The role of triple therapy in genotype 1: naïve patients

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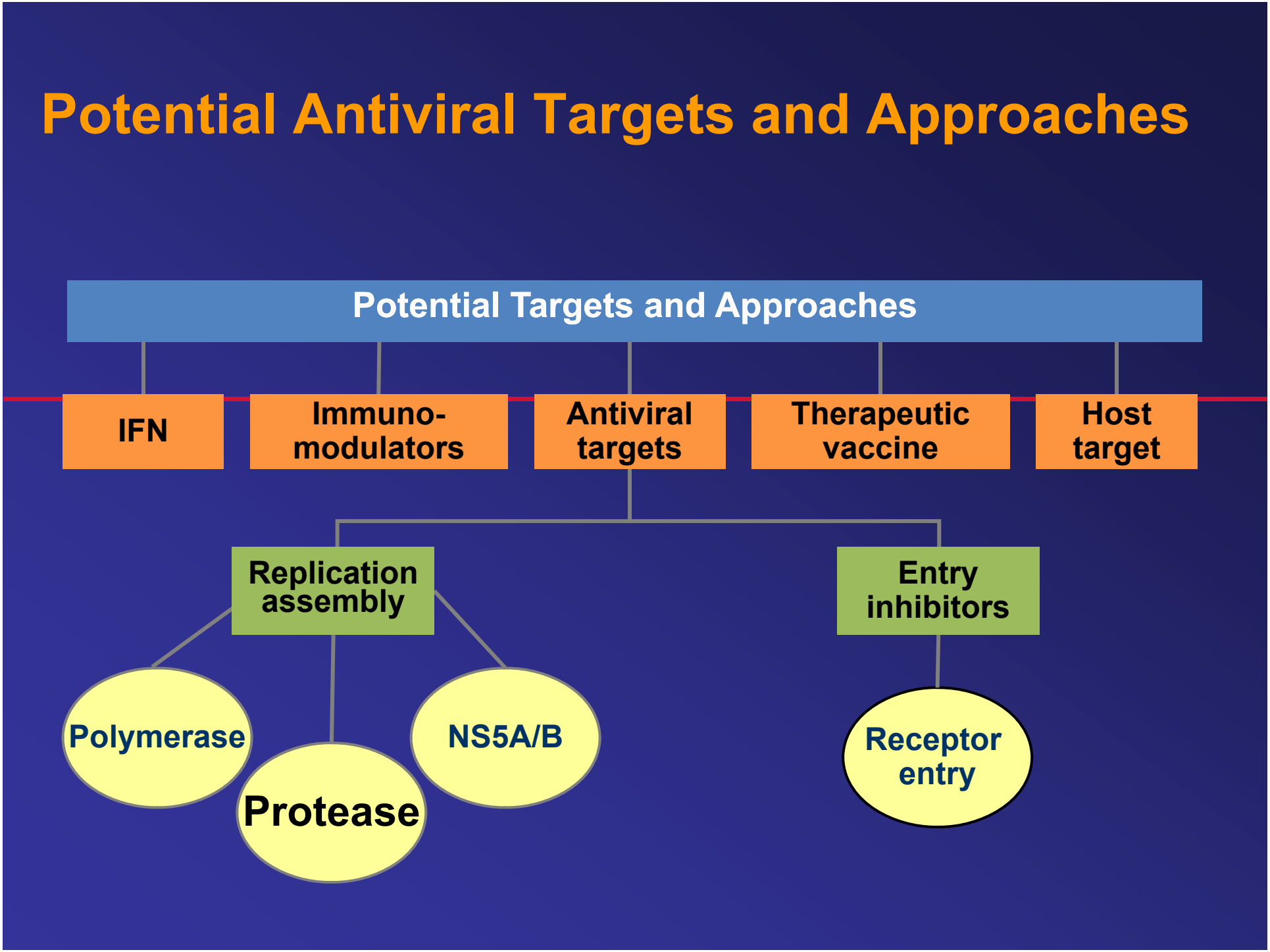
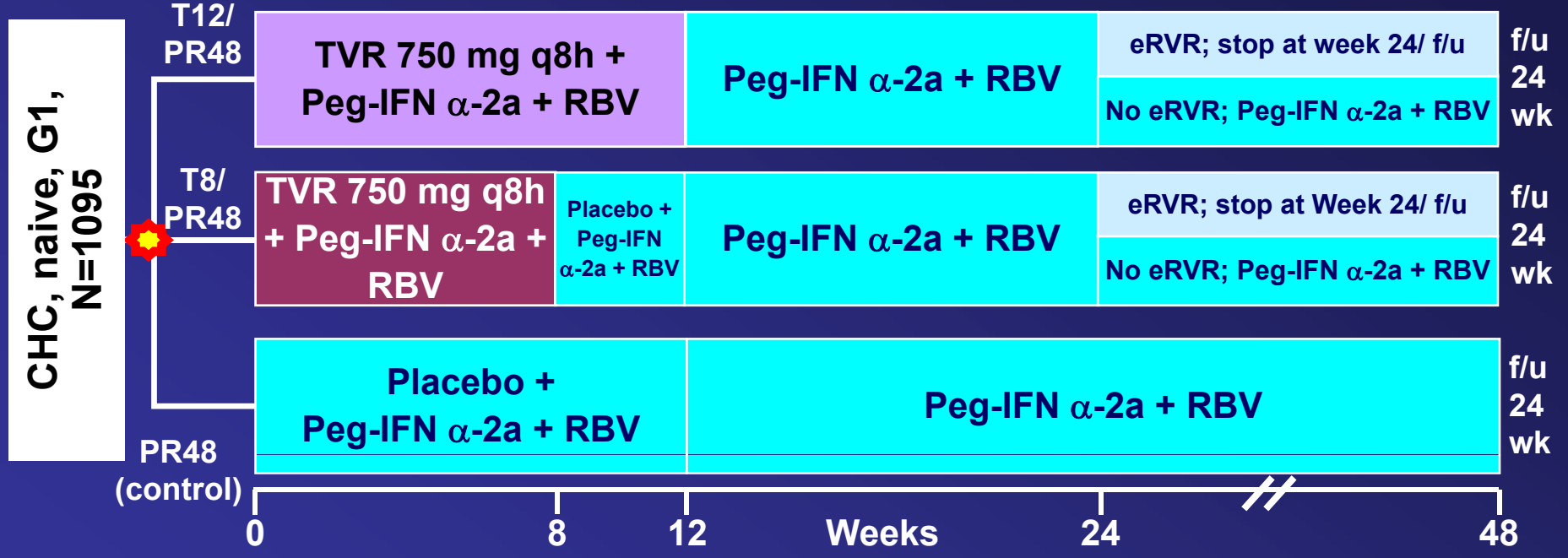
Potential Antiviral Targets and Approaches



Telaprevir and Boceprevir

- Anticipated FDA approval June 2011
- G1 naive patients registration trials:
  - ADVANCE: telaprevir
    - SVR 75%, TVR optimized for 12 weeks duration
  - ILLUMINATE: telaprevir
    - SVR 72%; supports response guided therapy
  - SPRINT-2: boceprevir
    - SVR 67%; supports response guided therapy
- Issue of safety and resistance are manageable

ADVANCE: telaprevir + Peg-IFN α-2a in G1 treatment-naive patients



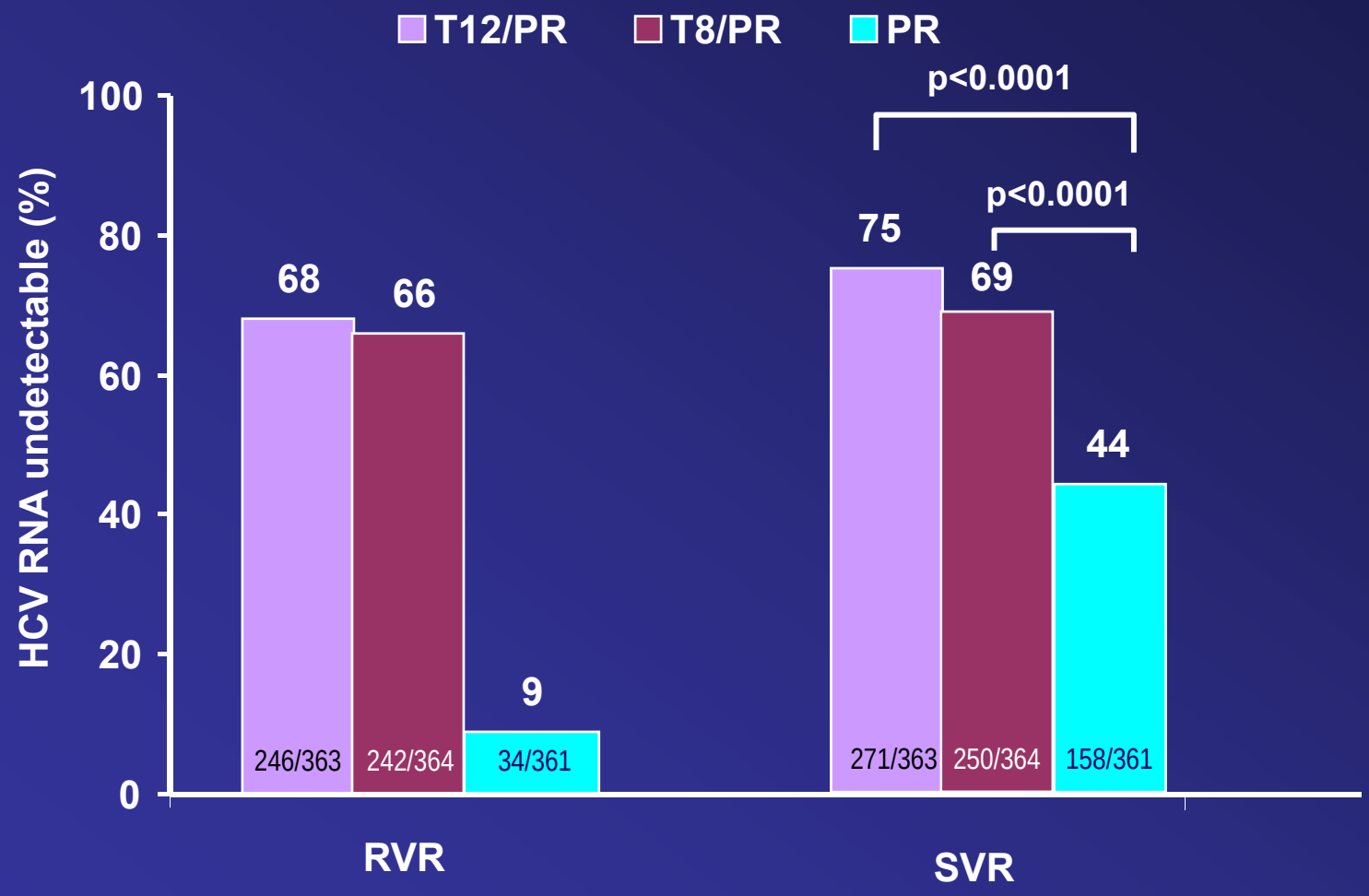
Randomization 1:1:1 (stratified by G1 subtype and viral load)

- ~ 60% North American population
- ~ 20% African Americans, Hispanics/Latinos
- ~ 20% Advanced fibrosis/cirrhosis

- Treatment duration for TVR arms:
  - Pts with eRVR (undetectable HCV RNA at wk 4 AND wk 12): receive 24 wks of therapy
  - Patients without eRVR will continue on P/R for a total of 48 weeks

Jacobson IM, et al. Hepatology 2010; 52 (S1) [abstract 211]

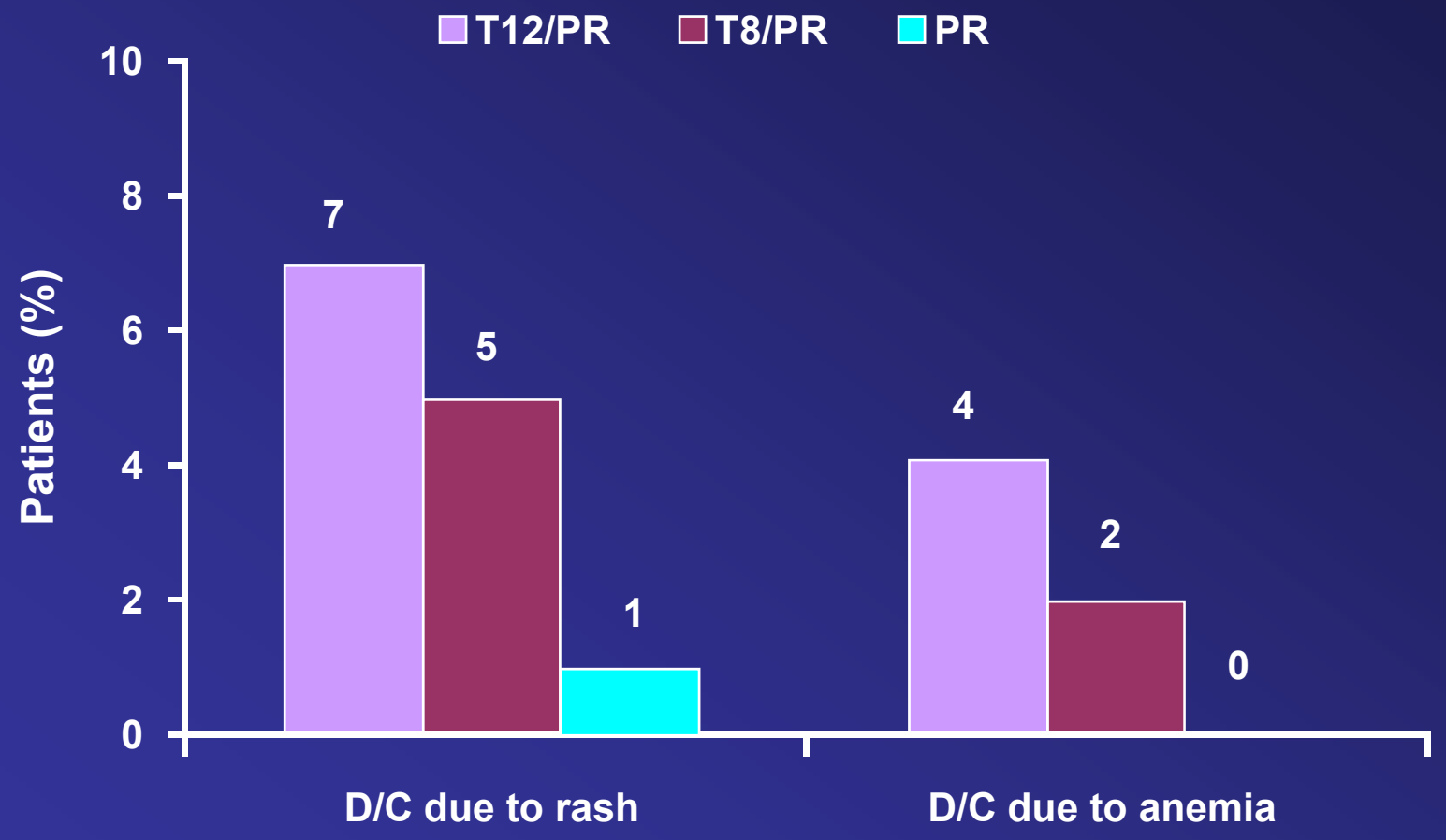
ADVANCE: higher RVR and SVR rates with telaprevir



ITT population

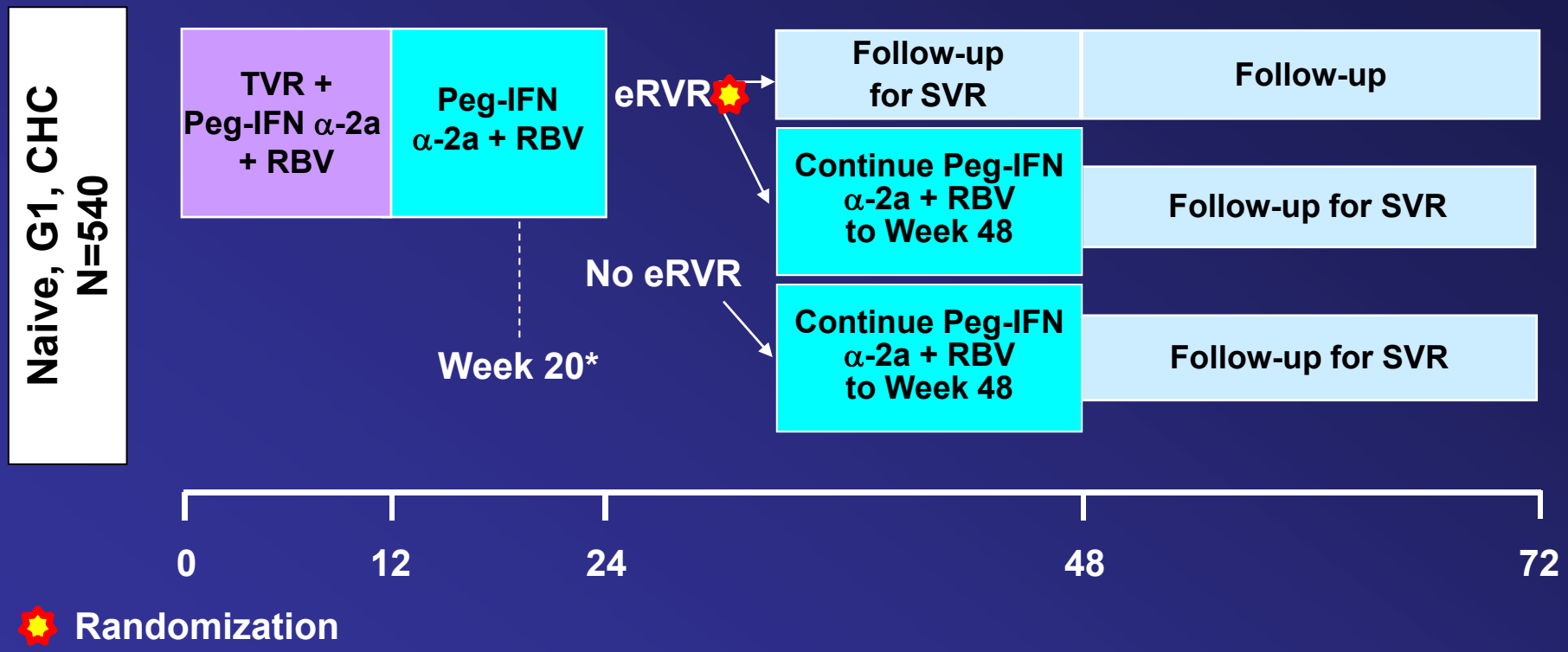
Jacobson IM, et al. Hepatology 2010; 52 (S1) [abstract 211]

ADVANCE: discontinuation due to rash and anemia



Jacobson IM, et al. Hepatology 2010; 52 (S1) [abstract 211]

ILLUMINATE study design: telaprevir + Peg-IFN α-2a in G1 treatment-naive patients

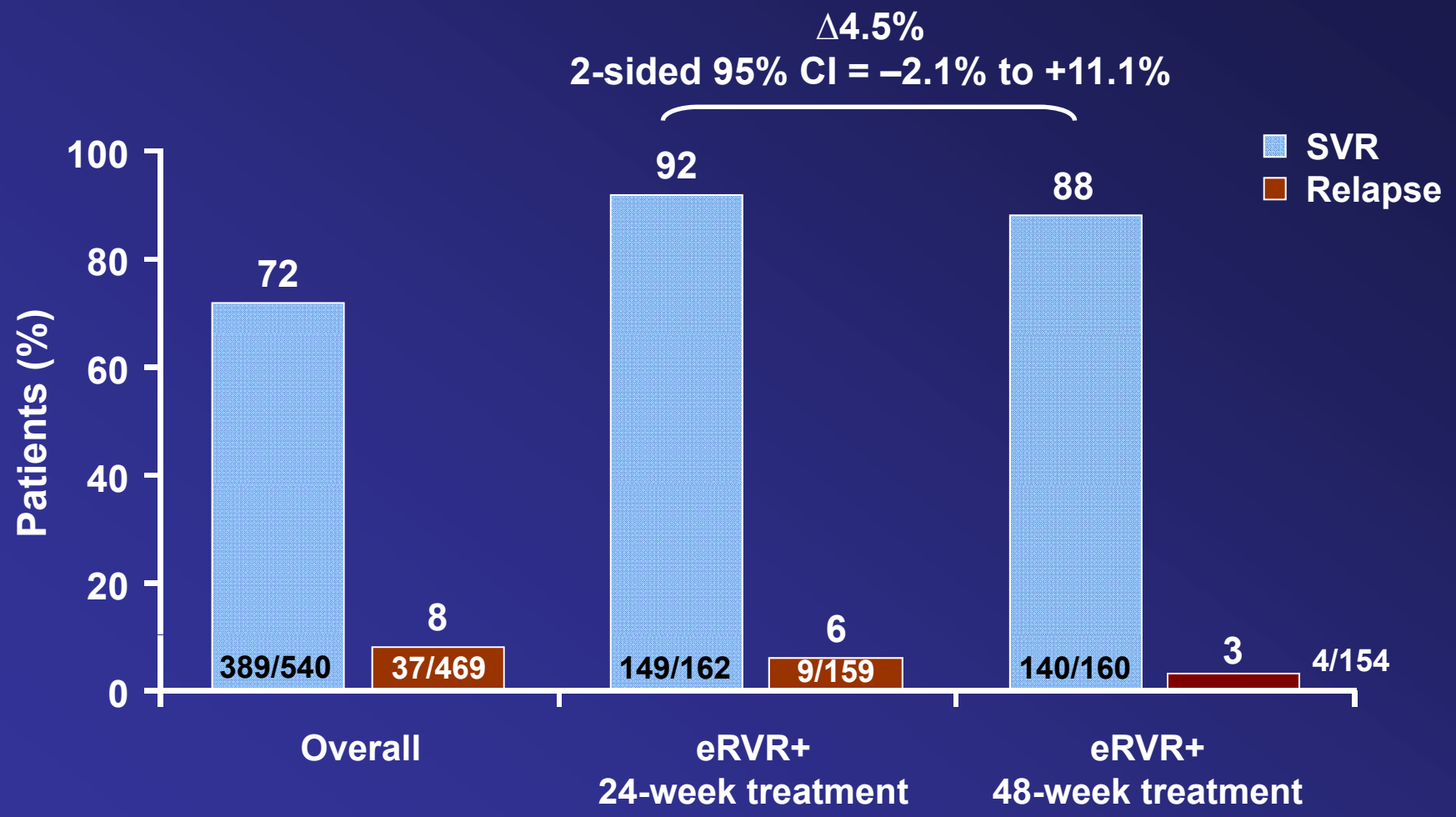


* Patients who achieved eRVR and completed week 20 visit were randomized to receive an additional 4 weeks or 28 weeks of Peg-IFN α-2a/RBV

eRVR = extended rapid viral response (undetectable HCV RNA at week 4 AND week 12)

Sherman KE, et al. Hepatology 2010; 52 (S1) [abstract LB-2]

ILLUMINATE: group efficacy results (ITT)



eRVR = 65%

Sherman KE, et al. Hepatology 2010; 52 (S1) [abstract LB-2]

ILLUMINATE: adverse events leading to study drug discontinuations

	Total
	N=540
Discontinuations of all study drugs during telaprevir treatment phase, %	
Any AE	7
Rash events	1
Anemia events	1
Discontinuations of telaprevir during telaprevir treatment phase, %	
Any AE	12
Rash events	7
Anemia events	2

Overall treatment phase

- 17% of patients in the ITT discontinued all study drugs due to AEs

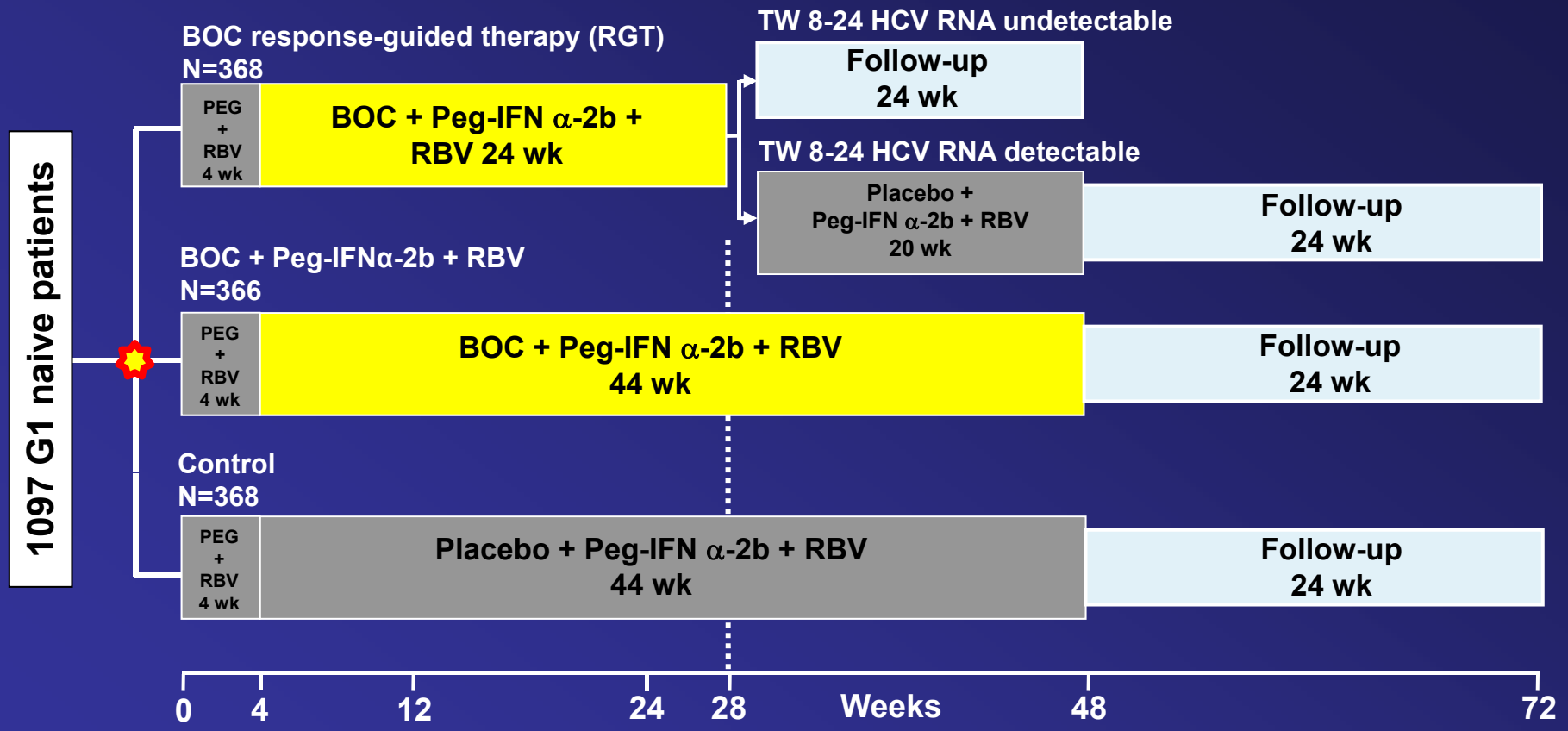
Sherman KE, et al. Hepatology 2010; 52 (S1) [abstract LB-2]

Lessons from ADVANCE and ILLUMINATE trials

- 24 week response-guided therapy is appropriate in patients with an eRVR (defined at week 4 and 12)
- Approximately 2/3 of treatment-naive patients are eligible for shorter duration of treatment
- 12 weeks of TVR (vs 8 weeks) is required for optimal virologic response

1. Sherman KE, et al. Hepatology 2010; 52 (S1) [abstract LB-2]
2. Jacobson IM, et al. Hepatology 2010; 52 (S1) [abstract 211]

SPRINT-2: study design: boceprevir + Peg-IFN α-2b in G1 treatment-naive patients



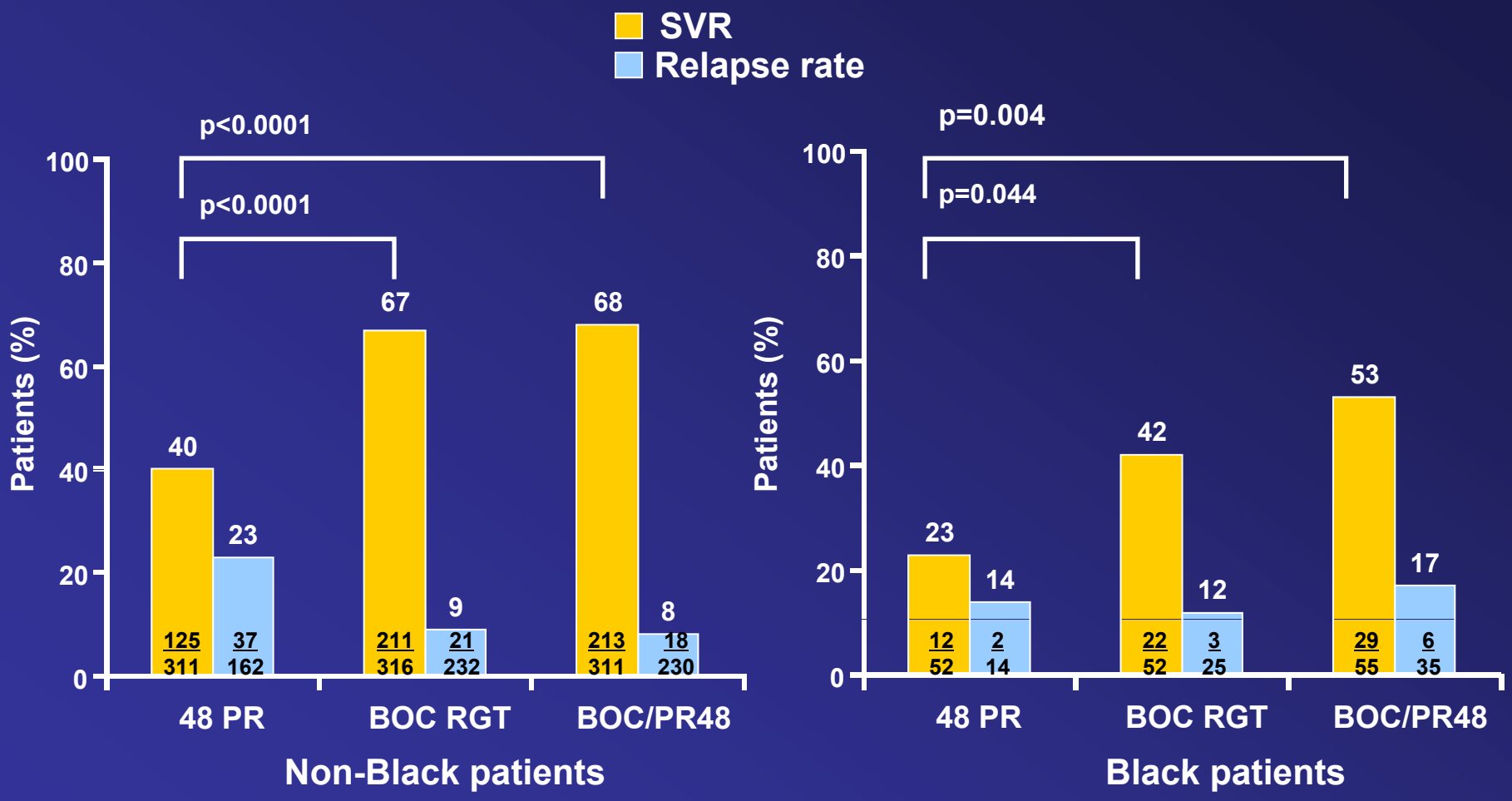
Randomization

Cohort 1 = 938 non-Black patients; Cohort 2 = 159 Black patients

BOC = boceprevir (800 mg PO tid); PEG = Peg-IFN α-2b (1.5 µg/kg/wk); RBV = ribavirin (600–1400 mg/d)

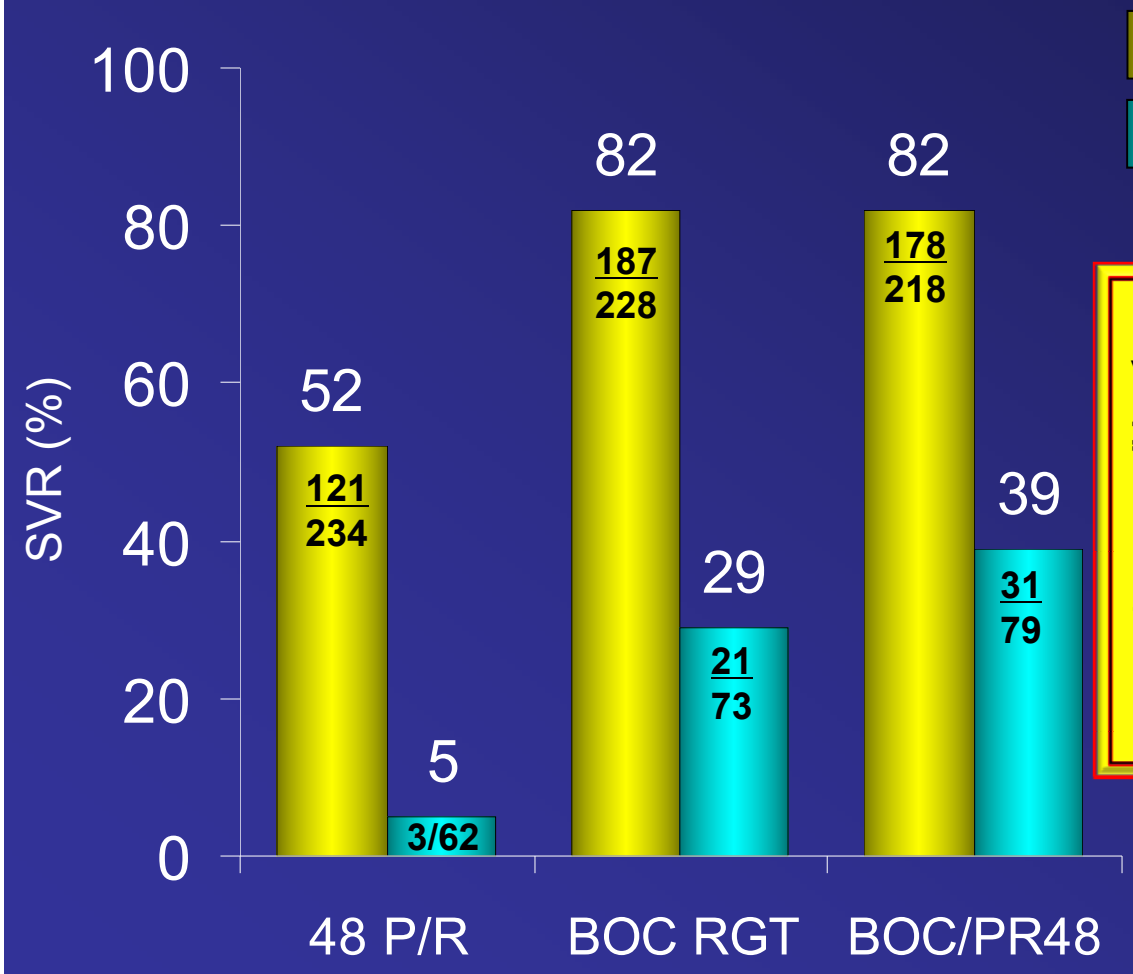
Poordad F, et al. Hepatology 2010; 52 (S1) [abstract LB-4]

SPRINT-2: SVR and relapse rates (ITT)



Poordad F, et al. Hepatology 2010; 52 (S1) [abstract LB-4]

SVR Based on Week 4 PR Lead-In in Non-Black Patients



Boceprevir Resistance-associated Variants*:

≥ 1 $\log_{10}$ decline:

BOC RGT: 4% (9/232)

BOC/PR48: 4% (9/231)

< 1 $\log_{10}$ decline:

BOC RGT: 47% (45/95)

BOC/PR48: 35% (33/94)

* Boceprevir resistance-associated variants determined with population sequencing

SPRINT-2: safety

The five most common treatment-emergent AEs

Patients (%)	BOC RGT n=368	BOC/PR48 n=366	PR48 n=363
Fatigue	52	57	59
Headache	45	43	42
Nausea	46	42	40
Anemia	49	49	29
Dysgeusia	37	43	18

- Treatment discontinuations due to anemia occurred in ≤2% of patients; EPO was used in more BOC recipients (43%) vs. controls (24%)
- Treatment discontinuations due to adverse events overall were 12% and 16% for the BOC RGT and BOC + PR groups, respectively, compared with 16% for the control group (PR48)

Poordad F, et al. Hepatology 2010; 52 (S1) [abstract LB-4]

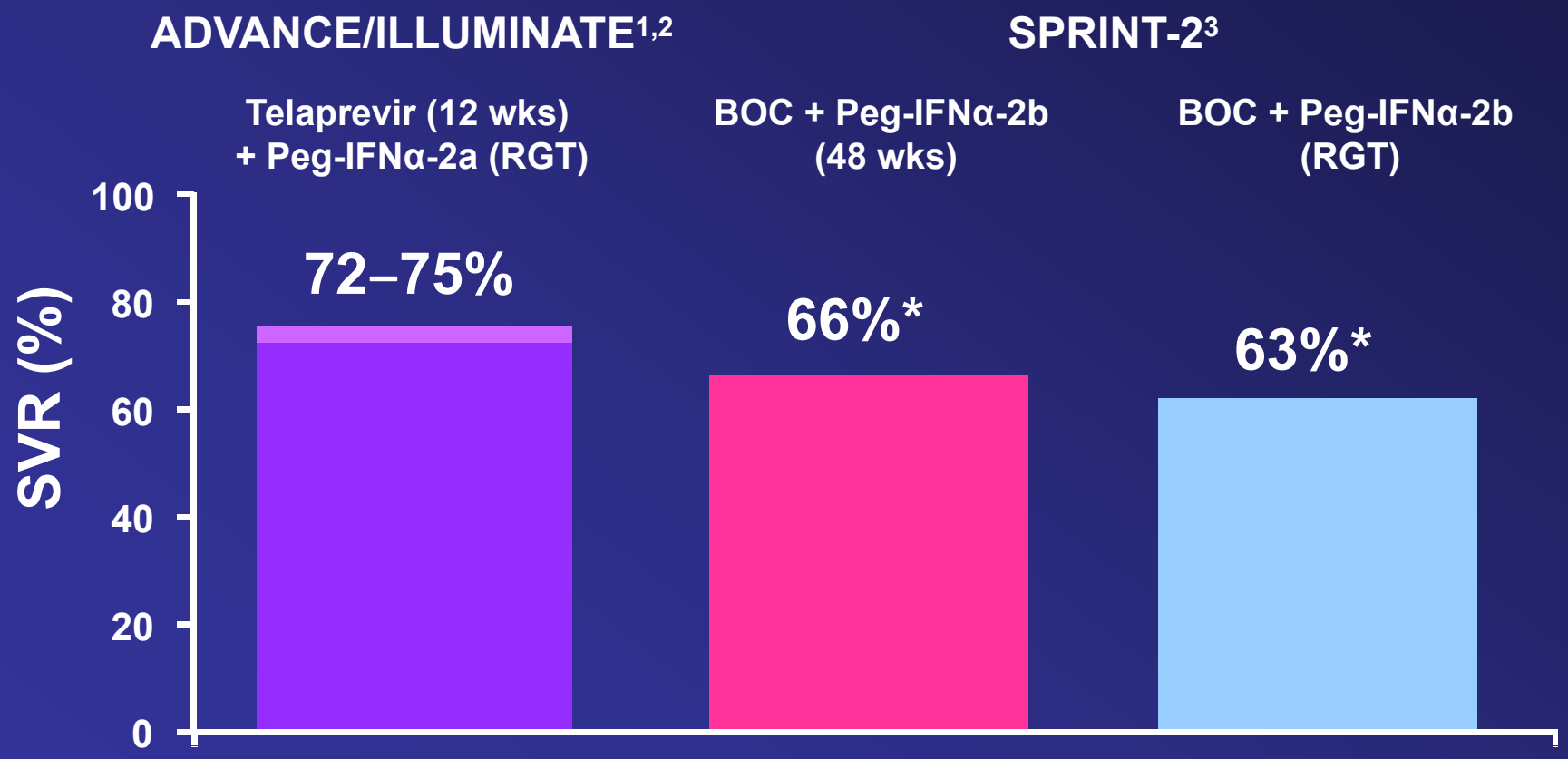
Lessons from the SPRINT-2 trial

- 24-week triple therapy (RGT) is as effective as 44 weeks (BOC/PR48) in non-Black patients
  - Approximately 1/2 of treatment-naive patients are eligible for shorter duration of treatment
- Resistance-associated variants were identified and correlated with week 4 viral load decline
- Anemia and dysgeusia occurred more often in the boceprevir groups than the control groups

Poordad F, et al. Hepatology 2010; 52 (S1) [abstract LB-4]

Summary of Phase 3 Trials

Naive patients

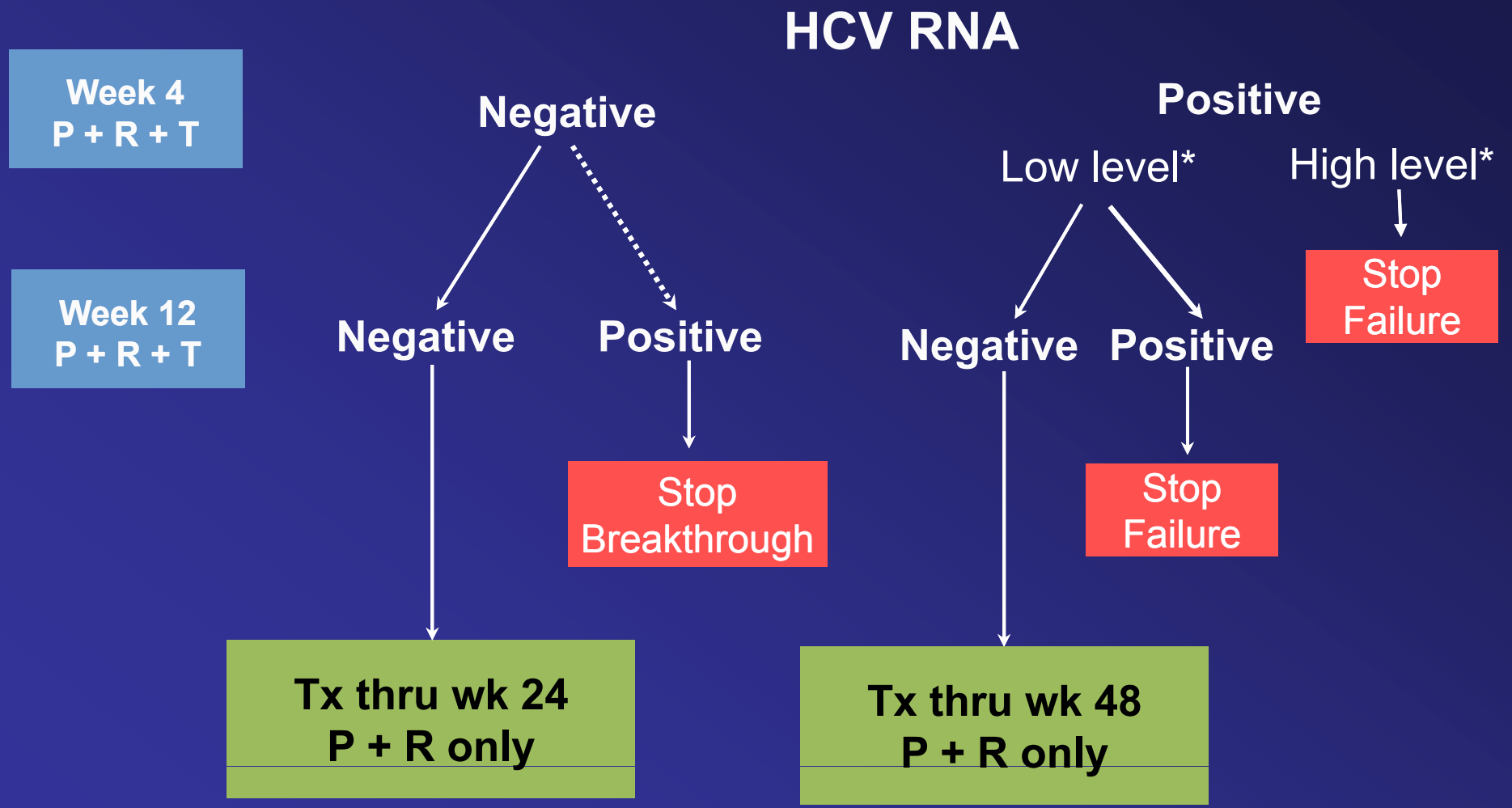


* Combined Black and non-Black populations

1. Jacobson IM, et al. Hepatology 2010; 52 (S1) [abstract 211]
2. Sherman KE, et al. Hepatology 2010; 52 (S1) [abstract LB-2]
3. Poordad F, et al. Hepatology 2010; 52 (S1) [abstract 797]

Telaprevir Response-Guided Therapy

Treatment-Naive Patients G1

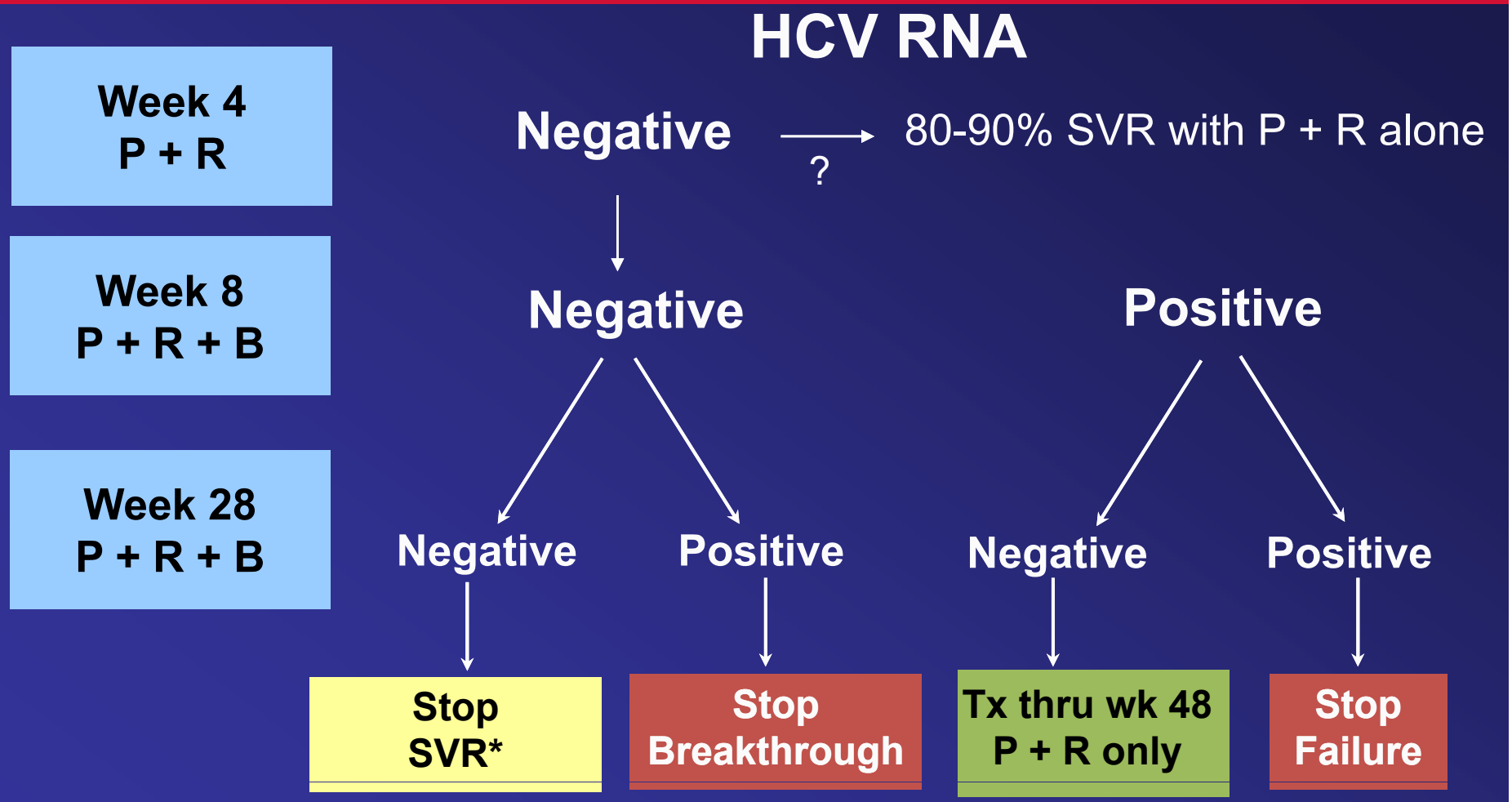


Abbreviations: P, peginterferon; R, ribavirin; T, telaprevir.

* Likely < or > 100 -1,000 IU/ml

Boceprevir Response-Guided Therapy

Treatment-Naive Patients G1



Abbreviations: B, boceprevir; P, peginterferon; R, ribavirin.

* Unclear in Black pts

Summary for Naïve Genotype 1
Expectations for New Therapies

- Higher response rates: genotype 1 SVR
  - 65-75% naïve
  - Response-guided therapy with extended RVR
- But...
  - Resistance will be a new factor
    - Close viral monitoring, viral subtyping
  - Adding a third drug = greater adverse effects
    - Strategies needed to optimize adherence, dose reduction, and side effect management