Update sul trattamento dell'infezione da HCV:
problemi clinici e gestionali
Milano, 2 ottobre 2015 - Starhotel Echo

CISAI
Coordinamento Italiano Studio Allergie e Infezione da HIV

Il trattamento HCV nei diversi stadi di malattia

Il paziente cirrotico: Rischi e opportunità

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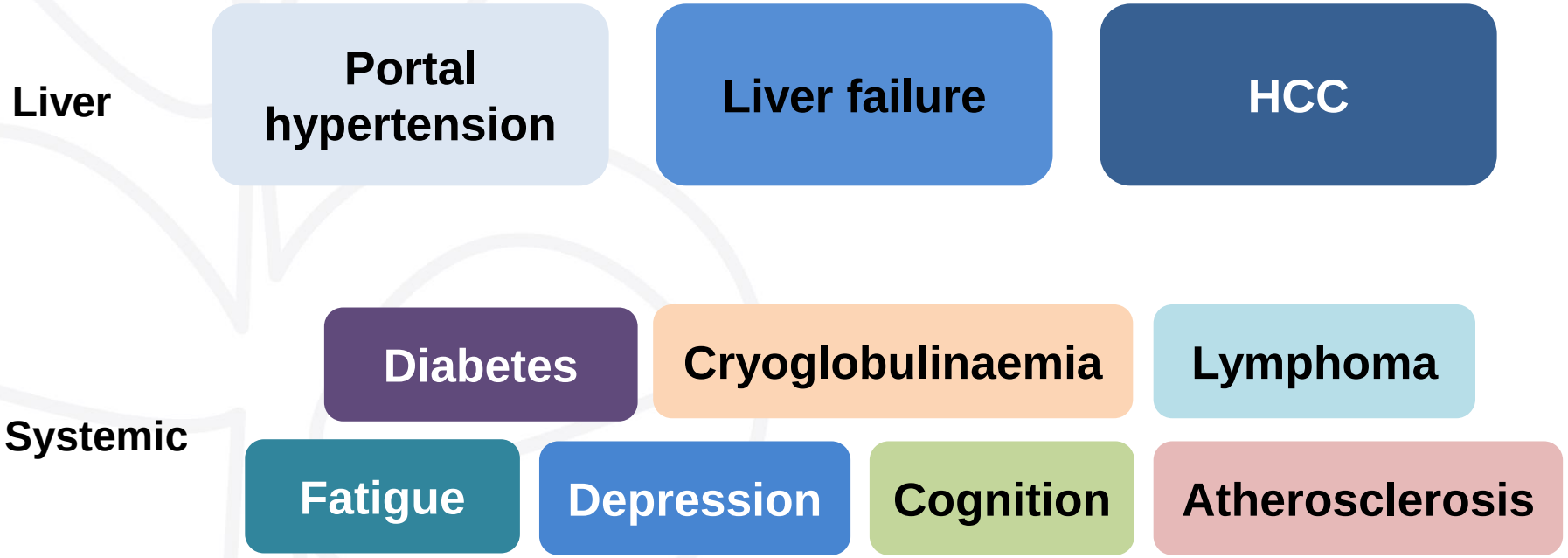
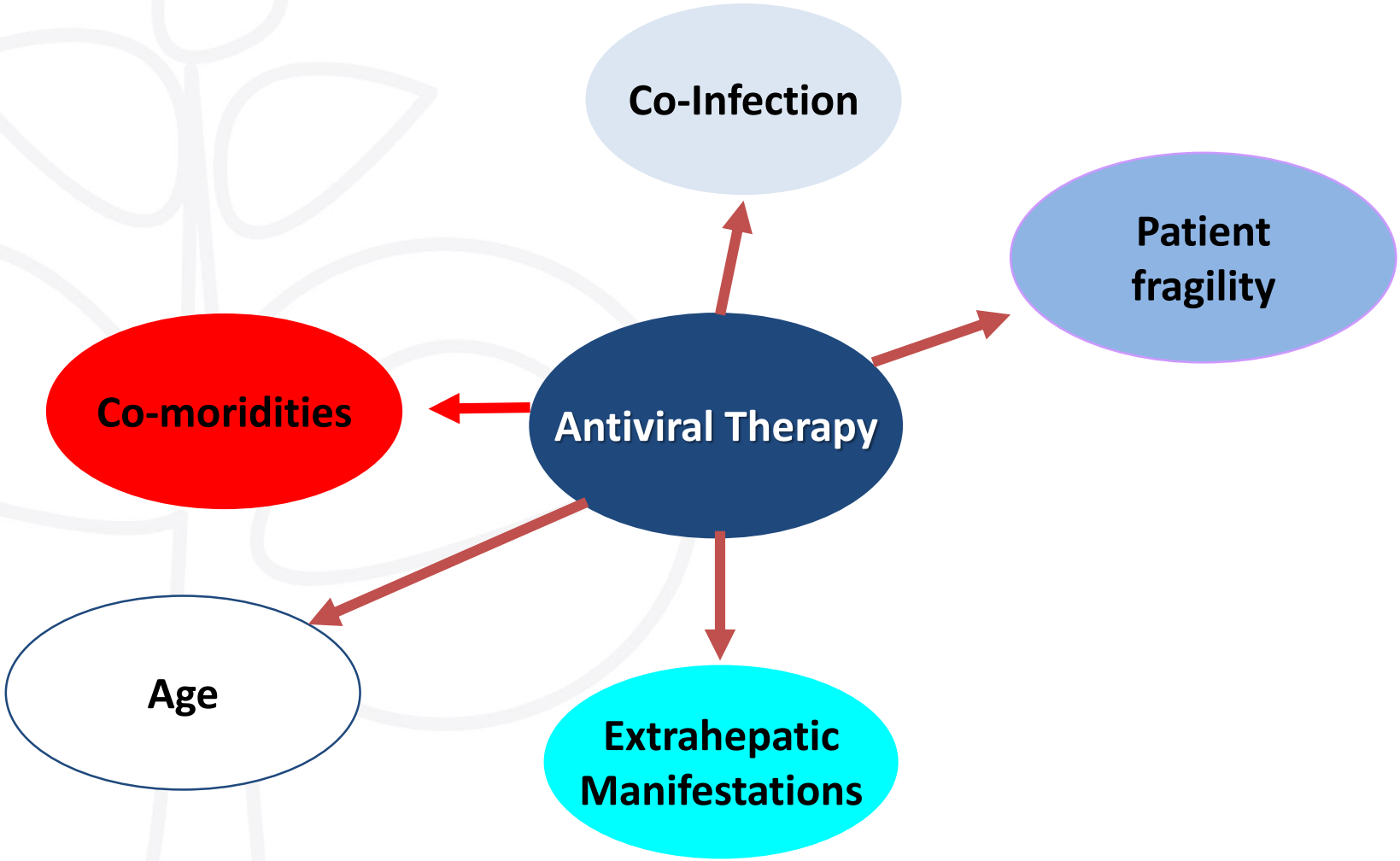
Città della Salute e della Scienza di Torino
Università di Torino

Chronic Hepatitis C: not just a disease….



Negro F, Forton D, Craxì A, Sulkowski MS, Feld JJ, Manns MP, Extra-hepatic Morbidity and Mortality of Chronic Hepatitis C, *Gastroenterology* (2015), doi: 10.1053/j.gastro.2015.08.035.

Cirrhosis & HCV Therapy: risks and opportunities

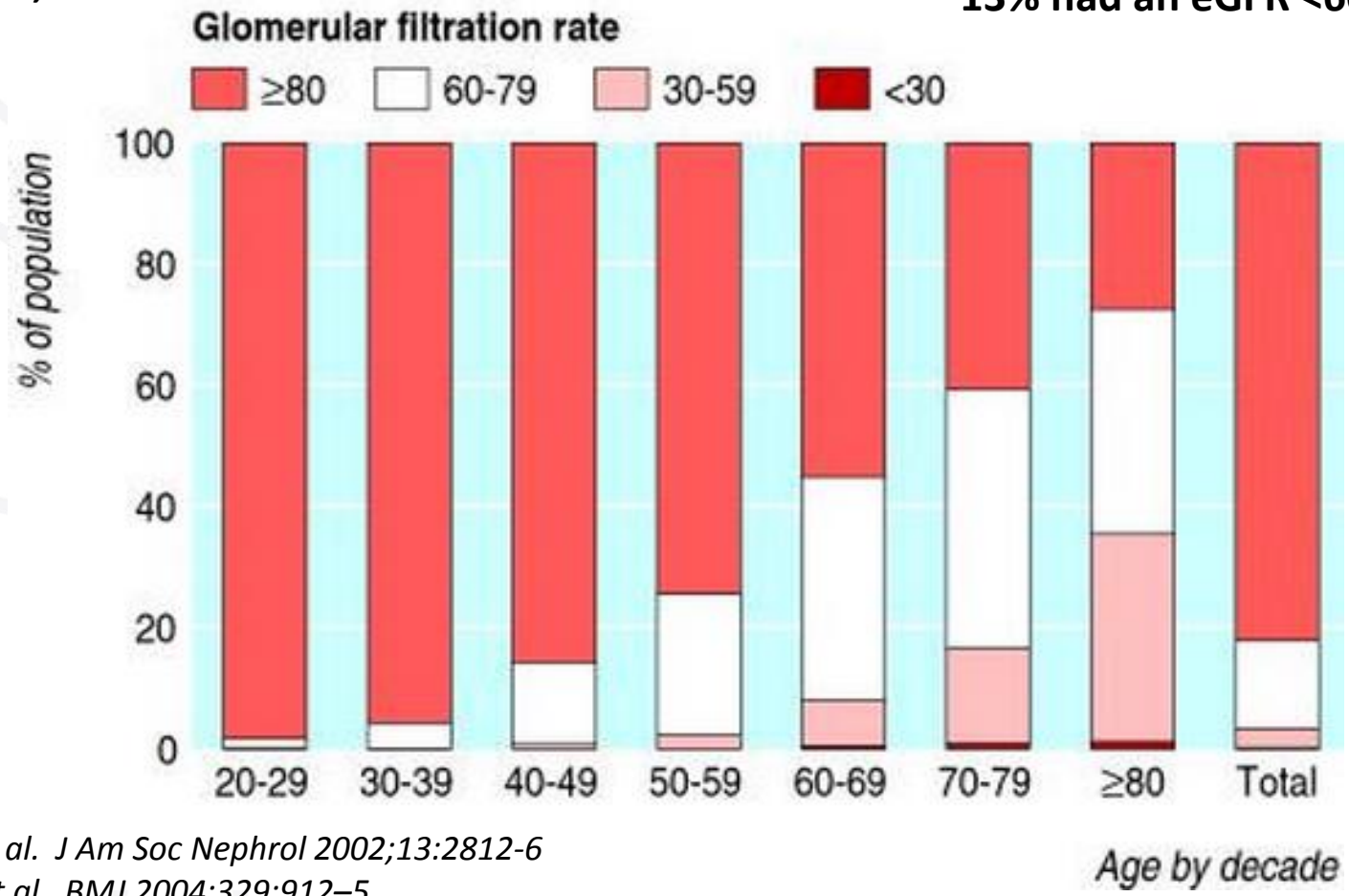


Distribution of predicted glomerular filtration rate by MDRD Formula by age in non diabetic adults

Third National Health and Nutrition Examination Survey (NHANES III)

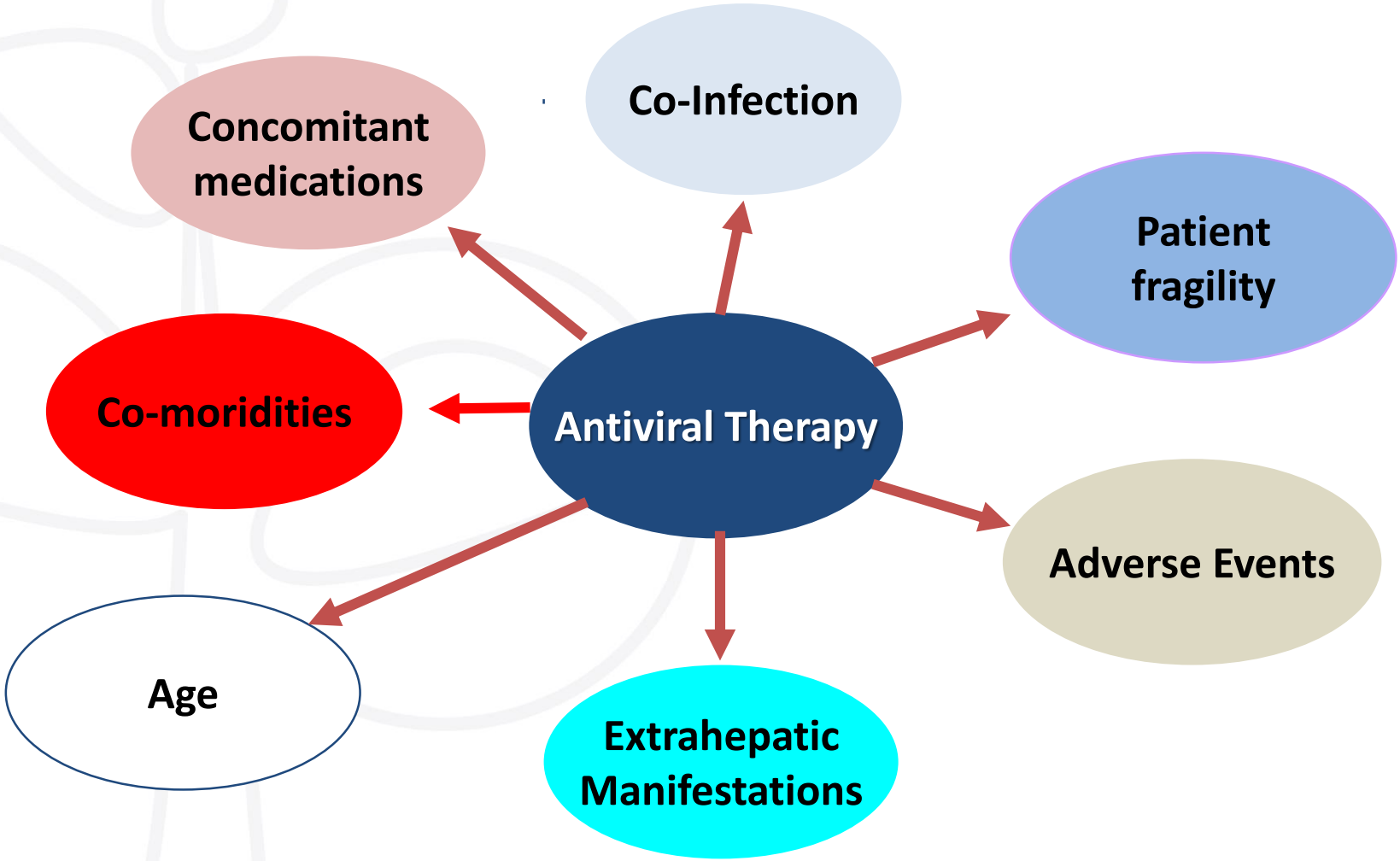
N = 13,251

13% had an eGFR <60

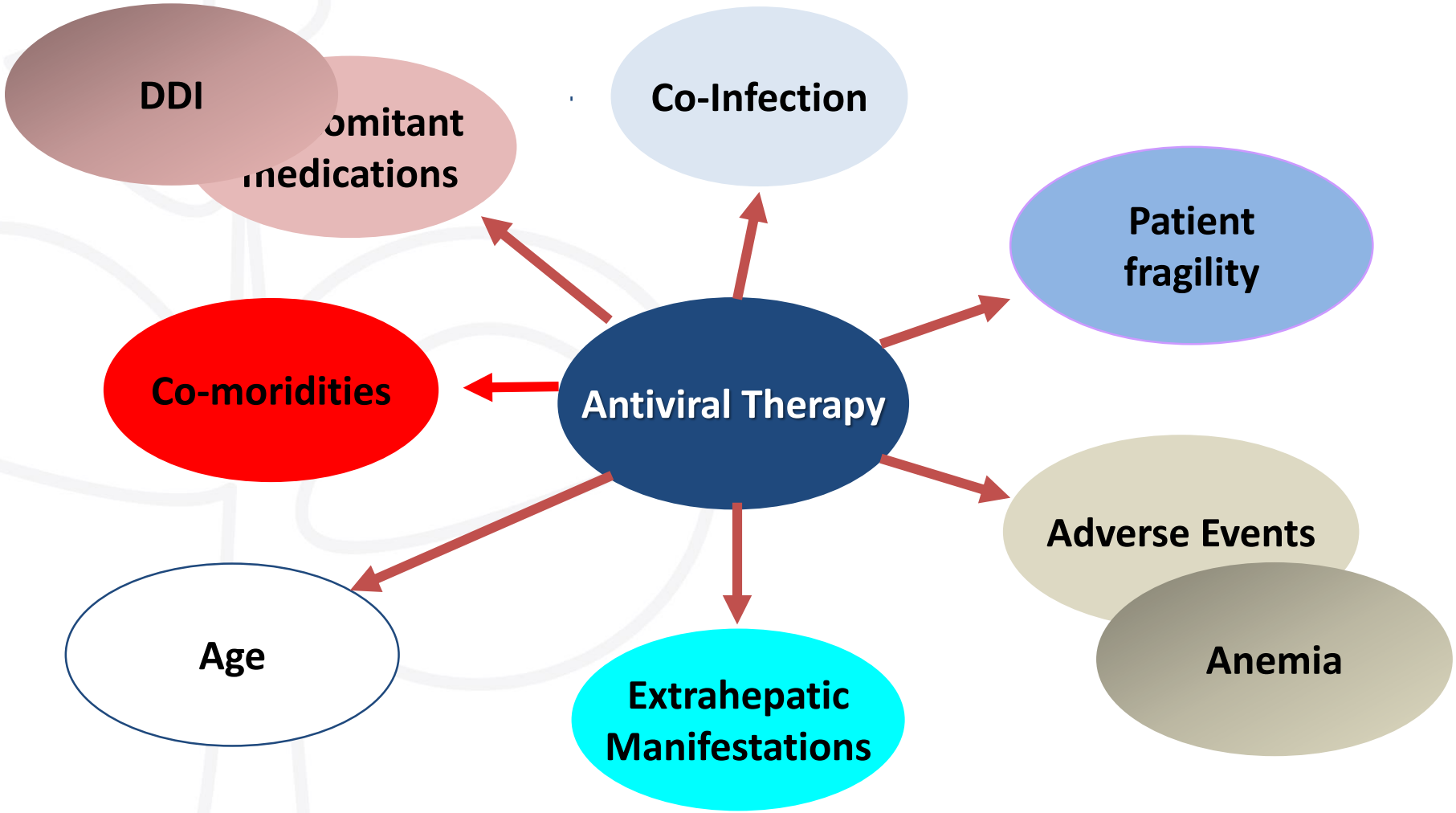


Clase CM et al. J Am Soc Nephrol 2002;13:2812-6
Clase CM et al, BMJ 2004;329:912–5

Cirrhosis & HCV Therapy: risks and opportunities



Cirrhosis & HCV Therapy: risks and opportunities

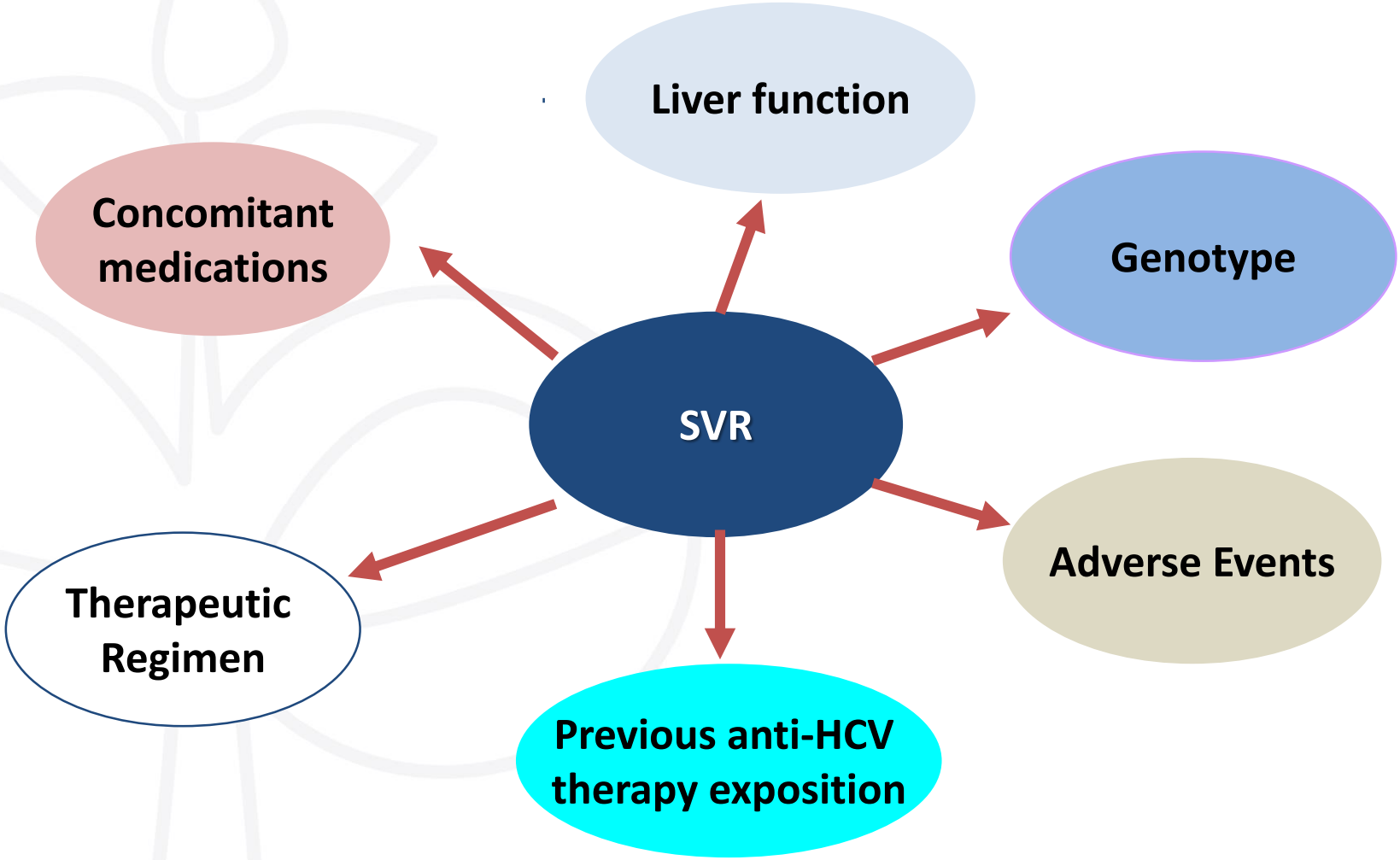


Serious Adverse Events (SAEs), Death and Liver Transplantation

	SOF RBV (n=88)	SOF SMV (n=114)	SOF SMV RBV (n=32)	Total (n=234)
TOTAL PATIENTS WITH SAEs N (%)	**27 (26.47)**	**8 (6.84)**	**9 (26.47)**	**44 (17.39)**
Hepatic Decompensation*	10 (19.6)	2 (1.71)	4 (11.76)	16 (6.32)
Infections	7 (7.14)	2 (1.71)	1 (2.94)	10 (4.00)
Died, n (%)	0 (0.0)	2 (1.7)	1 (2.9)	3 (1.2)
Unspecified	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.4)
Hepatic Failure	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.4)
Shock	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.4)
Received liver transplant on treatment, n (%)	4 (4.6)	3 (2.6)	5 (15.6)	12 (5.1)

***Hepatic encephalopathy, Variceal bleeding, Hepatic failure , Hepatic hydrothorax, bacterial peritonitis**

Cirrhosis & HCV Therapy



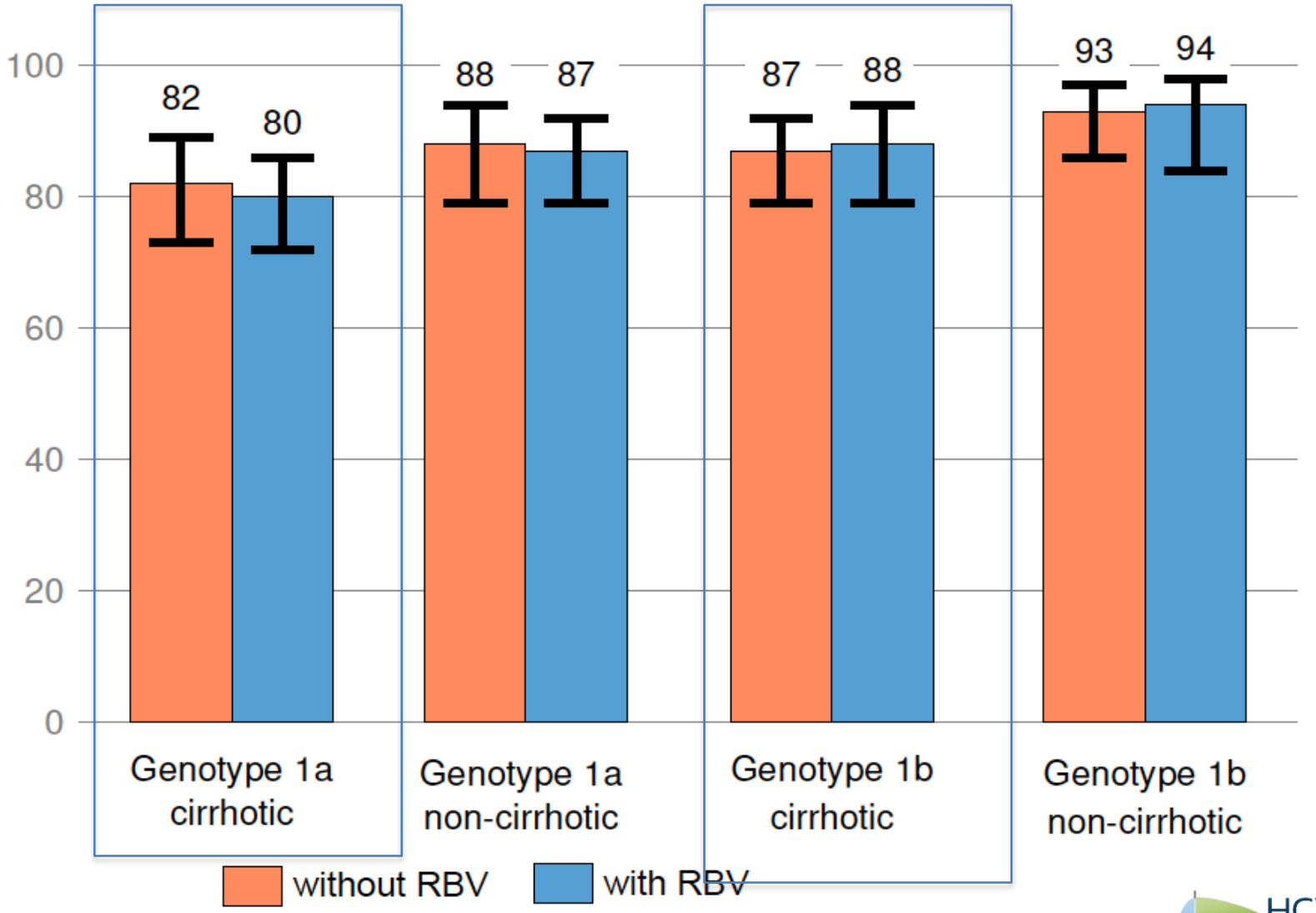
New DAAs in GT 1 cirrhotic patients: high rates of SVR with short duration regimens

	Duration (weeks)	SVR (Compensated)	SVR (Decompensated)
SOF + PEG-IFN + RBV	12–24	81%[1]	43% (3/7)*[2]
SOF + RBV	24–48	36–78%[3–5]	68% (CTP B)
SOF + SMV	12–24	86–100%[7,8]	7/7 [17] (CTP B) 79%[20]
SOF + DCV ± RBV	12- 24	94-100%[18]	60-86%[19]
PTV/RTV OMV + DSV ± RBV	12–24	89–100%[9]	No data
SOF LDV ±RBV	12–24	86–100%[10–14]	60–90%[15,16]

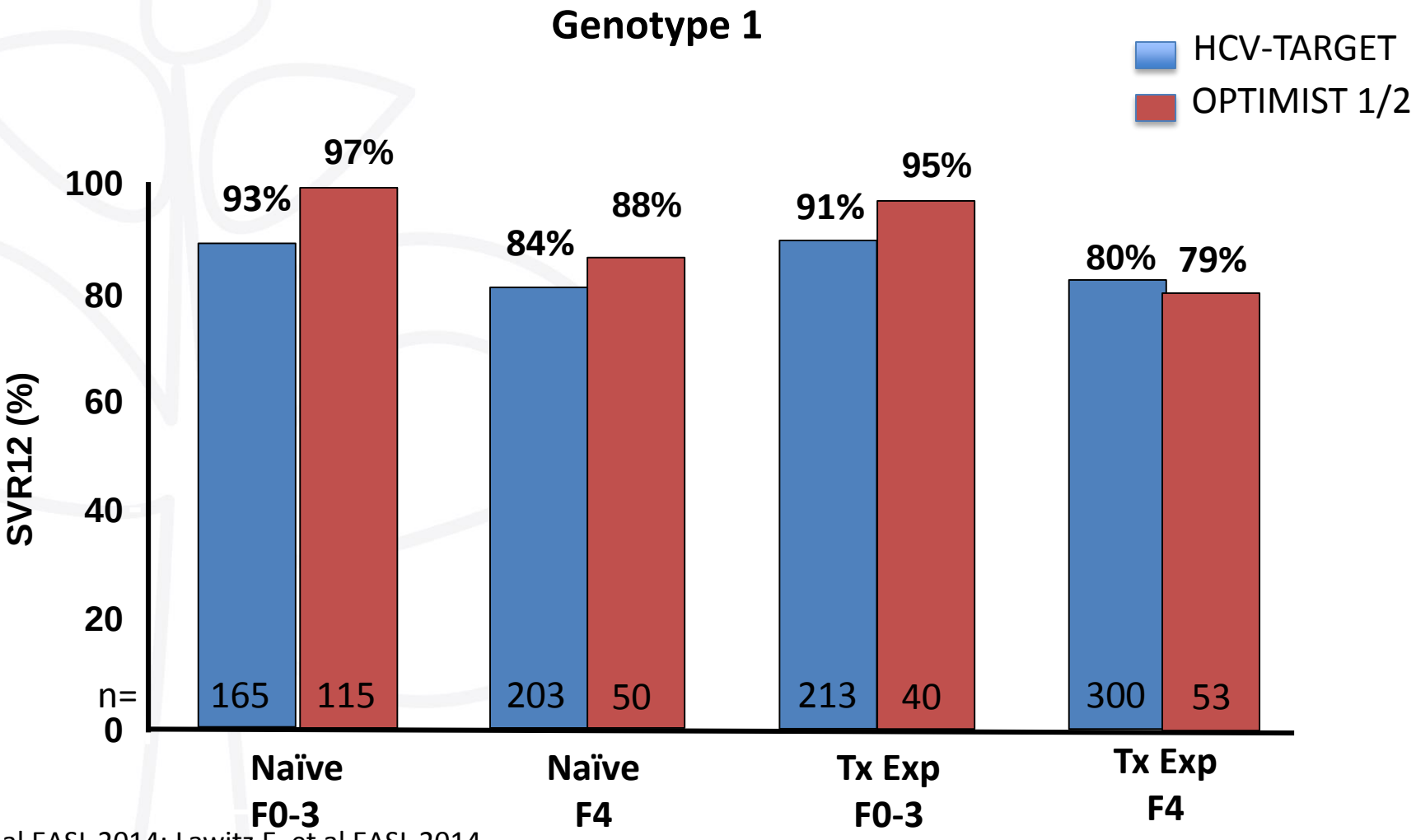
1. Lawitz E, et al. N Engl J Med 2013;368:1878–87; 2. Forns X, et al. Hepatology 2015;61:1485-94; 3. Gilead Sciences Europe Ltd. SOVALDI▼ (sofosbuvir), SmPC, March 2015;
4. Sulkowski MS, et al. JAMA 2014;312:353–61; 5. Molina JM, et al. Lancet. 2015;385:1098–106; 6. Afdhal N, et al. EASL 2014; Oral #68; 7. Lawitz E, et al. Lancet 2014;384:1756–65; 8. Janssen Products LP. OLYSIO▼(simeprevir), US PI, November 2014;
9. AbbVie Ltd. VIEKIRAX▼ (ombitasvir/paritaprevir/ritonavir), SmPC, January 2015;
10. Afdhal N, et al. N Engl J Med 2014;370:1889–98; 11. Gilead Sciences Europe Ltd. HARVONI▼ (ledipasvir/sofosbuvir), SmPC, November 2014; 12. Afdhal N, et al. N Engl J Med 2014;370:1483–93; 13. Reddy KR, et al. Hepatology 2015. doi: 10.1002/hep.27826; 14. Bourlière M, et al. Lancet Infect Dis 2015;15:397–404;
15. Flamm S, et al. AASLD 2014; Oral #239; 16. Reddy KR, et al. AASLD 2014; Oral #8
17. Reddy KR EASL 2015 Abst 0007. 18. Pol S et al EASL 2015 Abst LB03 19. Foster G et al EASL 2015 Abst 0002
20. Agel B et al AASLD 2014 Abst 19.

- *Post-transplant patients (n=22);
- †On-treatment response 95% at Week 24;
- ‡See late breaker presentation (S. Pol; Abstract L03) at this meeting. DCV: daclatasvir; DSV: dasabuvir; GT: genotype; LDV: ledipasvir; OMV: ombitasvir; PEG-IFN: pegylated interferon; PI: prescribing information; PTV: paritaprevir; RBV: ribavirin; RTV: ritonavir; SmPC: Summary of Product Characteristics; SMV: simeprevir; SOF: sofosbuvir

HCV-TARGET: Adjusted SVR4 for SOF/SMV±RBV: Impact of Cirrhosis and Genotype



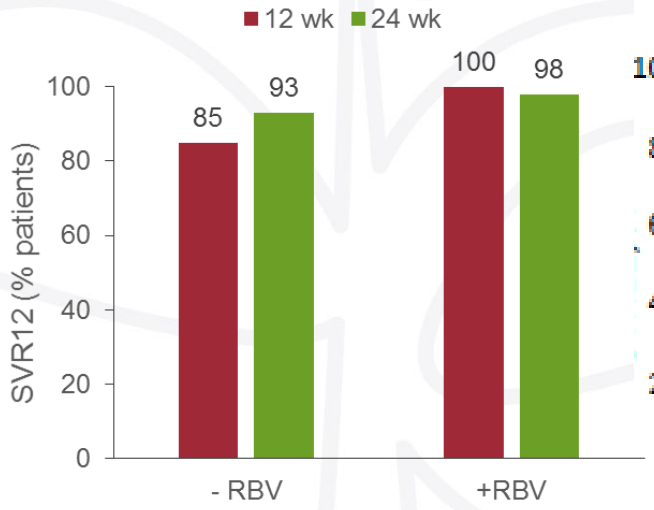
Sofosbuvir + Simeprevir for 12 weeks Real World vs Phase III



Kwo P, et al EASL 2014; Lawitz E, et al EASL 2014

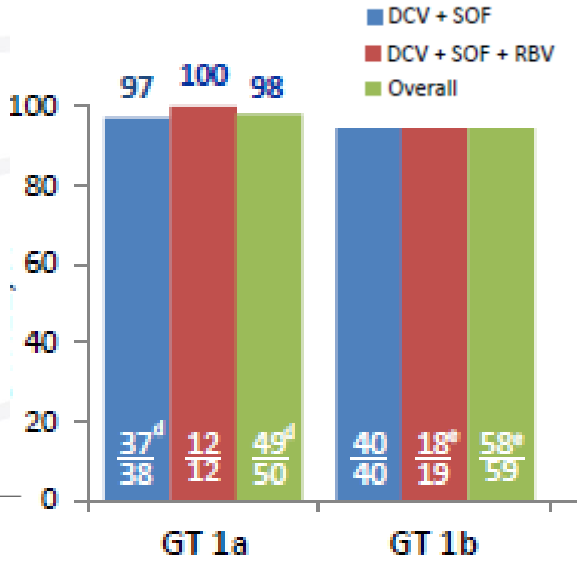
Real world data demonstrates similar outcomes to clinical trials with III DAA gen

ANRS CO22 HEPATHER[1]



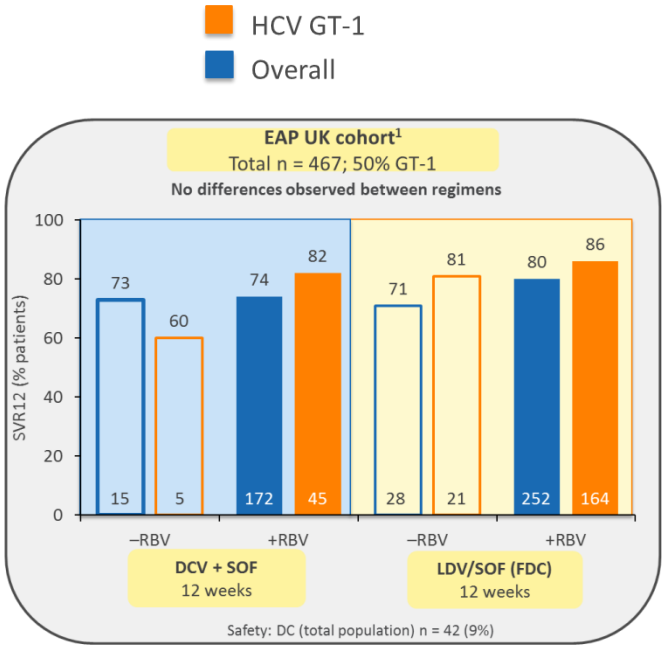
DCV + SOF

EU CUP[2]



DCV + SOF ± RBV

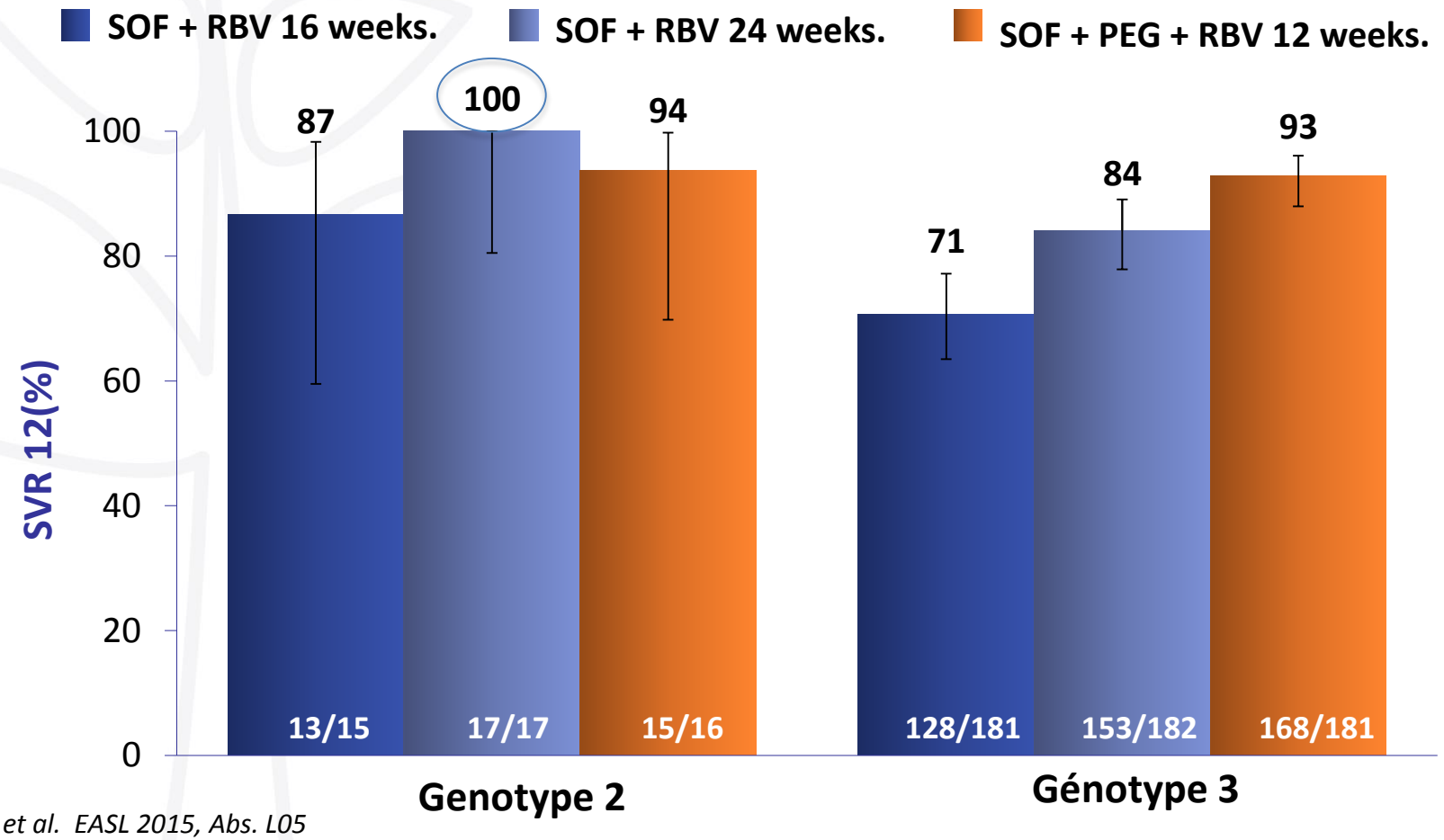
EAP UK cohort



1. Pol S, et al. EASL 2015 Abstract L03; 2. Welzel T., et al. EASL 2015 Abstract P0772. 3. Foster G et al. EASL 2015, Oral O002.

SOF + RBV or SOF + PEG + RBV in GT-2/3 treatment-experienced cirrhotic patients

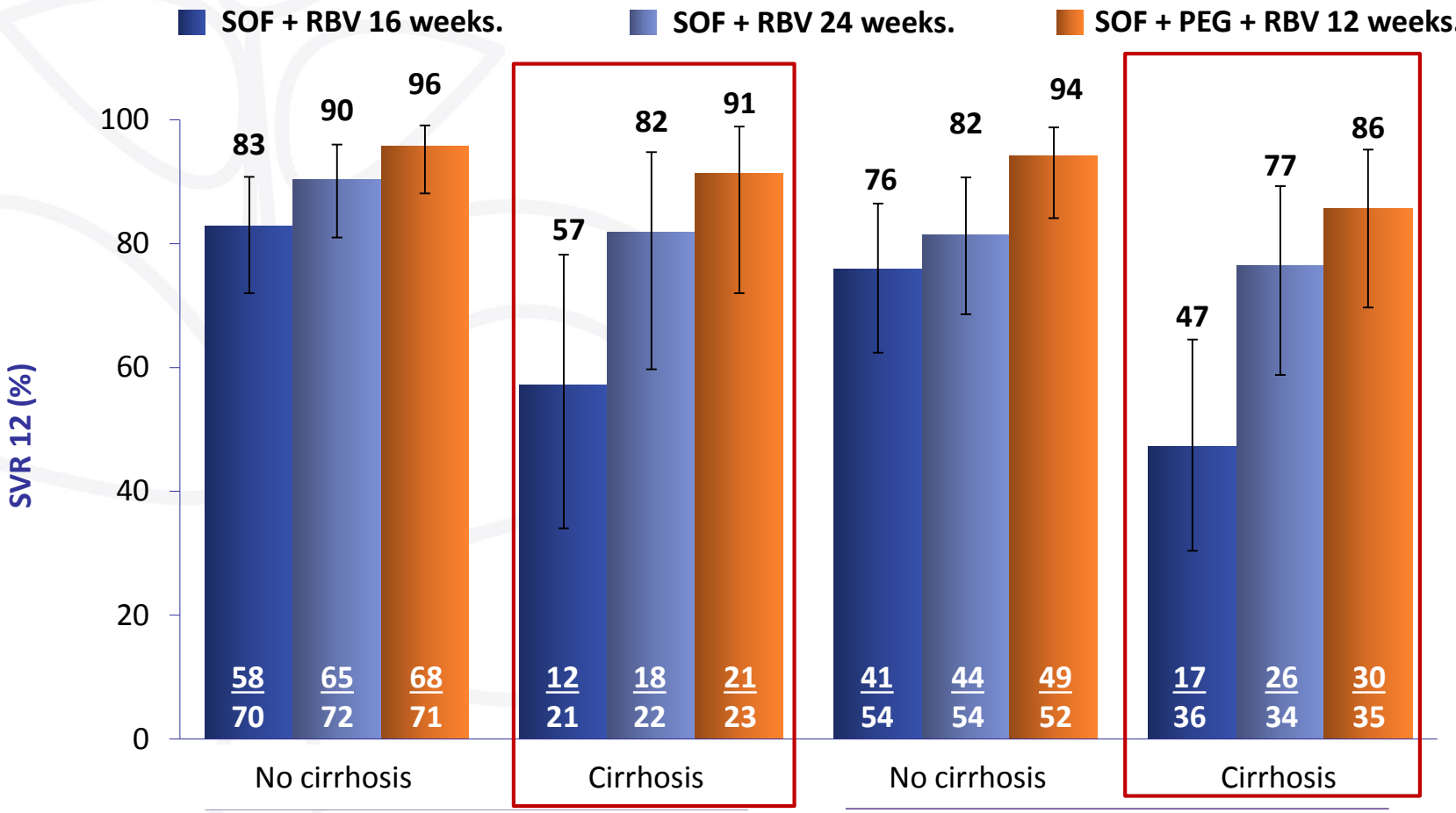
SVR 12



Foster G et al. EASL 2015, Abs. L05

HCV Gt 3: still a difficult genotype

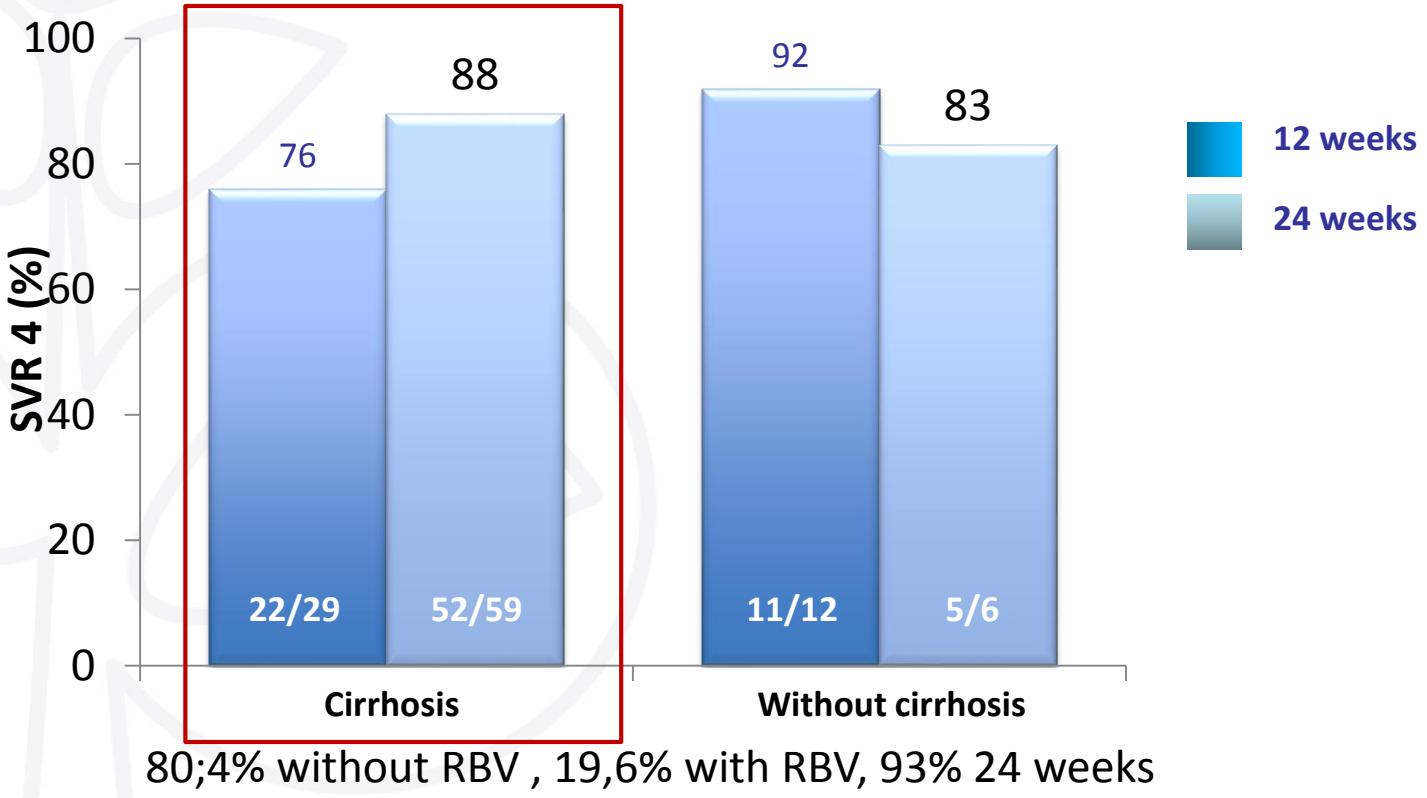
SVR 12 according to fibrosis stage and patients status



Foster G et al. EASL 2015, Abs. LC

SOF + DCV in GT-3 patients from EAP in France

SVR 4 according to treatment duration and fibrosis stage

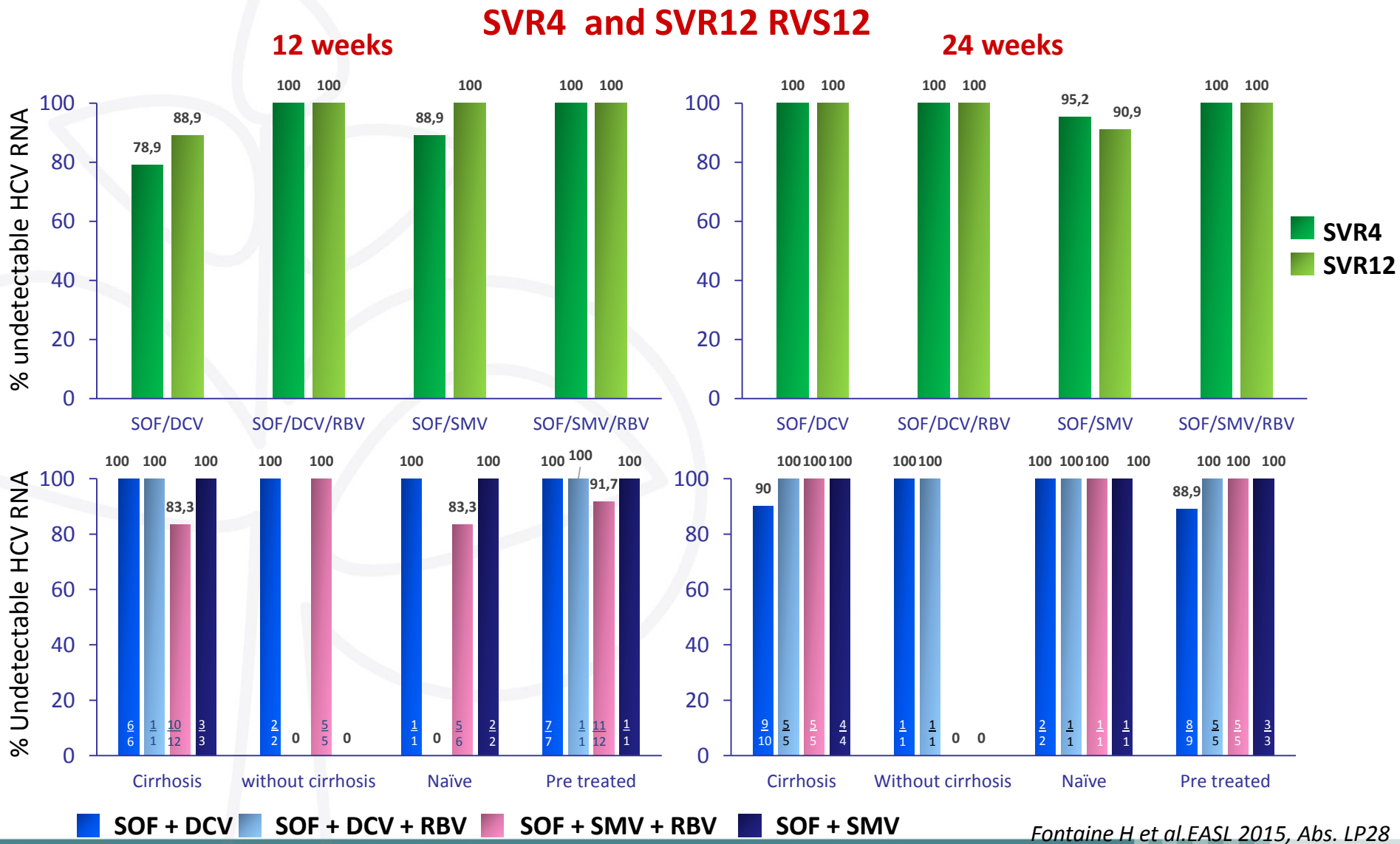


80;4% without RBV , 19,6% with RBV, 93% 24 weeks

➔ **12 weeks without cirrhosis, 24 weeks with cirrhosis**

Hézode C et al. EASL 2015, Abs. LP05

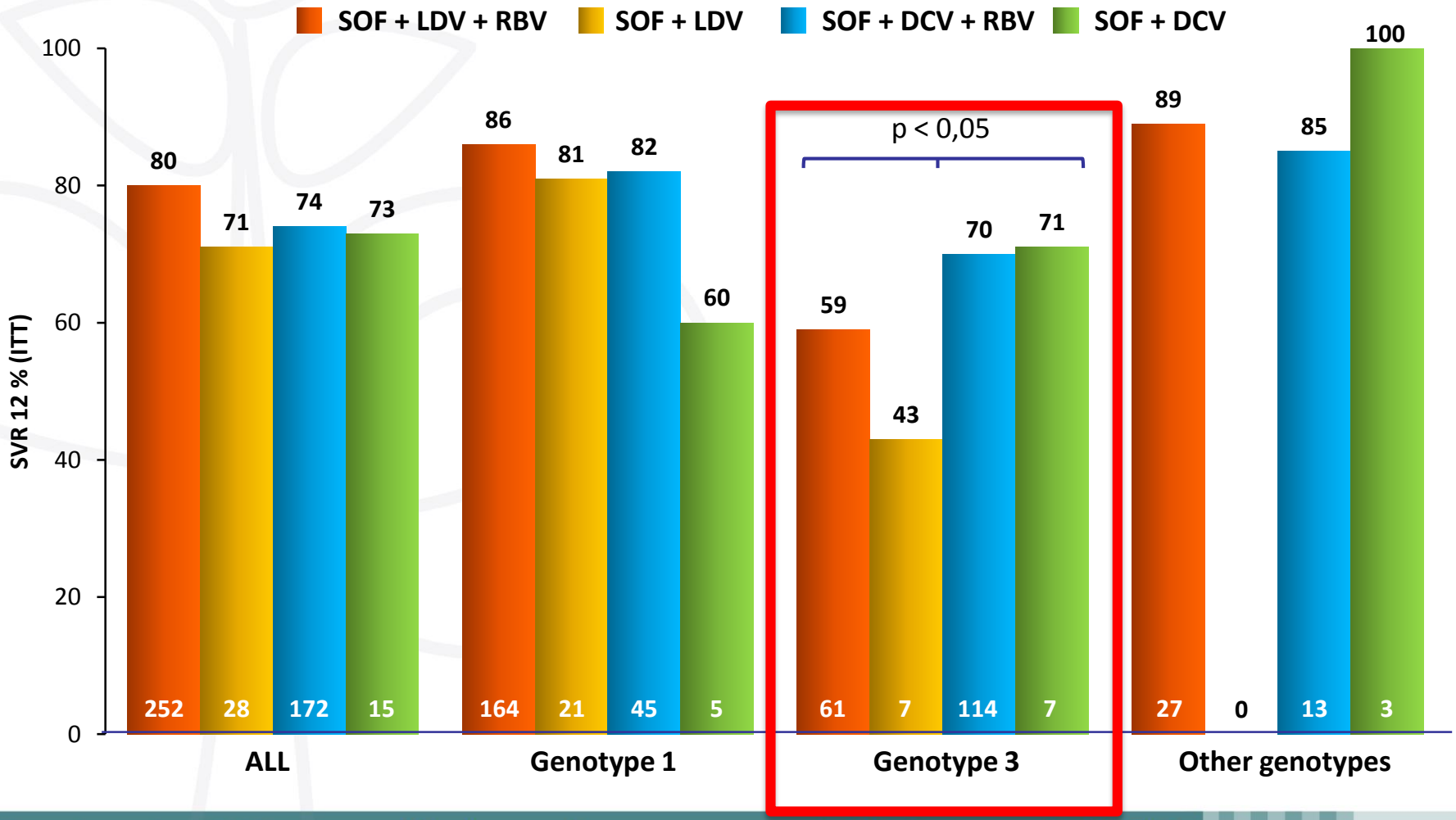
GT- 4 : SOF-based regimen in the HEPATHER cohort



Fontaine H et al.EASL 2015, Abs. LP28

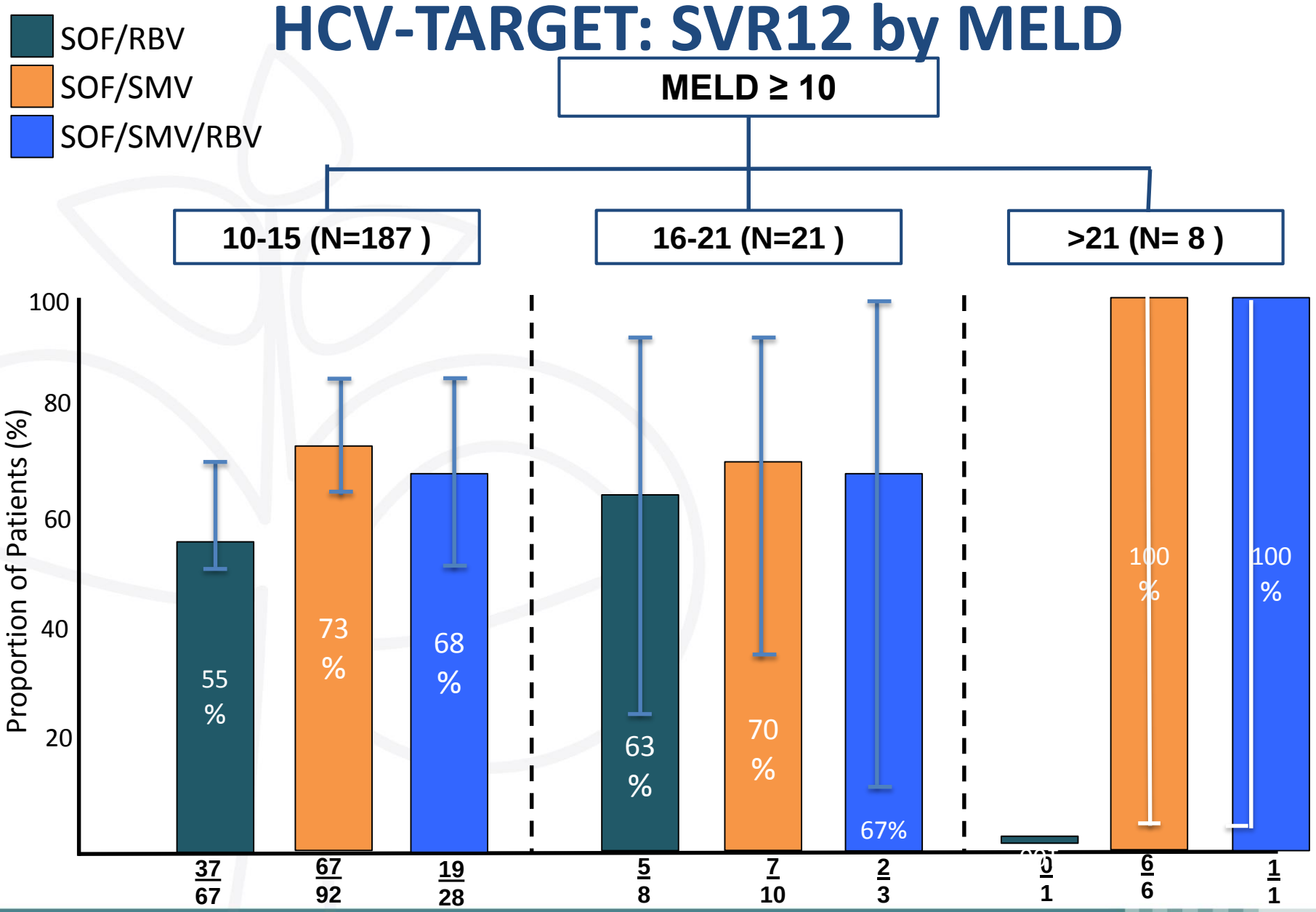
Decompensated Cirrhosis. UK EAP NS5B + NS5A +/- RBV

SVR 12 according to genotype and treatment options



Foster G et al. EASL 2015, Abs. O002

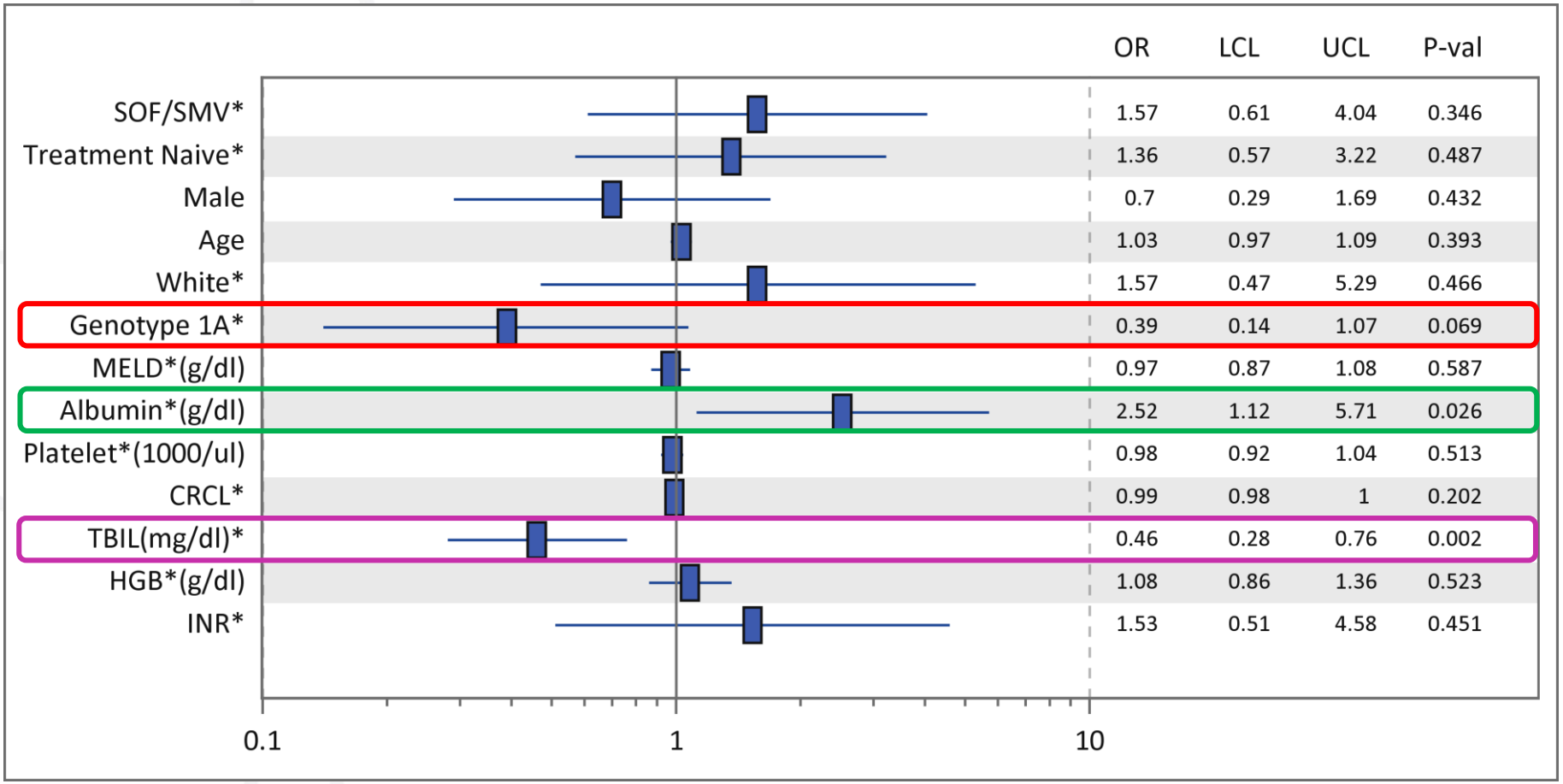
HCV-TARGET: SVR12 by MELD



*Crude SVR12 in patients with available outcome

Predictors of Response: Multivariate Analysis

Odds ratios, 95% CL, and p-value



Among GT 1 SOF/SMV+ -RBV patients with available virological outcomes;
Patients who discontinued early due to non virological reasons or where lost to follow up where excluded
***Estimated with logistic regression with the predictor of interest, age and gender in the model**

Liver - Risk:Benefit

	Number of patients (%)	Albumin >35	Albumin <35
Age <65	Harmed – SAE/MELD worse by 2	14 (14%)	94 (33%)
	Helped MELD improved by 2	29 (28%)	53 (18%)
	TOTAL	102	288
Age >65	Harmed- SAE/MELD worse by 2	9 (32%)	14 (33%)
	Helped MELD improved by 2	4 (14%)	6 (14%)
	TOTAL	28	43

Foster G et al. EASL 2015, Abs. O002

Liver - Risk:Benefit

	Number of patients (%)	Albumin >35	Albumin <35
Age <65	Harmed – SAE/MELD worse by 2	14 (14%)	94 (33%)
	Helped		

In decompensated cirrhosis:

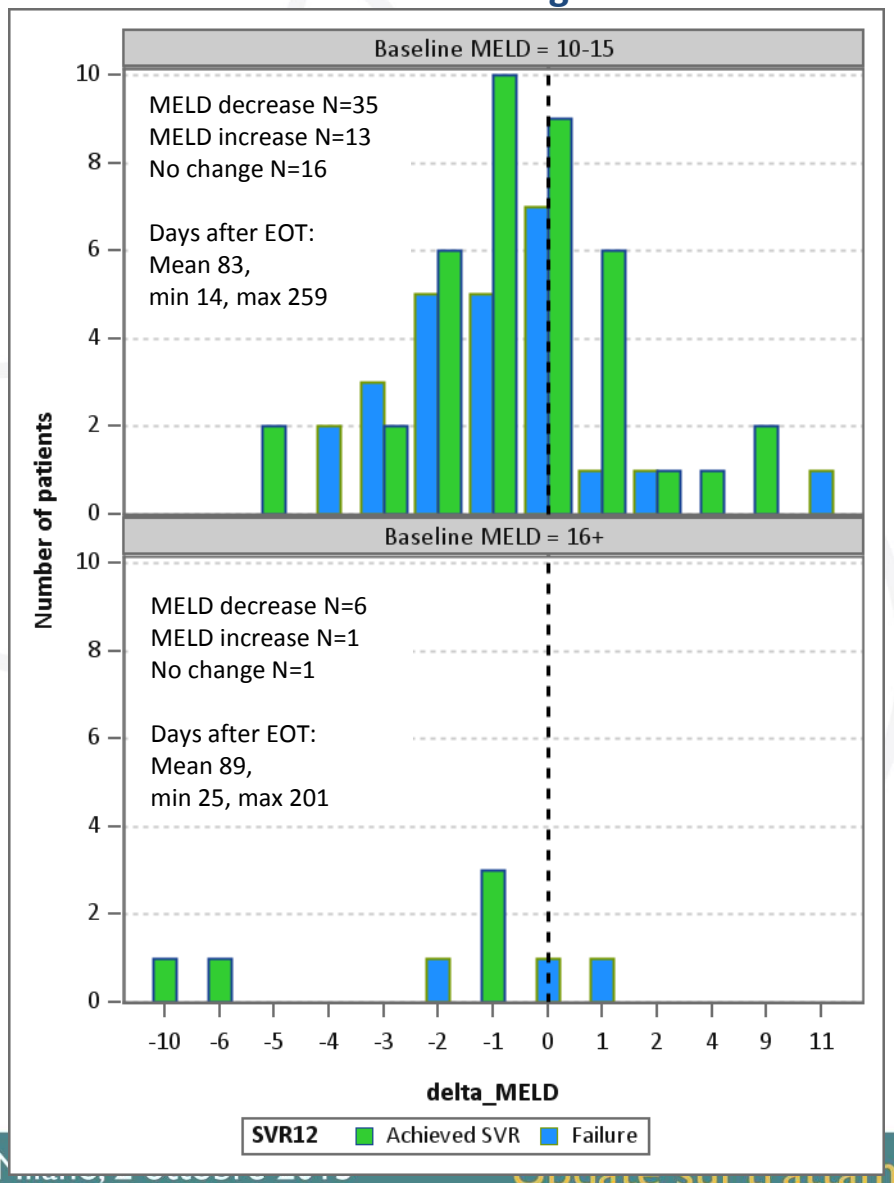
For patients younger than 65 years if the albumin is > 35 g/L improvement in liver function is more likely than harm

	Helped MELD improved by 2	4 (14%)	6 (14%)
	TOTAL	28	43

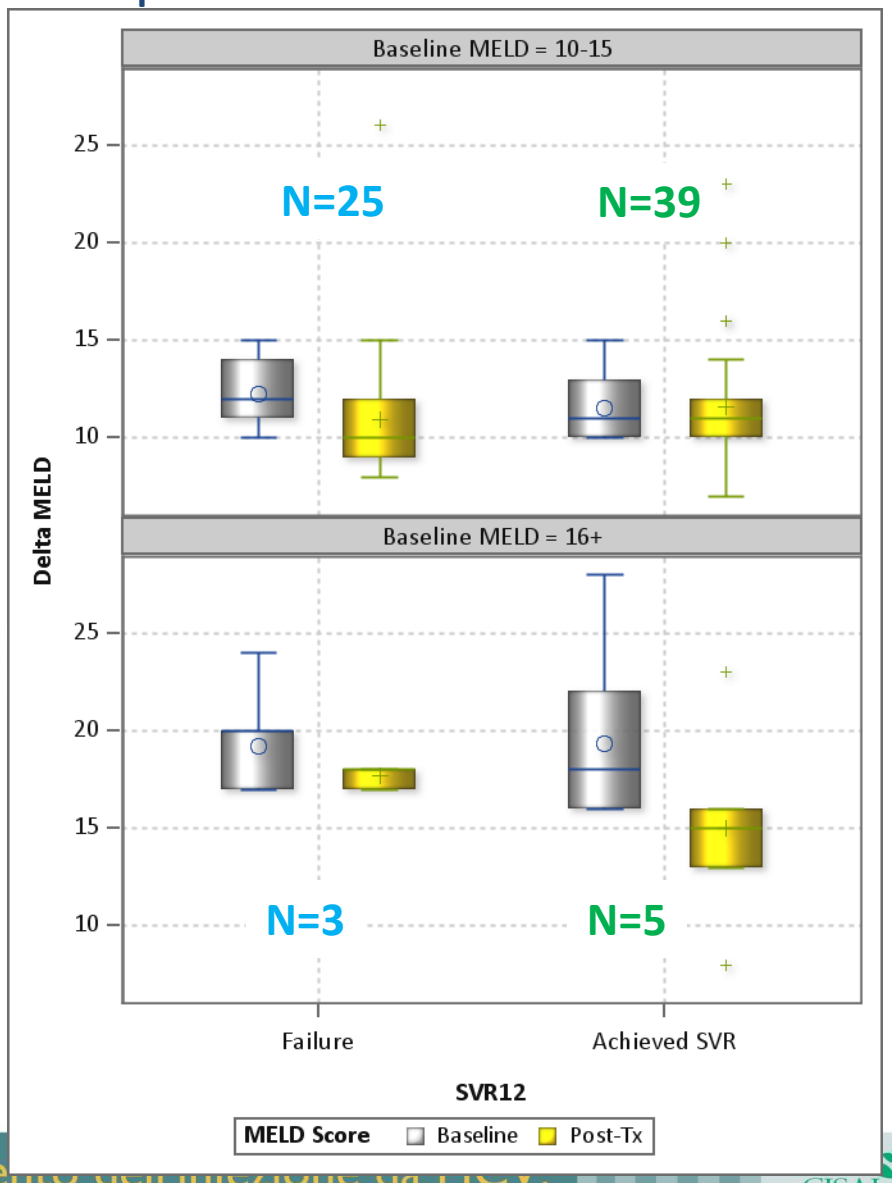
Foster G et al. EASL 2015, Abs. O002

Change in MELD score

Change from Baseline to Follow up week 2 or later



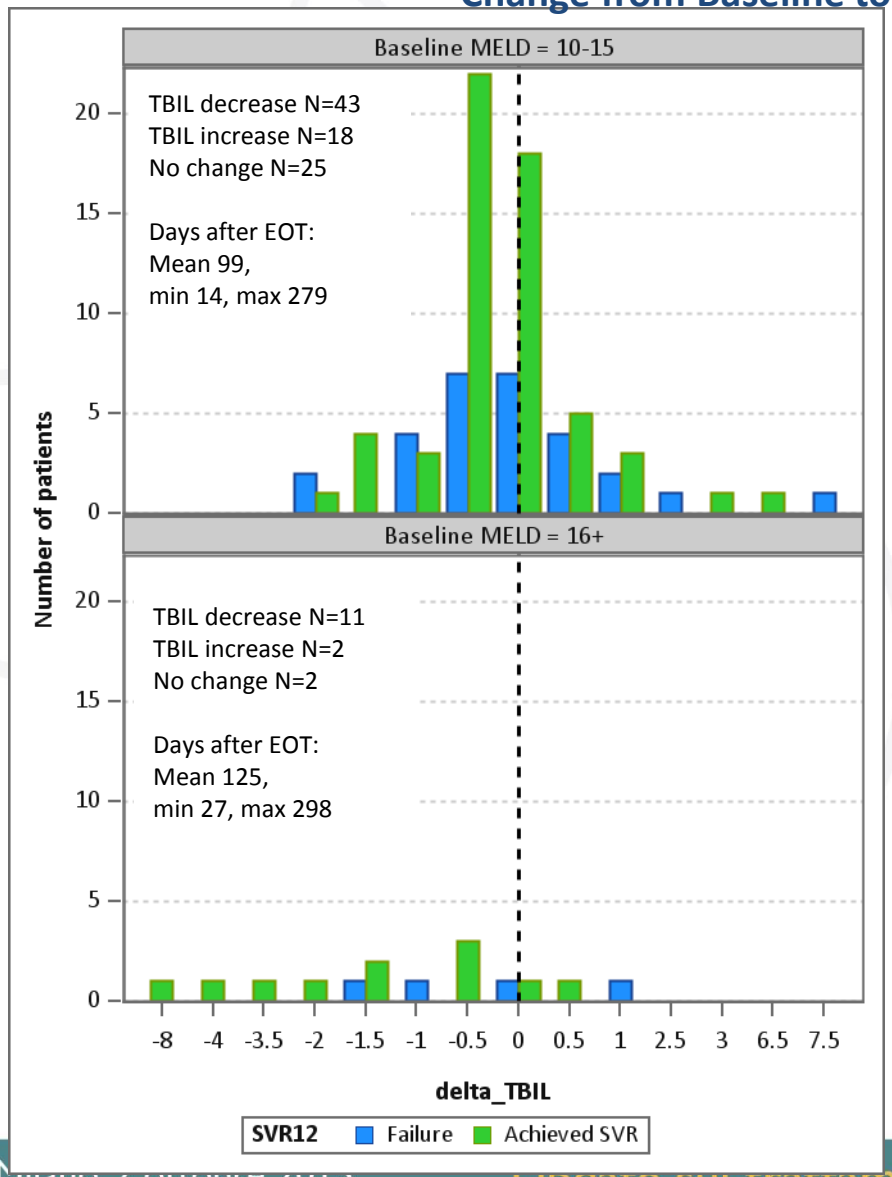
Pre-treatment to post-treatment value change among individual patients



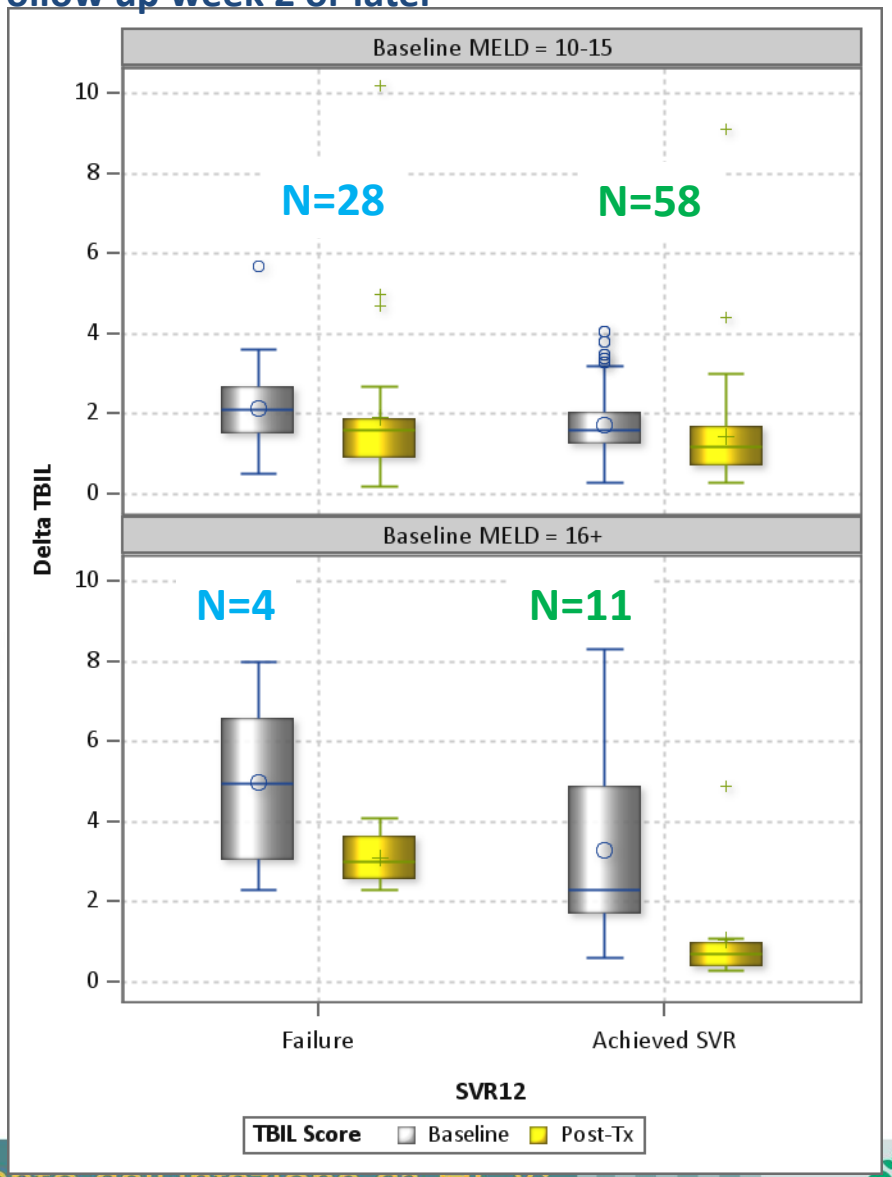
Change from pre-treatment to post-treatment value by treatment outcome

Change in Total Bilirubin

Change from Baseline to Follow up week 2 or later



Pre-treatment to post-treatment value change among individual patients

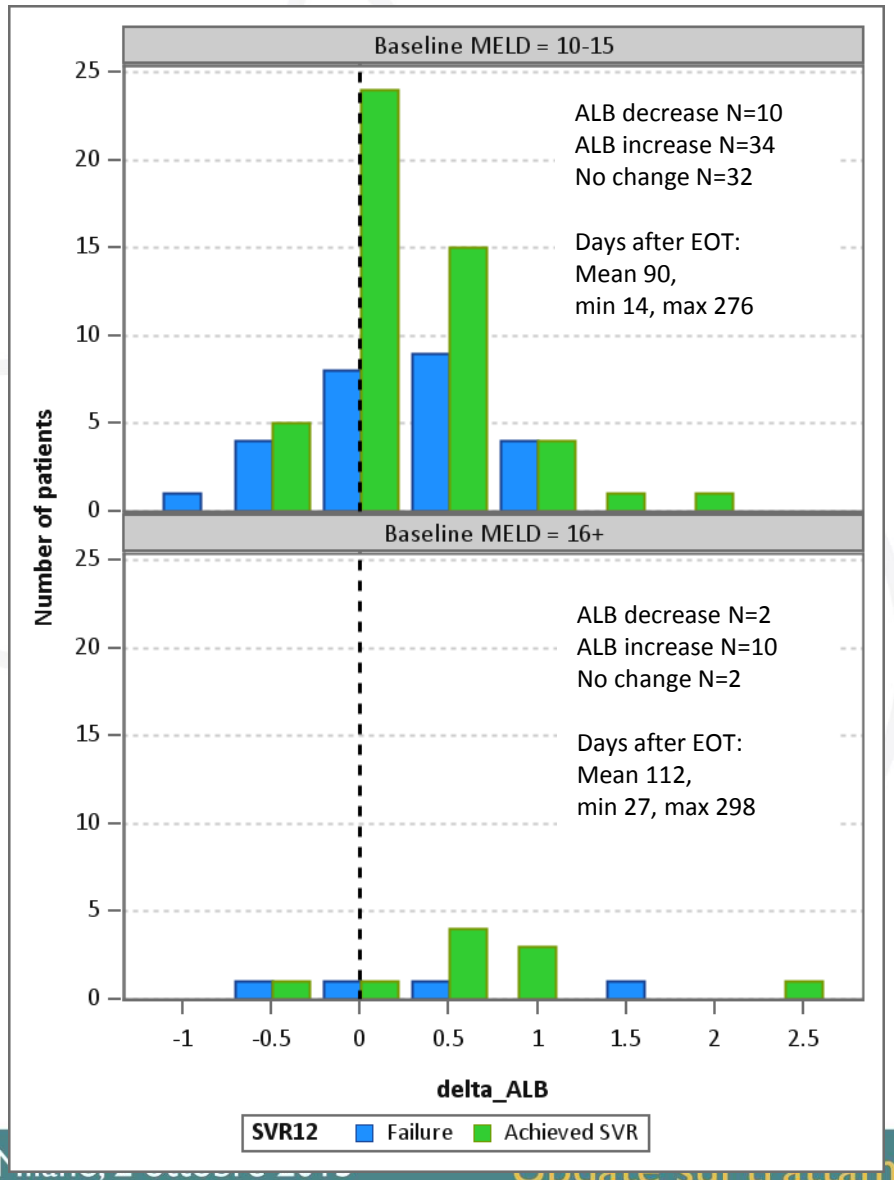


Change from pre-treatment to post-treatment value by treatment outcome

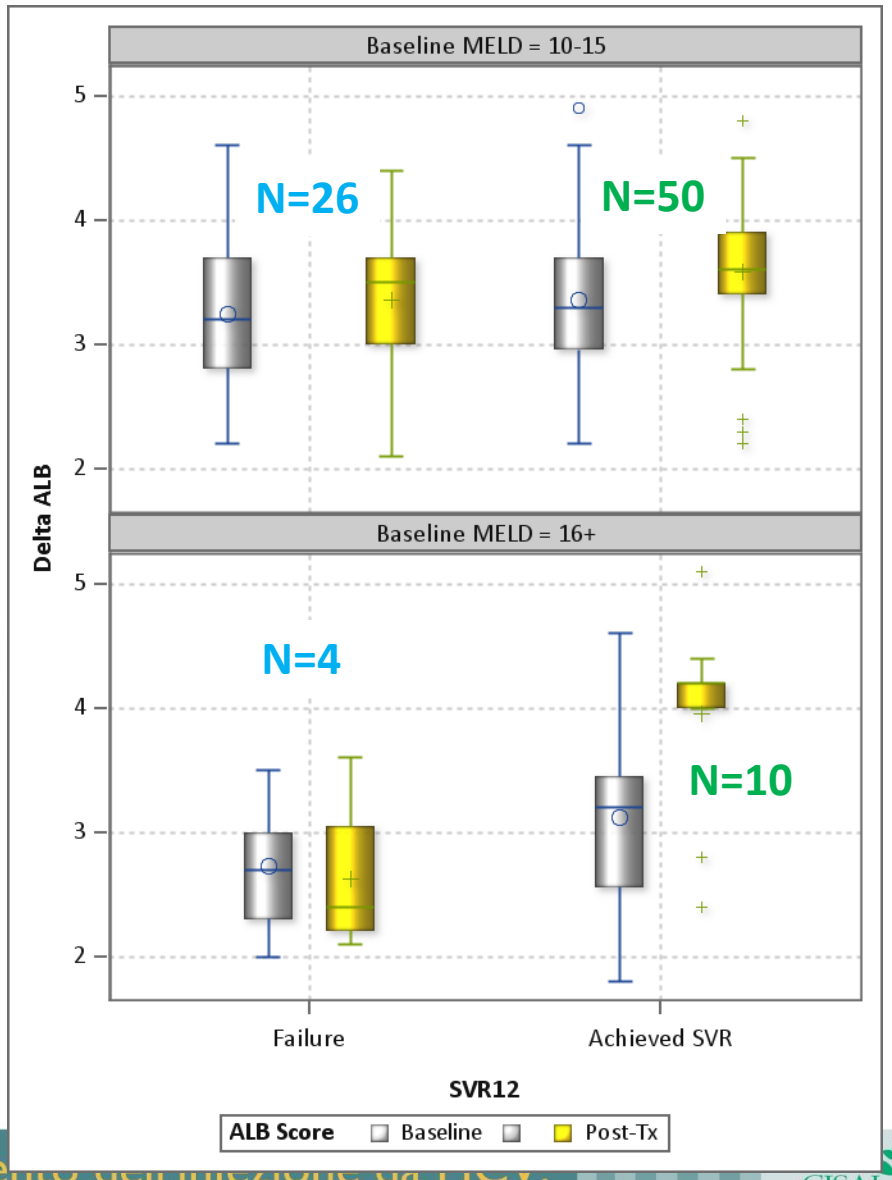
MELD change largely driven by Bilirubin. Data on Creatinine and INR not shown

Change in Albumin

Change from Baseline to Follow up week 2 or later

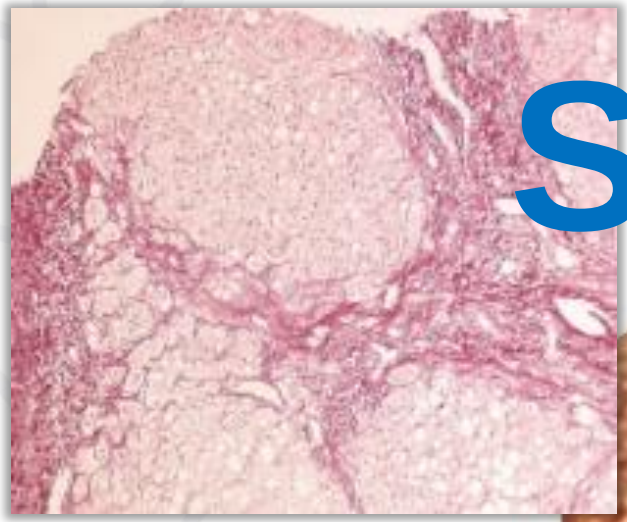


Pre-treatment to post-treatment value change among individual patients



Change from pre-treatment to post-treatment value by treatment outcome

SVR



Deaths associated with different diseases in Italy

Disease	n. deaths/yr
Colon and rectum cancers	20,269
Breast cancers	13,222
Chronic obstructive pulmonary disease	21,527
Nephritis and nephrosis	8744
Liver cancer	9753
Cirrhosis of the liver	8165

- 60% related to HCV

Comparison of the number of deaths associated with selected diseases compared to liver diseases based on death certificates (age-standardized) in Italy (population 59,6 millions)

Blachier M, J Hepatol 2013;58(3):593-608

Clinical benefits in HCV Cirrhotic Patients Achieving a Sustained Virological Response (SVR)

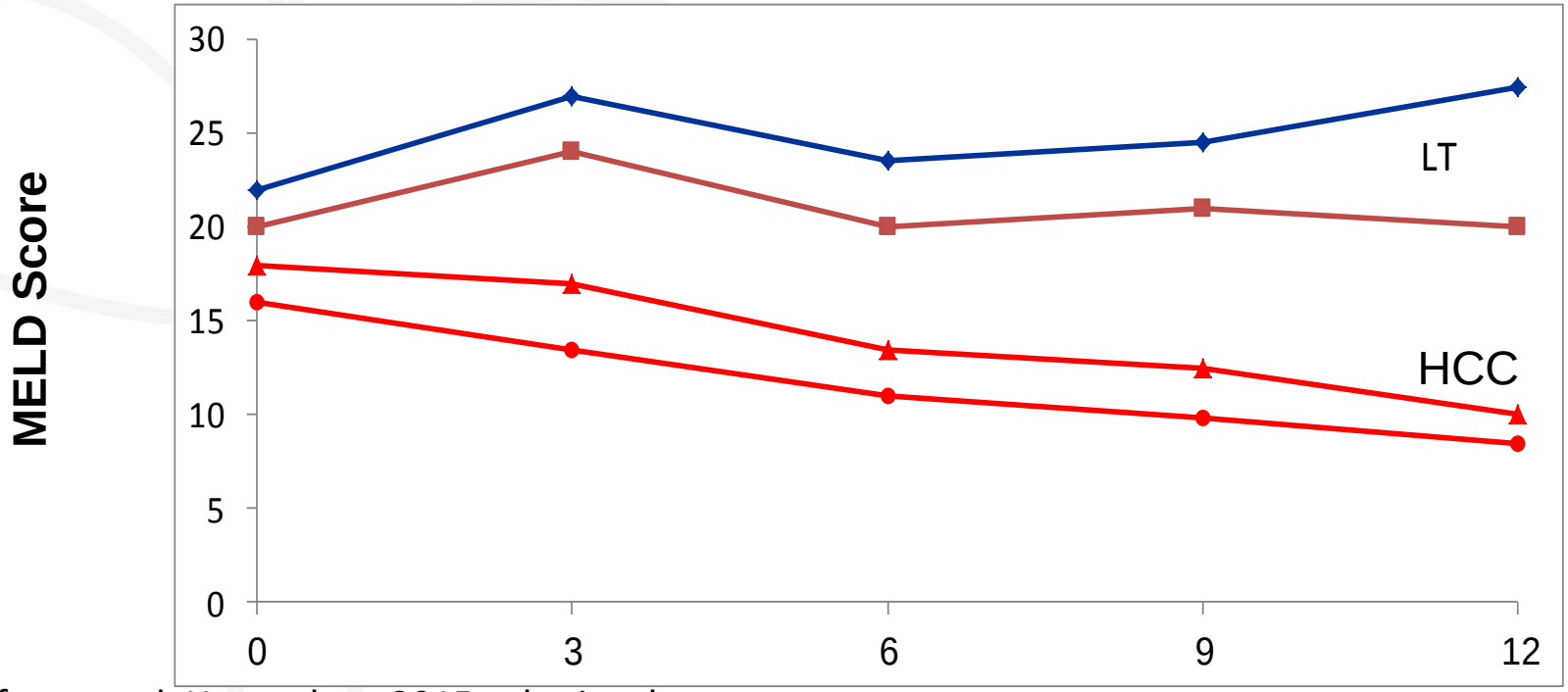
Clinical benefits of a SVR

- Regression of cirrhosis
- Reduction of all-cause/liver-related mortality
- Prevention/attenuation of portal hypertension-related events
- Prevention of hepatocellular carcinoma (HCC) (?)
- Prevention of HCV Related Extrahepatic Disease

Courtesy of Prof . M. Colombo

SVR May Not Cure the Liver. The Point of No Return

- 120 patients with advanced cirrhosis treated with SOF+SMV for 12 weeks
- Overall SVR=81%
- **Patients with MELD >20 did not appear to improve**
- HCC developed in some patients that appeared to improve



Shiffman et al, Hepatology 2015 submitted

Therapy in cirrhotic patients: Conclusions

- **Cirrhosis most important predictor of response**
- **Efficacy:**
  - Very high SVR
  - Real world data generally consistent with phase II-III trial data (approximately 8% less)
    - Genotype 3 has suboptimal response
- **Predictor of response:**
  - Genotype 1a
  - Albumin levels
  - History of prior decompensation
  - Prior therapy failure
- **Safety:**
  - Very low discontinuation rate (around 3%) and SAE rates
  - AEs of all-oral regimens were much lower than those with PEG

Therapy in decompensated cirrhosis: Conclusions

- **SVR varied by genotype and regimen**
  - **Genotype 1: 52-74 % (TARGET) 82-86% (UK EAP)**
    - Geno-1a: 66%, 71% (SMV SOF + RBV)
    - Geno-1b: 87%, 50% (SMV SOF + RBV)
  - **Genotype 2: 81 %**
  - **Genotype 3: 39% (TARGET), 70-71% (UK EAP)**
- **Abbvie regimen not (actually) indicated for lack of data**
- **Negative Predictors of SVR were genotype 1a and elevated bilirubin, while higher albumin was associated with better outcome**
- **MELD score and Serum Albumin improved or remained stable in the majority of patients**

Therapy in advanced fibrosis: Conclusions

EASL Guidelines. Post-treatment Follow-up of Patients who Achieve an SVR

- Patients with **pre-existing cofactors** for liver disease (notably, history of alcohol drinking and/or type 2 diabetes) should be carefully and periodically subjected to a thorough clinical assessment,……
- The exact duration of **HCC surveillance** in patients with advanced fibrosis or cirrhosis who achieve an SVR is unknown in the current state of knowledge, but is probably indefinite (B1).