

29th Viral Hepatitis Prevention Board Meeting

Madrid, November 2006

Treatment of chronic hepatitis C

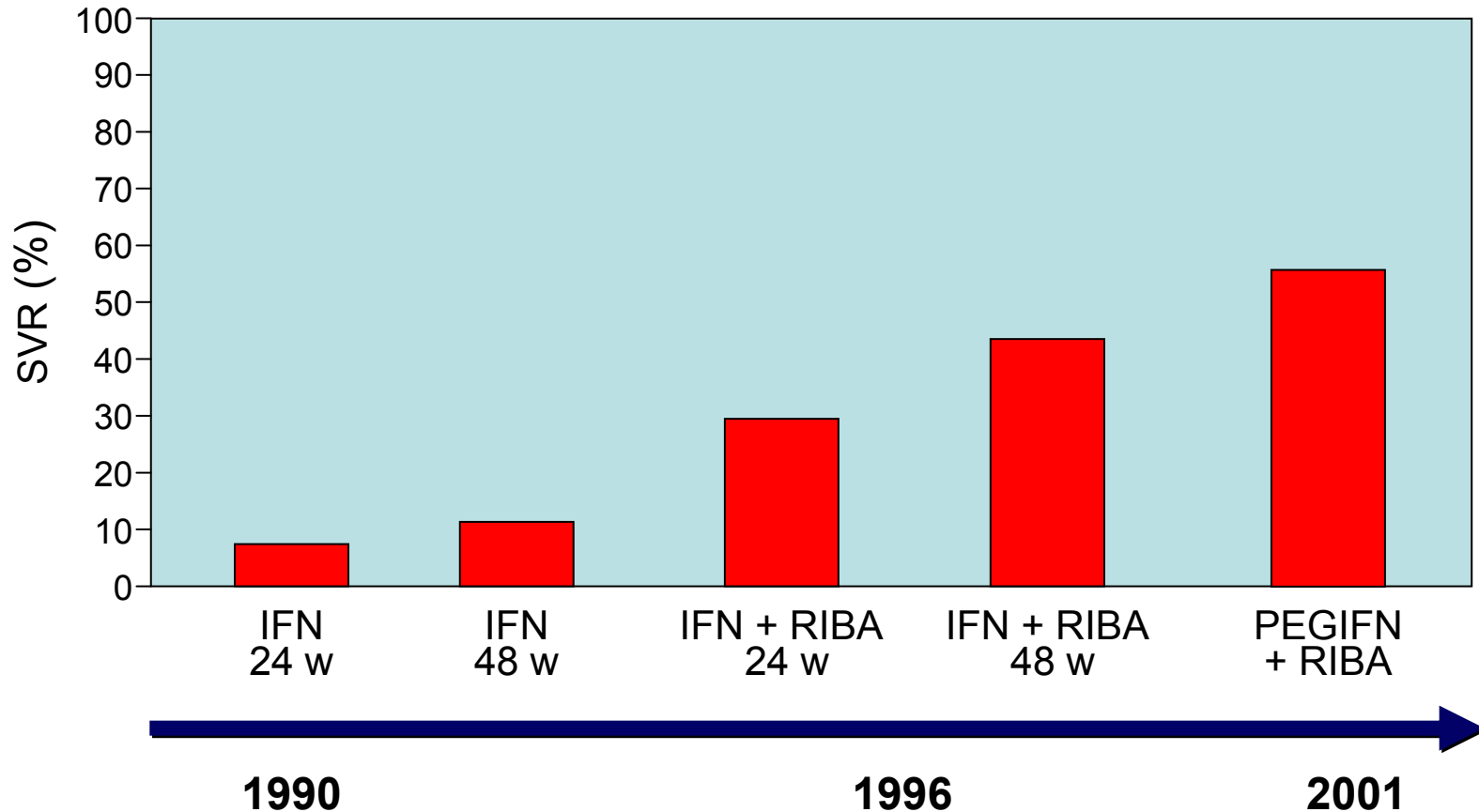
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Spain**

CHRONIC HEPATITIS C

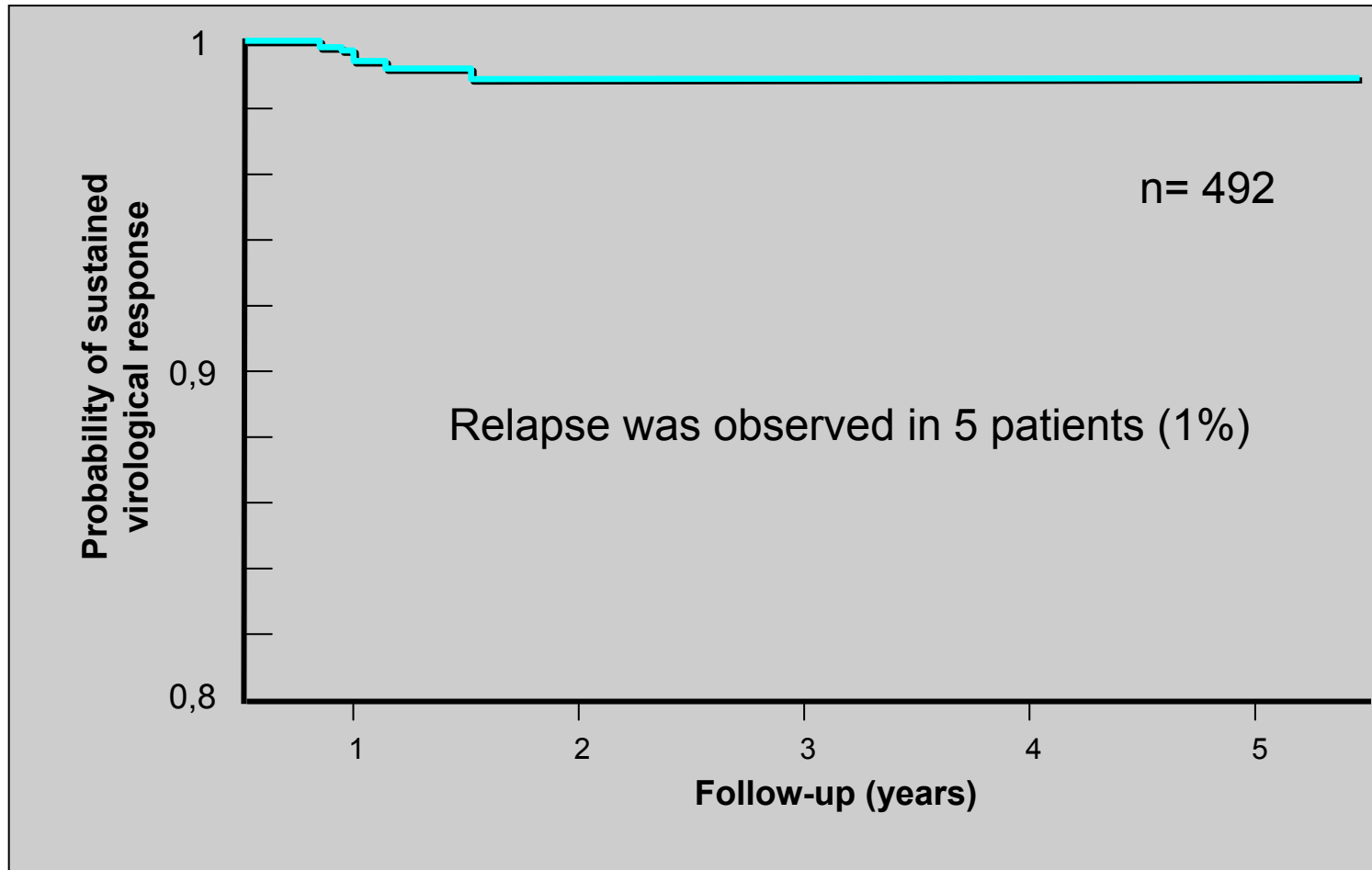
- Extremely common
- Variable outcome
- Most frequent cause of chronic liver disease including chronic hepatitis, hepatic cirrhosis and hepatocellular carcinoma
- Leading reason for liver transplantation.

ADVANCES IN THE TREATMENT OF CHRONIC HEPATITIS C

Rate of sustained virological response (SVR) according to the therapeutic regime



SUSTAINED VIROLOGIC RESPONSE TO INTERFERON-ALPHA-2b +/- RIBAVIRIN THERAPY AT 6 MONTHS RELIABLY PREDICTS LONG-TERM CLEARANCE OF HCV AT 5-YEAR FOLLOW-UP



TREATMENT OF CHRONIC HEPATITIS C

Recommended therapy: Peginterferón + Ribavirin

Duration according to HCV genotype

Sustained virological response: 45% in genotype 1 or 4

80% in genotype 2 or 3.

Problems: Relatively low efficacy

Frequent side effects

High cost

Perspectives: More rationale use of PEGIFN –RIBA

New therapies

TREATMENT OF CHRONIC HEPATITIS C

Factors related to response

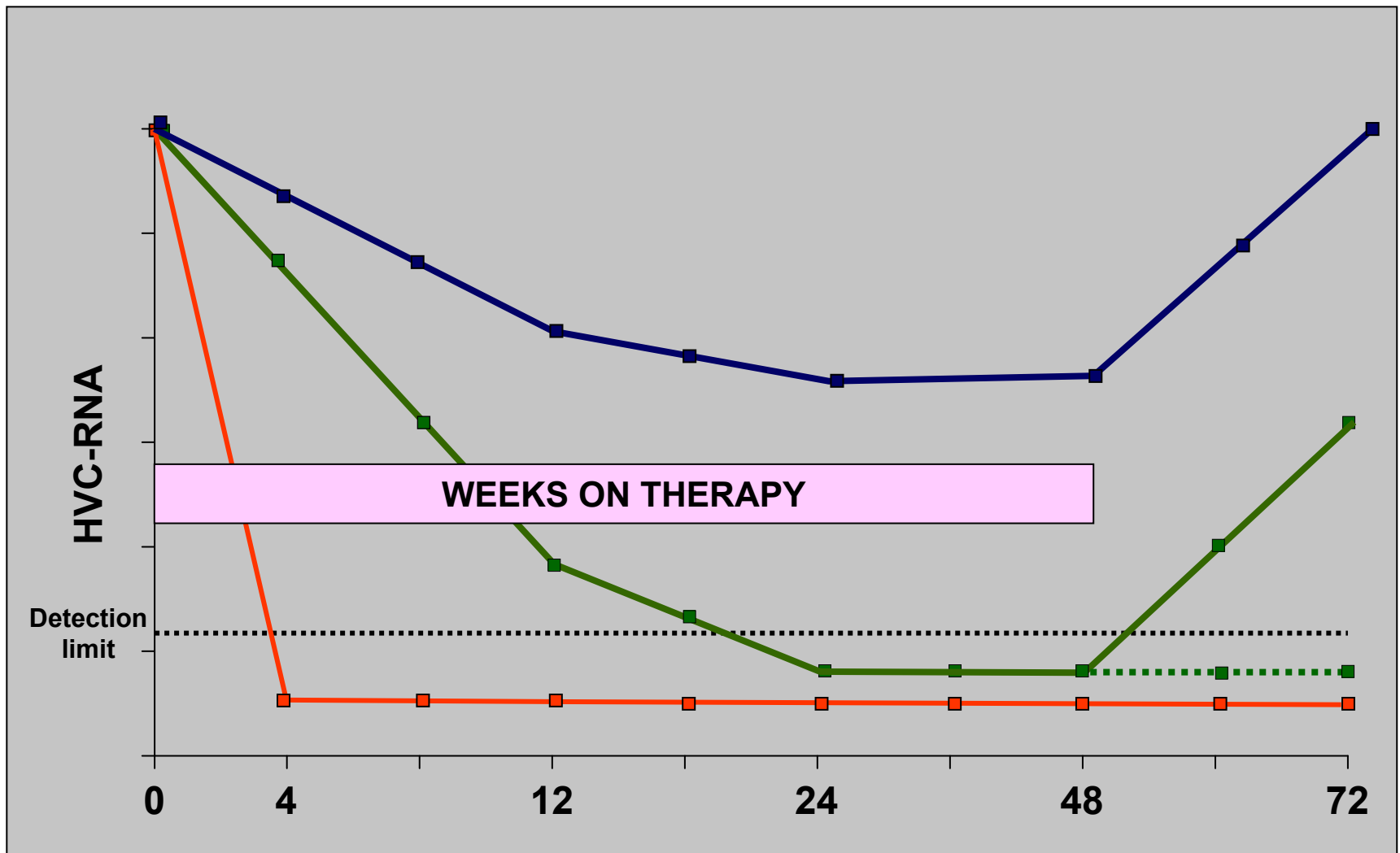
- HCV genotype
- HCV viremia
- Severity of liver fibrosis
- Race, sex
- Body weight
- Insulin resistance
- Viral kinetics during therapy

TREATMENT OF CHRONIC HEPATITIS C

Factors related to response

- HCV genotype
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- Viral kinetics during therapy

Schematic representation of the types of virological response to therapy of patients with genotype 1 chronic hepatitis C



■—■ Rapid response

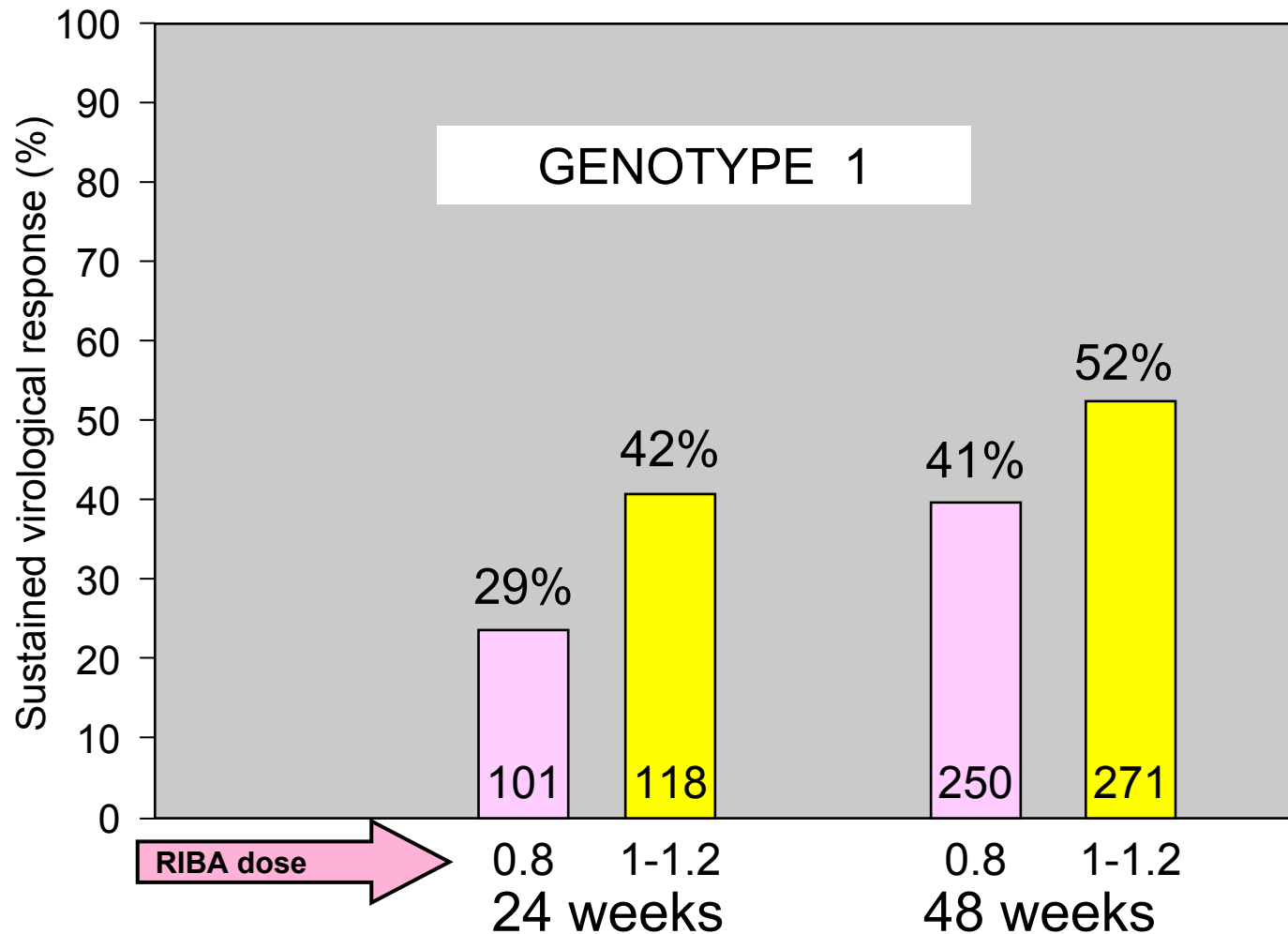
■—■ Slow response

■—■ No response

Could standard therapy be modified
according to the initial virological
response?

PEG (40 KD)- IFN (α -2a) IN COMBINATION WITH RIBAVIRIN AS A THERAPY FOR CHRONIC HEPATITIS C

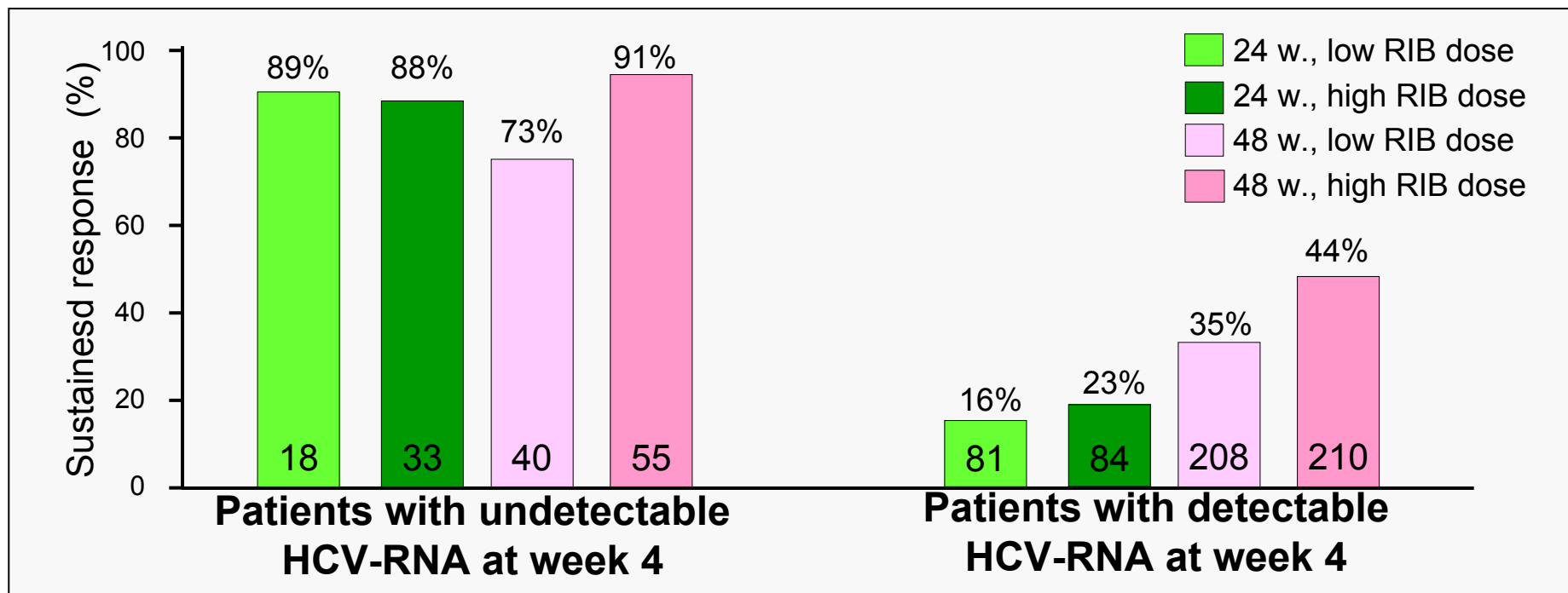
Evaluation of treatment duration and ribavirin dose



Early identification of HCV Genotype 1 patients responding to 24 weeks Peginterferon α -2a (40kd)/Ribavirin therapy

Identification of factors associated to sustained virological response in 740 genotype 1 patients from a previous randomized study ([Hadziyannis et al., Ann Intern Med 2004](#))

Factor		OR	IC 95%	p
Baseline HCV-RNA	<200x10 ³ vs >600x10 ³	2.7	1.1 - 6.3	.026
Virological response at week 4	Yes vs No	23.7	9.1 – 61.7	<.0001

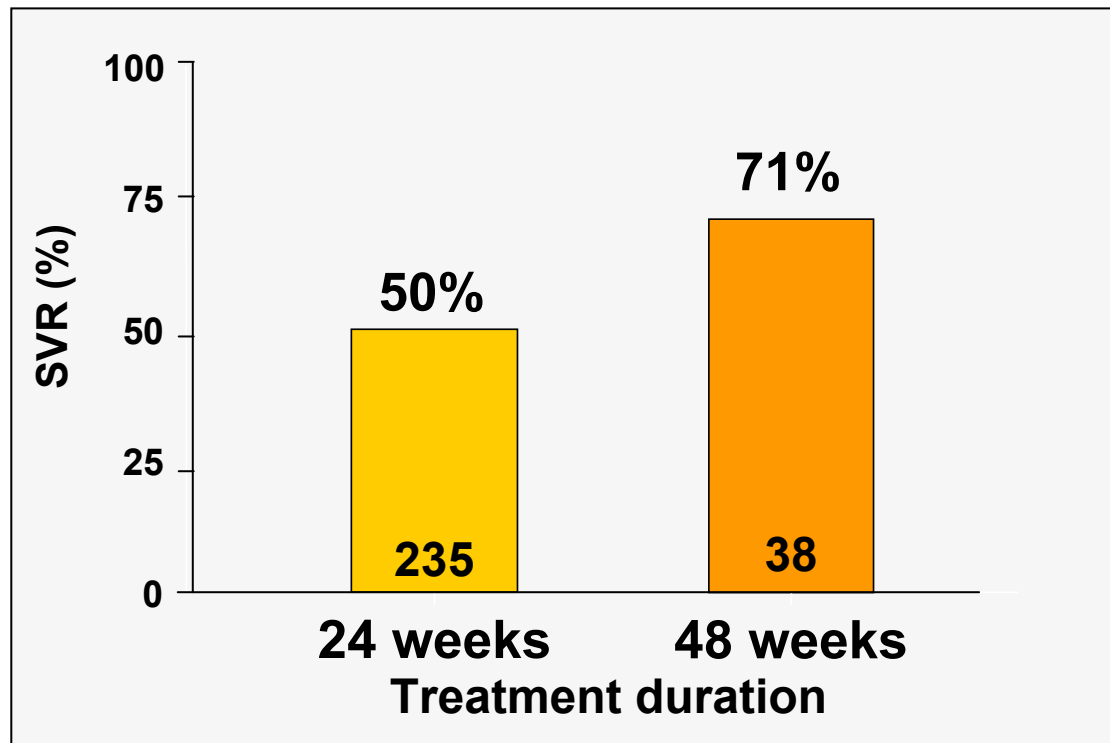


Efficacy of 24 weeks of treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia

235 patients with baseline viremia $\leq 600,000$ IU/mL

Therapy: Peg-IFN α -2b (1.5 μ g/kg) + RBV (800-1400 mg) , 24 weeks

Historic control: Cohort of comparable patients treated for 48 weeks in a previous study (Manns et al., Lancet 2001)

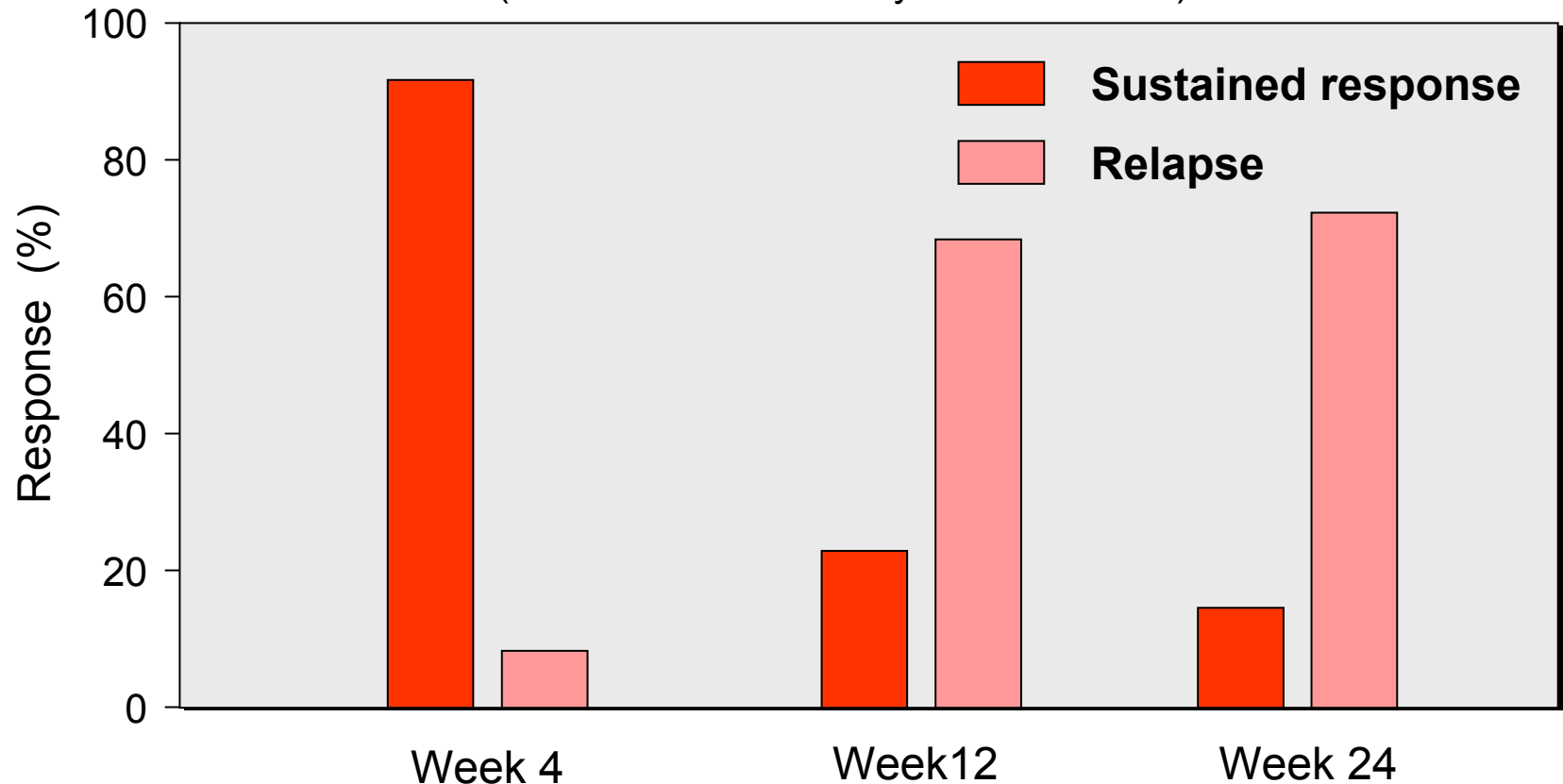


Zeuzem et al.
J Hepatology 2006

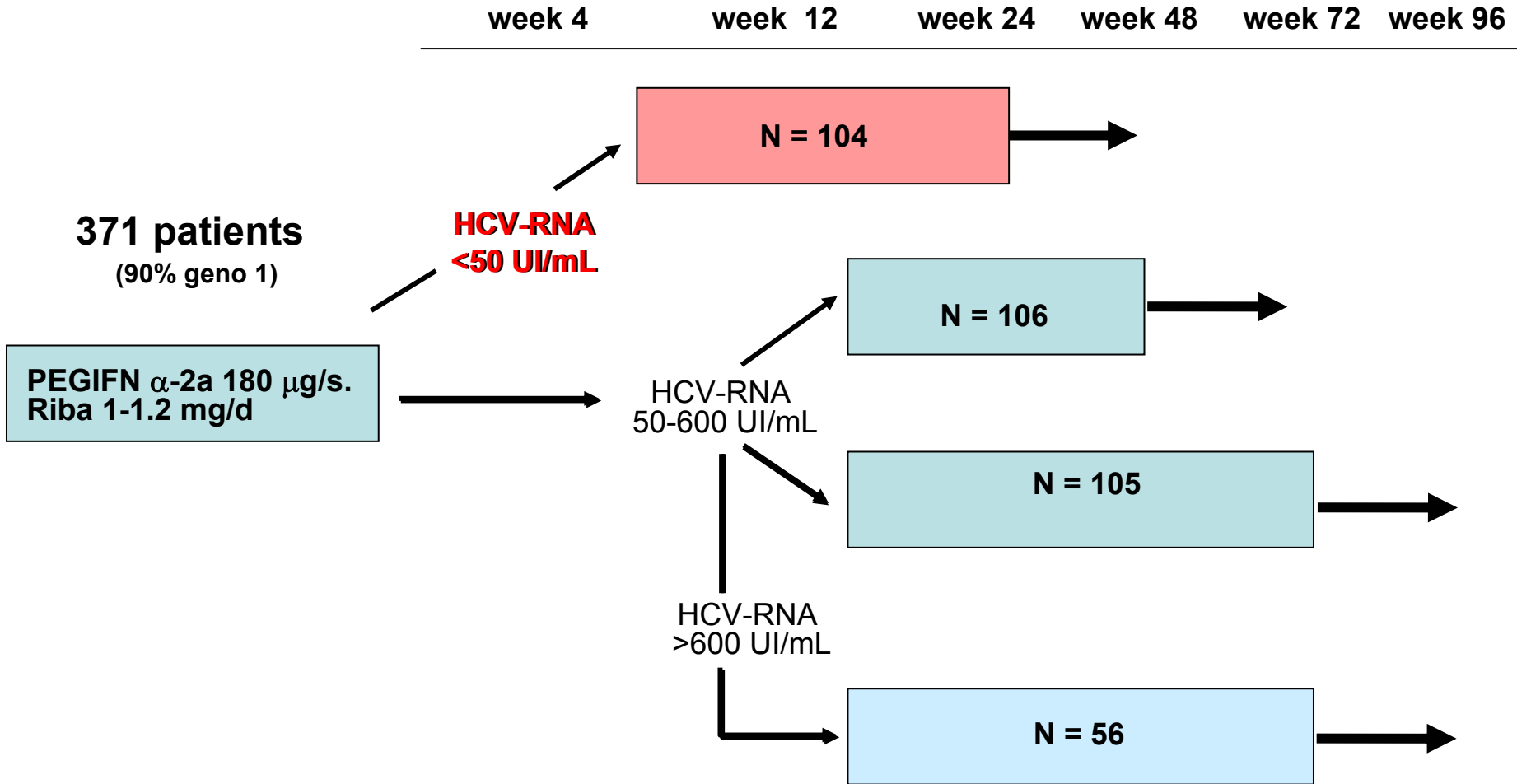
Efficacy of 24 weeks of treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia

Relationship with time on therapy till clearance of HCV-RNA

(Less than 29 IU/mL by real time PCR)



24-week Peginterferon alfa-2a plus ribavirin regimen appears effective in patients with genotype 1 or 4 HCV who respond early to treatment



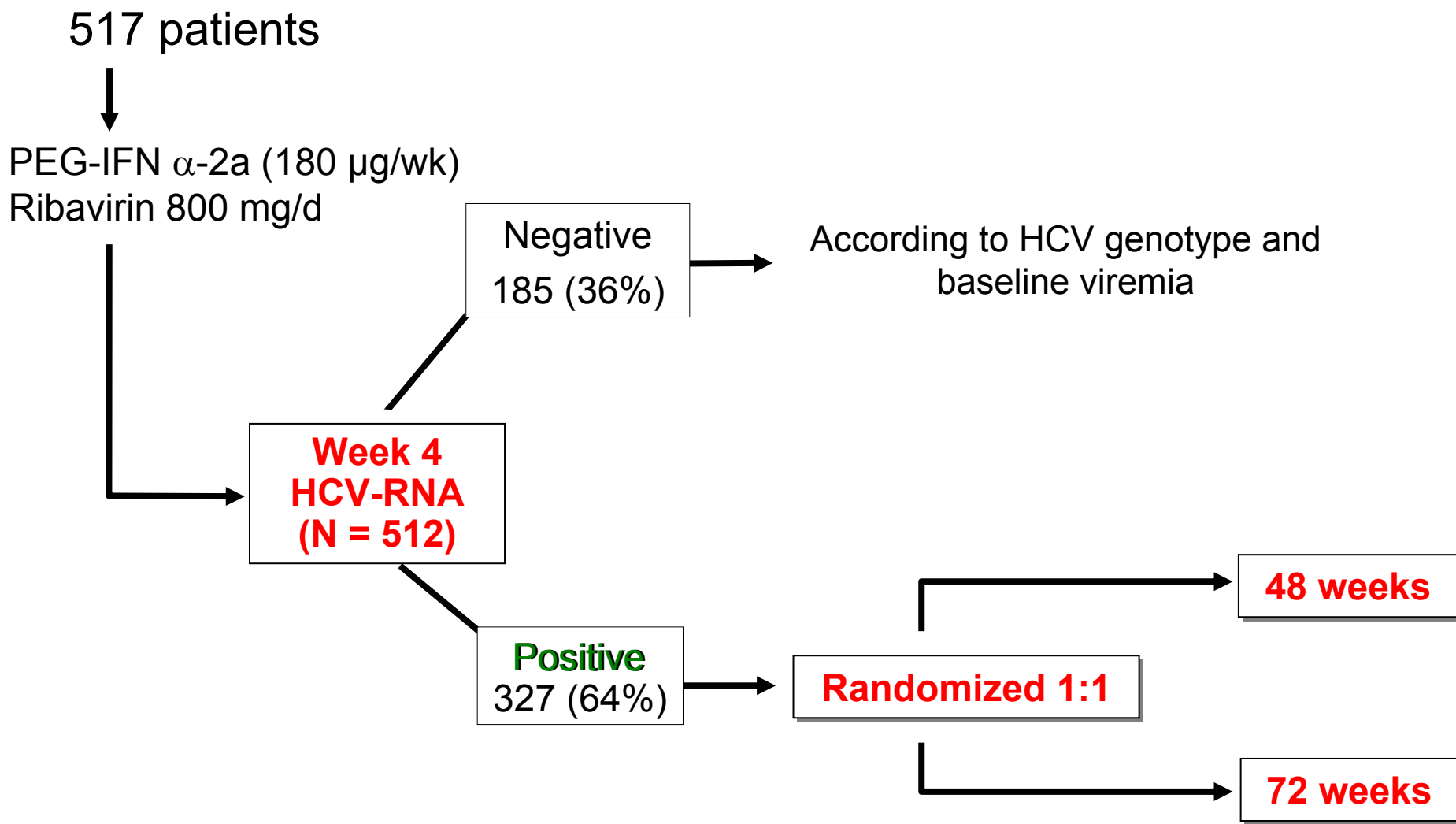
24-week Peginterferon alfa-2a plus ribavirin regimen appears effective in patients with genotype 1 or 4 HCV who respond early to treatment

Sustained virological response (SVR) in super-responders¹

	SVR (%)
Global	77
Baseline viremia <600.000 UI/mL	93
≥600.000 UI/mL	74
Fibrotic stage 0-2	90
3-4	79

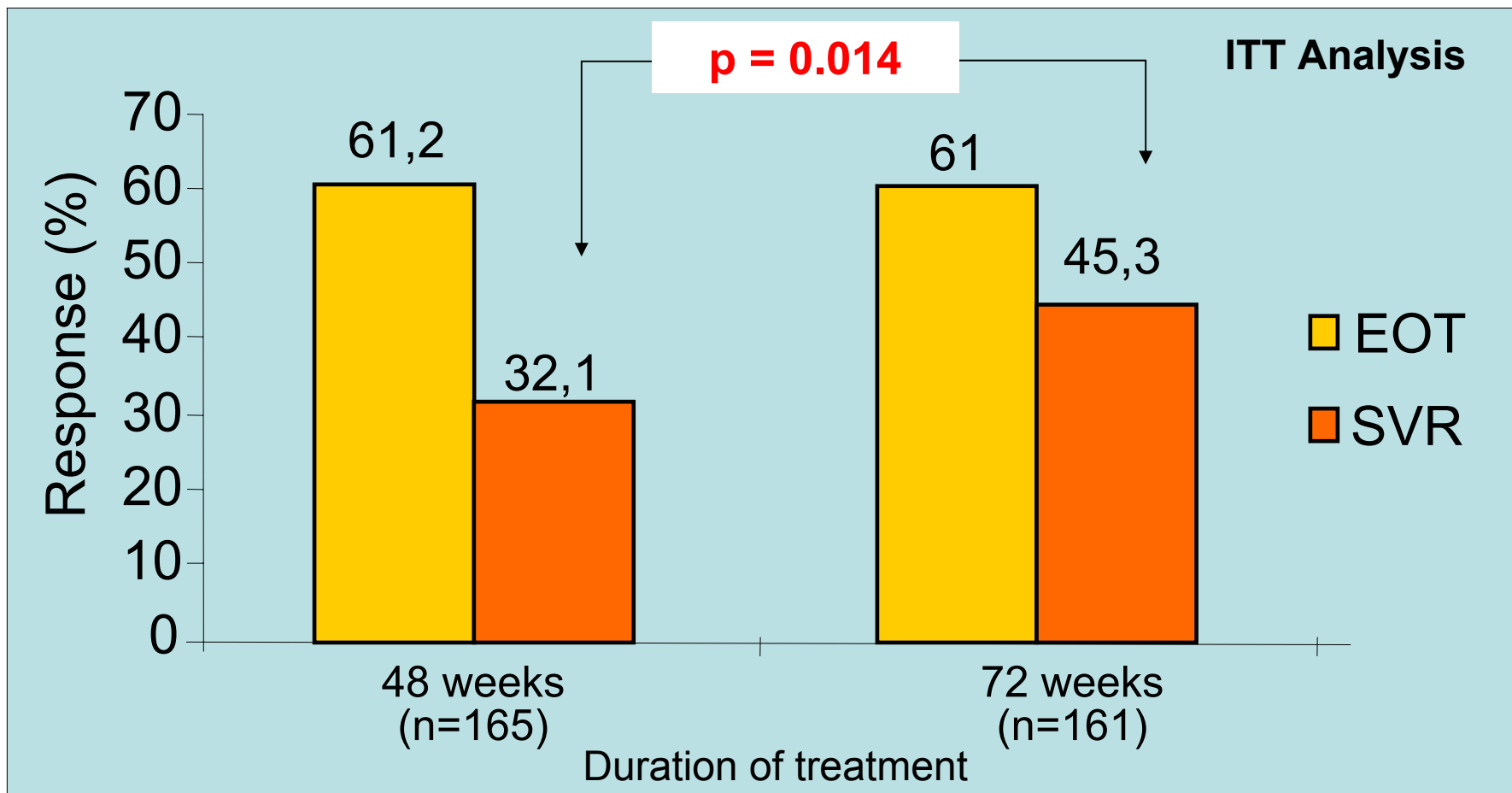
1: Defined by HCV-RNA <50 IU/mL at week 4

Peginterferon α -2a plus ribavirin for 48 versus 72 weeks in patients with detectable HCV-RNA at week 4th of treatment



Peginterferon α -2a plus ribavirin for 48 versus 72 weeks in patients with detectable HVC-RNA at week 4th of treatment

End of treatment (EOT) response and sustained virological response (SVR)



Who may benefit from extended duration therapy ?

Rate of sustained virological response according to viral kinetics during therapy in non-responders at week 4

Treatment duration	HCV-RNA-VHC at week 12		
	All patients	Negative	Positive > 2 log drop
48 weeks	53/165 (32%)	30/58 (52%)	5/31 (16%)
72 weeks	73/161 (45%)	45/74 (61%)	11/25 (44%)

Ribavirin: 800 mg

S.Tapias et al., Gastroenterology 2006

48 sem.	54/99 (57%)	47/59 (80%)	7/19 (31%)
72 sem.	46/78 (59%)	36/44 (82%)	10/13 (77%)

Ribavirin 1.000 – 1200 mg

Ferenci et al., AASLD 2006

Effects of shortening therapy duration in genotype 2 or 3 infected patients

	Num.	RVR	Sustained response	
			RVR	No RVR
Dalgard et al., 2004	122	78%	90% (14)	56% (24)
Mangia et al., 2005	213	63%	86% (12)	64% (24)
Wagner et al., 2005	153	93%	82% (16)	36% (24)
Shiffmann et al., 2006	1463	---	82% (16)	27% (16)
			90% (24)	49% (24)

RVR: Rapid virological response (HCV-RNA undetectable at week 4)

Red figures in brackets indicate treatment duration

Treatment of chronic hepatitis C

- Currently recommended Pegylated interferon plus ribavirin combination therapy is acceptably effective but not fully satisfactory as a treatment for chronic hepatitis C.
- Individualizing therapy duration according to HCV genotype, baseline viremia, liver fibrosis, and viral kinetics early during therapy is an attractive strategy.
- More effective, safer and cheaper therapies are urgently required.