

Actualités

Hépatite chronique C

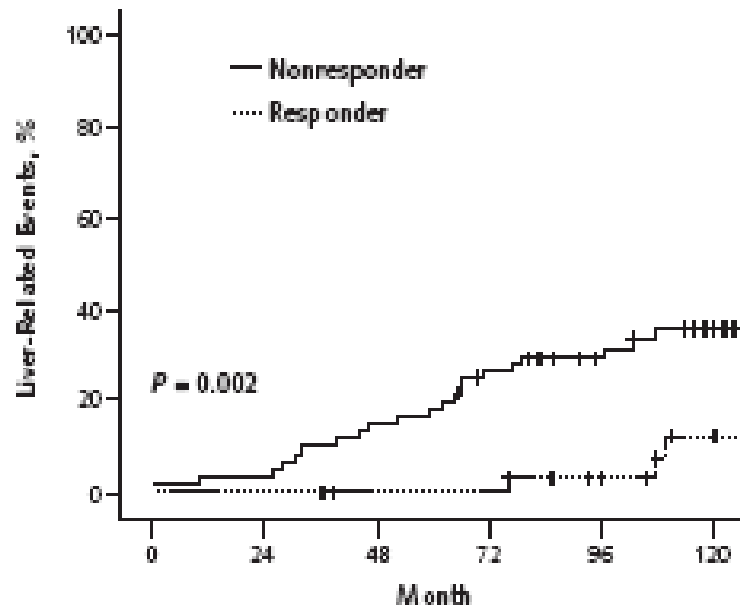
Christophe Hézode
Hôpital Henri Mondor - Créteil



Paris, le 25 janvier 2011

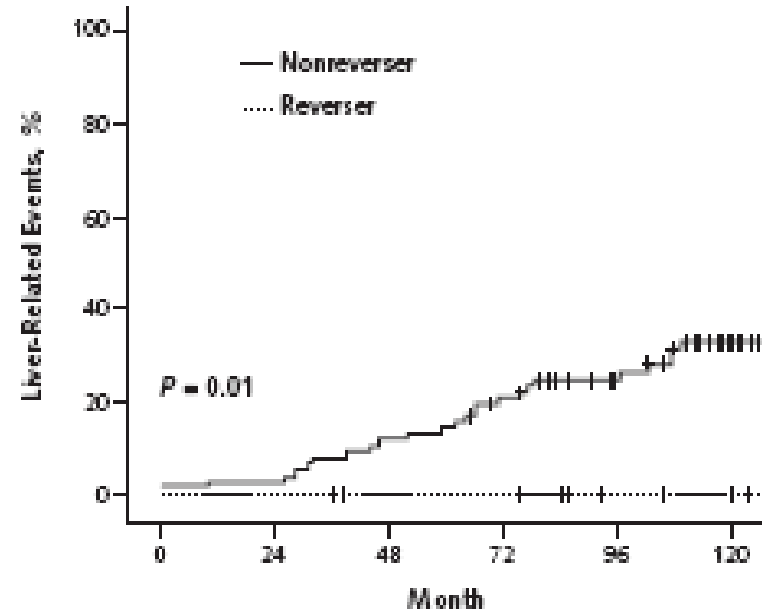
Impact sur la mortalité et les complications hépatiques : Réponse virologique/Régression de cirrhose

Réponse virologique soutenue



Number at risk	0	24	48	72	96	120
Nonresponders	61	59	52	43	32	22
Responders	35	35	33	33	27	18

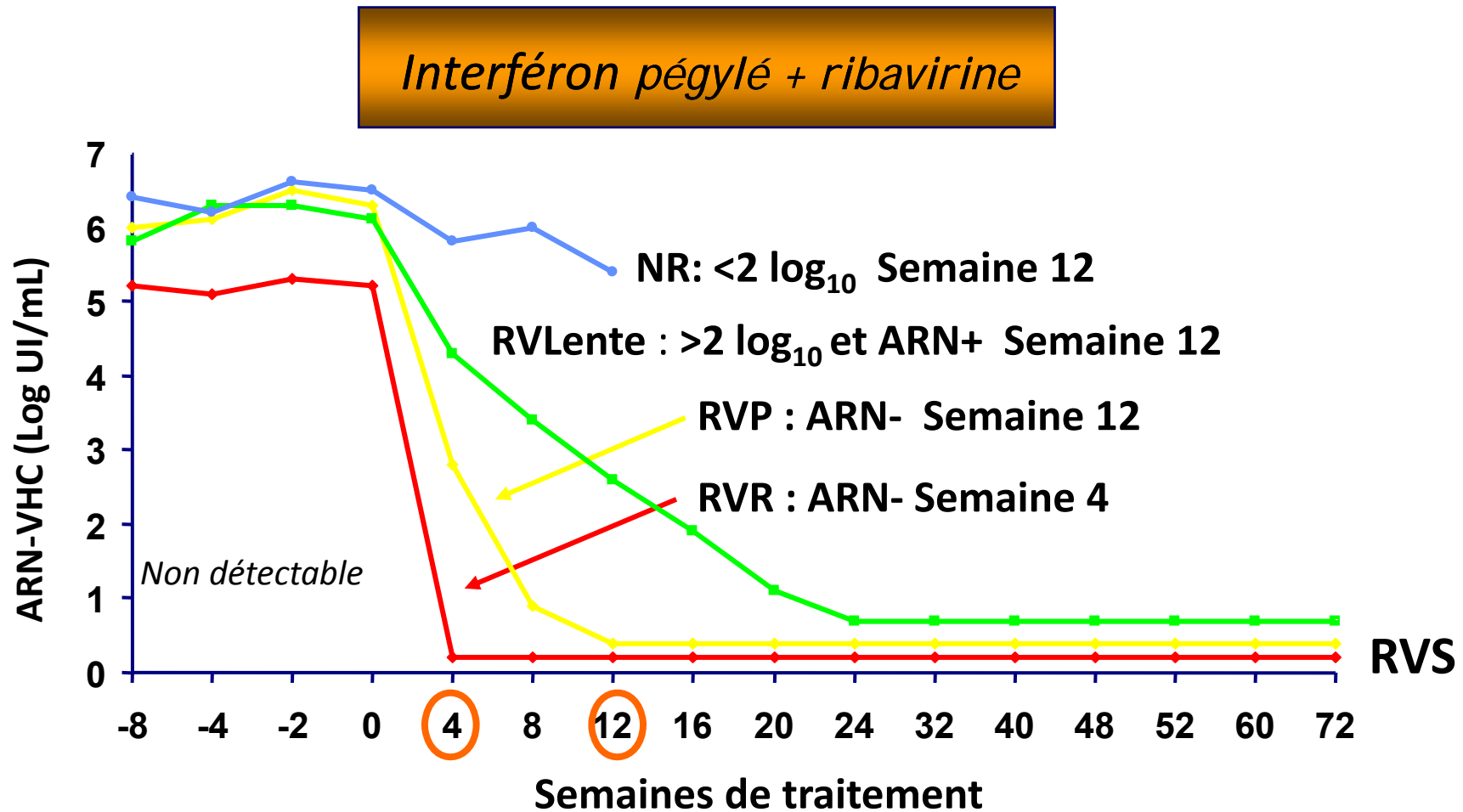
Régression de la cirrhose



Number at risk	0	24	48	72	96	120
Nonreversers	78	76	69	60	47	30
Reversers	18	18	16	16	12	10

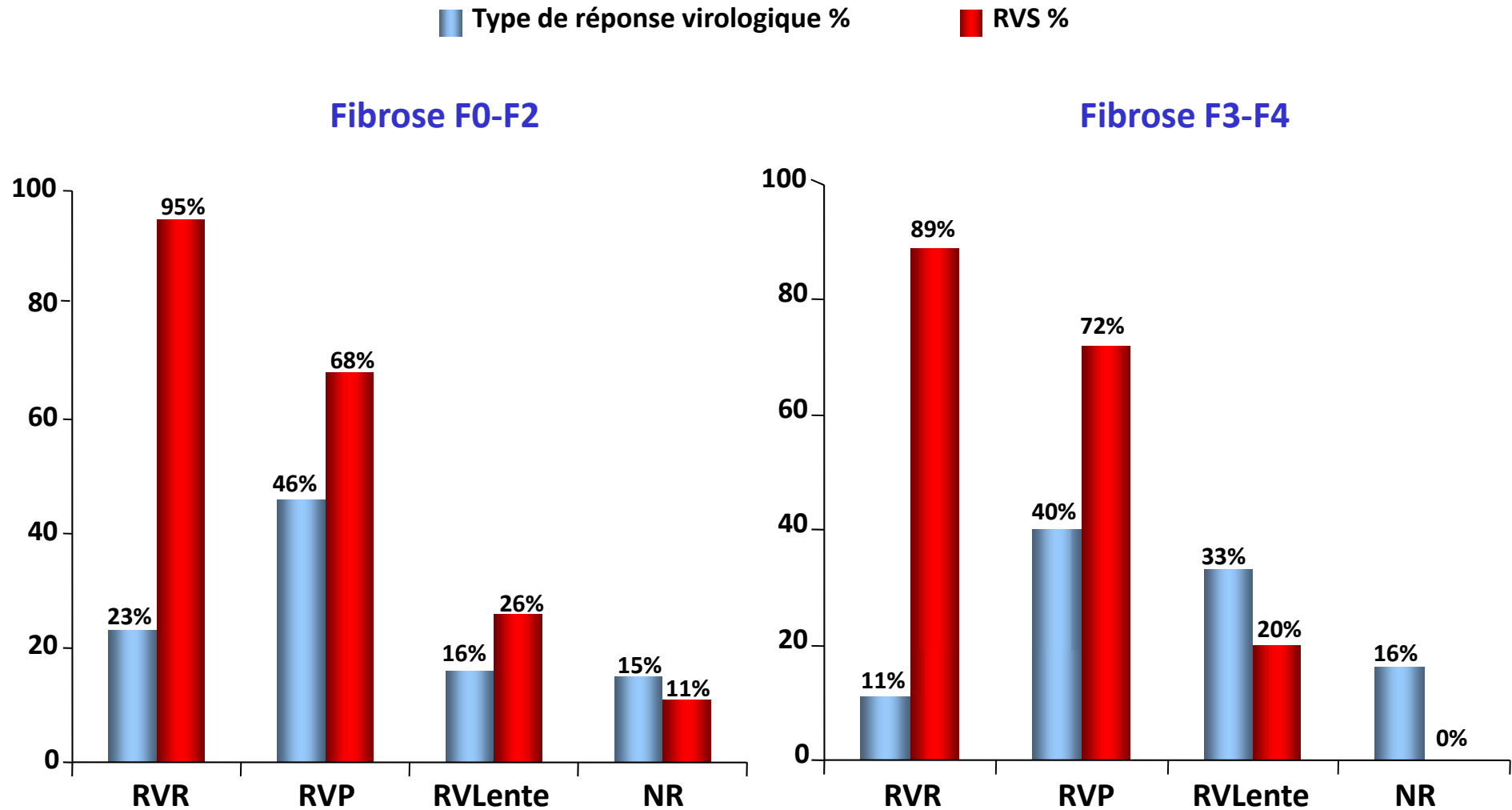
Hépatite chronique C

Types de réponse virologique



Génotype 1 et 4 : IFN-PEG α 2a + RBV 48 semaines

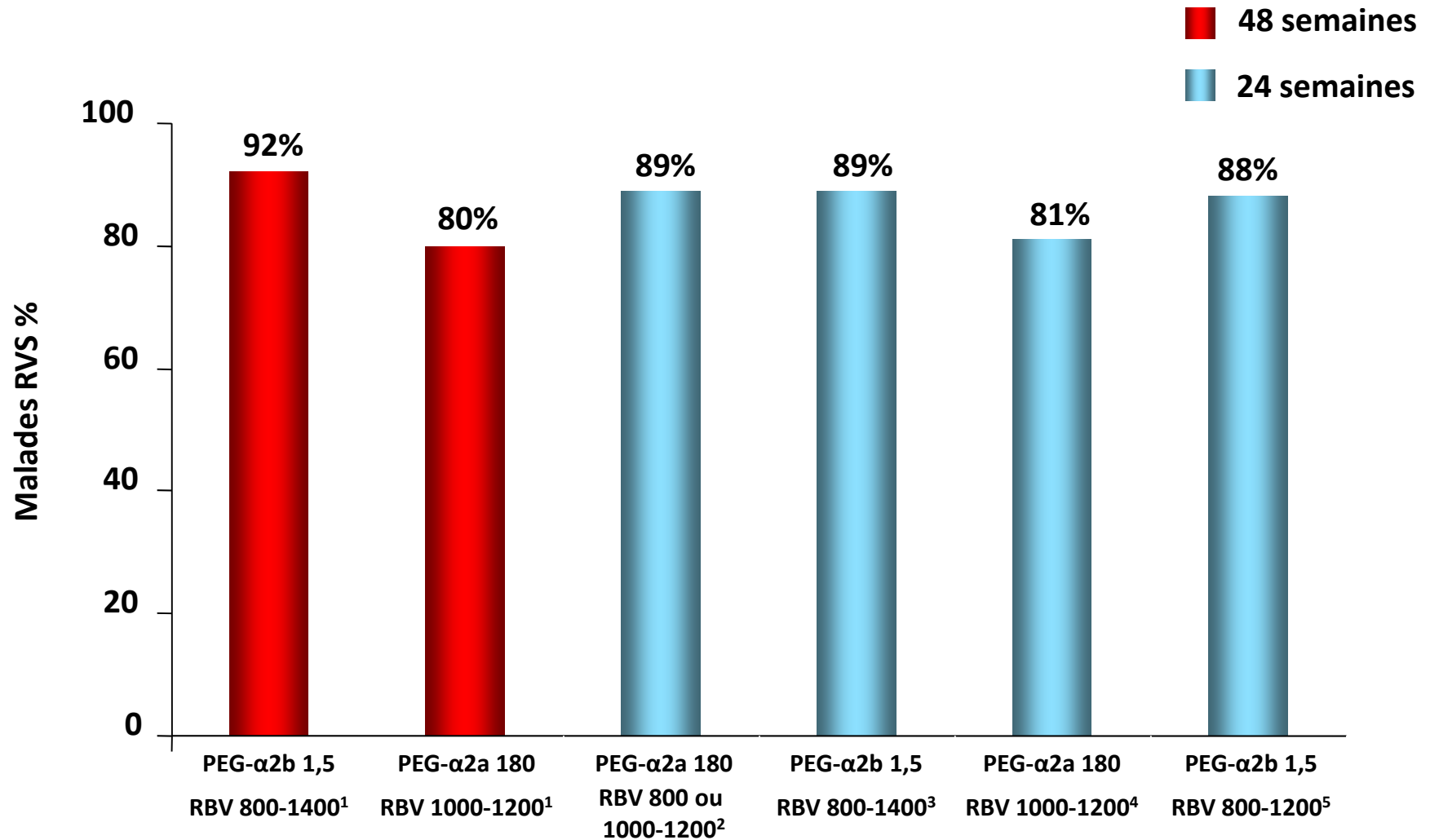
Type de réponse et RVS



RVR=ARN-VHC<50UI/ml à S4; RVP=ARN-VHC≥50UI/ml à S4 et <50UI/ml à S12
 RVLente=ARN-VHC≥50UI/ml à S4 et S12, mais ↓≥2 log à S12; NR= ↓ARN-VHC<2 log à S12

Traitement « à la carte »

Réponse Rapide : 24 semaines c'est suffisant

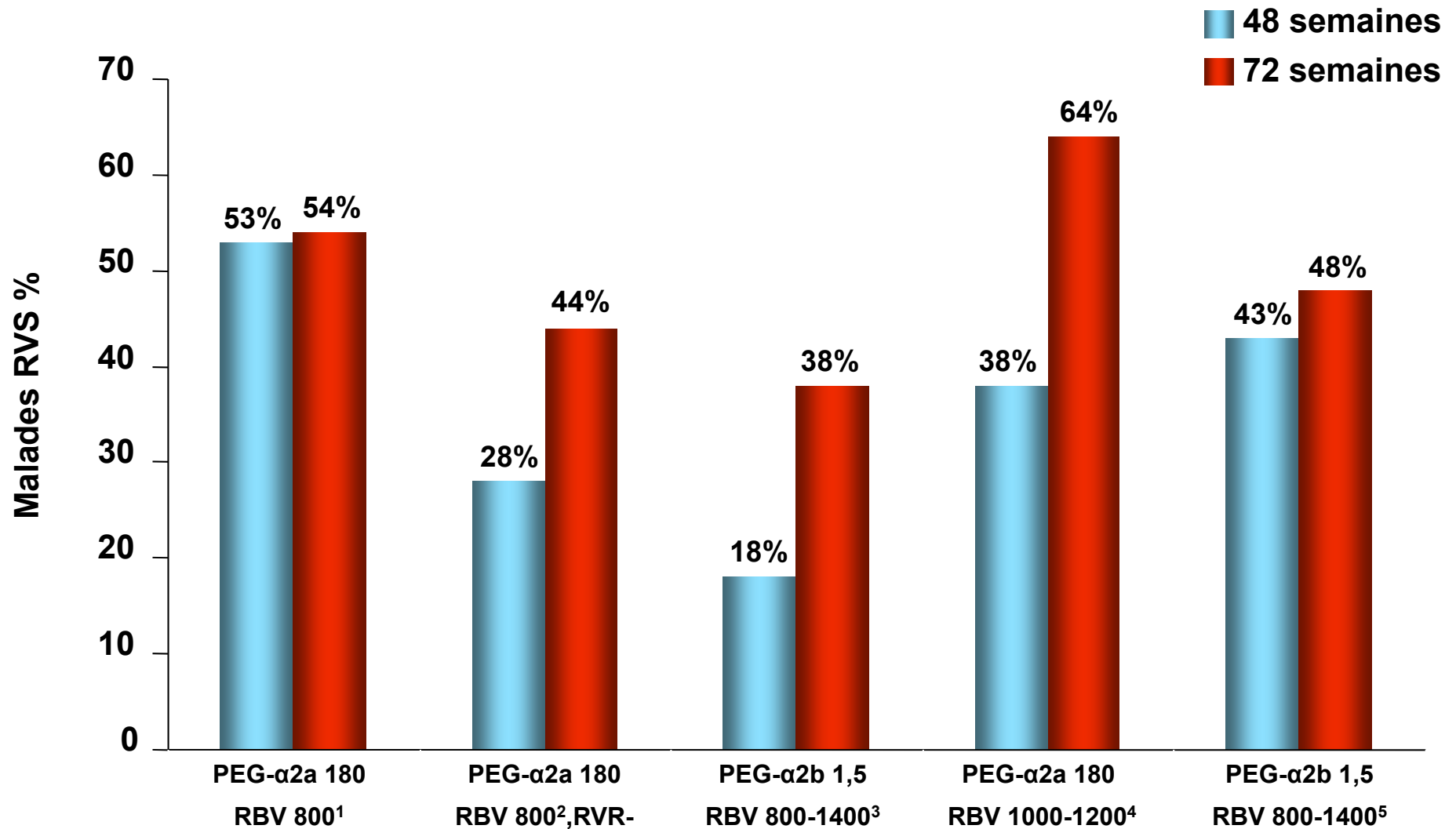


¹McHutchison JG et al, NEJM 2009; ²Jensen DM et al, Hepatology 2006; ³Zeuzem S et al, J Hepatol 2006;

⁴Ferenci P et al, Gastroenterology 2008; ⁵Craxi A et al (PREDICT), AASLD 2009.

Traitement sur Mesure

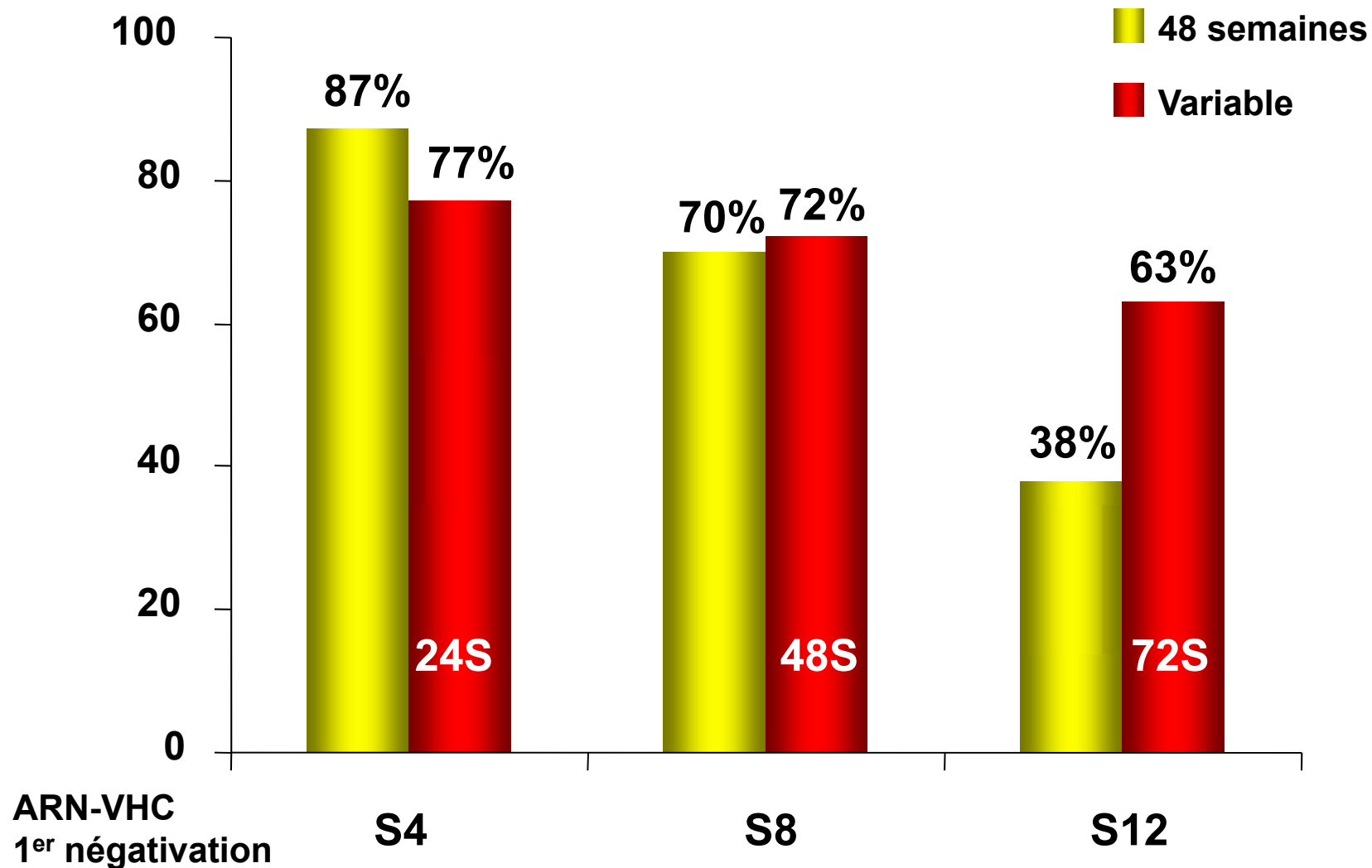
Réponse Lente : 72 semaines font mieux ?



¹Berg T et al, Gastroenterology 2006; ²Sanchez-Tapias J et al, Gastroenterology 2006; ³Pearlman BL et al, Hepatology 2007; ⁴Mangia A et al, Hepatology 2008; ⁵Buti M et al, EASL 2009

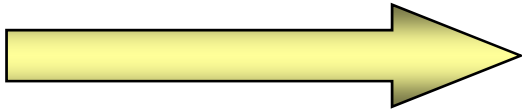
Traitement sur Mesure

en fonction de la 1ère négativation de l'ARN-VHC

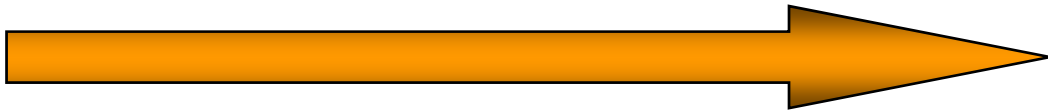


Traitement sur Mesure Génotype 1

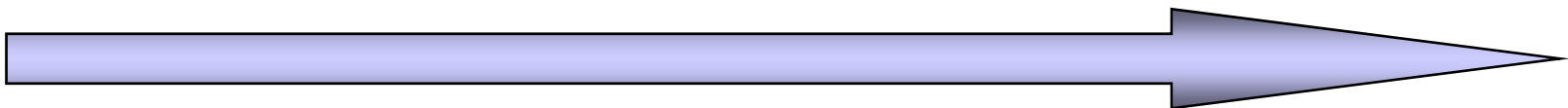
Charge virale initiale faible
Réponse Virologique Rapide



ARN-VHC indétectable à S12 (1^{ère} fois)

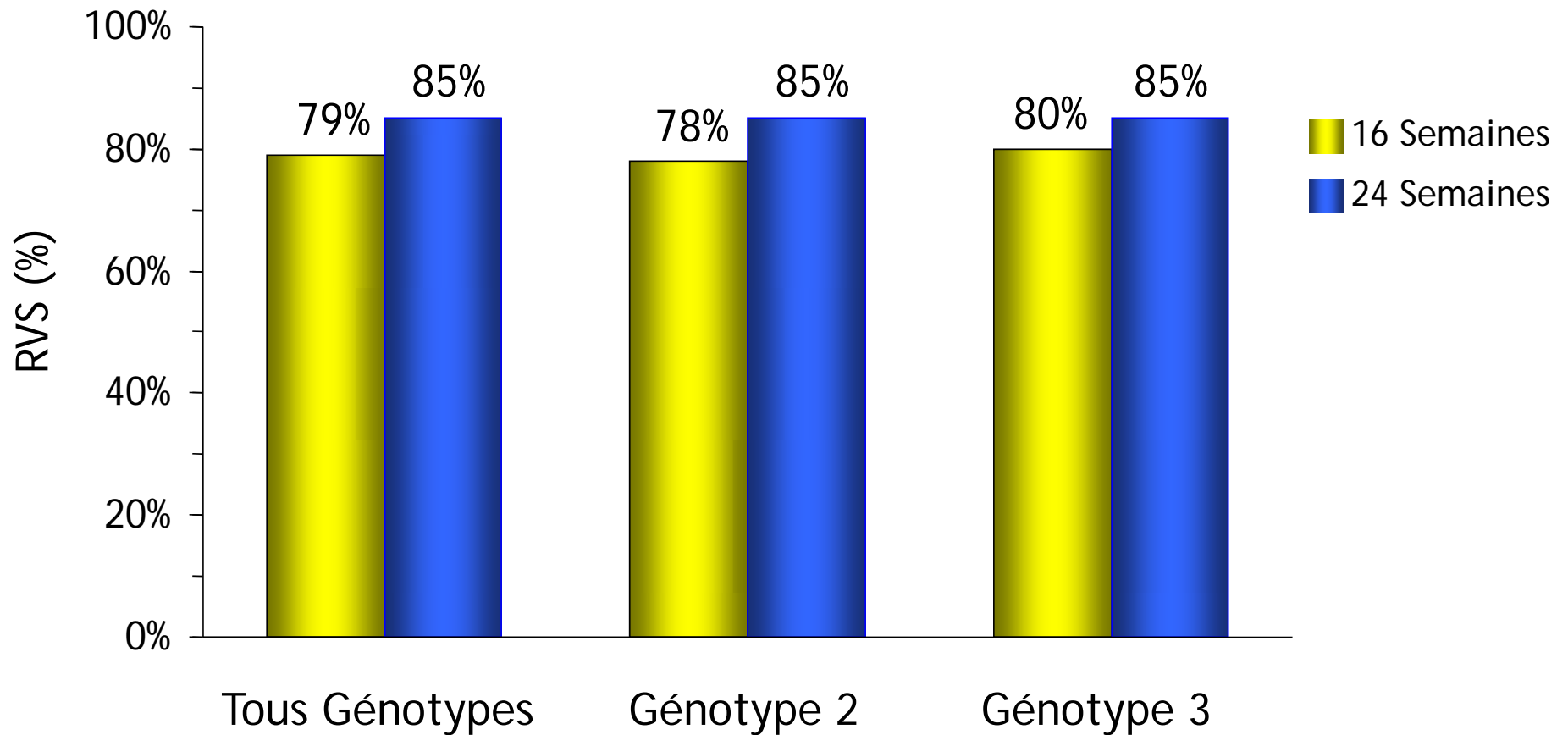


Réponse Virologique Lente
ARN-VHC indétectable entre S12 et S24



0 24 Semaines 48 Semaines 72 Semaines
Durée du traitement

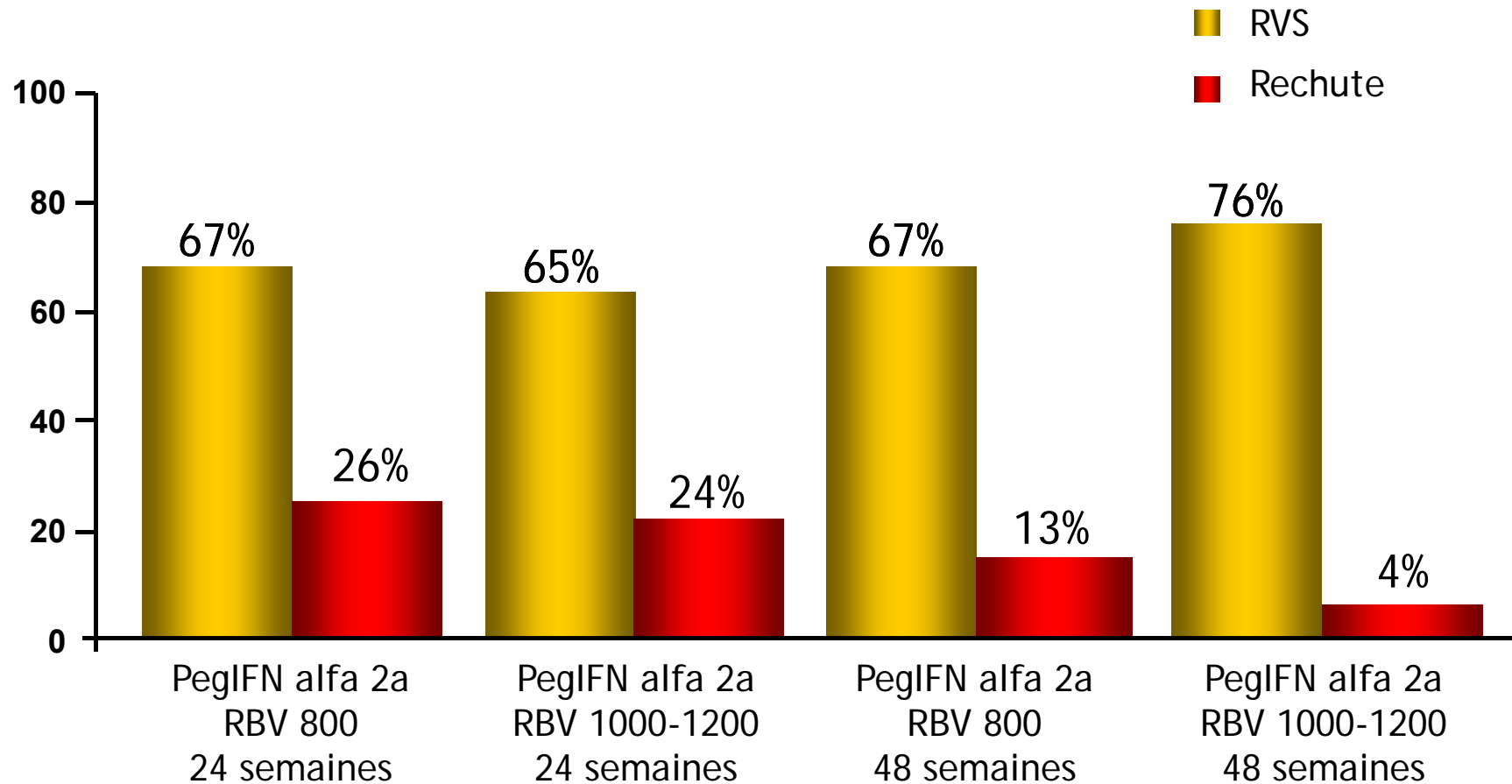
Génotypes 2 ou 3, Peut on traiter moins longtemps les répondeurs virologiques rapides* ?



*ARN-VHC < 50 UI/mL à S4

Shiffman ML et al. N Engl J Med 2007;357:124-34

Génotypes 2 ou 3, Faut-il traiter plus longtemps en absence de réponse virologique rapide* ?

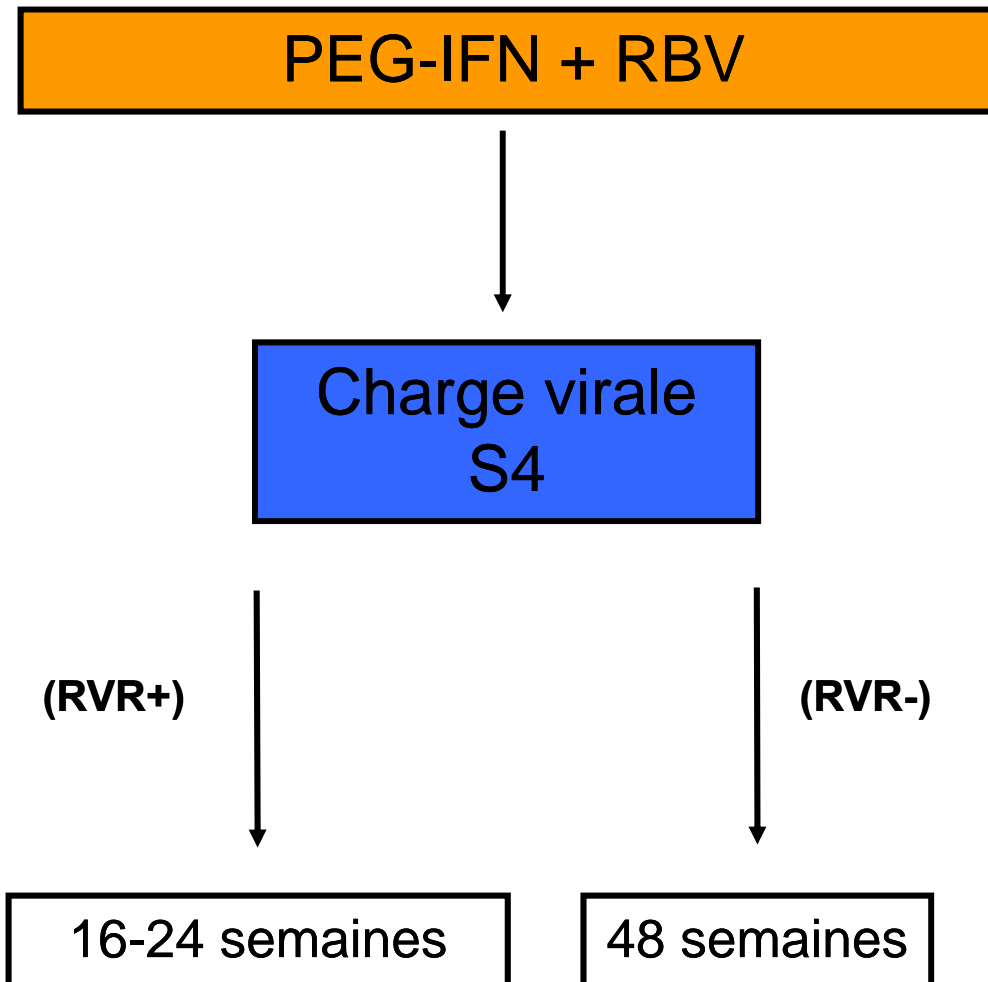


*ARN-VHC > 50 IU/mL à S4

*Fried MW et al. N Engl J Med. 2002;347:975-982.
Hadziyannis SJ et al. Ann Intern Med. 2004;140:346-355.
Willems B et al. EASL2007 Abstract 8.*

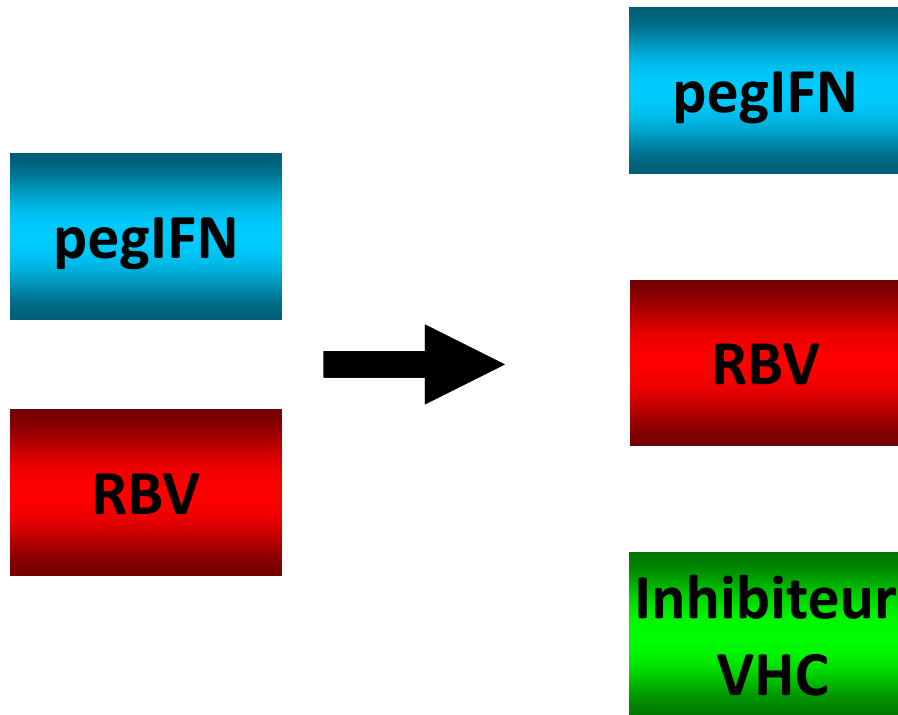
Algorithme de traitement

Génotypes 2 ou 3



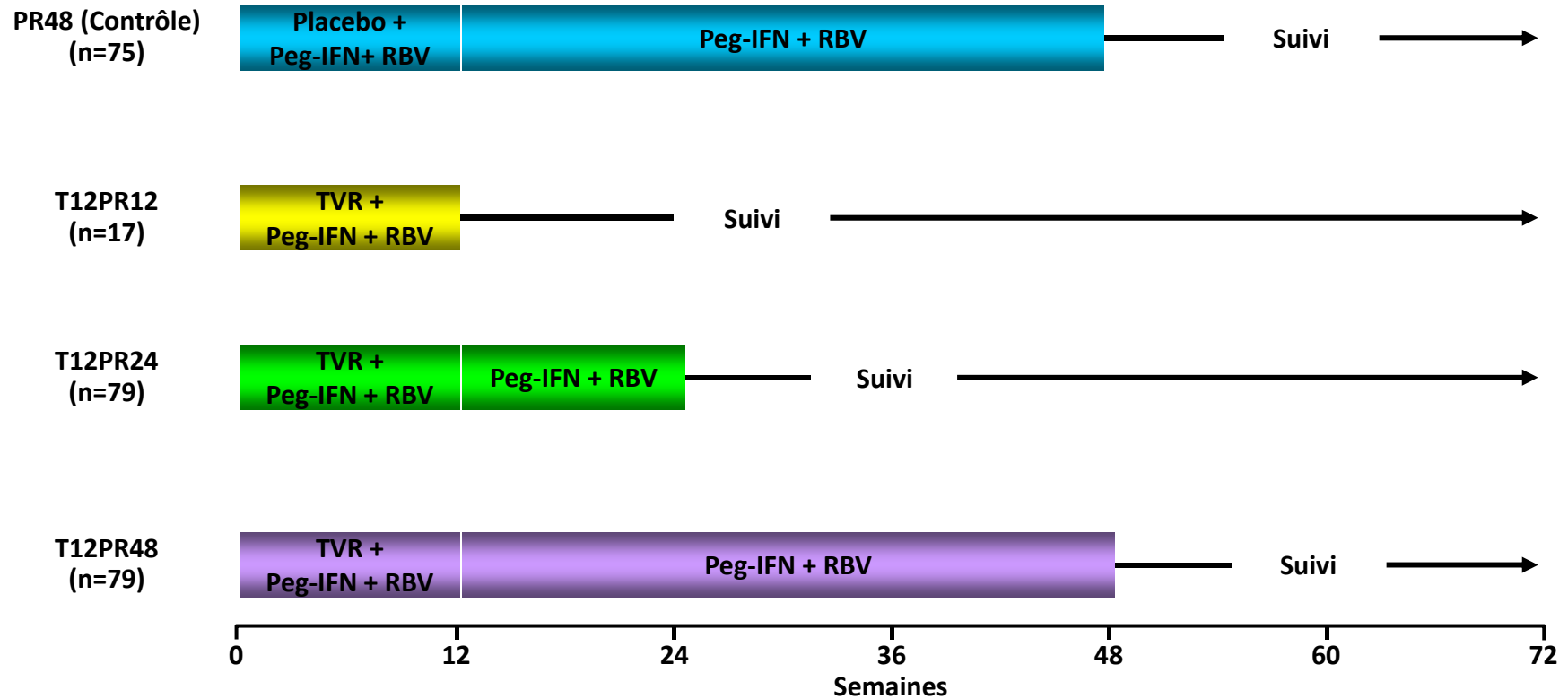
Traitement de 2012

Traitement futur pour le VHC



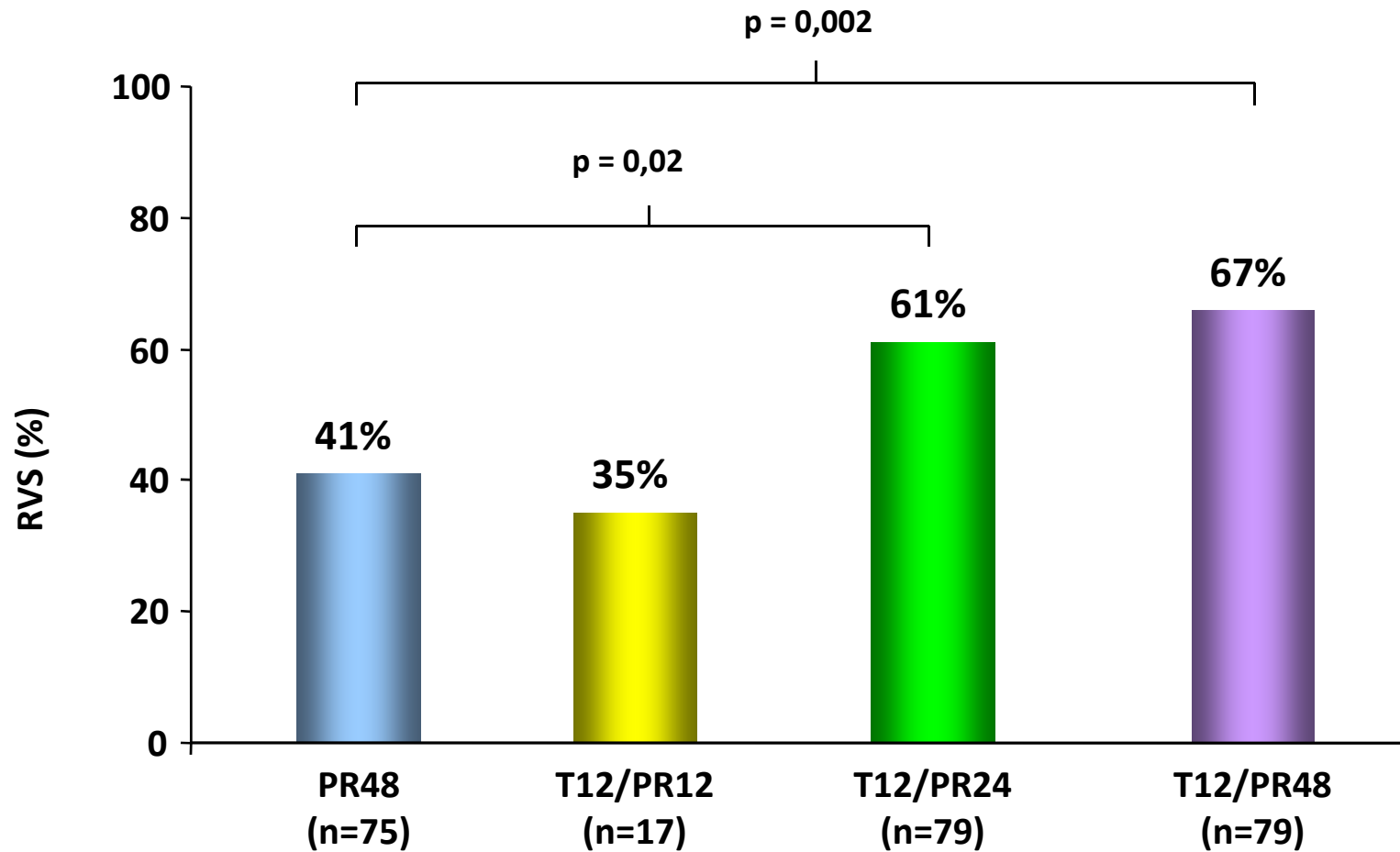
Télaprevir Génotype 1 Naïfs

PROVE1: Schéma de l'étude

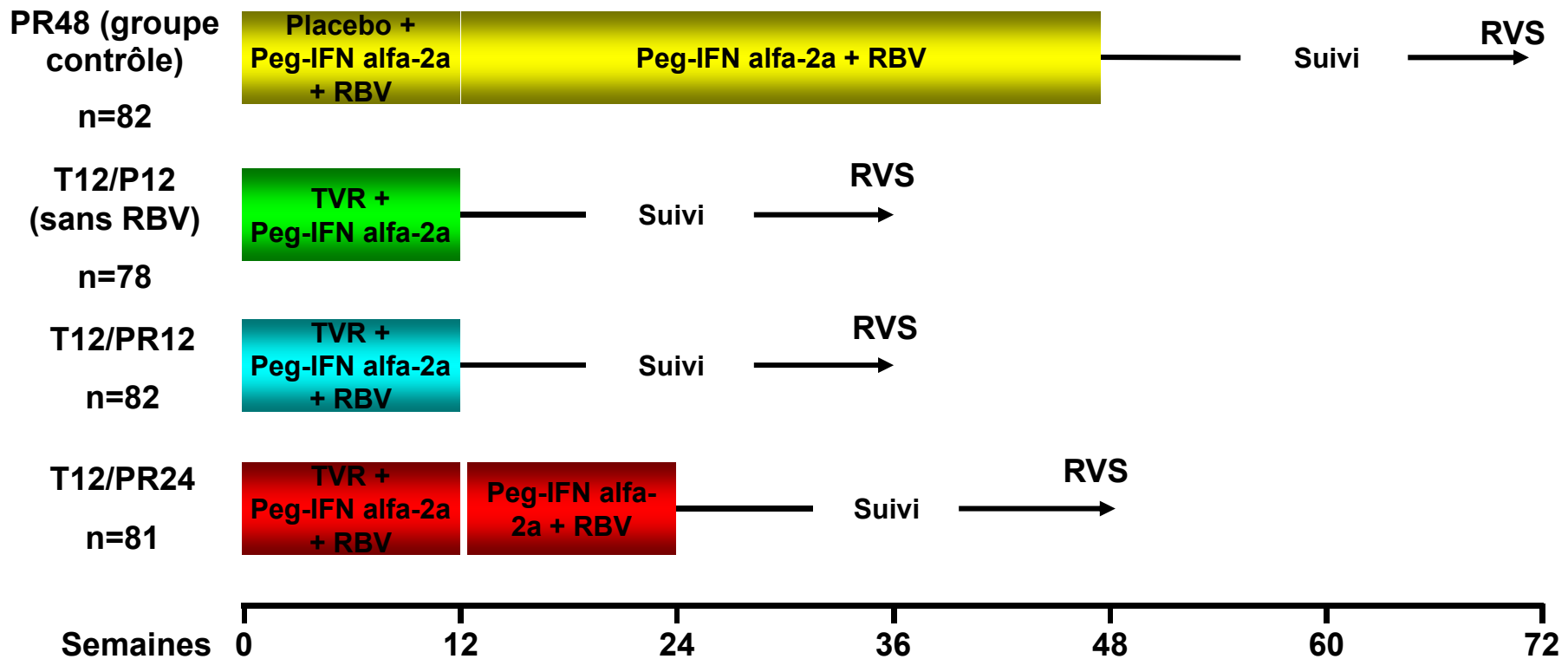


Essai PROVE1, Phase II

Génotype 1, Naïfs, US



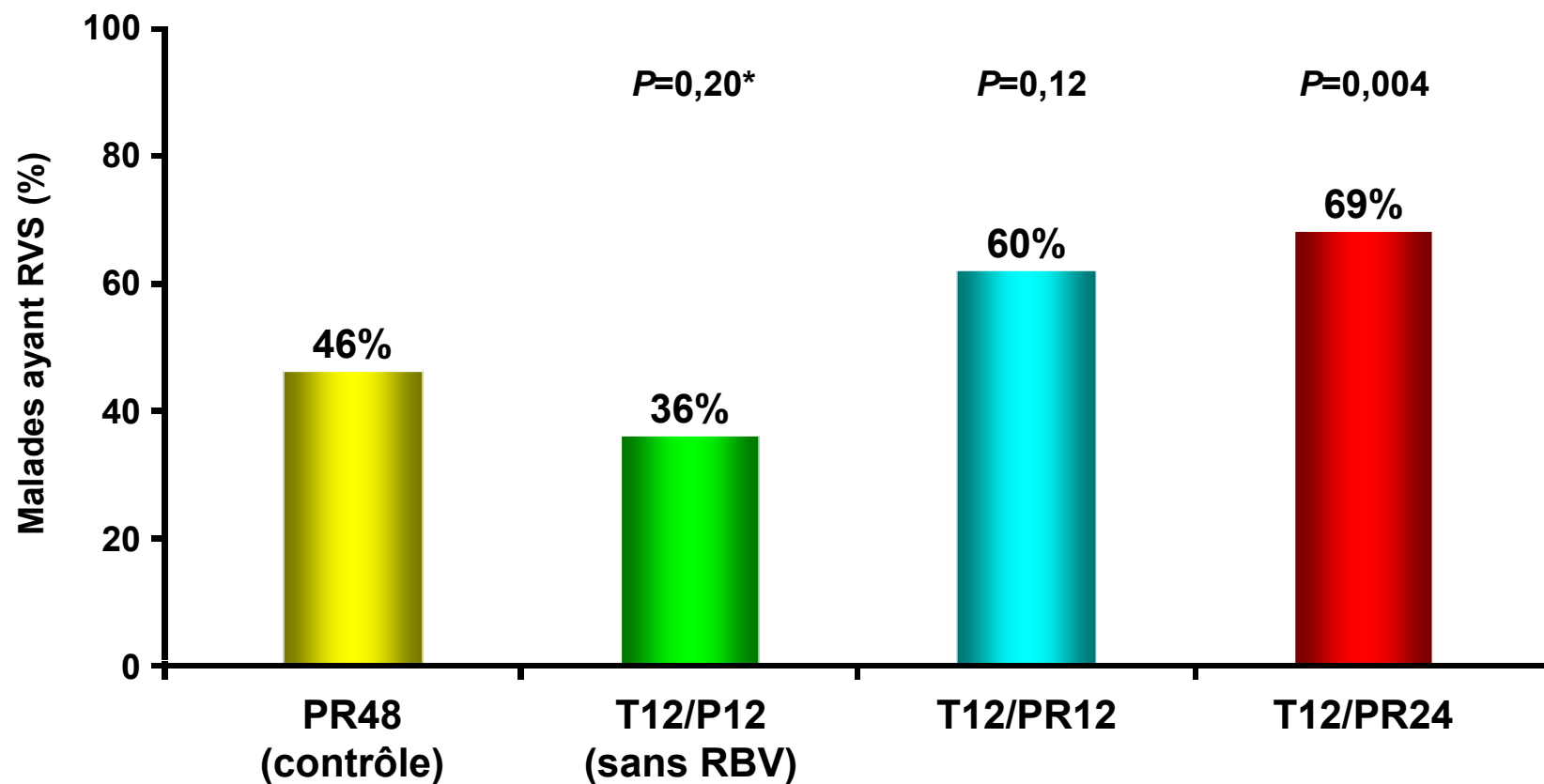
PROVE2: Schéma de l'étude



P = Peg-IFN alfa-2a 180 µg/semaine;

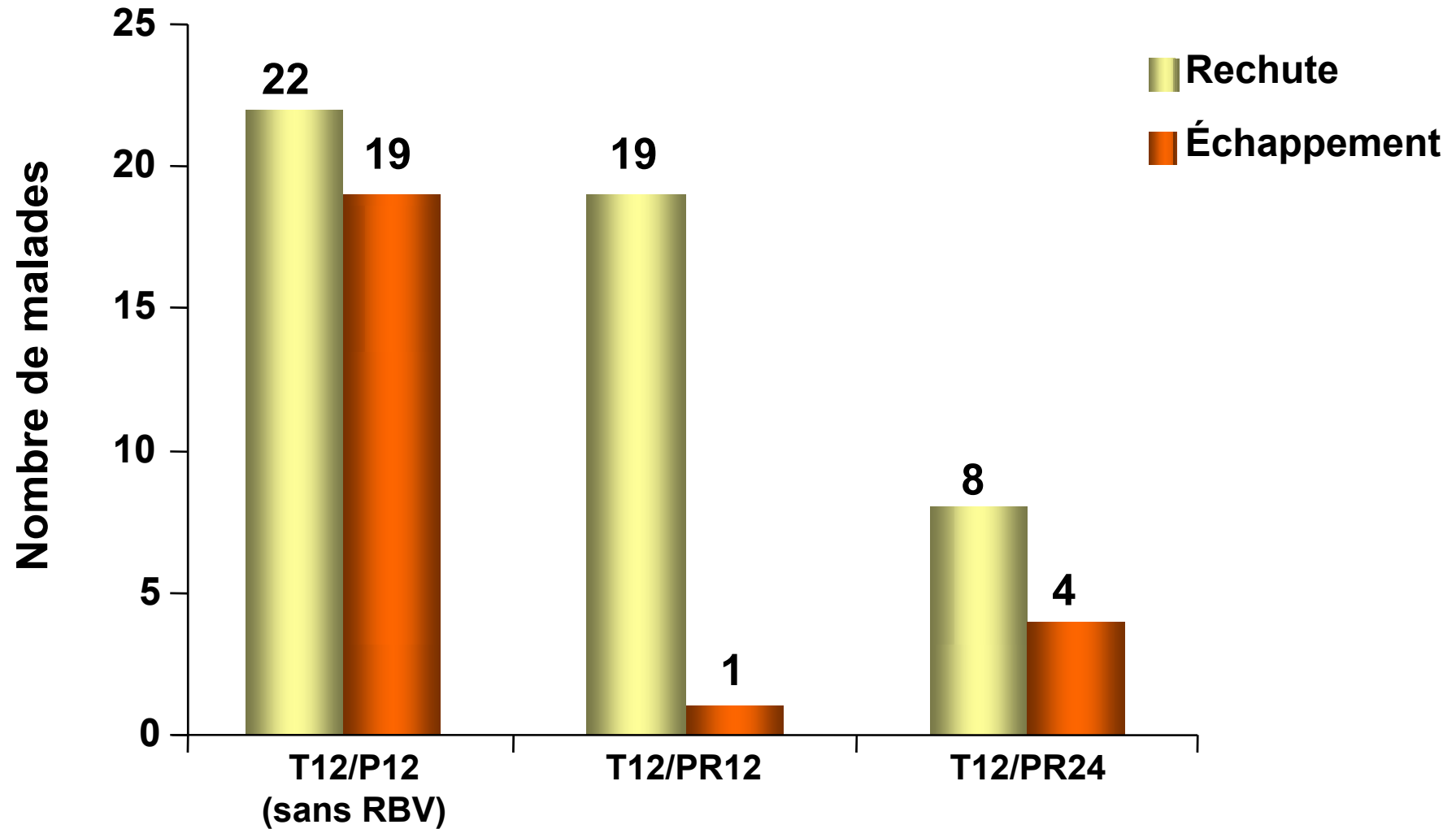
R = RBV 1000 ou 1200 mg/jour; T = TVR 750 mg toutes les 8h

Prove2 : Efficacité en terme de RVS

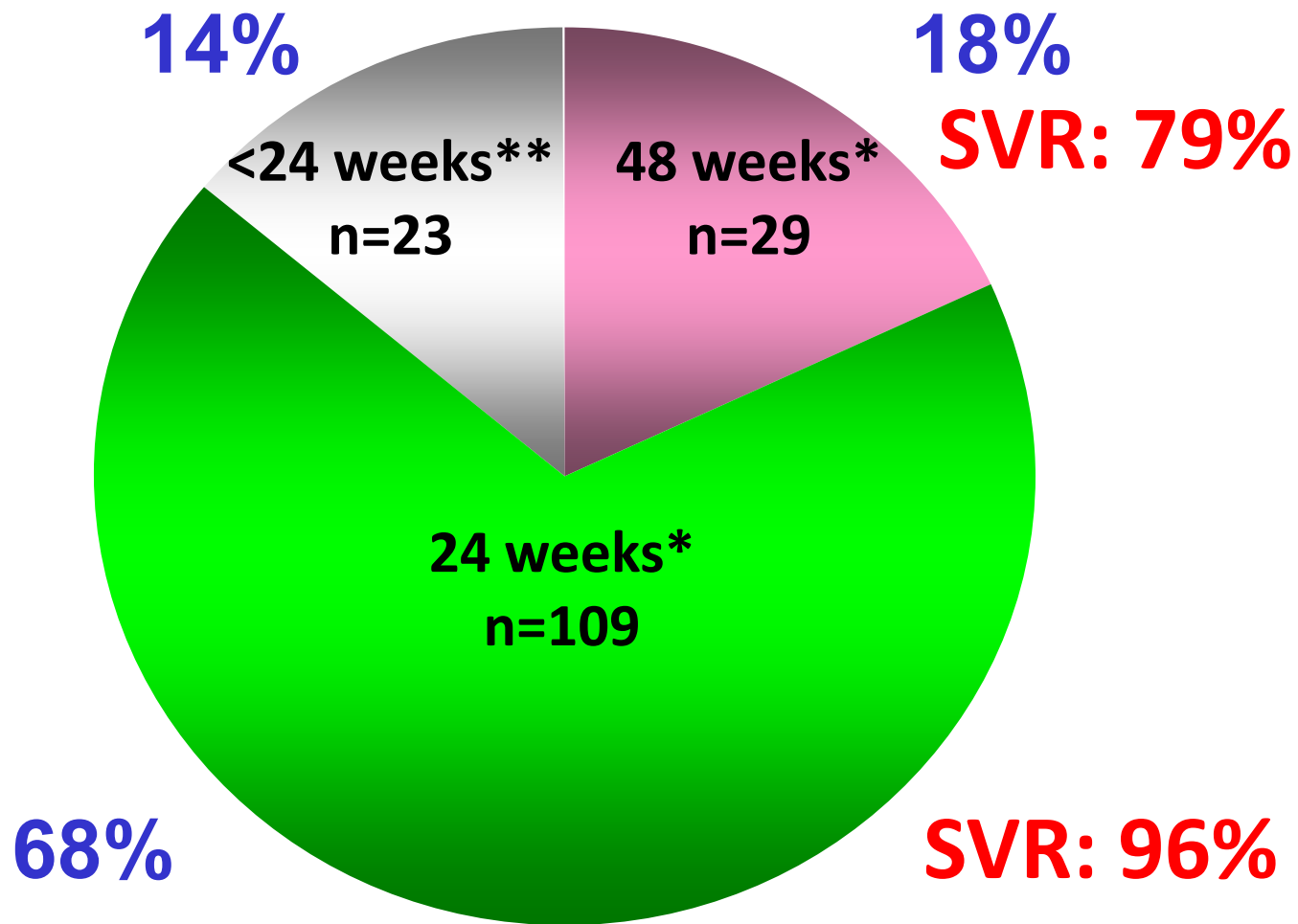


**versus* PR48 (contrôle), test exact de Fischer bilatéral

Prove2 : Échappement et Rechute



C208: response guided treatment SVR according Treatment Duration

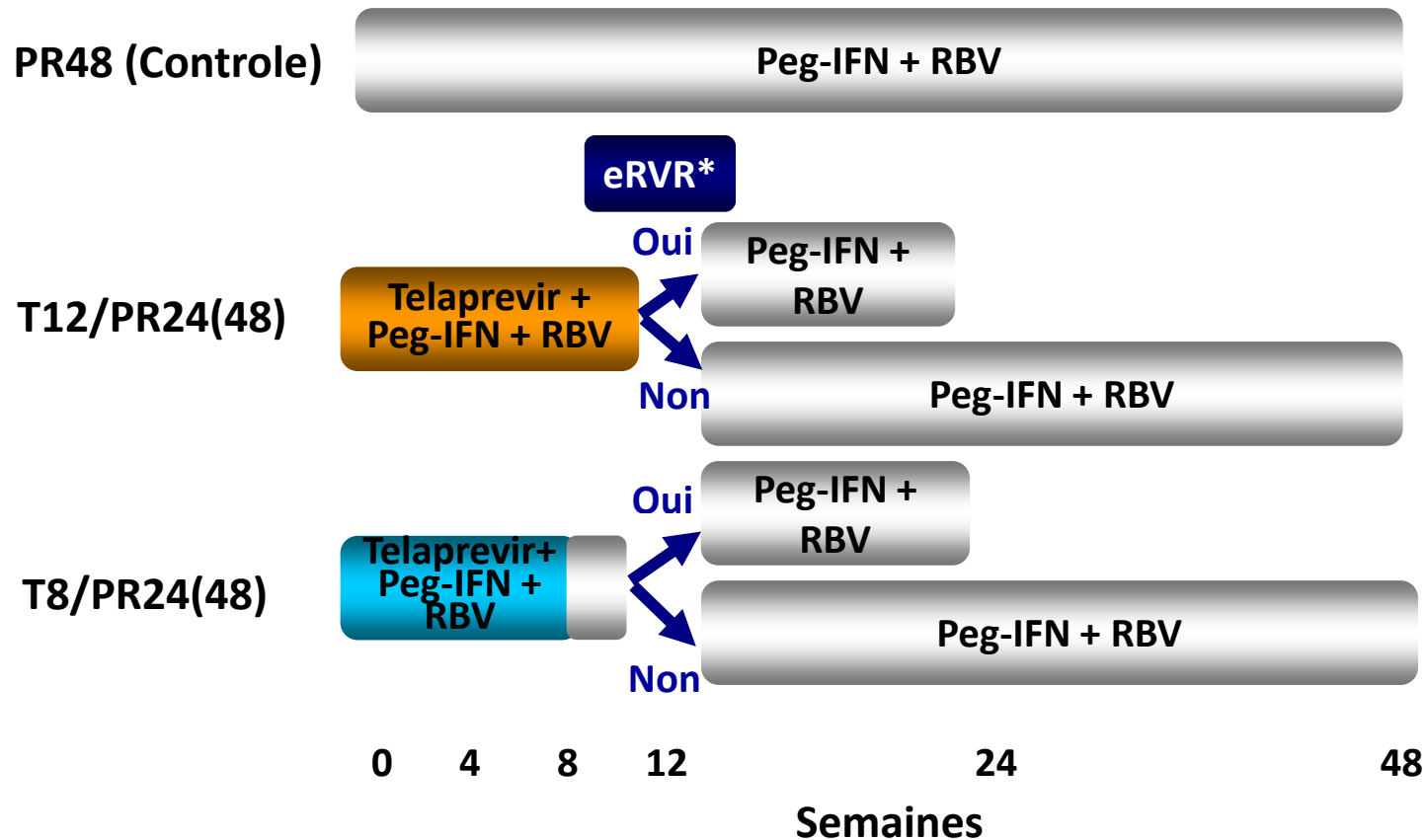


*Based on the assigned intention to treat. Some patients discontinued earlier

**23 pts discontinued <24 weeks: 8 for virological reasons, 11 due to adverse event (AE), 4 due to other reasons

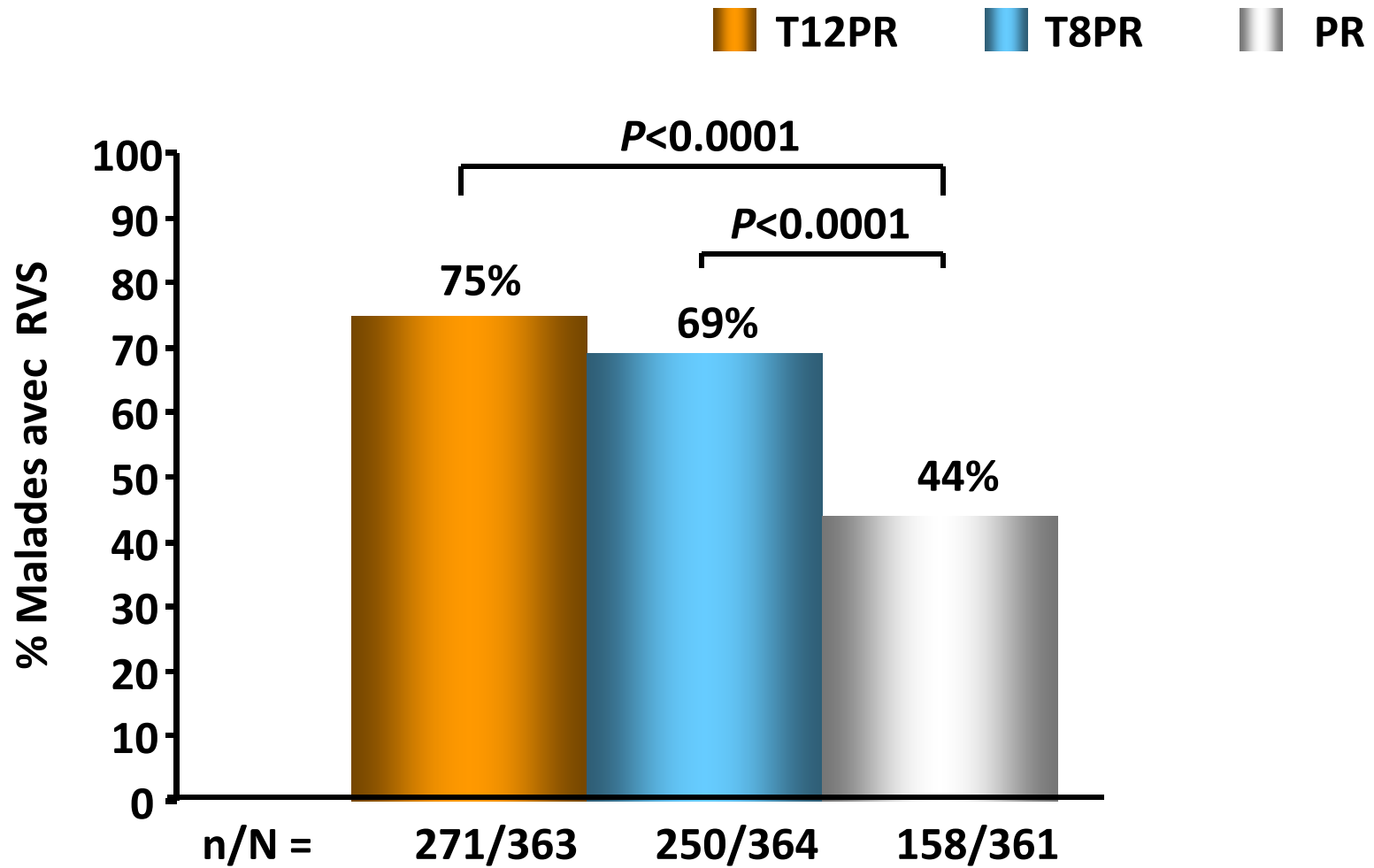
Forns X, et al. J Hepatol 2010;52:S26

Advance : Phase III, G1 malades naïfs

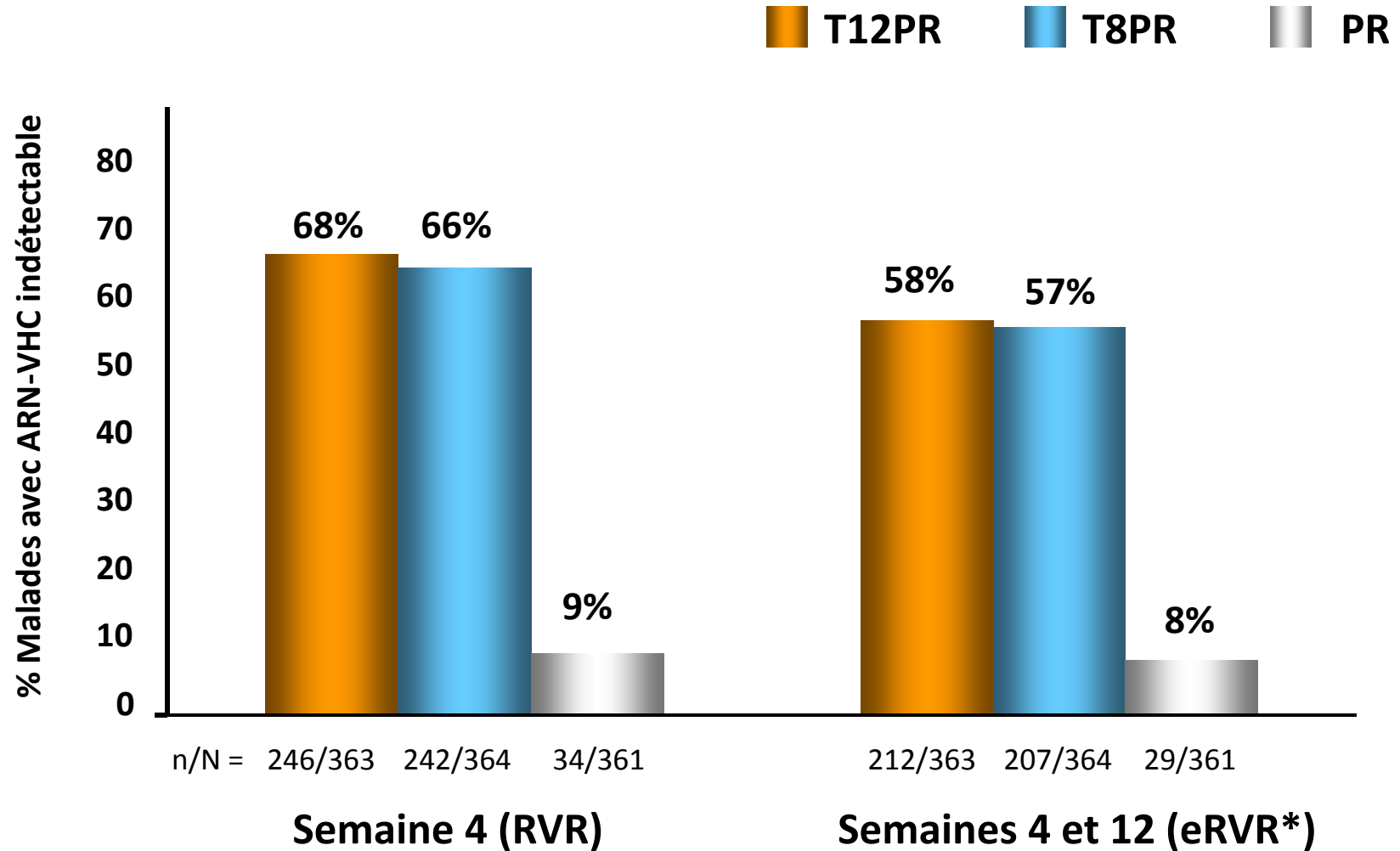


* eRVR = RVR étendue = ARN-VHC indétectable aux semaines 4 et 12

Advance : Phase III, G1 malades naïfs



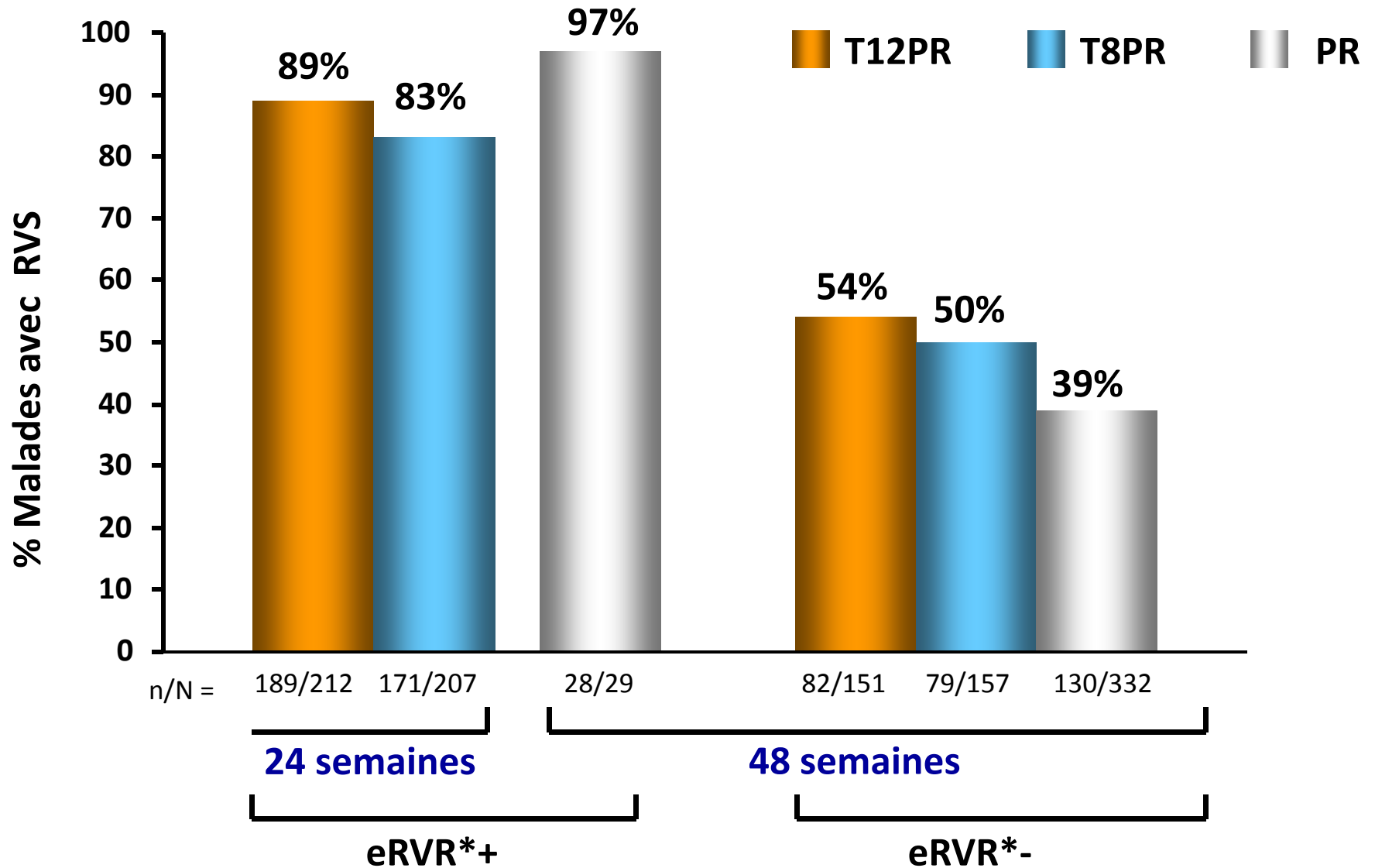
Advance : Phase III, G1 malades naïfs



* eRVR = RVR étendue = ARN-VHC indétectable aux semaines 4 et 12

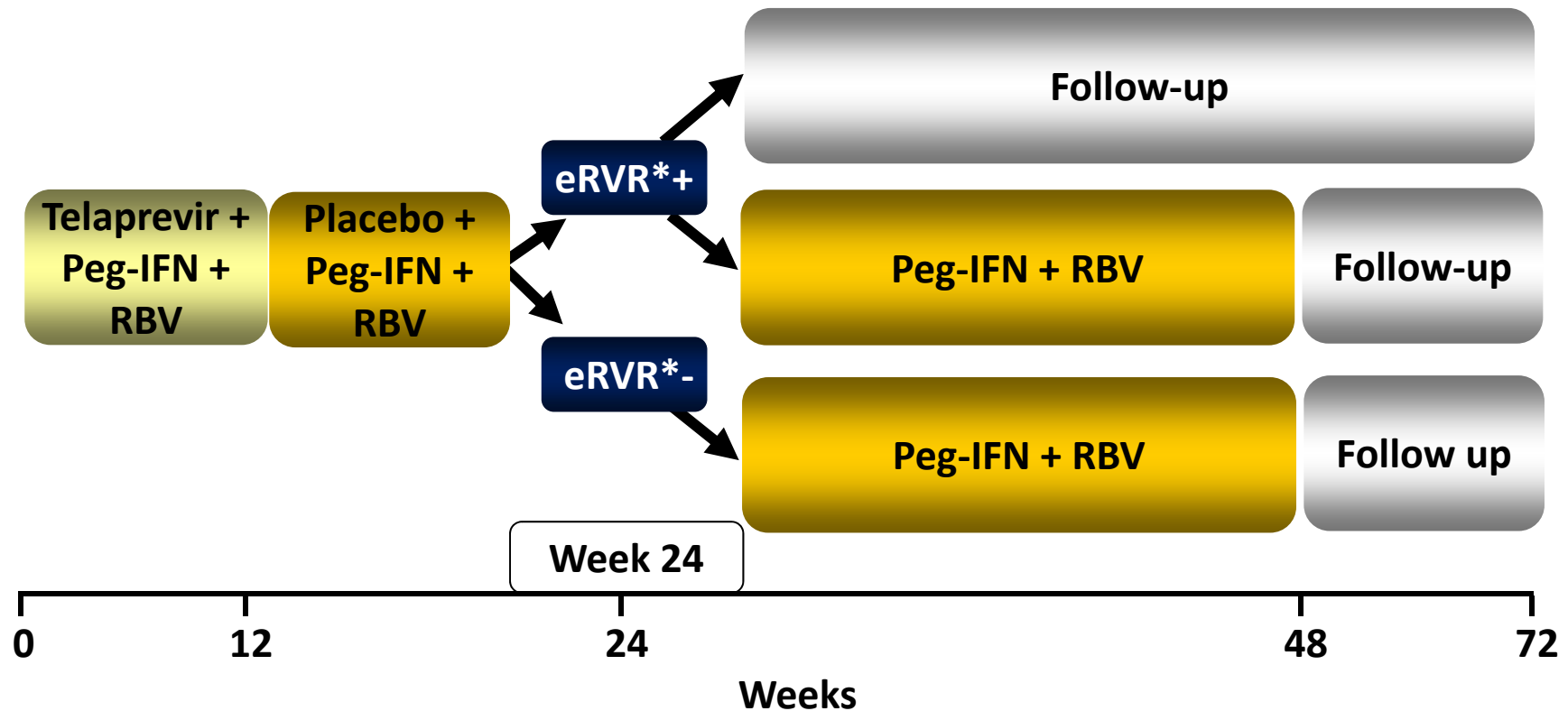
Jacobson I et al, AASLD 2010

Advance : RVS selon la eRVR*



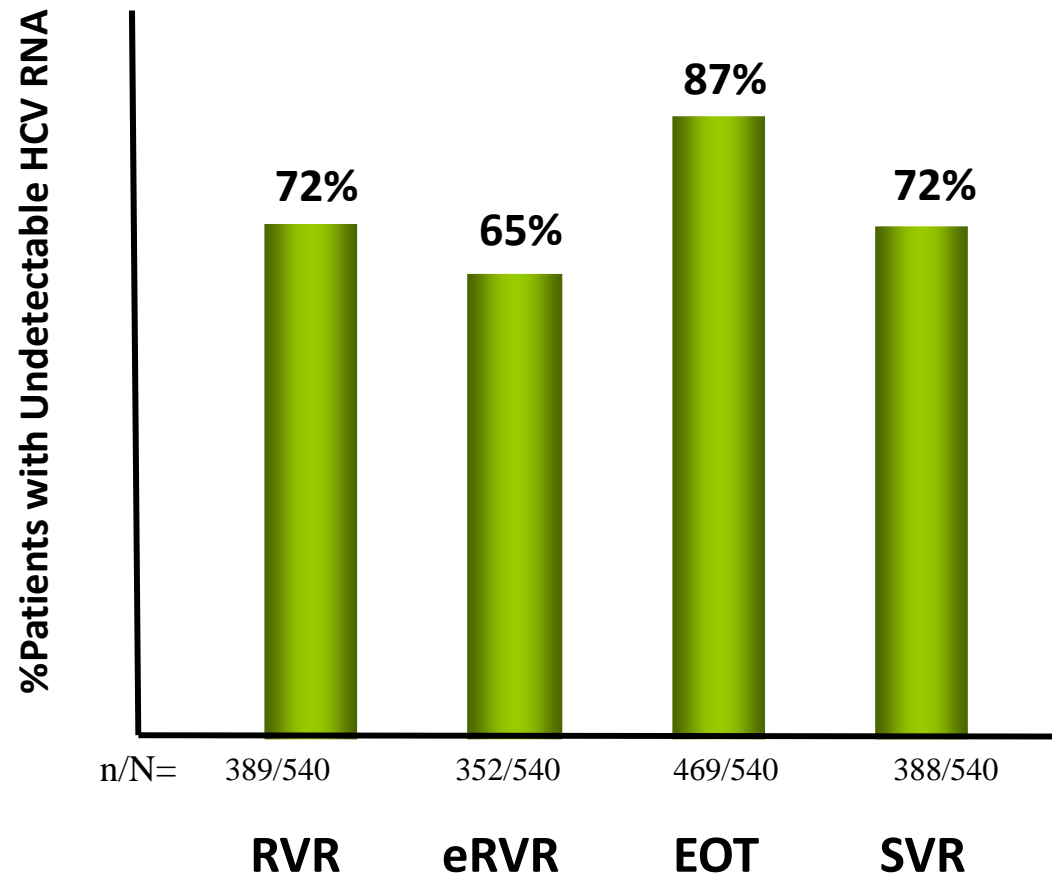
* eRVR = RVR étendue = ARN-VHC indétectable aux semaines 4 et 12

ILLUMINATE: Study design, Phase III trial *Genotype 1, Naïve Patients*



* eRVR = extended RVR, undetectable at weeks 4 and 12

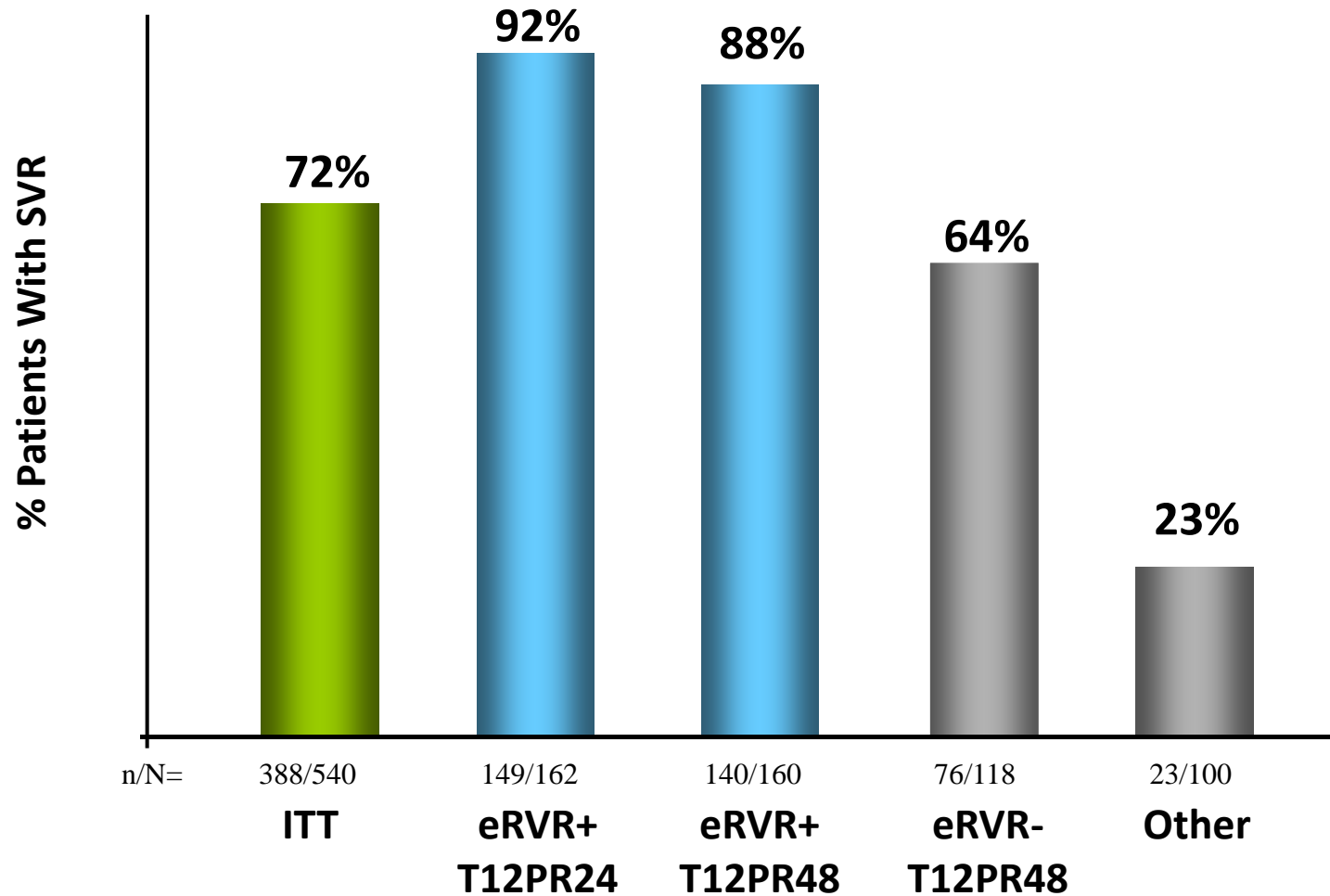
Undetectable HCV RNA over time (ITT)



RVR = rapid viral response, undetectable HCV RNA at week 4,
eRVR = extended rapid viral response, undetectable at week 4 and week 12,
EOT = end of treatment, SVR = sustained virologic response

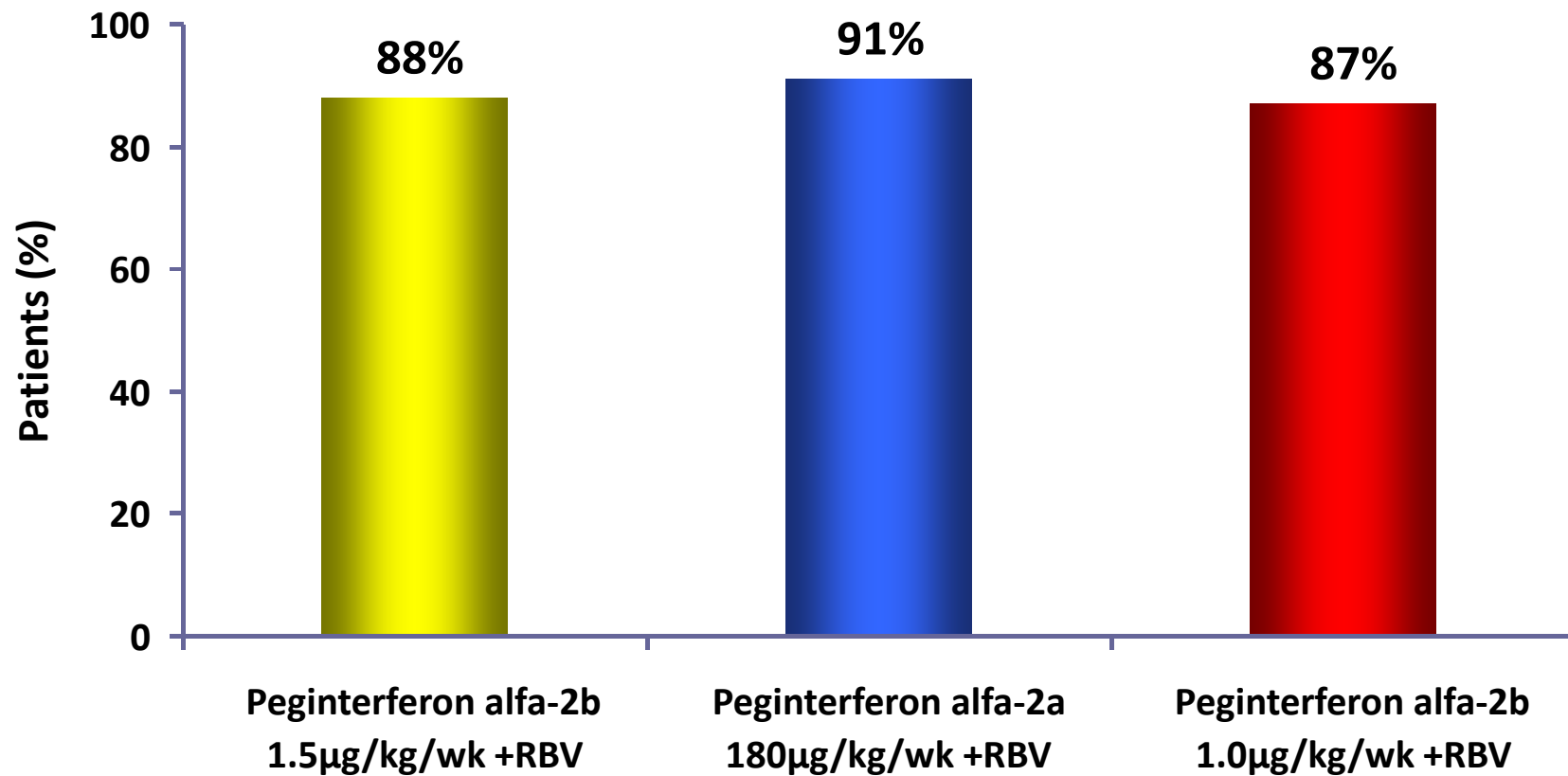
SVR Rates in All Treatment Groups

Δ 4.5%
(2-sided 95% CI = -2.1% to +11.1%)



Télaprevir Génotype 1 en Echec

IDEAL: Concordance between Week 4 and Week 12 as the Definition for Null Response



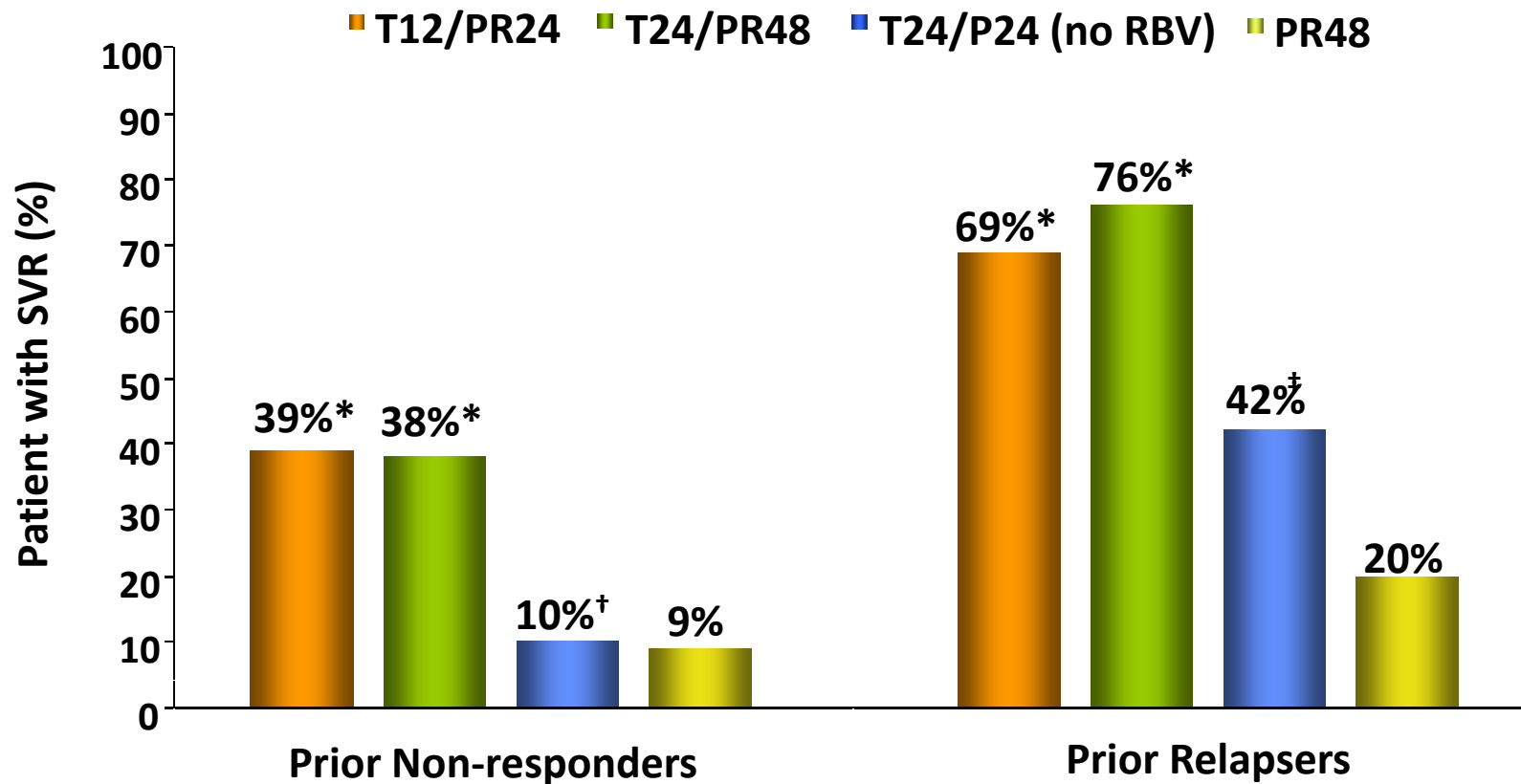
IDEAL: Concordance between Week 4 and Week 12 as the Definition for Null Response

	Week 4 response	Week 12 response	
		Null*	Non-Null
Peginterferon alfa-2b 1.5µg/kg/wk +RBV (n=900)	<1 log ₁₀ decline	150	56 (27.2%)
	≥1 log ₁₀ decline	55	639
Peginterferon alfa-2a 180µg/kg/wk +RBV (n=945)	<1 log ₁₀ decline	148	65 (30.5%)
	≥1 log ₁₀ decline	22	710
Peginterferon alfa-2b 1.0µg/kg/wk +RBV (n=932)	<1 log ₁₀ decline	235	51 (17.8%)
	≥1 log ₁₀ decline	69	577

172/705 (24.4%) patients had <1 log₁₀ decline at W4 and ≥2 log₁₀ decline at W12

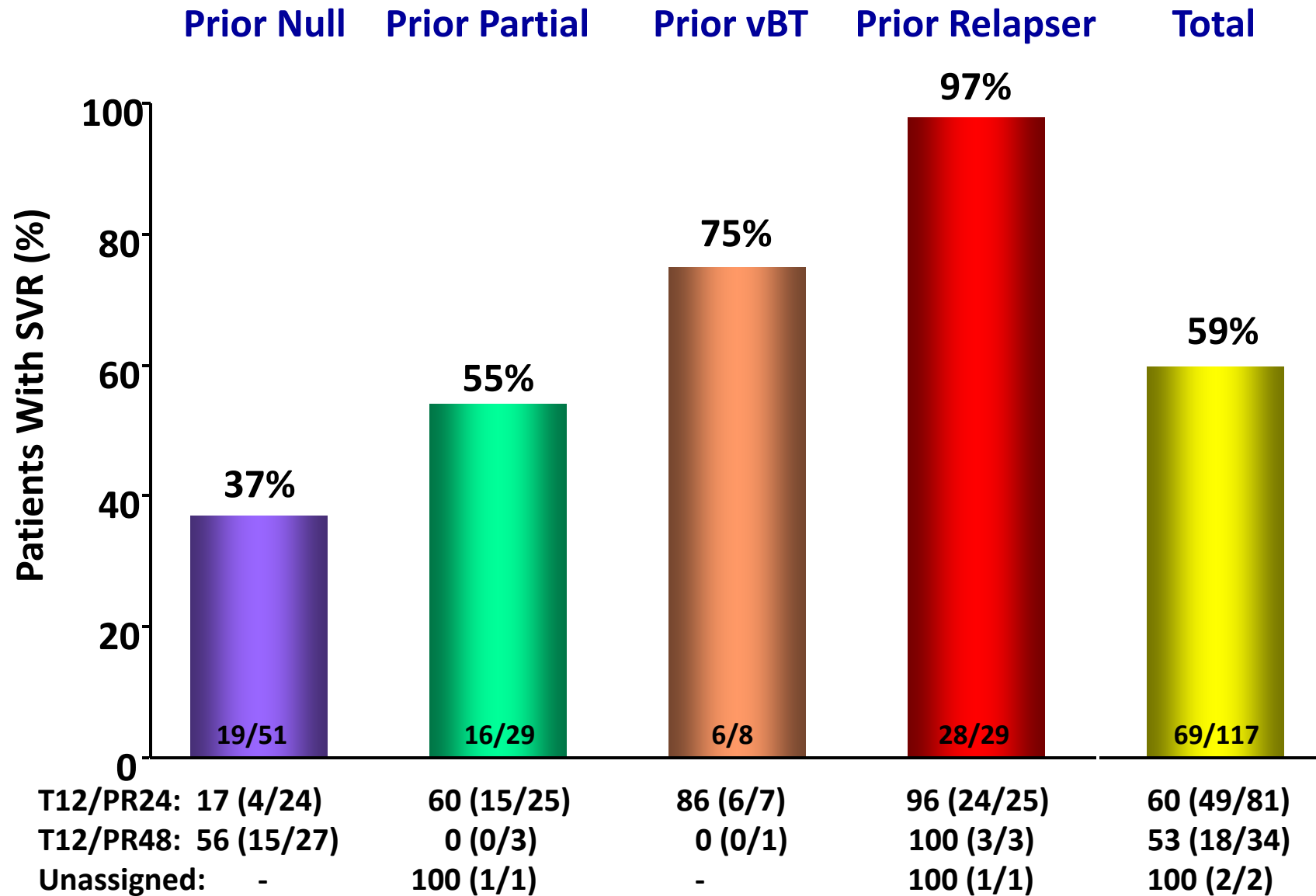
* < 2 log₁₀ decrease from baseline

PROVE3: SVR by Prior Response and Treatment Group (ITT)



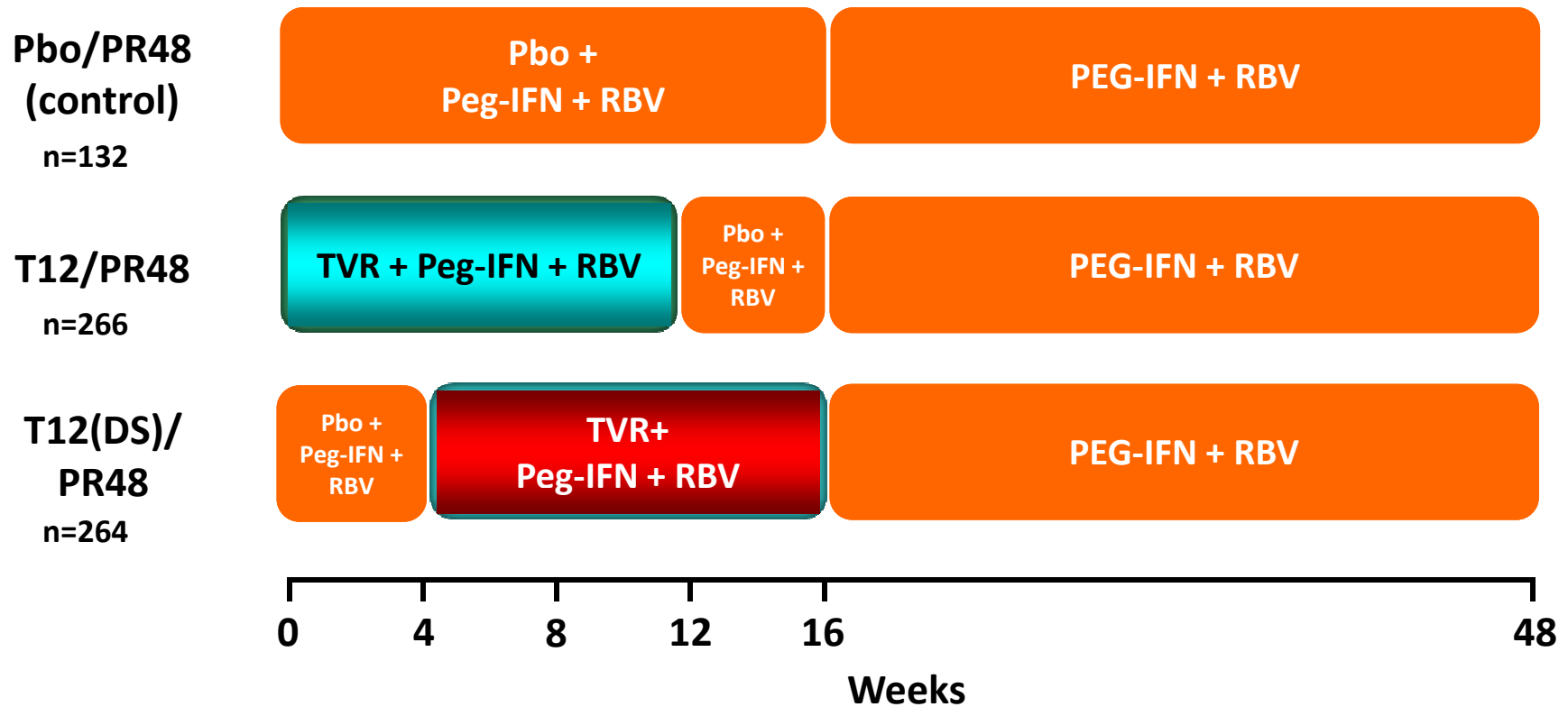
P value shown is versus PR48 control group; * $P < 0.001$; † $P = 0.471$; ‡ $P = 0.029$

107 Rollover trial: SVR Rates



Berg, et al. J Hepatol 2010;52:S2

REALIZE: Study Design



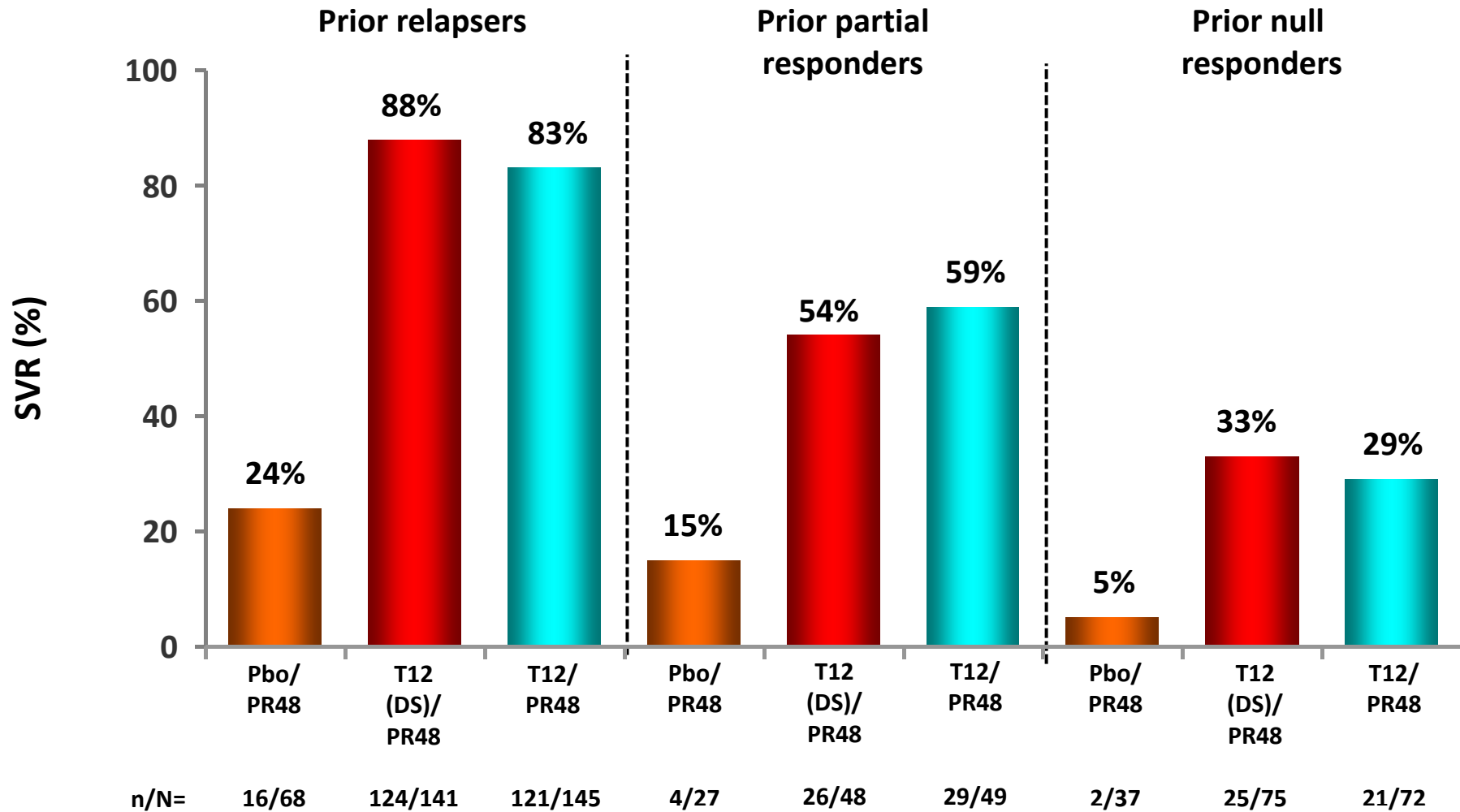
*Randomization stratified by viral load and prior response; stopping rules applied for TVR (Week 4, 6, and 8) and Peg-IFN/RBV (Week 12, 24, and 36)

P = Peg-IFN alfa-2a 180µg/week; Pbo = placebo
R = RBV 1000–1200mg/day; T = TVR 750mg every 8 hours

ClinicalTrials.gov identifier: NCT00703118

Press release, 7 September 2010

REALIZE: SVR in Prior Partial Responders, Null Responders and Relapsers



*p<0.001 vs Pbo/PR48

Press release, 7 September 2010

Télaprevir Tolérance

Prove2 : Tolérance

Symptômes (%)	PR48 (n=82)	T12/PR24 (n=81)	T12/PR12 (n=82)	T12/P12 (n=78)
Rash	35	49	44	47
Nausées	40	48	48	31
Syndrome grippal	52	39	39	36
Prurit	35	51	63	59
Céphalées	45	44	39	47
Insomnie	39	28	34	14
Diarrhée	28	25	32	26
Anémie	17	27	18	9
Peau sèche	35	26	26	28
Asthénie	32	46	52	38
Dyspnée	16	22	26	14
Toux	26	18	17	10
Arthralgie	17	10	10	26

Adverse Events leading to Discontinuation and Most Common Adverse Events

% of Patients with	T12PR N=363	T8PR N=364	PR (control) N=361
Any Adverse Event*	99	99	98
Fatigue	57	58	57
Pruritus	50	45	36
Headache	41	43	39
Nausea	43	40	31
Rash	37	35	24
Anemia	37	39	19
Insomnia	32	32	31
Diarrhea	28	32	22
Influenza-like illness	28	29	28
Pyrexia	26	30	24

- Reported in $\geq 25\%$ of patients regardless of severity in any treatment arm, events occurring at $\geq 10\%$ points in any T group vs PR (shaded in grey)
- 7%, 8% and 4% of pts in T12PR, T8PR and PR discontinued all drugs due to adverse events during TVR/Pbo phase
- 11%, 7% and 1% of pts in T12PR, T8PR and PR discontinued TVR/Pbo only during TVR/Pbo phase

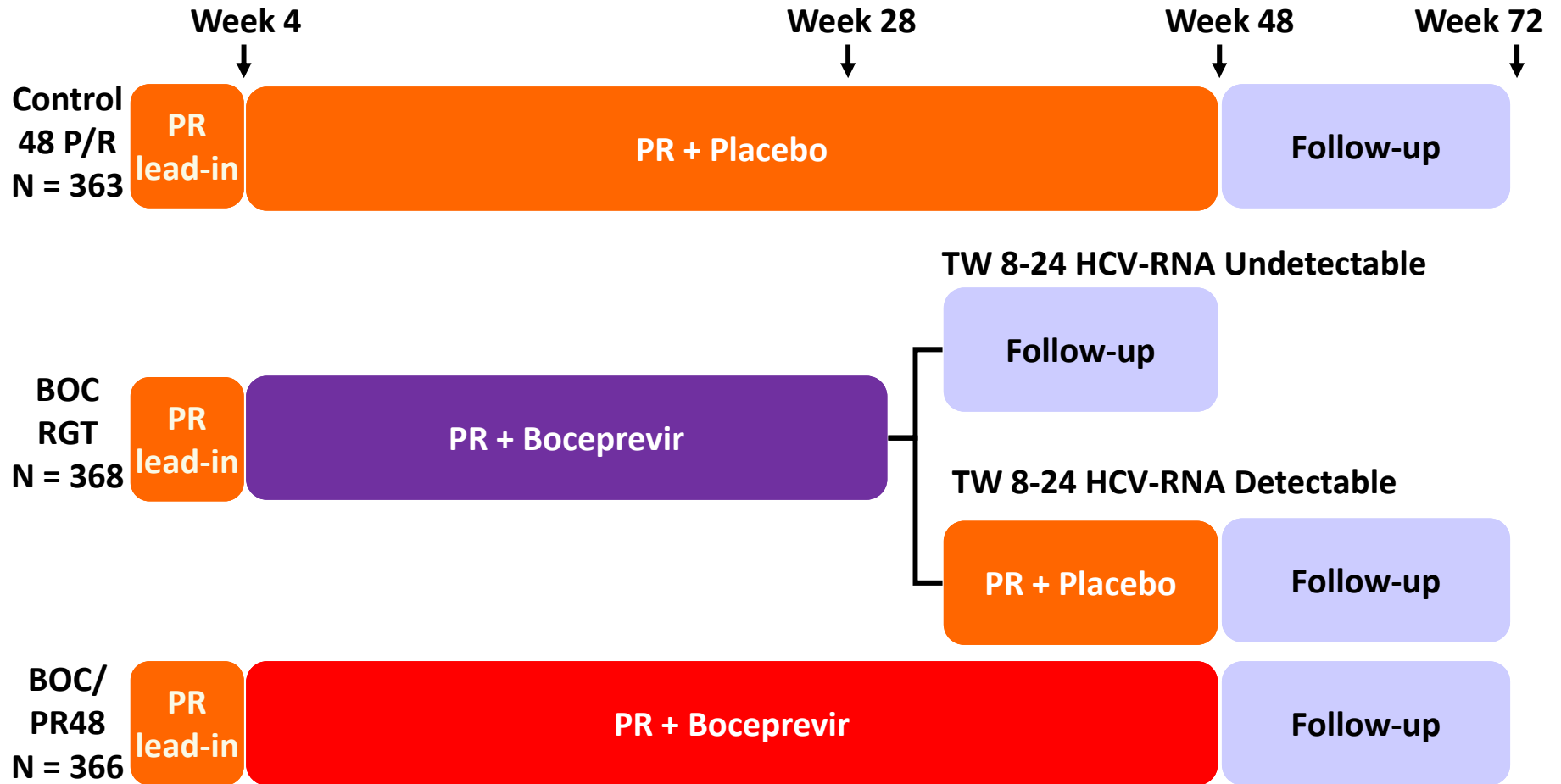
Rash Events During Telaprevir/Placebo Phase

% of Patients with	T12PR N=363	T8PR N=364	PR (control) N=361
Rash events	56	53	37
Severe rash events	6	3	1
Discontinuation of telaprevir/placebo only due to rash events	7	5	1
Discontinuation of all study drugs due to rash events	1.4	0.5	0

- Rash was primarily eczematous and resolved upon cessation of therapy
- Moderate and severe rash were managed by sequentially discontinuing telaprevir, followed by ribavirin and, if indicated, peginterferon for continued progression

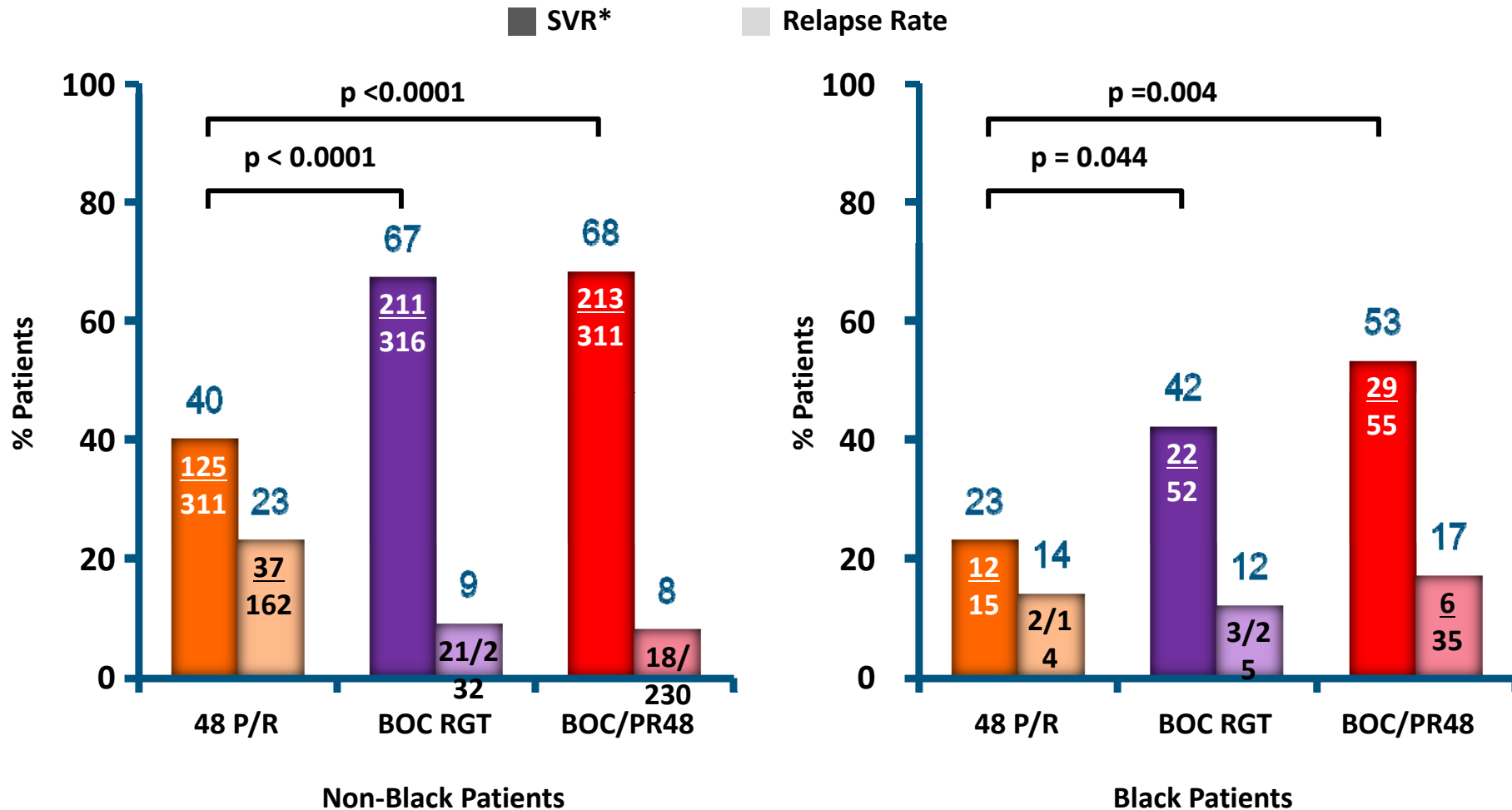
Bocéprevir Génotype 1 Naïfs

SPRINT-2: Study Design



Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose Boceprevir dose of 800 mg thrice daily

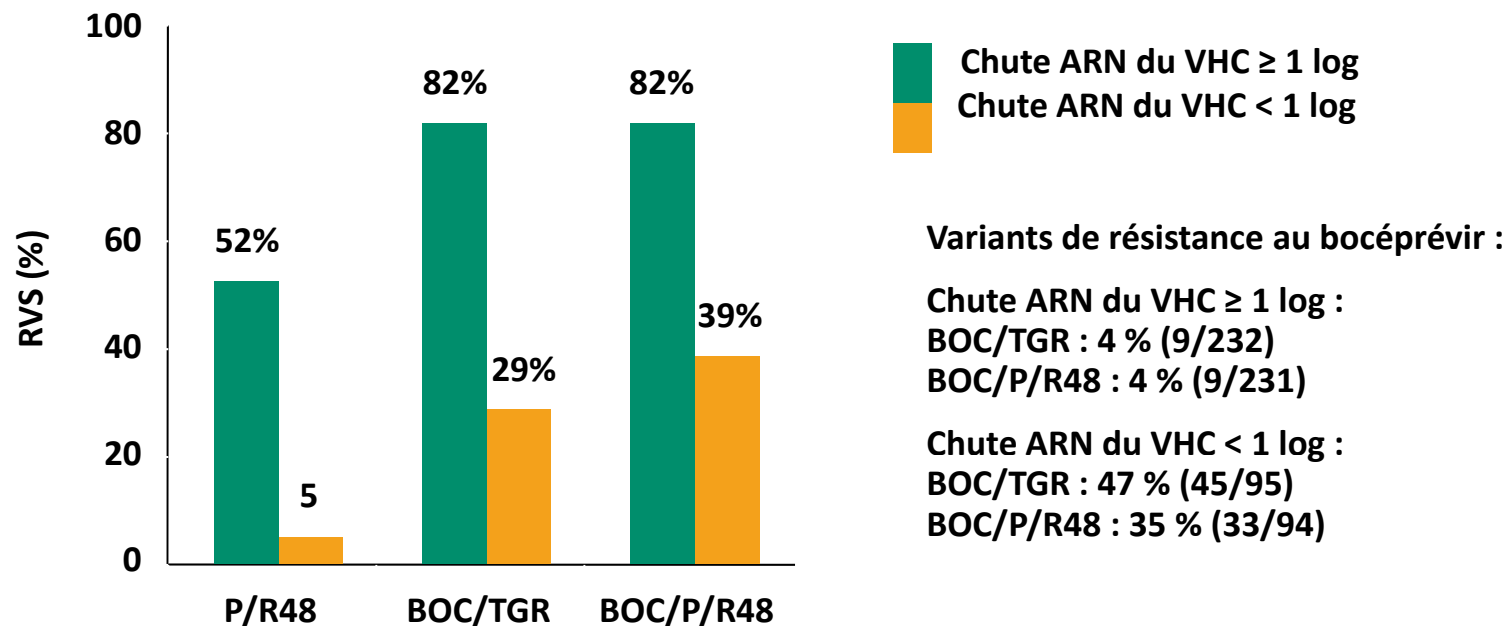
SPRINT 2: SVR and Relapse Rates (ITT)



*SVR was defined as undetectable HCV RNA at the end of the follow-up period. The 12-week post-treatment HCV RNA level was used if the 24-week post-treatment level was missing (as specified in the protocol). A sensitivity analysis was performed counting only patients with undetectable HCV RNA documented at 24 weeks post-treatment and the SVR rates for Arms 1, 2 and 3 in Cohort 1 were 39% (122/311), 66% (207/316) and 68% (210/311), respectively and in Cohort 2 were 21% (11/52), 42% (22/52) and 51% (28/55), respectively

SPRINT-2 – Bocéprévir (BOC) + PEG-IFN + RBV chez les patients naïfs de génotype 1 : résultats de l'étude de phase III

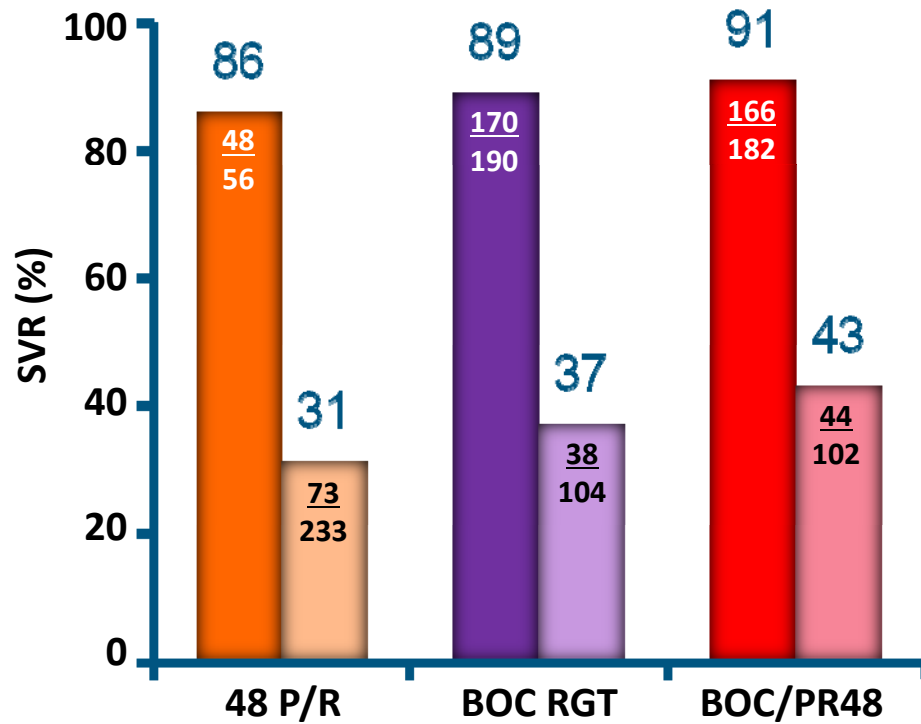
- Taux de RVS en fonction de la réponse à S4 après la phase de *lead-in*



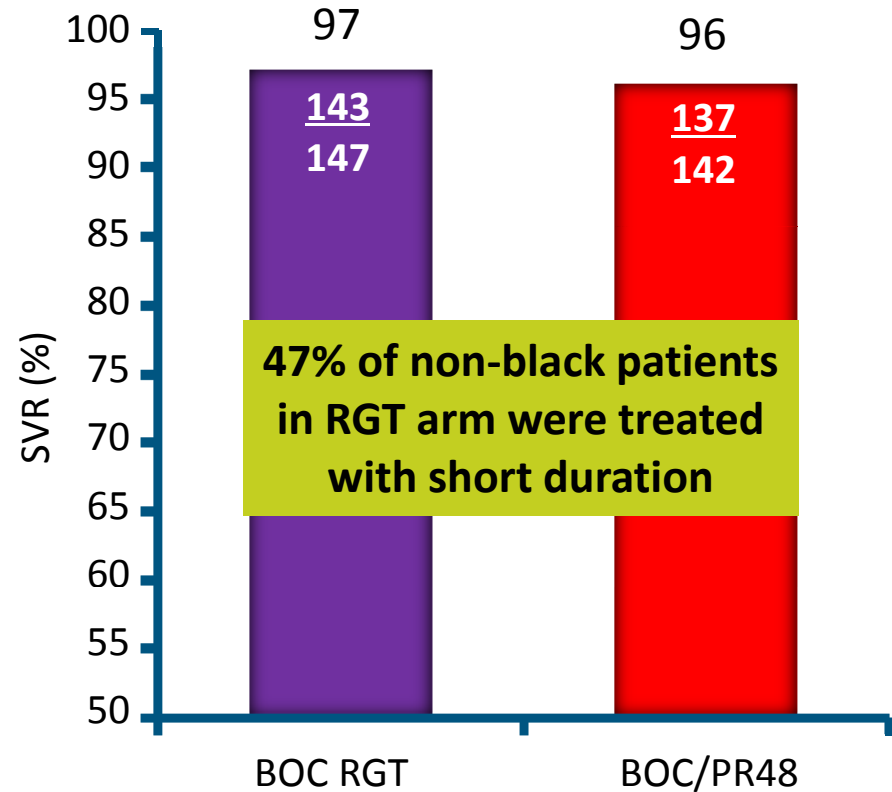
- Intérêt de la réponse virologique à S4 pour évaluer les chances de guérison
- Corrélation entre la réponse virologique à S4 et la probabilité de sélectionner des variants résistants

SVR Based on Week 8 HCV RNA in Non-Black Patients

- Undetectable HCV RNA at Week 8 **58%**
- Detectable HCV RNA at Week 8



SVR in patients with undetectable HCV RNA between Weeks 8-24

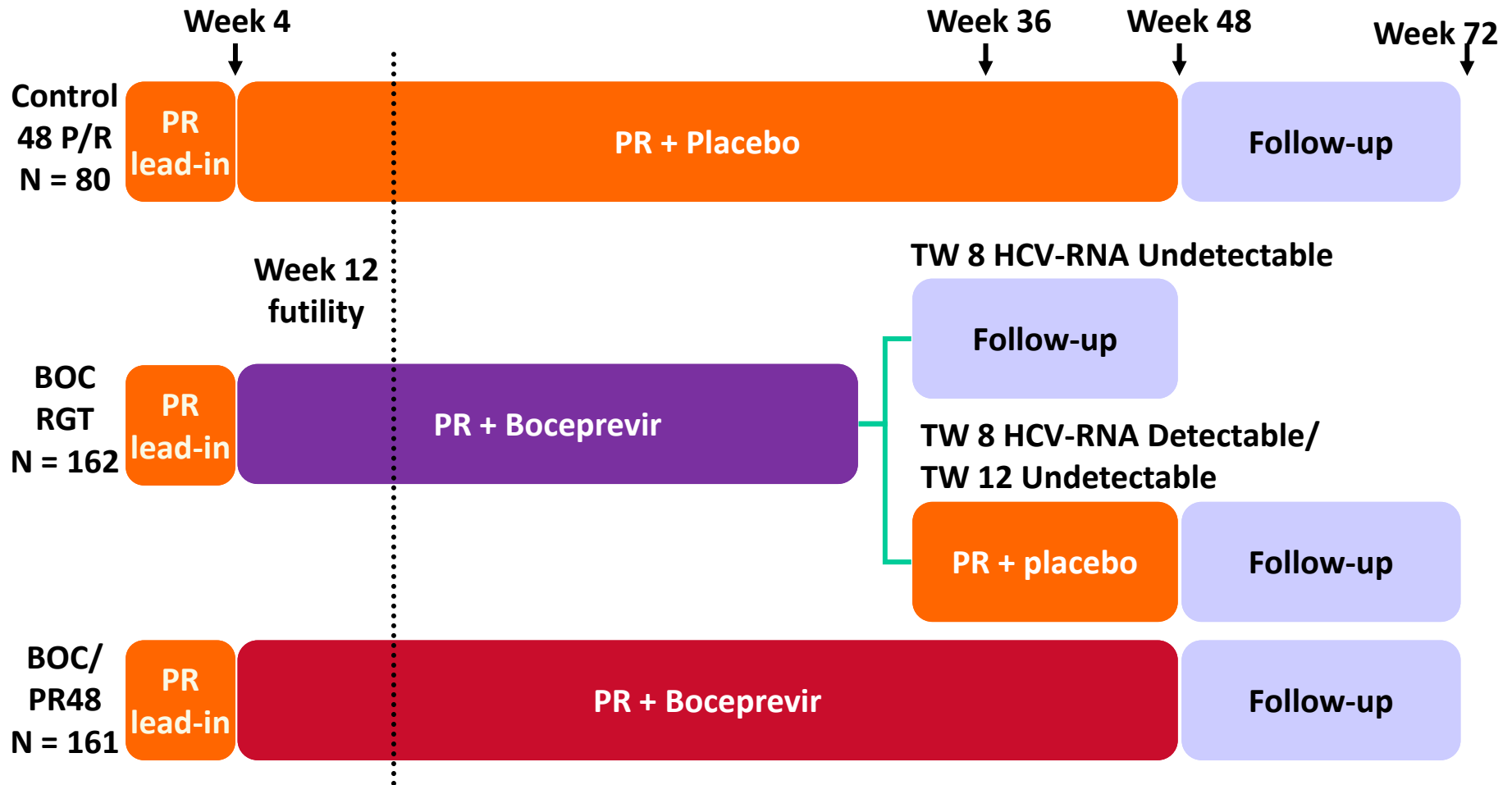


SPRINT-2: Safety Profile Over Entire Course of Therapy

	48 P/R n=363	BOC RGT n=368	BOC/PR48 n=366
Median treatment duration, days	203	197	335
Deaths	N=4	N=1	N=1
Serious AEs	9%	11%	12%
Discontinued due to AEs	16%	12%	16%
Dose modification due to AEs	26%	40%	35%
Hematologic parameters			
Neutrophil count (<750 to $500/\text{mm}^3$ / $<500/\text{mm}^3$)	14% / 4%	24% / 6%	25% / 8%
Hemoglobin (<10 to 8.5 g/dL / <8.5 g/dL)	26% / 4%	45% / 5%	41% / 9%
Discontinuation due to anemia	1%	2%	2%
Dose reductions due to anemia	13%	20%	21%
Erythropoietin use	24%	43%	43%
Mean (median) days of use	121 (109)	94 (85)	156 (149)

Bocéprevir Génotype 1 Echec

RESPOND-2: Study Design

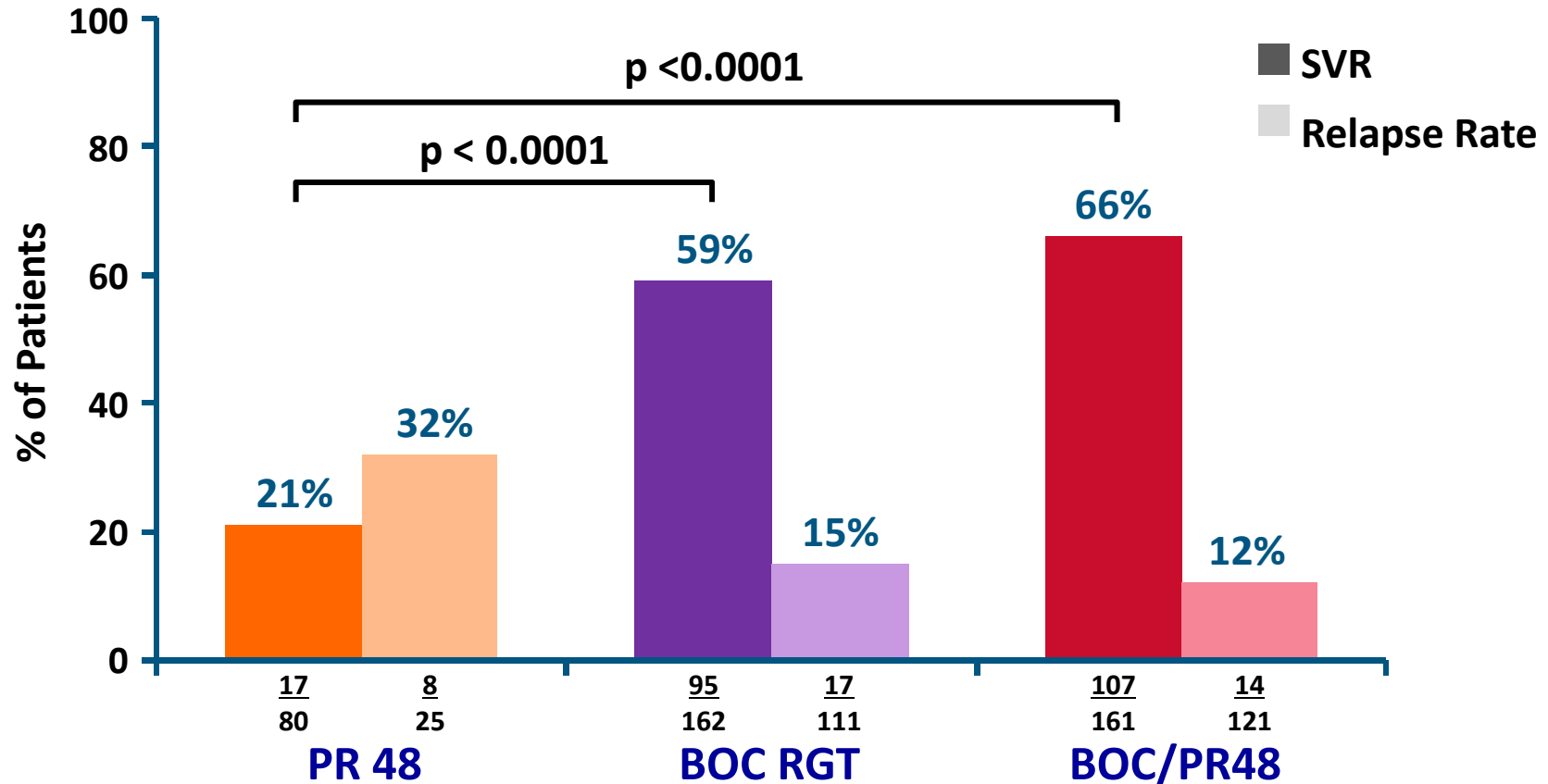


HCV-RNA measured by the Cobas TaqMan assay (Roche). Patients with detectable HCV-RNA (LLD=9.3 IU/mL) at week 12 were considered treatment failures.

Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly; plus Ribavirin (R) using weight based dosing of 600-1400 mg/day in a divided daily dose; Boceprevir dose of 800 mg thrice daily

RESPOND-2: SVR and Relapse Rates

Intention to treat population



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

12-week HCV-RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161) respectively

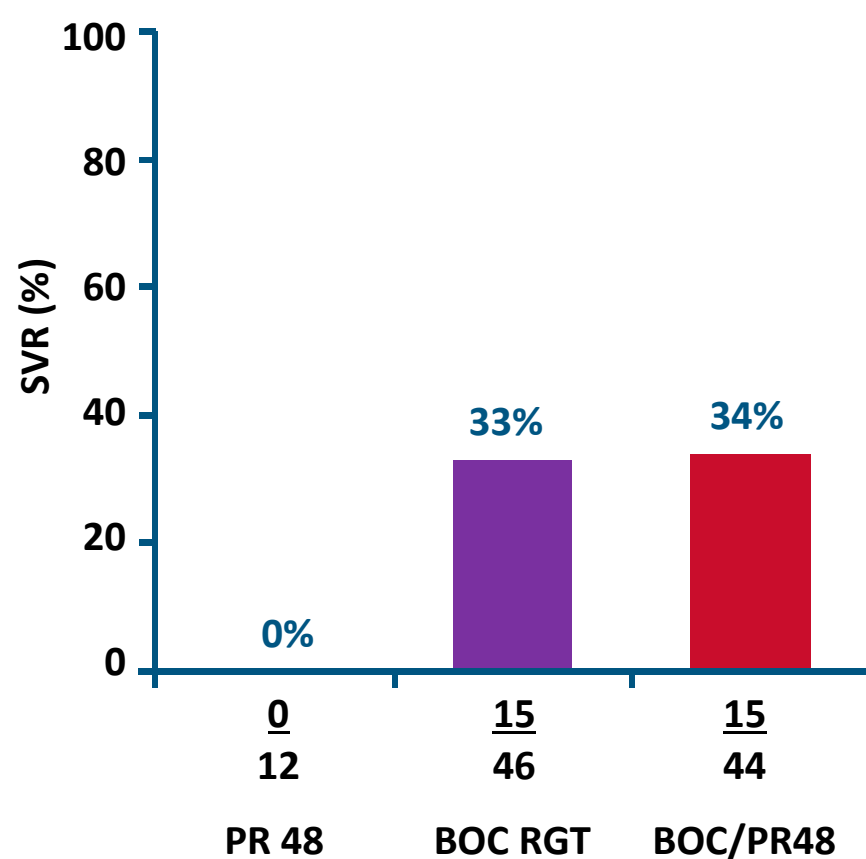
RESPOND-2: SVR by Historical Response Non-responders and Relapsers*

	Arm 1: 48 P/R N = 80	Arm 2: BOC RGT N = 162	Arm 3: BOC/PR48 N = 161
Partial-responder – n/n (%)	2/29 (6.9%)	23/57 (40.4%)	30/58 (51.7%)
Relapser – n/n (%)	15/51 (29.4%)	72/105 (68.6%)	77/103 (74.8%)

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

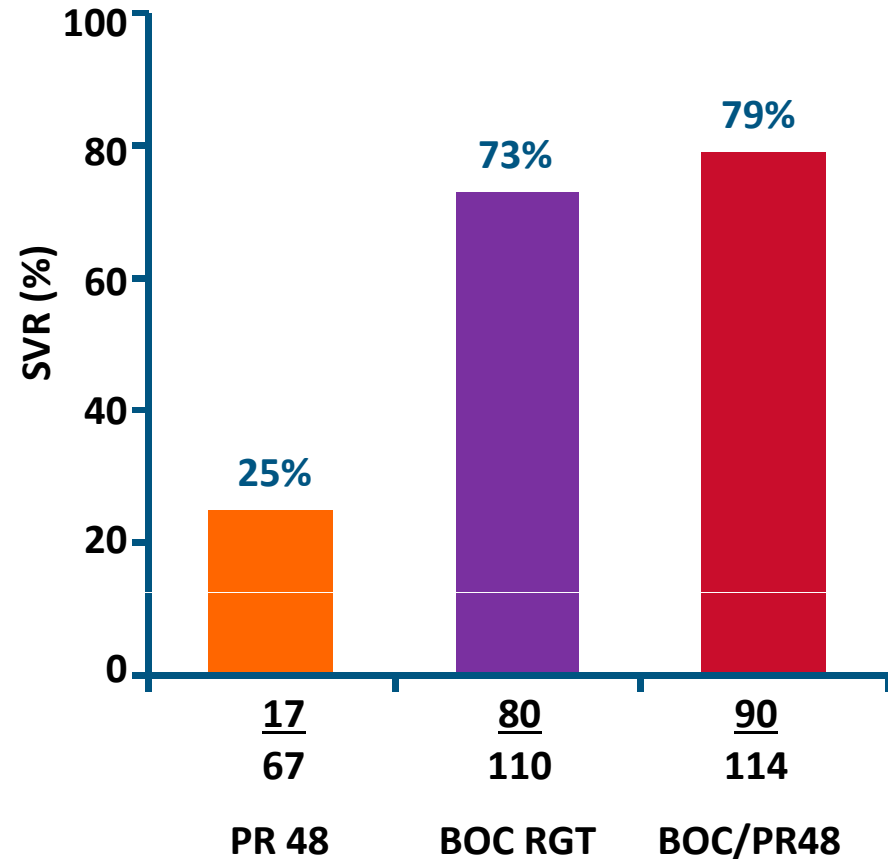
RESPOND-2: SVR by Week 4

PR Lead-In Response



Poorly Responsive to IFN

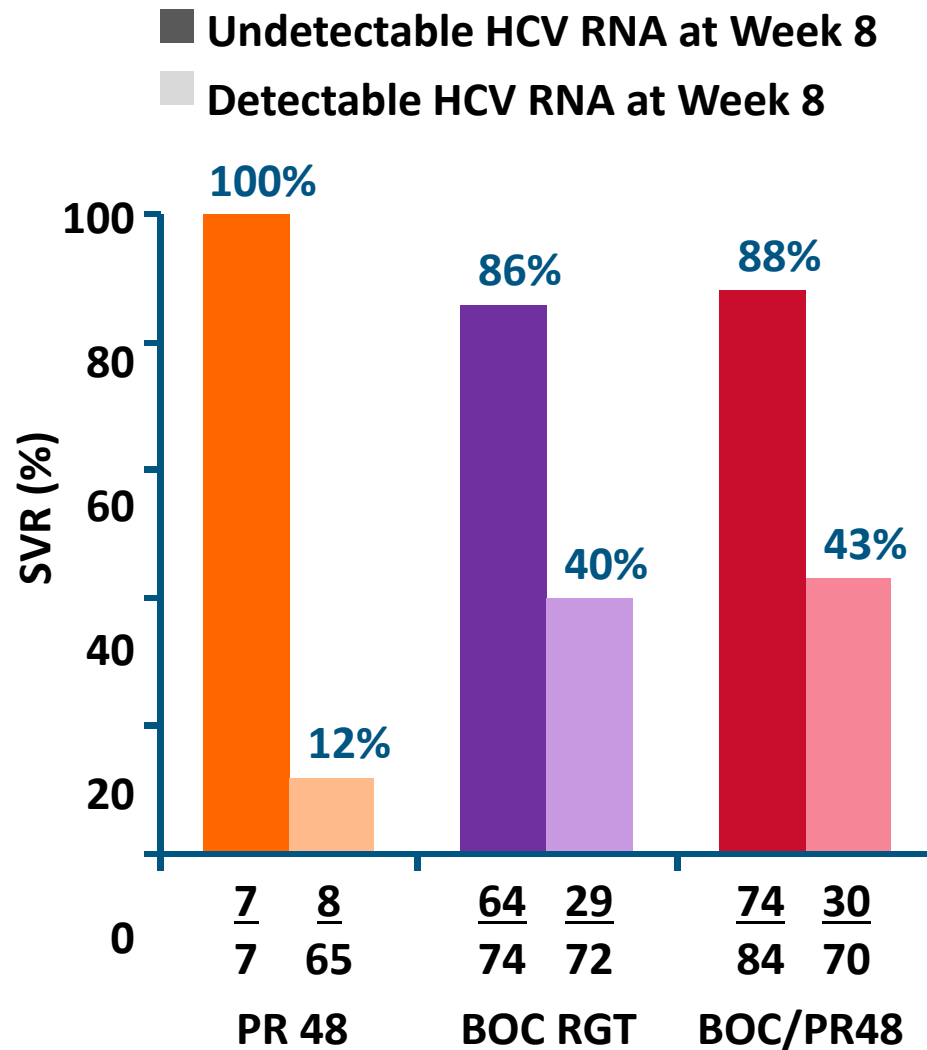
<1 log₁₀ viral load decline
at treatment week 4



Responsive to IFN

≥1 log₁₀ viral load decline
at treatment week 4

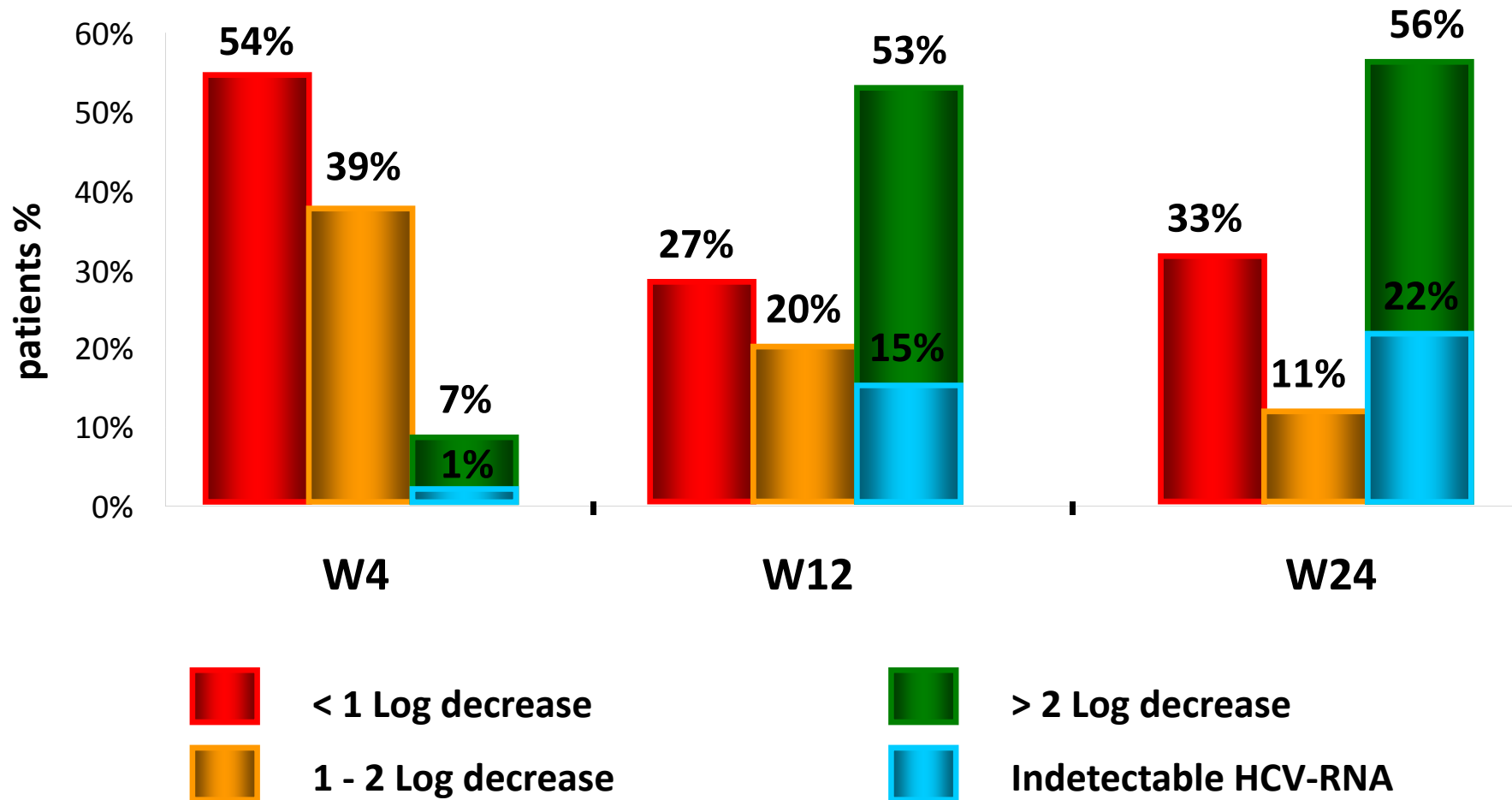
RESPOND-2: SVR by Week 8 HCV RNA Response (ITT)



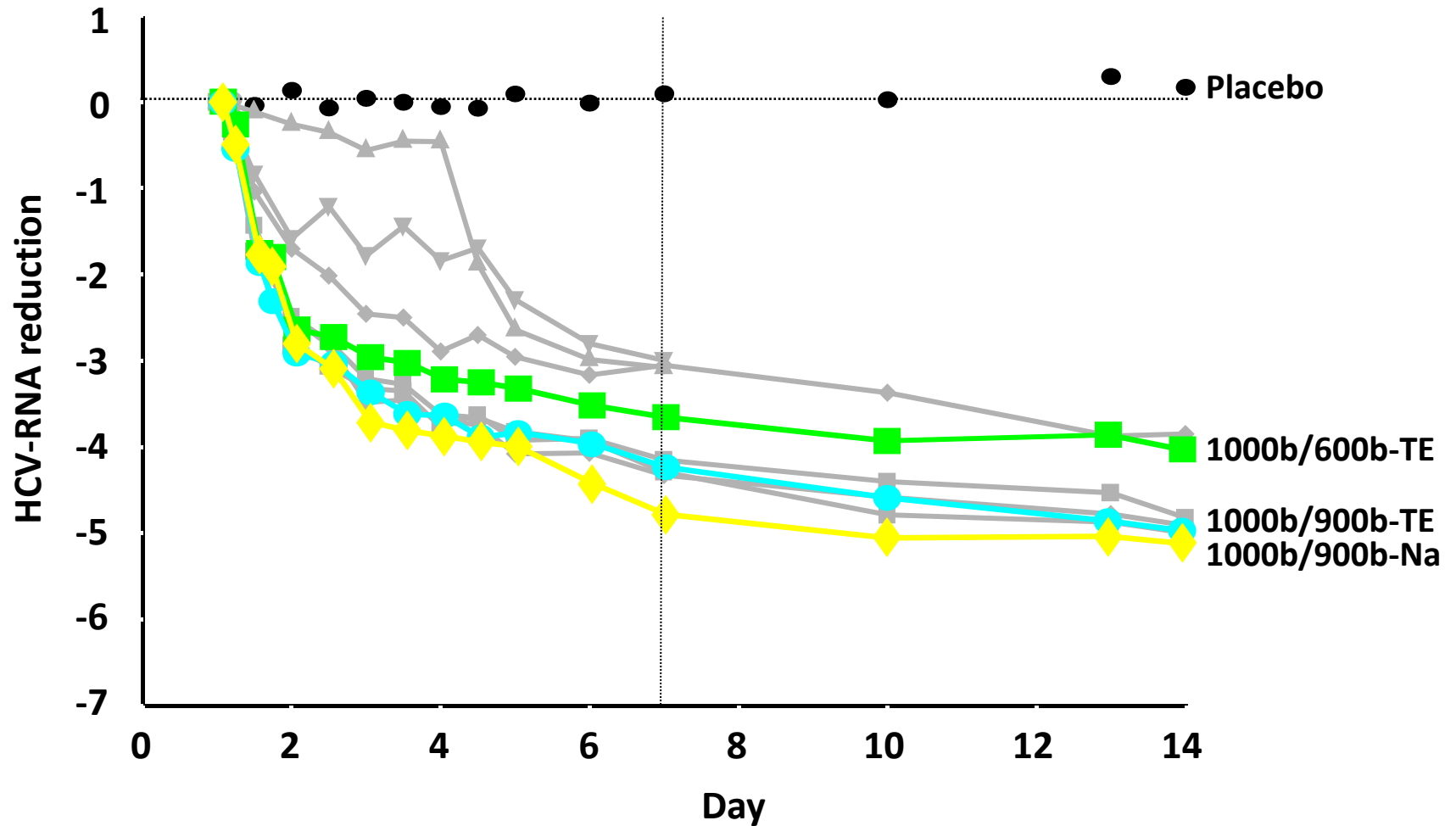
- 46% of patients in BOC RGT arm were eligible for shorter therapy

**Comment prévenir l'échec de la
trithérapie ?**

SYREN Trial: Virological Responses at week 4, week 12, week 24

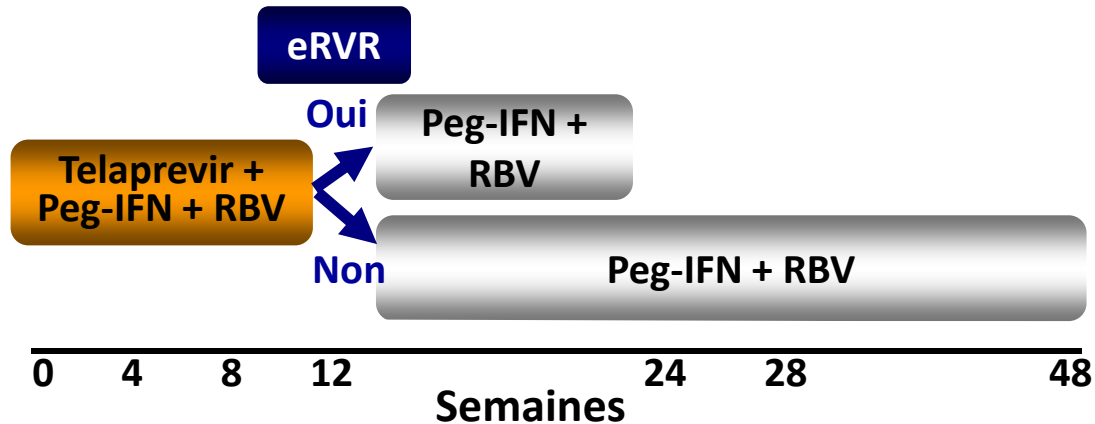


Combinaison R7128/R7227 *INFORM* Trial



Conclusions : Malades génotype 1 Naïfs

Télaprevir

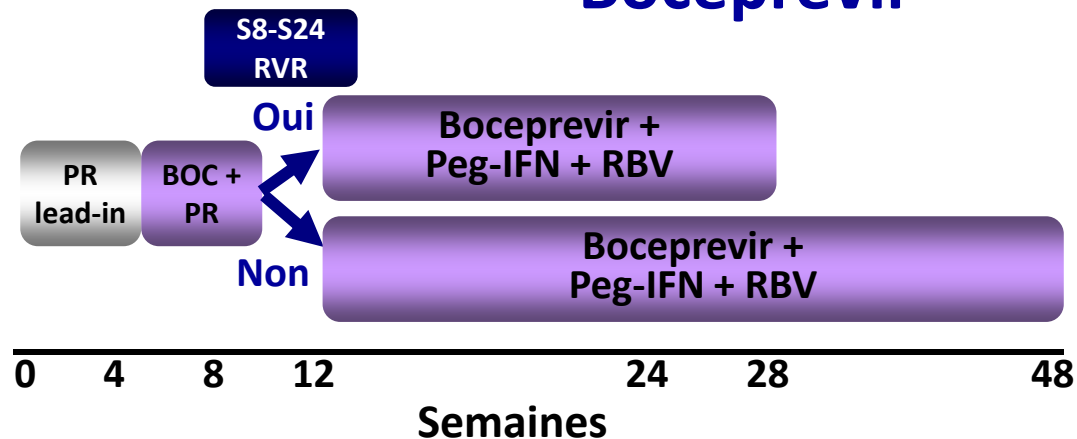


Durée courte (24S): 59-65%
RVS : 89-92%

RVS : 54-64%

Arrêt de tous les traitements
du au rash: 1-1,4%

Bocéprevir



Durée courte (28S): 47%*
RVS : 97%

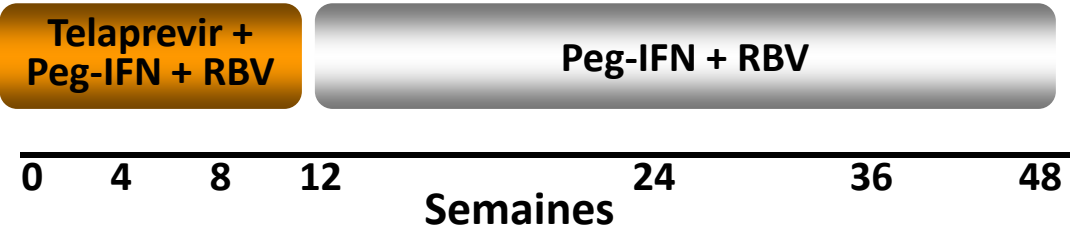
RVS : 43%

Anémie <10g/dl: 50%
Utilisation EPO : 43%

* Malades non de race noire

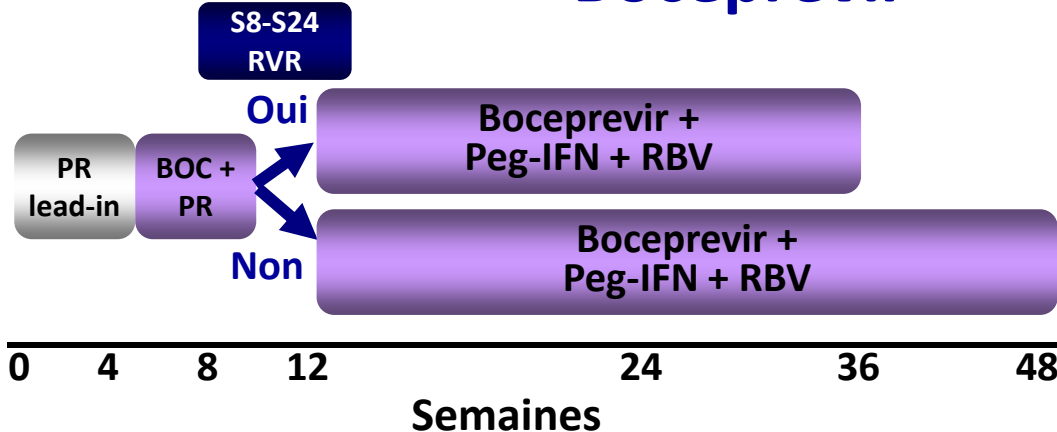
Conclusions : Malades génotype 1 en échec

Télaprevir



RVS :
Rechuteurs : 86%
Répondeurs partiels : 57%
Répondeurs nuls : 31%

Bocéprevir*



Durée courte (36S): 46%*
RVS : 86%
RVS : 43%

* Résultats uniquement chez les rechuteurs et répondeurs partiels