Curso de Biologia Molecular para Clínicos: VIH y Hepatitis

Novedades Terapeuticas

Boceprevir

Vigo, 04 Febrero 2012

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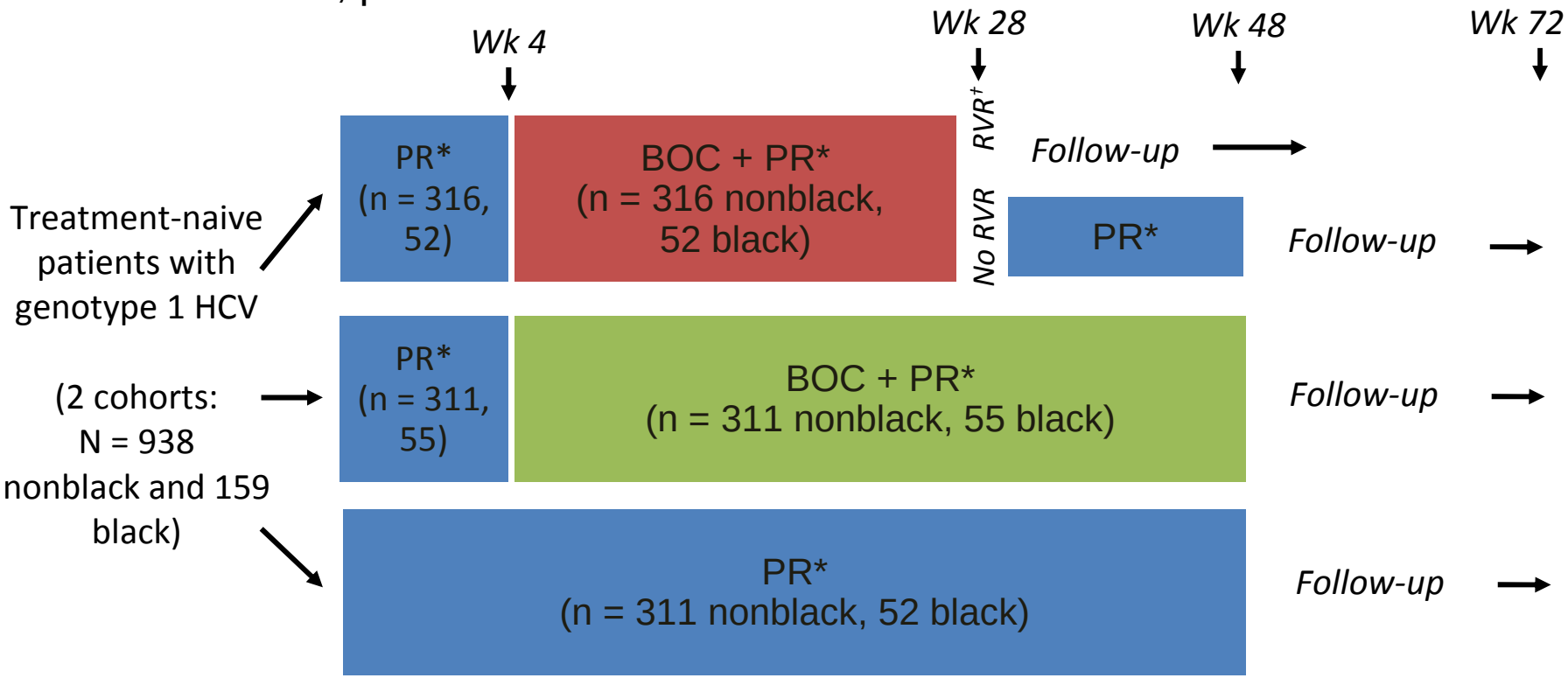
Definitions of Virologic Response

Response	*Definition*
SVR	HCV RNA undetectable by sensitive assay 24 wks after treatment end
RVR	HCV RNA undetectable at Wk 4
EVR	> 2 $\log_{10}$ IU/mL reduction in HCV RNA at Wk 12
cEVR	HCV RNA detectable at Wk 4, but undetectable at Wk 12
Null response	HCV RNA decline < 2 $\log_{10}$ IU/mL from baseline at Wk 12
Partial response	HCV RNA decline > 2 $\log_{10}$ IU/mL from baseline at Wk 12, but HCV RNA detectable at Wks 12 and 24
Viral breakthrough	HCV RNA detectable at any time during treatment after being undetectable
Relapse	HCV RNA detectable after withdrawing treatment in a patient who was undetectable at end of treatment
New response categories with PI-based therapy	
eRVR with boceprevir	HCV RNA undetectable at Wks 8 and 24 of therapy
eRVR with telaprevir	HCV RNA undetectable at Wks 4 and 12 of triple therapy
Week 8 response	Among boceprevir-treated patients, HCV RNA undetectable at Wk 8 of the overall treatment course (ie, after 4 wks of pegIFN/RBV lead-in and 4 wks of triple therapy)
Lead-in RVR	HCV RNA undetectable at Wk 4 for patients who had a pegIFN/RBV lead-in phase of therapy

Phase III SPRINT-2: Boceprevir + PegIFN/RBV in GT 1 Tx-Naive Patients

- Randomized, placebo-controlled trial

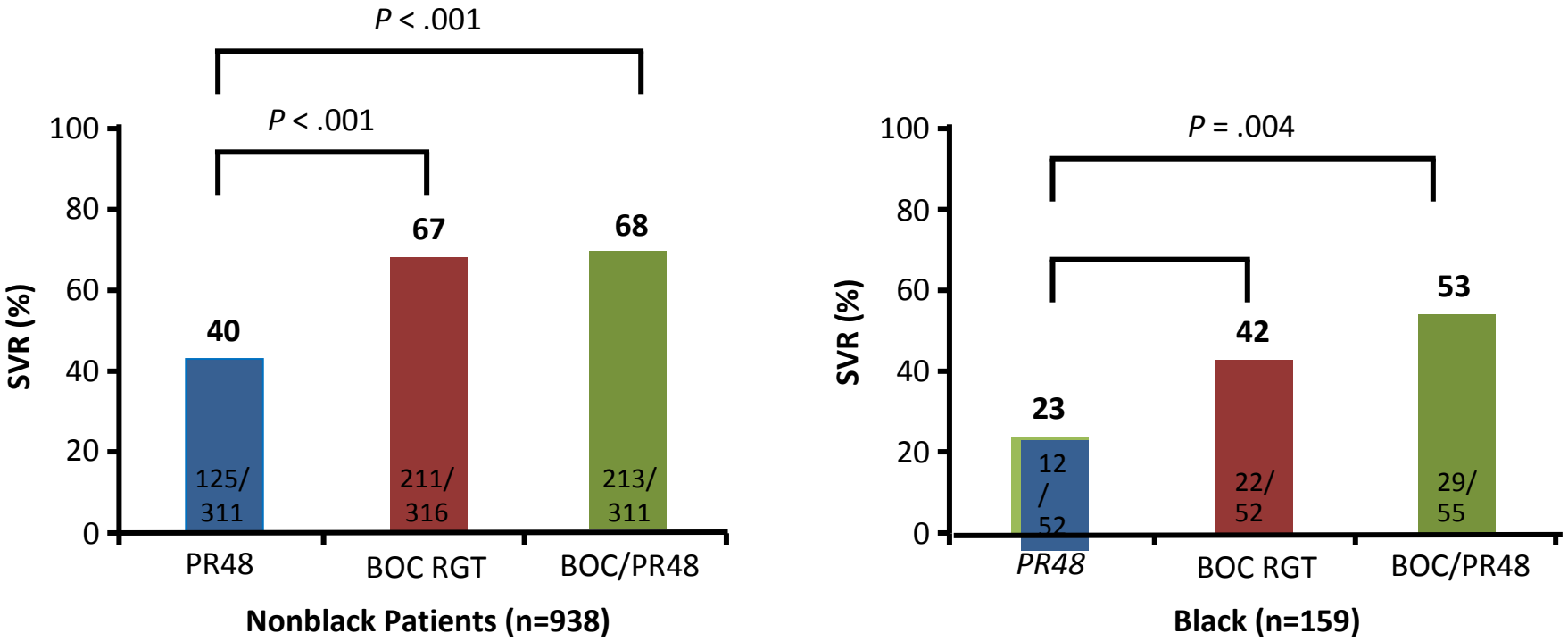


*BOC 800 mg q8h; pegIFN alfa-2b 1.5 µg/kg/wk; weight-based RBV 600-1400 mg/day.
†Undetectable HCV RNA at Wk 4 of BOC treatment (ie, at Wk 8) and at all subsequent assays.

Poordad F, et al. N Eng J Med. 2011;364:1195-1206.

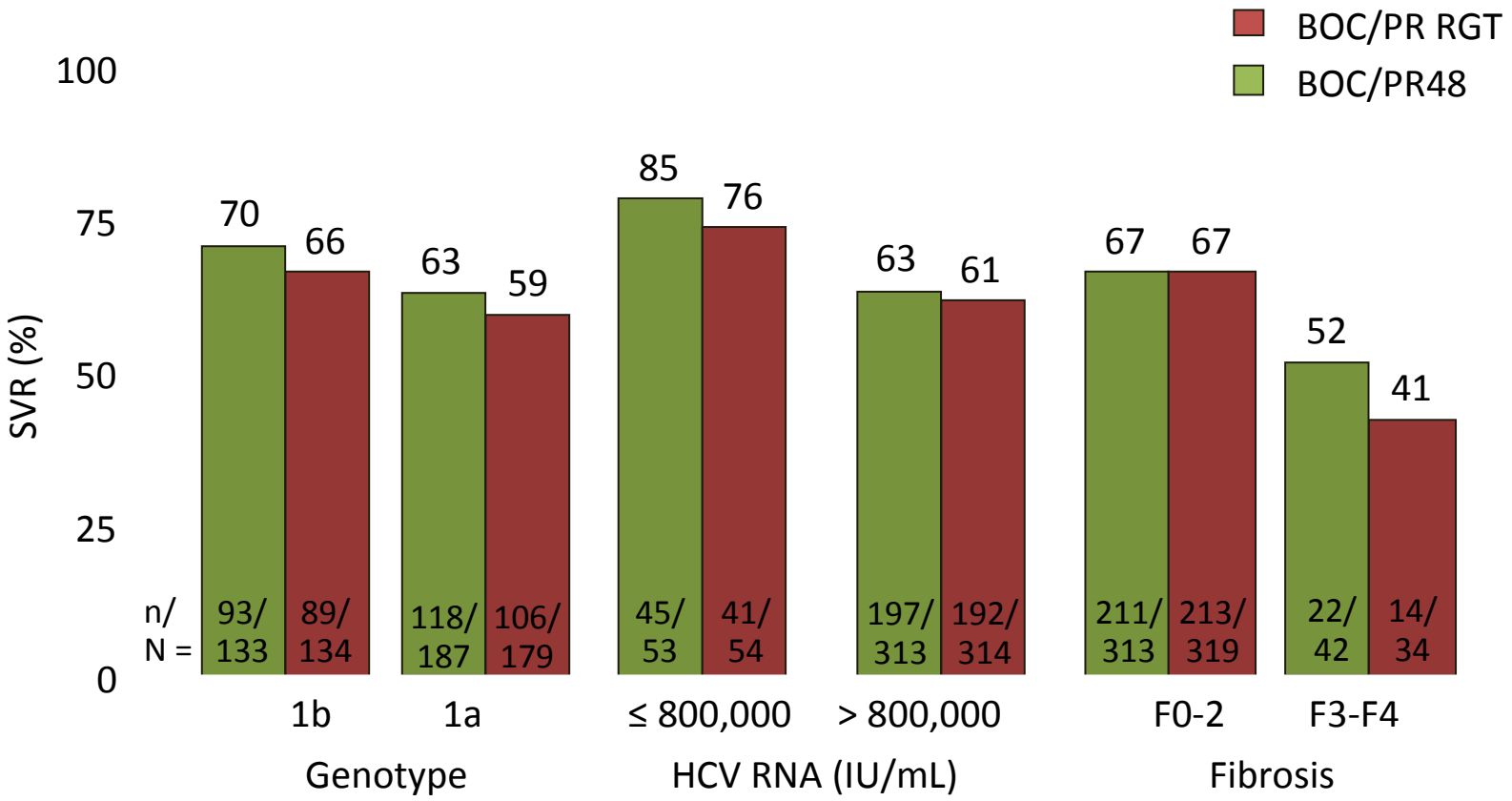
Boceprevir + PR: SVR Rates

SPRINT-2: BOC + PegIFN/RBV in Genotype 1 Treatment-Naive Patients



Adapt. de Poordad F, et al. N Engl J Med. 2011;364:1195-1206.

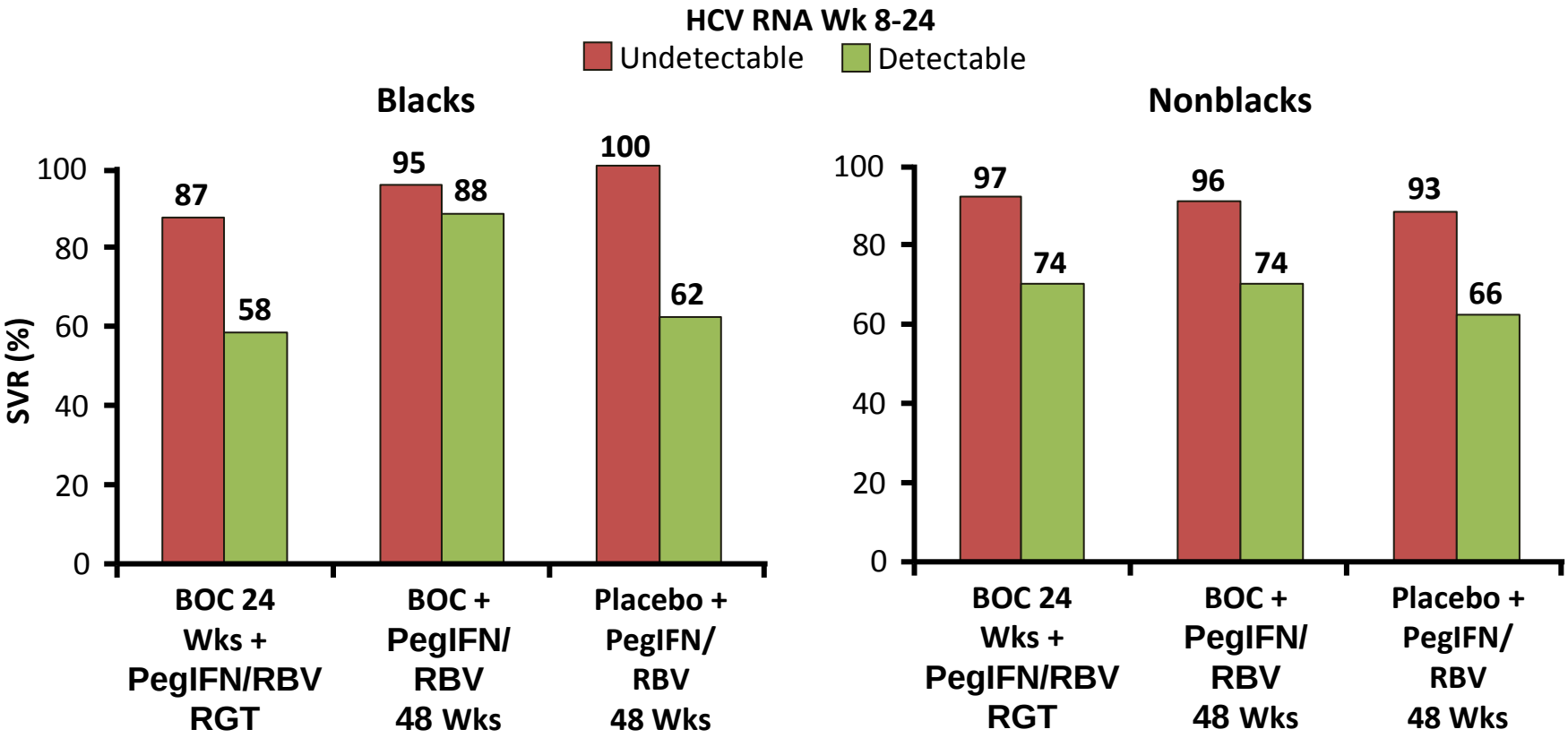
SPRINT-2: Influence of Baseline Patient and Virus Factors on SVR



Poordad F, et al. N Engl J Med. 2011;364:1195-1206. Reddy KR, et al. EASL 2011. Abstract 466.

SPRINT-2 Data Show Importance of Early Response to Boceprevir-based Therapy

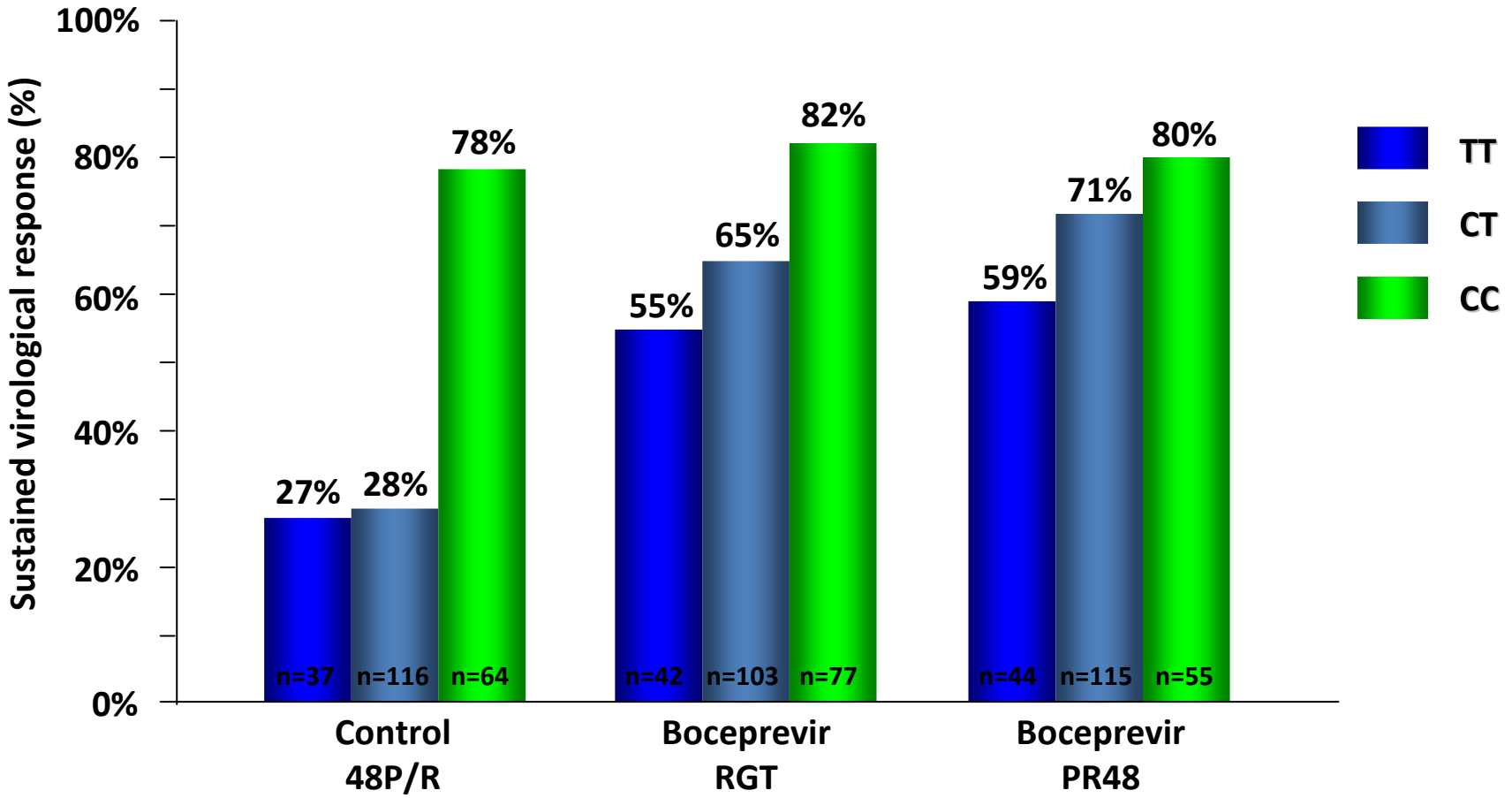
- Results support extended therapy approach for patients who respond later to therapy



Poordad F, et al. N Engl J Med. 2011;364:1195-1206.

IL28B and Boceprevir Regimens

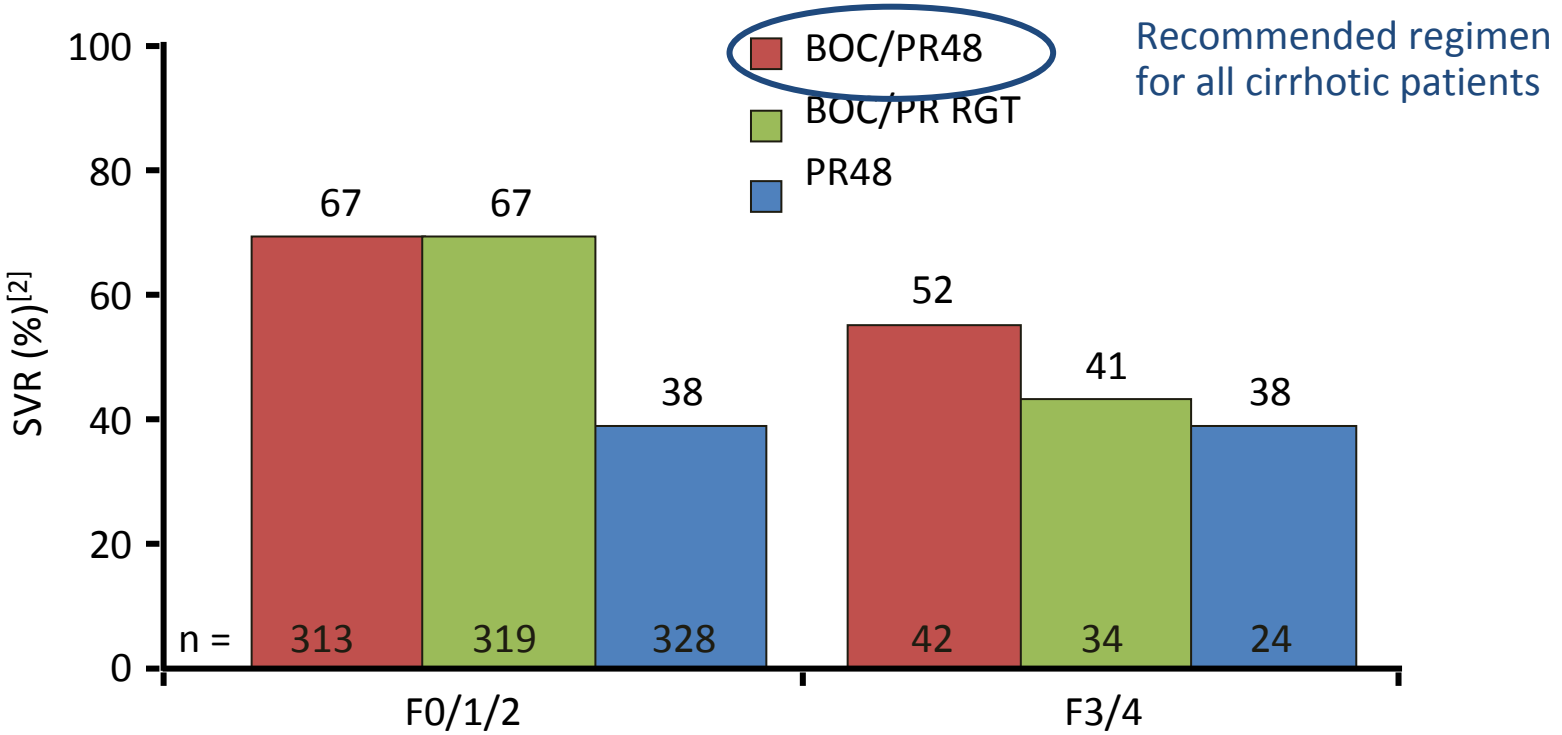
SPRINT-2 Phase 3 Clinical Trial



Poordad et al., EASL 2011, oral presentation

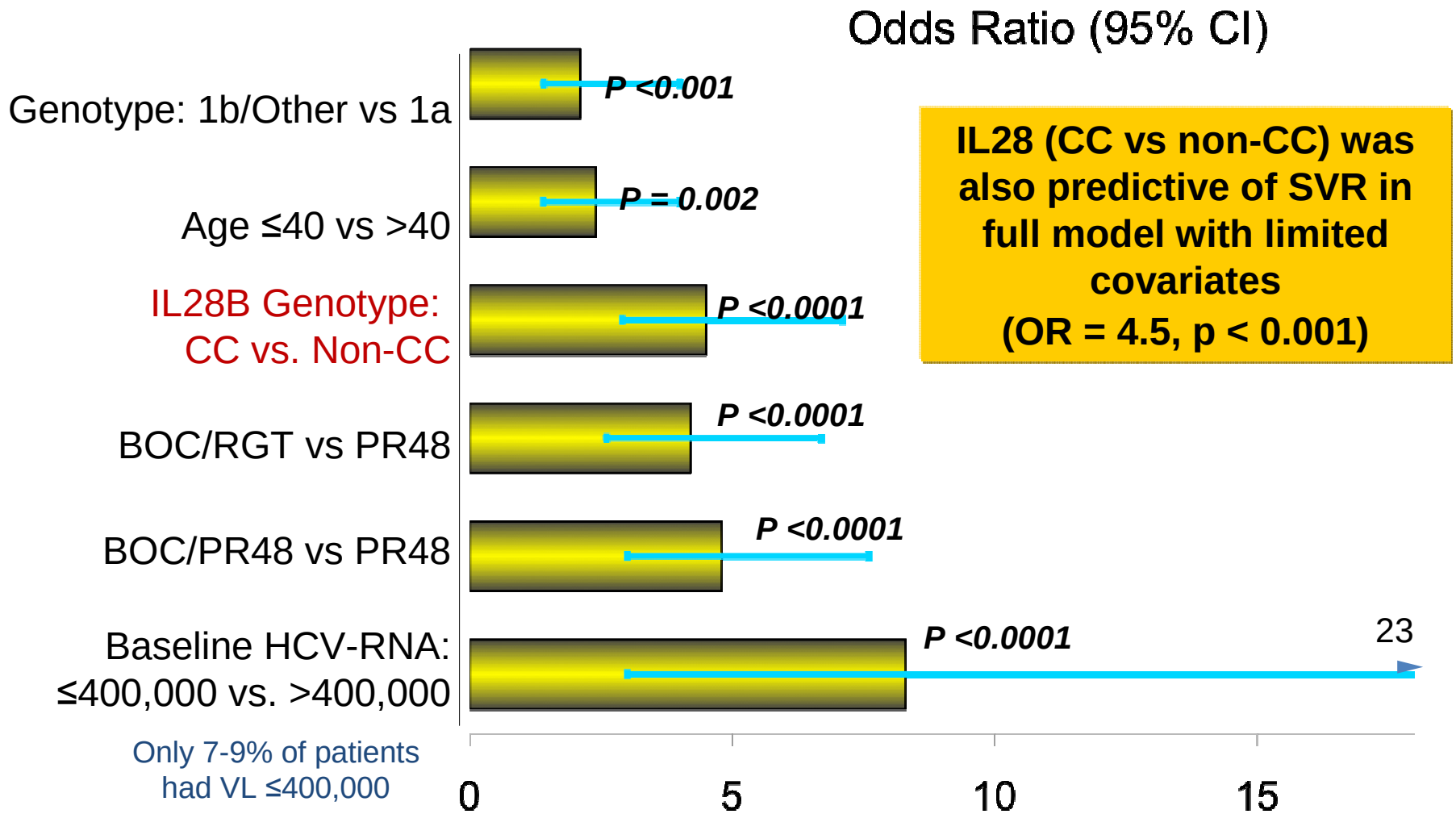
SPRINT-2: SVR to Boceprevir-Based Tx According to Fibrosis/Cirrhosis

- Phase III: genotype 1, treatment naive
  - Odds ratio for SVR with no cirrhosis vs cirrhosis: 2.5 (*P* = .003)[1]



Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 2. Bruno S, et al. EASL 2011. Abstract 7. Graphics used with permission.

SPRINT-2: predictors of response to PEGIFN + RBV ± BOC (Multiple Stepwise Logistic Regression Model)



IL28 (CC vs non-CC) was also predictive of SVR in full model with limited covariates (OR = 4.5, p < 0.001)

Only 7-9% of patients had VL ≤400,000

Only covariates remaining significant at α=0.05 after adjustment for the other variables were retained in the model as shown in the figure. Factors entered but not retained in the model were, region, race, gender, weight, BMI, steatosis, platelets, ALT, statin use, and fibrosis

Poordad F et al. N Engl J Med 2011: 364: 1195-1206

Recommended Treatment Duration With BOC in Tx-Naive Patients

All patients start with pegIFN/RBV for 4 wks

At Wk 4, BOC added to pegIFN/RBV for a duration determined by response at Wks 8 and 24

HCV RNA at Wk 8	HCV RNA at Wk 24	Recommendation
Undetectable	Undetectable	Complete BOC + pegIFN/RBV at Wk 28
Detectable	Undetectable	▪ Continue BOC + pegIFN/RBV through Wk 36, then ▪ PegIFN/RBV through Wk 48

- Stop all therapy if HCV RNA > 100 IU/mL at Wk 12 or detectable at Wk 24

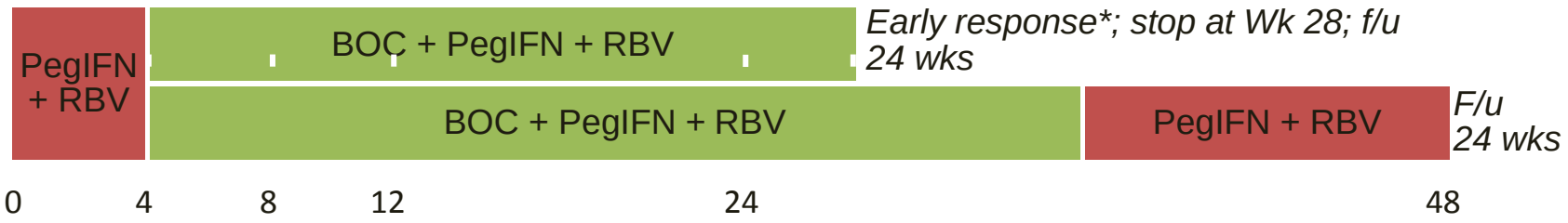
Boceprevir [package insert]. 2011.

New Standard of Care for Genotype 1 Treatment-Naive Patients

Recommendation: Optimal treatment for all genotype 1 treatment-naive patients is BOC or TVR + pegIFN/RBV

- BOC and TVR should not be used without pegIFN/RBV

Boceprevir[1,2]



*Undetectable HCV RNA at Wk 8 of therapy (Wk 4 of triple therapy).

1. Boceprevir [package insert]. May 2011. 2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.

Futility Rules for BOC + PegIFN/RBV in Tx-Naive Patients

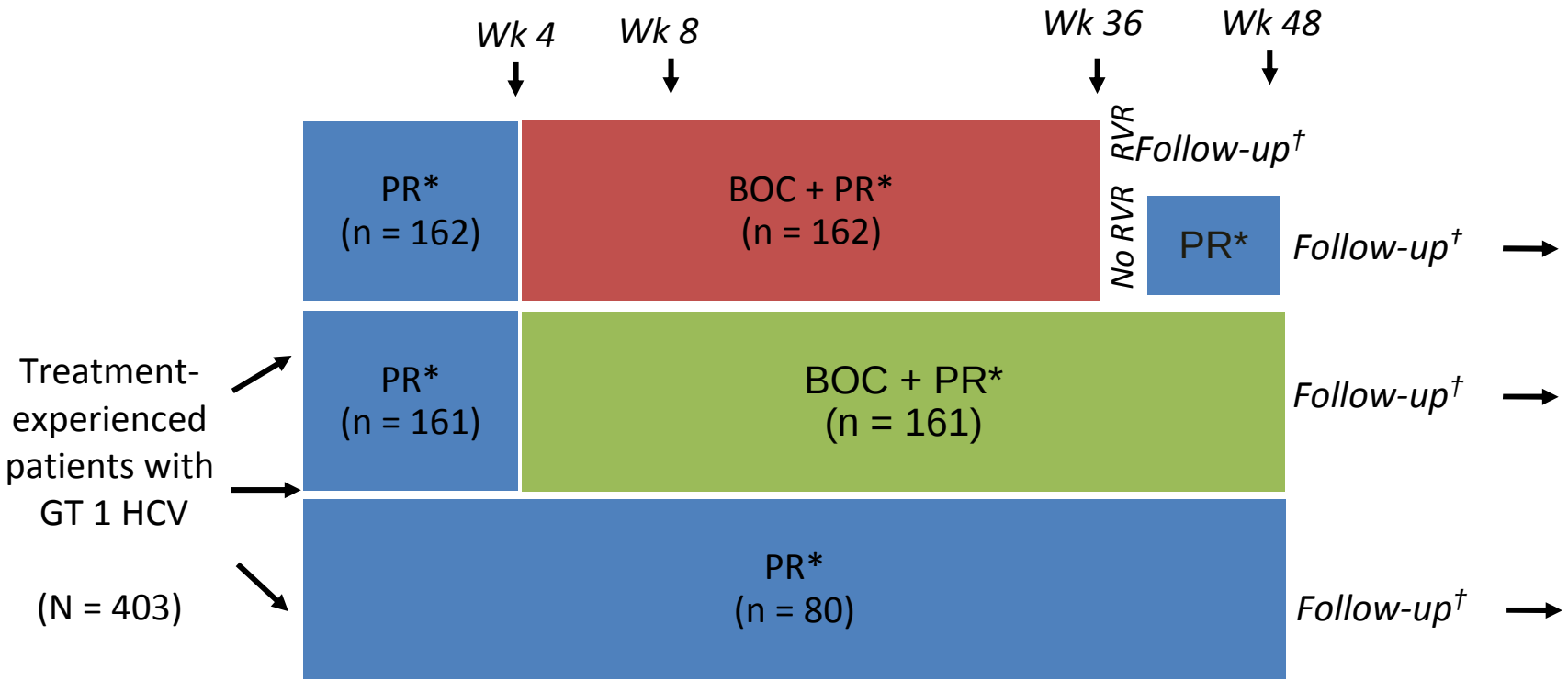
Recommendation: All therapy should be discontinued in patients with the following:

BOC[1,2]		
Time Point	**Criteria**	**Action**
Wk 12	HCV RNA ≥ 100 IU/mL	Discontinue all therapy
Wk 24	HCV RNA detectable	Discontinue all therapy

Assay should have a lower limit of HCV RNA quantification of ≤ 25 IU/mL and a limit of HCV RNA detection of approximately 10-15 IU/mL.

Adaptado de Boceprevir [package insert]. May 2011. 2. Ghany MG, et al. Hepatology. 2011;54:1433-1444.

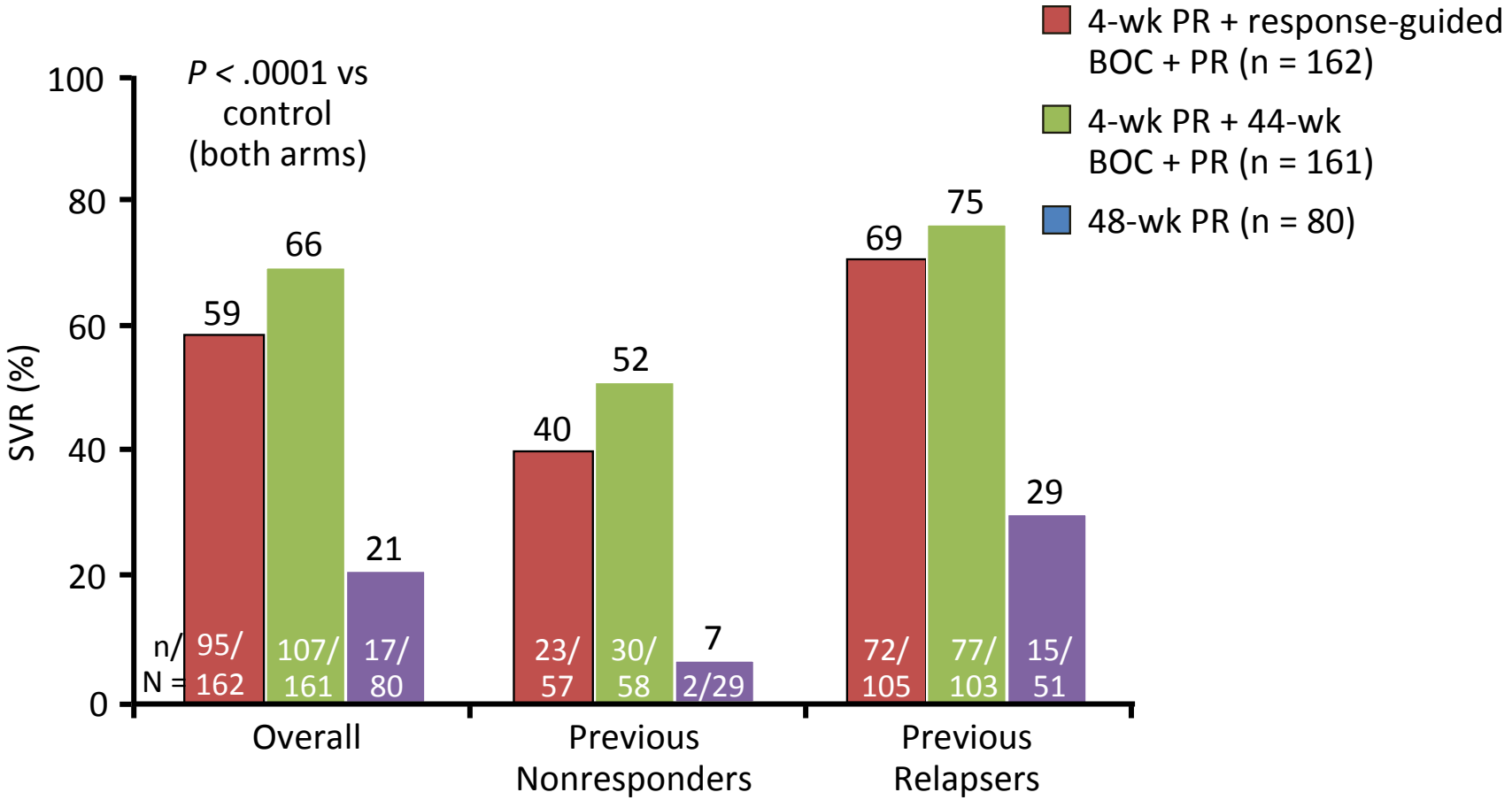
Phase III RESPOND-2: Boceprevir in GT 1 Previous Nonresponders to PegIFN/RBV



*BOC 800 mg TID; pegIFN alfa-2b 1.5 µg/kg/wk; weight-based RBV 600-1400 mg/day.
†Follow-up for 24 wks after completion of therapy.

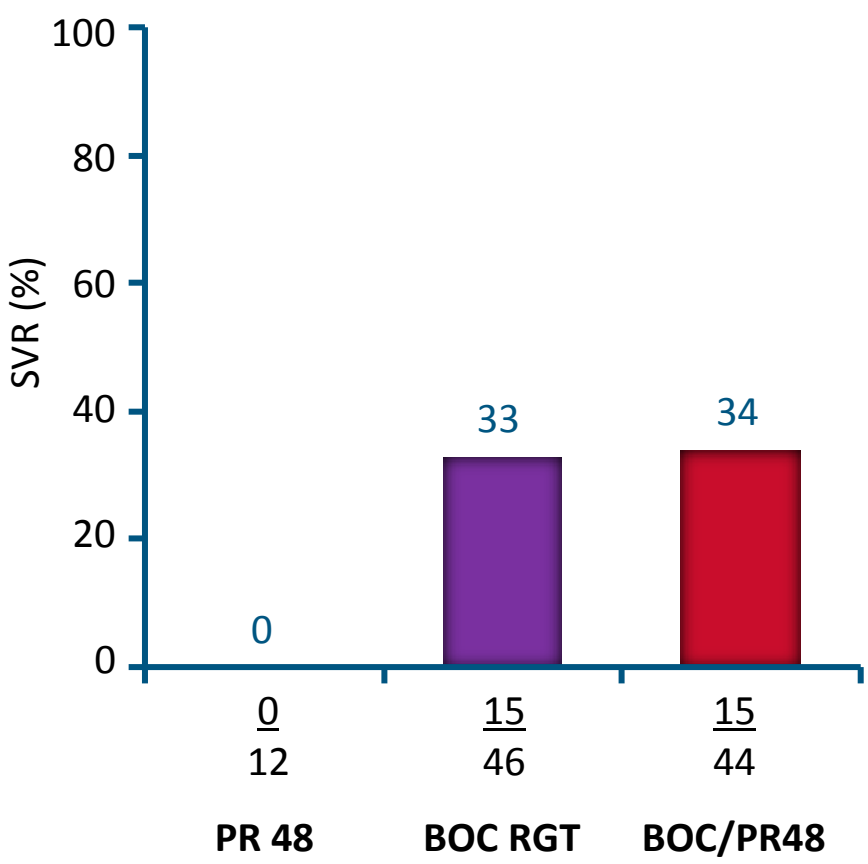
Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

RESPOND-2: SVR Rates According to Treatment Arm and Previous Response



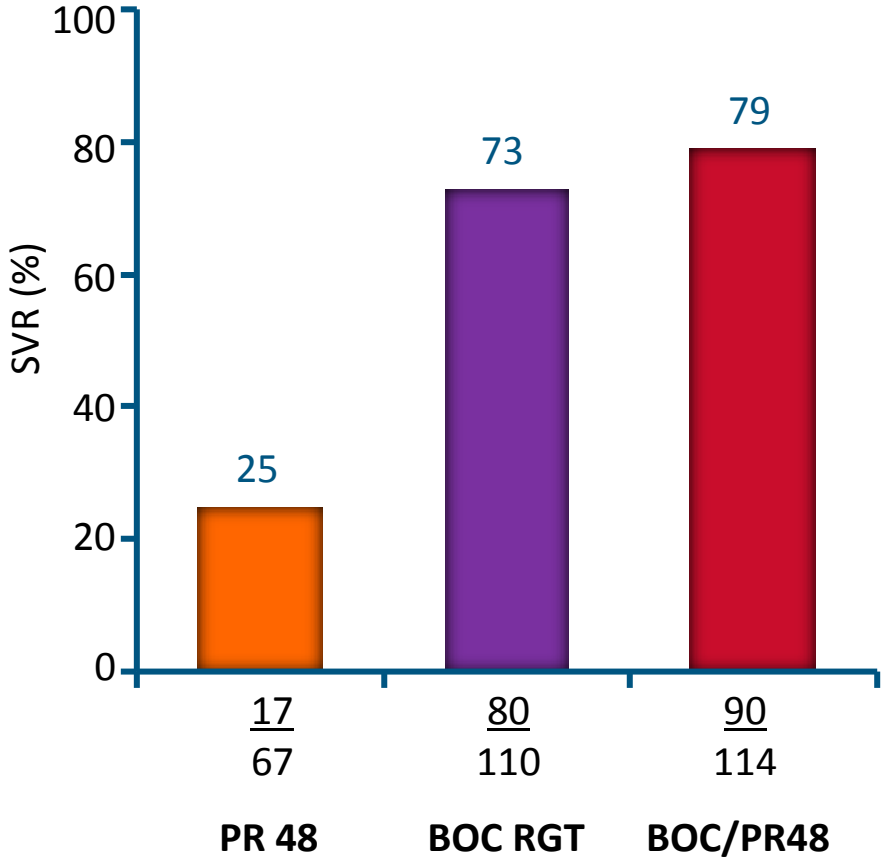
Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

RESPOND-2: SVR by Week 4
PR Lead-In Response



Poorly Responsive to IFN (n=102)

<1 log_{10} viral load decline
at treatment week 4

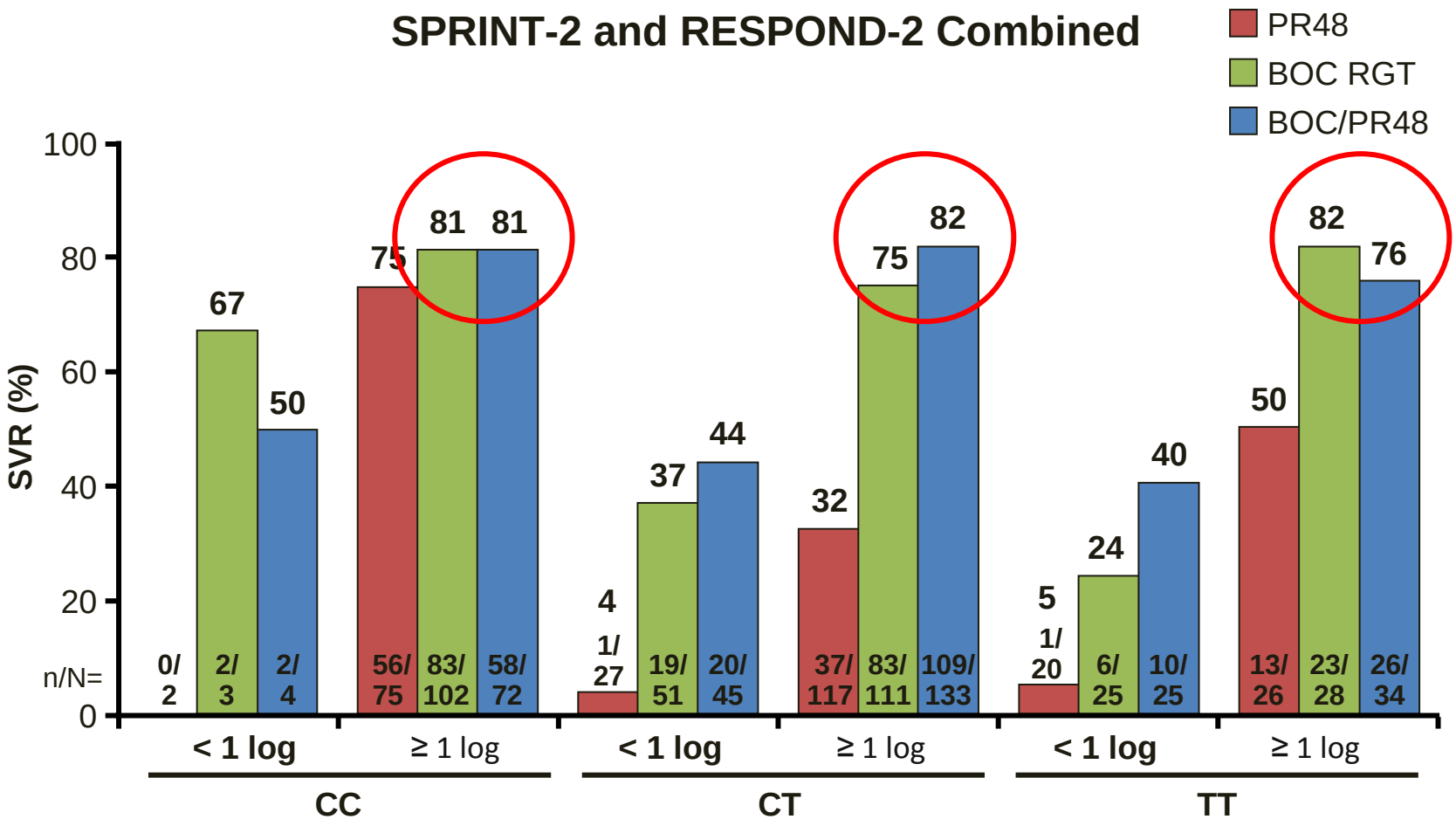


Responsive to IFN (n=294)

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

Bacon BR, et al. N Engl J Med. 2011;364:1207-1217

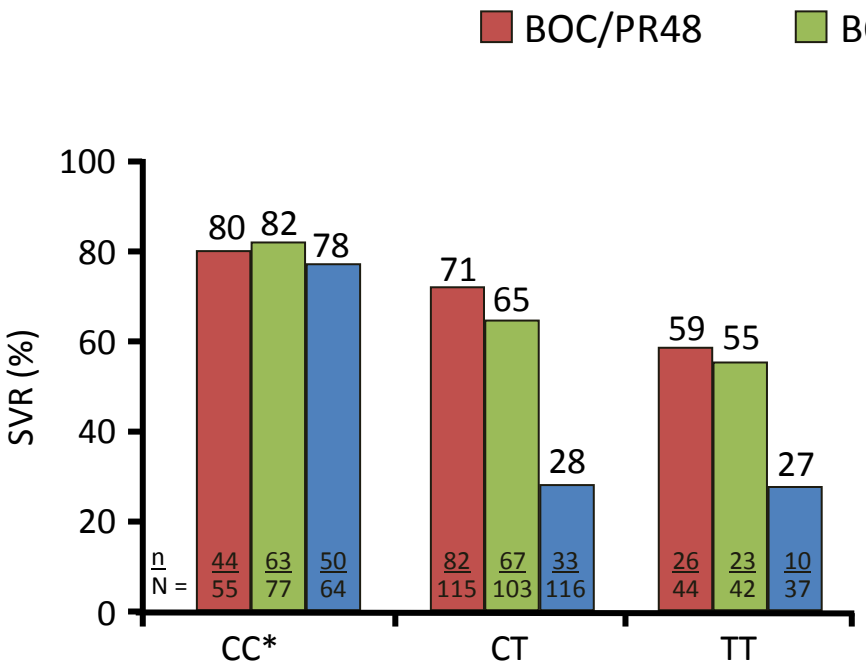
Early IFN Response (Lead-in) Further Defines Likelihood of SVR for Non-CC Pts



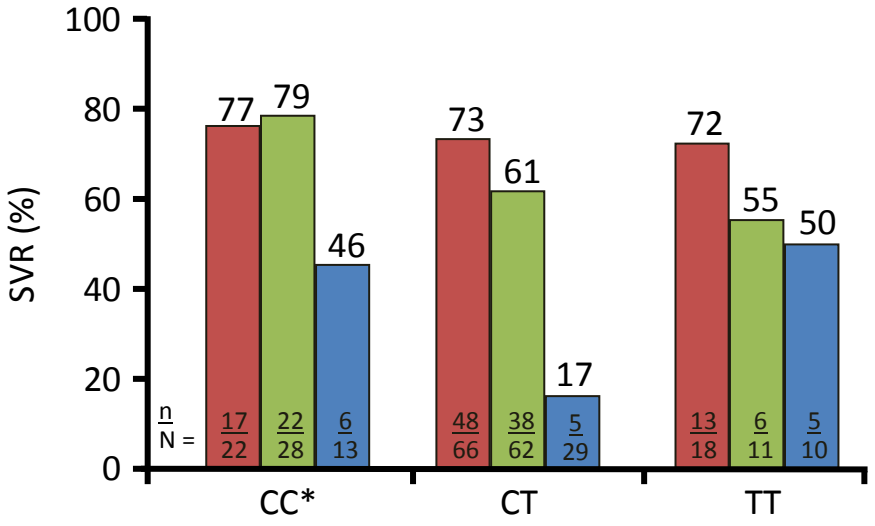
Poordad F, et al. EASL 2011. Abstract 12.

Subanalysis of Phase III Boceprevir Trials: *IL28B* as a Predictor of Response

- **SPRINT-2:** GT 1, treatment naive
- **RESPOND-2:** GT 1 relapsers and partial responders to pegIFN/RBV



*~ 90% eligible for short duration therapy.

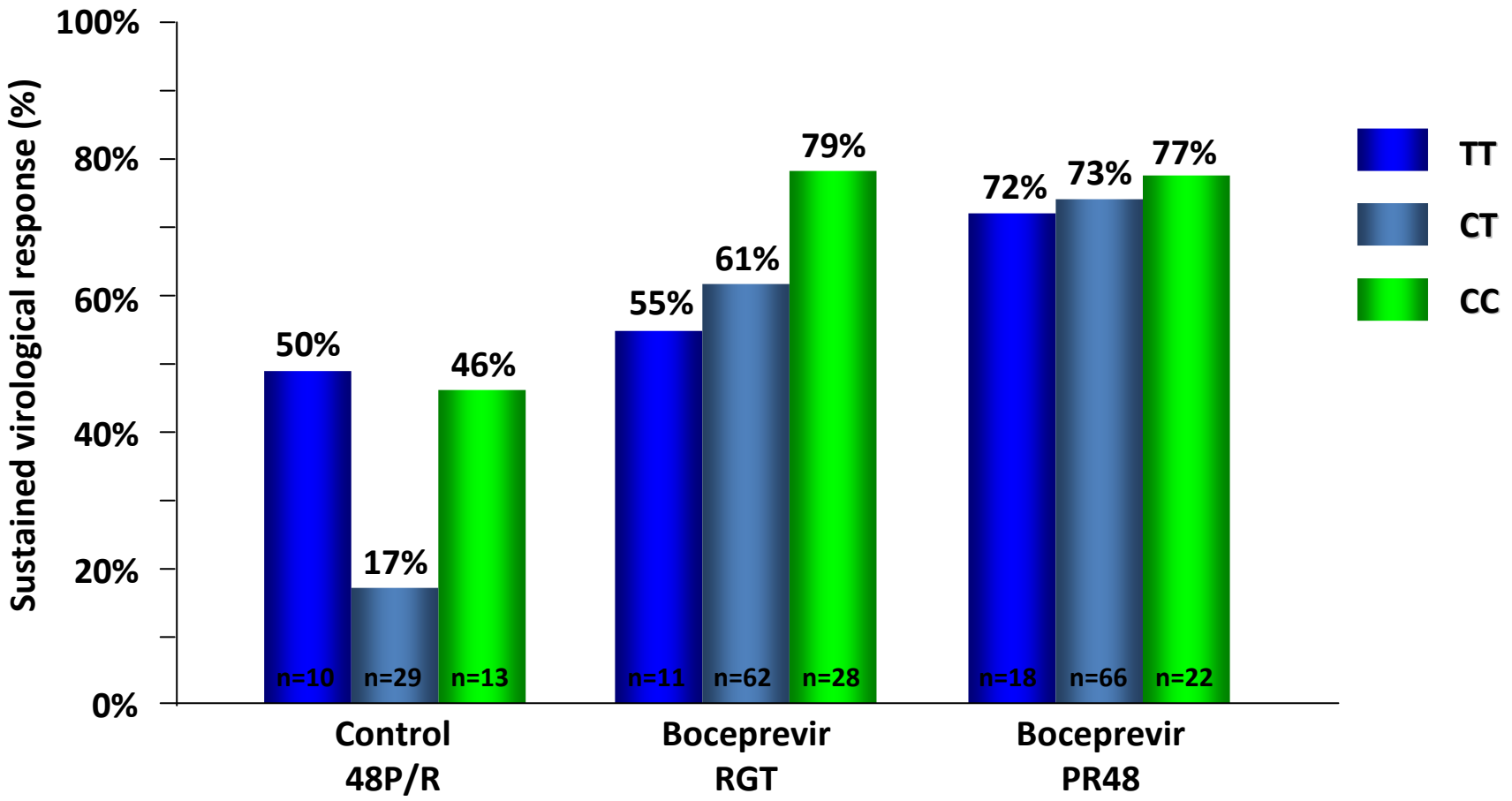


*~ 80% eligible for short duration therapy.

Poordad F, et al. EASL 2011. Abstract 12. Graphics used with permission.

IL28B and Boceprevir Regimens

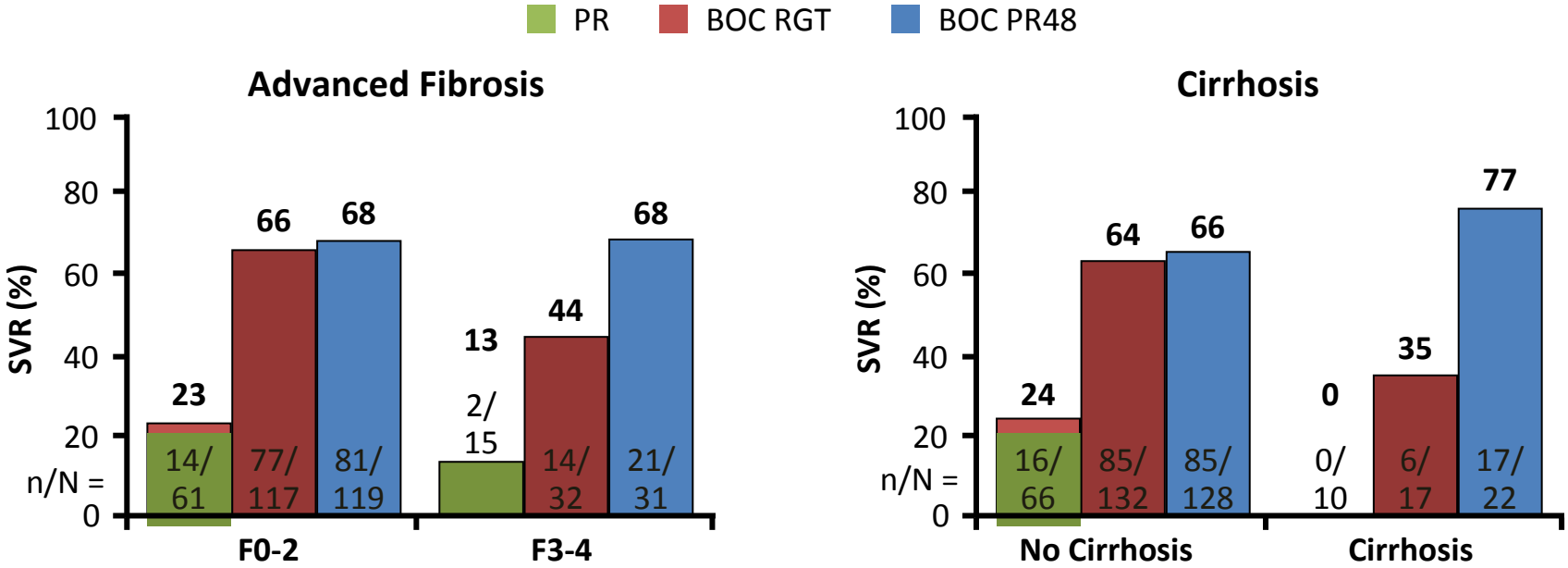
RESPOND-2 Phase 3 Clinical Trial



Bacon BR et al., EASL 2011, oral presentation

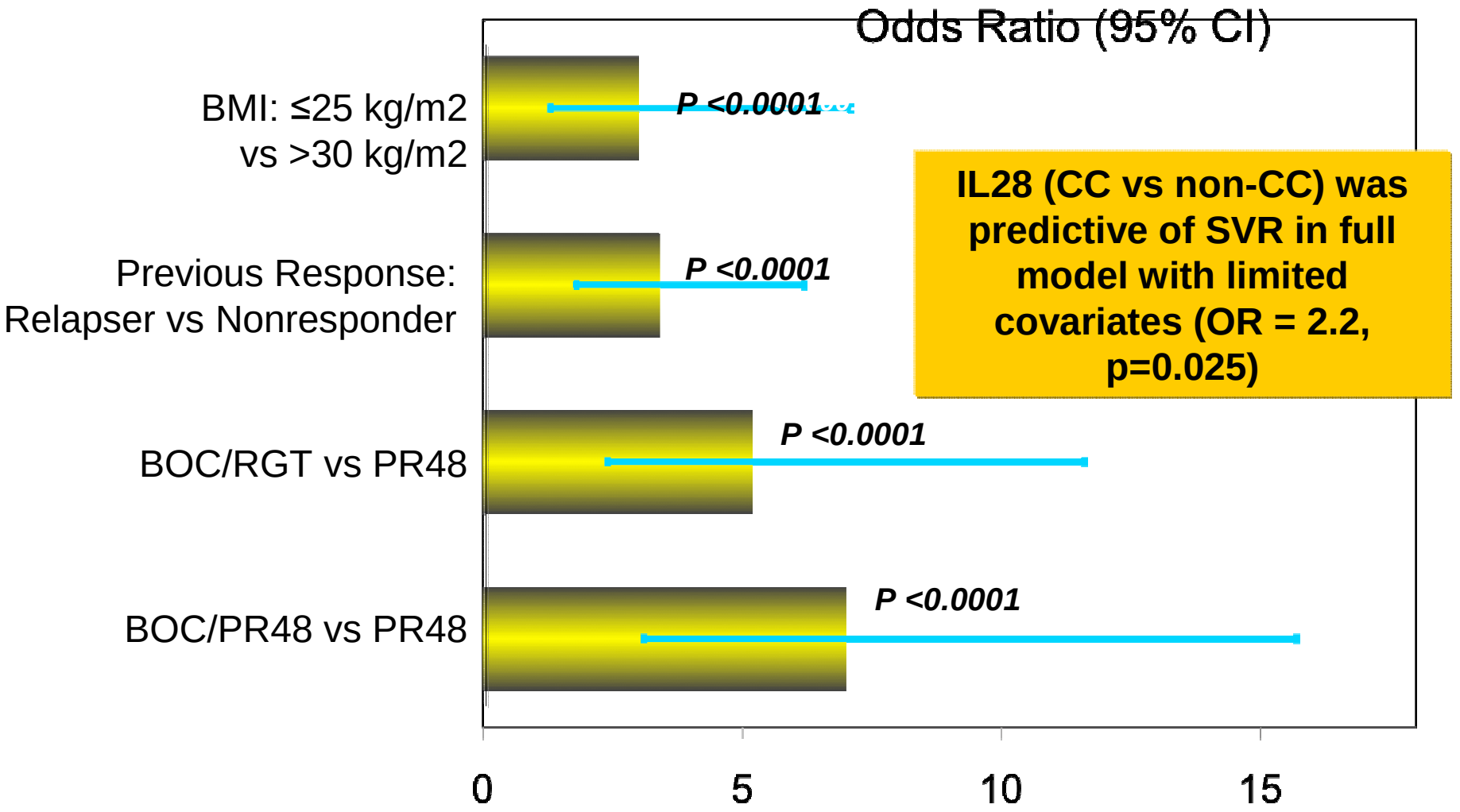
Treatment-Experienced Patients With Advanced Fibrosis or Cirrhosis

- Package inserts for both boceprevir **recommend fixed duration therapy** rather than response-guided approach in cirrhotics
  - Supported by RESPOND-2 study data evaluating impact of response-guided therapy on SVR in cirrhotic patients



Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

RESPOND-2: IL-28B CC Polymorphism as a Predictor of SVR (Multiple Stepwise Logistic Regression Model)



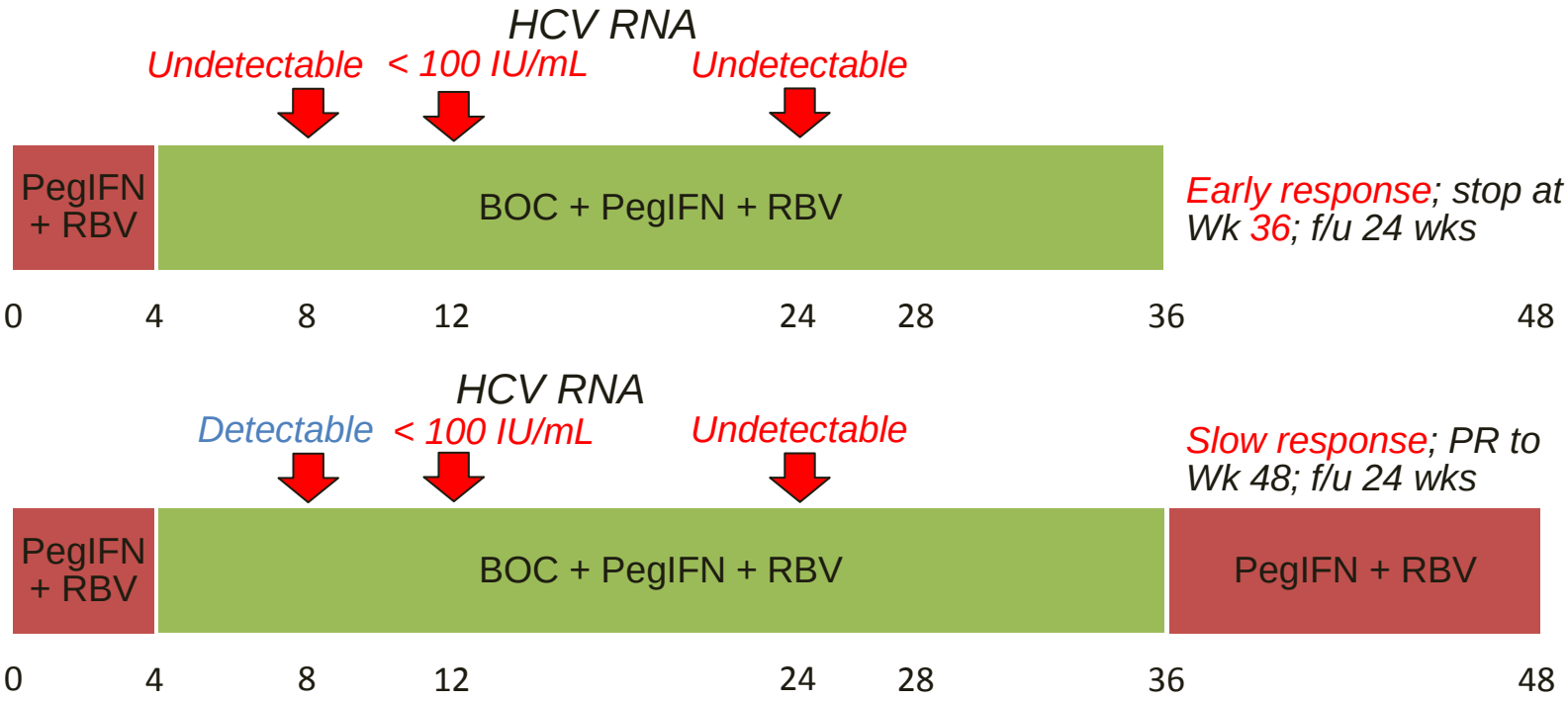
IL28 (CC vs non-CC) was predictive of SVR in full model with limited covariates (OR = 2.2, p=0.025)

Other predictors: low VL, absence of cirrhosis, W4 response

Bacon BR., et al. N Engl J Med 2011; 364:1207-1217.

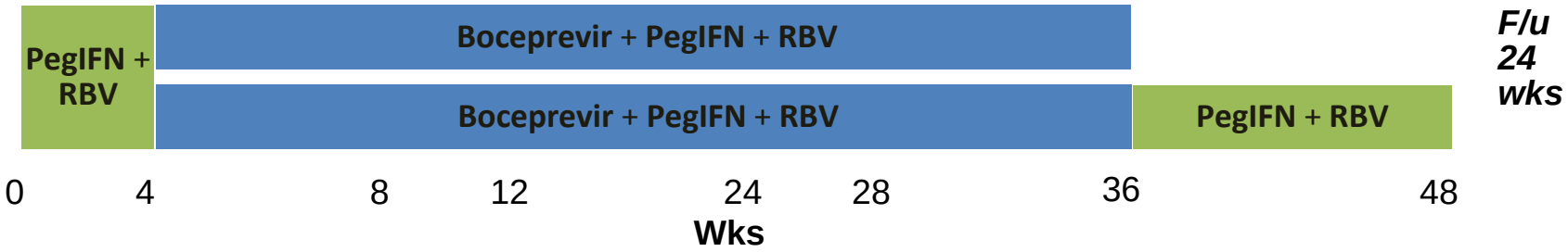
Response-Guided Therapy Paradigm With BOC + PegIFN/RBV in Tx-Exp Patients

Recommendation: **Response-guided therapy** can be considered for previous **relapsers**, may be considered for previous **partial responders**, but **NOT for previous null responders**



Boceprevir [package insert]. May 2011. Ghany MG, et al. Hepatology. 2011;54:1433-1444.

Boceprevir + PegIFN/RBV: Genotype 1 Noncirrhotic Tx-Experienced Patients



Partial Responders, Relapsers: Duration Based on Wks 8 and 24 HCV RNA*

- If undetectable at both time points, continue 3-drug regimen to Wk 36
- If detectable at Wk 8 but undetectable at Wk 24, continue 3-drug regimen to Wk 36, then administer pegIFN/RBV to Wk 48

- **All cirrhotic patients should receive lead-in then boceprevir + PR for 44 wks**
- Futility: stop all 3 drugs if Wk 12 HCV RNA ≥ 100 IU/mL or Wk 24 HCV RNA detectable
- **Wk 4 < 1 log HCV RNA reduction** associated with greater risk of developing resistance associated variants and lower SVR rates: consider **boceprevir + PR for 44 wks after lead-in, no RGT**
- If considered for treatment, previous **null responders** should receive **lead-in then boceprevir + PR for** 44 wks

*Assay should have a lower limit of HCV RNA quantification ≤ 25 IU/mL.

Boceprevir [package insert]. May 2011.

Boceprevir Regimens – Treatment experienced and cirrhotics

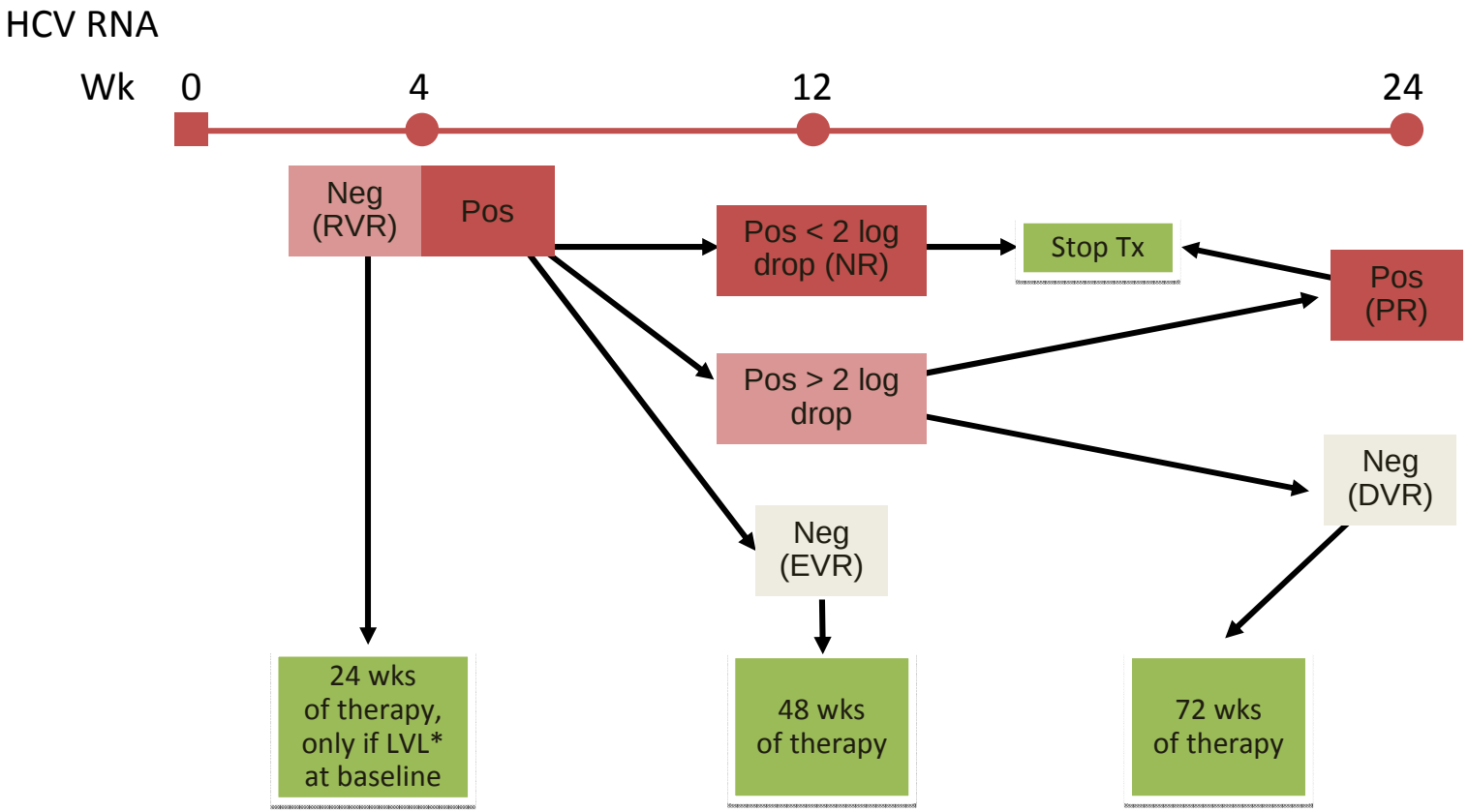
- **Previous partial responders and relapsers**
  - 4-wk **lead-in period** of pegIFN/RBV alone, then **triple therapy** with BOC 800 mg TID + pegIFN/RBV for **32 weeks**
    - Followed by **additional 12 wks of pegIFN/RBV alone** for **slow responders**

- **Previous null responders and all cirrhotic patients**
  - 4-wk **lead-in period** of pegIFN/RBV alone, then **triple therapy** with BOC 800 mg TID + pegIFN/RBV for **44 weeks**

*Treatment duration covered in detail in next section.

Boceprevir [package insert]. 2011.

EASL: Response-Guided Therapy in Patients With Genotype 1 Infection



*HCV RNA < 400,000-800,000 IU/mL

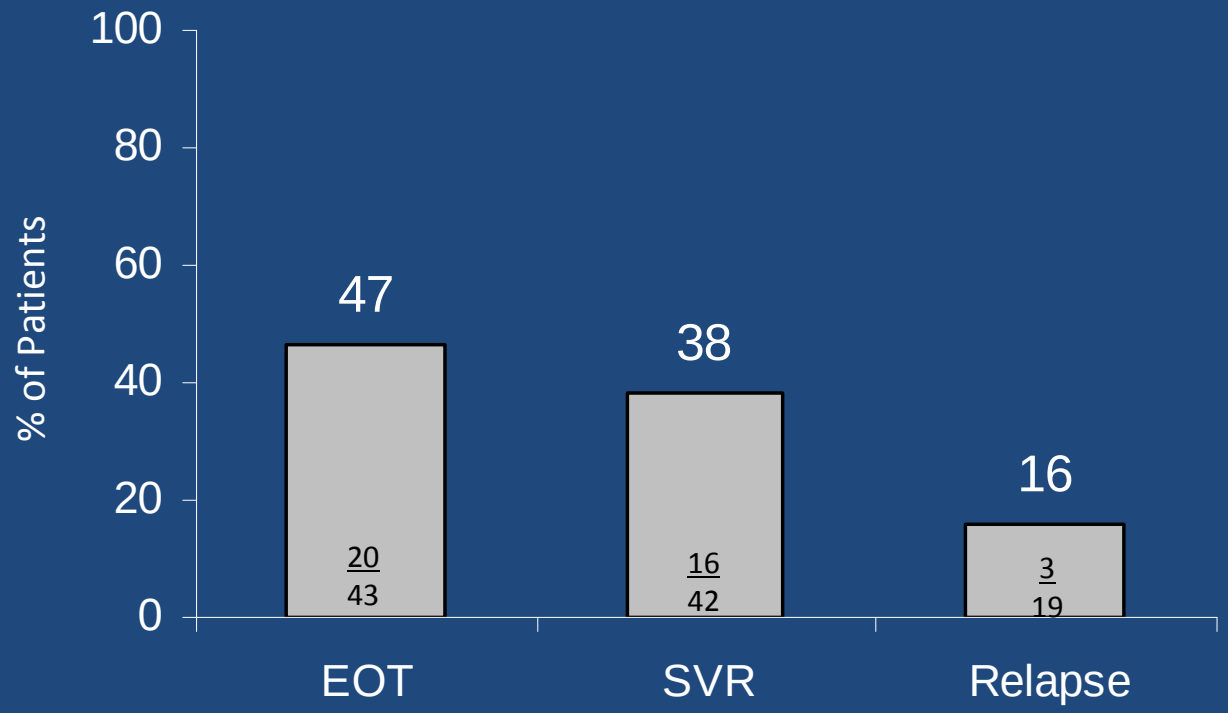
Craxi A, et al. J Hepatol. 2011;[Epub ahead of print].

Efficacy of Boceprevir in Prior Null Responders to Peginterferon/Ribavirin: The PROVIDE Study

J. Vierling[1], S. Flamm[2], S. Gordon[3], E. Lawitz[4], J-P Bronowicki[5], M. Davis[6], E. Yoshida[7], L.D. Pedicone[8], W. Deng[8], M. Treitel[8], C. Brass[8], J. Albrecht[8], and I. Jacobson[9]

[1]Baylor College of Medicine, Houston, TX ; [2]Northwestern Feinberg School of Medicine, Chicago, IL; [3]Henry Ford Hospital, Detroit, MI, USA; [4]Alamo Medical Research, San Antonio, TX; [5]University Henri Poincare of Nancy, Vandoeuvre-lès-Nancy, France; [6]South Florida Center of Gastroenterology, Wellington, FL; [7]University of British Columbia and Vancouver General Hospital, Vancouver, BC, Canada; [8]Merck Sharp & Dohme Corp., Whitehouse Station, NJ; [9]Weill Cornell Medical College, New York, NY;

Responses in Prior Null Responders*



*Of 48 prior Null Responders from SPRINT-2 and RESPOND-2, 3 discontinued during the 4-week lead-in phase, 2 are ongoing treatment (1 entering TW3, 1 entering TW18 of BOC/PR) and 1 is in follow-up phase

EOT = end of treatment.
SVR = sustained virologic response
Relapse = an undetectable HCV RNA level at EOT, but with a detectable HCV RNA level during the follow-up period

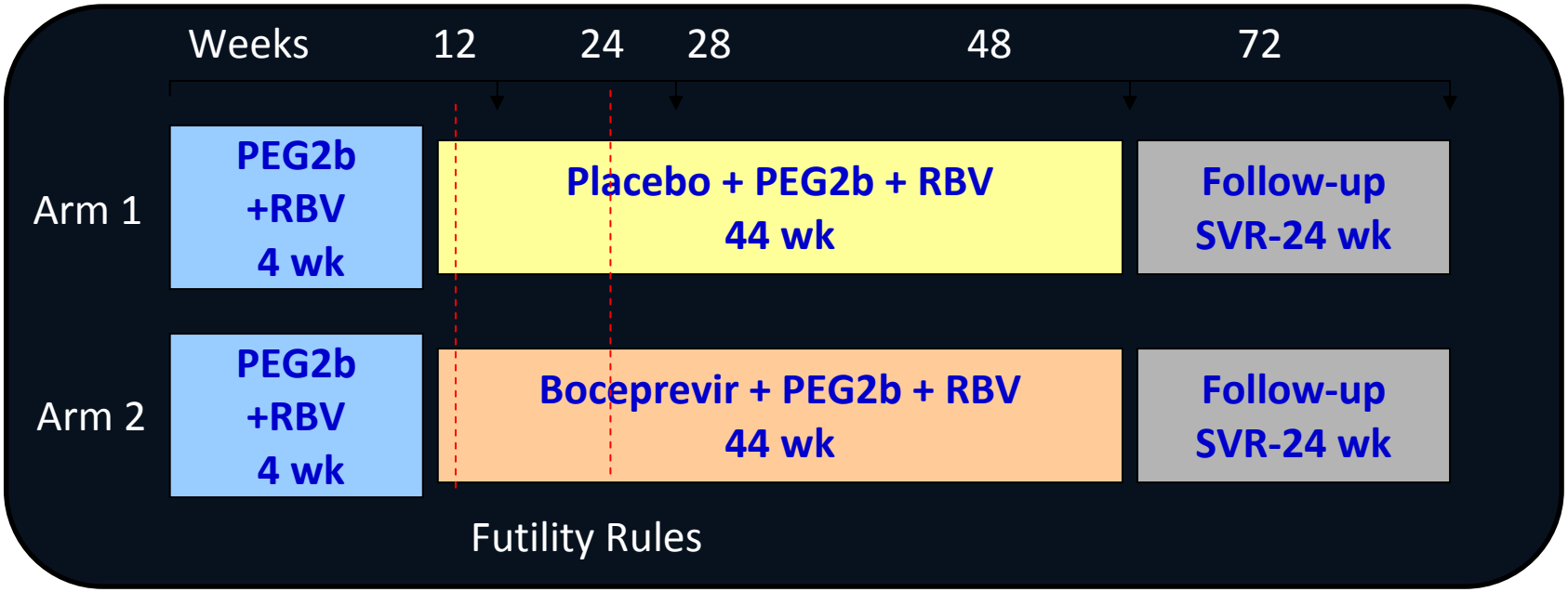
Boceprevir plus PegINF/RBV for the treatment of HCV/HIV co-infected patients.

M Sulkowski[1], S Pol[2], C Cooper[3], H Fainboim[4], J Slim[5], A Rivero[6], S Thompson[7], W Greaves[7], J Wahl[7], J Mallolas[8]

[1]John Hopkins University School of Medicine, Baltimore, MD; [2]Hopital Cochin, Paris, France; [3]The Ottawa Hospital, Ottawa, ON, Canada; [4]F. J. Muñiz Hospital De Infecciosas, Buenos Aires, Argentina; [5]Saint Michael's Medical Center, Newark, NJ; [6]Hospital Universitario Reina Sofia, Córdoba, Spain; [7]Merck Sharp & Dohme, Whitehouse Station, NJ; [8]Hospital Clinic i Provincial Barcelona, Spain

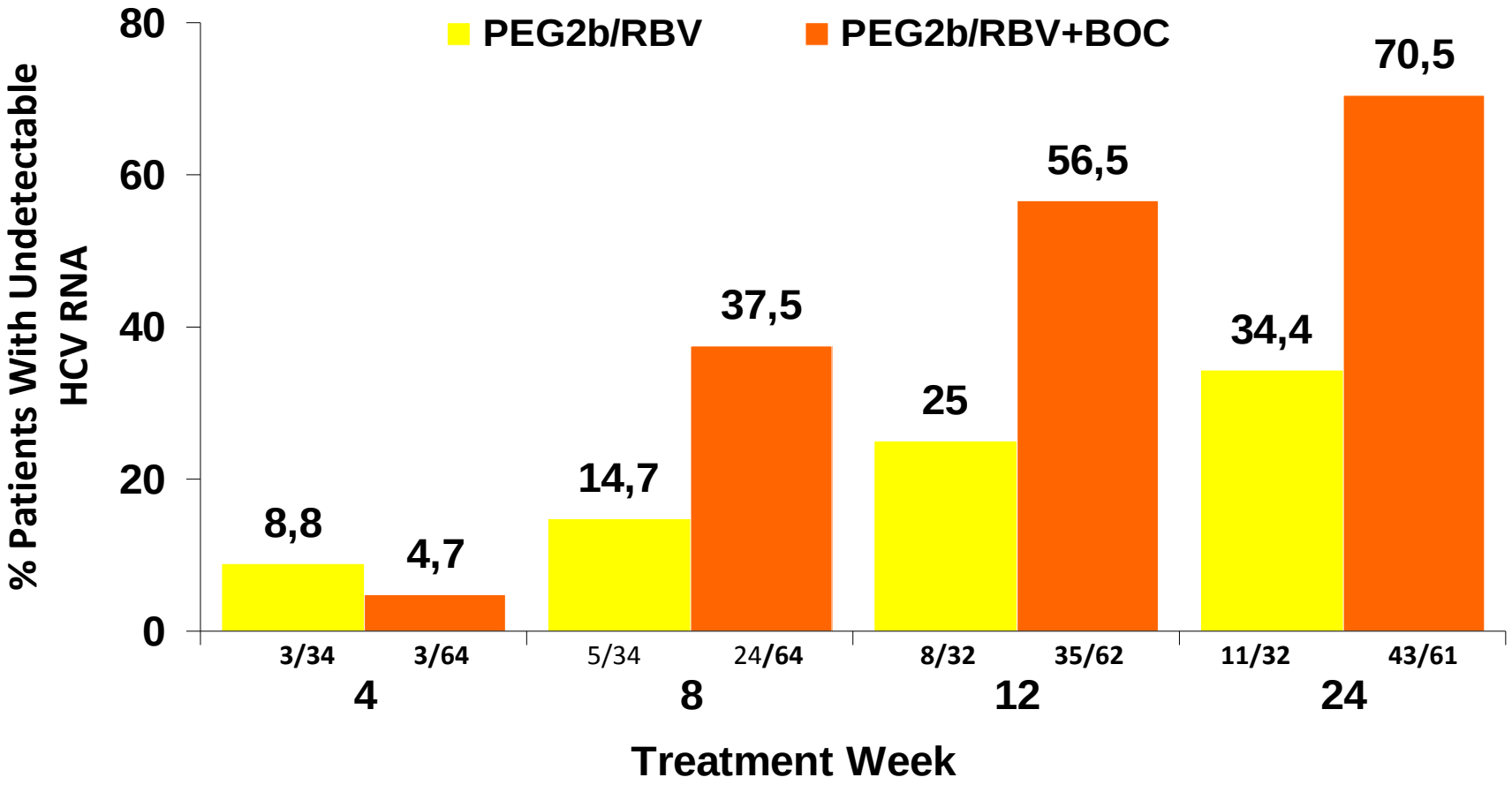
Late Breaker Oral Abstract LB-37
Infectious Diseases Society of America (IDSA) 49th Annual Meeting
Boston MA
October 22nd, 2011

Study design



- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomization (experimental: control)
  - Boceprevir dose 800 mg, TID
- 4-week lead-in with PEG2b/RBV for all patients
  - PEG-2b 1.5 µg/kg QW; RBV 600-1400 mg/day divided BID
- Control arm subjects with HCV-RNA ≥ LLQ at TW 24 were offered open-label PEG2b/RBV+BOC via a cross-over arm

Virologic response over time (% HCV RNA undetectable)

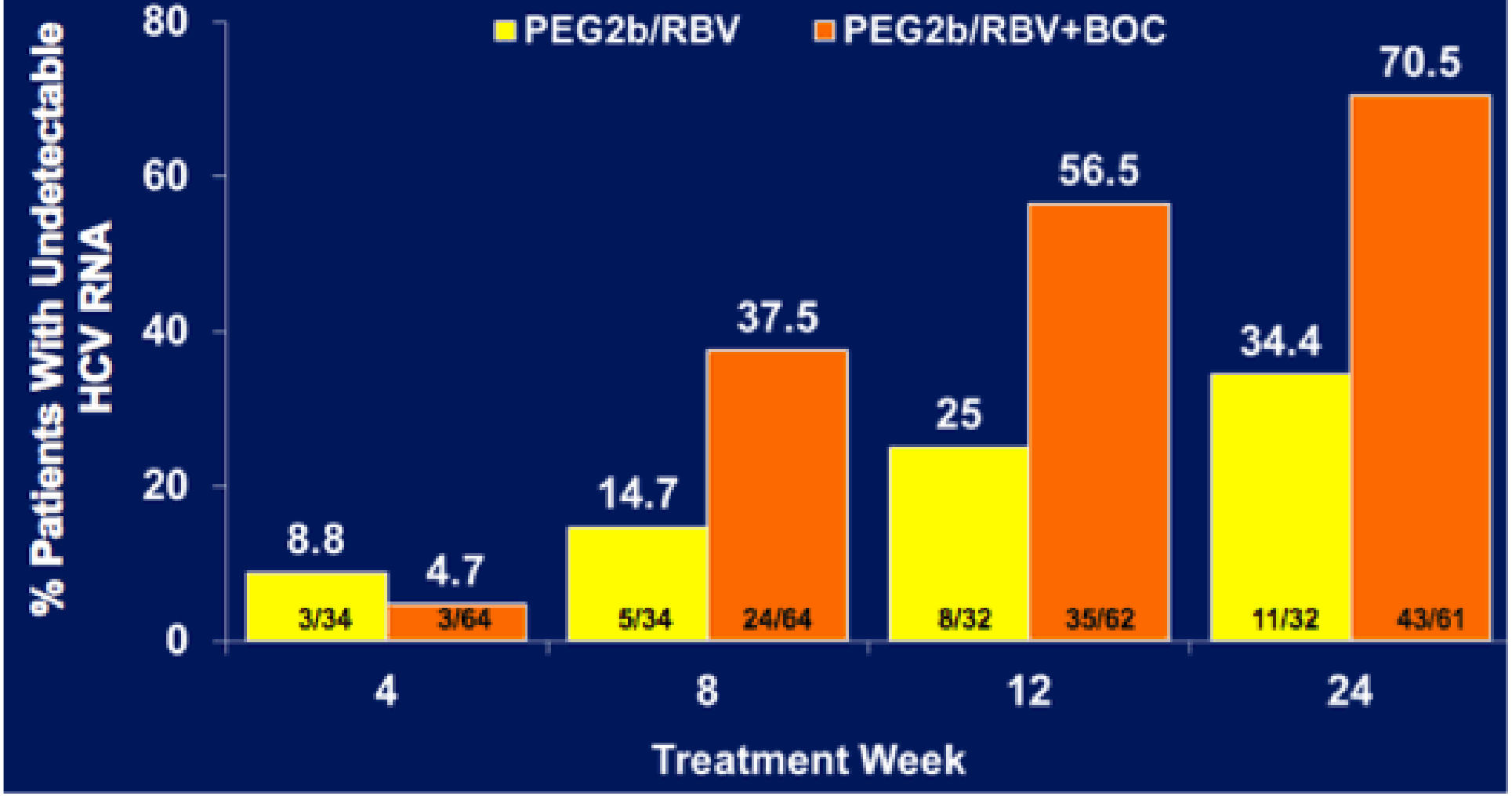


Percentage of Patients with Undetectable HCV RNA* Through TW48/EOT						
	Control P/R		Boceprevir BOC+ P/R		BOC vs. Control	
	n/N (%)	**95% CI**	**n/N (%)**	**95% CI**	**Difference (%)**	**95% CI**
Week 4	**3 /34 (8.8)**	**(0.0, 18.4)**	**3 /64 (4.7)**	**(0.0, 9.9)**	**-4.1**	**(-15.0, 6.7)**
Week 8	**5 /34 (14.7)**	**(2.8, 26.6)**	**27 /64 (42.2)**	**(30.1, 54.3)**	**27.5**	**(10.5, 44.5)**
Week 12	**8 /34 (23.5)**	**(9.3, 37.8)**	**38 /64 (59.4)**	**(47.3, 71.4)**	**35.8**	**(17.2, 54.5)**
Week 24	**11/34 (32.4)**	**(16.6, 48.1)**	**47/64 (73.4)**	**(62.6, 84.3)**	**41.1**	**(22.0, 60.2)**
Week 48†	**10/34 (29.4)**	**(14.1, 44.7)**	**39/61 (63.9)**	**(51.9, 76.0)**	**34.5**	**(15.0, 54.0)**

*As determined by Roche Taqman v2, LOD 9.3 IU/mL
† Excludes 3 subjects still on BOC+P/R at time of analysis

Virologic Response Over Time (% HCV RNA Undetectable)

Efficacy and safety as expected from data in HIV-



Summary of safety

	PEG2b/RBV (N = 34)	PEG2b/RBV + BOC (N = 64)
Days on study, median	**166**	**211**
Any AE, n (%)	**34 (100)**	**63 (98)**
Serious AEs, n (%)	**7 (21%)**	**5 (8%)**
Treatment-related Treatment-emergent AEs, n (%)	**34 (100%)**	**61 (95%)**
Study Discontinuation Due to an AE, n (%)	**3 (9%)**	**9 (14%)**
Any Drug Modification Due to an AE, n (%)	**7 (21%)**	**12 (19%)**

Most common AE with a difference of ≥10% between groups*

	PEG2b/RBV (N=34)	PEG2b/RBV + BOC (N=64)
Days on study, median	**166**	**211**
Neutropenia, (%)	**3%**	**13%**
Dysgeusia, (%)	**15%**	**25%**
Vomiting, (%)	**15%**	**25%**
Pyrexia, (%)	**21%**	**34%**
Headache, (%)	**12%**	**28%**
Decreased Appetite, (%)	**18%**	**30%**

*A difference of ≥10% for patients receiving PEG2b/RBV+BOC when compared with PEG2b/RBV.

Clinical Infectious Diseases Advance Access published December 14, 2011

INVITED ARTICLE HIV/AIDS

Kenneth H. Mayer, Section Editor

Provisional Guidance on the Use of Hepatitis C Virus Protease Inhibitors for Treatment of Hepatitis C in HIV-Infected Persons

David L. Thomas,[1] John G. Bartlett,[1] Marion G. Peters,[2] Kenneth E. Sherman,[3] Mark S. Sulkowski,[1] and Paul A. Pham[1]

[1]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; [2]Department of Medicine, University of California, San Francisco School of Medicine; and [3]Department of Medicine, University of Cincinnati School of Medicine, Ohio

In May 2011, hepatitis C virus (HCV) protease inhibitors (PIs) were approved by the US Food and Drug Administration to treat persons with genotype 1 chronic hepatitis C virus (HCV) infection, but not those dually infected with human immunodeficiency virus (HIV). Although critical safety and efficacy data are lacking, the availability of the drugs and substantial medical need justify the off-label use of HCV PIs in select HIV/HCV-coinfected persons. Pending results of ongoing investigations, this article represents provisional guidance on the use of HCV PIs in HIV-infected persons.

Antiretroviral therapy in candidates for PEG IFN + RBV + BOC or TPV

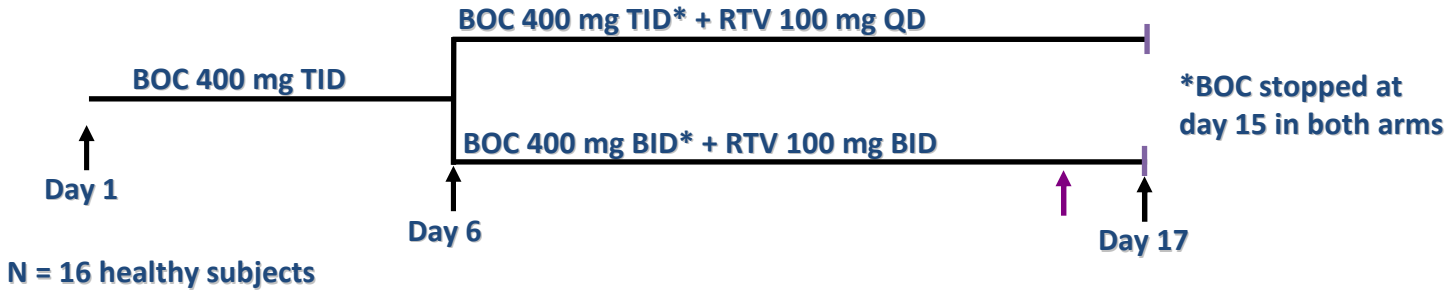
CLASS	Antiretrovirals	TELAPREVIR	BOCEPREVIR
NRTI	AZT, ddI, d4T	Avoid coadministration	Avoid coadministration
	ABC: No data but DDI not anticipated	?	?
	FTC, LAM,TDF	Can be combined	Can be combined
PI	LPV/R , DRV/R, FPV/R,	Avoid coadministration	Can be combined
	ATZ/R	Can be combined	Can be combined
NNRTI	EFV	1125 mg tid (+12000 €)	Avoid coadministration
	NVP RPV ETV: No data	Avoid coadministration	Avoid coadministration
II	RAL	Can be combined	Can be combined

Management of HIV-HCV coinfected genotype-1 patients according to fibrosis stage and prior treatment outcome: what I'm going to do

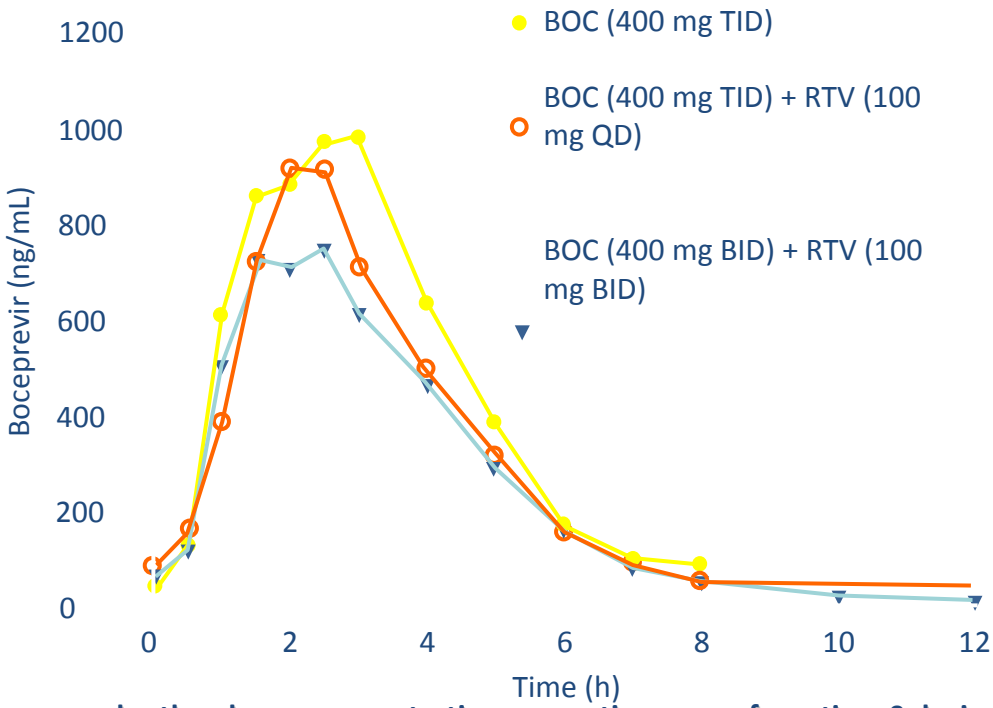
Fibrosis Stage	B.L & on Treatment predictors		Naïve	EXPERIENCED			
METAVIR	IL28B	RVR		Relapsers	Partial resp.	Null resp.	Unclassified*
F0-F1	Good	YES	P + R	Consider P+R+B/T	Defer	Defer	Defer
		NO					
	Poor	YES					
		NO	Defer				
F2-F3	Good*	YES	P+R	P+R+B/T	P+R+B/T		P+R+B/T* If > 1 Log decline after lead in
		NO	P+R+B/T				
	Poor	ANY					
F4	Any	>1 Log decrease	P+R+B/T			P+R+B/T*	
		< 1 Log decrease				Defer*	

* Lead in phase

Ritonavir: no effect on BOC



N = 16 healthy subjects

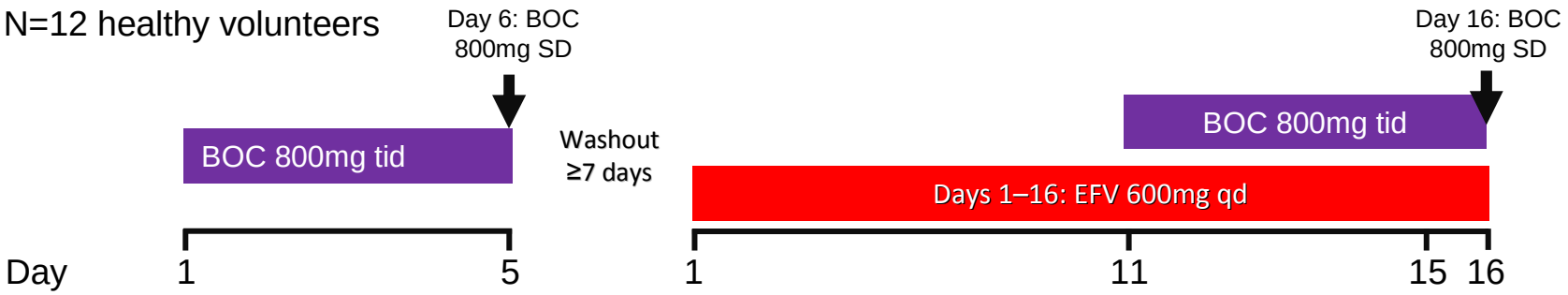


BOC + RTV (100 mg QD) vs BOC
$AUC_{(T)}$ ratio estimate
81% (90% CI: 73–91)
C_{max} R.E.
73% (90% CI: 57–93)

BOC + RTV (100 mg BID) vs BOC
$AUC_{(T)}$ ratio estimate
82% (90% CI: 75–88)
C_{max} R.E.
x% (90% CI: y–z)

$AUC_{(T)}$, area under the plasma concentration versus time curve from time 0 dosing interval; BID, two time a day; BOC, boceprevir; CI, confidence interval; RTV, ritonavir; TID, three times a day.

Boceprevir exposure decreased by efavirenz



	Treatment	LSmean*	Ratio estimate, % (90% CI)
BOC AUC_{0-8h}, ng•h/mL	BOC	6913	**81 (75–89)**
	BOC + EFV	5630	
EFV AUC_{0-24h}, ng•h/mL	EFV	78667	**120 (115–126)**
	EFV + BOC	94655	

Modified from Kassera C, et al. CROI 2011. Abstract 118

SD: single dose; *model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment and volunteer

- **<u>Results:</u>**

  By TW48, 2/64 patients and 3/34 patients in the boceprevir/PEG/RBV and control (PEG/RBV) groups, respectively had HIV virologic failure. The addition of boceprevir to PEG/RBV was associated with higher rates of undetectable HCV RNA AT at all time points, including TW48. The safety profile was consistent with that observed in HCV-monoinfected patients.

- **Recommendation:**

  In light of the PK data generated in healthy volunteers, Merck believes that these pharmacokinetic interatcions may be clinically significant for patients infected both with chronic HCV and HIV. **Accordingly, use of boceprevir in combination with RTV-boosted HIV protease inhibitors should be limited to a clinical trials** setting in wich patients are properly consented and closely monitored.

MSD, Protocol 5411

- **Results:**

  Co-administration of boceprevir with ritonavir (RTV)-boosted atazanavir, lopinavir, or darunavir reduced mean trough concentrations of the respective PIs by 49%, 43%, and 59%, respectively. Mean reductions of 34-44% and 25-36% were observed in AUC and Cmax, respectively. Co-administration of atazanavir/RTV with boceprevir did not alter boceprevir AUCτ, but co-administration of boceprevir with lopinavir/RTV or darunavir/RTV decreased boceprevir AUCτ by 45% and 32%, respectively.

MSD, Protocol 08384

BOC metabolism and excretion

- Victim (boceprevir metabolism and excretion)
  - Extensively metabolized by two distinct pathways
    - AKR
    - CYP3A4
  - P-gp substrate
  - Primary route of excretion is hepatic/fecal

- Perpetrator
  - Boceprevir is a strong reversible CYP3A4 inhibitor
  - Boceprevir does not induce CYP450 enzymes

AKR=aldoketo reductase; CYP=cytochrome P450; P-gp=P-glycoprotein.

Drug-Drug Interactions Represent a Clinical Challenge*

Drug Class	Contraindicated With BOC[1]	Contraindicated With TVR[2]
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Alfuzosin
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	N/A
Antimycobacterials	**Rifampin**	**Rifampin**
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agents	Cisapride	Cisapride
Herbal products	*Hypericum perforatum* (St John's wort)	*Hypericum perforatum*
HMG CoA reductase inhibitors	Lovastatin, simvastatin	Atorvastatin, lovastatin, simvastatin
Oral contraceptives	Drospirenone	N/A
Neuroleptic	Pimozide	Pimozide
PDE5 inhibitor	Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension	Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension
Sedatives/hypnotics	Triazolam; orally administered midazolam	Orally administered midazolam, triazolam

*Studies of drug-drug interactions incomplete.

1. Boceprevir [package insert]. May 2011. 2. Telaprevir [package insert]. May 2011.

DDI: Boceprevir as Victim

No clinically concerning effect of co-administered drugs on Boceprevir

	Co-administered Drug	Mean $AUC_{(\tau)}$ Ratio[†]
AKR inhibitors	Ibuprofen Diflunisal	1.04 ↔ 0.96 ↔
CYP3A4/P-gp inhibitors	Ketoconazole Ritonavir Clarithromycin*	2.31 ↑ 0.81 ↔ 1.21 ↔
CYP3A4 inducers	Efavirenz	0.81 ↔
Other	Tenofovir Peginterferon α-2b[‡] Ribavirin[§]	1.08 ↔ 1.00 ↔ ~0.92 ↔

[†] Ratio estimate of Boceprevir PK parameters (in combination vs. alone); ↓=<0.8; ↔=≥0.8 and ≤1.25; ↑=>1.25.
[‡] Data from P03527.
[§] From Phase 3 in presence of Peg α-2b.
* In presence of diflunisal, compared with boceprevir + diflunisal
AUC=area under the concentration-time curve; AKR=aldoketo reductase; CYP=cytochrome P450; PK=pharmacokinetic; Peg α-2b=peginterferon alfa-2b.

New DDI studies with BOC

- Cyclosporine

  C_{max} increased by about 2-fold and AUC_{inf} increased by about 2.7-fold (geometric mean)

- Tacrolimus

  C_{max} increased by about 10-fold and and AUC_{inf} increased by about 17-fold (geometric mean)

- Atorvastatin

  C_{max} increased by about 2.7-fold and AUC_{inf} increased by about 2.3-fold (geometric mean)

- Pravastatin

  C_{max} increased by about 1.5-fold, and and AUC_{inf} increased by about 1.6-fold (geometric mean)

  –

- Escitalopram

  C_{max} reduced by about 19% and AUC_{inf} reduced by about 21% (geometric mean)

Boceprevir-Related Adverse Events in Clinical Trials

- Most notable adverse events occurring more frequently with boceprevir-based therapy vs pegIFN/RBV alone
  - Anemia, neutropenia, and dysgeusia

Adverse Event, %	Boceprevir + PegIFN/RBV	PegIFN/RBV
Treatment-naive patients	(n = 1225)	(n = 467)
▪Anemia	50	30
▪Neutropenia	25	19
▪Dysgeusia	35	16
Treatment-experienced patients	(n = 323)	(n = 80)
▪Anemia	45	20
▪Dysgeusia	44	11

Boceprevir [package insert]. May 2011.

Safety of Boceprevir in Phase 3 studies

AE	P/R n=547 %	BOC/PR n=1548 %
Fatigue	57	57
Headache	43	44
Nausea	40	45
Insomnia	31	32
Pyrexia	31	31
Anemia	29	49
Chills	29	33
Rash/skin eruption	27	30
Alopecia	25	26
Influenza-like illness	25	22
Myalgia	24	23
Pruritus	23	21
Decreased appetite	23	25
Irritability	22	23
Depression	20	20
Diarrhea	18	23
Neutropenia	18	23
Dysgeusia	15	37
Other events of interest		
Rash	17	16
Anorectal discomfort	1	1
Hemorrhoids	3	4
Total bilirubin (mg/dL)		
2.60 to 5.09 x ULN (WHO grade 2)	2	1
5.10 to 10.0 x ULN (WHO grade 3)	0	0
>10.0 x ULN (WHO grade 4)	0	0

Discontinuation of BOC:

- SPRINT-2: 13/734
- Dose reduction: 21%

- RESPOND-2: 5/161

Discontinuation of BOC: none

UNL = upper limit of normal

Red = >10% difference between arms

Yellow = 5 to 10% difference between arms

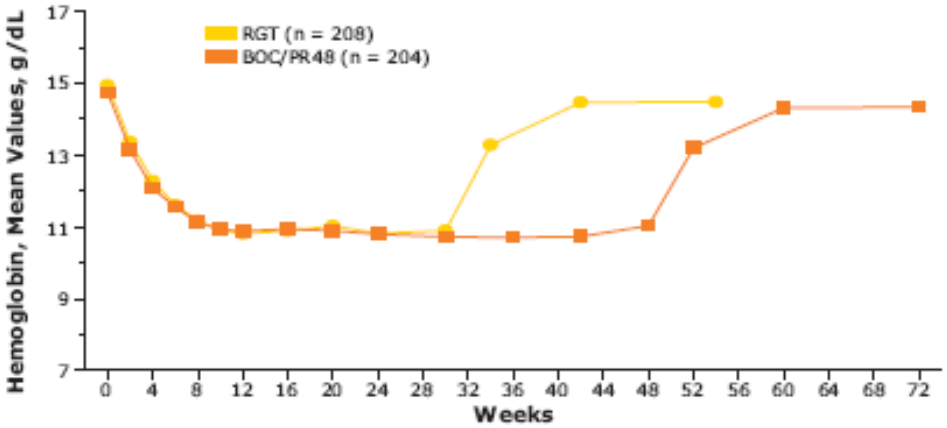
Green = <5% difference between arms

Adapt M.P. Manns et al, EASL 2011 (Poster 449)

Incidence of anemia in phase 3 studies

	Anemia*	EPO
SPRINT-2	**363/726** (50%)	**282/726** (39%)
RESPOND-2	**158/323** (49%)	**126/323** (39%)
Total	**521/1049** (50%)	**408/1049** (39%)

*** Anemia: Hb<10g/dL or as reported by the investigator as an AE**



Change in Hb levels with time among early responders.*

*Early responders = treatment week 8 HCV RNA undetectable.

F. Poordad, et al. NEJM 2011, B. R. Bacon, et al. NEJM 2011 , M.P. Manns et al, AASLD 2011 (Poster 963)

Management of anemia in phase 3 studies

→ **Hb <10 g/dL** → RBV reduction (200mg)

↘

EPO (40000U s.c./week)

↗

→ **Hb <8.5 g/dL** → RBV interruption

Initiation of EPO therapy	EPO Dose adjustments
EPO provided by Sponsor and used at the discretion of the investigator	No EPO when Hb ≥12 g/dL
Initial dose: 40,000 U epoeitin alfa SC once weekly	Reduce dose by 25 to 50% when Hb increase >1 g/dL within 2 weeks or Hb increase >2 g/dL within 4 weeks

P. Y. Kwo, et al. The Lancet 2010, F. Poordad, et al. NEJM 2011, B. R. Bacon, et al. NEJM 2011

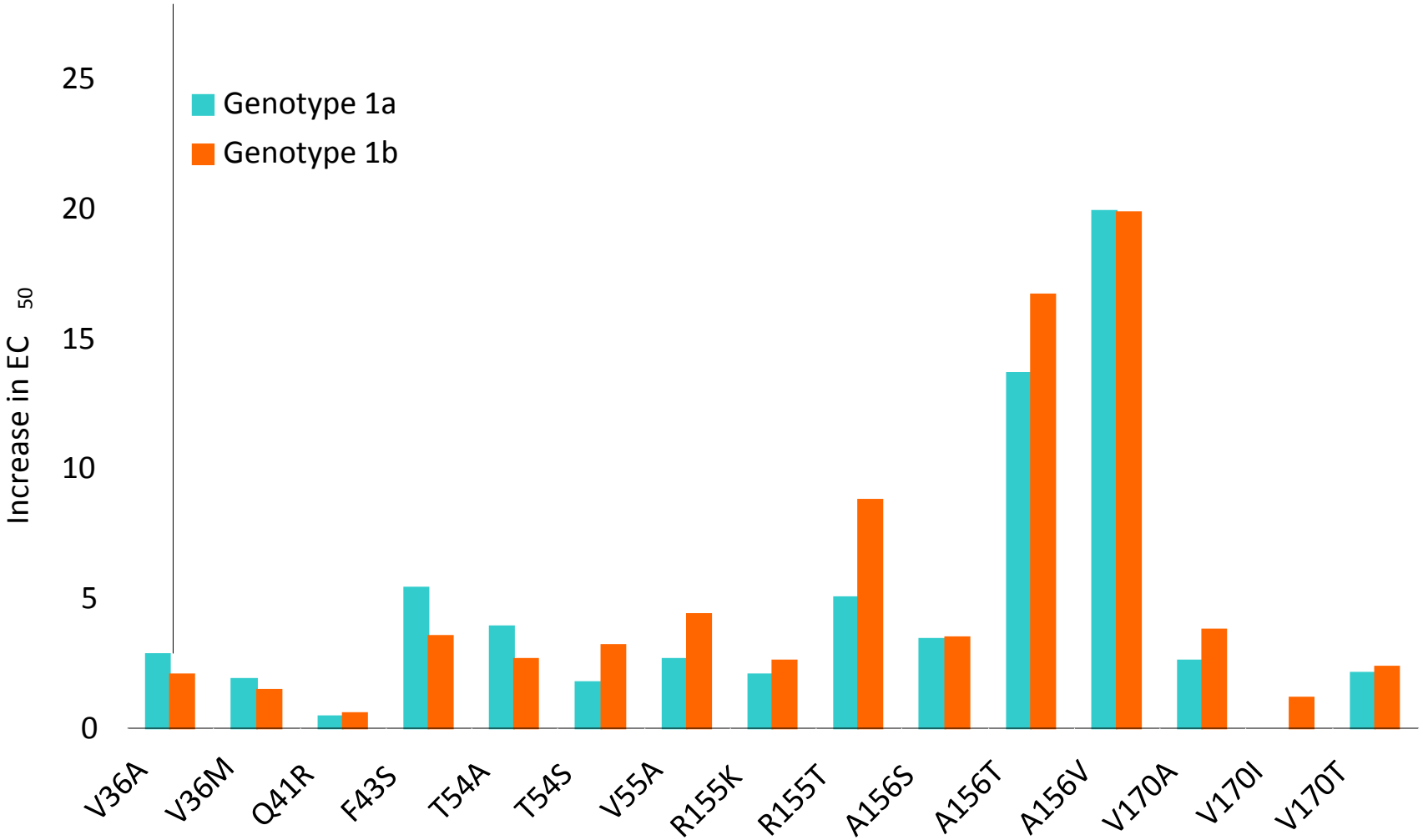
Treatment-Emergent Substitutions During PI-Based Therapy

- Pooled analyses of subjects who had on-treatment failure or relapse during clinical trials with boceprevir or telaprevir
  - Patterns of treatment-emergent substitutions varied by subtype 1a vs 1b
  - Resistance **most common among previous null responders and patients with subtype 1a**

HCV Genotype 1 Subtype	Treatment-Emergent Substitutions	
	Telaprevir[1]	Boceprevir[2]
1a	V36M R155K Combination of V36M and R155K	V36M T54S R155K
1b	V36A T54A/S A156S/T	T54A/S V55A A156S I/V170A

1. Telaprevir [package insert]. May 2011. 2. Boceprevir [package insert]. May 2011.

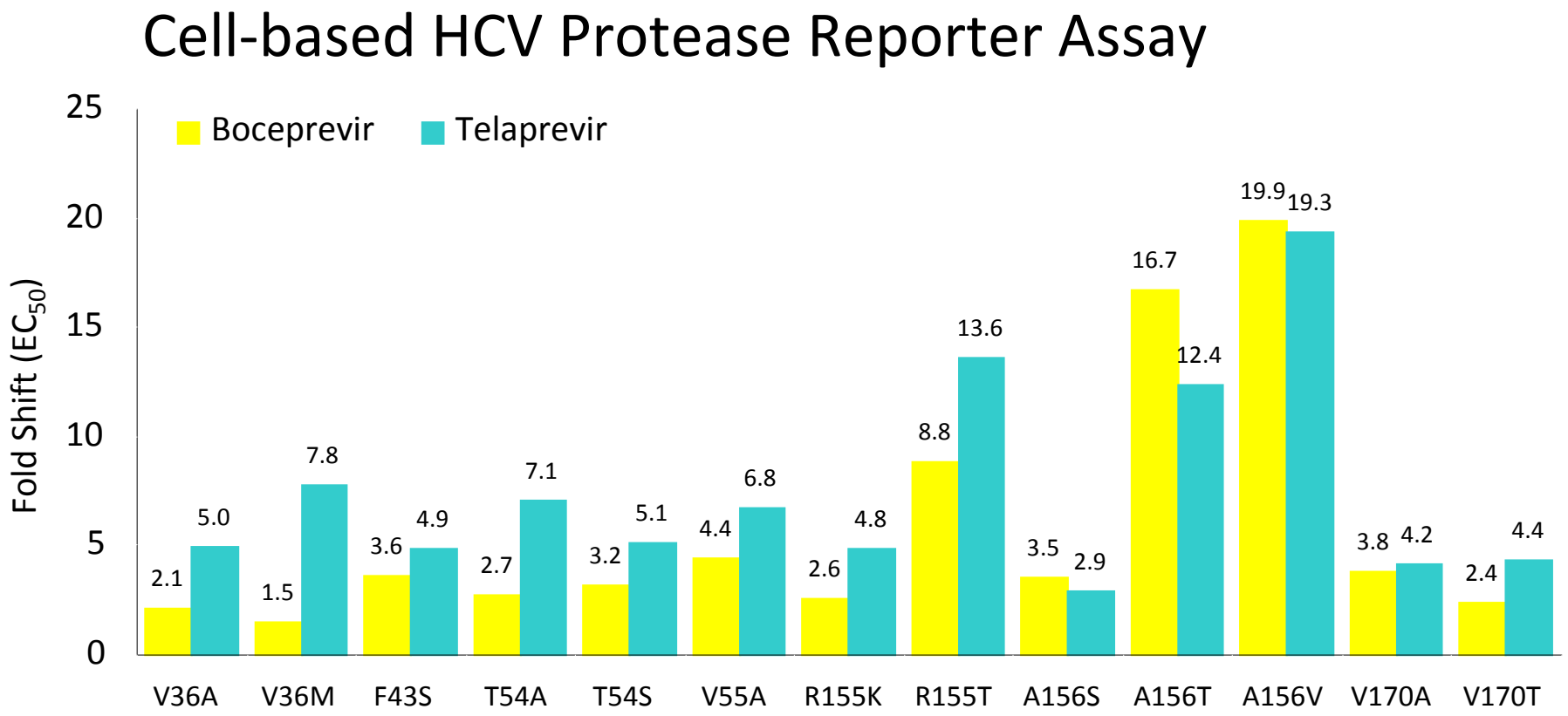
In vitro characterization of BOC NS3 RAVs in cell based HCV Protease Reporter Assay



Testing was not completed for genotype 1a V170I.

RAVs=resistance associated amino acid variants; SEAP=secreted alkaline phosphatase; EC_{50}=50% effective concentration.

BOC and TLV have overlapping resistance profiles in vitro



SEAP=secreted alkaline phosphatase; EC_{50}=50% effective concentration