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

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For the RESPOND-2 Investigators

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I have financial relationships within the last 12 months relevant to my presentation with:

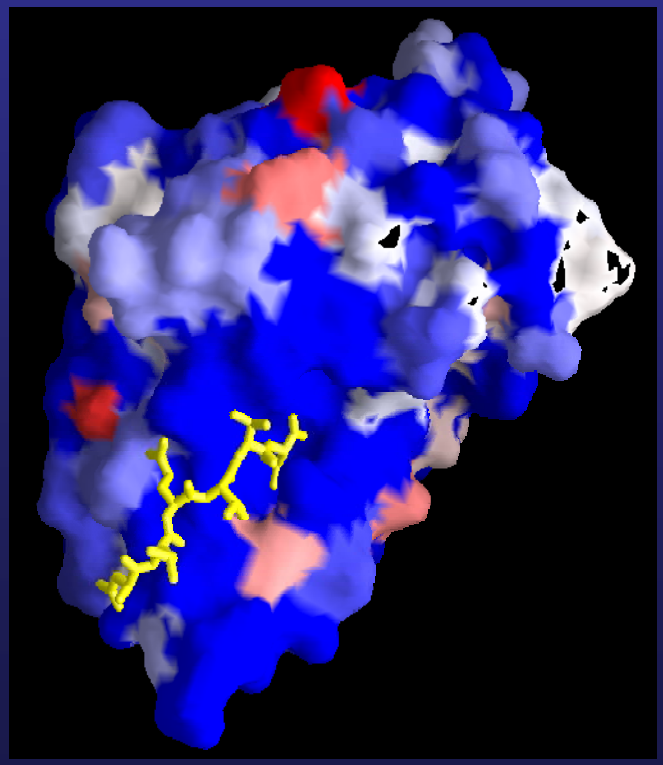
Schering Plough (now part of Merck); Roche Laboratories; Bristol-Myers Squibb; Three Rivers Pharmaceuticals; Valeant; Vertex ; Human Genome Sciences; Novartis; ISIS; Wyeth; and Romark Laboratories

AND

My presentation does include investigational use of Boceprevir

Background

- Of the six major HCV genotypes, genotype 1 is the least responsive to currently approved therapies, with sustained virologic response rates of less than 50%
- Boceprevir (SCH503034) is a structurally novel, peptidomimetic ketoamide protease inhibitor that binds reversibly to the HCV NS3 active site
  - Demonstrated antiviral activity in treatment naïve, and previously treated, genotype 1 patients in Phase 2 studies[1-2]



1. Kwo PY et al Lancet 2010;376:705.
2. Schiff E et al J Hepatol 2008;48:S46.

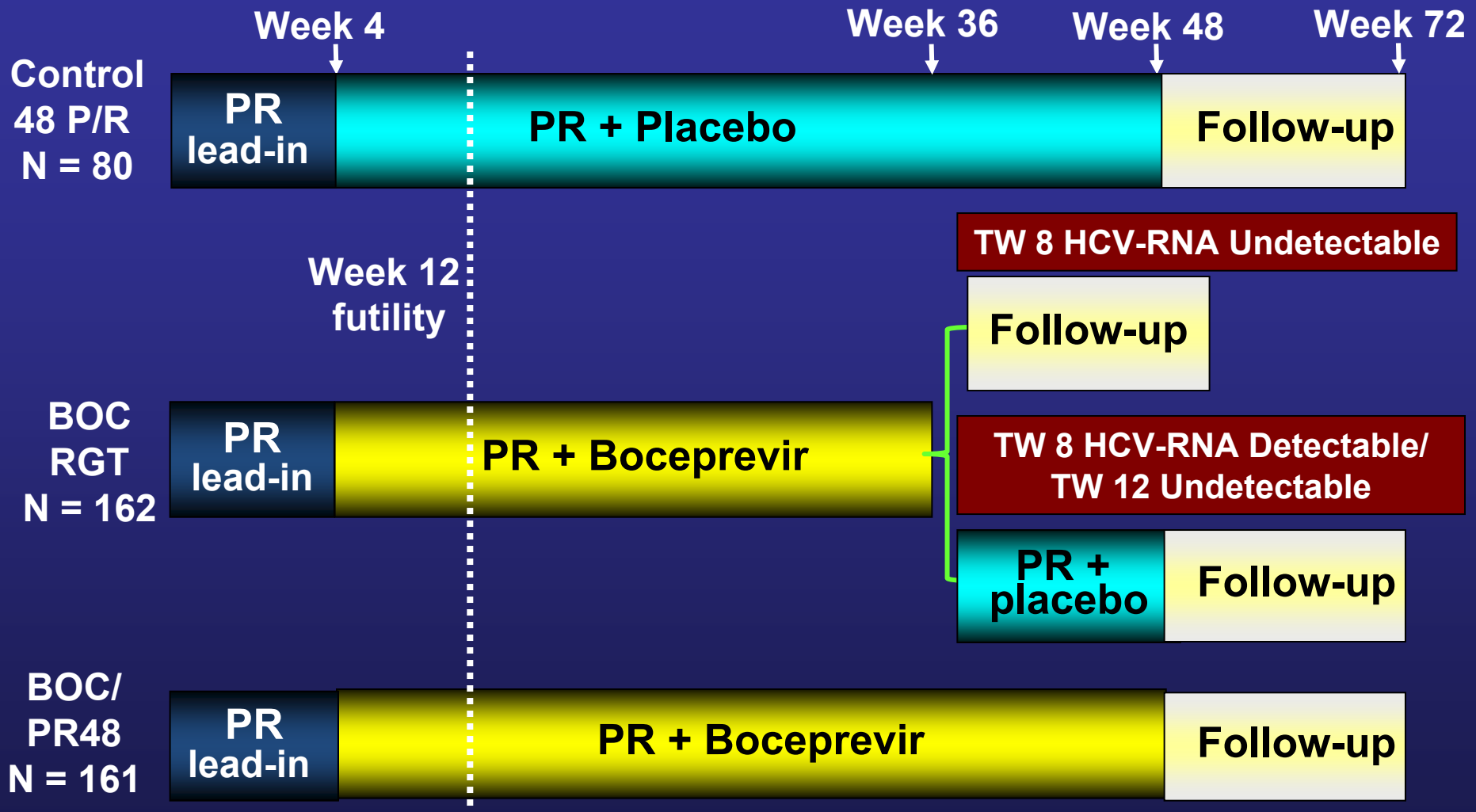
Study Objectives

- Compare safety/efficacy of two treatment strategies with boceprevir added to peginterferon/ribavirin (PR) versus PR alone in genotype 1 patients who failed treatment with PR

- Evaluate safety/efficacy independently in two patient populations, historic PR non-responders (decrease of HCV-RNA ≥ 2-$\log_{10}$ by week 12 of prior therapy but with detectable HCV-RNA throughout the course of therapy) and relapsers

- Explore response-guided therapy [RGT] *vs*. 44 weeks of therapy with boceprevir regimen (BOC/PR48)

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

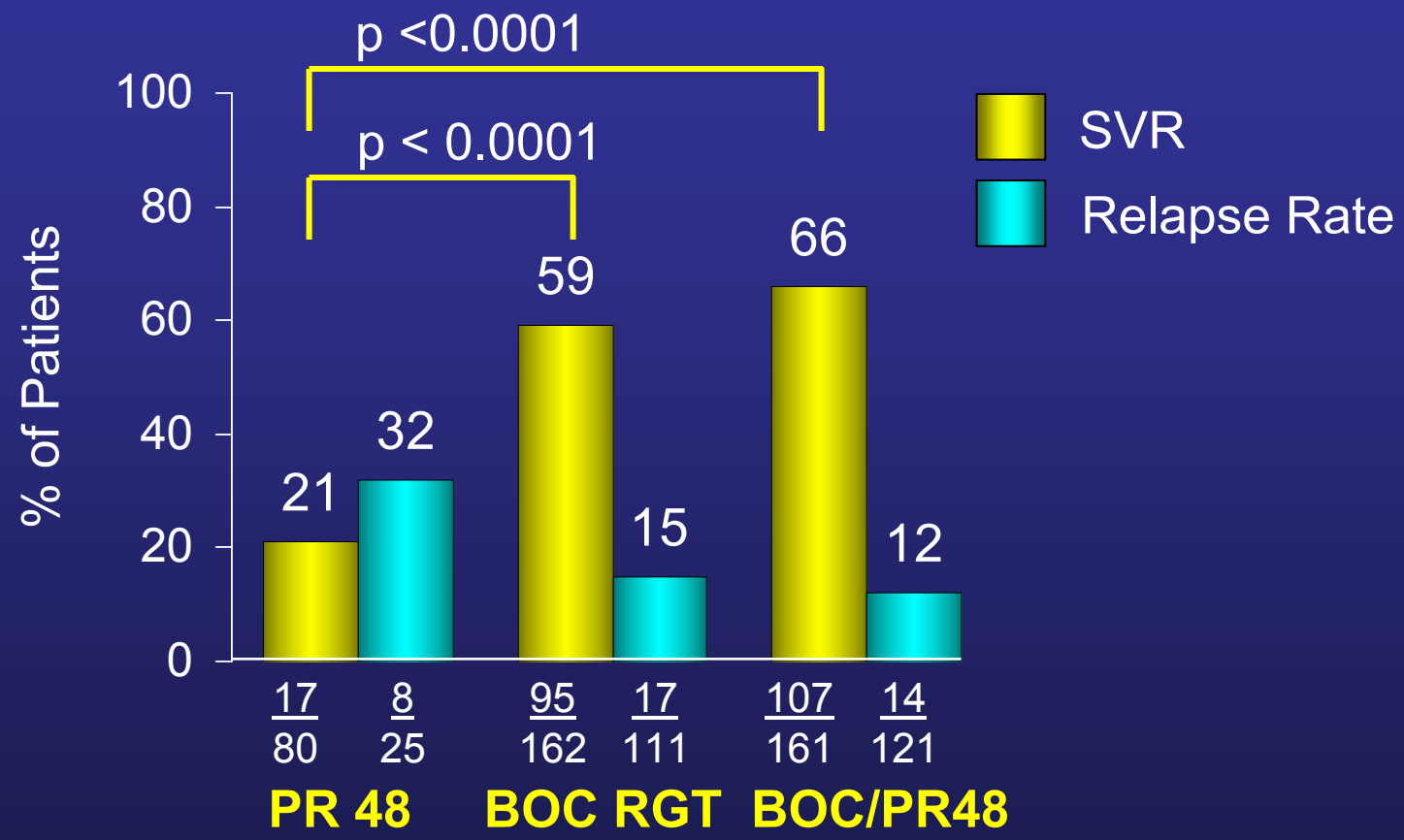
Baseline Characteristics

	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

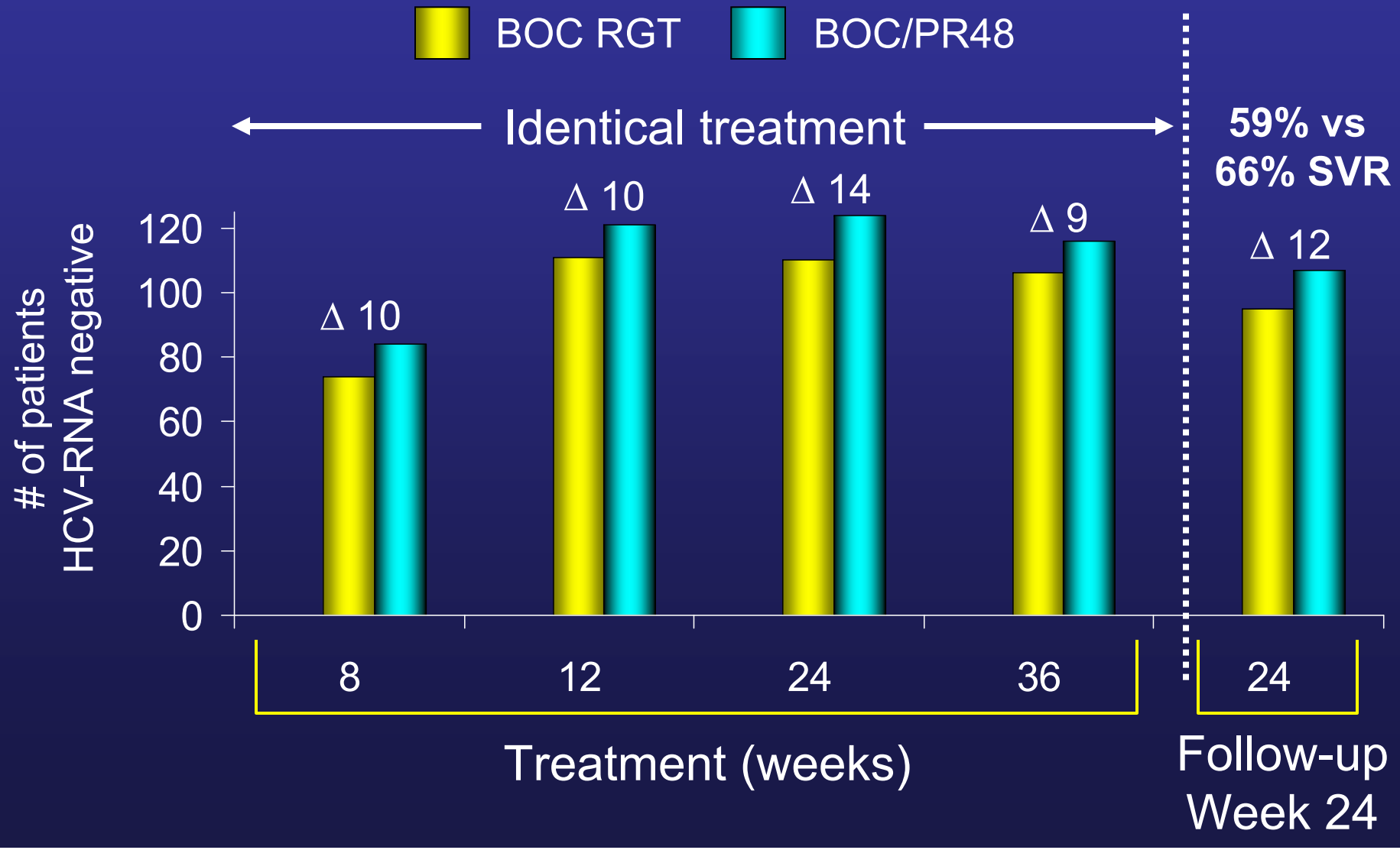
Intention to treat population



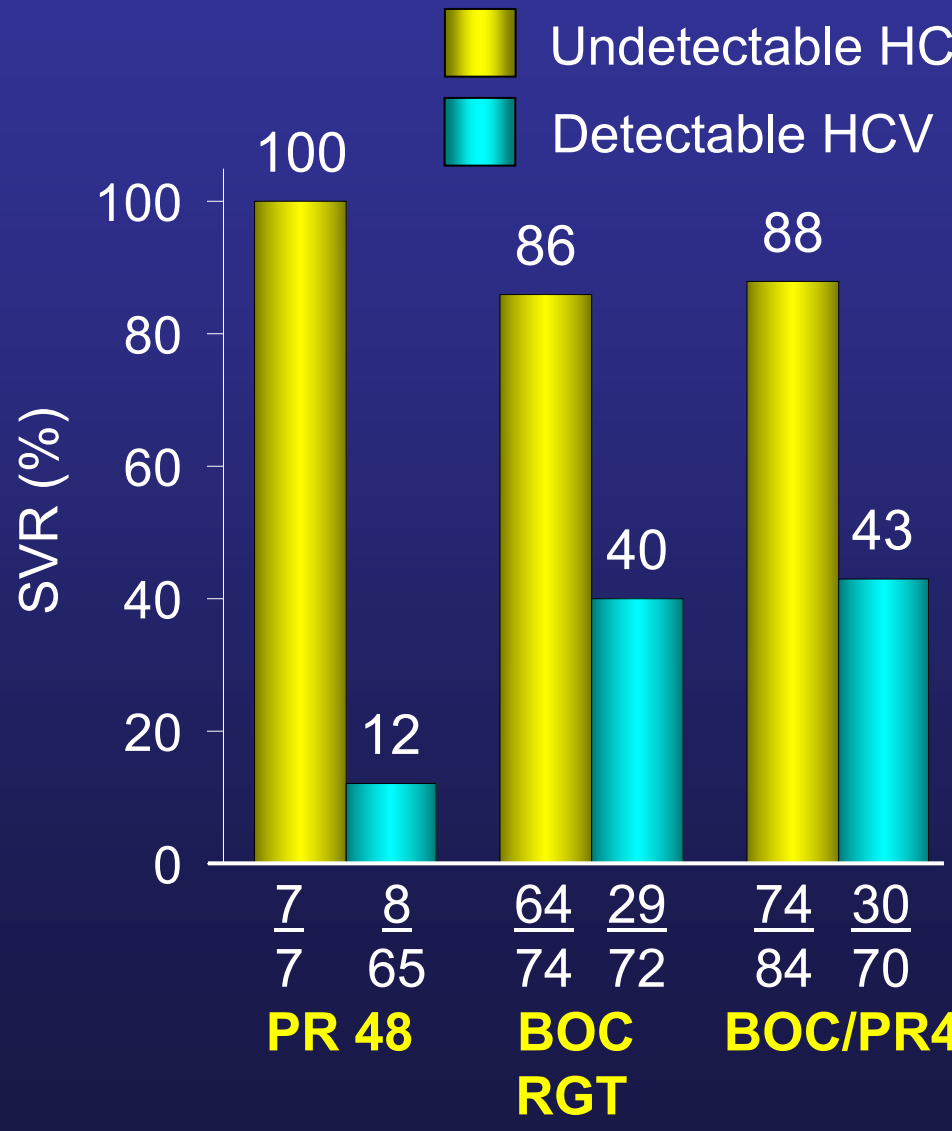
SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])

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.

BOC RGT vs BOC/PR48
Is there a Difference in Response?



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)**

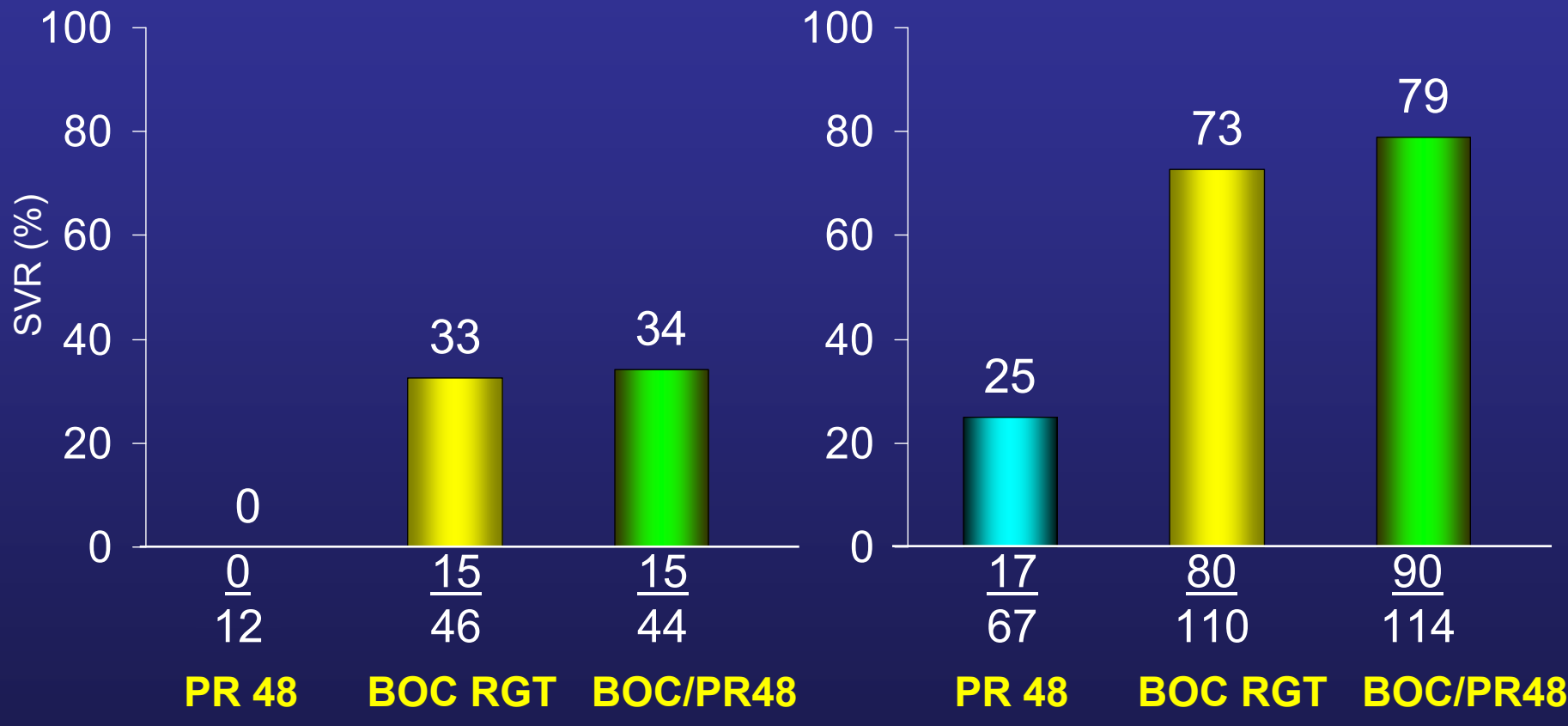
*Non-responders had a decrease in plasma HCV-RNA of at least 2-$\log_{10}$ by week 12 of prior therapy but with detectable HCV-RNA throughout the course of therapy. Relapsers had undetectable HCV-RNA at end of prior therapy without subsequent attainment of a sustained virologic response.

PR 4 Week Lead-In As a Predictor of Response

- Interferon responsiveness may not remain constant over time
- Viral load decline of <1 $\log_{10}$ after 4 weeks of PR is significantly correlated to a <2 $\log_{10}$ decline after 12 weeks of treatment[1]
  - Phase 3 trial (IDEAL) of PR alone - only 4% (31/750) of patients with <1 $\log_{10}$ decline after 4 weeks of PR achieved SVR[2]
- Lead-in allows real time assessment of patient's interferon responsiveness vs. historic response
- 26% (102/393) of RESPOND-2 patients had a < 1 $\log_{10}$ decline in HCV viral load at week 4

1. Poordad F, et al. AASLD, Boston, MA, 2010, abstract # 797
2. McHutchison JG, et al. NEJM. 2009; 360:1827-1838

SVR 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

Safety Profile Over Entire Course of Therapy

	48 PR N = 80	BOC RGT N = 162	BOC/PR48 N = 161
Median treatment duration, days	104	252	336
Deaths	N=0	N=1	N=0
Serious AEs	5%	10%	14%
Discontinued due to AE	3%	8%	12%
Dose modification due to AE	14%	29%	33%
Hematologic parameters			
Neutrophil count (<750 to 500/mm^3 / <500/mm^3)	9% / 4%	19% / 6%	20% / 7%
Hemoglobin (<10 to 8.5 g/dL / <8.5 g/dL)	24% / 1%	43% / 5%	35% / 14%
Discontinuation due to anemia	0%	0%	3%
Dose reductions due to anemia	8%	19%	22%
Erythropoietin use	21%	41%	46%
Mean (median) days of use	65 (55)	135 (155)	130 (90)
Boceprevir Resistance Assoc Variants % (n/n)			
< 1 $\log_{10}$ Decline Wk 4 Lead-In	NA	28% (13/46)	32% (14/44)
≥ 1 $\log_{10}$ Decline Wk 4 Lead-In		8% (9/110)	6% (7/112)

Most Common Treatment-Related Adverse Events
>15% of patients in any treatment arm

Adverse Events (%)	Arm 1 (PR48) n=80	Arm 2 (RGT) n=162	Arm 3 (BOC/PR48) n=161
Fatigue	50	54	57
Headache	48	41	39
Nausea	38	44	39
Chills	30	35	30
Influenza like illness	25	23	23
Myalgia	24	28	21
Pyrexia	21	27	29
Anemia	20	43	46
Insomnia	20	30	29
Dyspnea	18	18	25
Pruritus	18	19	19
Decreased appetite	16	22	29
Alopecia	16	26	18
Asthenia	16	19	24
Cough	15	17	22
Diarrhea	15	23	23
Arthralgia	14	19	22
Irritability	13	19	22
Dysgeusia	11	43	45
Dry Skin	8	21	22

Summary and Conclusions

- **Triple therapy was generally well-tolerated**
  - **Anemia and dysgeusia occurred more often in the boceprevir groups than the control group**
- **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**

Acknowledgements

RESPOND-2 Investigators, alphabetical by country

Belgium - J. Delwaide, Y. Horsmans, H. Van Vlierberghe

Canada - F. Anderson, SV. Feinman, J. Heathcote, P. Marotta, A. Ramji, F. Wong, K. Peltakian and K. Kaita

France - L. Alric, S. Ben Ali, M-A. Bigard, M. Bourliere, N. Boyer-Darrigrand, J-P. Bronowicki, V. De Ledinghen, C. Hezode, P. Lebray, P. Marcellin, M. Maynard–Muet, S. Pol, T. Poynard, A. Tran, C. Trepo, R. Truchi, A. Vallet-Pichard

Germany - T. Berg , R. Guenther, A. W. Lohse, M. P. Manns, C. Niederau, W. E. Schmidt, U. Spengler, H. Wedemeyer, S. Zeuzem

Italy - G. Carosi, M. Colombo, A. Craxì, M. Rizzetto, A.L. Zignego, M. Zuin

Puerto Rico - A. Reymunde

Spain - M Buti Ferret, R. Esteban

USA - N. Afdhal, B. Bacon, L. Balart, M. Bennett, T. Box, T. Boyer, M. Davis, S. Flamm, B. Freilich, J. Galati, G. Galler, A. Gibas, E. Godofsky, S. Gordon, J. Herrera, S. Herrine, I. Jacobson, J. King, P. Kwo, E. Lawitz, W. Lee, J. Levin, V. Luketic, J. McCone, J. McHutchison, K. Mullen, T. Morgan, A. Muir, F. Nunes, A. Nyberg, L. Nyberg, M.P. Pauly, C. Peine, F. Poordad, N. Ravendhran, R. Reindollar, T. Riley, L. Rossaro, R. Rubin, M. Ryan, E. Schiff, K. Sherman, M. Shiffman, R. Strauss, J. Vierling, R. Yapp

Study Pathologist – Dr Zachary Goodman

Merck - Drs Heather L Sings and Lisa Pedicone