

Learning Objectives

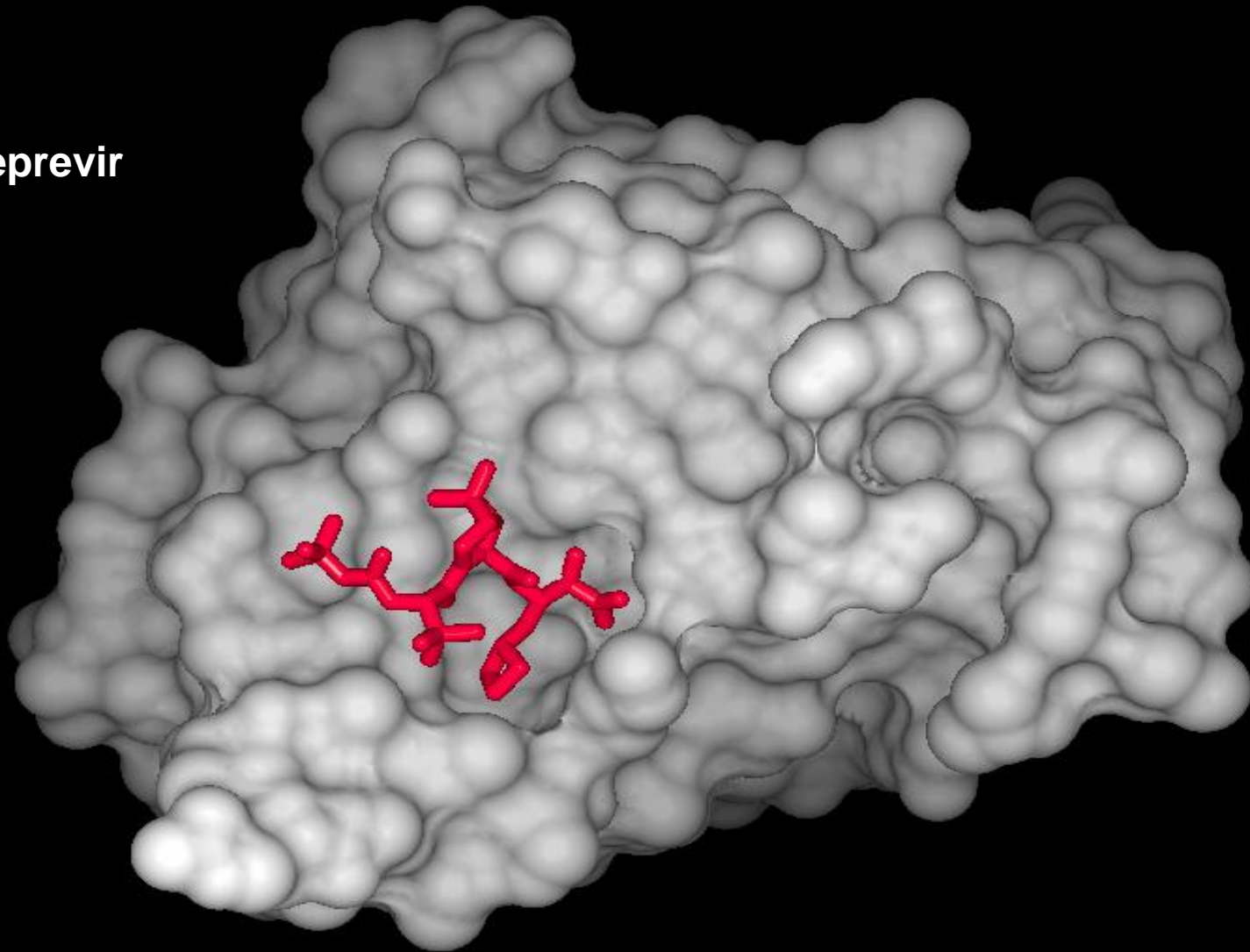
1. Review current therapy with protease inhibitors for chronic hepatitis C.
2. Appreciate nuances of current-generation treatment (predictors of response, complexity of regimens, drug-drug interactions, resistance).
3. Understand limitations of current-generation antiviral therapy.

Assumptions

1. This audience is well acquainted with these data.
2. Some of the basics have already been covered (predictors, AE profiles, IL28B, resistance, stopping rules).
3. This will be an eclectic review based on huge data sets.

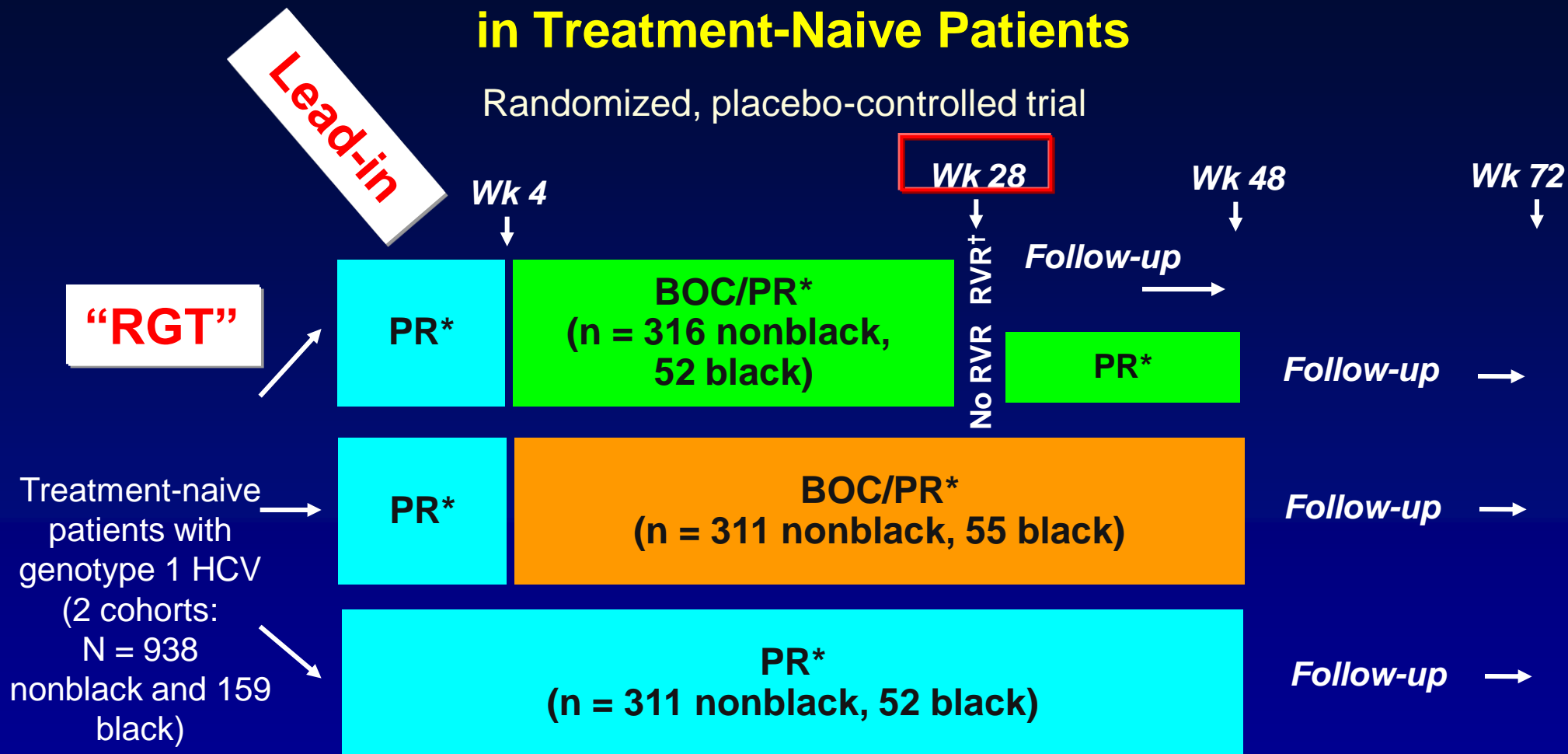
NS3/4A Protease Inhibitors

Boceprevir



Phase III SPRINT-2: BOC + PEG IFN/RBV in Treatment-Naive Patients

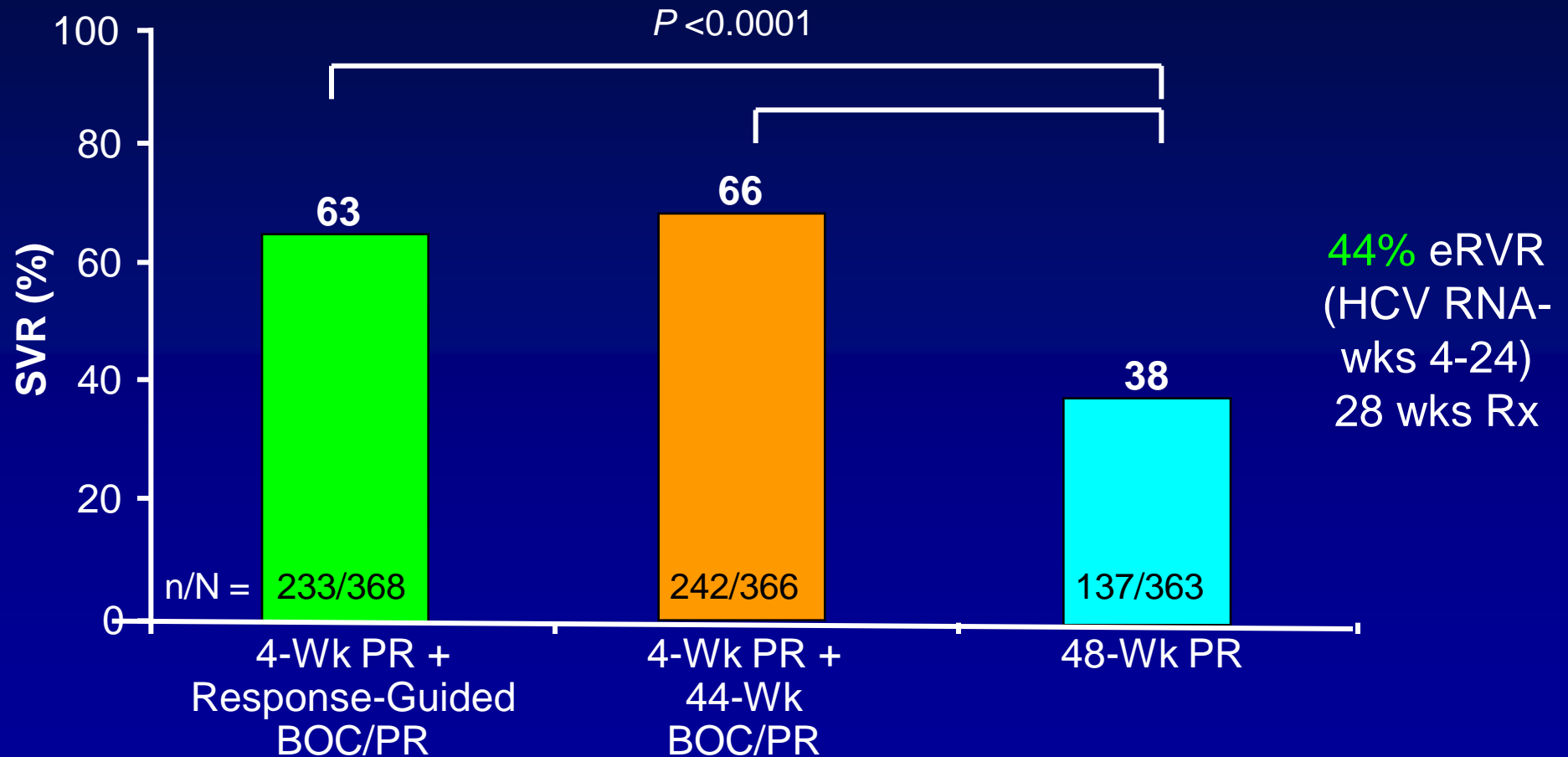
Randomized, placebo-controlled trial



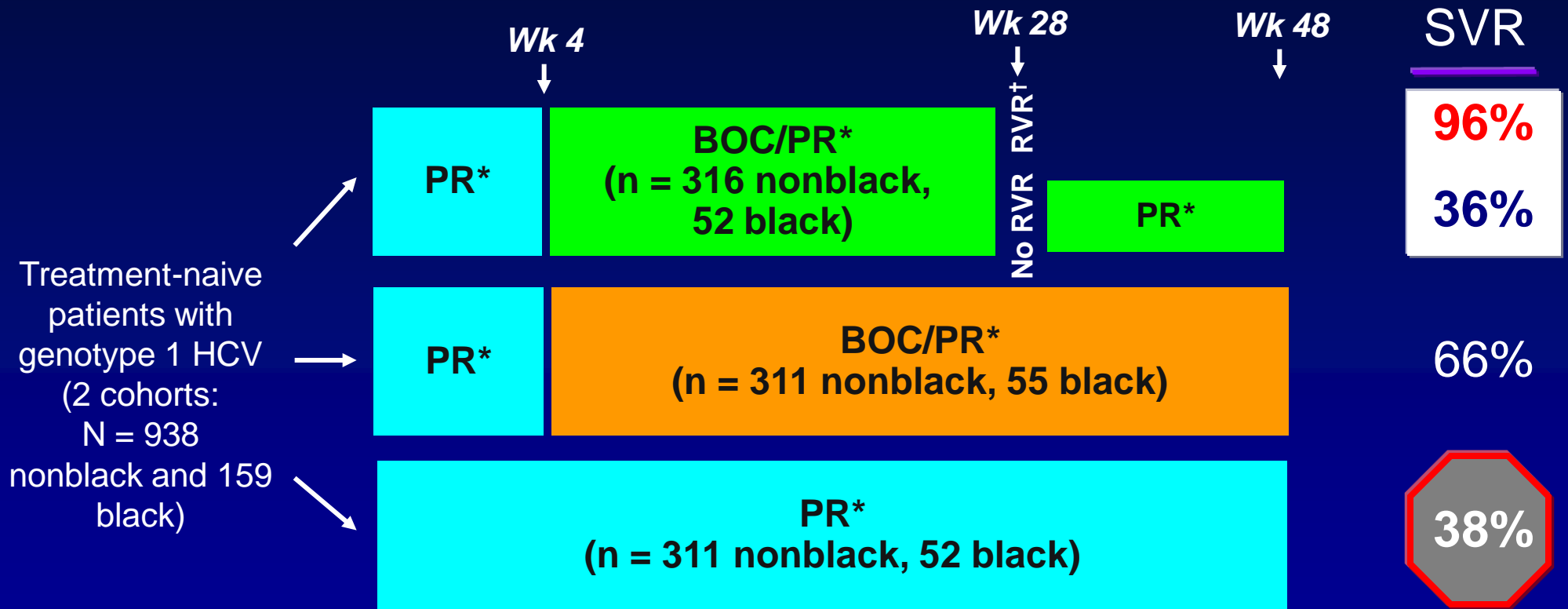
*BOC 800 mg q8h; PEG IFN alfa-2b 1.5 µg/kg/wk; weight-based RBV 600-1400 mg/day

†Undetectable HCV RNA at Wk 4 of BOC treatment (Week 8) and at all subsequent assays

SPRINT-2: SVR



Phase III SPRINT-2: BOC + PEG IFN/RBV in Treatment-Naive Patients



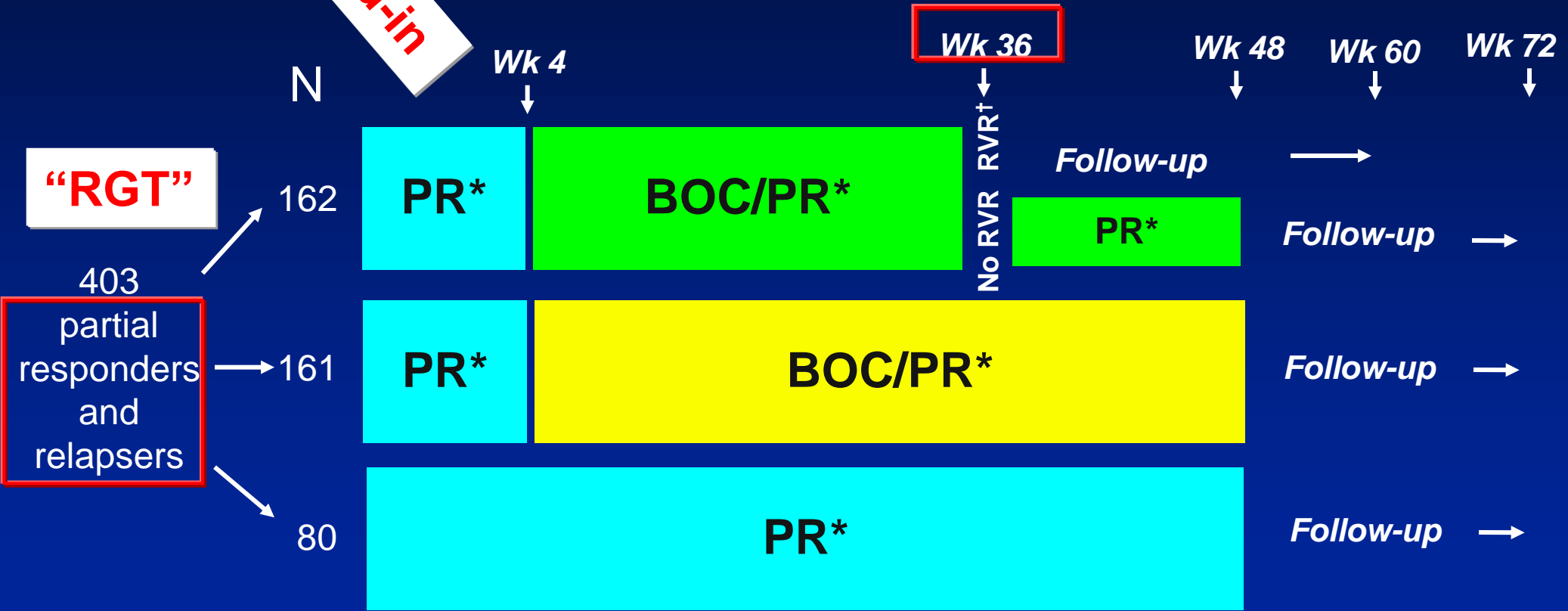
*BOC 800 mg q8h; PEG IFN alfa-2b 1.5 µg/kg/wk; weight-based RBV 600-1400 mg/day

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Phase III RESPOND-2: BOC + PEG IFN/RBV in Treatment-Experienced Patients

Randomized, placebo-controlled trial

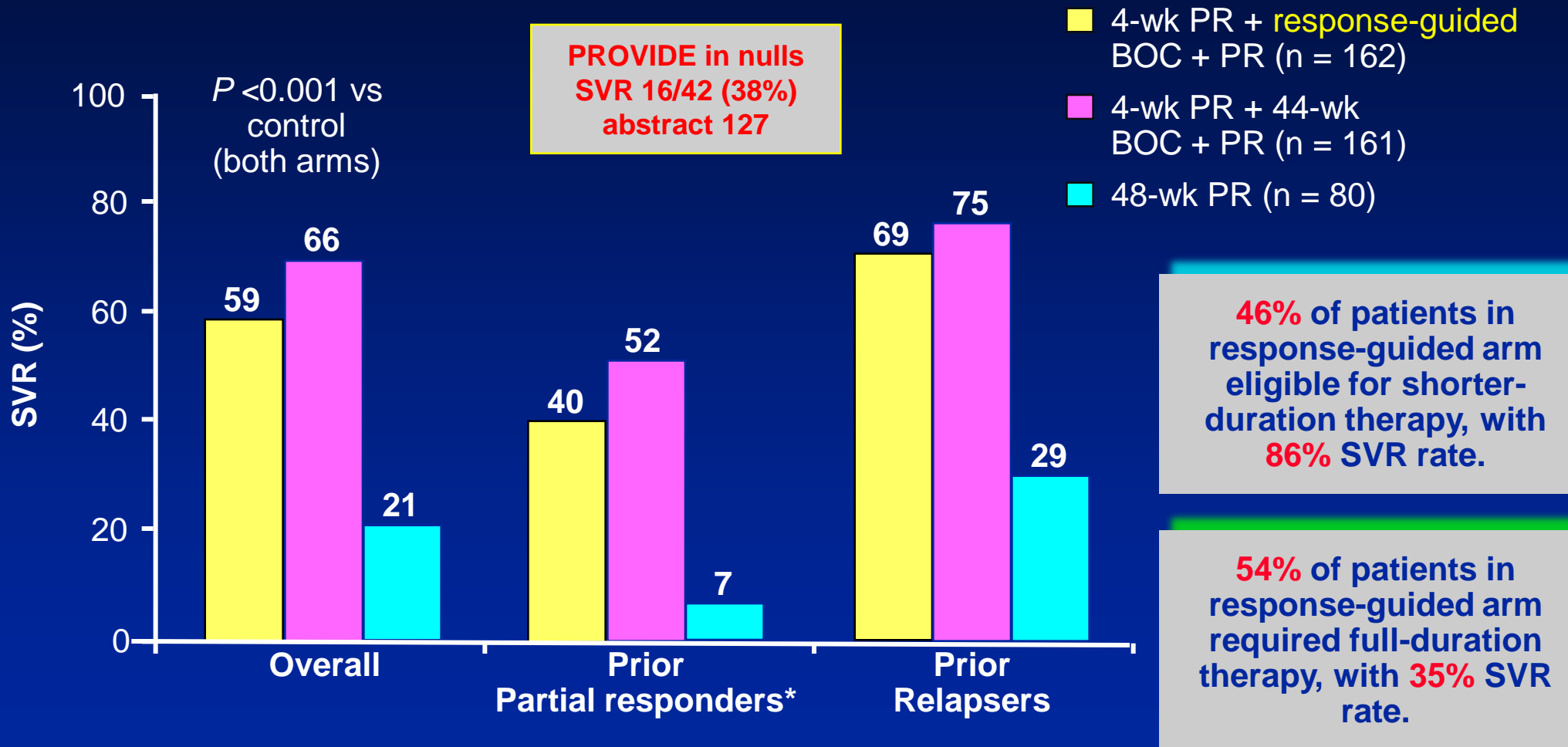
Lead-in



*BOC 800 mg q8h; PEG IFN alfa-2b 1.5 µg/kg/wk; weight-based RBV 600-1400 mg/day

†Undetectable HCV RNA at Wk 4 of BOC treatment (Week 8) and at all subsequent assays

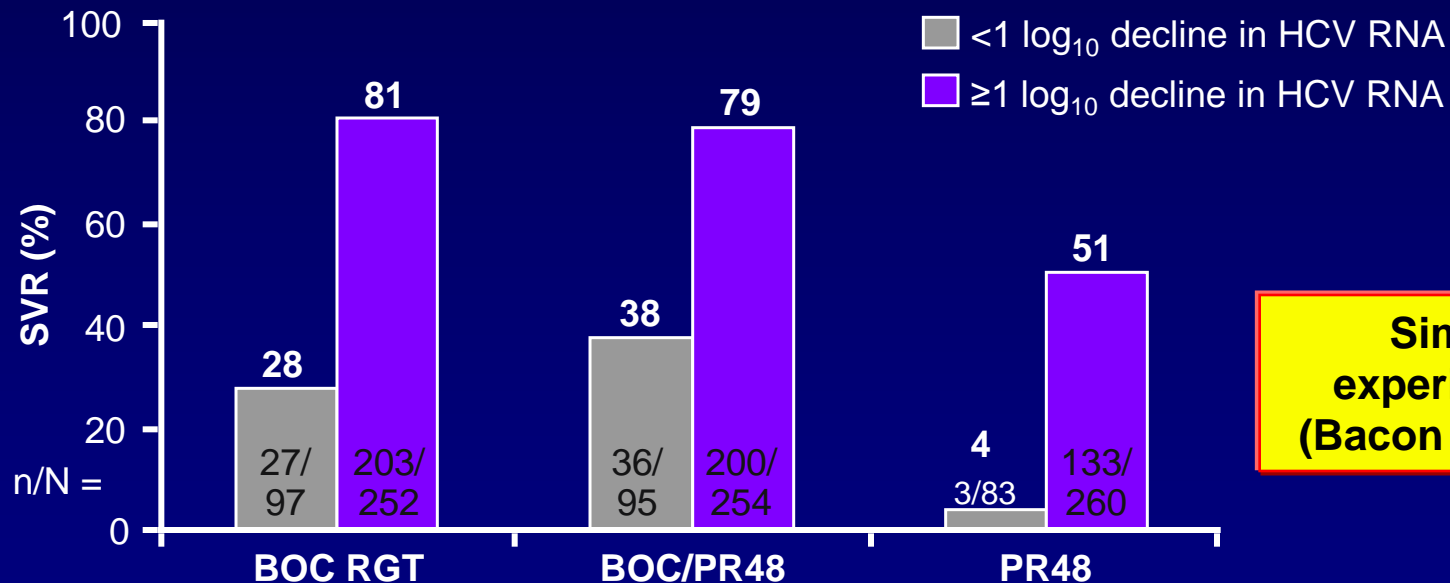
RESPOND-2: SVR Rates According to Treatment Arm and Prior Response



SPRINT-2: Response to 4-Wk PEG IFN/RBV Lead-in

4-wk PR lead-in response = strongest predictor of SVR in multivariate analysis (OR: 9.0; $P < 0.001$).

When 4-wk lead-in included in model, *IL28B* no longer significantly predictive of SVR.

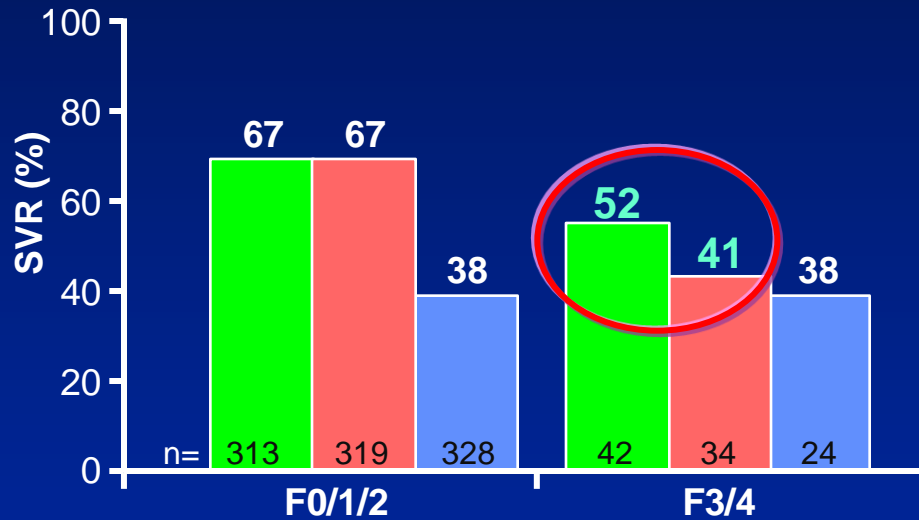


Similar for experienced pts (Bacon NEJM 2011)

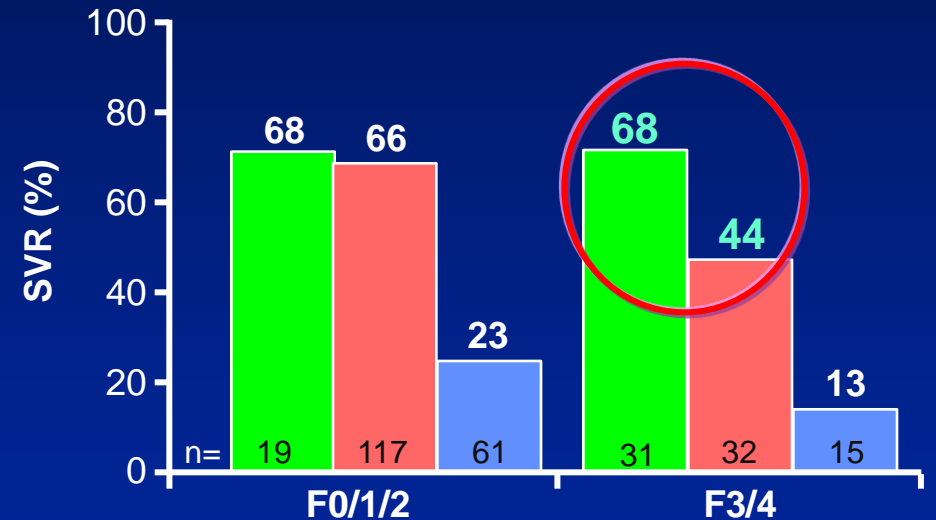
Subanalysis of Phase III Boceprevir Trials: SVR in Advanced Fibrosis/Cirrhosis

- BOC 48
- BOC RGT (triple 24/32)
- PEG/RBV 48

SPRINT-2: treatment-naive



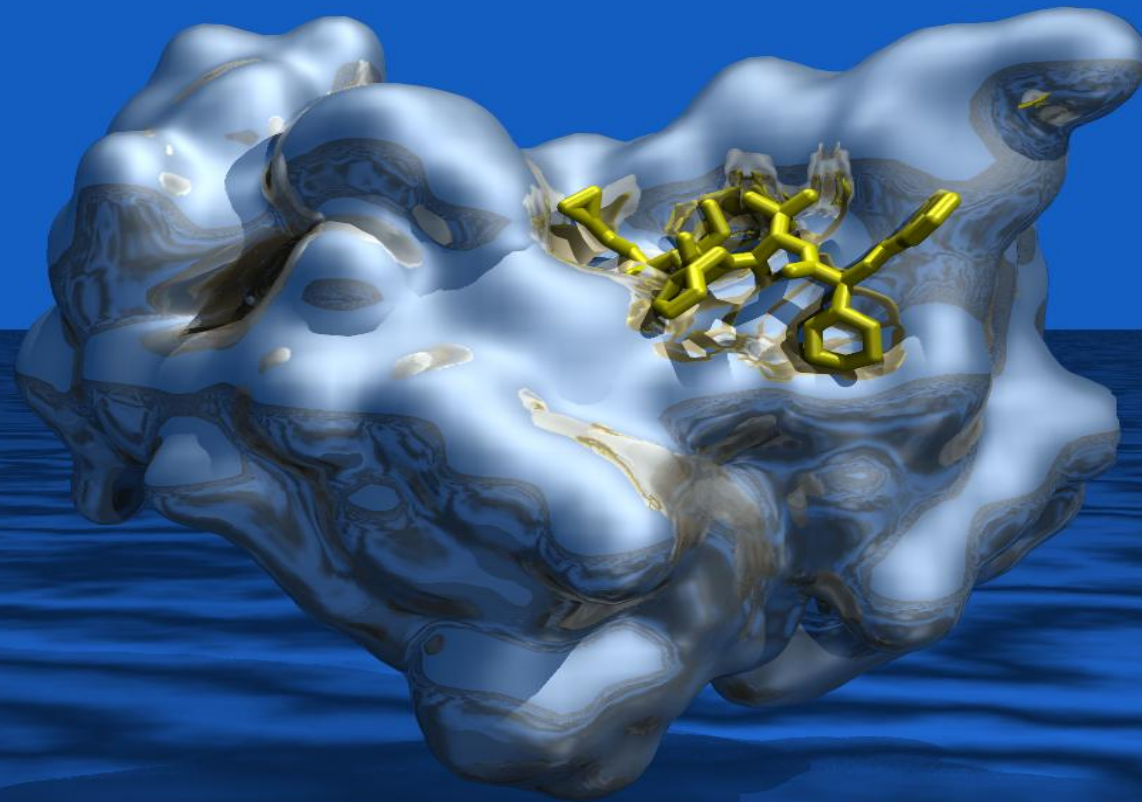
RESPOND-2: relapsers, partial responders



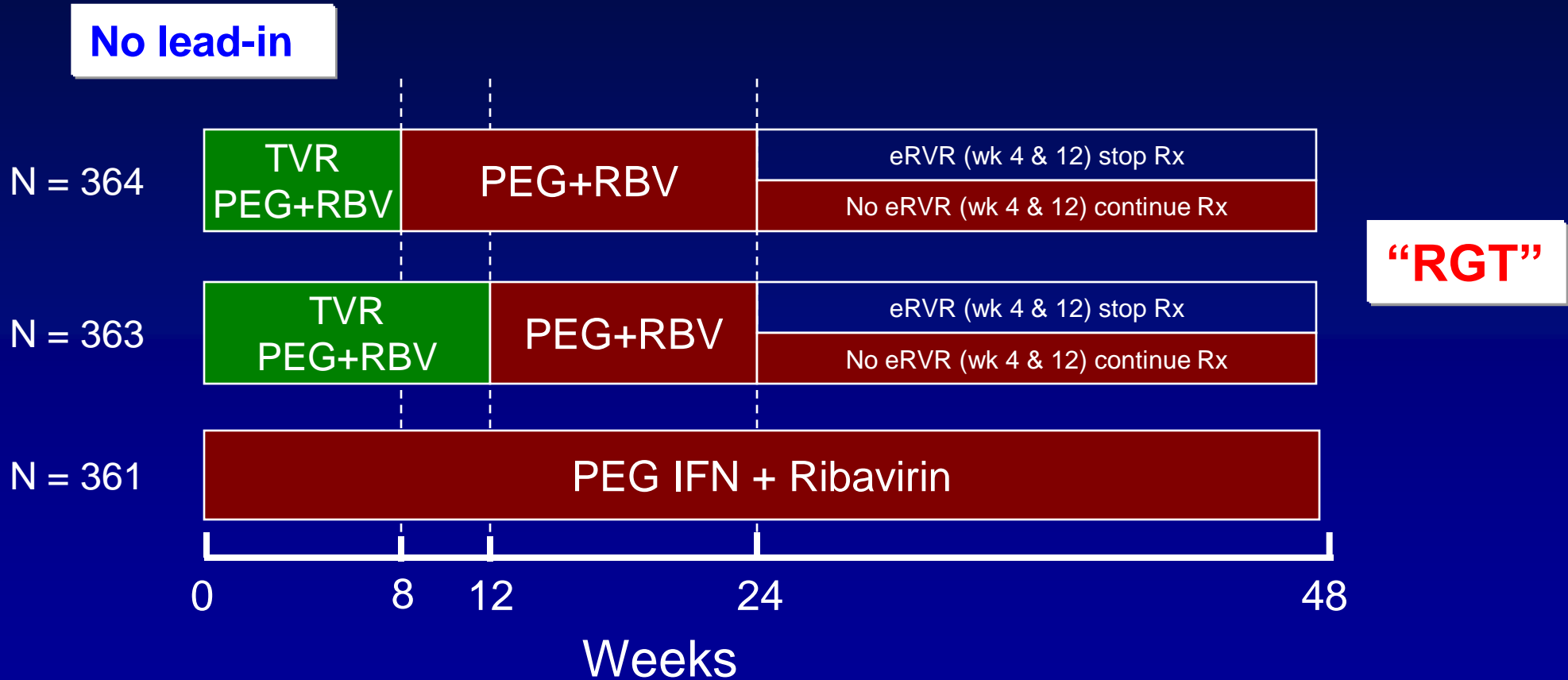
Patients with F3/4 did better with full yr of therapy vs response-guided therapy.

NS3/4A Protease Inhibitors

Telaprevir (VX-950)



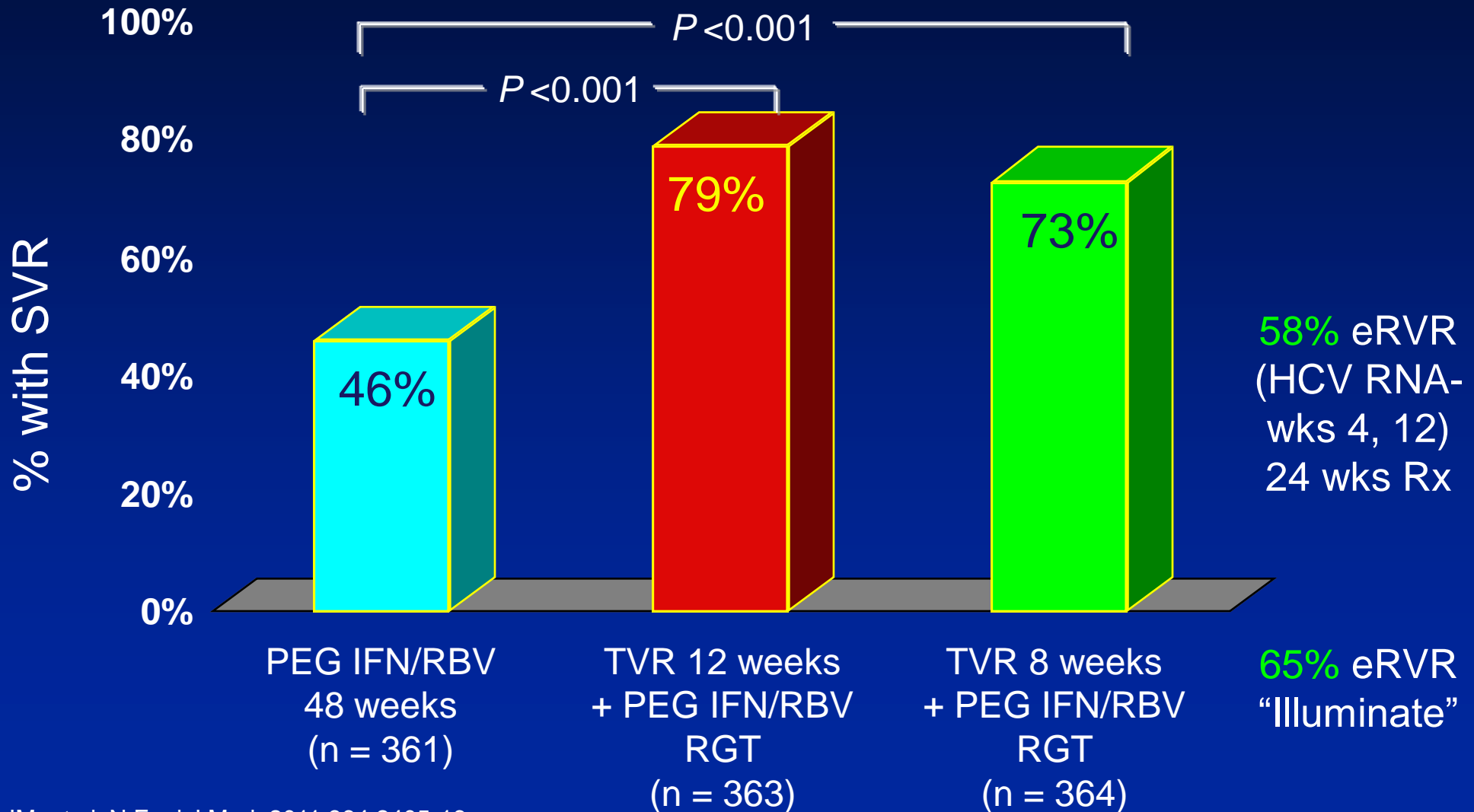
Telaprevir - “ADVANCE” Phase-III Trial in Rx-Naïve Subjects with Chronic Hepatitis C (Genotype 1)



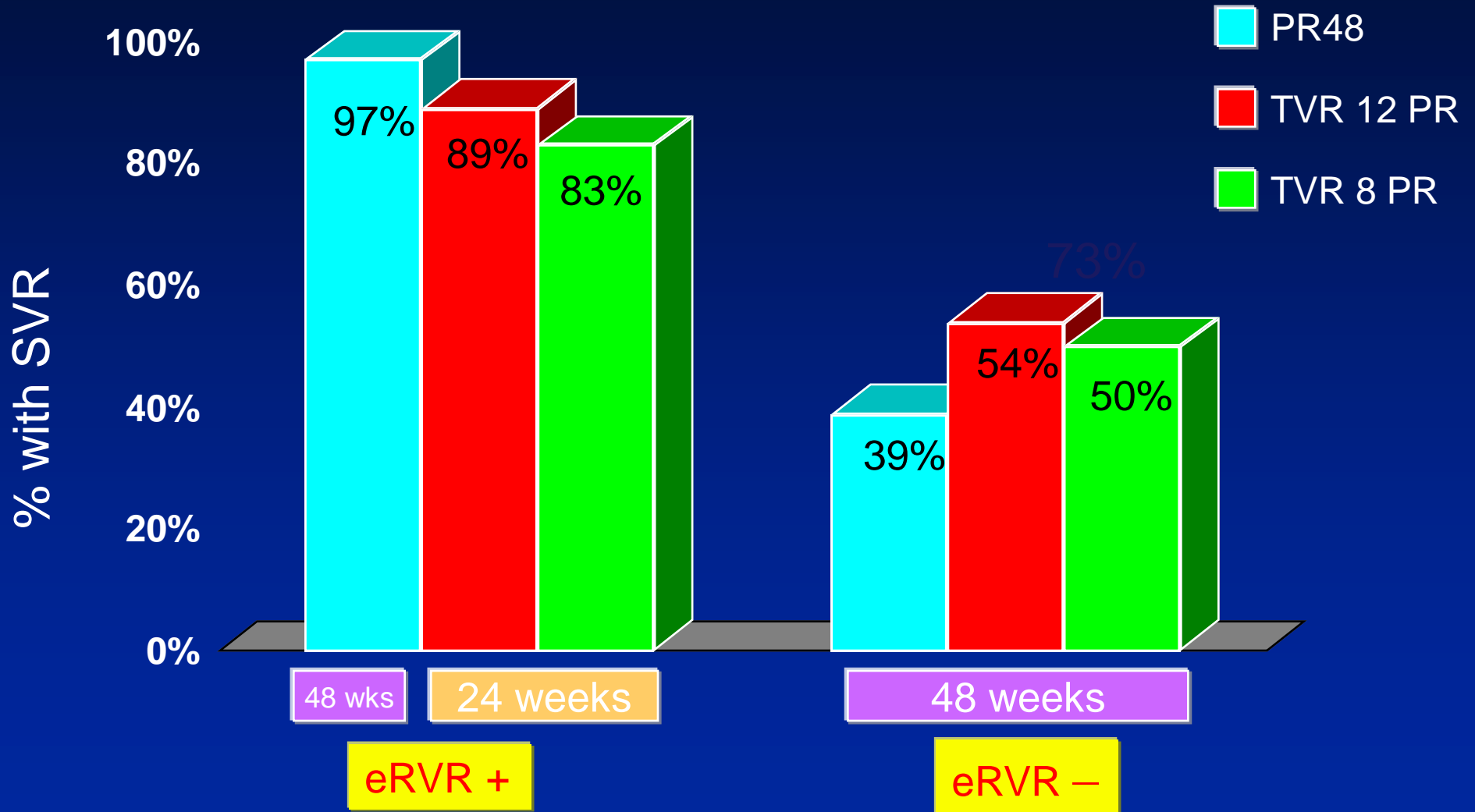
eRVR = lower level of detection
HCV RNA <10 IU/ml

Telaprevir - "ADVANCE"

Phase-III Trial in Rx-Naïve Subjects with Chronic Hepatitis C (Genotype 1)



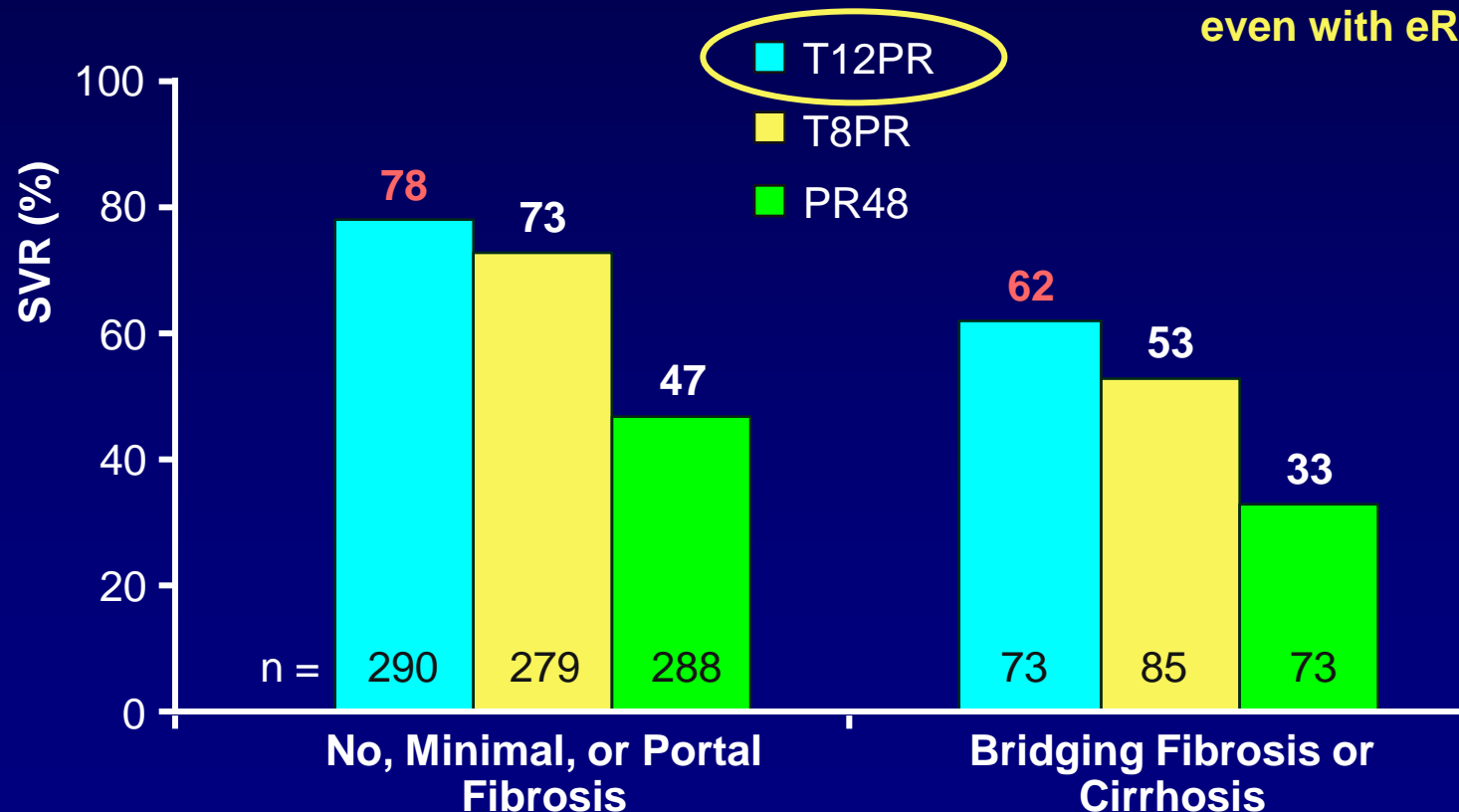
Telaprevir - "ADVANCE" Phase-III Trial in Rx-Naïve Subjects With Chronic Hepatitis C (Genotype 1)



ADVANCE: SVR to Telaprevir-Based Rx According to Fibrosis/Cirrhosis

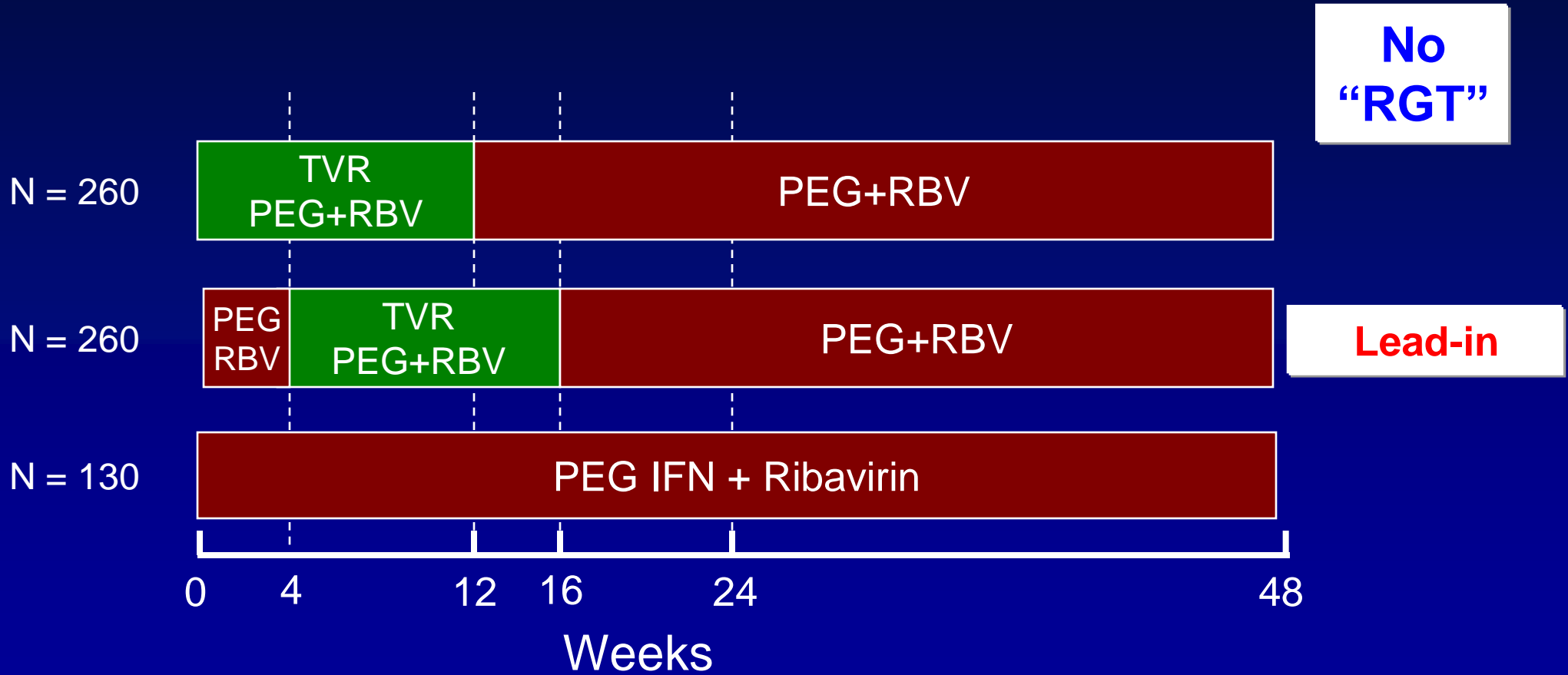
Treatment naive

Cirrhotic patients may benefit from 48-week T12PR (not RGT), even with eRVR.

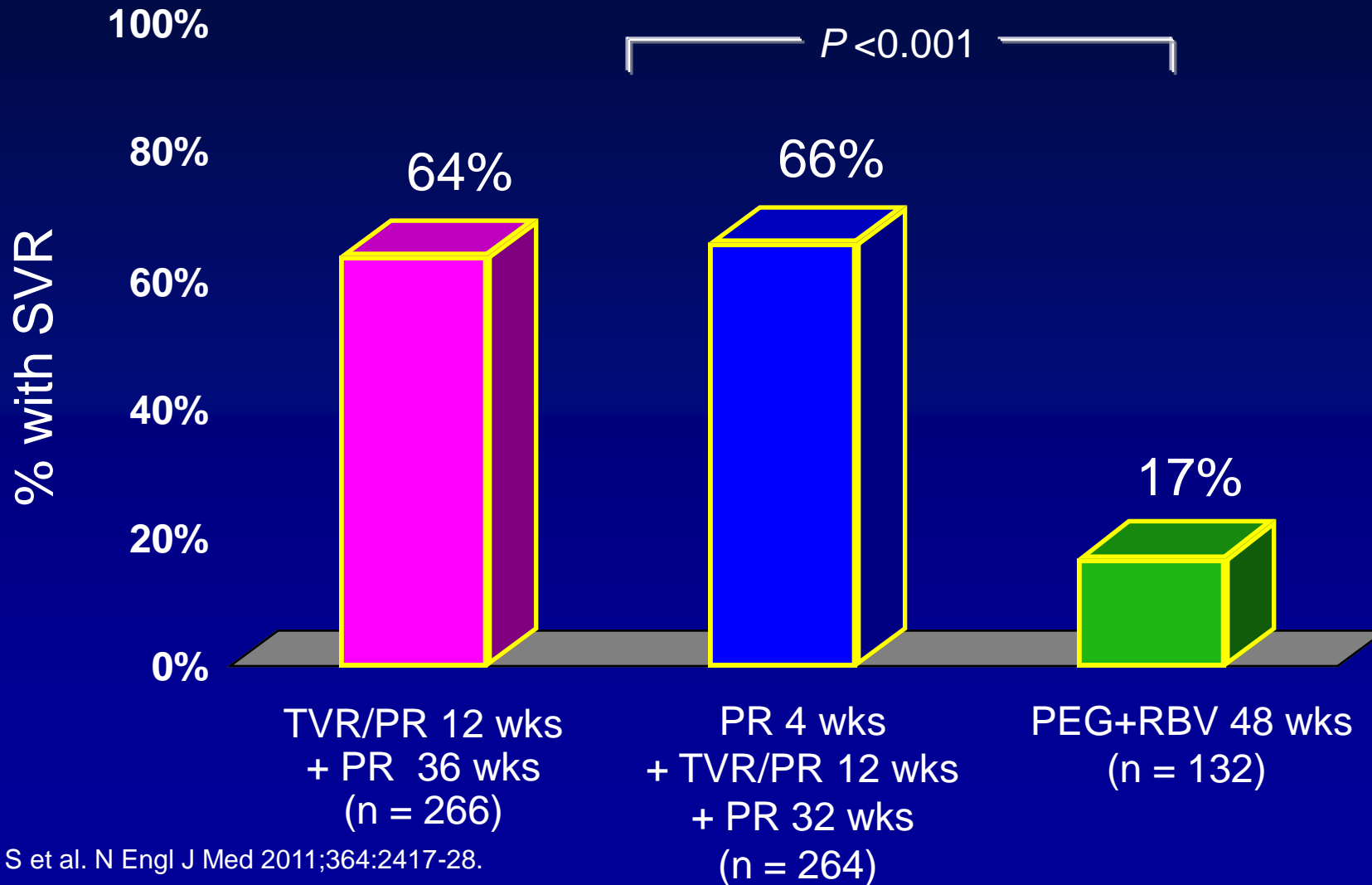


Telaprevir - "REALIZE"

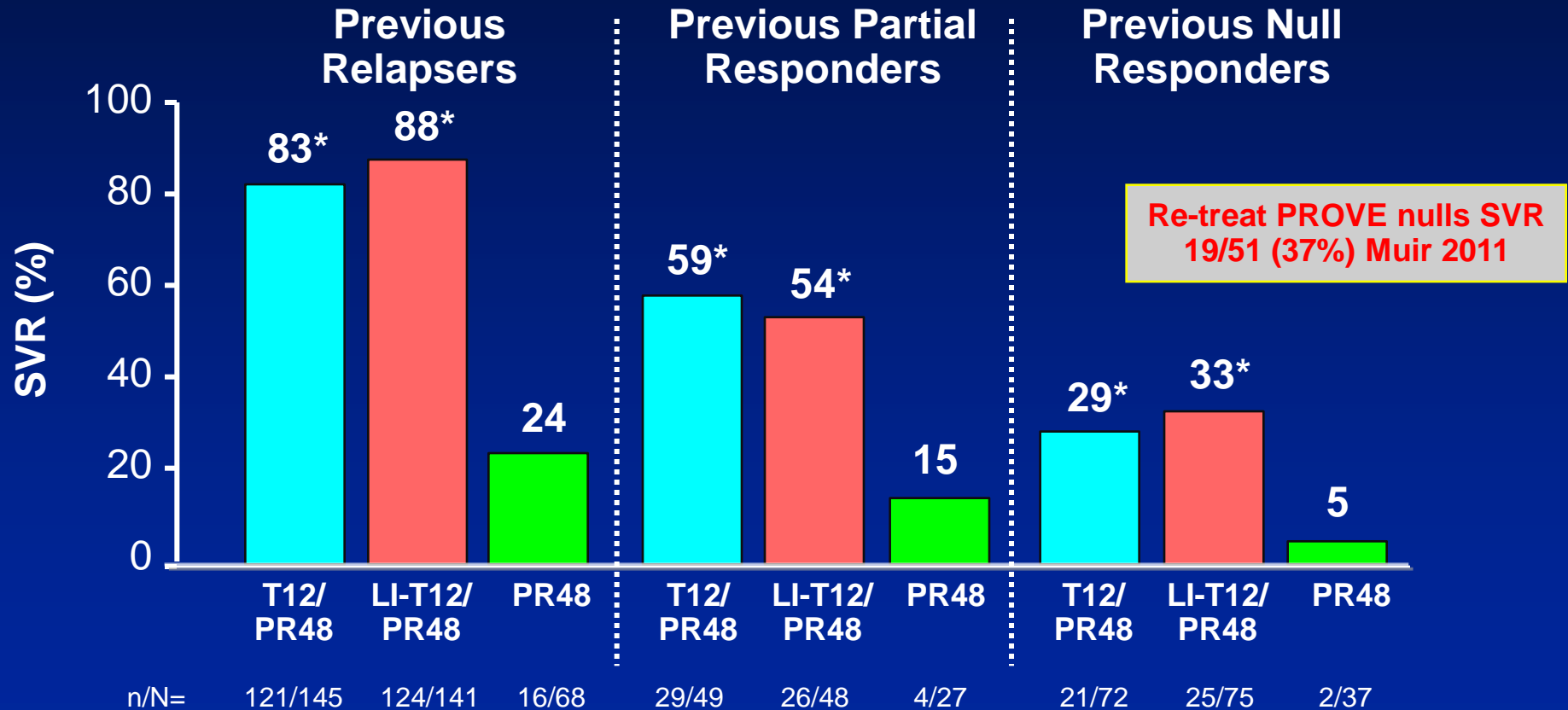
Phase-III Trial in 632 Rx-Experienced Subjects with Chronic Hepatitis C (Genotype 1)



Telaprevir “REALIZE” Nonresponder Retreatment



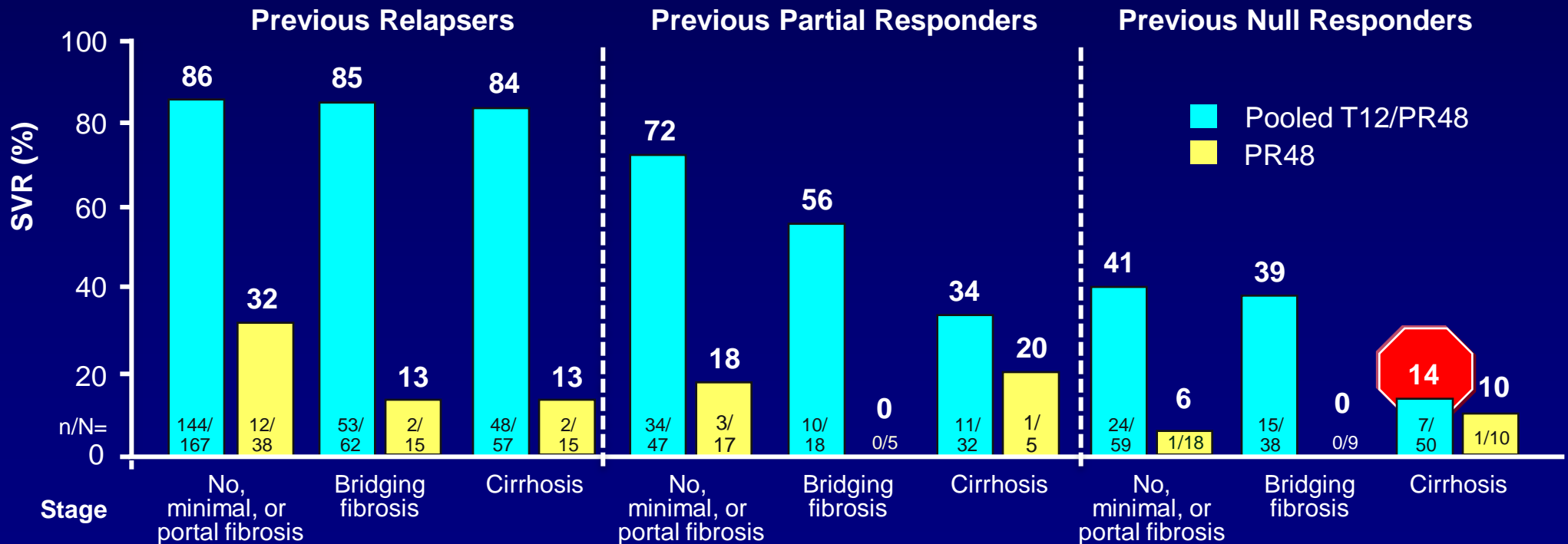
REALIZE: SVR According to Previous Response



* $P < 0.001$ vs PR48
LI, lead-in.

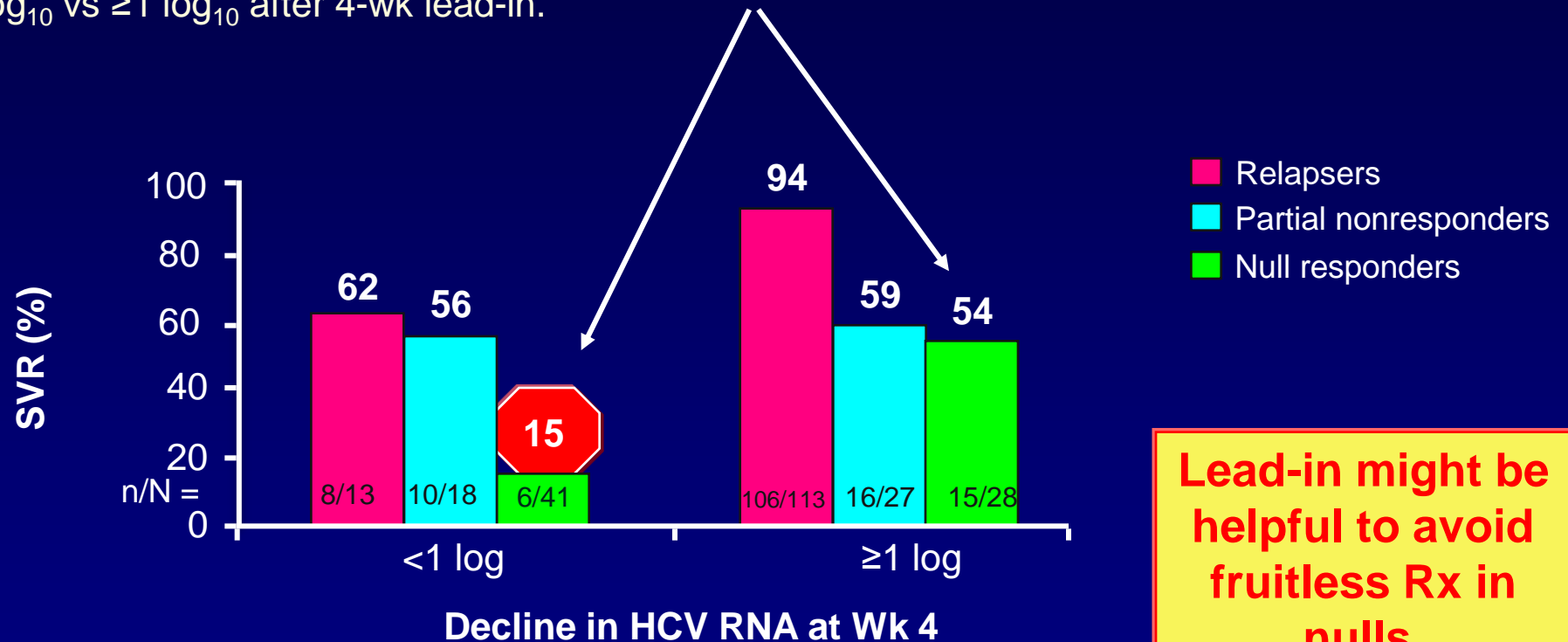
REALIZE: Treatment-Experienced Patients With Advanced Fibrosis or Cirrhosis

- Previous relapsers (independent of fibrosis stage) had high SVR rates following treatment with telaprevir + PEG IFN/RBV.
- For previous null responders with cirrhosis, SVR rates similar to PEG IFN/RBV alone.



REALIZE: Lead-in vs Previous Response Category as Predictors of Response to TVR

- Previous response category a stronger predictor of SVR than response to lead-in.
- Previous null responders, however, had a >3-fold lower likelihood of SVR if HCV RNA decreased by $<1\log_{10}$ vs $\geq 1\log_{10}$ after 4-wk lead-in.



Advantages of TVR and BOC in Naïve Pts

Parameter	TVR ^[1]	BOC ^[2]
PR lead-in	No	Yes: 4 wks
PEG IFN alfa	2a	2b
PI dosing requirements	TID* with fatty meal	TID with food
PI pills daily	6 (2 x 375 mg)	12 (4 x 200 mg)
Wholesale cost (not incl PEG/RBV)	\$49,200	\$1,100/wk (\$26,400-\$48,400)
Duration of PI triple therapy	12 wks followed by 12-36 wks PR	24-32 (44 in cirrhotics) wks after 4 wks PR lead-in
Qualification for shortened therapy (response guided)	eRVR (Wk 4 and 12)	RVR (Wk 8 of Rx = Wk 4 BOC; then Wk 24)
Qualified for shortened therapy, %	58-65 (24 wks)	44 (28 wks)
SVR (vs PR), % SVR in eRVR-neg, %	73-79 (46) 54%	63-66 (38) 36%
Relapse, %	9	9
Drug-drug interactions	12 wks	24-36 wks (up to 44 in cirrhotics)
Adverse events more frequent in PI arms	Rash , anemia, pruritus, nausea	Anemia , dysgeusia

^[1] Jacobson IM, et al. NEJM 2011;364:2405-16. ^[2] Poordad F, et al. NEJM 2011;364:1195-206.

*potential for BID

Comparisons of TVR and BOC in Experienced Pts

Parameter	TVR ^[1]	BOC ^[2]
Duration of PI triple therapy, relapsers	12 wks followed by 12-36 wks PR	4 wks PR lead-in 32 wks B/P/R ± 12 PR (eRVR-neg) [44 wks triple in cirrhotics]
Duration of PI triple therapy, partial/null responders	12 wks followed by 36 wks PR (no RGT)	4 wks PR lead-in 32 wks B/P/R ± 12 PR (eRVR-neg) [44 wks triple in cirrhotics and nulls]
Qualification for shortened therapy (RGT)	NA (relapsers eRVR)	eRVR (Wk 8 of Rx = Wk 4 BOC; then Wk 24)
SVR relapsers, % (vs PR)	83-88 (24)	69-75 (29)
Relapsers qualified for shortened therapy, %	NA	~46*
SVR partial responders, % (vs PR)	54-59 (15)	40-52 (7)
Partial responders qualified for shortened therapy, %	NA	~46*
SVR null responders, % (vs PR)	31-37 (5)	38

*for relapsers and partial responders combined

^[1] Zeuzem S et al. N Engl J Med 2011;364:2417-28.

^[2] Bacon BR et al. NEJM 2011; 364:1207-17.

Other Limitations of PI-Based Therapy

- ◆ Contraindications (e.g., IFN intolerance, pregnancy, decompensated cirrhosis)
- ◆ Genotype-specific, subtype 1b > 1a
- ◆ Limited data—HIV, transplantation
- ◆ Drug-drug interactions
- ◆ Tolerability issues (worse adverse event profile)
- ◆ Especially poor tolerability in cirrhotic experienced pts (SAEs 40-57%, abstract 46)
- ◆ Complexity of regimens and strict stopping rules
- ◆ Barriers to adherence
- ◆ Potential for resistance

Take Home Points

- TVR and BOC nearly double SVR in naïve pts; improve outcome in treatment-experienced pts (6-fold increase SVR for prior nulls).
- Fibrosis stage, IL28B, ethnicity, GT1 subtype, and especially early response are predictors of SVR.
- Response-guided therapy permits truncation of treatment in 44-65% of Rx-naïve and 46% (BOC) of treatment-experienced pts. (recommended for treatment-naïve pts and relapsers).
- Full-course Rx preferred for cirrhotics (except relapsers?), null responders, slow responders.
- Tolerability issues: TVR - rash, pruritus; BOC - anemia
- Drug-drug interactions, pill burden, complex regimens complicate therapy.
- Protease inhibitors select for resistant variants (revert eventually in most).
- It's a great start, but the best is yet to come.