IU/ml at week 4 and <15 IU/ml at week 12 completed treatment after 24 weeks.

Drug Dosing
Simeprevir: 150 mg once daily
Peginterferon alfa-2a (PEG): 180 mcg/week
Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75kg

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

QUEST-1: Proportion of Patients with SVR12

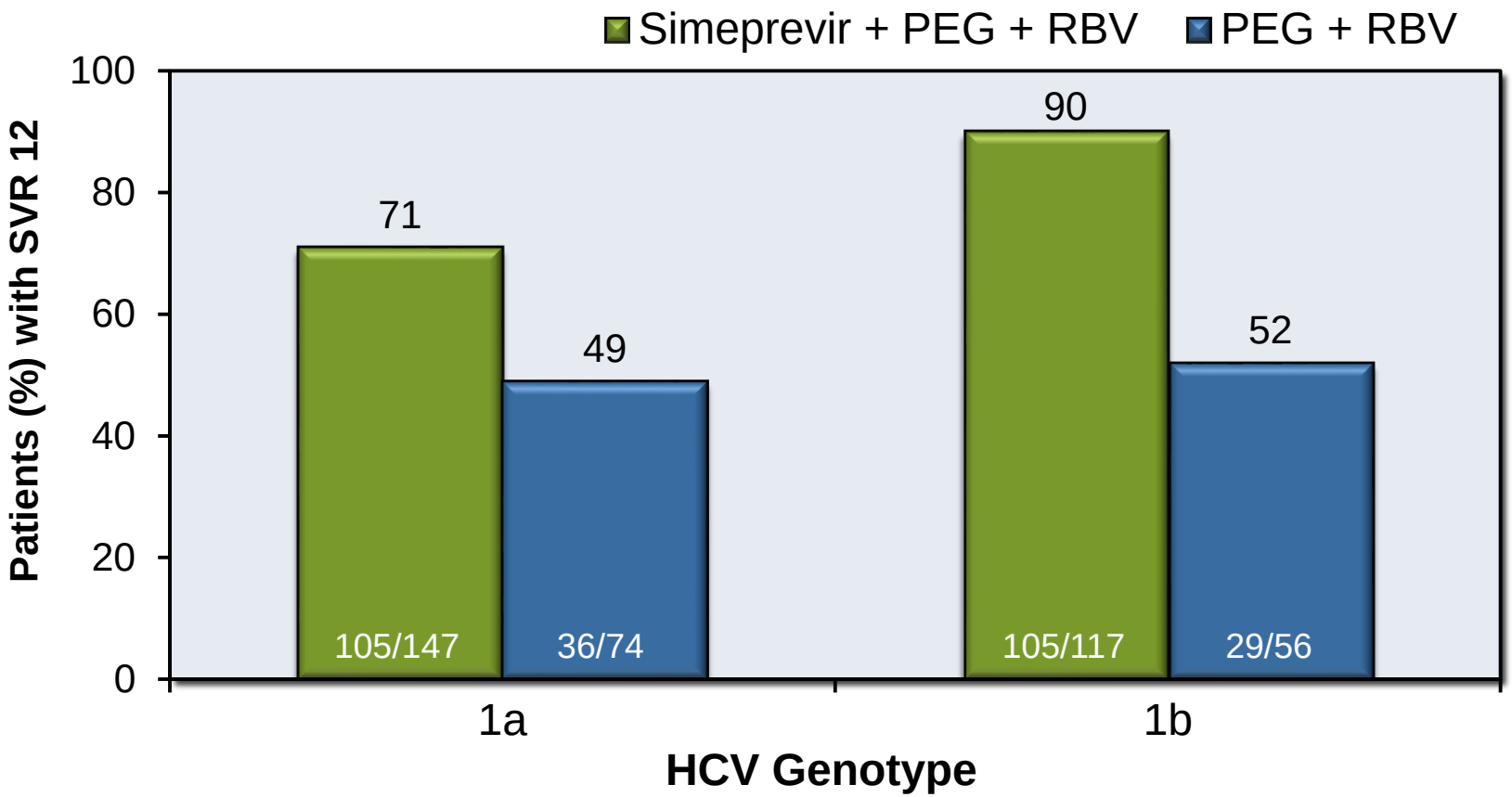


Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

SVR12 by HCV Genotype 1 Subtype



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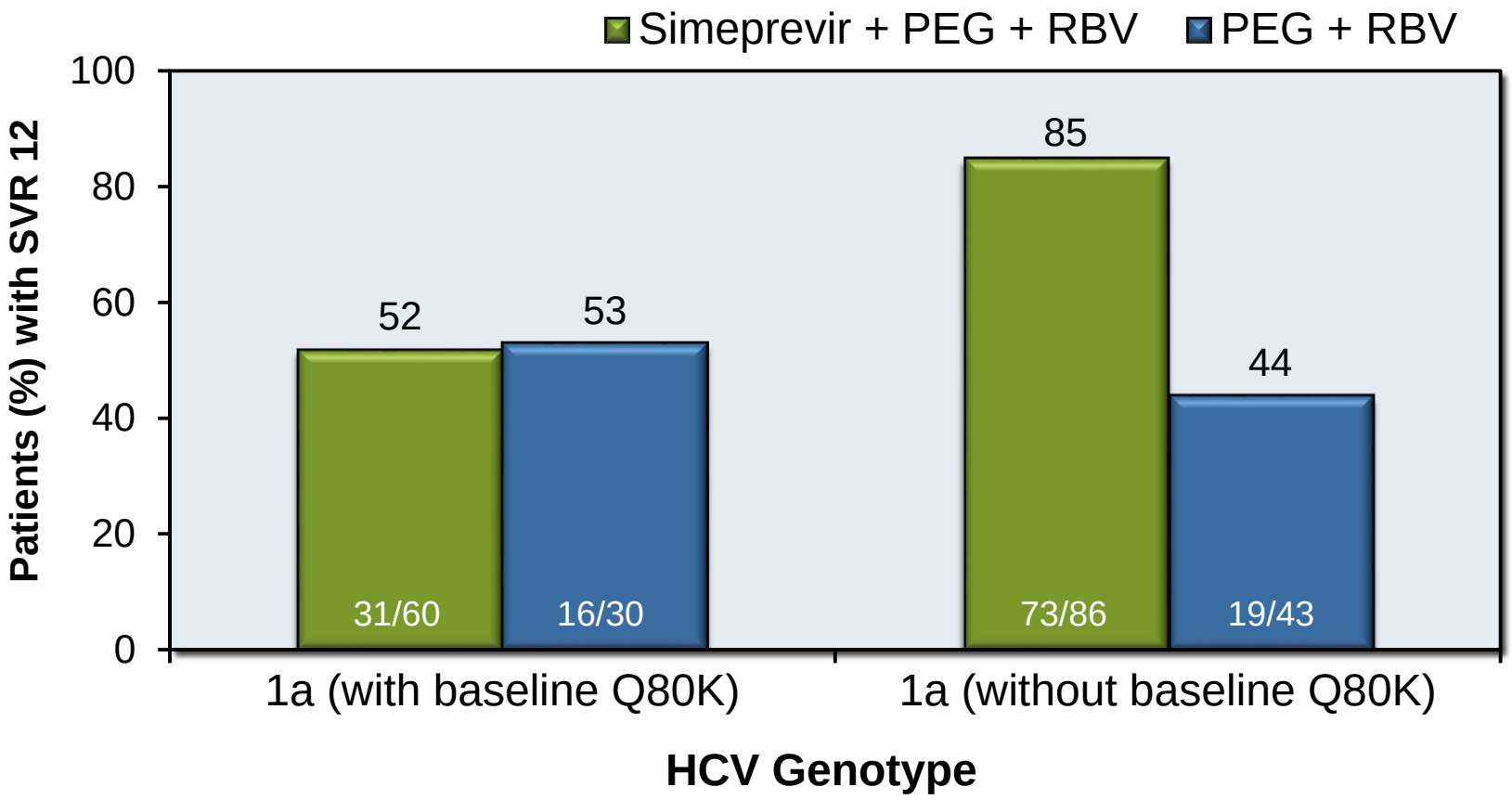
Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

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



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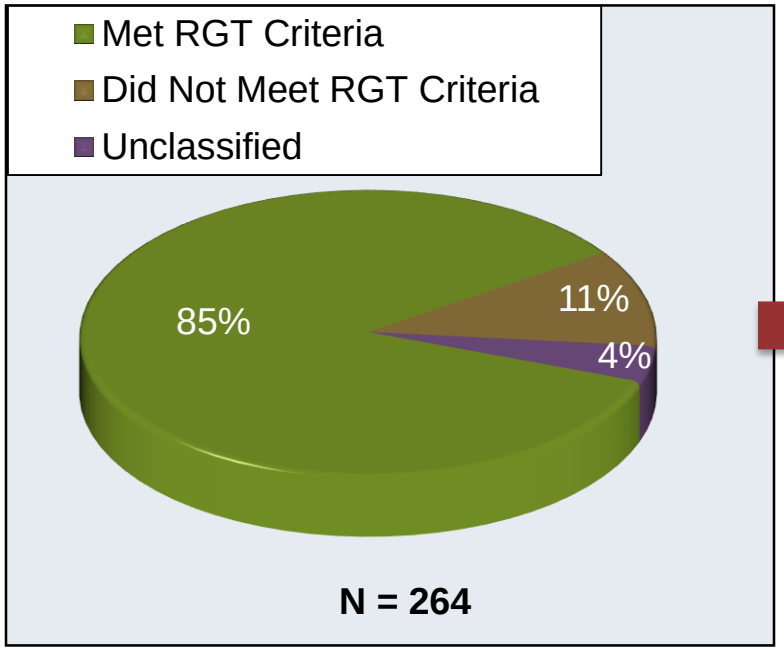
Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

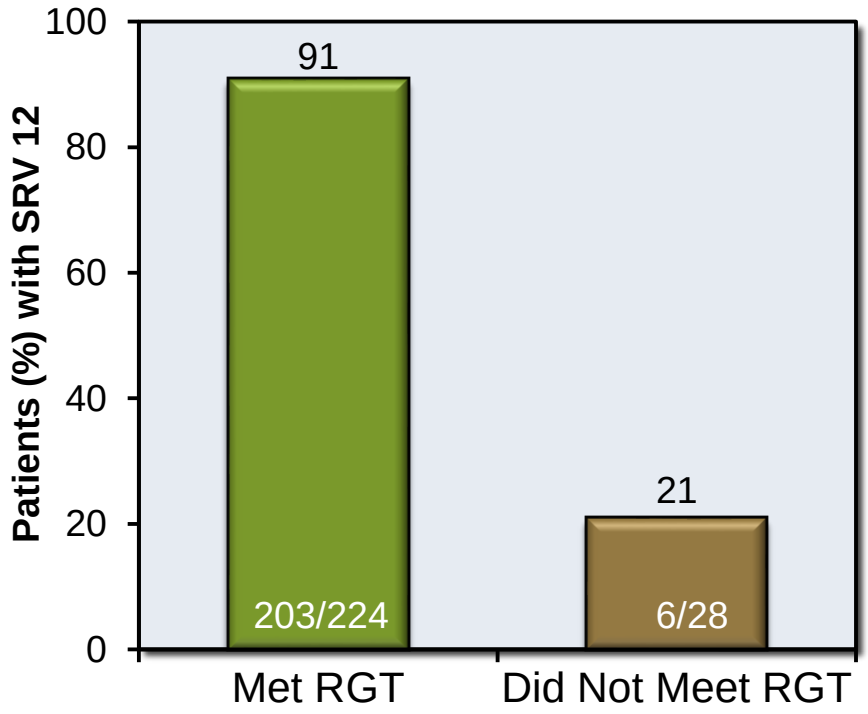
Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

SVR12 Response in Simeprevir Arm Based on Achievement of RGT Criteria

Patients (%) who Met RGT Criteria



SVR12 Based on Meeting RGT

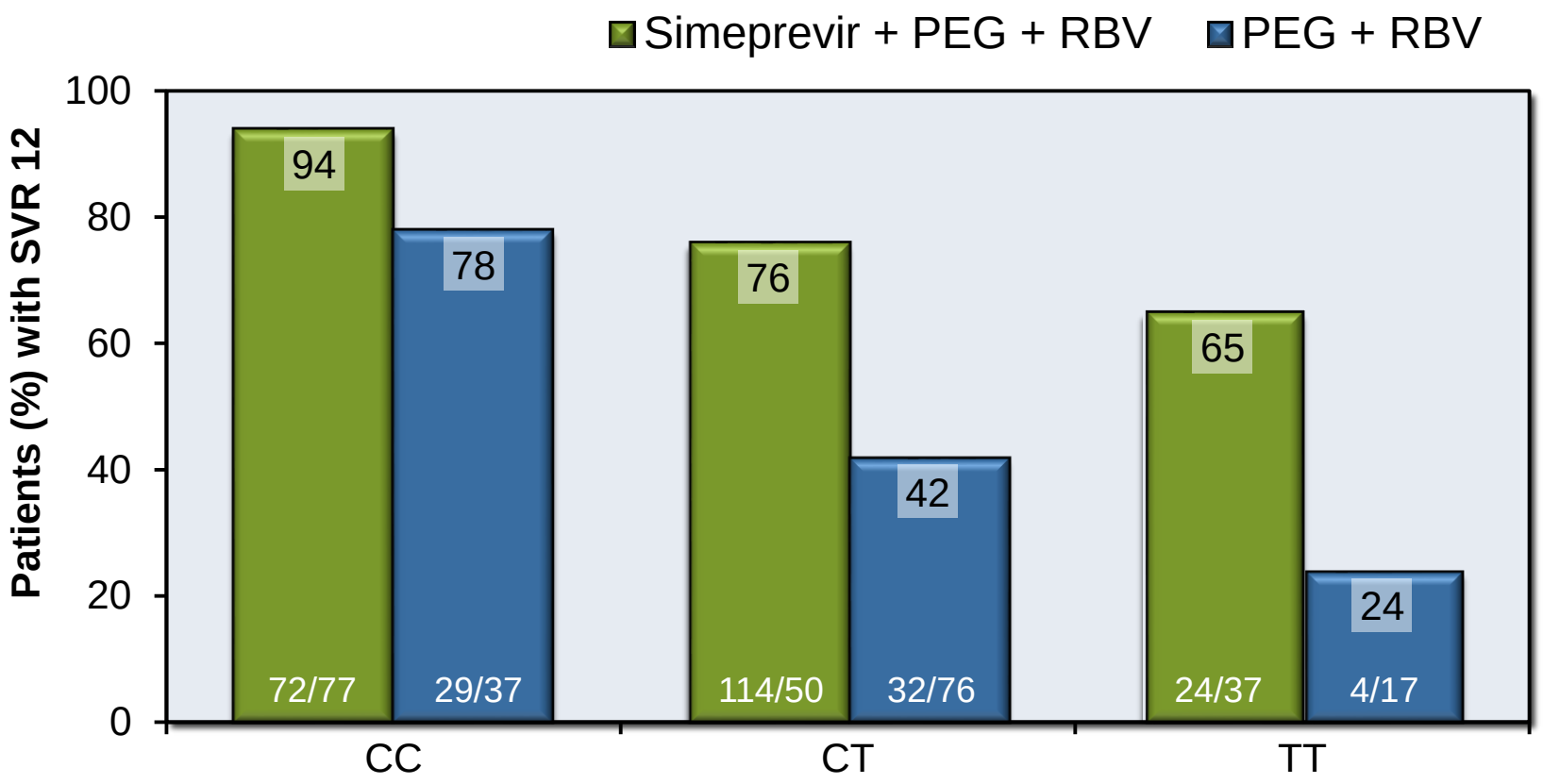


RGT= response-guided therapy: in simeprevir study arm, patients with HCV RNA<25 IU/ml at week 4 (undetectable or detectable) and <25 IU/ml at week 12 (undetectable) stopped treatment after 24 weeks

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

QUEST 1: SVR12 by Host *IL28B* Genotype



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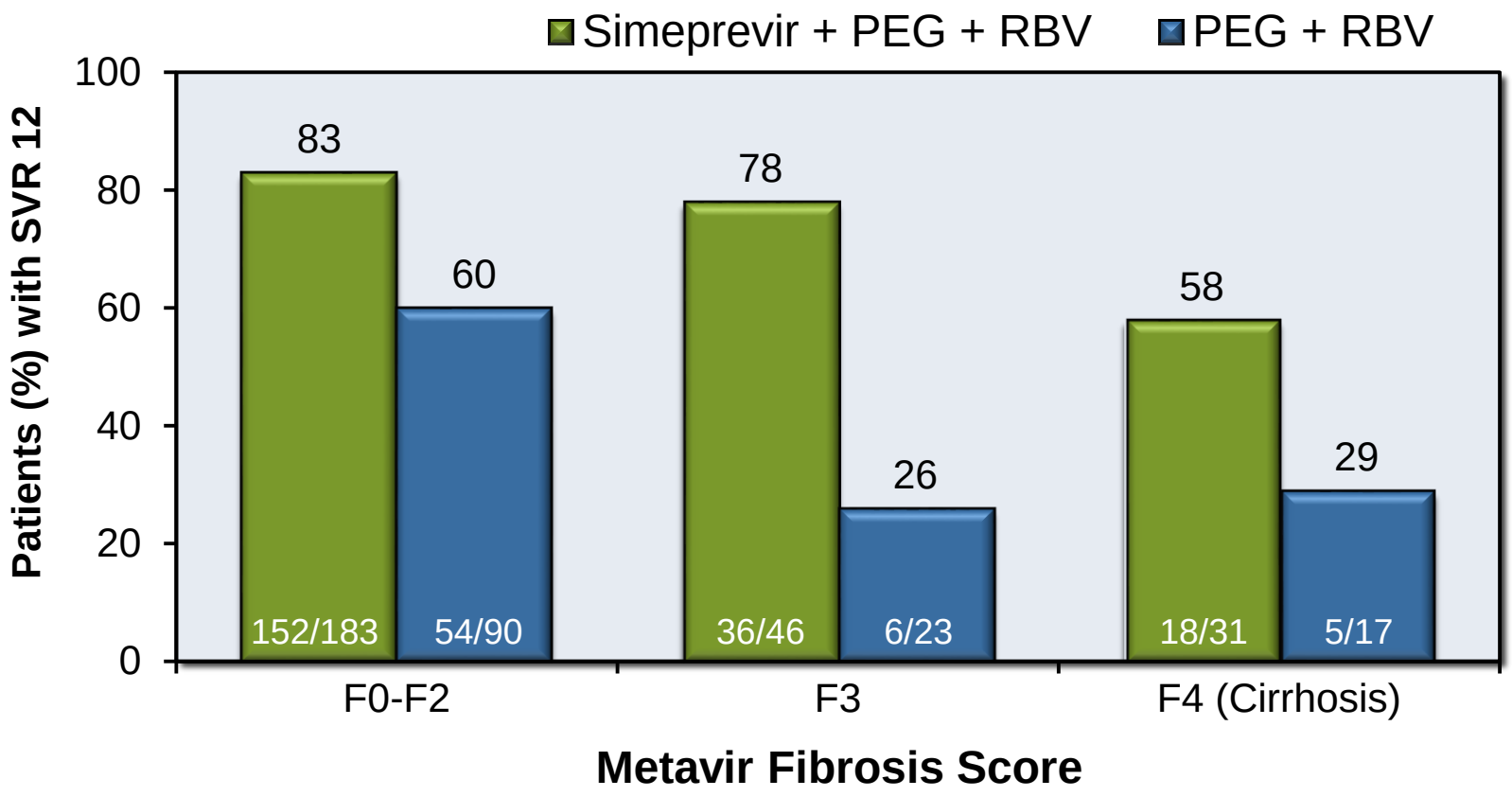
Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

QUEST 1: SVR12 by Liver Fibrosis (Metavir Score)



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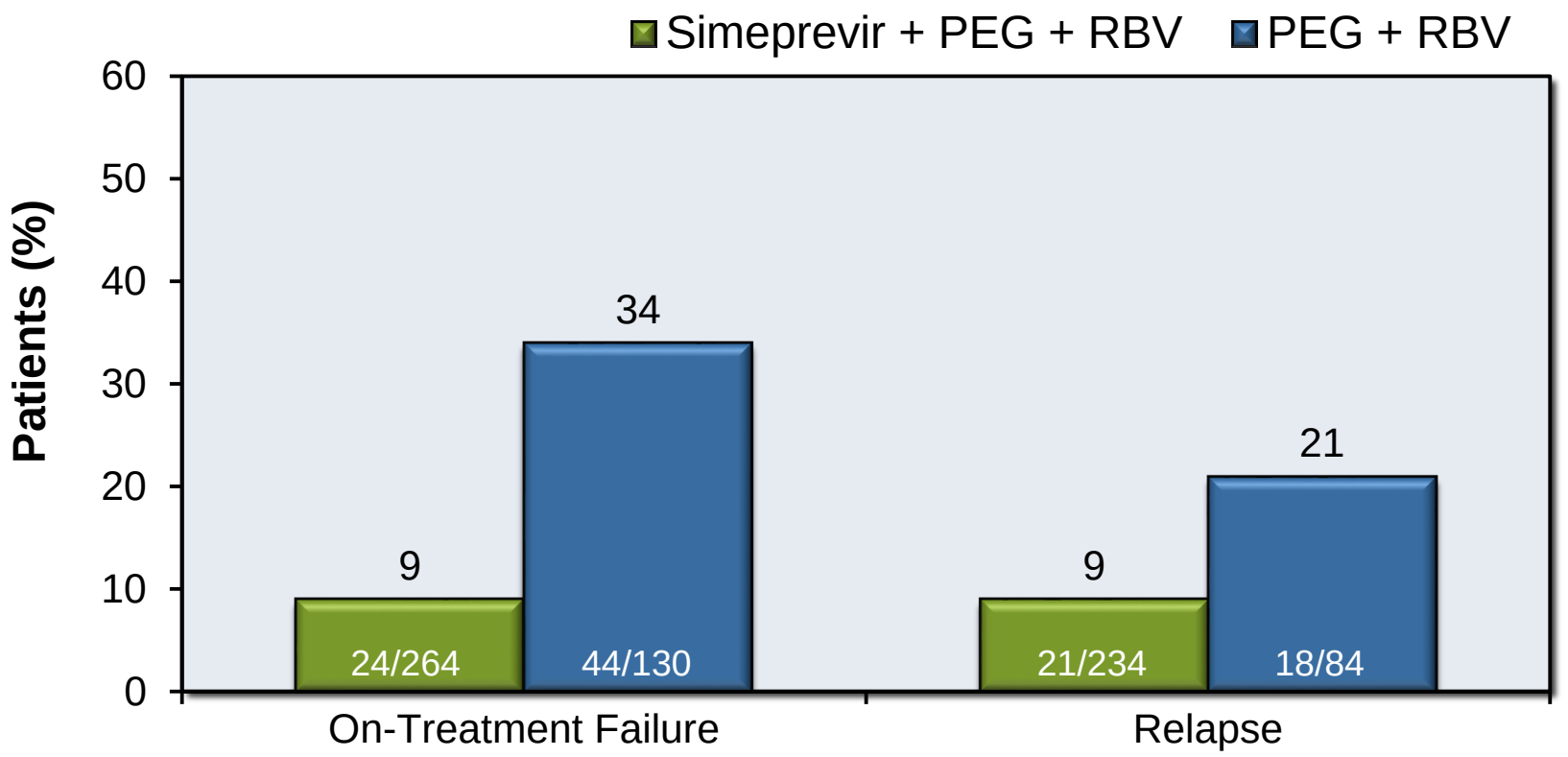
Hepatitis web study

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

On-Treatment Failure or Relapse



Stopping rules: (1) Stop simeprevir or placebo if HCV RNA>1000 at week 4; (2) Stop all therapy if HCV RNA < 2 $\log_{10}$ IU/mL reduction at week 12; (3) Stop all therapy if HCV RNA ≥25 IU/mL at week 24 or 36.
On-treatment failure: Detectable HCV RNA at end of treatment.

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Results

Emergent Protease 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 35 (92%) of 38
- Genotype 1A: Most common mutation = R155K alone or in combination with mutations at codons 80 and/or 168
- Genotype 1B: Most common mutation = D168V

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1
QUEST-1 Trial: Adverse Effects

QUEST 1: Event	Simeprevir + PEG + RBV (n=264)	Placebo + PEG + RBV (n=130)
Discontinuation (due to adverse event)	3%	2%
Grade 3 adverse event	25%	33%
Grade 4 adverse event	3%	5%
Fatigue	42%	41%
Headache	33%	39%
Pruritus	30%	20%
Rash (any type)	34%	32%
Anemia	20%	21%
Photosensitivity condition	3%	<1%
Neutropenia	24%	18%
Bilirubin increase	9%	5%

Source: Jacobson IM, et al. Lancet. 2014;384:403-13.

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Conclusions

Interpretation: “Simeprevir once daily with peginterferon alfa 2a and ribavirin shortens therapy in treatment-naive patients with HCV genotype 1 infection without worsening the adverse event profiles associated with peginterferon alfa 2a plus ribavirin.”

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This slide deck is from the University of Washington's *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online

www.hepatitisc.uw.edu

Hepatitis Web Study

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

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Hepatitis web study