Boceprevir

FDA Antiviral Drugs
Advisory Committee Meeting
April 27, 2011

Merck Research Laboratories

Merck Presentation

Laurie J. MacDonald, MD	Introduction
Janice K. Albrecht, PhD	Clinical Efficacy
Clifford Brass, MD, PhD	Resistance and Clinical Safety
Keith Gottesdiener, MD	Benefit/Risk

Unmet Need for Hepatitis C Therapies

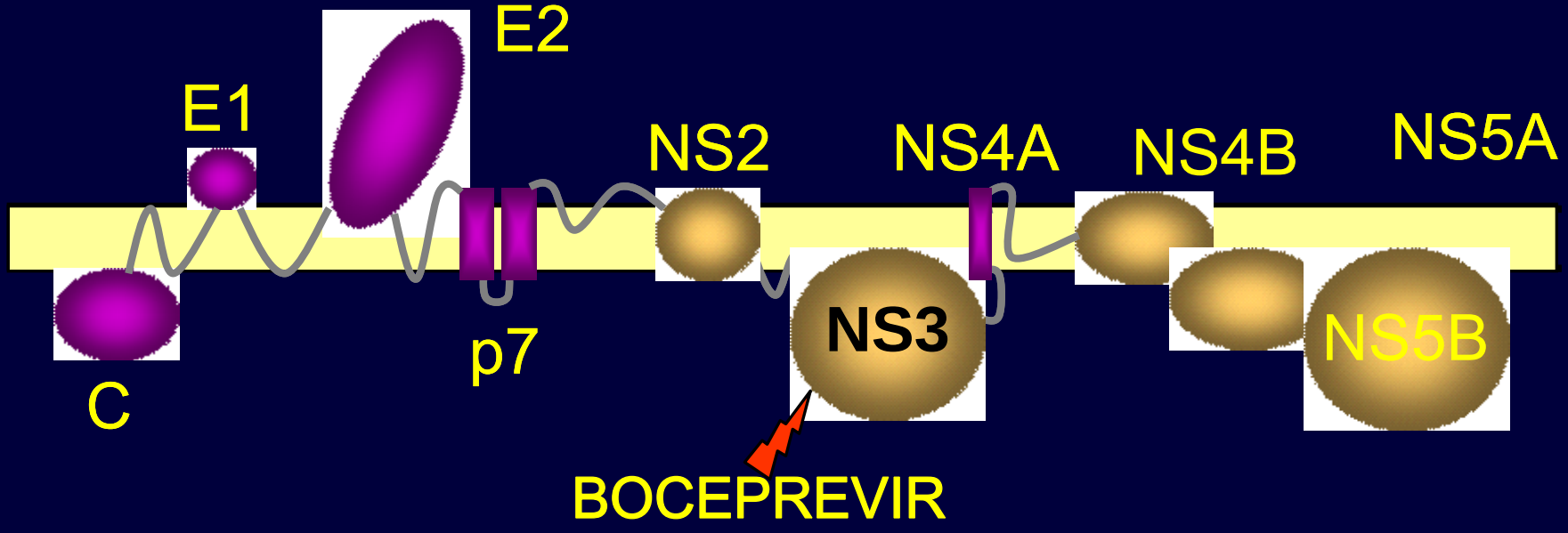
- Chronic hepatitis C (CHC) is a major public health issue
- In the U.S., ~3.2 million are chronically infected with hepatitis C virus (HCV)
  - HCV genotype 1 is most common and least responsive to current therapies
    - African-Americans and patients with cirrhosis have even lower response rates
  - HCV is a leading cause of liver cirrhosis, hepatocellular carcinoma and is the leading indication for liver transplantation

Limitations of Current HCV Therapies

- Goal of treatment is sustained virologic response (SVR)
  - Undetectable HCV-RNA 24 weeks after end-of-treatment
- Current standard-of-care therapy for CHC genotype 1
  - 48-week course of peginterferon combined with ribavirin
    - Often poorly tolerated, side effects may prevent patients from completing 48-weeks
- Only 40% of genotype 1 patients achieve SVR with current standard-of-care
- Direct acting antiviral agents are ushering in a new era in HCV therapy

Mechanism of Action of Boceprevir

- Hepatitis C is single-stranded RNA virus
  - Genome codes for synthesis of a single large polyprotein
  - NS3 protease processes the polyprotein into viral proteins
- Boceprevir is a protease inhibitor of the ketoamide class
  - Potent inhibitor of HCV replication (IC_{90} 200 nM)
  - Binds reversibly to the active site of the HCV NS3 protease



Boceprevir Phase 2/3 Clinical Program

Phase 2

RESPOND-1
(Treatment Failure)
N=357

SPRINT-1
(Treatment-Naïve)
N=595

Pivotal Phase 3

RESPOND-2
(Treatment Failure)
N=403

SPRINT-2
(Treatment-Naïve)
N=1097

Additional Studies

PEG α-2a
(Treatment Failure)
N=201

HIV/HCV Co-infection
(Treatment-Naïve)
Ongoing

EPO – Anemia Management
Ongoing

Rollover Studies

PROVIDE
Boceprevir Treatment
Ongoing

Long-Term Follow-up
Ongoing

Boceprevir: Phase 3 Results

- Overall favorable benefit/risk profile
- Boceprevir efficacy
  - Superior SVR rates compared to standard-of-care
    - Treatment-naïve and previous treatment failure
  - Response-guided therapy – early responders receive shorter durations of therapy
- Boceprevir safety profile
  - Largely reflects standard-of-care
  - Incremental hematologic side effects are manageable and not treatment limiting

Proposed Indication and Dosage and Administration

- Boceprevir is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients with compensated liver disease
  - Previously untreated patients
  - Patients who have failed previous therapy
- Dosage and administration
  - The recommended dosage of boceprevir is 800 mg TID (every 7-9 hours) with food
  - Response-guided therapy

Merck Consultants

Bruce Bacon, MD	Professor of Medicine St Louis University School of Medicine
Gary Koch, PhD	Professor of Biostatistics University of North Carolina at Chapel Hill
Fred Poordad, MD	Associate Professor of Medicine David Geffen School of Medicine – UCLA
Jerry L. Spivak, MD	Professor of Medicine/Oncology Johns Hopkins University School of Medicine

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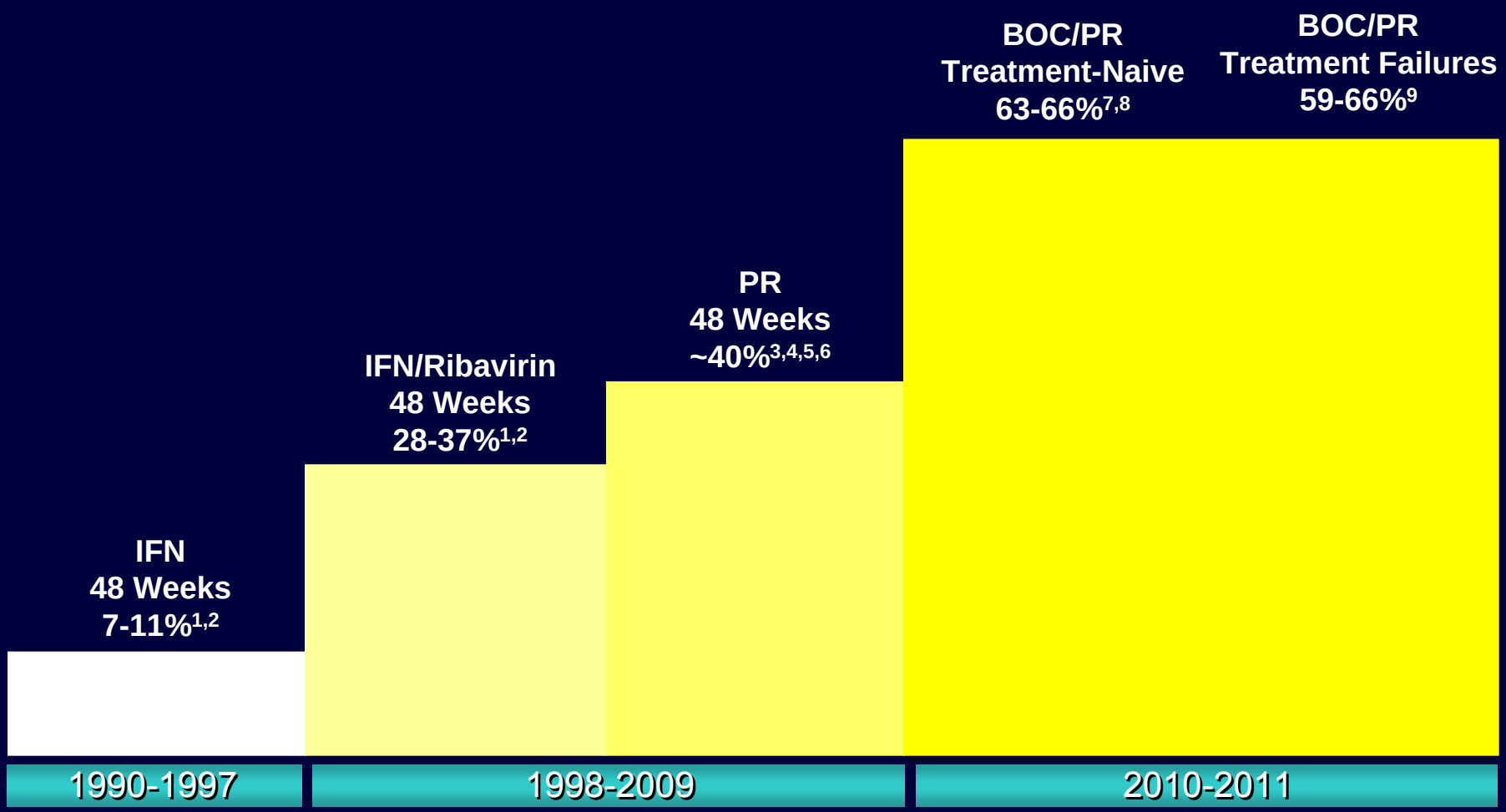
Efficacy

Dr. Janice K. Albrecht

Progress in Treating Chronic HCV Genotype 1



[1]McHutchison, NEJM (339) 1998; [2]Poynard, Lancet (352) 1998; [3]Manns, Lancet (358), 2001; [4]Lindsay, Hepatology (34) 2001; [5]Fried, NEJM (347), 2002; [6]McHutchison, NEJM (361) 2009; [7]Kwo, Lancet (376) 2010; [8]Poordad, NEJM (364) 2011; [9]Bacon, NEJM (364) 2011.

HCV=hepatitis C virus; IFN=interferon; PR=peginterferon α-2b + ribavirin; BOC/PR48=boceprevir/PR.

Efficacy Outline

- Phase 2 outcomes used to design Phase 3 program
- Treatment strategies in Phase 3
- Study design
- Key study results
  - SPRINT-2: treatment-naïve
  - RESPOND-2: previous treatment failures
- Treatment recommendations

Phase 2 Outcomes Used to Design Phase 3 Program

- Boceprevir significantly increases sustained virologic response (SVR)
  - 28 and 48 week treatment more efficacious than peginterferon α-2b/ ribavirin control
- Early response predicts treatment duration
  - Early responders – HCV-RNA undetectable at TW8
    - Similar SVR whether treated for 28 or 48 weeks
- Data support that 800 mg TID is on or near the plateau of both the
  - Dose/exposure curve
  - Exposure/response curve
- Lead-in: 4 week of PR
  - Defines patient interferon responsiveness
  - Important prognostic factor for response
  - Lead-in included as a component of Phase 3 program

TW=treatment week; PR=peginterferon α-2b + ribavirin.

Two Boceprevir Treatment Strategies for Phase 3 Studies

- Boceprevir added to peginterferon α-2b/ribavirin 48 weeks
  - 4 weeks of lead-in and 44 weeks of triple therapy
- Response-guided therapy
  - Treatment duration based on time to HCV-RNA undetectability
  - Early responders: Undetectable HCV-RNA by TW8†
  - Late responders: 1st undetectable HCV-RNA result occurred after TW8

† TW4 of boceprevir.
TW=treatment week.

Phase 3 Pivotal Studies
HCV Genotype 1

- SPRINT-2: treatment-naïve
- RESPOND-2: previous treatment failures

SPRINT-2 Treatment-Naïve Patients Boceprevir/Peginterferon α-2b/Ribavirin

- Multi-center, double-blind for boceprevir, randomized, Phase 3 study
- Treatment regimens
  - Standard-of-care control
    - Peginterferon α-2b 1.5 µg/kg QW SC plus
    - Ribavirin 600-1400 mg/day PO
  - Boceprevir containing regimens
    - Boceprevir 800 mg TID PO (every 7-9 hours) plus peginterferon/ribavirin

SPRINT-2 Treatment-Naïve Patients Study Design

Peginterferon α-2b/Ribavirin 48 Weeks (PR Control)

PR

Boceprevir Response-Guided Therapy (RGT)

PR

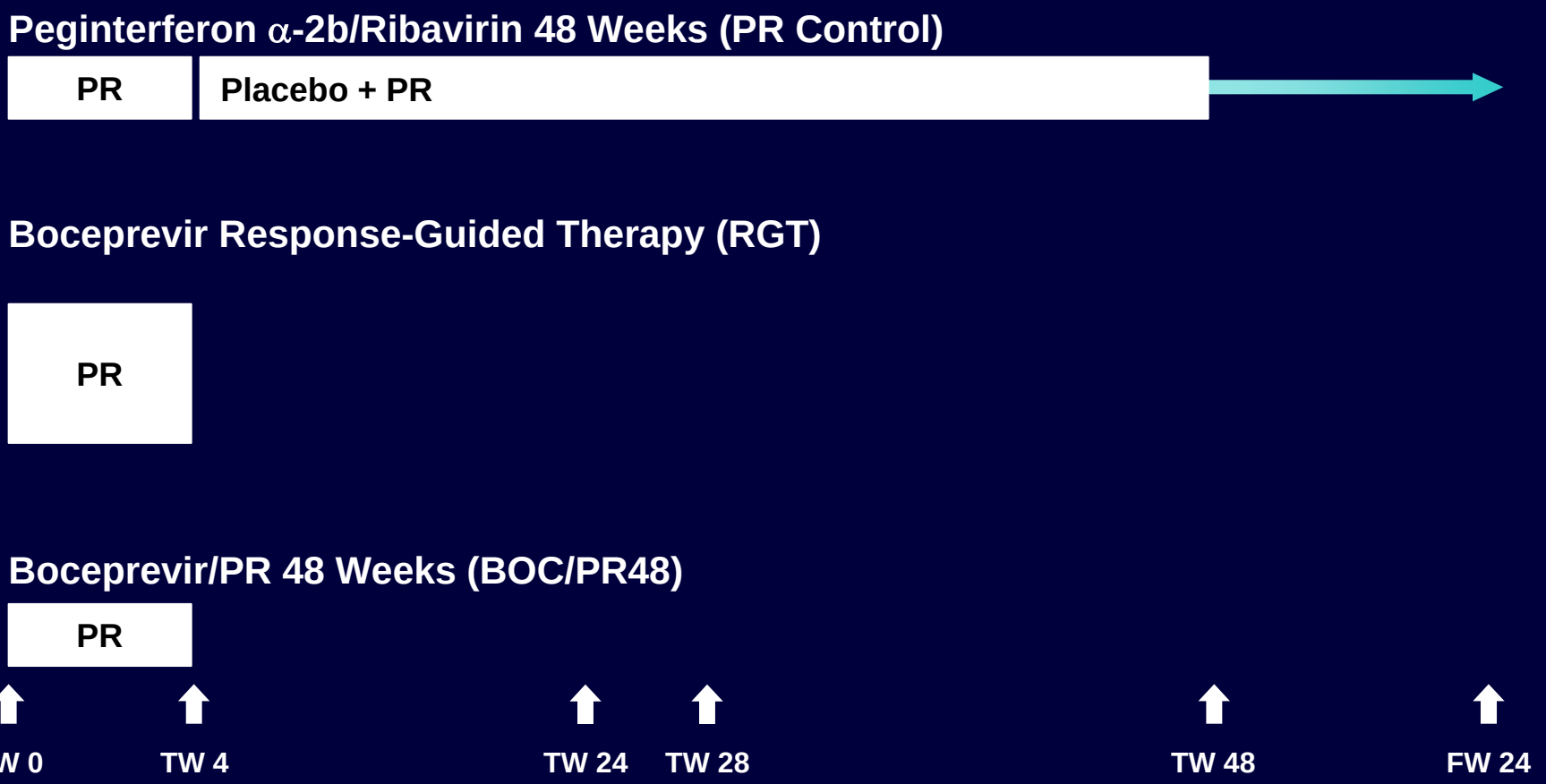
Boceprevir/PR 48 Weeks (BOC/PR48)

PR

TW 0 **TW 4** **TW 24** **TW 28** **TW 48** **FW 24**

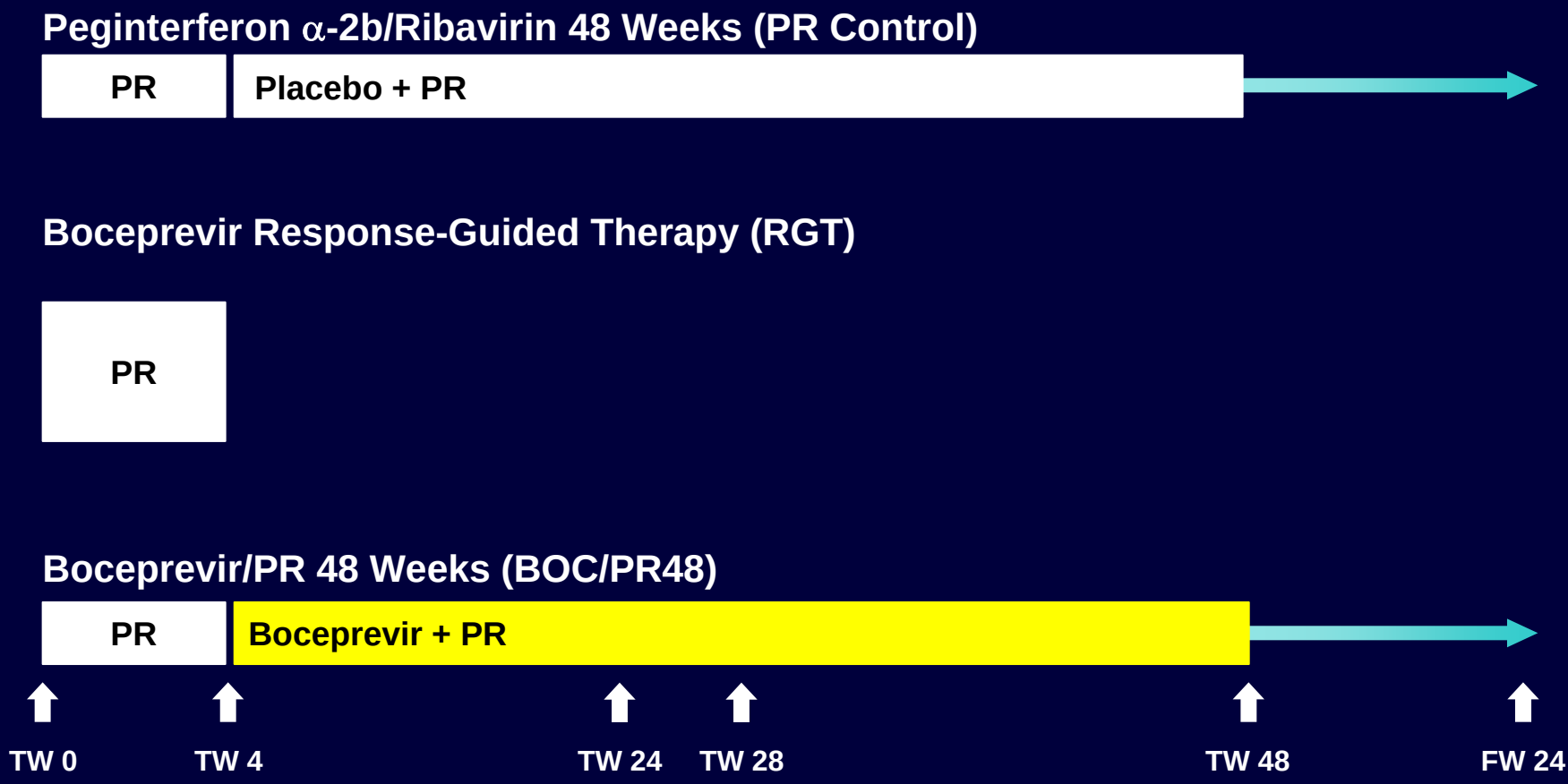
PR=peginterferon α-2b + ribavirin; TW=treatment week; FW=follow-up week.

SPRINT-2 Treatment-Naïve Patients Study Design



PR=peginterferon α-2b + ribavirin; TW=treatment week; FW=follow-up week.

SPRINT-2 Treatment-Naïve Patients Study Design



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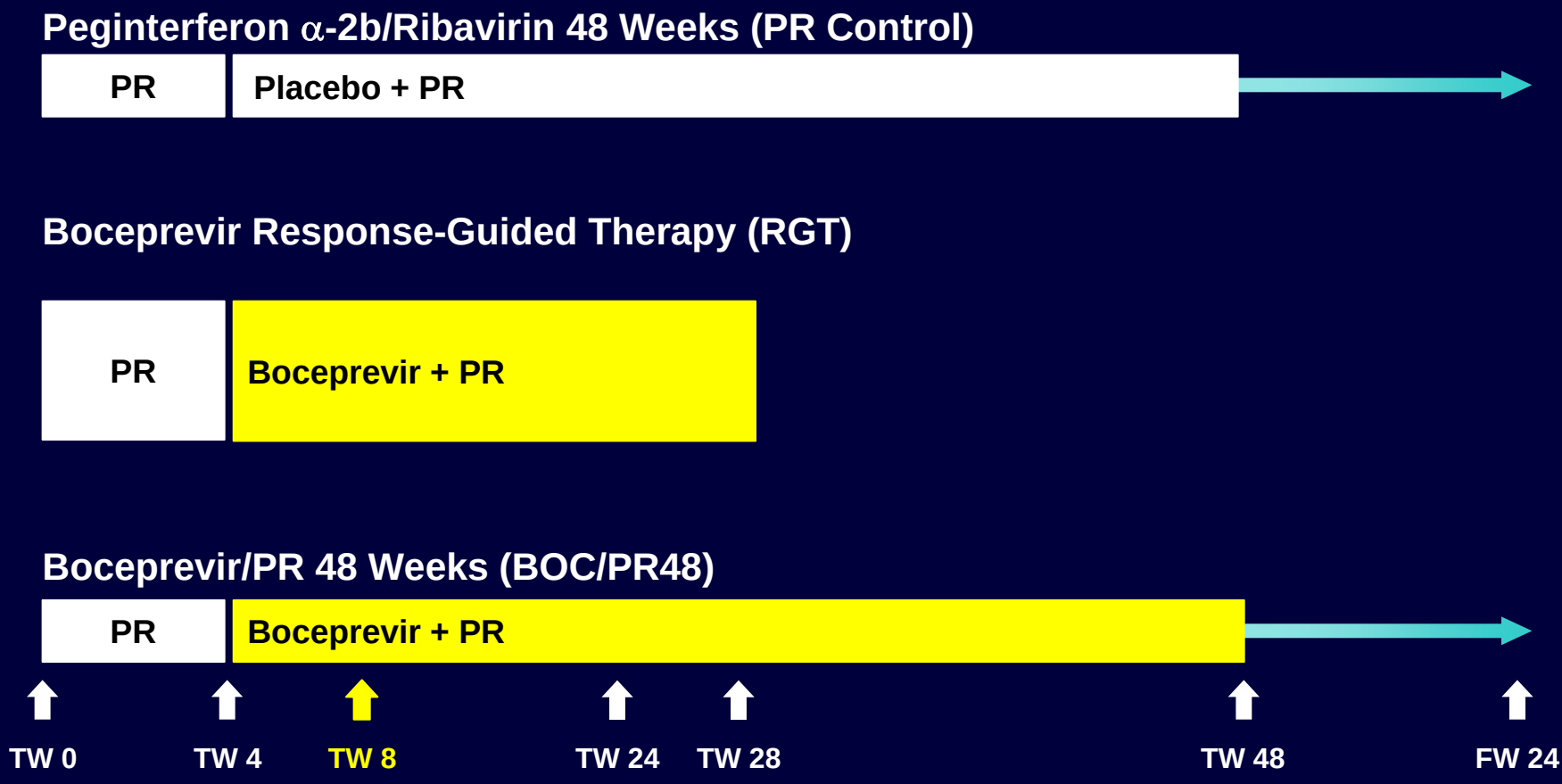
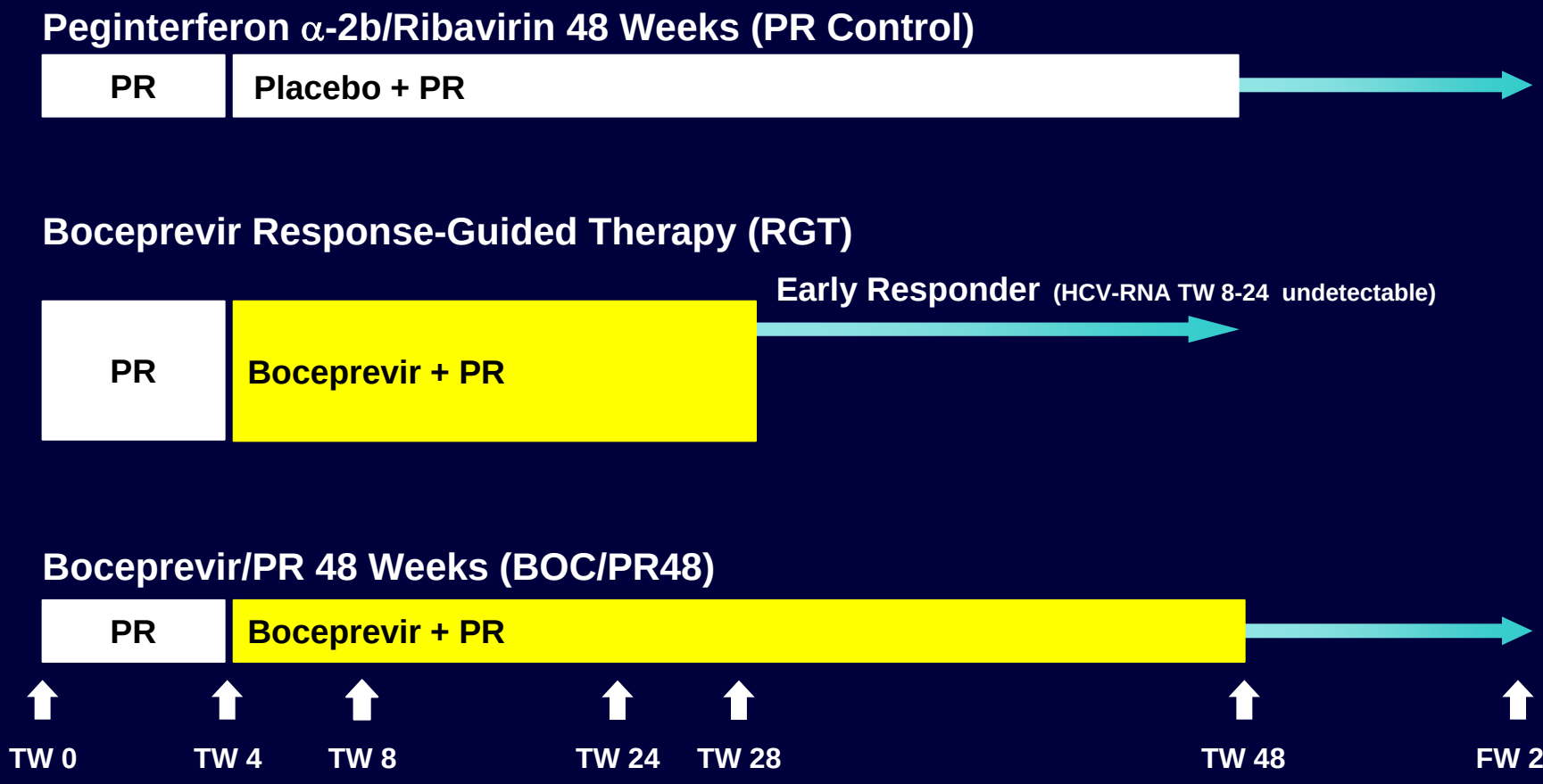
SPRINT-2 Treatment-Naïve Patients Study Design



PR=peginterferon α-2b + ribavirin; TW=treatment week; FW=follow-up week.

SPRINT-2 Treatment-Naïve Patients Study Design



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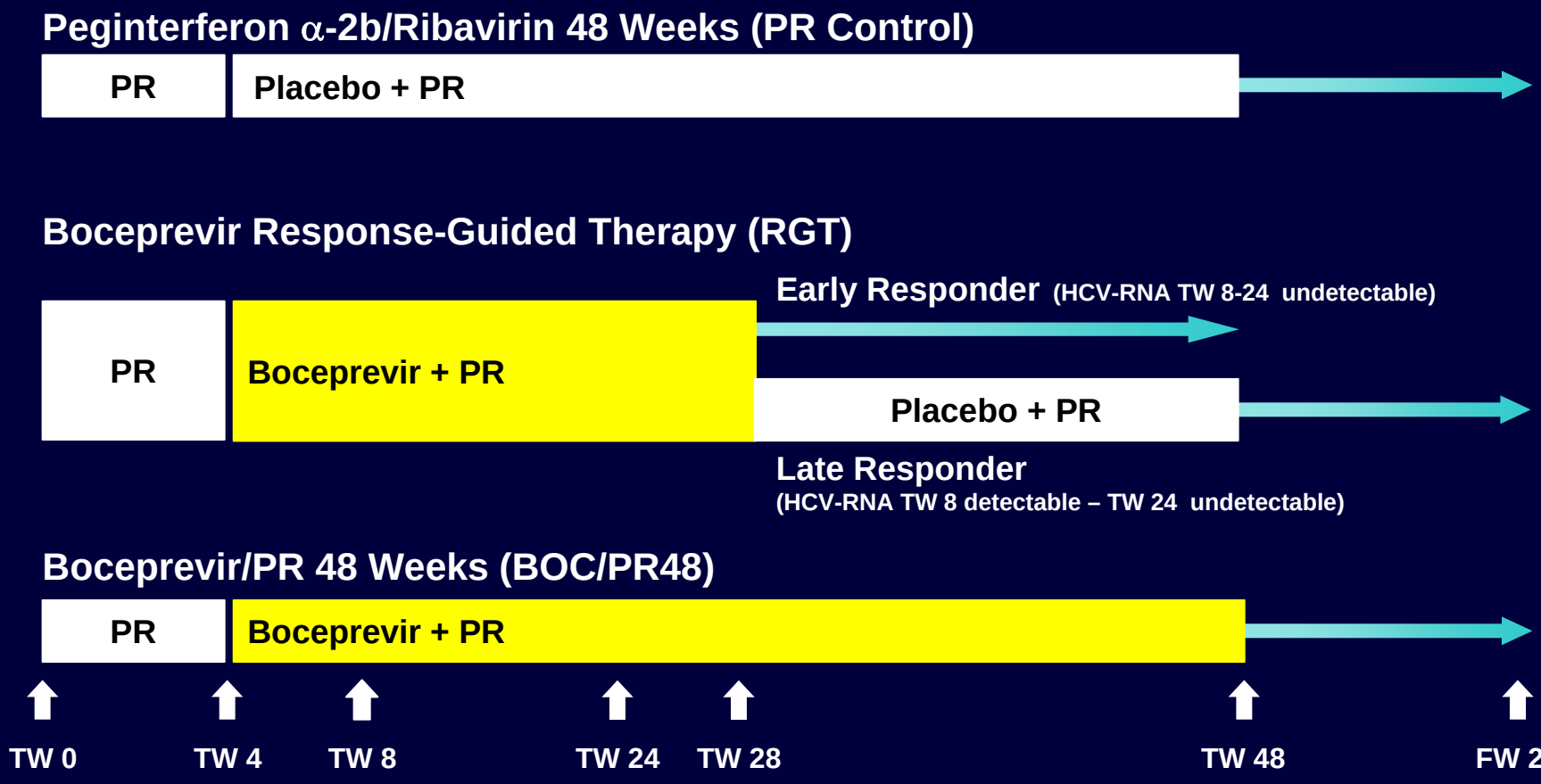
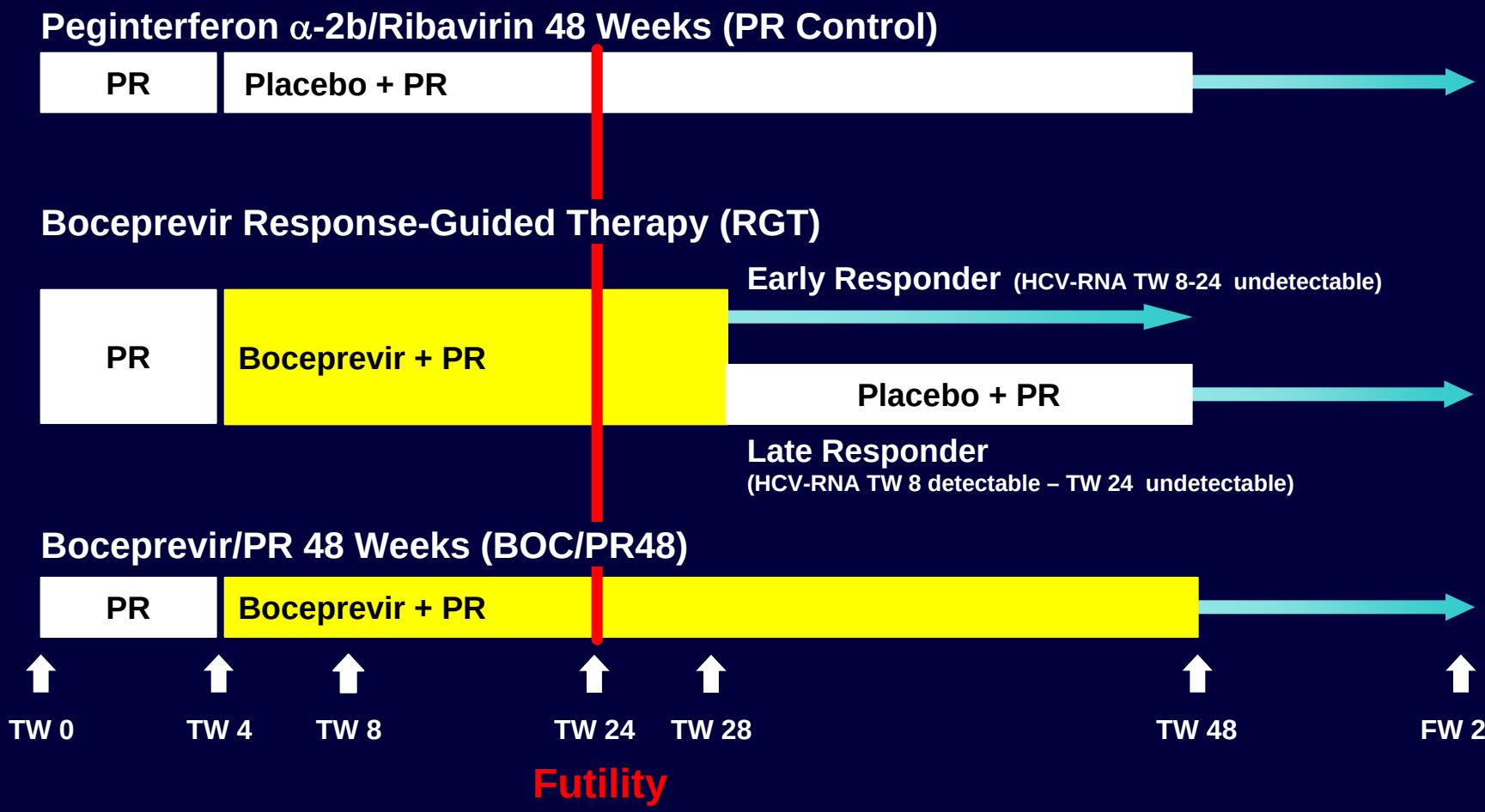


PR=peginterferon α-2b + ribavirin; TW=treatment week; FW=follow-up week.

SPRINT-2 Treatment-Naïve Patients Study Design



PR=peginterferon α-2b + ribavirin; TW=treatment week; FW=follow-up week.

SPRINT-2 Treatment-Naïve Patients Study Design

- Pre-specified patient cohorts
  - Cohort 1: Non-Black (N=938)
  - Cohort 2: Black (N=159)
- Randomization
  - 1:1:1 (363:368:366)
- Stratification variables
  - Baseline viral load: > vs. ≤400,000 IU/mL
  - Genotype: 1a vs. 1b
- HCV-RNA
  - Roche TaqMan 2.0 LLD 9.3 IU/mL
  - Used to define undetectable at all decision points
- Futility rule
  - Detectable HCV-RNA at TW24
- Liver histology
  - Central pathologist
  - Assessed by METAVIR score
    - F0: no fibrosis
    - F1: portal fibrosis without septae
    - F2: portal fibrosis with some septae
    - F3: septal fibrosis without cirrhosis
    - F4: cirrhosis

IU=international units; LLD=lower limit of detection.

SPRINT-2 Treatment-Naïve Patients Study Endpoints

- Primary efficacy endpoint
  - Sustained virologic response (SVR)
    - Undetectable plasma HCV-RNA 24 weeks post treatment
  - Population: full analysis set (FAS)
    - All randomized patients receiving one dose of any study drug
  - Primary comparisons
    - BOC/PR48 vs. PR48
    - RGT vs. PR48
- Key secondary endpoint (mITT)
  - SVR in patients receiving one dose of boceprevir or placebo
    - Excludes patients who discontinued during the PR lead-in

mITT=modified intention-to-treat.

SPRINT-2 Baseline Characteristics

	Cohort 1 (Non-Black) N=938			Cohort 2 (Black) N=159		
	PR48 n=311	RGT n=316	BOC/ PR48 n=311	PR48 n=52	RGT n=52	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)	29 (4)	29 (5)	31 (6)
HCV genotype (%)†						
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).

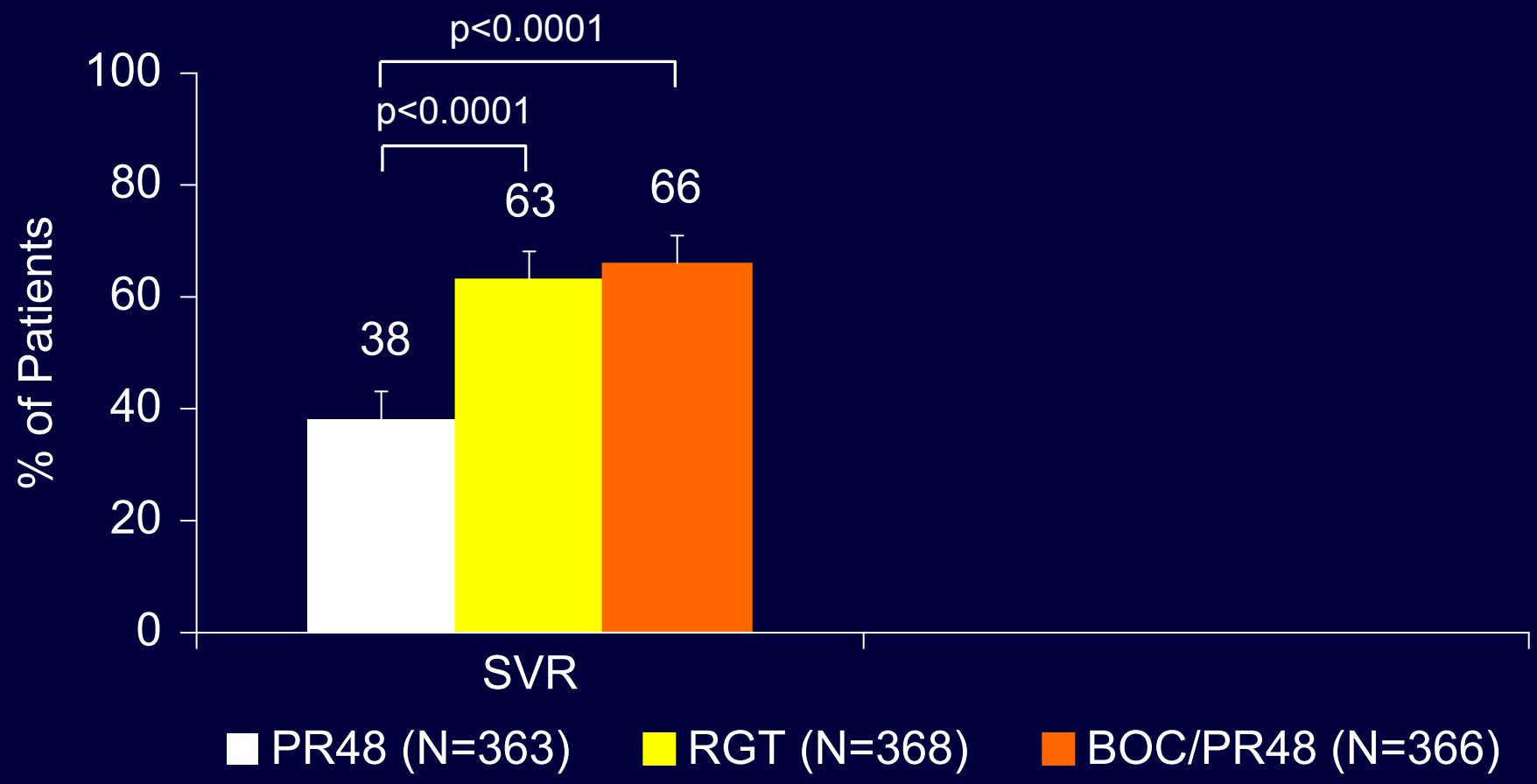
SPRINT-2 Treatment-Naïve Patients
Patient Disposition - All Cohorts

Screened N=1472
Randomized and Treated N=1097

	PR48 n=363	RGT n=368	BOC/PR48 n=366
	n (%)	n (%)	n (%)
PR Lead In Discontinued:	19 (5)	18 (5)	12 (3)
Discontinued Between TW4 & TW28:	150 (41)	106 (29)	104 (28)
RGT 28		162 (44)	
RGT 48		82 (22)	
For those patients who received boceprevir placebo (N=344):			
	n (%)		
Completed Treatment:	159 (44)		
Discontinued Treatment:			
Due to AE:	42 (12)		
Due to Treatment Failure:	117 (34)		
Due to Other:	26 (8)		
For those patients who received boceprevir (N=350):			
		n (%)	
Completed Treatment:		229 (62)	
Discontinued Treatment:			
Due to AE:		35 (10)	
Due to Treatment Failure:		55 (16)	
Due to Other:		31 (9)	
For those patients who received boceprevir (N=354):			
			n (%)
Completed Treatment:			215 (59)
Discontinued Treatment:			
Due to AE:			51 (14)
Due to Treatment Failure:			47 (13)
Due to Other:			41 (12)

PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks; TW=treatment week;AE=adverse event.

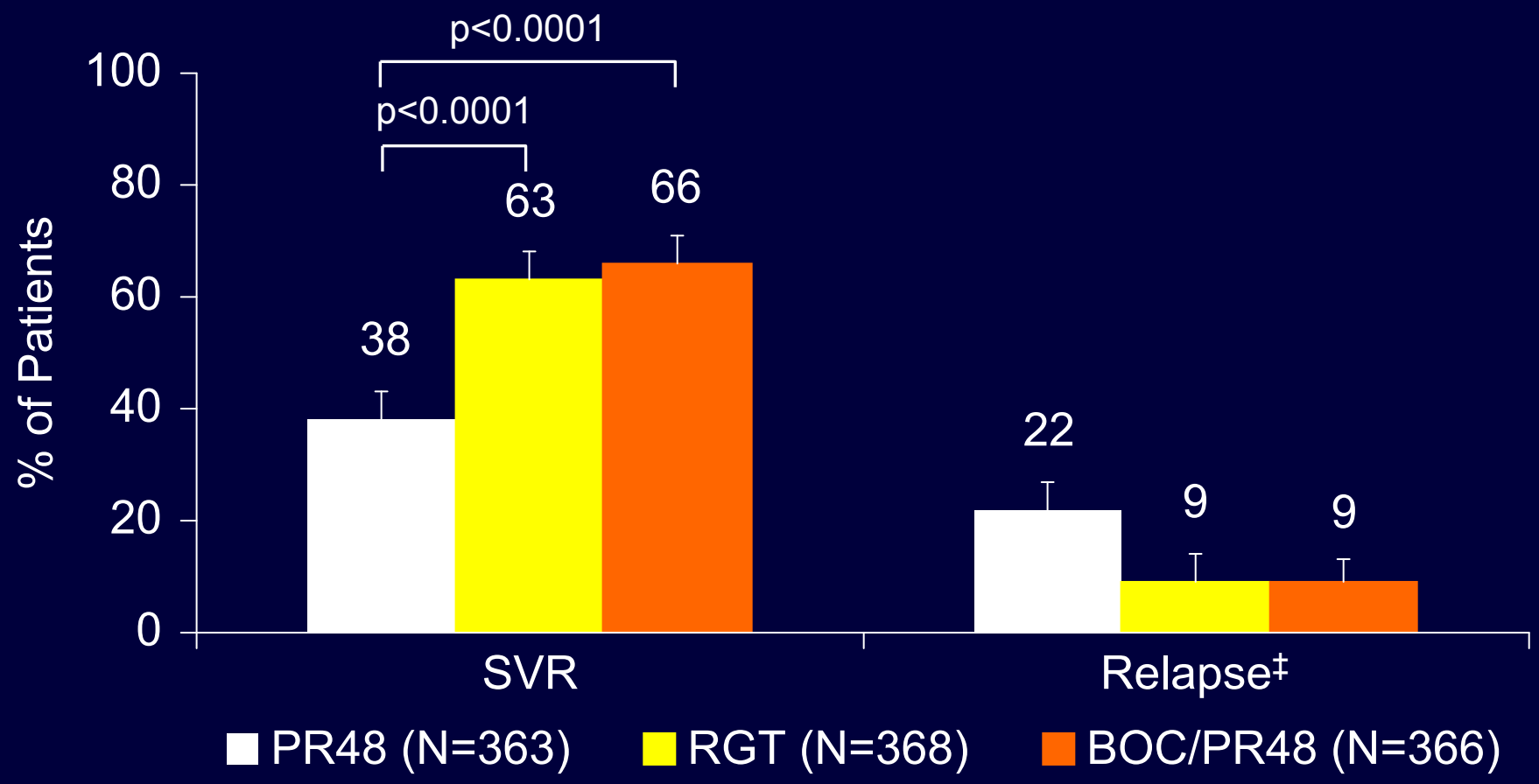
SPRINT-2 Treatment-Naïve Patients Primary Endpoint: SVR All Cohorts†



† Full Analysis Set.

SVR=sustained virologic response; PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks.

SPRINT-2 Treatment-Naïve Patients SVR and Relapse All Cohorts†

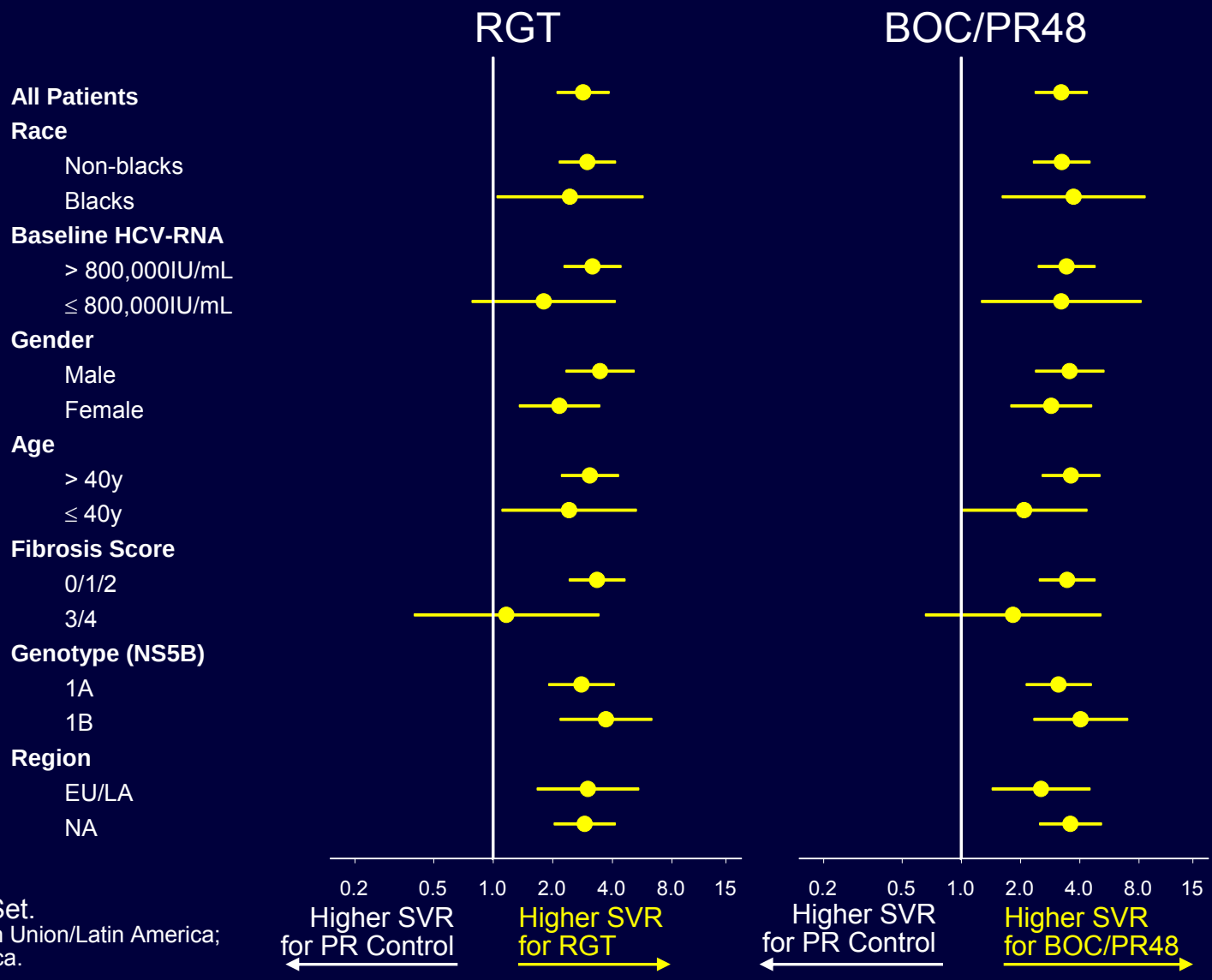


† Full Analysis Set.

‡ Relapse is computed on patients who were undetectable at end of treatment and were not missing data at end of follow-up.

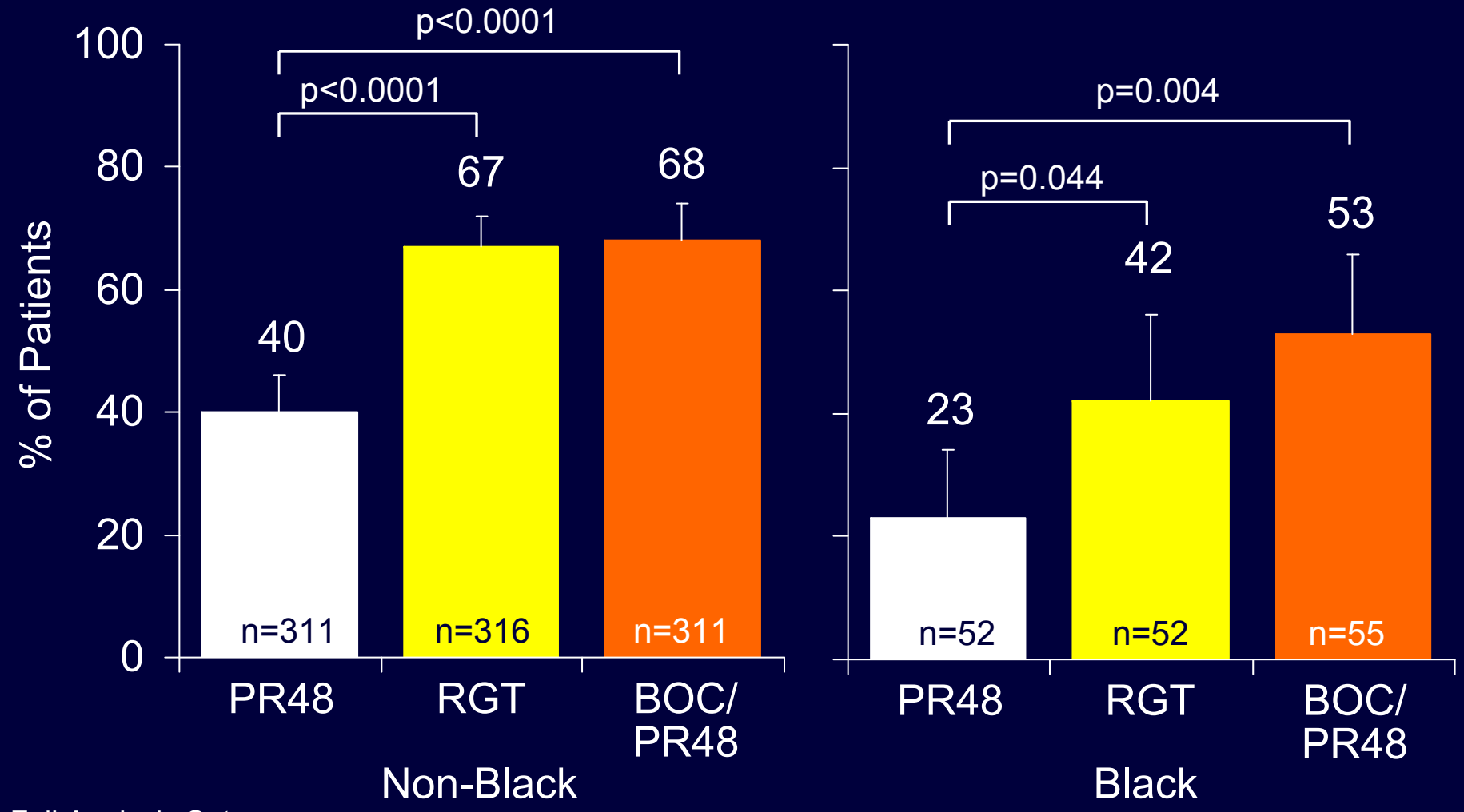
SVR=sustained virologic response; PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks.

SPRINT-2: RGT, BOC/PR48 vs. Control
Odds Ratio (95% CI) for SVR by Subgroups



Full Analysis Set.
EU/LA=European Union/Latin America;
NA=North America.

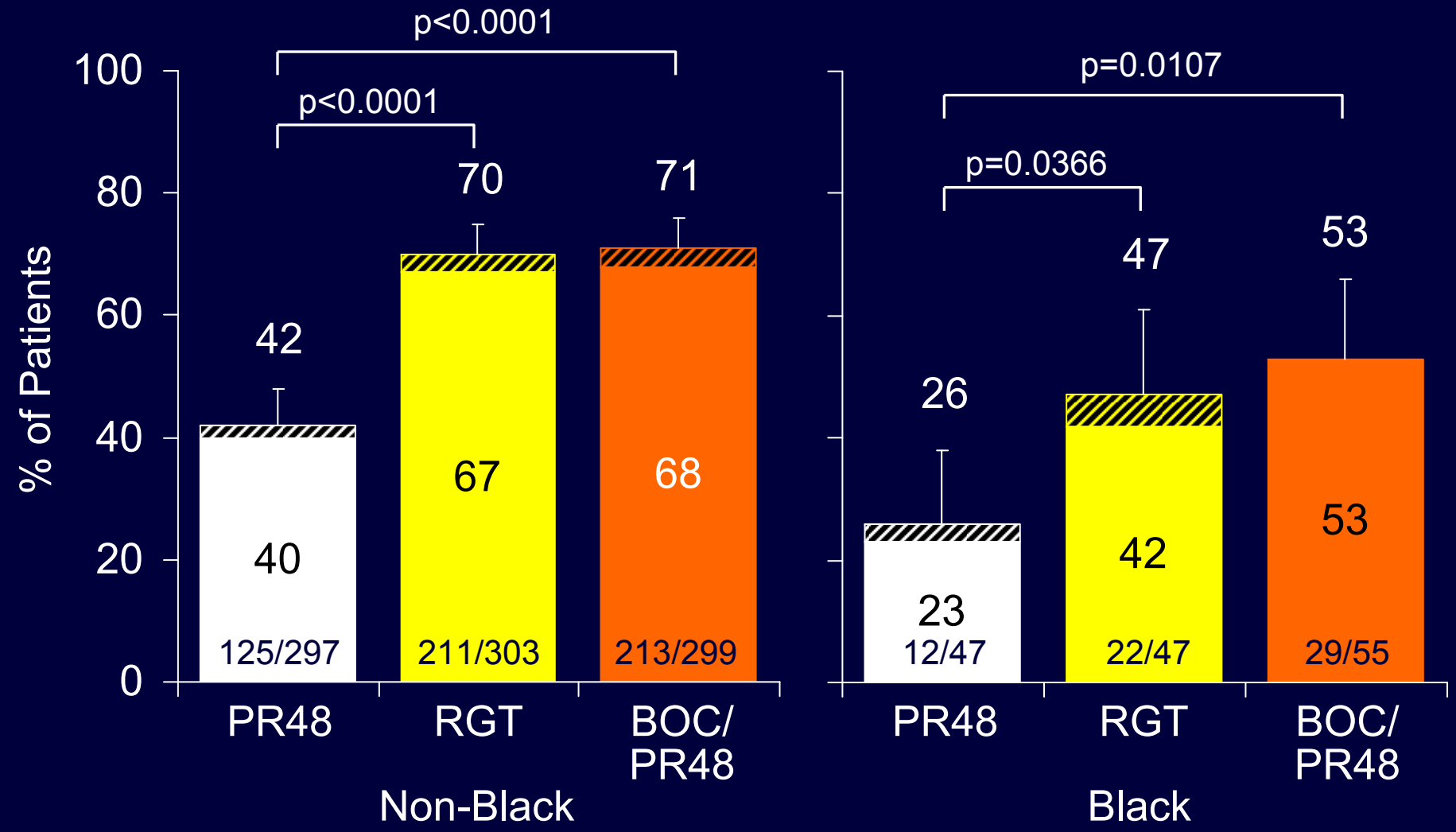
SPRINT-2 Treatment-Naïve Patients SVR Rates by Non-Black vs. Black



Full Analysis Set.

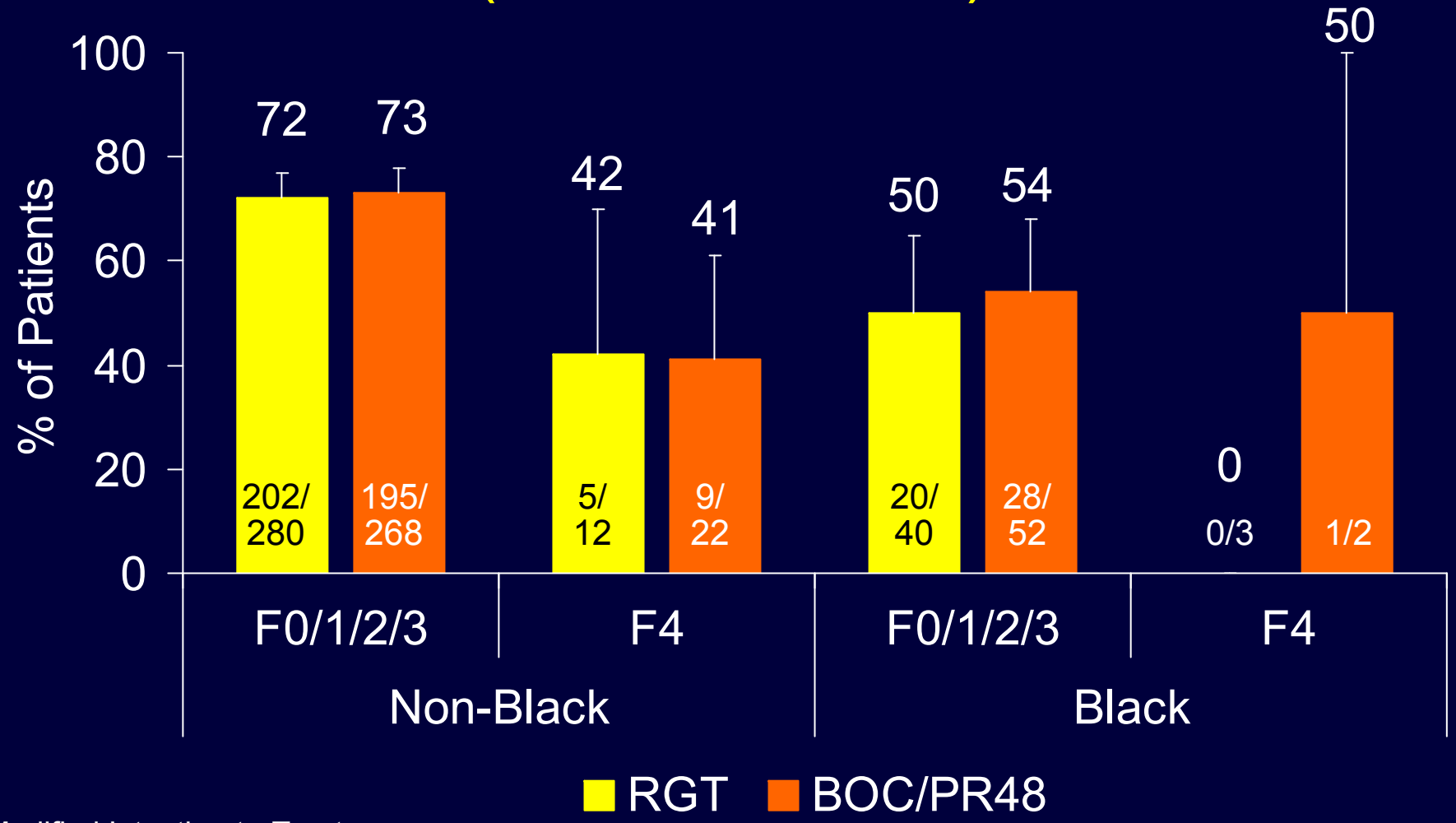
SVR=sustained virologic response; PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks.

SPRINT-2 Treatment-Naïve Patients SVR Rates by Cohort (mITT)



SVR=sustained virologic response; mITT=modified intention-to-treat; PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks.

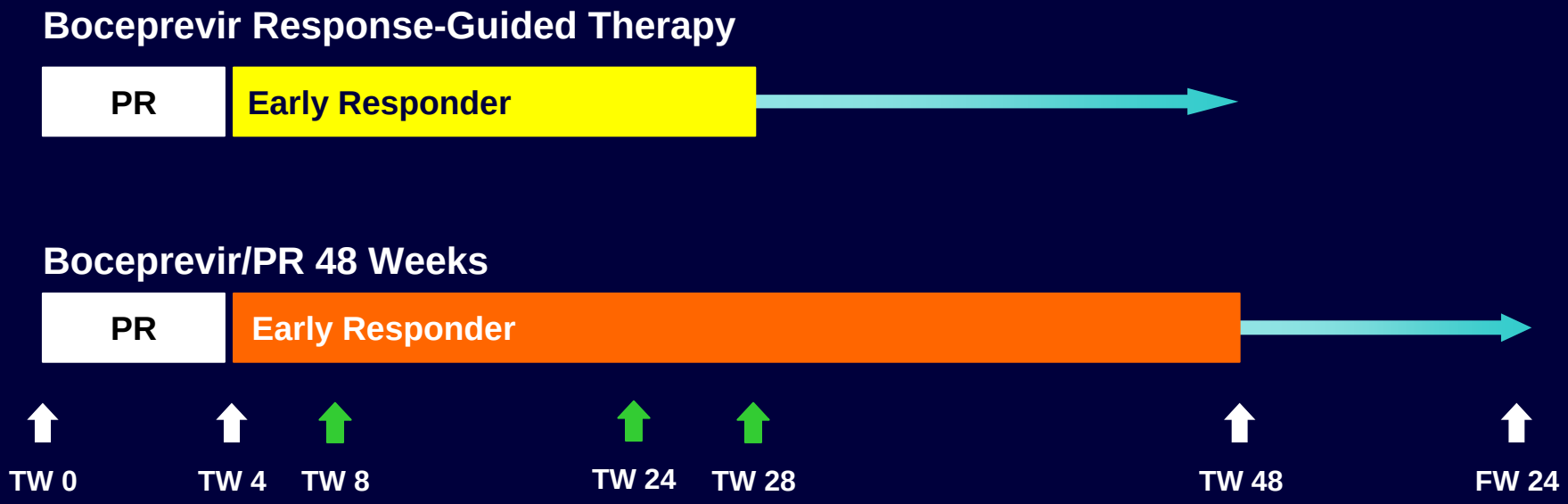
SPRINT-2: Overall SVR in RGT & BOC/PR48 by Race and METAVIR Fibrosis Score (F0/1/2/3 vs. F4)



Modified Intention-to-Treat.

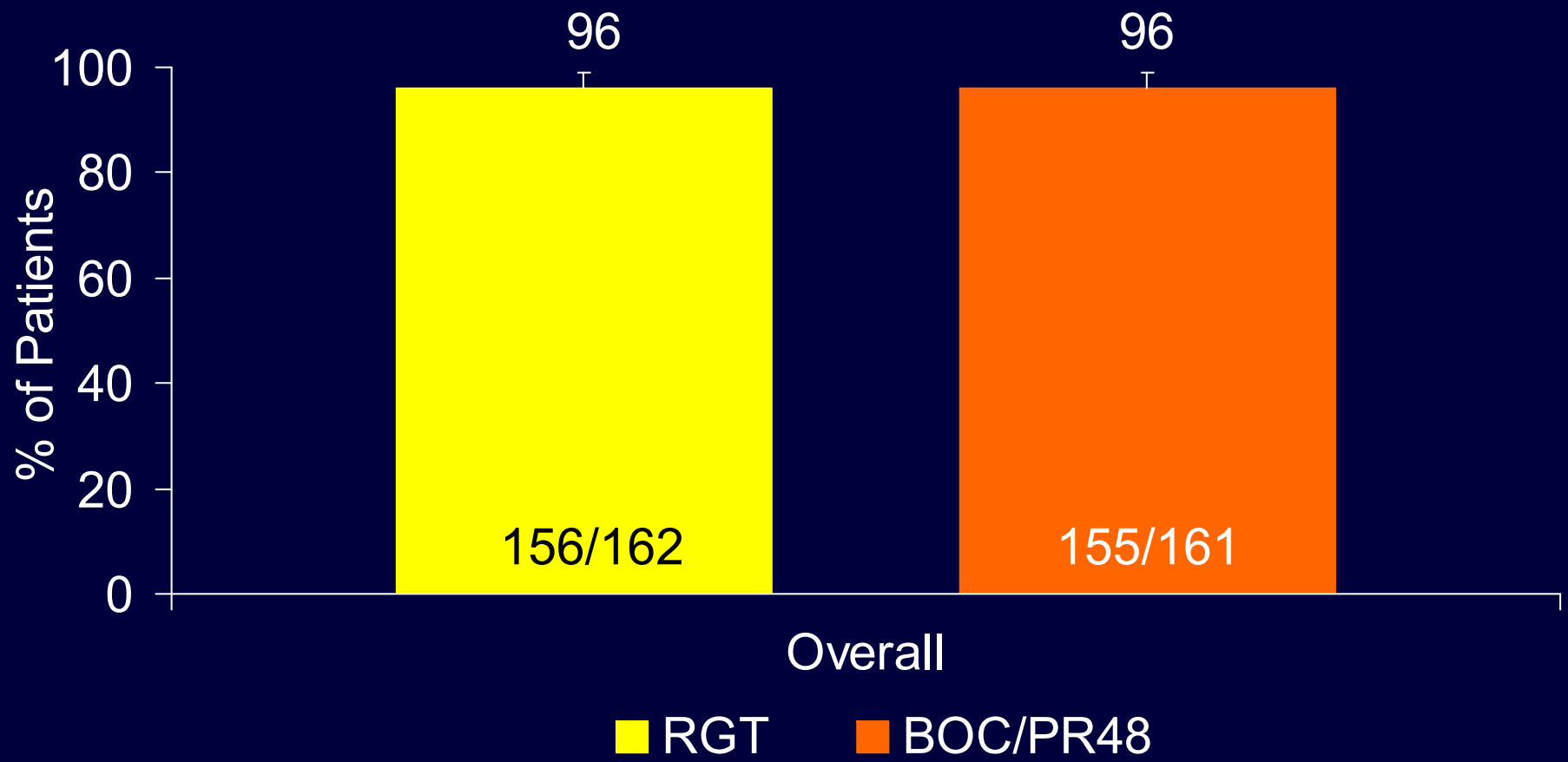
SVR=sustained virologic response; FAS=full analysis set; RGT=response-guided therapy; BOC/PR48=boceprevir/peginterferon α-2b + ribavirin 48 weeks.

SPRINT-2 Treatment-Naive Patients Early Responders: TW 8-TW 24 HCV-RNA Undetectable



HCV-RNA undetectable at TW8 through TW24, and received at least 28 weeks of therapy.
TW=treatment week.

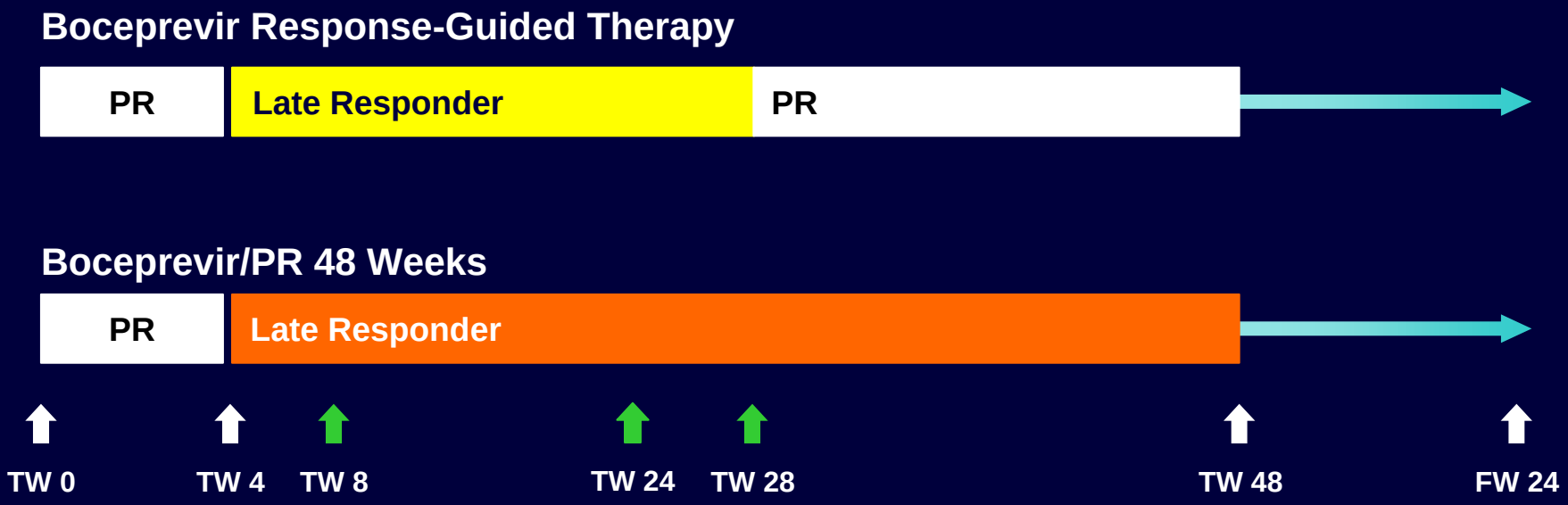
SPRINT-2 Treatment-Naïve Patients
SVR in Early Responders†
All Cohorts



- 44% of patients met the criteria for early response

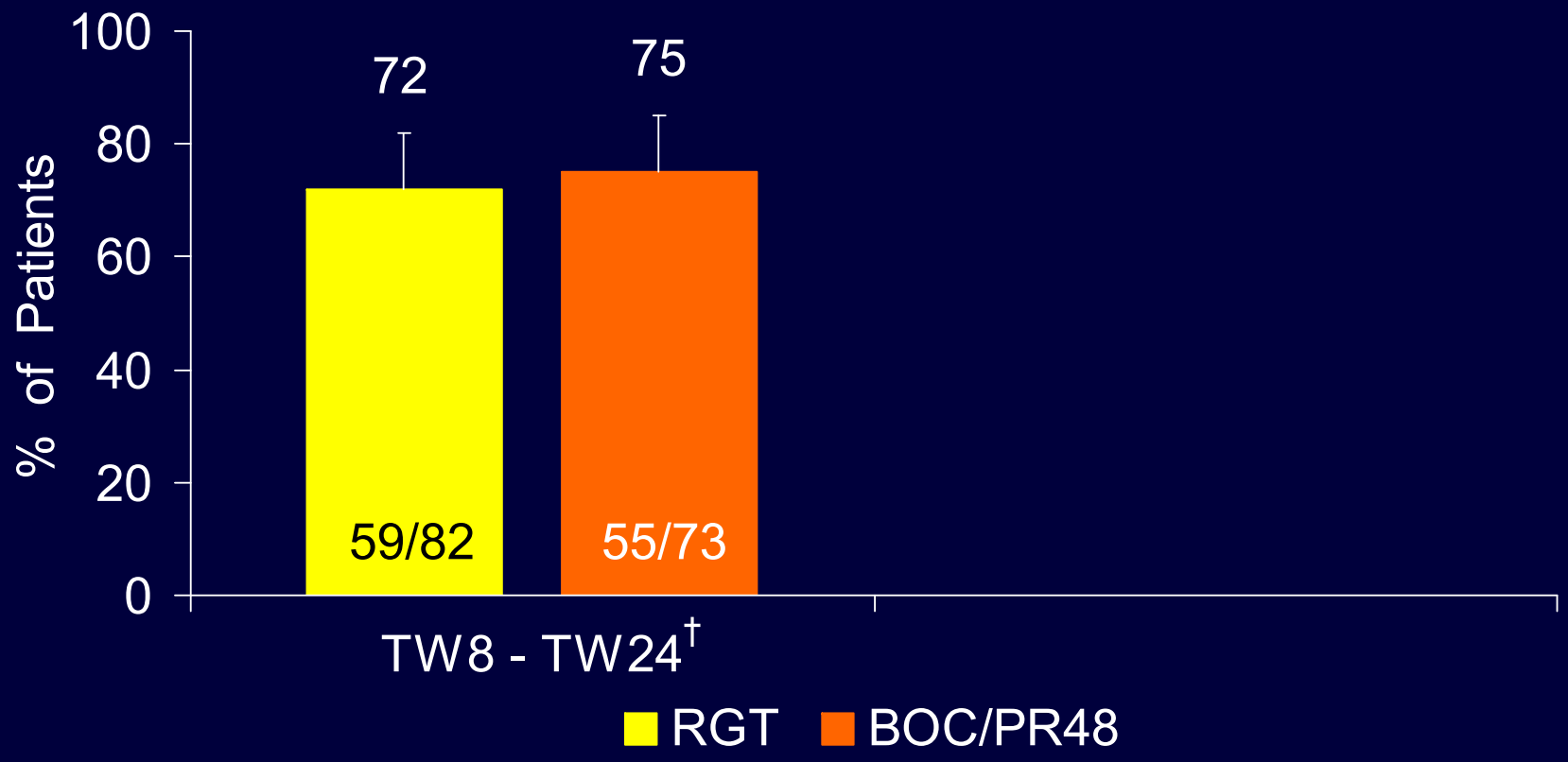
† HCV-RNA undetectable at TW8 through TW24, and received at least 28 weeks of therapy.

SPRINT-2 Treatment-Naïve Patients Late Responders: HCV-RNA TW 8 Detectable and TW 24 Undetectable



HCV-RNA detectable at TW 8, undetectable at TW 24, and received at least 28 weeks of therapy.
TW=treatment week.

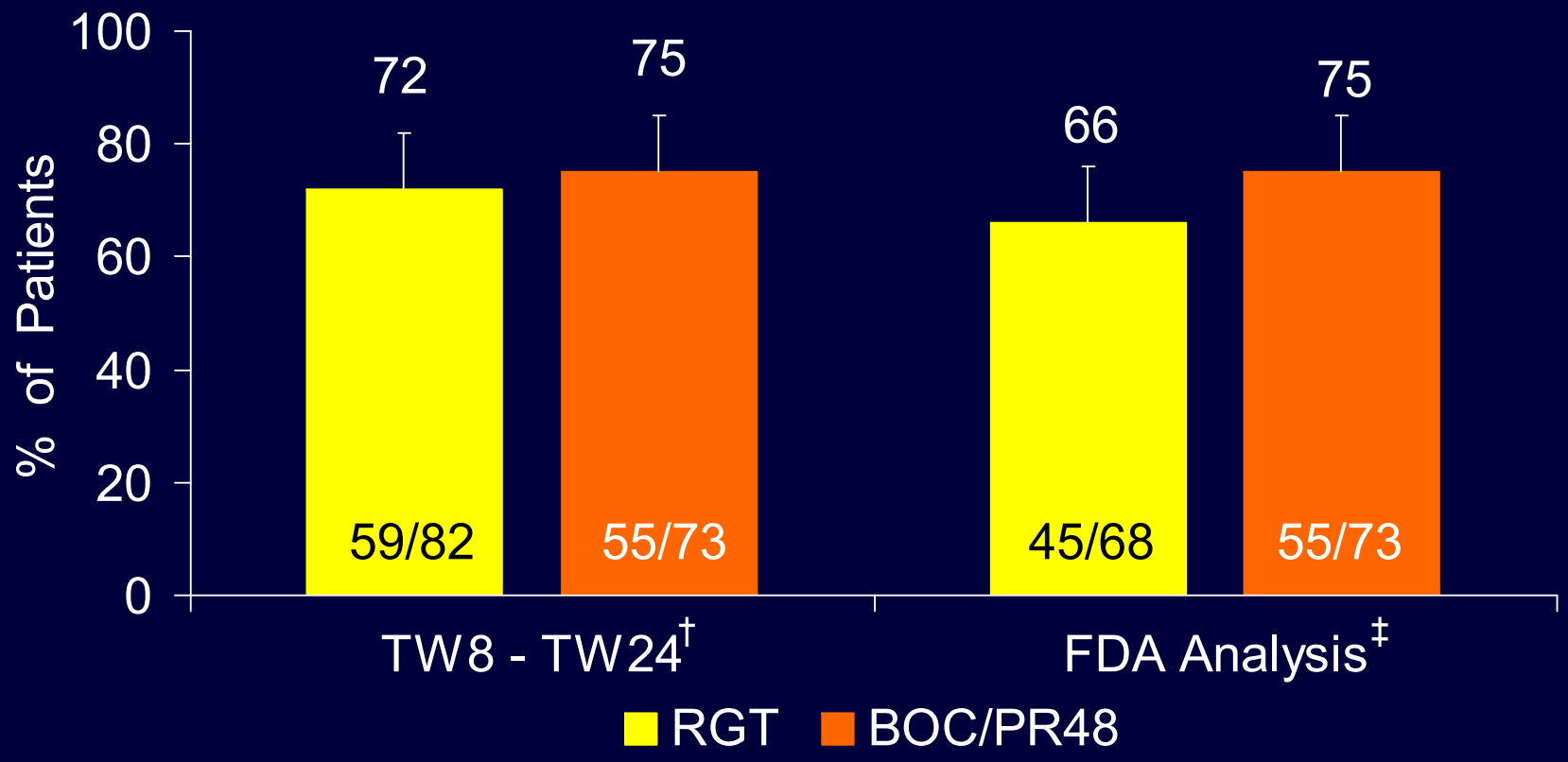
SPRINT-2: SVR in Late Responders† in RGT and Corresponding BOC/PR48



† HCV-RNA detectable at TW8 - undetectable at TW24, and received at least 28 weeks of therapy.

RGT=response-guided therapy; BOC/PR48=boceprevir/peginterfero α-2b + ribavirin 48 weeks; SVR=sustained virologic response; HCV=hepatitis C virus; RNA=ribonucleic acid; TW=treatment week.

SPRINT-2: SVR in Late Responders† in RGT and Corresponding BOC/PR48



† HCV-RNA detectable at TW8 - undetectable at TW24, and received at least 28 weeks of therapy.
‡ 14 patients in the RGT arm with false positive HCV-RNA results between TW8 and TW24 were removed from the numerator and denominator.

RGT=response-guided therapy; BOC/PR48=boceprevir/peginterfero α-2b + ribavirin 48 weeks; SVR=sustained virologic response; HCV=hepatitis C virus; RNA=ribonucleic acid; TW=treatment week.

SPRINT-2 Treatment-Naïve Patients Conclusions

- Addition of boceprevir to PR standard-of-care results in a statistically significant increase in efficacy in treatment-naïve patients
- Using RGT, 44% of patients receive only 28 weeks of treatment and achieve a SVR rate of 96%
- Boceprevir/PR also significantly improves efficacy in the difficult to treat black patients
  - RGT is the recommended regimen
- Boceprevir/PR also improves efficacy in the difficult to treat cirrhotic patients
  - Patients with cirrhosis may need 44 weeks of boceprevir treatment

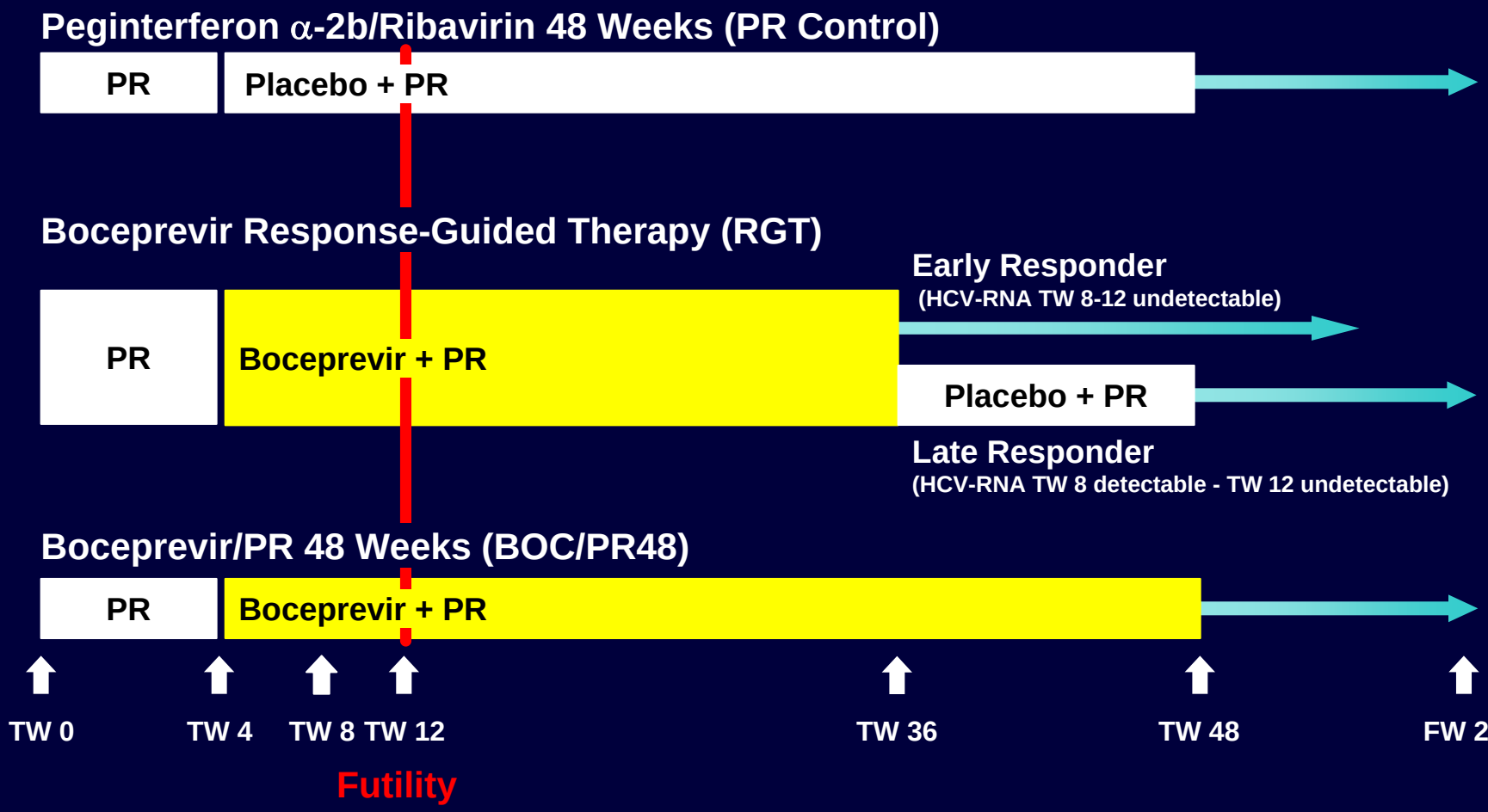
RESPOND-2

Previous Treatment Failure

RESPOND-2 Previous Treatment Failure Boceprevir/peginterferon α-2b/ribavirin

- Multi-center, double-blind for boceprevir, randomized, Phase 3 study
- Treatment regimens
  - Standard-of-care control
    - Peginterferon α-2b 1.5 µg/kg QW SC plus
    - Ribavirin 600-1400 mg/day PO
  - Boceprevir containing regimens
    - Boceprevir 800 mg TID PO (every 7-9 hours) plus peginterferon/ribavirin

RESPOND-2 Previous Treatment Failure Patients Study Design



TW=treatment week; FW=follow-up week.

RESPOND-2 Previous Treatment Failure Patients Study Design

- Primary Endpoint (FAS)
  - SVR 24 weeks post treatment
- Secondary Endpoint (mITT)
  - Excludes dropouts during PR 4 week lead-in
- Randomization
  - 1:2:2 (80:162:161)
- Population/Stratification variables
  - Historical Non-responder (≥2 log decline TW12) vs. relapse
  - Genotype: 1a vs. 1b
- Futility rule
  - Detectable HCV-RNA at TW12
- HCV-RNA
  - Roche TaqMan 2.0 LLD 9.3 IU/mL
  - Used to define undetectable at all decision points

FAS=full analysis set; mITT=modified intention-to-treat; LLD=lower limit of detection.

RESPOND-2 Previous Treatment Failure Patient Subpopulations

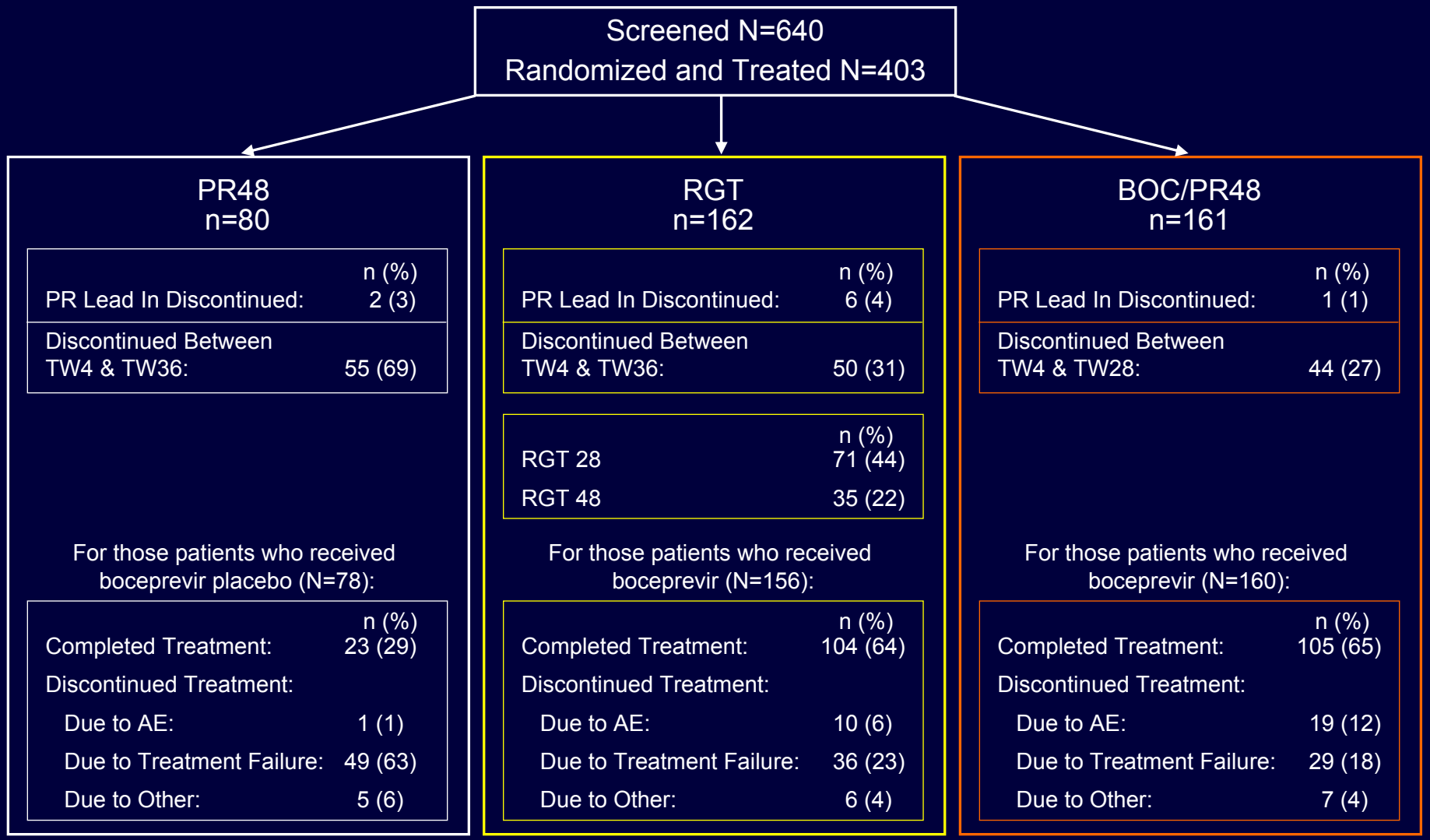
- Classification is based on interferon responsiveness
- Historical response to previous treatment
  - Relapsers
    - HCV undetectable at the end-of-treatment becoming positive when therapy is discontinued
  - Non-responders
    - ≥2 log decline at TW12 - included
      - Partial responders
    - <2 log decline at TW12 - excluded
      - Null responders

RESPOND-2: Baseline Characteristics

	PR48 N=80	RGT N=162	BOC/PR48 N=161
Mean age (years)	53	53	52
Male (%)	73	60	70
Black (%)	15	11	12
Region (%)			
North America	64	72	74
Europe	36	28	26
Latin America	0	1	0
BMI – mean (SD)	28 (4)	29 (5)	28 (5)
HCV genotype (%)†			
1a	58	58	60
1b	43	41	38
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

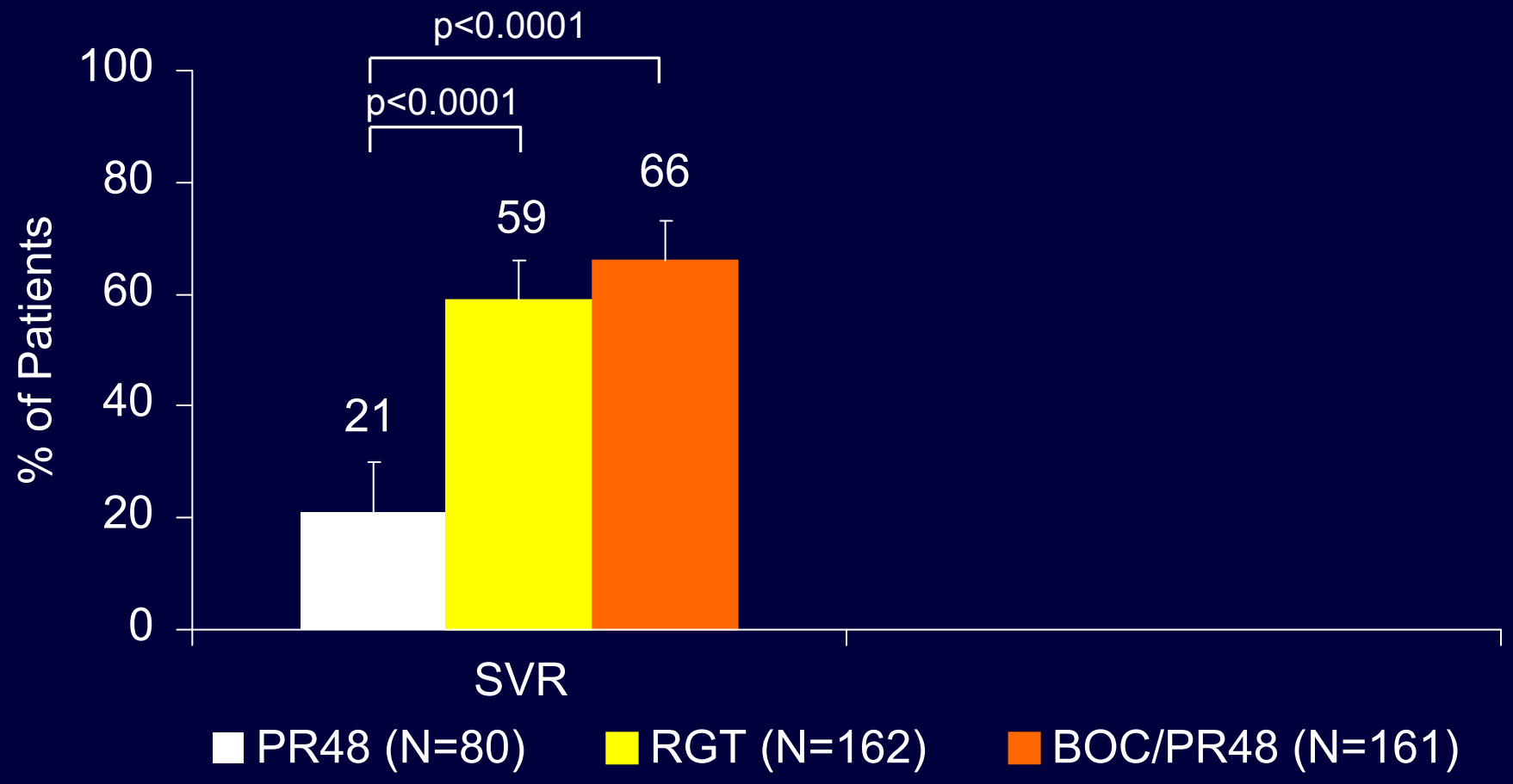
† Subtyping performed by NS5B sequencing (Virco, Mechelen, Belgium).

RESPOND-2 Previous Treatment Failure Patient Disposition



PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks; TW=treatment week;AE=adverse event.

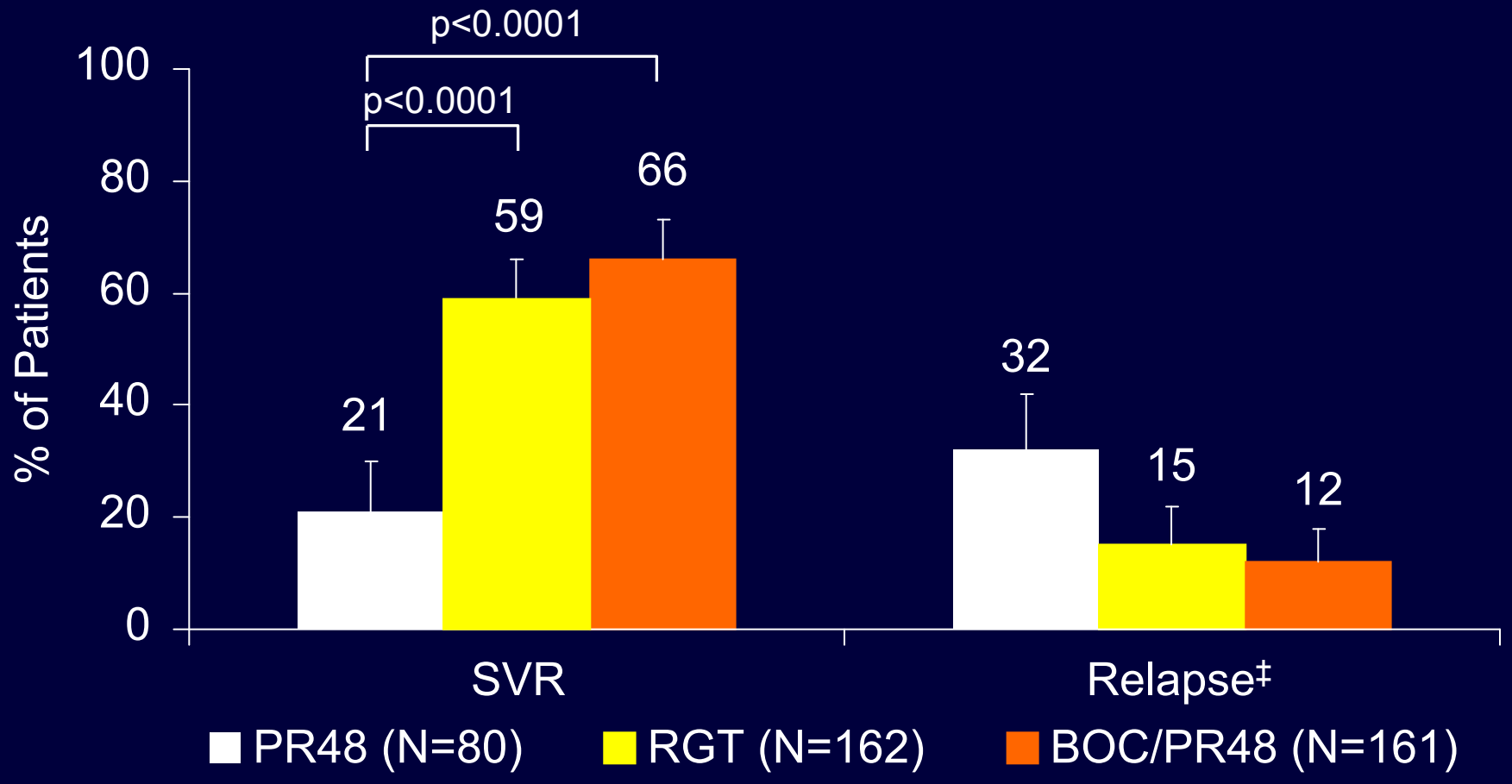
RESPOND-2 Previous Treatment Failure† Primary Endpoint: SVR



† Full Analysis Set.

SVR=sustained virologic response; PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks.

RESPOND-2 Previous Treatment Failure† Primary Endpoint: SVR and Relapse

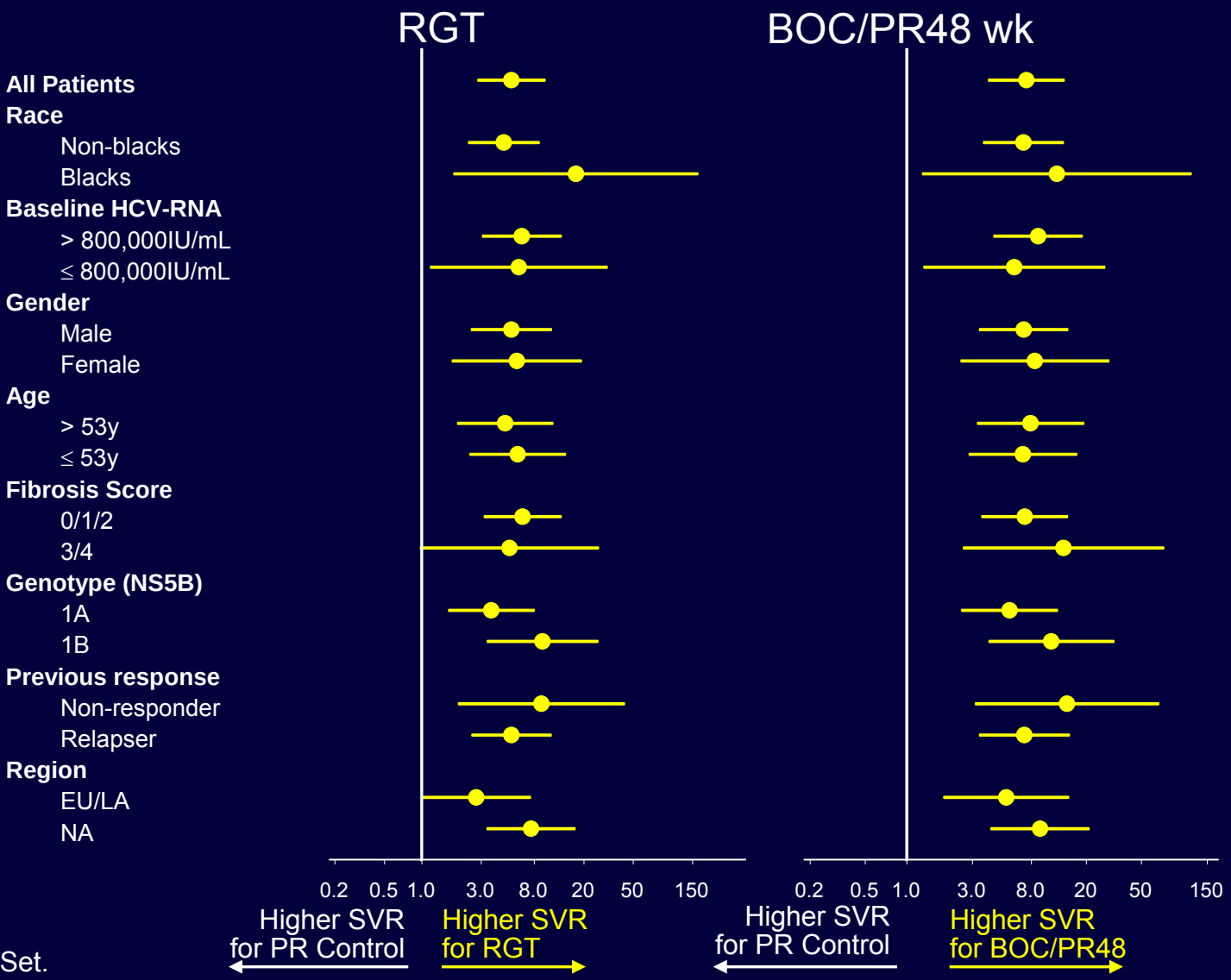


† Full Analysis Set.

‡ Relapse is computed on patients who were undetectable at end-of-treatment and were not missing data at end-of-follow-up.

SVR=sustained virologic response; PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks.

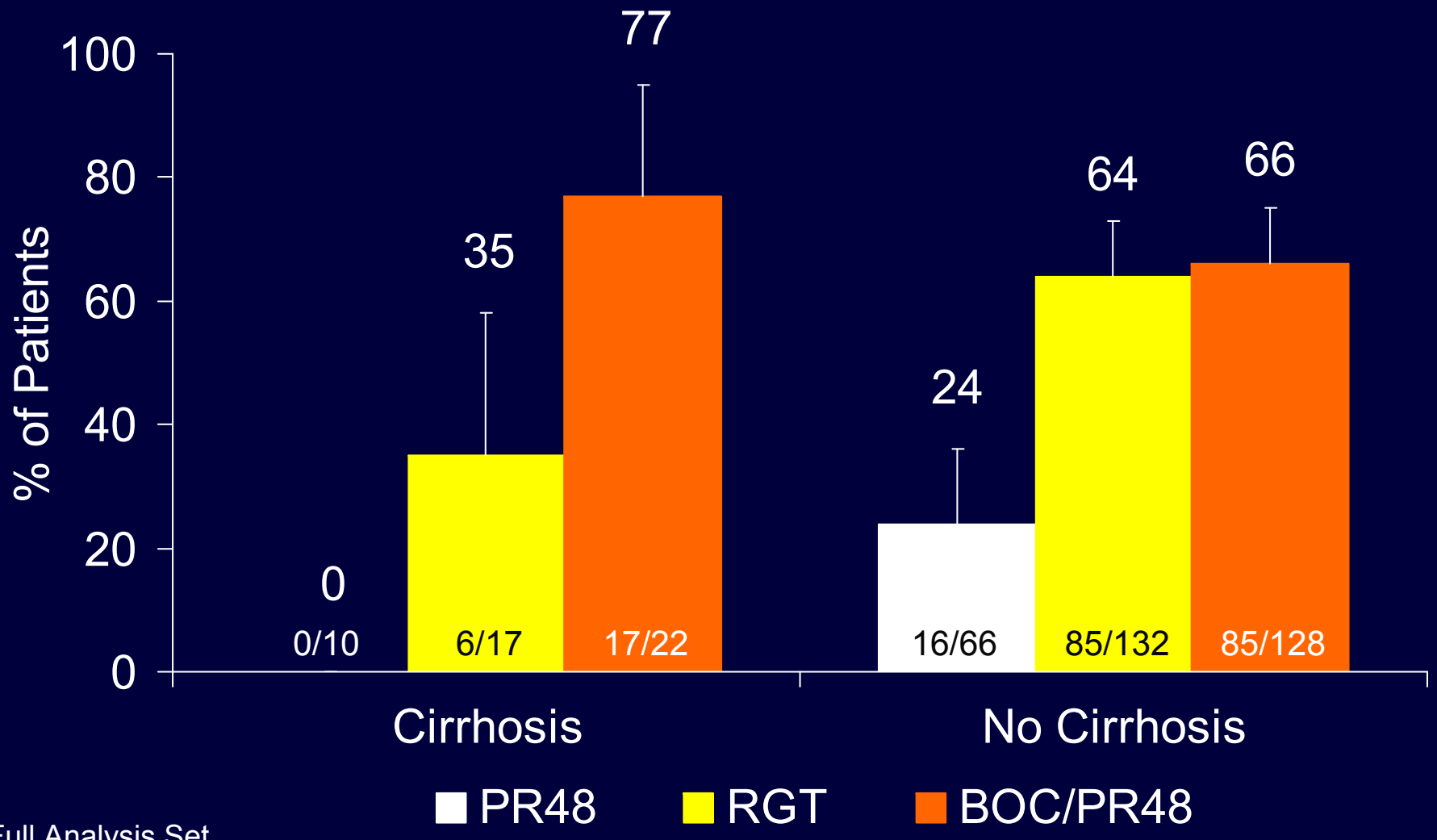
RESPOND-2: RGT, BOC/PR48 vs. Control
Odds Ratio (95% CI) for SVR by Subgroups



Full Analysis Set.

RESPOND-2: Previous Treatment Failure

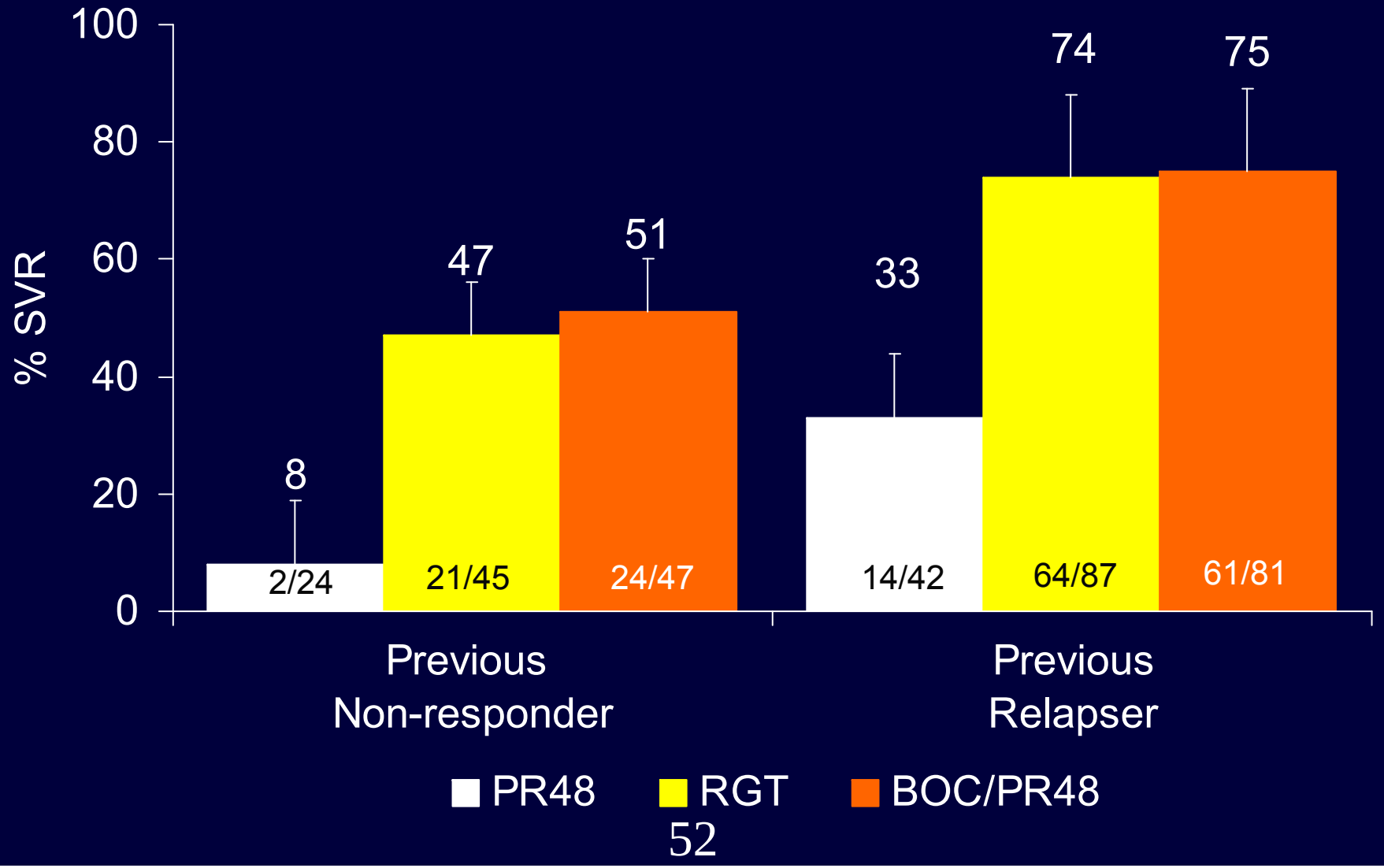
SVR by Cirrhotics (F4) vs. Non-cirrhotics (F0/1/2/3)



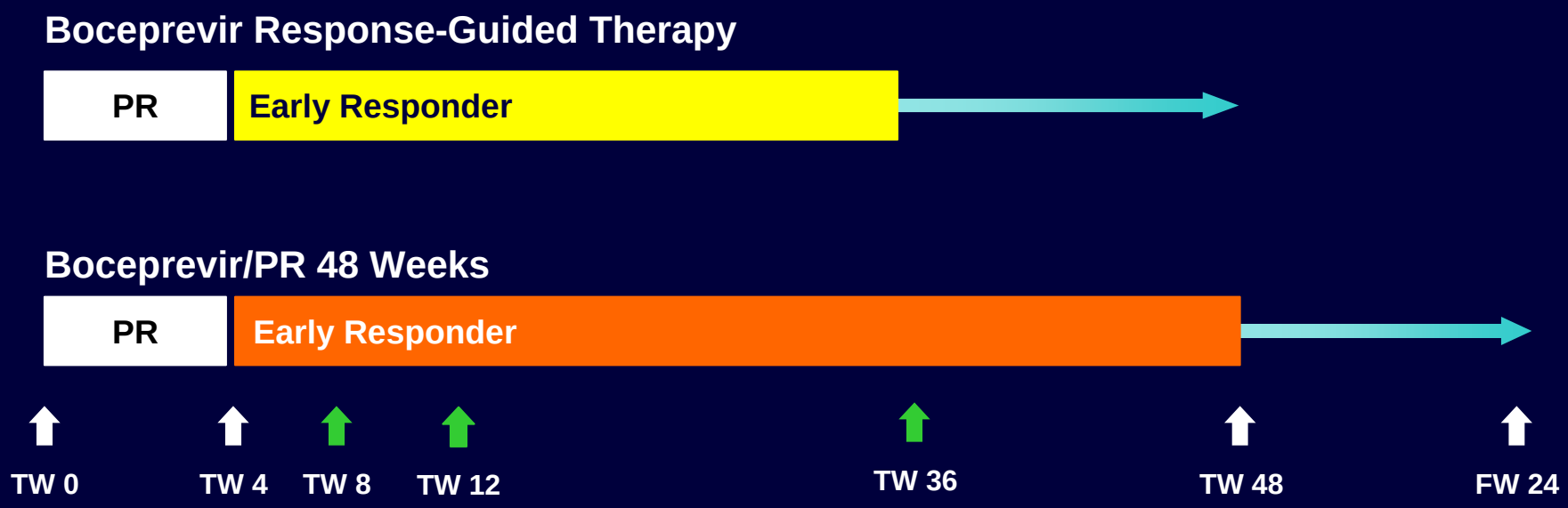
Full Analysis Set.

RESPOND-2: SVR by Historical Response to Previous Treatment

METAVIR F0/1/2/3



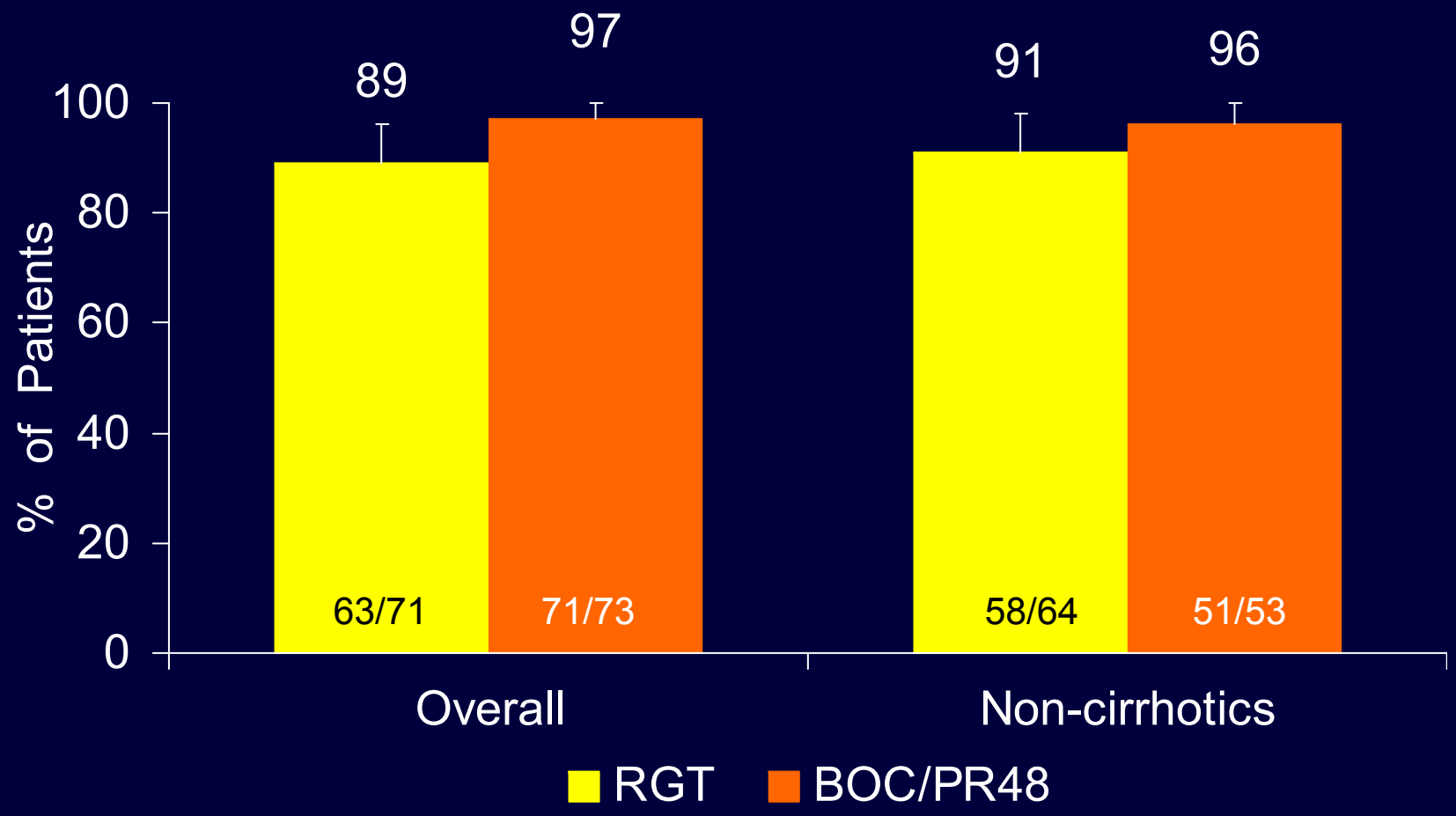
RESPOND-2 Previous Treatment Failure Early Responders: TW 8-12 HCV-RNA Undetectable



HCV-RNA undetectable at TW 8 through TW 12, and received at least 36 weeks of therapy.

TW=treatment week; FW=follow-up week.

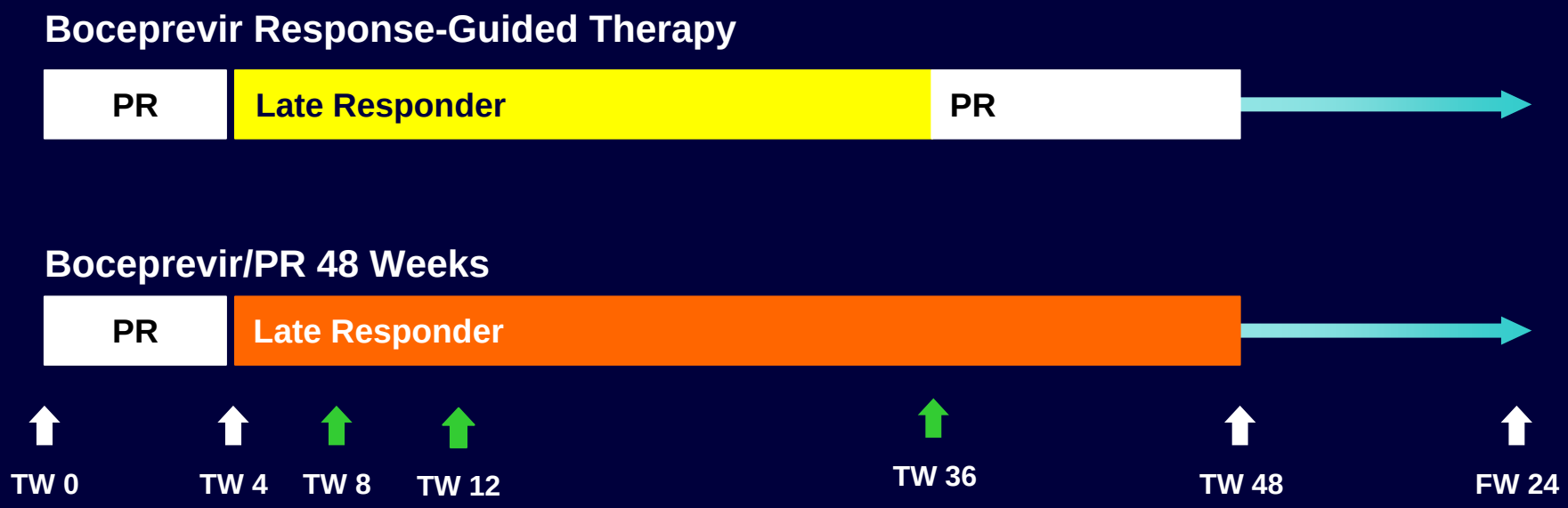
RESPOND-2: SVR in Early Responders† in RGT and Corresponding BOC/PR48



- 44% of patients met the criteria for early response

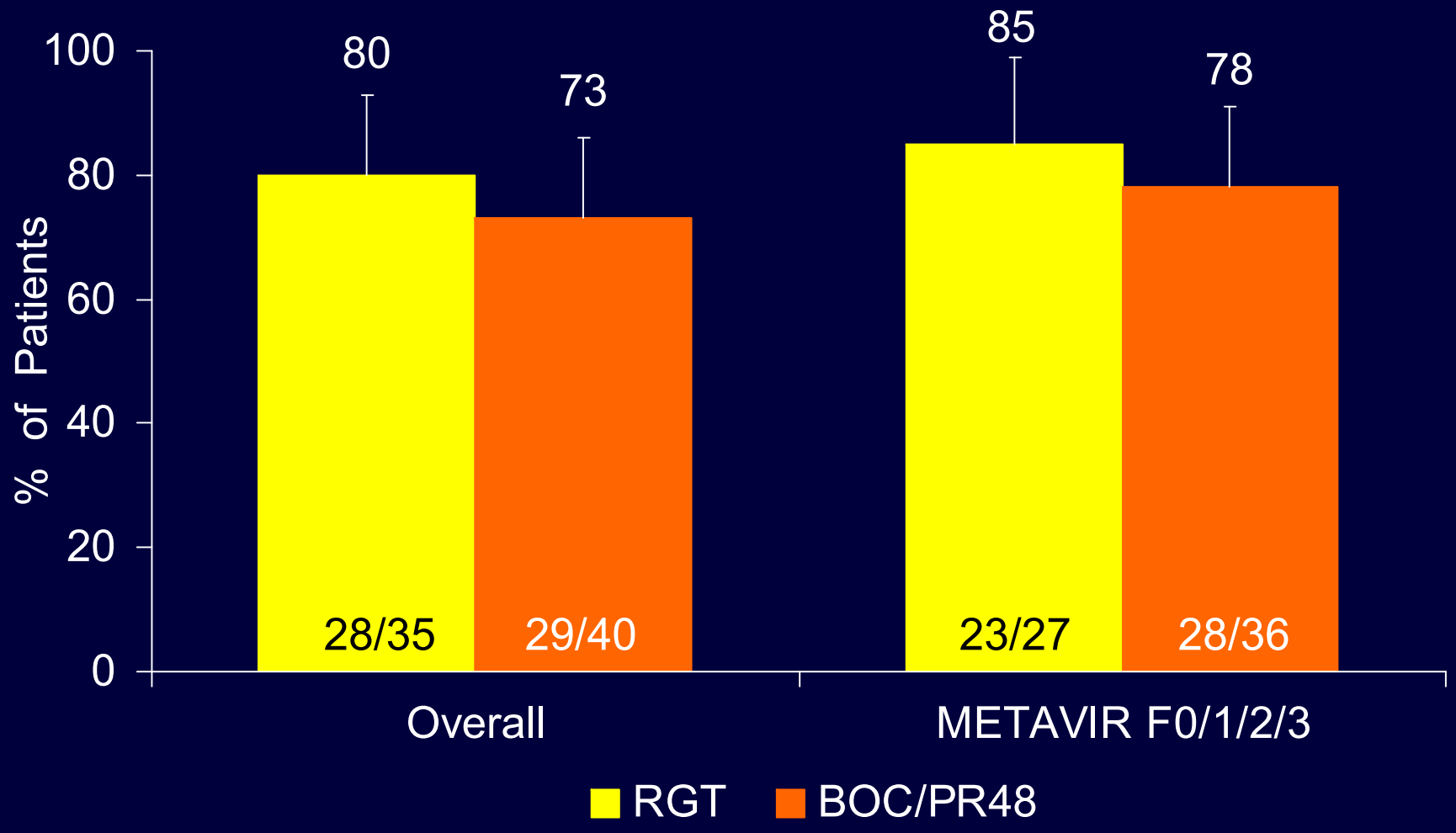
† HCV-RNA undetectable at TW8 through TW12, and received at least 36 weeks of therapy.

RESPOND-2 Previous Treatment Failure Late Responders: HCV-RNA TW 8 Detectable and TW 12 Undetectable



HCV-RNA detectable at TW8, undetectable at TW12, and received at least 36 weeks of therapy.
TW=treatment week; FW=follow-up week.

RESPOND-2: SVR in Late Responders† in RGT and Corresponding BOC/PR48



† HCV-RNA detectable at TW8 and undetectable at TW12, and received at least 36 weeks of therapy.

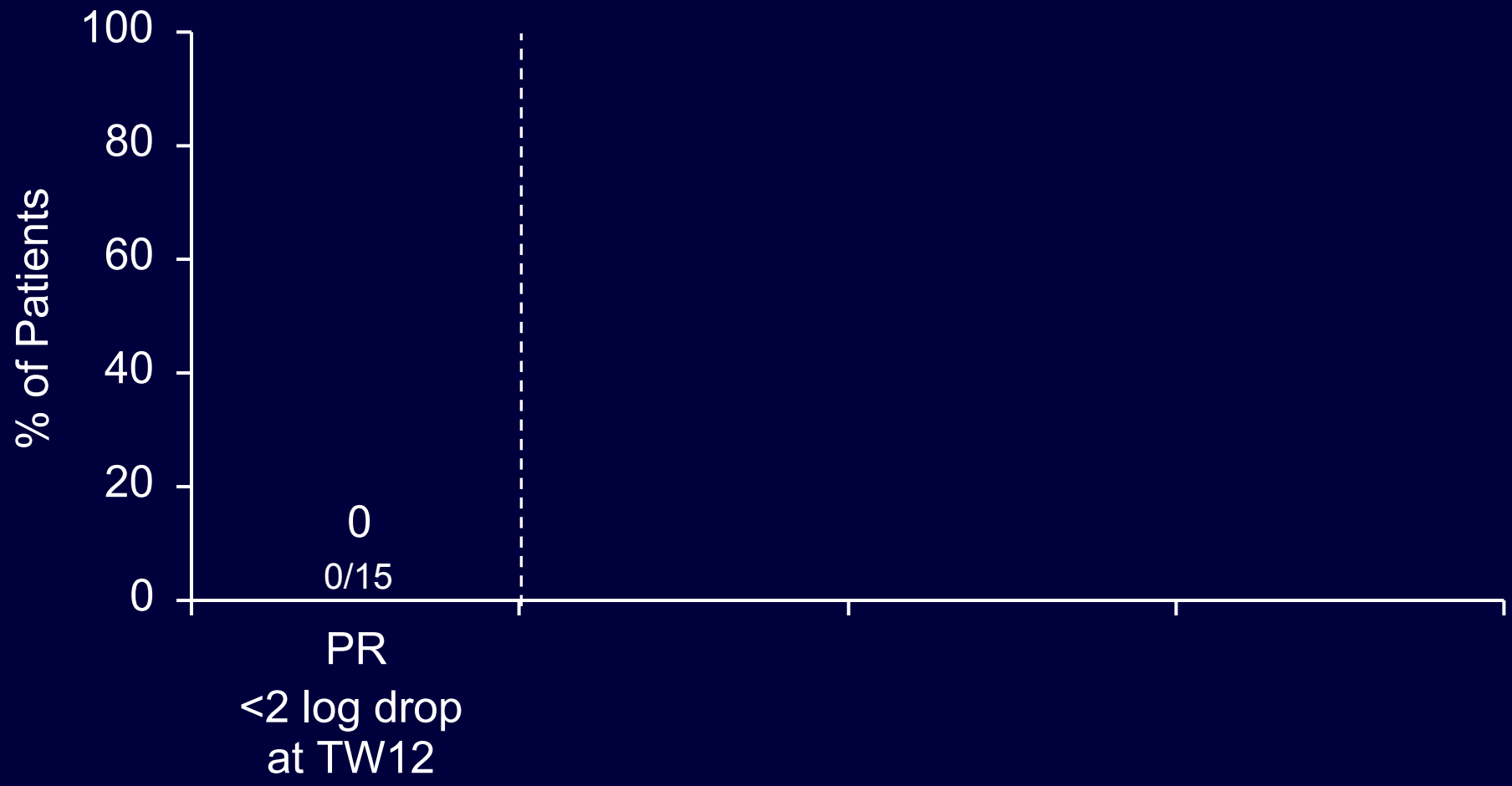
Patients With Poor Interferon Response

Data in Patients With Poor Interferon Response

- Null responders are defined by their poor interferon response <2 $\log_{10}$ decline at TW12
- SPRINT-2 and RESPOND-2 included patients with poor interferon response, defined by:
  - PR control groups (both studies): 20% of patients had <2 log decline at TW12 “null” responders
  - Both TW4 (<1 log) and TW12 (<2 log; historical null responders) define patients who are unlikely to respond to Peg/Ribavirin
- PROVIDE Data: Boceprevir treatment of null responders from the control arms of boceprevir Phase 3 studies

RESPOND-2: SVR in Poorly IFN Responsive Patients

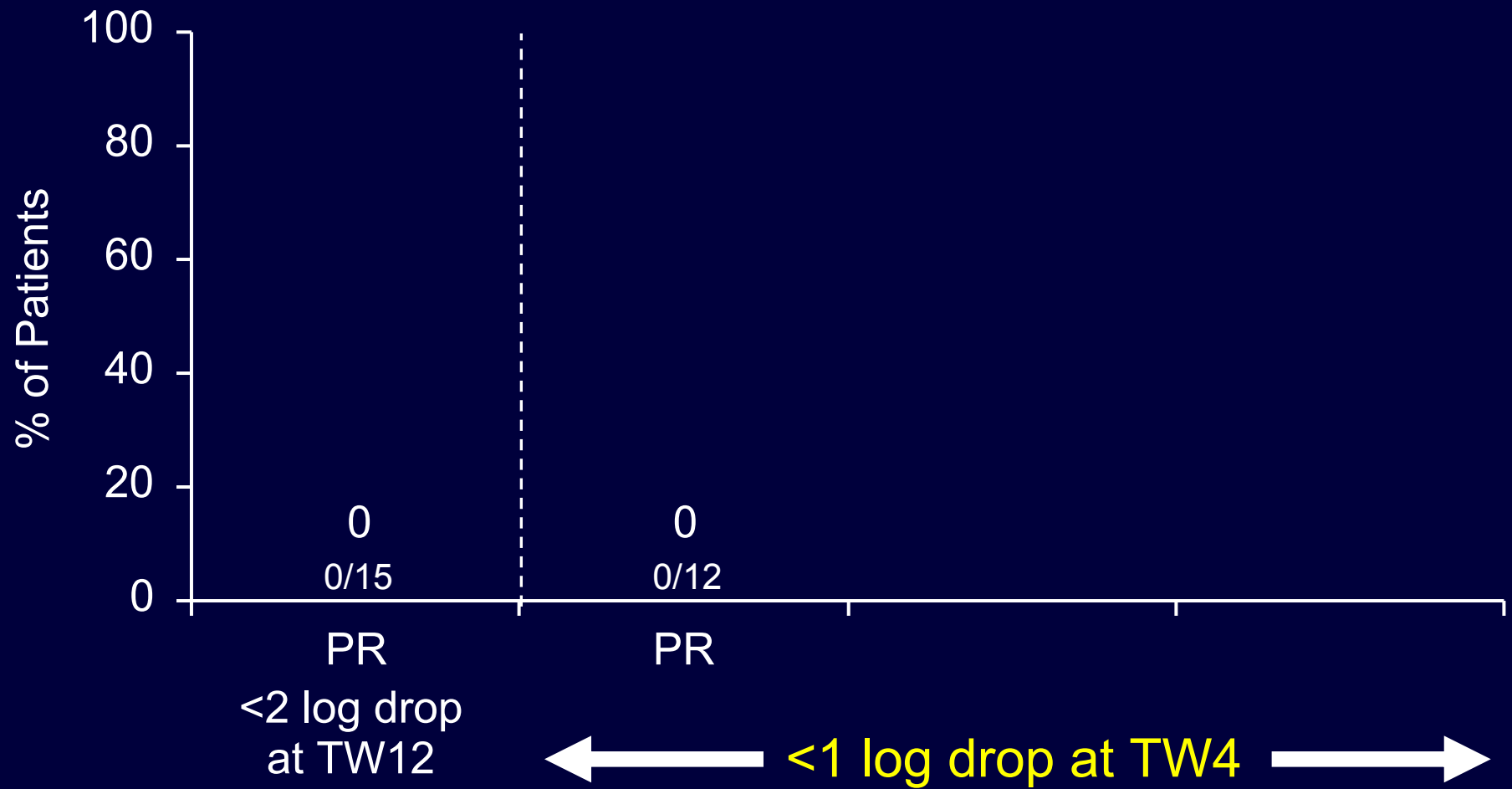
<2 Log Drop at TW12 in PR Control Arm



SVR=sustained virologic response; IFN=interferon; PR=peginterferon α-2b + ribavirin.

RESPOND-2: SVR in Poorly IFN Responsive Patients

<1 Log Drop at TW4 PR Control Arm

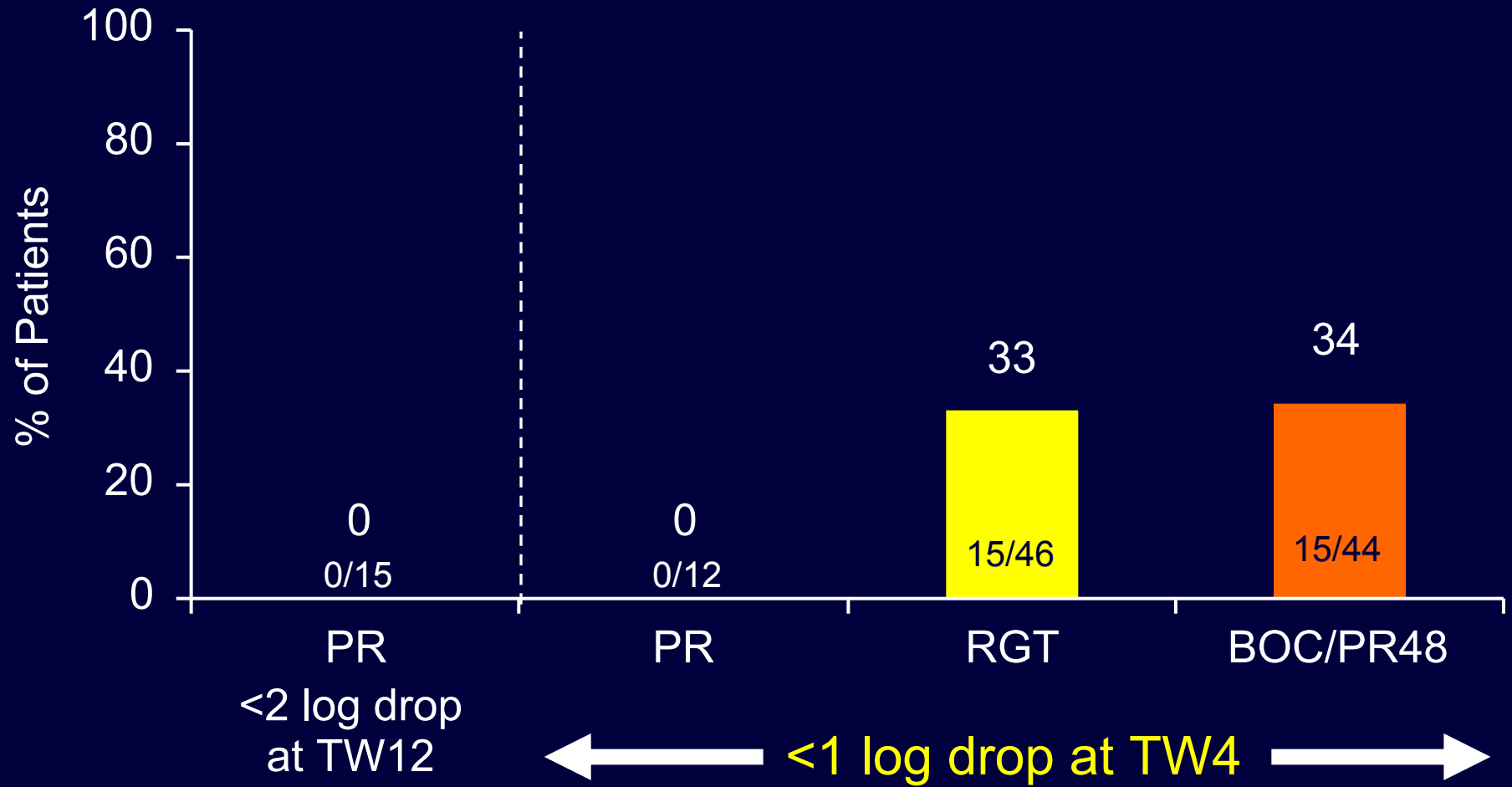


SVR=sustained virologic response; IFN=interferon; PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks.

SVR=sustained virologic response; IFN=interferon; PR=peginterferon α-2b + ribavirin.

RESPOND-2: SVR in Poorly IFN Responsive Patients

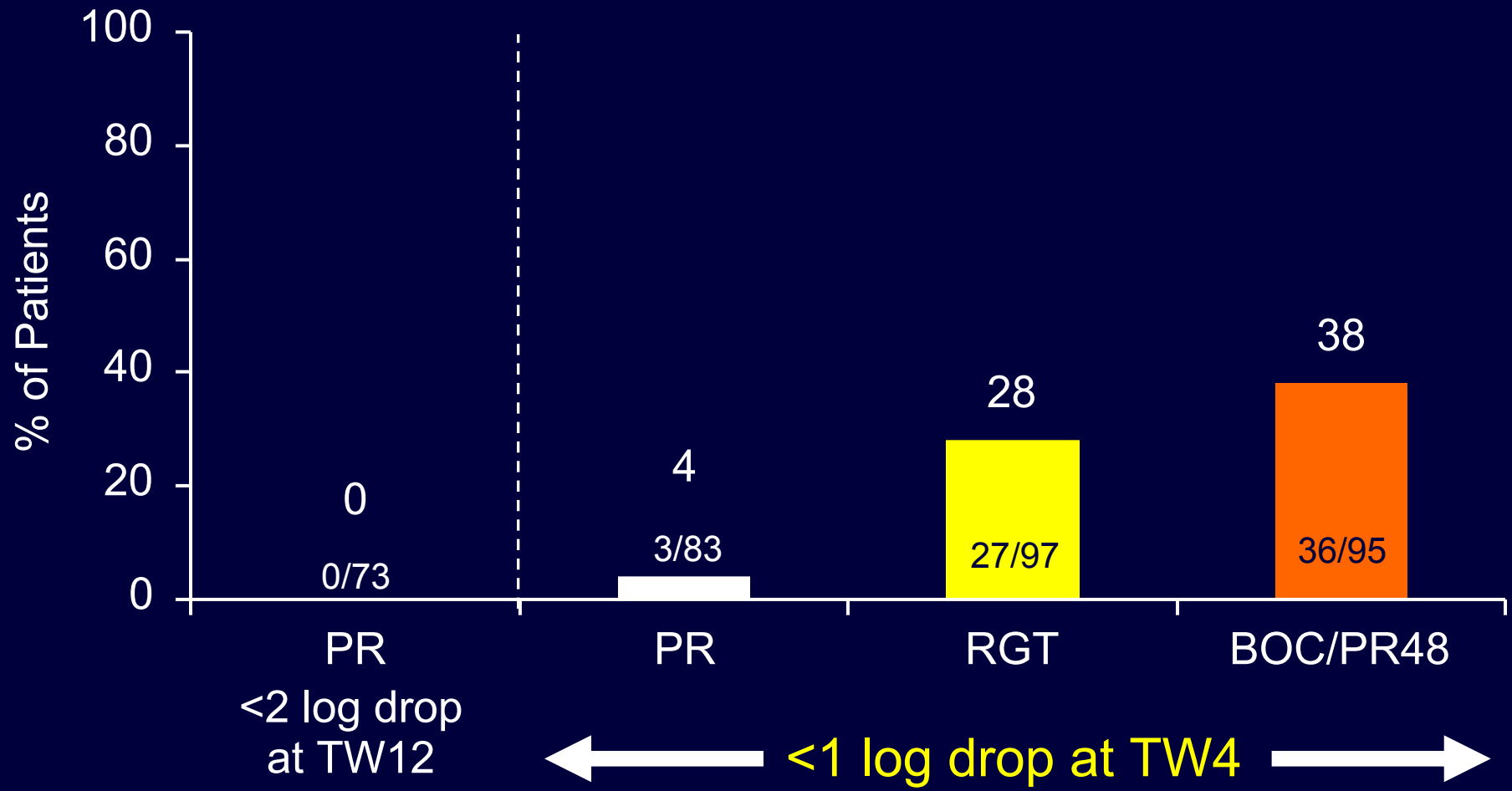
<2 Log Drop at TW12 and <1 Log Drop at TW4 in PR Control Arms,
<1 Log Drop at TW4 in RGT and BOC/PR48



SVR=sustained virologic response; IFN=interferon; PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks.

SPRINT-2: SVR in Poorly IFN Responsive Patients

<2 Log Drop at TW12 and <1 Log Drop at TW4 in PR Controls,
<1 Log Drop at TW4 in RGT and BOC/PR48



SVR=sustained virologic response; IFN=interferon; PR48=peginterferon α-2b + ribavirin 48 weeks; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks.

PROVIDE Study

Boceprevir Treatment of Null† Responders from the Control Arms of Boceprevir Phase 3 Studies

Weeks of BOC	% (n/N) Undetectable HCV-RNA
44 (EOT)	39 (15/38)

- EOT in patients with <1 log decline TW4 in the boceprevir arms of the Phase 3 studies: ~44%

† <2 log TW 12.
Data provided to FDA but not reviewed.
BOC=boceprevir; EOT=end-of-treatment.

Use of Boceprevir to Treat Patients With Poor Response to Interferon

- TW4 definition is a good surrogate for poor IFN response and a useful alternative to the historical TW12 definition
- A broad range of treatment failure and treatment-naïve patients were enrolled in the Phase 3 boceprevir program, including hard-to-treat patients comparable to the conventional “null” definition
- Boceprevir added to PR therapy resulted in an increase of ~30% in SVR in these difficult-to-treat patients

IFN=interferon.

RESPOND-2 Previous Treatment Failure Conclusions

- Adding boceprevir to PR for the Treatment Failure population resulted in a statistically significant ~3-fold increase in SVR
- RGT allowed a shorter duration of treatment in 44% of patients (early responders) who achieved an 89% SVR
- Regardless of a patient's historic response classification the addition of boceprevir substantially increased SVR:
  - Highest responses in relapsers
  - Robust response in non-responders
  - RGT is the optimal regimen
- Boceprevir/PR also improves efficacy in the difficult to treat cirrhotic patients
  - Patients with cirrhosis may need 44 weeks of boceprevir treatment

PR=peginterferon α-2b + ribavirin; SVR=sustained virologic response; RGT=response-guided therapy; BOC/PR48=boceprevir/PR48 weeks.

Efficacy Conclusions

Boceprevir/Peginterferon/Ribavirin

Boceprevir/Peginterferon/Ribavirin Efficacy Conclusions

- Addition of boceprevir to PR standard-of-care results in significant increases in SVR in both naïve and treatment failure patients
- Boceprevir/PR increases SVR in all subgroups, including patients with poor interferon response
- RGT allows the early responder to receive a shorter duration of therapy with efficacy equal to adding boceprevir to the standard peginterferon/ribavirin 48 week regimen
- RGT is the recommended regimen for both treatment-naïve and previous treatment failure patients
  - Patients with cirrhosis may need 44 weeks of boceprevir treatment

PR=peginterferon α-2b + ribavirin; SVR=sustained virologic response; RGT=response-guided therapy.

Resistance and Clinical Safety

Dr. Clifford Brass

Resistance and Safety

- Resistance
- Clinical Safety
  - Common Adverse Events
  - Adverse Events of Special Interest
- Clinical Pharmacology
- Benefit/Risk Conclusion

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Introduction to Resistance

- Boceprevir is a direct acting antiviral agent targeting HCV NS3 protease
- Loss of drug susceptibility and resistance to HCV NS3 PIs is associated with amino acid variants in the NS3 coding region
- Resistance associated amino acids variants (RAVs) cause decreased susceptibility to boceprevir
  - Identified in vitro and in vivo mapping to NS3
- RAVs characterized in pivotal Phase III trials
  - Baseline, TW8, time of failure
  - Followed post therapy to evaluate persistence

PI=protease inhibitor.

Resistance Associated Amino Acid Variants (RAVs)

- Putative RAVs were identified as amino acid changes appearing:
  - In replicons selected for boceprevir resistance in vitro
  - In viruses isolated from HCV-infected patients treated with boceprevir
- Putative RAVs engineered into genotype 1a and 1b proteases (NS3) and tested for susceptibility to boceprevir
  - V36, Q41, F43, T54, V55, R155, A156, V158, V170, M175
- In vitro, RAVs demonstrated ~2-300 fold decreased sensitivity to boceprevir

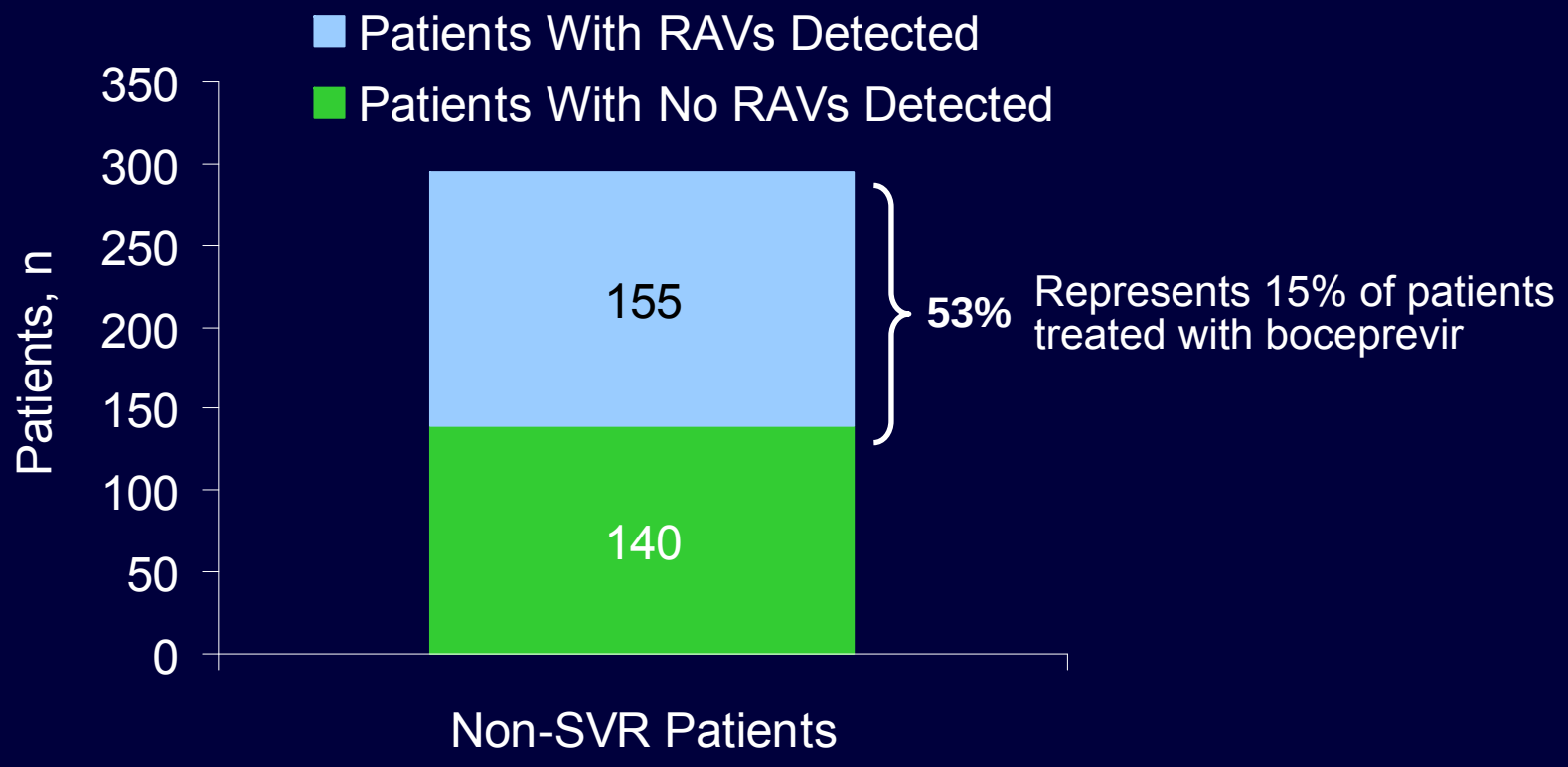
Methodology for Assessing RAVs
SPRINT-2 and RESPOND-2

- RAVs were detected by population sequencing
  - 96% patients had samples sequenced at baseline
  - 86% post-baseline samples sequenced in non-SVR patients
- Population sequencing has a detection limit of ~20%
  - Sequencing performed at >1000 IU/mL
- NS3 coding region was sequenced†
- All subsequent slides show data from patients receiving boceprevir in SPRINT-2 and RESPOND-2

† Note: The entire NS3/4A coding region was sequenced.
RAV=resistance associated amino acid variant; IU=international units.

RAVs Detected in Non-SVR Patients

SPRINT-2 and RESPOND-2



Most Frequently Detected RAVs

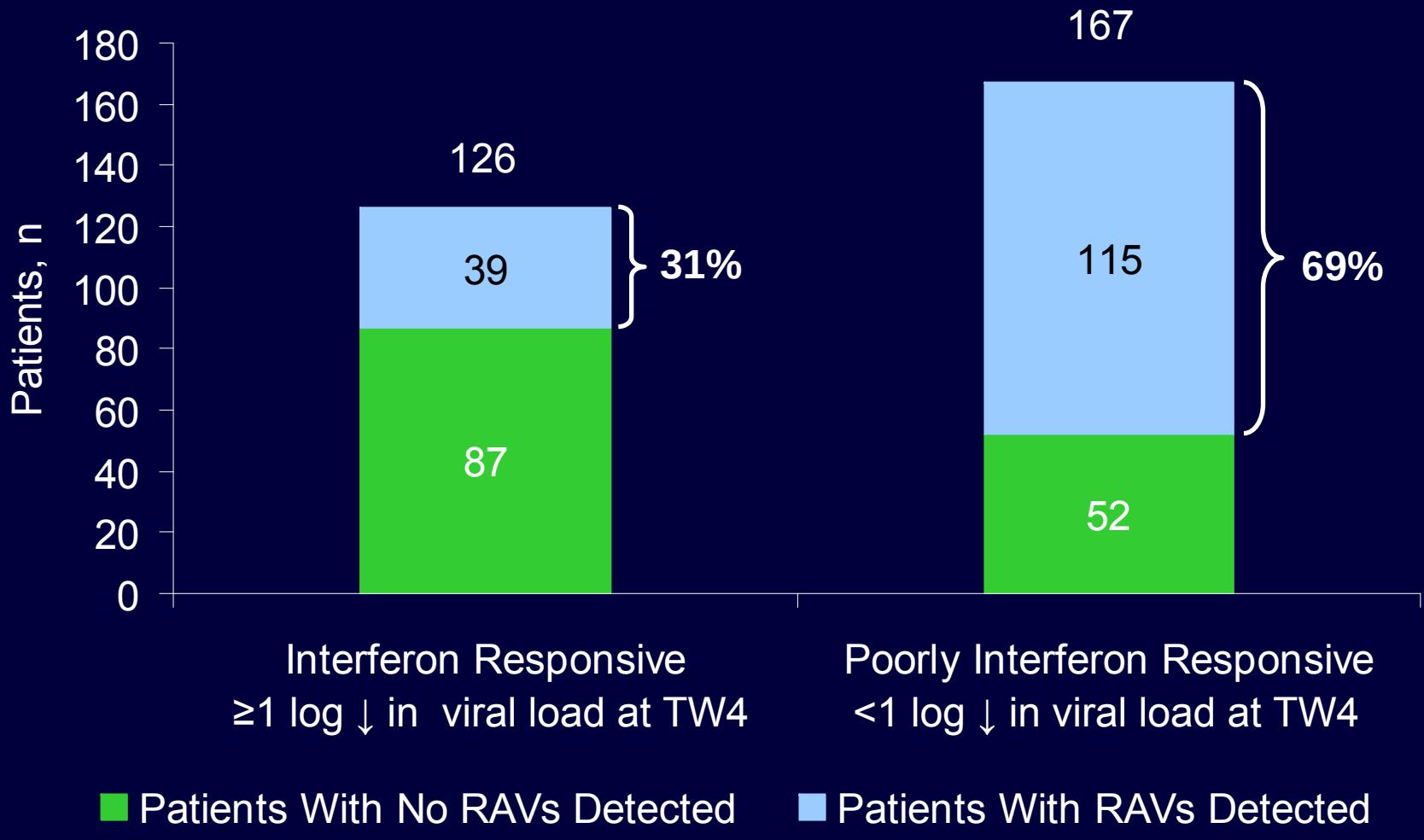
Genotype 1a; V36M, R155K

Genotype 1b; T54A/S, A156S, V170A

48 non-SVR patients had no sequence data.

RAV=resistance associated amino acid variant; SVR=sustained virologic response.

RAVs Detected in Non-SVR Patients
by Interferon Responsiveness at TW4



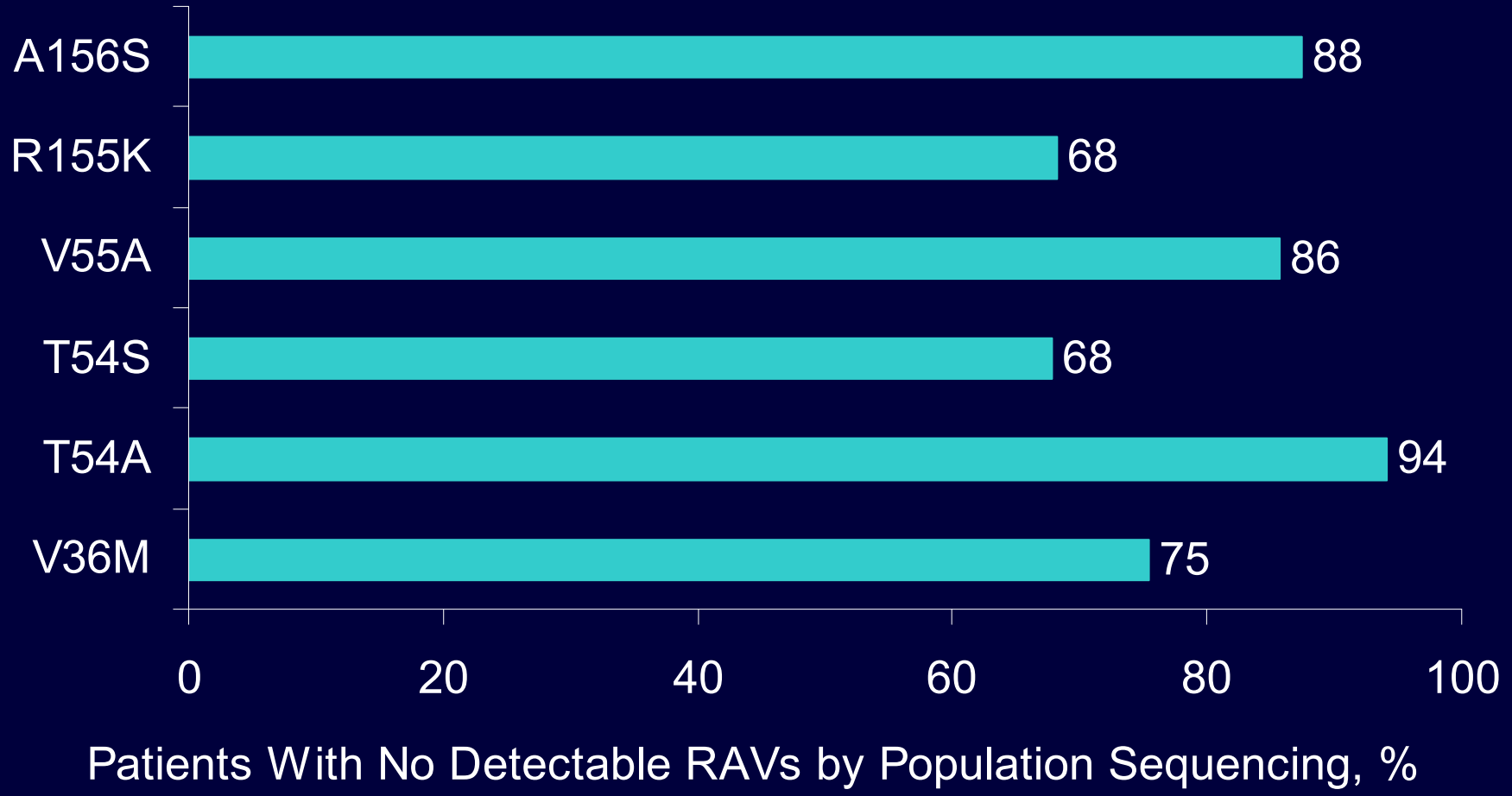
8 Patients missing TW4 viral load data and 42 with no sequence data are not included.
RAV=resistance associated amino acid variant; SVR=sustained virologic response; TW=treatment week.

SVR Rates Are Similar in Patients With/Without Baseline RAVs Detected

Patient Category	Total n, (%)	Number of Patients With SVR	% SVR
Patients With Baseline RAVs Detected	66 (7)	43	65
Patients Without Baseline RAVs Detected	914 (93)	608	67

RAV=resistance associated amino acid variant; SVR=sustained virologic response.

Most Common RAVs†: Detectability Declines During Follow-Up



† In non-SVR patients with detectable RAVs at treatment failure in SPRINT-2 and RESPOND-2. As of latest follow-up time point (Range 6-14 Months).

Resistance Summary
Data From SPRINT-2 and RESPOND-2

- Overall, the presence of RAVs at baseline was not predictive of outcome
- 53% of non-SVR patients had viruses with RAVs detected post-baseline
- In treatment failures, the most common RAVs differed by genotype
  - Genotype 1a: V36M and R155K
  - Genotype 1b: T54A/S, A156S and V170A
- RAVs detected in non-SVR patients declined over time
  - The majority of patients did not have RAVs 6-14 months post-therapy, percentage differed based on the RAV selected (68-94%)
  - Studies to evaluate whether RAVs return to pre-treatment levels are ongoing
- Clinical significance of RAVs is unknown

RAV=resistance associated amino acid variant; SVR=sustained virologic response.

Resistance and Safety

- Resistance
- Clinical Safety
  - Common Adverse Events
  - Adverse Events of Special Interest
- Clinical Pharmacology
- Benefit/Risk Conclusion

NDA Safety Database

- **Key studies:** evaluated boceprevir 800 mg TID (every 7-9 hours)
  - Phase III: SPRINT-2 (n=1097) and RESPOND-2 (n=403)
  - Phase II: SPRINT-1 (Treatment-naïve, open-label, n=595)
- 2095 patients received at least one dose of study drug in three key studies
  - RGT and BOC/PR48 were pooled
  - Exposure was 3:1
    - 1548 BOC/PR
    - 547 PR control
  - 78% received ≥24 weeks of therapy
  - Total exposure to boceprevir ~840 patient-years

RGT=response-guided therapy; BOC=boceprevir; PR=peginterferon α-2b + ribavirin.

Safety Overview of the Key Studies

	All Patients	
	PR N=547	BOC/PR N=1548
Median Treatment Duration (Days)	198	201
	n (%)	n (%)
Treatment-Related Adverse Event (AE)	533 (97)	1532 (99)
Serious AE	43 (8)	164 (11)
Death†	4 (1)	4 (<1)
Dose Modification (Any Drug) Due to AE‡	132 (24)	605 (39)
Treatment Discontinuation Due to AE	67 (12)	205 (13)

Key studies: SPRINT-1, SPRINT-2, RESPOND-2.
Note: Patients may have had more than one adverse event.
† Deaths are included in serious AE count; ‡ Excludes patients who discontinued due to adverse events.
PR=peginterferon α-2b + ribavirin; BOC/PR=boceprevir/PR.

Most Common Treatment-Related AEs

Adverse Event	PR N=547 n (%)	BOC/PR N=1548 n (%)
Fatigue	312 (57)	889 (57)
Anemia	158 (29)	755 (49)
Nausea	217 (40)	690 (45)
Headache	234 (43)	683 (44)
Dysgeusia	82 (15)	568 (37)
Chills	161 (29)	515 (33)
Insomnia	170 (31)	498 (32)
Pyrexia	168 (31)	485 (31)
Alopecia	139 (25)	404 (26)
Decreased Appetite	125 (23)	386 (25)
Myalgia	129 (24)	354 (23)
Diarrhea	100 (18)	353 (23)
Neutropenia	96 (18)	350 (23)
Influenza-Like Illness	135 (25)	339 (22)

PR=peginterferon α-2b + ribavirin; BOC/PR=boceprevir/PR.

Most Common Treatment-Related AEs

Events Common to Interferon and Ribavirin

Adverse Event	PR N=547 n (%)	BOC/PR N=1548 n (%)
Fatigue	312 (57)	889 (57)
Anemia	158 (29)	755 (49)
Nausea	217 (40)	690 (45)
Headache	234 (43)	683 (44)
Dysgeusia	82 (15)	568 (37)
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PR=peginterferon α-2b + ribavirin; BOC/PR=boceprevir/PR.

Most Common Treatment-Related AEs

Adverse Events More Common With Boceprevir

Adverse Event	PR N=547 n (%)	BOC/PR N=1548 n (%)
Fatigue	312 (57)	889 (57)
Anemia	**158 (29)**	**755 (49)**
Nausea	217 (40)	690 (45)
Headache	234 (43)	683 (44)
Dysgeusia	**82 (15)**	**568 (37)**
Chills	161 (29)	515 (33)
Insomnia	170 (31)	498 (32)
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PR=peginterferon α-2b + ribavirin; BOC/PR=boceprevir/PR.

Resistance and Safety

- Resistance
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Adverse Events of Special Interest

- Hematologic effects
  - Anemia (Hgb <10 g/dL)
  - Neutropenia
  - Thrombocytopenia
- Dysgeusia
- Skin rash

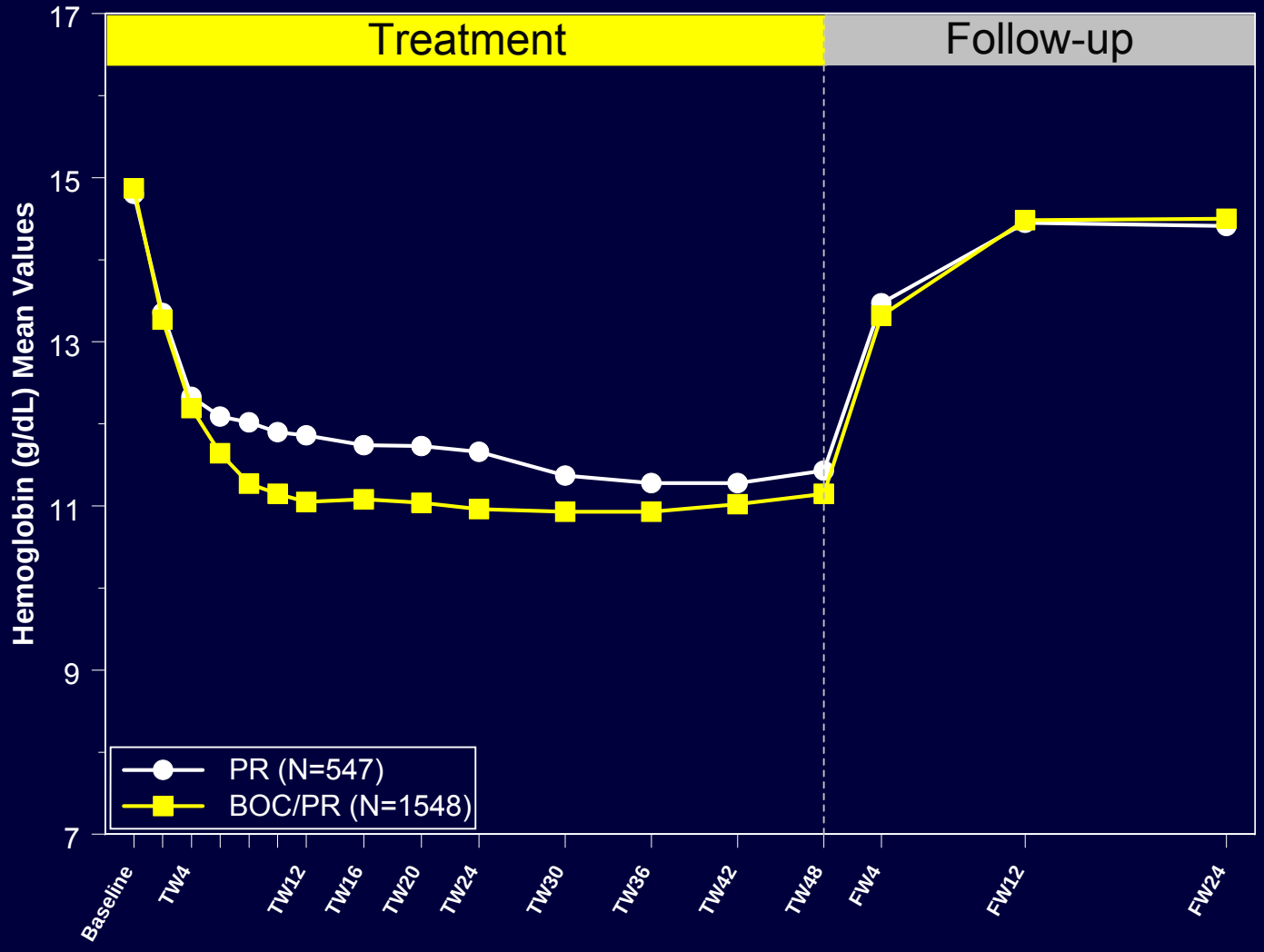
Hgb=hemoglobin.

Hemoglobin Reductions and Boceprevir

- Recognized with peginterferon/ribavirin: ↓ Hgb ~3 g/dL
  - Peginterferon marrow suppressive
  - Ribavirin causes hemolytic anemia
- No hemoglobin decrease with 2-mo. boceprevir monotherapy
- Incremental hemoglobin decrease of ~1 g/dL with addition of boceprevir to peginterferon/ribavirin backbone
- Anemia management effective using same tools as for SOC
- Low incidence of discontinuations due to anemia
  - 1% in both PR and BOC/PR
- Hemoglobin returned to baseline post therapy

PR=peginterferon α-2b + ribavirin; BOC=boceprevir; SOC=standard-of-care.

Mean Hemoglobin Over Time in the Key Studies

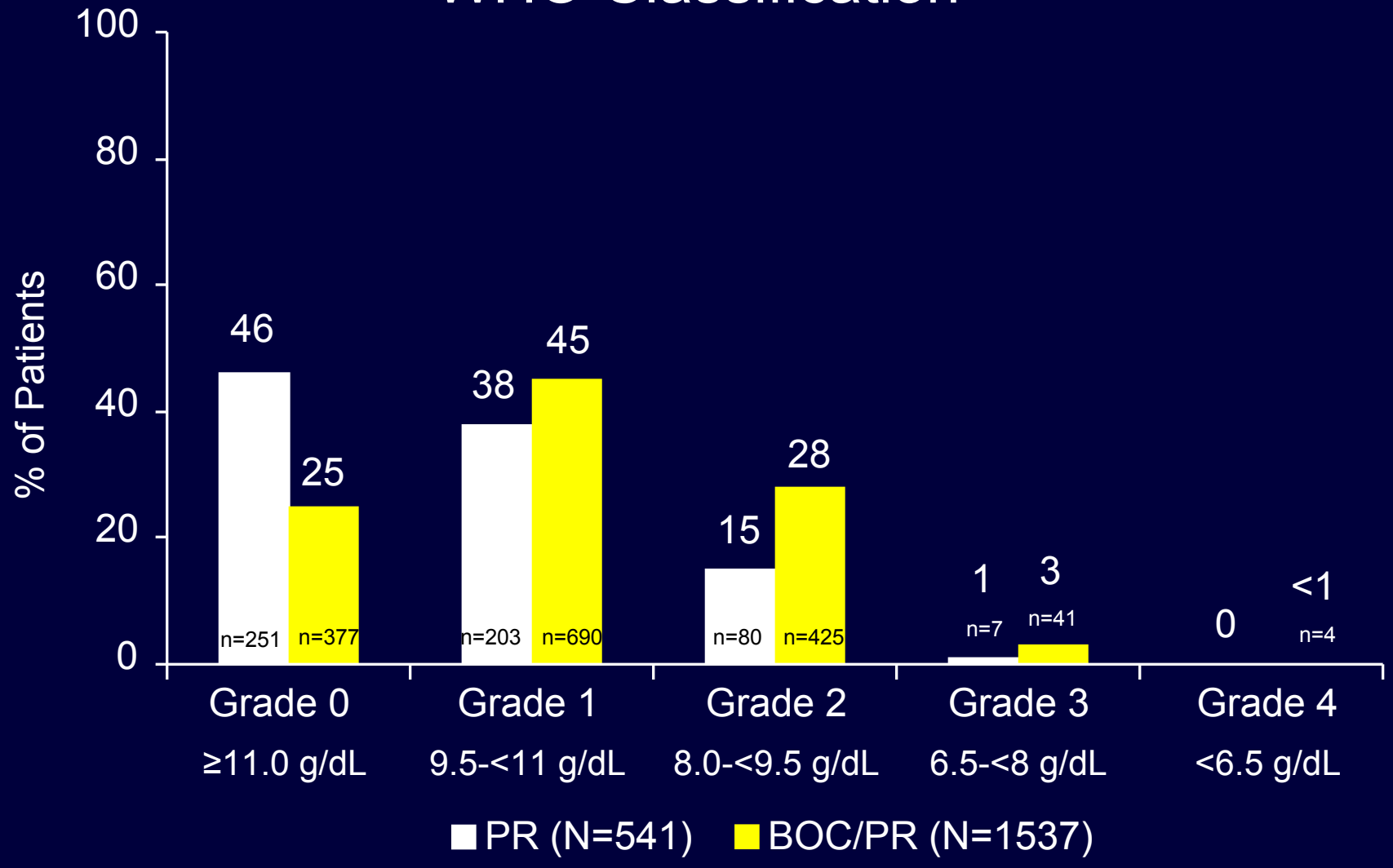


Key studies: SPRINT-1, SPRINT-2 and RESPOND-2.

PR=peginterferon α-2b + ribavirin; BOC/PR=boceprevir/PR.

Nadir Hemoglobin Values During Treatment

WHO Classification



Key studies: SPRINT-1, SPRINT-2, RESPOND-2.

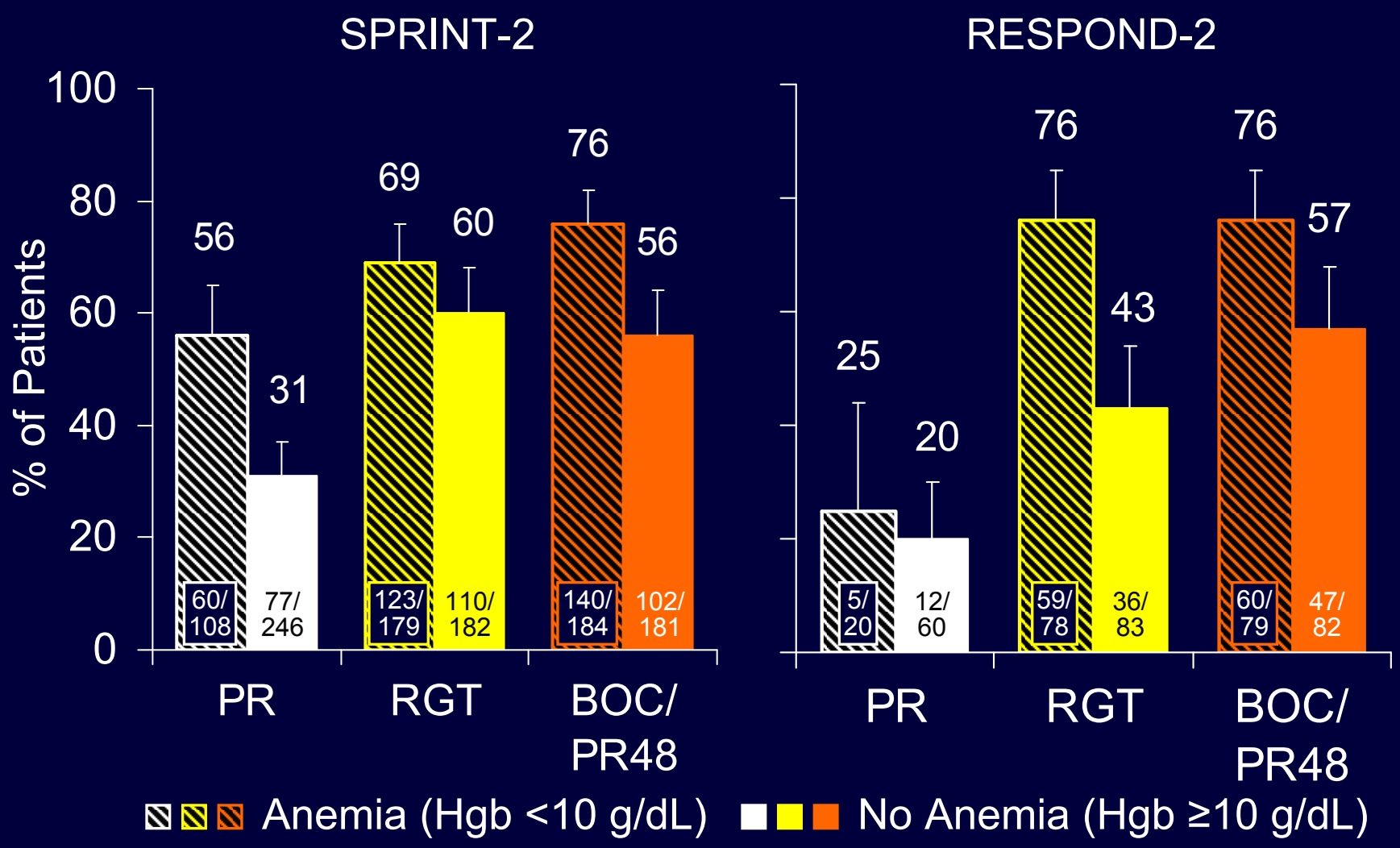
WHO=World Health Organization; PR=peginterferon α-2b + ribavirin; BOC/PR=boceprevir/PR.

Anemia Management
Patients With Hgb <10 g/dL

	PR N=547 n (%)	BOC/PR N=1548 n (%)
Patients With Hgb <10 g/dL	153 (28)	744 (48)
RBV Dose Reduction Only	15 (3)	54 (3)
EPO Only	57 (10)	247 (16)
EPO and RBV Dose Reduction	49 (9)	340 (22)
None	32 (6)	103 (7)
Any RBV Dose Reduction	64 (12)	394 (25)
Any EPO	106 (19)	587 (38)

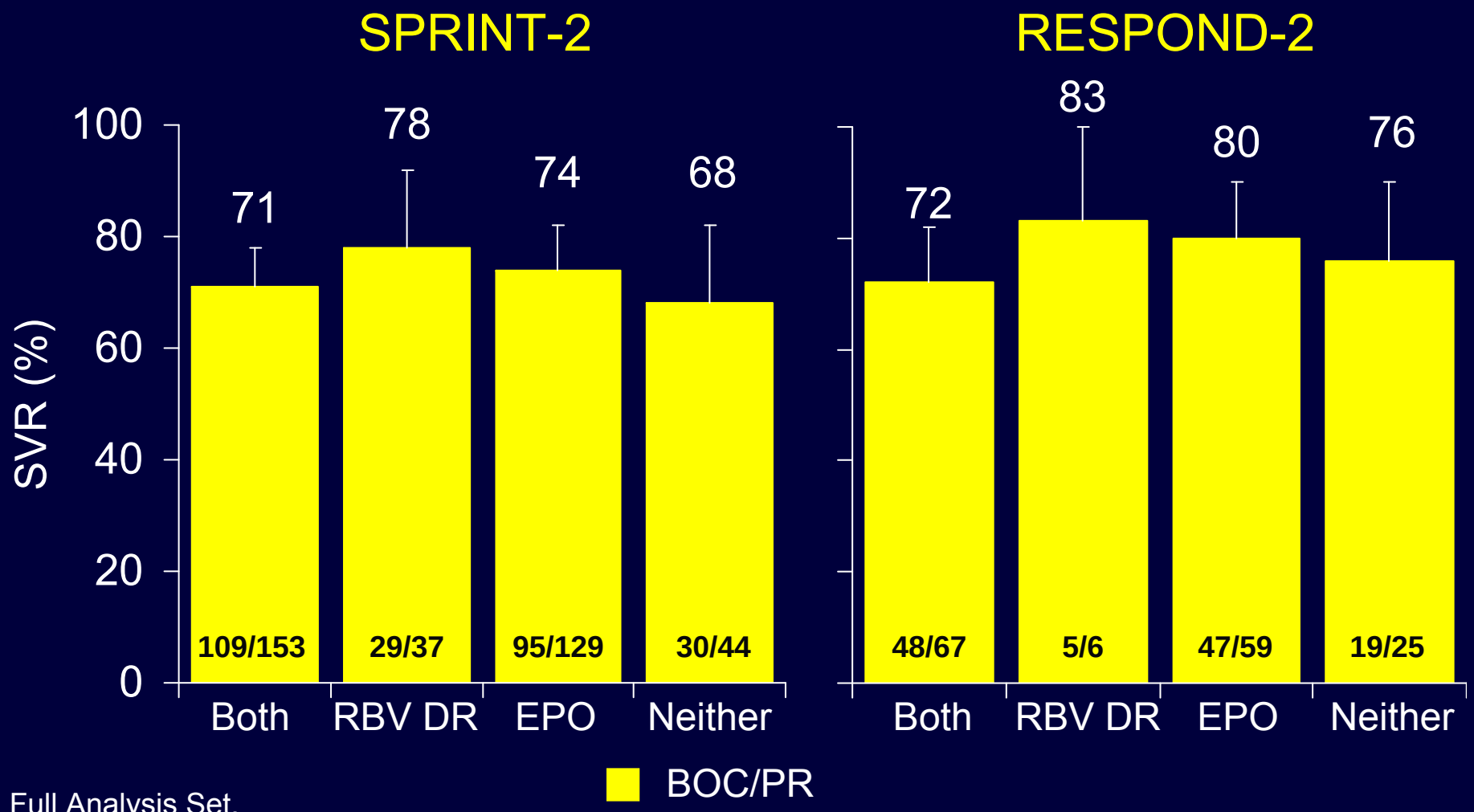
Key studies: SPRINT-1, SPRINT-2, RESPOND-2.
Hgb=hemoglobin; RBV=ribavirin; EPO=erythropoietin.

Patients With Anemia Had Higher SVRs



Full Analysis Set.

SVR in Patients With Hgb <10 g/dL by EPO and/or Ribavirin Dose Reduction



Full Analysis Set.
Note: BOC/PR includes patients pooled from Response-Guided Therapy and BOC/PR48 treatment group.
RBV=ribavirin; DR=dose reduction; EPO=erythropoietin.

Summary of Adverse Events Reported As Anemia†

	All Patients	
	PR N=547 n (%)	BOC/PR N=1548 n (%)
Treatment-Related Adverse Event	158 (29)	756 (49)
Dose Modification (Any Study Drug) Due to AE§	71 (13)	406 (26)
Transfusion	2 (<1)	39 (3)
Serious Adverse Event (AE)‡	1 (<1)	14 (1)
Treatment Discontinuation Due to AE	4 (1)	23 (1)

Key studies: SPRINT-1, SPRINT-2, RESPOND-2.

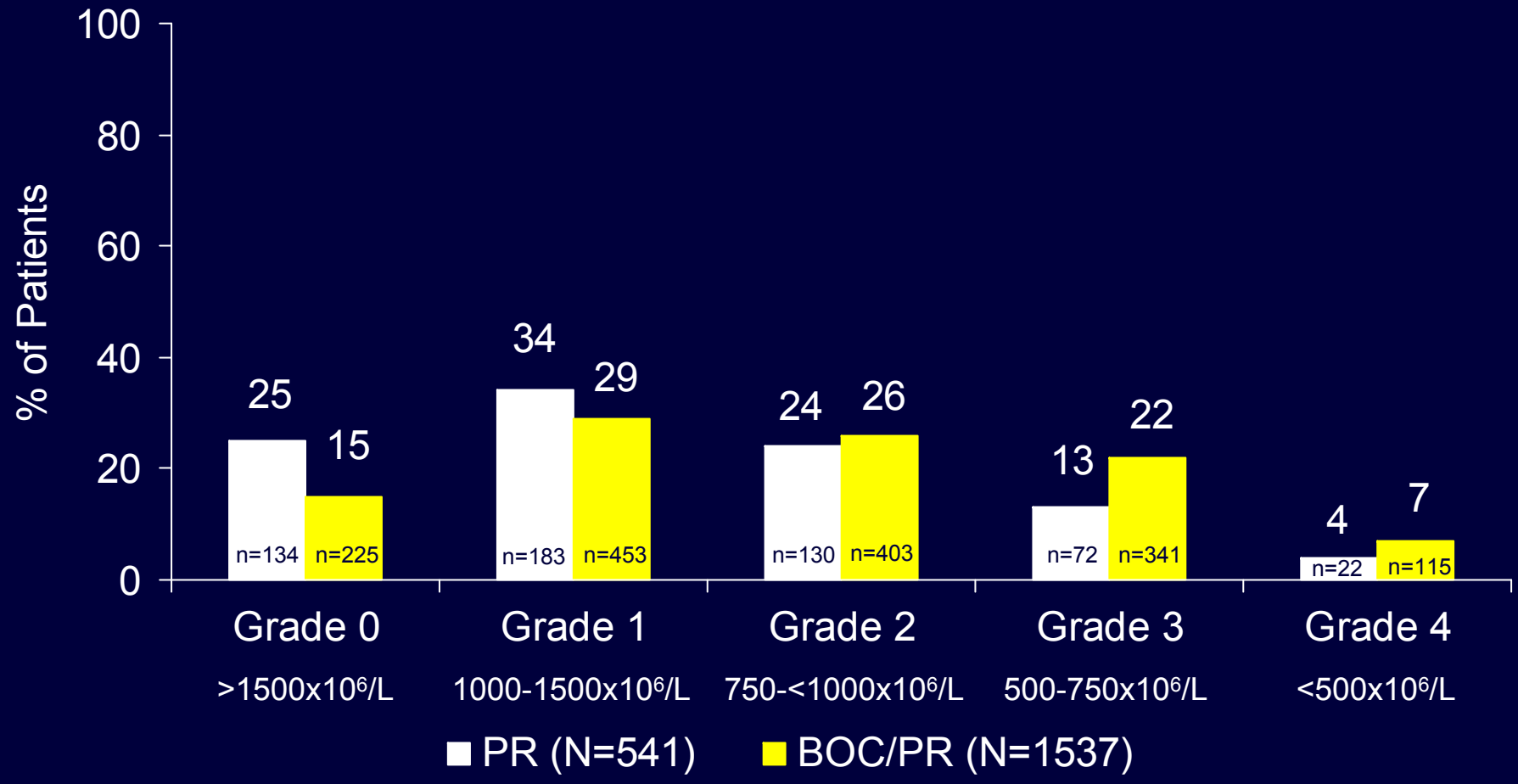
† Table reflects the proportion of patients reporting AEs associated with the preferred terms anemia and hemolytic anemia. Patients may have had more than one adverse event.

‡ Deaths are included in serious AE count.

§ Excludes patients who discontinued due to adverse events.

Nadir Neutrophil Values During Treatment

WHO Classification



Key studies: SPRINT-1, SPRINT-2, RESPOND-2.

WHO=World Health Organization.

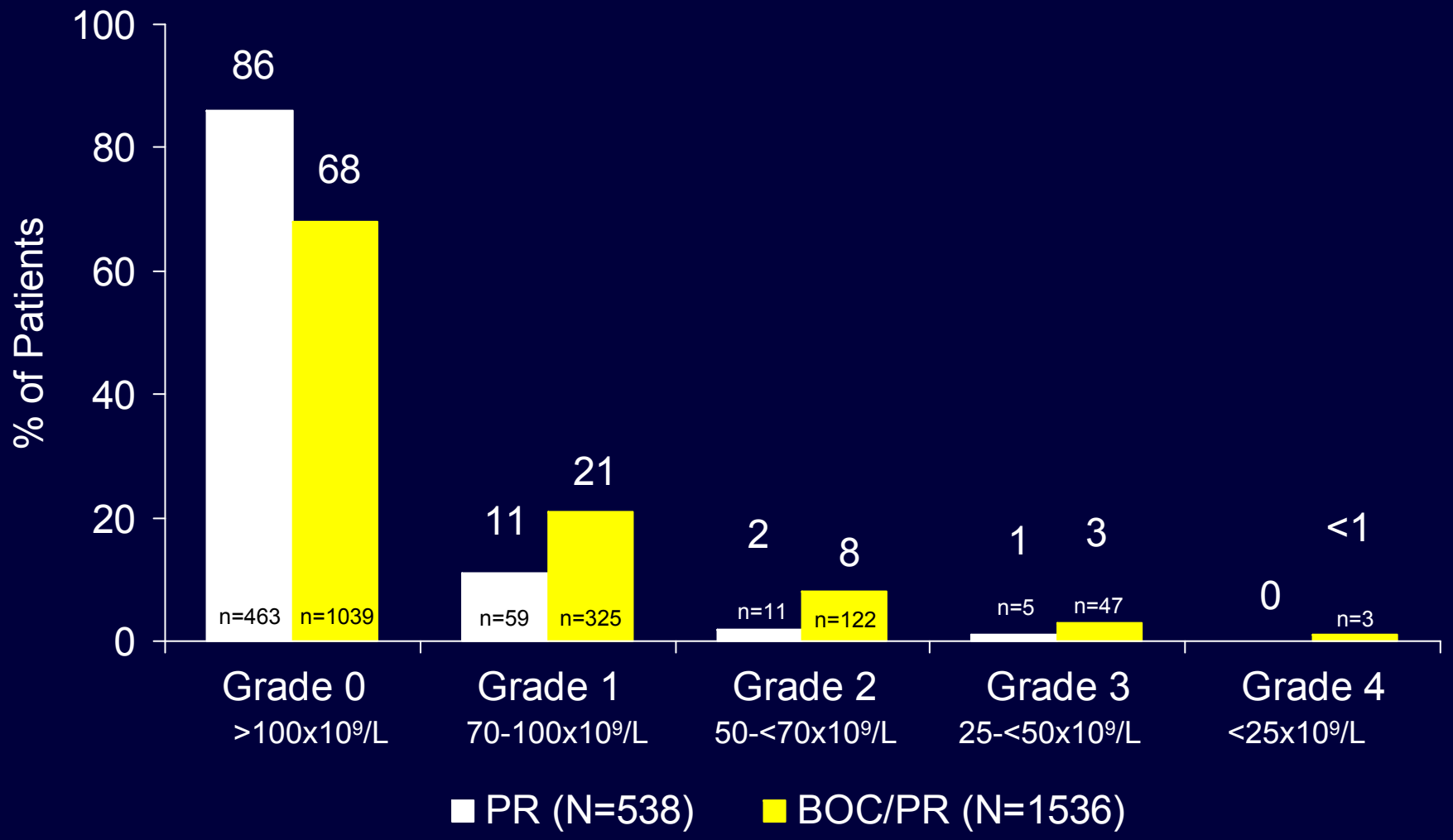
Summary of Adverse Events Reported As Neutropenia

	All Patients	
	PR N=547 n (%)	BOC/PR N=1548 n (%)
Treatment-Related Adverse Event (AE)	96 (18)	350 (23)
Serious AE	0	7 (<1)
G-CSF Use	32 (6)	144 (9)
Dose Modification (Any Study Drug) Due to AE†	46 (8)	208 (13)
Treatment Discontinuation Due to AE	0	11 (1)

Key studies: SPRINT-1, SPRINT-2, RESPOND-2.
† Excludes patients who discontinued due to adverse events.
G-CSF=granulocyte-colony stimulating factor.

Nadir Platelet Values During Treatment

WHO Classification



Key studies: SPRINT-1, SPRINT-2, RESPOND-2.

WHO=World Health Organization.

Dysgeusia in the Key Studies

- Transient/reversible
- Verbatim terms include
  - Metallic taste in mouth
  - Earthy after-taste
  - Bitter taste in mouth
- Rarely required dose modifications (4; <1%)
- Rarely required study drug discontinuation (1/1508; <1%)
- No serious adverse events of dysgeusia
- Associated with increased gastrointestinal symptoms
  - Nausea, vomiting, and diarrhea

Key studies: SPRINT-1, SPRINT-2 and RESPOND-2.

Rash in the Key Studies

- Incidence of rash similar in PR and BOC/PR arms (27% vs. 30%)
- Rash description consistent with ribavirin rash
  - No mucosal involvement
  - No Stevens-Johnson Syndrome or TEN
- Rash not severe
  - 1% dose reduction in both PR and BOC/PR
  - <1% drug discontinuations in both PR and BOC/PR arms
  - 1 serious AE: erythematous rash, no hospitalization
    - Resolved on full dose boceprevir
  - No death

Key studies: SPRINT-1, SPRINT-2 and RESPOND-2.
TEN=toxic epiderrnal necrolysis.

Boceprevir Safety by Demographic Group

- Difference between boceprevir and PR Arms examined by
  - Age
  - Gender
  - Race
  - BMI
  - Comorbid conditions (cirrhosis, diabetes, hypertension, psychiatric disorders, IVDU)
- Increased incidence of anemia on boceprevir
  - Elderly > younger
  - Females > males
  - Cirrhotics > non-cirrhotics
- Increase incidence of thrombocytopenia on boceprevir in cirrhotics

IVDU=intravenous drug use.

Response-Guided Therapy Provides Safety Advantages

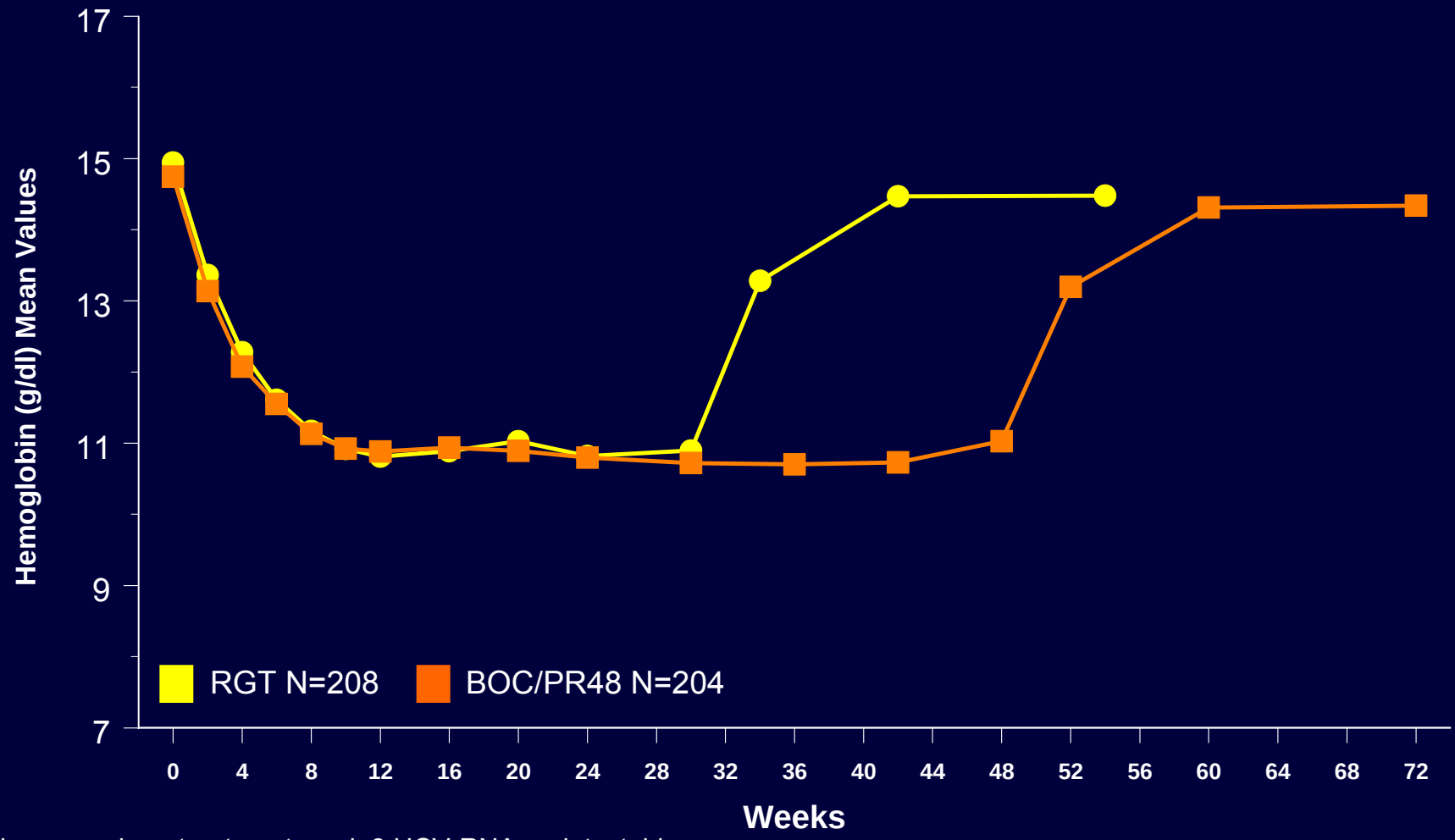
- Response-guided therapy designed to limit drug exposure
  - RGT vs. BOC/PR48 Arm
- Anticipated to reduce:
  - Discontinuations due to AEs
  - Duration of AEs

SPRINT-2: RGT Safety Advantages Early Responders - RGT vs. BOC/PR48

- Mean BOC/PR exposure reduced 37%
- Mean erythropoietin exposure reduced 46%
- Similar rate of serious AEs: 10% vs. 11%
- Fewer study drug discontinuations: 9% vs. 17%
- Severe anemia (<8 g/dL) reduced: 1% vs. 5%
- Weeks of depression (moderate/severe) reduced:
  - 16 wks vs. 30 weeks

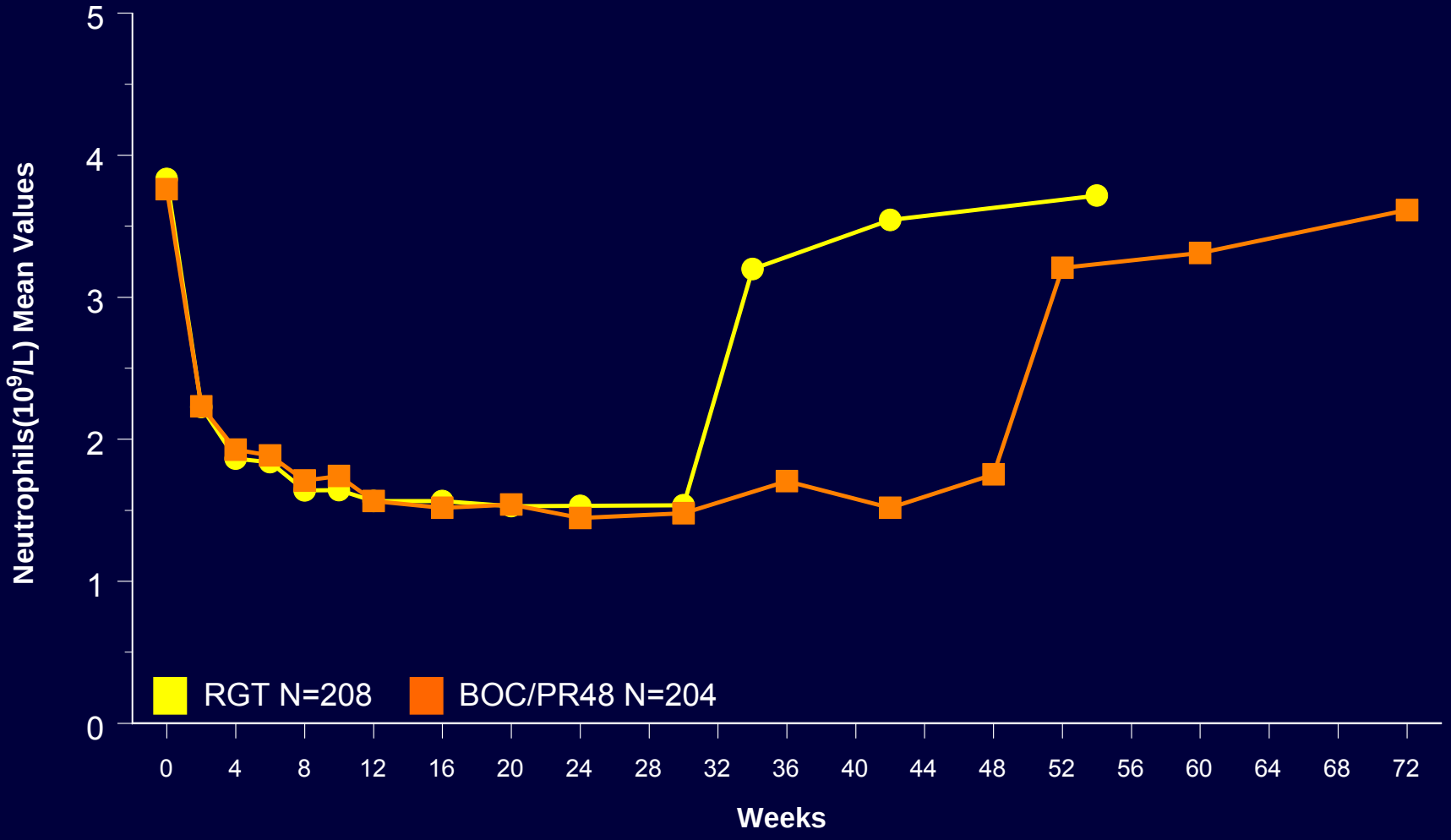
HCV-RNA treatment week 8 undetectable.
RGT=response-guided therapy; BOC/PR48=boceprevir/peginterferon α-2b + ribavirin 48 weeks.

SPRINT-2: RGT Safety Advantages
Early Responders - RGT vs. BOC/PR48
Changes in Hemoglobin Over Time



Early responders=treatment week 8 HCV-RNA undetectable.
RGT=response-guided therapy; BOC/PR48=boceprevir/peginterferon α-2b + ribavirin 48 weeks.

SPRINT-2: RGT Safety Advantages
Early Responders - RGT vs. BOC/PR48
Changes in Neutrophil Counts Over Time



† Early responders=treatment week 8 HCV-RNA undetectable.

Resistance and Safety

- Resistance
- Clinical Safety
  - Common Adverse Events
  - Adverse Events of Special Interest
- Clinical Pharmacology
- Benefit/Risk Conclusion

Boceprevir Absorption, Metabolism, Excretion

- Absorption
  - Rapidly absorbed: median T_{max} ~2 hrs
  - Less than dose proportional increases in steady state exposure
  - No accumulation
  - Food increases exposure ~40% - 60%
- Metabolism & Excretion
  - Extensively metabolized by two distinct pathways
    - Aldo keto reductase (AKR)
    - CYP3A4/5
  - Mean plasma $t_{½}$ of ~3.4 hours
  - Primary route of excretion is hepatic/fecal
- Boceprevir: strong reversible CYP3A4 inhibitor
  - Not a CYP450 isoenzyme inducer

Drug-Drug Interactions: Boceprevir As Victim

	Co-administered Drug	Mean AUC(τ) Ratio†
AKR inhibitors	Ibuprofen	1.04 ↔
	Diflunisal	0.96 ↔
CYP3A4/P-gp inhibitors	Ketoconazole	2.31 ↑
	Ritonavir	0.81 ↔
	Clarithromycin‡	1.21 ↔
CYP3A4 inducers	Efavirenz	0.81 ↔
Other	Tenofovir	1.08 ↔
	Peginterferon α-2b	1.00 ↔
	Ribavirin	~0.92 ↔

† Ratio estimate of boceprevir PK parameters (in combination vs. alone);
↓ = ratio estimate <0.8; ↔ = ratio estimate ≥0.8 and ≤1.25; ↑ = ratio estimate >1.25.
‡ In presence of diflunisal, compared with boceprevir + diflunisal.
AKR=aldo keto reductase; P-gp=P-glycoprotein; AUC=area under the curve.

Drug-Drug Interactions: Boceprevir As Perpetrator

	Co-administered Drug	Mean AUC(τ) Ratio†
CYP3A4 substrates	Midazolam	5.30 ↑
Other	Drospirenone/ Ethinyl estradiol	1.99 ↑ 0.76 ↓
	Efavirenz	1.20 ↔
	Tenofovir	1.05 ↔
	Peginterferon α-2b	0.99 ↔
	Ribavirin‡	~1.02 ↔

Phase 3 sub-analyses: similar safety profile when CYP3A4 substrates (e.g., benzodiazepines) or inhibitors (e.g., azoles) administered with boceprevir

† Ratio estimate of concomitant drug PK parameters (in combination with Boceprevir vs. alone); ↓ = ratio estimate <0.8; ↔ = ratio estimate ≥0.8 and ≤1.25; ↑ = ratio estimate >1.25.
AUC=area under the curve.

Special Populations

- No dose adjustment required for patients with:
  - Hepatic impairment
    - Mild, moderate, severe
  - Renal insufficiency
    - Including end stage renal disease
  - Different demographic factors
    - Including race (e.g., Asian) and gender

Cardiac Conduction

- Thorough QT study
  - Randomized, placebo- and active-controlled, evaluator-blind, four-way crossover
  - Multiple doses of 800 mg TID and 1200 mg TID
- Boceprevir had no clinically relevant effects on cardiac conduction
- Study validated with positive control (moxifloxacin)

Safety Conclusions

- Boceprevir added to SOC is safe and generally well tolerated
  - Treatment duration not limited by toxicity
- Safety profile largely reflects the safety profile of peginterferon and ribavirin
  - Exceptions:
    - Incremental increase in hematologic effects and dysgeusia
- No dose adjustment of boceprevir required for DDIs or special populations, including hepatic impaired
- RGT leads to decreased duration of exposure to all 3 study drugs for many patients

SOC=standard-of-care; DDI=drug-drug interaction.

Benefit/Risk Conclusion

Keith Gottesdiener, MD

Resistance and Safety

- Resistance
- Clinical Safety
  - Common Adverse Events
  - Adverse Events of Special Interest
- Clinical Pharmacology
- Benefit/Risk Conclusion

Demonstrated Benefits

- Meets the urgent need for more effective treatment for chronic HCV genotype 1 infection
- Boceprevir plus standard-of-care therapy markedly improves SVR rates
  - Treatment-naïve: ~2x increase in SVR
  - Previous treatment failure: 3x increase in SVR
  - Decrease in relapse rate
  - Consistent benefit across all subpopulations including Blacks and patients with hepatic fibrosis
- RGT decreases drug exposure in almost 50% of patients
- Durability of SVR has been shown for more than 2 years

SVR=sustained virologic response.

Clinical Safety

- Extensive safety database
  - 2095 patients treated in Key Studies
- Safety profile largely reflects standard-of-care PR therapy
- Boceprevir added to SOC is safe and generally well tolerated
  - Low discontinuation rates due to AEs
- AEs monitorable, manageable, and reversible
  - Consistent with current practice
- Safety demonstrated for up to 44 weeks of treatment
  - No toxicities that limit treatment duration

AE=adverse event; PR=peginterferon α-2b + ribavirin; SOC=standard-of-care.

Risks

- Incremental increase in anemia beyond that associated with standard-of-care
  - Anemia manageable with same tools used with SOC therapy: ribavirin dose reduction and/or EPO
- Inhibitor of CYP3A4
  - CYP3A4 substrates with narrow therapeutic index should be avoided
- Contraindicated in pregnancy due to use with ribavirin
- Resistance associated amino acid variants
  - Clinical implications unknown

SOC=standard-of-care; EPO=erythropoietin.

Early Futility Rules

- SPRINT-2 designed with TW24 futility rule
  - Patients with detectable HCV RNA discontinued
- Post-hoc evaluation of alternative futility rules conducted by the sponsor, with these goals:
  - Preserve SVR for patients who might achieve SVR
  - Stop therapy in patients unlikely to achieve SVR
  - Harmonize futility rules to reduce complexity
- Proposal for early futility rule:
  - Discontinue therapy if patient has HCV RNA levels:
    - >100 IU/mL at TW12
    - Detectable at TW24
  - Similar rule for both Naïve and Treatment Failure patients

Favorable Benefit/Risk for RGT

Early Responders Have High SVR

SVR	Treatment-Naïve	Treatment Failure
Overall BOC/PR (FAS)	63-66%	59-66%
Early Responders		
RGT	96%	89%
BOC/PR48	96%	97%

Incremental Benefit
Decreased exposure to PR
↓ duration of AEs, less severe anemia

Incremental Risk
Patients with cirrhosis
may need 44 weeks of boceprevir treatment

RGT=response-guided therapy; SVR=sustained virologic response; FAS=full analysis set; BOC/PR48=boceprevir/peginterferon α-2b + ribavirin 48 weeks; PR=peginterferon α-2b + ribavirin.

Dosage and Administration

- Initial 4 weeks peginterferon alpha and ribavirin
- Add boceprevir 800 mg TID (every 7- 9 hours)
- Response-guided therapy is the optimal regimen

	Treatment-Naive	Treatment Failure	
	All patients	Relapser/Partial Responder	Null Responder†
Early Responder	PR4/ BOC + PR24	PR4/ BOC + PR32	PR4/ BOC+PR44
Late Responder	PR4/ BOC + PR32/PR12	PR4/ BOC + PR32/PR12	

- Cirrhotics to receive PR4/BOC+PR44

† If approved for an indication; historical null responder (previous treatment failure at TW12 <2 log decline).
TW = Treatment Week; BOC=boceprevir; PR=peginterferon/ribavirin.

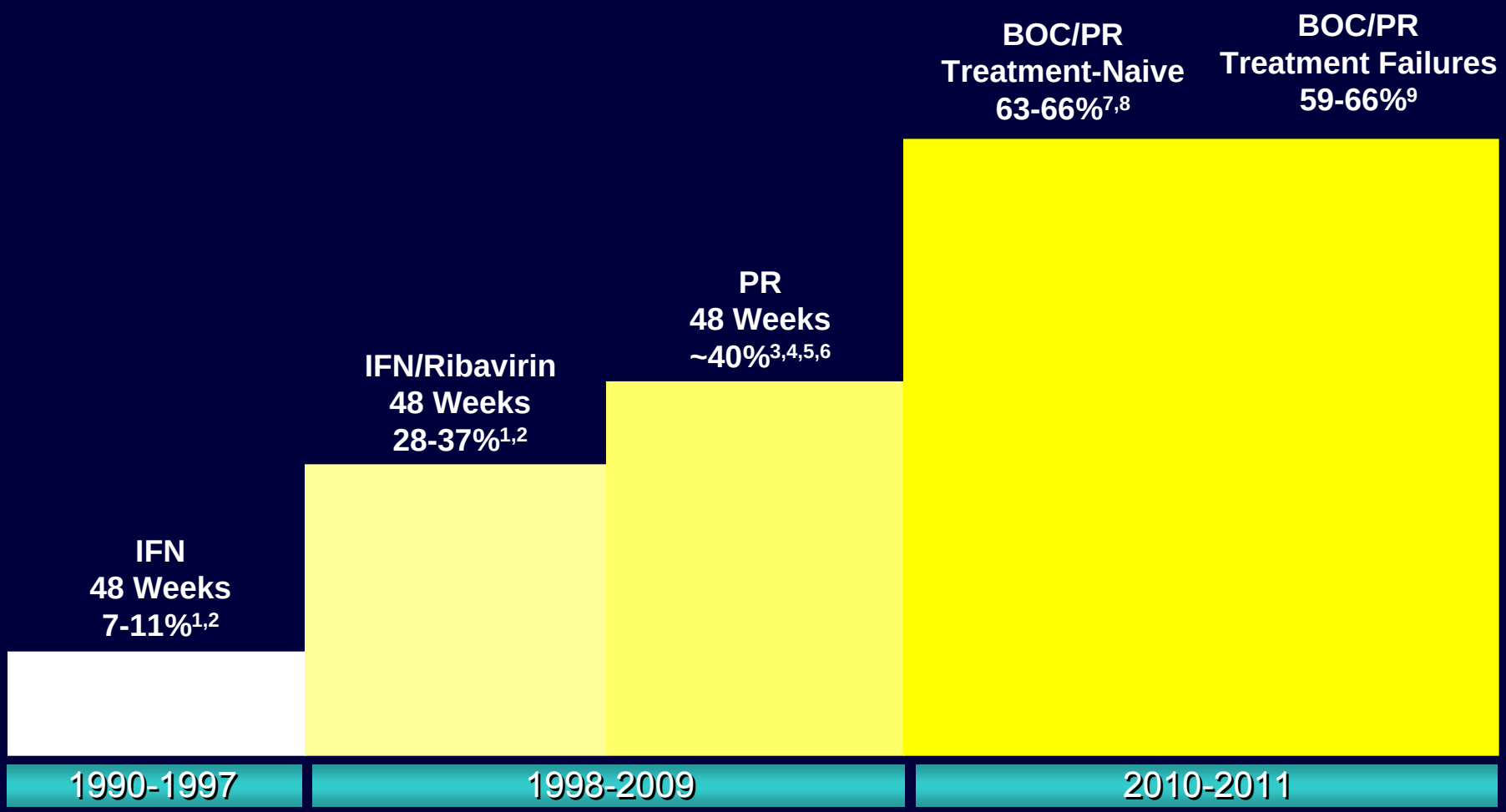
Overall Boceprevir Benefit/Risk

Data indicate that benefits of Boceprevir outweigh the risks and support the proposed indication:

Boceprevir is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients with compensated liver disease

- *Previously untreated patients*
- *Patients who have failed previous therapy*

Progress in Treating Chronic HCV Genotype 1



[1]McHutchison, NEJM (339) 1998; [2]Poynard, Lancet (352) 1998; [3]Manns, Lancet (358), 2001; [4]Lindsay, Hepatology (34) 2001; [5]Fried, NEJM (347), 2002; [6]McHutchison, NEJM (361) 2009; [7]Kwo, Lancet (376) 2010; [8]Poordad, NEJM (364) 2011; [9]Bacon, NEJM (364) 2011.

HCV=hepatitis C virus; IFN=interferon; PR=peginterferon α-2b + ribavirin; BOC/PR48=boceprevir/PR.