UPEC
UNIVERSITÉ PARIS-EST CRÉTEIL

FACULTÉ
DE MÉDECINE

GROUPE HOSPITALIER
HENRI MONDOR
ALBERT CHENEVIER - GEORGES CLEMENCEAU
JOFFRE-DUPUYTREN - EMILE ROUX

Hepatitis C: Results in Real life

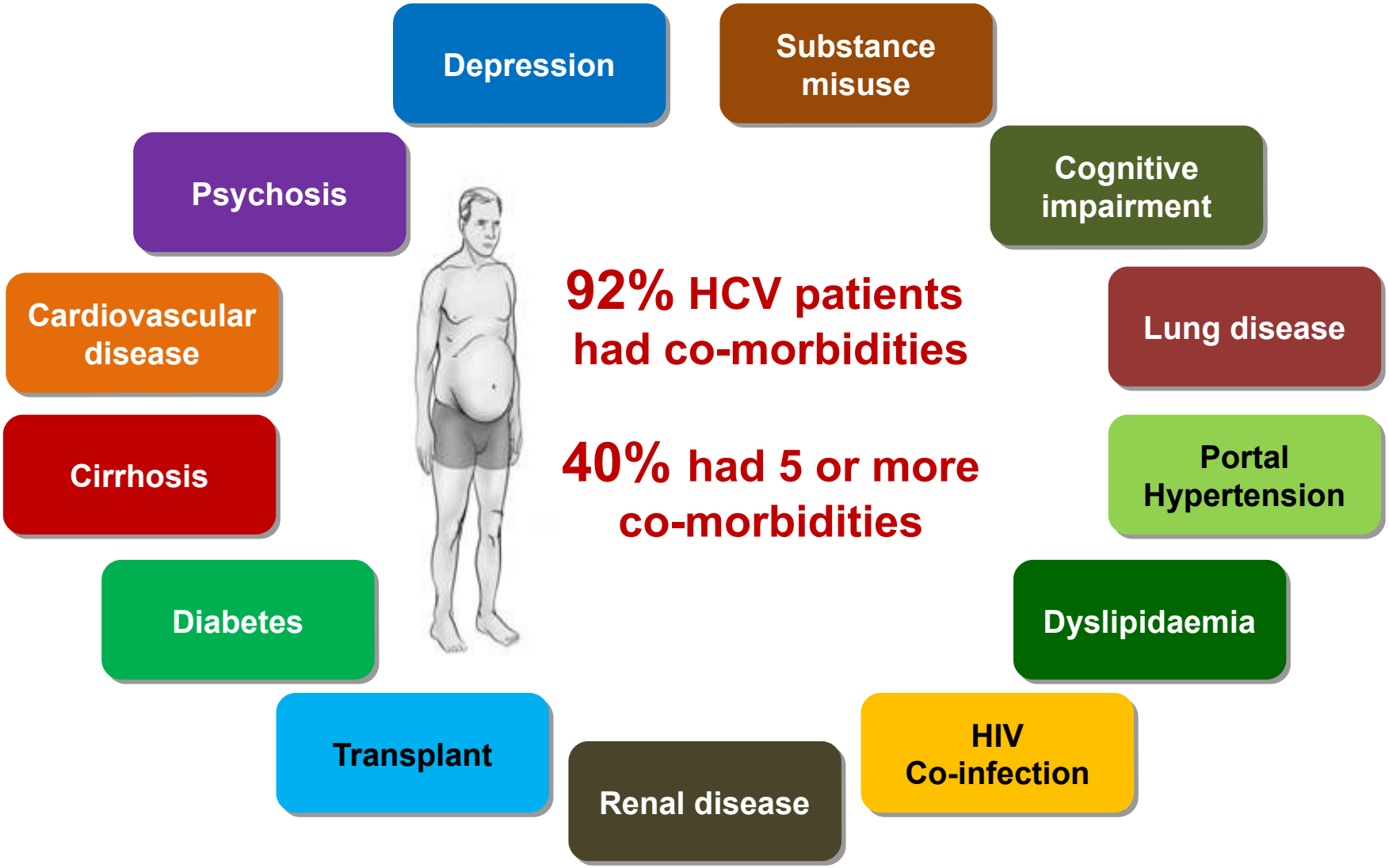
Christophe Hézode, Henri Mondor Hospital, Paris-Est University, Créteil, France

Links of interest and Disclaimer

Adviser, speaker, investigator for:

Abbvie, BMS, Gilead, Janssen, MSD

Co-morbidities, multiple medications and DDIs

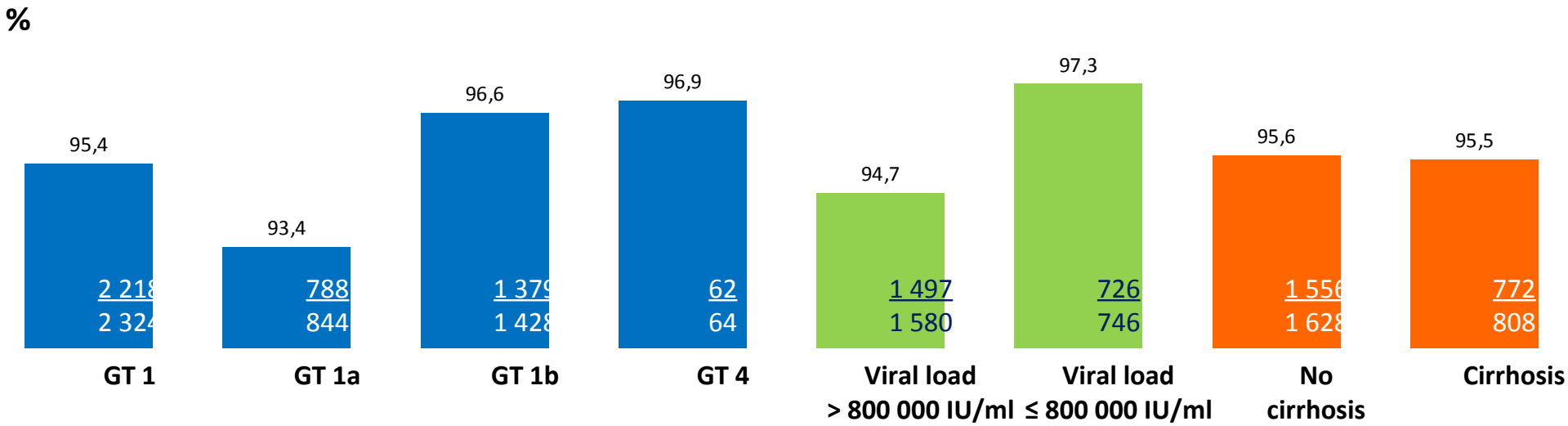


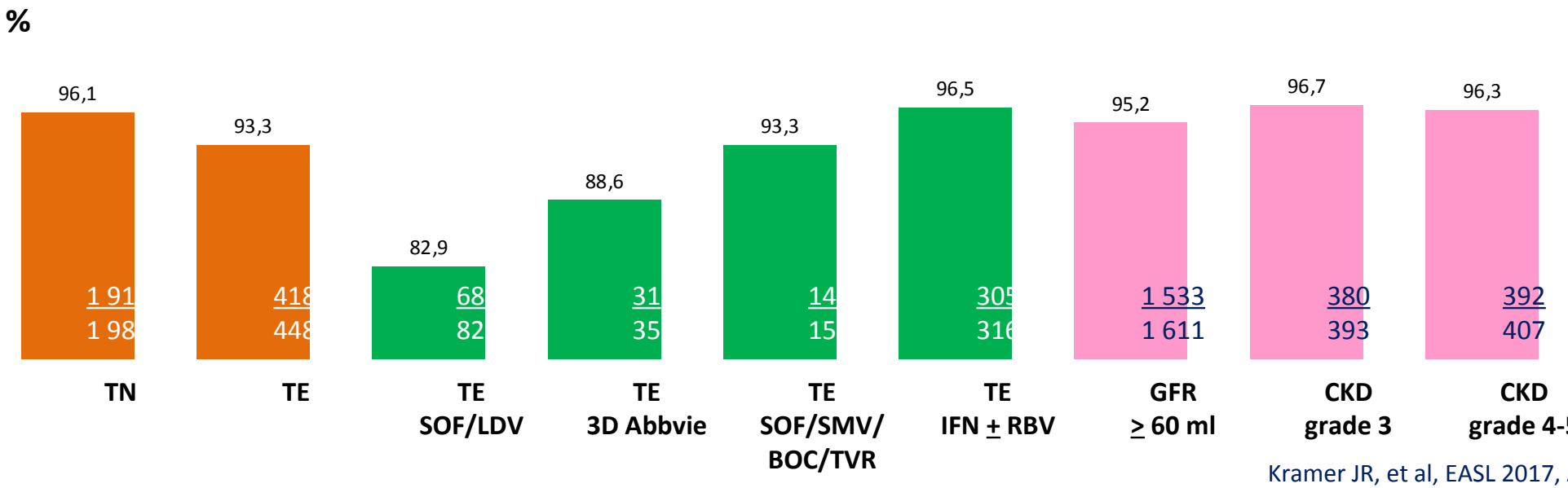
Vutien P, et al. AASLD 2014; Poster 1481

Grazoprevir and elbasvir in US veterans

~93% treated for 12 weeks and without RBV

SVR (Evaluable population): 95.6 % (2 328/2 436)





Kramer JR, et al, EASL 2017, Abs. PS-095

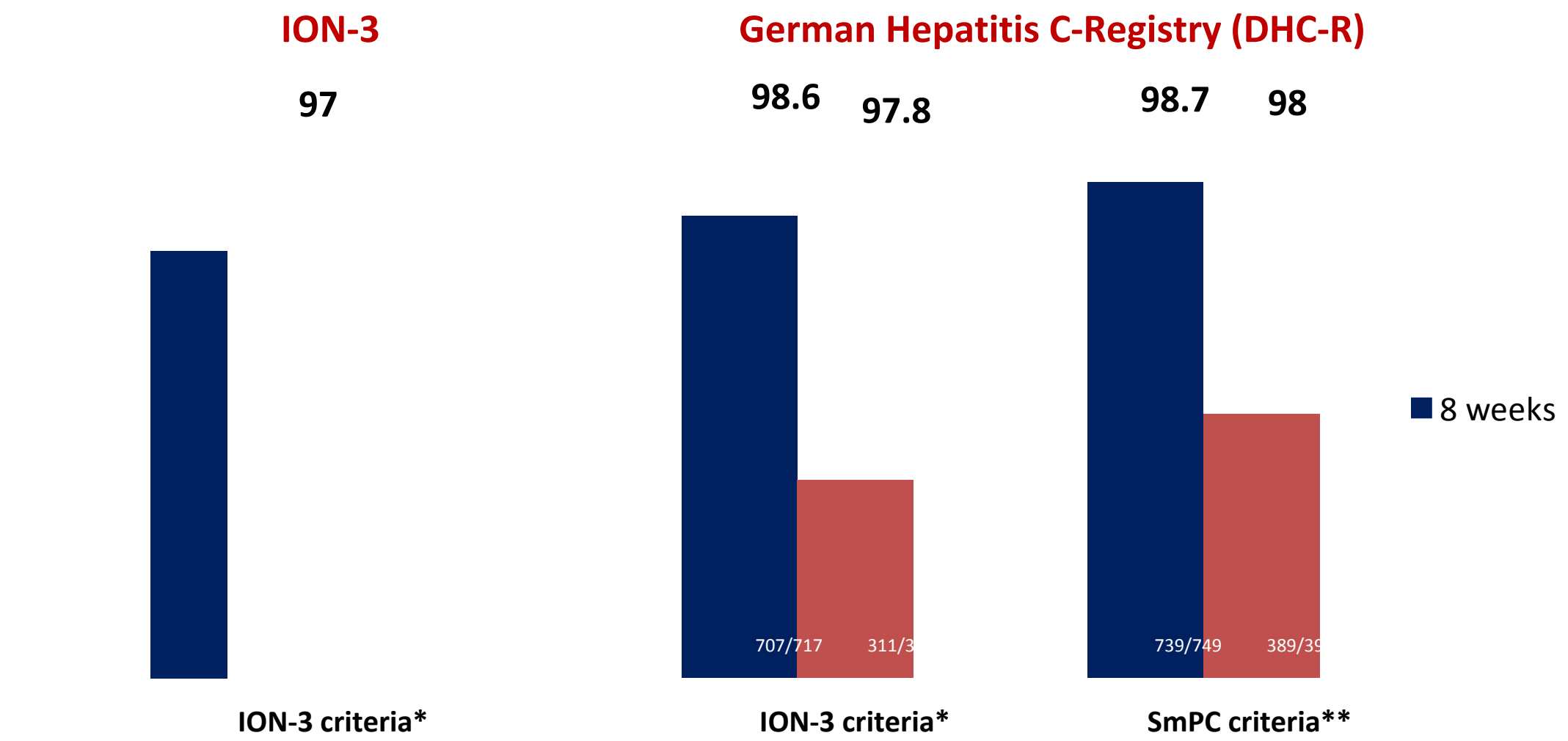
Genotype 1 patients

EASL treatment recommendations for DAA-naïve GT 1 patients treated with SOF + 1st generation NS5A inhibitor

Patients	SOF + LDV No cirrhosis	SOF + LDV with cirrhosis	SOF + DCV All patients
GT 1b TN	8-12 weeks		
GT 1b TE			
GT 1a TN	8-12 weeks		
GT 1a TE			

EASL Recommendations on treatment of hepatitis C. Available at: http://www.easl.eu/medias/cpg/HCV2016/English-report.pdf

LDV/SOF for 8 weeks in non-cirrhotic GT 1 patients



Real-world cohorts support ION-3 clinical trial data in >6000 GT 1 patients

*TN, NC, VL<6 millions
**TN, NC

Kowdley KV, et al. N Engl J Med 2014;370:1879-88; Buggisch P, et al. J Hepatol 2018, in press

EASL treatment recommendations for DAA-naïve GT 1 patients treated with SOF + 1st generation NS5A inhibitor

Patients	SOF + LDV No cirrhosis	SOF + LDV with cirrhosis	SOF + DCV
GT 1b TN	8-12 weeks	12 weeks	12 weeks
GT 1b TE	12 weeks	12 weeks	12 weeks
GT 1a TN	8-12 weeks	12 weeks	12 weeks
GT 1a TE	12 weeks with RBV* or 24 weeks	12 weeks with RBV* or 24 weeks	12 weeks with RBV* or 24 weeks

*Add RBV only in patients with RASs that high-level resistance to NSAA inhibitors at baseline if RAS testing available

EASL Recommendations on treatment of hepatitis C. Available at: http://www.easl.eu/medias/cpg/HCV2016/English-report.pdf

HEPATHER ANRS CO-22 cohort: SOF + DCV +/- RBV in G1 patients

	SOF+ DCV (n=599)		SOF+ DCV+ RBV (n=169)	
	12w	24w	12w	24w
SVR12 N % 92	146/159	415/432 96	32/34 94	132/135 98
SVR12 in cirrhotics N % 89	80/90	320/335 96	23/25 92	100/102 98
SVR12 in Non cirrhotics N % 98	62/63	95/97 98	9/9 100	32/33 97
SVR12 in treatment-naïve patients N % 88	57/65	41/47 87	3/3 100	10/11 100
SVR12 in treatment-experienced patients N % 95	89/94	374/385 97	29/31 94	122/124 98
SVR12 – HCV Genotype 1a N % 94	68/72	196/205 96	13/14 93	82/84 98
SVR12 – HCV Genotype 1b N % 89	73/82	198/205 97	17/18 94	44/45 98

Pol S, et al. J Hepatol 2017;66:39-47

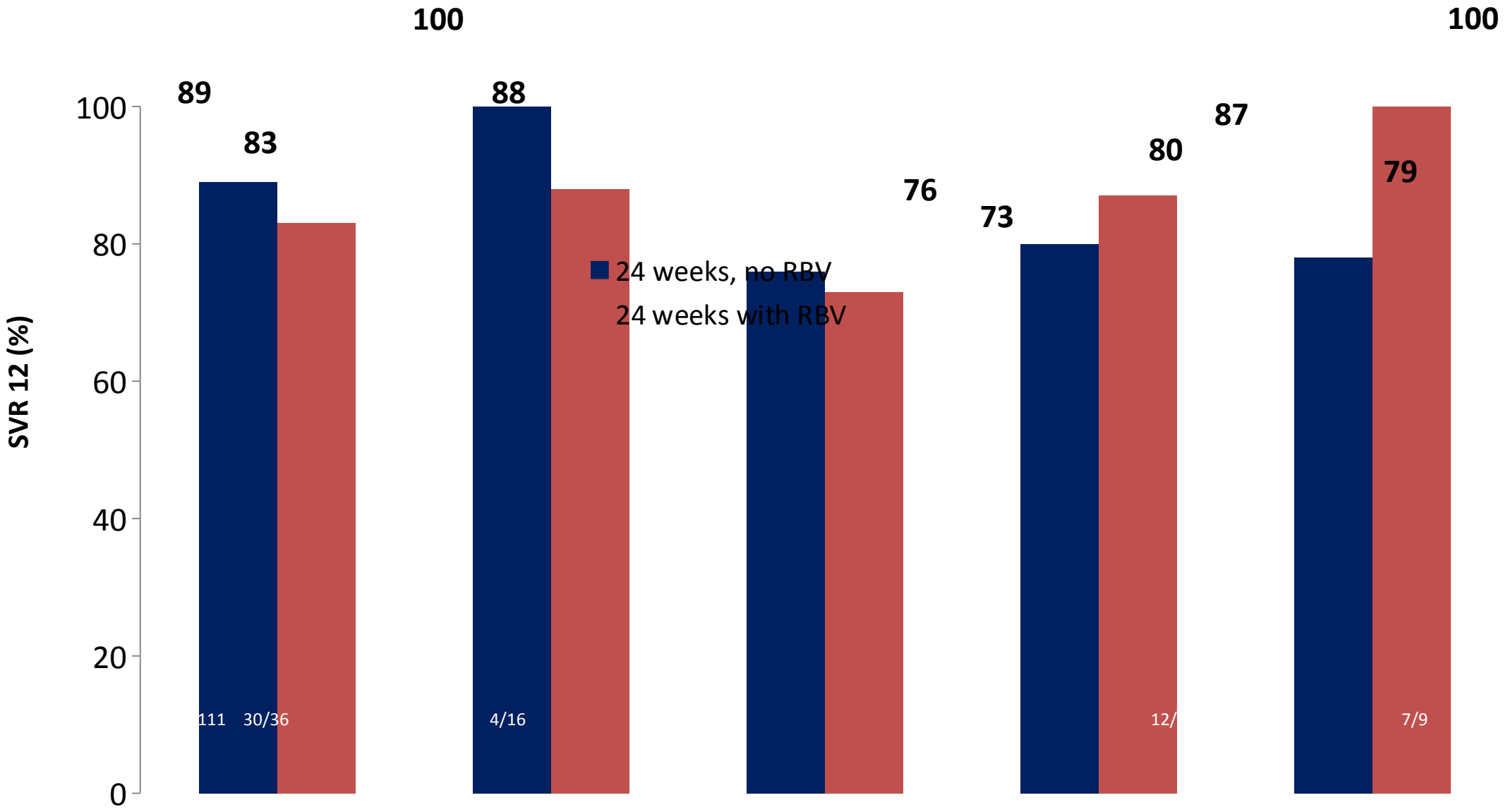
Genotype 3 patients

EASL treatment recommendations for DAA-naïve GT 3 patients

Patients	SOF + DCV	SOF + VEL
GT 3 TN No cirrhosis	12 weeks	
GT 3 TE No cirrhosis	12 weeks with RBV or 24 weeks	
All GT 3 Compensated cirrhosis	24 weeks with RBV	
All GT 3 Decompensated cirrhosis	24 weeks with RBV	

EASL Recommendations on treatment of hepatitis C. Available at: http://www.easl.eu/medias/cpg/HCV2016/English-report.pdf

SOF + DCV ± RBV for 24 weeks DAA-naïve GT 3 patients with cirrhosis included in 2 real-life cohorts



Hézode C, et al. Liver Int 2017;37:1314-24

Welzel TM, et al. Gut 2016;65:1861-70

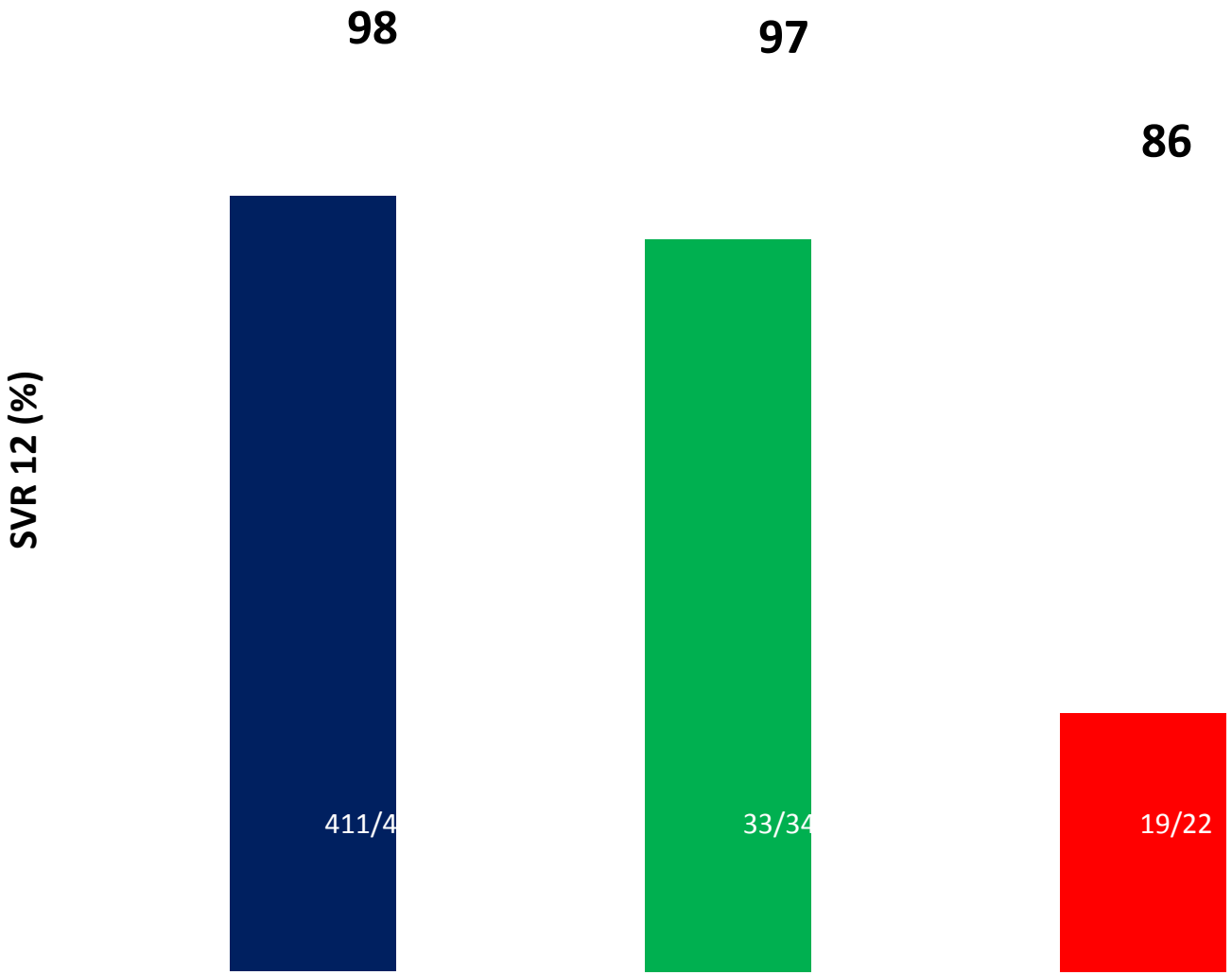
EASL treatment recommendations for DAA-naïve GT 3 patients

Patients	SOF + DCV	SOF + VEL
GT 3 TN No cirrhosis	12 weeks	12 weeks
GT 3 TE No cirrhosis	12 weeks with RBV or 24 weeks	12 weeks with RBV* or 24 weeks
All GT 3 Compensated cirrhosis	24 weeks with RBV	12 weeks with RBV* or 24 weeks
All GT 3 Decompensated cirrhosis	24 weeks with RBV	12 weeks with RBV or 24 weeks

*Add RBV only in patients with NS5A RAS Y93H at baseline if RAS testing available

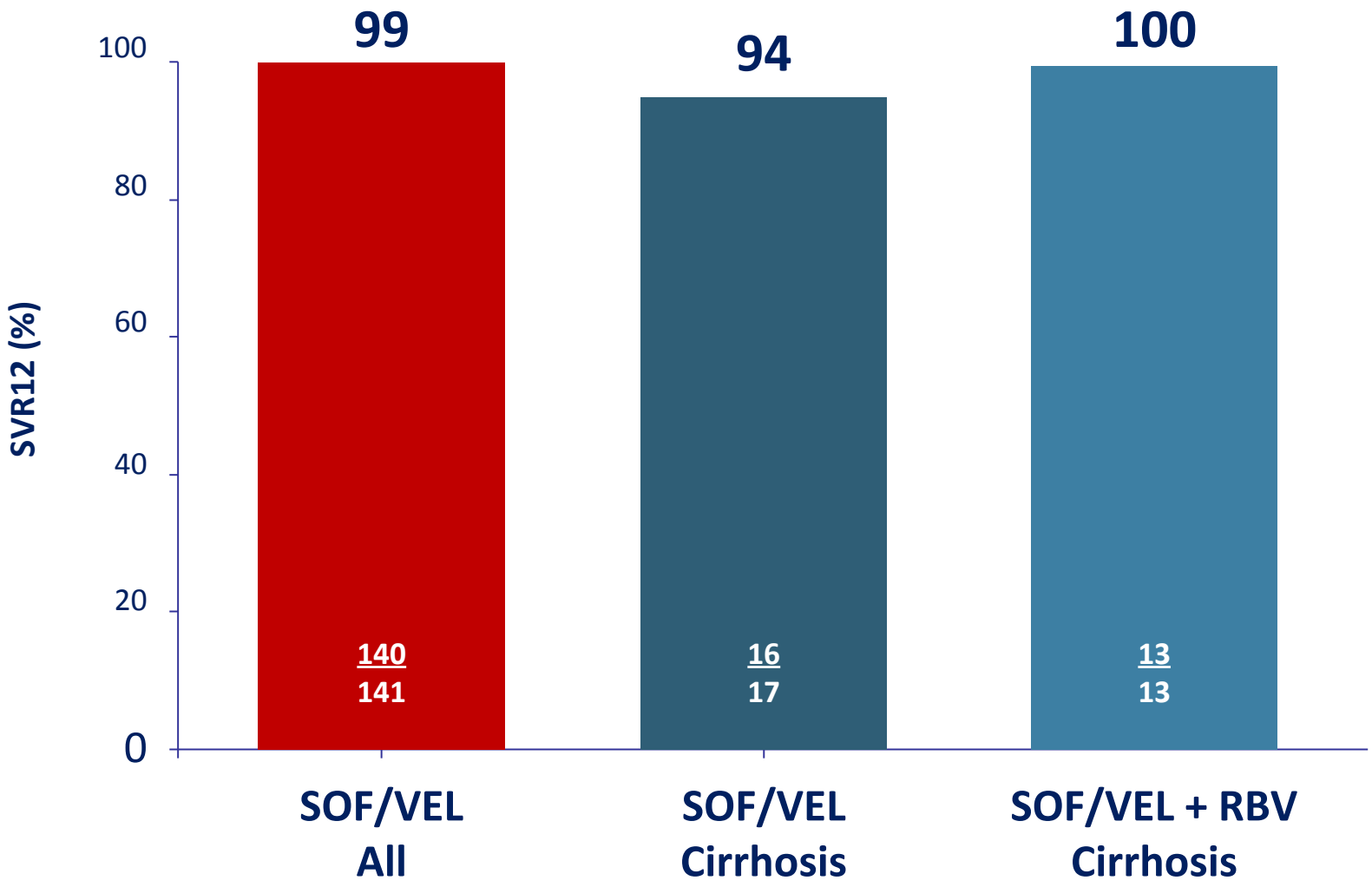
EASL Recommendations on treatment of hepatitis C. Available at: http://www.easl.eu/medias/cpg/HCV2016/English-report.pdf

Impact of NS5A RAS on efficacy of SOF + VEL for 12 weeks in DAA-naïve GT 3 patients (pooled analysis)



Hézode C, et al. J Hepatol 2017, Dec 5

GECCO Cohort: SOF + VEL in GT 3 patients with cirrhosis. With or without RBV?



Christensen S, et al. AASLD 2017, Abs. 63

Safety

Extreme bradycardia in patients receiving amiodarone and SOF/DCV

1) **<u>Cardiac asystole 30 min after receiving SOF + DCV</u>**

   Amiodarone, SOF + DCV stopped

   10 days later, normal cardiac evaluation

3) **<u>Extreme sinus node dysfunction 2 hours after receiving SOF + DCV</u>**

   Amiodarone and propranolol stopped, SOF + DCV continued for 3 days: Sinus bradycardia recorded 2 hrs after intake of SOF + DCV

   SOF + DCV stopped and no bradycardia observed

   New administration of SOF + DCV on day 13: bradycardia 2 hrs after intake

   Amiodarone stopped, rechallenge 8 weeks after and no bradycardia

Renet S, et al. Gastroenterology 2015;149:1378-80

3 cases of severe bradyarrhythmia*

	Patient 1	Patient 2	Patient 3
Liver disease	Cirrhosis Child C MELD 23	Cirrhosis Child A	Cirrhosis Child A
DAAs	SOF + DCV	SOF + SMV Followed by SOF + RBV	SOF + DCV
Other medications	Propranolol Furosemide Esomeprazole	Etanercept/Fluindione Amiodarone/Levothyroxine Bromazepam/Cholecalciferol Spironolactone/Omeprazole	Efavirenz Emtricitabine Tenofovir
Rhythm abnormality	Sinus-node dysfunction with junctional escape rhythm (ventricular rate, 30 beats/min) without resolution after discontinuation of propranolol treatment	Sinus bradycardia with syncope, with spontaneous resolution after discontinuation of antiviral treatment and recurrence during the second course	Intermittent third-degree atrioventricular block with syncope
Interval between day 1 and AE	10 days	1 day 6 days (reintroduction)	6 days
Pacemaker implantation	Yes (Day 4)	Yes (6 days after recurrence of the bradyarrhythmia)	Yes (Day 1)
Virologic response	SVR MELD 13, Child A6	SVR	SVR

*Among 415 patients treated with SOF + DCV, or SMV, or RBV

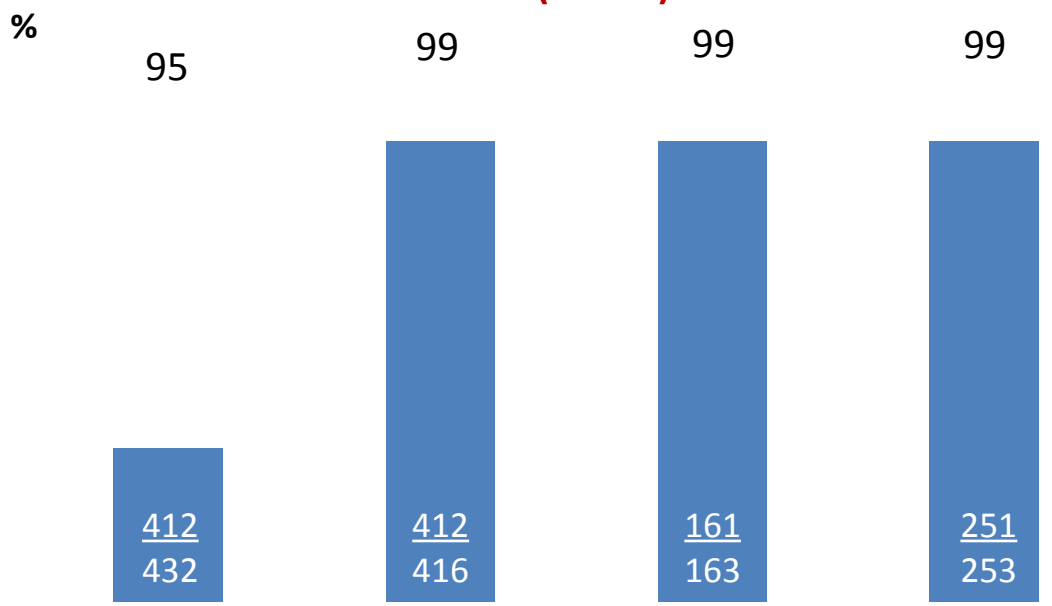
Fontaine H, et al. N Engl J Med 2015; 373:19

Real-life cohort from Israel: 3D ± RBV in GT1 patients

Patients characteristics (n=661)

Mean age (years)	60
G1b (%)	86
PR experienced (%)	62
Cirrhosis (%)	62
Cirrhosis with OV (%)	28
Platelets < 90 000 (%)	28
Albumin < 35g/l	25
Cirrhosis with MELD > 10 (%)	10

SVR12 (n=432)



Safety (n=661)

SAEs, n (%)	25 (3.8)
Early discontinuation due to AEs, n (%)	20 (3)
Death	1 (0.2)

*patients excluded from analysis due to non virologic failure

Hepatic decompensation (n=8)

Predictors (univariate) :

Age > 75

Platelets < 90 000

Albumin <35

Child-Pugh ≥ 7

MELD >10

Prior history of decompensation

Zuckerman E, et al. EASL 2016, Abs. PS004

Off-label and EASL recommended combination can be dangerous

SOF + DCV + SMV + RBV for 24 weeks → **SVR12**

Genotype	Fibrosis stage	Outcome
1a	F4 Child A5	Relapse
1a	F4 Child A6	Relapse
1a	F4 Child A6	Discontinuation SAE*
1a	F4 Child A6	SVR12
1b	F4 Child A6	Discontinuation SAE and Death*
1b	F4 Child A5	SVR12
1b	F3	SVR12
2	F4 Child A5	SVR12
4	F3	SVR12
4	F3	SVR12
6	F3	SVR12

*** SAEs: Pulmonary arterial hypertension Wk 3 (n=1) ; Multi-organ failure related to mitochondrial toxicity Wk4 (n=1)**

Hézode C, et al. Clin Inf Dis 2017;64:1615-18

Potential risk of HBV reactivation in patients with HCV-HBV coinfection

Cohort Study	Patients, n	Reactivation / Clinical reactivation
HBsAg positive patients		
Wang et al	10	3 (30%) / 3 (100%)
Calvaruso et al	4	3 (75%) / 0
Yeh et al	7	4 (57.1%) / 1 (25%)
Belperio et al	84	25 (29.8%) / 6 (24%)
Patients with occult HBV infection		
Wang et al	124	0
Calvaruso et al	37	0
Yeh et al	57	0
Sulkowski et al	103	0
Belperio et al	173	4 (2.3%) /1 (25%)
Kawagishi et al	84	5 (5.9%) / 1 (20%)

Calvaruso V et al. J Hepatol 2017;67:898-901

HBV/HCV Co-Infection: SOF + ledipasvir for 12 weeks (clinical trial)

n, %	BL HBV DNA <LLOQ n=37 (%)	BL HBV DNA ≥LLOQ n=74 (%)
Increase to ≥LLOQ	31 (84)	
+ ALT >2x ULN	0	
Increase >1 log10 IU/mL		39 (53)
+ ALT >2x ULN		5 (7)

ULN: male 43 U/L; female 34 U/L.

- SVR12 was 100% (111/111)
- 4 patients initiated therapy for HBV, including one patient with HBV reactivation since week 8 and concomitant ALT elevation > 2 x ULN at post treatment week 48 and clinical signs and symptoms associated with HBV reactivation
- No liver decompensation, liver failure or liver transplant

Liu CJ, Gastroenterology 2017, Nov 21

Summary

DAAs combinations are highly effective and well tolerated in the real-world setting and globally, data from the real-life cohorts confirm those observed in clinical trials

Large real-life cohorts validate sofosbuvir and ledipasvir for 8 weeks in treatment-naïve patients without cirrhosis

However, in some subgroups of patients it remains difficult to define optimal regimens (treatment duration, use of RBV,…) based on real-life cohorts

In real-life, the majority of HCV patients has co-morbidities and multiple medications leading to potential DDIs

Real-life cohorts are useful to highlight safety concerns