NEW OPTIONS IN HCV THERAPY:

UPDATE FROM AASLD 2014

Case 1: A 52-year-old man with HCV genotype 1b and ascites

- LF, 52-year-old Hispanic male with known cirrhosis
- Cirrhosis on liver biopsy in 2007
- Treatment failure PEG / RBV – null response
- 2012 – new onset ascites, controlled with diuretics
- 2013 – encephalopathy, started on lactulose and rifaximin
- 2014 – ascites requiring paracentesis every 4–6 weeks
- Past history:
  - Diabetes for 3 years
  - Alcohol abuse – none since 2007
- Medications:
  - Metformin 1 gm/day
  - Aldactone 200 mg, Lasix 80 mg
  - Rifaximin 550 mg bid
  - Lactulose 30 cc tid
  - Nadolol 20 mg/day

- Social History:
  - Alcohol 1–2 units per week
  - History of IVDU 35 years ago
  - Nonsmoker for 35 years
- Physical exam:
  - BP 95/566; BMI 29
  - 3-finger splenomegaly
  - Ascites
- Investigations:
  - CBC: WBC 2.8/µL, neutrophils 1.2/µL
  - HgB 11.3 g/dL
  - Platelets 43,000×10^3/µL
  - Albumin 2.6 g/dL, INR 1.7, bilirubin 2.3 mg/dL
  - Creatinine 1.6 mg/dL

- Investigations:
  - Ultrasound shows coarse liver and enlarged spleen, 15.3 cm
  - MRI – nodular liver, no enhancing lesions, 3-cm hemangioma
  - Ascites – moderate
  - FibroScan 44.7 kPa
  - Endoscopy Grade 3 varices
- Summary:
  - Child-Pugh 9
  - MELD 15
  - CrCl 48 mL/min
  - Prior PEG/RBV failure

Questions

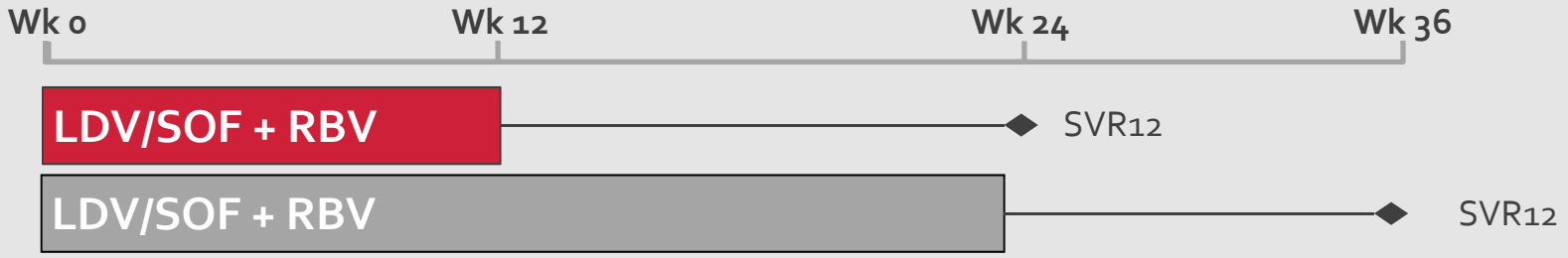
1. Would you treat this patient?
2. Does he meet the current criteria for prioritization for treatment?
3. Are Child-Pugh of 9, MELD 15, and CrCl a contraindication to any treatments?
4. Would you use RBV?
5. What outcomes can we expect? SVR? Improved liver function?
6. Instead, should the patient be put on transplant list and treated post-transplant?

NEW OPTIONS IN HCV THERAPY:

UPDATE FROM AASLD 2014

Decompensated Cirrhosis and Post-transplant

LDV/SOF + RBV for the treatment of HCV in patients with decompensated cirrhosis: Preliminary results of a prospective, multicenter study

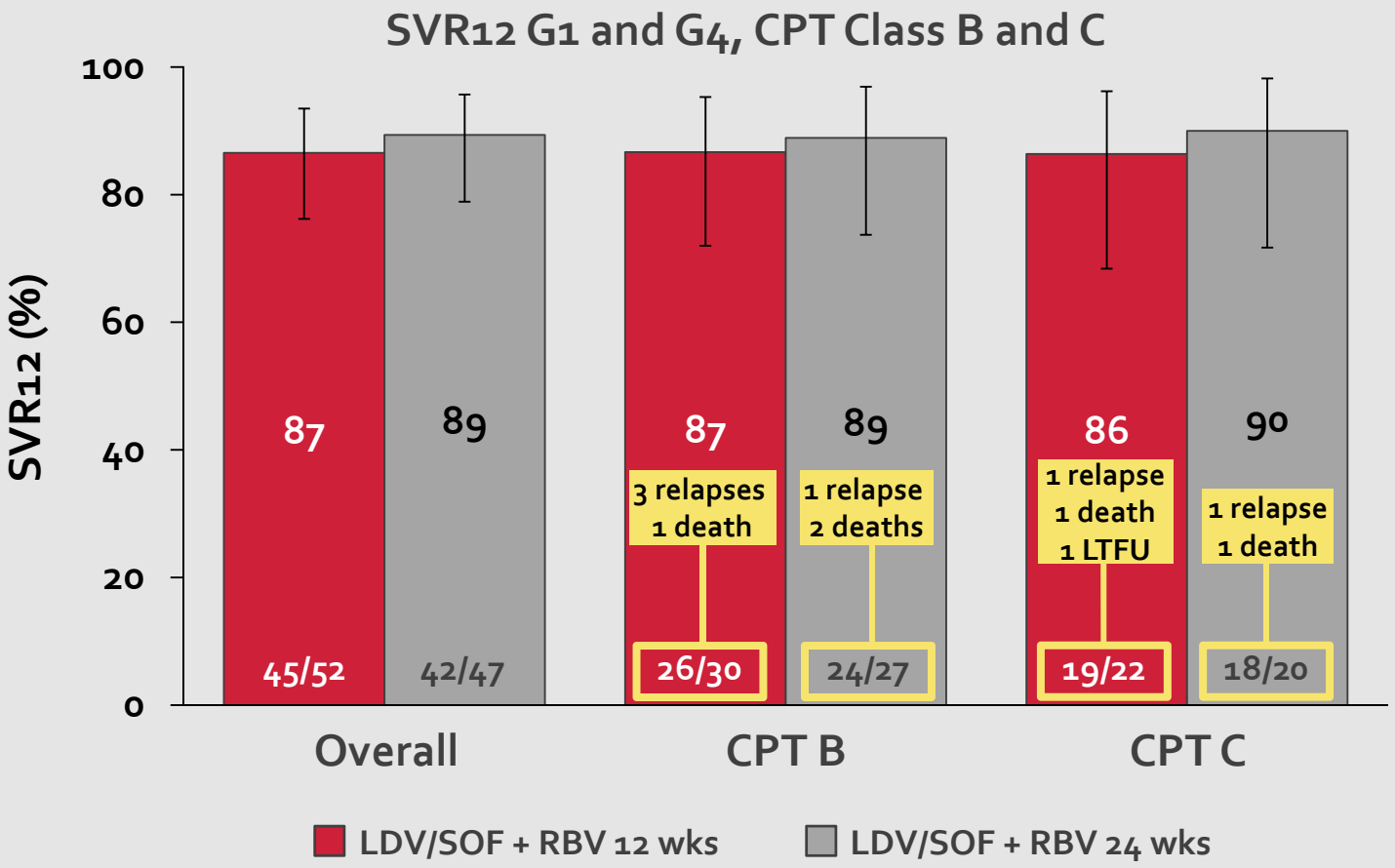


- 108 patients randomized 1:1 to 12 or 24 weeks of treatment
- G1 or G4 treatment-naïve or treatment-experienced patients with decompensated cirrhosis
  - CPT class B (7–9) or C (score 10–12)

Flamm SL, et al. AASLD 2014, Boston. #239

LDV/SOF + RBV for the treatment of HCV in patients with decompensated cirrhosis: Preliminary results of a prospective, multicenter study (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

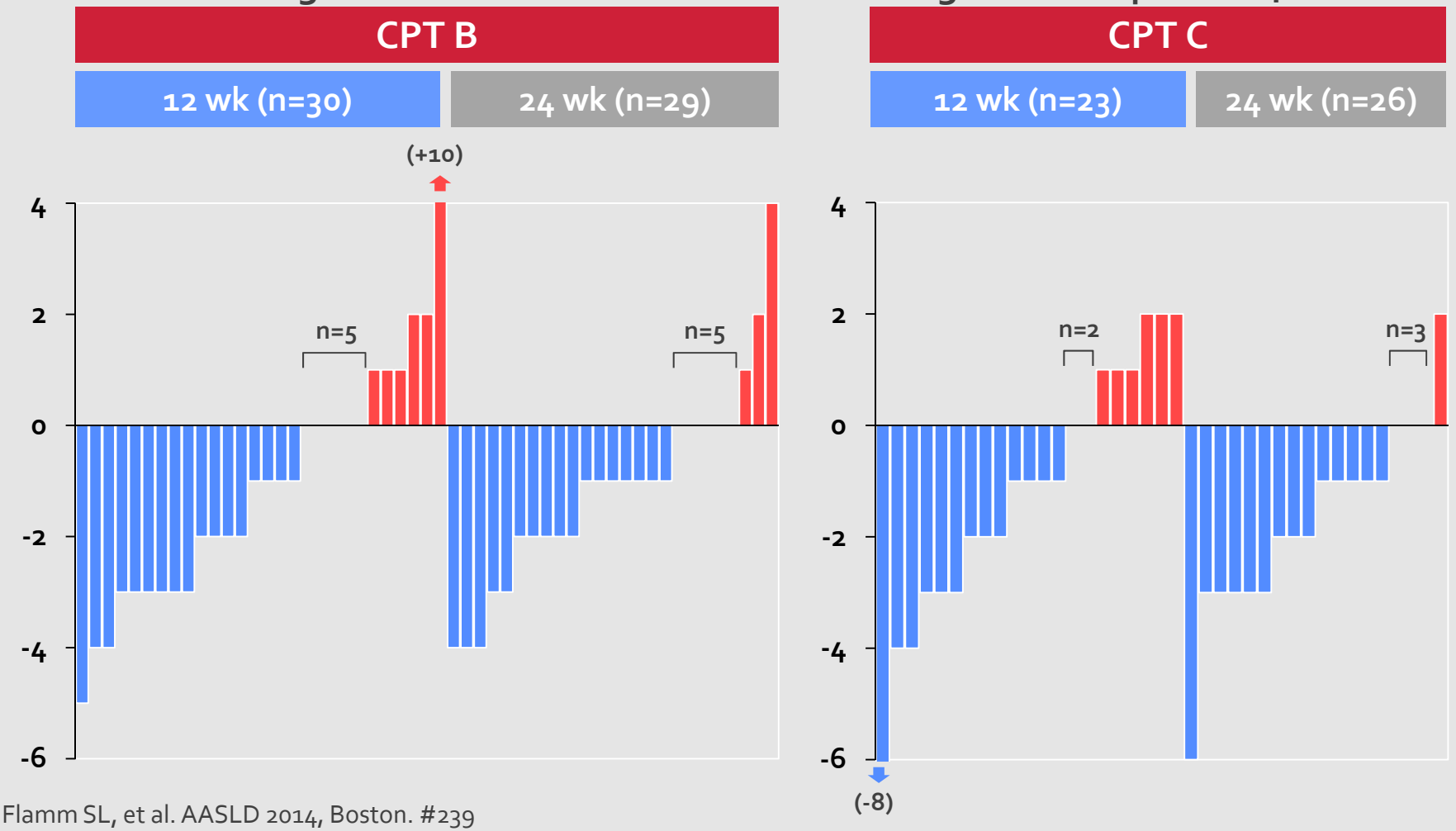


Flamm SL, et al. AASLD 2014, Boston. #239

LDV/SOF + RBV for the treatment of HCV in patients with decompensated cirrhosis: Preliminary results of a prospective, multicenter study (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

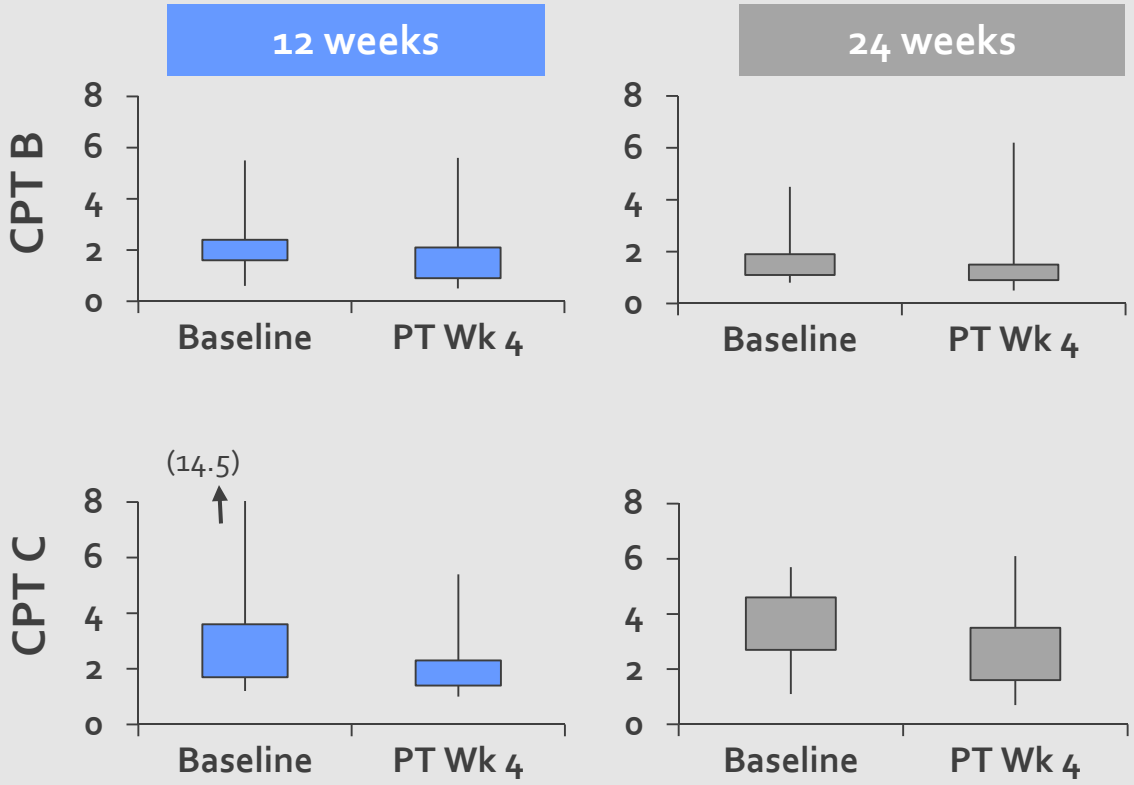
Change in MELD score from Baseline through follow-up Week 4



Flamm SL, et al. AASLD 2014, Boston. #239

LDV/SOF + RBV for the treatment of HCV in patients with decompensated cirrhosis: Preliminary results of a prospective, multicenter study (cont)

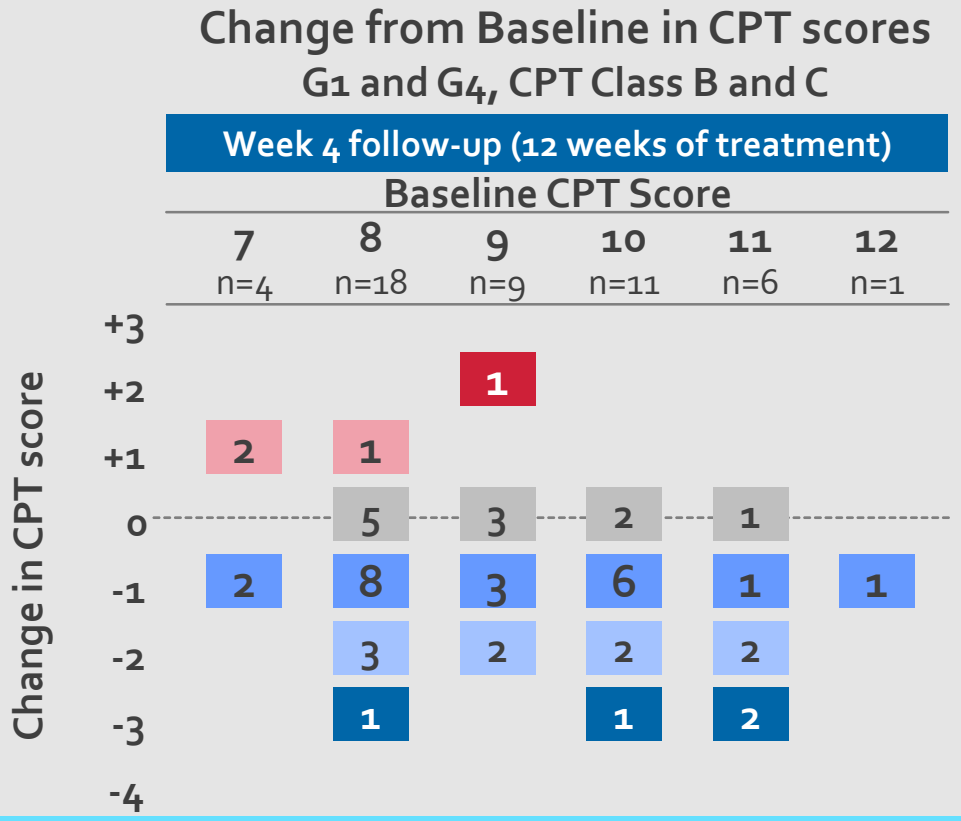
Median total bilirubin (CPT B/C):
Change from Baseline to follow-up Week 4



Flamm SL, et al. AASLD 2014, Boston. #239

LDV/SOF + RBV for the treatment of HCV in patients with decompensated cirrhosis: Preliminary results of a prospective, multicenter study (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



- LDV/SOF + RBV for 12 weeks: high SVR12 in HCV patients with G1 and G4 and advanced liver disease
  - Extending duration to 24 weeks did not increase response rate
- Virologic response was associated with improvements in bilirubin, albumin, MELD and CPT scores in both CPT class B and C patients
- LDV/SOF + RBV for 12–24 weeks was safe and well-tolerated in CPT class B and C patients

Flamm SL, et al. AASLD 2014, Boston. #239

The use of SMV and SOF to treat HCV G1 in the liver transplant setting: The experience in 3 US centers

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

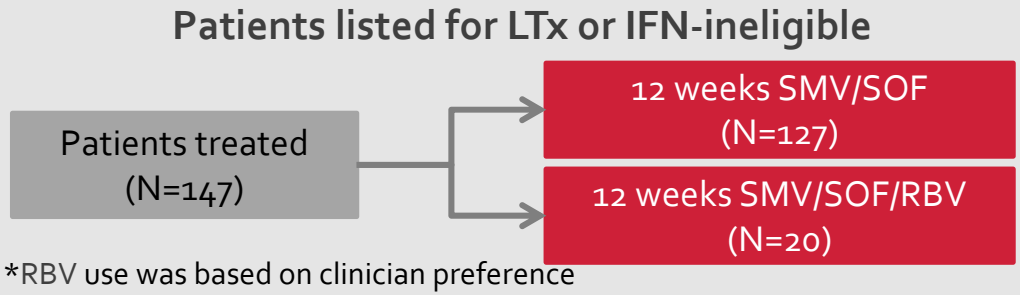
Patient characteristics (N=147)

Mean age (range)	59 years (47–7)
Male, n (%)	90 (61)
Listed for transplant, n (%)	93 patients (63)
Median MELD (range)	12 (7–17)
HCV genotype 1a, n (%)	103 (70)
eGFR >30 mL/min, n (%)	147 (100)
Treatment status	
Naïve, n (%)	51 (35)
Treatment experienced, n (%)	96 (65)
Peg/RBV, n	69
Peg/RBV/PI, n	27
Cirrhosis, n (%)	114 (78)
CTP A/B, n (%)	80/20
IL-28 status	
CC genotype, n (%)	31 (21)
Non-CC genotype, n (%)	77 (52)
Missing genotype, n (%)	39 (27)

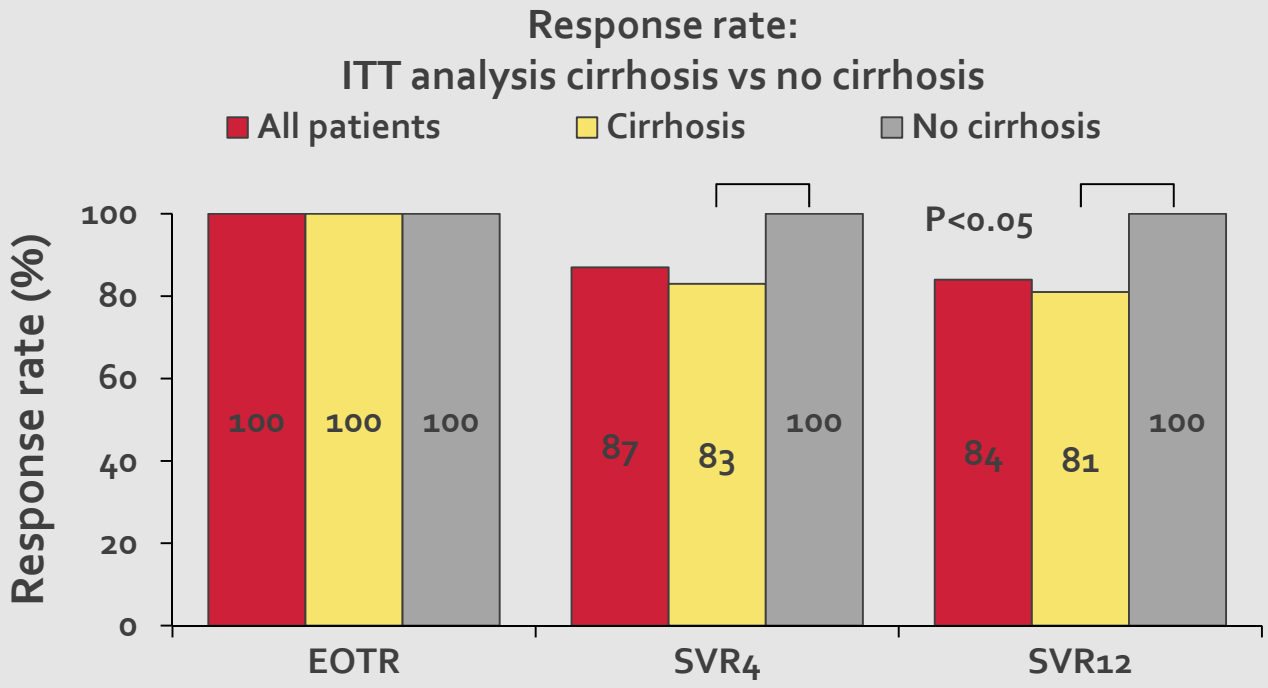
Aqel B, et al. AASLD 2014, Boston. #19

The use of SMV and SOF to treat HCV G1 in the liver transplant setting: The experience in 3 US centers (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



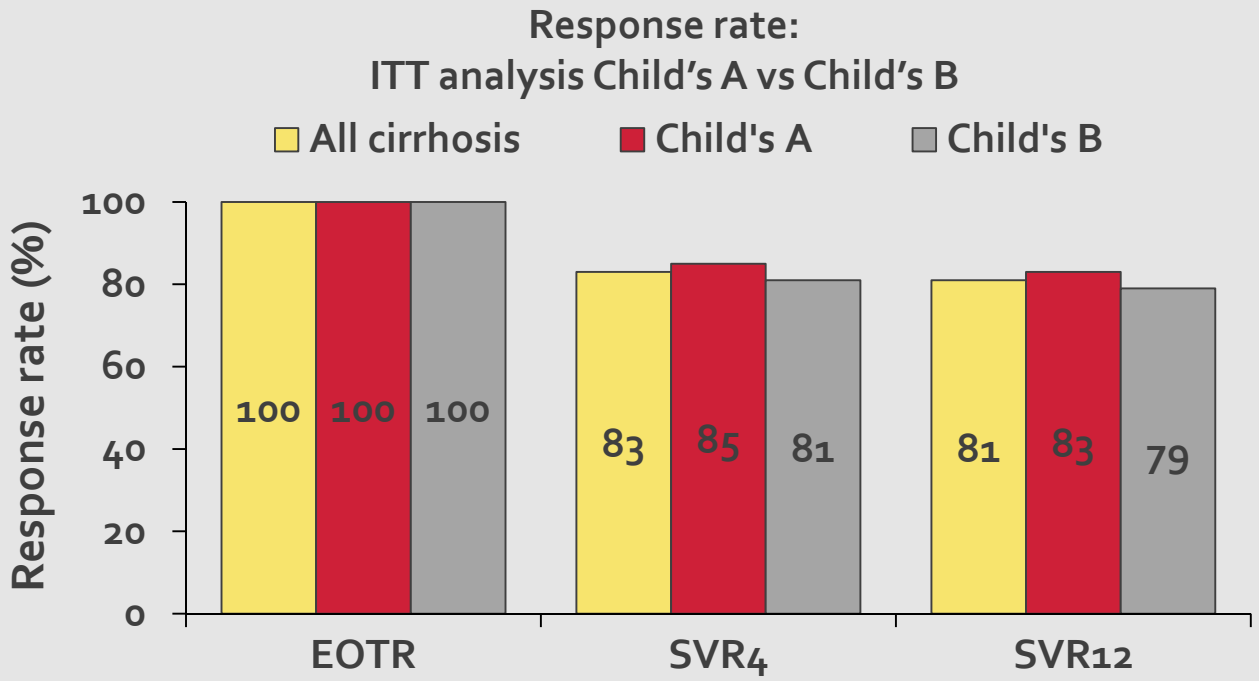
*RBV use was based on clinician preference



Aquel B, et al. AASLD 2014, Boston. #19

The use of SMV and SOF to treat HCV G1 in the liver transplant setting: The experience in 3 US centers (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



- No difference in response rate:
  - RBV vs no RBV
  - HVL vs LVL
  - Naïve vs treatment-experienced
  - G1a vs G1b
  - Listed for LTx 93 cases - SVR 12–83%

Aquel B, et al. AASLD 2014, Boston. #19

The use of SMV and SOF to treat HCV G1 in the liver transplant setting: The experience in 3 US centers (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

- 100% (13/13) of virologic failures had cirrhosis vs 78% (68/88) of SVR4, p<0.05

Adverse events	
Any adverse events, n	15 (10%)
Hyperbilirubinemia	4 patients (3%)
Grade 1–2 (bilirubin 1–2x ULN) Completed 12 weeks	2 patients (1%)
Grade 3–4 (bilirubin >3x ULN) Treatment stopped (Wk 8, Wk 11) Both achieved SVR4	2 patients (1%)
Anemia (Grade 1–2)	2 patients (1%)

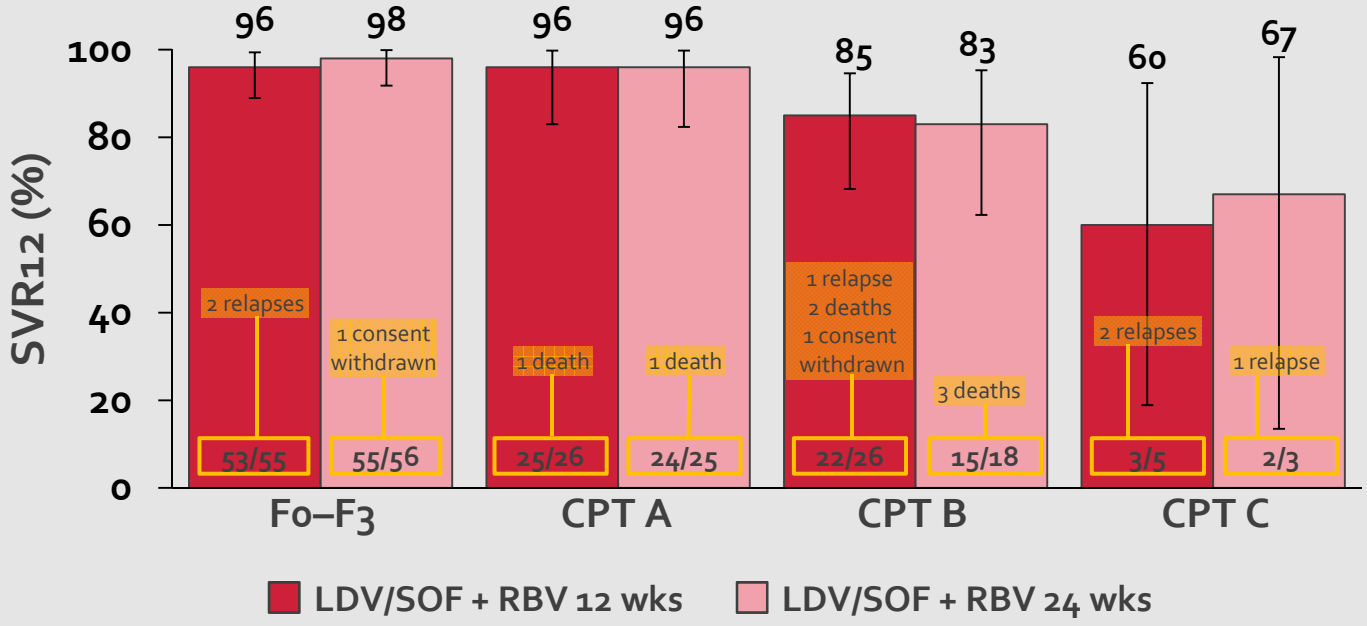
- Low SVR in decompensated patients
- Few cases of hyperbilirubinemia (3%)
- SMV/SOF: very effective therapy
  - May not need RBV in non-cirrhotic, easy-to-treat patient
  - More convenient regimens are available
- SVR4 is a surrogate of SVR12?

Aquel B, et al. AASLD 2014, Boston. #19

LDV/SOF + RBV for the treatment of HCV in patients with post-transplant recurrence: Preliminary results of a prospective, multicenter study

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

- 223 post-transplant patients
- G1 or G4 treatment-naïve or treatment-experienced
- Stratified at Screening: Fo–F3, CPT A, B, C
- RBV dose escalation in CPT B and C

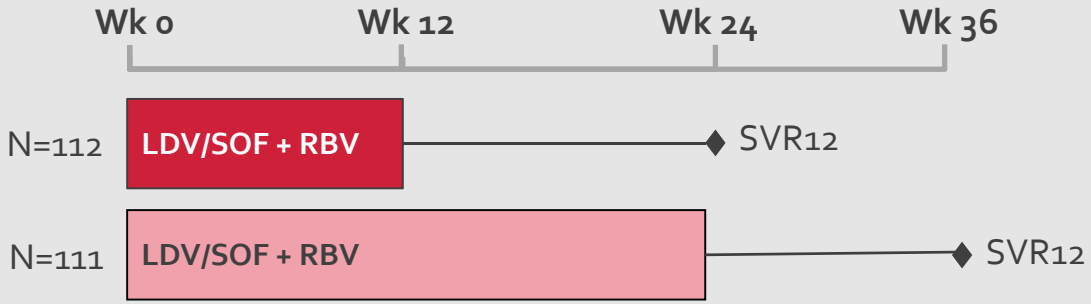


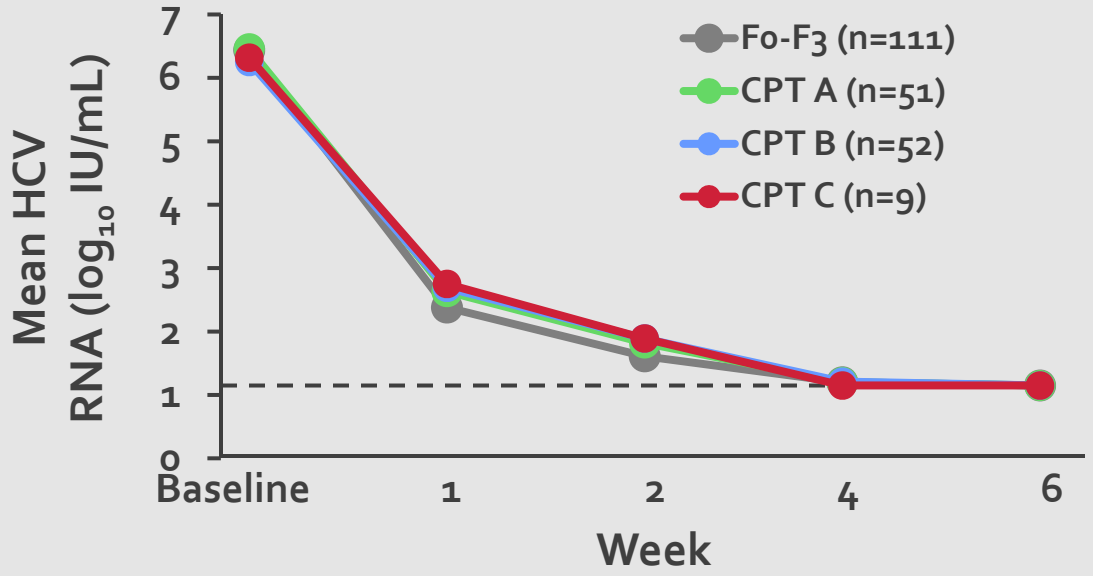
- 6 virologic failures (relapse)

Reddy K, et al. AASLD 2014, Boston. #8

LDV/SOF + RBV for the treatment of HCV in patients with post-transplant recurrence: Preliminary results of a prospective, multicenter study (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014





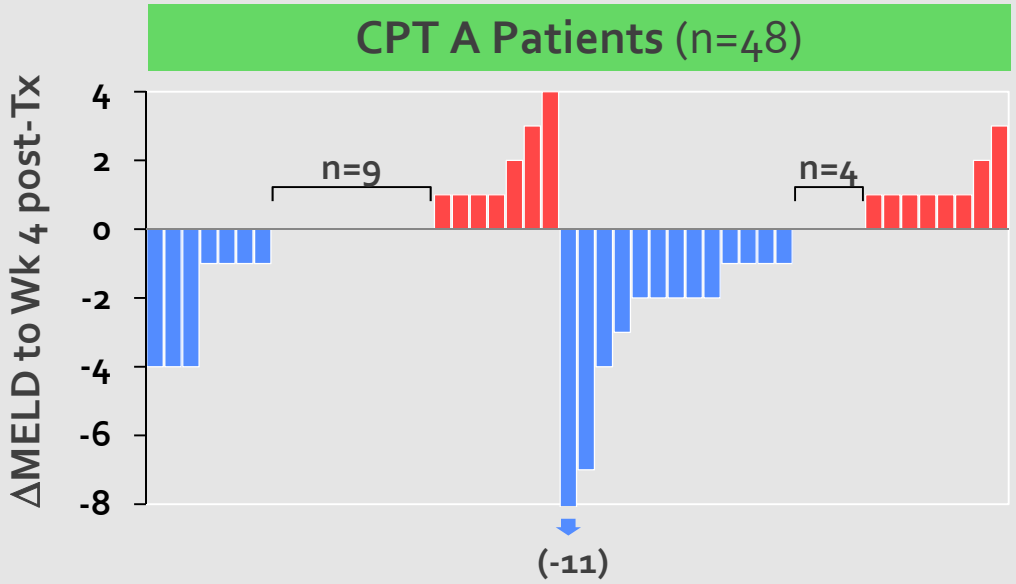
Reddy K, et al. AASLD 2014, Boston. #8

LDV/SOF + RBV for the treatment of HCV in patients with post-transplant recurrence: Preliminary results of a prospective, multicenter study (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

Efficacy

- Significant improvement in albumin, bilirubin in both 12- and 24-week arms and CPT A or B
- Overall improvement in MELD



- In recurrent HCV, LDV/SOF+RBV for 12 or 24 weeks had high SVR, including advanced disease
- Early improvements in bilirubin, albumin, and MELD
- Safe and well-tolerated including RBV S/Es

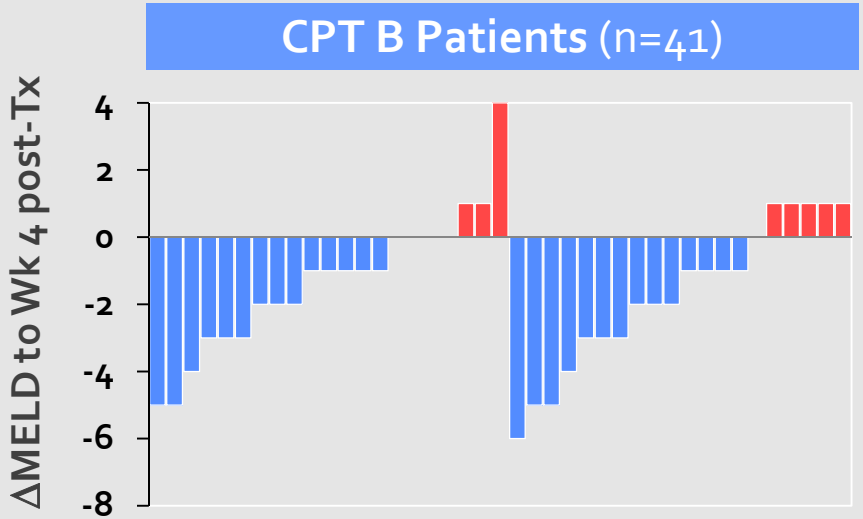
Reddy K, et al. AASLD 2014, Boston. #8

LDV/SOF + RBV for the treatment of HCV in patients with post-transplant recurrence: Preliminary results of a prospective, multicenter study (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

Safety

- 7 deaths (4 on treatment)
- 46 SAEs (6 treatment-related)
- 6 treatment-related discontinuations



- No on-treatment virologic failure
- Same rate of viral decline in CPT-c.f. SOF/RBV
- Reduce the need for re-transplantation?
- Only 12-week duration needed?

Reddy K, et al. AASLD 2014, Boston. #8

Multicenter experience using SOF and SMV ± RBV to treat HCV G1 after liver transplantation

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

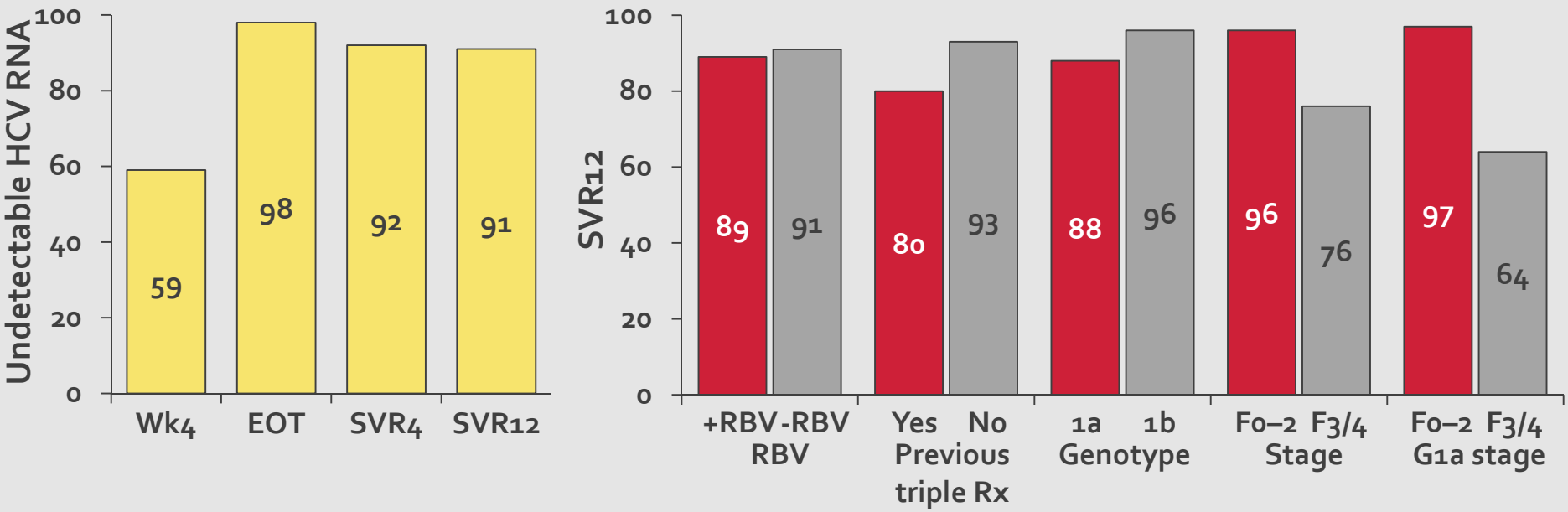
- **109 transplant recipients with HCV⇨ SOF/SMV ± RBV for 12 weeks**

- Mean age 61 ± 6 years
- Median 29 months post-OLT
- 82% treatment failures (12% PI)
- 29% F3/4; 11% FCH
- 98 on Tac, 9 CyA, 1 SIR

- Minimal effect on Tac levels, no rejection
- 42% anemia in RBV patients
  - 100% dose reduction; 50% EPO
- One case of acute pancreatitis (Day 5)
- 1 case acute lung injury (D14)⇨ died

Pungpapong S, et al. AASLD 2014, Boston. #9

Multicenter experience using SOF and SMV ± RBV to treat HCV G1 after liver transplantation (cont)



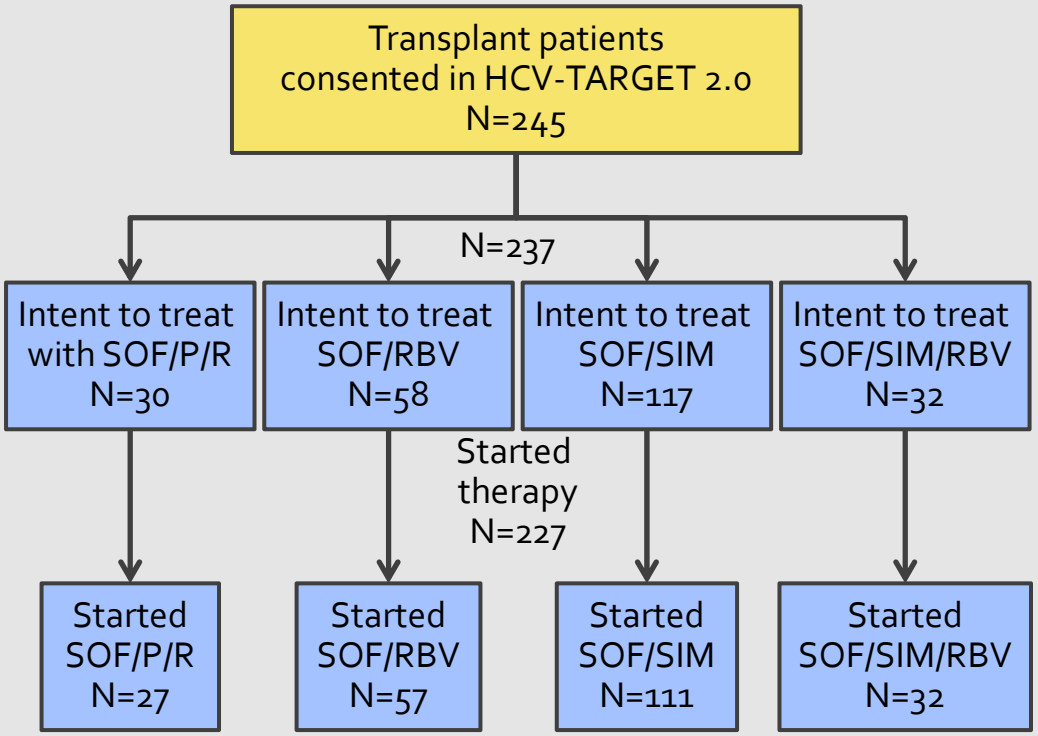
- SOF/SMV ± RBV for 12 weeks - SVR 91%
- Relationship to SAEs?
- Reduced efficacy in G1a ⇨ Impact of Q80K?
- RBV-associated toxicity with no added benefit

Pungpapong S, et al. AASLD 2014, Boston. #9

Safety and efficacy of new DAA-based therapy for HCV post-transplant: Interval results from the HCV-TARGET longitudinal, observational study

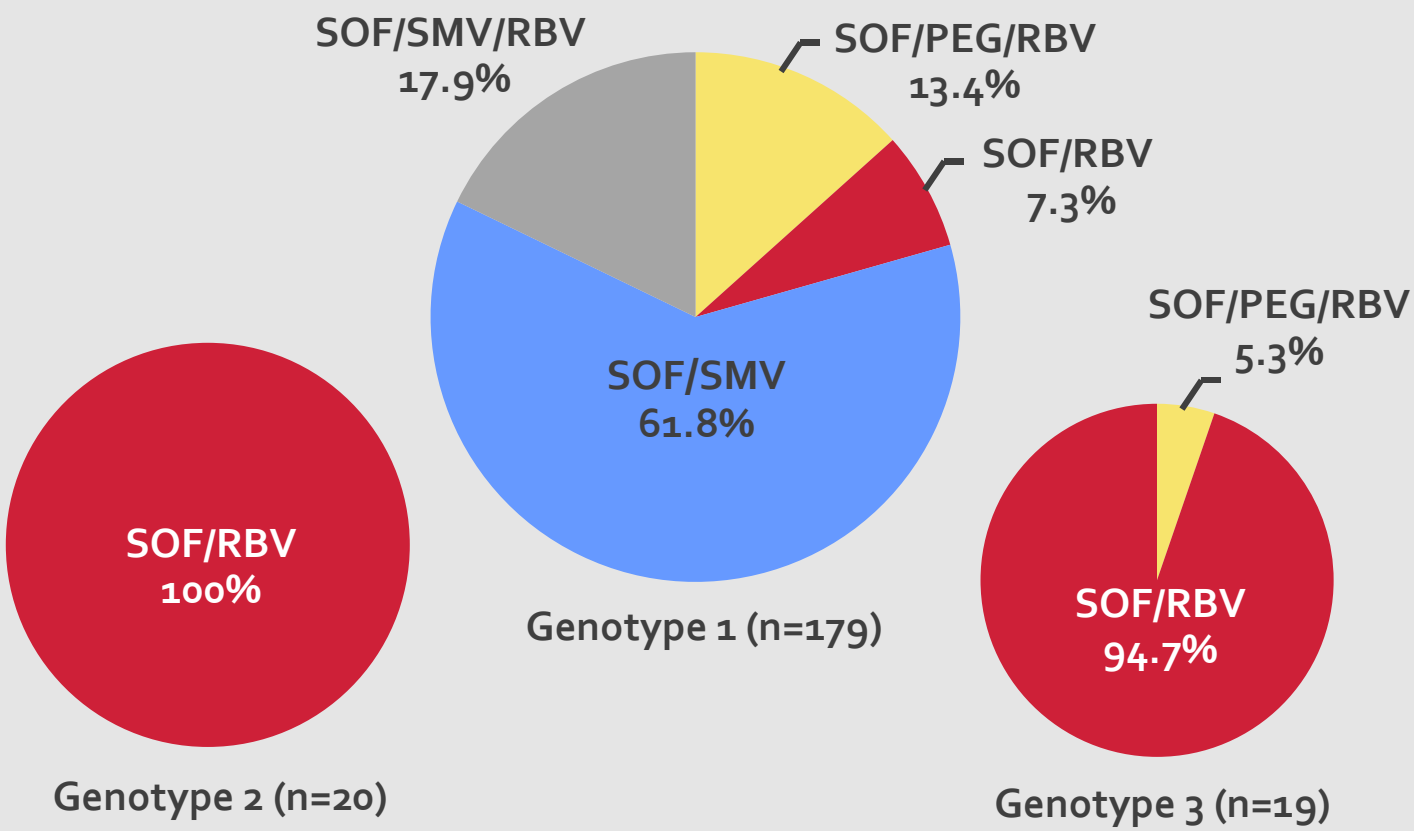
NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

- HCV-TARGET 2.0: US/Canada/ Germany real-world study of SOF treatment post-OLT
  - 245 patients across 53 centers
  - Data from all treatment-recipients started on SOF
  - Mean age 60 (20% >65 yrs)
  - 56% cirrhosis; 31% MELD >10
  - SVR4 data on 159



Brown RS, et al. AASLD 2014, Boston. #LB-4

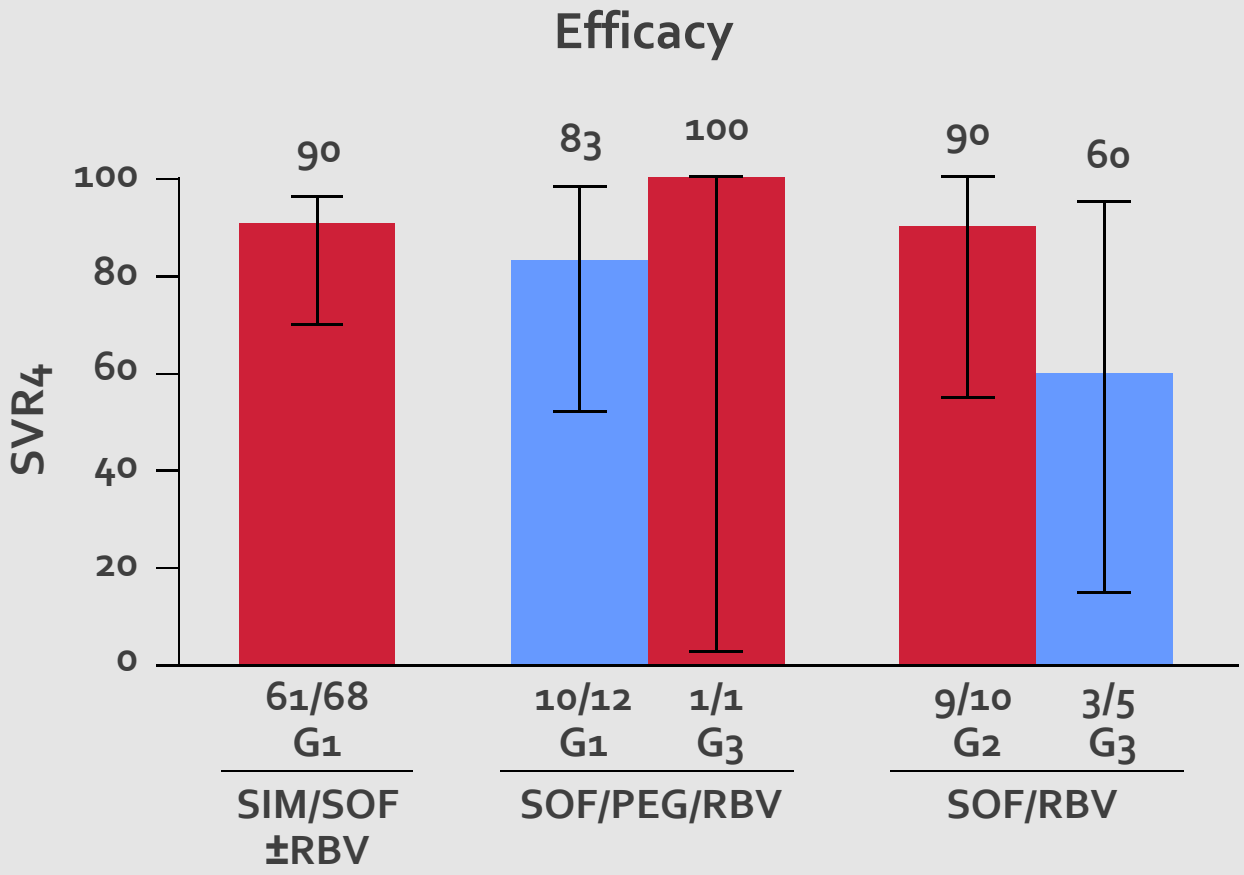
Safety and efficacy of new DAA-based therapy for HCV post-transplant: Interval results from the HCV-TARGET longitudinal, observational study (cont)



Brown RS, et al. AASLD 2014, Boston. #LB-4

Safety and efficacy of new DAA-based therapy for HCV post-transplant: Interval results from the HCV-TARGET longitudinal, observational study (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014



Brown RS, et al. AASLD 2014, Boston. #LB-4

Safety and efficacy of new DAA-based therapy for HCV post-transplant: Interval results from the HCV-TARGET longitudinal, observational study (cont)

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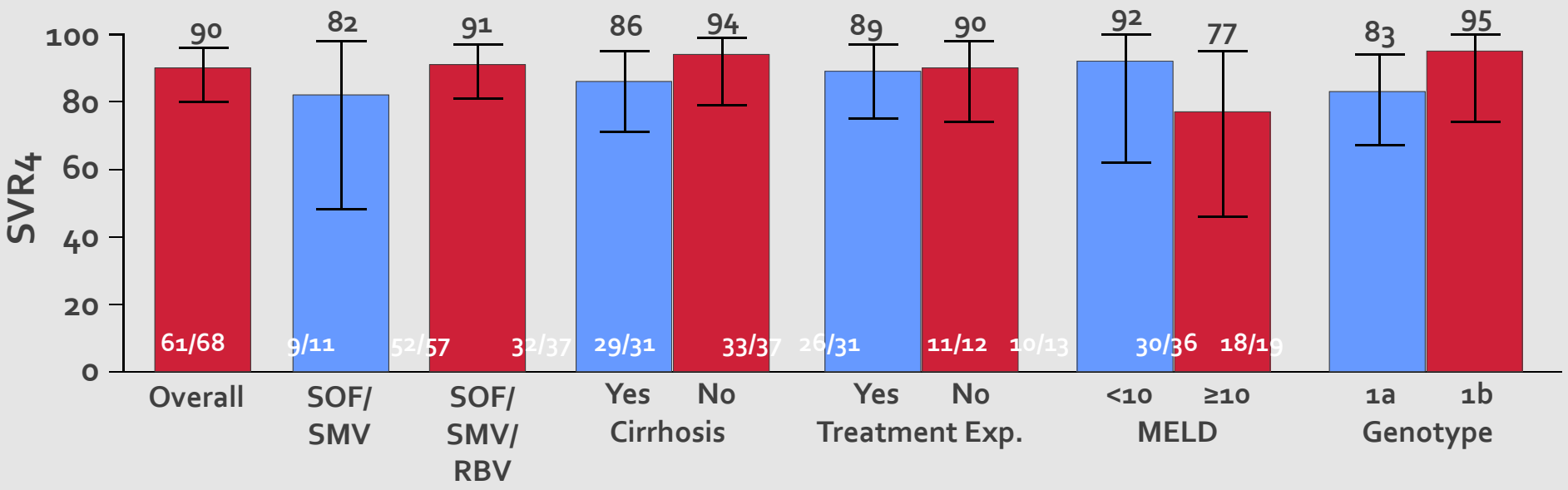

Brown RS, et al. AASLD 2014, Boston. #LB-4

Safety and efficacy of new DAA-based therapy for HCV post-transplant: Interval results from the HCV-TARGET longitudinal, observational study (cont)

NEW OPTIONS IN HCV THERAPY: UPDATE FROM AASLD 2014

Safety

	SOF PEG RBV (N=27)	SOF RBV (N=57)	SOF SMV ± RBV (N=143)	Total* (N=227)
Completed treatment, n (%)	**24 (88.9)**	**31 (54.4)**	**102 (74.4)**	**157 (69.2)**
Ongoing treatment, n (%)	3 (11.1)	24 (42.1)	28 (25.2)	63 (27.8)
D/C prematurely, n (%)	**0**	**2 (3.5)**	**4 (3.5)**	**7 (3.1)**
AE, n (%)	0	1 (1.8)	3 (2.7)	5 (2.2)
Death, n (%)	0	0	2 (1.8)	3 (1.3)

- AEs, mild and manageable
- SAEs 8.5%

- SOF-based therapy safe and effective post-OLT, despite >50% with advanced graft disease
- Lower SVR in 1a due to Q80K?
- Benefit of RBV in 12 week SIM/SOF
- Should treat earlier when IMS lowered but before onset of cirrhosis?

Brown RS, et al. AASLD 2014, Boston. #LB-4