Treating now vs. post transplant

Pros (for treating pre transplant)

- **If SVR efficacy means**
  - Better quality of life
  - Removal from waiting list
  - No post transplant recurrence
- **Few drug drug interactions**

Cons if treated pre transplant

- **Progression despite SVR**
- **Decreased response rates in advanced fibrosis/cirrhosis**
- **Longer duration for some**
- **Toxicity?**
- **Risk of decompensation**
- **Sudden progression**
- **Health costs advanced disease?**
- **Post transplant recurrent disease easily treated**
- **Resistance with treatment failure**

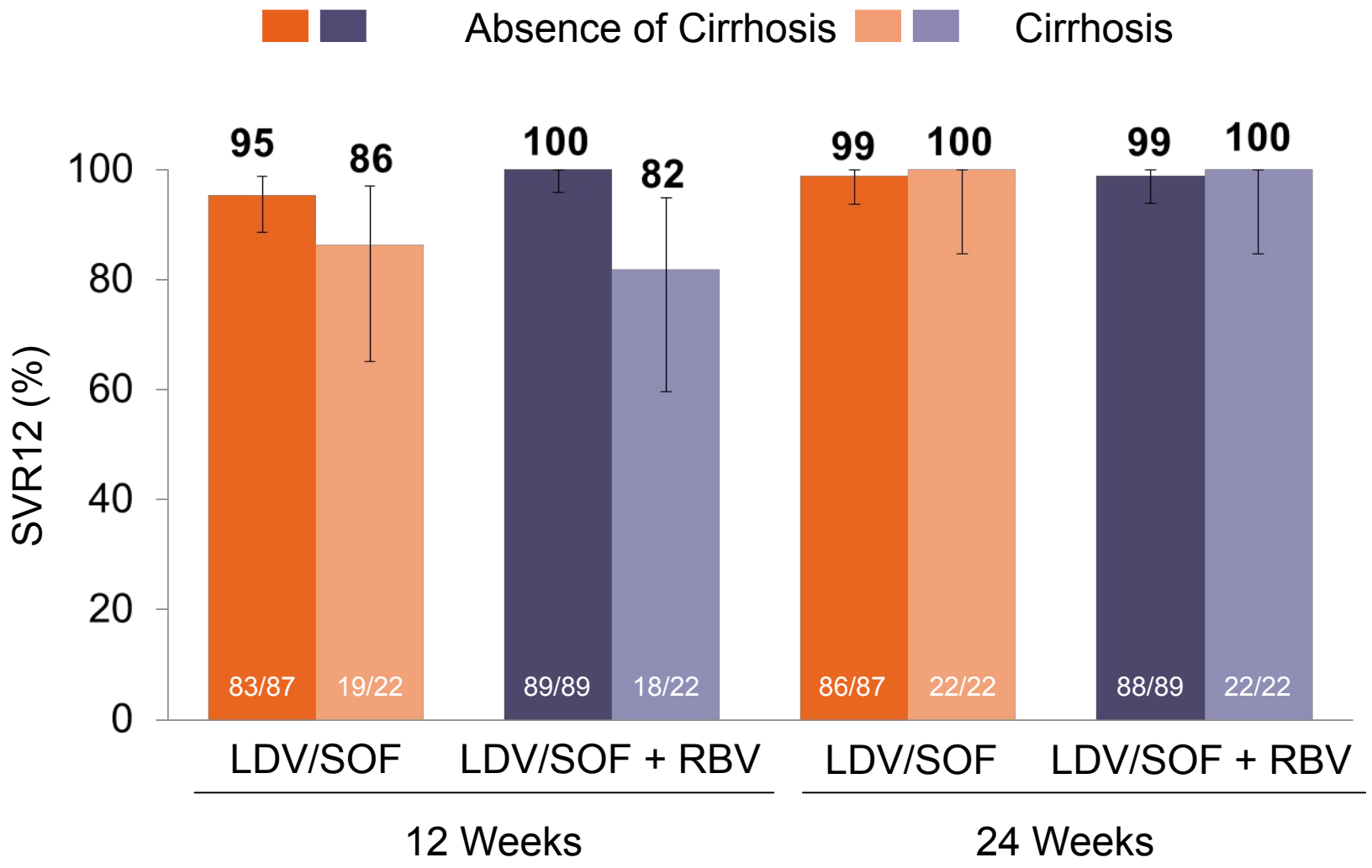
Scrutinising results in cirrhosis

- **Comparative results in patients with advanced cirrhosis**
- **Safety**
- **Resistance**
  - Retreatment options
- **Pharmacokinetics**
- **Overall evidence decision**

SVR12: Absence of Cirrhosis vs Cirrhosis

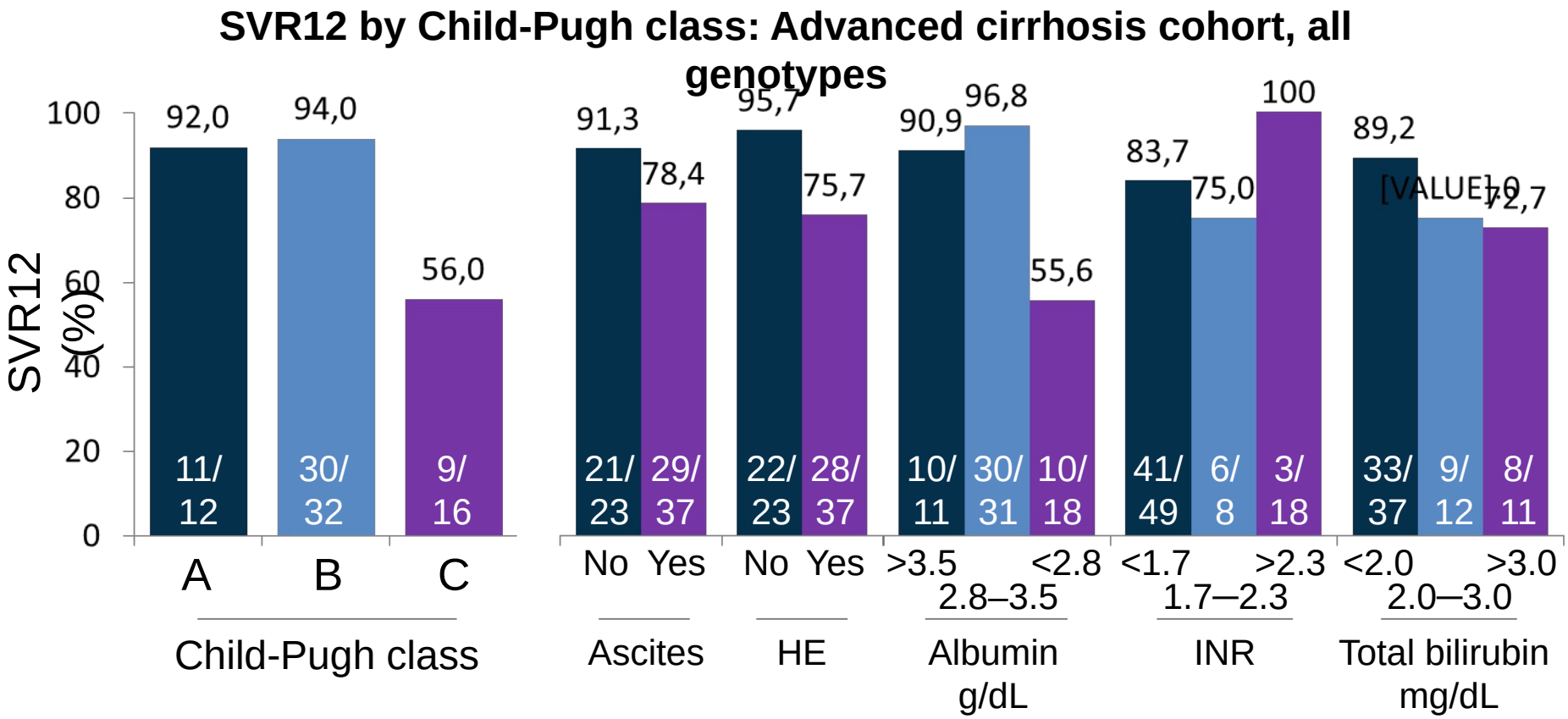
GT 1 Treatment-Experienced (ION-2)

Afdhal et al NEJM 2014



Error bars represent 95% confidence intervals.

ALLY-1: DCV, SOF + RBV combination for HCV patients with advanced cirrhosis or post-transplant recurrence

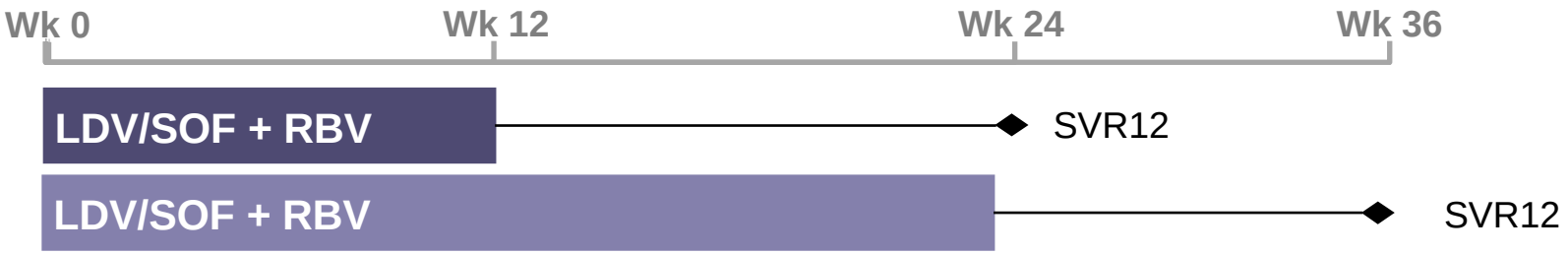


- Post-transplant results similar to SOLAR trials
- CP C patients have reduced SVR secondary to relapse of unclear mechanism
- Effect on long-term outcomes critical to make decision of whether to treat CP C

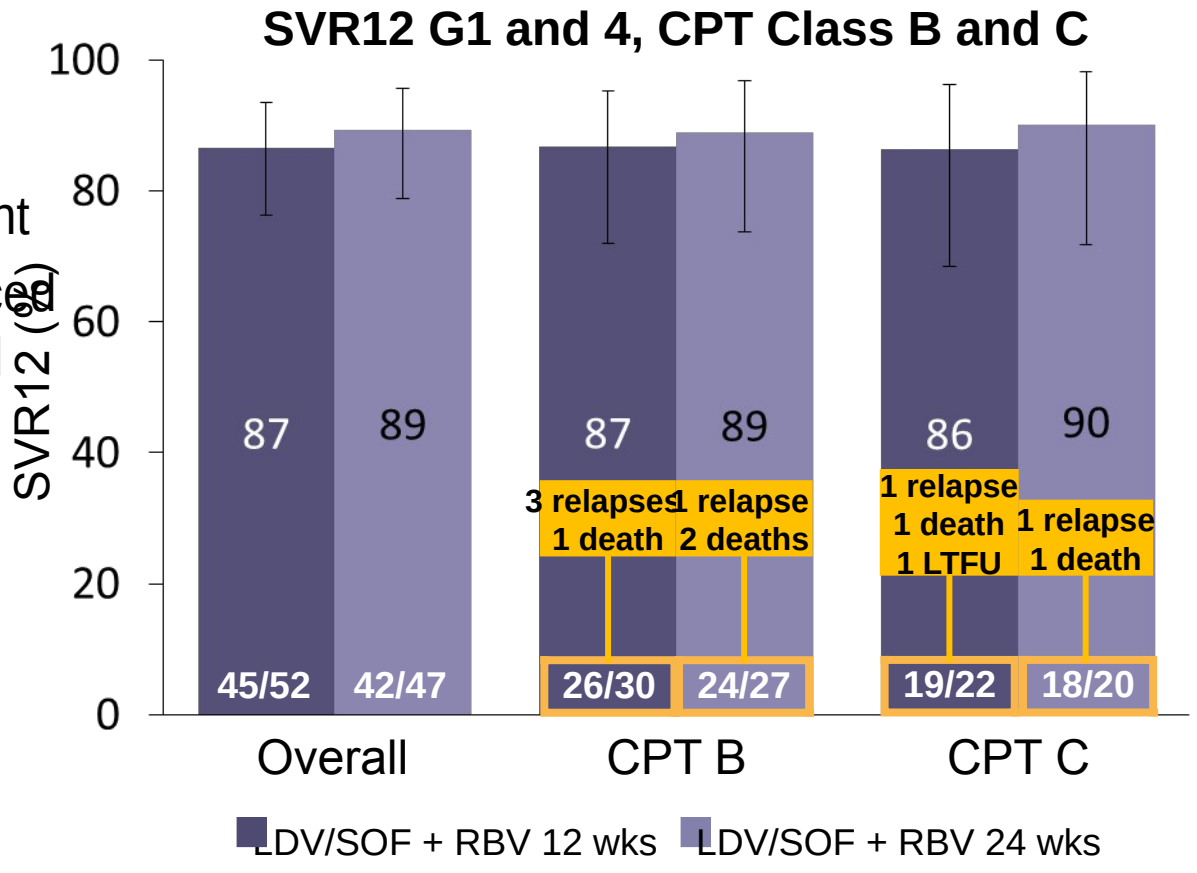
Poordad F, et al. EASL 2015, Vienna. #LO8

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

Flamm SL, et al. AASLD 2014, Boston. #239 Charlton Gastroenterology 2015

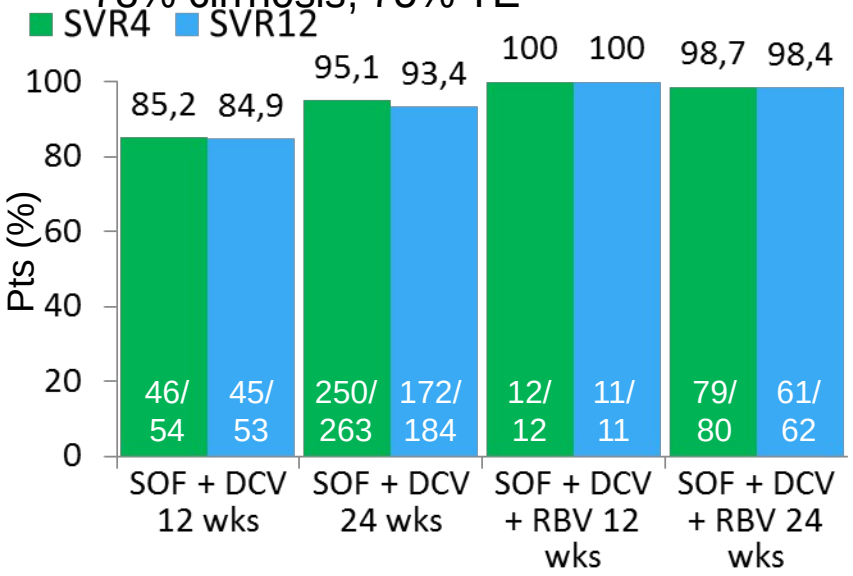


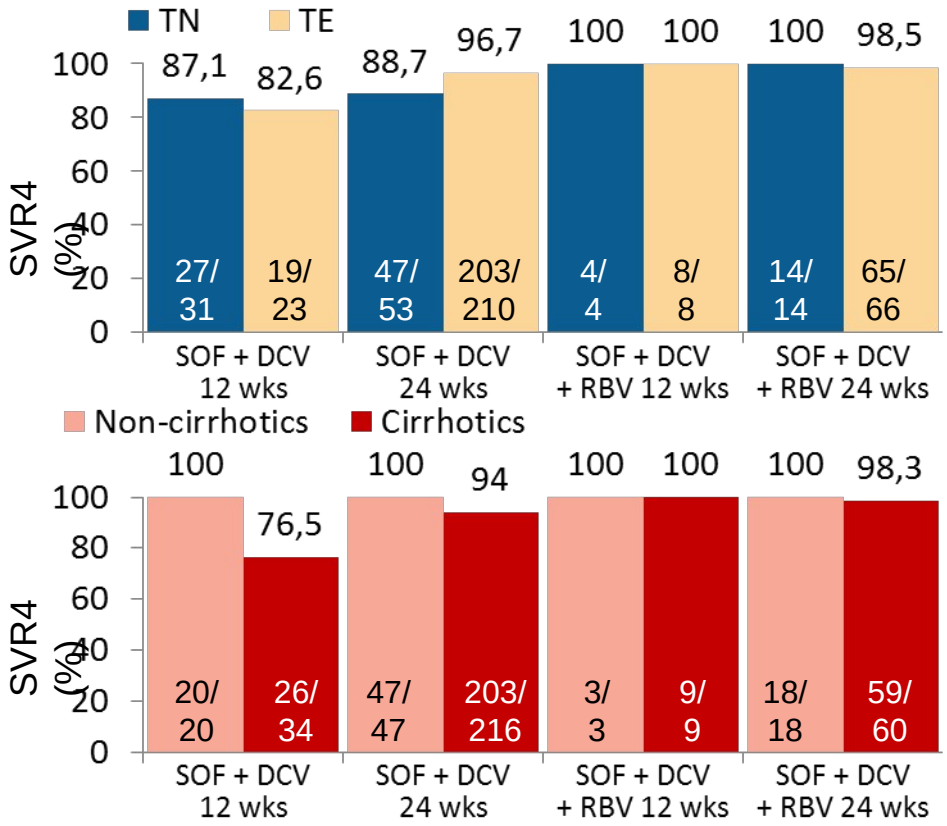
- 108 patients randomized 1:1 to 12 or 24 weeks of treatment
- G1 or 4 tx-naïve or experienced patients with decompensated cirrhosis
  - CPT class B (7–9) or C (score 10–12)



DCV + SOF in G1 monoinfected patients from French observational cohort ANRS CO22 HEPATHER

- Real-world French database
- 409 pts treated with DCV + SOF ± RBV
  - RBV n=92; no RBV n=317
  - 78% cirrhosis; 75% TE





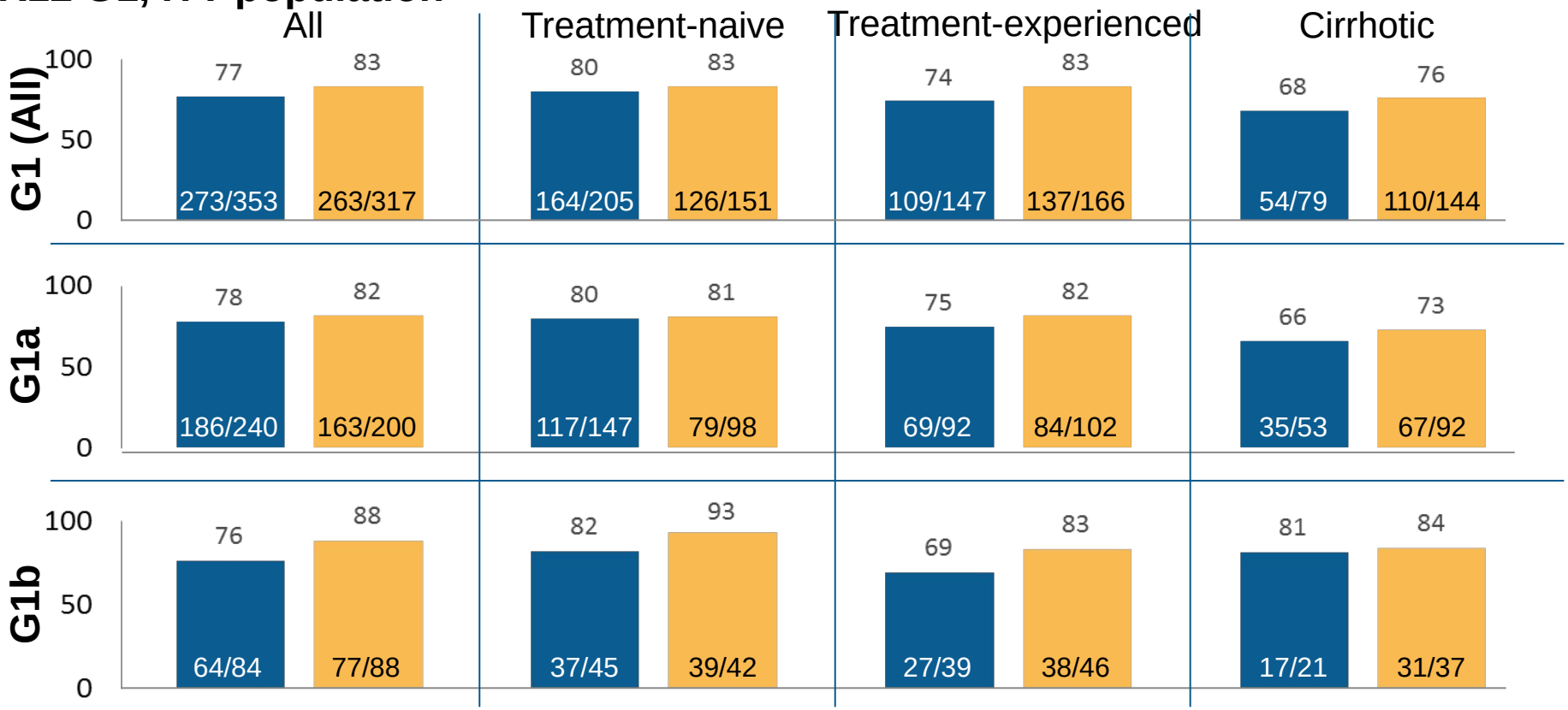
- Factors associated with failure:
  - No RBV
  - 12-week duration
  - Cirrhosis

- 100% SVR for non-cirrhotics with all regimens
- Without RBV, 24 weeks better than 12 for cirrhotics
- RBV may eliminate need for extra 12 wks (as for LDV/SOF)
- Authors recommended 12 wks DCV + SOF + RBV

Pol S, et al. EASL 2015, Vienna. #LO3

regimens containing SOF ± SMV in the TRIO network: Academic and community treatment of a real-world, heterogeneous population

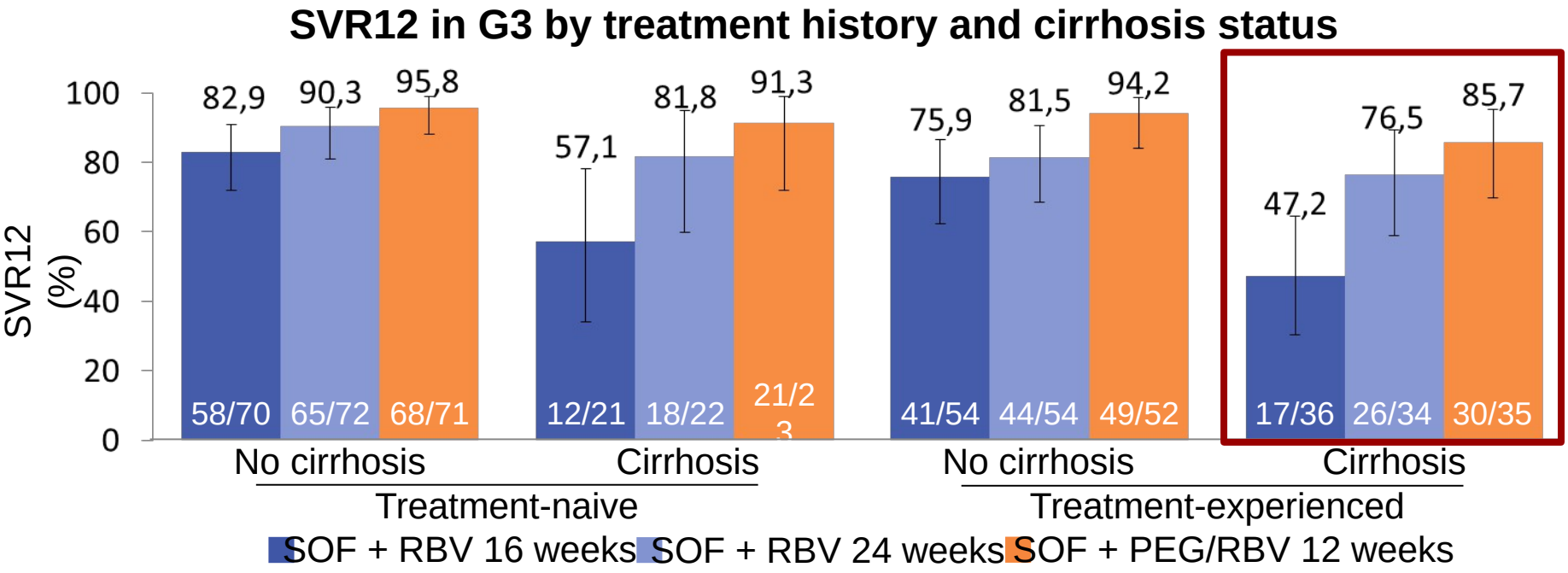
SVR12 G1, ITT population



- Both regimens performed less well than in clinical trials in cirrhosis pts
- G1a performed less well than G1b
- PR/SOF performed well in treatment failure non-cirrhotic at 74% as predicted by FDA

Dieterich D, et al. EASL 2015, Vienna. #P0775

BOSON: SOF + PEG-IFN/RBV for 12 weeks vs SOF + RBV for 16 or 24 weeks in G3 HCV-infected patients and treatment-experienced cirrhotic G2 patients



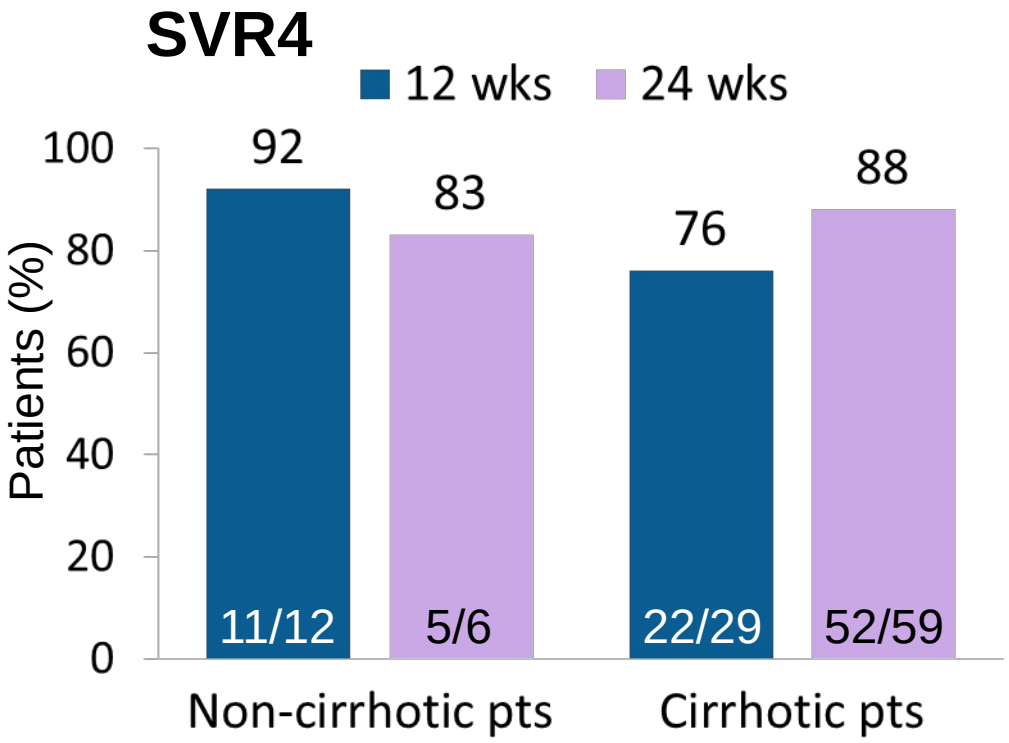
- SOF treatment-emergent variants L159F and V321A were observed in 9/78 (12%) pts:
  - L159F was present at baseline and at the time of virologic failure in 1 patient, and at the time of virologic failure in 6 patients
  - V321A emerged at the time of virologic failure in 2 patients

- Peg-IFN RBV with SOF still a treatment option for G3
- 16 week SOF + RBV for G3 did not meet expectation
- Newer DAAs with activity against G3 still a necessity

Foster GR, et al. EASL 2015; Vienna. #LO5

Daclatasvir (DCV) + sofosbuvir (SOF) ± ribavirin (RBV) in G3 patients: Interim analysis of a French multicenter compassionate use program

- 601 G3 pts received:
  - DCV + SOF for 12 wks (4%)
  - DCV + SOF + RBV for 12 wks (17%)
  - DCV + SOF for 24 wks (15%)
  - DCV + SOF + RBV for 24 wks (64%)
- Patients:
  - ≥F3 / extrahepatic manifestations / post-LT HCV recurrence / indication for liver or kidney transplant
  - Mostly male (75%), mono-infected (83%), cirrhotic (77%), treatment-experienced (73%
  - Median BL platelets 118.5 x
  - Median BL albumin 39.0 g/L

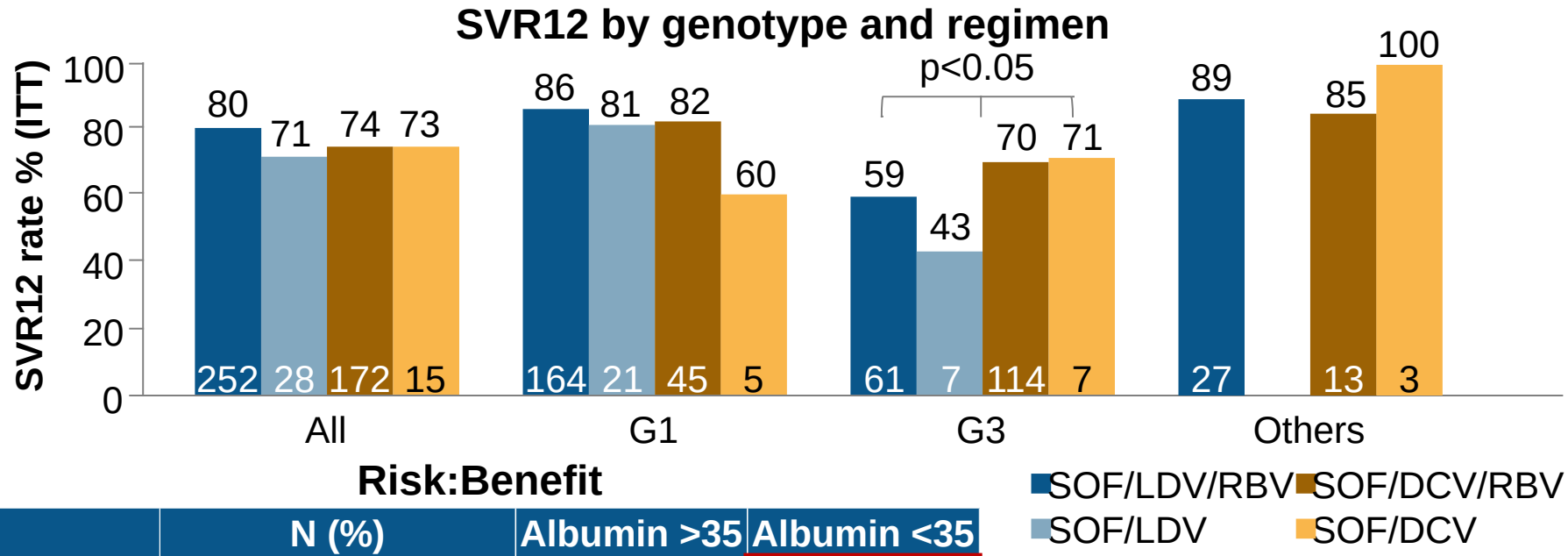


- d/c related to AEs (1 pt), death (2 pts), patient decision (1 pt)

- 12-week regimen effective for non-cirrhotic G3 pts
- Cirrhotics appear to benefit from 24 weeks
- Effect of RBV not included in analysis

Hezode C, et al. EASL 2015, Vienna. #LP05

Treatment of decompensated HCV cirrhosis in patients with diverse genotypes: 12 weeks SOF + NS5A inhibitors ± RBV is effective in HCV G1 and G3

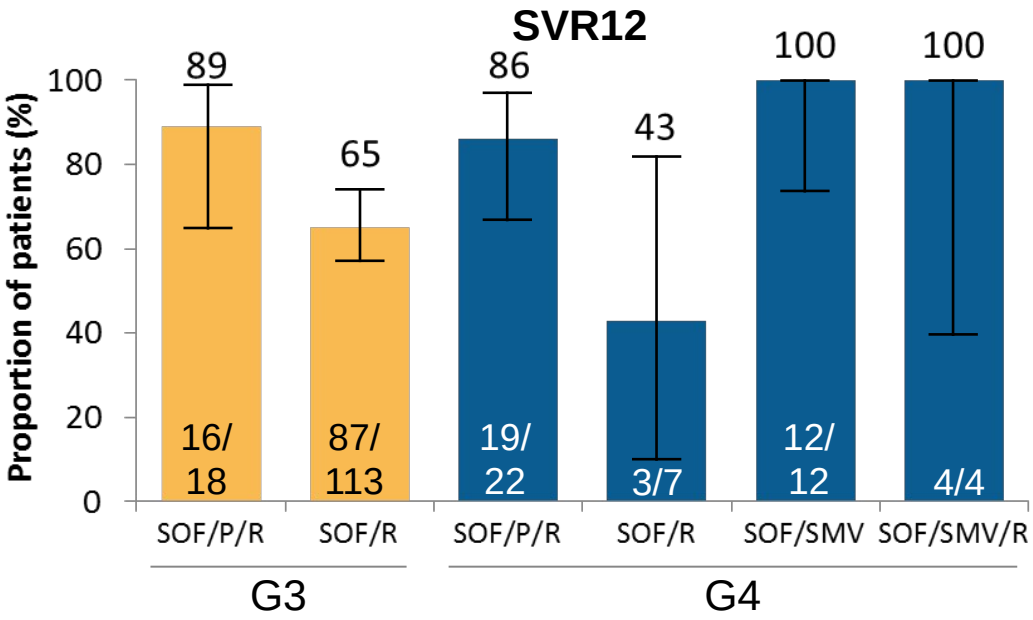


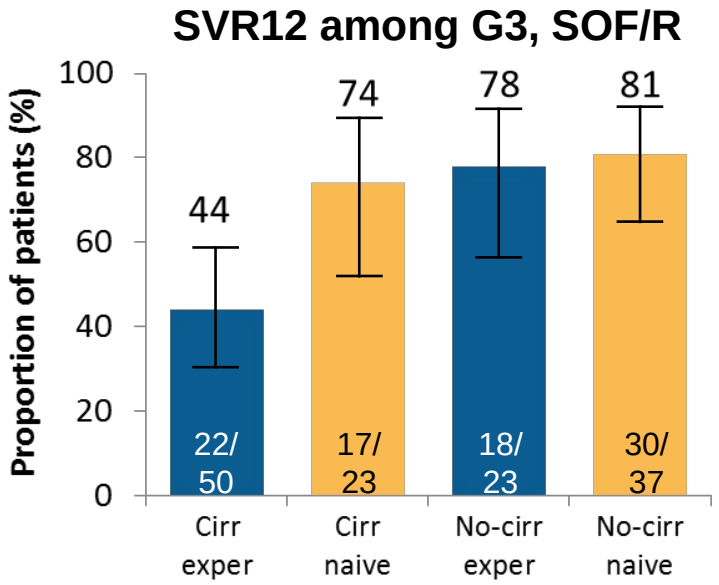
Risk:Benefit

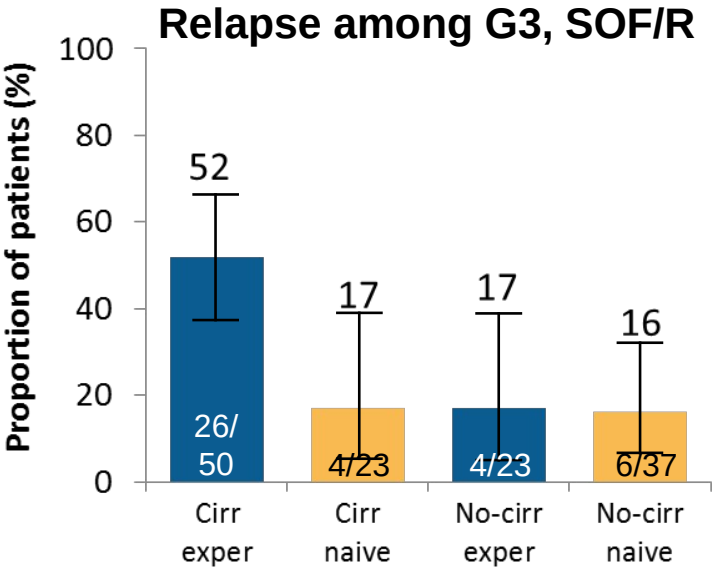
	N (%)	Albumin >35	Albumin <35
Age <65	'Harmed' SAE/MELD worse by 2	14 (14%)	94 (33%)
	Helped MELD improved by 2	29 (28%)	53 (18%)
	Total	102	288
Age >65	'Harmed' SAE/MELD worse by 2	9 (32%)	14 (33%)
	Helped MELD improved by 2	4 (14%)	6 (14%)
	Total	28	43

- Restricted regimen: 12 weeks SOF only
- Encouraging results in G1 somewhat concerning G3
- G3 SVR favored by SOF + DCV vs SOF + LDV, compared with EC_{50}s
- Estimates of risk benefit may

Safety and effectiveness of SOF-based regimens for the treatment of HCV G3 and 4 infections: Interim analysis of a prospective, observational study



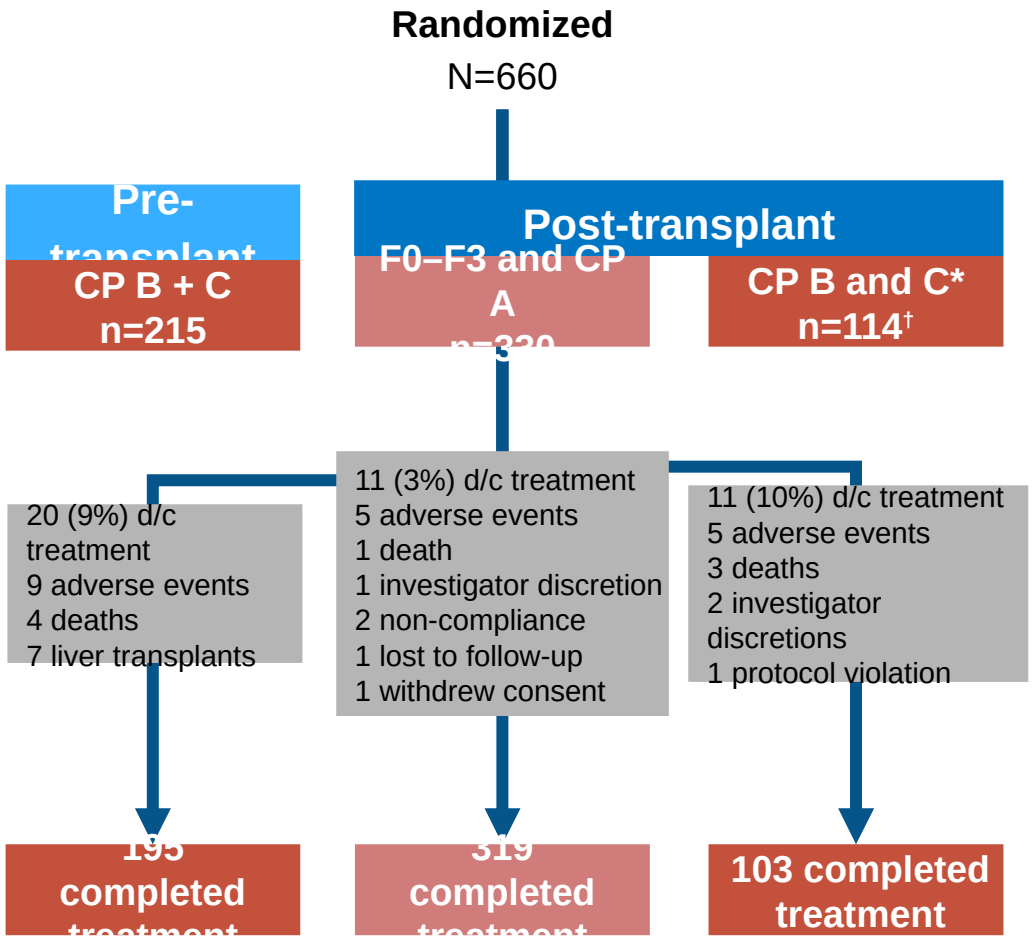




- G4 is more effectively treated with 2 oral DAAs
- G3 treatment with SOF/RBV was less effective in real-world
  - TE cirrhosis – only 44% SVR
  - Markers of advanced liver disease (MELD, albumin, platelet count) predictive of SVR

Alqahtani S, et al., EASL 2015, Vienna. #P0840

Integrated safety analysis of SOLAR 1 and 2:
LDV/SOF + RBV in >600 decompensated and post-LT patients with HCV infection



*17 post-transplantation CP C patients were enrolled
†One patient who was randomized was not dosed

Samuel D, et al. EASL 2015, Vienna. #P0774

Treatment-emergent deaths	Population	
Did not complete treatment		
Septic shock	Pre	CP B
Cardiac arrest in setting of sepsis	Pre	CP B
Oliguric renal failure	Pre	CP C
Septic shock	Pre	CP C
GI bleeding and liver failure	Pre	CP C
Multi-organ failure and septic shock	Pre	CP C
Cardiac arrest due to ischemic heart disease	Pre	CP C
Staphylococcus aureus sepsis	Pre	CP C
GI bleeding & liver failure	Post	CP A
Progressive multifocal leukoencephalitis	Post	CP A
Thoracic aorta aneurysm dissection	Post	CP B
Internal bleeding	Post	CP B
Multi-organ failure with sepsis	Post	CP B
Multi-organ failure due to decompensated cirrhosis	Post	CP B
Infiltrative multifocal hepatocarcinoma	Post	CP C
Intestinal ischemia	Post	CP C
Died ≤30 days after completing treatment		
Sepsis and multi-organ failure	Pre	CP B
Liver failure due to chronic liver rejection	Post	F0–F3
Myocardial infarction	Post	CP A

HCV-TARGET: Safety and efficacy of SOF-containing regimens in HCV-infected patients with reduced renal function

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)		
Early treatment discontinuation AE	1 (6)	2 (3)		
Death	1 (6)	0 (0)		

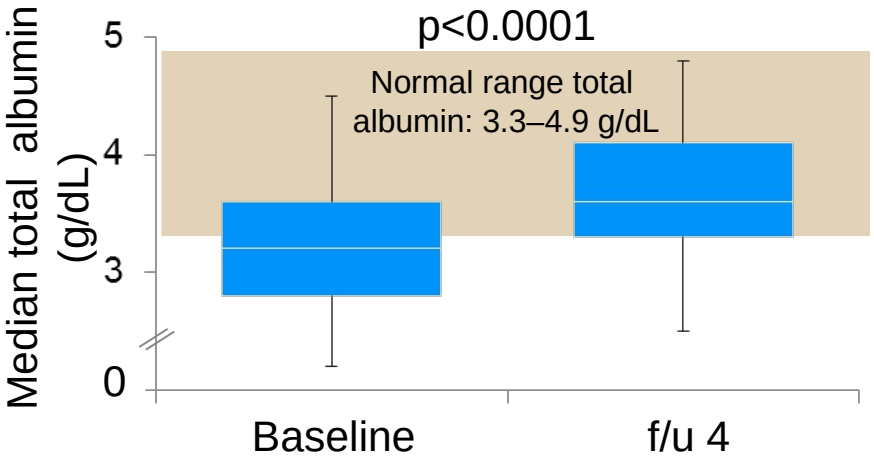
- In patients with eGFR <30 worsening renal function

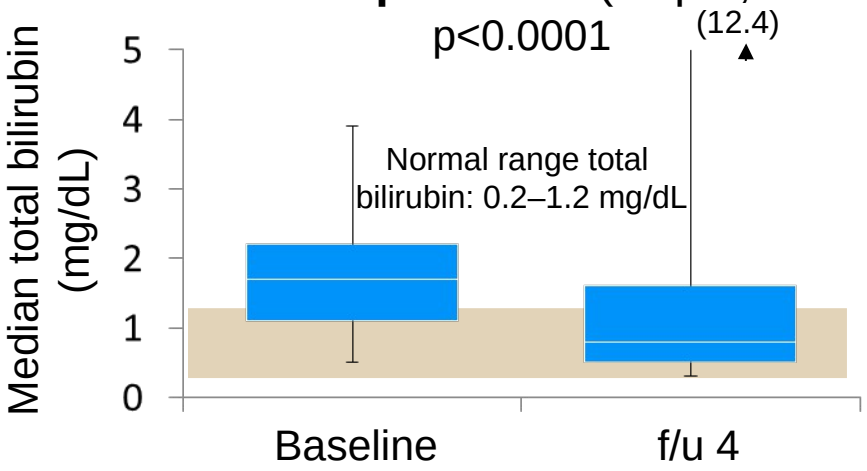
- More anemia and more monitoring with SOF-containing regimen
- Does not validate safety of DAA utilization

Saxena V, et al. EASL 2015, Vienna. #LP08

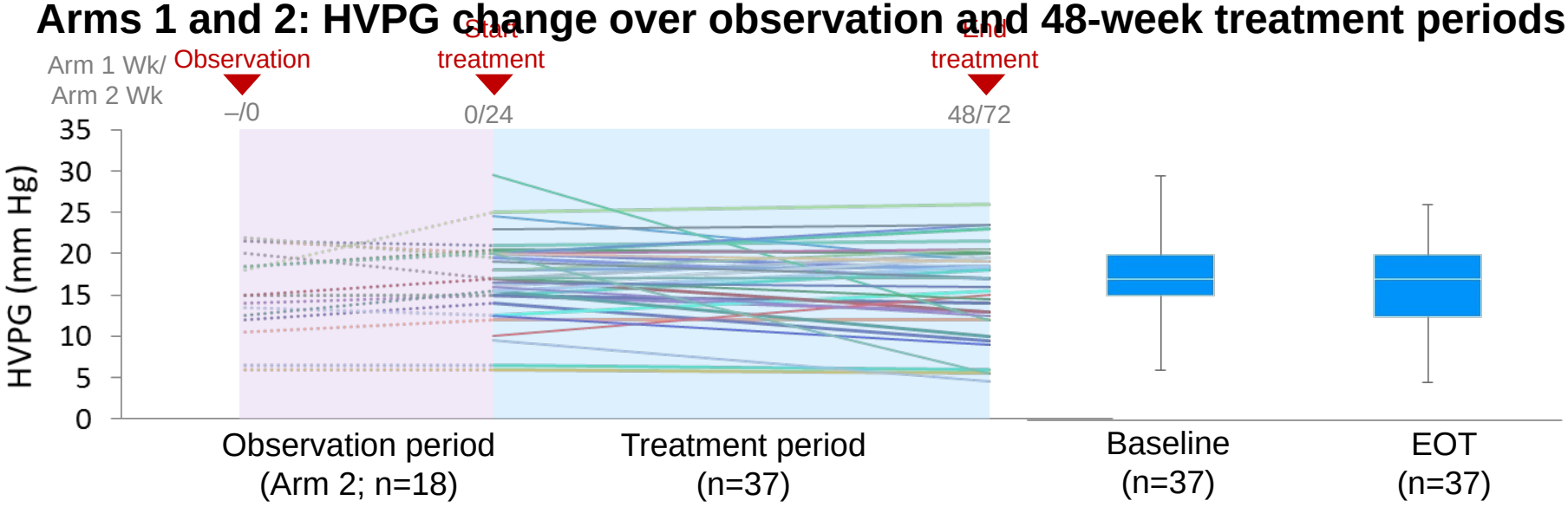
hepatic venous pressure gradient in HCV-infected patients with cirrhosis and portal hypertension

Median total albumin and bilirubin at baseline and follow-up Week 4 (all pts, N=96)





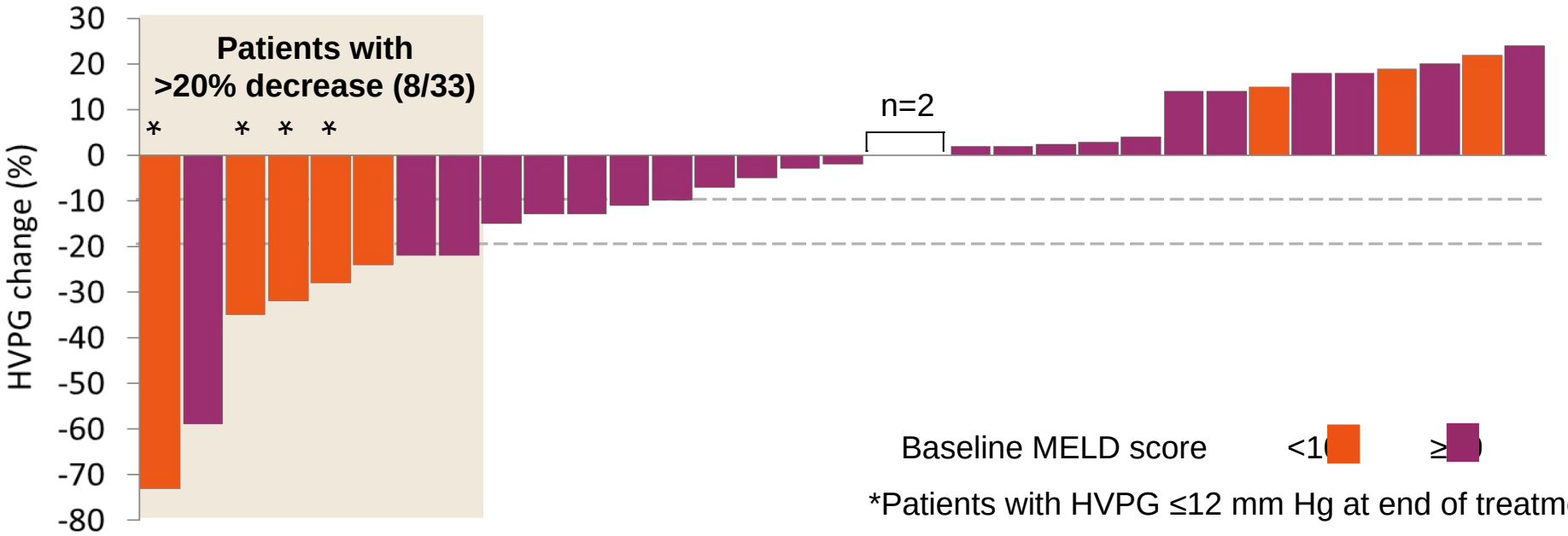
Arms 1 and 2: HVPG change over observation and 48-week treatment periods



Afdhal N, et al. EASL 2015, Vienna. #LP13

hepatic venous pressure gradient in HCV-infected patients with cirrhosis and portal hypertension

rms 1 and 2: HVPG % change after treatment in subset of patients with baseline HVPG ≥12 mm H



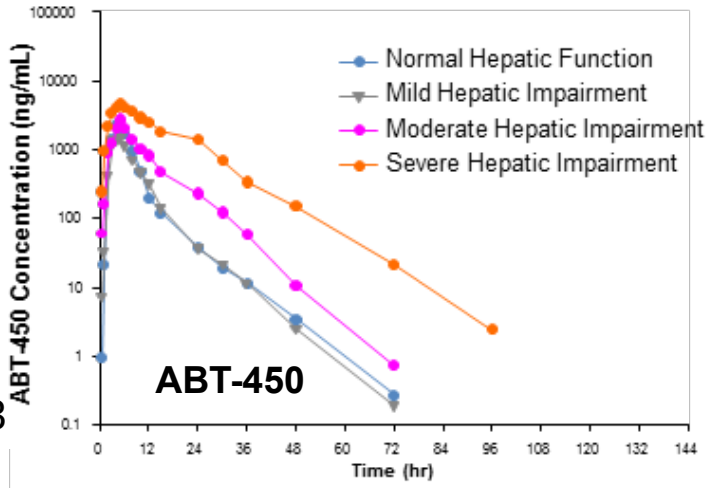
*Patients with HVPG ≤12 mm Hg at end of treatmer

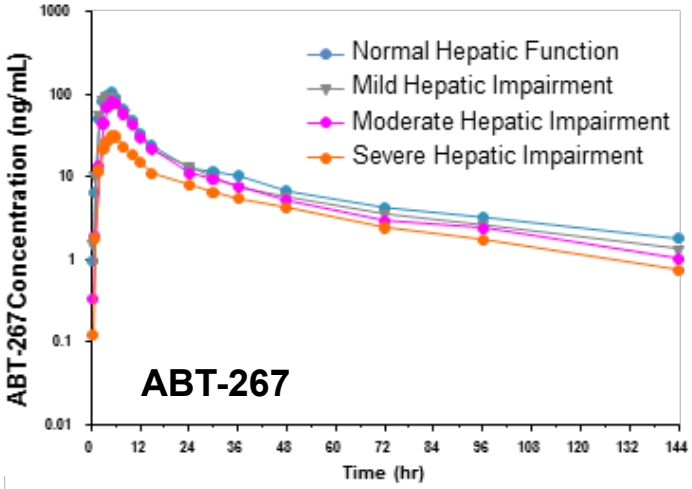
- SOF + RBV for 48 weeks: SVR rate of 72%
- Clinical improvement occurs after viral suppression more rapidly than remodeling of fibrosis and reduction in HVPG
- Effect of SVR12 and long-term viral suppression/cure on HVPG may manifest later, and is being explored in these patients 1 year post-treatment

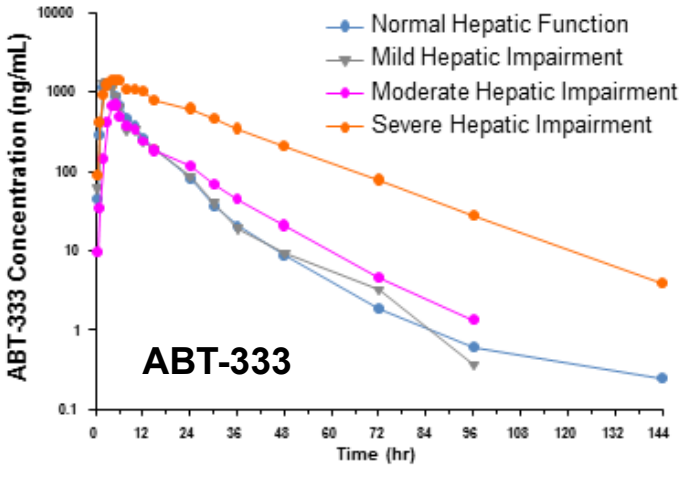
Afdhal N, et al. EASL 2015, Vienna. #LP13

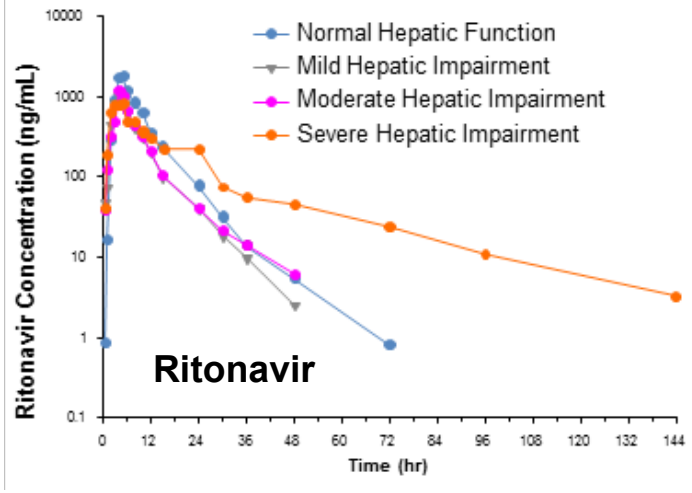
PK and safety of co-administered ABT-450/r, ABT-267 and ABT-333 as a single dose in subjects with normal hepatic function and in subjects with mild, moderate, and severe hepatic impairment

- **Mild impairment:** ABT-450, -333 and -267 exposures not clinically significantly different (AUCs up to ±30% different)
- **Moderate impairment:** ABT-333 and -267 exposures not clinically significantly different (AUCs ≤30% lower), ABT-450 exposures moderately higher (AUC 62% higher)
- **Severe impairment**: ABT-450 and -333 exposures significantly higher



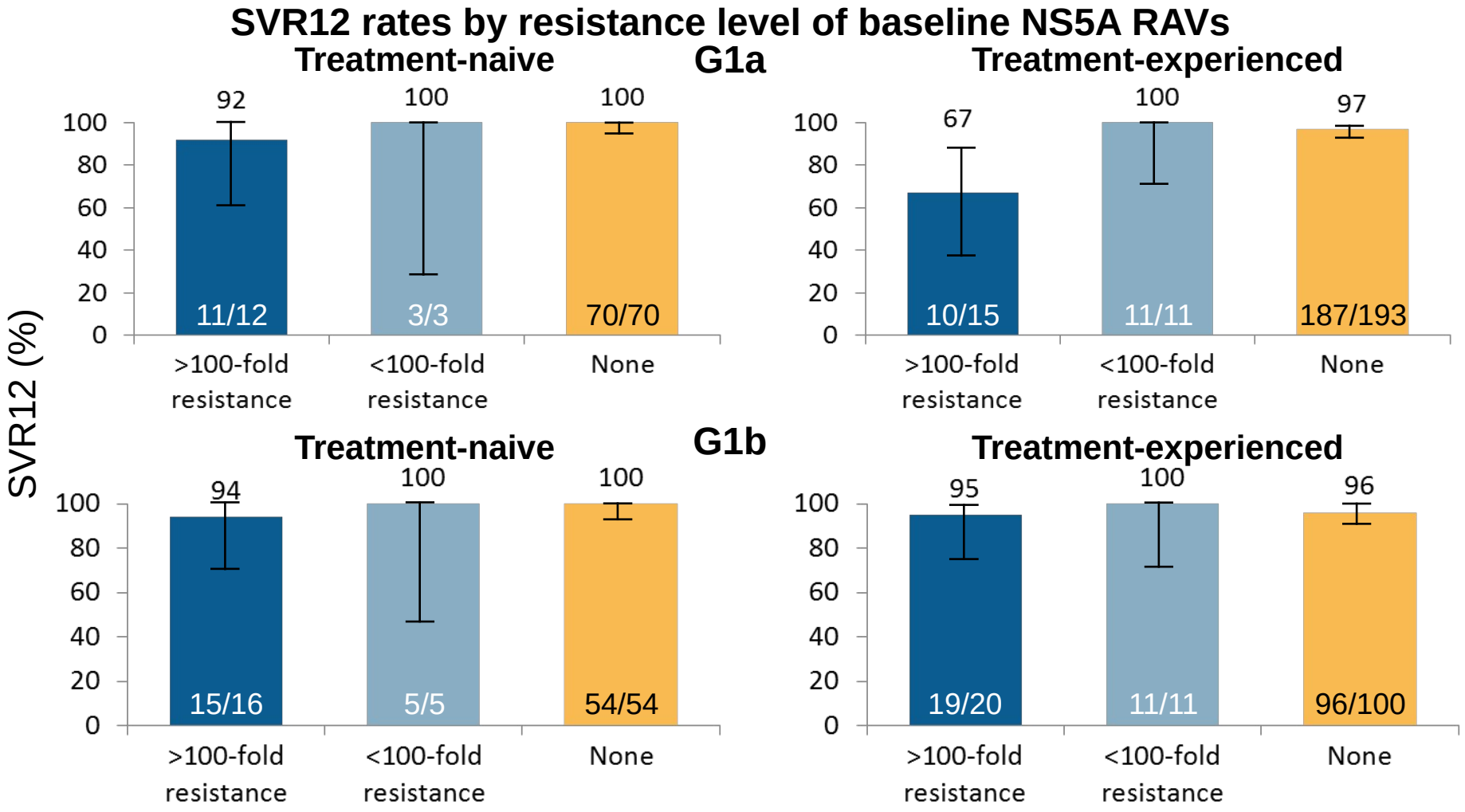






Khatri A, et al. AASLD 2012, Boston, #758

The prevalence and effect of HCV NS5A resistance-associated variants in subjects with compensated cirrhosis treated with LDV/SOF ± RBV



- NS5A RAVs important in G1 treatment-failure cirrhotics
- RBV, not ↑ duration, overcomes effective NS5A RAVs on relapse

Sarrazin C, et al. EASL 2015, Vienna. #P

Urgent lessons to be learned from DAA IFN free therapy in decompensated cirrhosis

- What degrees of cirrhosis impair response?
- What is the optimal duration of therapy for different stages of cirrhosis?
- Is mortality less than expected in this population
- Is the long term outcome better in Child Pugh C when treated pre transplant?
- What are the consequences of relapse?
- Are pre-existent resistant variants more critical in this group?
- Are there higher rates of adverse events in patients with decompensated cirrhosis?
- To what degree is disease reversible? Is the natural history of the disease altered? Is mortality lessened in this group