E.T Monothematic conference on
Hepatitis Viruses and Immunosuppression
Florence, march 10-12, 2011

IL28B nei genotipi non-1

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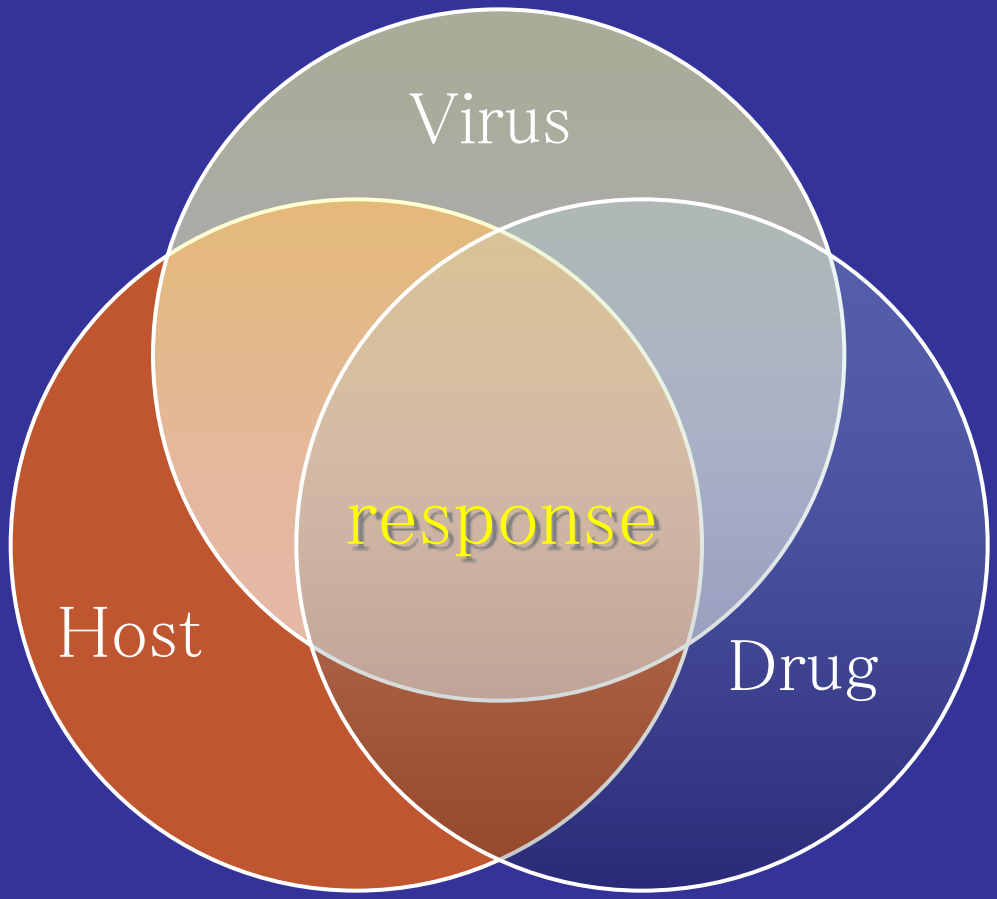
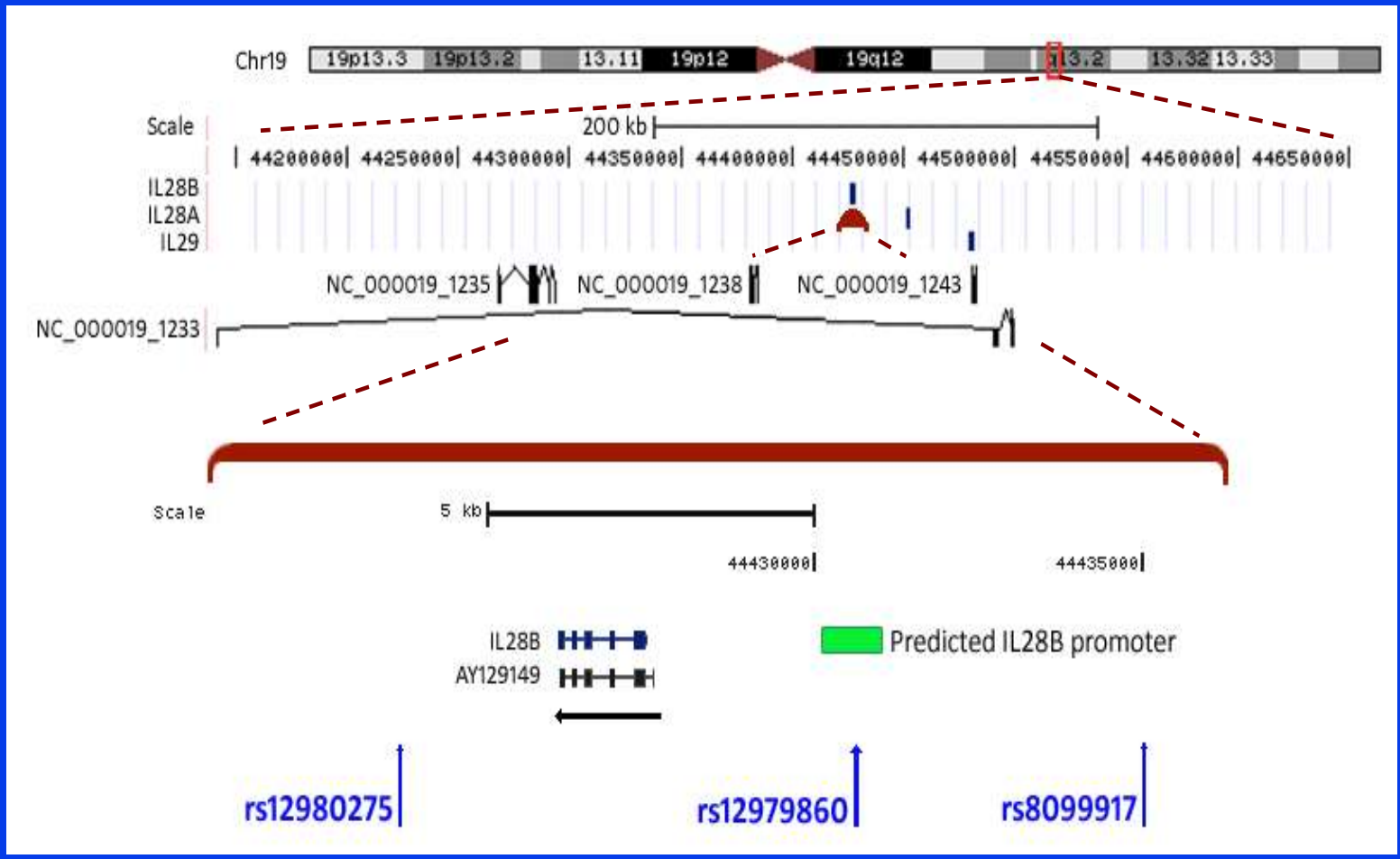
San Giovanni Rotondo

Viral factors, drugs, host factors associated with response to interferon tx



- Viral factors
  - HCV genotype
  - HCV-RNA levels
  - HCV mutations (core, ISDR)
- Drug factors
  - PEG-interferon
  - ribavirin
  - adherence of drugs
- Host factors
  - race
  - body weight
  - age
  - sex
  - SNPs

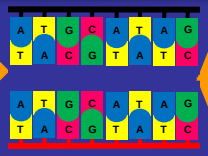
rs12979860 localized within *IL28B* promotor



Both SNPs around *IL28B* gene are significant predictors in Europeans

Blood samples

SNPs



80%

20%

Prediction 80 ~ 90%

Major allele → SVR → PEG-IFN plus ribavirin (protease inhibitor)

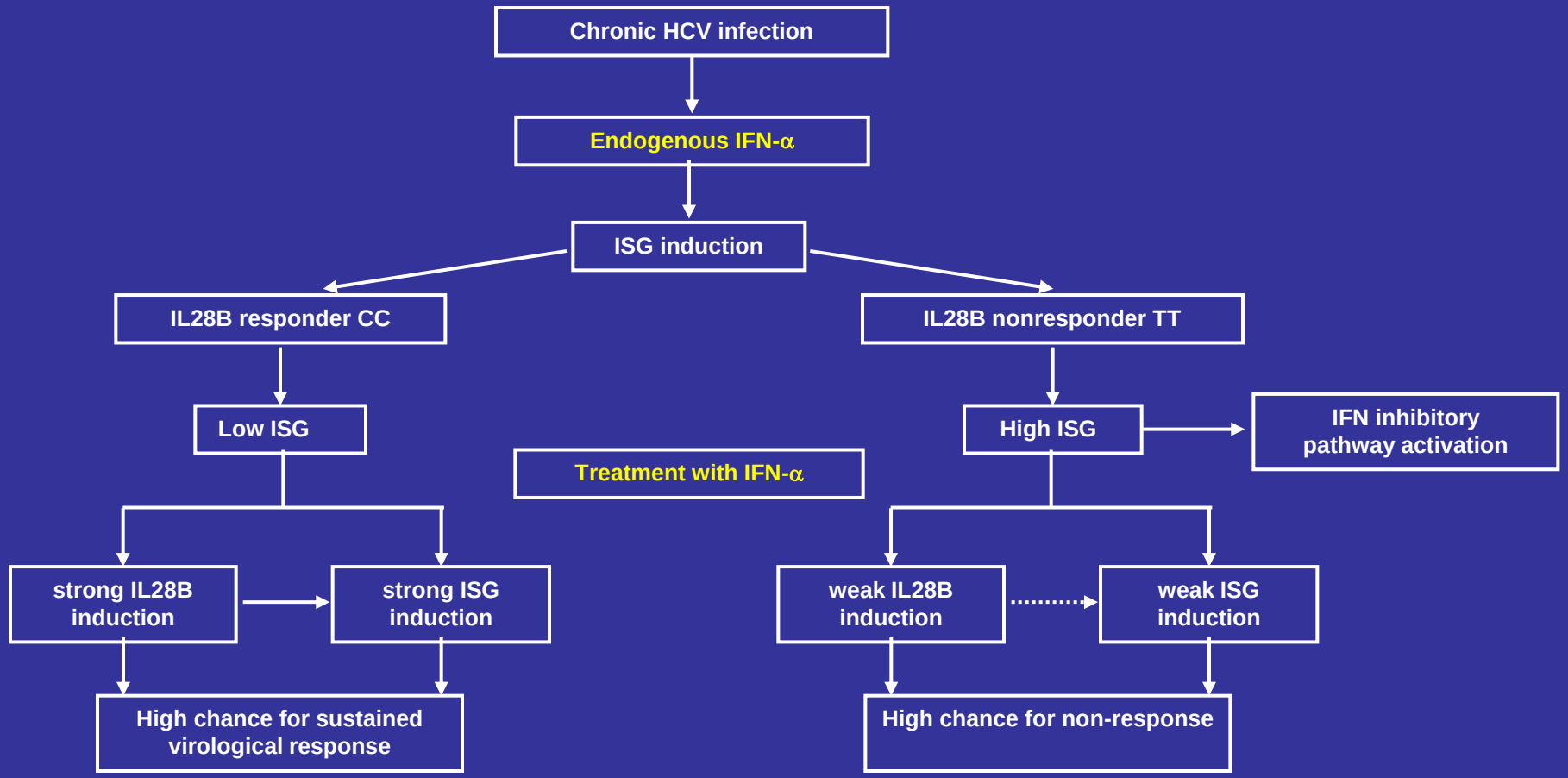
rs12979860 (CpG SNP)

rs8099917 (Three nine)

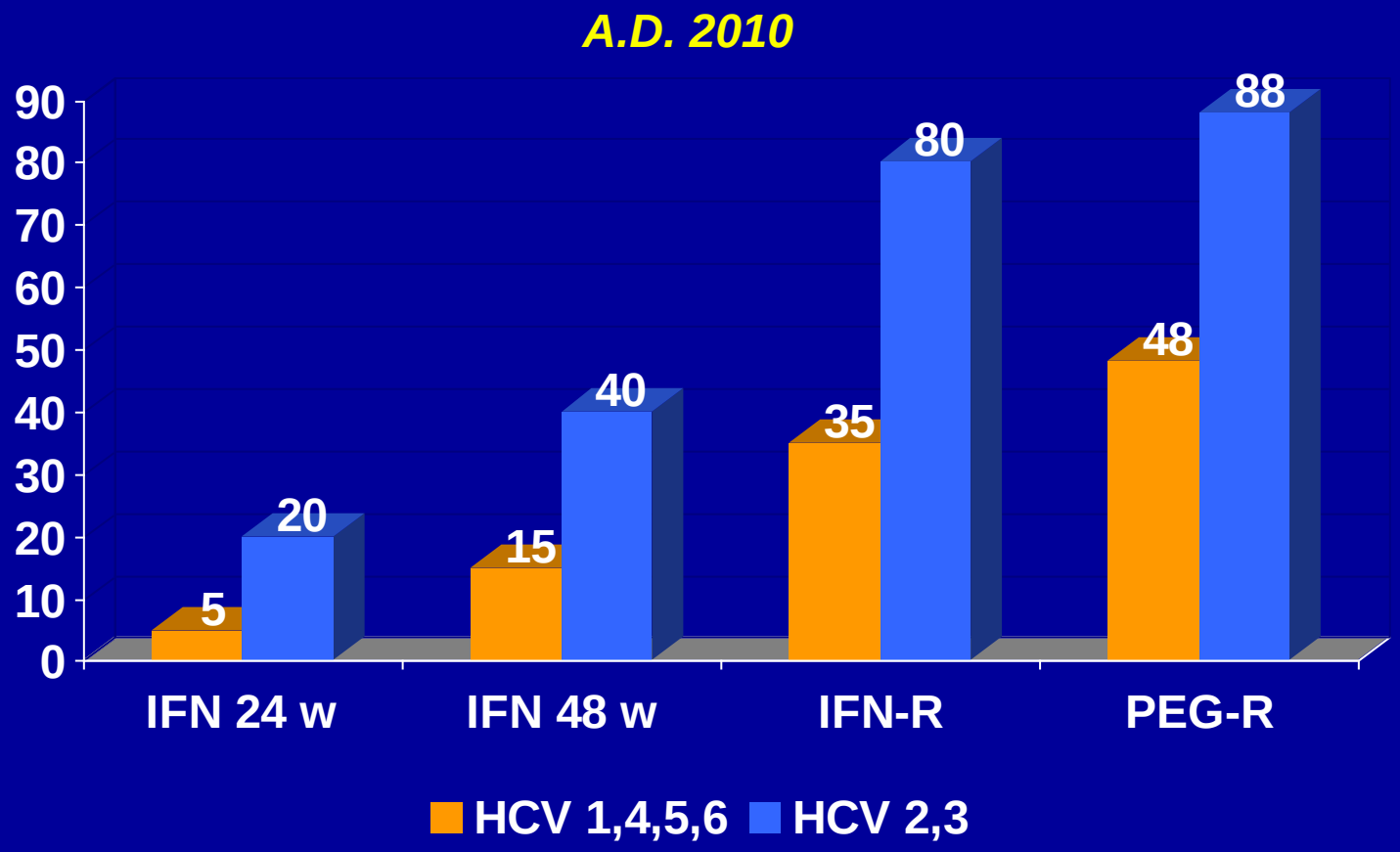
Prediction 80 ~ 90%

Hetero or minor allele → NR → New drugs

Role of IL28B variants in chronic HCV-1 infection



Increase in SVR rates according to HCV genotype over time



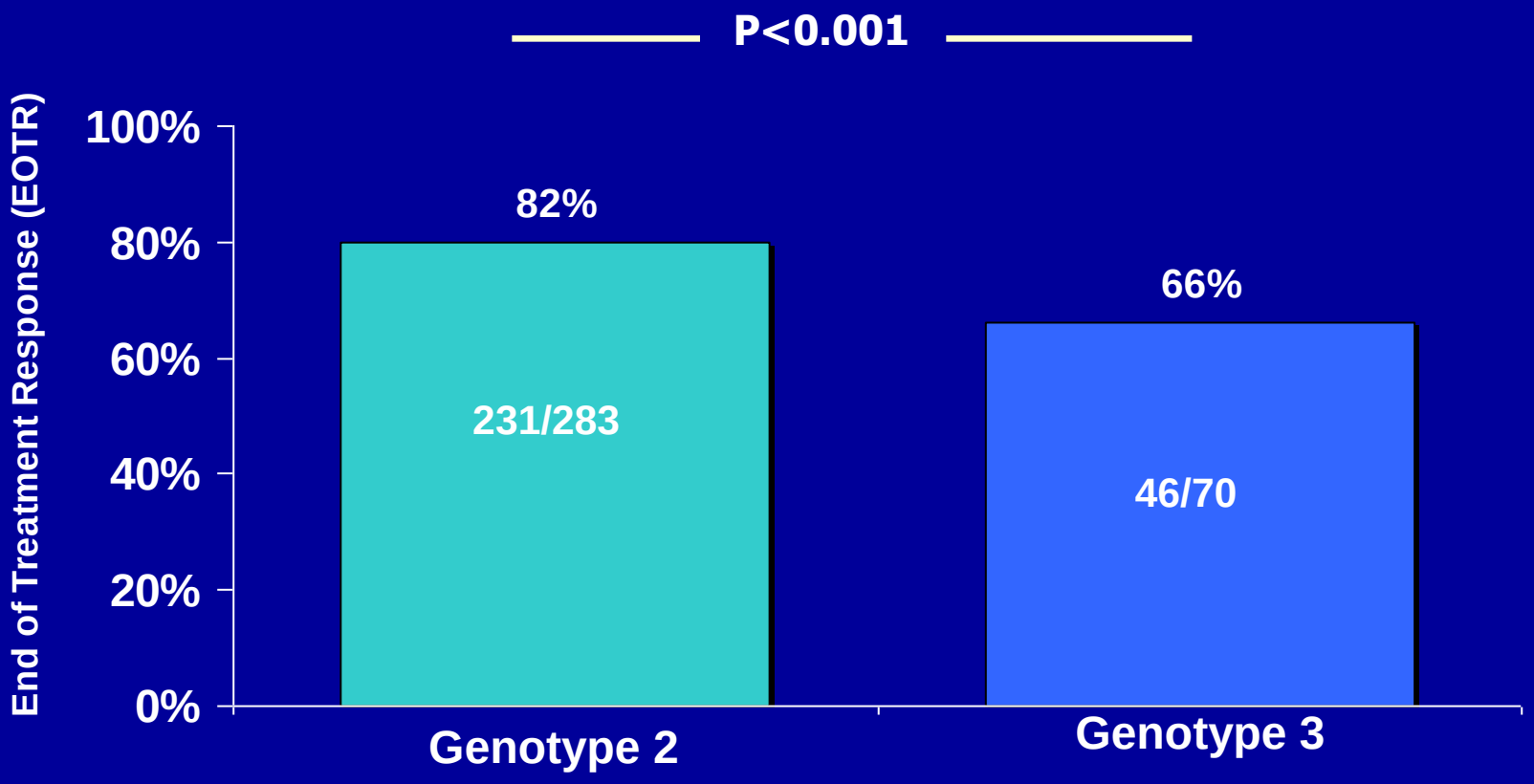
Poynard, Lancet 2003

- Do we need other predictors?

Differences in SVR Between HCV Genotype 2 and 3 after 24 weeks Tx

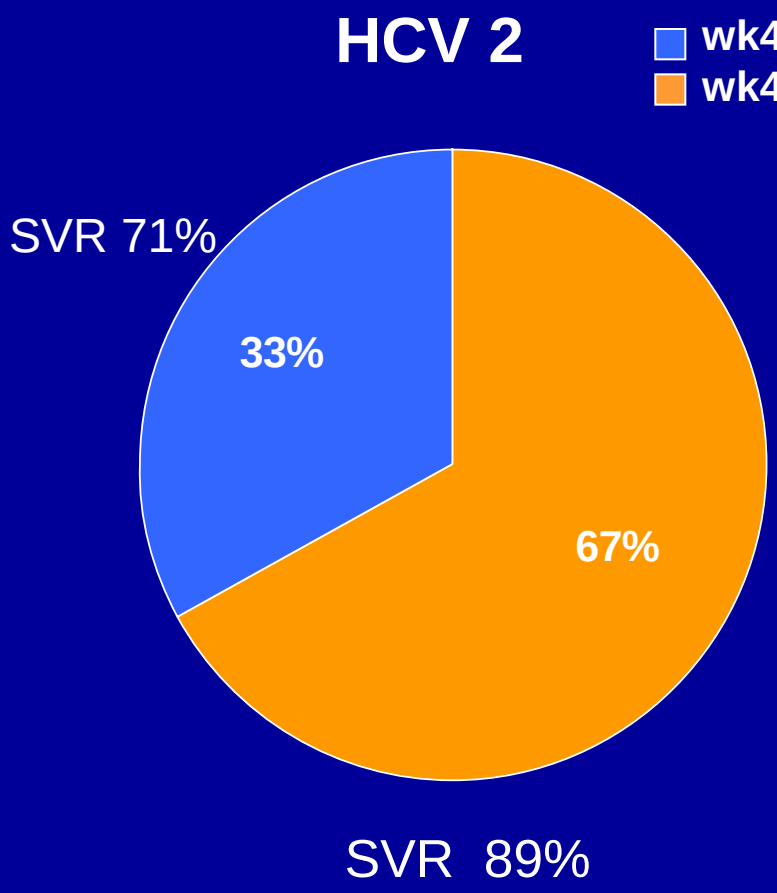
Author	Peg+Rbv	HCV-2		HCV-3		Δ
		No.		No.		
Zeuzem	α2b + wbd	42	93%	183	79%	14%
Powis	α2a + 800	67	81%	101	70%	11%
Dalgard	α2b + wbd	31	97%	119	92%	5%
Shiffman	α2a + 800	356	75%	369	66%	9%
Lagging	α2a + 800	49	82%	139	78%	4%

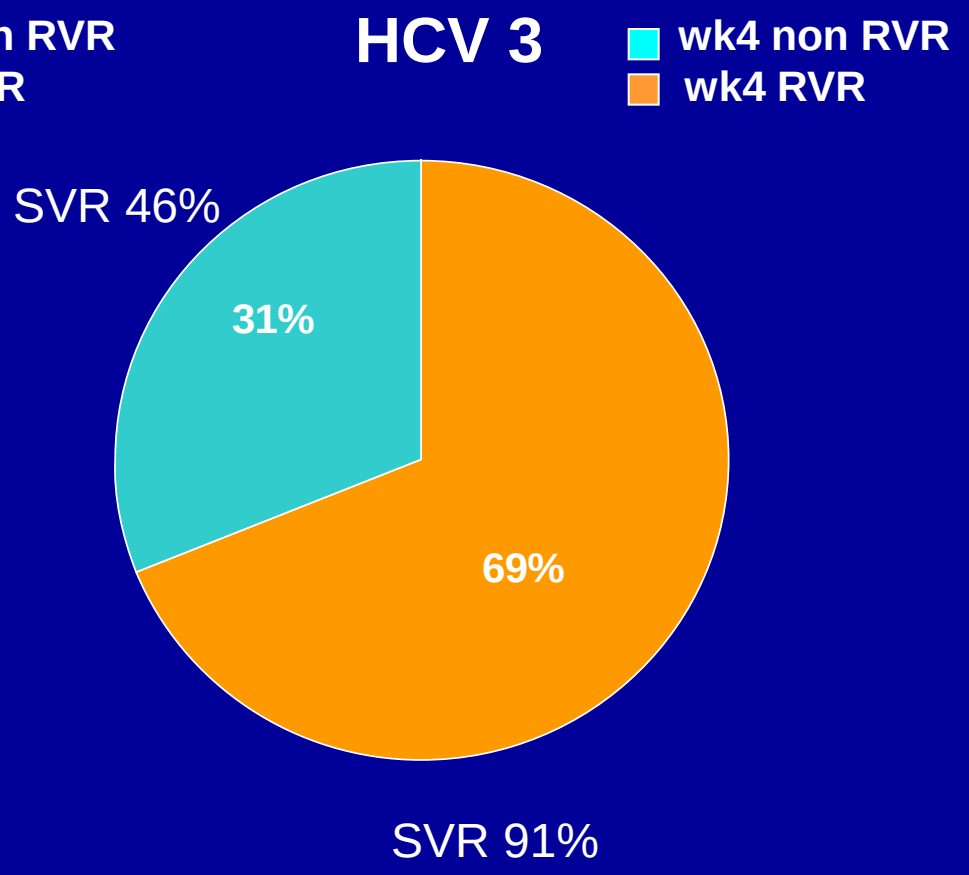
Genotype 2 and 3 SVR



Mangia et al NEJM 2005

SVR rates in pts without RVR

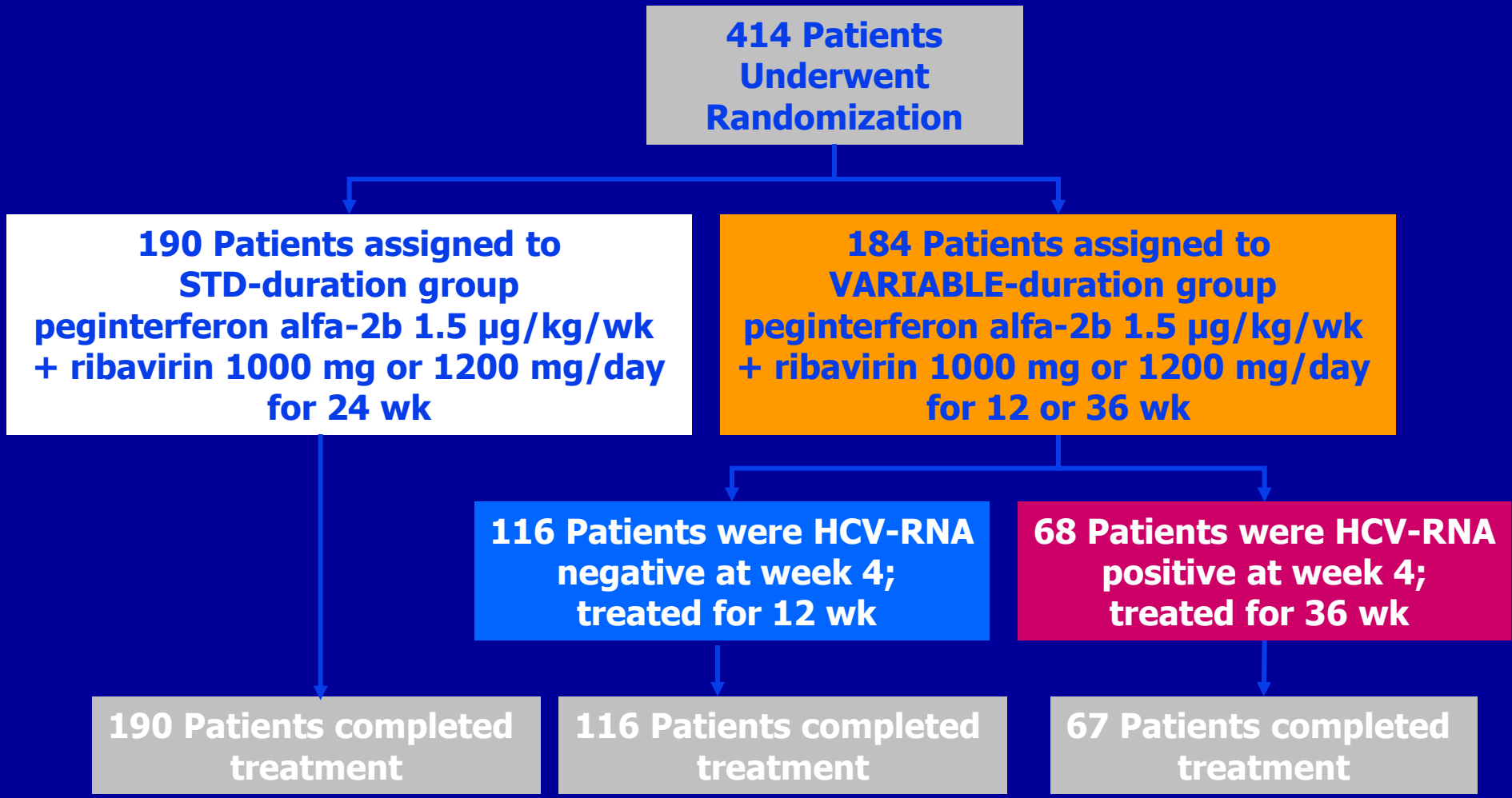




Andriulli et al DLD 2006

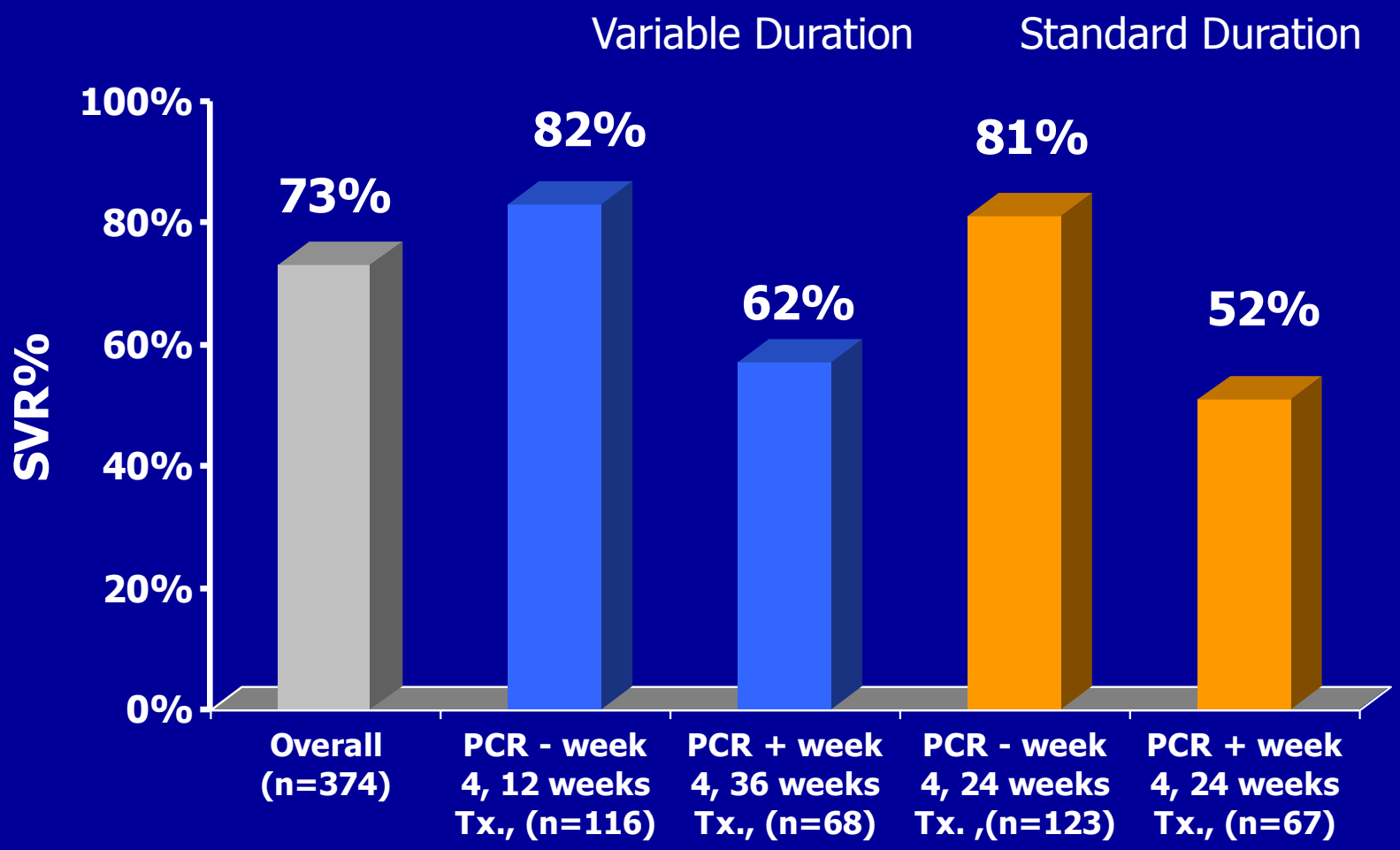
How to increase SVR in HCV 3 patients without RVR ?

Individualized treatment duration for pts with HCV 3



Mangia et al, J Hepatol 2010

Sustained Virologic Response in pts with HCV 3 on individualized tx



Mangia A et al J Hepatol 2010

- Does genetic help us in identifying pts with highest likelihood of SVR?

Gastroenterology

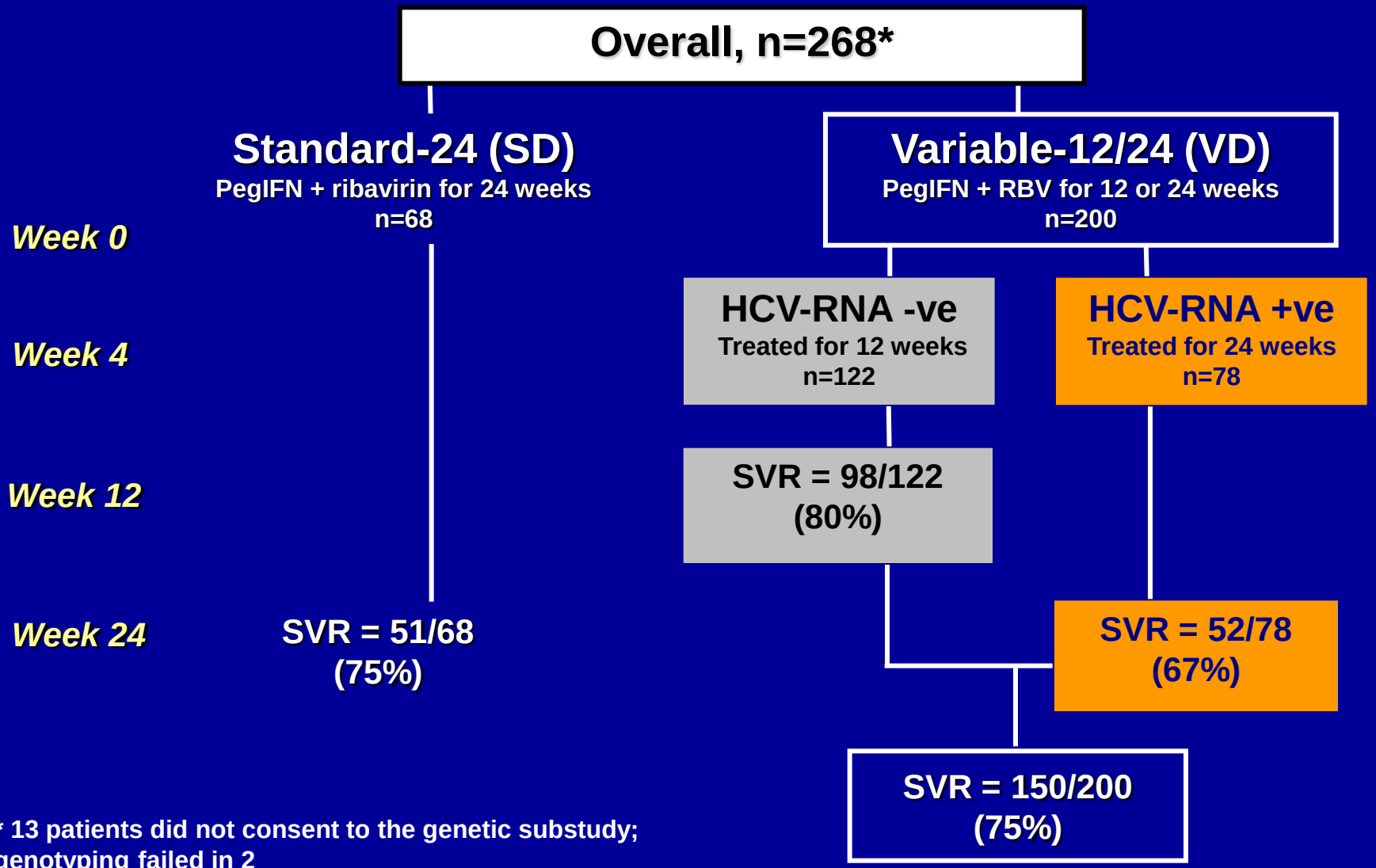
OFFICIAL JOURNAL OF THE AGA INSTITUTE

An *IL28B* Polymorphism Determines Treatment Response of Hepatitis C Virus Genotype 2 or 3 Patients Who Do Not Achieve a Rapid Virologic Response

Mangia A, Thompson AJ, Santoro R *et al*.. 2010;139:821-827.

Original study protocol

Mangia, NEJM, 2005



* 13 patients did not consent to the genetic substudy; genotyping failed in 2

First International Course of Translational Hepatology, Florence, 2011

Adherence

- In the original study only 1 pt of 133 treated for 12 wks and 8 of 150 treated for 24 weeks had to discontinue treatment
- Only 5 of 9 non adherent patients agreed to have the genetic evaluation. All of them received 24 weeks of treatment, 2 in the standard and 3 in the variable treatment arm

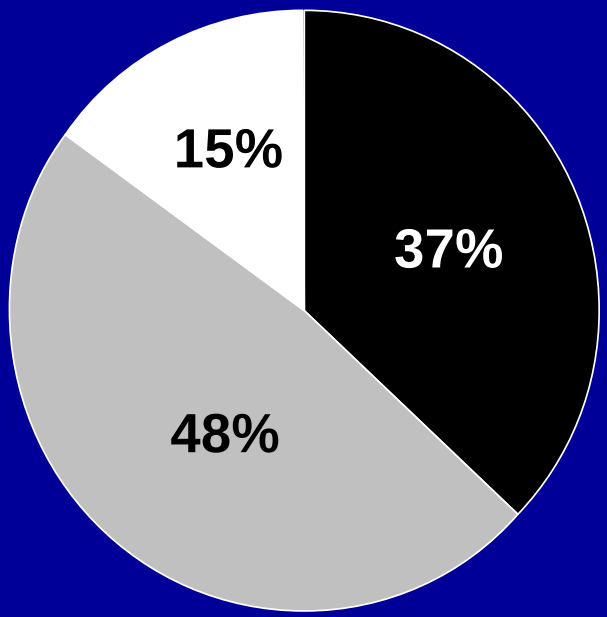
Results - patient characteristics

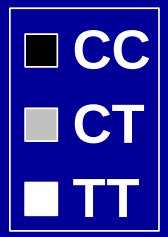
	Overall		Standard duration (SD)		Variable duration (VD)		P** SD vs VD
	N	(%)	N	(%)	N	(%)	SD vs VD
N	268		68		200		
Male Gender	155	57.8%	39	57.0%	116	58.0%	0.9256
Age ≥ 40	208	78.0%	50	73.5%	158	79.0%	0.3498
Caucasian ethnicity	268	100%	68	100%	200	100%	*
BMI ≥ 27	112	41.8%	28	41.2%	75	37.5%	0.5903
Genotype 2	213	79.5%	53	77.9%	160	80.0%	0.7165
Genotype 3	55	20.5%	15	22.1%	40	20.0%	*
HCV RNA > 800,000 IU/mL	100	37.5%	20	29.4%	80	40.2%	0.1125
ALT > 3 x ULN	61	23.0%	21	30.9%	40	20.3%	0.074
Mod-severe steatosis*	61	25.0%	22	34.9%	44	24.2%	0.0975
Scheuer F3-4	52	19.5%	17	25.0%	35	17.6%	0.1827

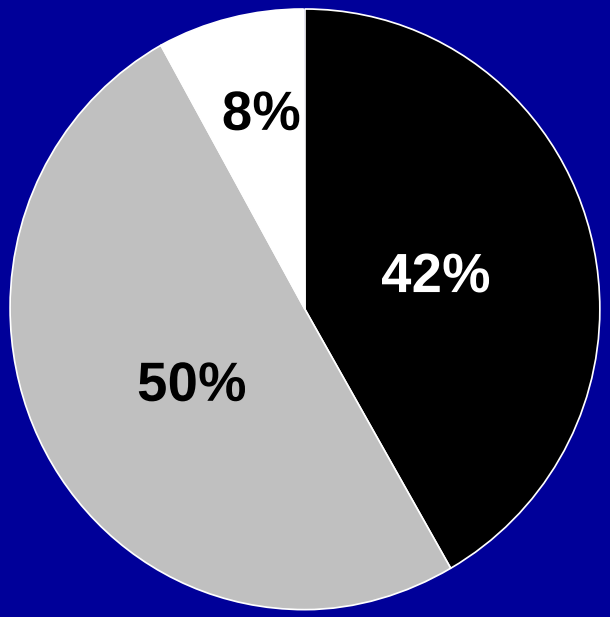
* Hepatic steatosis grade not available in 23 patients
** No significant differences were noted between the standard and variable duration treatment arms

IL28B-type frequency in G2/3 CHC pts and healthy Italian controls

P=0.08







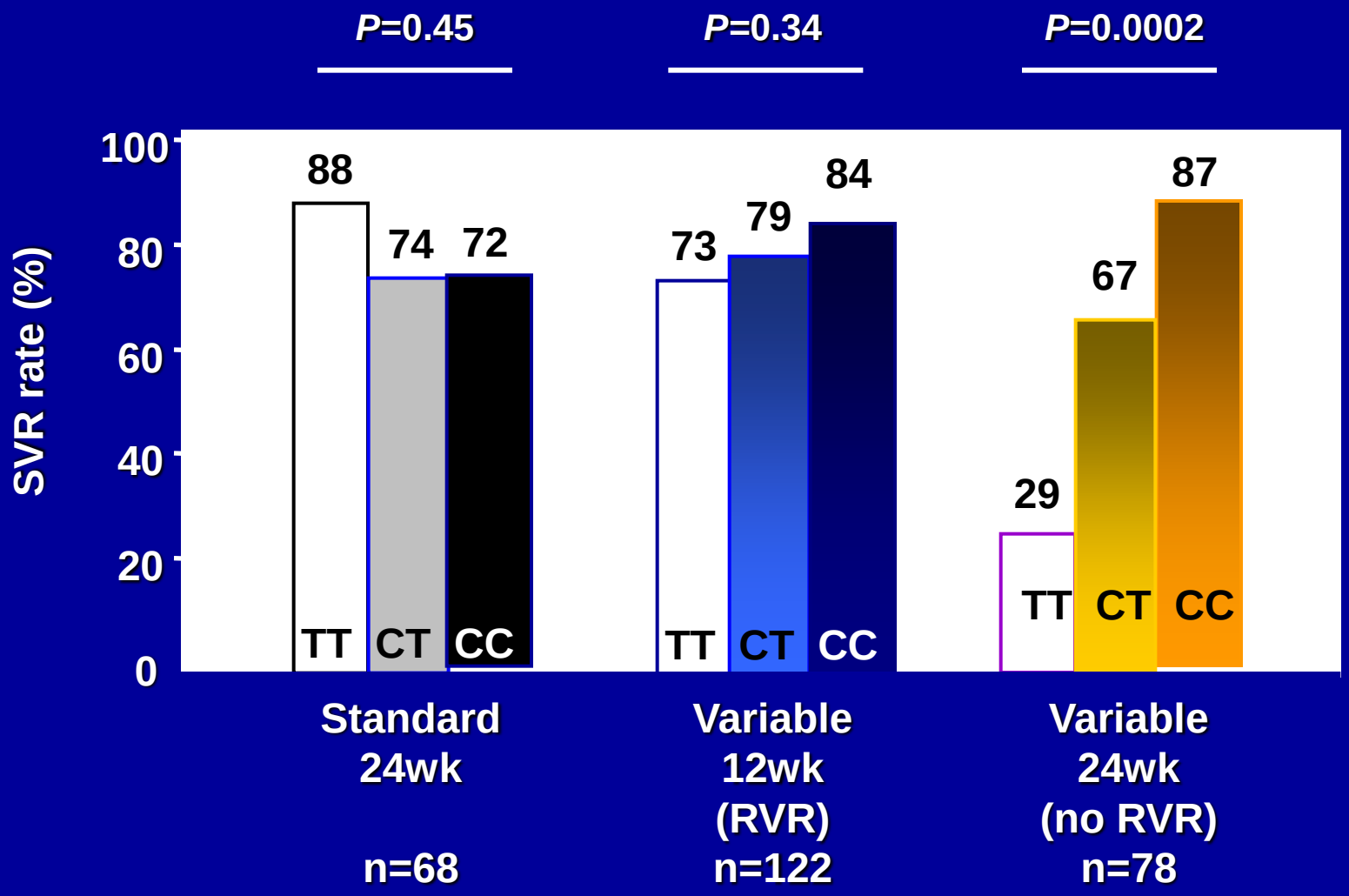
C allele frequency = 0.61

C allele frequency = 0.67

HCV G2/3, n = 268

Healthy control, n = 178

IL28B-type is associated with increased SVR in non-RVR patients



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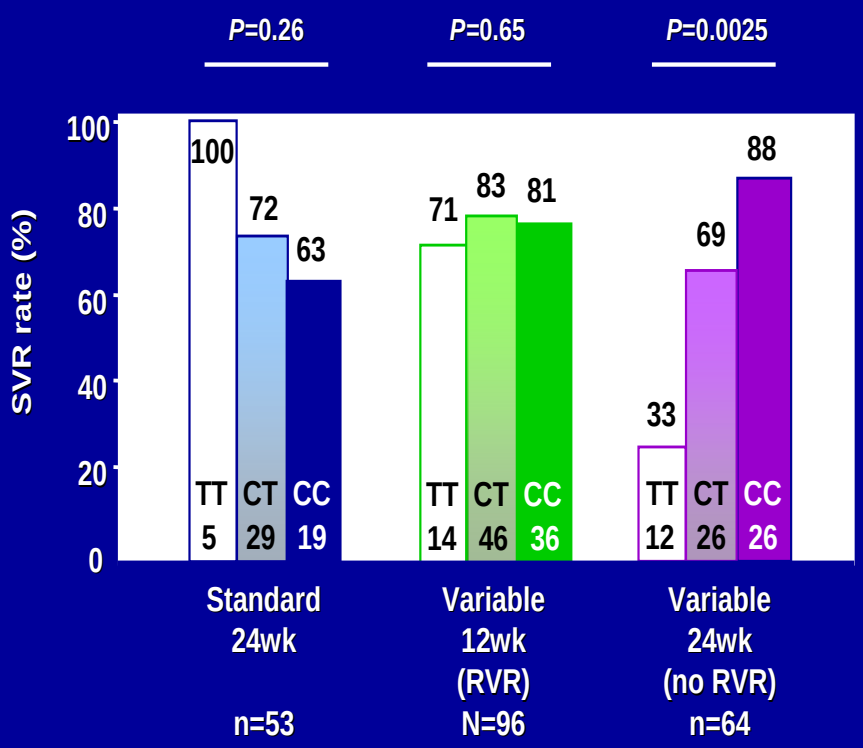
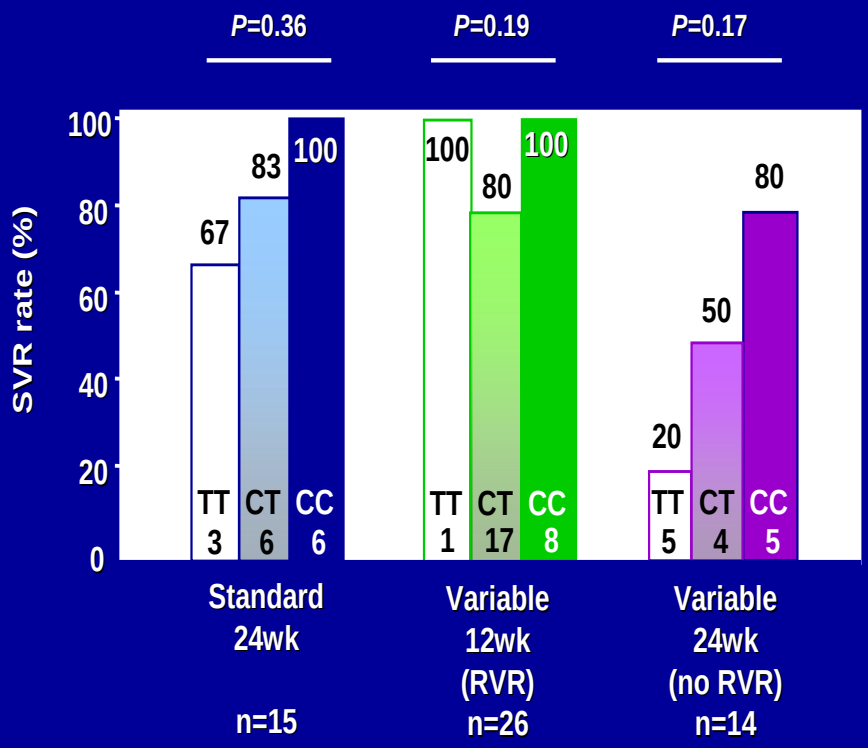
SVR by HCV genotype



HCV genotype 2, n=213



HCV genotype 3, n=55

MLR of predictors of SVR including RVR

Baseline predictors + RVR		OR	95% CI		P
Univariable	*RVR*	3.25	1.83 -	5.75	5.49×10^{-5}
	Combined IL28B-type+RVR	2.07	1.57 -	2.74	2.6×10^{-7}
	BMI < 27	2.14	1.22 -	3.75	0.0079
	Scheuer F0-2	2.56	1.34 –	4.88	0.0042
Mutivariable	*Combined IL 28B-type* +RVR	2.02	1.5 2 -	2.69	1.13×10^{-6}
	Scheuer F0-2	2.02	1.01 -	4.04	0.0456

Limitations of our study

- The study was not powered for a comparative analysis of patients with RVR enrolled in the standard or in the short treatment
- Few genotype 3 patients were enrolled in the original study

IL28B variants and SVR in pts with HCV genotype 2 & 3

	Pts #	Race	Type of study	Association	Healthy controls
McCharthy **Gastroenterology 2010**	45	Caucasian	Cross sectional	Yes	No
Rauch[1] **Gastroenterology 2010**	230	Caucasian	Cross sectional	No	No
Mangia **Gastroenterology 2010**	260	Caucasian	RCT	Yes in Non RVR	Yes

rs 12989860 CC

[1]rs809991 7TT

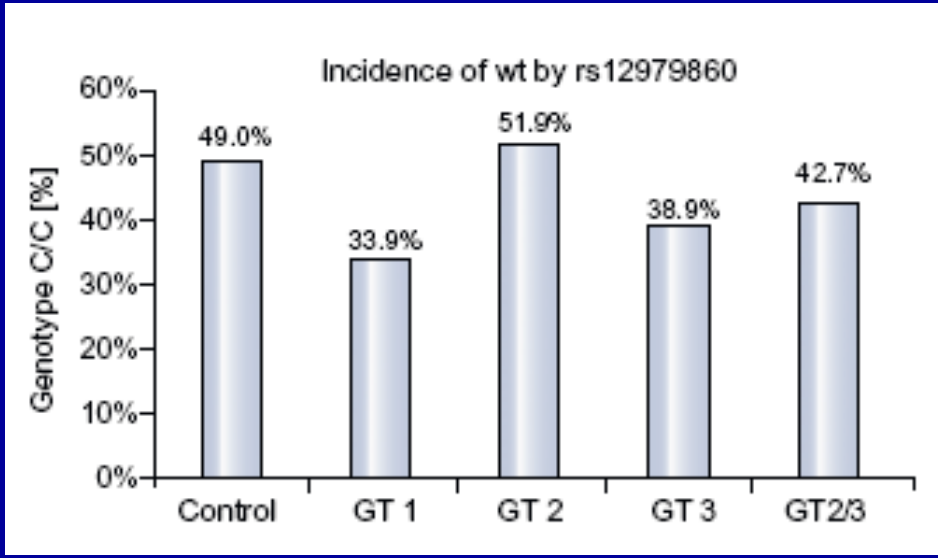
Frequencies of the IL28B rs12979860 CC genotypes according to wk-4 response

	Total population	SVR overall	SVR wk4+ve*	SVR wk4-ve
CC	114 (43%)	87%	34/40 (95%)	4/4 (100%)
CT	122 (46%)	71%	32/37 (86%)	3/11 (27%)
TT	31 (12%)	73%	5/7 (71%)	3/4 (75%)

*$p=0.05$

Sarrazin et al J Hepatol 2011

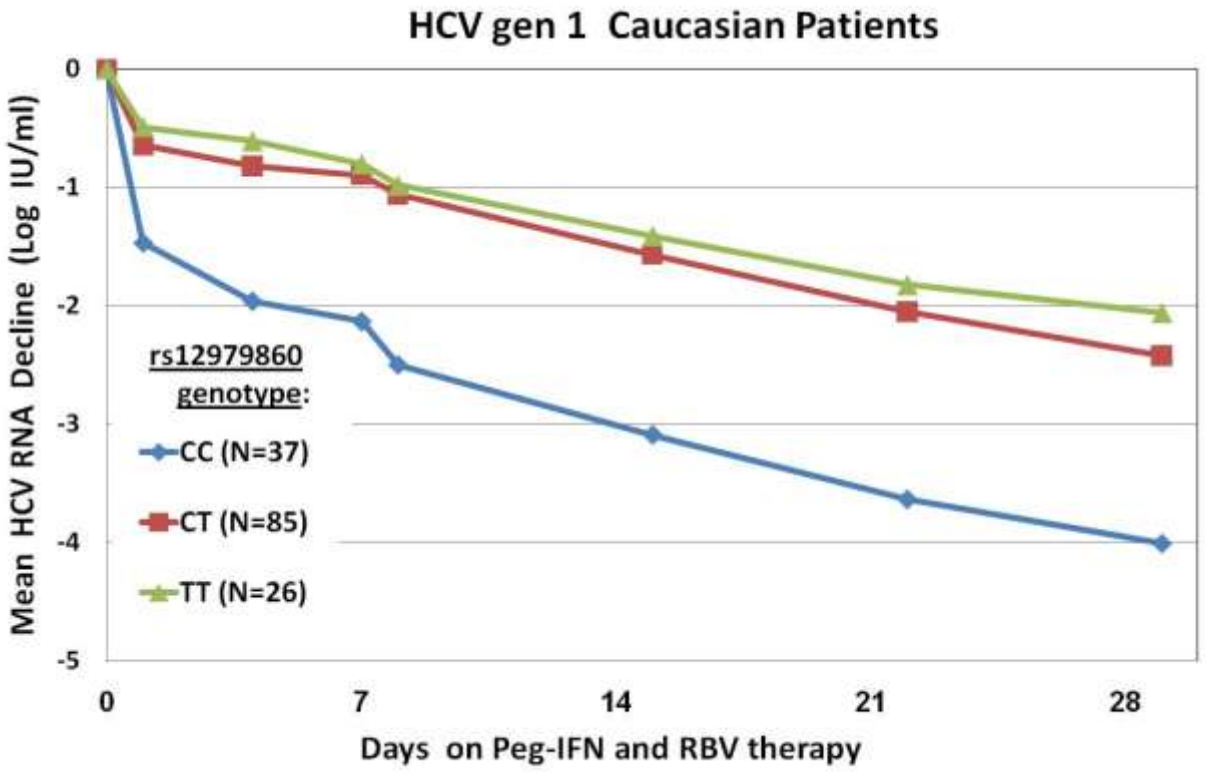
Frequencies of the IL28B rs12979860 CC genotypes in HCV 1, 2, and 3 infected patients compared to healthy controls



Sarrazin C et al. J Hepatol 2011 in press

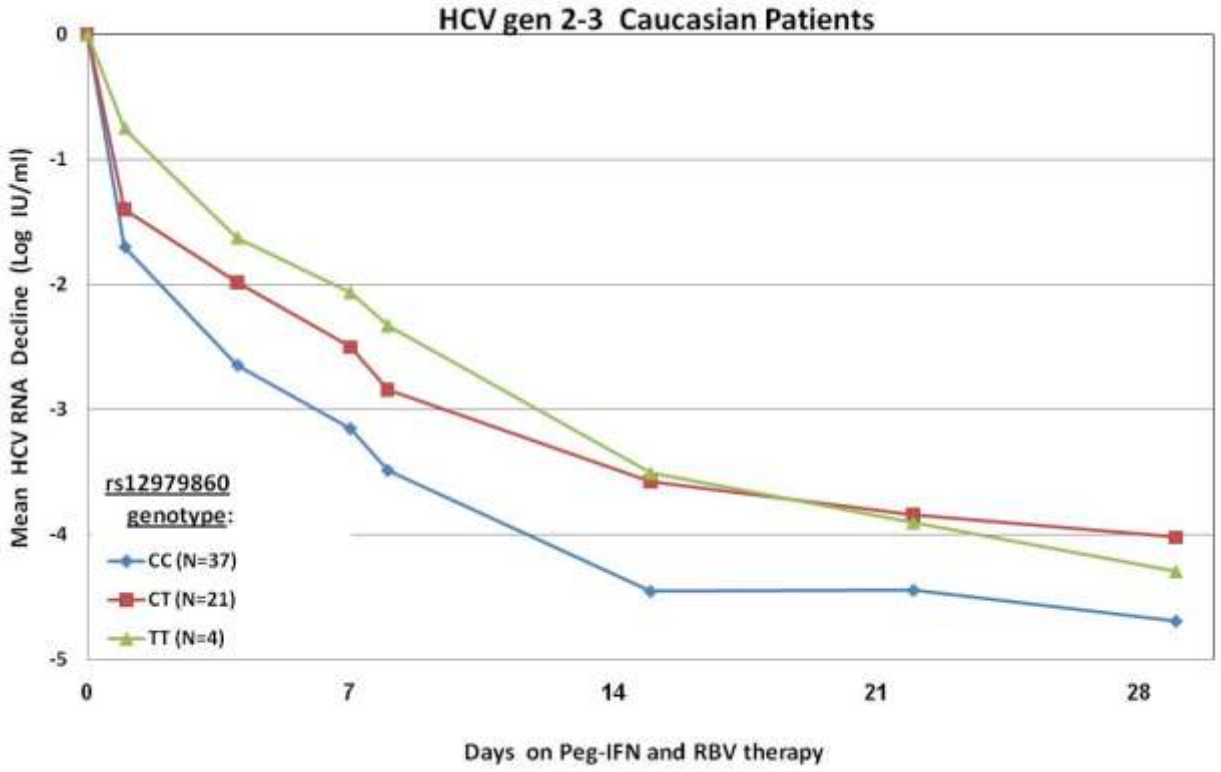
- Viral kinetics and IL28B

IL28B polymorphism predict reduction of HCV RNA from the first day of tx



(Neumann et al., EASL 2010)

Viral Kinetics According to to SNP rs12979860 in HCV 2 and 3



Neumann et al., EASL 2010

Summary

- *IL28B* genetic variation influences SVR in patients with genotype 2/3 with attenuated effect size as compared to genotype 1
- *IL28B* variation seemed most important for influencing SVR in non-RVR patients
  - TT – low response rate
  - CT – intermediate response rate
  - CC – high response rate
- The C allele frequency was lower in CHC pts compared to matched healthy controls, suggesting a role in spontaneous clearance

Diagnostic Applications: Personalized Tx in HCV 2 and 3

Encourage patients with CC to continue treatment

Wait for alternative therapies in non RVR patients with CT or TT

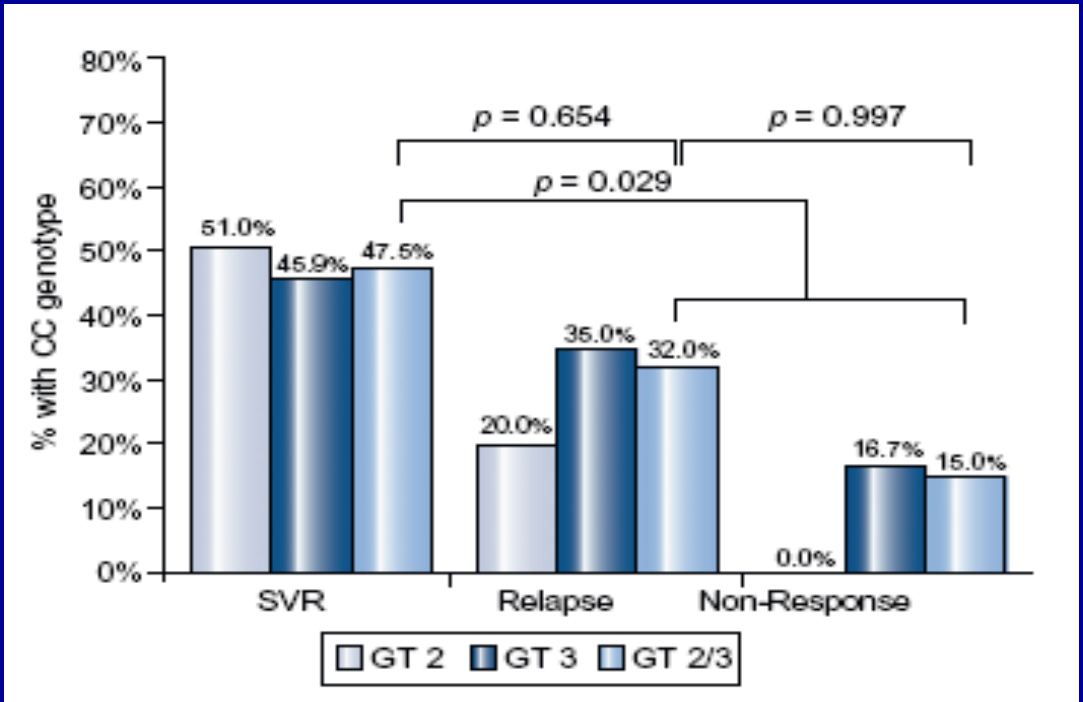
Future scenarios

Prospective study using IL28B

to individualize treatment duration in patients without RVR

to investigate the impact of *IL28B* on DAA effective for G2

Frequency of rs12979860 CC genotype in HCV 2, HCV 3, and 2/3 infected pts and association to different treatment outcomes



Sarrazin C et al. J Hepatol 2010 in press

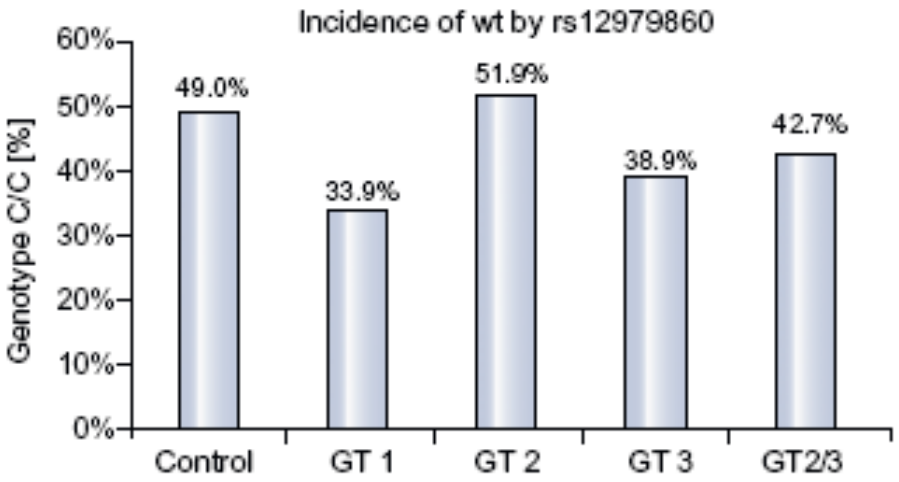


Fig. 3. Frequencies of the IL28B rs12979860 CC genotypes in HCV genotype 1, 2, and 3 infected patients compared to healthy controls

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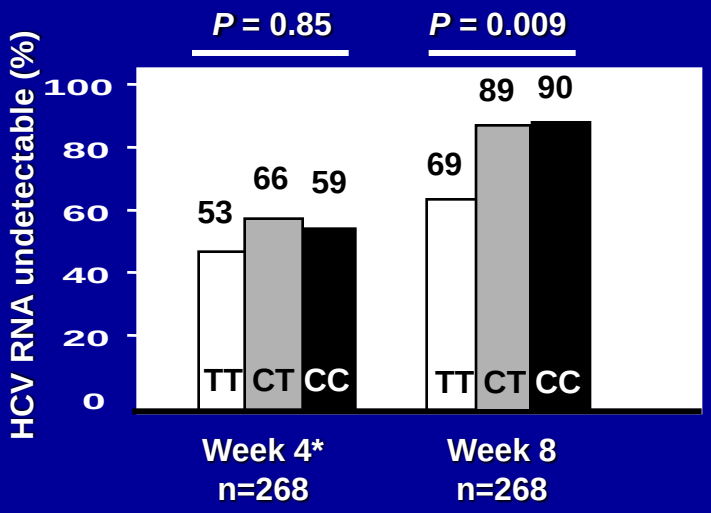
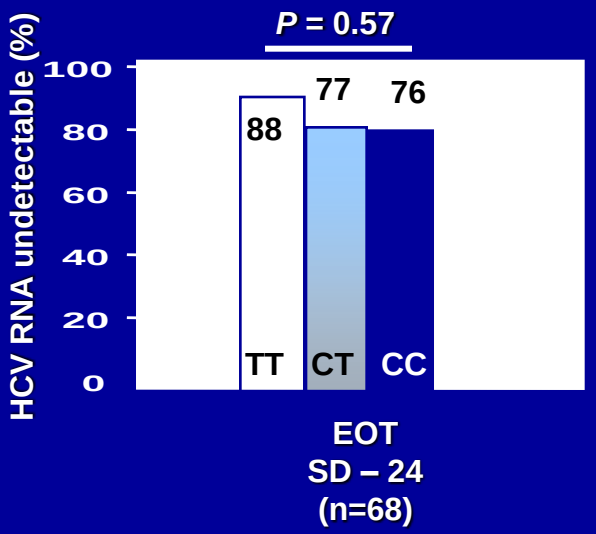
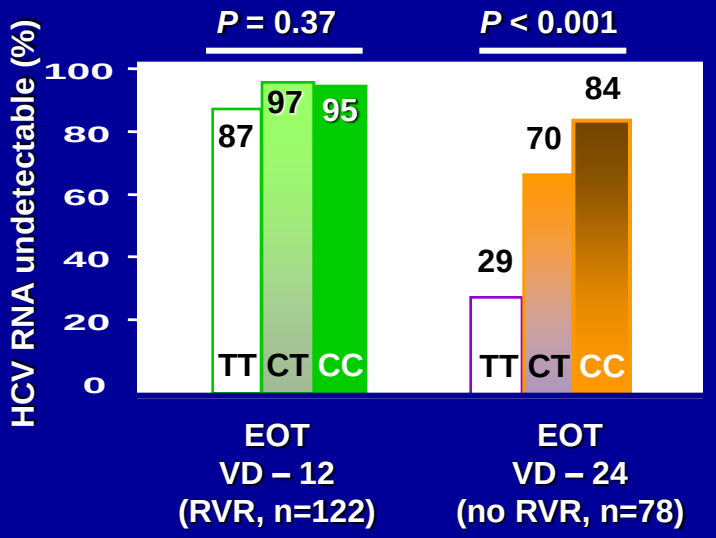
IL28B-type and on-treatment / end-of-treatment virological responses

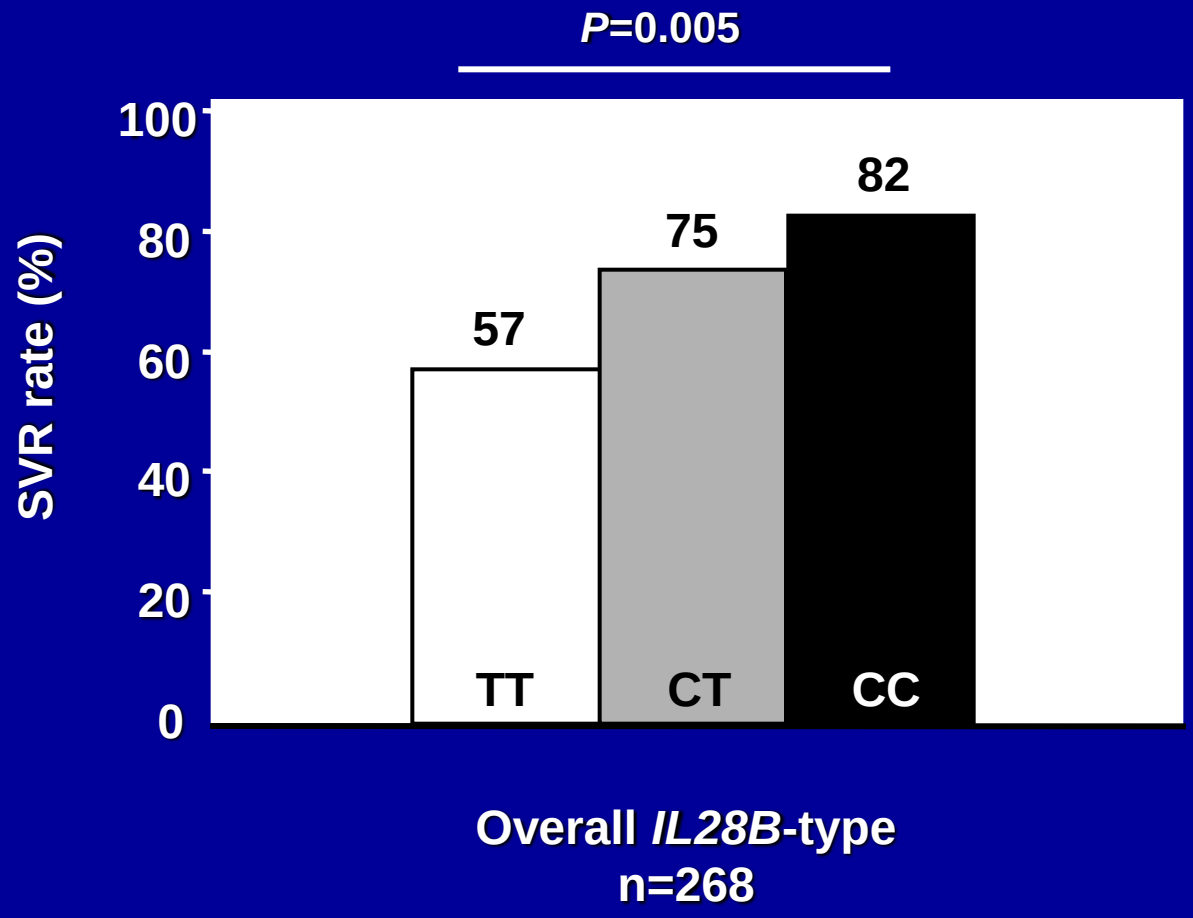


* Quantitative wk 4 HCV RNA levels not available





IL28B-type is associated with increased SVR in pts with G2/3 CHC



Results

- IL28B and SVR
- IL28B vs RVR
- Role of IL 28 B in genotypes 2 and 3 separately
- MLR results

IL28B-type is a baseline predictor of SVR

Baseline predictors		OR	95% CI	P
Univariable	*IL28B*-type	1.80	1.20 - 2.71	0.0046
	BMI < 27	2.14	1.22 - 3.75	0.0079
	Scheuer F0-2	2.56	1.34 - 4.88	0.0042

Baseline predictors		OR	95% CI	P
Multivariable*	*IL28B*-type	1.76	1.16 - 2.66	0.0077
	BMI < 27	1.88	1.05 - 3.37	0.0334
	Scheuer F0-2	2.35	1.21 - 4.56	0.0118

*Co-variates: *IL28B*-type, BMI ≥ 27, Scheuer F0-2 vs F3-4, ± HCV RNA > 800,000 IU/mL

Performance of IL28B

	Sensitivity	Specificity	PPV	NPV	LR +	LR –
TT vs non-TT	88.6%	25.37%	78.0%	42.5%	1.2	0.4
CC vs non-CC	40.8%	73.1%	82.0%	29.1%	1.5	0.8
RVR vs no RVR	68.6%	59.7%	83.6%	38.3%	1.7	0.5

First International Course of Translational Hepatology, Florence, 2011

	No of patients			
CC	114 (43%)	87%	34/40 (95%)	4/4 (100%)
CT	122 (46%)	71%	32/37 (86%)	3/11 (27%)
TT	31 (12%)	73%	5/7 (71%)	3/4 (75%)

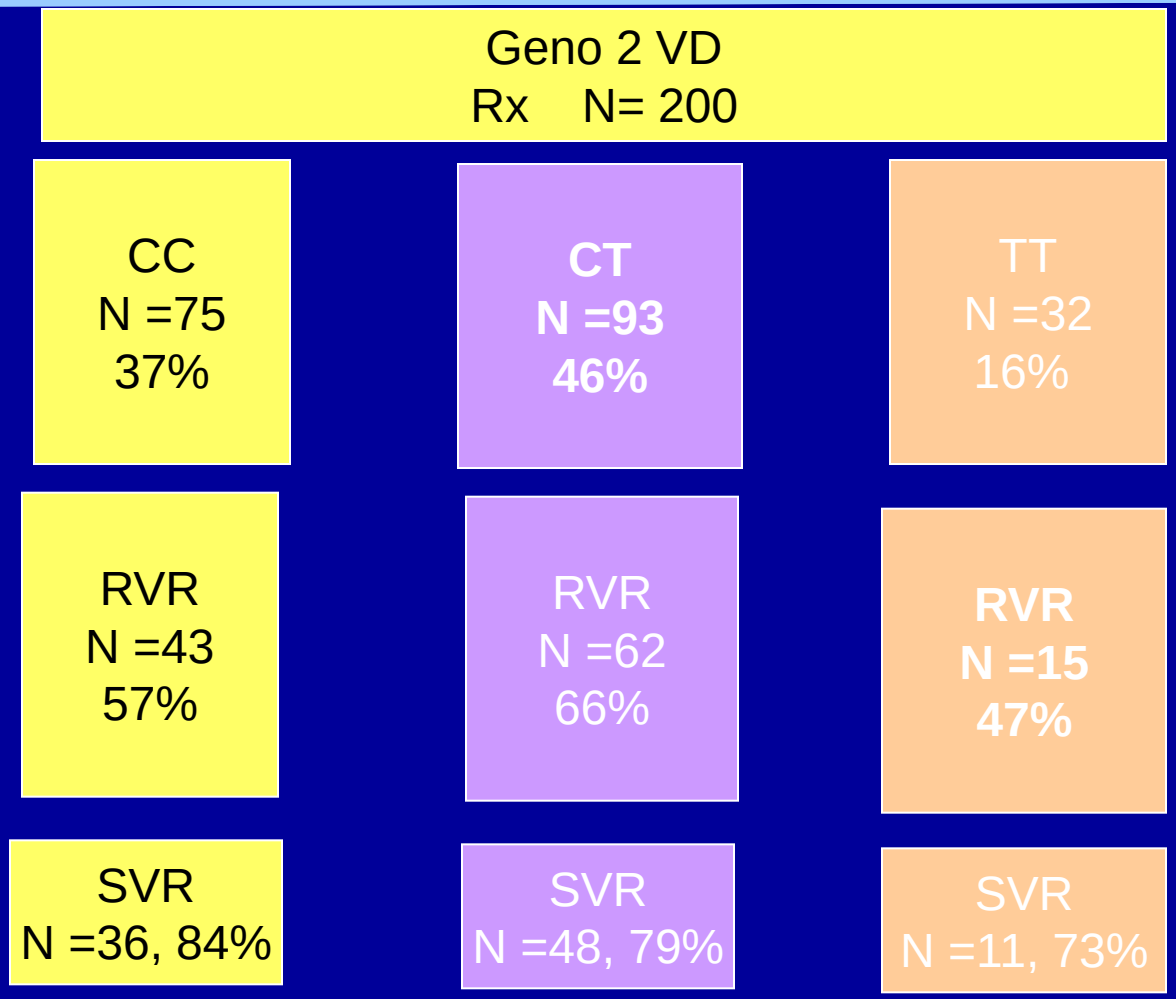
Sarrazin C et al 2010

Comparison of the four GWAS

Study	Ancestry (sample size)	Genotyping platform	Case/Control	Associated SNPs
Ge et al.	Cauc/Afric/Hisp (N=1615)	Illumina 610-Quad	R/NR	rs12979860 (OR=3.10)
Suppiah et al.	Cauc (N1=293) (N2=555)	Illumina CNV370-Quad	R/NR	rs8099917 (OR=1.98)
Tanaka et al.	Jap (N1=154) (N2=172)	Affymetrix 6.0	NVR/VR	rs8099917 (OR=12.10)
Rauch et al	Cauc (N=1362)	Illumina 1M,550,610	R/NR SC	rs8099917 (OR=2.31)

R/NR – sustained virological response/no sustained virological response
NVR – null virological responders
VR – virological responders (subject who respond to treatment, but do not necessary clear the virus)

RVR in HCV-2 and -3 VD arm



Future scenarios

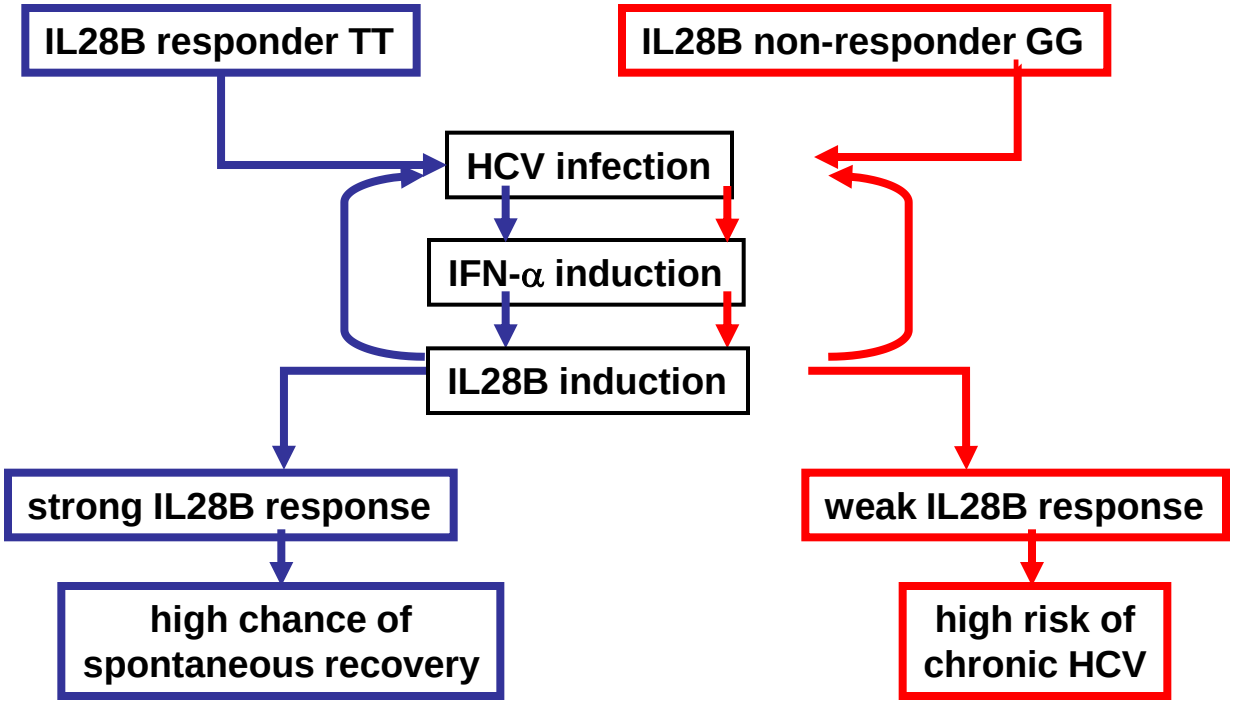
Evaluation of personalized treatment duration in genotype 2/3 HCV integrating:

- Week 4 virological response
- *IL28B*-type

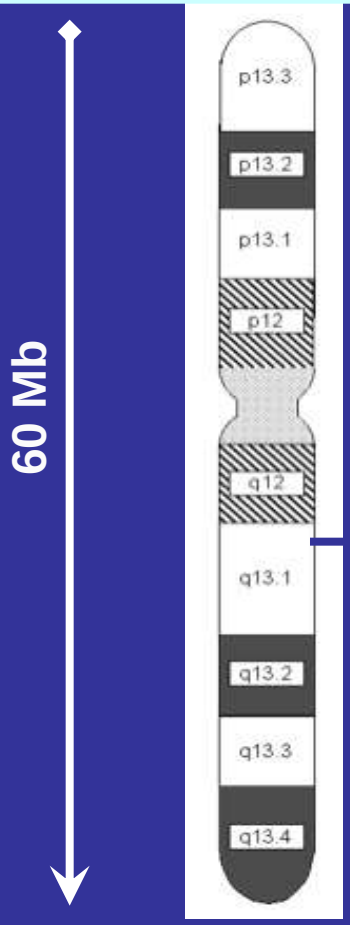
Prospective study using IL28B to individualize treatment duration in patients without RVR

Impact of *IL28B*-type on DAA effective for G2 to be investigated

Role of IL28B polymorphism in acute HCV infection



IL28b gene polymorphism predicts SVR



- IFN lambda proteins encoded by the *IL28A/B* and *IL29* genes
- These IFNs signal through a unique receptor, but share common downstream signaling with type 1 IFNs, including IFN-α

IL28B gene

3 kb

Polymorphism rs12979860

Ge D, et al. *Nature.* 2009;461:399-401.
Chromosome 19 graphic courtesy of Oak Ridge National Laboratory. Available at: http://www.ornl.gov/sci/techresources/meetings/ecr2/olsen.gif. Accessed on: October 21, 2009.