Clinical Overview

Drug Development Advisory Group
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Ira M. Jacobson, M.D.
Vincent Astor Professor of Medicine
Chief, Division of Gastronterology and Hepatology
Medical Director, Center for the Study of Hepatitis C
Weill Cornell Medical College

The Beginning of a New Era

What We Hope Is Coming In 2011

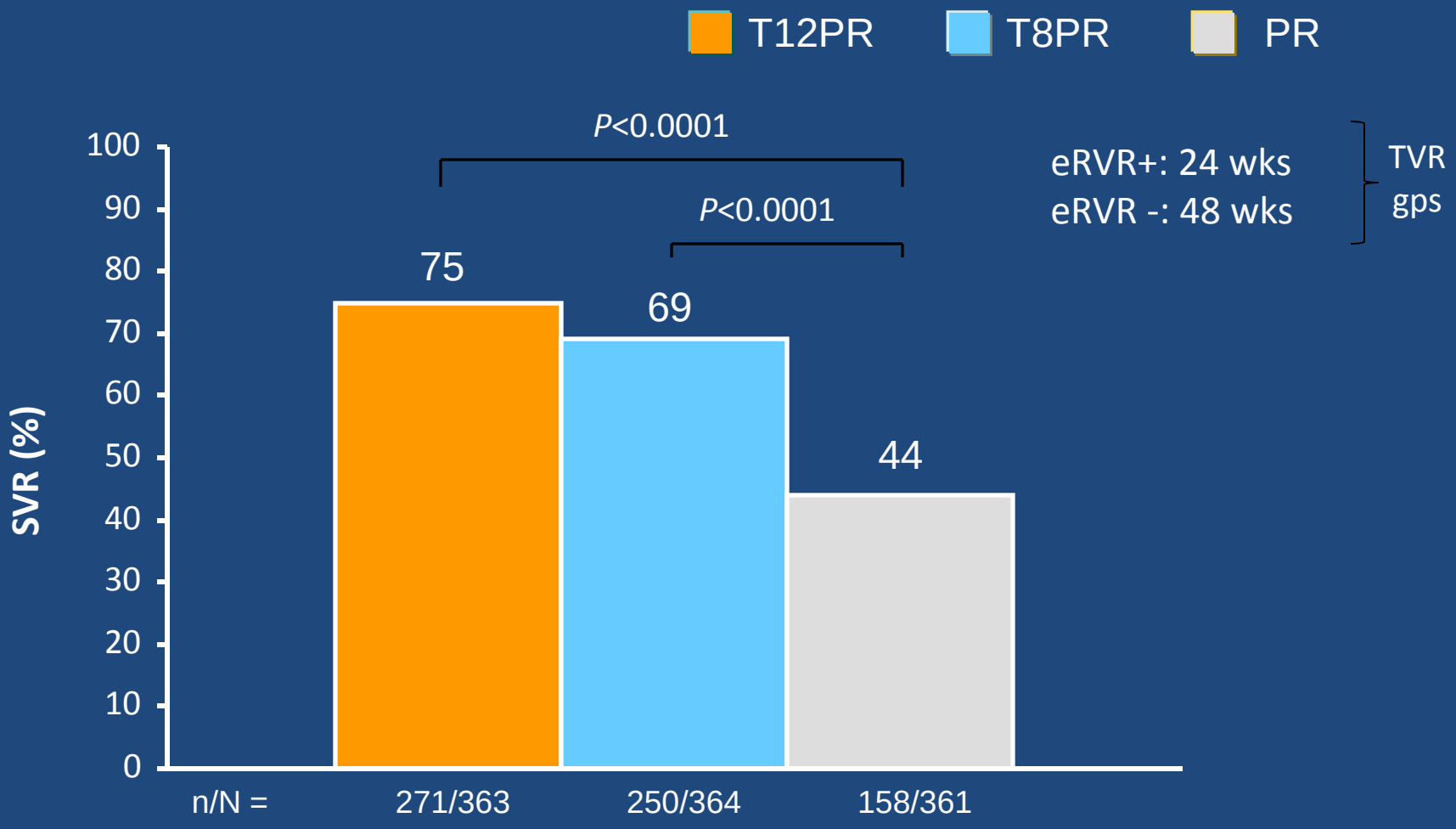
SVR >70% Genotype 1

Response-guided therapy

Increased side effects

Resistance

ADVANCE Trial: Telaprevir + PegIFN alfa-2a/RBV (PR) vs PR Alone: G1 Naive



T=Telaprevir 750 mg q8h; P=Peg IFN alfa-2b 180 ug/wk;RBV=Ribavirin 1000-1200 mg/d

Jacobson IM, et al. *Hepatology.* 2010;52(suppl 1):112A. Abstract 211.

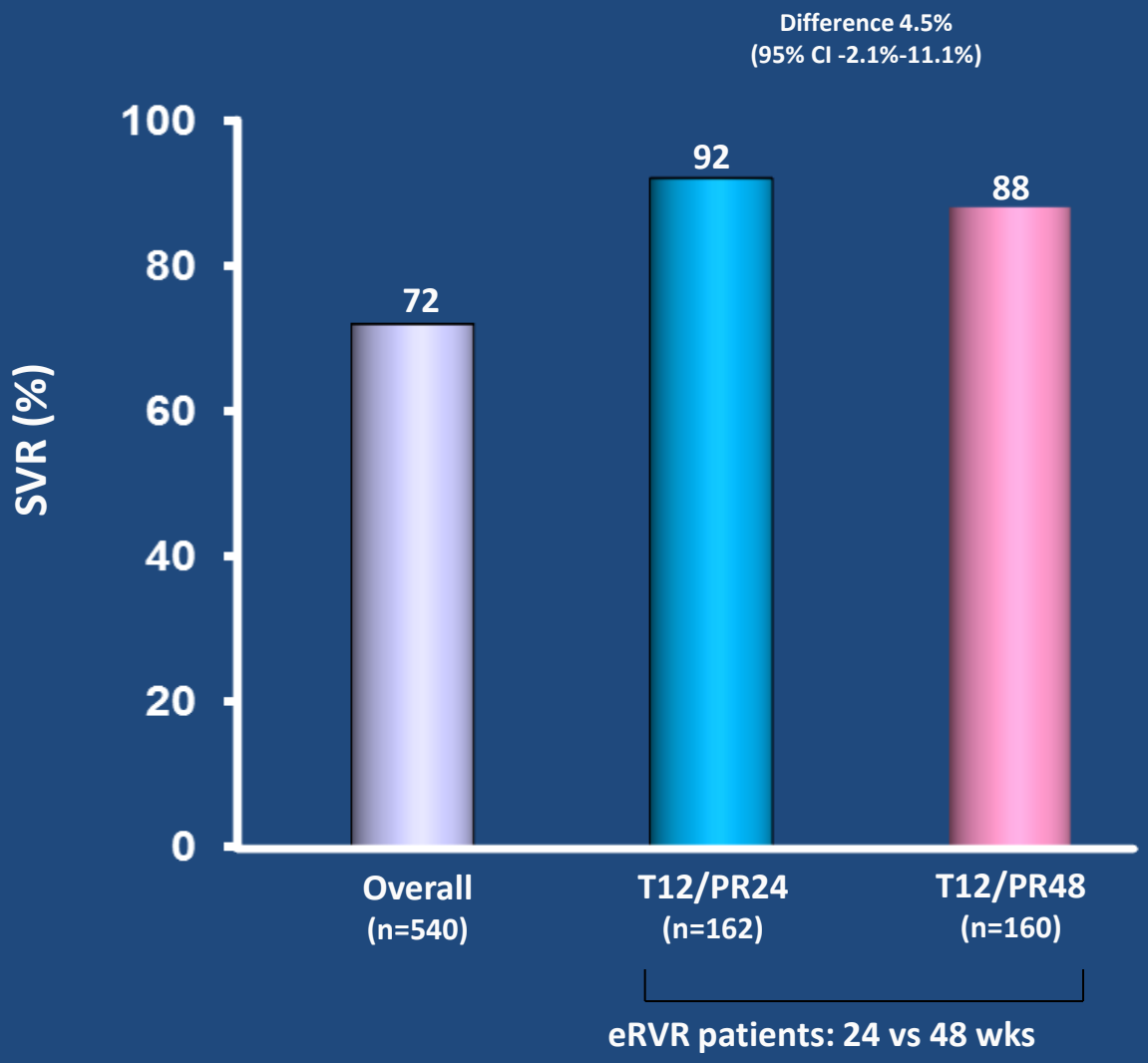
ADVANCE Study: Adverse Events

	T12 (n=363)	T8 (n=364)	PR48 (n=361)
Discontinuation (%)			
Adverse events			
- Overall treatment phase*	10	10	7
- TVR/Pbo only	11	7	4
Adverse events (%)			
Pruritus	50	45	36
Nausea	43	40	31
Rash	37	35	24
Anemia	37	39	19
Diarrhea	28	32	22

*Lower overall d/c rates for AEs than in phase 2 was associated with sequential d/c of meds

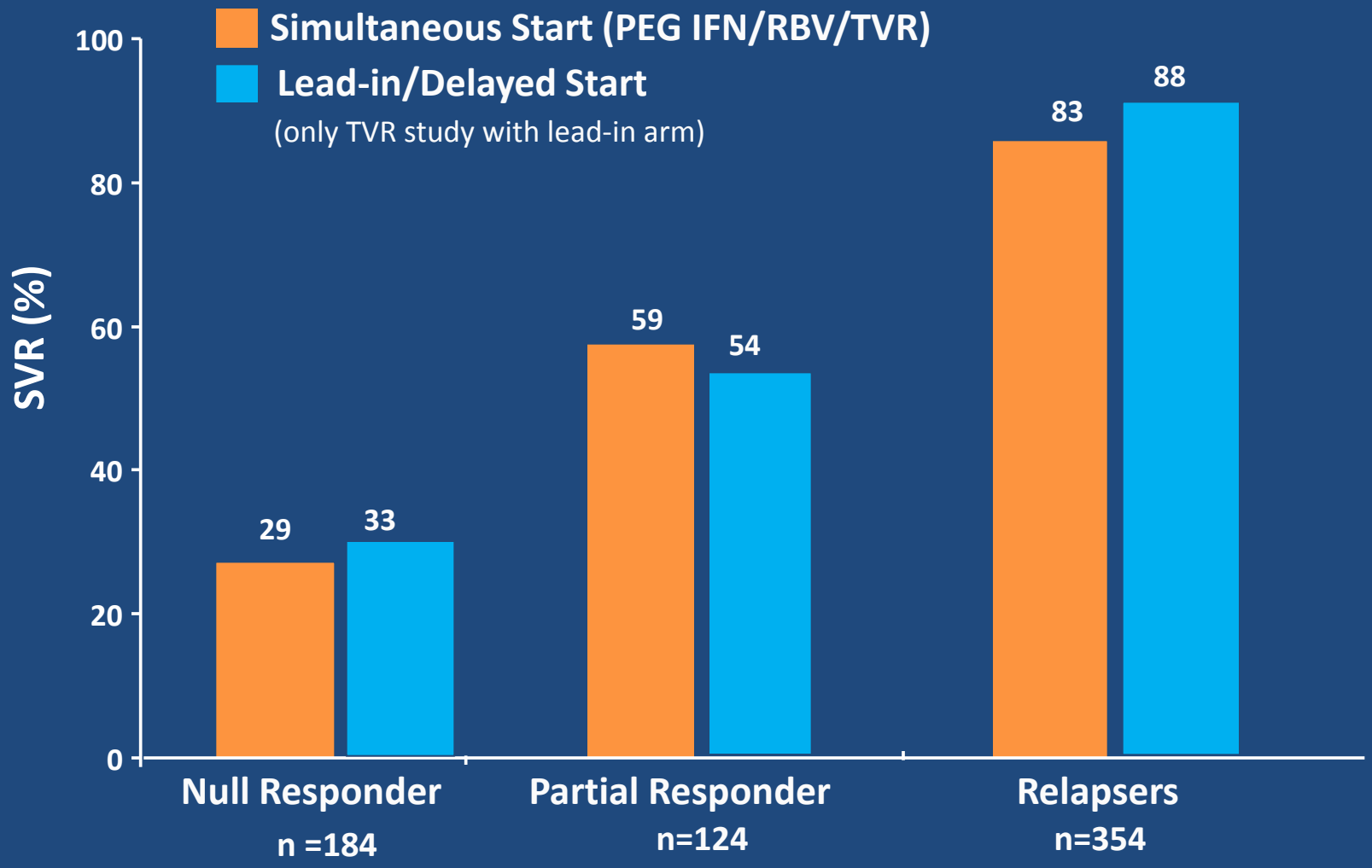
Jacobson IM, et al. *Hepatology.* 2010;52(suppl 1):112A. Abstract 211.

ILLUMINATE Study: T12PR24 vs T12PR48 For Patients With eRVR



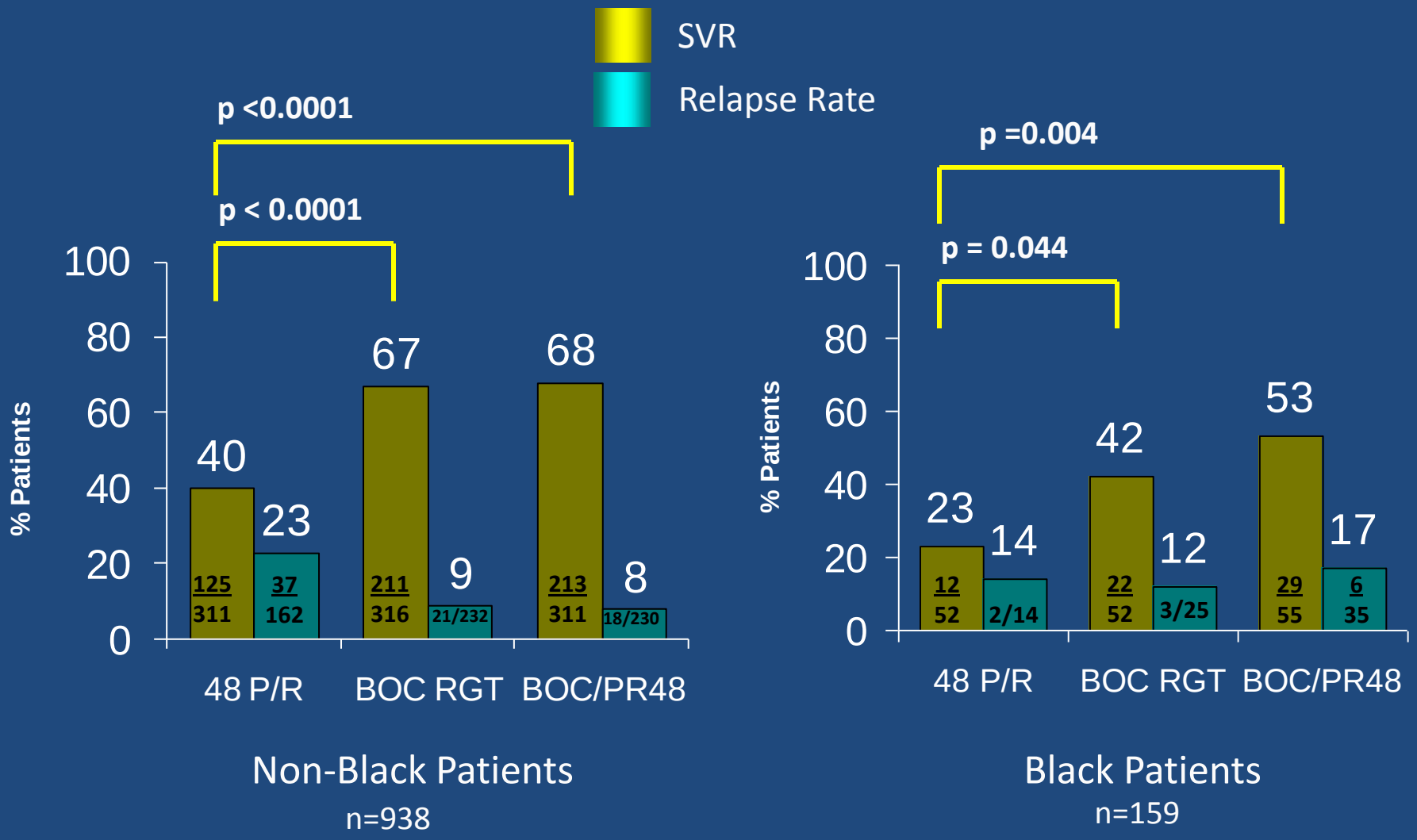
Sherman KE, et al. *Hepatology.* 2010;52(suppl 1):106A. Abstract LB2.

REALIZE Study: T12PR48 For G1 Patients Who Failed PegIFN/RBV



NATAP. Press release. Sept. 7, 2010. Available at: http://www.natap.org/2010/HCV/090710_01.htm. Graphic courtesy of Dr. David R. Nelson.

SPRINT 2: Boceprevir + PegIFN alfa-2b/RBV Response-Guided vs 48 Wks vs PR Alone



B=Boceprevir 800 mg tid;P=PegIFN alfa-2b 1.5/ug/wk;R=Ribavirin 600-1400 mg/d

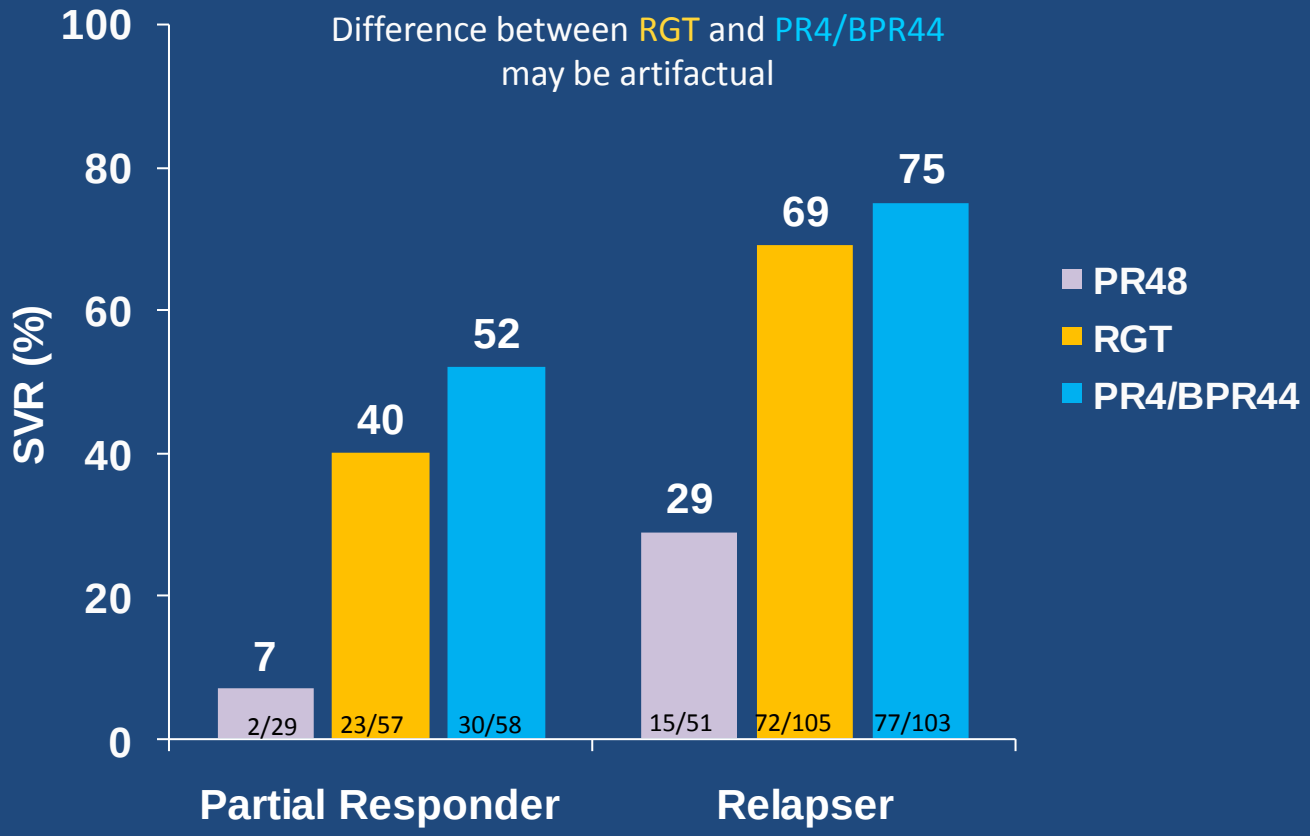
Poordad F, et al. *Hepatology.* 2010;52(suppl 1):107A. Abstract LB4.

SPRINT-2: Adverse Events

	BOC/PR48 (n=366)	BOC RGT (n=368)	PR48 (n=363)
Discontinuation (%)			
Adverse events	16	12	16
Adverse events (%)			
Anemia	49	49	29
Dysgeusia	43	37	18
Anemia (%)			
Discontinuation	2	2	1
Dose reduction	21	20	13
Erythropoietin use	43	43	24

Poordad F, et al. *Hepatology.* 2010;52(suppl 1):107A. Abstract LB4.

RESPOND-2—BOC (RGT or 48 wk) + PR vs PR Alone in Treatment Failure Patients



Abbreviations: B, boceprevir 800 mg TID; P, PEG IFN α-2b 1.5 µg/kg/wk; R, ribavirin 600–1400 mg/d; RGT, response-guided therapy 36 vs 48 wks;
Bacon BR, et al. *Hepatology.* 2010;52:Abstract 216.

Protease Inhibitors: Resistance Considerations

- Resistance emerges quickly with monotherapy
- G1a = ∅1b
- Rates of emergent resistance low in naïve patients, but higher in prior nonresponders
  - Particular implications for prior null responders
- Potential to "blow" class

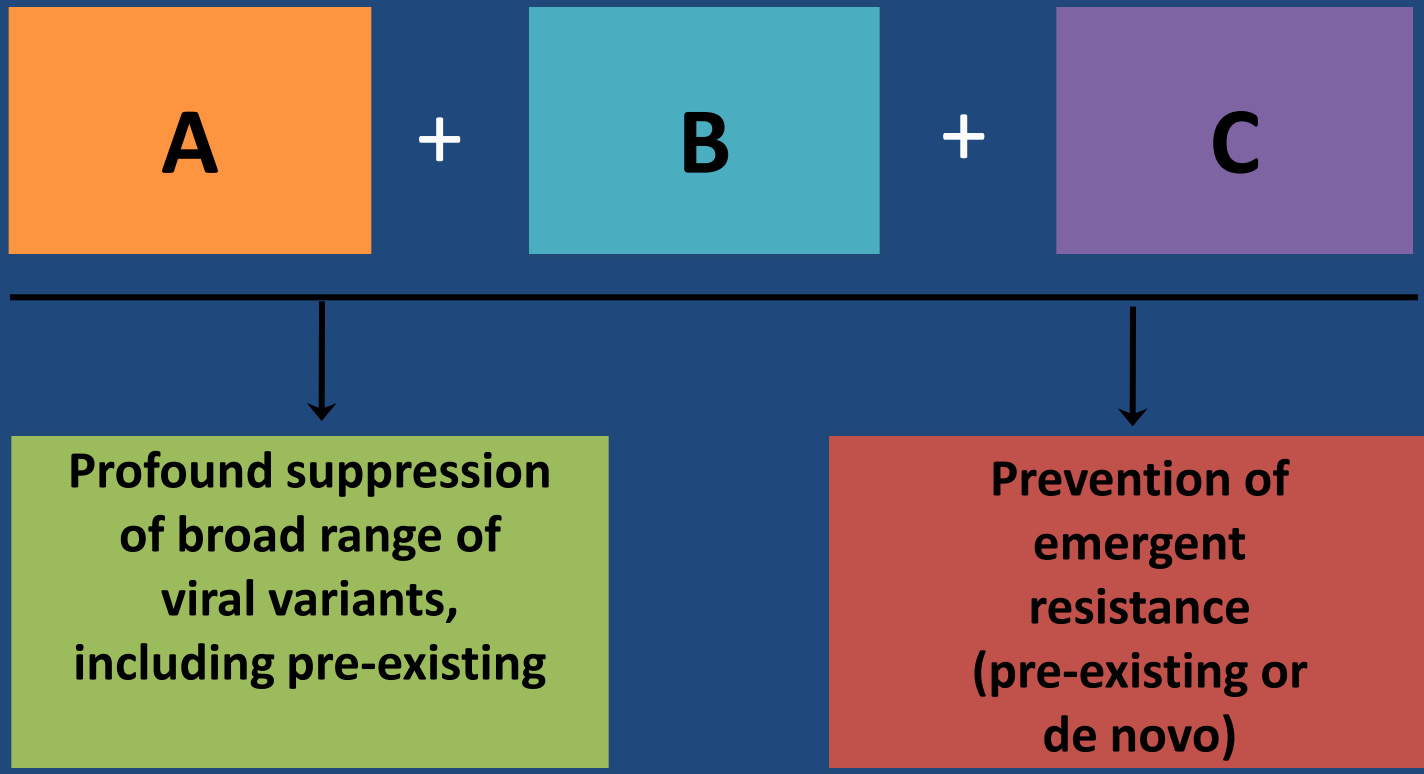
- HCV is not archived
- Resistant variants are less fit than wild-type
  - High level resistant variants are least fit
- Increasing data suggest that resistant variants wane or become undetectable with sufficient passage of time

- *Resistance issues should not impact on status of protease inhibitors as new standard of care*
- *Resistance should be discussed with patients and taken into consideration in selected situations, e.g. null responders with mild fibrosis*

The Three Schools of Thought on the Future of HCV Therapy

Graphic courtesy of Dr. Ira Jacobson.

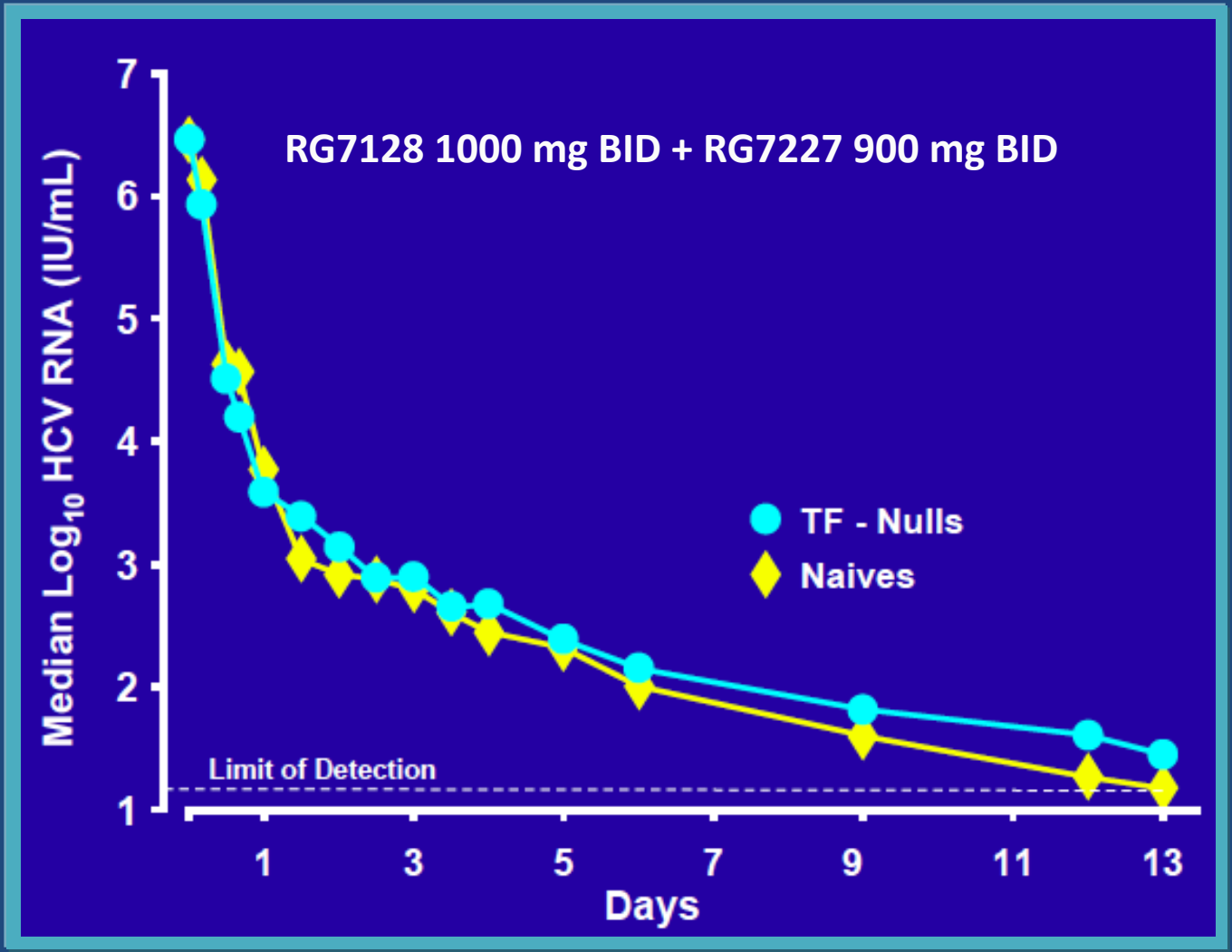
The Goal of IFN-Free Combination Regimens



- Different drugs may contribute variably to each of these goals
- Not all components have to be DAA agents (eg, cyclophilin antagonists)
- Ribavirin needs to be studied as an adjunct

Graphic courtesy of Dr. Ira Jacobson.

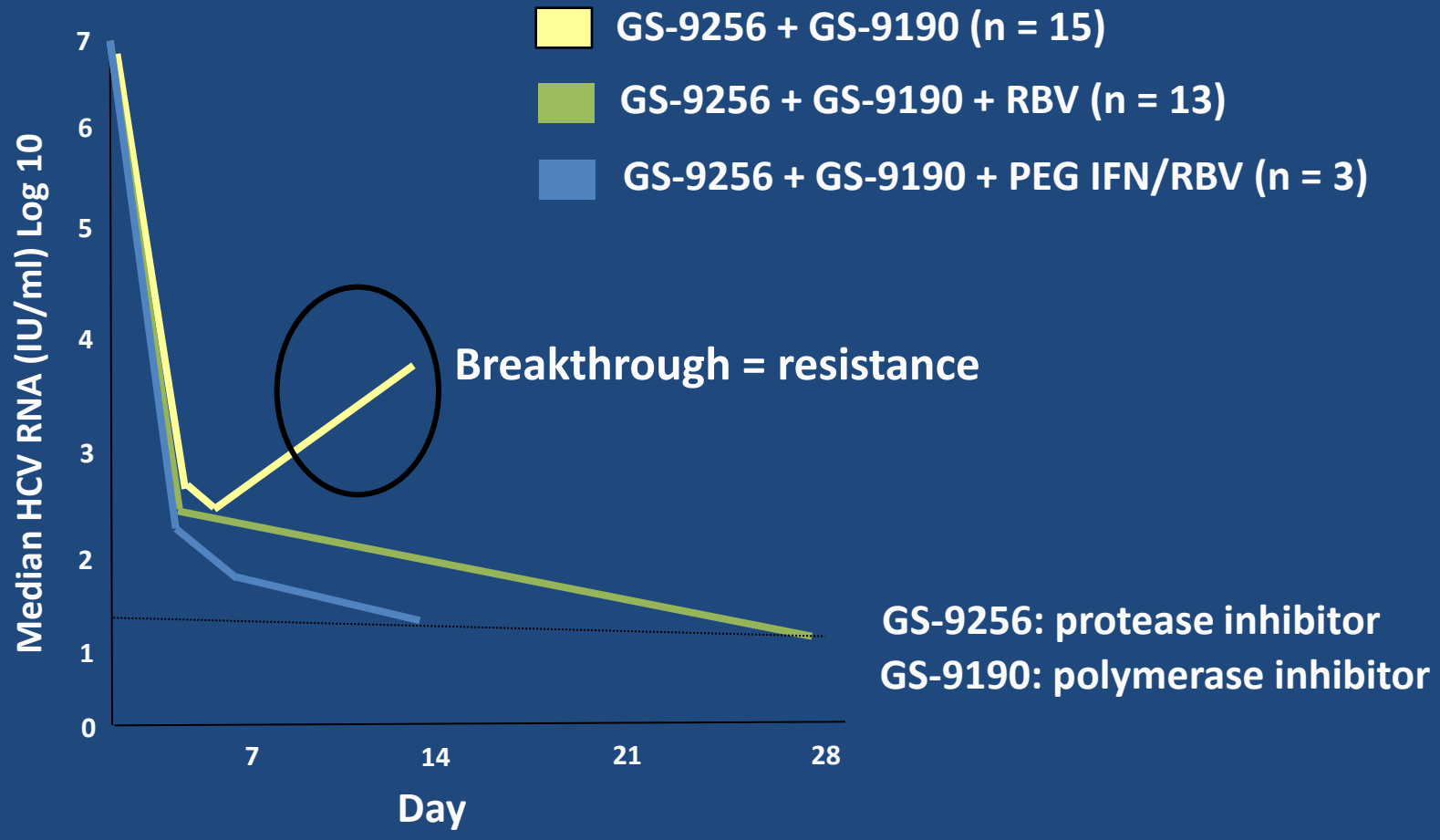
Nucleoside (RG7128) + Protease Inhibitor(RG7227) G1 Interferon-Naive and Null Responders



Gane EJ, et al. Lancet 2010;376:1467-75

Interferon-Free Regimen

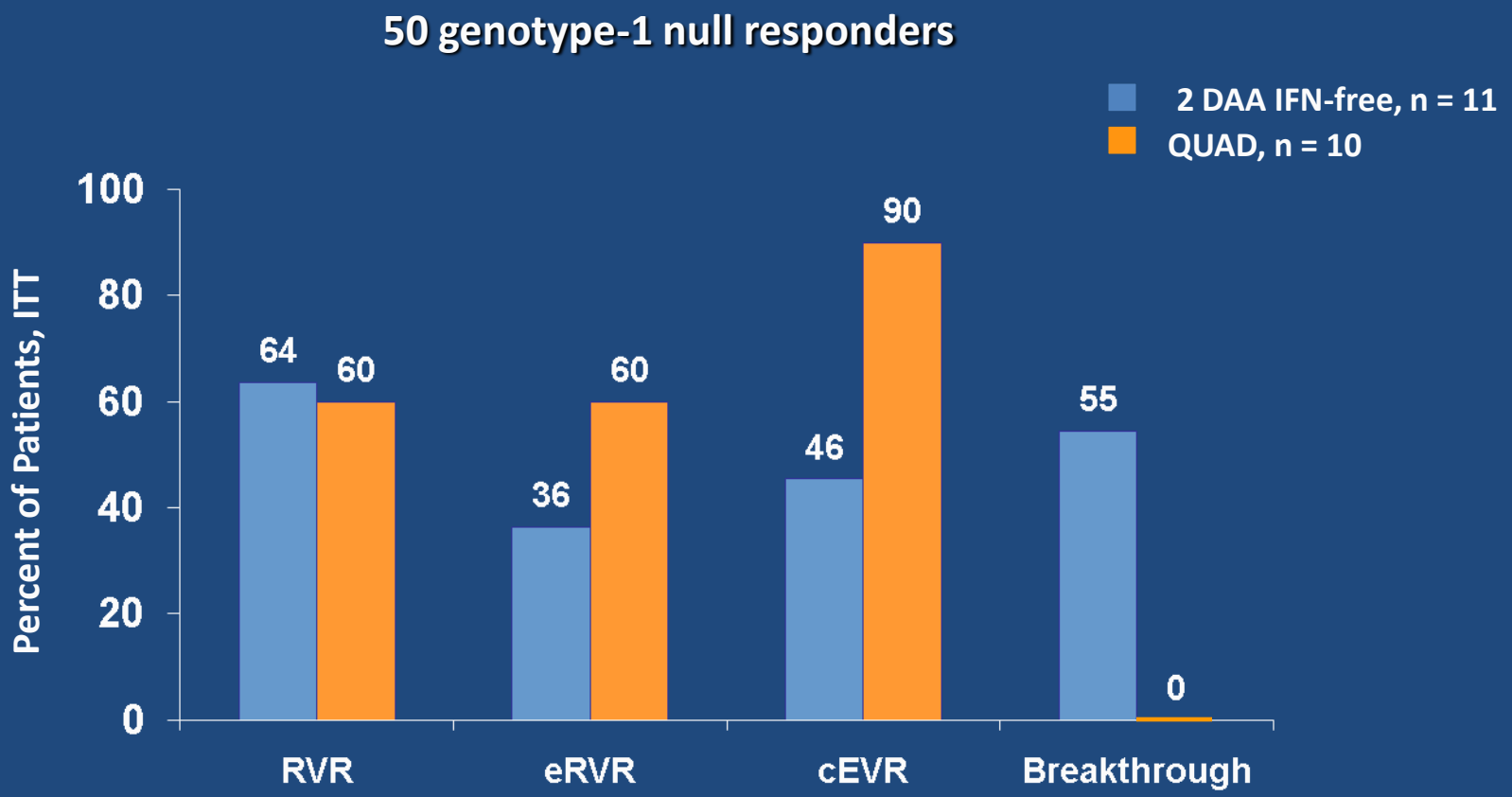
Protease + Polymerase + Ribavirin



Zeuzem S, et al. *Hepatology.* 2010;52:Abstract LB-1.

Protease Inhibitor (BMS-650032) Plus NS5AI Inhibitor (BMS-790052) ± PR

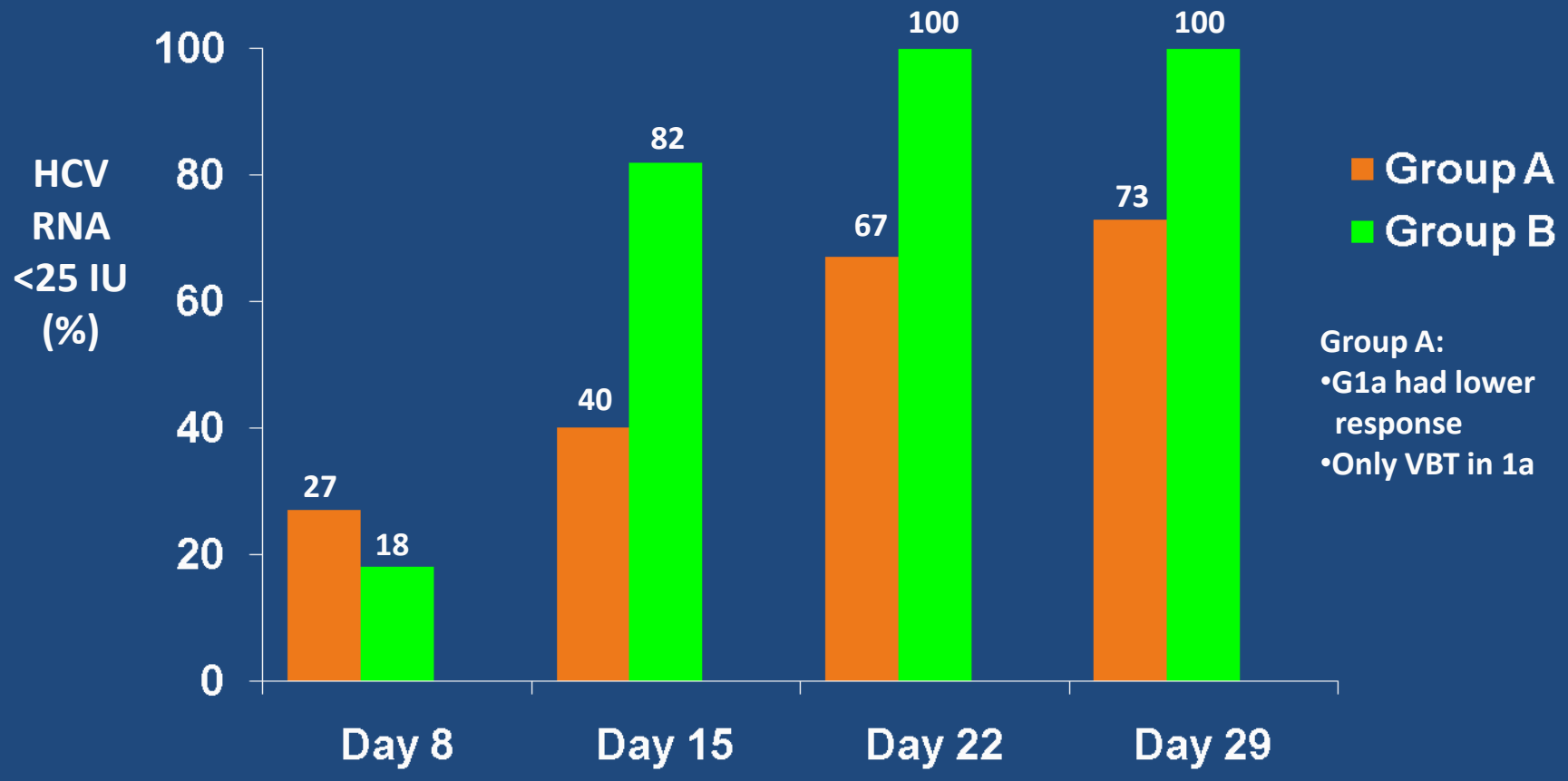
Interim Analysis



Lok AS, et al. *Hepatology.* 2010;52:Abstract LB-8. Graphic courtesy of Dr. David R. Nelson.

Protease Inhibitor (BI201335) + Polymerase Inhibitor (BI207127) + Ribavirin

Group A: BI201335 120 mg qd+BI207127 400 mg tid+RBV 1000-1200 mg/d
Group B: BI201335 120 mg qd+BI207127 600 mg tid+RBV 1000-1200 mg/d



Group A:
- **G1a had lower response**
- **Only VBT in 1a**

Zeuzem S et al, Hepatology 2010;52(Suppl):LB-7

Recent DAA Studies

- At least one component of a dual regimen must have high barrier to resistance
- Ribivarin as adjunctive 3rd drug appears potentially valuable
- Three drug regimens might still work without a high genetic barrier drug
- Other factors being equal (potency, safety), a high genetic barrier component of a DAA regimen will always be attractive

Resistance Isn’t Good, But Just How Bad Is It?

EXTEND: Interim Analysis of 56 Patients Who Failed SVR in Phase 2 Telaprevir Studies

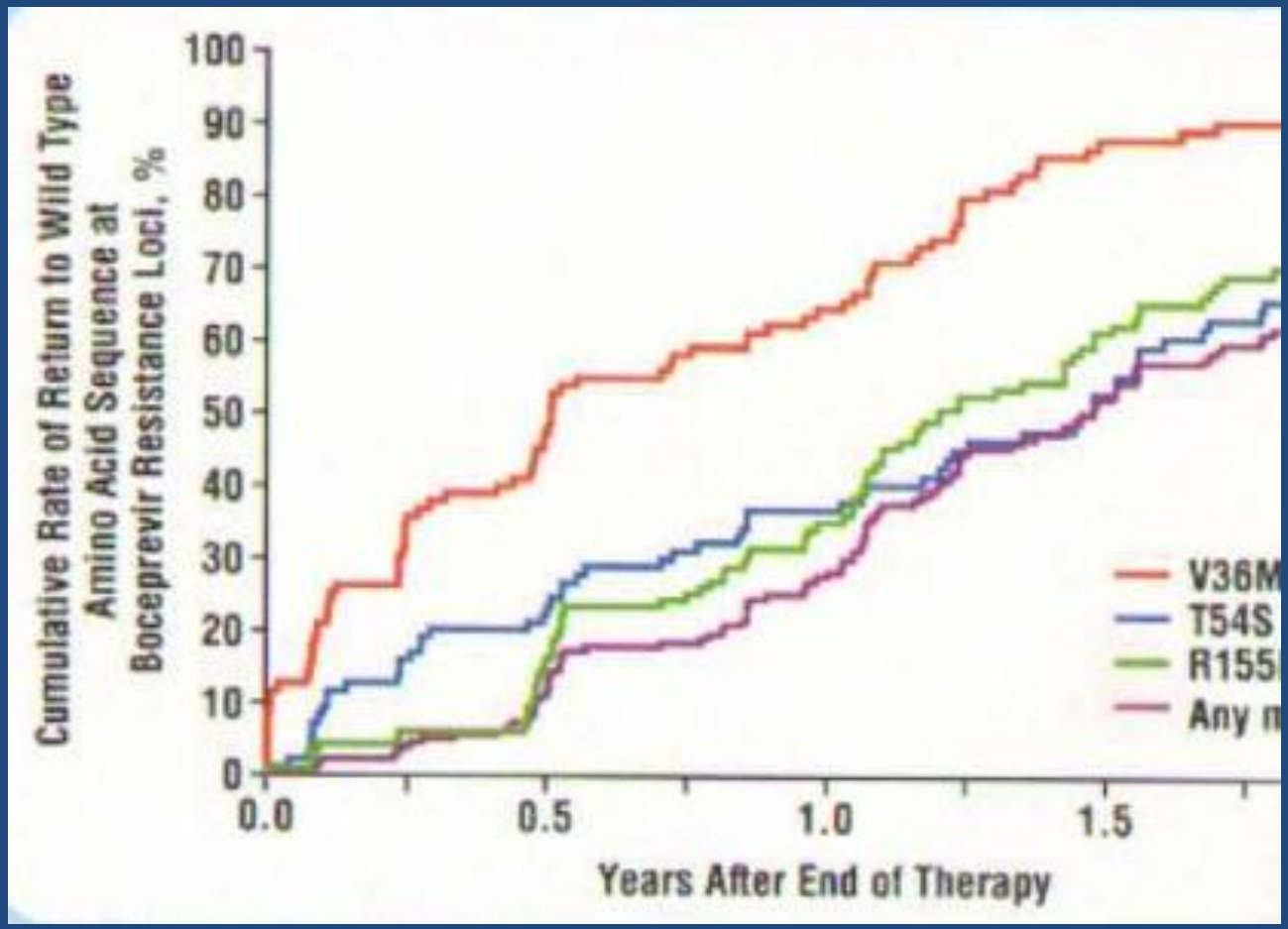
- 99% of patients who achieved SVR with telaprevir-based regimen in Phase 2 studies had a durable response
  - Median time to follow-up: 22 months after SVR

- In patients who did not achieve SVR during telaprevir treatment, resistant variants were replaced by WT virus:
  - 89% of subjects no longer had detectable resistant variants (median follow-up time: 25 months from end of prior study)

  - Clonal sequencing performed in representative samples indicated that HCV populations returned to pre-treatment state

Zeuzem S et al, AASLD 2010

Rate of Return to Wild Type Virus From SPRINT-1 (Boceprevir)



Majority of patients with pre-existent mutations had SVR*

Vierling J et al, EASL 2010; *Vierling J et al, AASLD 2010

The Future May Be Coming Faster Than We Thought

- Combinations of antivirals are being studied at a pace unanticipated until recently
- We must not hold this out to patients who are good treatment candidates as a near term possibility
- We may soon have proof of concept that SVR can be attained with antiviral combinations – a “sea change” would occur
- Resistance may not have the long term ramifications that it does with other viruses
  - We should balance legitimate concerns about resistance with the need to help the enormous numbers of patients who cannot take interferon