FIRST INTERNATIONAL COURSE
ON TRANSLATIONAL HEPATOLOGY
FOCUS ON HCV DISEASE
FLORENCE, MARCH 9-11, 2011

MASVE

Presidents of the Course
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Honorary President
Prof. Paolo Gentilini

The Future of ANTI-HCV treatment: "Results of experimental trials"

Savino Bruno. MD

Internal Medicine and Liver Unit
A.O. Fatebenefratelli e Oftalmico, Milan

Financial interests disclosed: Sponsored research, speakers board: Roche, Merck. International Advisory Board for HCV: Merck

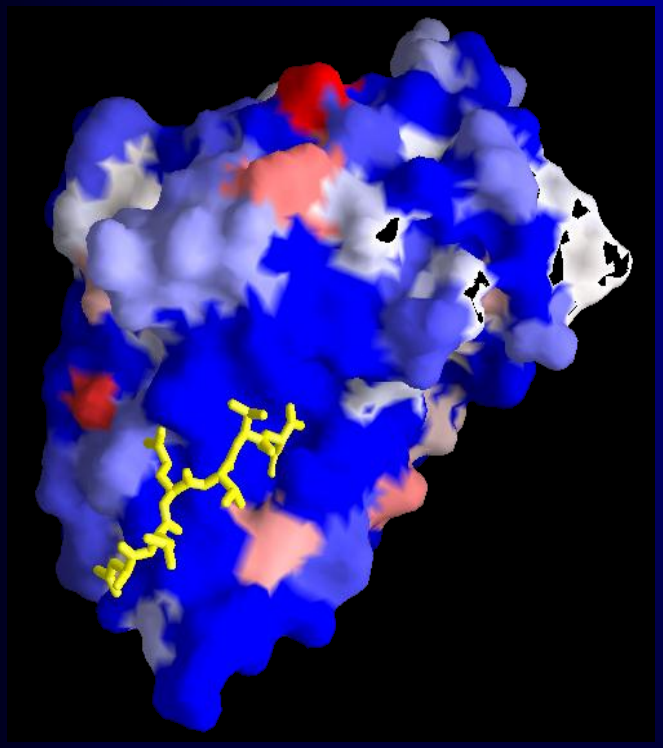
Today's talk

- Review efficacy of Boceprevir and Telaprevir in
  - Naïve patients
  - Previous non responders and relapsers
- Discuss the new lexicon
- Evaluate the concepts of Lead-in Phase and of Response Guided Therapy
- Evaluate SE management and of the impact of emergence of resistance associated variants (RAV)

EFFICACY IN TREATMENT NAIVE PATIENTS

Boceprevir (BOC)

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

The NEW ENGLAND JOURNAL of MEDICINE

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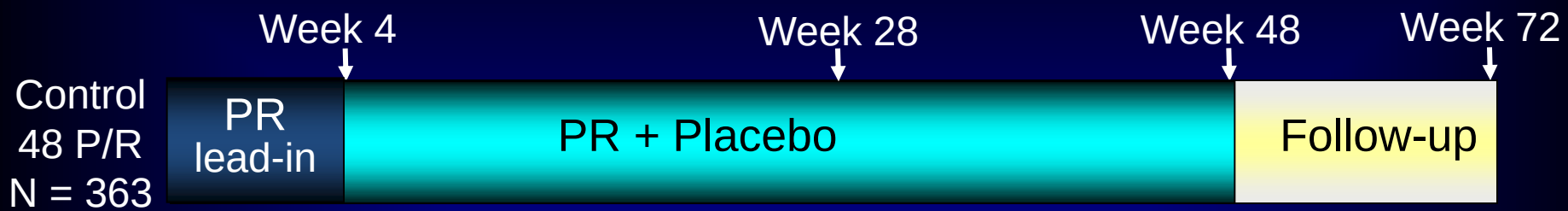
Boceprevir for Untreated Chronic HCV Genotype 1 Infection

Fred Poordad, M.D., Jonathan McCone, Jr., M.D., Bruce R. Bacon, M.D., Savino Bruno, M.D., Michael P. Manns, M.D., Mark S. Sulkowski, M.D., Ira M. Jacobson, M.D., K. Rajender Reddy, M.D., Zachary D. Goodman, M.D., Ph.D., Navdeep Boparai, M.S., Mark J. DiNubile, M.D., Vilma Sniukiene, M.D., Clifford A. Brass, M.D., Ph.D., Janice K. Albrecht, Ph.D., and Jean-Pierre Bronowicki, M.D., Ph.D., for the SPRINT-2 Investigators*

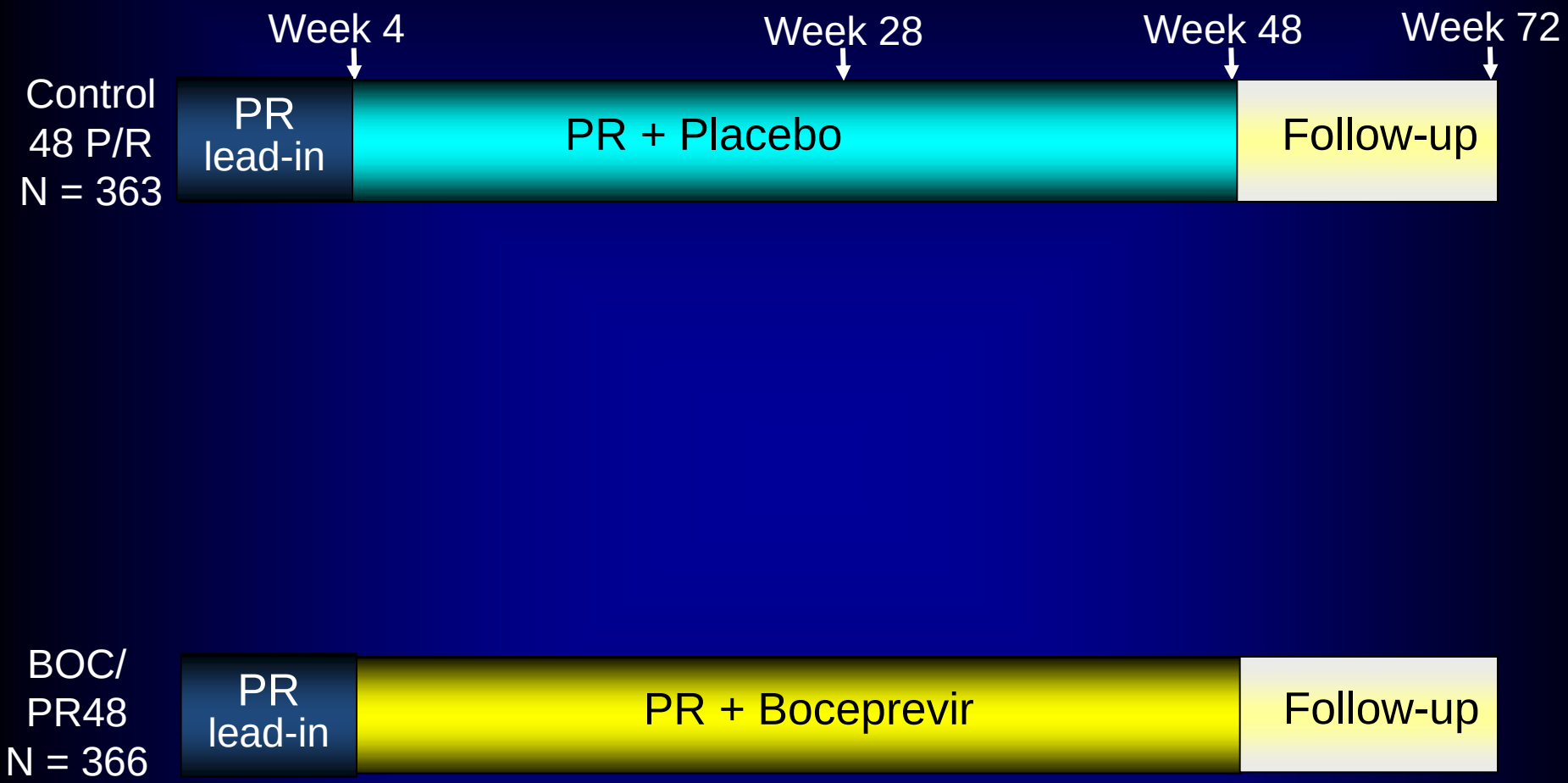
SPRINT 2: Study Design



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

Boceprevir dose of 800 mg thrice daily

SPRINT 2: Study Design



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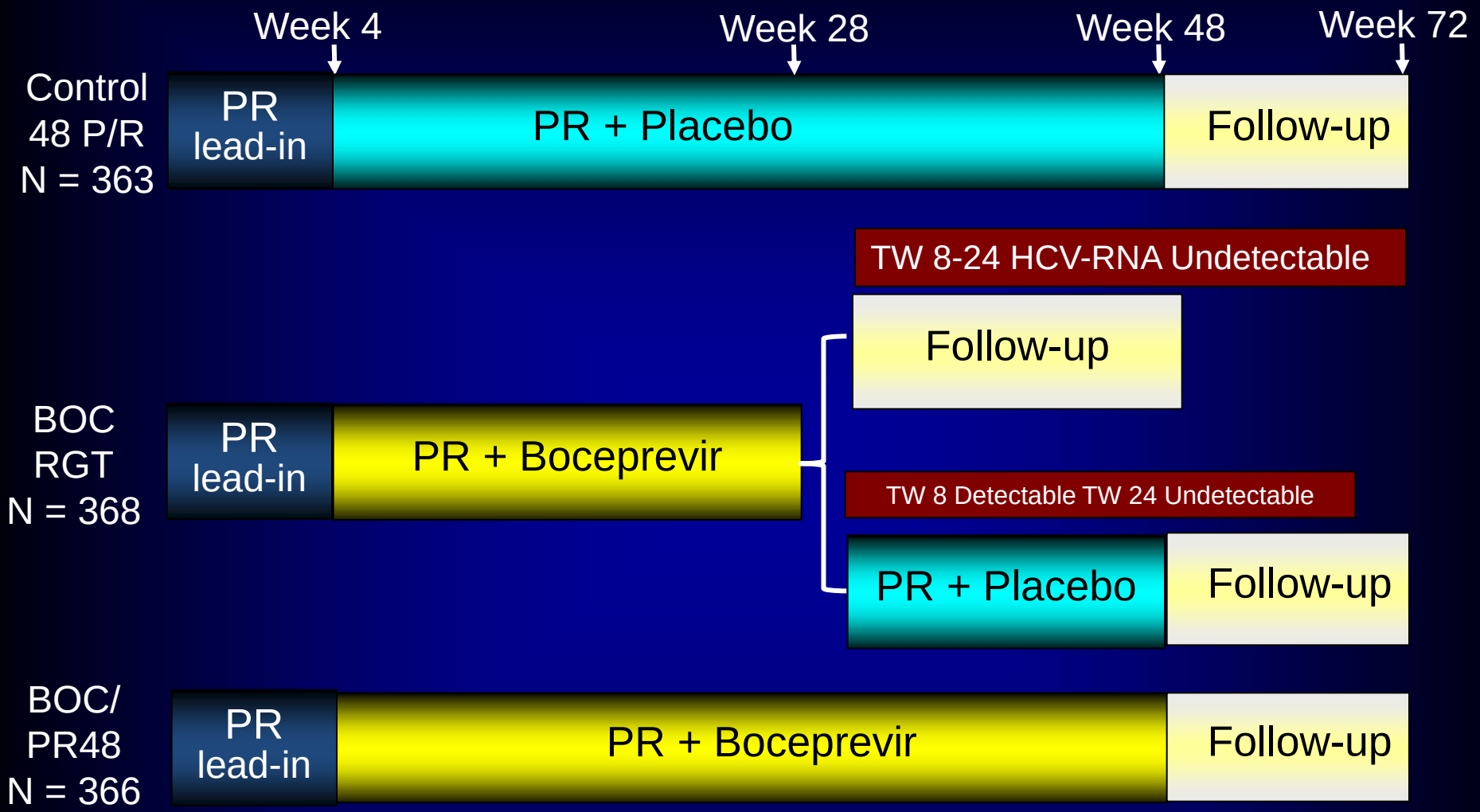


Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose

Boceprevir dose of 800 mg thrice daily

SPRINT 2: Study Design

Prespecified cohorts
- Cohort 1: Non-blacks (N=938)
- Cohort 2: Blacks (N=159)

Stratification variables
- Baseline viral load:
  > *vs.* ≤ 400,000 IU/mL
- HCV subtype: 1a *vs.* 1b

HCV RNA
- TaqMan 2.0 (LLQ=25 IU/mL; LLD=9.3 IU/mL)
- LLD used to define undetectable at all decision points

Pre-specified endpoints

Primary
- SVR 24 in ITT population

Key Secondary
- SVR 24 in mITT population: all patients who received >1 dose of boceprevir/placebo

Stopping rule
- Detectable HCV RNA at 24 wks

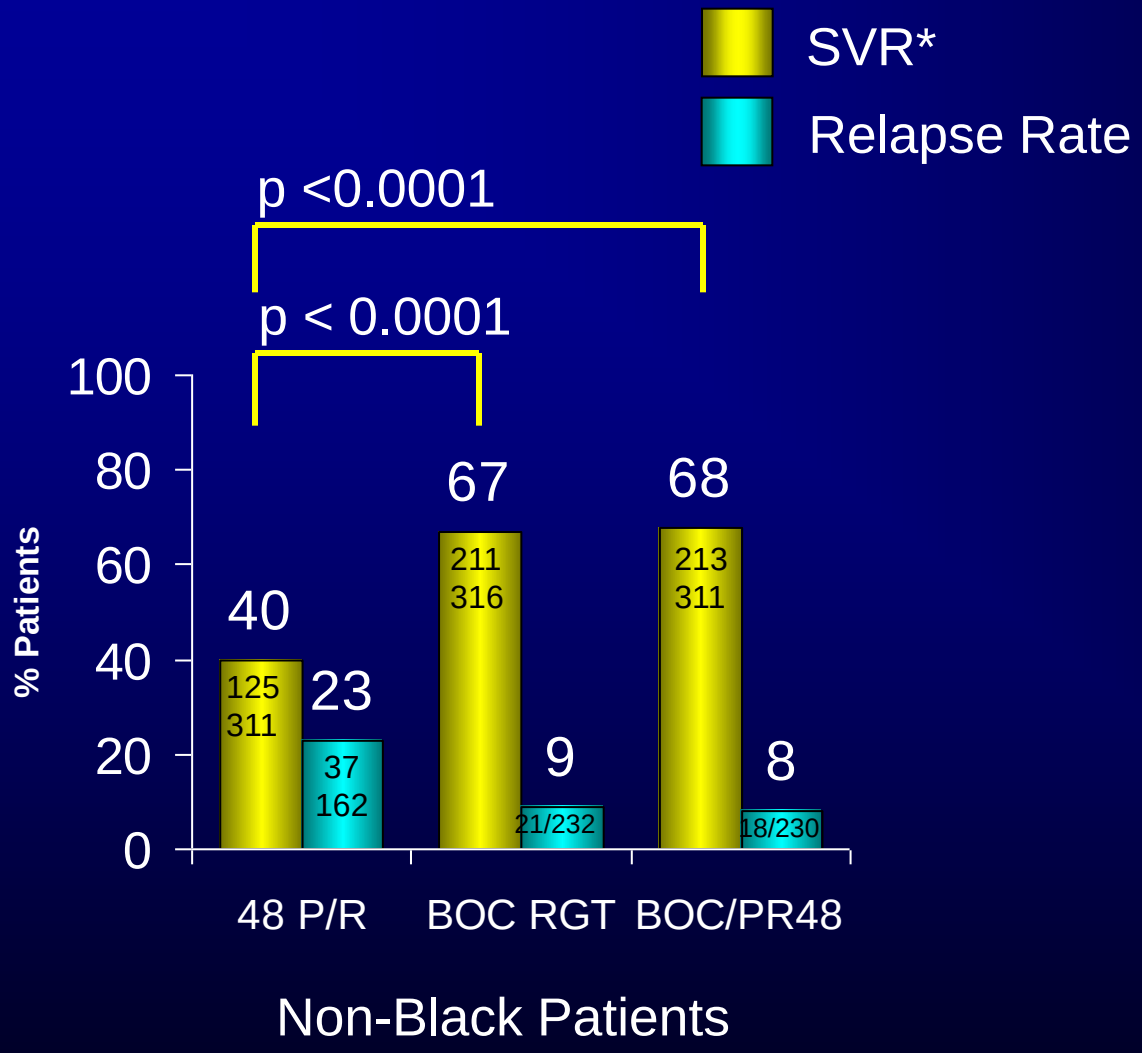
LLQ=Lower limit of quantitation; LLD=Lower limit of detection; SVR=Sustained virologic response; ITT=Intent-to-treat; mITT=Modified ITT; IU=International units

Baseline Characteristics

	Cohort 1 (Non-black)		
	Arm 1: 48 P/R N = 311	Arm 2: BOC RGT N = 316	Arm 3: BOC/ PR48 N = 311
Mean age (years)	48	49	49
Male (%)	55	63	60
Region (%)			
North America	65	72	70
Europe	32	25	27
BMI – mean (SD)	27 (5)	28 (5)	27 (5)
HCV subtype (%)*			
1a	60	62	63
1b	36	35	33
HCV RNA level			
>400,000 IU/mL (%)	92	91	93
METAVIR F3/F4 (%)	7	8	12

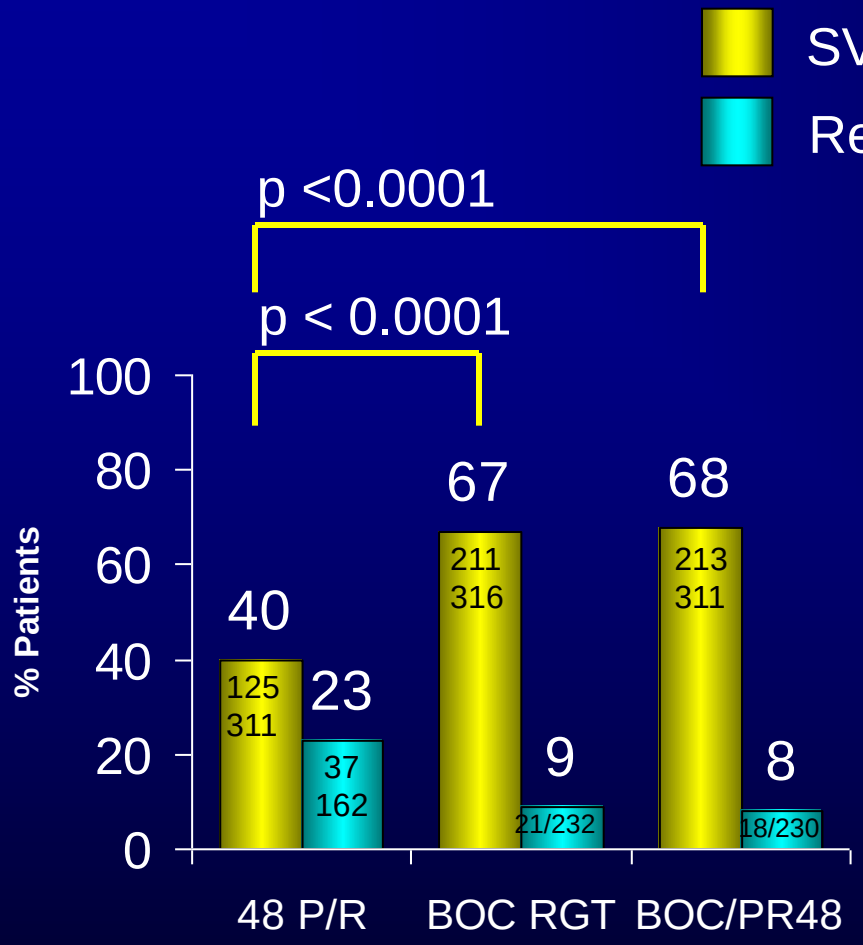
* Subtyping performed by NS5B sequencing (Virco, Mechelen, Belgium)

SPRINT 2: SVR and Relapse Rates (ITT)

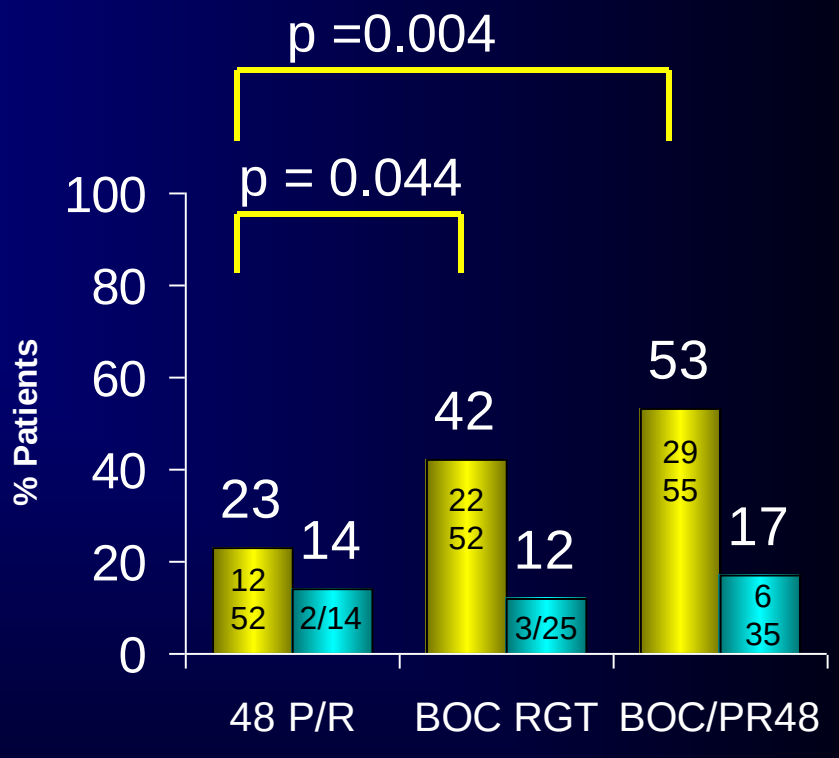


Non-Black Patients

SPRINT 2: SVR and Relapse Rates (ITT)



Non-Black Patients



Black Patients

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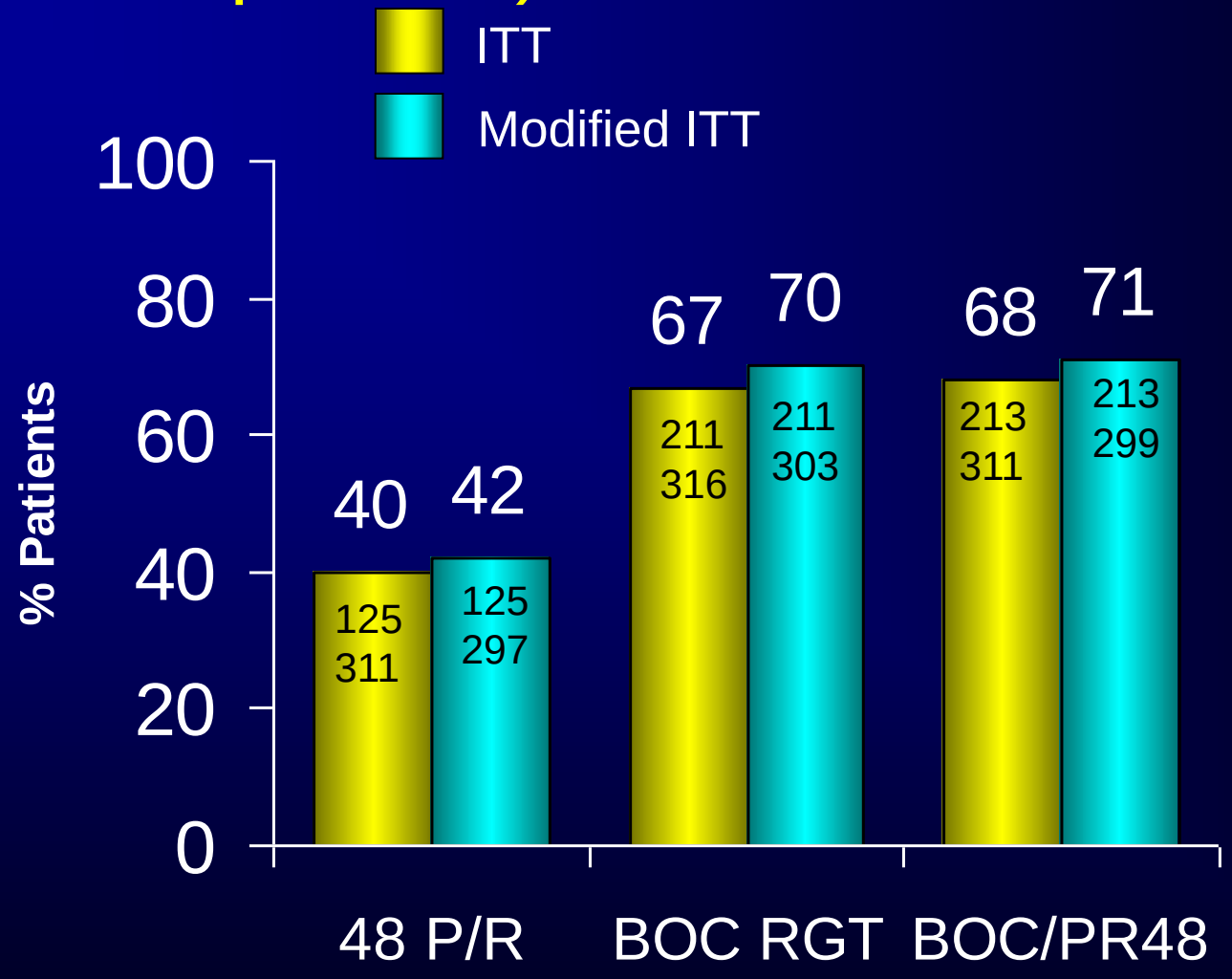
*SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented 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), respectively and in Cohort 2 were 21% (11/52), 42% (22/52) and 51% (28/55), respectively.

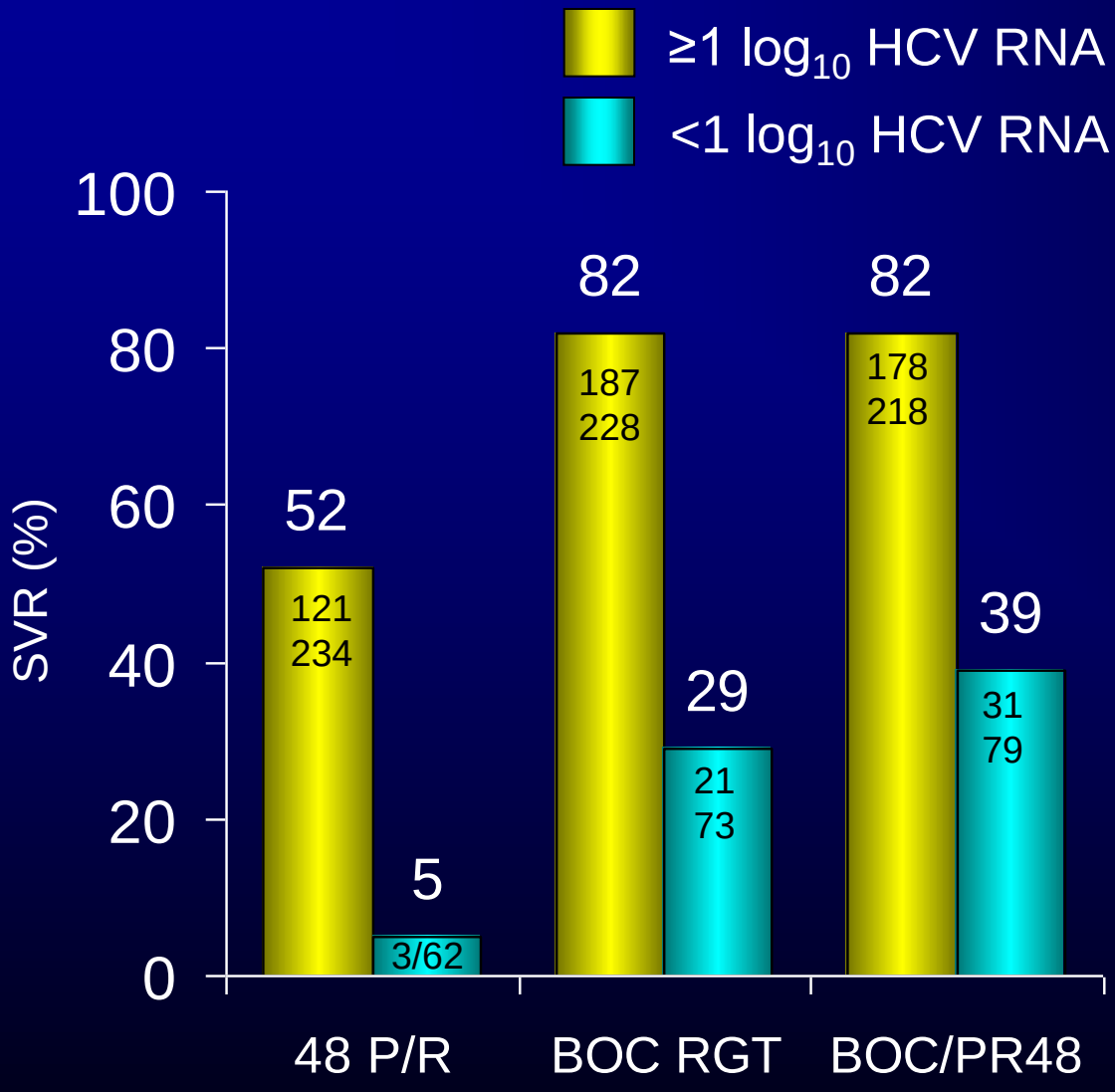
SVR: ITT and mITT (at least one dose of BOC/placebo) in Non-Black Patients



SVR by HCV RNA detectability at Week 4

	Non blacks			Blacks		
	SOC N=311	**BOC RGT** N=316	**BOC/P R48** N=311	**SOC** N=52	**BOC RGT** N=52	**BOC/P R48** N=55
Undetectable	**96 %** 27/28	**89 %** 16/18	**90 %** 18/20	**100 %** 2/2	**100 %** 1/1	**0** 0
Detectable	**36 %** 97/268	**68 %** 192/283	**69 %** 191/277	**22 %** 10/45	**45 %** 21/47	**52 %** 27/52

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



* Boceprevir resistance-associated variants determined with population sequencing

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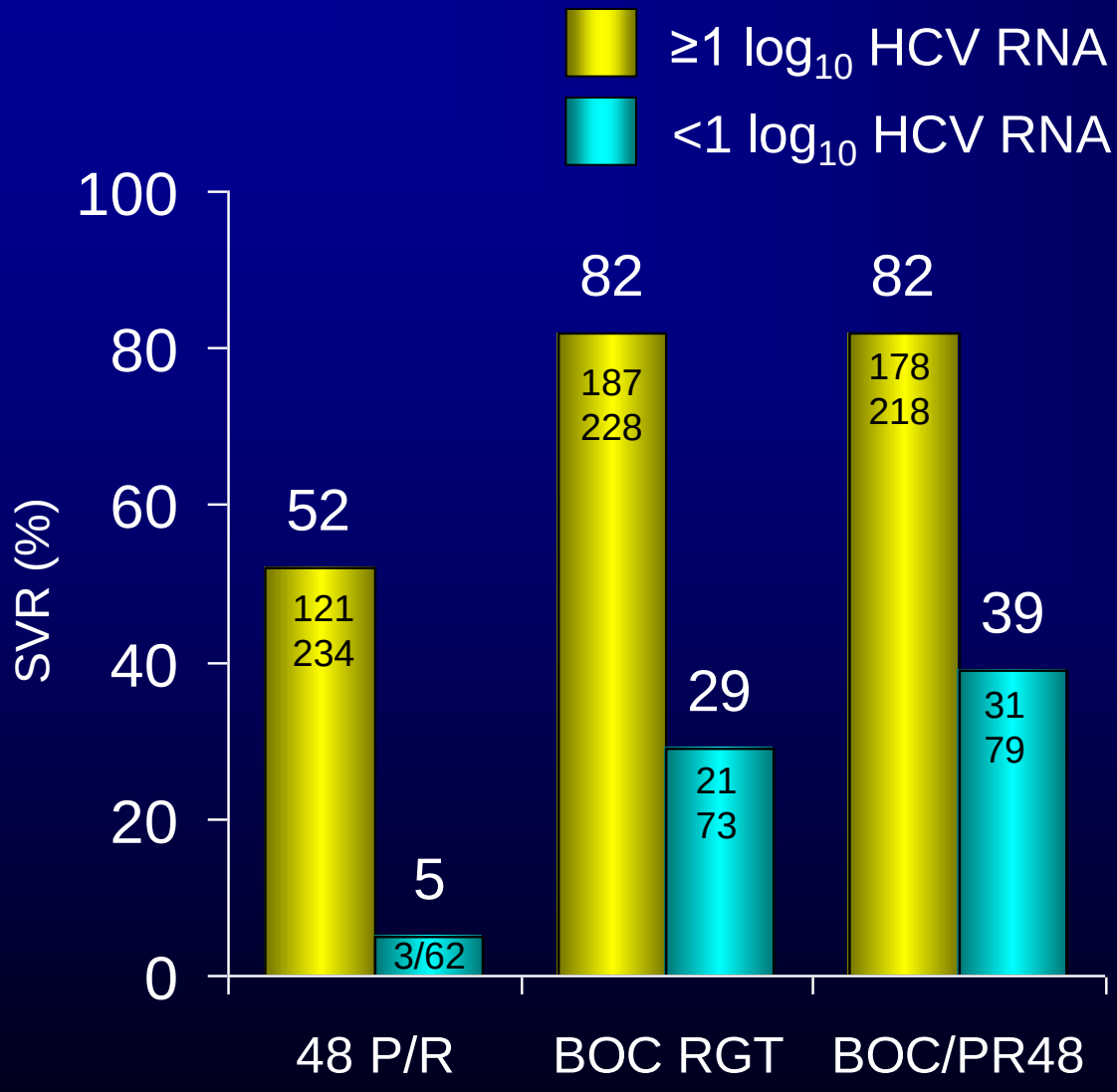
SVR Based on Week 4 PR Lead-In in Non-Black Patients



72 % of all patients

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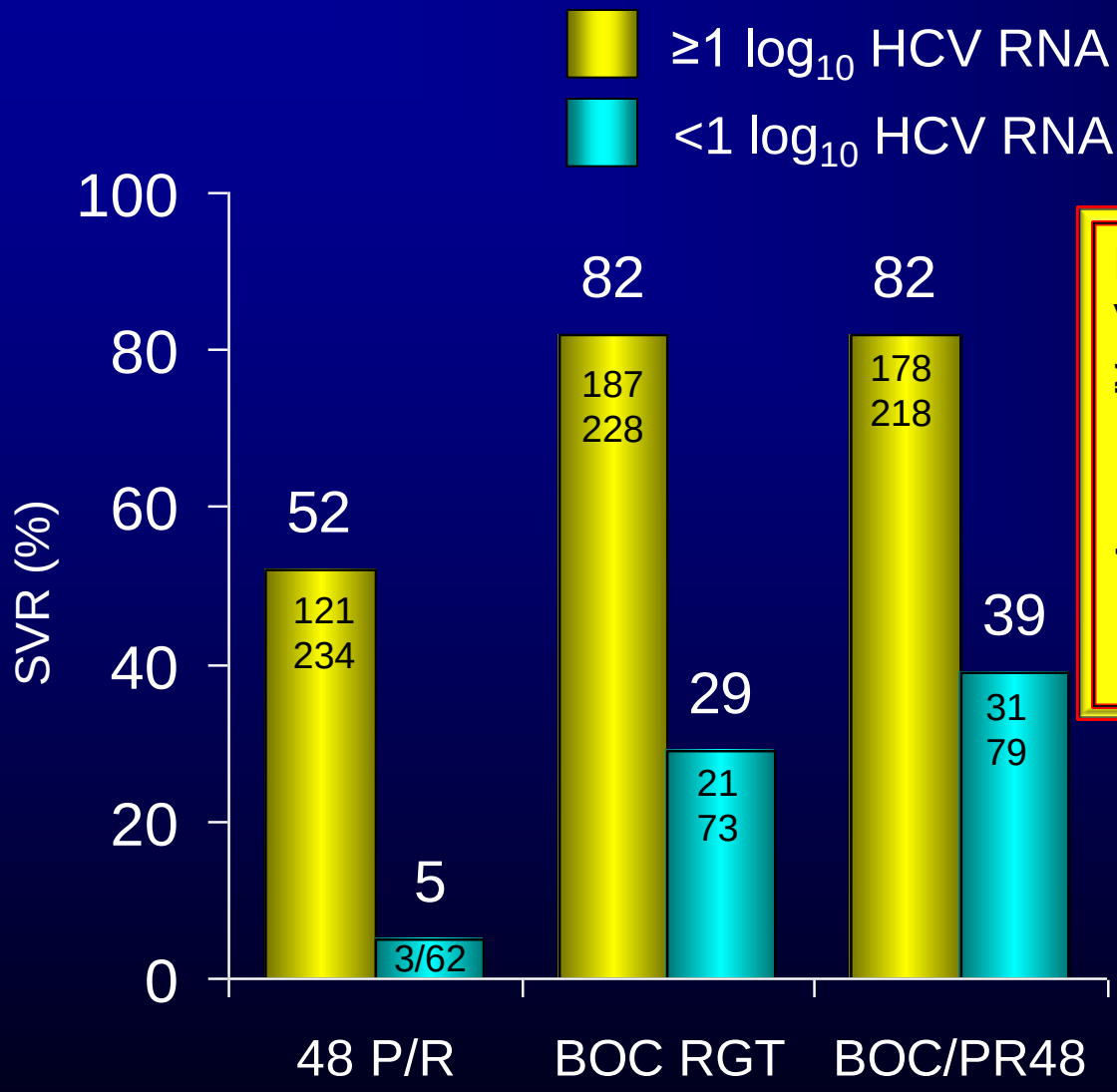
* Boceprevir resistance-associated variants determined with population sequencing

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)

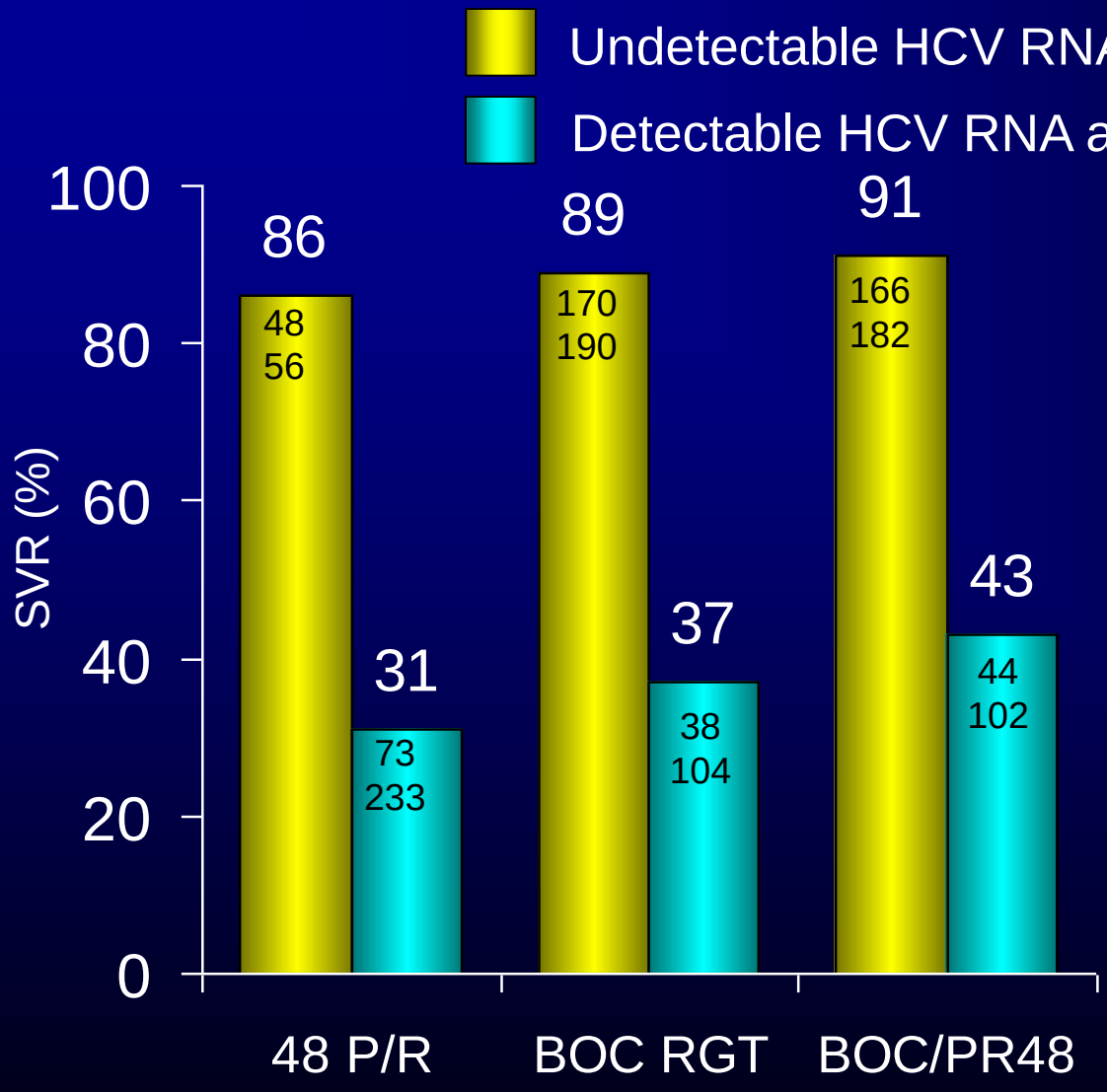
< 1 log_{10} decline:

BOC RGT: 47% (45/95)

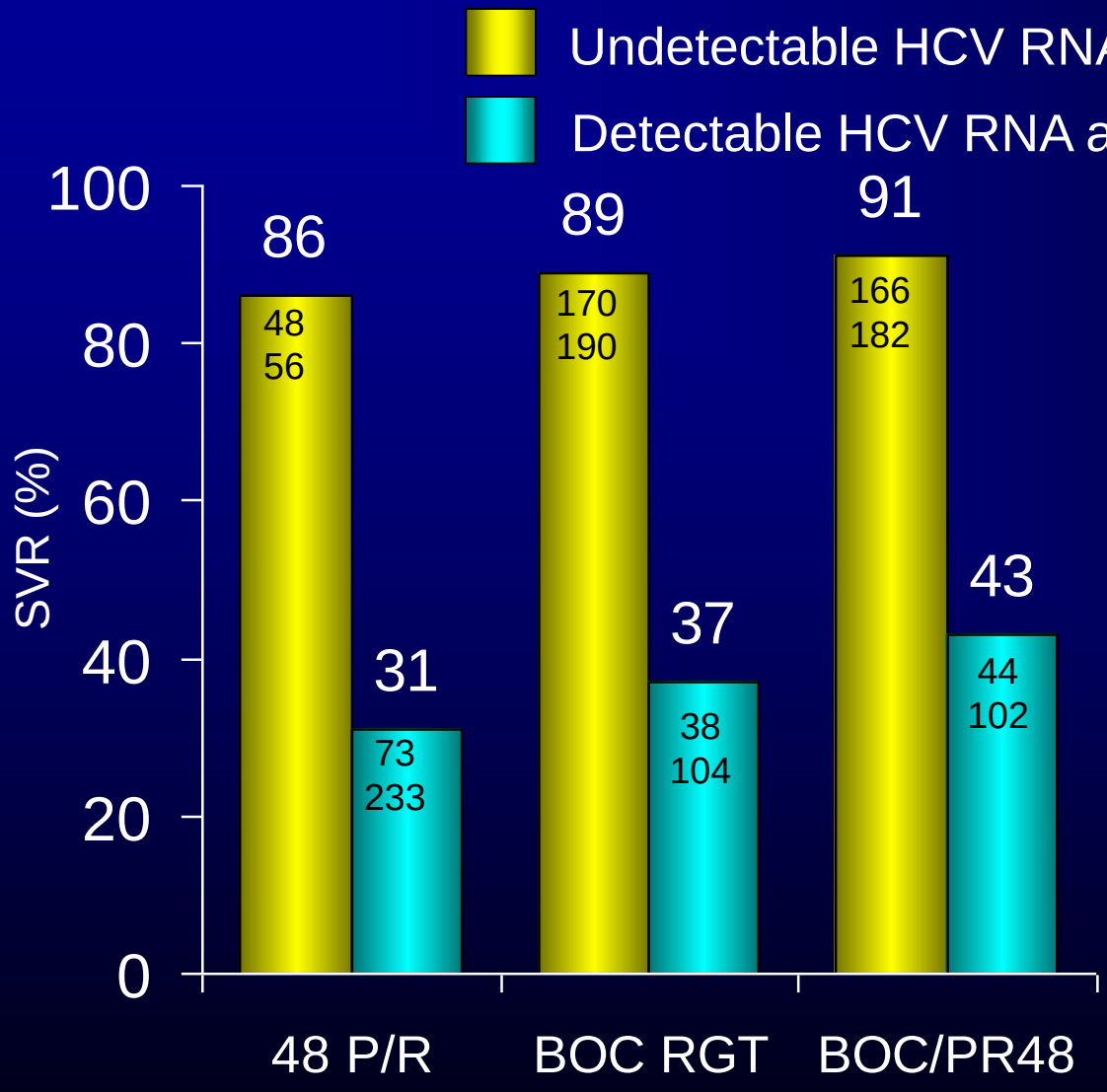
BOC/PR48: 35% (33/94)

* Boceprevir resistance-associated variants determined with population sequencing

SVR Based on Week 8 HCV RNA in Non-Black Patients



SVR Based on Week 8 HCV RNA in Non-Black Patients



Baseline predictors of SVR: multivariate analysis

Variables†	Odds Ratio (95% Confidence Interval)	Chi-Square P-value
Treatment: Arm 3 vs. Arm 1	3.5 (2.6, 4.8)	<0.0001
Treatment: Arm 2 vs. Arm 1	3.1 (2.3, 4.3)	<0.0001
Baseline HCV RNA level: ≤400,000 vs. >400,000 IU/mL	3.7 (2.1, 6.8)	<0.0001
Race: Black (Cohort 2) vs. Nonblack (Cohort 1)	0.5 (0.3, 0.7)	<0.0001
Fibrosis score: F0/1/2 vs. F3/4	1.9 (1.2, 3.0)	0.0037

In an expanded model which included on-treatment response, HCV RNA level at Week 4 (the end of the lead-in treatment period with peginterferon/ribavirin): undetectable or ≥1 log decline from baseline vs. <1 log decline from baseline had the highest odds ratio of 9.3 (6.5, 13.3) with p<0.0001.

Summary - Efficacy

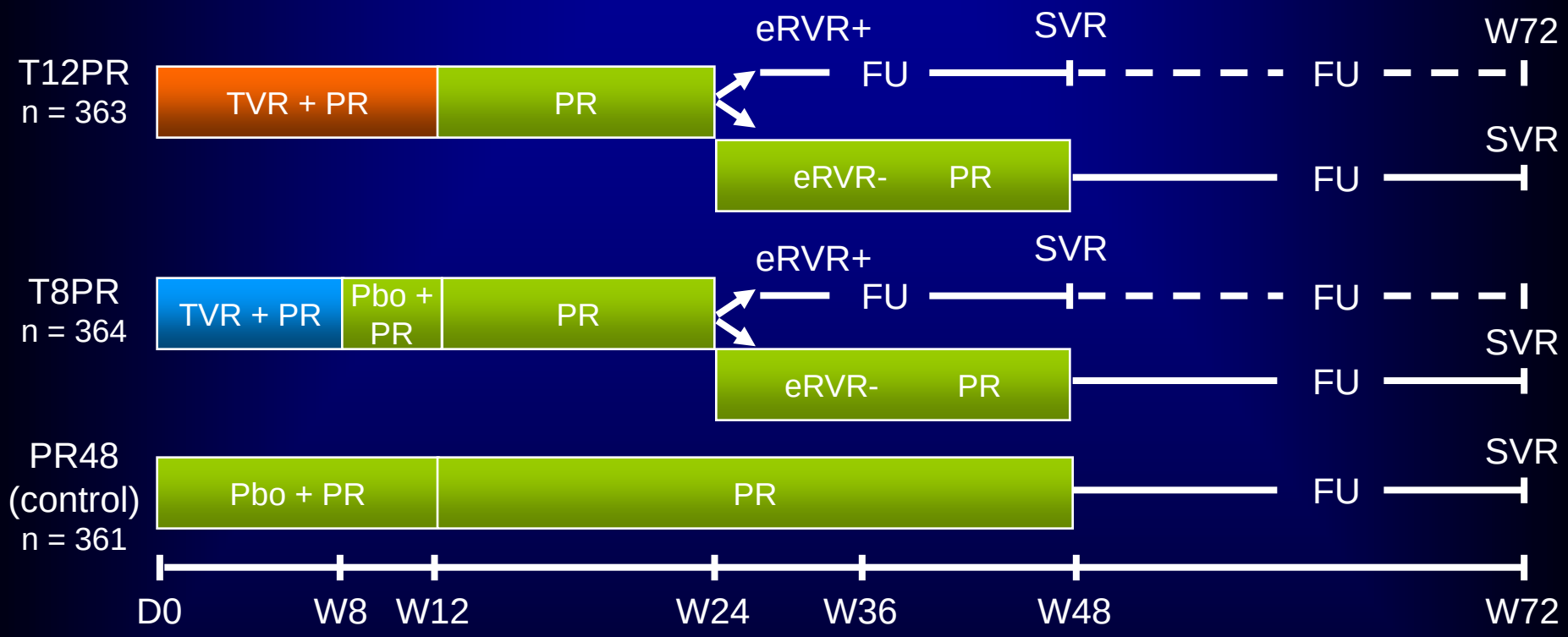
- 24 weeks of boceprevir (RGT paradigm) is as effective as 44 weeks of boceprevir (BOC/PR48) for treatment-naïve patients
  - 78 - 89% SVR in all BOC treated patients with undetectable HCV RNA by week 8
    - 60% have undetectable HCV RNA by week 8 in Cohort 1 (Non-Blacks)
  - An additional 20 weeks of PR ‘tail’ is only required for patients who first became undetectable after week 8 (4+24+20)
- PR Lead-in allows for
  - Prediction of SVR based on degree of early response
  - Determination of probability of developing boceprevir resistance-associated variants

Telaprevir in Treatment-Naïve Patients *ADVANCE Final Results*

I Jacobson. AASLD 2010 a211

Jacobson AASLD 2010, a211

Study design



P: PEG-IFNα-2a 180 µg/sem. + RBV 1000-1200 mg/j
T: telaprevir 750 mg/8 h
eRVR: HCV RNA < 25 UI/ML at W4 and W12

Jacobson AASLD 2010, a211

ADVANCE Stopping Rules

Time	Criteria for Stopping	Action
Week 4	HCV-RNA > 1000 IU/mL	DC TVR, Continue PR
Week 12	HCV-RNA < 2log decline	DC all Treatment
Week 24-40	HCV- RNA Detectable	DC all Treatment

Jacobson AASLD 2010, a211

Baseline characteristics

	T12PR N = 363	T8PR N = 364	PR N = 361
Males (%)	59	58	58
Caucasians (%)	90	87	88
Black (%)	7	11	8
Age (median)	49	49	49
BMI (median)	26	26	26
HCV RNA ≥ 800000 (%)	77	77	77
G1 subtypes (%)	59	58	58
1a	41	41	42
1b	<1	1	1
1, unknown			
Bridging fibrosis (%)	14	16	14
Cirrhosis (%)	6	7	6

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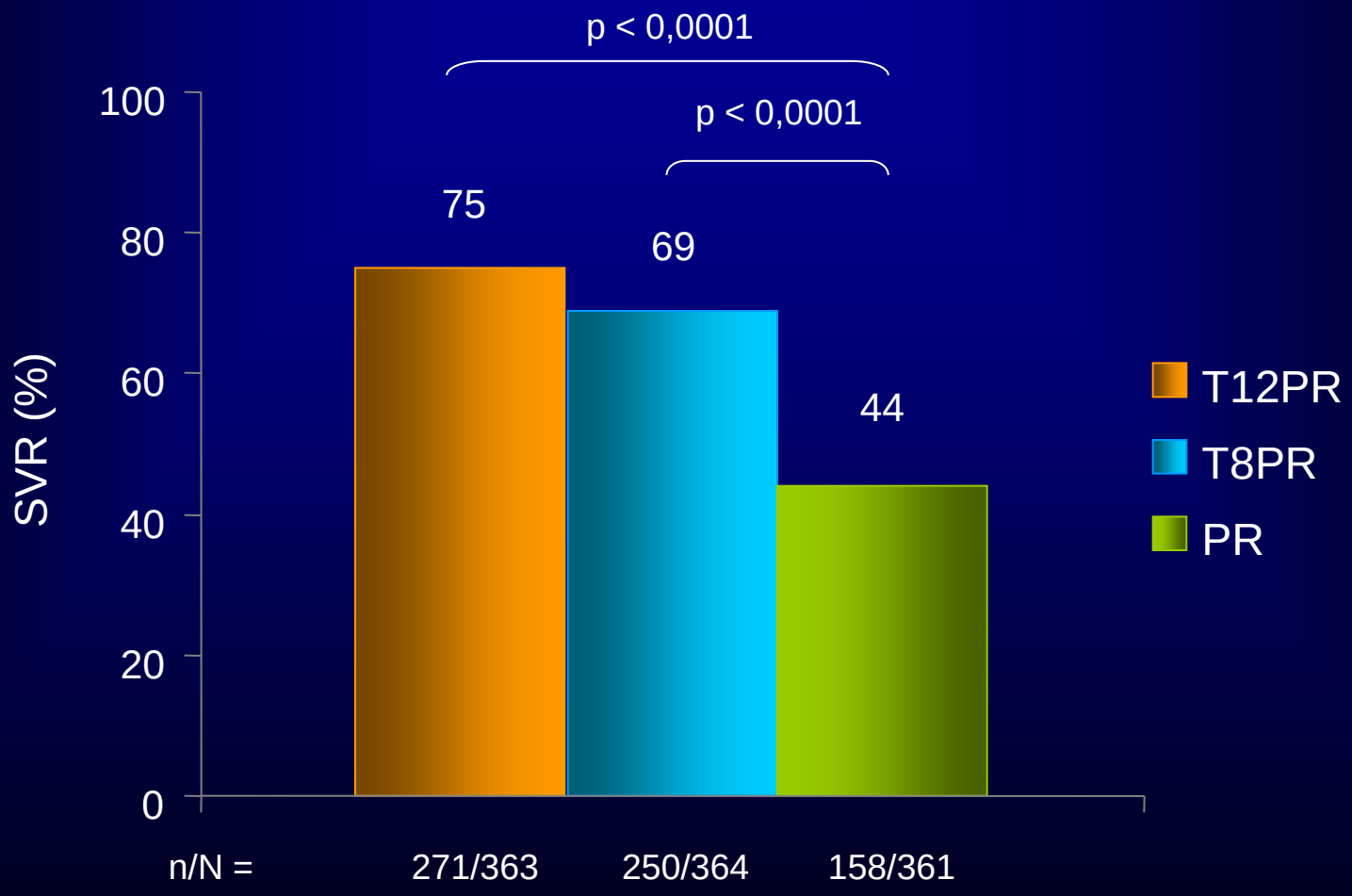
Sustained Virological Response



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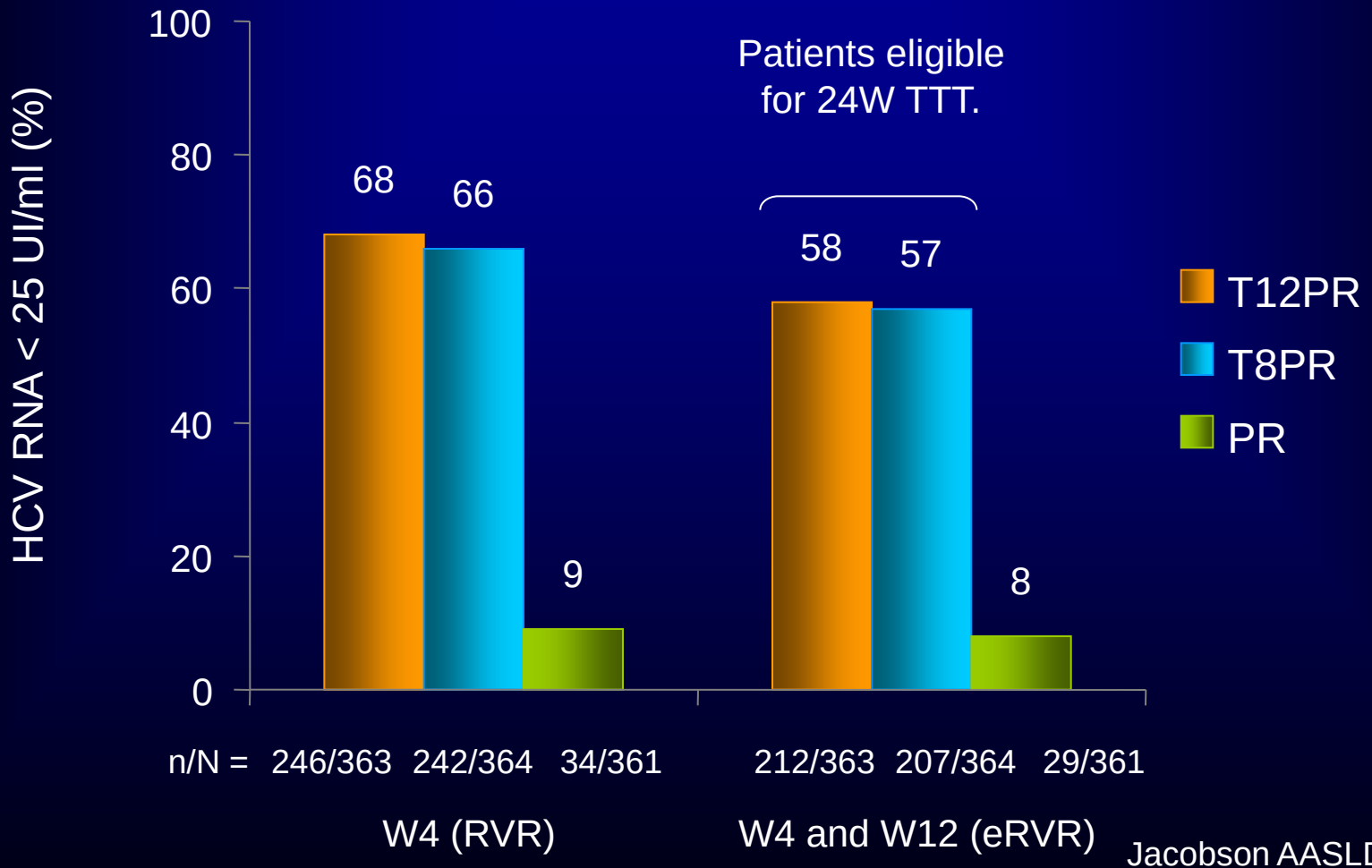
Virological response during treatment



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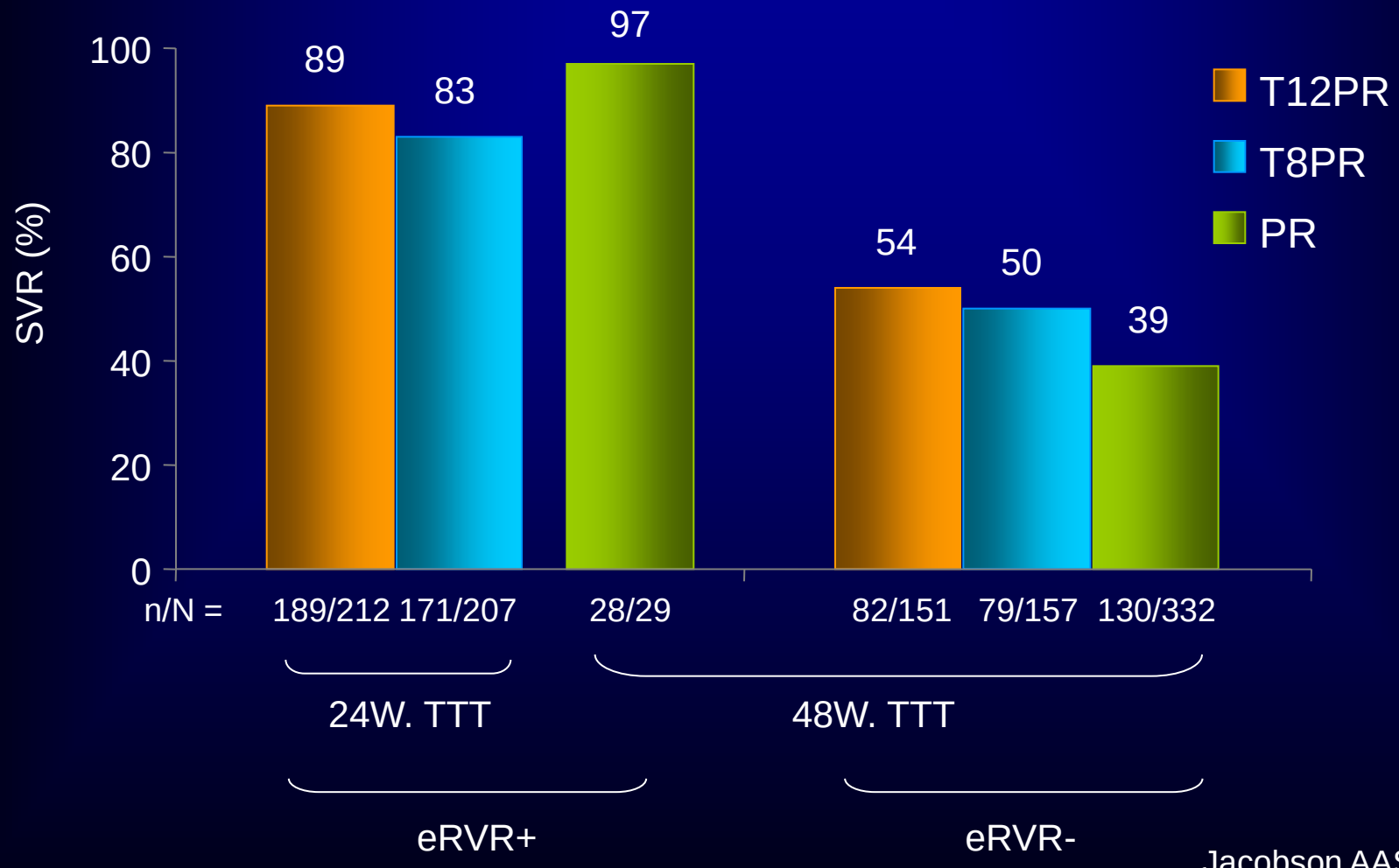
SVR according to eRVR



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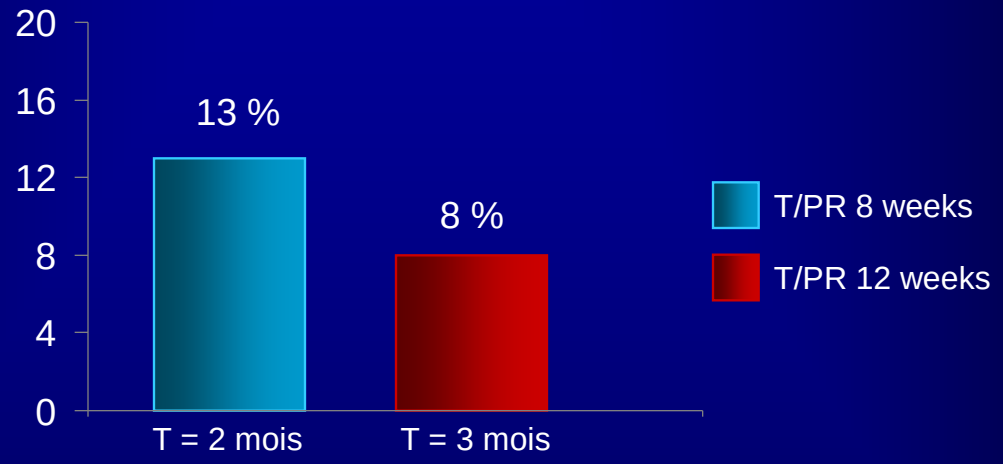
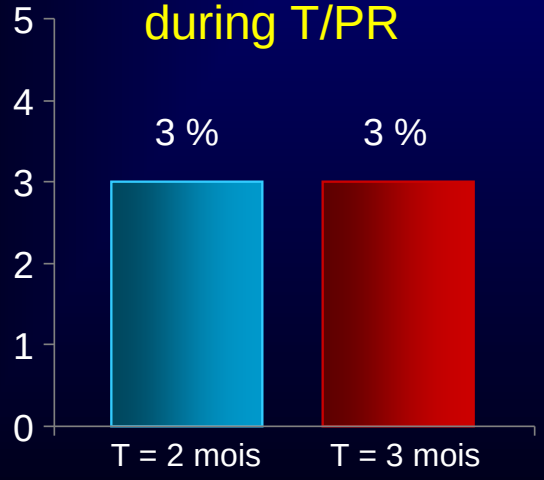
ADVANCE: treatment failure

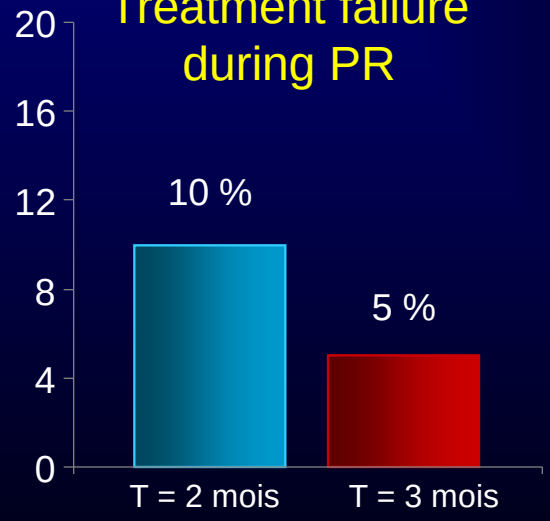
Global treatment failure



Treatment failure during T/PR



Treatment failure during PR



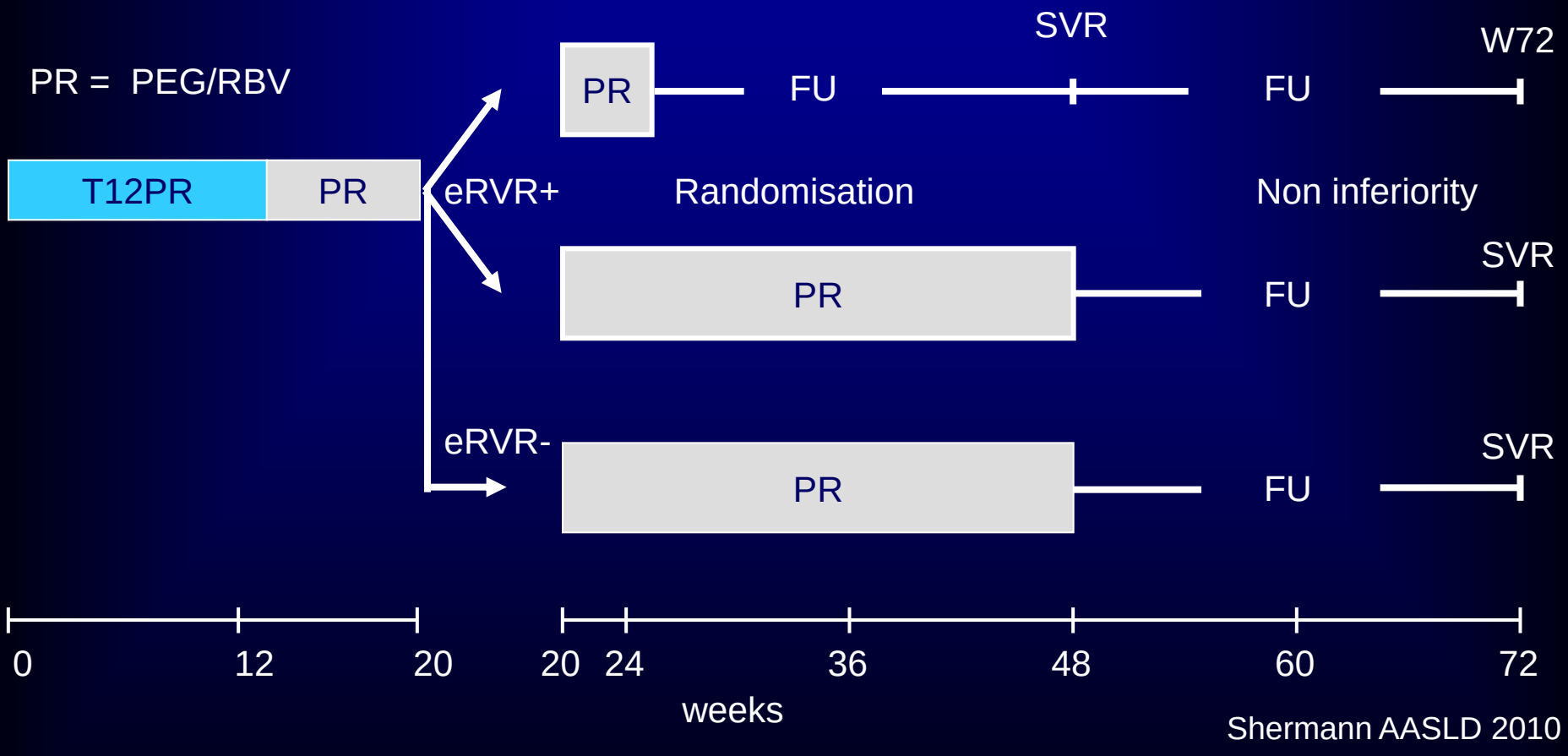
Kieffer TL AASLD 2010

Telaprevir in Treatment-Naïve Patients *Illuminate Results*

Shermann. AASLD 2010

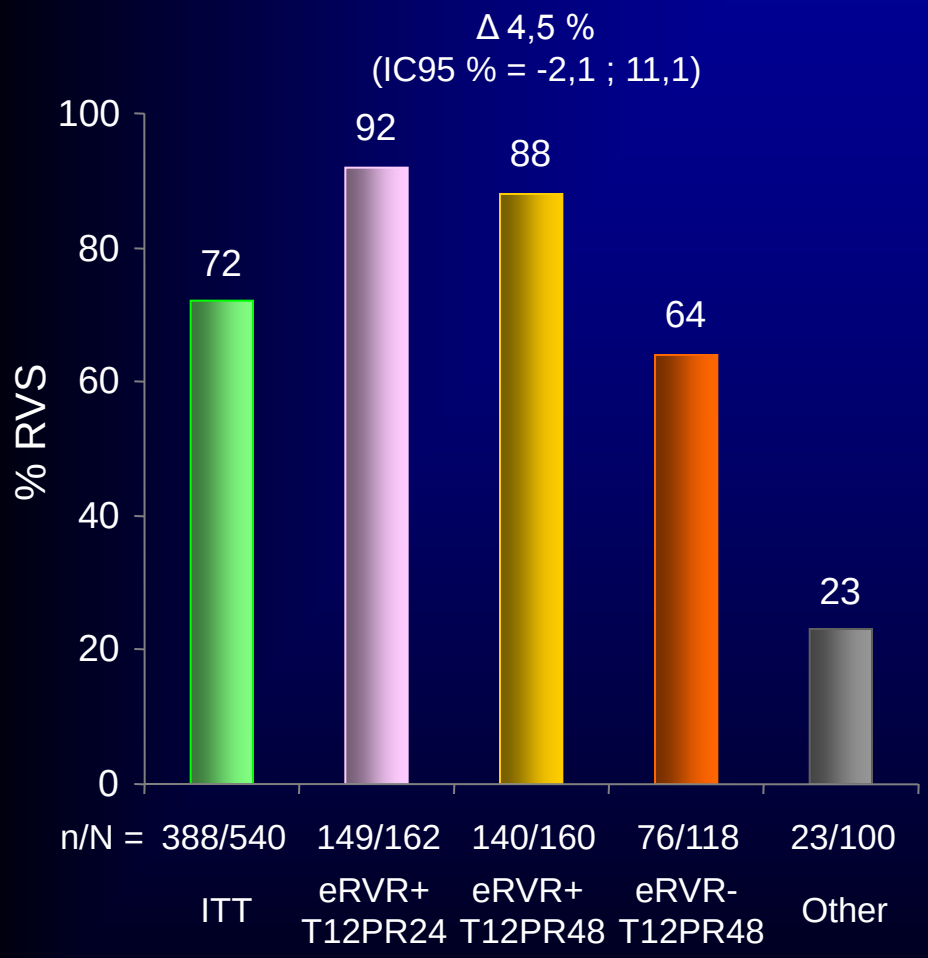
Jacobson AASLD 2010

Illuminate study: Study design

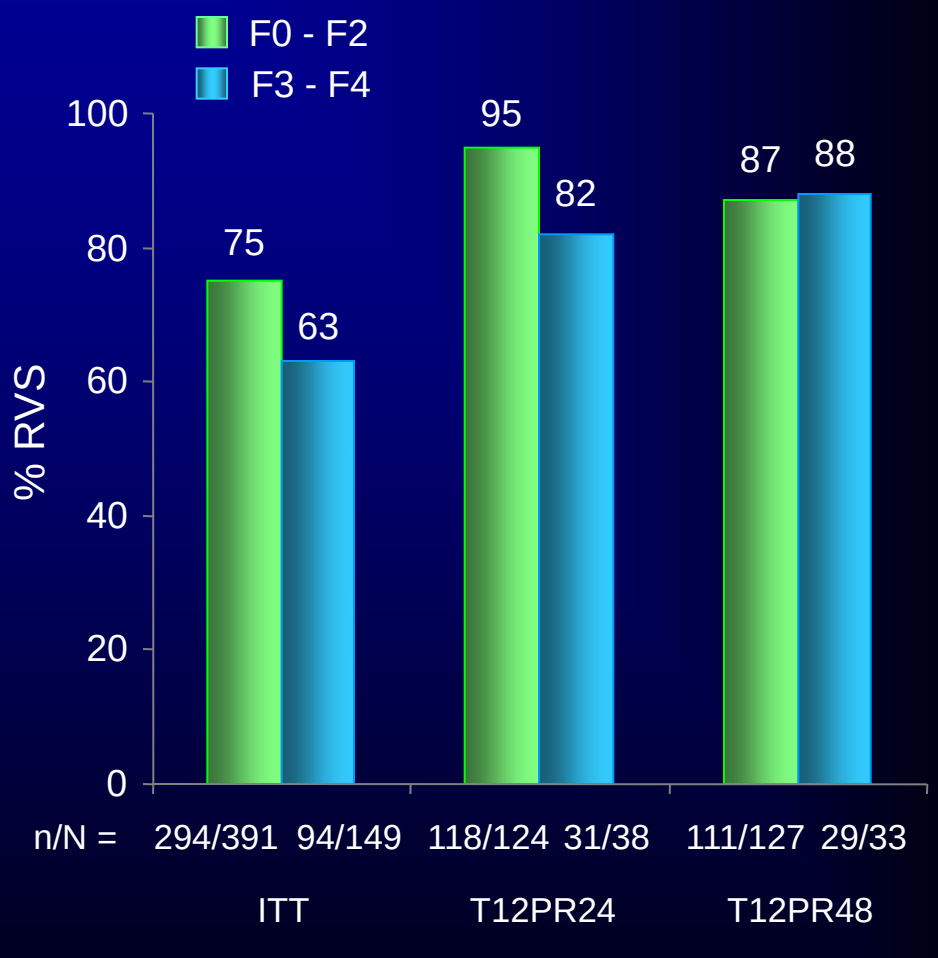


Illuminate: SVR

SVR



SVR according to fibrosis



Shermann AASLD 2010

EFFICACY IN PREVIOUS NON RESPONDERS OR RELAPSERS

HCV RESPOND-2 Final Results

High Sustained Virologic Response Among Genotype 1 Previous Non-Responders and Relapsers to Peginterferon/Ribavirin when Re-Treated with Boceprevir Plus PEGINTRON (Peginterferon alfa-2b)/Ribavirin

Bruce R. Bacon, Stuart C. Gordon, Eric Lawitz, Patrick Marcellin, John M. Vierling, Stefan Zeuzem, Fred Poordad, Navdeep Boparai, Margaret Burroughs, Clifford A. Brass, Janice K. Albrecht, and Rafael Esteban

For the RESPOND-2 Investigators

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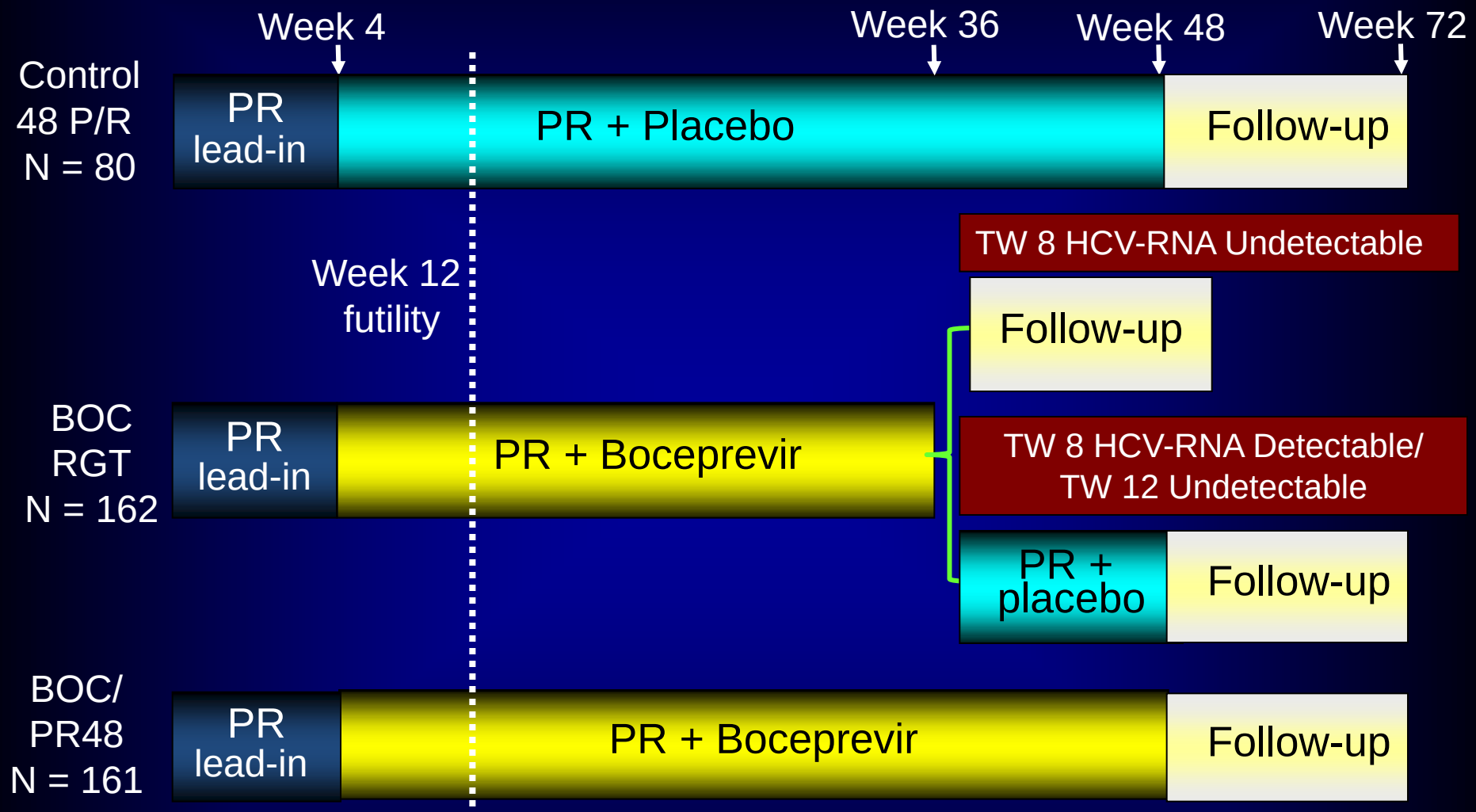
Study Arms and Dosing Regimen



HCV-RNA measured by the Cobas TaqMan assay (Roche). Patients with detectable HCV-RNA (LLD=9.3 IU/mL) at week 12 were considered treatment failures.
Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus Ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose
Boceprevir dose of 800 mg thrice daily

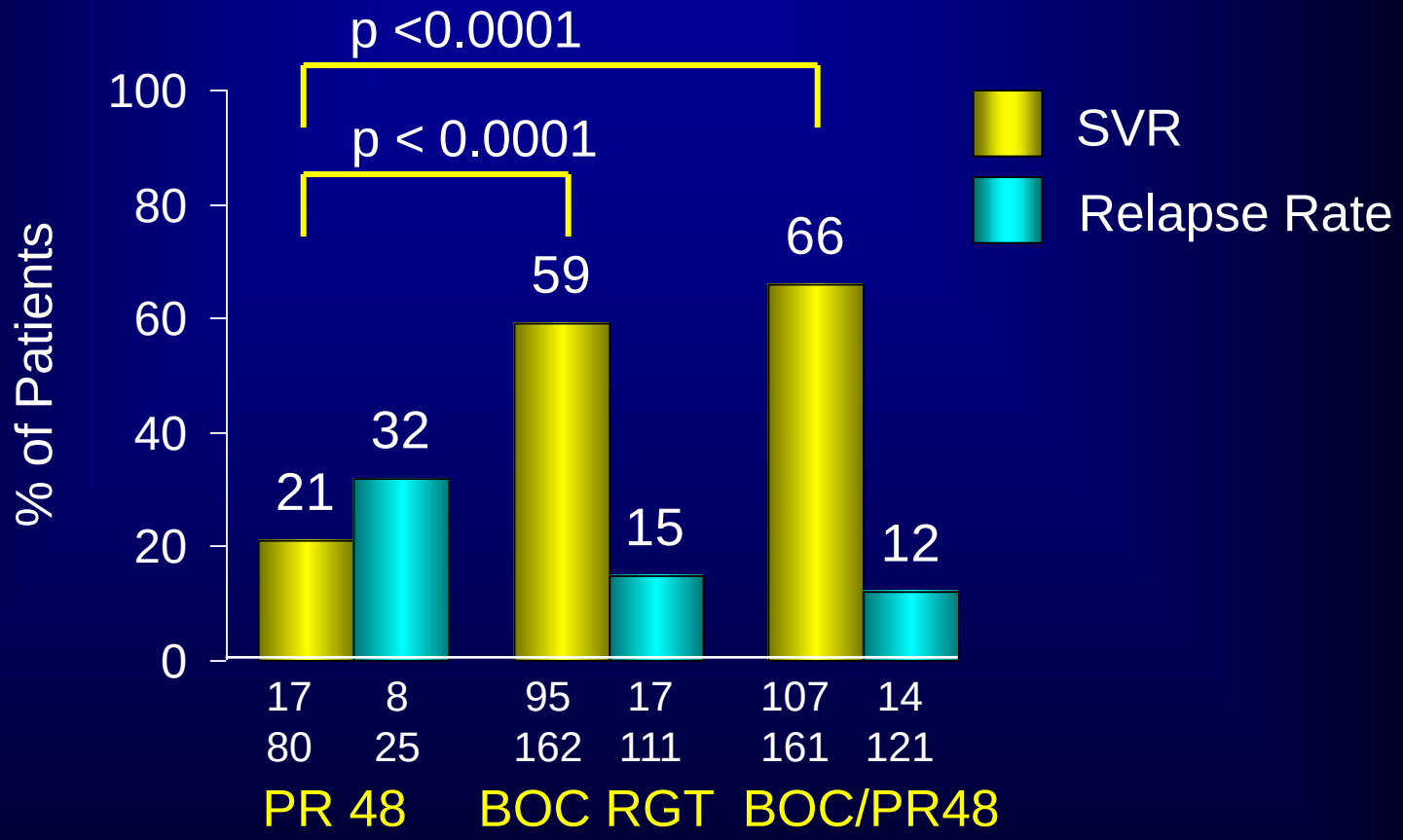
Baseline Characteristics

	Arm 1: 48 P/R N = 80	Arm 2: BOC RGT N = 162	Arm 3: BOC/PR48 N = 161
Mean age (years)	52.9	52.9	52.3
Male (%)	73	60	70
Black (%)	15	11	12
Region (%)			
North America	64	71	75
Europe	36	28	26
Latin America	0	1	0
BMI – mean (SD)	28 (4)	29 (5)	28 (5)
HCV subtype (%)*			
1a	48	46	48
1b	45	46	42
HCV RNA level >800,000 IU/mL (%)	81	91	88
METAVIR F3/F4 (%)	19	20	19
Non-responder (%)	36	35	36
Relapser (%)	64	65	64

*Subtyping performed by NS5B sequencing (Virco, Mechelen, Belgium)

RESPOND-2 SVR and Relapse Rates

Intention to treat population



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

12-week HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161), respectively.

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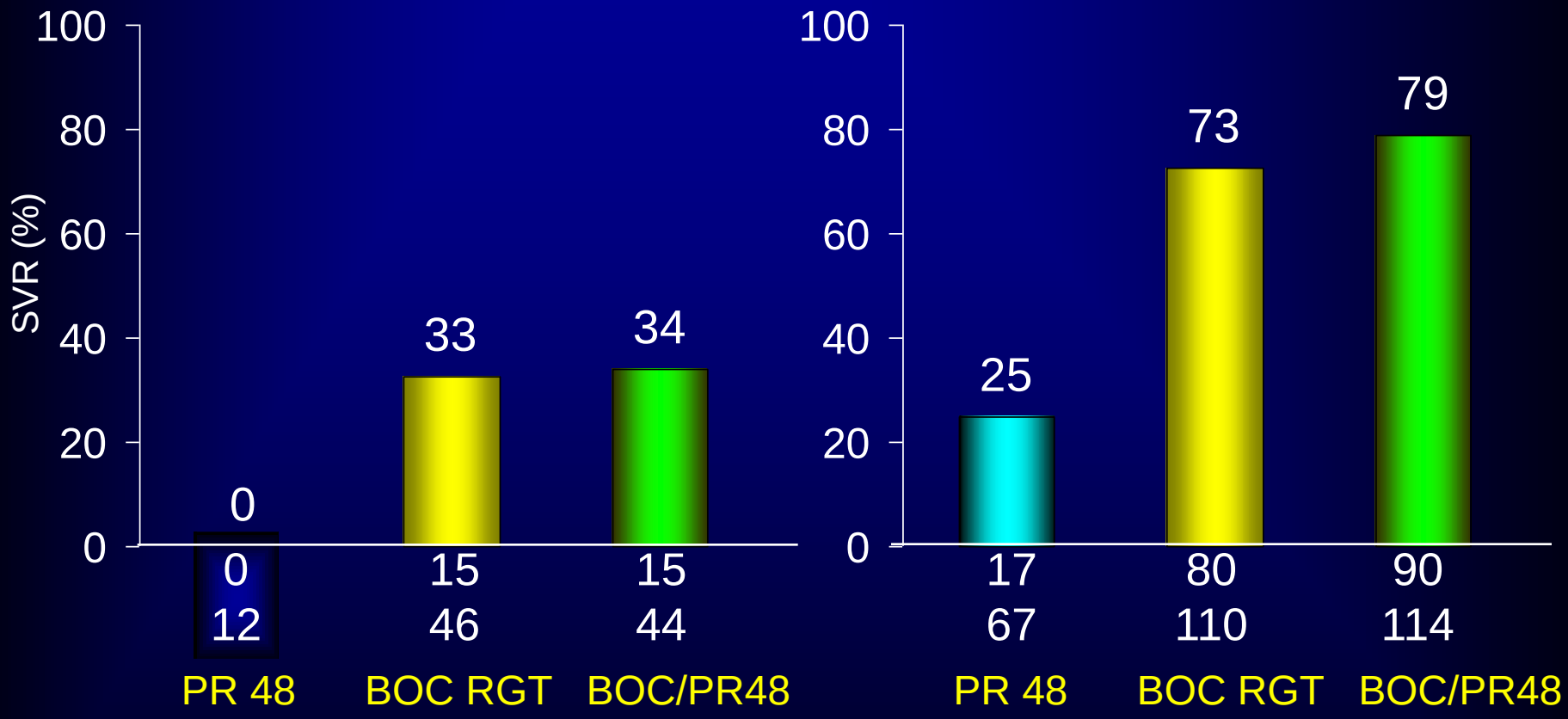
SVR by Week 4 PR Lead-In Response



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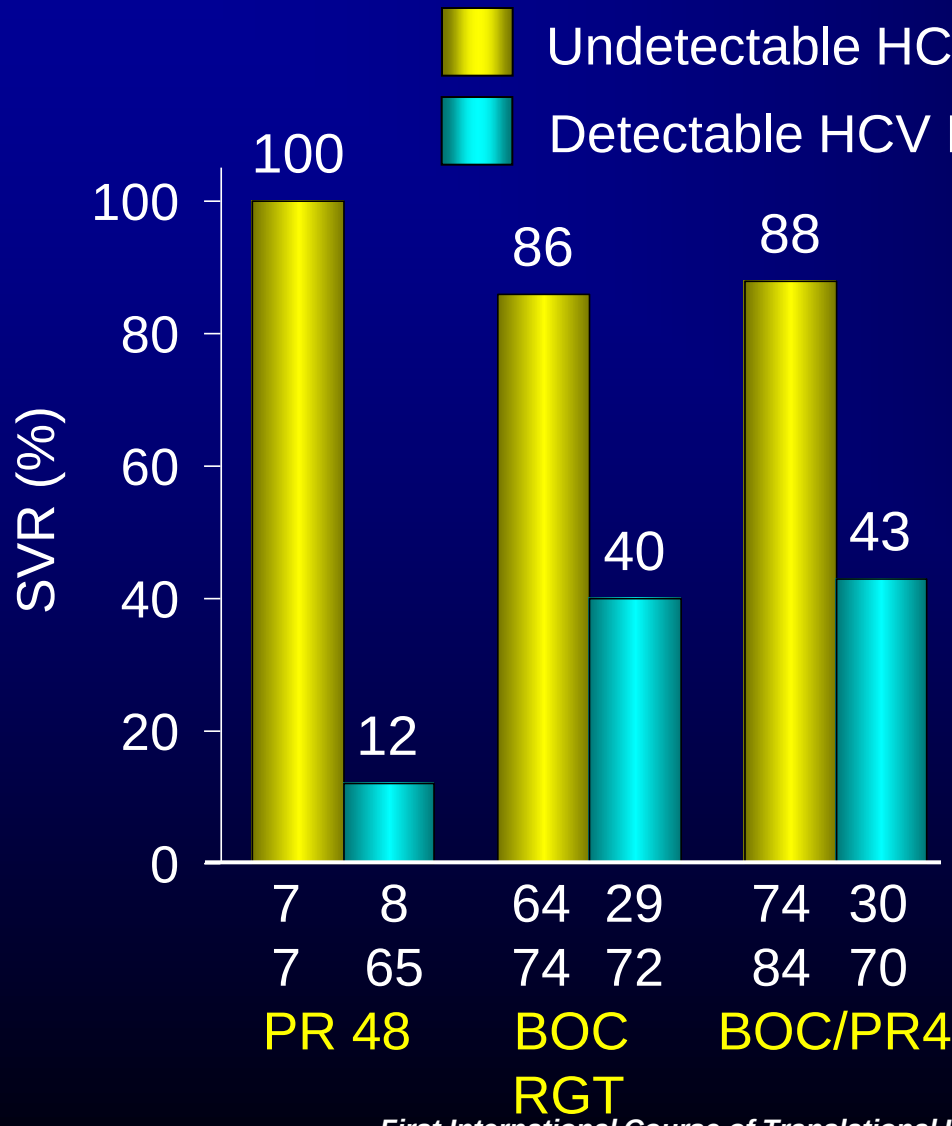
SVR by Week 8 HCV RNA Response
Intention to Treat Population



- 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%)

SVR by Historical Response Non-responders and Relapsers*

	Arm 1: 48 P/R N = 80	Arm 2: BOC RGT N = 162	Arm 3: BOC/PR48 N = 161
Non-responder – n/n (%)	**2/29 (6.9)**	**23/57 (40.4)**	**30/58 (51.7)**
Relapser – n/n (%)	**15/51 (29.4)**	**72/105 (68.6)**	**77/103 (74.8)**

*Non-responders had a decrease in plasma HCV-RNA of at least 2-$\log_{10}$ by week 12 of prior therapy but with detectable HCV-RNA throughout the course of therapy. Relapsers had undetectable HCV-RNA at end of prior therapy without subsequent attainment of a sustained virologic response.

PR 4 Week Lead-In As a Predictor of Response

- **26% (102/393) of RESPOND-2 patients had a < 1 log_{10} decline in HCV viral load at week 4**
- **Interferon responsiveness may not remain constant over time**
- **Lead-in allows real time assessment of patient's interferon responsiveness vs. historic response**

Summary and Conclusions

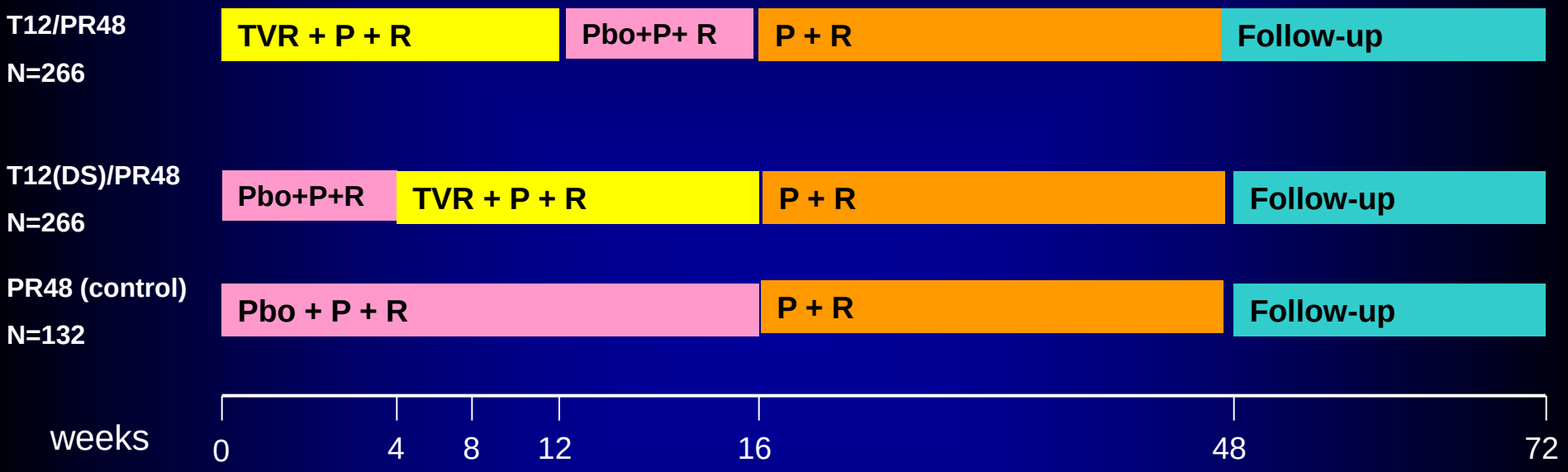
- **Boceprevir added to PR significantly increased SVR compared to PR control**
  - **Can be used to treat patients with all categories of interferon responsiveness**
- **RGT and BOC/PR 48 were equally effective for treatment failure patients**
- **PR lead-in allows for real time assessment of patient's interferon responsiveness**
  - **Poorly responsive: 33-34% achieved SVR vs 0% in control**
  - **Responsive: 73-79% achieved SVR vs 26% in control**

REALIZE: Study Objectives

- International, randomized, double-blind, multicenter, placebo-controlled Phase III trial
  - Trial included relapsers, partial and null responders (patients with <2 log_{10} HCV RNA decline at Week 12 with Peg-IFN/RBV therapy)
- Primary objective:
  - To evaluate superior efficacy (proportion of patients achieving an SVR) of TVR-based therapy compared with standard treatment in patients within the prior relapser and prior non-responder (partials/ nulls) group
- Key secondary objectives
  - Evaluation of effect of Peg-IFN/RBV lead-in on efficacy of TVR-based treatment
  - Assessment of safety and tolerability of TVR-based treatment

SVR = sustained virologic response (i.e. undetectable plasma HCV RNA 24 weeks after the last planned intake of study medication using the COBAS TaqMan® assay (Roche,Switzerland), version 2.0 (lower limit of quantification 25 IU per milliliter); **TVR** = telaprevir

Telaprevir in HCV G1 patients with prior null response, partial response or relapse



Peginterferon alfa-2a (P) administered subcutaneously at 180 µg once weekly; ribavirin (R) 1,000-1,200 mg/day; telaprevir (TVR) 750 mg every 8 hours.

REALIZE TRIAL: study design

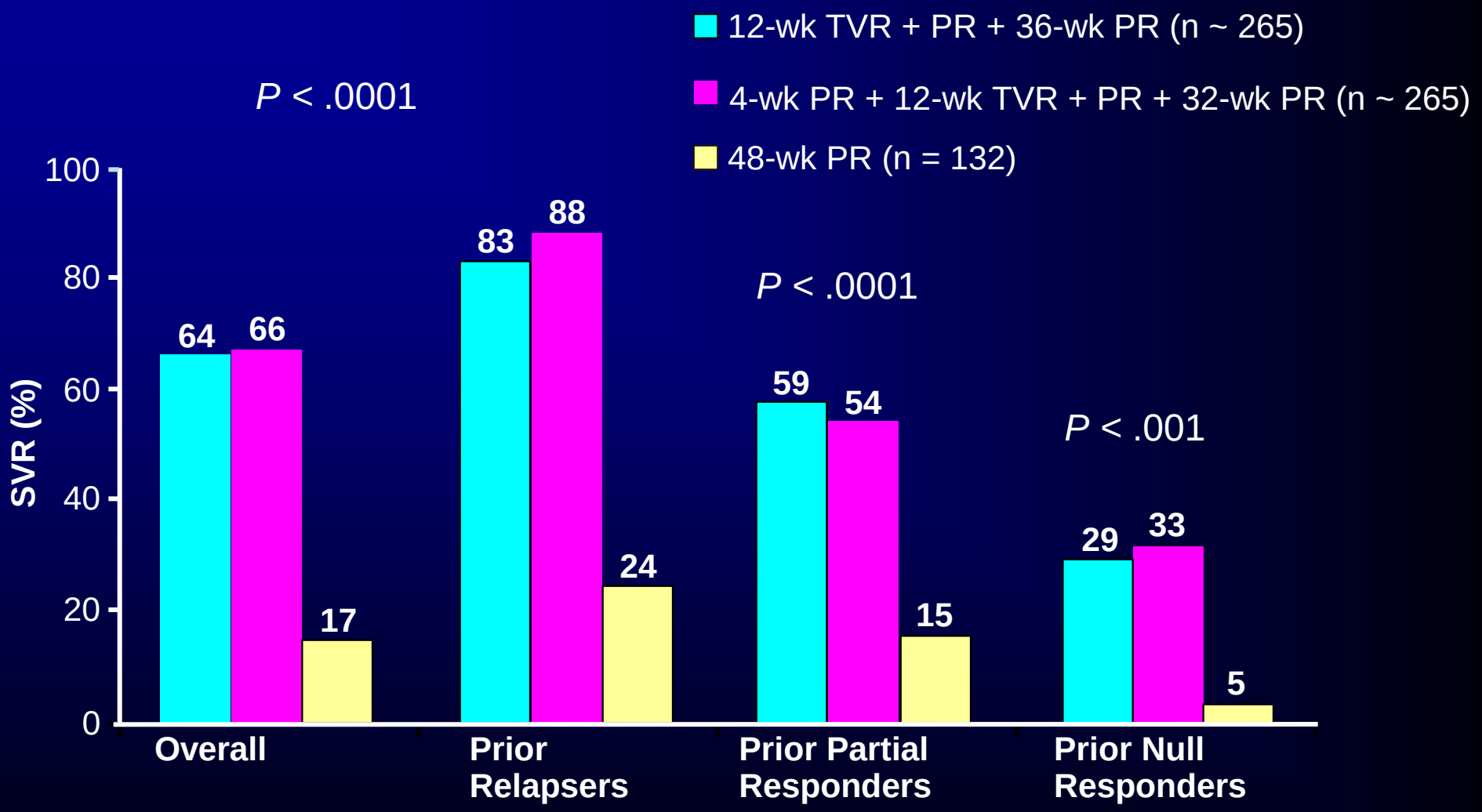
Foster GR, et al. APASL 2011

REALIZE: Baseline Characteristics

Characteristic	T12/PR48 (n=266)	T12(DS)/PR48 (n=264)	Pbo/PR48 (n=132)
Male, n (%)	183 (69)	189 (72)	88 (67)
Caucasian race, n (%)	246 (92)	252 (95)	117 (89)
Black race, n (%)	11 (4)	8 (3)	11 (8)
Years of age, median (range)	51 (23–69)	51 (24–70)	50 (21–69)
HCV RNA ≥800,000 IU/mL, n (%)*	238 (89)	234 (89)	114 (86)
HCV genotype, n (%)‡			
1a	136/262 (52)	149/262 (57)	67/128 (52)
1b	126/262 (48)	113/262 (43)	61/128 (48)
Prior response, n (%)			
Null responder	72 (27)	75 (28)	37 (28)
Partial responder	49 (18)	48 (18)	27 (20)
Relapser	145 (55)	141 (53)	68 (52)
Bridging fibrosis, n (%)§	60 (23)	58 (22)	29 (22)
Cirrhosis, n (%)§	72 (27)	67 (25)	30 (23)

*Determined using the COBAS TaqMan HCV assay version 2.0; ‡Determined by NS3 sequencing; §Defined by local pathologists

REALIZE: SVR rates according to treatment arm and prior response



Foster GR, et al. APASL 2011

REALIZE: Conclusions

- TVR/Peg-IFN/RBV was superior to Peg-IFN/RBV in treatment-experienced populations including null responders, partial responders and relapsers
- A lead-in strategy using TVR-based regimen did not improve SVR rates or reduce on-treatment virologic failure and relapse rates
- Safety data were comparable to previous TVR studies. Adverse events leading to permanent discontinuation of telaprevir (mainly anemia and rash) were more frequent in the pooled telaprevir group than in the control group

SAFETY

BOCEPREVIR

Safety Profile Over Entire Course of Therapy

	48 PR n=363	BOC RGT n=368	BOC/PR48 n=366
Median treatment duration, days	203	197	335
Deaths	N=4	N=1	N=1
Serious AEs	9%	11%	12%
Discontinued due to AEs	16%	12%	16%
Dose modification due to AEs	26%	40%	35%
Hematologic parameters			
Neutrophil count (<750 to 500/mm^3 / <500/mm^3)	14% / 4%	24% / 6%	25% / 8%
Hemoglobin (<10 to 8.5 g/dL / <8.5 g/dL)	26% / 4%	45% / 5%	41% / 9%
Discontinuation due to anemia	1%	2%	2%
Dose reductions due to anemia	13%	20%	21%
Erythropoietin use	24%	43%	43%
Mean (median) days of use	121 (109)	94 (85)	156 (149)

Most Common Treatment-Related Adverse Events*

Adverse Event	Arm 1 (PR48); n=363 (%)	Arm 2 (RGT); n=368 (%)	Arm 3 (BOC/PR48); n=366 (%)
Fatigue	59	52	57
Headache	42	45	43
Nausea	40	46	42
Anemia	29	49	49
Dysgeusia	18	37	43
Chills	28	36	33
Pyrexia	32	33	30
Insomnia	32	31	32
Alopecia	27	20	28
Decreased Appetite	25	26	24
Pruritis	26	23	25
Neutropenia	21	25	25
Influenza Like Illness	25	23	22
Myalgia	26	21	24
Rash	22	24	23
Irritability	24	22	22
Depression	21	23	19
Diarrhea	19	19	23
Dry Skin	18	18	22
Dyspnea	16	18	22
Dizziness	15	21	17

*Reported in >20% of patients in any treatment arm and listed by decreasing overall frequency

Summary - Safety

- Anemia and dysgeusia occurred more often in the boceprevir groups than the control groups (20% and 19-25% higher, respectively)
- Discontinuation due to anemia occurred in ≤2% of patients
- SVR was higher in patients with anemia in the 3 arms
- 43 % patients received EPO

TELAPREVIR

ADVANCE: Adverse events

% of patients	T12PR	T8PR	PR
Any AE	99	99	98
Fatigue	57	58	57
Pruritus	50	45	36
Headache	41	43	39
Nausea	43	40	31
Rash	37	35	24
Anemia	37	39	19
Insomnia	32	32	31
Diarrhea	28	32	22
Influenza-like sd	28	29	28
Pyrexia	26	30	24

Adverse events

% of patients	T12PR	T8PR	PR
Rash events	56	53	36
Severe rash events	6	3	1
Discontinuation of telaprevir/placebo only due to rash events	7	5	1
Discontinuation of all drugs due to rash events	1.4	0.5	0
Discontinuation of telaprevir/placebo due to AE during Tela/placebo phase	11	7	1
Discontinuation of all drugs due to AE during Tela/placebo phase	7	8	4

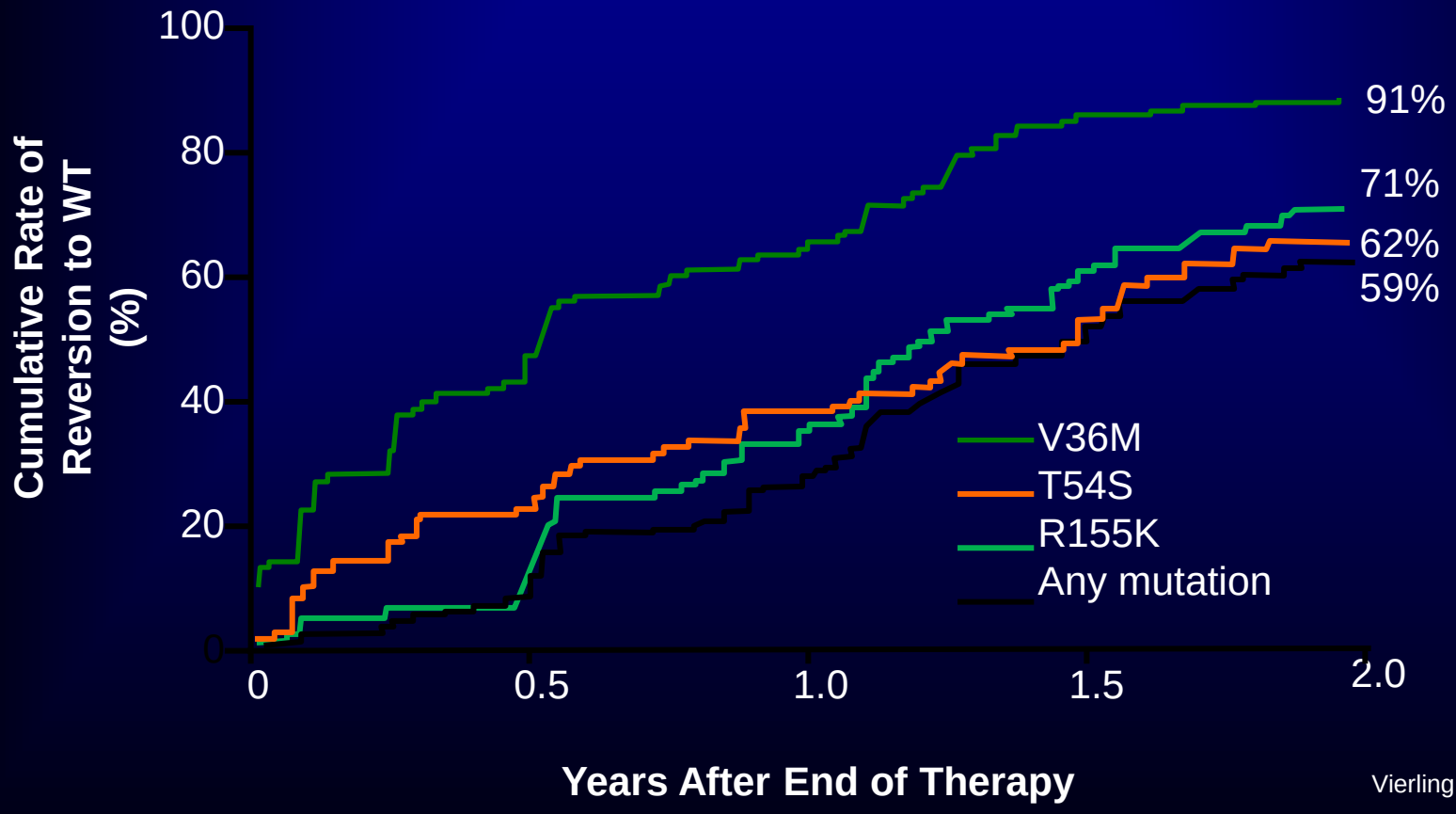
RASH induced by telaprevir

- Are not comparable with the rash induced by PR
- Follow up +++
- Use of steroid
- Dermatological follow up

Resistance Associated Variants (RAV)

Boceprevir Long-term Follow-up (2Y)

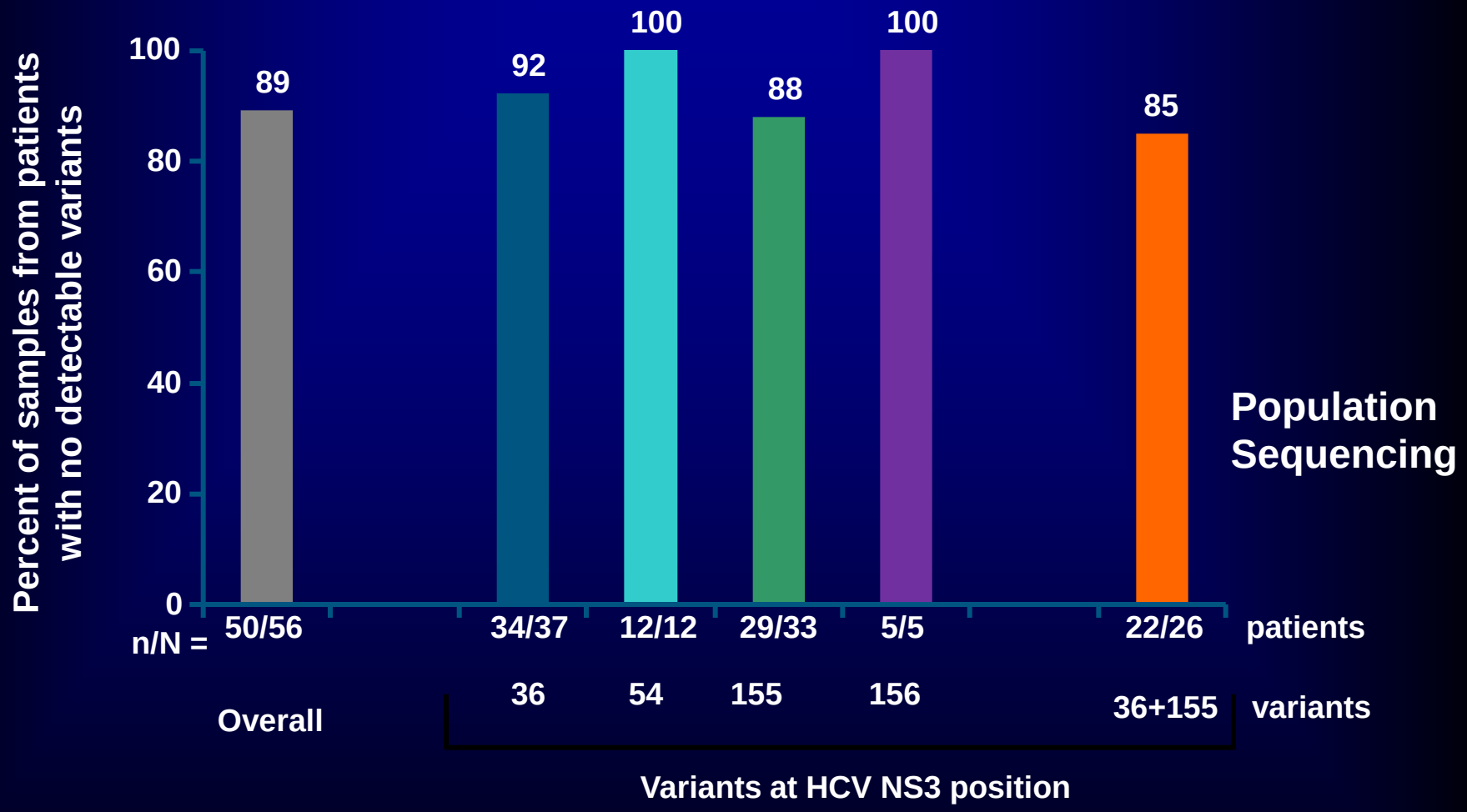
- No late relapse was confirmed in the 290 subjects who previously had SVR
- 174 subjects who did not achieve SVR were followed for ≥2 years (overall number of non-SVR patients?)
- No of patients (x/174, y%) with resistance mutations?



Vierling JM, et al. EASL 2010

EXTEND STUDY:

89% of Patients with resistance observed during PR+TPV No Longer Have Detectable Resistant Variants



- Median follow-up time from end of prior study of 25 months (range 7-36)

Variant categories are not mutually exclusive

Similarities and Differences in Phase III Studies of TVR and BOC

Parameter	TVR	BOC
PR lead-in	No	Yes: 4 wks
Peginterferon alfa formulation	2a	2b
PI dosing requirements	TID; administer with fatty meal	TID
Duration of PI triple therapy Naives	8-12 wks followed by 16-12 (RGT) or 40 wks PR	24 (RGT) or 44 wks after 4 wks PR lead-in
Duration of PI triple therapy Non Responders	8-12 wks followed by 36-40 wks PR Null Responders Included	32 (RGT) or 44 wks after 4 wks PR lead-in Null Responders excluded
Qualification for shortened therapy (response guided)	eRVR	RVR (Wk 4 after addition of BOC; Wk 8 with triple therapy ongoing)
Qualified for shortened therapy, %	58 (24 wks)	44 (28 wks)
SVR, %	69-75	63-66
Relapse, %	9	9
Adverse events more frequent in PI arms	Rash, anemia, pruritus, nausea	Anemia, dysgeusia

INFORM-1: Dual Polymerase and Protease Inhibitors R7128 and R7227 For HCV G1.
14-Day Response Rates in Tx-Naive and Tx-Experienced G1 HCV Pts

R7128/R7227 Doses, mg	n	Pt Population	HCV RNA		
			Median Change From Baseline, Log_{10} IU/mL	< LLOQ, %	
				< 40 IU/mL	< 15 IU/mL
500/100 TID	8	Naive	-3.9	13	13
500/200 TID	8	Naive	-5.2	63	25
1000/100 TID	7	Naive	-4.8	71	29
1000/200 TID	8	Naive	-4.8	63	25
1000/900 BID	8	Naive	-5.1	88	63
1000/600 BID	8	Exp, non-null	-4.0	50	13
1000/900 BID	8	Exp, null	-4.9	50	25

- No serious adverse events, treatment-related discontinuations, or grade 3/4 laboratory abnormalities observed in any treatment arm. No evidence of emergent drug resistance during treatment

Gane EJ, et al. The Lancet 2010

Take Home

The lead –in phase paradigm

- Limit exposure to direct-acting antiviral agents (DAA) to those who can tolerate peg-interferon and ribavirin therapy
- Determine tolerance to and compliance with peginterferon/ribavirin
- May allow the identification of patients:
- - not requiring DAA (best strategy and cost/benefit: 48 weeks SOC, RGT triple, very short triple therapy, 12 weeks?, remains to be determined)

  - at higher risk of developing RAV/likelihood of SVR (Risk/benefit of DAA treatment remains to be determined)