Boceprevir Combined with Peginterferon alfa-2b/Ribavirin for Treatment-Naïve Patients with HCV Genotype 1

SPRINT-2 Final Results

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For the SPRINT-2 Investigators

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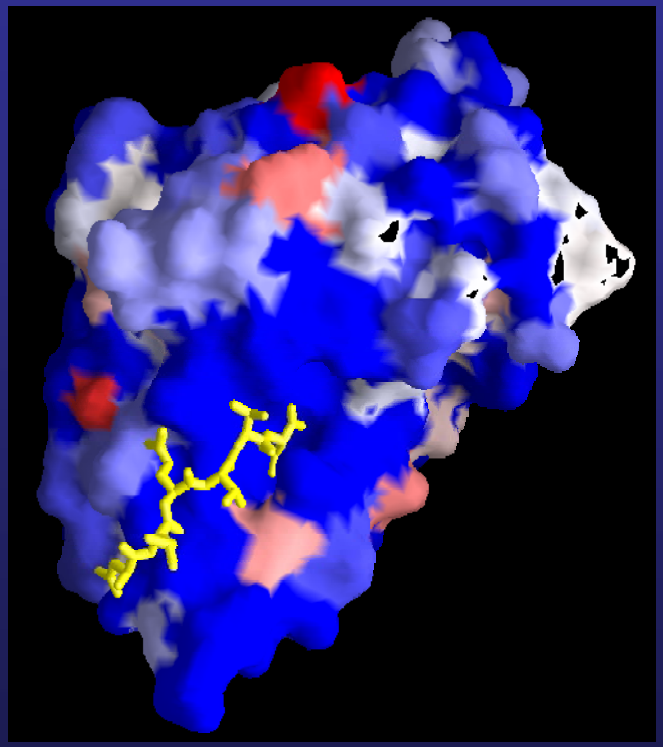
Cedars-Sinai Medical Center, Los Angeles, CA

I have been an investigator, consultant, and/or speaker within the last 12 months for:

Schering-Plough (now part of Merck), Vertex, Genentech, Bristol-Myers Squibb, Gilead, Pfizer, Salix, Idenix, Valeant, Tibotec and Abbott.

My presentation discusses investigational uses of boceprevir.

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



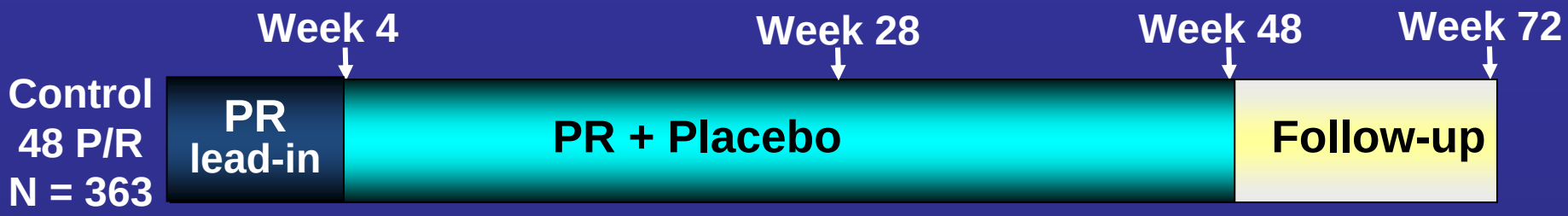
Effective against Genotype 1

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

Study Objectives

- Compare safety/efficacy of two treatment strategies with boceprevir added to peginterferon/ribavirin (PR) versus PR alone in previously untreated genotype 1 patients
- Evaluate safety/efficacy independently in two patient populations, non-black and black
- Explore response-guided therapy with 24 weeks therapy with a boceprevir regimen (BOC RGT) *vs*. 44 weeks of therapy with a boceprevir regimen (BOC/PR48) following 4 week lead-in with PR

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

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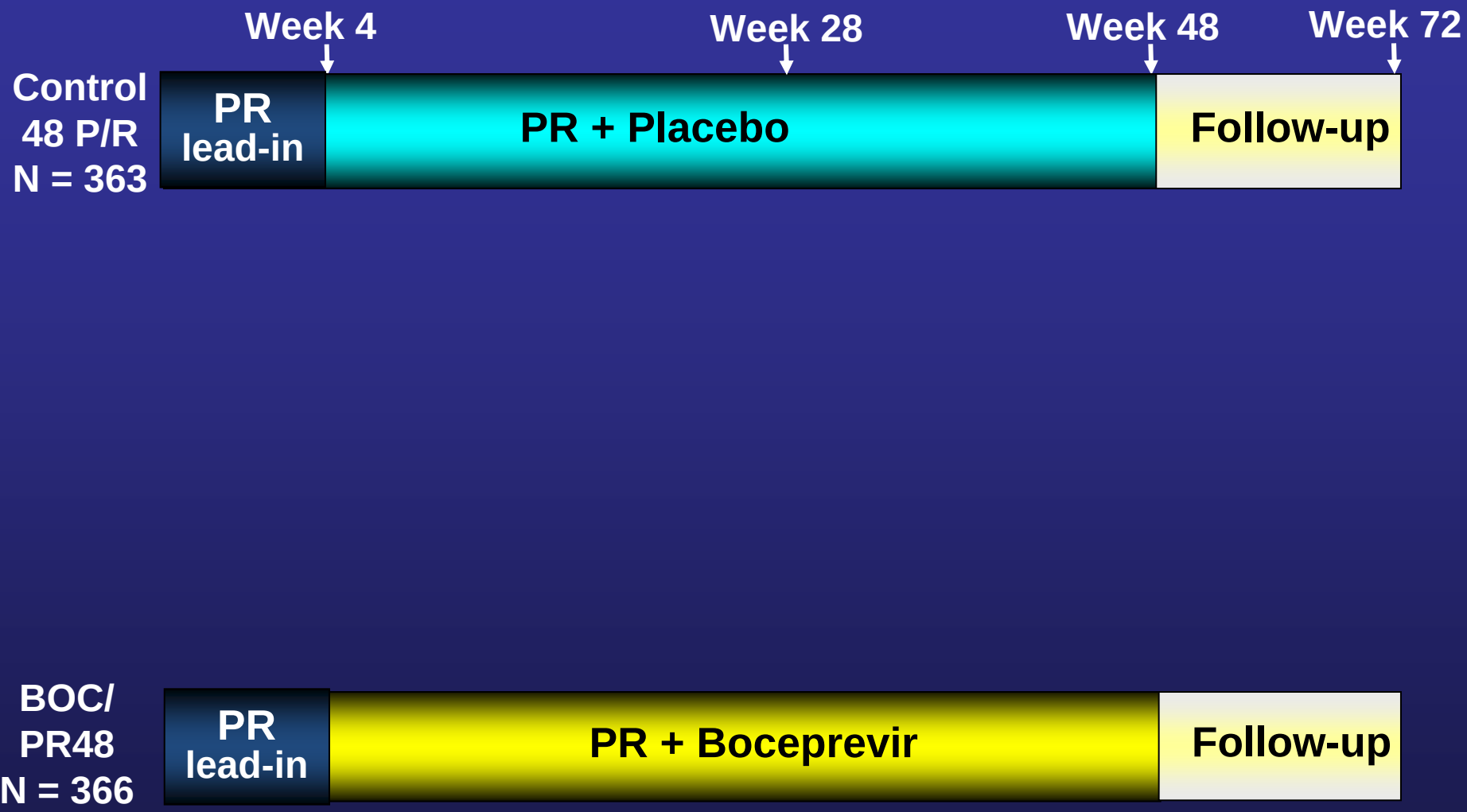

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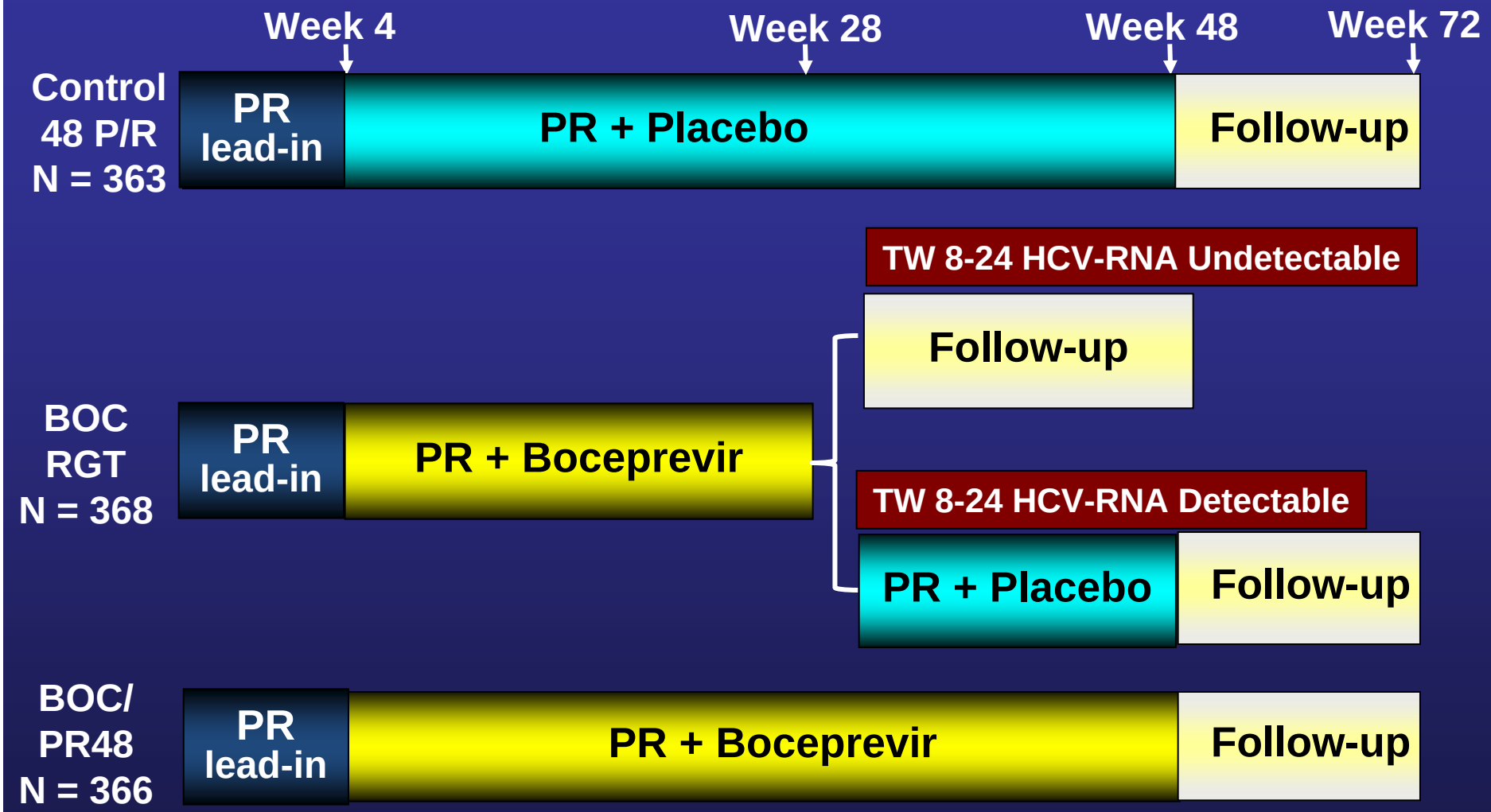

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Boceprevir dose of 800 mg thrice daily

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

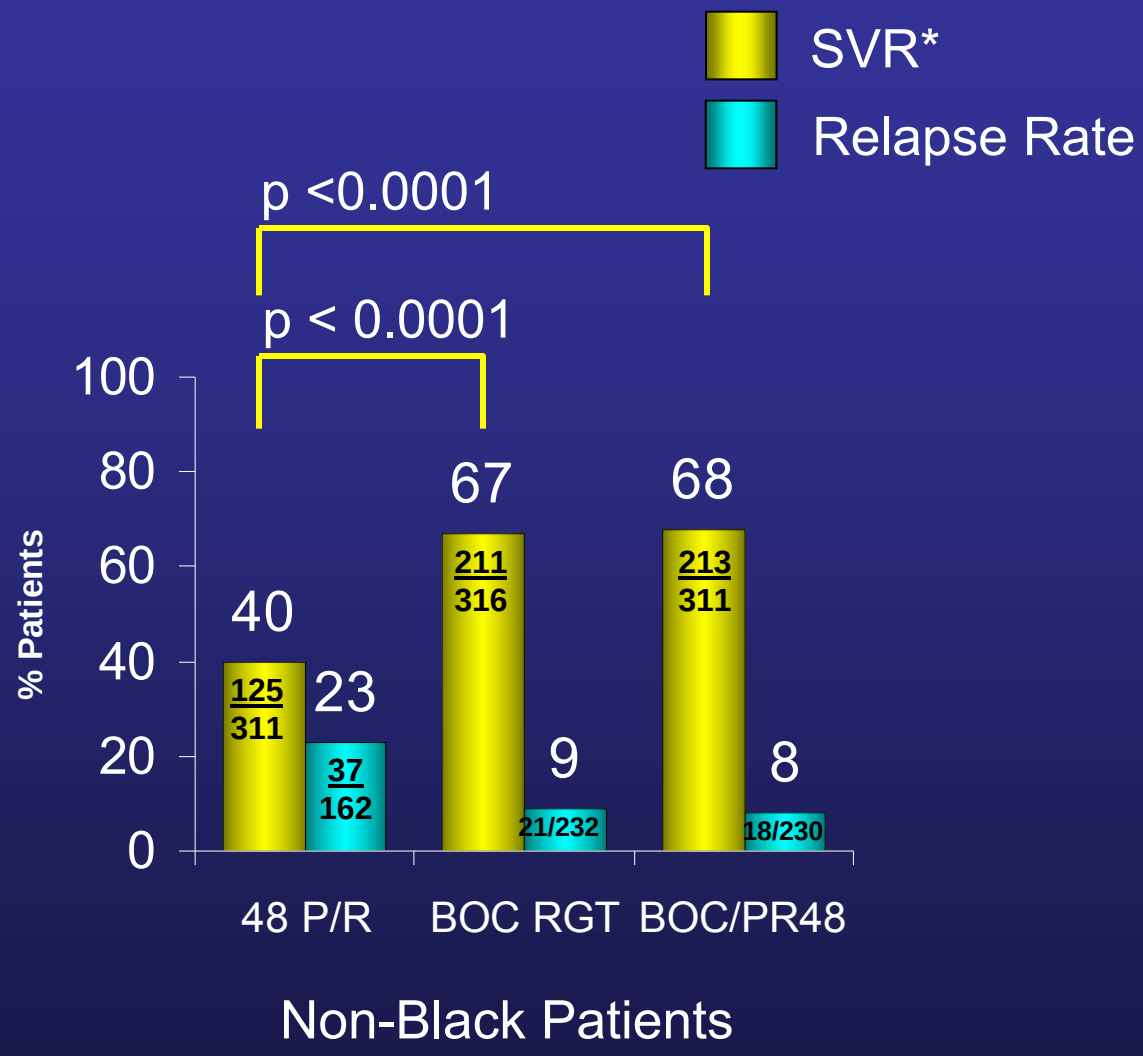
LLQ=Lower limit of quantitation; LLD=Lower limit of detection; SVR=Sustained virologic response; ITT=Intent-to-treat; mITT=Modified ITT; IU=International units

Baseline Characteristics

	Cohort 1 (Non-black)			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
Mean age (years)	48	49	49	51	52	51
Male (%)	55	63	60	67	56	60
Region (%)						
North America	65	72	70	98	98	95
Europe	32	25	27	2	2	5
BMI – mean (SD)	27 (5)	28 (5)	27 (5)	28 (4)	29 (5)	31 (6)
HCV subtype (%)*						
1a	60	62	63	79	75	73
1b	36	35	33	17	25	24
HCV RNA level						
>400,000 IU/mL (%)	92	91	93	100	94	96
METAVIR F3/F4 (%)	7	8	12	2	15	11

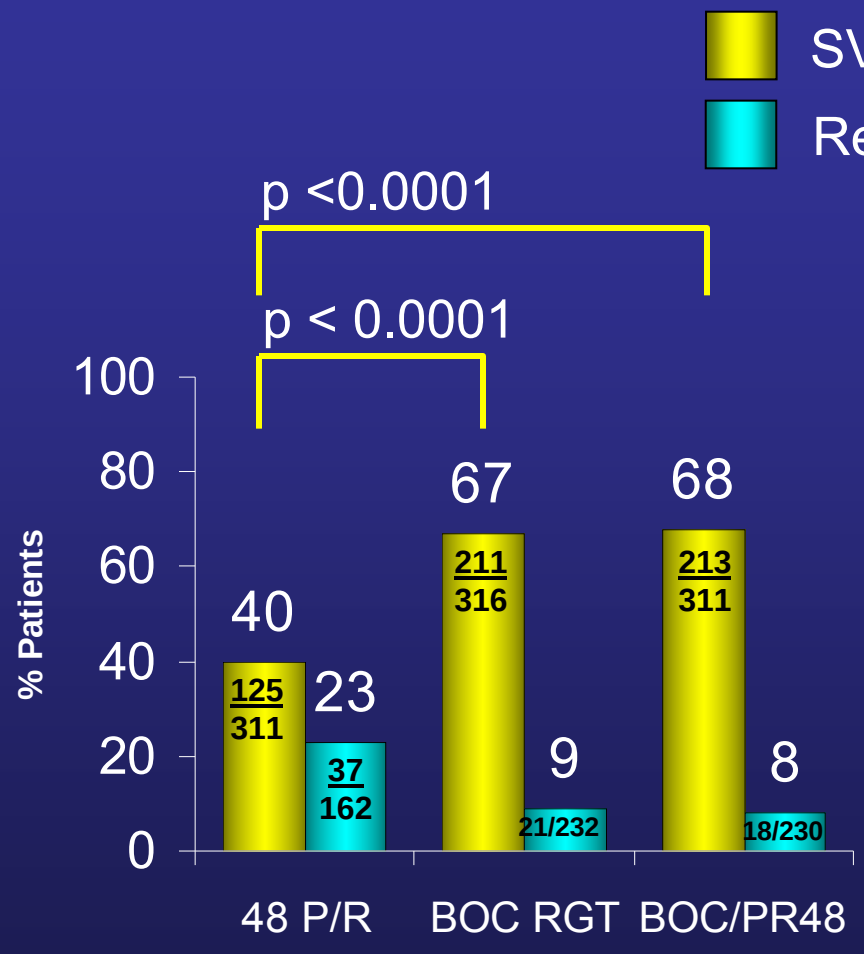
* Subtyping performed by NS5B sequencing (Virco, Mechelen, Belgium)

SPRINT 2: SVR and Relapse Rates (ITT)

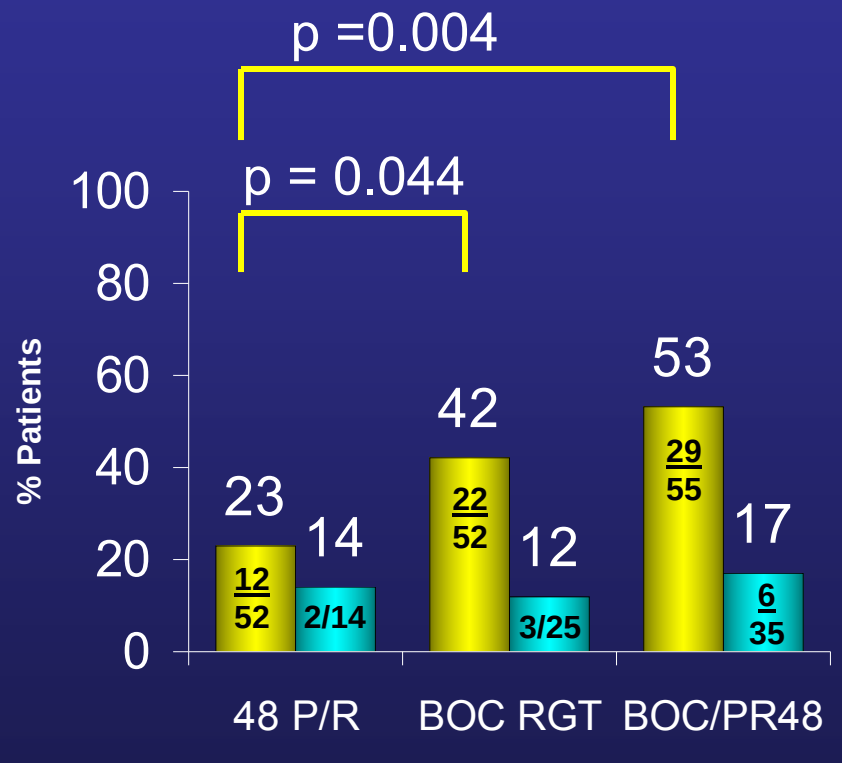


Non-Black Patients

SPRINT 2: SVR and Relapse Rates (ITT)



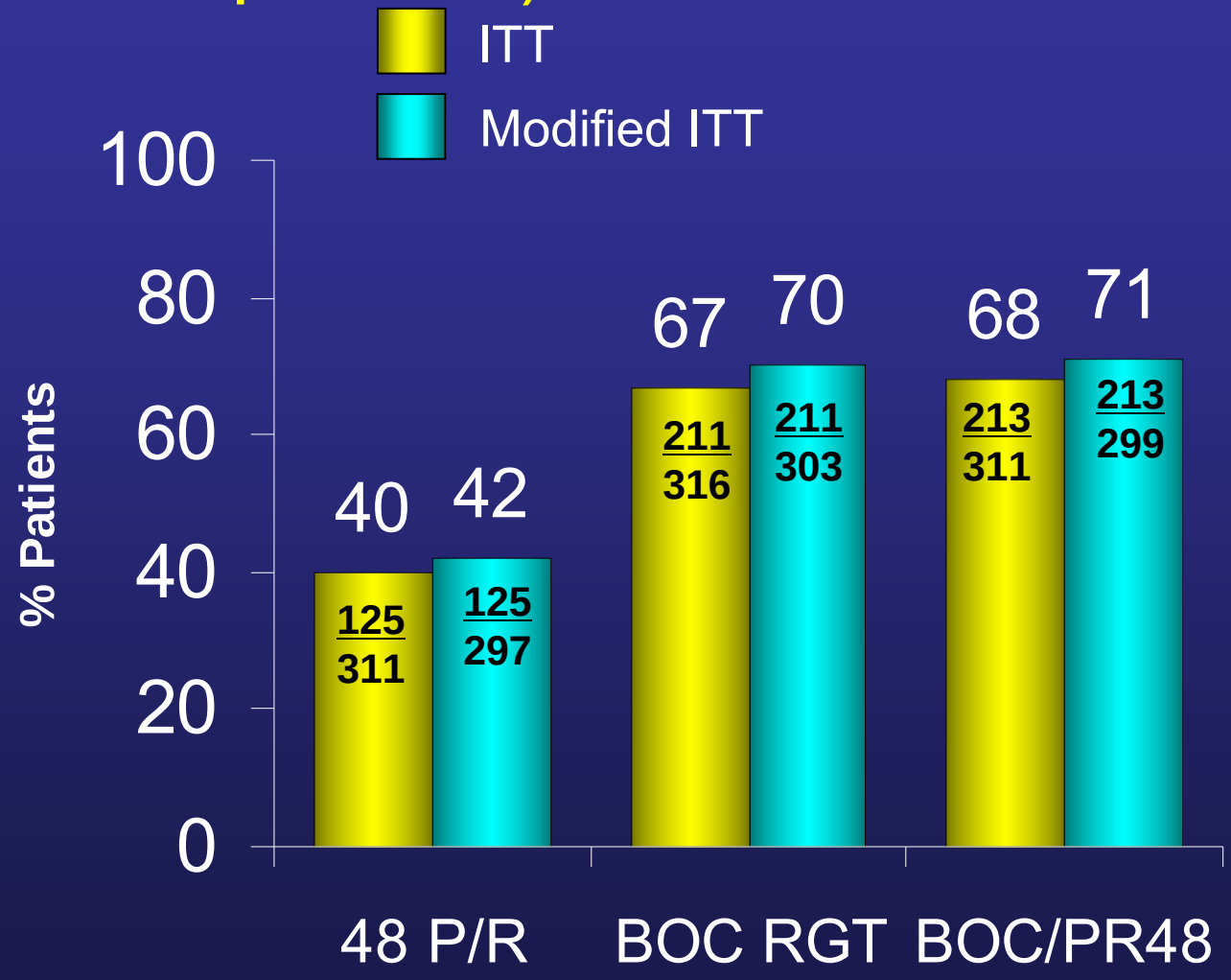
Non-Black Patients



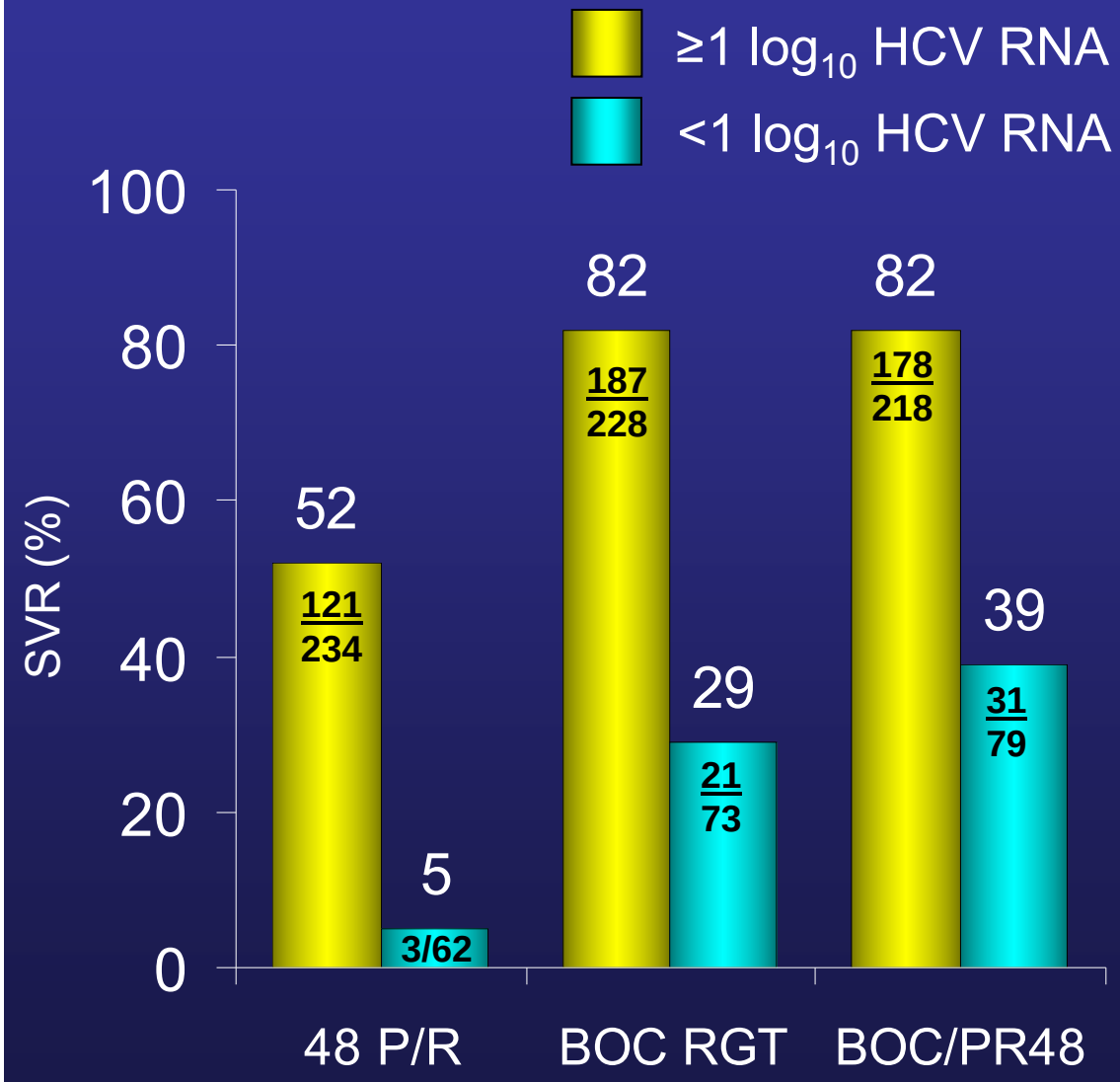
Black Patients

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



* Boceprevir resistance-associated variants determined with population sequencing

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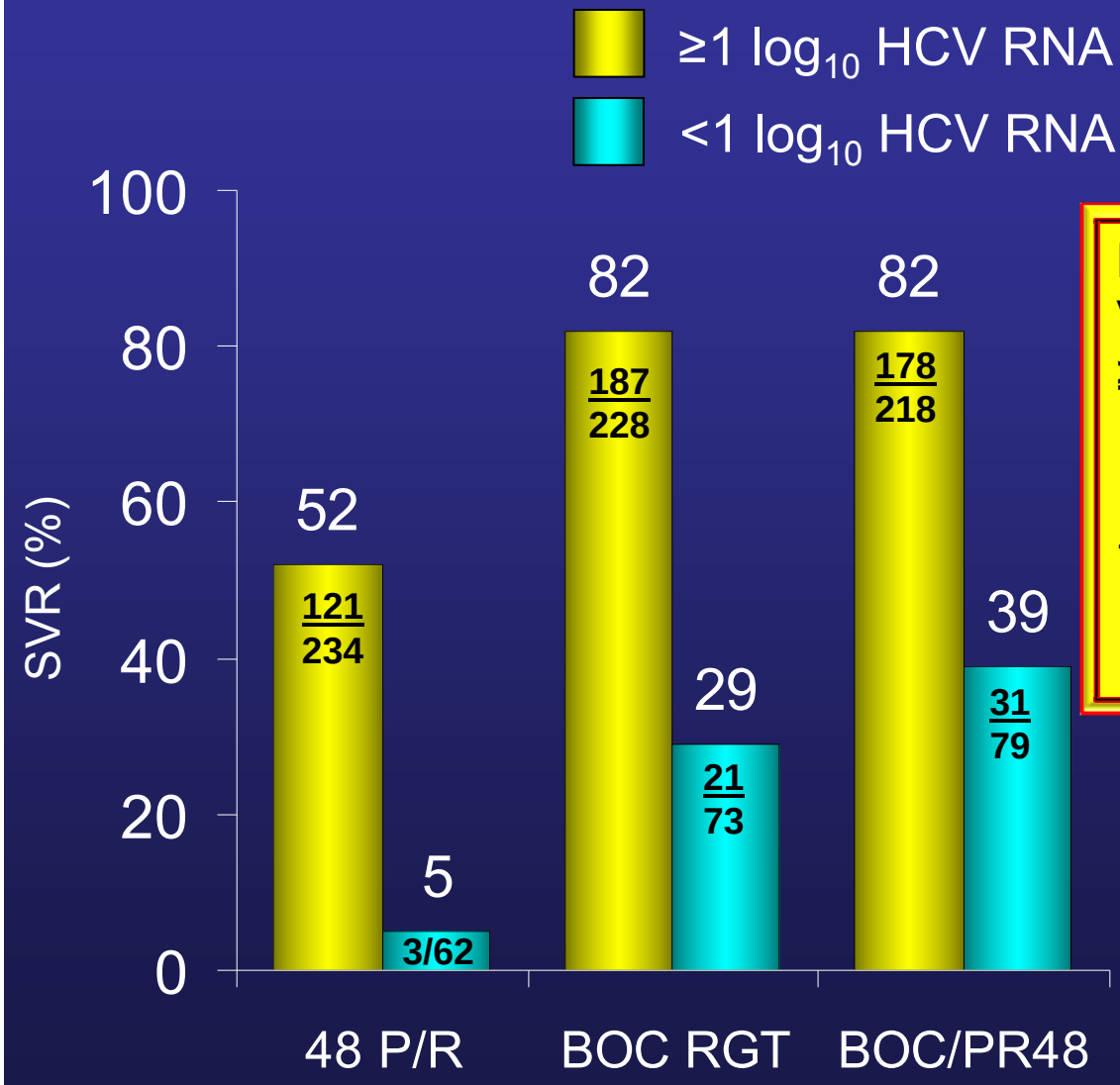


Boceprevir Resistance-associated Variants*:

≥ 1 $\log_{10}$ decline:

BOC RGT: 4% (9/232)

BOC/PR48: 4% (9/231)

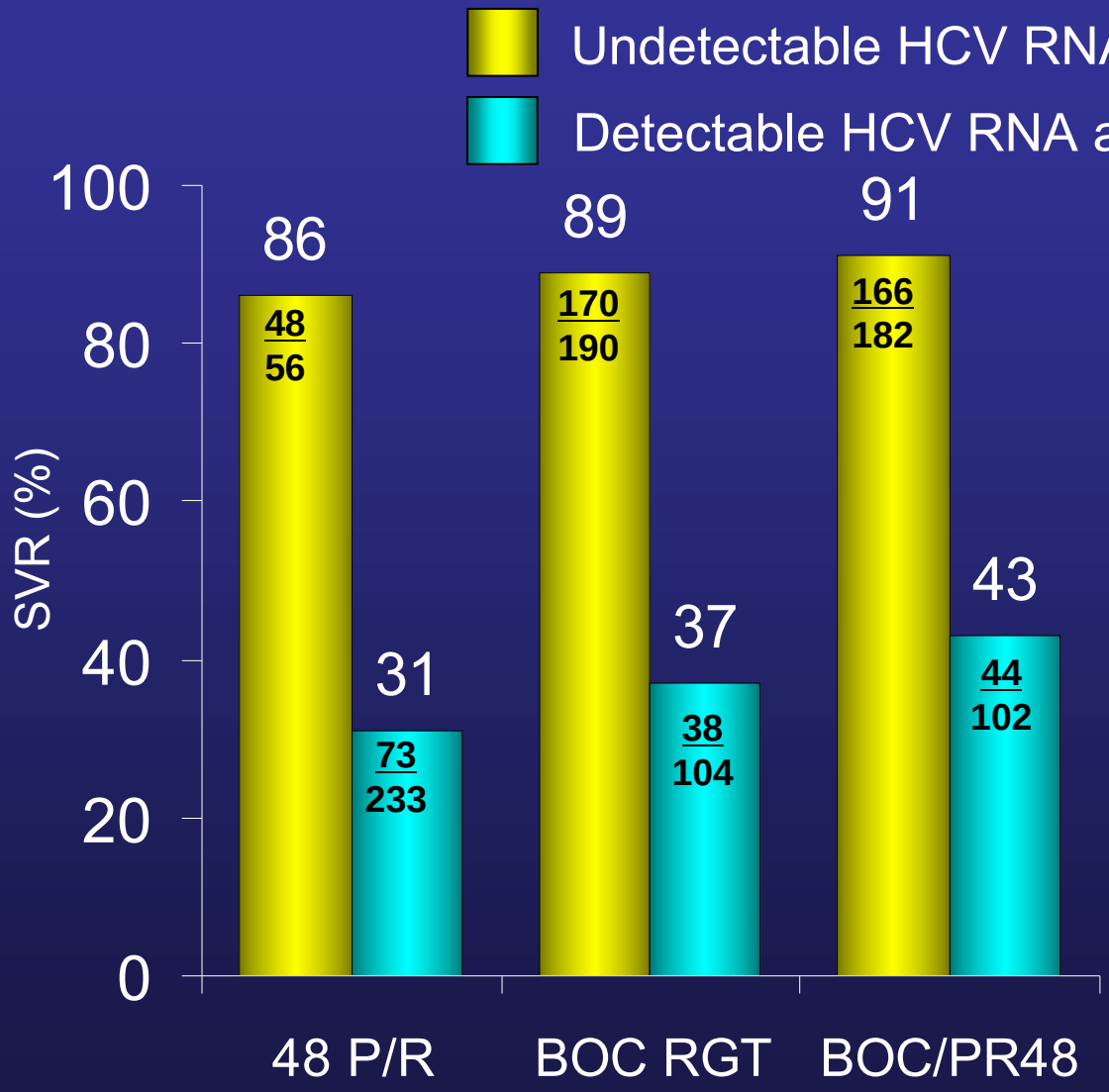
< 1 $\log_{10}$ decline:

BOC RGT: 47% (45/95)

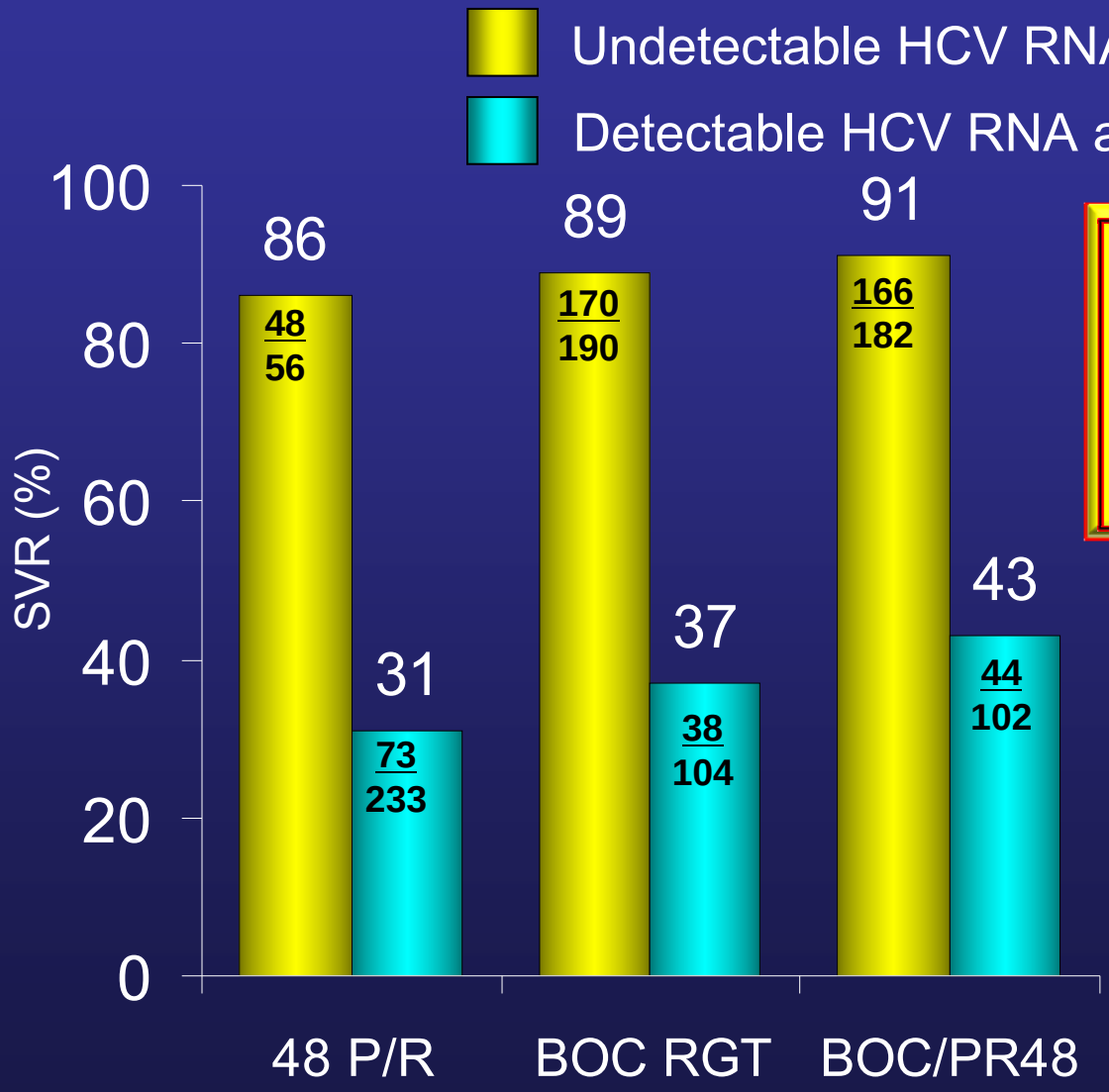
BOC/PR48: 35% (33/94)

* Boceprevir resistance-associated variants determined with population sequencing

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

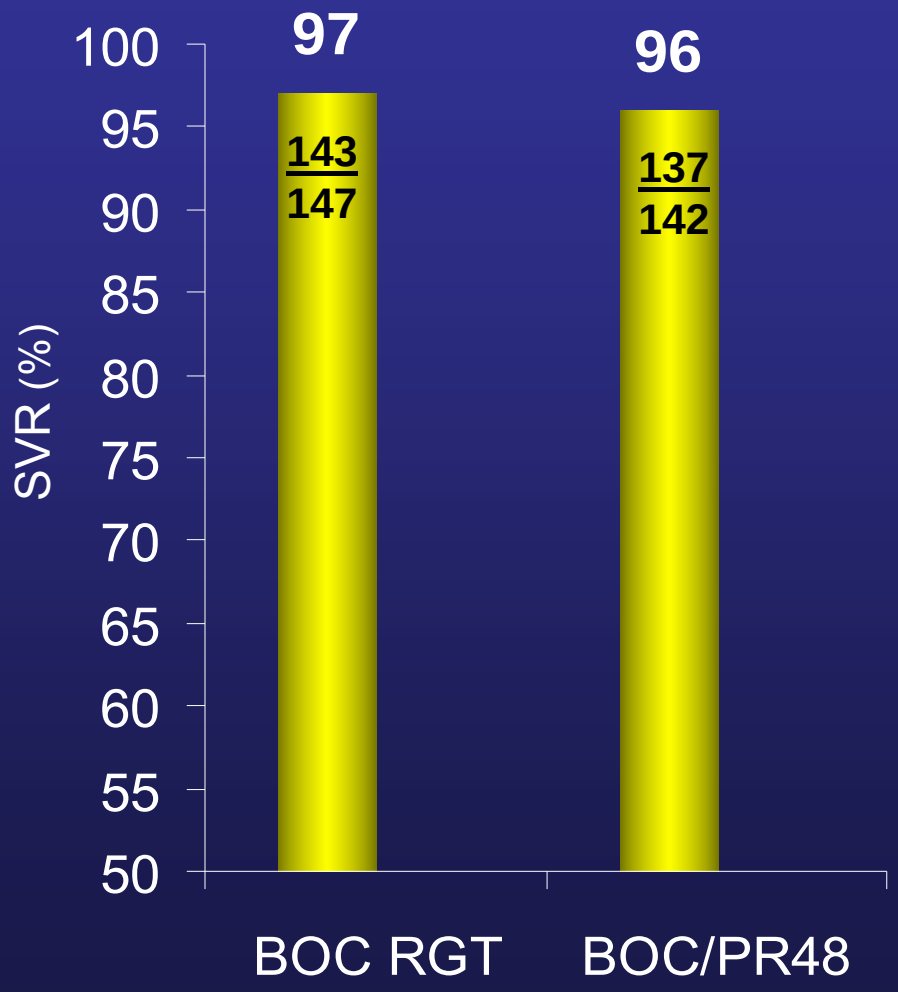


SVR Based on Week 8 HCV RNA in Non-Black Patients

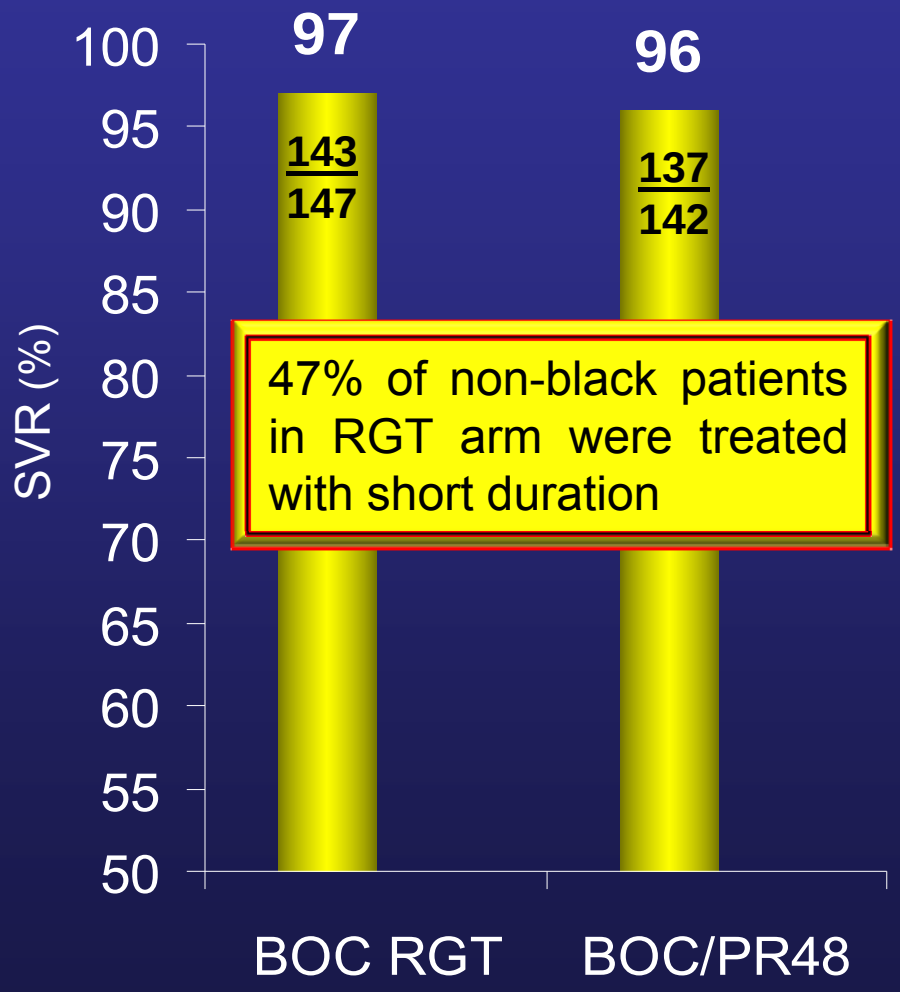


>3 times as many patients (60%) on BOC regimens achieved undetectable HCV RNA at Week 8 compared to control

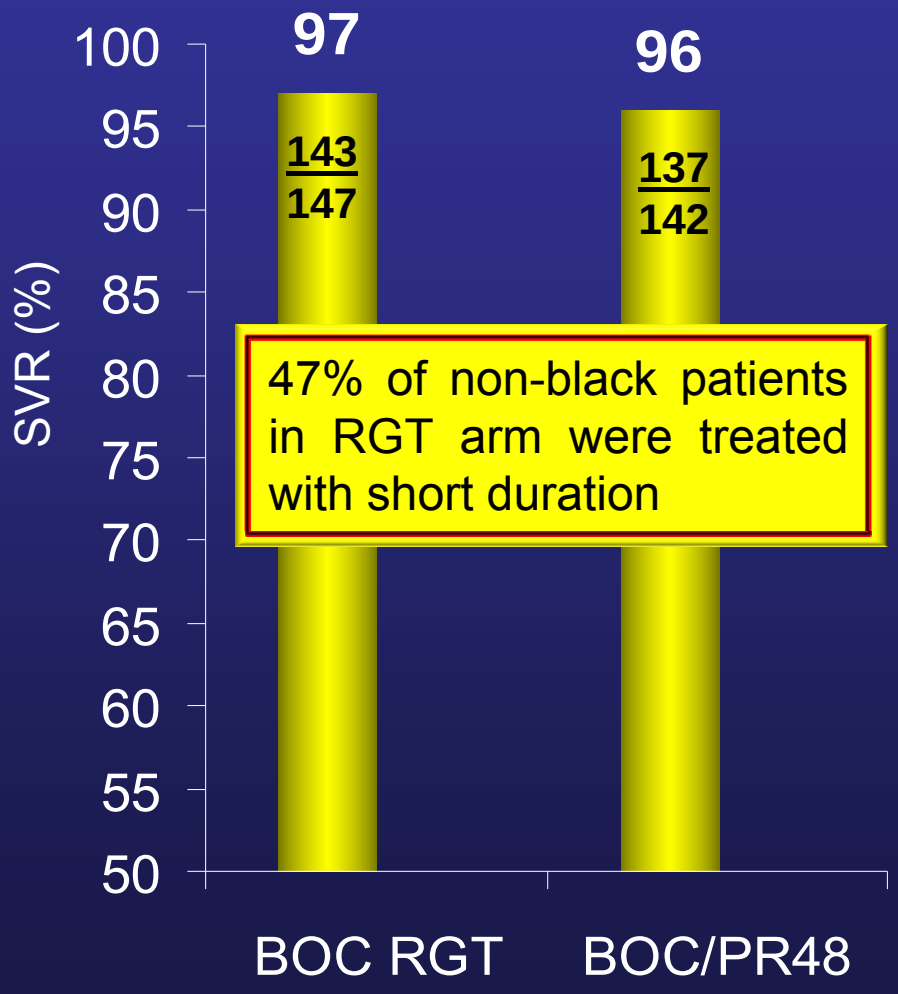
SVR in Non-Black patients with undetectable HCV RNA between Weeks 8-24



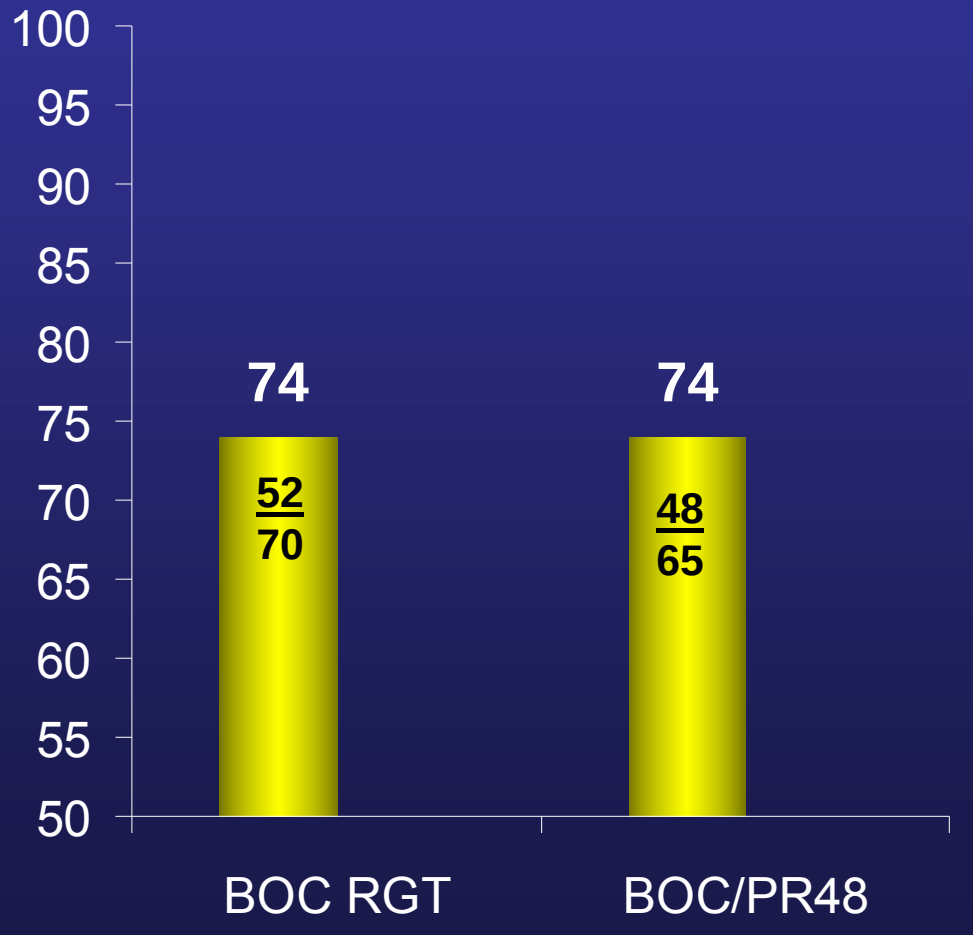
SVR in Non-Black patients with undetectable HCV RNA between Weeks 8-24



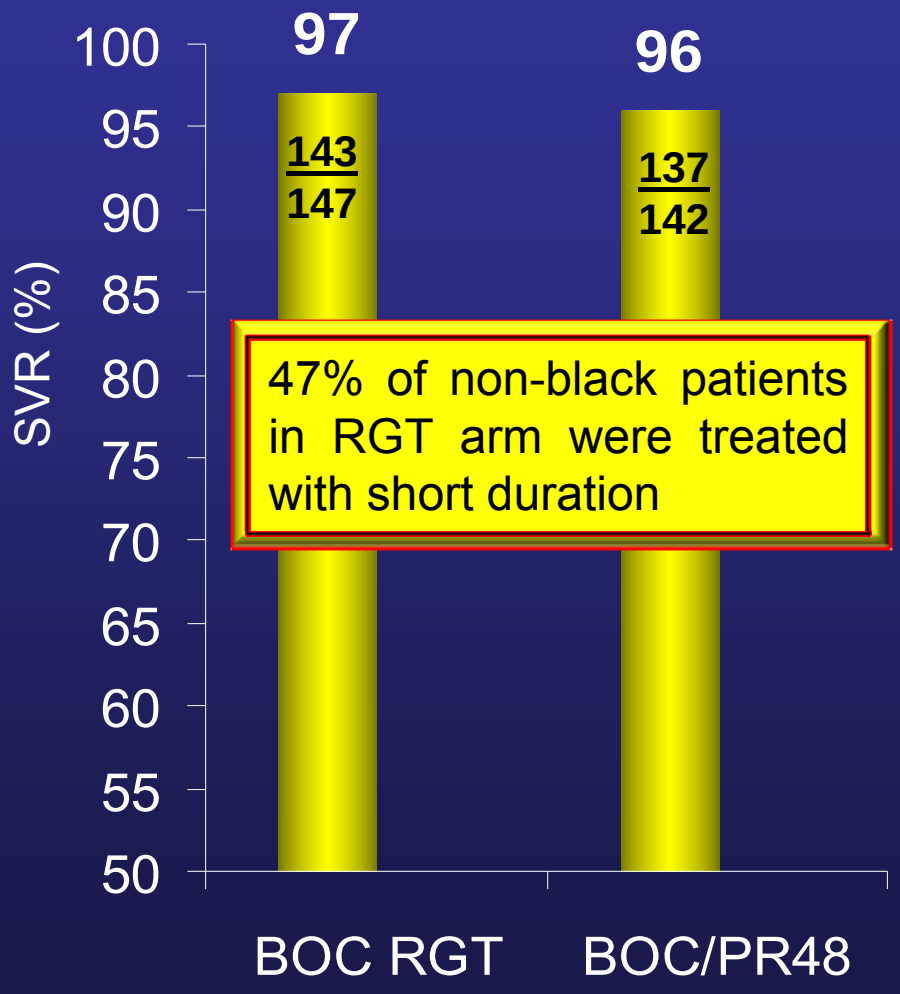
SVR in patients with undetectable HCV RNA between Weeks 8-24



SVR in patients with detectable HCV RNA at least once between Weeks 8-24



SVR in patients with undetectable HCV RNA between Weeks 8-24



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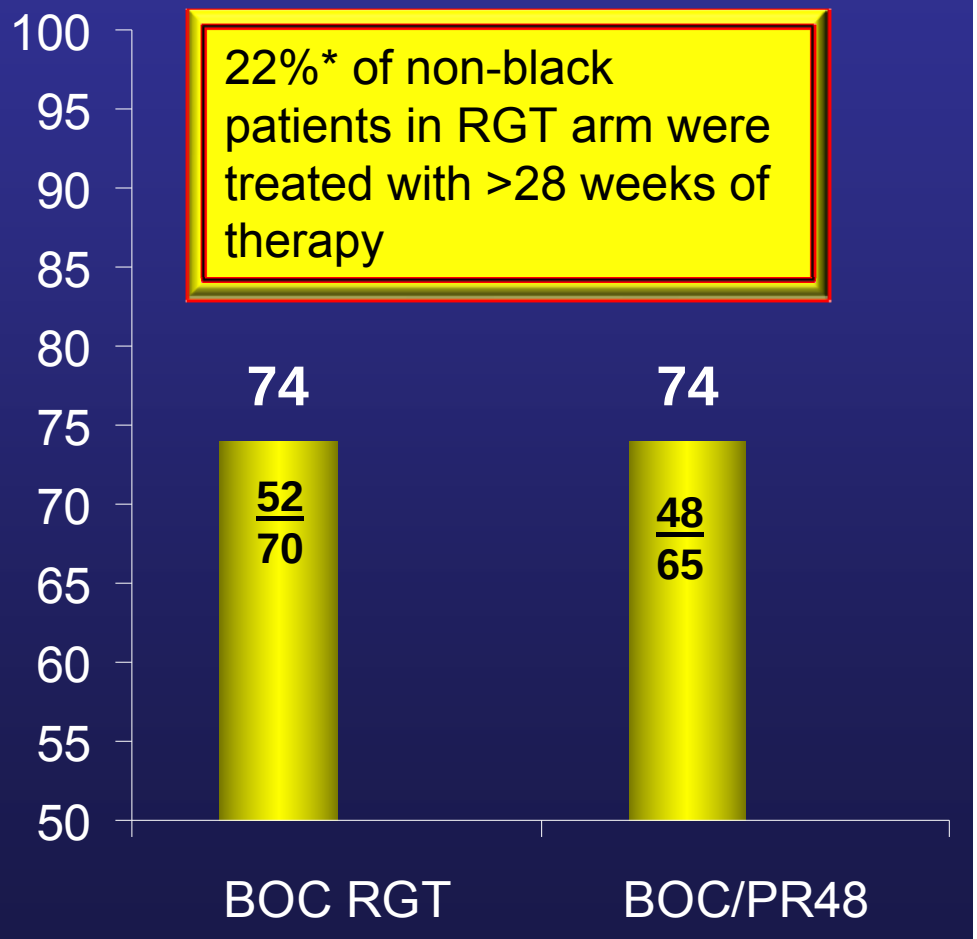
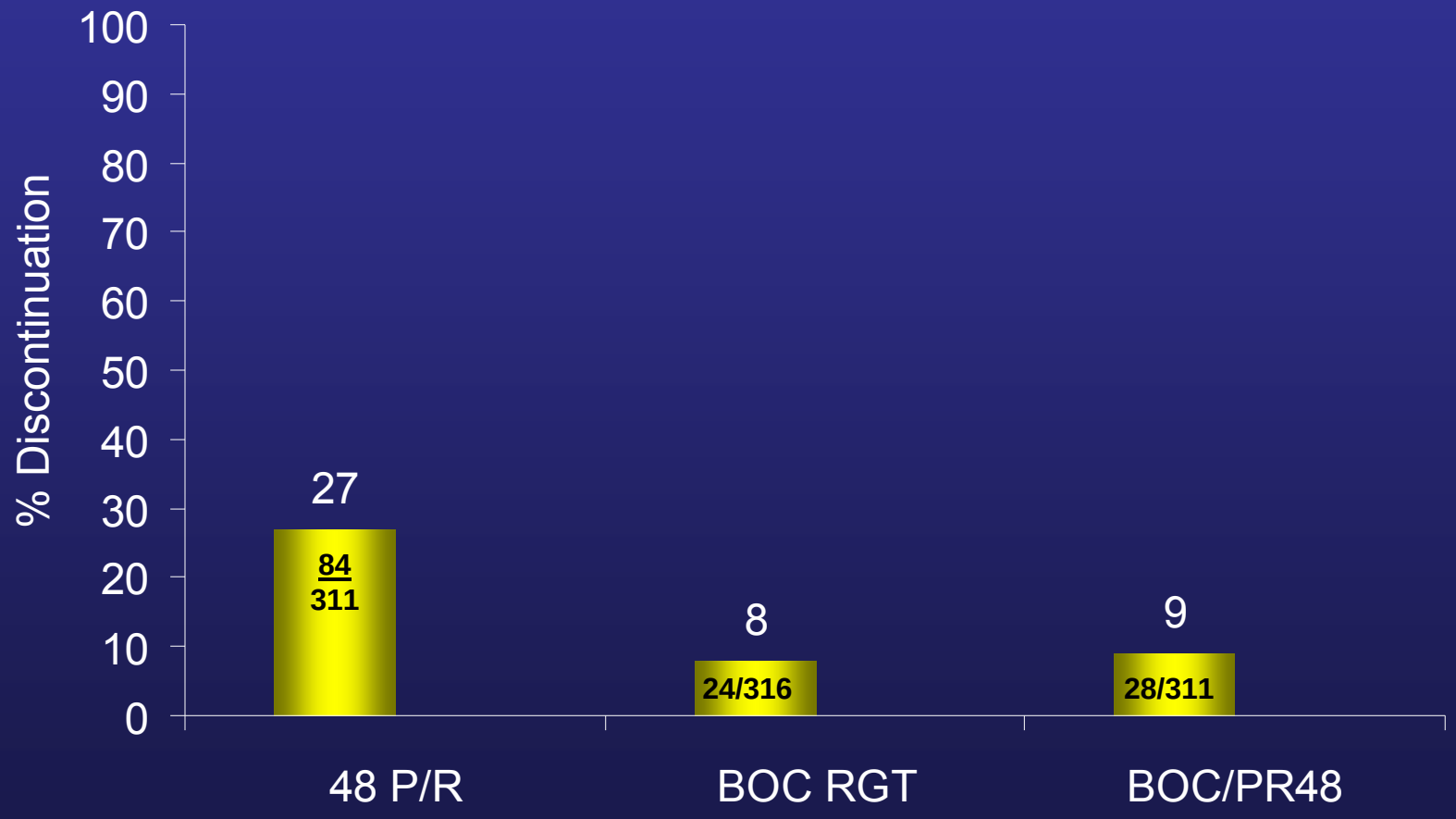


* Remaining patients discontinued prior to treatment week 28 due to futility, adverse events or non-medical reasons

Treatment discontinuations due to stopping rule at Week 24 in Non-Black patients



SVR Results in Cohort 2 (Blacks)

	% SVR (n/N)		
	48 P/R	BOC RGT	BOC/PR48
ITT	23 (12/52)	42 (22/52)	53 (29/55)
Modified ITT	26 (12/47)	47 (22/47)	53 (29/55)
Week 4 Lead-In Response			
≥ 1 $\log_{10}$ decrease	46 (12/26)	67 (16/24)	61 (22/36)
< 1 $\log_{10}$ decrease	0 (0/21)	25 (6/24)	31 (5/16)
Week 8 Viral Load			
Undetectable	75 (3/4)	78 (14/18)	82 (18/22)
Detectable	21 (8/38)	32 (8/25)	28 (8/29)
Viral Load Week 8 – 24			
Undetectable	100 (3/3)	87 (13/15)	95 (18/19)
Detectable ≥ 1 time	62 (8/13)	58 (7/12)	88 (7/8)
Discontinuations due to Week 24 Stopping Rule	46 (24/52)	17 (9/52)	15 (8/55)

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; EPO was used in 19% more boceprevir recipients compared to controls

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

Conclusions

- A regimen of PR containing boceprevir for 24 weeks significantly increased SVR over PR Control
- RGT using HCV RNA response at week 8 determines the duration of PR therapy
- PR Lead-in provides useful prognostic information

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