Renal Failure

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Epidemiology of HCV in Patients on Hemodialysis

- In US, estimated HCV prevalence of 8% , in France 14% and in Spain 22%
- Overall, HCV prevalence 5X greater in HD patients than in general population
- Risk factors for HCV infection among hemodialysis patients:
  - Number of years on dialysis
  - Number of blood product transfusions
  - Injection drug use
  - History of organ transplantation

Finelli L, et al. Semi Dial. 2005;18:52-61.

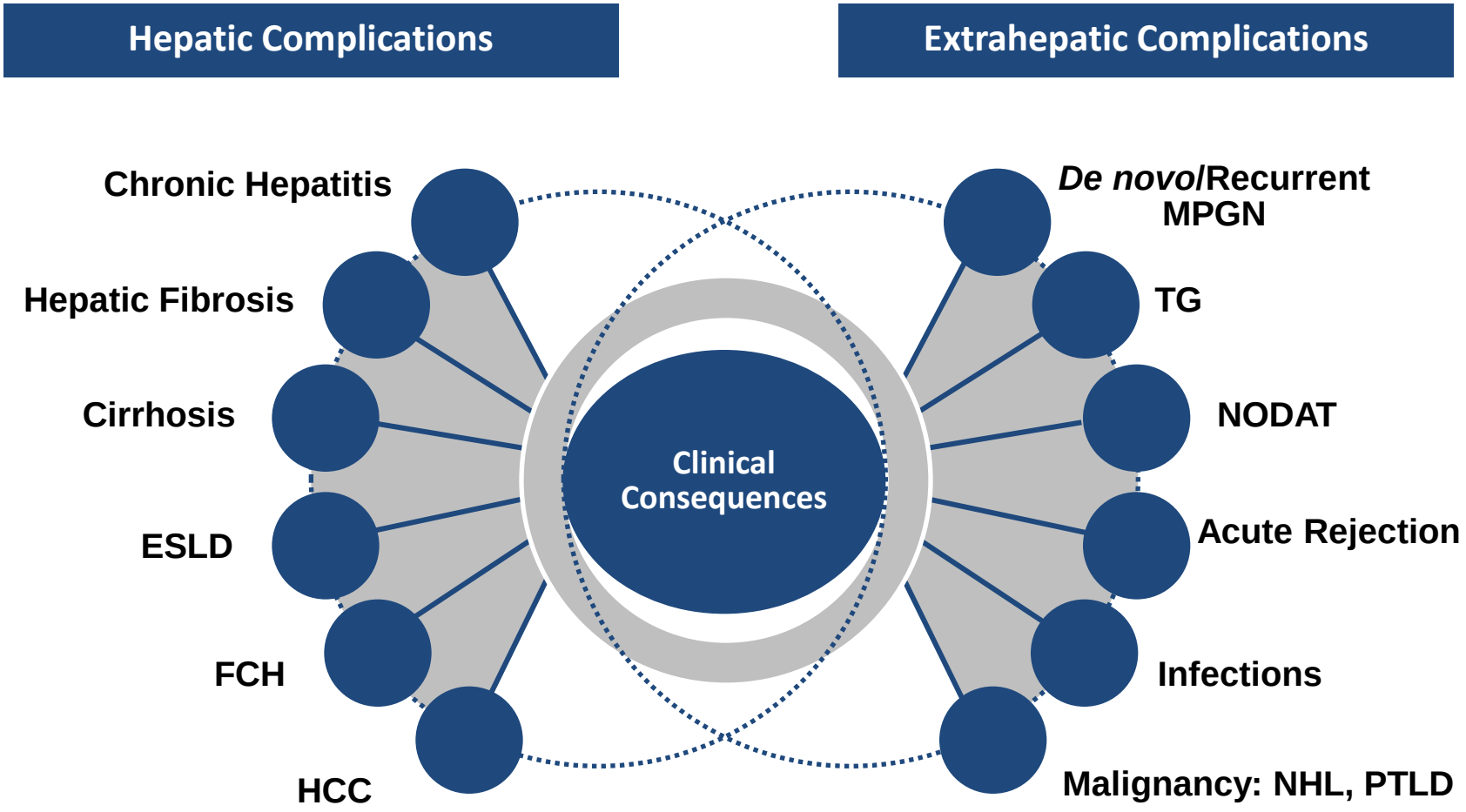
Natural History of HCV Infection in Hemodialysis Patients

Impact of Hepatitis C Infection on Hemodialysis Patients:

- Increased overall risk of mortality
- Increased risk of cirrhosis
- Increased incidence of hepatocellular cancer

Fabrizi F, et al. J Viral Hepat. 2007;14:697-703.

Clinical Consequences of HCV Infection After Kidney Transplantation



Hepatitis C Virus Infection and Kidney Transplantation in 2014
What's New?
S. Baid-Agrawal; M. Pascual; D. Moradpour; R. Somasundaram; M. Muche
American Journal of Transplantation. 2014;14(10):2206-2220.

HCV therapy in Chronic Kidney Disease

- Interferon based regimens poorly tolerated and limited efficacy
- Interferon implicated in renal graft loss
- Ribavirin induced anemia in CKD and limits its use

Stages of Chronic Kidney Disease

CKD Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney Damage with Normal or ↑ GFR	≥90
2	Kidney Damage with Mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney Failure	<15 (or dialysis)

NKF KDOQI Clinical Practice Guidelines for Chronic Kidney Disease

Dosing Considerations: Patients with Renal Impairment

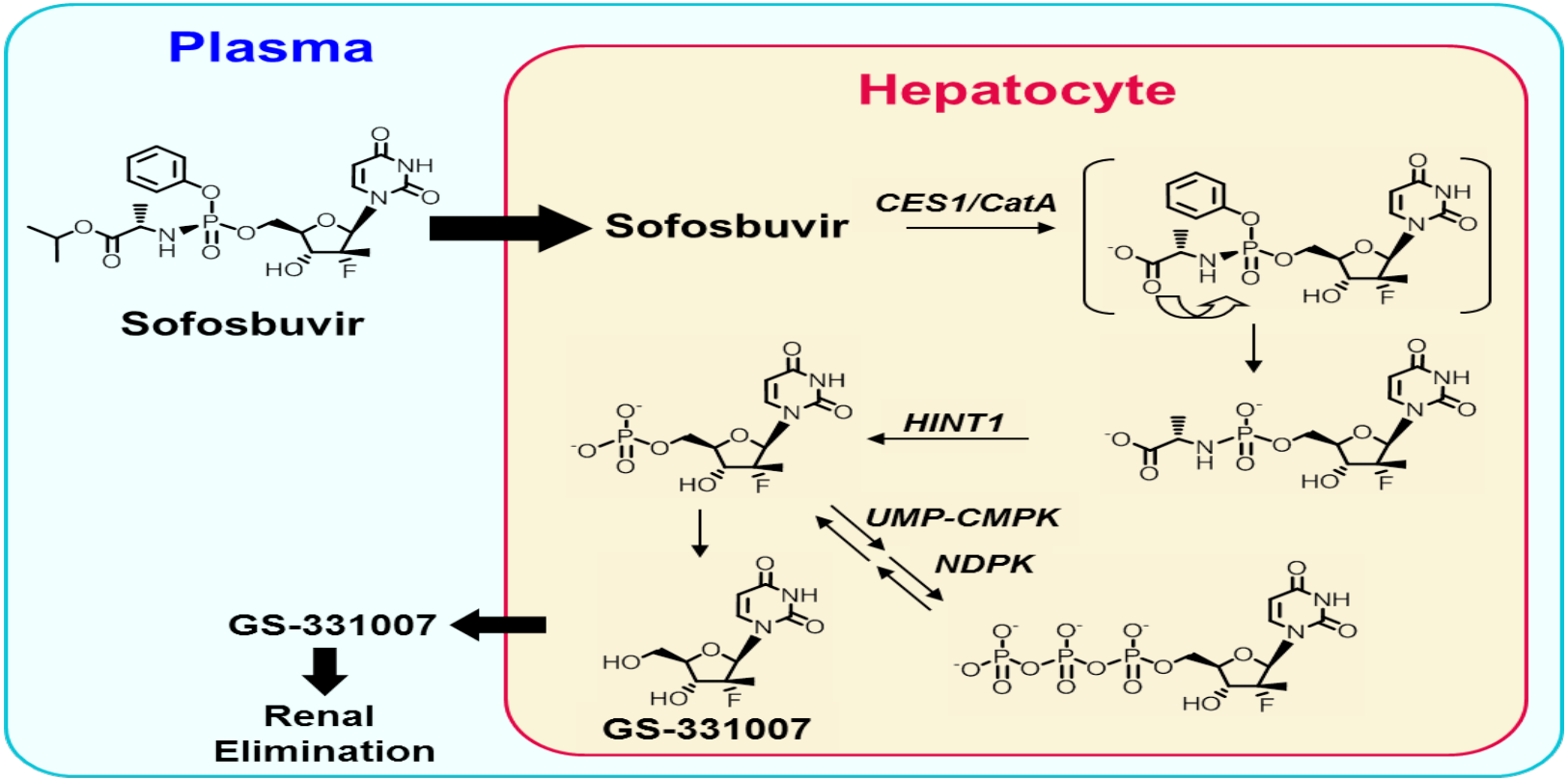
eGFR/CrCl	OMV/PTV/RTV + DSV	LDV/SOF	SMV + SOF, DCV + SOF	RBV	GZR/EBR
30-50 mL/min	No adjustment needed	No adjustment needed	No adjustment needed	Alternating 200 mg and 400 mg every other day	No adjustment needed
15-30 mL/min	**No adjustment needed**	Safety and efficacy not established	**No adjustment needed for SMV or DCV;** Safety and efficacy of SOF not established	200 mg/day	No adjustment needed
<15 mL/min or hemodialysis	Safety and efficacy not established	Safety and efficacy not established	Safety and efficacy not established	200 mg/day	No adjustment needed

In noncirrhotic pts for whom tx is urgent and renal transplant not an immediate option:

Recommended Recommended if RBV intolerant/ineligible, in consultation with expert

OMV/PTV/RTV + DSV [package insert]; LDV/SOF [package insert]; AASLD/IDSA/IAS-USA. Recommendations for testing, managing, and treating hepatitis C; DCV [package insert]; RBV [package insert]; AASLD/IDSA. HCV guidelines; Roth D, et al. Lancet 2015 (C-SURFER Study).

Sofosbuvir Metabolism



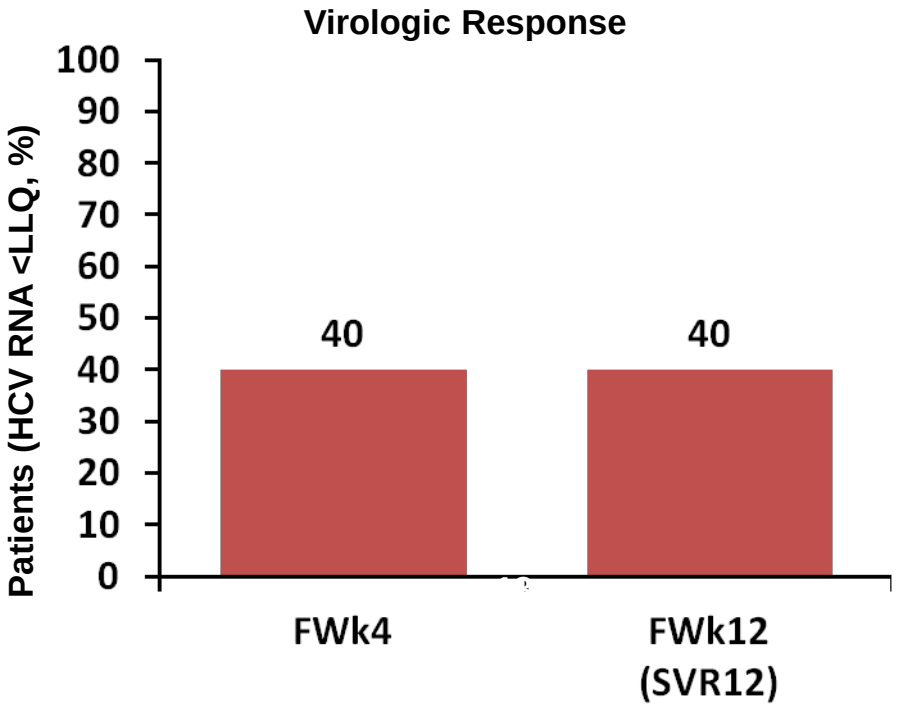
After 400 mg of oral Sofosbuvir, the systemic exposure of SOF and GS-331007 are ~4% y >90% respectively

Herbst DA. Expert Opin Invest Drugs 2013;22:527–36; Kirby B, et al. AASLD 2013. Washington, DC. #1106 .

SOFOSBUVIR 200mg +RBV 200 mg x 24 weeks in GT 1 and GT3, non-cirrhosis and GFR < 30 mL/min

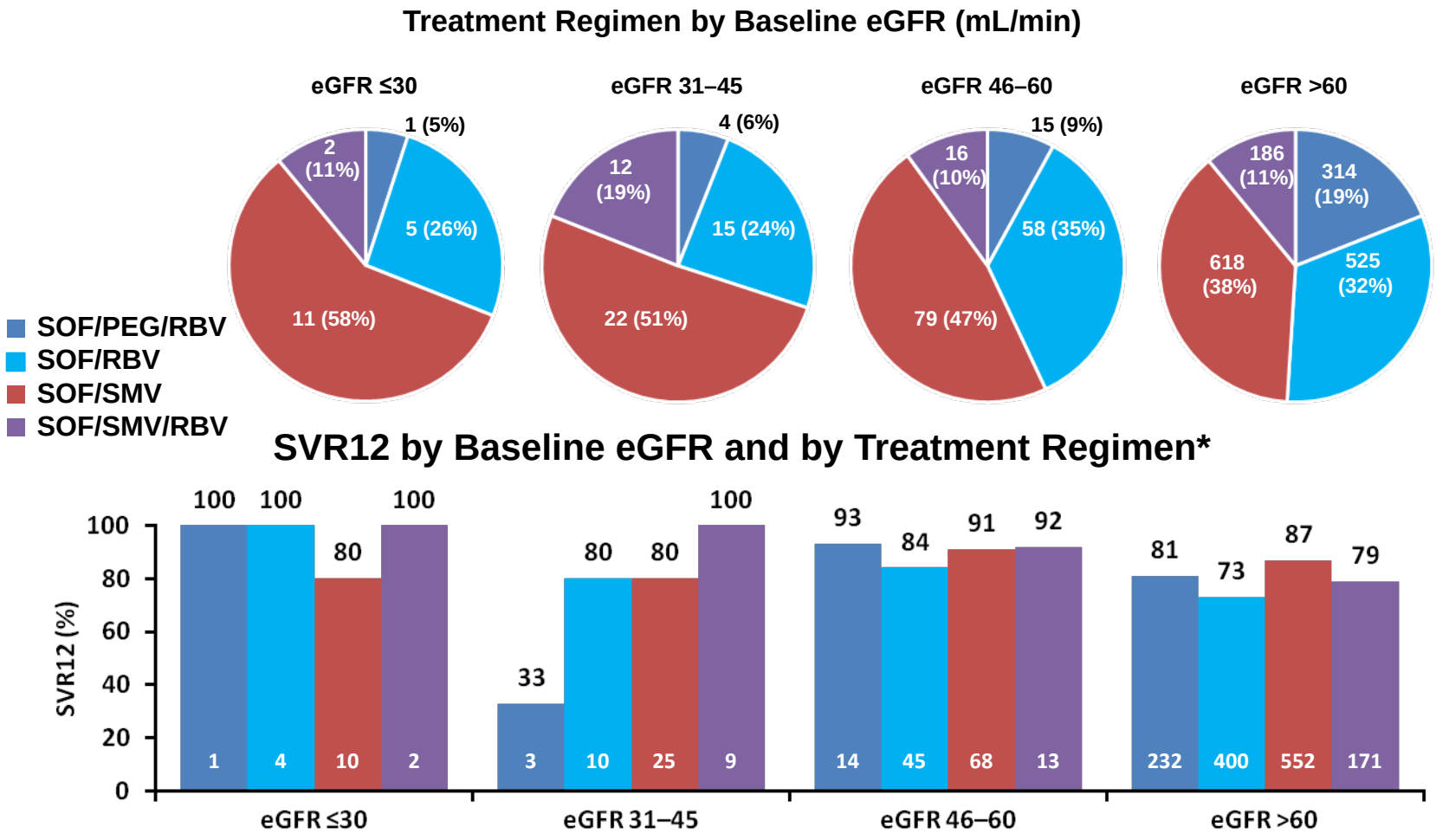
Side Effects

	SOF+ RBV N=10
Adverse Events	10
Grade 3 AEs	2
SAE	2
Anemia	
Hemoglobin, < 10 g/dL	7
Hemoglobin, < 8.5g/dL	4
RBV Dose reduction	5
Epoetin Use	6



Gane E et al. AASLD 2014

HCV-TARGET: Safety and Efficacy of SOF-Containing Regimens in Patients with Reduced Renal Function



*Among patients with known outcome

Saxena V, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Abstract LP08.

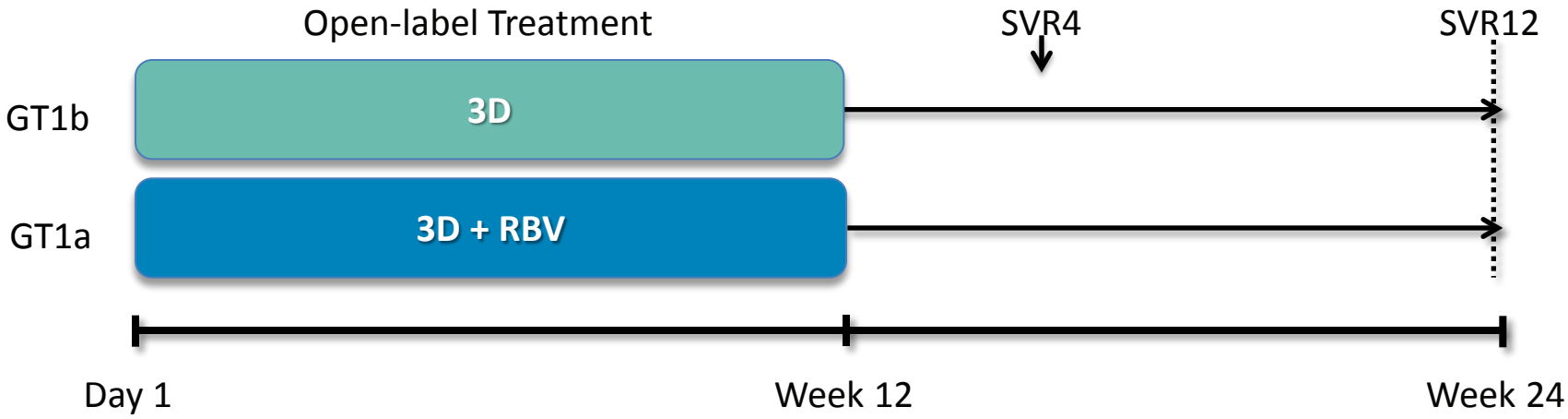
HCV-TARGET: Safety Outcomes by Baseline eGFR

Dichotomous = n (%) Continuous = mean (range)	eGFR ≤30 n=17	eGFR 31–45 n=56	eGFR 46–60 n=157	eGFR >60 n=1559
Common AEs				
Fatigue	3 (18)	19 (34)	56 (36)	543 (35)
Headache	1 (6)	9 (16)	19 (12)	274 (18)
Nausea	3 (18)	8 (14)	33 (21)	247 (16)
Anemia AE	6 (35)	16 (29)	37 (24)	246 (16)
Required transfusion(s)	2 (12)	5 (9)	3 (2)	31 (2)
Erythropoietin start on treatment	1 (6)	8 (14)	14 (9)	50 (3)
RBV				
Reduction in RBV due to anemia	3 (38)	8 (30)	33 (42)	185 (19)
RBV discontinuation	0 (0)	4 (15)	1 (1)	12 (1)
Worsening renal function	5 (29)	6 (11)	4 (3)	14 (1)
Renal or urinary system AEs	5 (29)	6 (11)	13 (8)	84 (5)
Any serious AEs	3 (18)	13 (23)	8 (5)	100 (6)
Cardiac serious AEs	1 (6)	2 (4)	8 (5)	53 (3)
Early treatment discontinuation	1 (6)	4 (6)	6 (4)	68 (4)
Early treatment discontinuation AE	1 (6)	2 (3)	4 (2)	39 (3)
Death	1 (6)	0 (0)	2 (1)	10 (1)

- High rates of SVR independent of baseline renal function
- In patients with eGFR <30 worsening renal function
- More anemia and more monitoring with SOF-containing regimen
- Does not validate safety of DAA utilization

Saxena V, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Abstract LP08.

3D FOR TREATING HCV GT1 INFECTION IN PATIENTS WITH SEVERE RENAL IMPAIRMENT OR END-STAGE RENAL DISEASE: THE RUBY-I STUDY



- Treatment-naïve adults
- Chronic kidney disease with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m

Pockros et al EASL, 2015

RUBY-I: Safety of OMB/PTV/RTV + DSV for GT1 Patients with Severe Renal Impairment or ESRD

Baseline Characteristics

	3D ± RBV N=20
Male, n (%)	17 (85)
Black, n (%)	14 (70)
Age, years; median (range)	60 (49–69)
Hispanic or Latino ethnicity, n (%)	3 (15)
Degree of fibrosis, n (%)	
F0–F1	10 (50)
F2	6 (30)
F3	4 (20)
HCV VL, $\log_{10}$ (IU/mL); median (range)	6.6 (5.5–7.6)
G1a, n (%)	13 (65)
Hemoglobin, g/dL; mean (SD)	12.6 (1.8)
CKD stage, n (%)	
4 (eGFR 15–30 mL/min/1.73 m^2)	7 (35)
5 (eGFR <15 mL/min/1.73 m^2 or dialysis)	13 (65)
On dialysis, n (%)	13 (65)
eGFR, mL/min/1.73 m^2; median (range)	10.9 (5.4–29.9)
Creatinine, mg/dL; median (range)	6.2 (2.2–10.8)

1. patient died

Pockros P, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Abstract LO1.
Pockros P et al. AASLD 2015

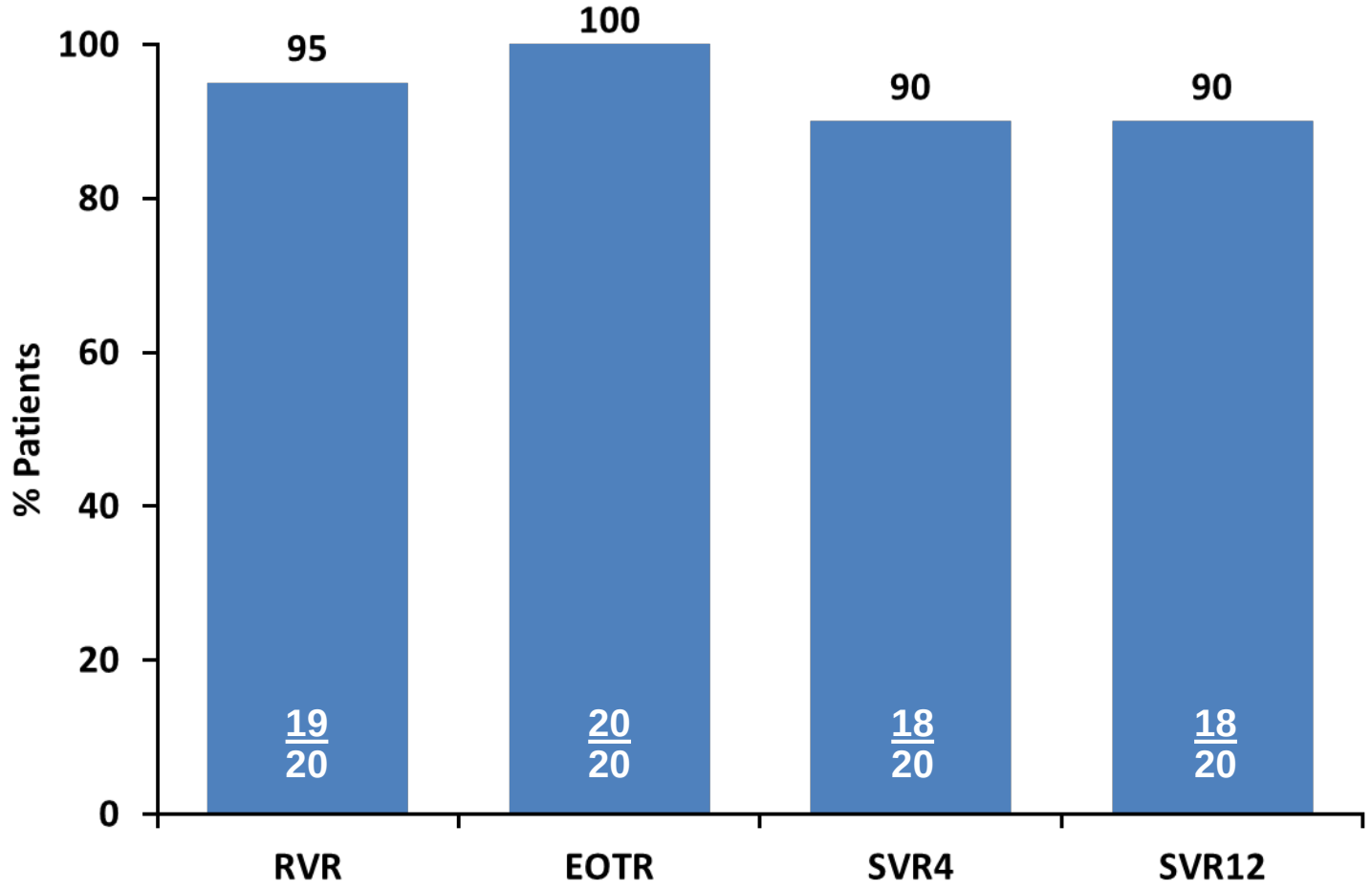
Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 & Renal Disease RUBY-I: SVR (ITT)

Drug Dosing

Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

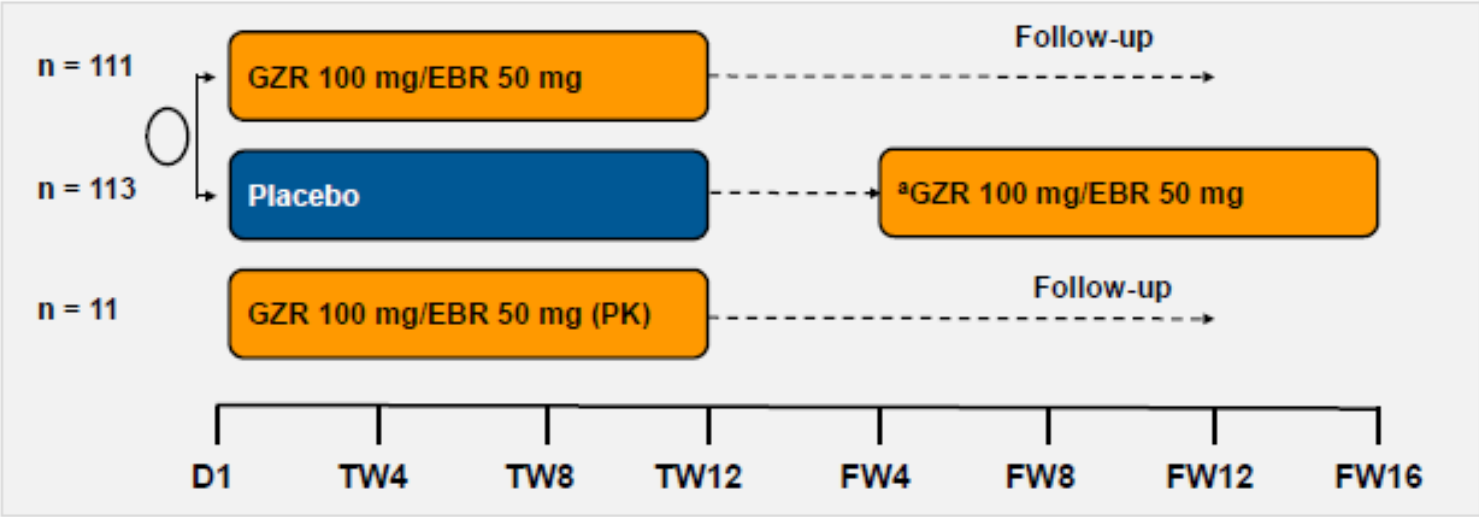
Ribavirin for patients not on hemodialysis: 200 mg once daily

Ribavirin for patients on hemodialysis: 200 mg given 4 hours before each hemodialysis session



Pockros P, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. 1039.

C-SURFER: GRAZOPREVIR PLUS ELBASVIR IN G1 TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS AND CHRONIC KIDNEY DISEASE



Key inclusion/exclusion criteria

- HCV GT1 infection, treatment-naive and treatment-experienced patients (including cirrhosis)
- CKD stage 4/5 (± hemodialysis dependence)
  - CKD stage 4 : eGFR 15-29 mL/min/1·73 m2
  - CKD stage 5: eGFR <15 mL/min/1·73 m2 or on dialysis.
  - target 20% non-hemodialysis patients

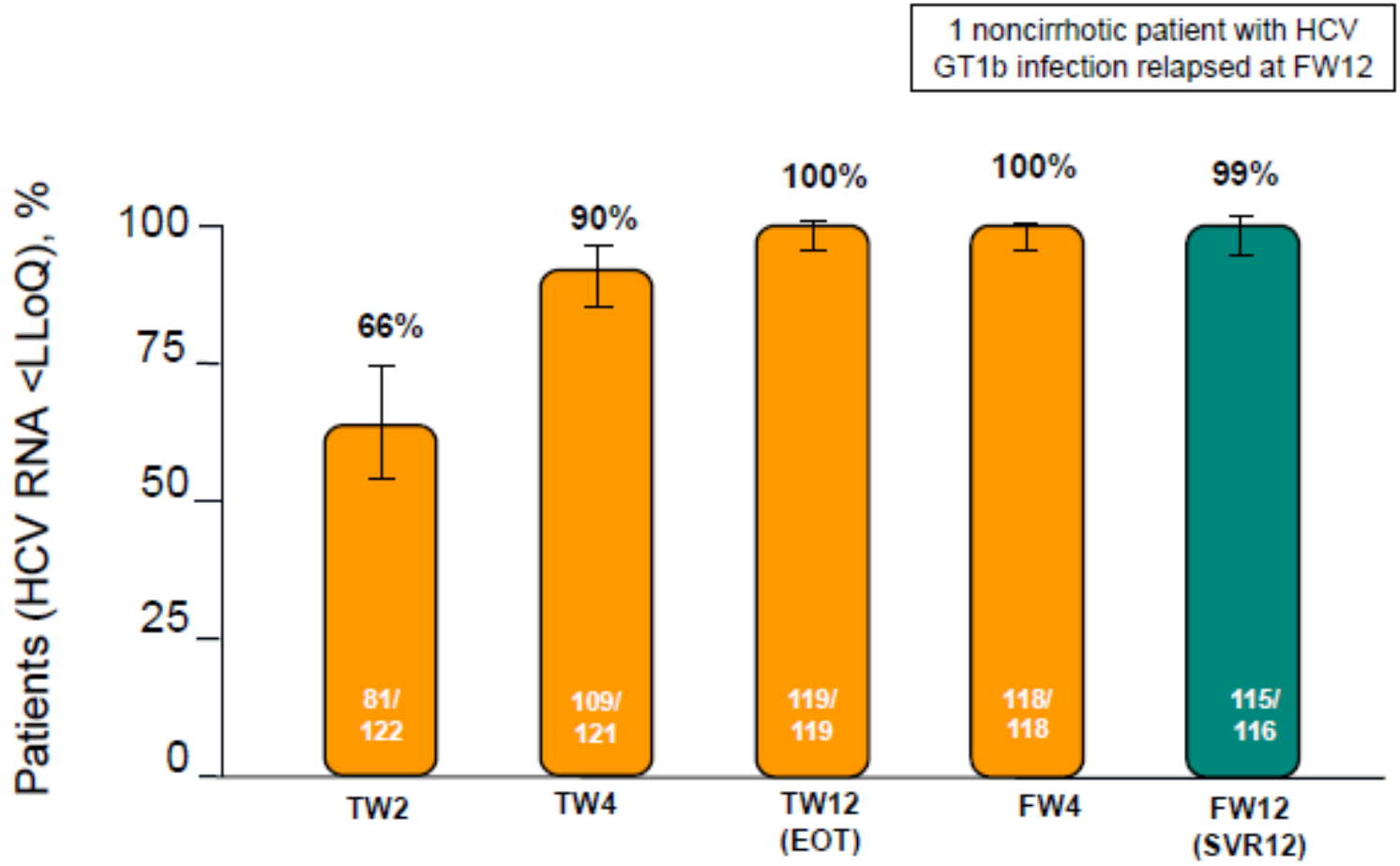
Roth et al. Lancet 2015

Demographics

Demographics	GZR + EBR (ITG + PK) 12 weeks (n = 122)	Placebo (DTG) 12 weeks (n = 113)
HCV genotype, n (%)		
G1a	63 (52)	59 (52)
G1b	58 (48)	53 (47)
G1 other	1 (<1)	1 (<1)
Treatment history, n (%)		
Naive	101 (83)	88 (78)
Experienced	21 (17)	25 (22)
Cirrhosis, n (%)	7 (6)	7 (6)
Diabetes, n (%)	44 (36)	36 (32)
Dialysis, n (%)	92 (75)	87 (77)
CKD stage, n (%)		
4	22 (18)	22 (19)
5	100 (82)	91(81)

Roth et al . Lancet , 2015

Figure 3. On-treatment virologic response[a] (ITG).



[a]Efficacy is presented for the modified full analysis set population (mFAS).

Roth et al Lancet 2015,

Safety

	GZR/EBR (ITG) 12 weeks (n = 111)	Placebo (DTG) 12 weeks (n = 113)
ALT, n (%)		
1.1-2.5 × baseline	2 (1.8)	36 (31.9)
>2.5-5 × baseline	1 (0.9)	6 (5.3)
>5× baseline	0 (0)	1 (0.9)
Alkaline phosphatase, n (%)		
1.1-2.5 × baseline	42 (37.8)	36 (31.9)
>2.5 × baseline	0 (0)	0 (0)
Hemoglobin		
Grade 1	27 (24%)	30 (26%)
Grade 2	14 (12%)	8 (7%)
Grade 3	4 (3,6%)	2 (1,8%)

Roth et al LAncet, 2015

SLKT Wait-listed Patients May Derive Benefit from Pre-Transplant HCV Cure

Characteristics of SLKT Wait-Listed Patients

Patient	Metavir Fibrosis Score	Free Hepatic Vein Pressure mm Hg	Wedge Pressure mm Hg	Hepatic Vein Portal Gradient (HVPG) mm Hg	HCV SVR 12	Transplant Decision
1	F3-4	9/5 (mean 7)	11	4	Y	KT Only
2	F4	12/10 (mean 11)	22	11	Y	KT Only
3	F4	8/4 (mean 6)	6	5	Y	KT Only
4	F3-4	8/5 (mean 5)	17	12	Y	KT Only
5	F4	15/6 (mean 10)	12	2	Y	KT Only
6	F4	11/5 (mean 8)	18	10	Y	KT Only
7	F4	17/14 (mean 15)	42	27	Relapse	SLKT
8	F3-4	6/1 (mean 3)	11	7	Y	KT Only
9	F4	NA	NA	NA	Relapse	SLKT

Conclusion: SLKT Wait-listed Patients Could Derive Benefit from Pre-Transplant HCV Cure as LT Could Be Avoided in Those With Compensated Cirrhosis and Devoid of Portal Hypertension

Frank C et al AASLD 2015.

Treatment of Hepatitis C in Patients with Renal Failure

- Renal disease severity should guide treatment decisions
- No dose adjustments with DAAs if GFR ≥ 30 mL/min
- Limited data with DAAs in patients with GFR <30 mL/min
- Renal transplant candidates should receive HCV treatment with DAAs
  - Either before or after transplantation, depending on clinical scenario