



# Optimal therapy in non-1 genotypes: genotype 2 and 3 patients

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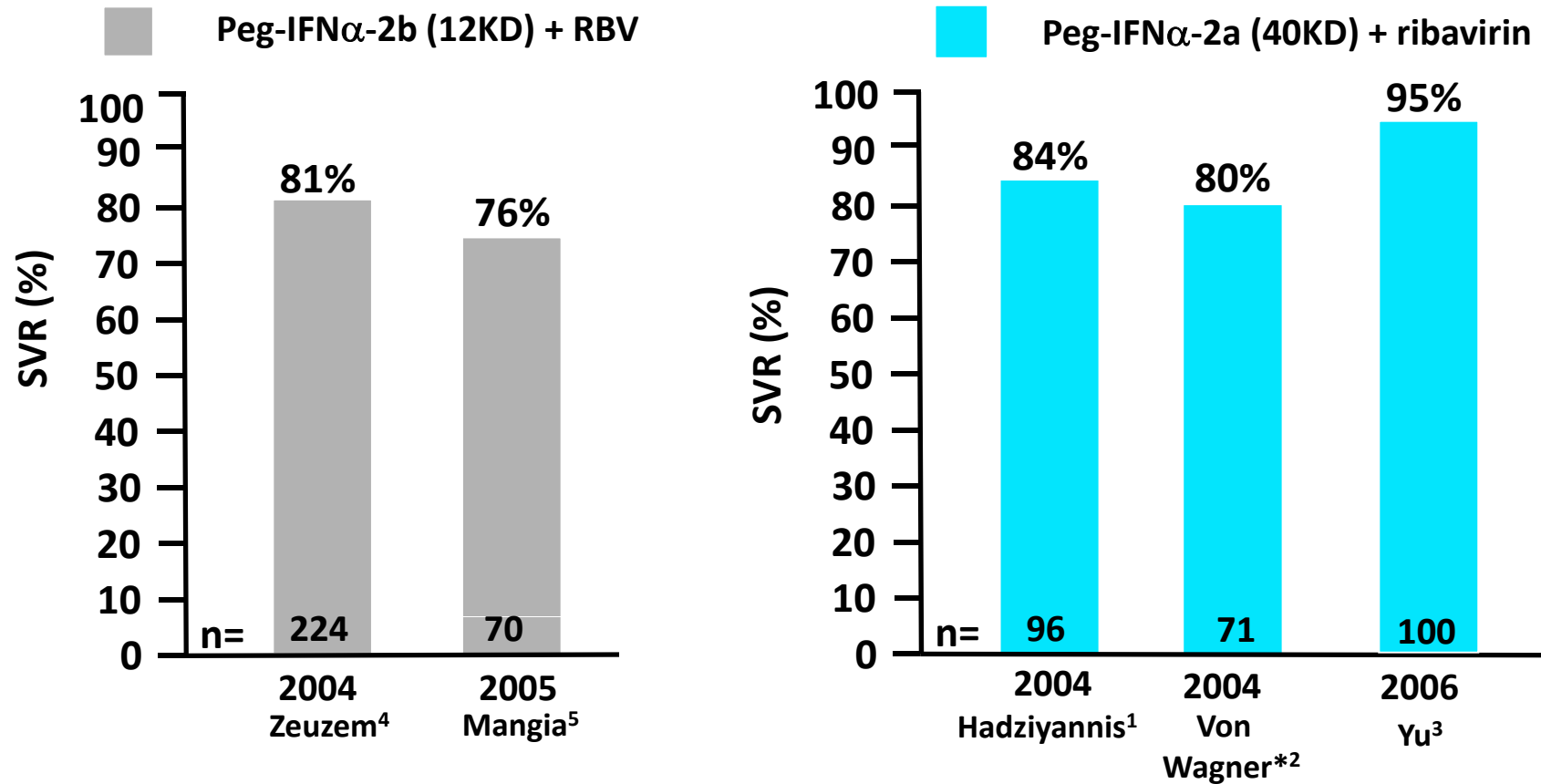
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# Peg IFN alpha plus ribavirin : SVR rate of >80% in genotype 2/3

24-week treatment duration

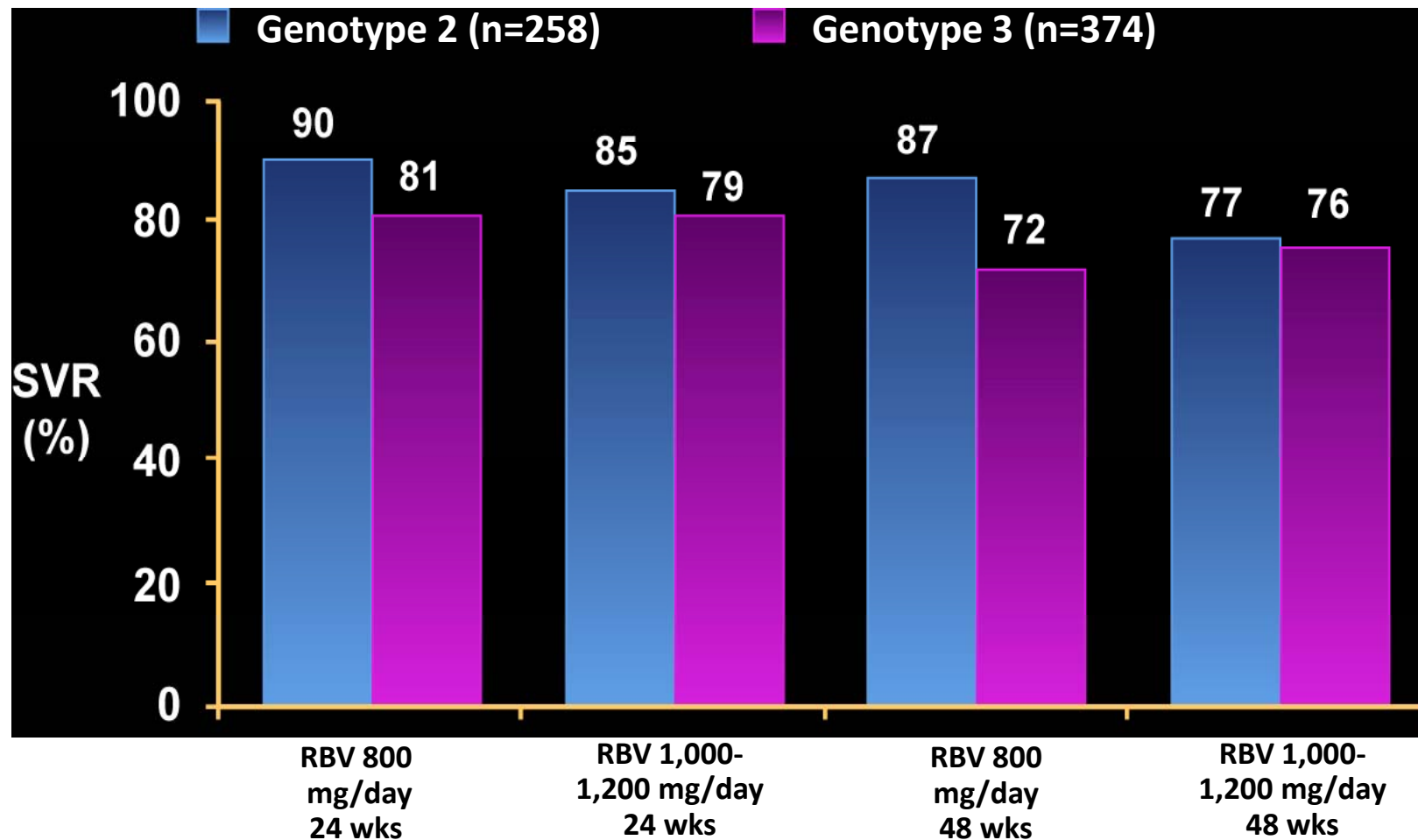


\*Patients had undetectable HCV RNA at week 4

1. Hadziyannis S, et al. *Ann Intern Med* 2004; 140: 346
2. Von Wagner M, et al. *Gastroenterology* 2005; 129: 522
3. Yu M-L, et al. *Gut* 2007; 56: 553
4. Zeuzem S, et al. *J Hepatol* 2004; 40: 993
5. Mangia A, et al. *N Engl J Med* 2005; 352: 2609



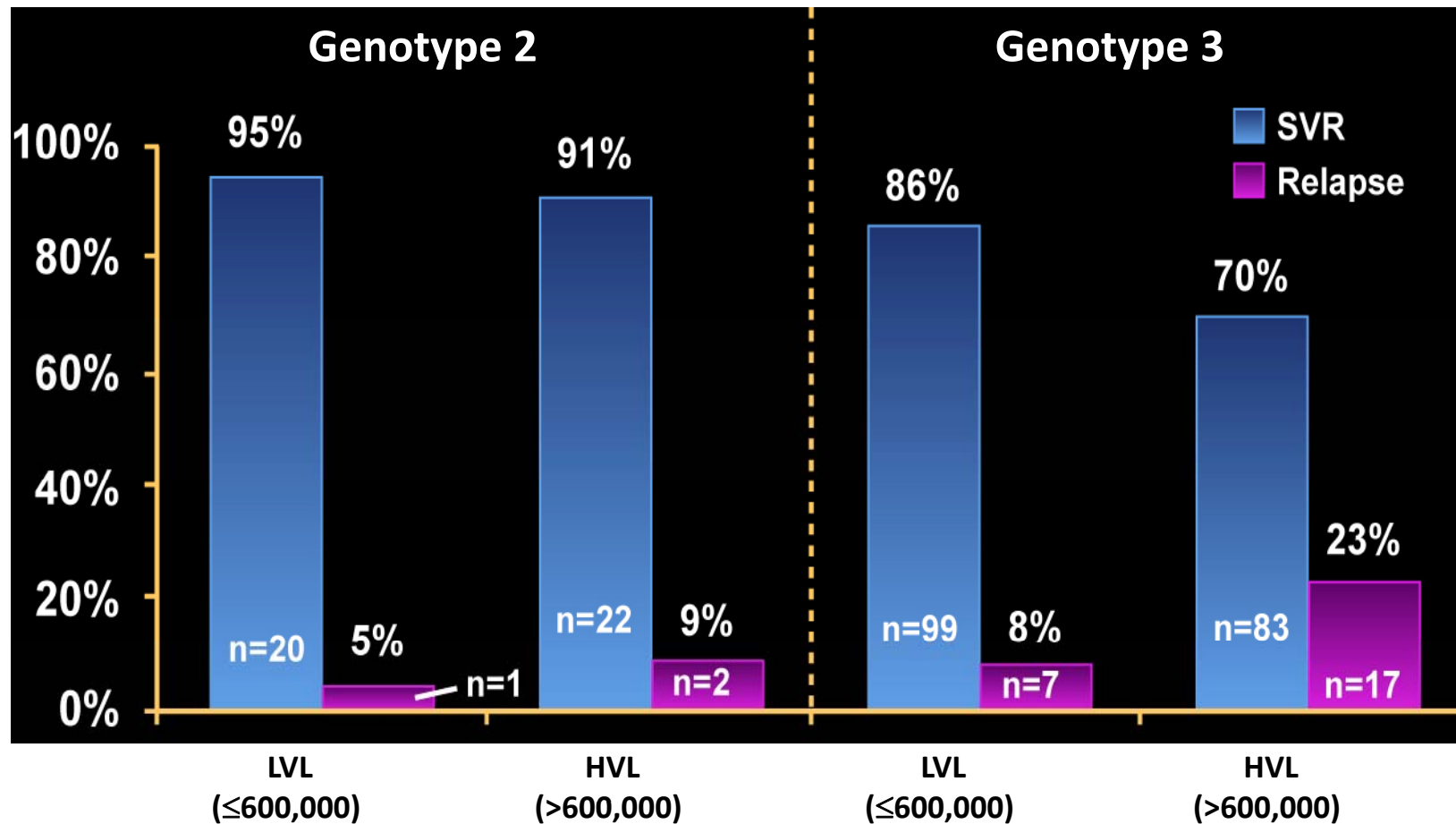
# SVR rates to PEG IFN alfa plus ribavirin for HCV genotypes 2 and 3





# SVR and relapse rates in HCV genotypes 2 and 3 according to viral load

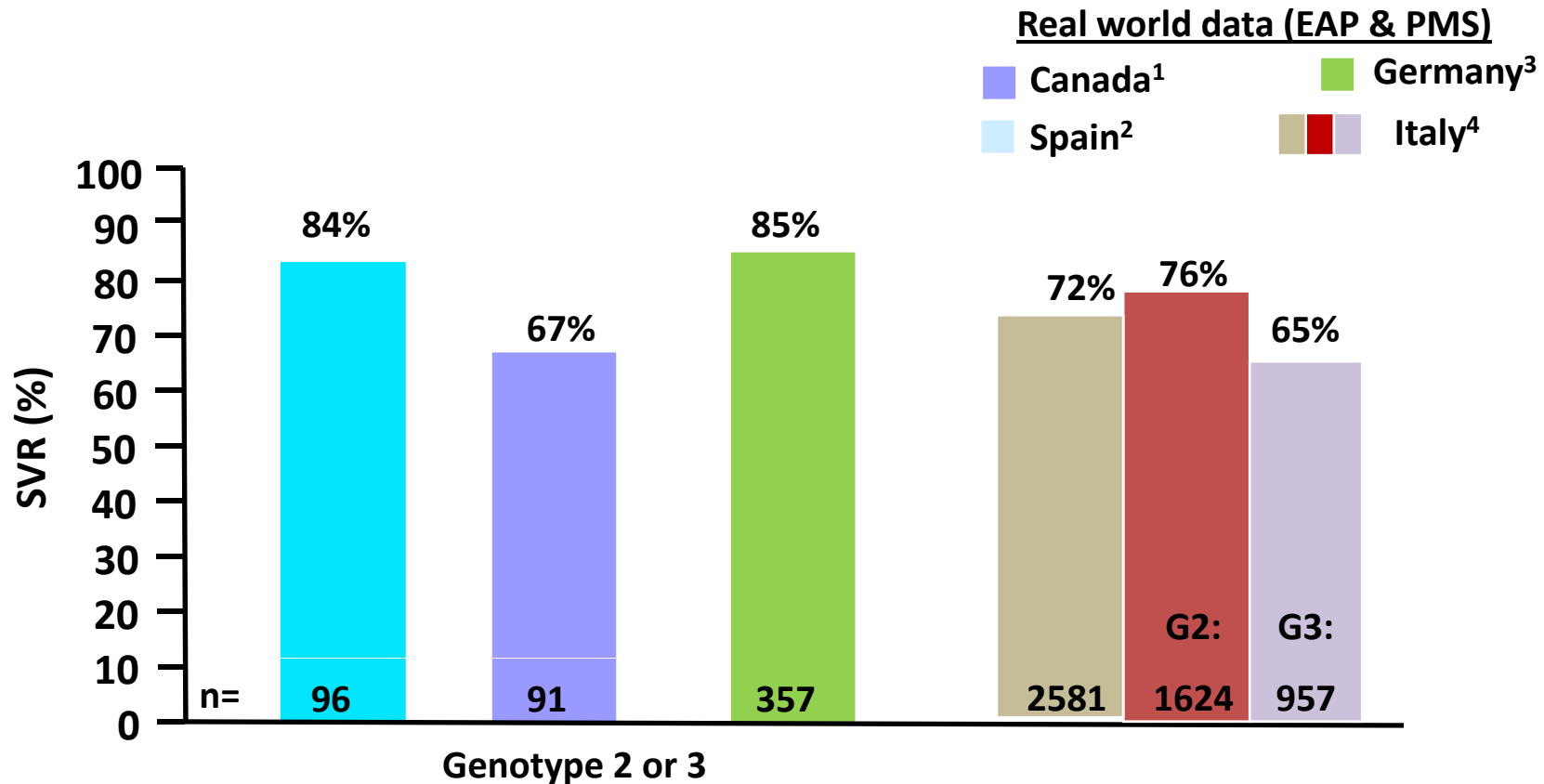
Peg-IFN  $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 800 – 1400 mg/day x 24 Weeks



Genotype 2 vs genotype 3 P=0.020



# Peg IFN plus ribavirin : SVR rates of pivotal trials are reproduced in real-life studies



1. Deschênes M, et al. 42nd EASL 2007; Abstract 615 (Poster)
2. Diago M, et al. 41st EASL 2006; Abstract 567
3. Zehnter E, et al. 56th AASLD 2005; Abstract 1233
4. PROBE study, Roche data on file, manuscript in preparation



# SVR to SoC HCV treatment in U.S. Veterans

Retrospective observational cohort study in 121 Department of V. A. facilities  
Patients: 5944 treated since October 2003 with Peg-IFN $\alpha$ 2a or Peg-IFN $\alpha$ 2b + Rbv

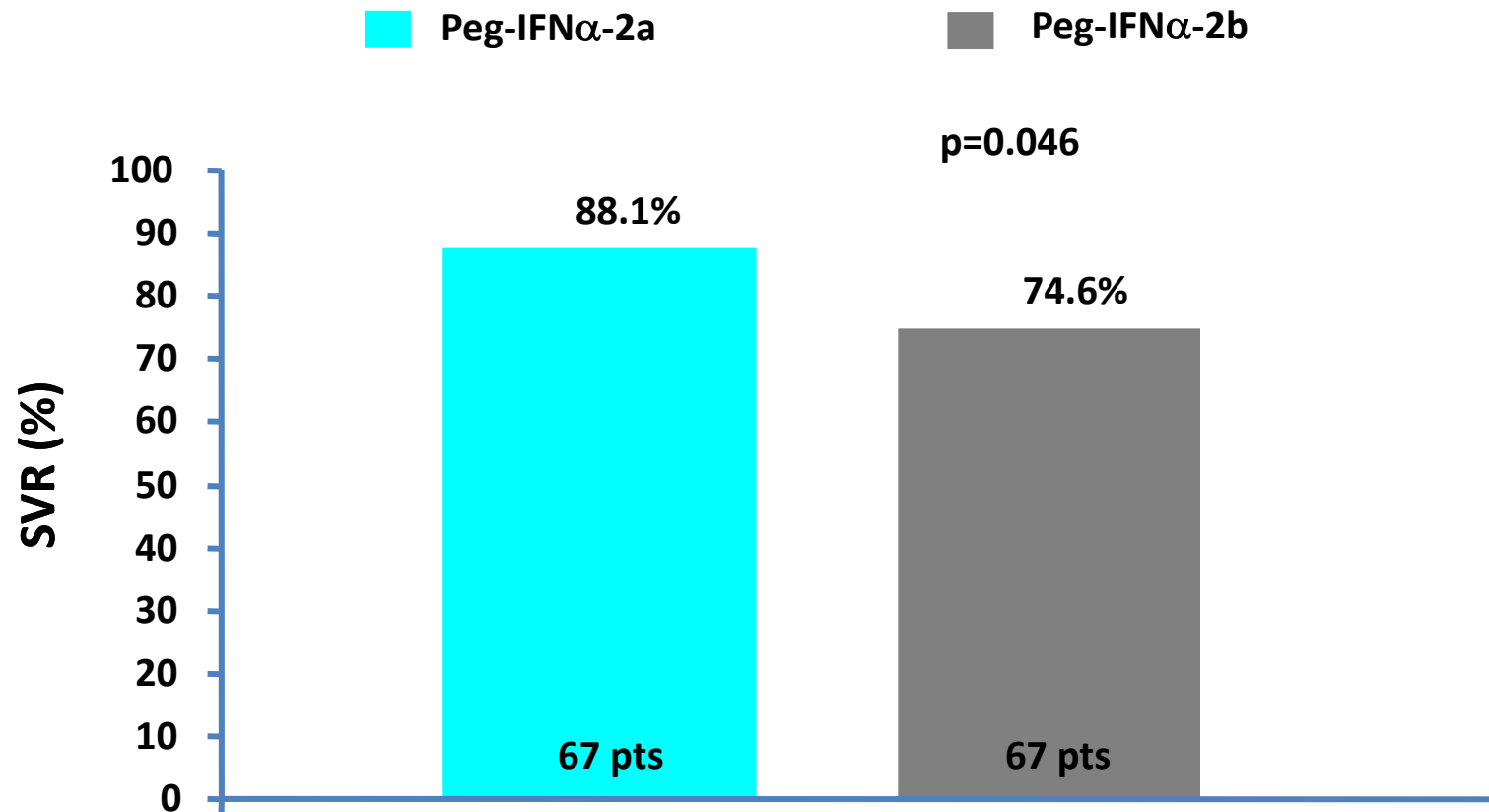
## SVR Rates

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	Peg-IFN $\alpha$ 2a	Peg-IFN $\alpha$ 2b	ALL
HCV-2	53%	52%	52%
HCV-3	52% ^	38%	43%

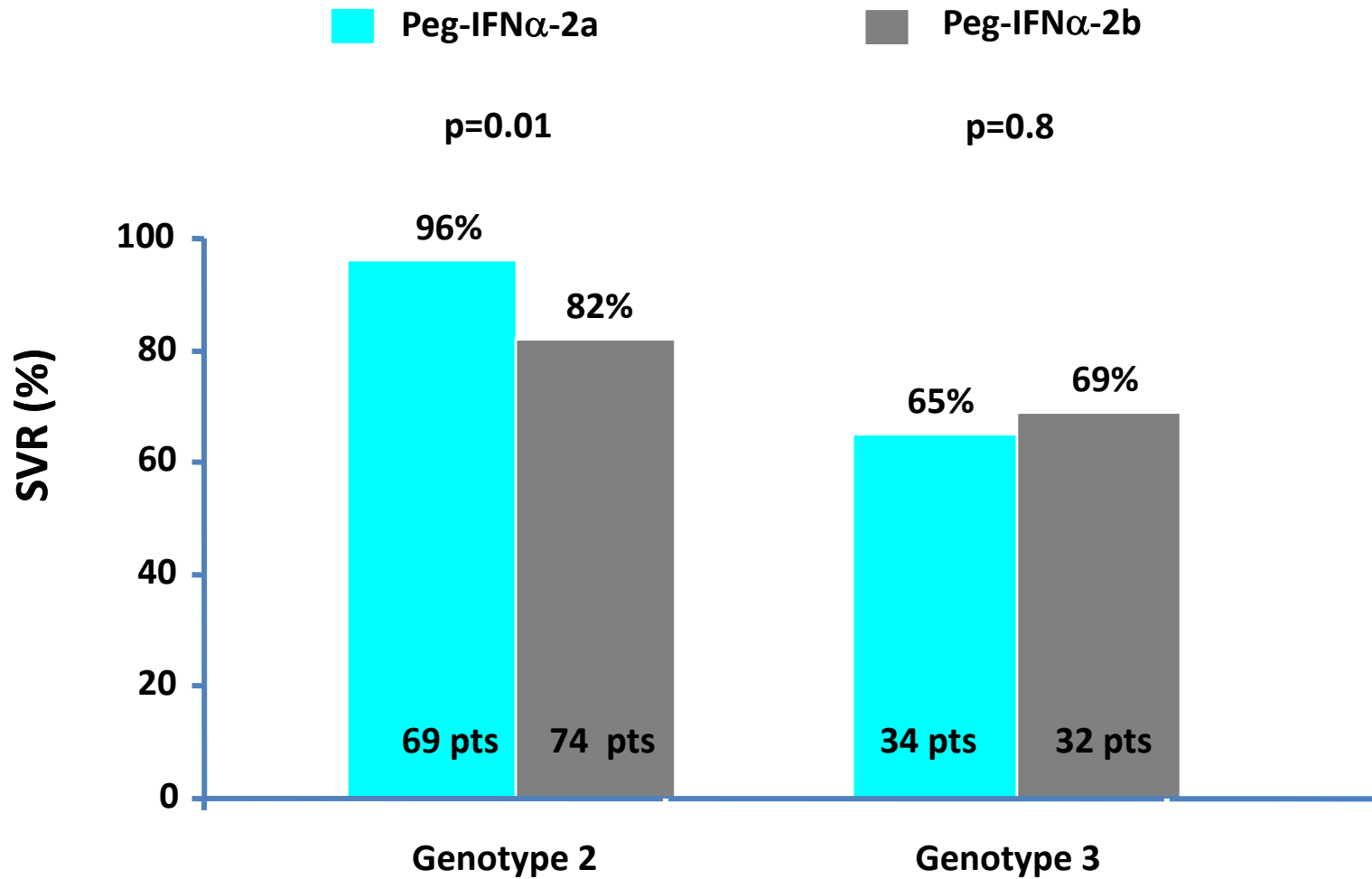


## Naples study: SVR rates with PEG IFN alfa-2a and PEG IFN alfa-2b in patients with HCV G2/G3





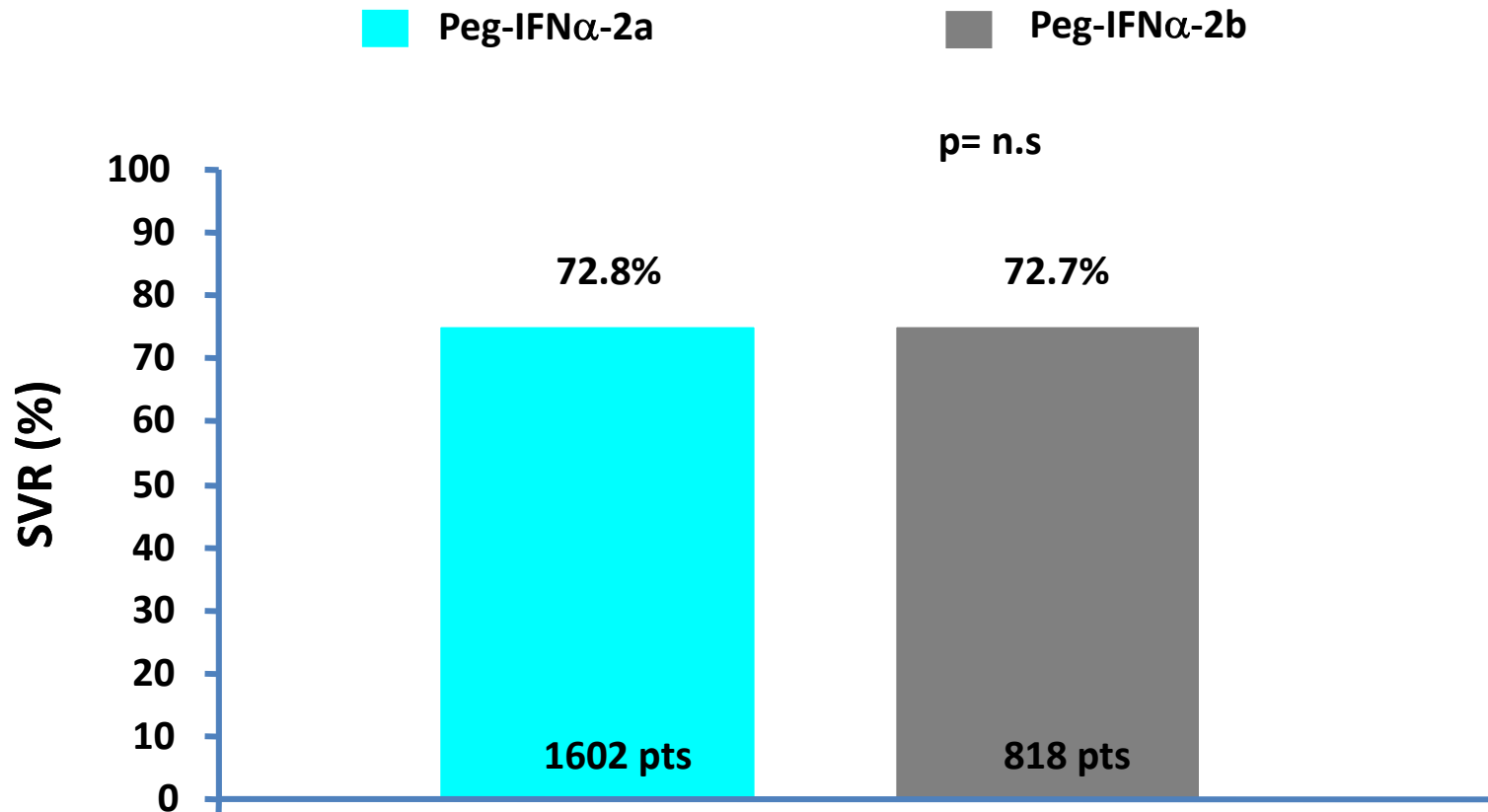
# MIST study: SVR rates with PEG IFN alfa-2a and PEG IFN alfa-2b in patients with HCV G2 and G3







# PROBE real-life study: SVR rates with PEG IFN alfa-2a and PEG IFN alfa-2b in patients with HCV G2/G3





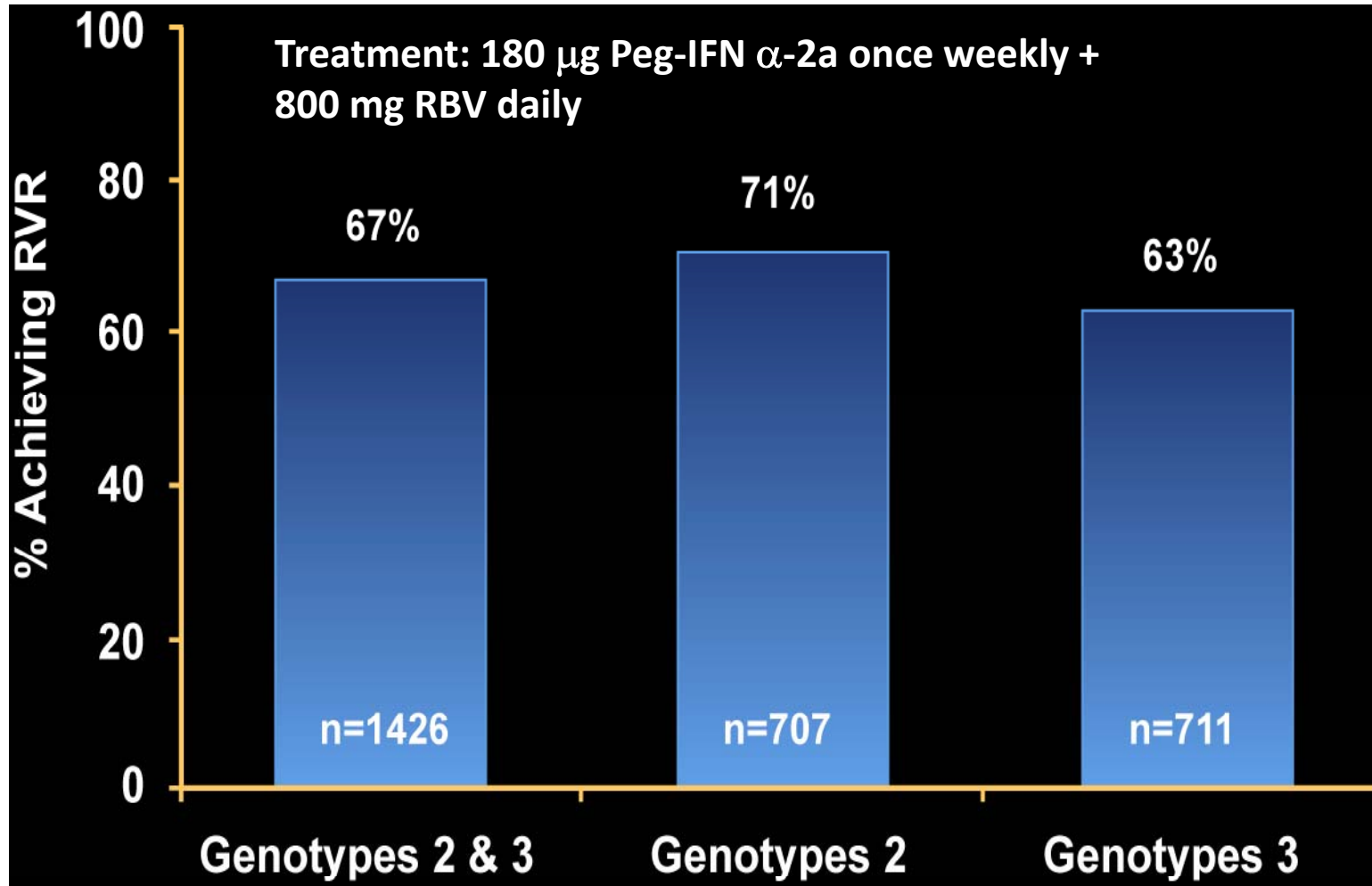
## Rapid Virological Response (RVR) as predictor of SVR: Subanalysis of 3 Phase III trials

Virological Response	G2 (n=395)	G3 (n=426)
RVR (< 50 IU/mL)	71%	60%
EVR (< 50 IU/mL)	24%	29%
pEVR ( $\geq 2 \log_{10}$ drop)	1%	3%
SVR	77%	68%
SVR in patients with RVR	86%	86%
SVR in patients with cEVR*	61%	54%
SVR in patients with pEVR°	-	-

\* Not including RVR; ° not including RVR or cEVR

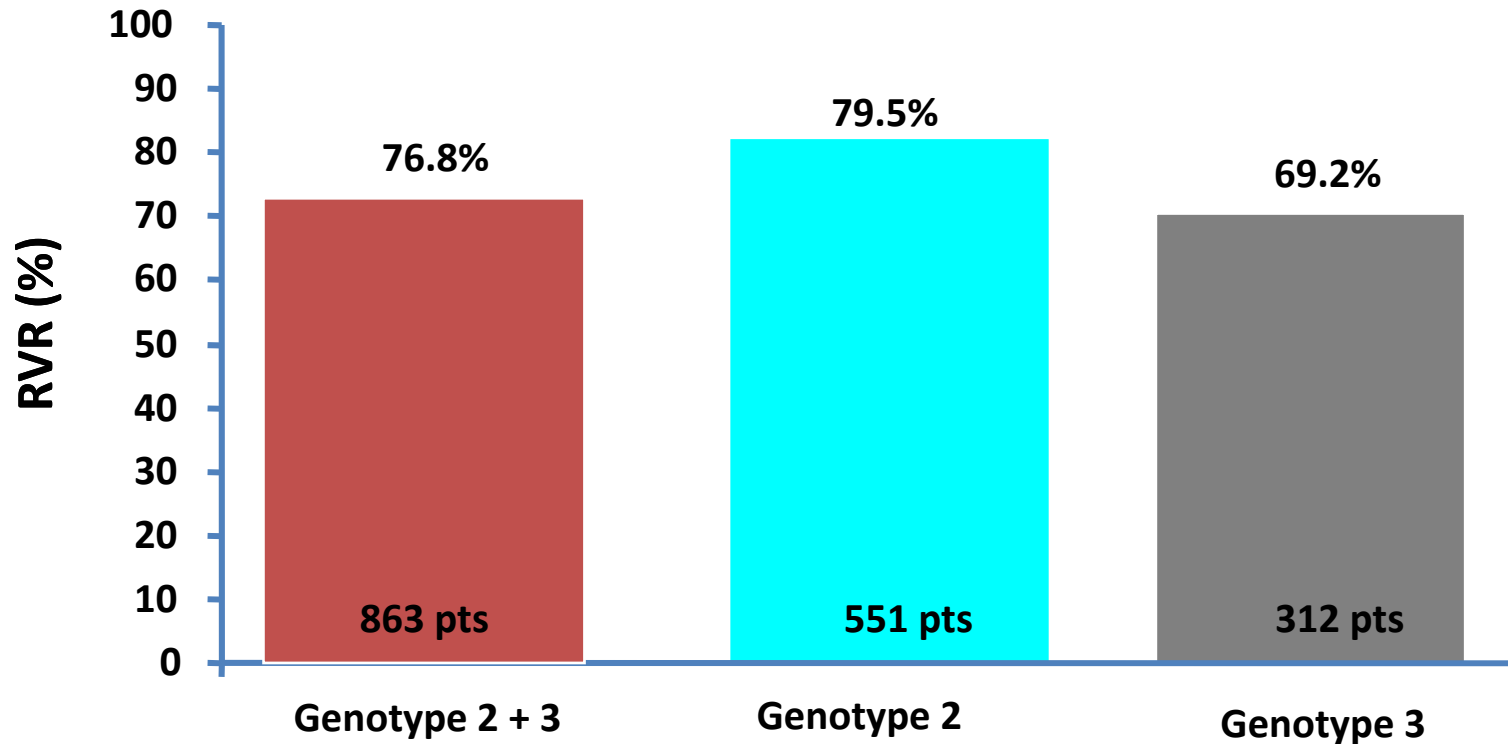


## RVR to SoC in patients with HCV genotype 2 or 3



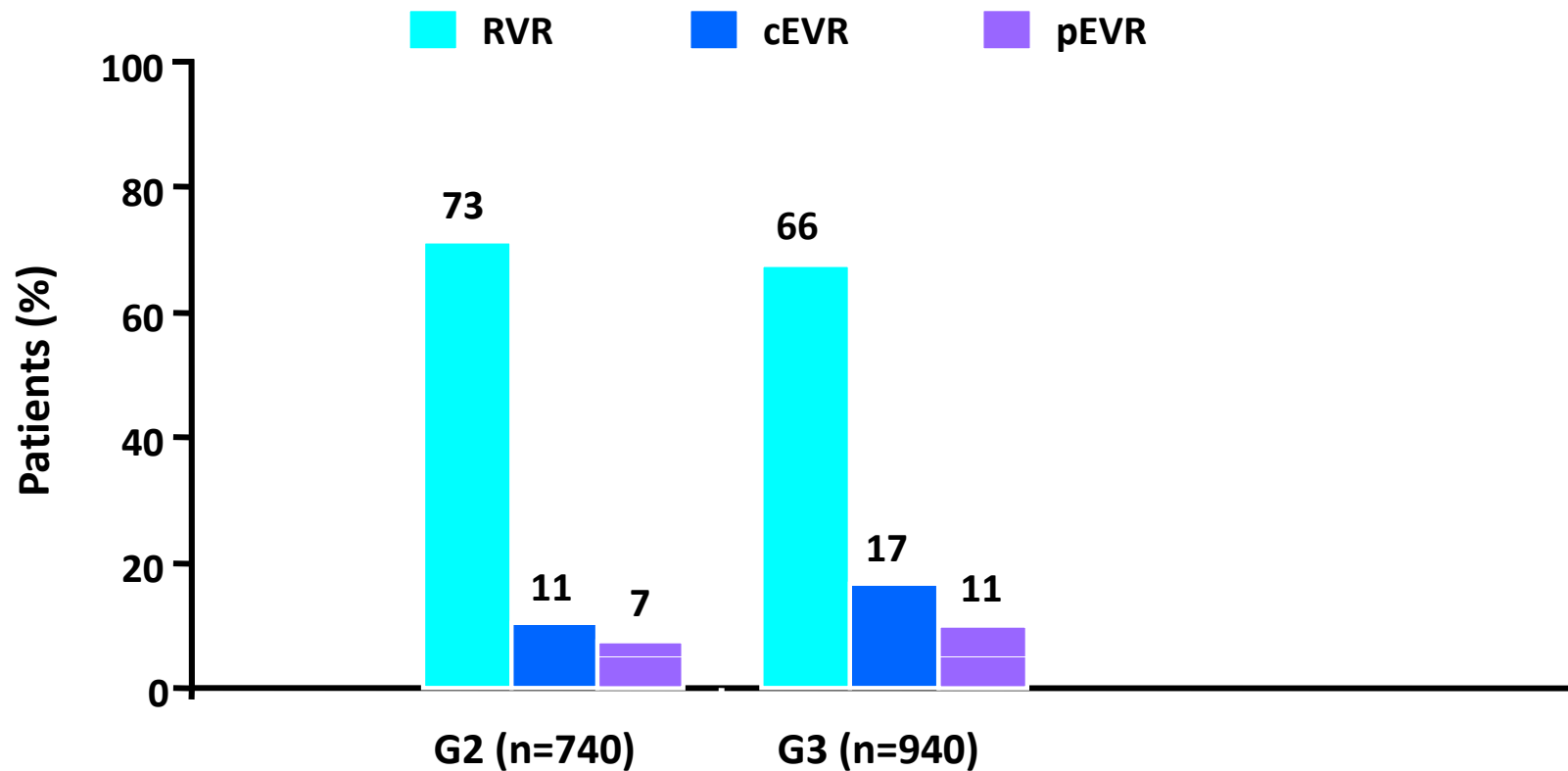


# PROBE real-life study: RVR rates in patients with HCV G2 and G3





# On-treatment early responses of HCV G2 and G3 in a real-life study

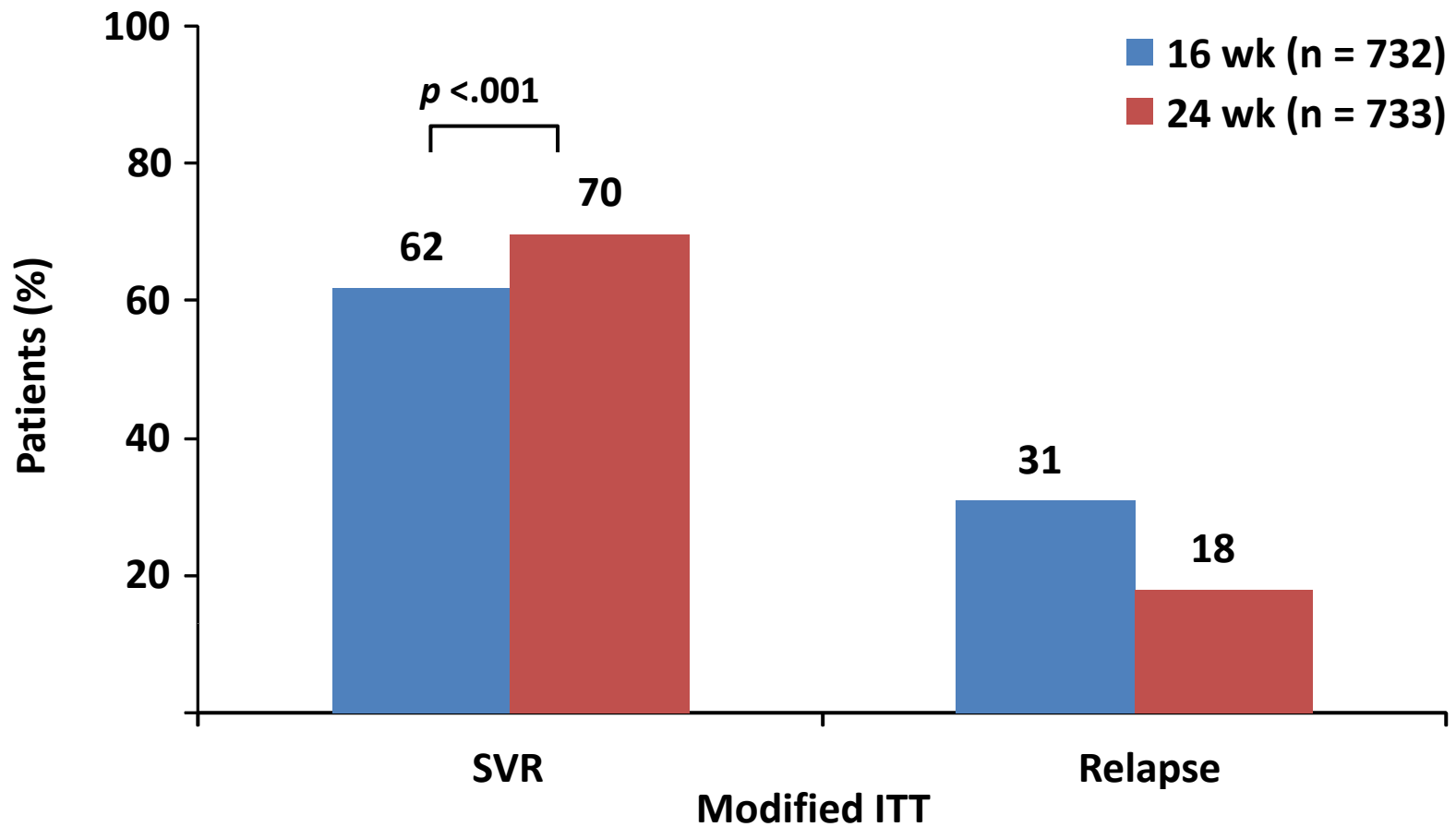


Ribavirin prescribed with either Peg-IFN  $\alpha$ -2a or Peg-IFN  $\alpha$ -2b in accordance with local label



# ACCELERATE: Treatment duration and outcomes

1469 treatment-naïve Gt 2/3 patients with elevated ALT,  
HCV RNA >600 IU/mL, and compensated disease



ALT, alanine aminotransferase; ITT, intention to treat.



# RVR and Short Therapy in G2 Patients

Study	Type	Randomization	Patients	RVR	SVR in pts with RVR and short therapy	SVR in pts with RVR and standard therapy	Therapy
Dalgard 2004	Randomized	RVR → 14 weeks No RVR → 24 weeks	23	91%	90.4%	50% (1/2)	PEGIFN α2b 1.5 RBV 800/1400
Mangia 2005	Randomized	<u>Standard group</u> : 24 weeks <u>Variable group</u> : RVR → 12 weeks NO RVR → 24 weeks	213	64%	87%	89%	PEGIFN α2b 1.0 RBV 1000/1200
Von Wagner 2005	Randomized	RVR → 16 weeks → 24 weeks	38	97%	94%	94%	PEGIFN α2a RBV 1000/1200
Shiffman 2007	Randomized	16 weeks 24 weeks	728	69.2%	78%	85%	PEGIFN α2a RBV 800
Yu 2007	Randomized	16 weeks 24 weeks	150	86.6%	100%	98%	PEGIFN α2a RBV 1000/1200
Dalgard 2008	Randomized	RVR → 14 weeks → 24 weeks	85	75%	93%	97%	PEGIFN α2b 1.5 RBV 800/1400
Lagging 2008	Randomized	12 weeks 24 weeks	104	N.A.	N.A.	N.A.	PEGIFN α2a RBV 800
Mecenate 2010	Randomized	RVR → 12 weeks → 24 weeks	116	79%	N.A.	N.A.	PEGIFN α2a RBV 800/1200

Low baseline viral load, absence of advanced fibrosis, younger age and absence of obesity are associated with SVR in G2 patients with RVR



# RVR and Short Therapy in G3 Patients

Study	Type	Randomization	Patients	RVR	SVR in pts with RVR and short therapy	SVR in pts with RVR and standard therapy	Therapy
Mangia 2005	Randomized	Standard group : 24 weeks Variable group: RVR → 12 weeks NO RVR → 24 weeks	70	59%	77%	100%	PEGIFN α2b 1.0 RBV 1000/1200
Dalgard 2004	Randomized	RVR → 14 weeks No RVR → 24 weeks	99	74.7%	89%	56%	PEGIFN α2b 1.5 RBV 800/1400
Von Wagner 2005	Randomized	RVR → 16 weeks → 24 weeks	113	91%	76.4%	75%	PEGIFN α2a RBV 1000/1200
Shiffman 2007	Randomized	16 weeks 24 weeks	726	61.8%	80%	85%	PEGIFN α2a RBV 800
Dalgard 2008	Randomized	RVR → 14 weeks → 24 weeks	343	70.3%	84%	92%	PEGIFN α2b 1.5 RBV 800/1400
Lagging 2008	Randomized	12 weeks 24 weeks	276	N.A.	N.A.	N.A.	PEGIFN α2a RBV 800
Mecenate 2010	Randomized	RVR → 12 weeks → 24 weeks	94	68.1%	N.A.	N.A.	PEGIFN α2a RBV 800/1200

Low baseline viral load, absence of advanced fibrosis, younger age and absence of obesity are associated with SVR in G3 patients with RVR





# Heterogeneity of short therapy studies in HCV G2/3

Design	No.	PegIFN + Rbv	Duration	RVR (LOD)
<b>Allocation by RVR</b>				
Dalgard 2004	122	alfa2b + wb	14 w	78% (50 IU)
Mangia 2005	283	alfa2b 1.0 + wb	12 w	63% (50 IU)
<b>Randomization by RVR</b>				
von Wagner 2005	153	alfa2a + wb	16 w	93% (600 IU)
Dalgard 2008	428	alfa2b + wb	14 w	71% (50 IU)
<b>Baseline Randomization</b>				
Shiffman 2007	1469	alfa2a + 800 mg	16 w	65% (50 IU)
Yu 2007	150	alfa2a + wb	16 w	87% (50IU)
Lagging 2008	382	alfa2a + 800 mg	12 w	60% (15 IU)



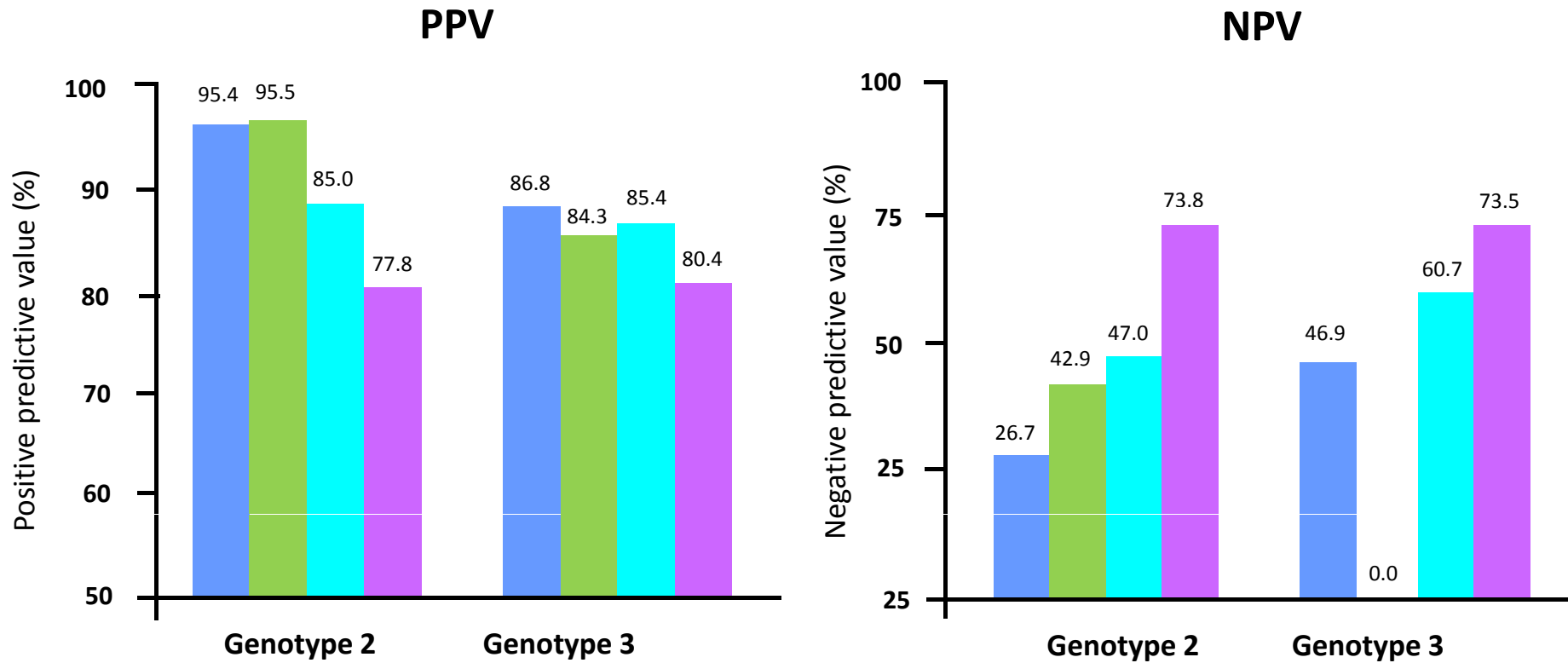
## Heterogeneity of short therapy studies in HCV G2/3

	Mangia	Shiffman	Yu	Lagging
Mean weight (kg)	69.4	81.6	65.8	78
Ribavirin (mg/day)	1,000-1,200	800	1,000-1,200	800
Ribavirin (mg/kg)	~14.4	~9.8	~15.2	~10.3
Relapse rate: (%)	8.9 vs 3.6	31 vs 18	6 vs 3.1	33 vs 12
Withdrawals: no. (%)	9 (3.2)	132 (9.0)	1 (0.7)	22 (5.8)



# The role of RVR in choosing treatment duration for HCV G2 and G3

- 24-week WBD RBV
- 14-16-week WBD RBV
- 24-week FD RBV
- 14-16-week FD RBV





SVR and relapse rates in 485 RVR genotypes 2 and 3 patients after short therapy (12 wks), according to the presence or absence of risk factors\*

	Total	SVR	Relapse
Pts without risk factors*	316	290 (91.8%)	26 (8.2%)
Pts with 1 or 2 risk factors*	169	128 (74.4%)	41 (25.6%)

\* BMI >30 and/or PLT <140,000

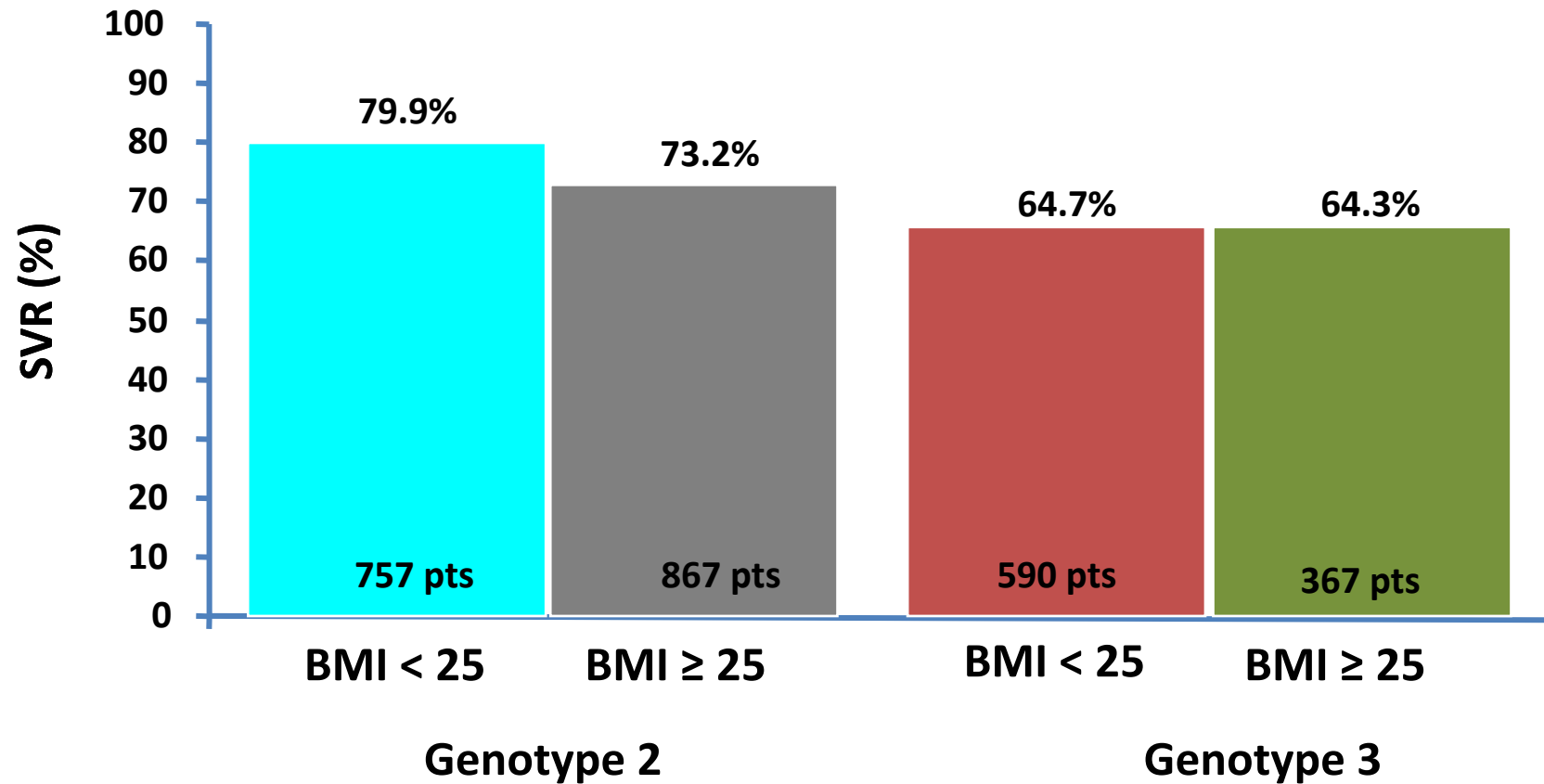


# Rates of relapse among subgroups of HCV 2/3 pts with RVR

	16 wks	24 wks	difference
HCV 2	39/233 (17)	10/204 (5)	11.8
HCV 3	28/206 (14)	13/180 (7)	6.4
HCV RNA ≤400.000 IU/ml	6/144 (5)	1/96 (1)	4.2
>400.000 IU/ml	61/325 (19)	22/288 (8)	11.1
Cirrhosis Yes	41/342 (12)	16/312 (5)	3.2
No	26/97 (27)	7/72 (10)	11.5
Body weight <65 kg	6/87 (7)	2/70 (3)	4.0
≥65 kg	61/352 (17)	21/314 (7)	10.6

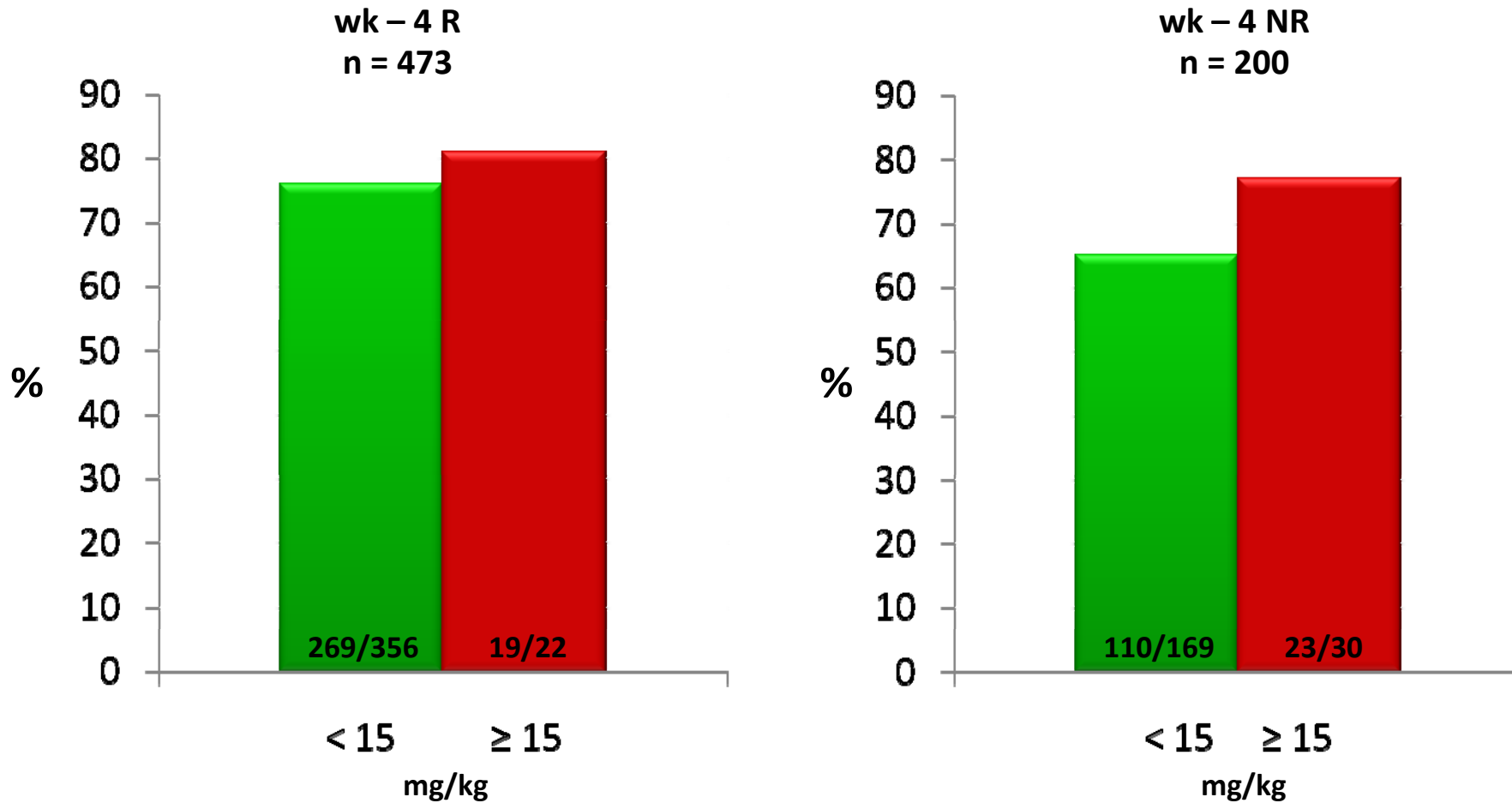


# PROBE real-life study: SVR rates in patients with HCV G2 and G3 according to BMI





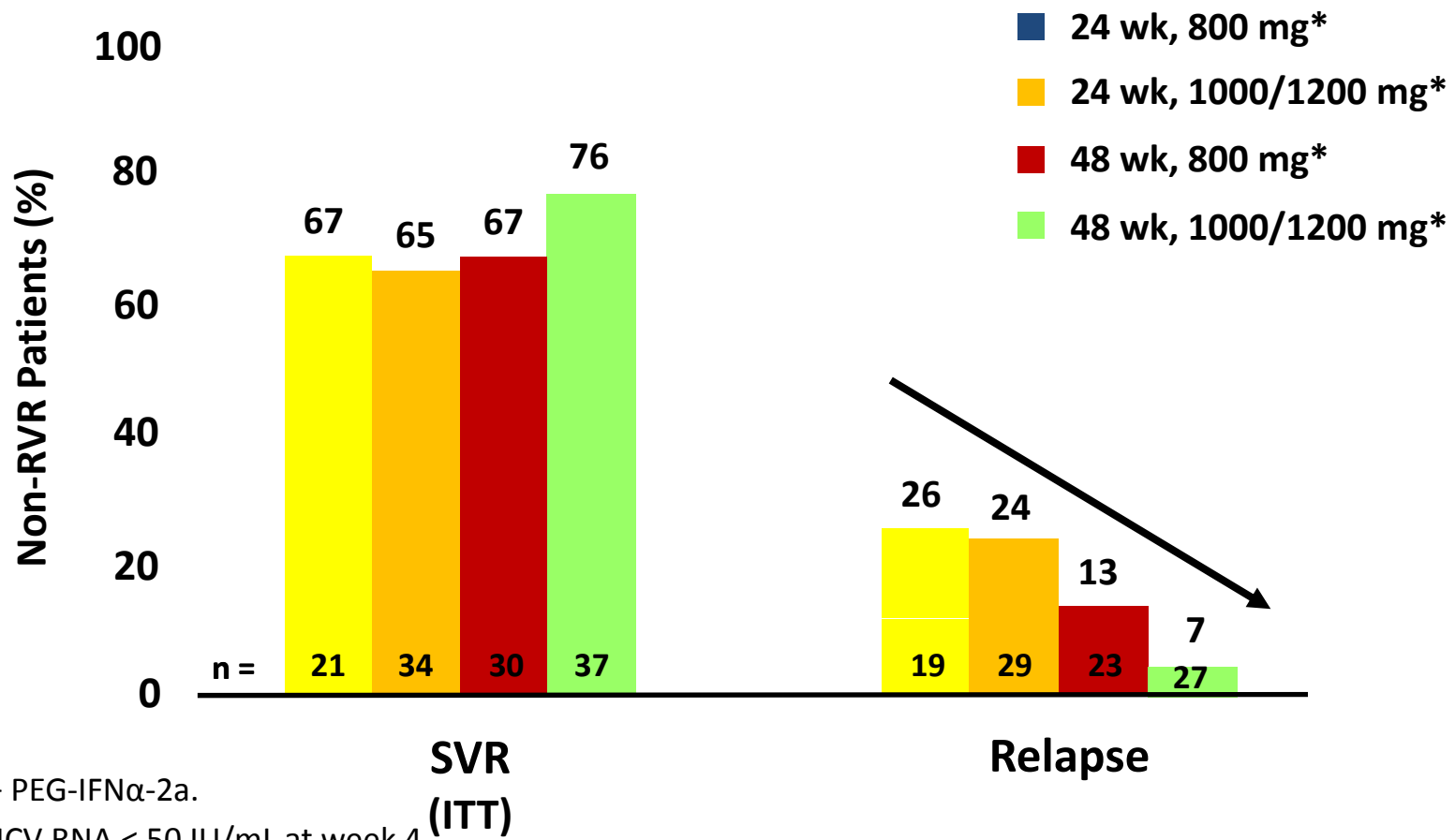
# SVR rates according to ribavirin dosage in 673 patients with HCV Genotype 2 and 3





# Non-RVR G 2 and G 3 patients: decreased relapse with 48 weeks treatment, weight-based RBV

Retrospective analysis of G 2/3 patients from two PEG-IFN $\alpha$ -2a pivotal trials



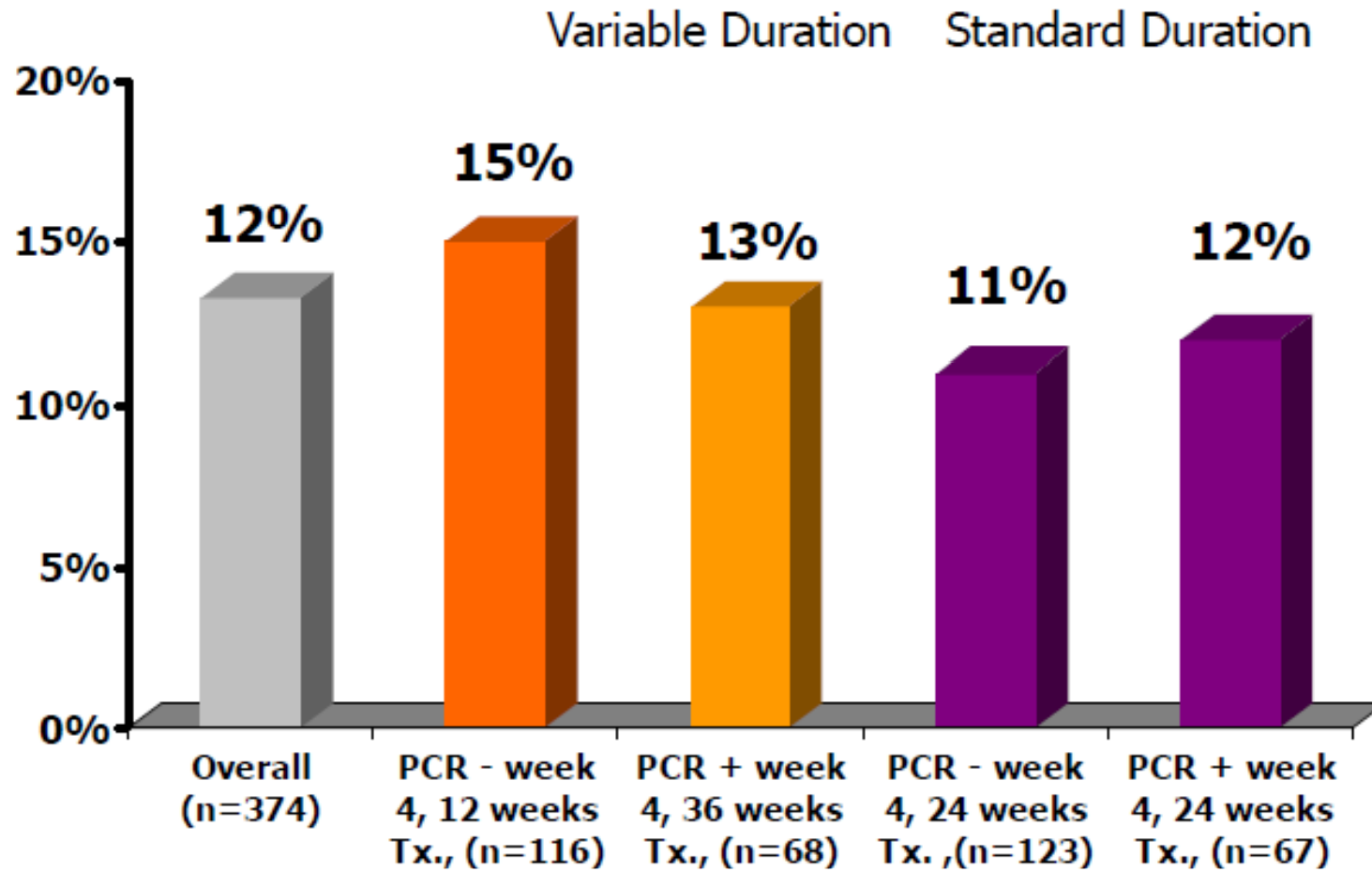
Willems B et al J Hepatol 2007;46:S6 Abstract 8

1. Hadziyannis S, et al. Ann Intern Med 2004; 140: 346  
2. Fried M, et al. N Engl J Med 2002; 347: 975



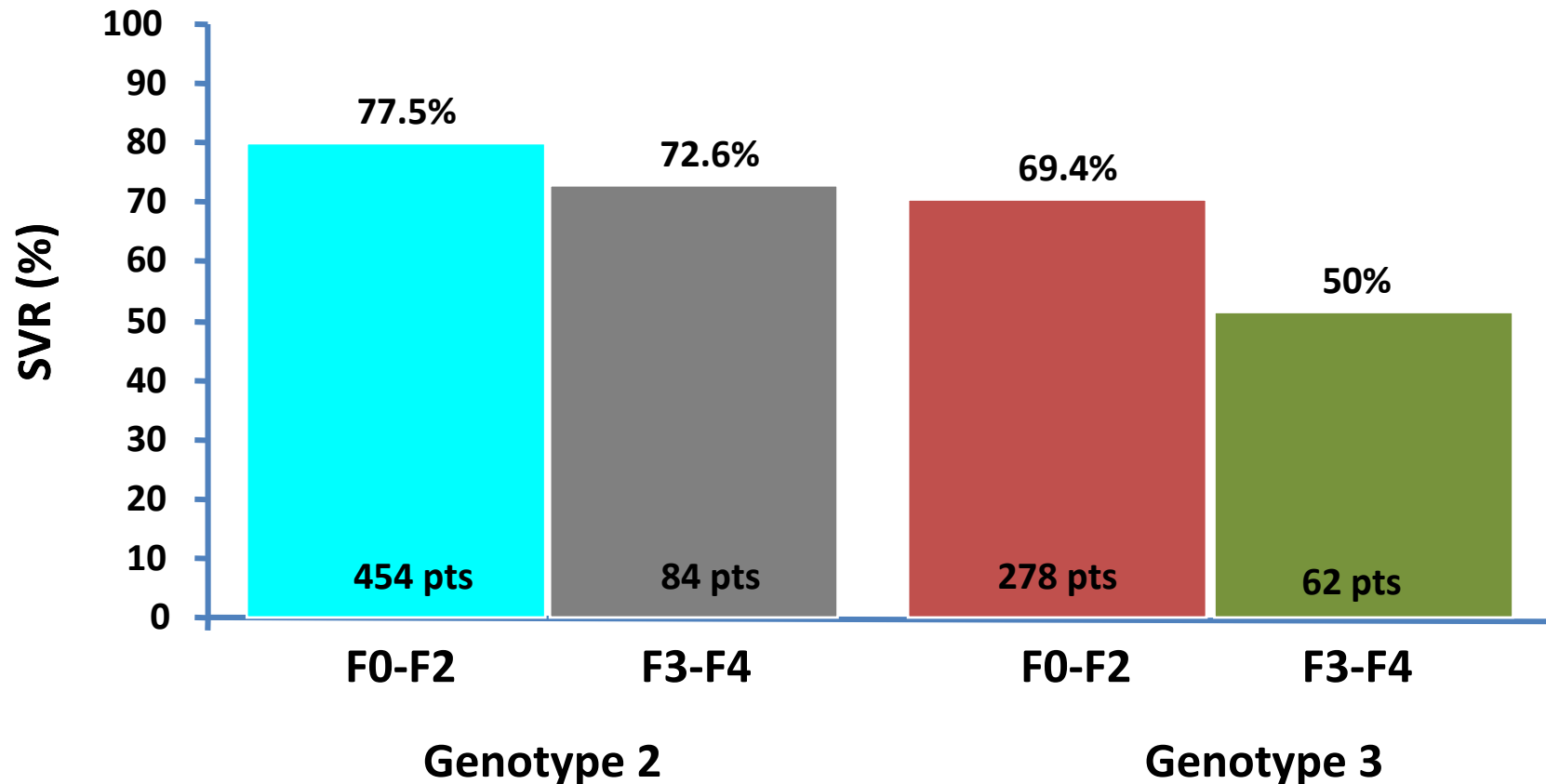


# % of Patients with HCV 3 Relapsing after Std or Extended Tx





# PROBE real-life study: SVR rates in patients with HCV G2 and G3 according to stage of fibrosis



*PROBE study, Roche data on file, manuscript in preparation*



## Treatment of cirrhosis (Child Pugh A5-B7) due to HCV genotypes 2 or 3 with SoC\*

	<b>Genotype 2 (41 pts)</b>	<b>Genotype 3 (18 pts)</b>	<b>P value</b>
<b>Age*</b>	59.6±7.8	43.4± 6.4	<b>&lt; 0.001</b>
<b>Sex (M)</b>	25(61.0%)	16(88.9%)	<b>0.032</b>
<b>Body weight (Kg)</b>	73.9 ± 14.5	78.3 ± 13.4	n.s.
<b>AST*</b>	116.0 ± 60.0	164.0 ± 102.0	<b>0.038</b>
<b>ALT*</b>	144.0 ± 68.0	232.0 ± 136.0	<b>0.002</b>
<b>PLT*</b>	105.8 ± 42.8	117.3 ± 54.2	n.s.
<b>AP%</b>	85.5± 21.8	86.5 ± 15.6	n.s.
<b>Bilirubin*</b>	0.95 ± 0.43	0.92 ± 0.35	n.s.
<b>Albumin*</b>	4.0 ± 0.5	4.2 ± 0.4	n.s.
<b>Oesophageal varices</b>	18 (43.9%)	8 (44.4%)	n.s.

\* PEG IFN alfa.2b 1,5 µg/wk plus ribavirin 800-1,400 mg/day for 48 weeks



## Treatment of cirrhosis (Child Pugh A5-B7) due to HCV genotypes 2 or 3 with SoC\*

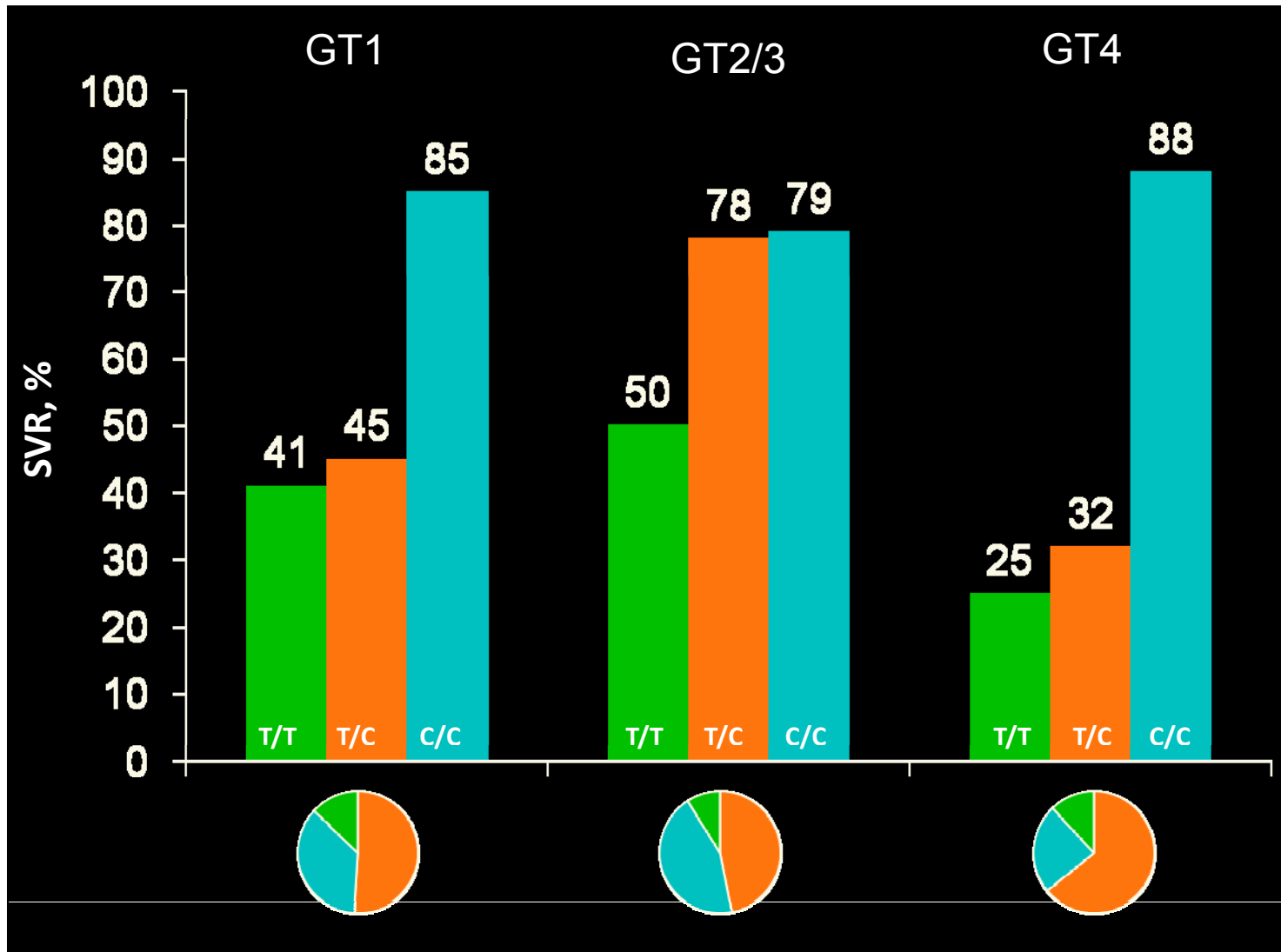
	<b>Genotype 2 (41 pts)</b>	<b>Genotype 3 (18 pts)</b>	<b>P value</b>
<b>RVR</b>	26 (63.4%)	14 (77.8%)	n.s.
<b>EVR</b>	34 (82.9%)	17 (94.4%)	n.s.
<b>ETR</b>	32 (78.0%)	16 (88.9%)	n.s.
<b>SVR</b>	25 (61.0%)	10 (55.6%)	n.s.

\* PEG IFN alfa.2b 1,5 µg/wk plus ribavirin 800-1,400 mg/day for 48 weeks

*Di Marco and Craxì, unpublished data*

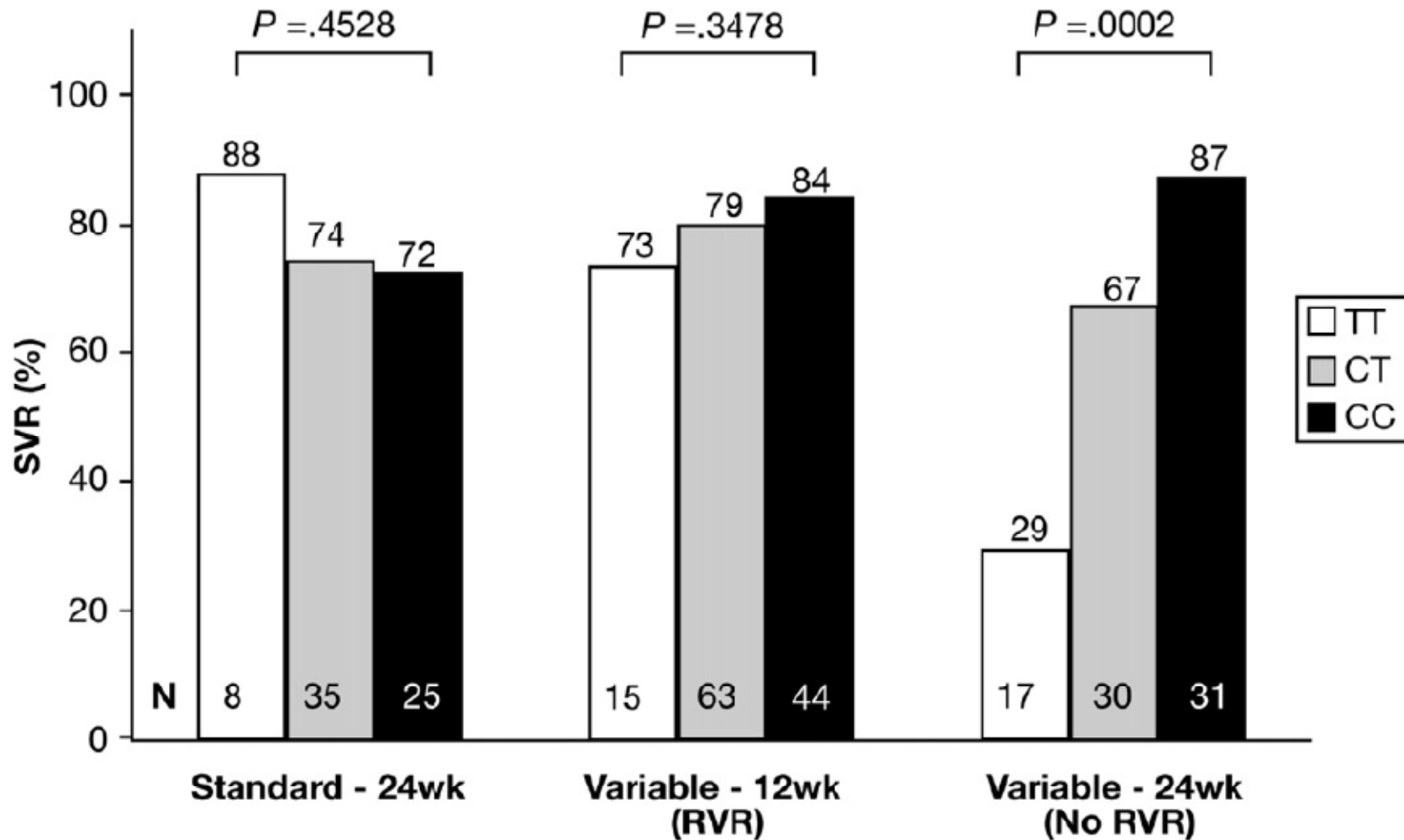


# IL28B polymorphism and treatment outcome





## IL28b genotype in HCV G 2/3 patients: predictability of SVR according to RVR





# Role of IL28B polymorphisms in the treatment of HCV genotype 2 infection in Asian patients

- rs8105790, rs8099917, rs4803219, and rs10853728 assessed as candidate SNPs in 482 Asian HCV G2 patients treated with SoC
- Patients with the rs8099917 TT genotype, in comparison with patients with GT/GG genotypes, had a significantly higher rate of RVR (85.2% versus 72.0%, P 5 0.017) but not of SVR (89.4% versus 86.0%)

**Table 3. Logistic Regression Analysis of Factors Associated With RVR and SVR**

Variable	OR	95% CI	P Value
<b>RVR</b>			
Baseline HCV RNA levels			
>400,000 IU/mL	1		
<400,000 IU/mL	4.27	2.31-7.87	<0.001
Liver fibrosis score (F0-F2 = 0, F3-F4 = 1)*	0.28	0.15-0.53	<0.001
rs8099917			
GT/GG genotype	1		
TT genotype	3.10	1.34-7.21	0.008
Pretreatment AST level (per 1 IU/L increase)	0.996	0.99-1.00	0.04
<b>SVR</b>			
Achievement of RVR			
No	1		
Yes	19.37	8.89-42.23	P < 0.001

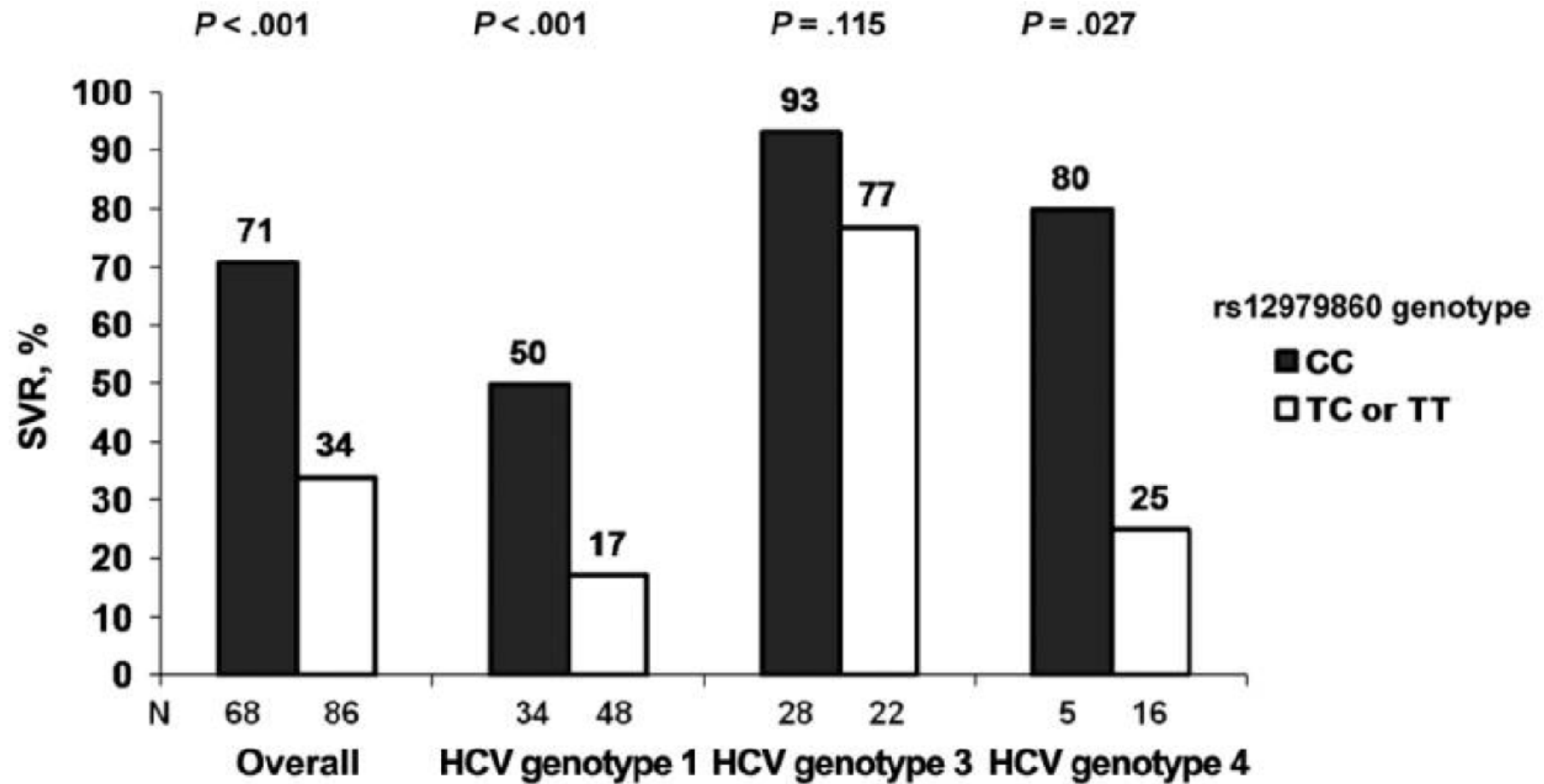
\*Data were available for 349 patients.

**Table 5. Impact of rs8099917 on the On-Treatment Response in HCV-2 Patients With or Without RVR**

Variable	rs8099917 TT Genotype	rs8099917 GT + GG Genotype	P Value
<b>RVR-positive</b>			
EOTVR, n/N (%)	367/368 (99.7)	36/36 (100.0)	1.00
SVR, n/N (%)	348/368 (94.6)	34/36 (94.4)	1.00
Relapse, n/N (%)	19/367 (5.2)	2/36 (5.6)	1.00
<b>RVR-negative</b>			
EVR, n/N (%)	57/64 (89.1)	13/14 (92.9)	1.00
EOTVR, n/N (%)	53/64 (82.8)	11/14 (78.6)	0.71
SVR, n/N (%)	38/64 (59.4)	9/14 (64.3)	0.73
Relapse, n/N (%)	15/53 (28.3)	2/11 (18.2)	0.71



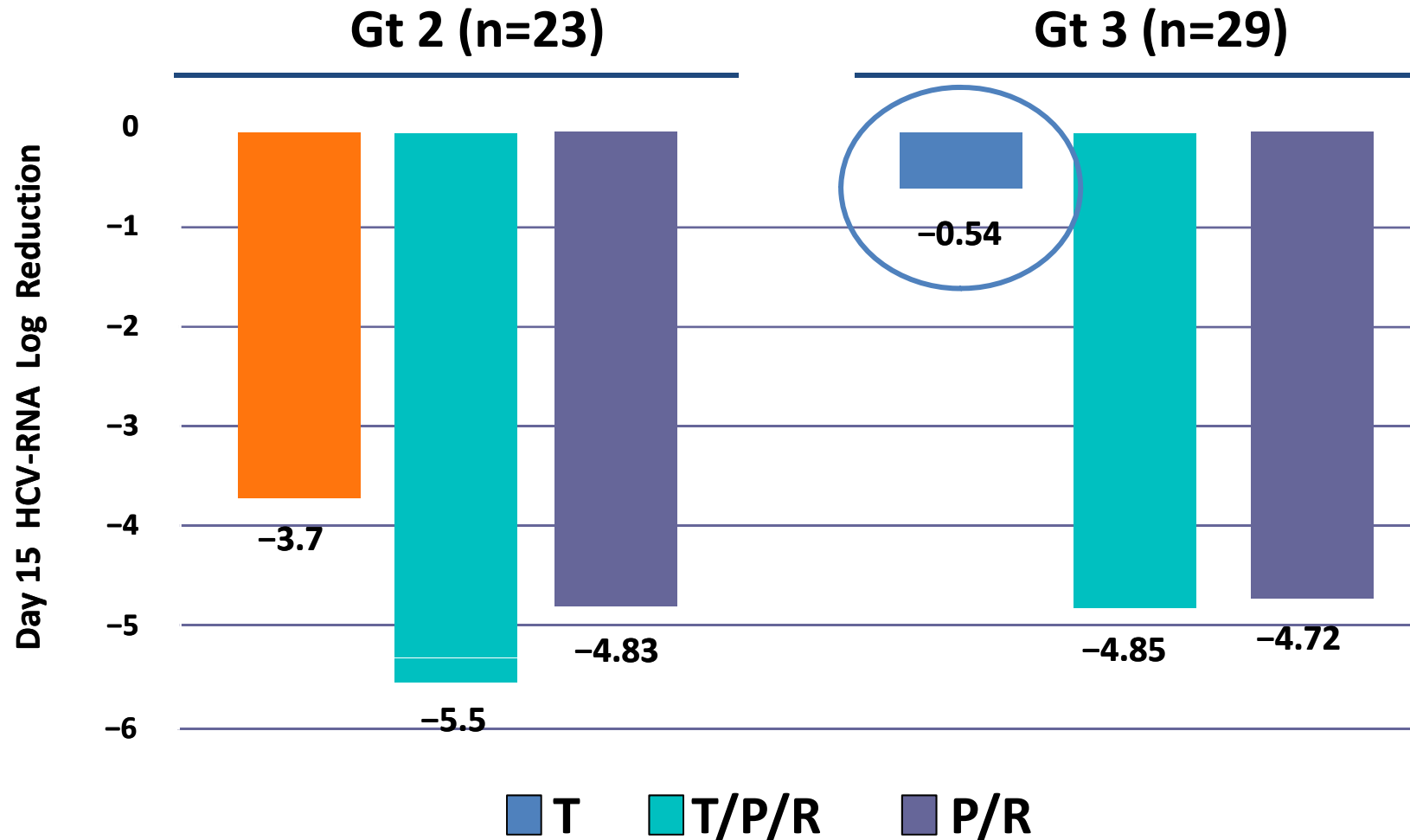
# IL28b genotype in HIV/HCV G3 patients: predictability of SVR







# Telaprevir in genotypes 2 and 3 (C209)



P, Peg-IFN $\alpha$ -2a 180  $\mu$ g/wk; R, ribavirin 800 mg/d; T, telaprevir q8h.





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## EASL HCV CLINICAL PRACTICE GUIDELINES

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