Tratamiento de la Hepatitis C

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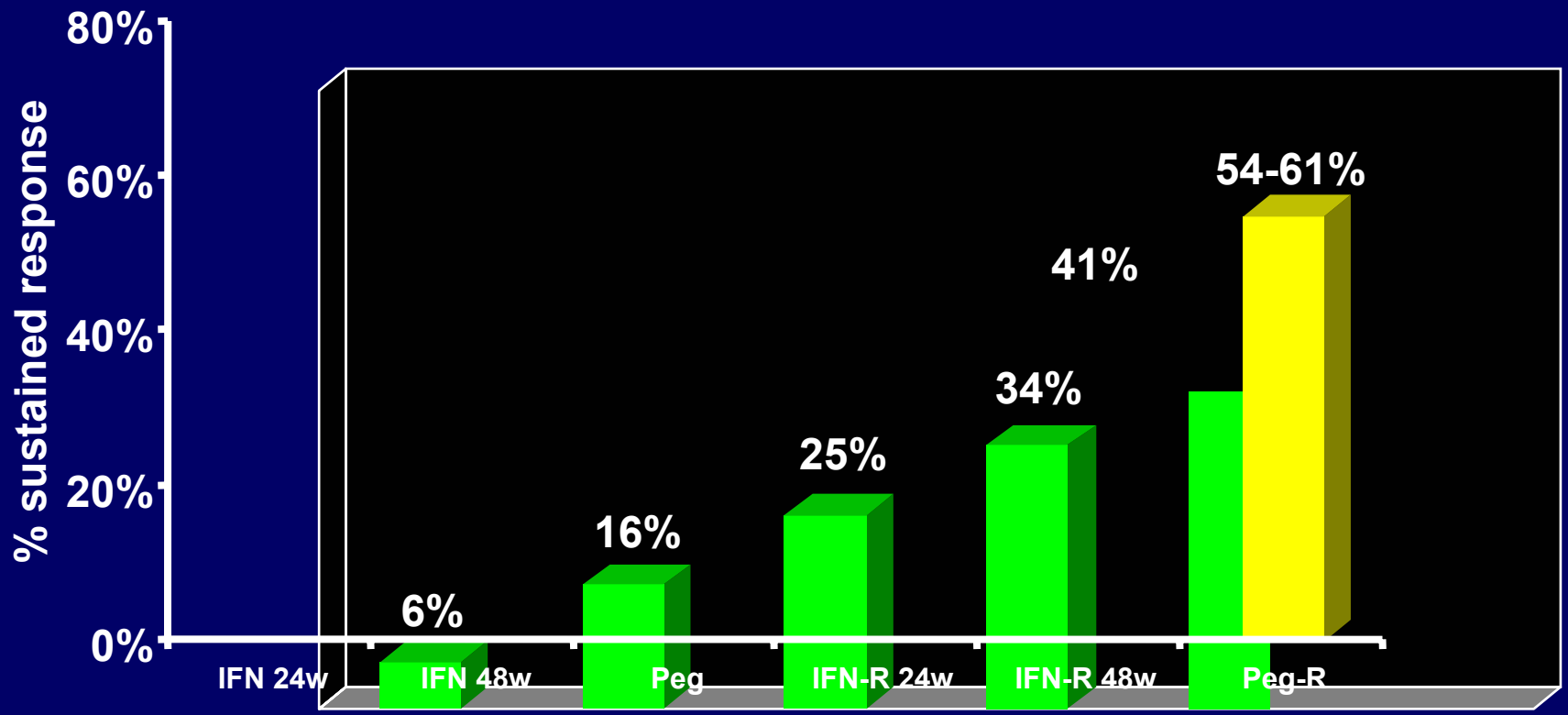
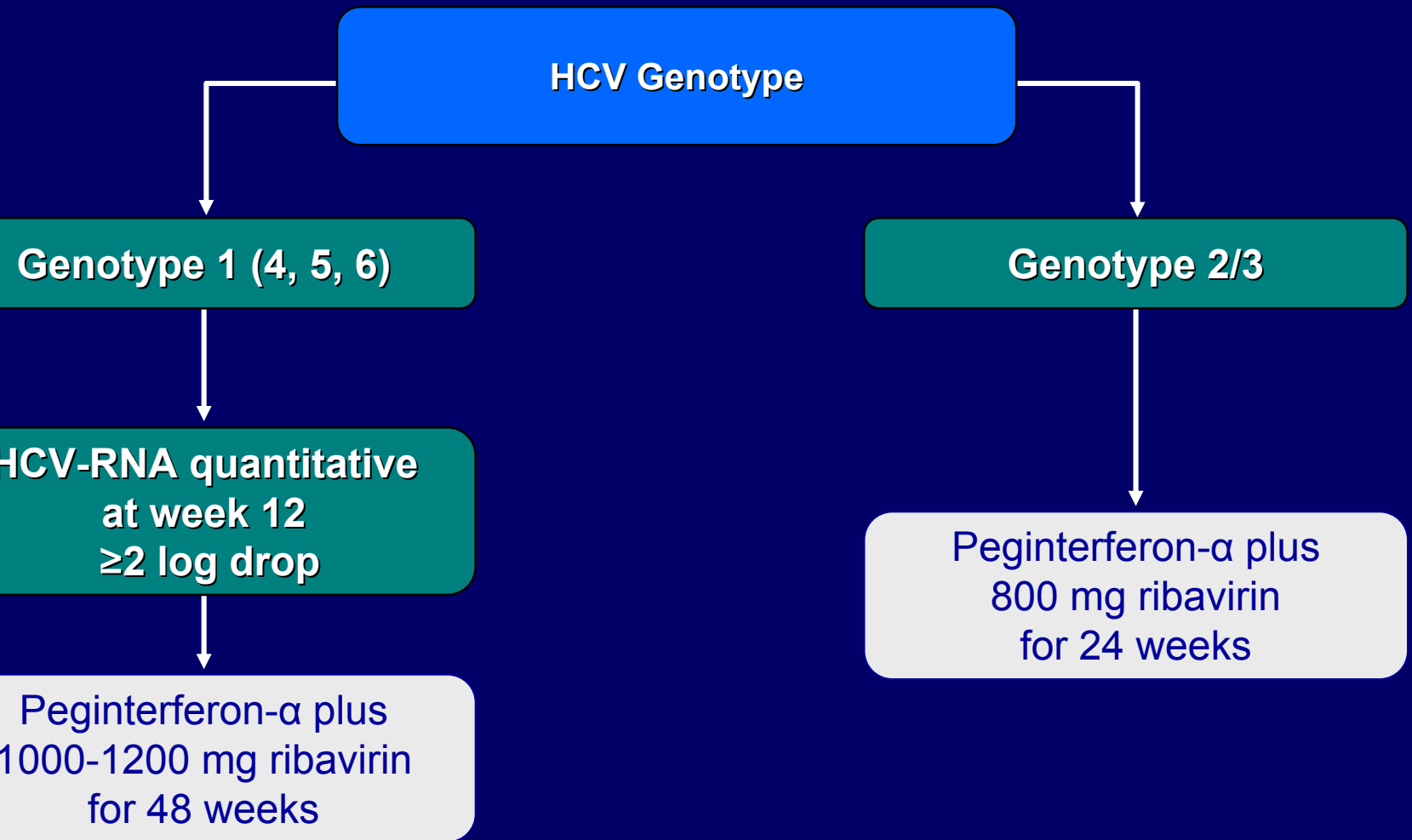
urrent HCV Therapy



Standard de Tratamiento: Peginterferon α + ribavirina



actors Related to Therapy Response

Virus

- Genotype
- Viral load

Treatment

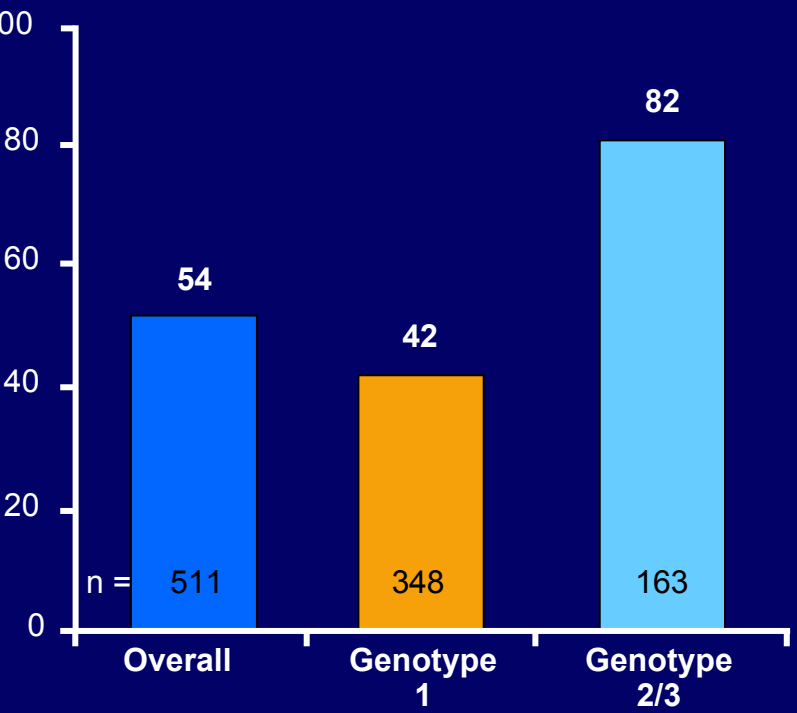
- Adherence
- Early Virologic Response
- Ribavirin Dosage
- Interfering agents (e.g., alcohol)

Patient

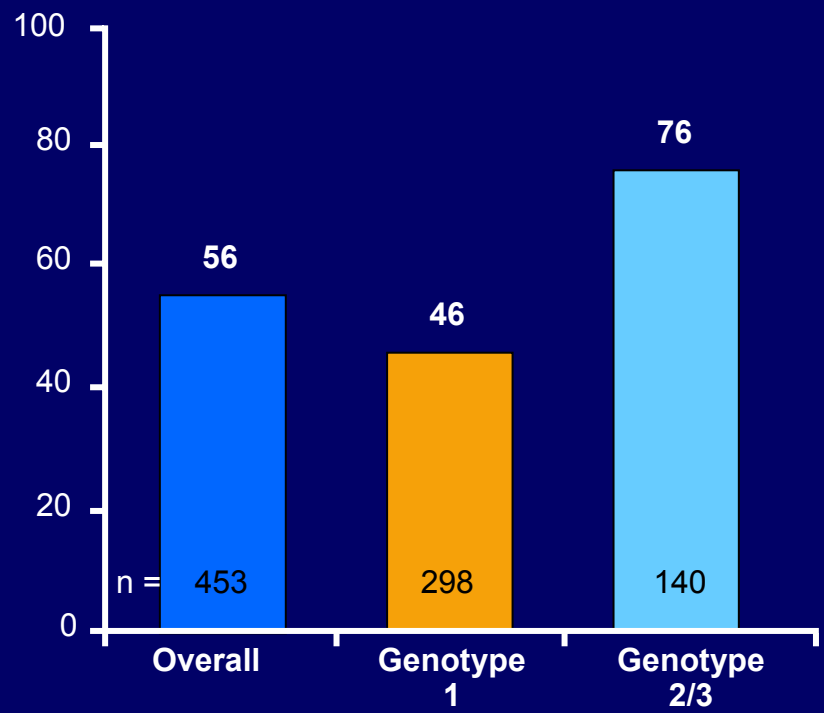
- Age
- Race
- Weight
- Cirrhosis
- Hepatic steatosis
- HIV co-infection
- Pre-treatment expression of IFN-response genes
- IL28b

pact of Genotype on SVR Rates

PegIFN alfa-2b 1.5 µg/kg/wk +
RBV 800 mg/day for 48 wks

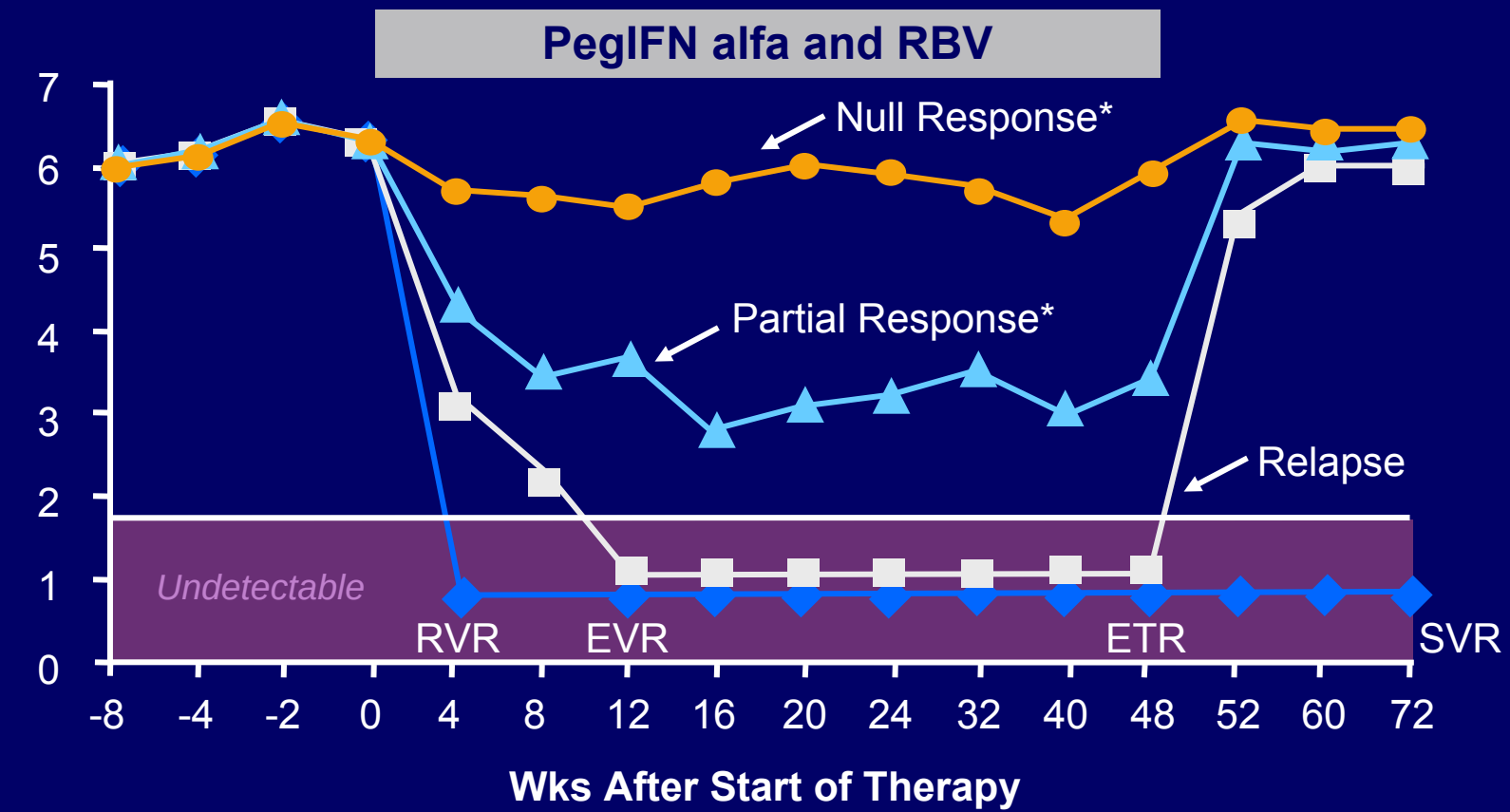


- **PegIFN alfa-2a 180 µg/wk + weight-based RBV (1000 or 1200 mg/d) for 48 wks**



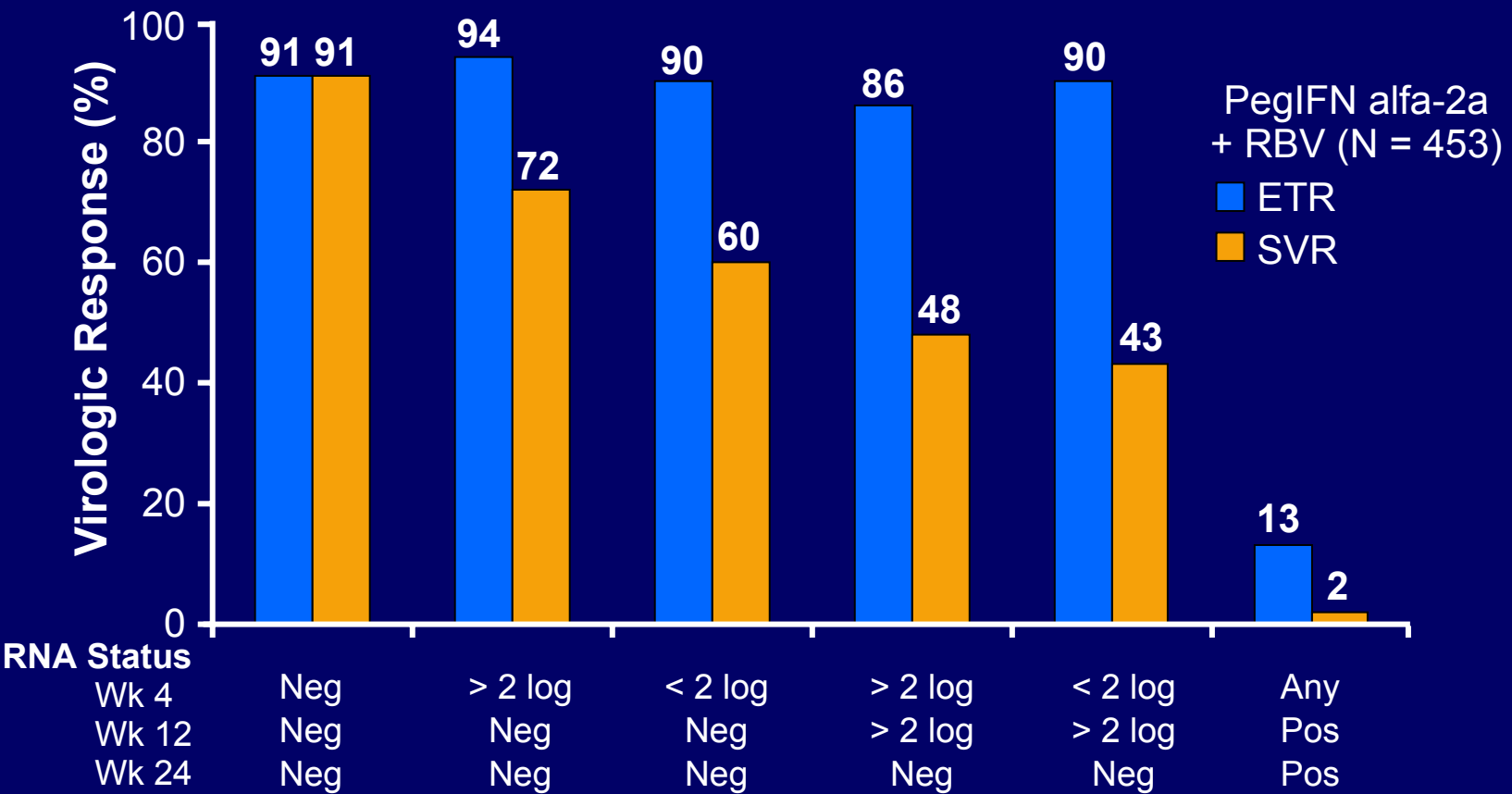
M, et al. Lancet. 2001;358:958-965. Fried MW, et al. N Engl J Med. 2002;347:975-982.

tterns of Virologic Response



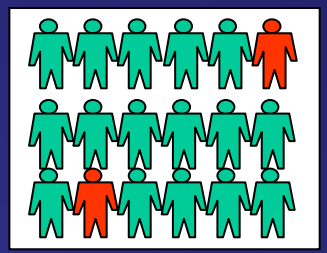
ubset of Nonresponse

al Kinetics and Outcome Importance of Rapid ologic Response

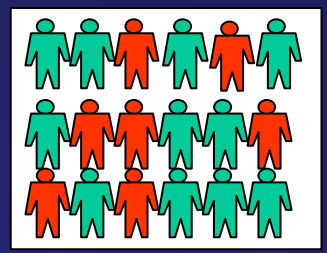


nted from Journal of Hepatology, 43, Ferenci P, et al, Predicting sustained virological responses in chronic hepatitis C
ts treated with peginterferon alfa-2a (40 KD)/ribavirin, 425-433, 2005, with permission from Elsevier.
www.sciencedirect.com/science/journal/01688278

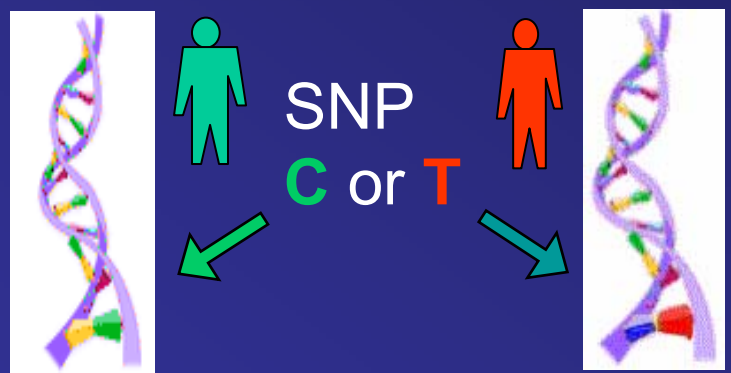
hat are Genome wide association ans (GWAS)?



Responders

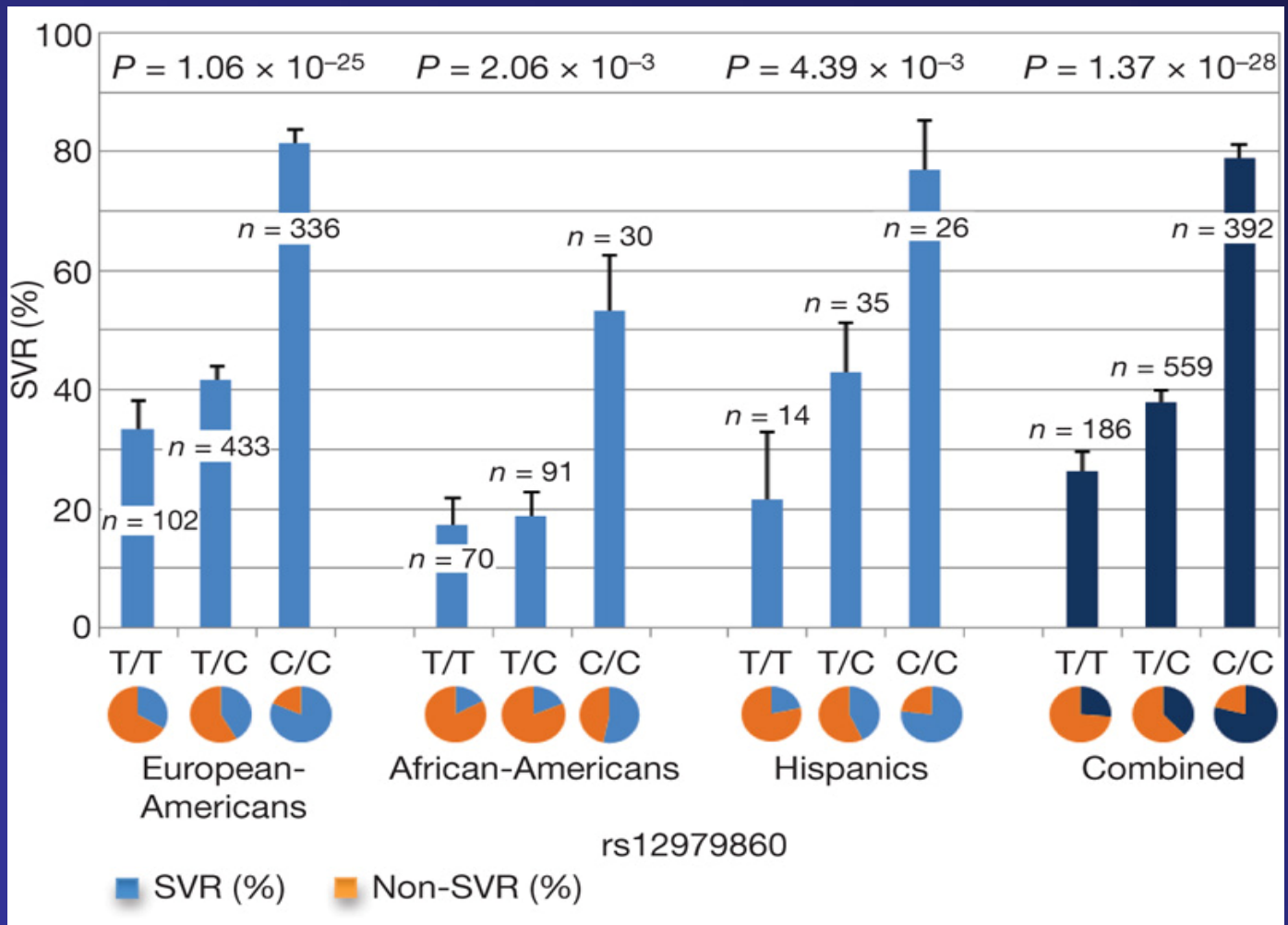


Non-responders



Pharmacogenetic Analysis of the rs12979860 C allele

VR by genotypes of rs12979860



son et al, AASLD 2009, oral (LB5); Nature Sept. 2009; 461: 399-401

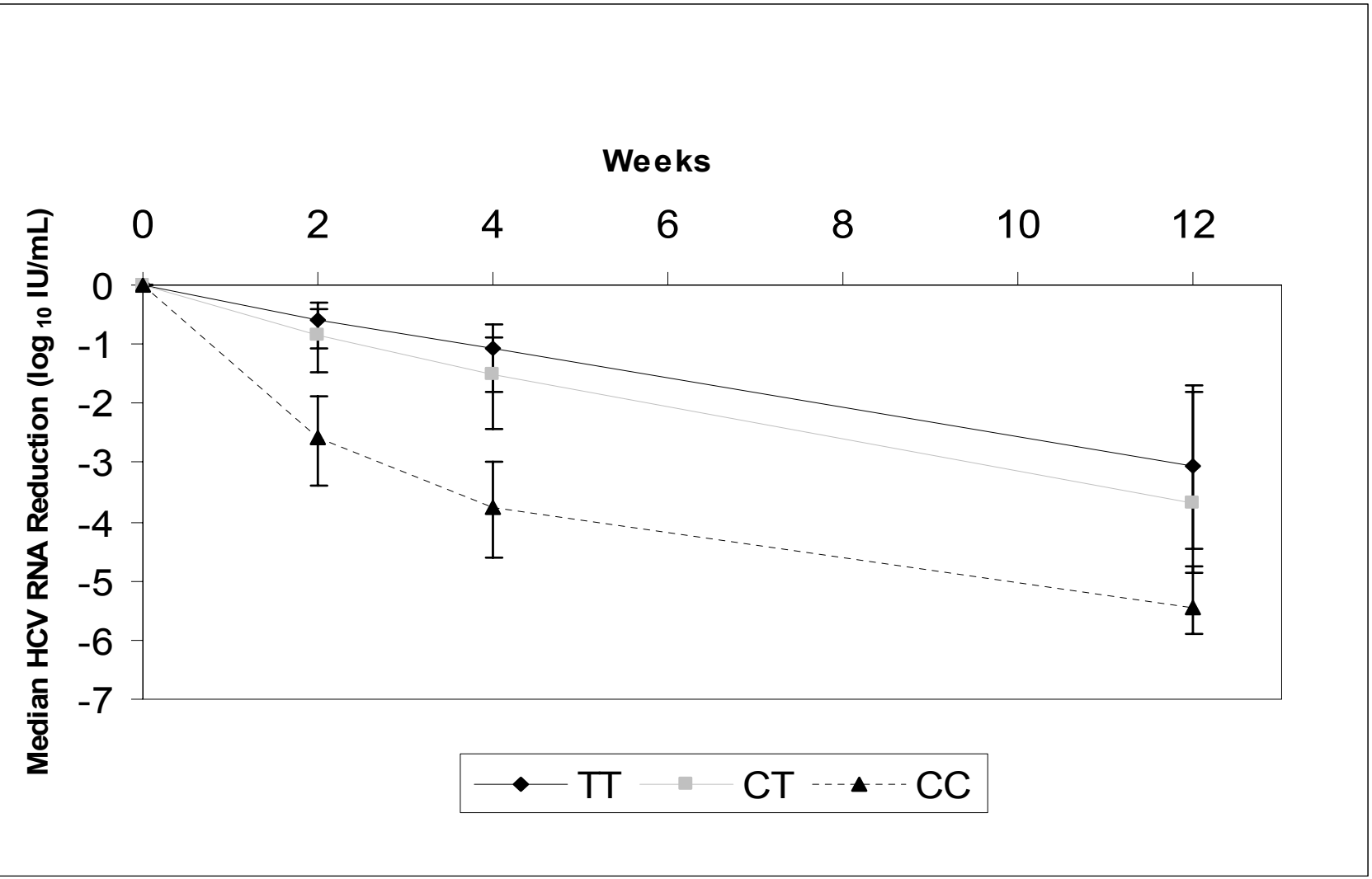
Multivariate Analysis of Baseline Predictors of SVR (Genotype 1 HCV)

ITT analysis of patients from IDEAL study who consented to genetic testing, regardless of adherence level

edictor	Adjusted Odds Ratio (95% CI)	*P* Value
2979860 CC	**5.2 (4.1-6.7)**	**< .0001**
V RNA level ≤ 600,000 IU/mL	3.1 (2.3-4.1)	< .0001
ite vs black	2.8 (2.0-4.0)	< .0001
panic vs black	2.1 (1.3-3.6)	.0041
TAVIR F0-F2	2.7 (1.8-4.0)	< .0001
sting blood sugar < 5.6 mmol/L	1.7 (1.3-2.2)	< .0001

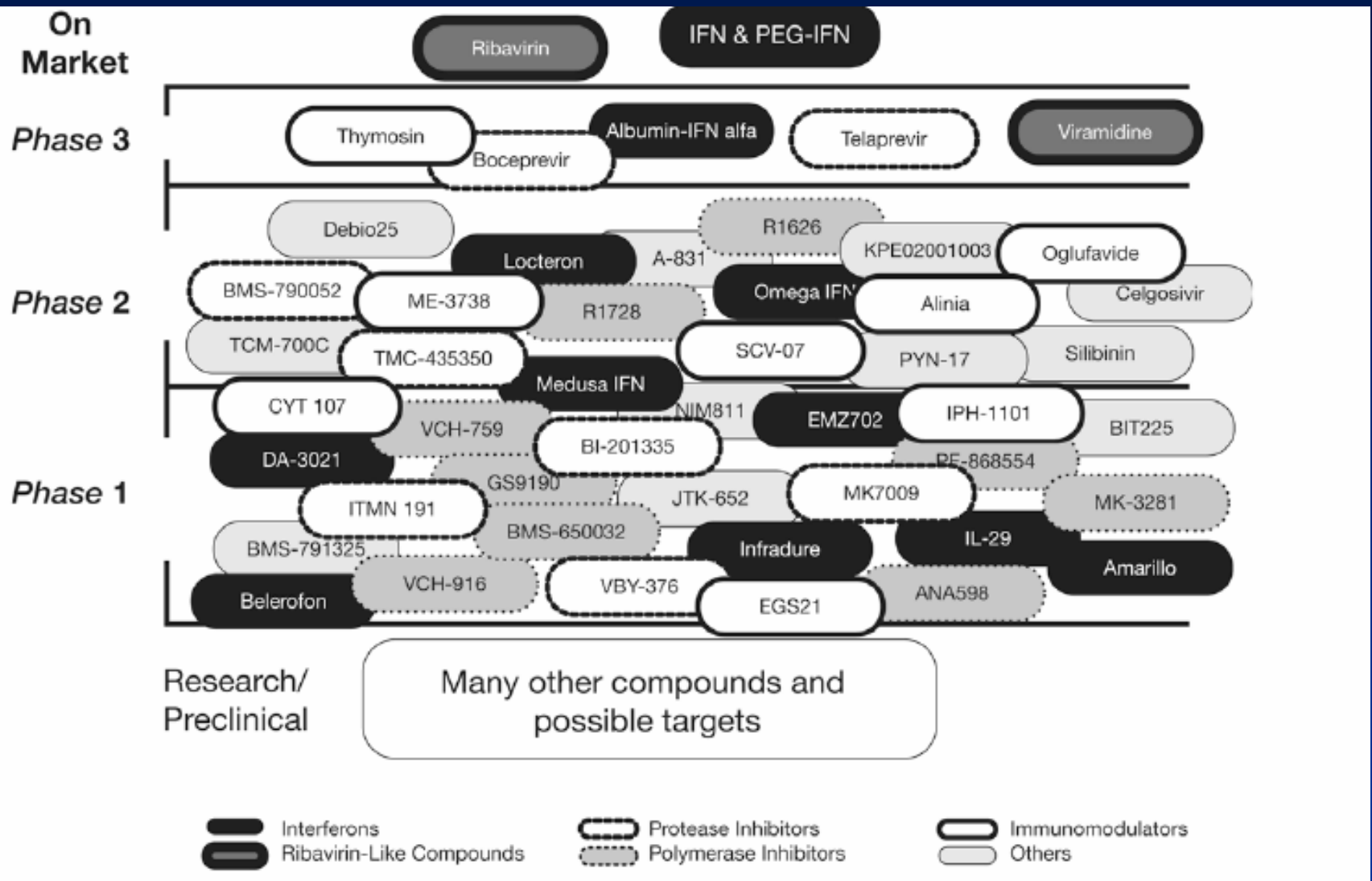
mpson AJ, et al. Gastroenterology. 2010;139:120-129.

HCV RNA decline in relation to IL28b in Genotype 1 patients under treament



pson A et al. Gastroenterology 2010

New Drugs for Hepatitis C

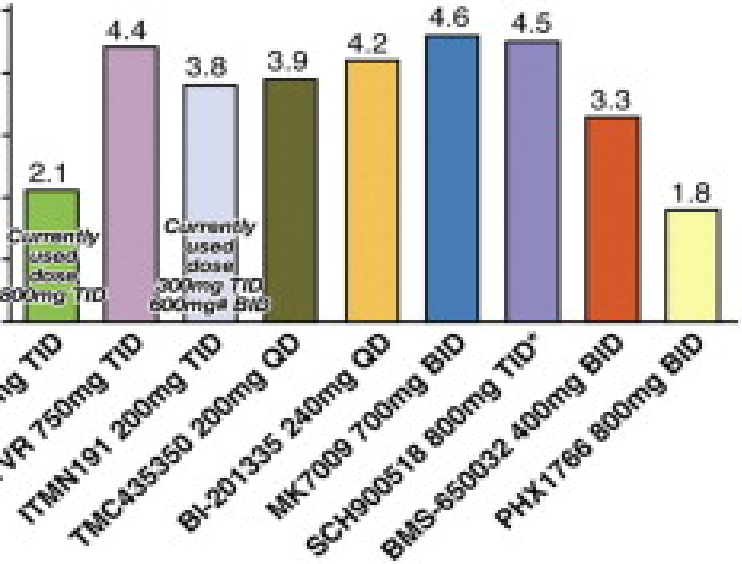


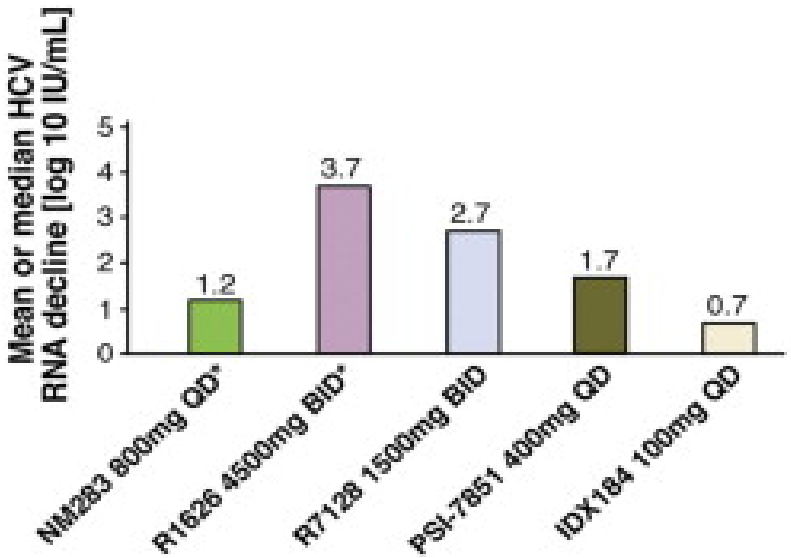
Thompson A et al J of Hepatol 2009

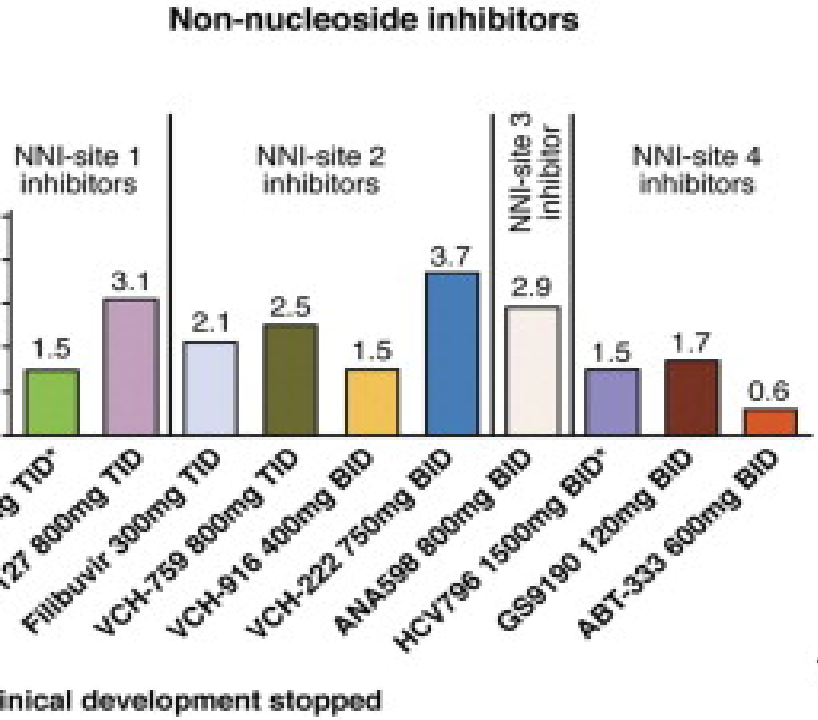
Types of drugs

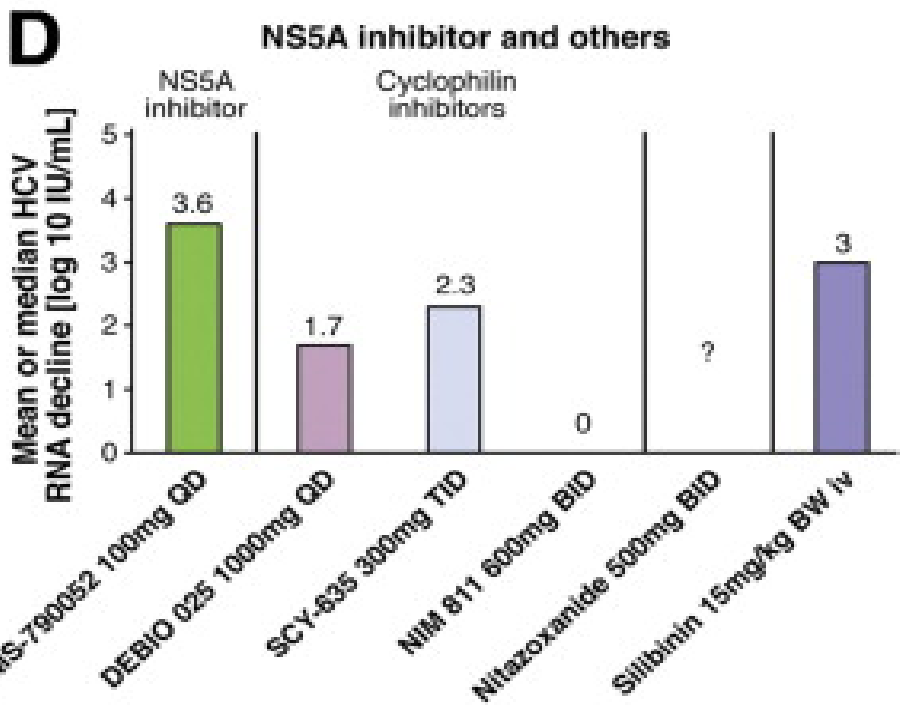
Type of drugs	Genetic Barrier/ AV Efficacy	*Other*
Protease Inhibitor	Low/ High	Only Gen 1
lymerase Inhibitor Nucleoside Analog	High / Low	Few in develop All genotypes
lymerase Inhibitor Non Nucleo	Low/ Medium	Genotype 1
Ciclofilin Inhibitor	No/ Low	

Charlton et al AASLD 2010.



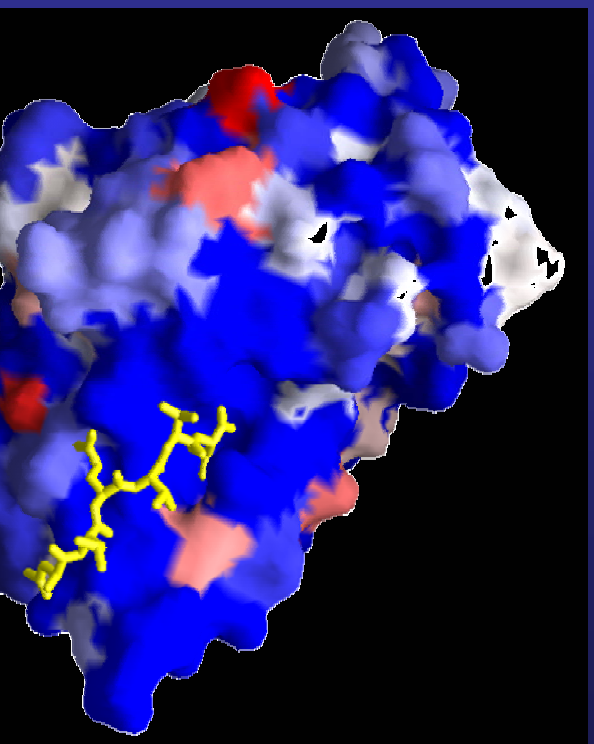






inical development stopped

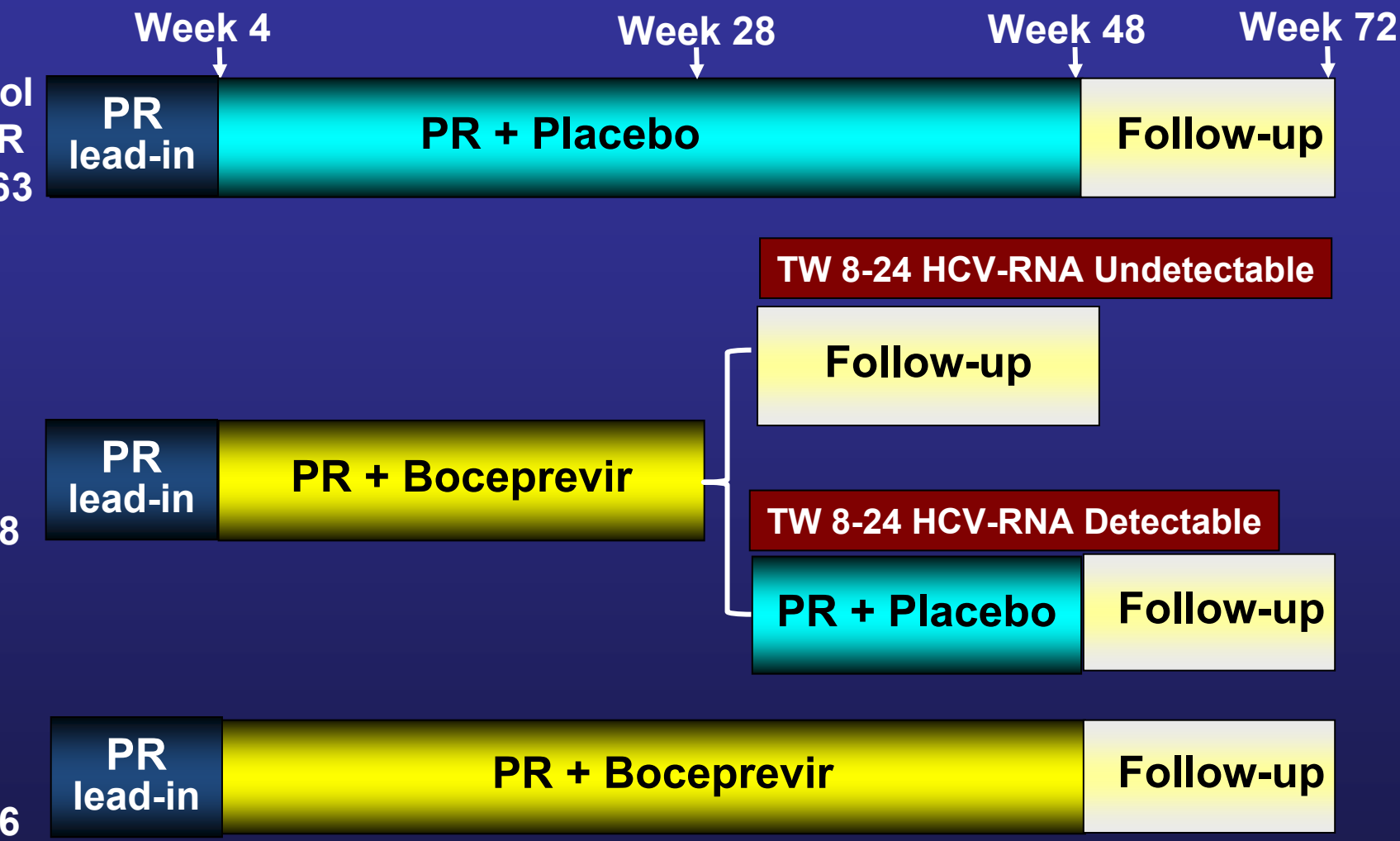
Boceprevir (BOC) is a linear peptidomimetic ketoamide serine NS3 protease inhibitor



Effective against Genotype 1

Demonstrated activity in treatment naïve and experienced populations in phase 2 clinical trials

SPRINT-2: Study Design



feron (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight based
f 600-1400 mg/day in a divided daily dose

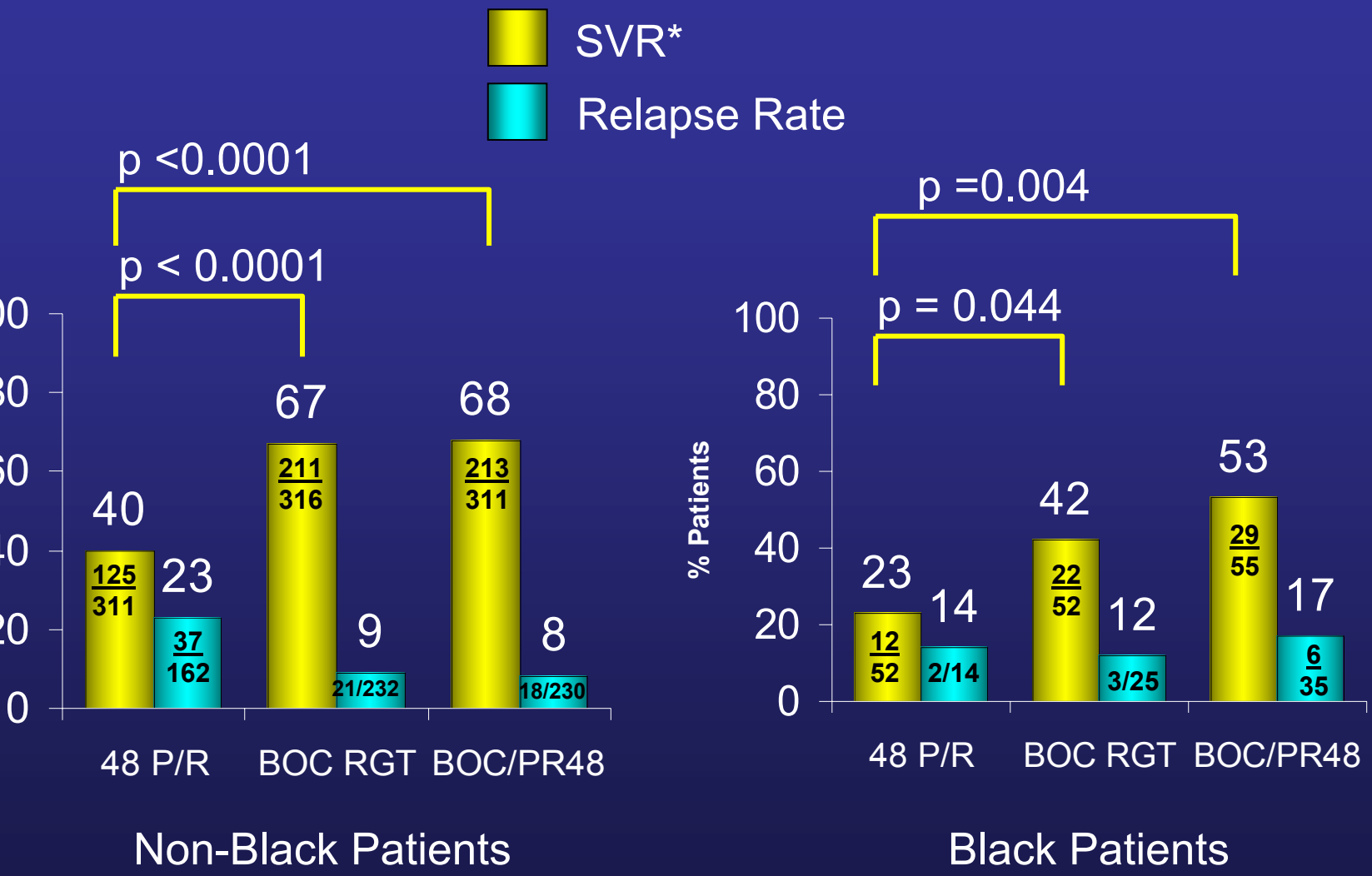
vir dose of 800 mg thrice daily

Baseline Characteristics

	Cohort 1 (Non-black)			Cohort 2 (Black)		
	Arm 1: 48 P/R N = 311	Arm 2: BOC RGT N = 316	Arm 3: BOC/ PR48 N = 311	Arm 1: 48 P/R N = 52	Arm 2: BOC RGT N = 52	Arm 3: BOC/ PR48 N = 55
n age (years)	48	49	49	51	52	51
e (%)	55	63	60	67	56	60
ion (%)						
orth America	65	72	70	98	98	95
urope	32	25	27	2	2	5
– mean (SD)	27 (5)	28 (5)	27 (5)	28 (4)	29 (5)	31 (6)
/ subtype (%)*						
a	60	62	63	79	75	73
b	36	35	33	17	25	24
/ RNA level						
0,000 IU/mL (%)	92	91	93	100	94	96
TAVIR F3/F4 (%)	7	8	12	2	15	11

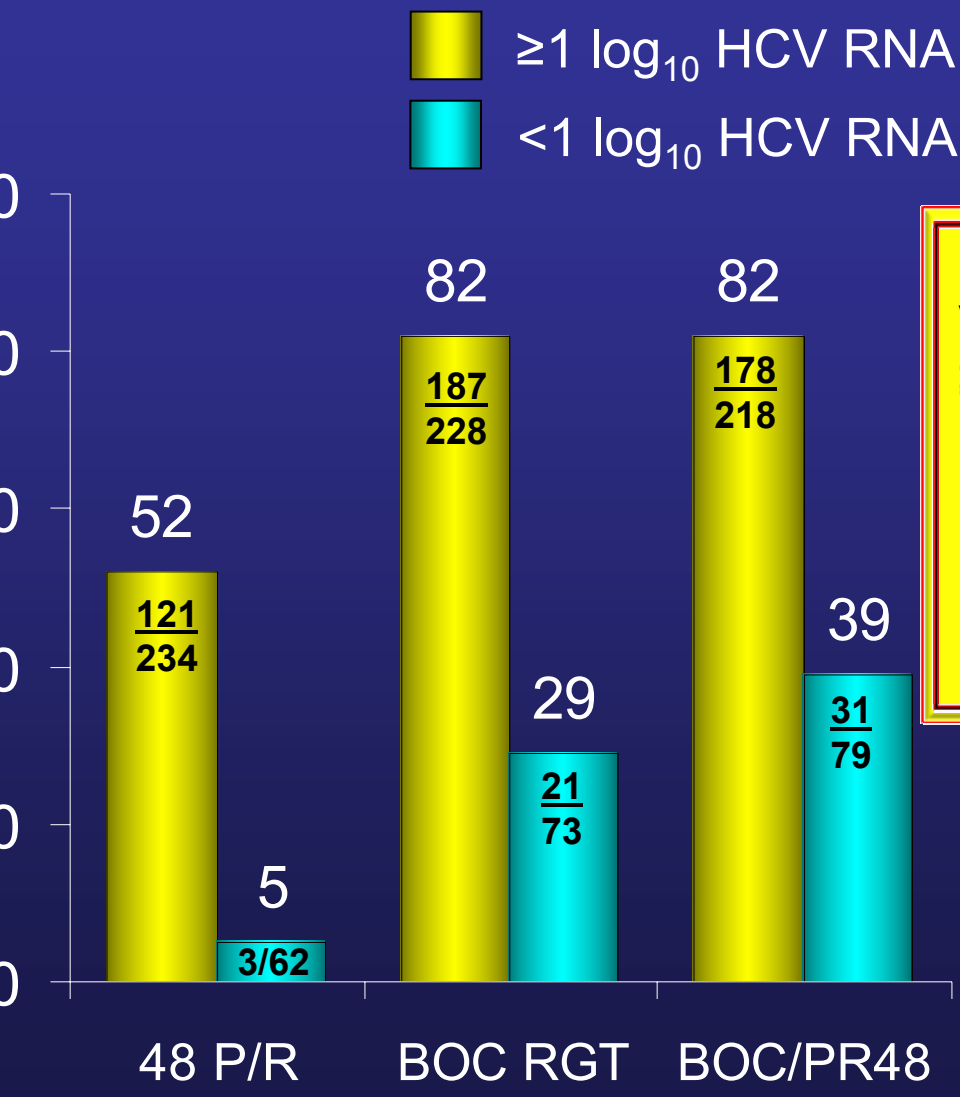
ping performed by NS5B sequencing (Virco, Mechelen, Belgium)

PRINT 2: SVR and Relapse Rates (ITT)



defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-evel was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA d at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39% (122/311), 66% (207/316) and 68% (210/311), y and in Cohort 2 were 21% (11/52), 42% (22/52) and 51% (28/55), respectively.

SVR Based on Week 4 PVR 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)

eprevir resistance-associated variants determined with population sequencing

Rationale for Lead-in Phase
4 weeks of PegIFN alfa-2b and ribavirin

- Achievement of steady-state drug levels
- Alpha interferon-mediated immune system activation
- Lower HCV burden

- May reduce the emergence of viral resistance by decreasing the pool of pre-existing viral quasi-species

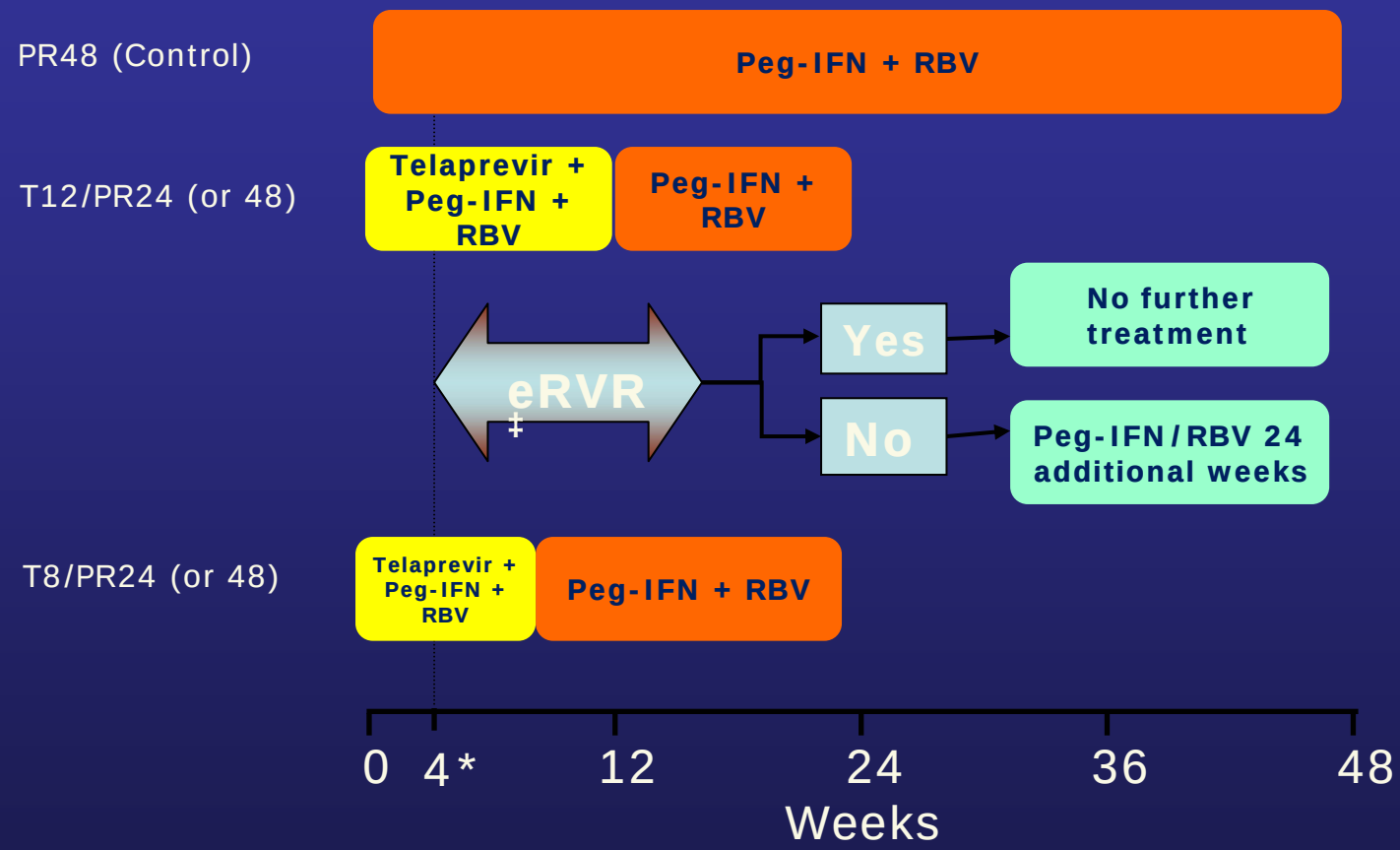
Boceprevir: Adverse Events and Discontinuations

Anemia and dysgeusia reported more frequently in BOC arms vs control in SPRINT-2[1-2]

tcome	4-Wk PR + Response-Guided BOC/PR (n = 368)	4-Wk PR + 44-Wk BOC/PR (n = 366)	48-Wk PR (n = 363)
verse event, %			
nemia[1]	49	49	29
EPO use	41	46	21
ysgeusia[2]	37	43	18
continuations due to verse events, %[1]	12	16	16
nemia[1]	2	2	1

1. Poordad F, et al. AASLD 2010.

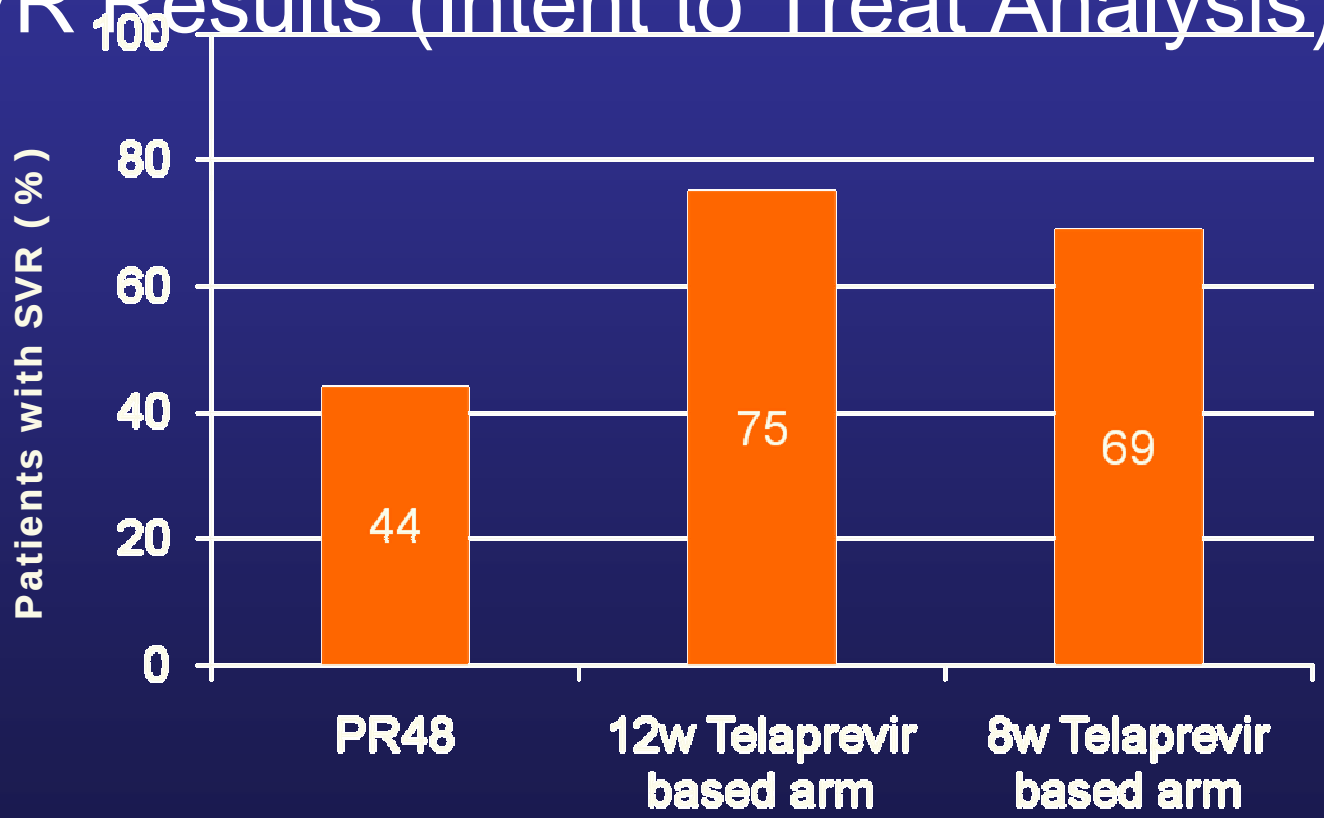
TELAPREVIR - ADVANCE



- * Stopping rule time point for Telaprevir
- ‡ eRVR = extended RVR, undetectable at W4 and 12

Efficacy Results from ADVANCE

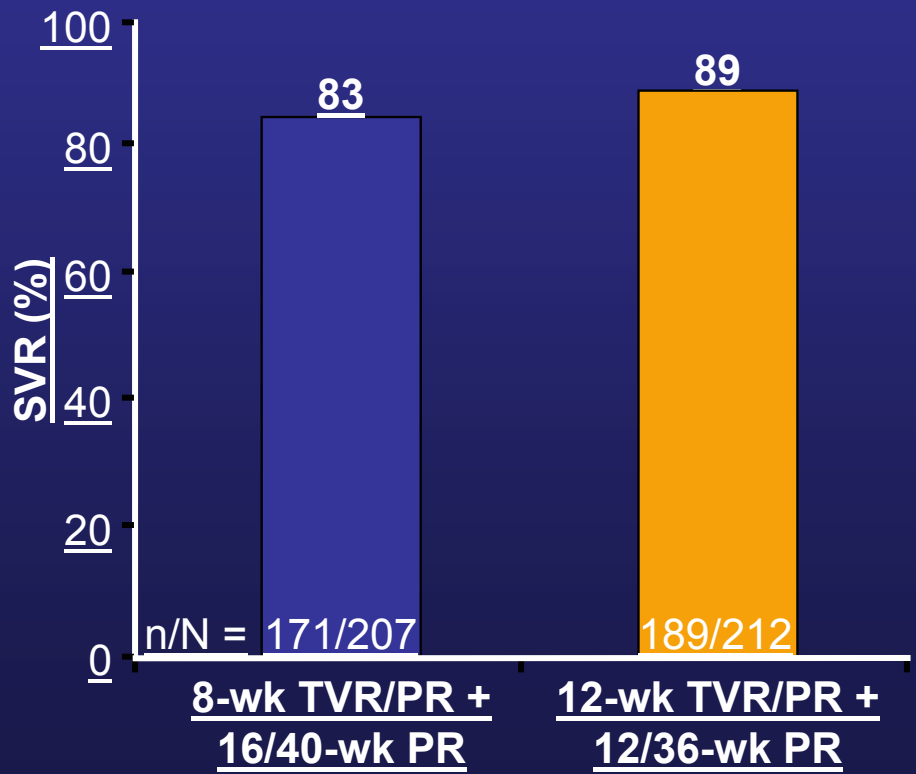
SVR Results (Intent to Treat Analysis)



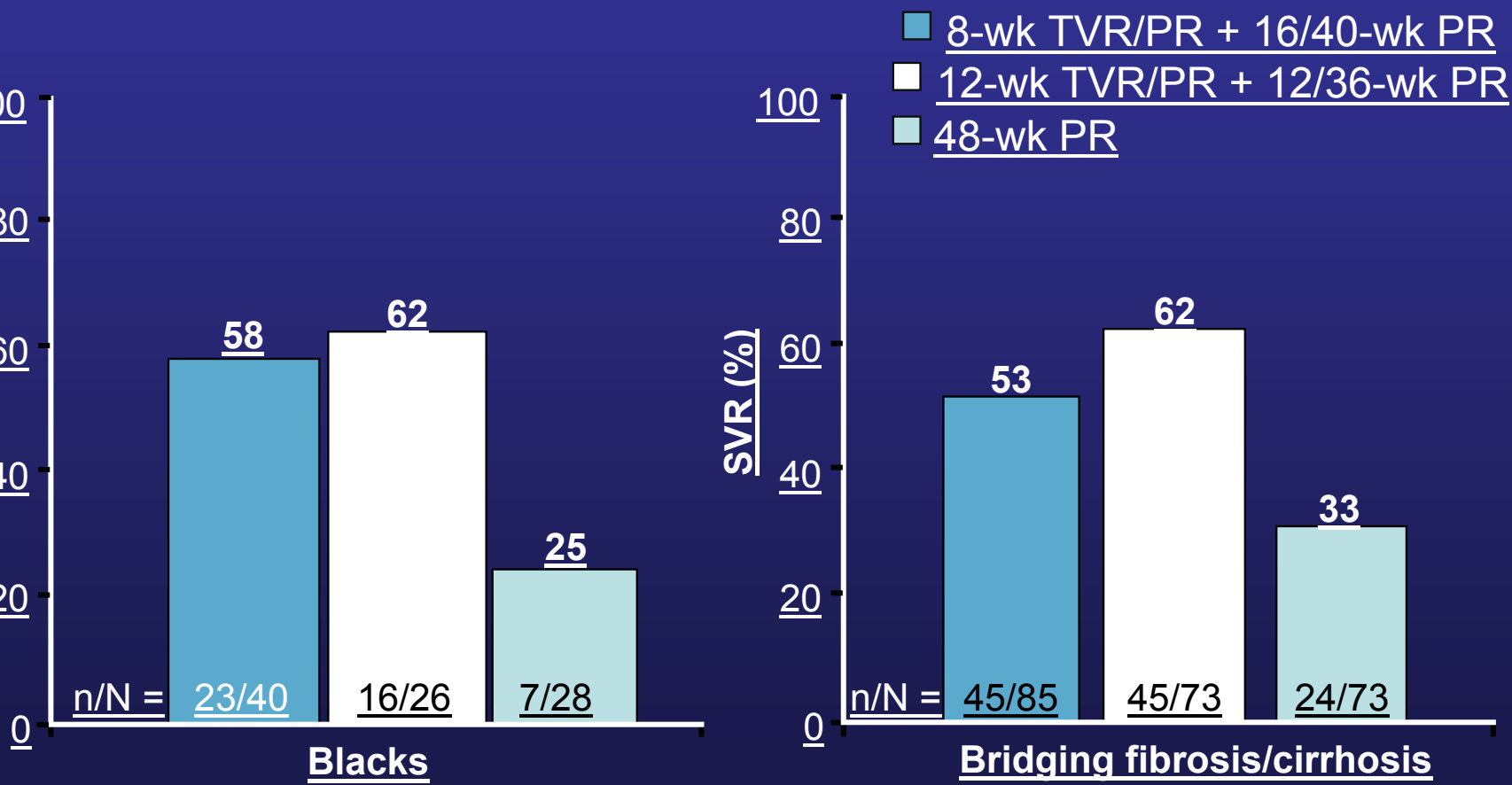
The SVR rates observed in the two telaprevir-based treatment arms were statistically significant when compared to the control arm ($p<0.0001$)

ADVANCE: SVR Rates in Patients Who Qualified For 24 Weeks of Therapy

57% and 58% of patients qualified for 24 weeks of therapy (assessment at Week 4) in 8-wk and 12-wk TVR arms, respectively



ADVANCE: Response Rates According to Race/Cirrhosis



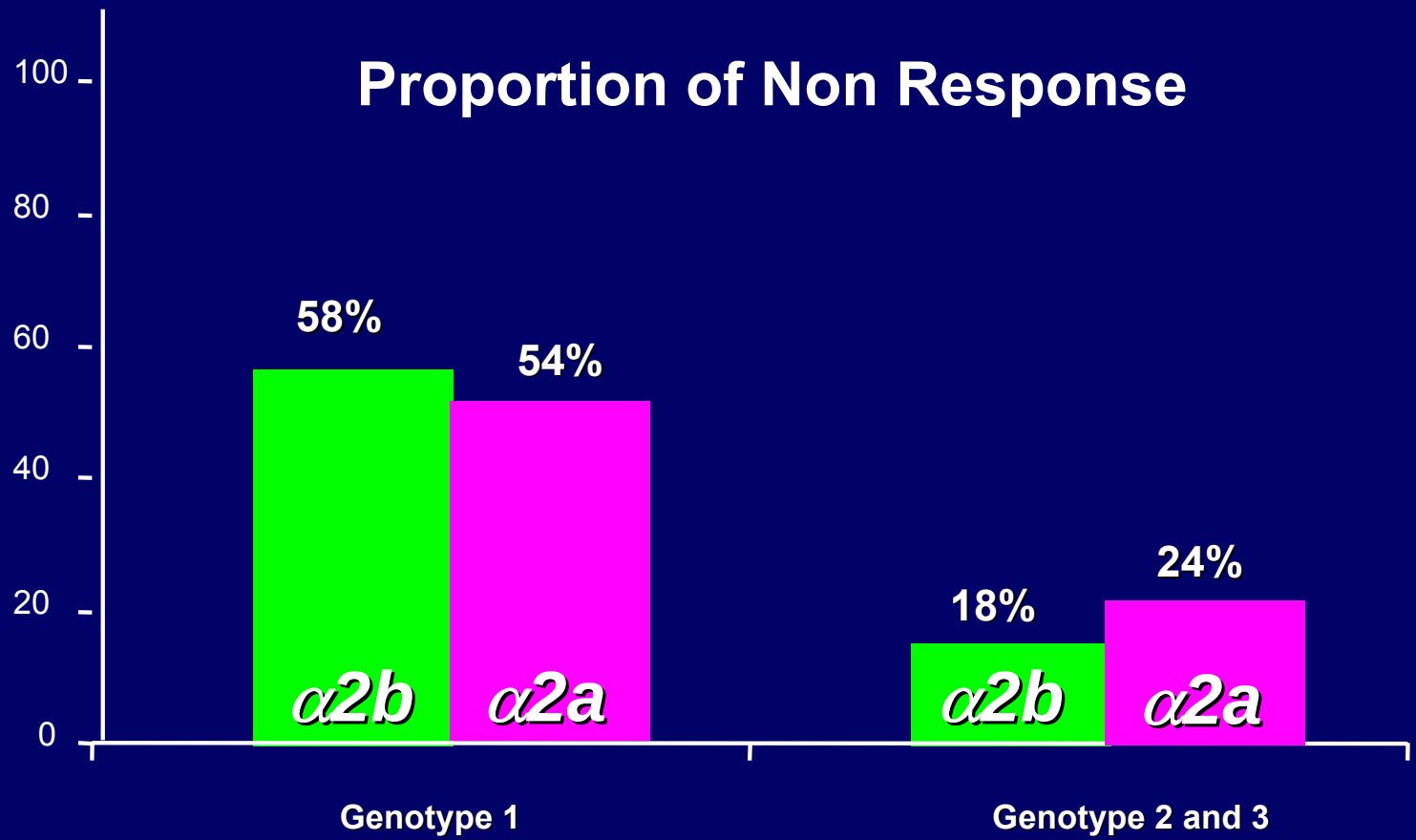
elaprevir: Discontinuations

Discontinuations due to adverse events in Phase III ADVANCE:

tcome, %	8-Wk TVR/PR + 16/40-Wk PR (n = 364)	12-Wk TVR/PR + 12/36-Wk PR (n = 363)	48-Wk PR (n = 361)
continuation of TVR/placebo due to h	7	11	1
continuation of all drugs due to AEs	8	7	4
nemia	3.3	0.8	0.6

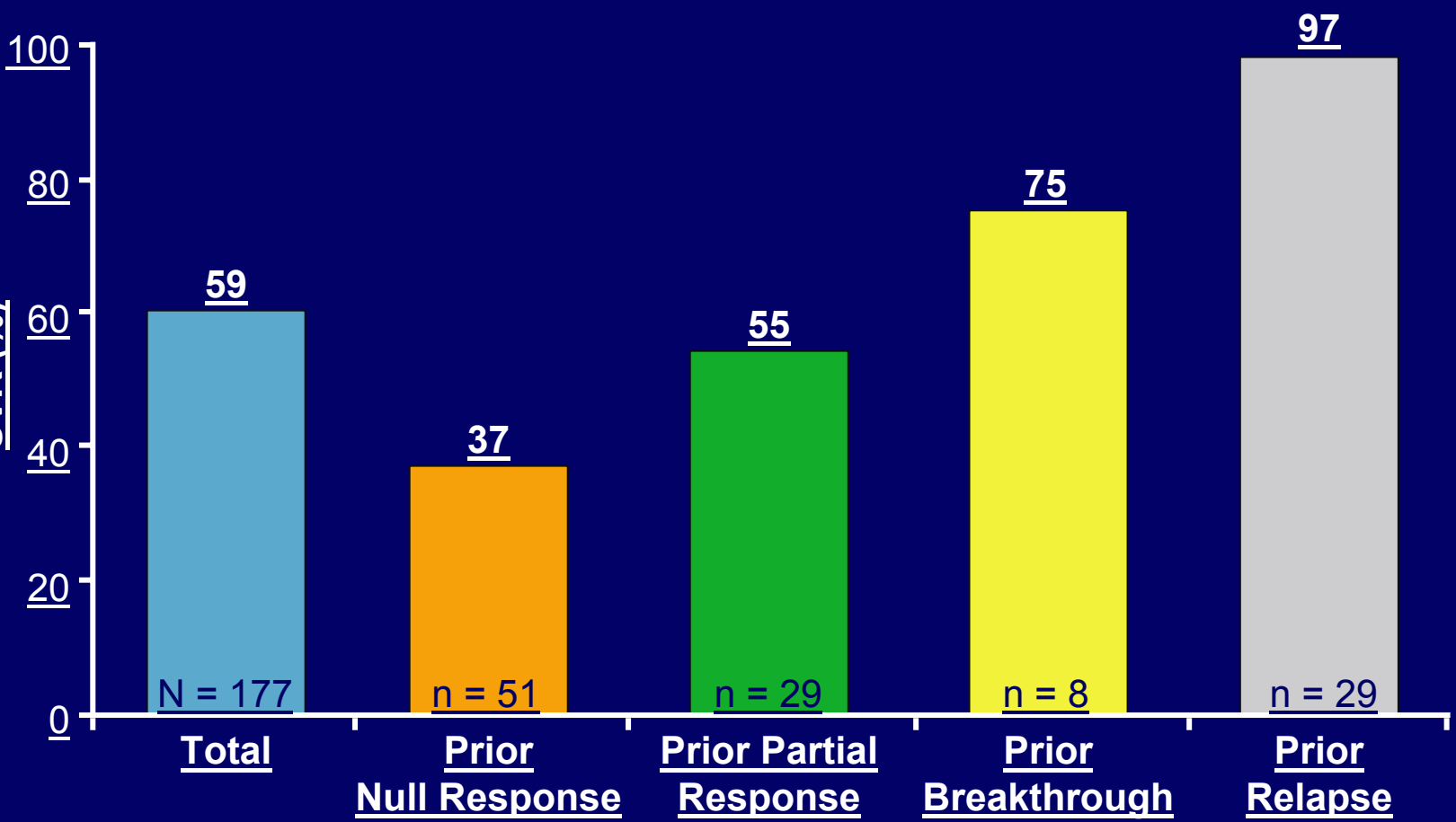
bson IM, et al. AASLD 2010. Abstract 211.

PegIFN alfa2 and Ribavirin in treatment of Chronic Hepatitis C



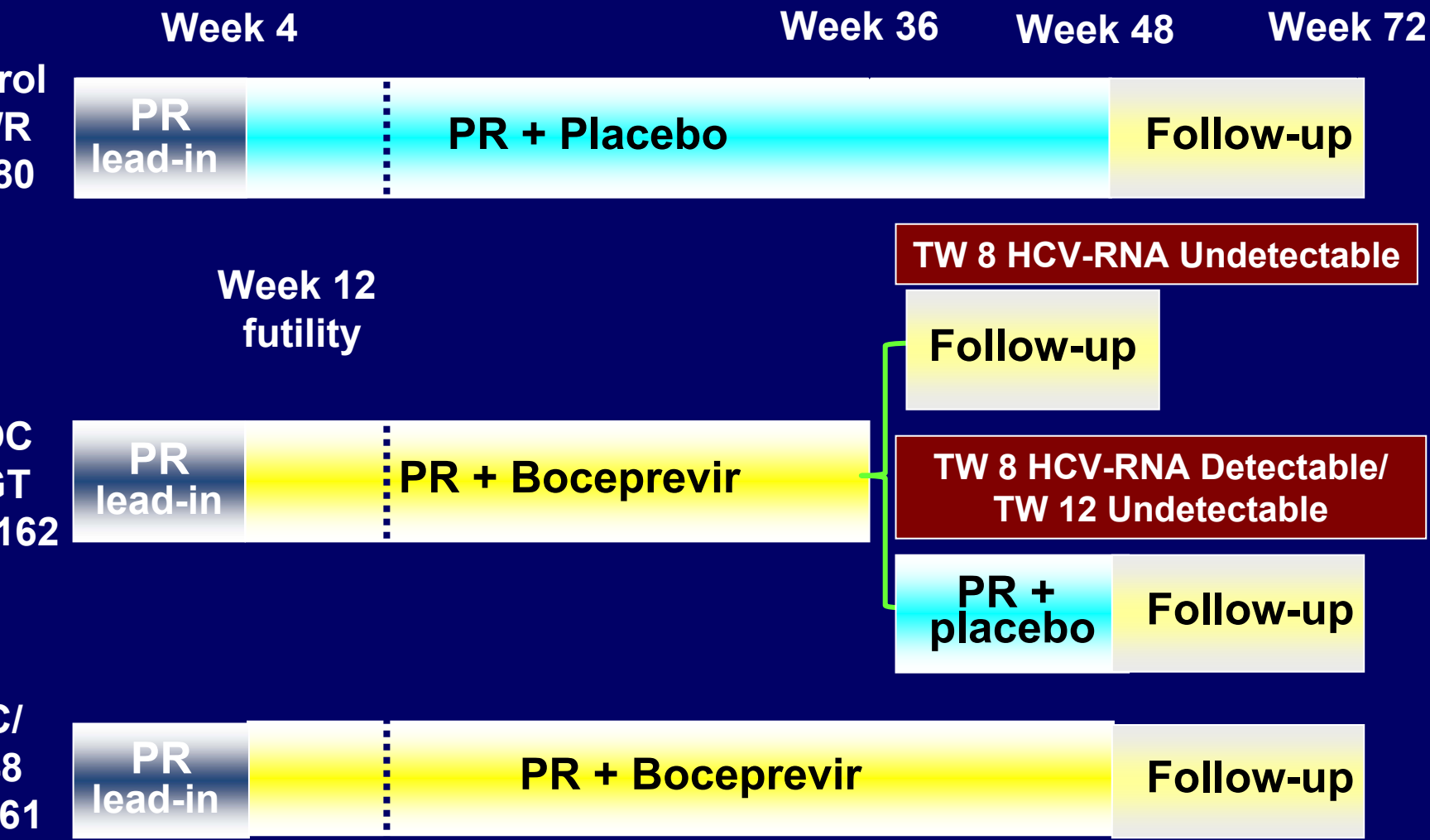
Manns et al. Lancet 2001 Fried et al N Eng J Med

udy 107: TVR/PR Retreatment of Pts With PR ilure in PROVE 1/2/3 Trials



T, et al. EASL 2010. Abstract 4. Graphic reproduced with permission.

Study Arms and Dosing Regimen



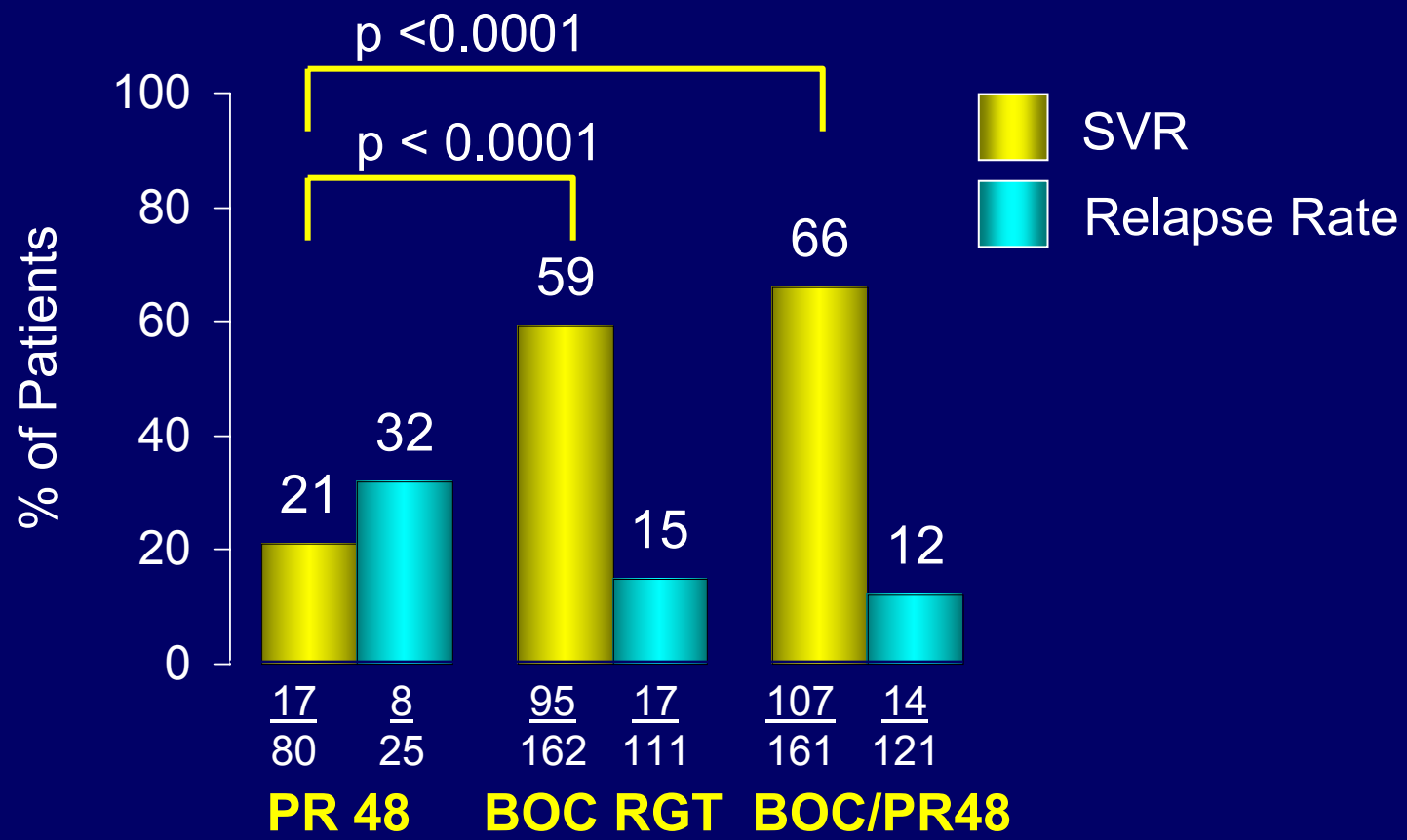
V-RNA measured by the Cobas TaqMan assay (Roche). Patients with detectable HCV-RNA (LLD=9.3 mL) at week 12 were considered treatment failures.

interferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus Ribavirin (R) g weight based dosing of 600-1400 mg/day in a divided daily dose

eprevir dose of 800 mg thrice daily

SPOND-2 SVR and Relapse Rates

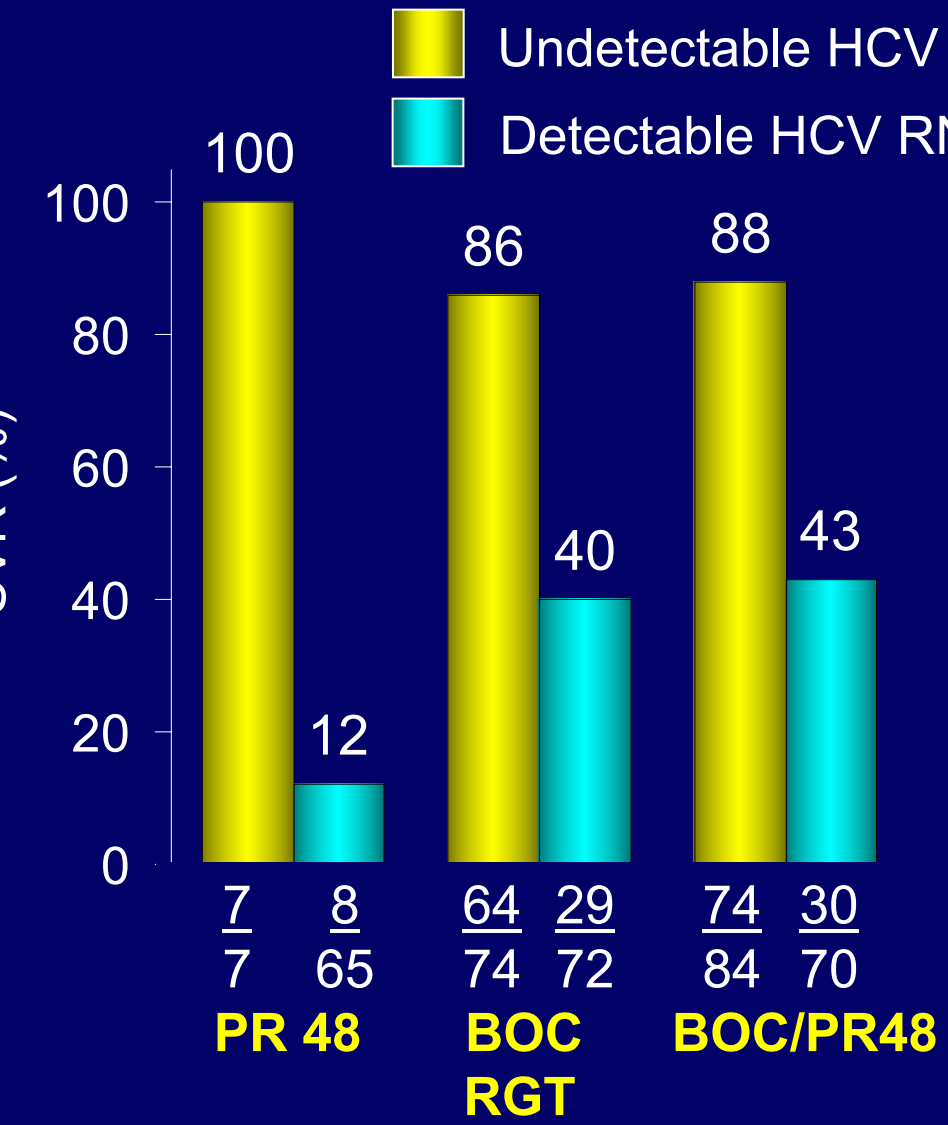
ntion to treat population



SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])

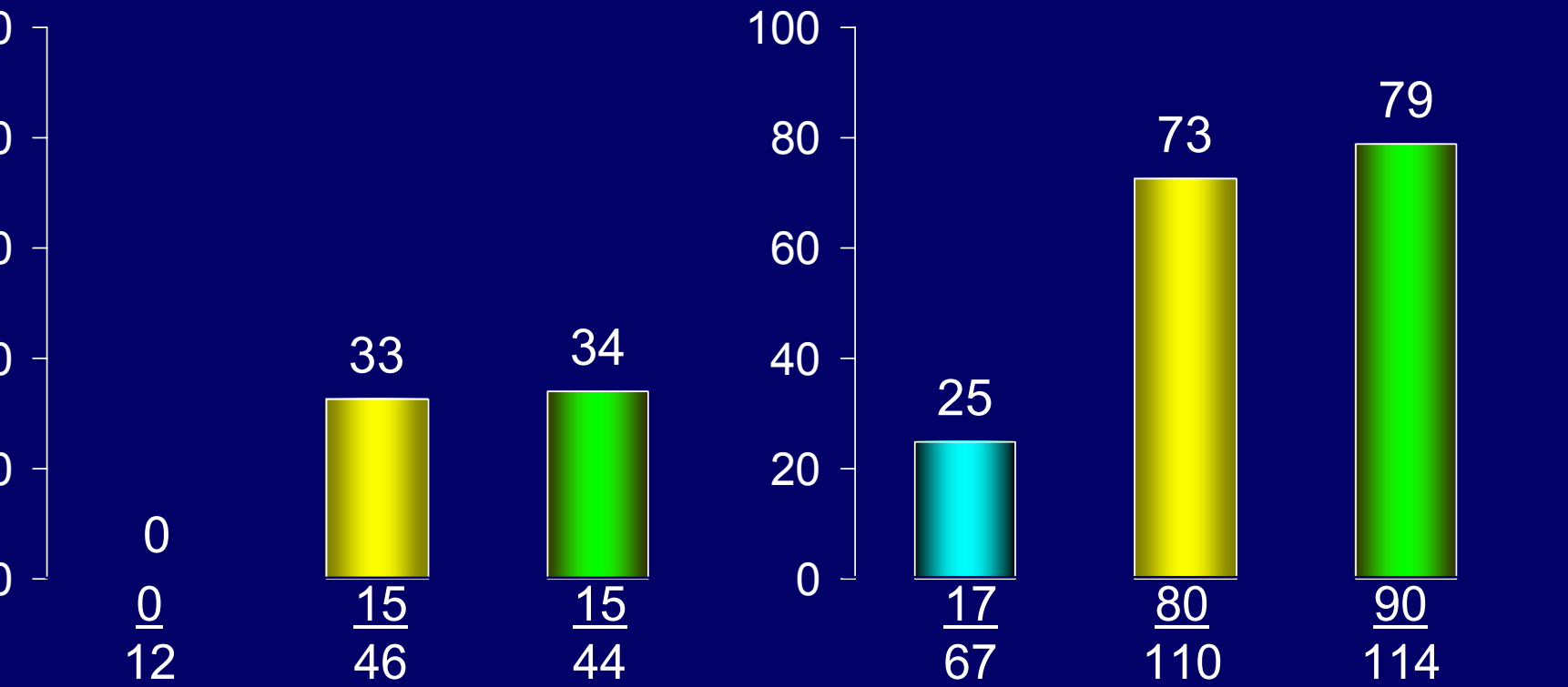
eek HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where ng data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% 62) and 66% (106/161), respectively.

R by Week 8 HCV RNA Response Intention to Treat ulation



- 46% of patients in BOC RGT arm were eligible for shorter therapy
- ~6 times as many patients on BOC regimens (46-52%) achieved undetectable HCV RNA at week 8 compared to control (9%)

R by Week 4 PR Lead-In Response



Poorly Responsive to IFN
<1 log_{10} viral load decline at treatment week 4

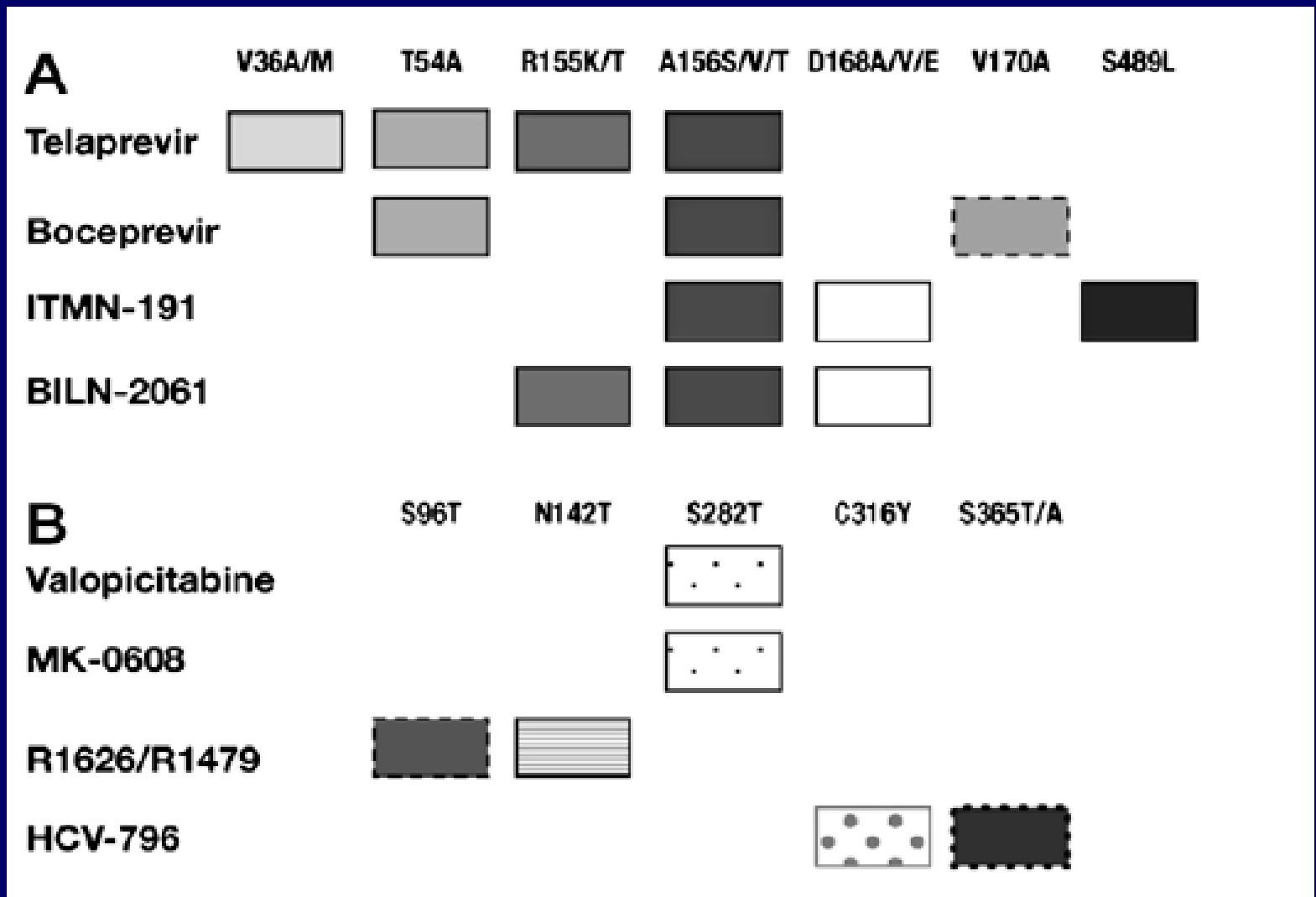
Responsive to IFN
≥1 log_{10} viral load decline at treatment week 4

ESPOND-2: Adverse Events Over ntire Treatment Course

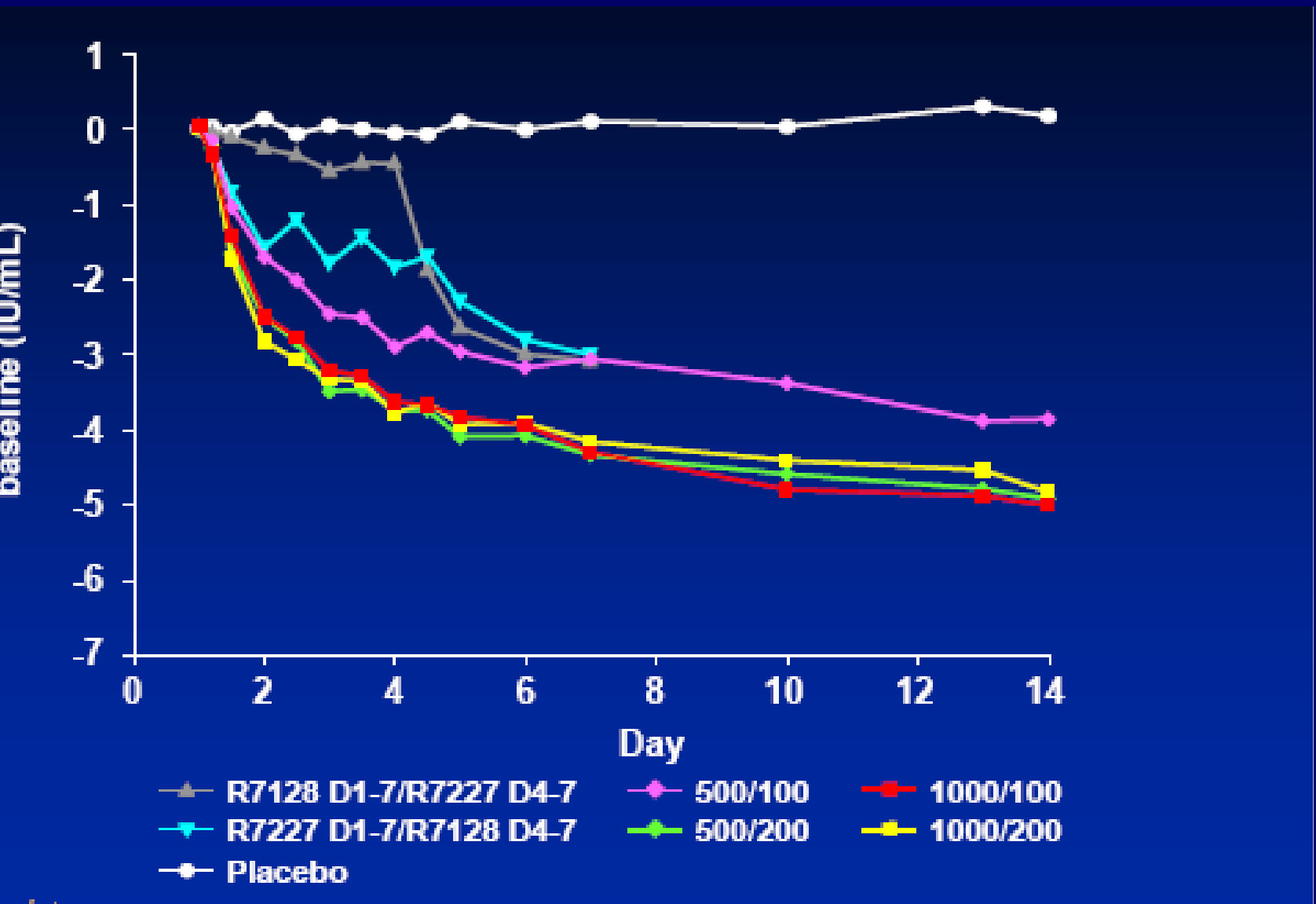
- Adverse events more common in BOC arms vs control
  - Anemia and dysgeusia

come	4-Wk PR + Response-Guided BOC + PR (n = 162)	4-Wk PR + 44-Wk BOC + PR (n = 161)	48-Wk PR (n = 114)
erse event, %[1]			
nemia	43	46	20
ysgeusia	43	45	11

In Vitro resistance to Protease (A) and Polymerase (B) Inhibitors



Combination of two oral drugs in HCV G-1Patients
Nucleoside Polymerase (R7128) and Protease (R7227) Inhibitor



Summary

Combination of Protease Inhibitors with PEG-IFN and RBV will increase SVR in genotype 1 patients from 40% to 60-70%

Relapse rate decline to 5-10%

Treatment duration may be shorten for a proportion of patients

Discontinuation rates may increase due to AEs

A new era in HCV therapy starts