MEDIZINISCHE KLINIK 1

UNIVERSITÄTS KLINIKUM FRANKFURT

Hepatitis C - Special Populations

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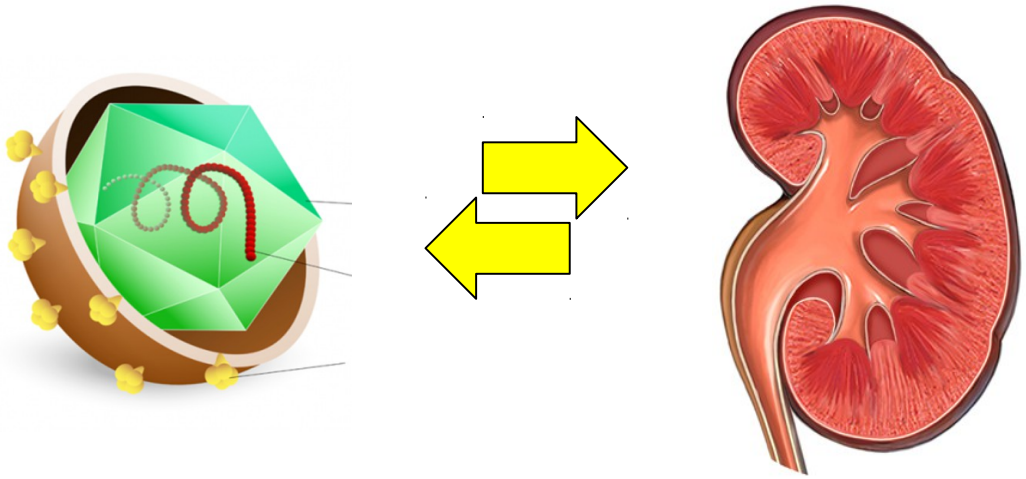
Less Special Populations in the DAA Era

Special Populations	IFN era	DAA era*
HCV/HIV coinfection	+	-
Compensated liver cirrhosis	+	-
Decompensated liver cirrhosis	N/A	(+)
Post-transplant (liver, kidney, etc.)	+	-
ESRD, hemodialysis	+	(+)
Cryoglobulinemia, vasculitis, etc.	+	-
Elderly patients	+	-
Children	+	-
PWID	+	-
Patients with psychiatric diseases	+	-
African American patients	+	-
etc.	+	-

* drug-drug interactions must still be considered

HCV and Chronic Kidney Disease

HCV can cause CKD
(mainly cryoglobulinemic membranoproliferative glomerulonephritis)



CKD is a risk for HCV
(blood transfusion, dialysis, renal transplant)

Stage	GFR (mL/min/1.73m2)
CKD 1	>89 (normal)
CKD 2	60-89 (mild)
CKD 3	30-59 (moderate)
CKD 4	15-29 (severe)
CKD 5	<15 (end-stage)

Clinical Trials in Patients with CDK

	HCV-1	HCV-2	HCV-3	HCV-4	HCV-5	HCV-6
Sofosbuvir + Ledipasvir	x	x	?	x	x	x
Sofosbuvir + Valpatasvir	x	x	x	x	x	x
Sofosbuvir + Daclatasvir	x	(x)	x	x	x	x
Sofosbuvir + Simeprevir	x	x		x	x	x
Paritaprevir/r + Ombitasvir ± Dasabuvir ± RBV	RUBY I (20 pts.) & RUBY II (18 pts.)					
Grazoprevir + Elbasvir	C-SURFER (116 pts.)					
Glecaprevir + Pibrentasvir	EXPEDITION-IV (114 pts.)					
Triple Therapies	x	x	x	x	x	x

RUBY-I: OBV/PTV/r + DSV ± RBV in Noncirrhotic G1 Patients with Severe RI or ESRD

-
-
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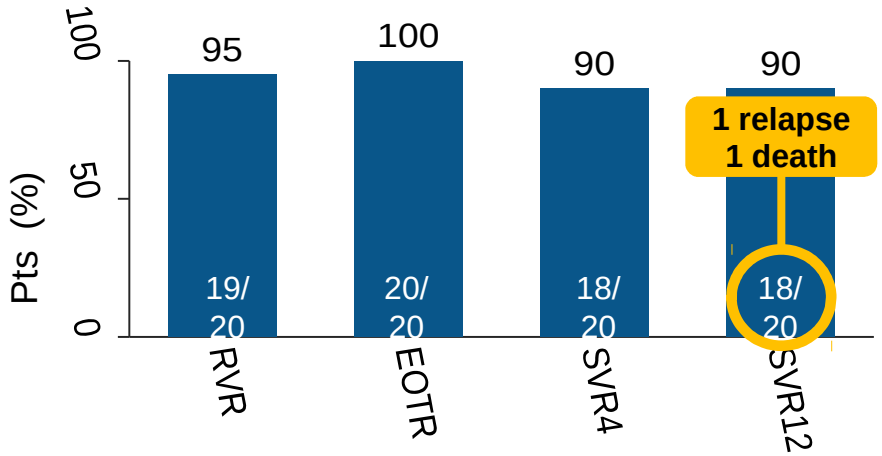
-

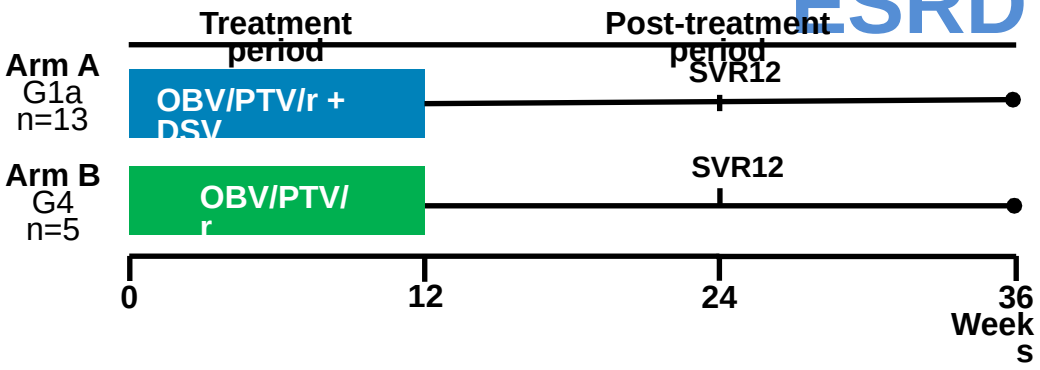
– Treatment-emergent RAVs:
  – NS3 (D168V) & NS5A (Q30R)

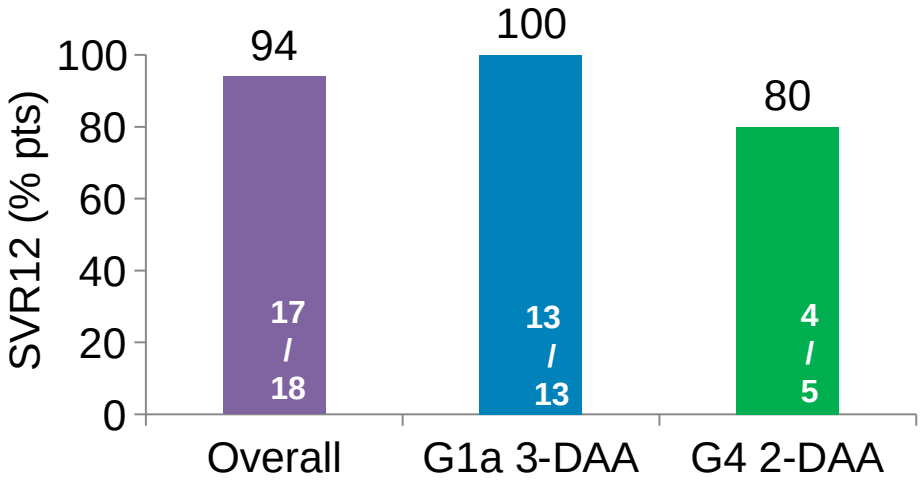


Safety

- No early d/c; 4 SAEs (not related)
- AEs more frequent with RBV
- Anemia (69%); fatigue (35%); diarrhea (25%); nausea (23%)
- ↓RBV dose: 69%; Hb <10 in 54%; Hb <8 in 8%
- ↑Bili <3 x ULN in 10%; no ↑ AST/ALT

OBV/PTV/r ± DSV Regimen in Patients with Severe RI or ESRD

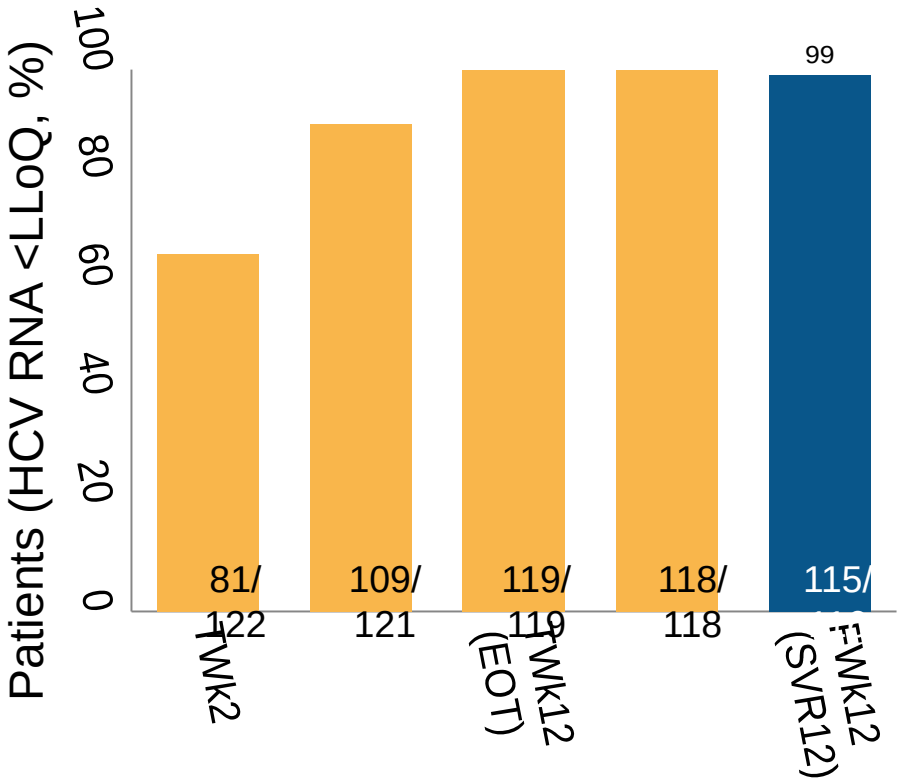




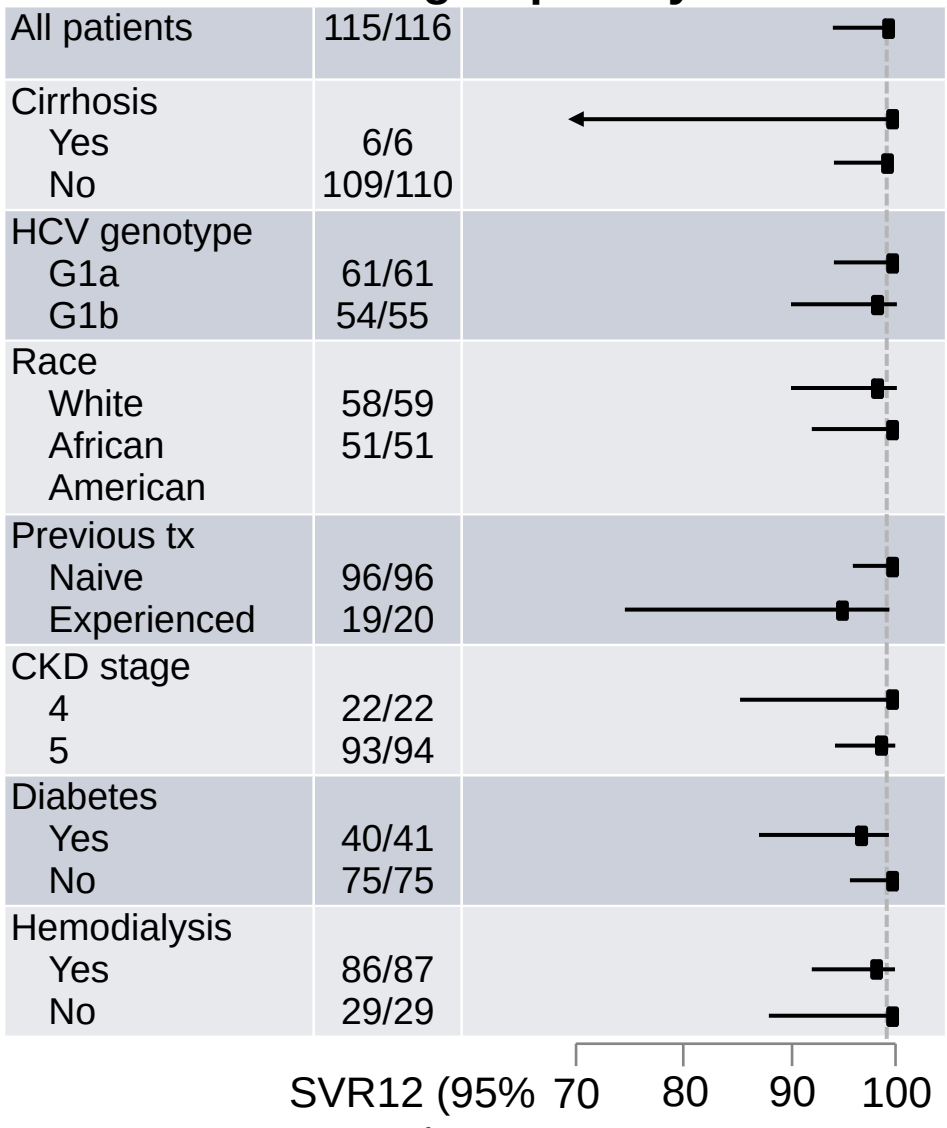
One G4 patient discontinued in wk 2 for elective renal tx

Event, n (%)	G1a (n=13)	G4 (n=5)
Any AE	13 (100)	5 (100)
Serious AE	3 (23)	1 (20)
Treatment-related SAE	0	0
d/c due to AE	1 (8)	1 (20)
AEs occurring in ≥15%		
Abdominal pain	4 (31)	0
Fatigue	3 (23)	1 (20)
Diarrhea	4 (31)	0
Headache	3 (23)	0
Hypertension	3 (23)	1 (20)
Nausea	4 (31)	0
Pruritus	2 (15)	1 (20)
Lab Abnormalities		
Hb Grade 2 (<10– 8)	4 (31)	2 (40)
Hb Grade 3 (<8 – 6.5)	0	0
ALT Grade 2 (>3 – 5 xULN)	0	0
ALT Grade 3 (>5 – 20 xULN)	1 (8)	1 (20)
Bilirubin Grade ≥2 (>1.5 xULN)	0	0

-experienced Patients with HCV G1 Infection and CKD

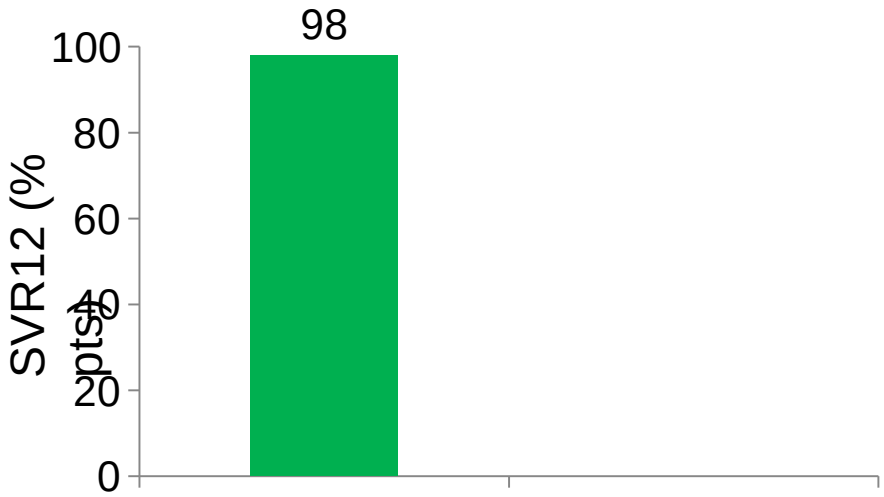


1 G1b, non-cirrhotic patient relapsed at FWk12



Roth D, et al, Lancet 2015; 385:1537-45

EXPEDITION-IV: Safety and Efficacy of G/P in G1–6 Adults with Renal Impairment



Breakthrough	0
Relapse	0
d/c	1
LTFU	1

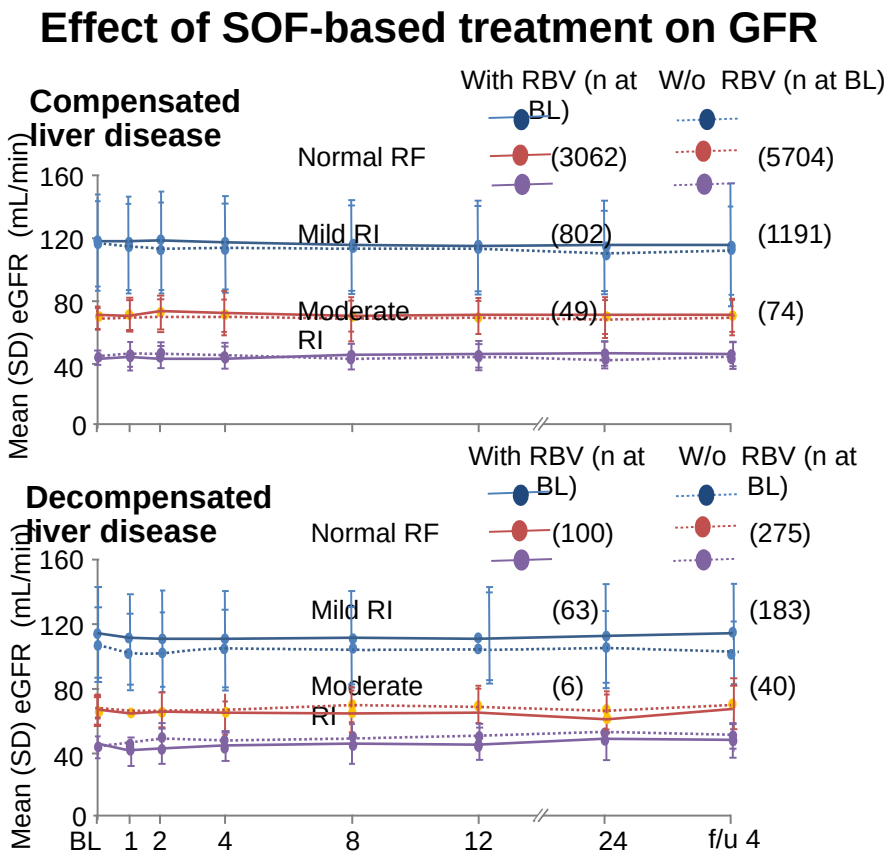
mITT=100%

Any AE	74 (71)
Serious AE	25 (24)
DAA-related SAEs	0
Treatment d/c due to AE	4 (4)
Hb Gr ≥3 (<8.0 – 6.5 g/dL)	5 (5)
AST Gr ≥2 (>5 – 20 × ULN)	0
ALT Gr ≥2 (>5 – 20 × ULN)	0
Bilirubin Gr ≥3 (>3 – 10 × ULN)	1 (1)

Clinical Trials in Patients with CDK

	HCV-1	HCV-2	HCV-3	HCV-4	HCV-5	HCV-6
Sofosbuvir + Ledipasvir	x	x	?	x	x	x
Sofosbuvir + Valpatasvir	x	x	x	x	x	x
Sofosbuvir + Daclatasvir	x	(x)	x	x	x	x
Sofosbuvir + Simeprevir	x	x		x	x	x
Paritaprevir/r + Ombitasvir ± Dasabuvir ± RBV	RUBY I & RUBY II					
Grazoprevir + Elbasvir	C-SURFER					
Glecaprevir + Pibrentasvir	EXPEDITION-IV					
Triple Therapies	x	x	x	x	x	x

Safety of SOF-based Regimens for HCV Treatment of Patients with Mild or Moderate RI

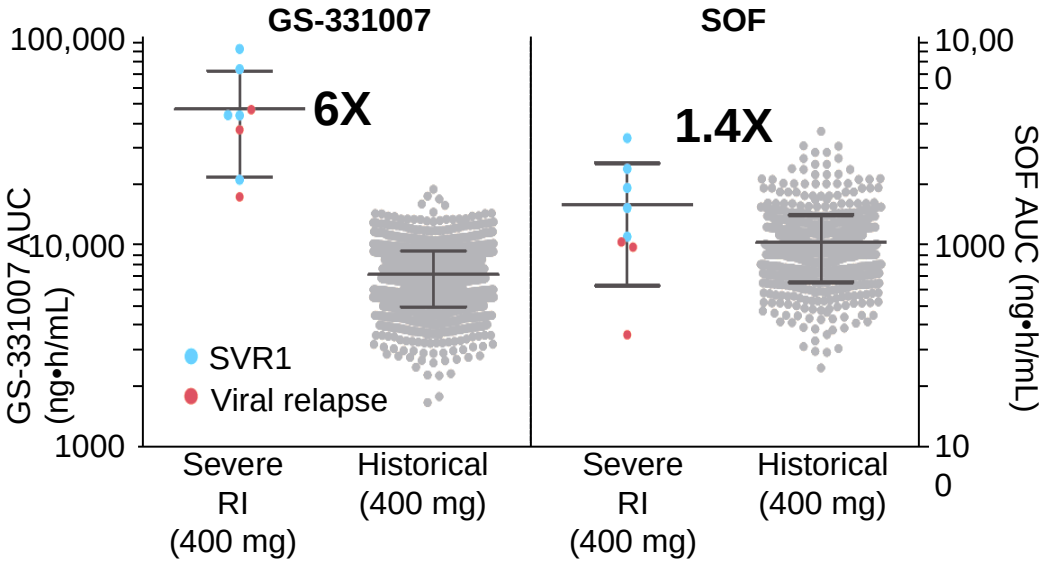


eGFR stable during SOF treatment regardless of RI

eGFR fluctuations only seen in transplant recipients

Renal AEs increased by RBV but not by baseline RI

Daily SOF 400 mg + RBV 200 mg for 24 Weeks in G1/3 Patients with Severe Renal Impairment



- No relationship observed between SOF, GS-331007 exposure (or RBV), and relapse

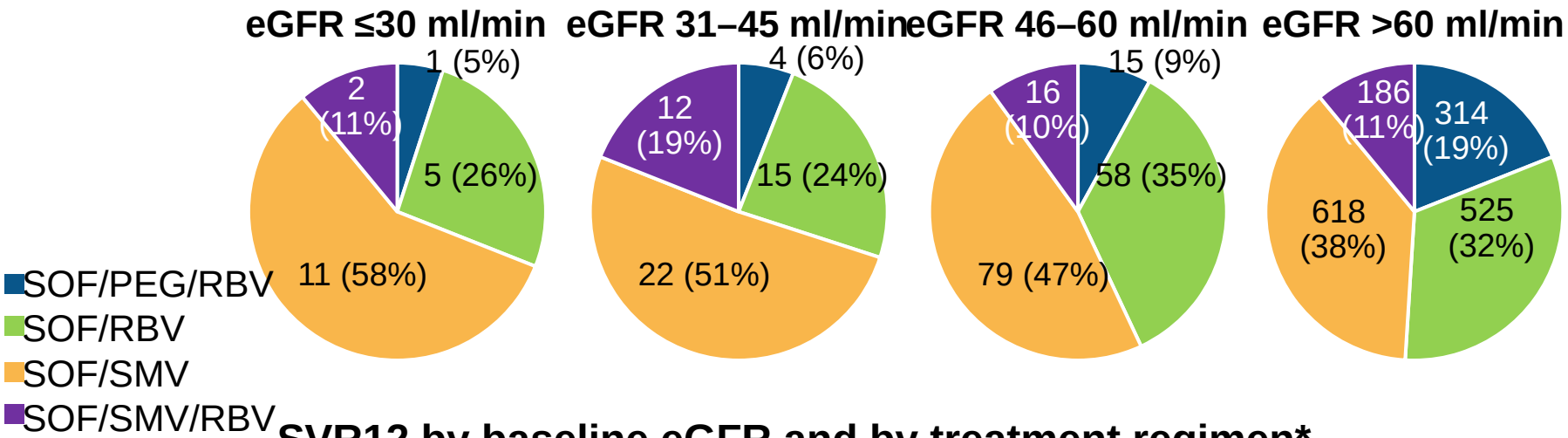
Safety

		SOF 200 mg	SOF 400 mg
AEs, n	Any AE	10	**9**
	Grade 3 AE	2	**3**
	Serious AE	2	**2**
	d/c due to AE	0	**2**
	Death	0	**0**
Labs, n	Hb <10	7	**9**
	Hb <8.5	4	**3**
	Δ CrCl	-3.1 mL/min	**+6.3 mL/min**
Echo	BL	57.1 ± 2.9	**56.4 ± 2.4**
	Week 24	58.1 ± 2.7	**55.9 ± 3.8**

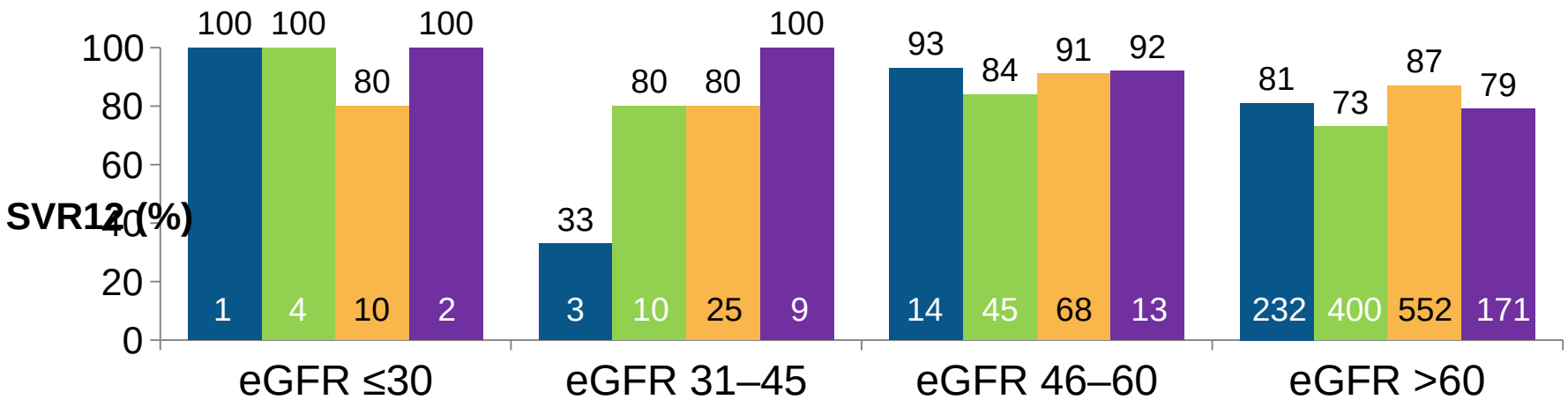
Martin P et al. AASLD 2015, San Francisco. #1128
Gane E, et al. AASLD 2014, Boston. #966

in HCV Infected Pts with Reduced Renal Function

Treatment regimen by baseline eGFR



SVR12 by baseline eGFR and by treatment regimen*



*Among patients with known outcome

Saxena V, et al., Liver Int 2016;36:807-16

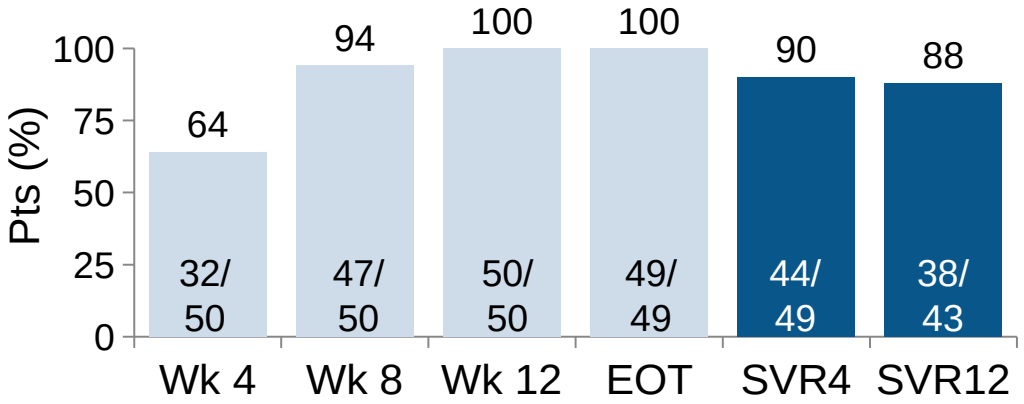
Regimens in HCV Infected Pts with Reduced Renal Function

Safety outcomes by baseline eGFR

Dichotomous = n (%) Continuous = mean (range)	eGFR ≤ 30 ml/min (n=17)	eGFR 31–45 ml/min (n=56)	eGFR 46–60 ml/min (n=157)	eGFR >60 ml/min (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)

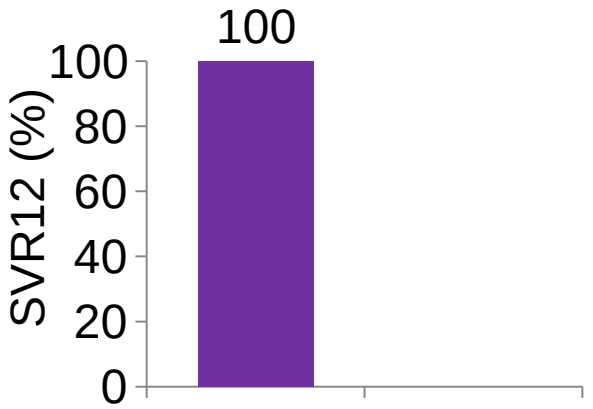
SOF-based antiviral therapy in HCV patients with severe renal failure

International Hepatitis Education Program



- SOF-based therapy effective, and safe, in renal failure, including dialysis
- Need for reduced SOF dose not established because no apparent

Use of LDV/SOF in patients with advanced chronic kidney disease (eGFR ≤30mL/min): A case series



(1 with RBV)

Adverse events

- Insomnia: 1
- Nausea/vomiting: 1
- Headache: 1
- Chest pain (Hx CAD): 1
- Anemia required transfusion or ESA: 2

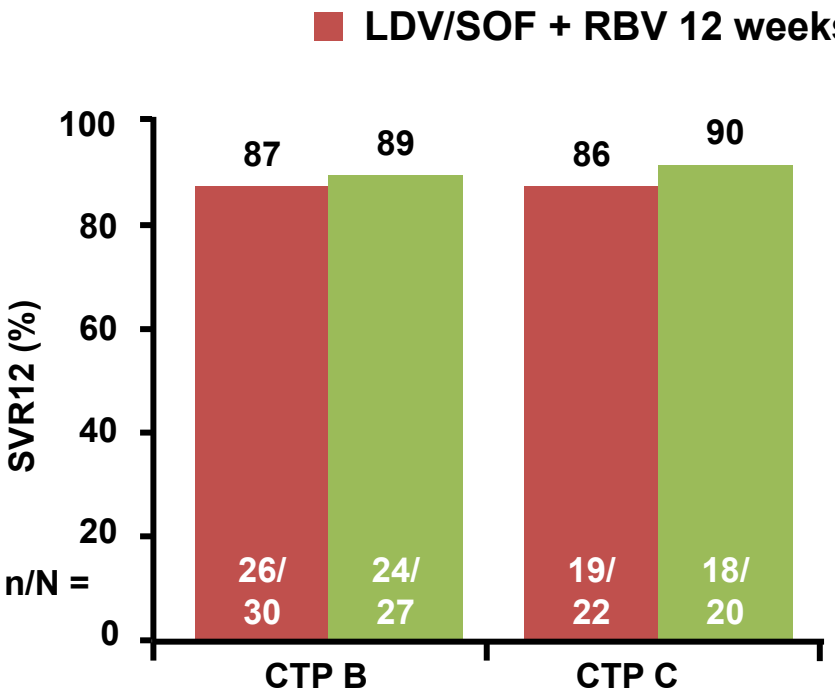
- 1 patient with cryo nephritis came off HD, at last report was on rituximab
- Of pts with severe renal impairment and post-tx f/u, 2 had increased eGFR and 4 had decreased eGFR
- Cannot rule out an effect on renal function in CKD-4 patients

Clinical Trials in Patients with Decompensated Liver Cirrhosis

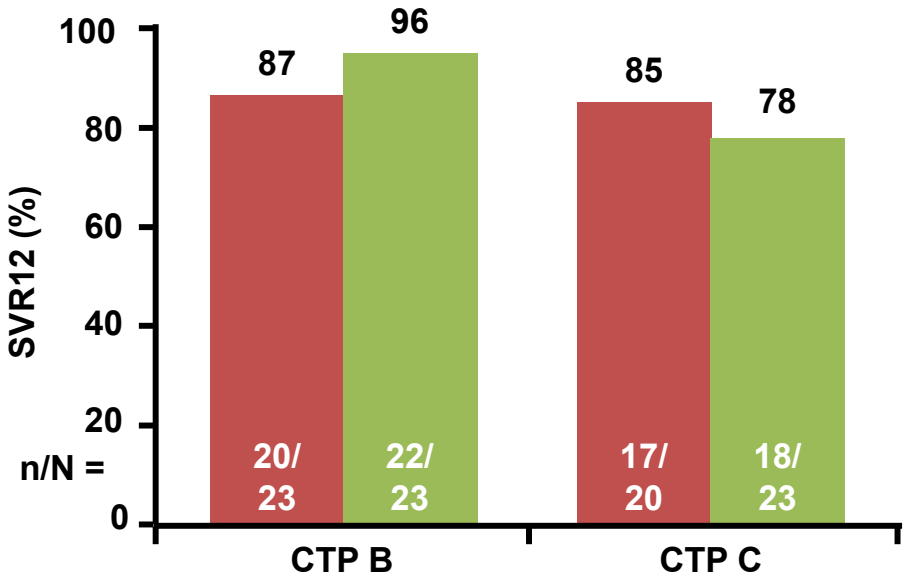
	HCV-1	HCV-2	HCV-3	HCV-4	HCV-5	HCV-6
Sofosbuvir + Ledipasvir	SOLAR-1 & -2					
Sofosbuvir + Valpatasvir	ASTRAL-4					
Sofosbuvir + Daclatasvir	ALLY-1					
Sofosbuvir + Simeprevir	NS3/4A protease Inhibitors and non-nucleosidic polymerase inhibitors **Contraindicated** in patients with decompensated liver cirrhosis					
Paritaprevir/r + Ombitasvir ± Dasabuvir ± RBV						
Grazoprevir + Elbasvir						
Glecaprevir + Pibrentasvir						
Triple Therapies						

SOLAR-1 and SOLAR-2: LDV/SOF + RBV in GT 1 or 4 with Decompensated Cirrhosis

Comparable Efficacy (SVR12) Between SOLAR-1 and SOLAR-2 Studies



SOLAR-1: GT 1 and 4

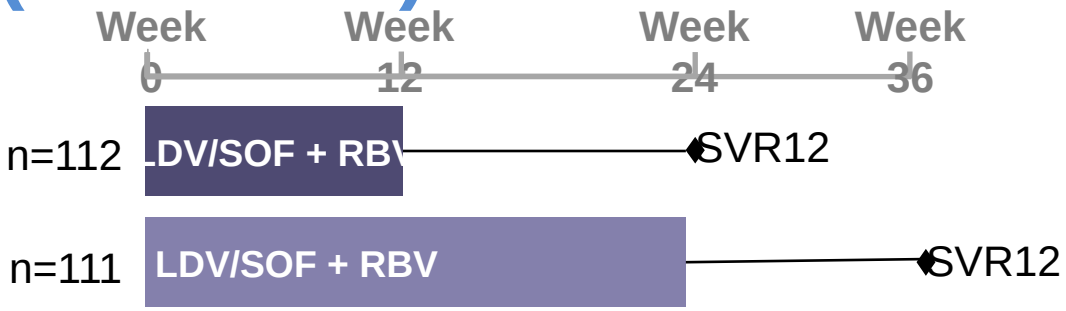


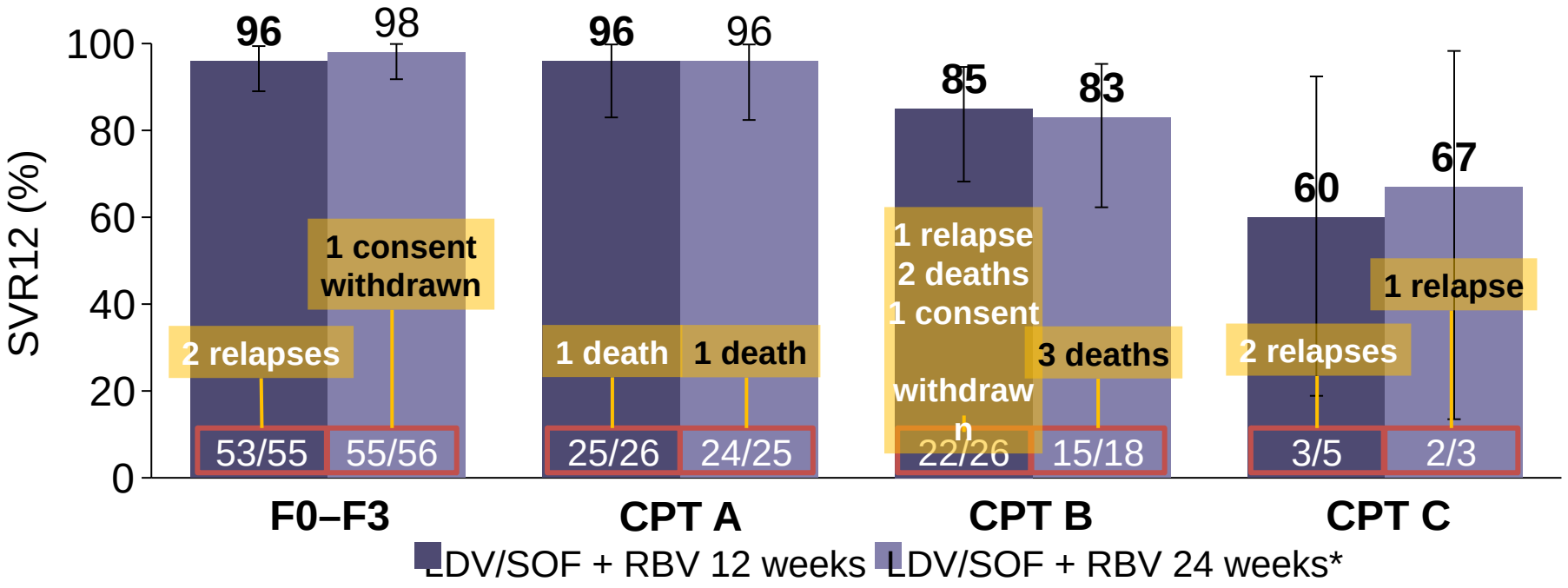
SOLAR-2: GT 1

Charlton M, et al., Gastroenterology 2015;149:649-59
Manns M, et al., Lancet Infect Dis 2016;16:685-97

LDV/SOF + RBV for the Treatment of HCV in Patients with Post-transplant Recurrence (SOLAR-1)

G1 or 4, treatment-naive or -experienced





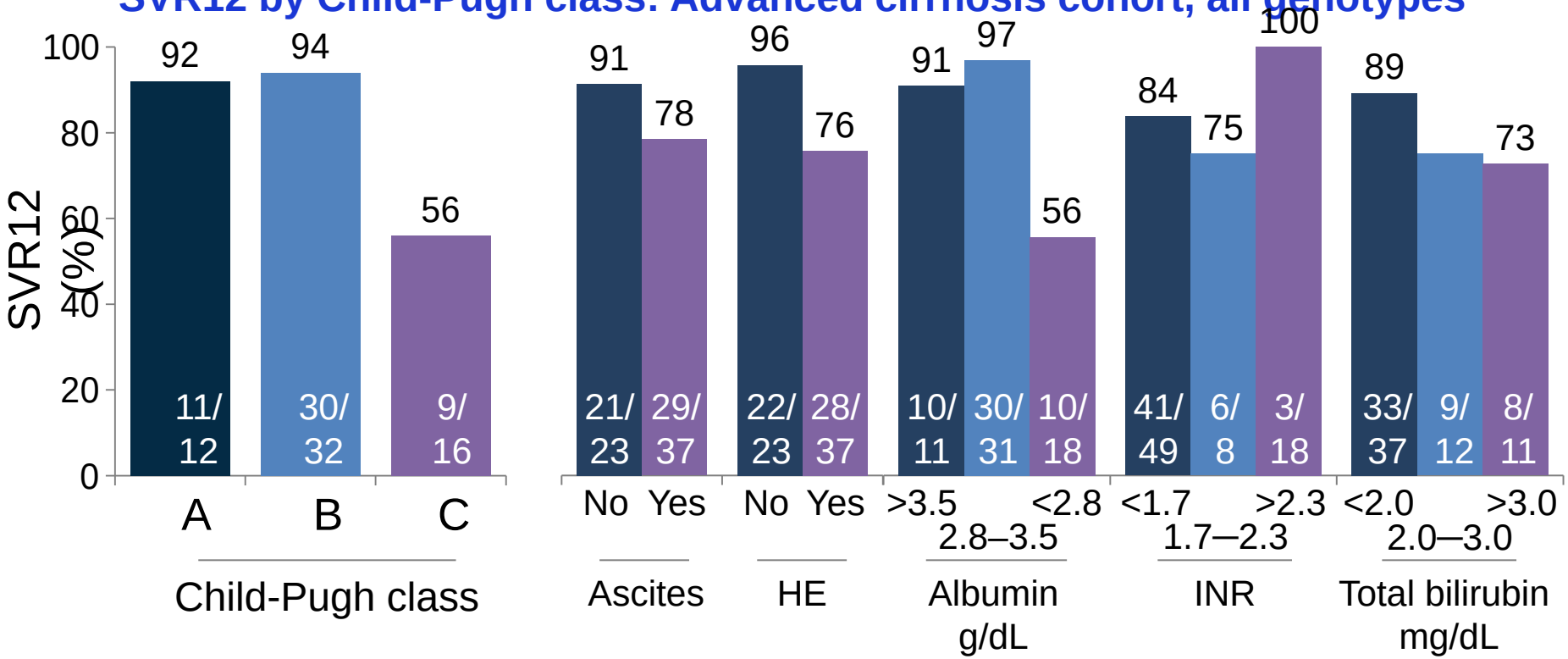
*8 CPT B 24-week and 1 CPT C 24-week pts had not reached the Wk 12 post-Tx visit

Charlton M, et al., Gastroenterology 2015;149:649-59

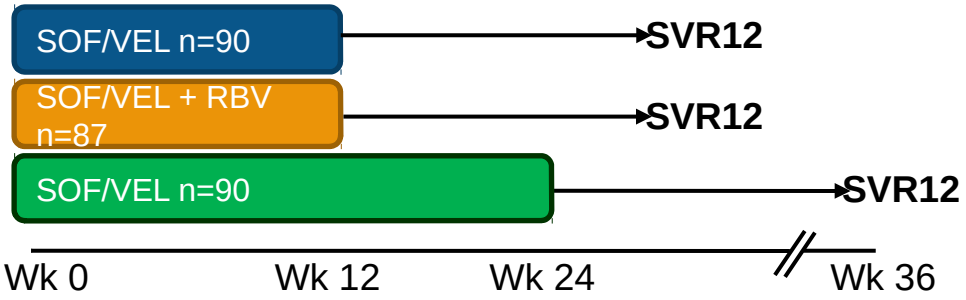
ALLY-1: DCV, SOF + RBV (600 mg) for HCV Patients with Advanced Cirrhosis or Post-LTX Recurrence

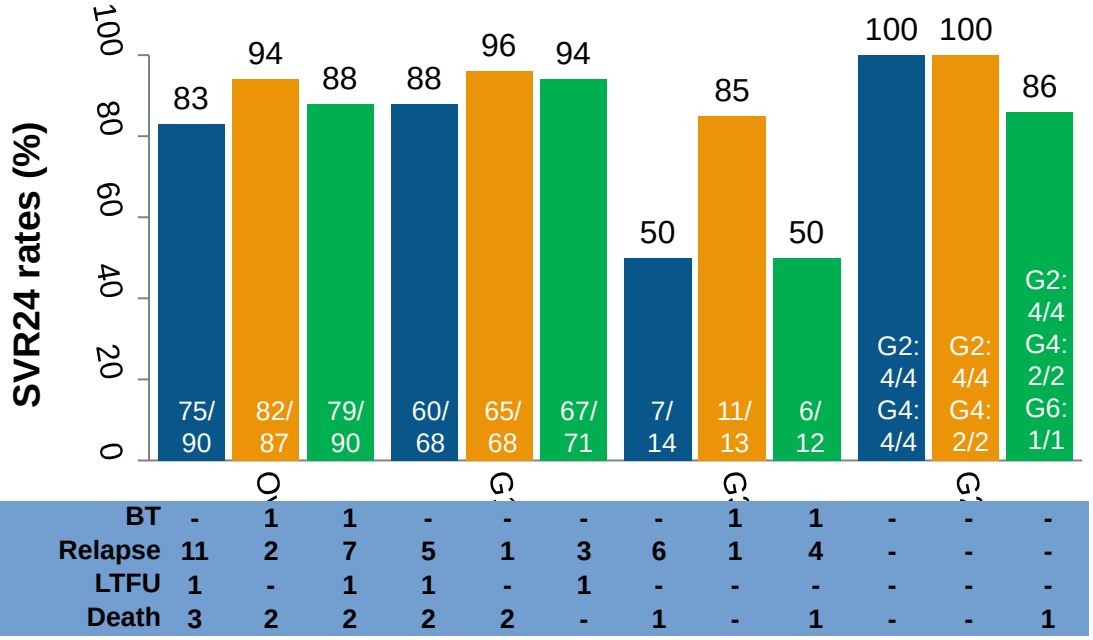
<u>Primary end point</u>: SVR12 in GT1 82% (advanced cirrhosis) and 95% (post-transplant)

SVR12 by Child-Pugh class: Advanced cirrhosis cohort, all genotypes

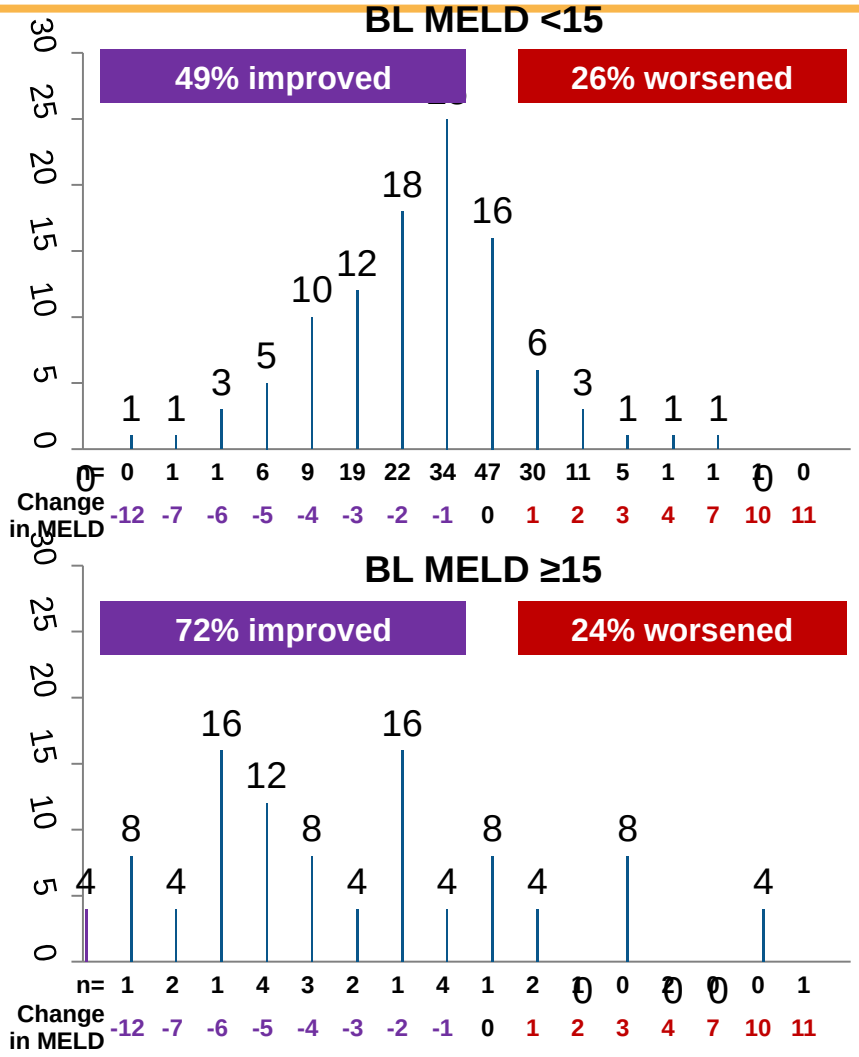


ASTRAL-4: SOF/VEL for HCV in Patients with Decompensated Cirrhosis





Baseline Clinical and Laboratory Parameters Associated with Clinical Benefits of SVR with SOF/VEL in Decompensated Cirrhotic Patients



Patients, n/n (%)	SVR12, n=127	SVR24, n=110
BMI		
<30 kg/m2	80/133 (60)	76/129 (59)
≥30 kg/m2	47/96 (49)	34/84 (40)
CPT		
A	8/14 (57)	6/13 (46)
B	112/205 (55)	99/191 (52)
C	7/10 (70)	5/9 (56)
MELD		
<15	105/203 (52)	92/188 (49)
≥15	22/26 (85)	18/25 (72)
Ascites		
None	27/48 (56)	24/42 (57)
Mild/moderate	99/175 (57)	83/165 (50)
Severe	1/6 (17)	3/6 (50)
Albumin		
≤3 g/dL	63/105 (60)	57/93 (61)
>3 g/dL	64/124 (52)	53/120 (44)
Encephalopathy		
None	62/87 (71)	49/80 (61)
Grades 1−2	65/142 (46)	61/133 (46)
Platelets		
<75 × 103/µL	61/96 (64)	54/91 (59)
≥75 × 103/µL	66/133 (50)	56/122 (46)

- Improvements in MELD score were driven largely by improvements in total bilirubin
- Lab improvements (albumin/bili) precede clinical improvements (ascites, encephalopathy)

Safety of Combined SOF/RBV Treatment in Patients with Advanced Cirrhosis

- SAE in 15/35 (43%) patients before (24 weeks) and in 12/35 (34%) patients during antiviral therapy, the majority in association with acute-on-chronic hepatic decompensation. Lactic acidosis occurred in 5/35 (14%) patients during therapy, while no event of lactic acidosis was observed prior to therapy. Lactic acidosis was severe (pH <7.3) in two patients.

- RBV in combination with SOF based antiviral therapy in patients with HCV associated advanced cirrhosis may be associated with the development of lactic acidosis. Impaired renal function, and higher MELD/Child-Pugh scores were identified as potential risk factors.

Welker et al., J Hepatol 2016;64:790-99

Conclusions

- Few „special populations“ left in HCV
- ESRD/hemodialysis
  - Paritaprevir/r + Ombitasvir ± Dasabuvir (HCV-1,-4)
  - Grazoprevir + Elbasvir (HCV-1,-4)
  - Glecaprevir + Pibrentasvir (pangenotypic)
- Decomp. Cirrhosis: Sofosbuvir +NS5A-inhibitor
- Safety of DAAs in these populations not yet fully defined – thorough surveillance during therapy
- No data in patients with ESRD and decompensated cirrhosis