Triple therapy : who and how

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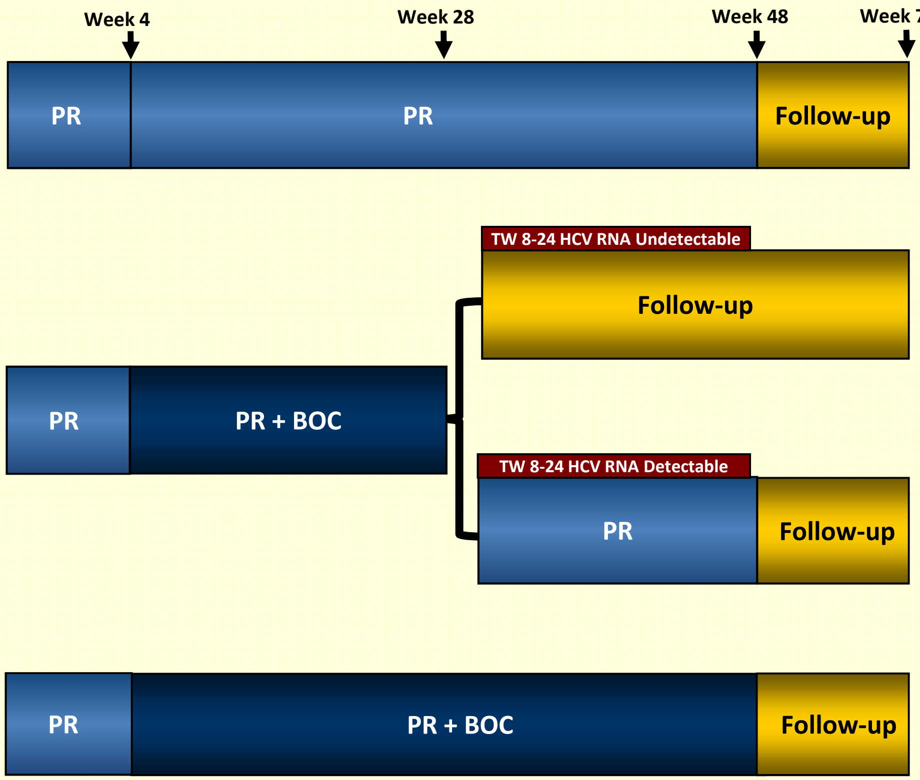
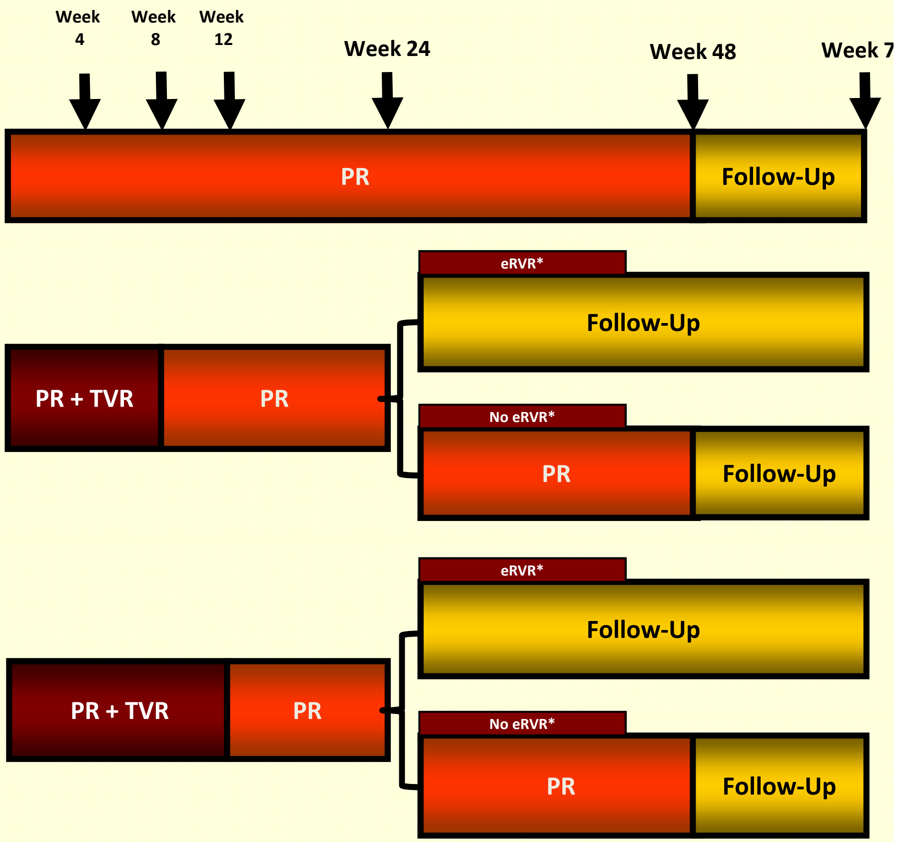
Two ideas of triple therapy

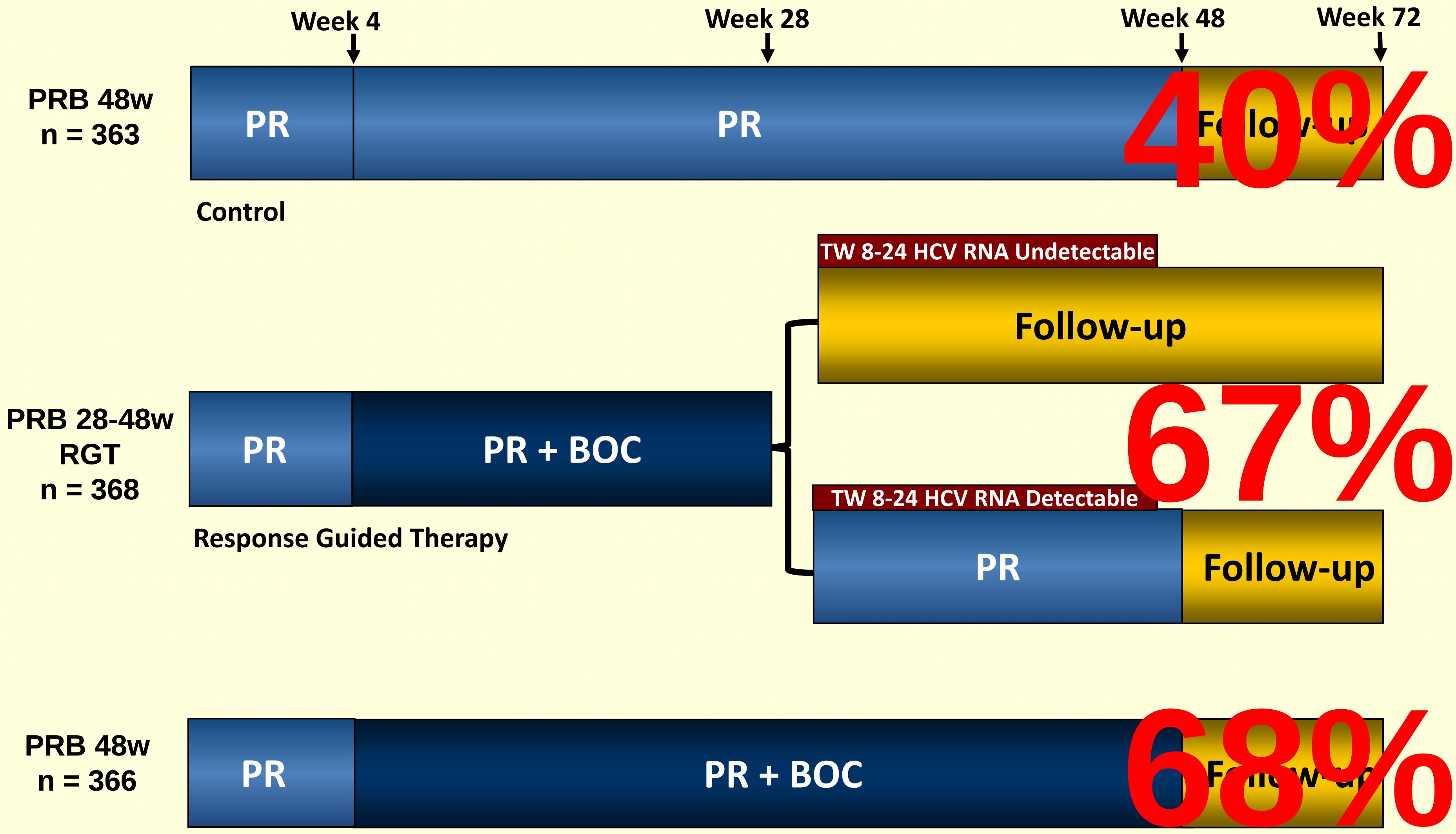
- lead-in → triple from 4 week
- PegIFN+RBV → low resistance risk
- triple therapy for 24 or 44 weeks

- triple from the begining
- triple therapy for 8 or 12 weeks
- strong suppression → low resistance risk





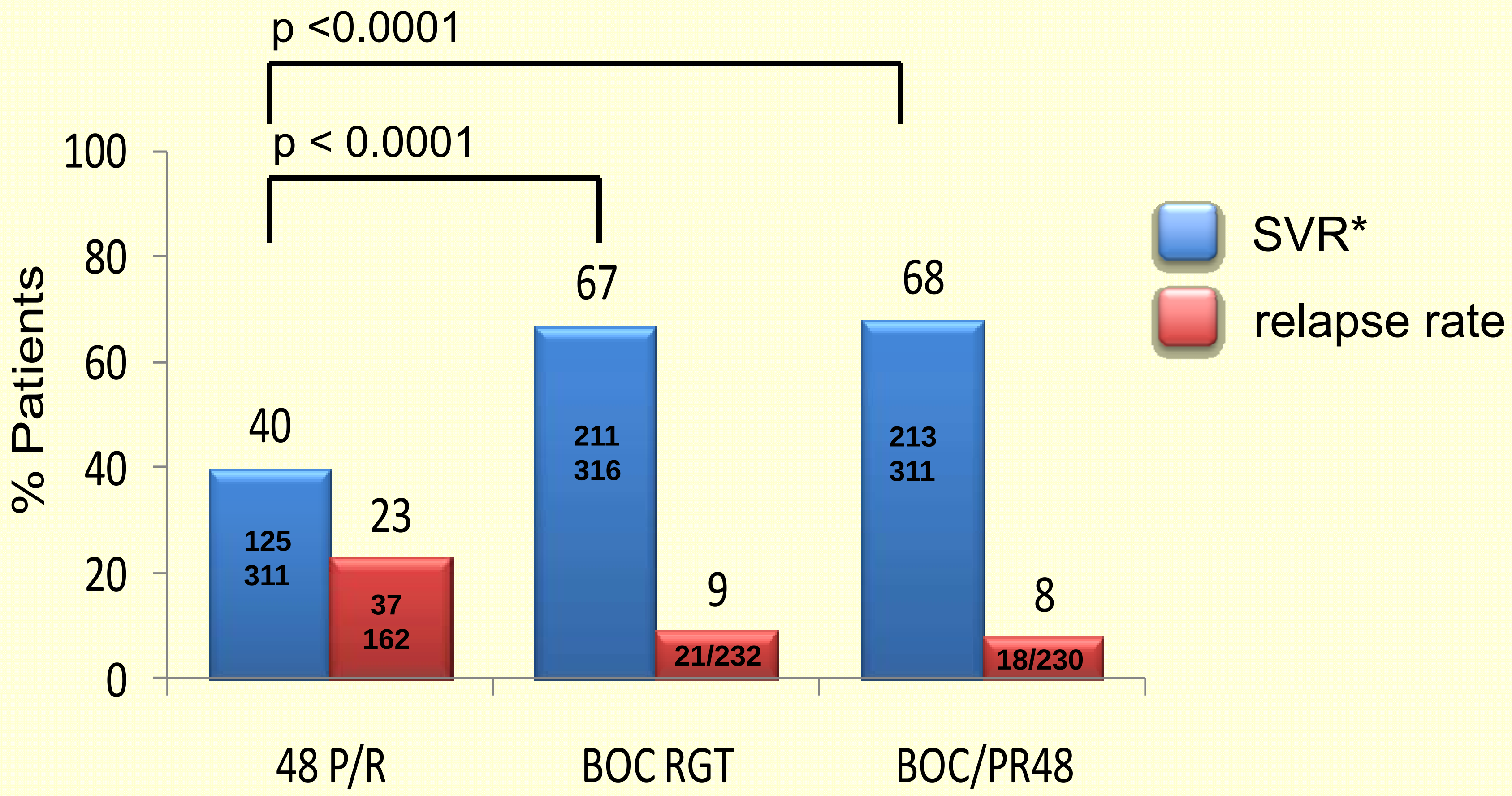
SPRINT 2: SVR (ITT - randomized)
a Phase 3 study of BOC in treatment-naïve G1 patients



Poordad F et al. AASLD 2010; 52, 4 (suppl): 107A

Total enrollment: 1099 patients

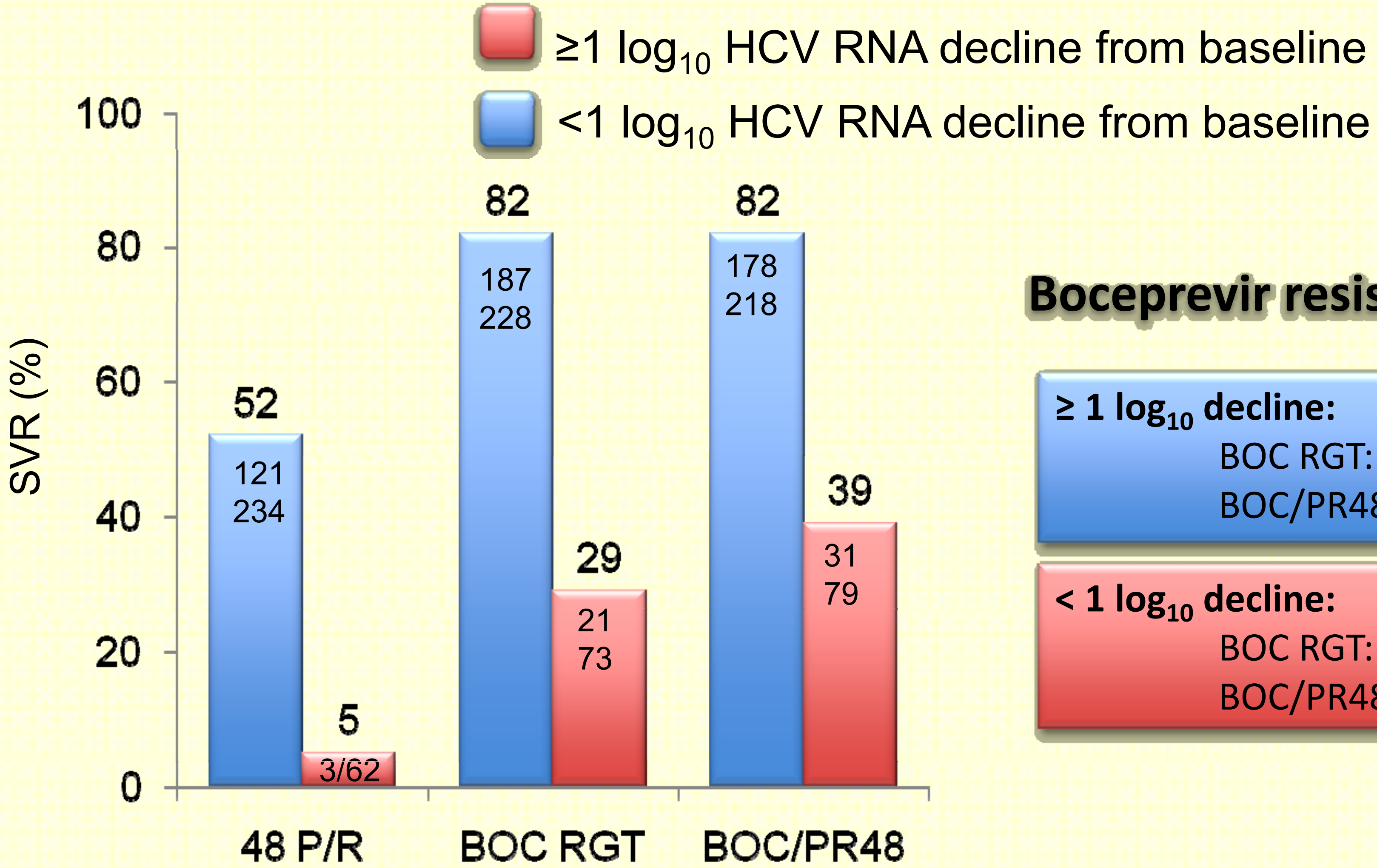
SVR and Relapse Rates (ITT)
in non-black G1 naïve patients



Response achieved at the end of treatment is more stable with triple therapy

Poordad F et al. AASLD 2010; 52, 4 (suppl): 107A

SVR based on week 4 PR lead-in
in non-black G1 naïve patients



Boceprevir resistance:

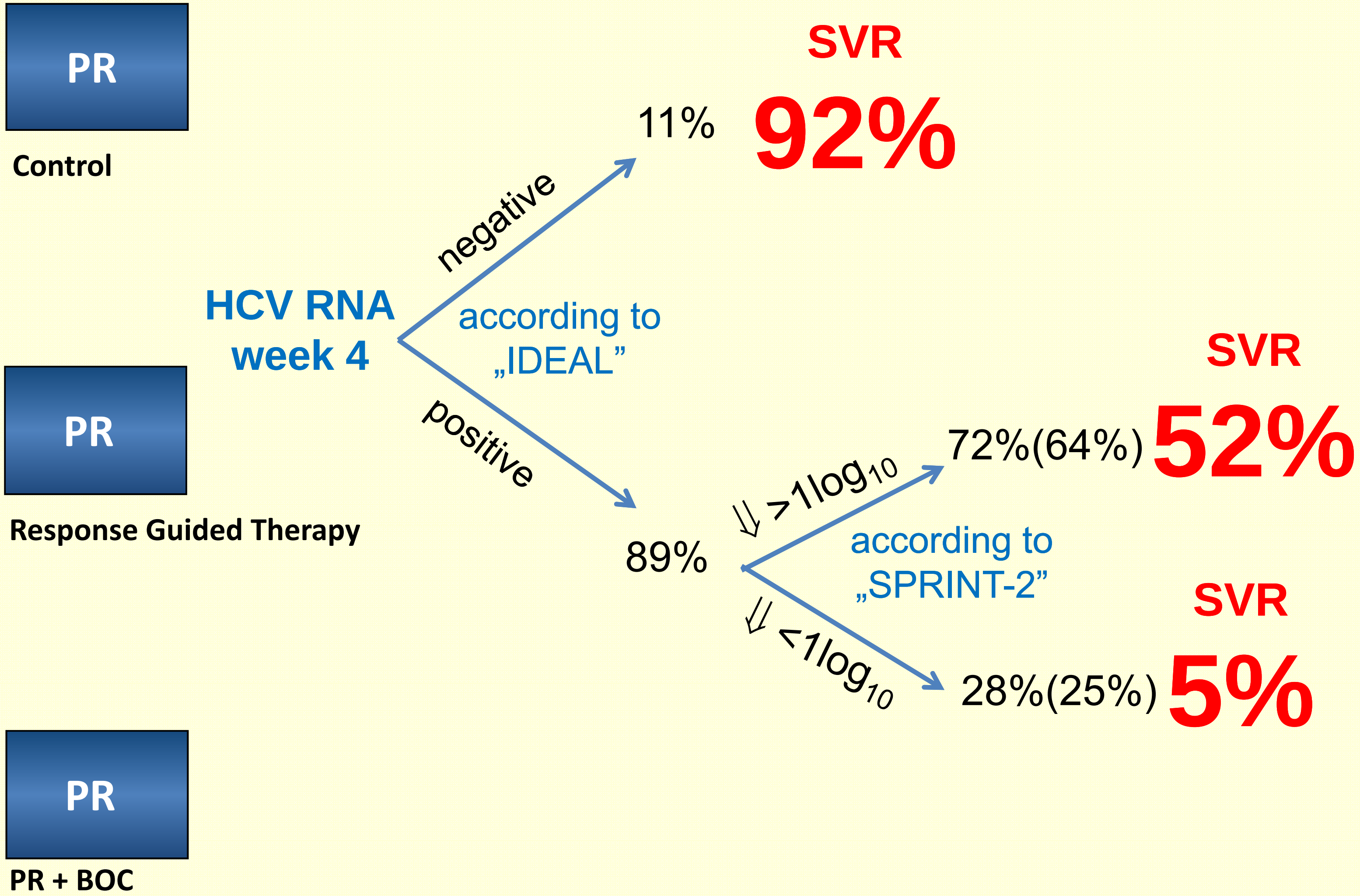
≥ 1 log_{10} decline:
BOC RGT: **4%**
BOC/PR48: **4%**

< 1 log_{10} decline:
BOC RGT: **47%**
BOC/PR48: **35%**

Chance of SVR in week 4 weak responders depends on BOC

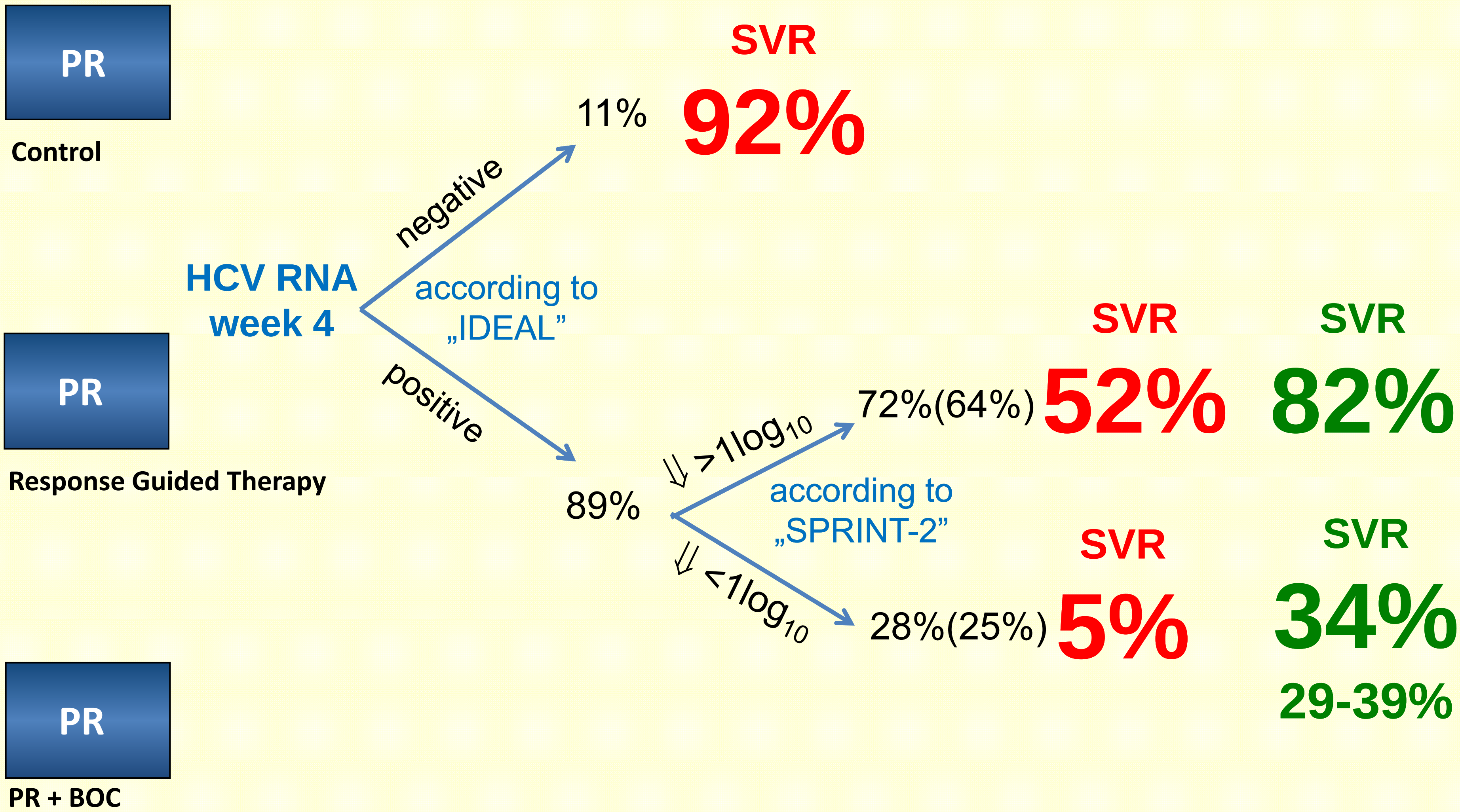
Poordad F et al. AASLD 2010; 52, 4 (suppl): 107A

HCV RNA decline at week 4
PegIFNα2b + RBV



HCV RNA decline at week 4

PegIFNα2b + RBV + BOC



How to treat: BOC-triple therapy in G1 naïve patients

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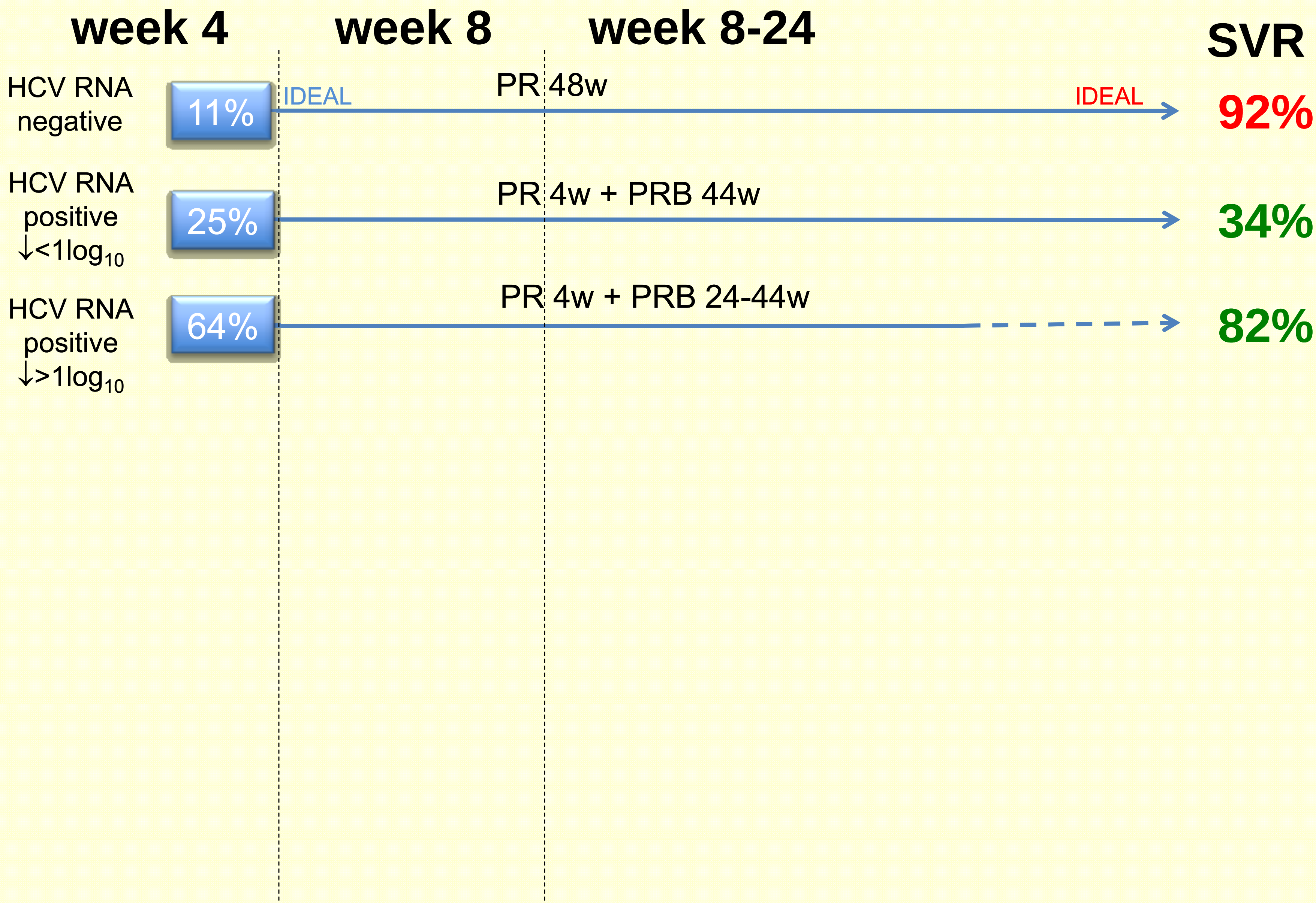
week 4 | week 8 | week 8-24 | SVR

HCV RNA negative — 11% — IDEAL — PR 48w — IDEAL → 92%

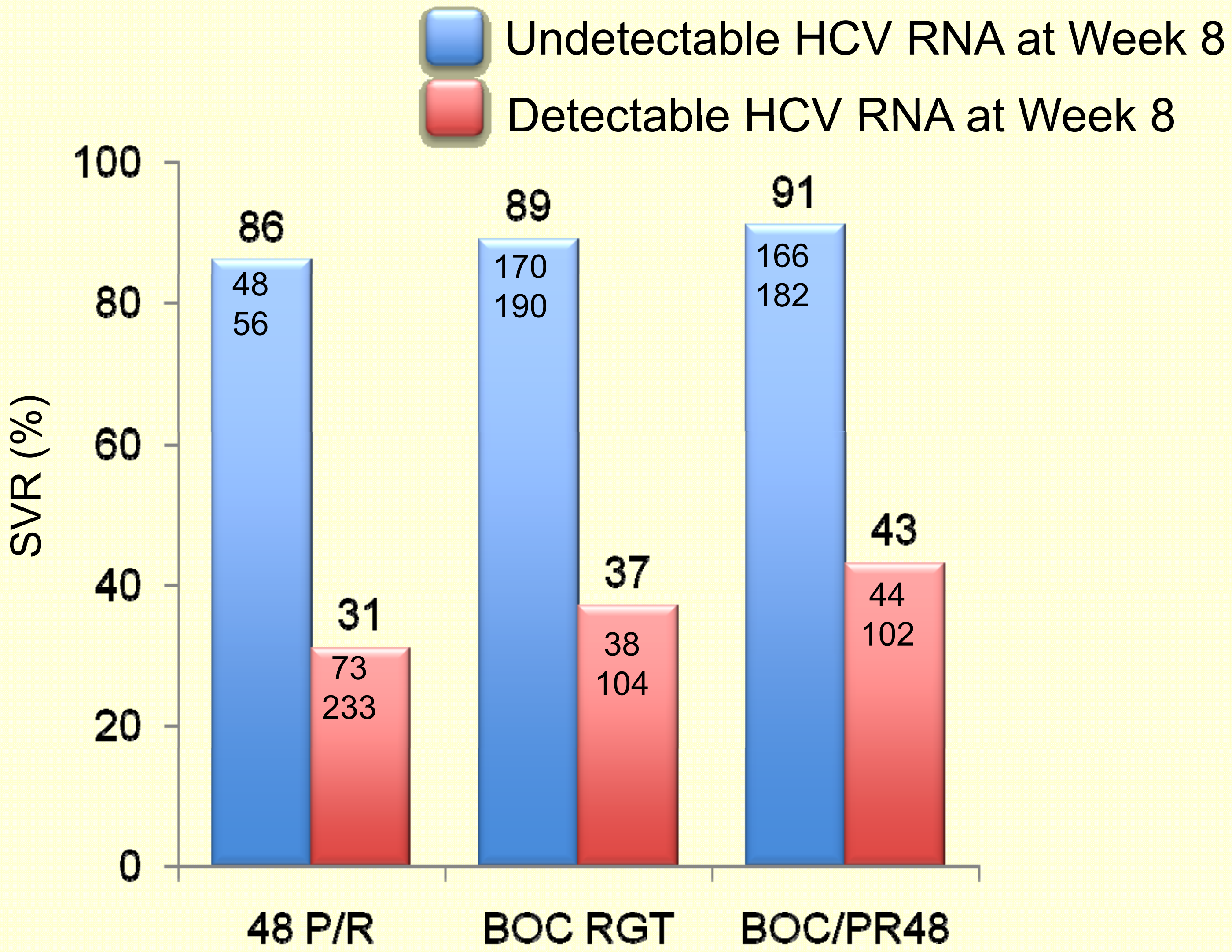
HCV RNA positive $\downarrow$>1log$_{10}$ — 64% — ? — PR 4w + PRB 24-44w → 82%

In „real life” decision on BOC for further therapy is impossible at week 4;
it can be done between weeks 4 and 8

How to treat: BOC-triple therapy in G1 naïve patients



SVR based on week 8 PR lead-in
in non-black G1 naïve patients



Poordad F et al. AASLD 2010; 52, 4 (suppl): 107A

8 weeks of PegIFNα2b + RBV +/- BOC

HCV RNA negative at week 8

Arm	Regimen	HCV RNA negative at week 8	SVR
Control	PR / PR	18%	86%
Response Guided Therapy	PR / PR + BOC	60%	89%
PR + BOC	PR / PR + BOC	59%	91%

% of patients who achieved undetectable HCV RNA in BOC arms compared to controls was >3 times higher

SVR in non-black patients with undetectable HCV RNA between weeks 8-24

PR	PR + BOC	→	HCV RNA negative between weeks 8 and 24 47%	→	SVR 97%

Response Guided Therapy

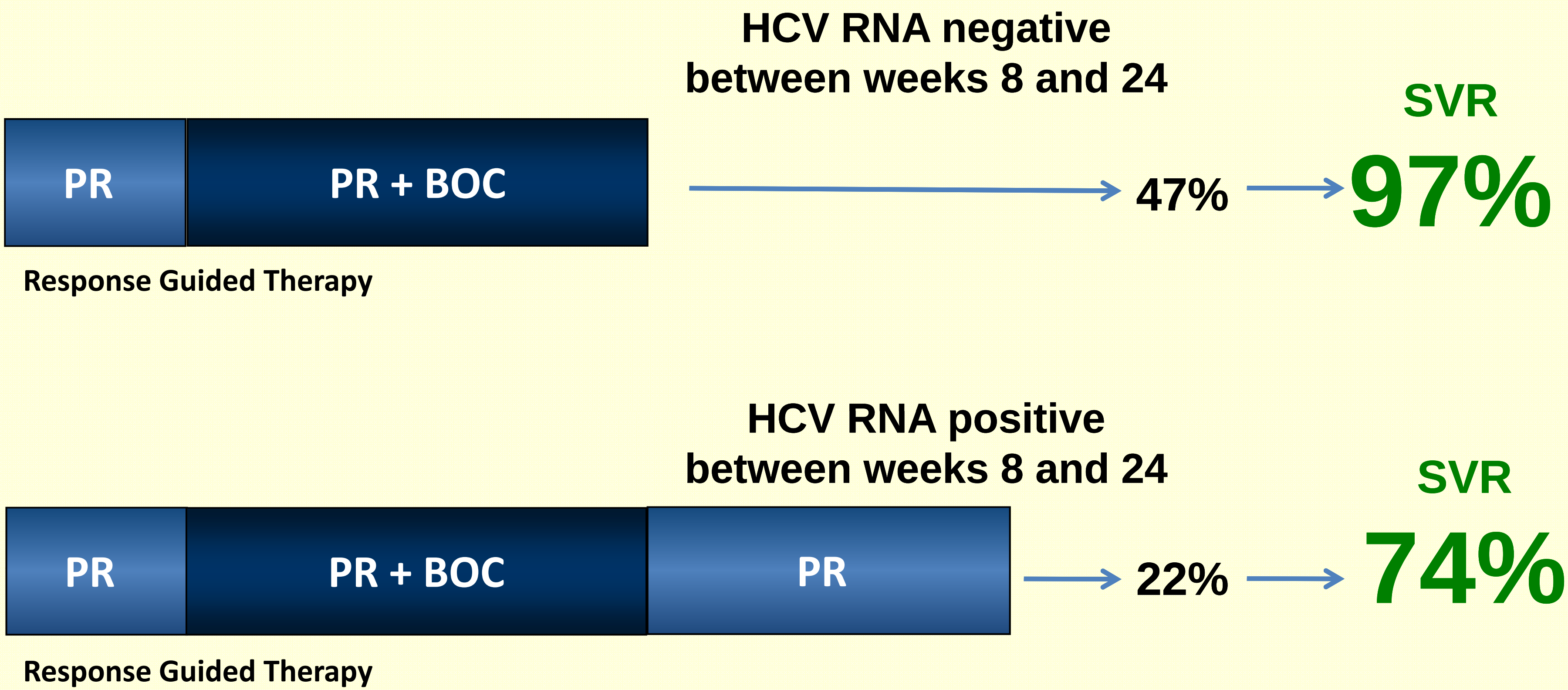
PR	PR + BOC	→	HCV RNA negative between weeks 8 and 24 46%	→	SVR 96%

PR + BOC

47% of non-black patients in RGT arm were eligible per protocol to be treated with short duration → PR4w + PRB24w resulting with SVR up to 97%

Poordad F et al. AASLD 2010; 52, 4 (suppl): 107A

SVR in non-black patients with detectable HCV RNA between weeks 8-24

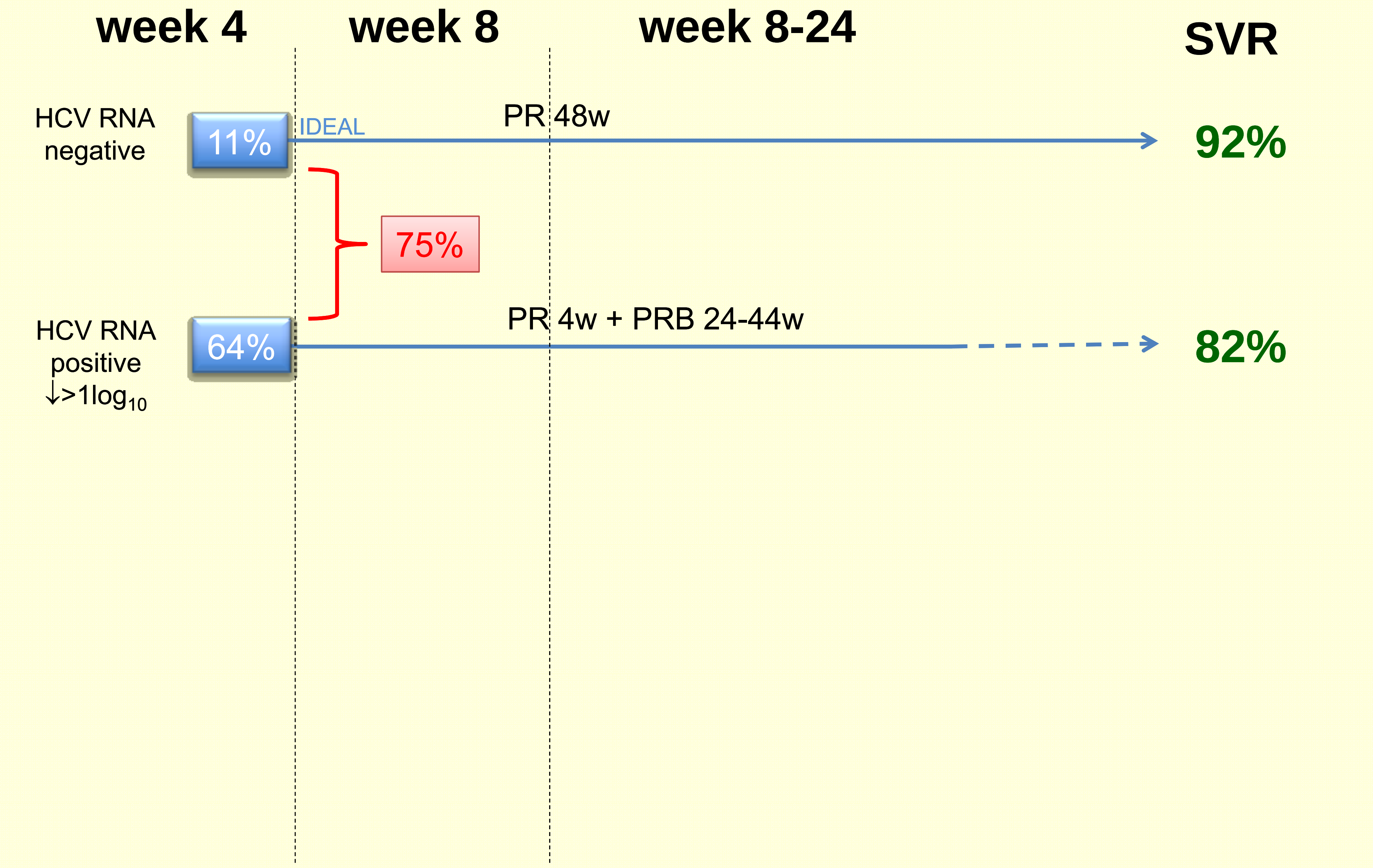


22%* of patients in RGT arm were HCV RNA(+) between weeks 8-24 and treated longer (>28 weeks) → PR4w + PRB24w + PR20w resulting with SVR 74%

* Remaining 31% patients discontinued prior to treatment week 28 due to adverse events, stopping rule (week 24) or non-medical reasons

Poordad F et al. AASLD 2010; 52, 4 (suppl): 107A

How to treat: BOC-triple therapy in G1 naïve patients



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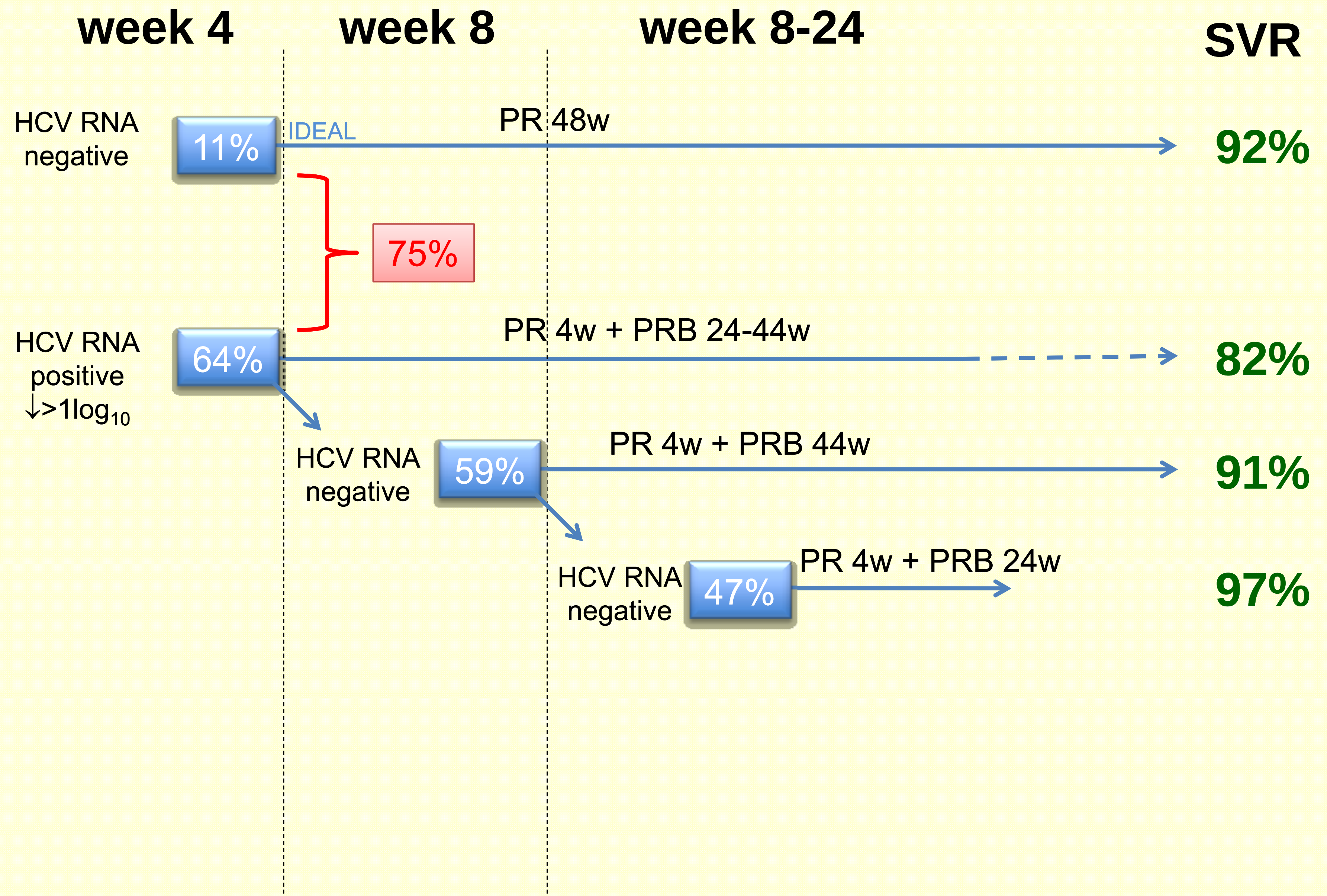

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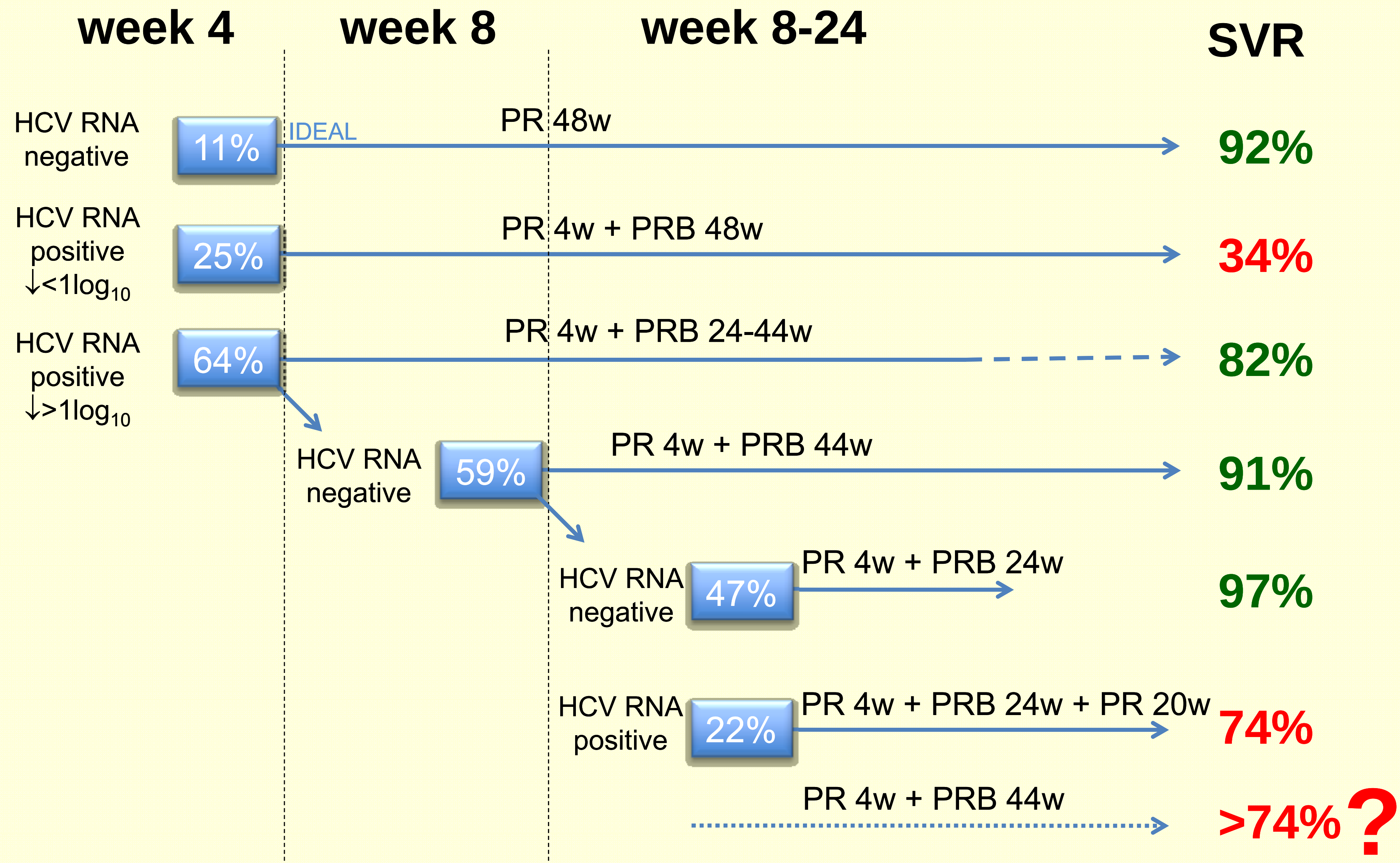
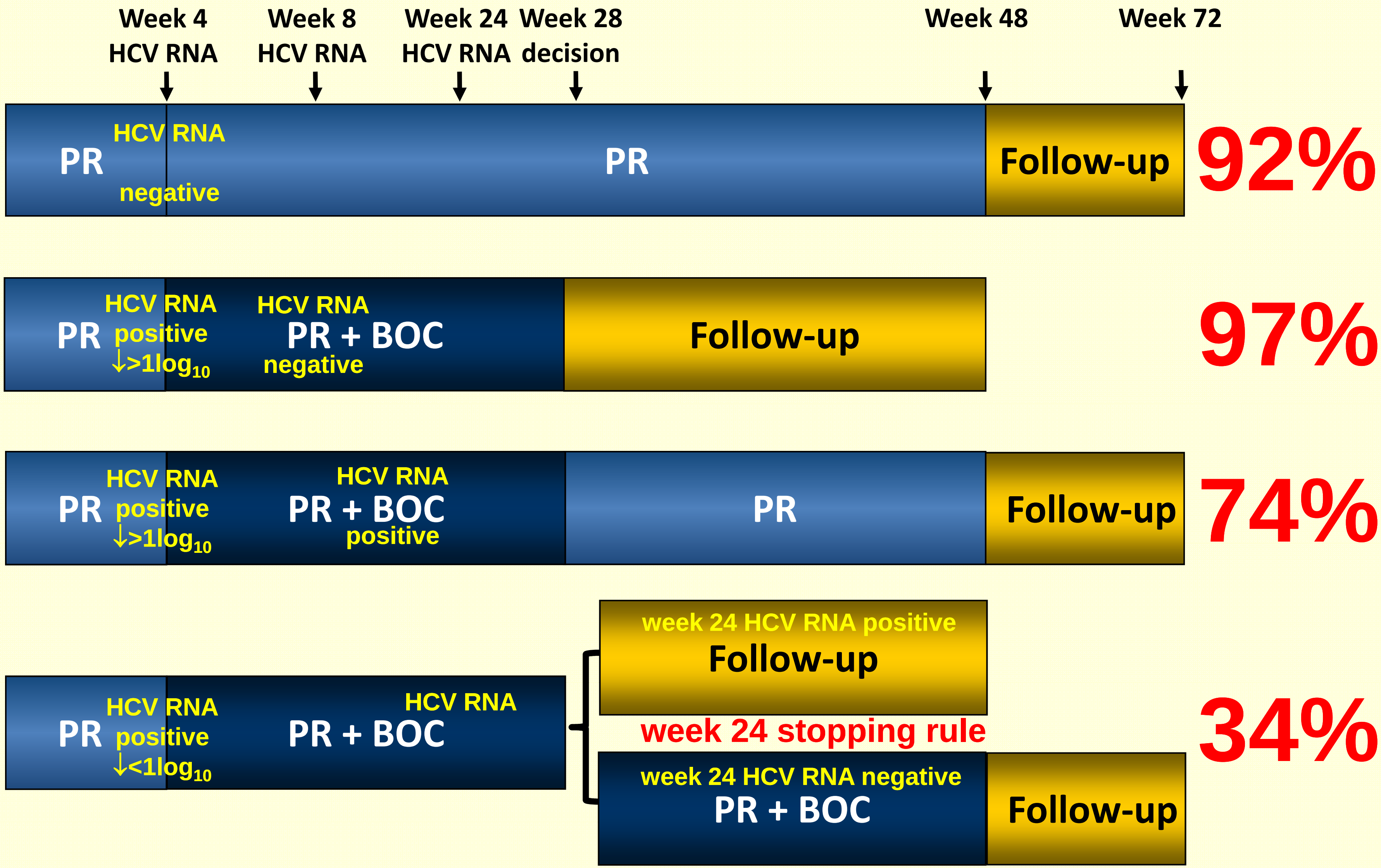
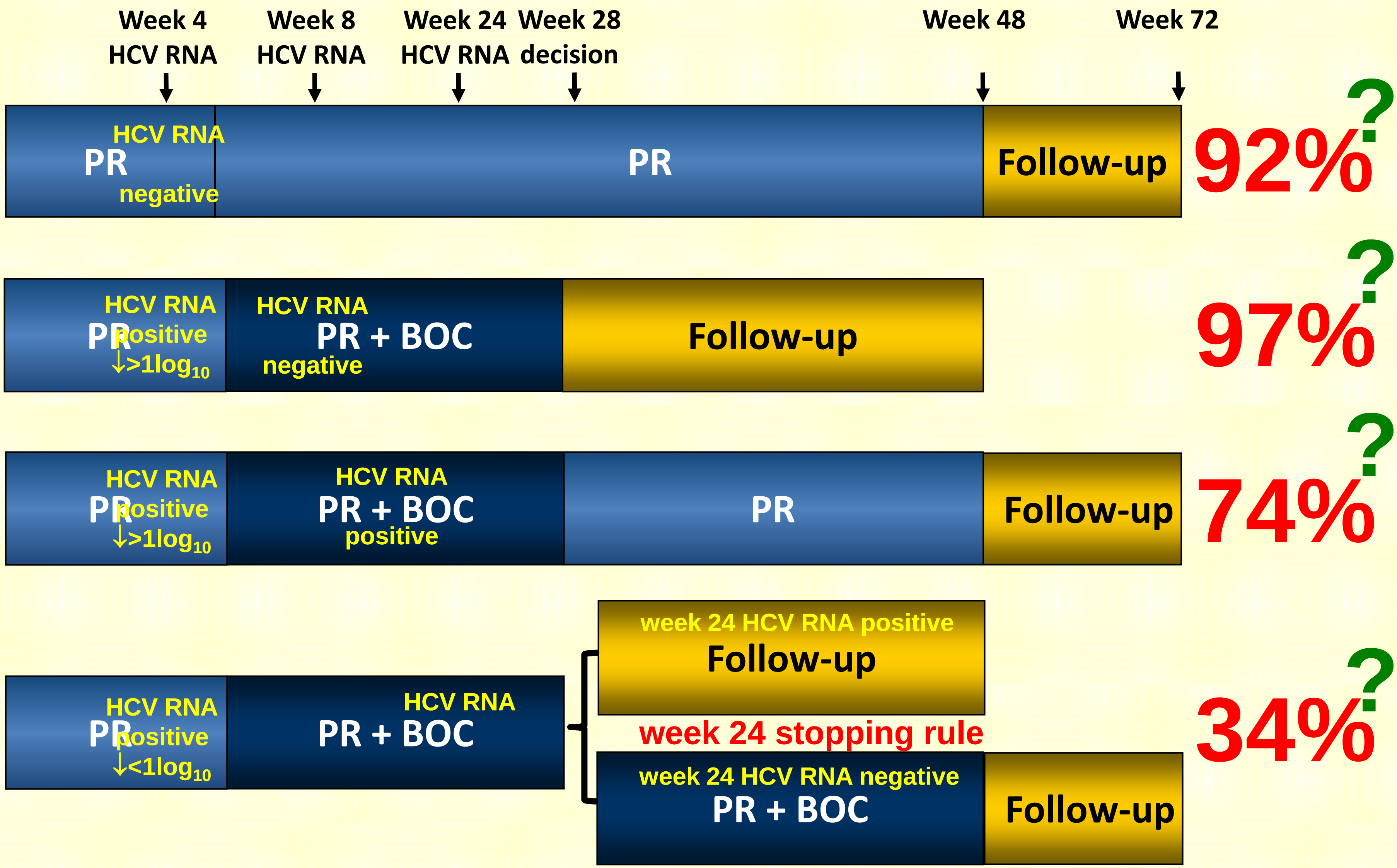


Can we achieve higher SVR extending triple therapy in week 8-24 HCV RNA(+)?

How to treat: BOC-triple therapy in G1 naïve patients



How to treat: BOC-triple therapy in G1 naïve patients



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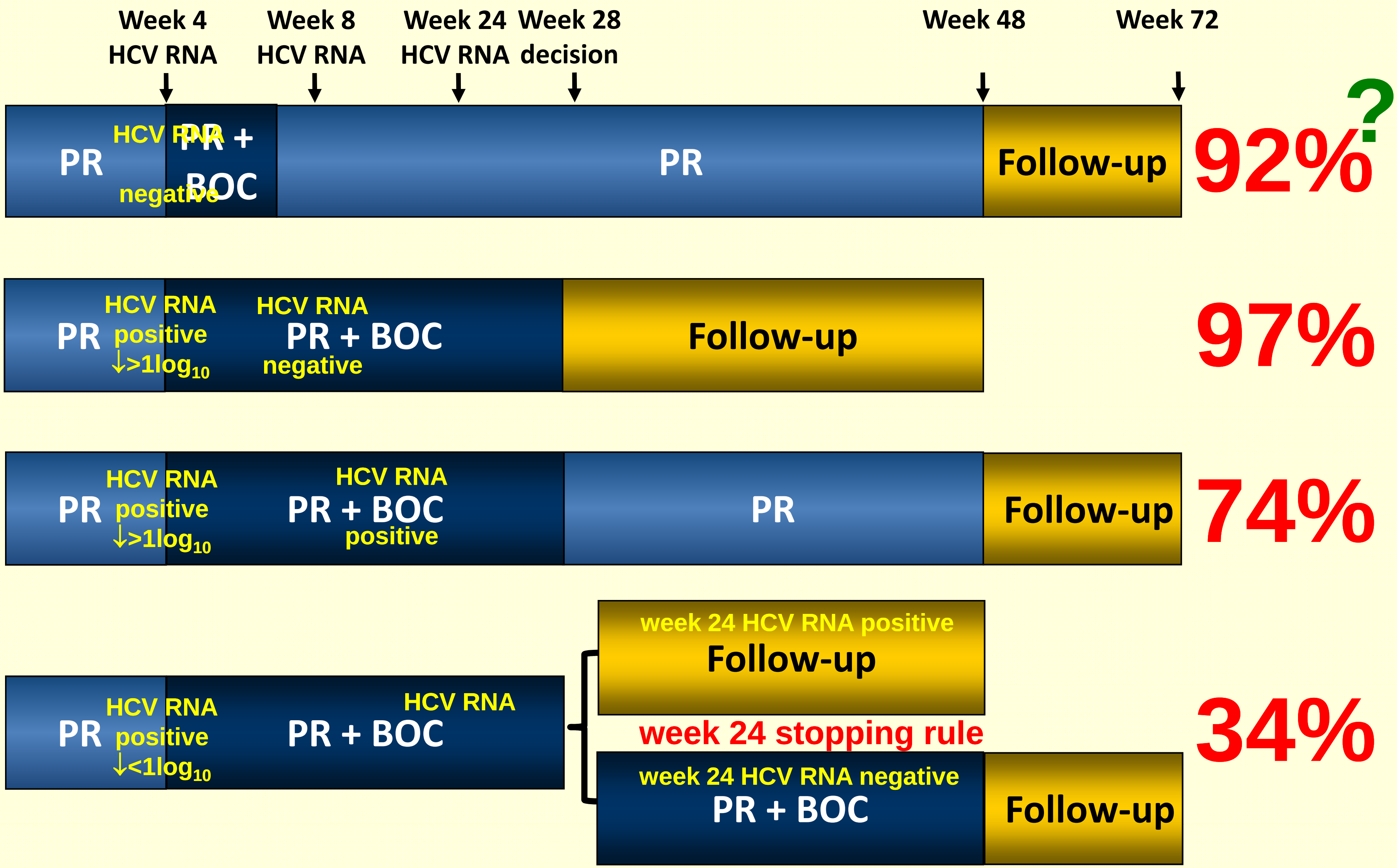
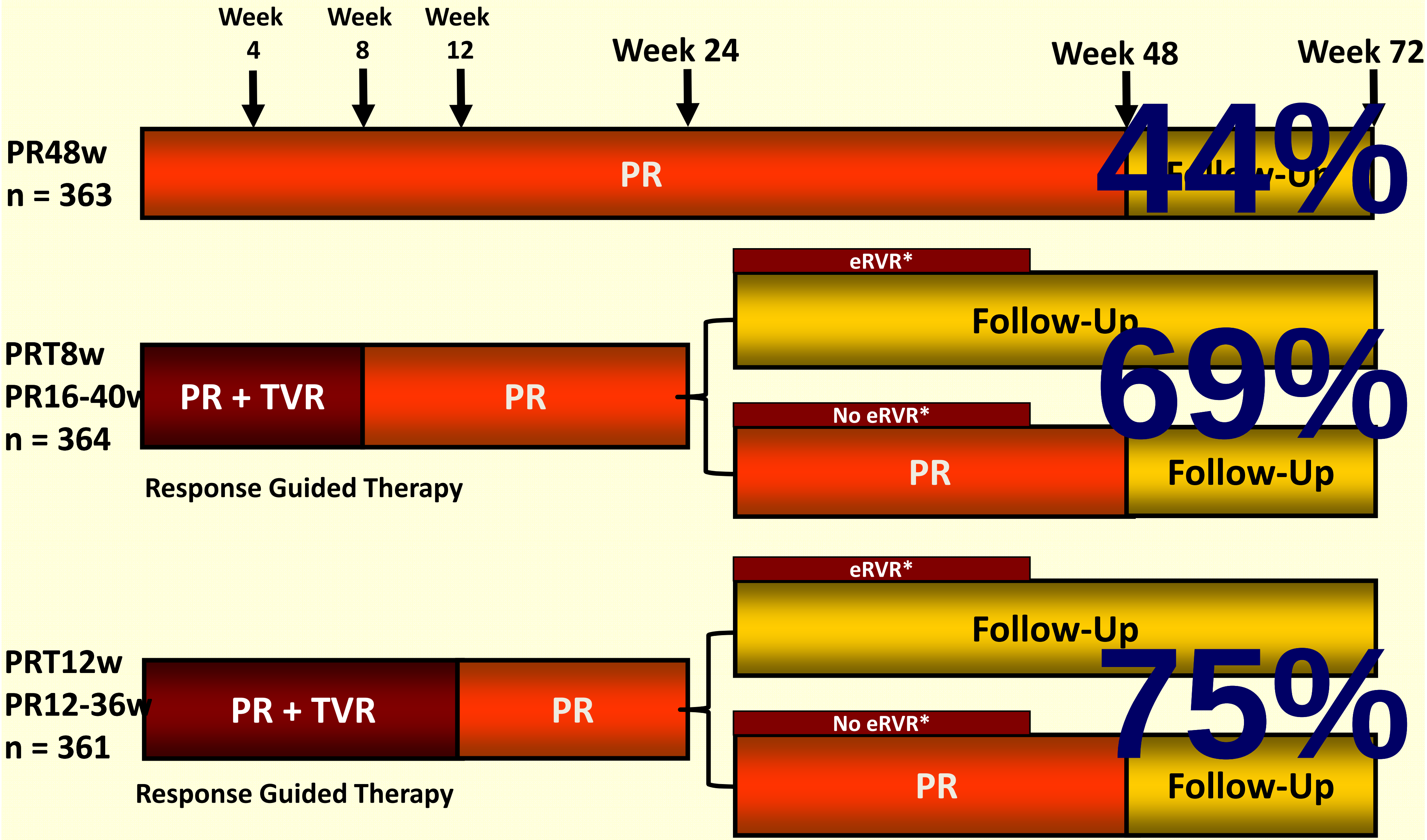


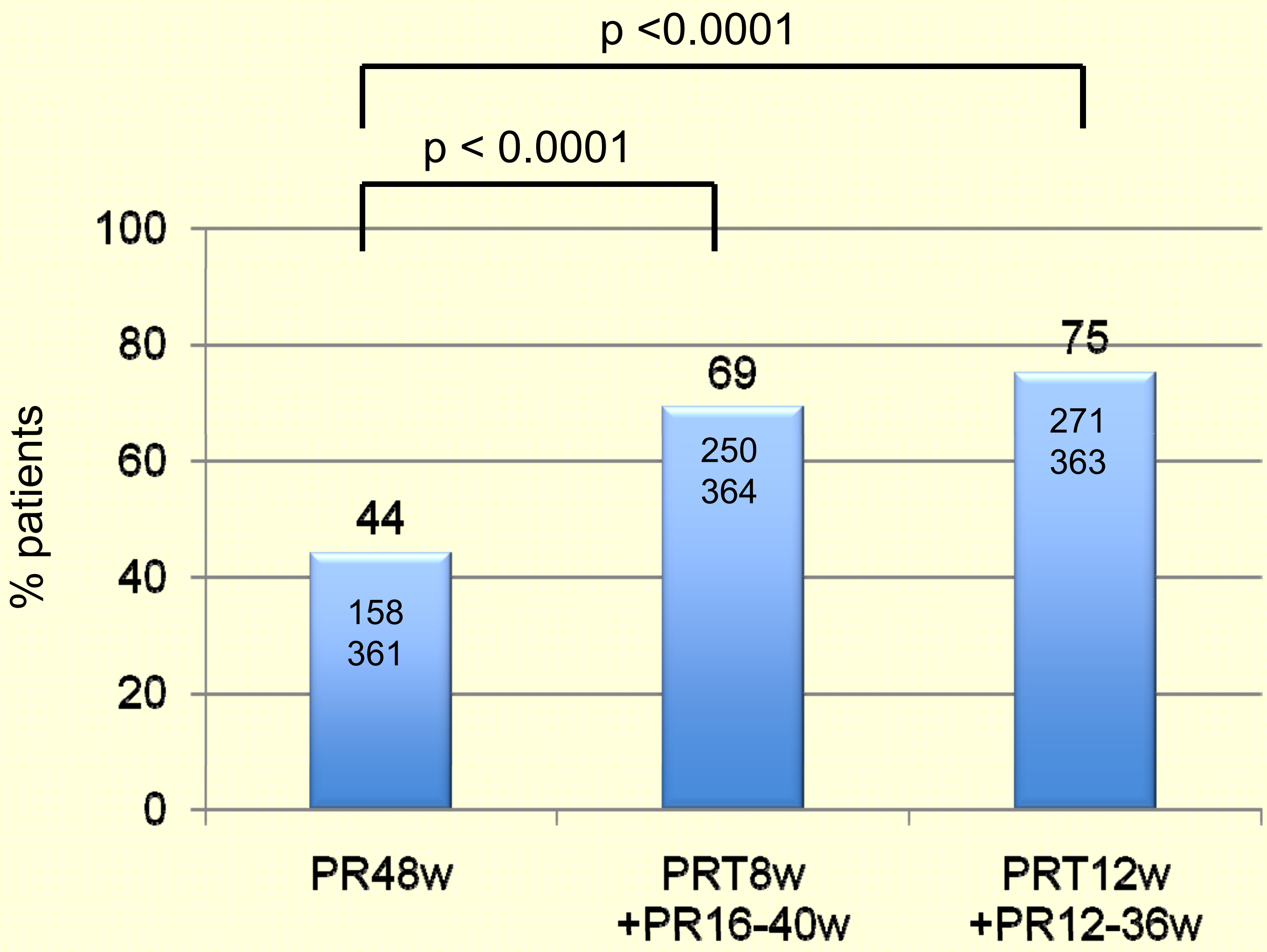
ADVANCE:
a Phase 3 study of TVR in treatment-naïve patients



*eRVR: Undetectable HCV RNA at weeks 4 and 12

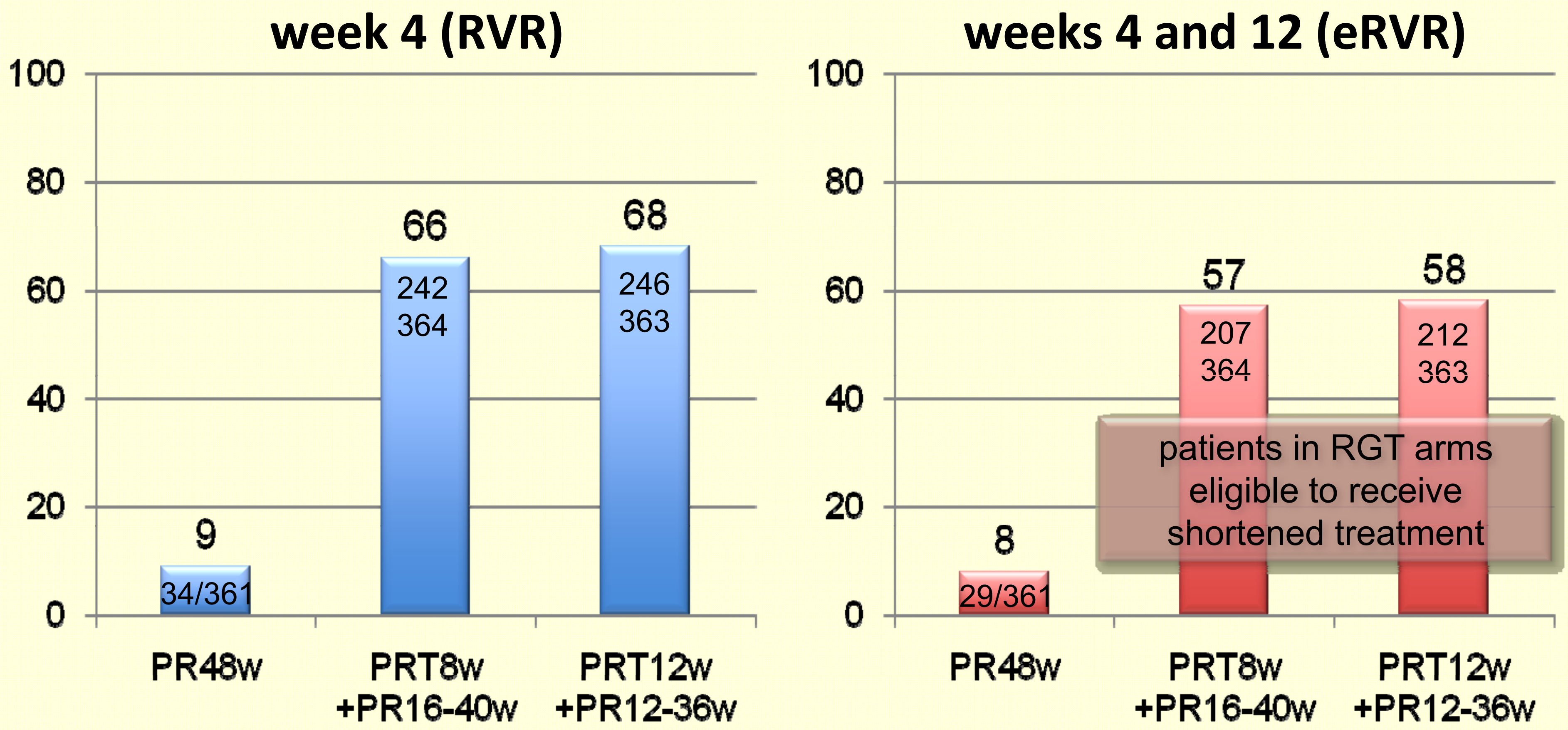
Jacobson I et al. AASLD 2010

SVR rates in TVR treated naïve patients compared to PegIFNα2a + RBV alone



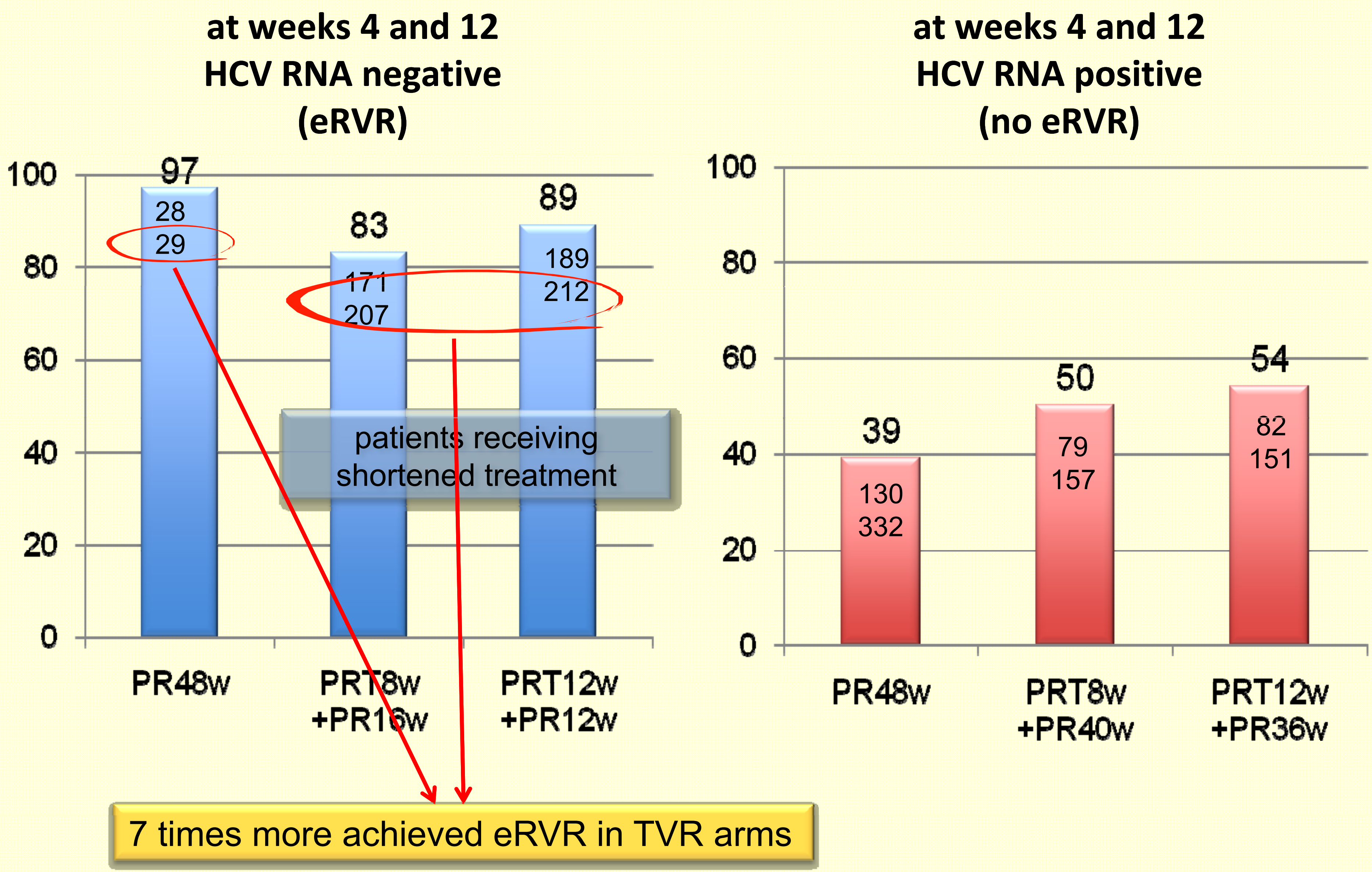
Jacobson I et al. AASLD 2010

Undetectable HCV RNA at week 4 (RVR) and weeks 4 and 12 (eRVR)



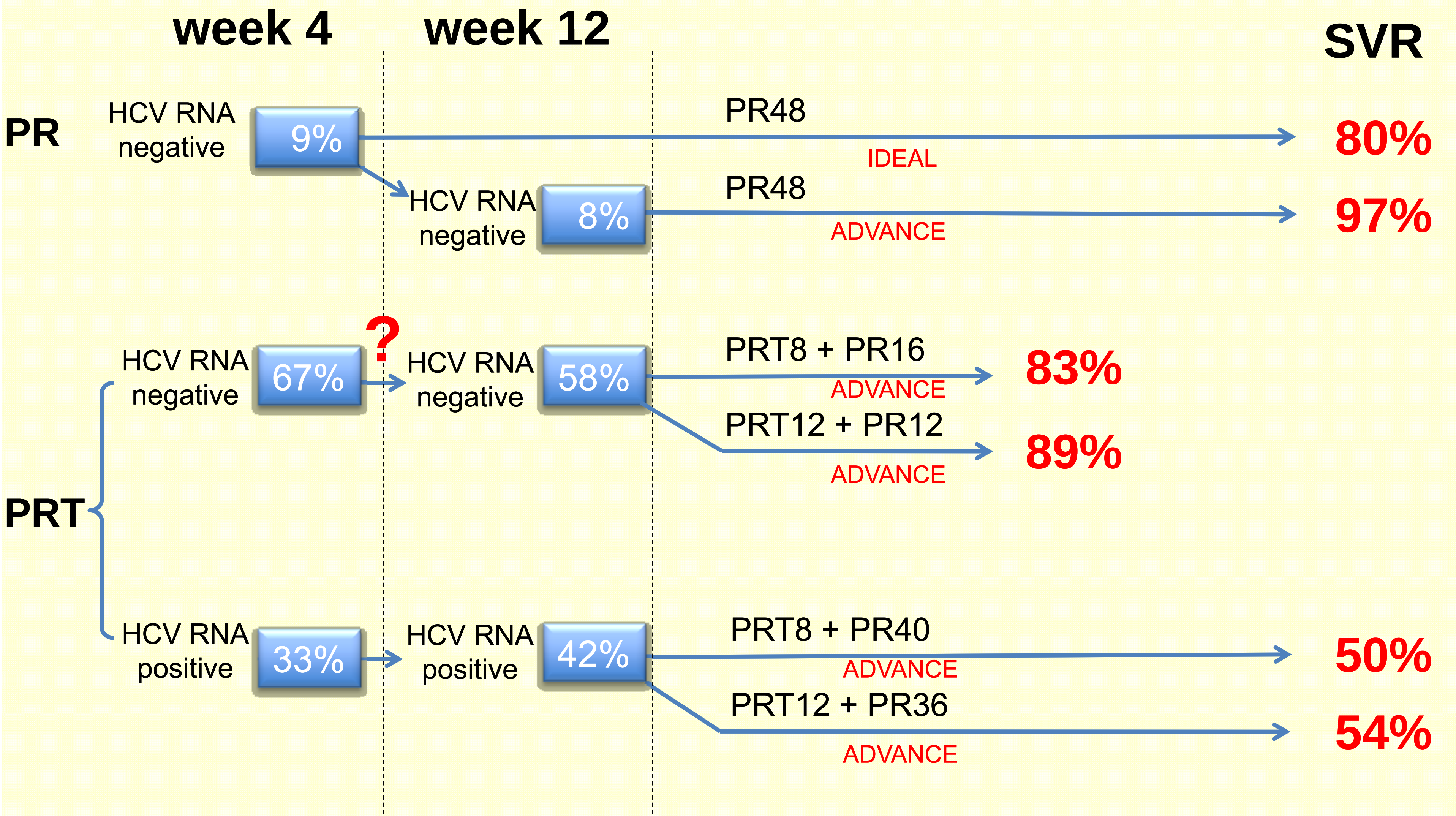
Jacobson I et al. AASLD 2010

SVR by eRVR status



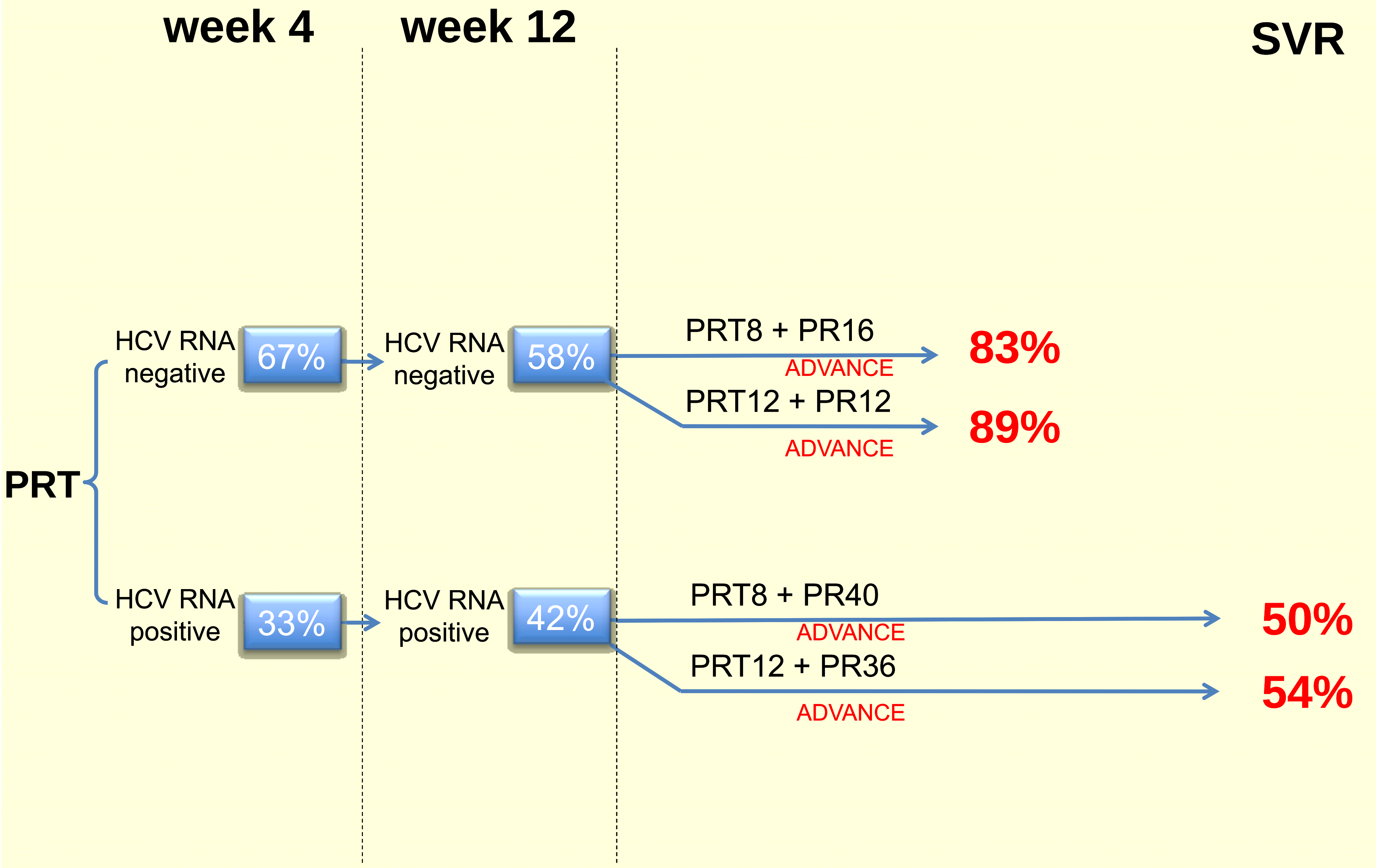
Jacobson I et al. AASLD 2010

How to treat: TVR-triple therapy in G1 naïve patients



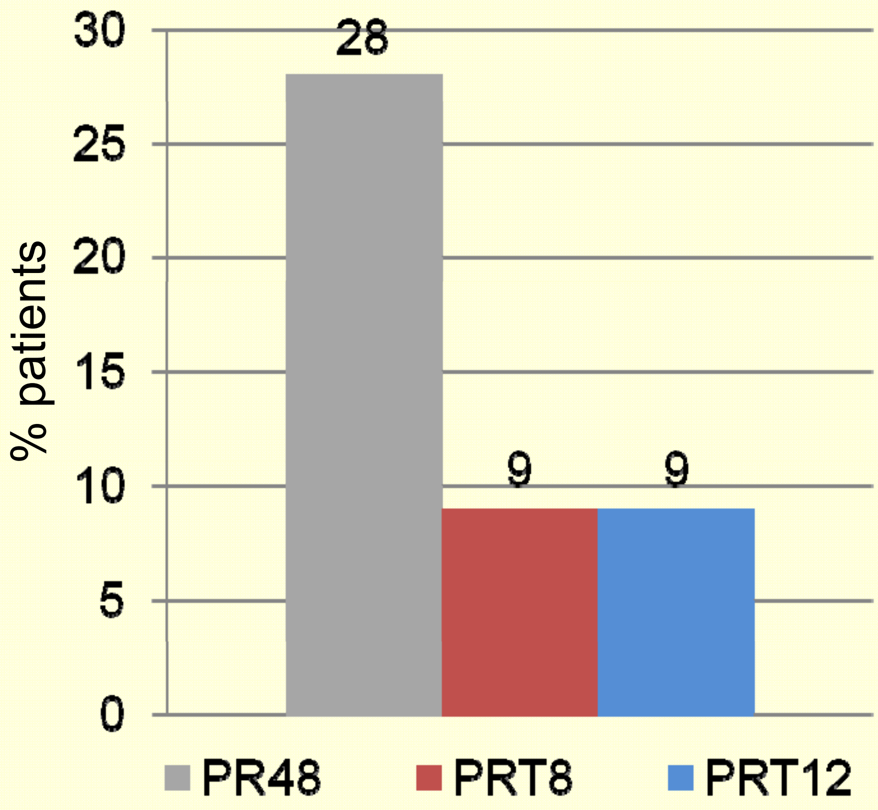
Should we stop TVR and continue on PR if HCV RNA negative at weeks 4?
in „real life" there will probably be need of additional 1-4 weeks untill receipt of virologic report

How to treat: TVR-triple therapy in G1 naïve patients



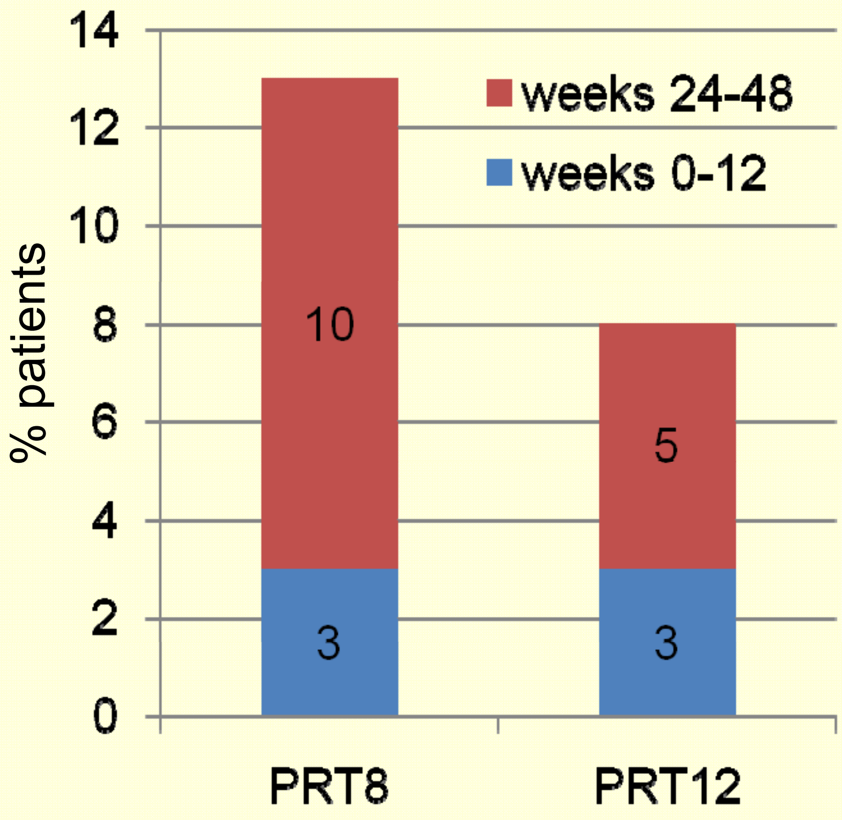
Relapse rate

undetectable HCV RNA at the last dose



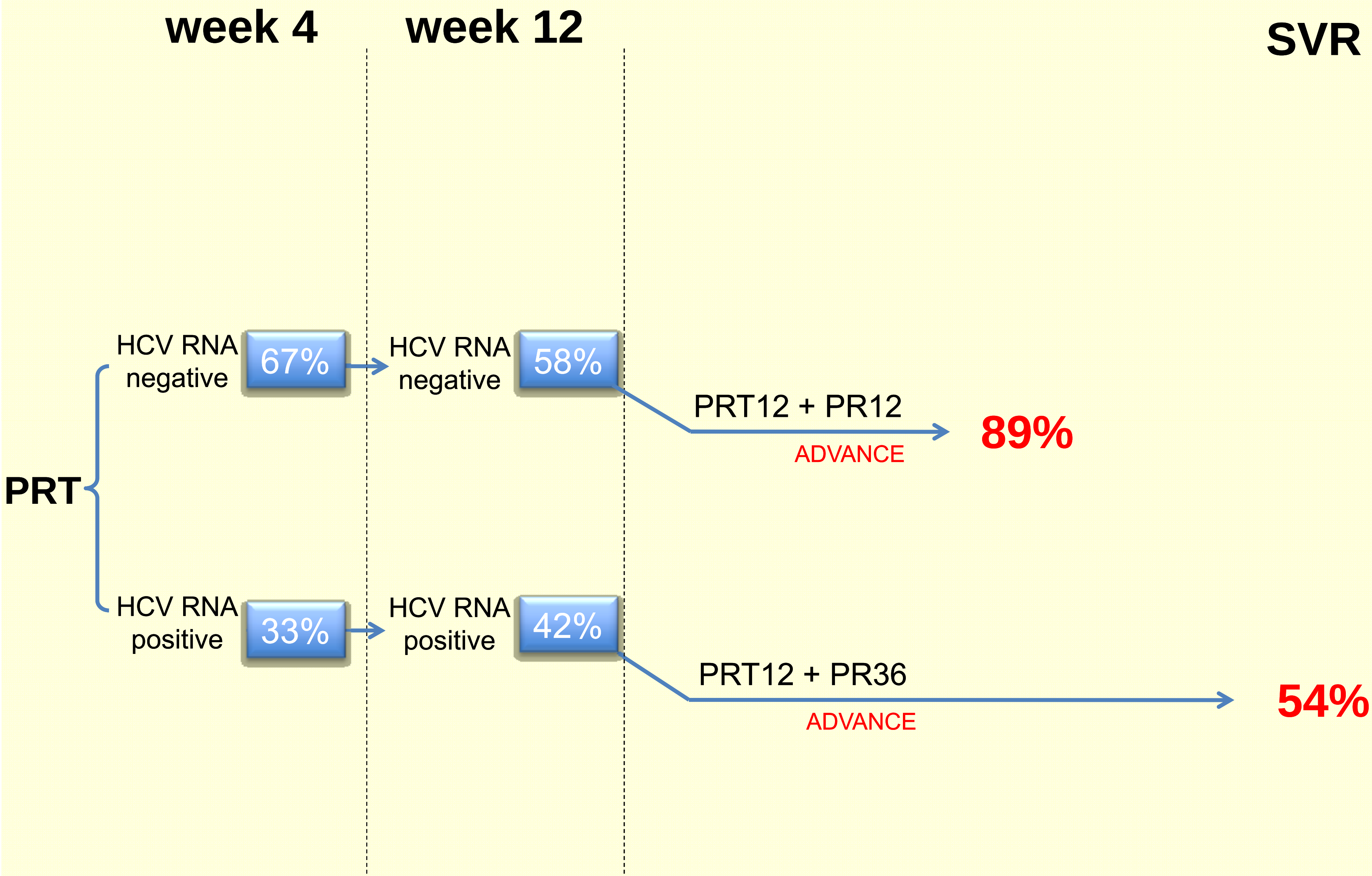
Virologic failure on treatment

- **met stopping rule**
- **HCV RNA>1000 IU/mL at 12w and ⇓ ≥2log10**
- **HCV RNA detectable at the end of treatment**

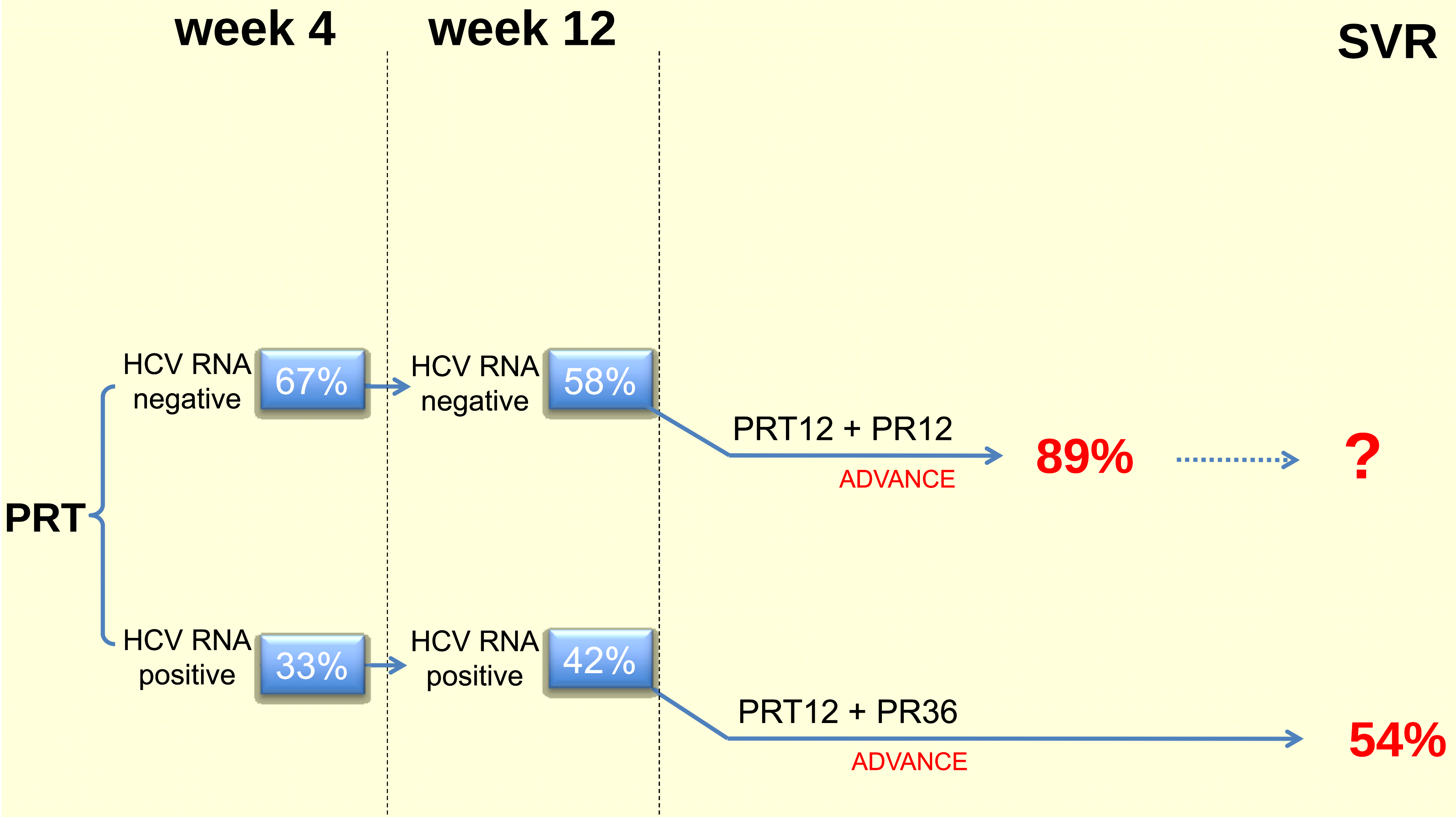


Jacobson I et al. AASLD 2010

How to treat: TVR-triple therapy in G1 naïve patients



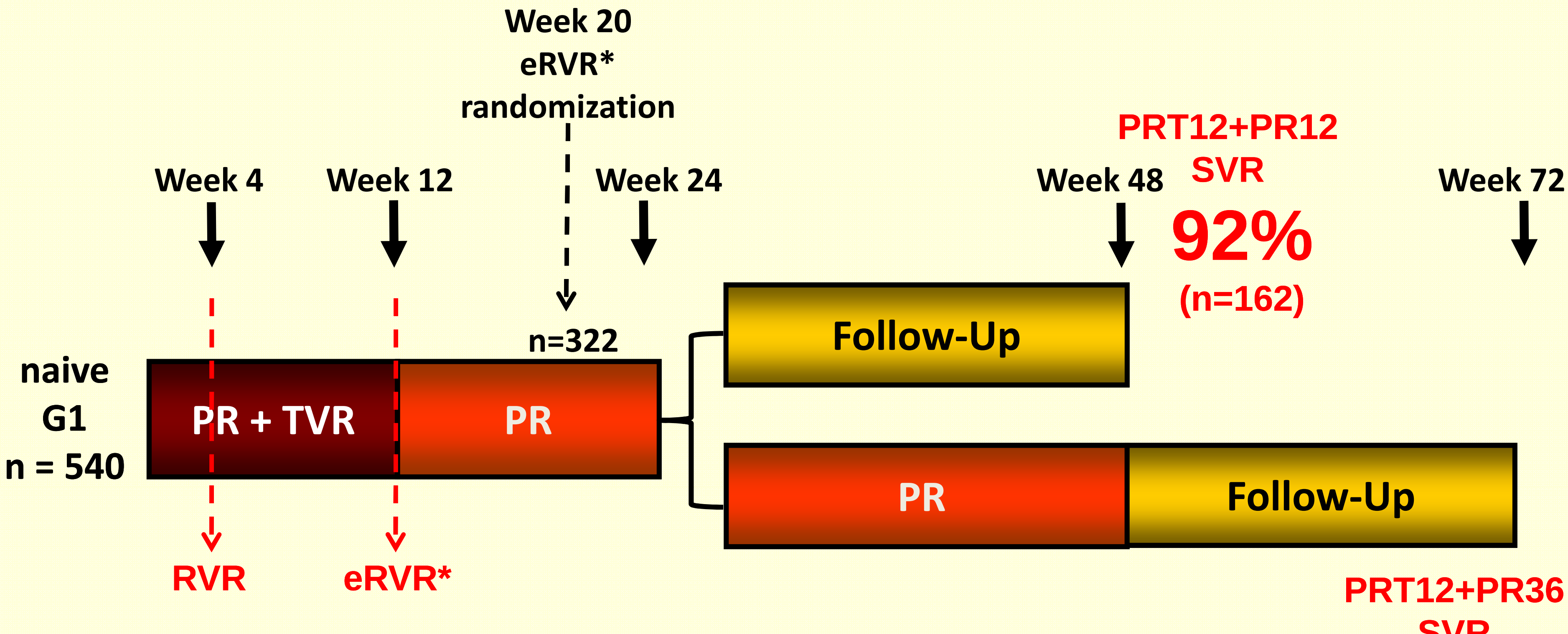
How to treat: TVR-triple therapy in G1 naïve patients



Can we achieve higher SVR extending treatment up to 48 weeks in patients HCV RNA negative in weeks 4 and 12?

ILLUMINATE:

TVR - based regimen for 24 vs 48 weeks in eRVR patients.

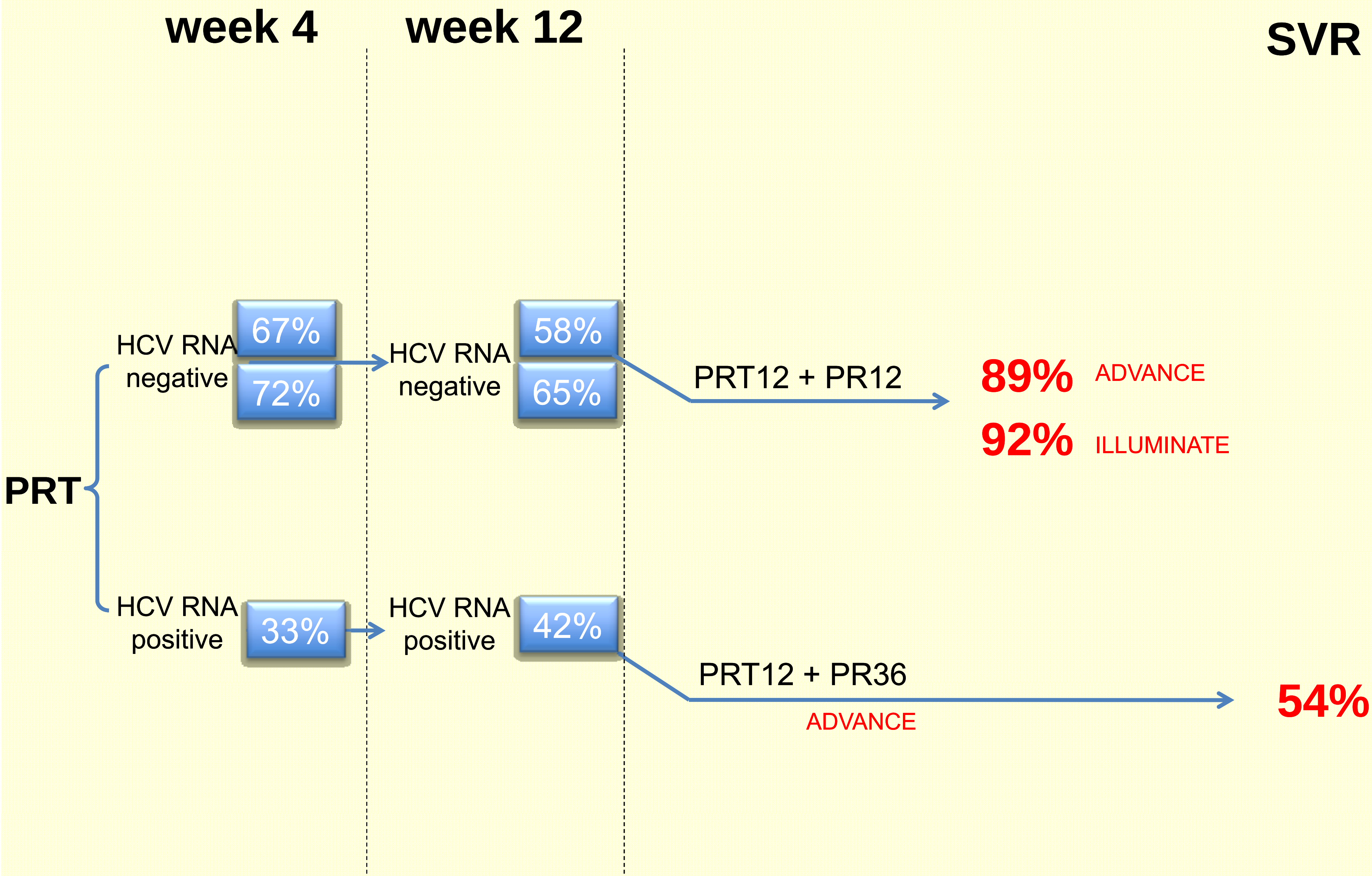


TVR-based regimen for 24 weeks is non-inferior to 48 weeks in patients who previously achieved eRVR

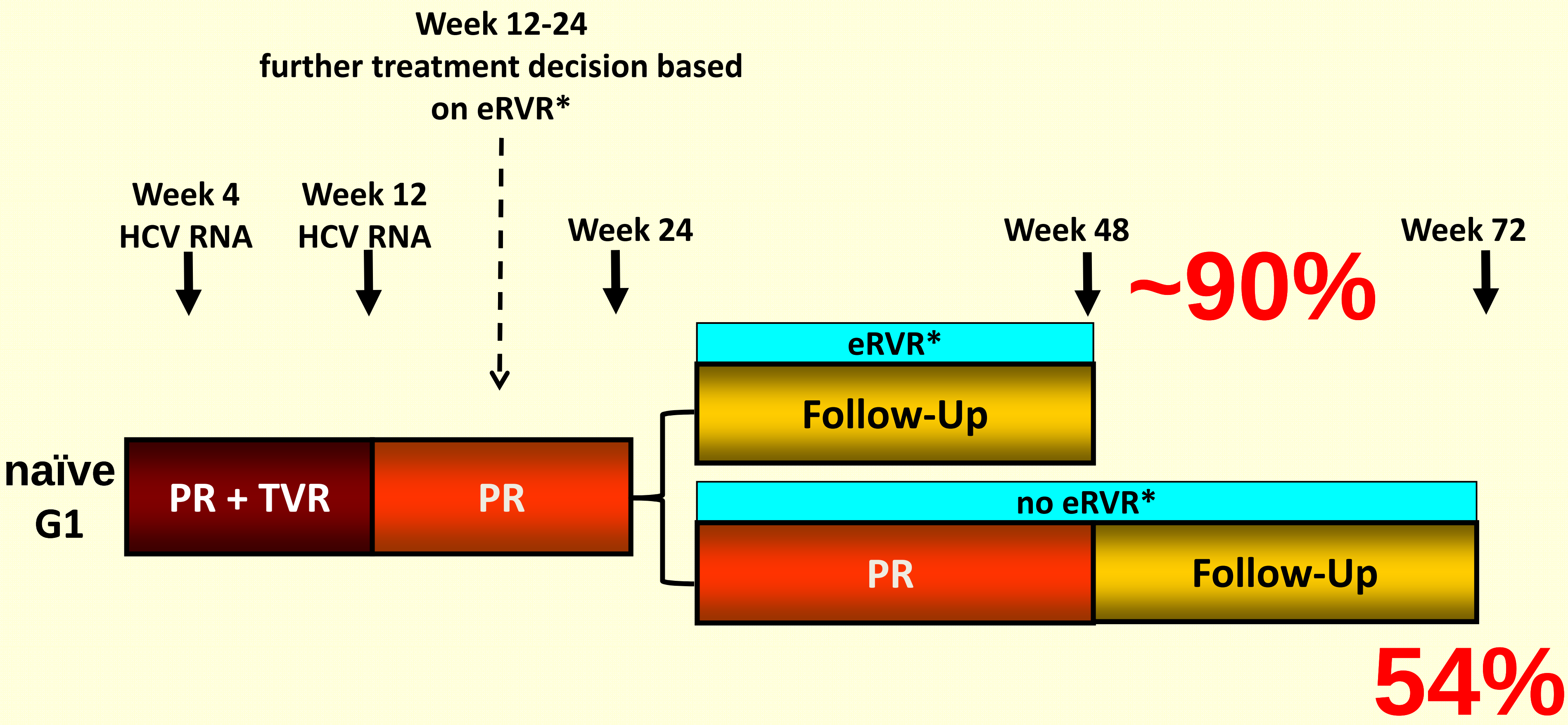
Sherman KE et al. AASLD 2010, LB-2, 401A.

*eRVR: Undetectable HCV RNA at weeks 4 and 12

How to treat: TVR-triple therapy in G1 naïve patients



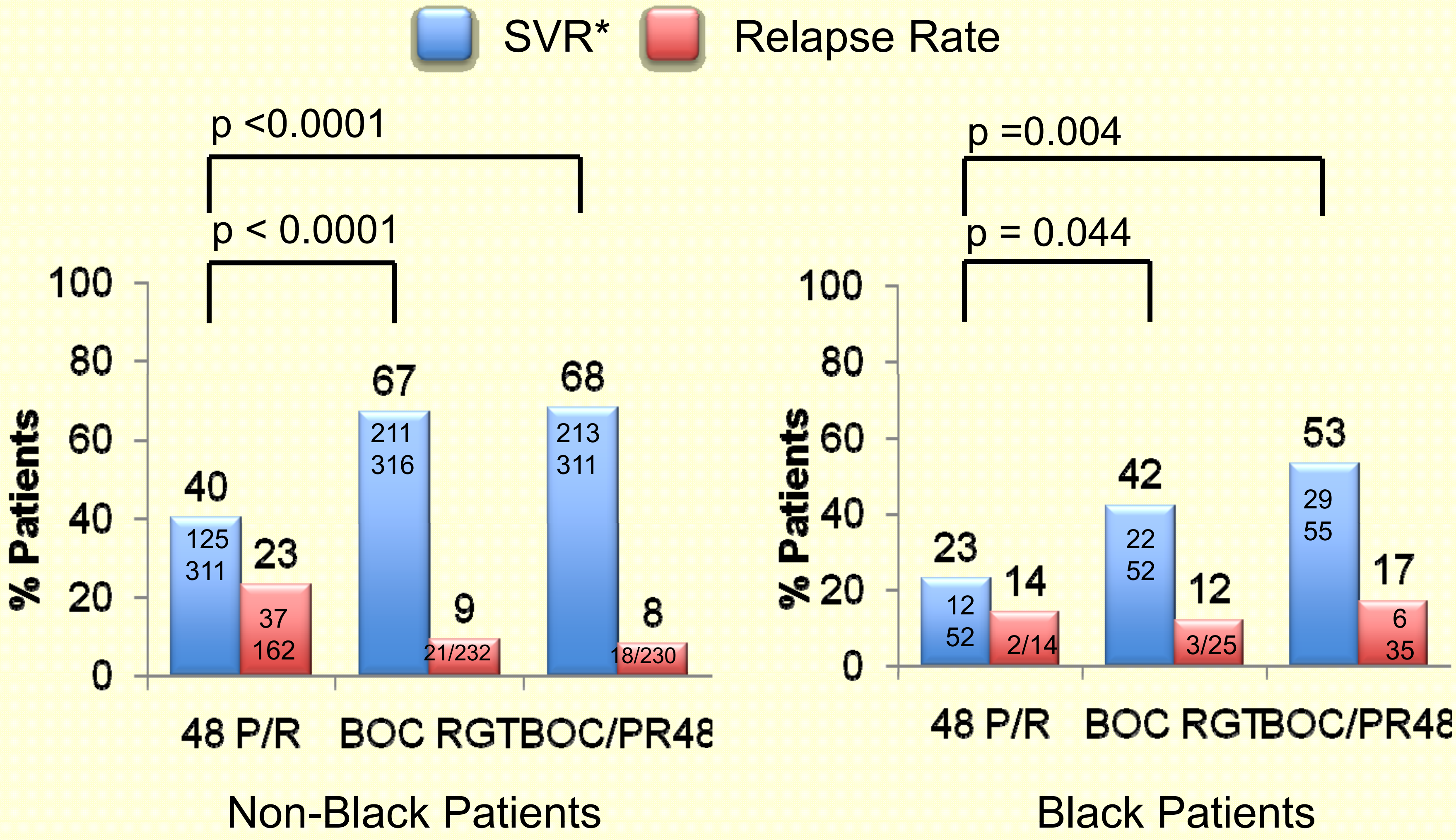
How to treat: TVR-triple therapy in G1 naïve patients



*eRVR: Undetectable HCV RNA at weeks 4 and 12

Who to treat:

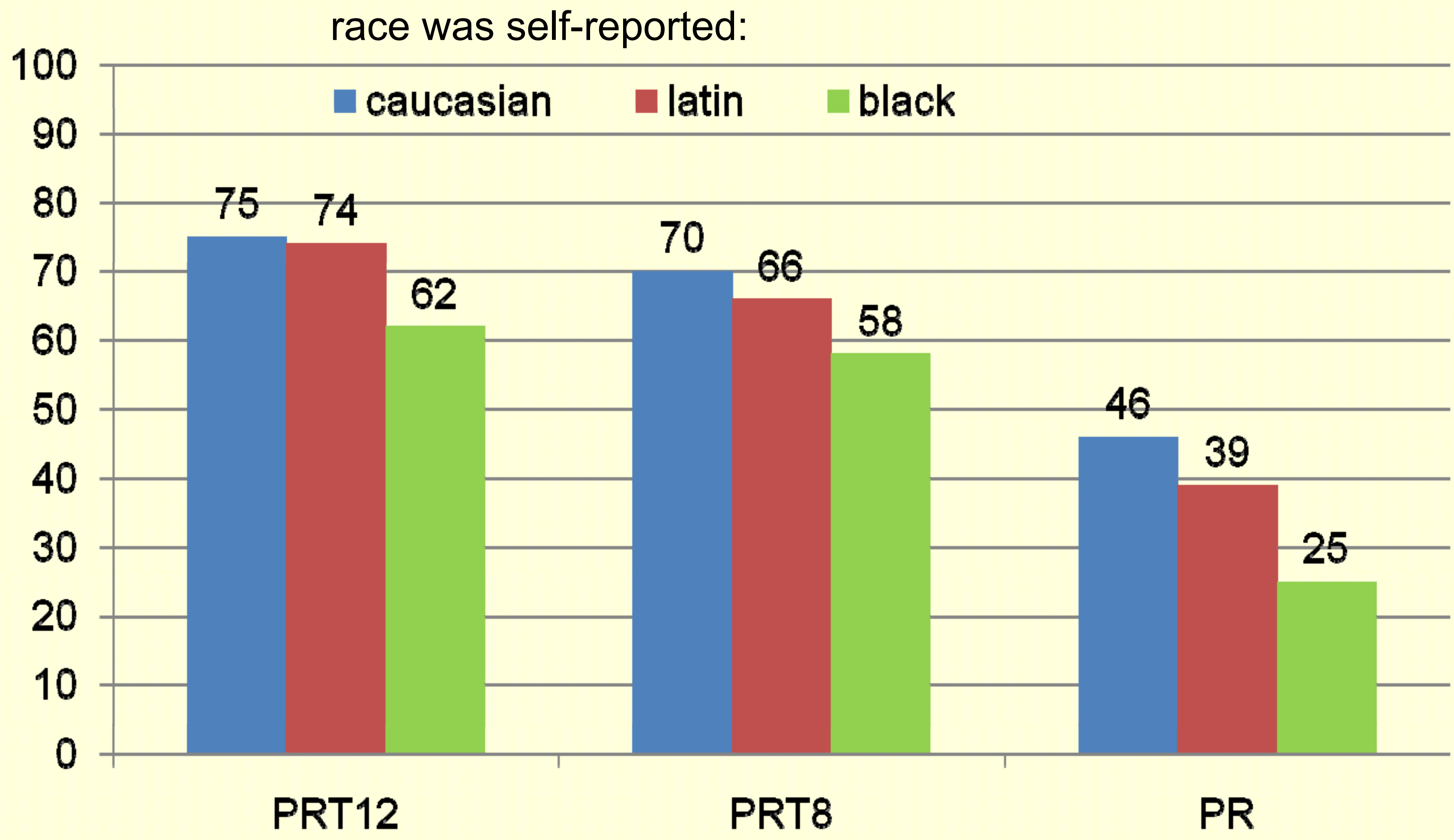
SVR and Relapse Rates in BOC treated non-black vs. black



Poordad F et al. AASLD 2010; 52, 4 (suppl): 107A

Who to treat:

SVR in TVR treated caucasian vs. black vs. latin

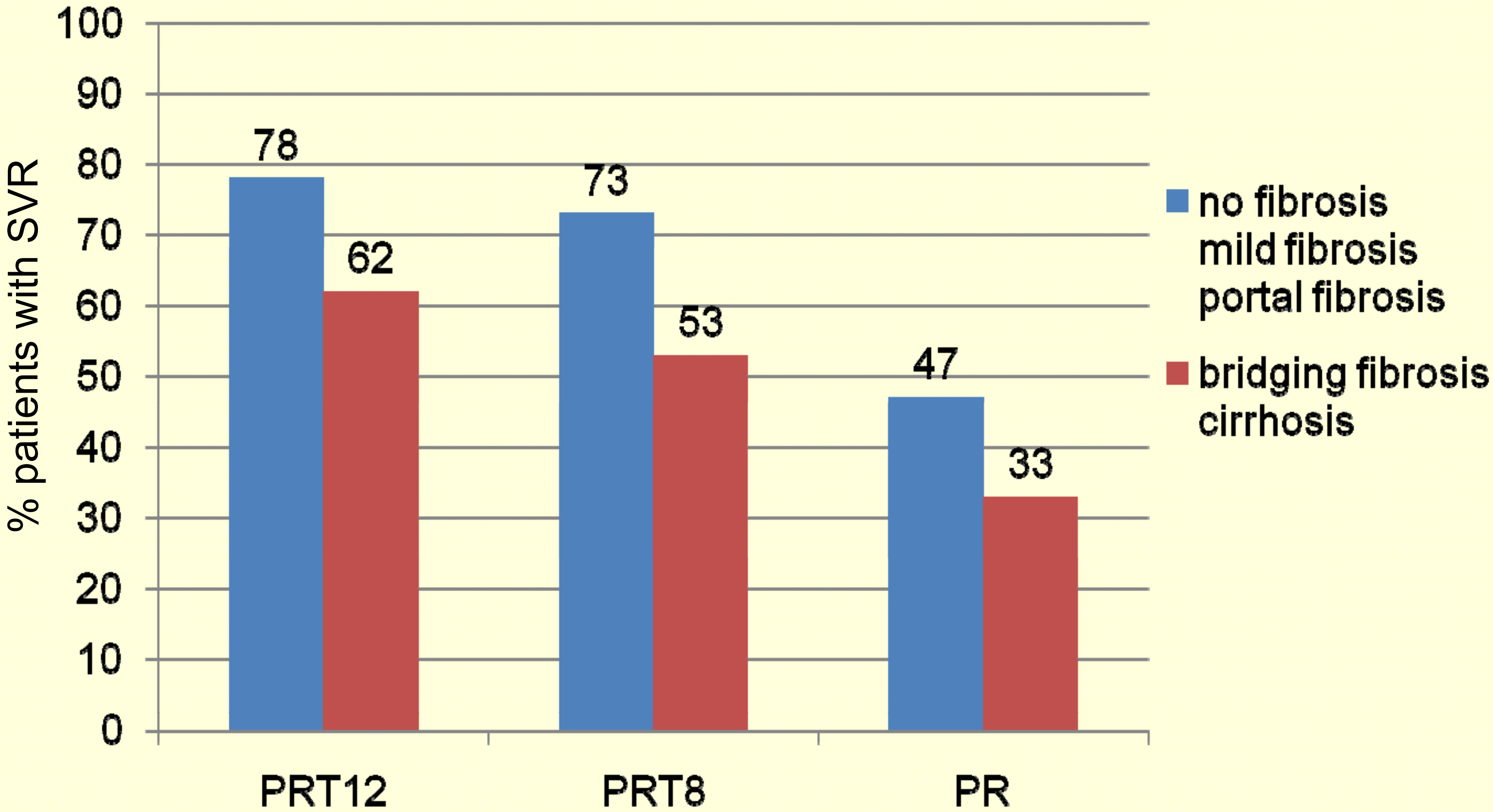


TVR-triple therapy increases SVR by 2.5 times compared SOC

Jacobson I et al. AASLD 2010

Who to treat:

SVR in TVR treated by fibrosis stage



In patients with advanced fibrosis TVR-triple therapy improve SVR in the same manner as in non-cirrhotics.

Jacobson I et al. AASLD 2010

AE due to triple therapy

BOC	BOC/PR48	BOC/RGT	PR
Hb<8.5 g/dL (ESA allowed) ?	9	5	4
Dysgeusia	43	37	18
TVR	**PRT12**	**PRT8**	**PR**
Hb<8.5 g/dL (ESA not allowed)	9	9	2
Dicontinuation due to rash	7	5	1

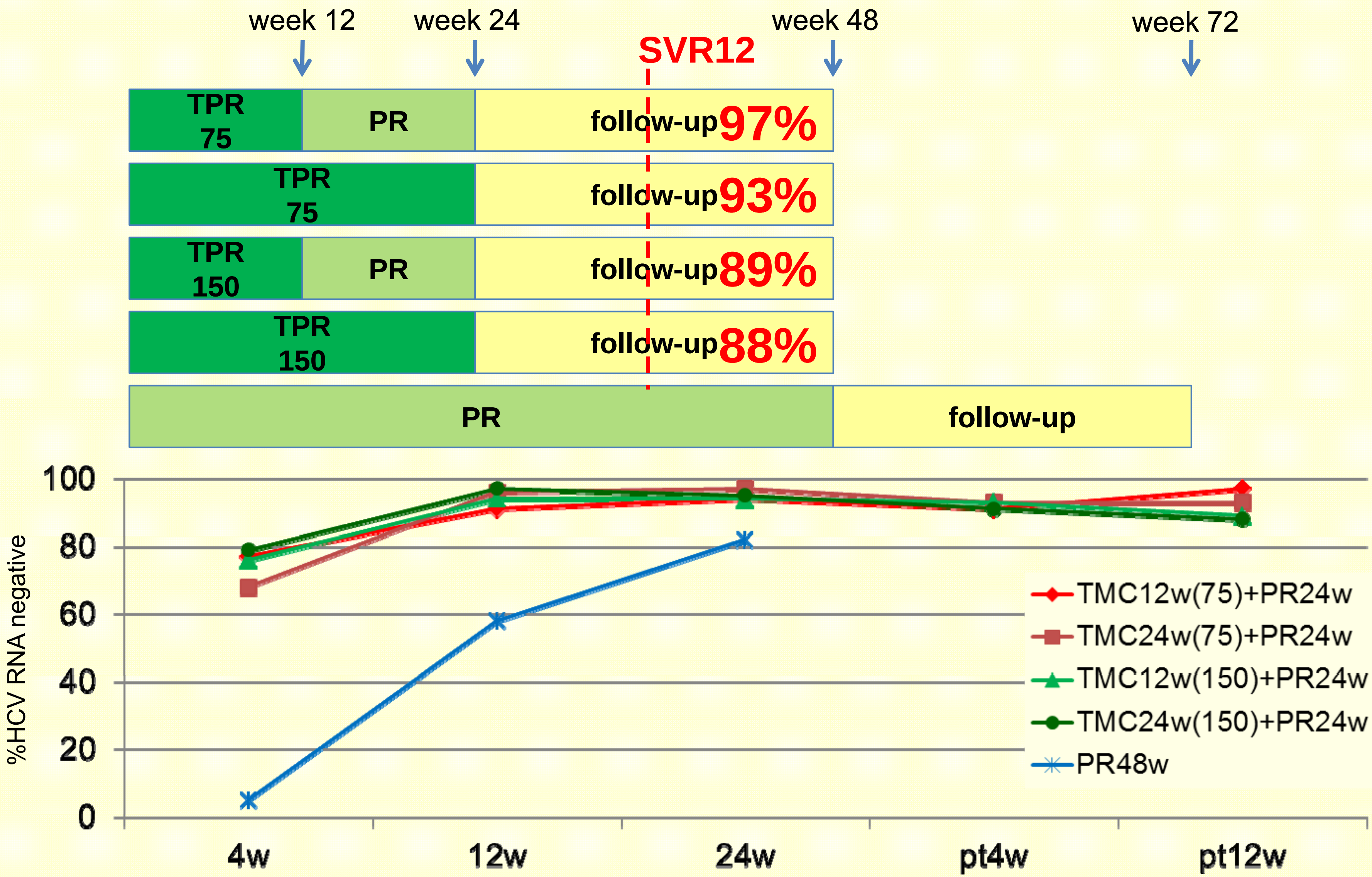
What happen if EAS can not be administered?
How it can affect anaemia and SVR rates?

Jacobson I et al. AASLD 2010

Poordad F et al. AASLD 2010; 52, 4 (suppl): 107A

TMC435 in triple therapy for G1 naïve patients

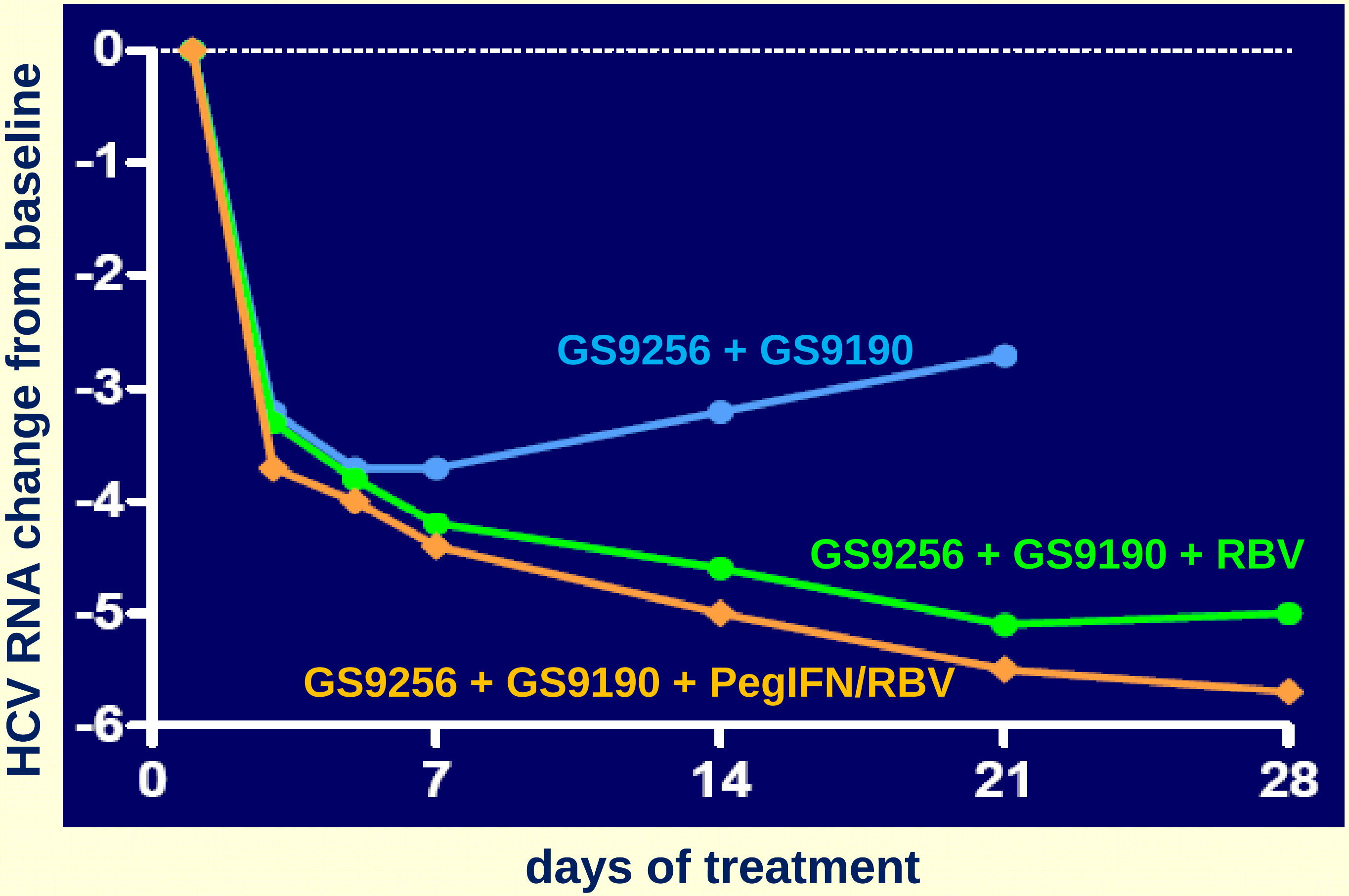
12 vs. 24 weeks of triple regimen and 75 vs. 150mg of TMC435



Fried MW et al. AASLD 2010; 52, 4 (suppl): 403A (LB5)

What about triple therapy with 2 DAA without PegIFN

GS-9190 (tegobuvir, polymerase inhibitor) + GS-9256 (protease inhibitor) for G1 naïve patients



Zeuzem S et al. AASLD 2010; 52, 4 (suppl): 400A (LB1)

Conclusions

1. BOC and TVR improve significantly efficacy of hepatitis C treatment in G1 naïve patients, including difficult to treat populations of blacks and cirrhotics.
2. Treatment algoritms for „real life” management need to be simplified to avoid suboptimal medication.
3. Direct acting antivirals (DAA) should be applied only if the patient is able to tolerate and accept treatment with PegIFN and ribavirin.
4. There is still need for drugs improving efficacy and shortening therapy in non-G1 patients.