PATIENT: PD

Didier Samuel

- 56-year-old male
- HCV cirrhosis
- GT 1a

This meeting has been organised and funded by Gilead Sciences Europe Ltd

Date of preparation: December 2014
HCV1/IHQ/14-09//1340(1)p

Patient: PD, Past medical history

Non responder to previous treatment with double therapy PEG-IFN + RBV

2009

- Liver transplantation for HCV cirrhosis

2013

- Liver biopsy - Metavir Score A2F2

PEG-IFN: pegylated interferon; RBV: Ribavirine; **BOC:** Boceprevir

Patient: PD,
Treatment: 2013

PEG-IFN + RBV + BOC

Evolution during treatment

- Week 16: viral load undetectable
- Week 21: viral breakthrough

Discontinuation of triple therapy

SOF: sofosbuvir; LDV: ledipasvir; RBV: ribavirin;

Patient: PD
Treatment: May 2014

Reevaluation A2F2 (Liver biopsy)
Fibrotest: F4

SOF/LDV + RBV (24 weeks)

Immunosuppressive treatment

- Prednisone (2 mg/d)
- Tacrolimus (3 mg/d)
- Mycophenolate mofetil (1 g/d)
- Aspirin (100 mg/d)

Evolution during treatment

- Week 4: viral load 37 IU/L
- Week 8: viral load below 12 IU/L (detectable)
- Week 8: HCV RNA undetectable until the end of treatment

SOF: sofosbuvir; LDV: ledipasvir; RBV: ribavirin;

Patient: PD
Findings

End of treatment

- Hb 11.6 g; platelets 92,000/mm3, ALAT 35 IU/L; GGT 110 IU/L
- Bilirubin 10 µmol; GGT 86 IU/L; creatinine 130 µmol
- Prothrombin 100%; WBC 2,400/mm3

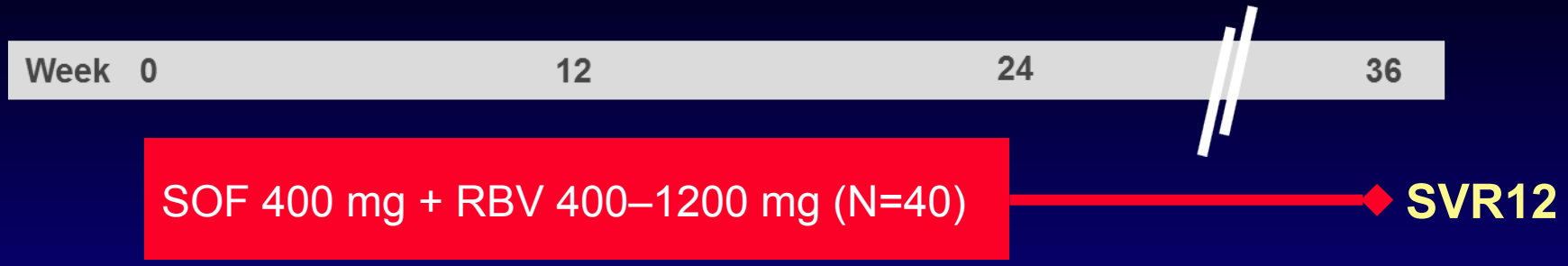
Week 12 post treatment

- SVR 12 achieved
- HCV RNA undetectable
- Hb 12.6 g; platelets 90,000; ALAT 26 IU/L

Conclusion

SVR achieved after SOF/LDV + RBV in liver transplant patient with probable cirrhosis, previously un responsive to Peg-IFN + BOC+RBV

Sofosbuvir + Ribavirin After Transplantation



- Patients with recurrent HCV post-liver transplant
  - Liver transplant ≥6 and ≤150 months prior to enrollment
  - Any HCV genotype
  - Naïve or treatment-experienced
  - CTP ≤7 and MELD ≤17
- Low, ascending-dose RBV regimen starting at 400 mg/day, escalated based on hemoglobin levels

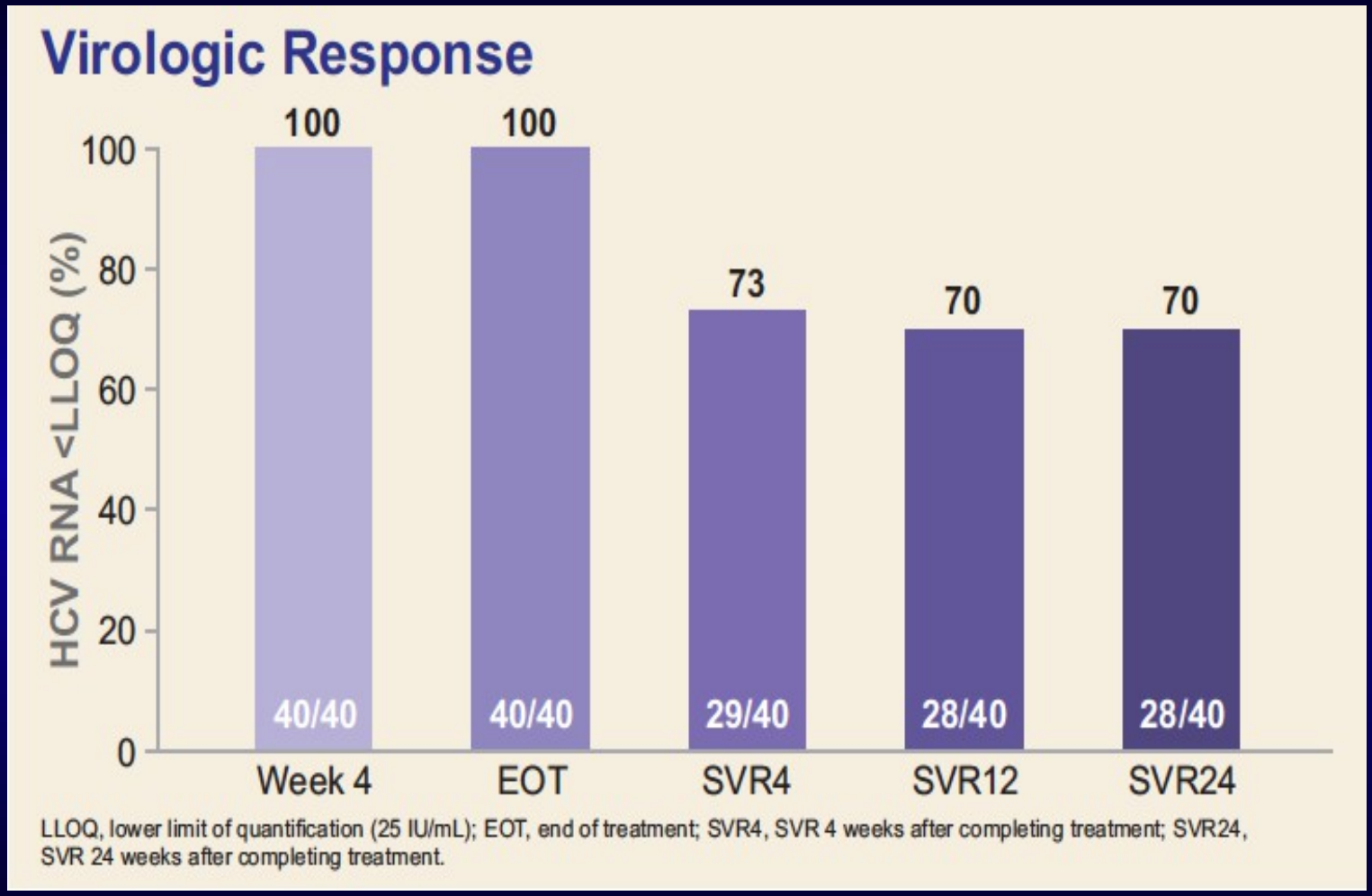
Sofosbuvir + Ribavirin After Transplantation

	SOF + RBV (N=40)
Male, n (%)	31 (78)
Median age, y (range)	59 (49-75)
White, n (%)	34 (85)
BMI <30 kg/m2, n (%)	30 (75)
Mean HCV RNA log10 IU/mL (range)	6.55 (4.49-7.59)
Genotype, n (%) 1a 1b 2 3 4	 22 (55) 11(28) 0 6 (15) 1 (3)
IL28B, n (%) CC CT TT	 13 (33) 16 (40) 11 (28)
Metavir-equivalent fibrosis stage, n (%) None or minimal (F0) Portal Fibrosis (F1-F2) Bridging Fibrosis (F3) Cirrhosis (F4)	 1 (3) 14 (35) 9 (23) 16 (40)
Prior HCV Treatment, n (%)	Yes 35 (88)
Median years since liver transplantation (range)	4.3 (1.02-10.6)

Charlton AASLD 2013

C.H.B.

Sofosbuvir + Ribavirin After Transplantation



Charlton Gastro 2015

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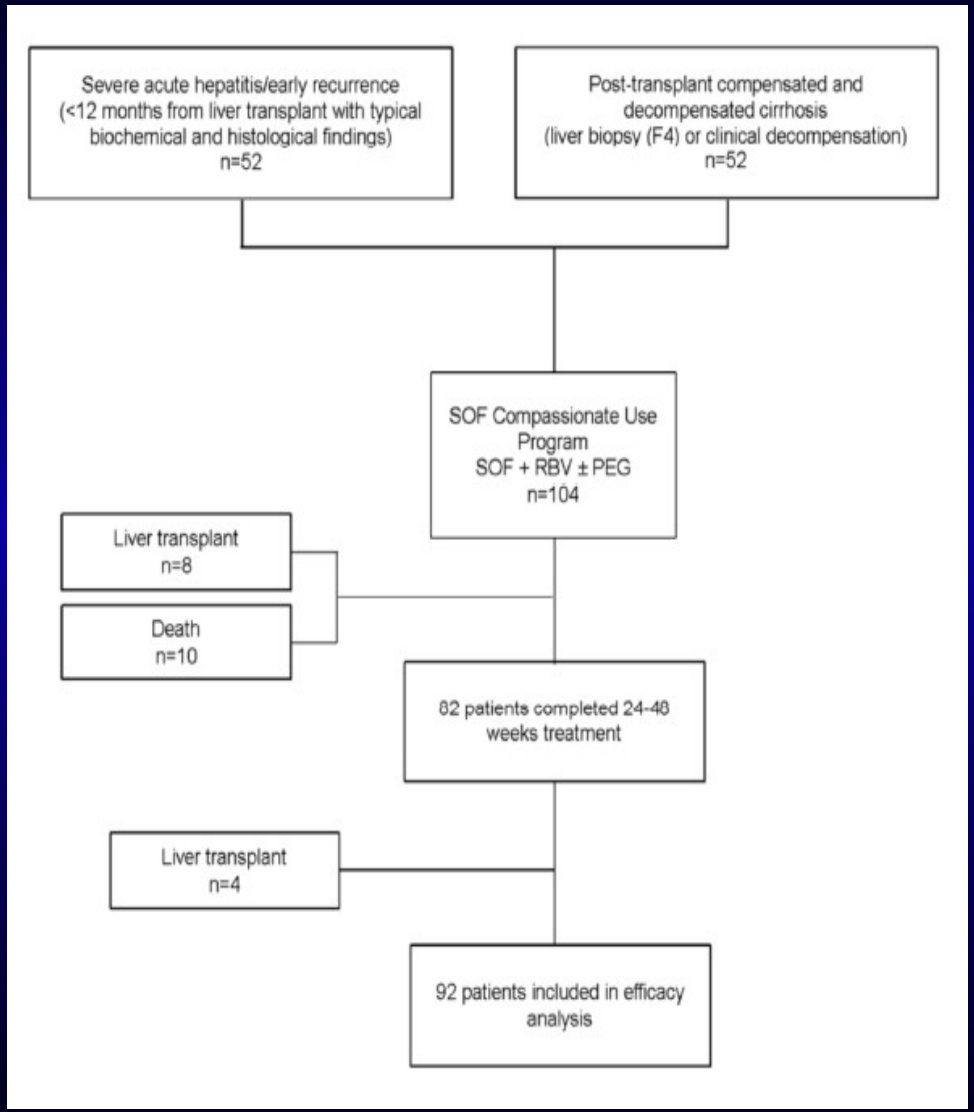
Compassionate Use Sofosbuvir + Ribavirin ± PegIFN in Liver Transplant Patients



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Compassionate Use Sofosbuvir + Ribavirin±PegIFN in Liver Transplant Patients

	Overall (N=104)	Acute hepatitis and early severe recurrence (N=52)	Compensated and decompensated cirrhosis (N=52)
Age, years (IQR)	55 (51-60)	54 (50-60)	56 (51-64)
Male, n (%)	76 (73)	39 (75)	37 (71)
Genotype, n (%)			
1a	36 (35)	22 (42)	14 (27)
1b	49 (47)	23 (44)	26 (50)
2	1 (1)	1 (2)	0
3	7 (7)	1 (2)	6 (12)
4	7 (7)	5 (10)	2 (4)
>1	4 (4)	0	4 (8)
HCV RNA, $\log_{10}$ IU/mL (IQR)	6.2 (5.3-7.0)	6.7 (5.5-7.5)	5.8 (5.1-6.4)
Months from OLT (IQR)[1]	16.8 (18-54)	8.4 (4.8-12.7)	53.1 (33.1-92.1)
Bilirubin, mg/dL median (IQR)	3.1 (1.3-9.7)	4.7 (1.5-19.2)	1.9 (1.2-4.8)
Albumin, g/dL median (IQR)	3.1 (2.7-3.5)	3.1 (2.6-3.6)	3.1 (2.7-3.5)
INR median (IQR)	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.4 (1.2-1.6)
Platelet count $\times 10^3$/mL median (IQR)	75 (52-119)	91 (59.3-134.5)	69 (50.3-99.3)
ALT, U/L median (IQR)	71.0 (39.3-167.0)	102.0 (38.5-200.8)	60.0 (39.5-101.3)
AST, U/L median (IQR)	124.5 (70.8-210.5)	145.5 (93.5-339)	101.0 (62.3-180.0)
ALP, U/L median (IQR)	164.0 (117.5-263.3)	190.0 (124.5)	148.0 (362.5)
GGT, U/L median (IQR)	144.0 (64.0-426.5)	383.0 (121.0-915.5)	112.7 (45-148.0)
Hemoglobin, g/dL median (IQR)	10.9 (9.6-12.5)	10.9 (9.4-12.2)	11.0 (9.8-12.9)
Creatinine, mg/dL median (IQR)	1.1 (0.9-1.4)	1.1 (0.9-1.4)	1.2 (0.9-1.4)
CPT (IQR)	8 (7-10)	N/A	8.0 (7-10)
MELD (IQR)	15 (11-21)	16 (10-22)	14 (11-19)
Antiviral regimens used			
SOF + RBV alone, n/N (%)	80/104 (77)	36/52 (69)	44/52 (85)
SOF + RBV + PEG, n/N (%)	24/104 (23)	16/52 (31)	8/52 (15)

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Compassionate Use Sofosbuvir + Ribavirin ± PegIFN in Transplant Patients: Virologic Response

Table 2. Response (HCV RNA <25 IU/mL) during and after treatment

	Overall (N=104)	Acute hepatitis and early severe recurrence (N=52)	Compensated and decompensated cirrhosis (N=52)
During treatment, % (n/n) %*			
At week 4	56/104 (54%)	24/52 (46%)	33/51 (65%)
At week 12	82/104 (79%)	42/50 (84%)	40/49 (82%)
At week 24	76/96 (73%)	38/48 (79%)	38/47 (81%)
In post-treatment follow-up, n (%)			
At week 4 (SVR4)	62/93 (67%)	38/48 (79%)	24/46 (52%)
At week 12 (SVR12)	54/92† (59%)	35/48† (73%)	19/44† (43%)
Virologic failure			
On-treatment failure	0	0	0
Relapse	19/92 (21%)	4/48 (8%)	15/44 (34%)
Lost to follow-up	2/92 (2%)	2/48 (4%)	0
Discontinuation due to SAE	3/92 (3%)	1/48 (2%)	2/44 (5%)
Discontinuation due to non-adherence	1/92 (1%)	0	1/44 (2%)
Death	13/92 (14%)	6/48 (13%)	7/44 (16%)

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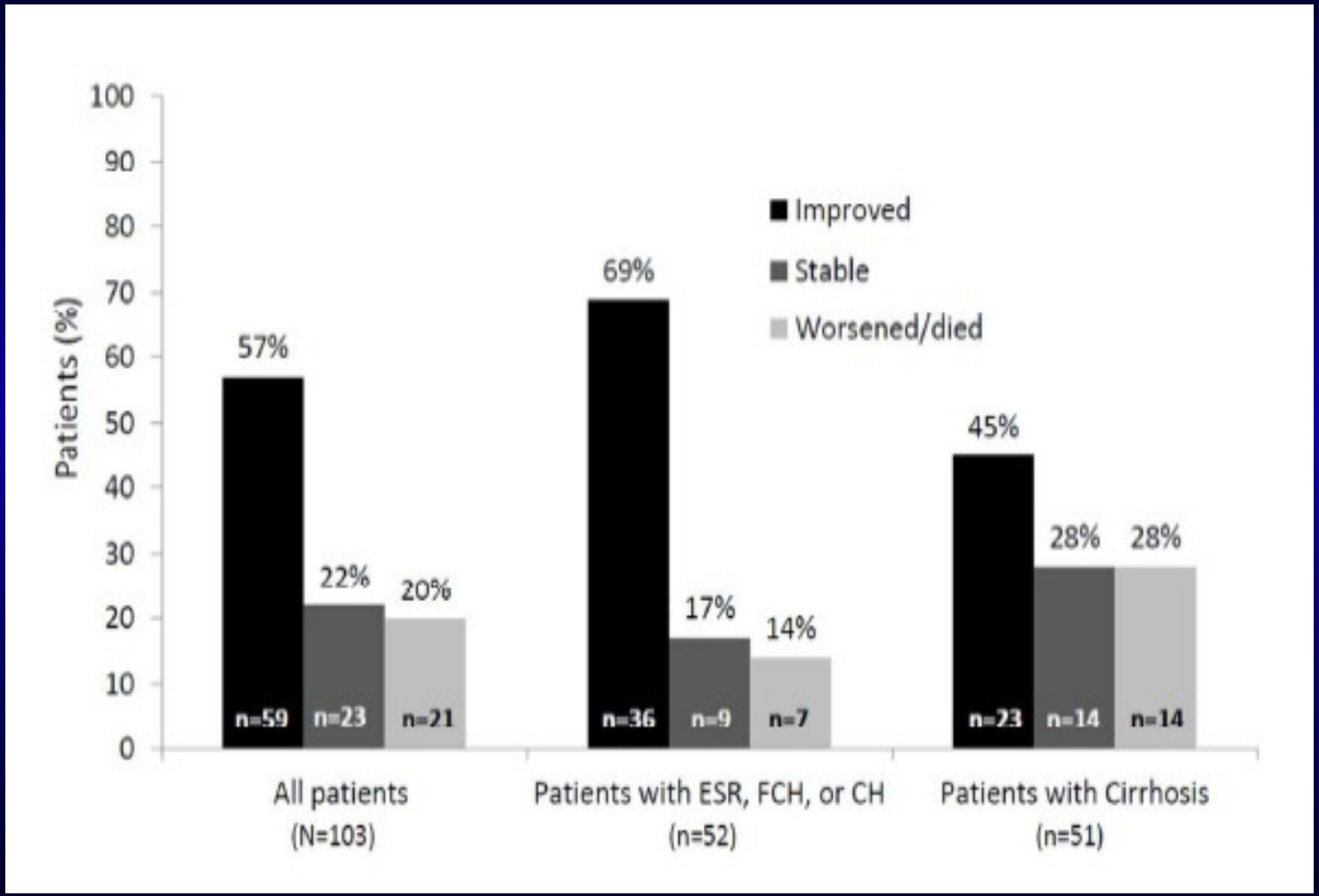
Compassionate Use Sofosbuvir + Ribavirin ± PegIFN in Transplant Patients: Virologic Response: Clinical Outcome



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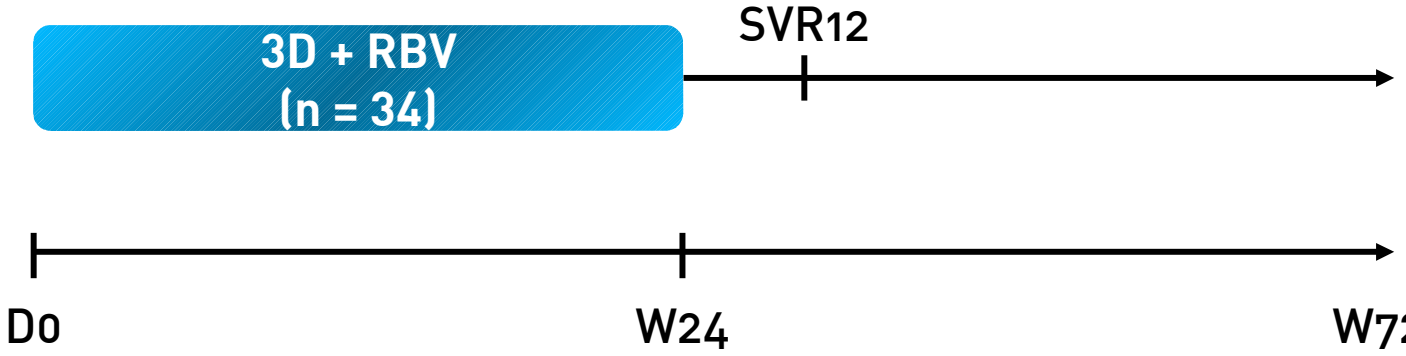
ABT450/Ritonavir/Ombitasvir + Dasabuvir + RBV in LT Recipients with Recurrent HCV GT 1

- Phase II Study on efficacy and tolerance of ABT-450/r/ombitasvir 150 mg/100m g/25 mg/d + dasabuvir 250 mg x 2/d in patients with HCV reinfection post-LT
- Patients G1, fibrosis ↙ F2 at Liver biopsy, no prior PEG/RBV after LT
- Dosing RBV free for the investigator
- CNI adaptation
  - Tacrolimus 0.5 mg/week or 0.2 mg/3 days
  - Ciclosporine 1/5 of initial daily dosing once a day



Kwo P, Etats-Unis, EASL 2014, Abs. 0114 actualise

ABT450/Ritonavir/Ombitasvir + Dasabuvir + RBV in LT Recipients with Recurrent HCV GT 1

Table 2. Response during and after Treatment.

Outcome	Patients with Outcome	
	no.	*% (95% CI)*
HCV RNA <25 IU/ml		
During treatment period		
At wk 4	34	100 (90–100)
At wk 24	34	100 (90–100)
After end of treatment		
At wk 4	33	97 (85–100)
At wk 12	33	97 (85–100)
At wk 24	33	97 (85–100)
Virologic failure during treatment	0	0 (0–10)
Relapse*	1	3 (0–15)

P Kwo NEJM 2015

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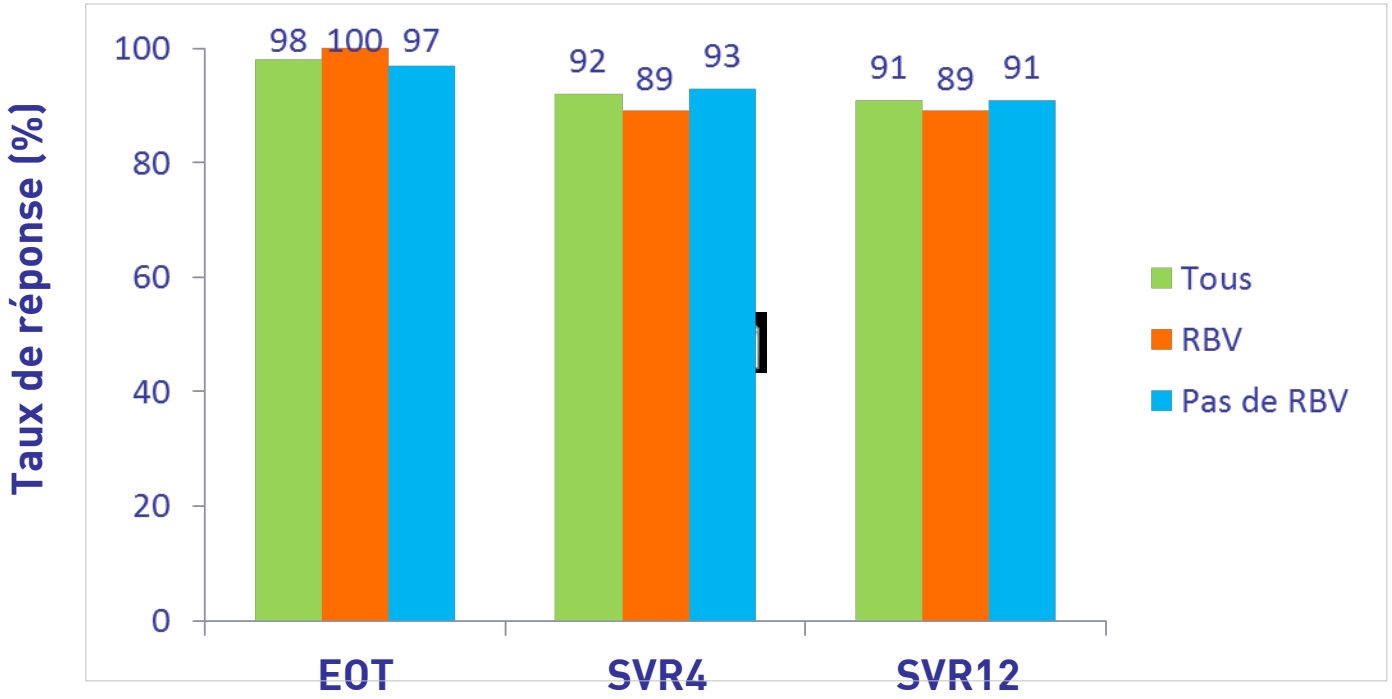
Sofosbuvir/Simeprévir ± RBV 12 weeks for HCV Recurrence Post-Transplantation

- Multicenter study, 109 transplant patients with histologically proven recurrent HCV.
- Delay post-LT : 29 months (median). Median FU : 23 weeks
- Cholestatic recurrence: 11 % ; METAVIR F3-F4 : 29 %

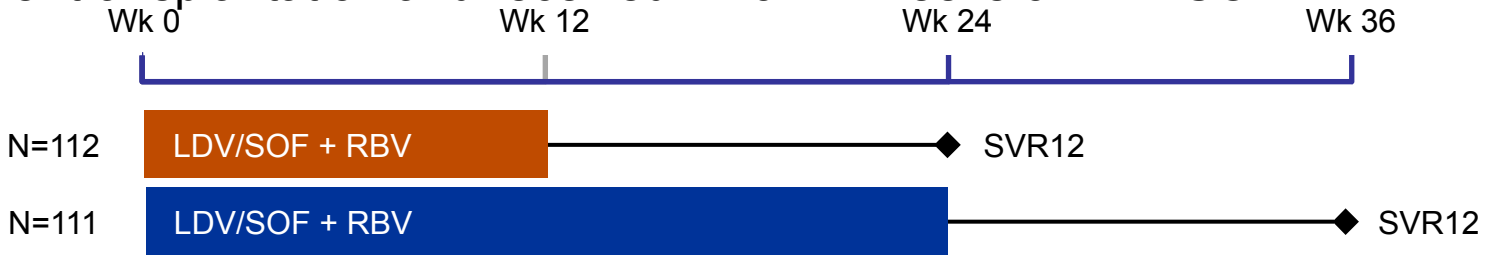
Virologic Response ITT



Pungpapong S, Etats-Unis, AASLD 2014, Abs. 9 actualis

LDV/SOF + RBV for treatment of HCV in patients with post-transplant recurrence

Prospective, multicentre study in TN and TE GT 1 and 4 patients, who were post-liver transplantation and received 12 or 24 weeks of LDV/SOF + RBV



223 patients randomised 1:1 to 12 or 24 weeks of treatment

- ↘3 months from liver transplant
- No hepatocellular carcinoma

Stratified at screening: F0–F3, CTP A, B, C

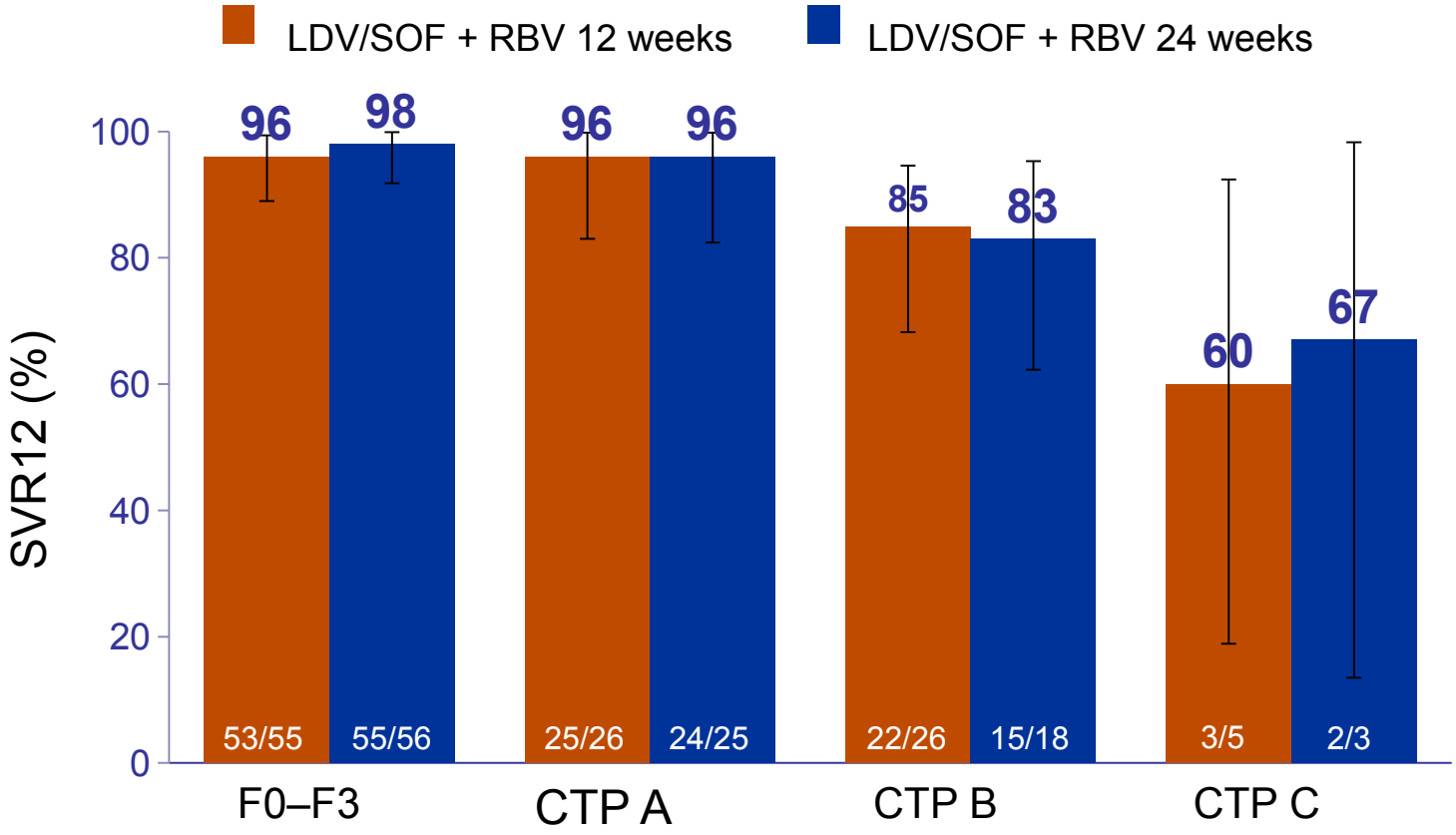
Broad inclusion criteria:

- Total bilirubin ↙10 mg/dL, Hb ↘10 g/dL
- CrCl ↘40 mL/min, platelets ↑ 30,000

RBV dosing

- F0–F3 and CTP A cirrhosis: weight-based (↓75 kg = 1000 mg; ↘75 kg = 1200 mg)
- CTP B and C cirrhosis: dose escalation, 600–1200 mg/d

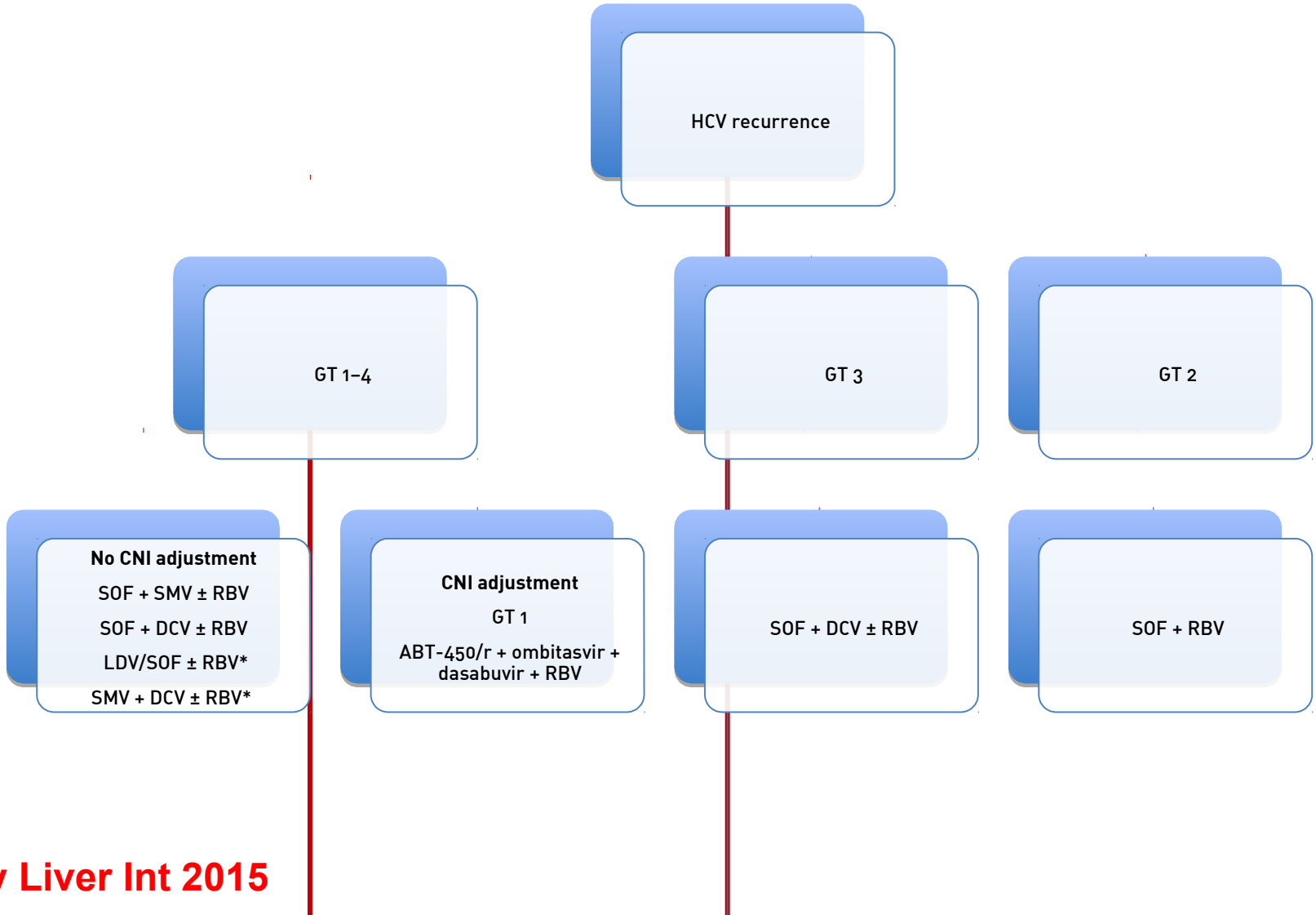
LDV/SOF + RBV in Post-Transplant Recurrence



SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

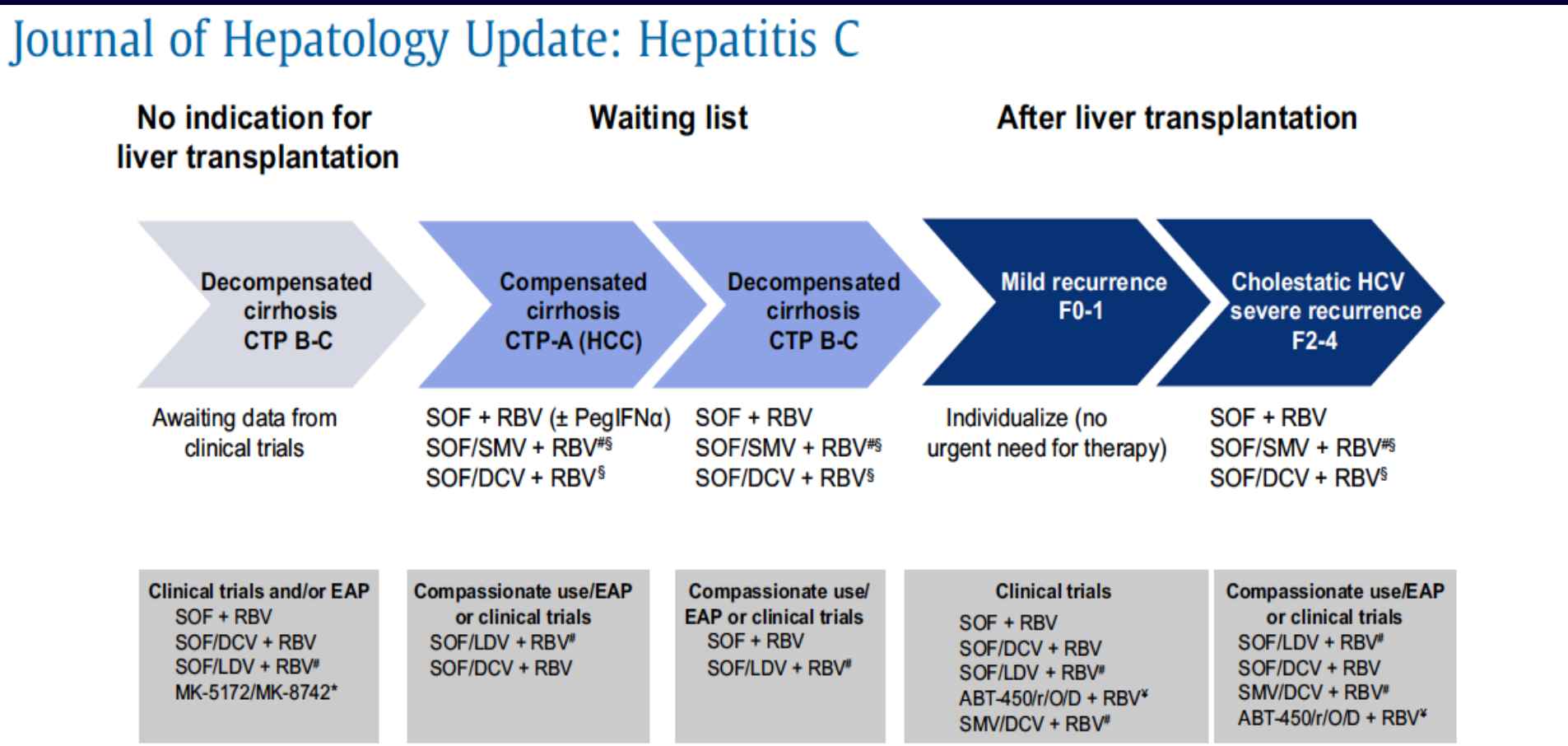
LDV/SOF + RBV for 12 weeks is not an EMA-recommended treatment regimen;
Reddy KR, et al. AASLD 2014, Oral #8. 90% exact confidence intervals

Figure 2: Alternative strategies to treat HCV recurrence after liver transplantation in 2014-2015



A Coilly Liver Int 2015

Management of Cirrhotic and Transplant Patients with DAA



Gamballi J Hepatol 2014

C.H.B.