

L'AGORÁ PENITENZIARIA 2015  
XVI Congresso Nazionale SIMSPe-ONLUS  
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3-5 Giugno 2015  
Hotel Regina Margherita  
Viale Regina Margherita 44, Cagliari  
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Università degli Studi di Sassari  
Dipartimento di Medicina Clinica e Sperimentale



# La terapia anti-HCV IFN-free: scenario attuale

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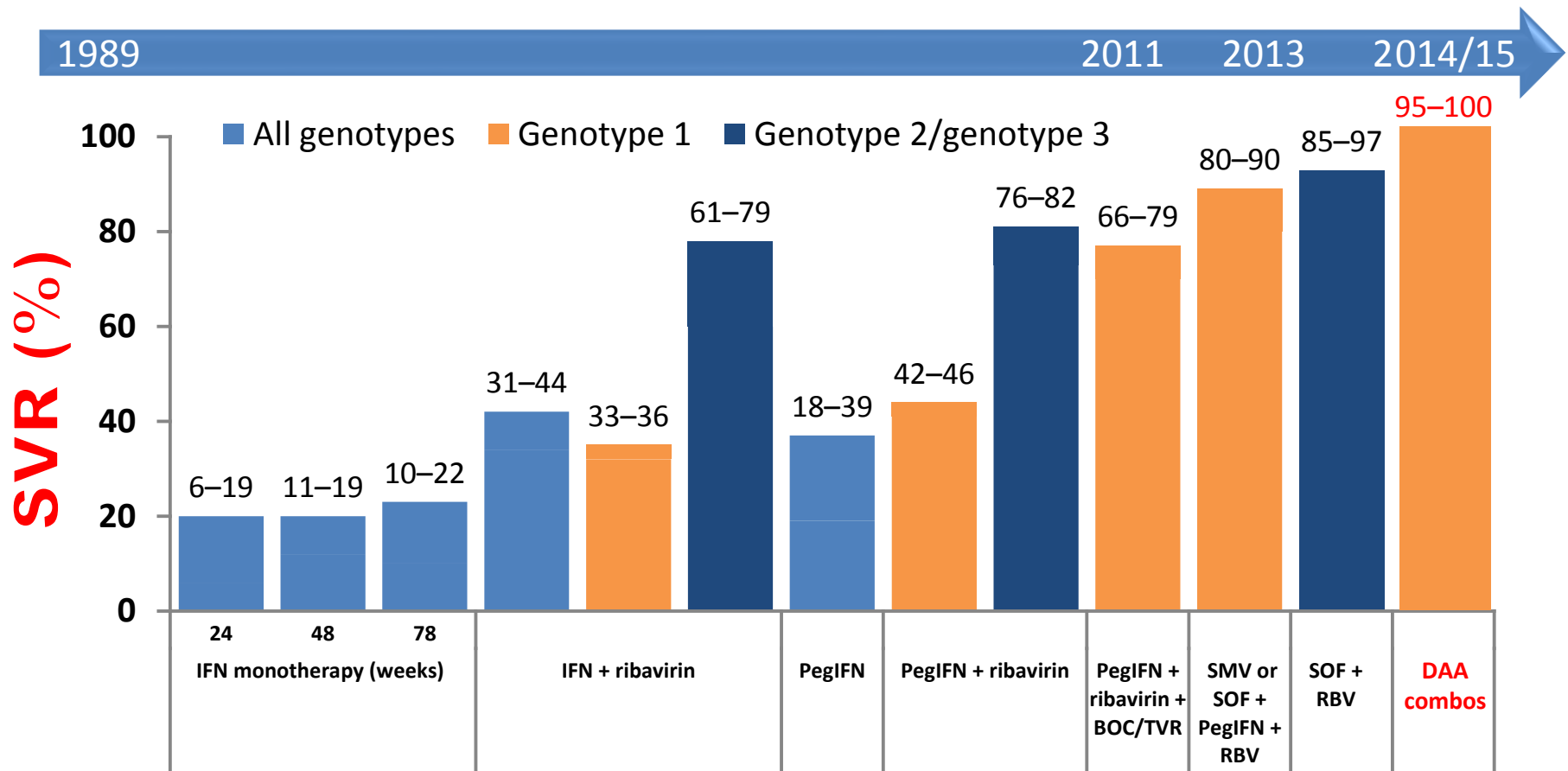
# La terapia anti-HCV IFN-free: scenario attuale (e futuro...)

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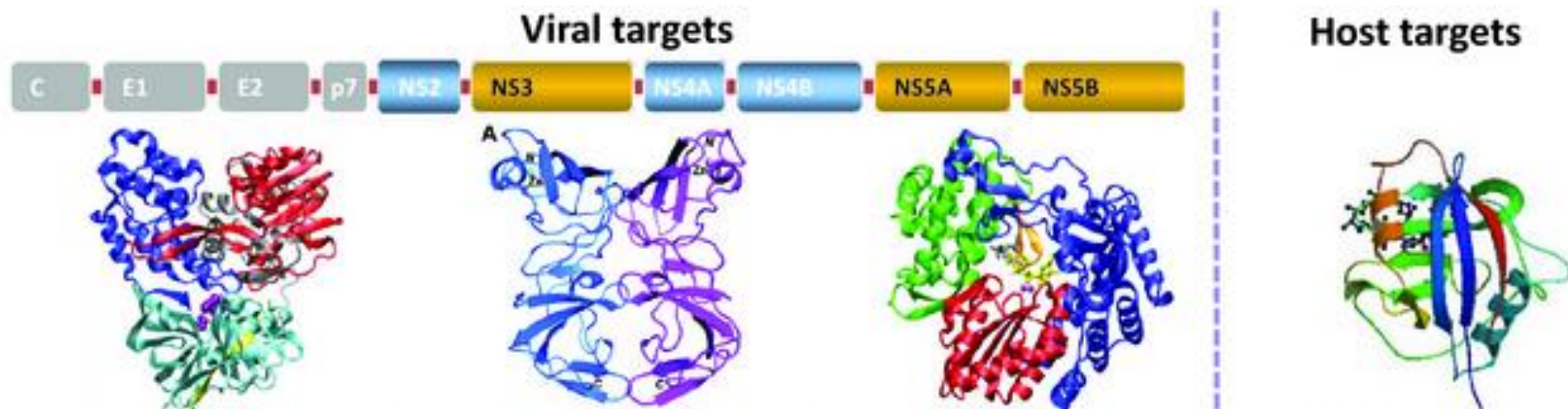
# Evolution of HCV treatment and SVR rates



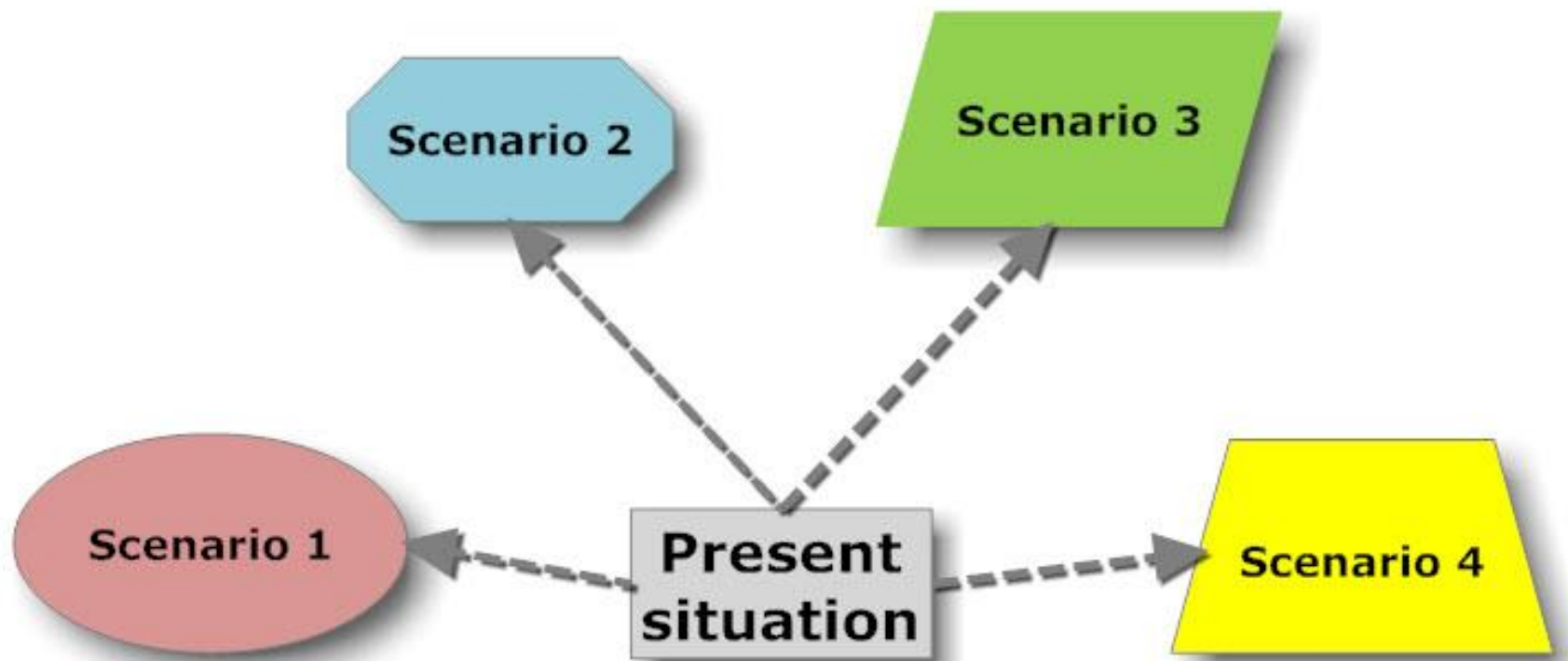
Davis GL, et al. *N Engl J Med* 1989; **321**:1501–1506; Poynard T, et al. *N Engl J Med* 1995; **332**:1457–1462; McHutchison JG, et al. *N Engl J Med* 1998; **339**:1485–1492; Poynard T, et al. *Lancet* 1998; **352**: 1426–1432; Zeuzem S, et al. *N Engl J Med* 2000; **343**:1666–1672; Lindsay KL, et al. *Hepatology* 2001; **34**:395–403; Pockros PJ, et al. *Am J Gastroenterol* 2004; **99**:1298–1305; Manns MP, et al. *Lancet* 2001; **358**:958–965; Fried MW, et al. *N Engl J Med* 2002; **347**:975–982; Poordad F, et al. *N Engl J Med* 2011; **364**:1195–1206; Jacobson IM, et al. *N Engl J Med* 2011; **364**:2405–2416; Simeprevir prescribing information, November 2013; Lawitz E, et al. *N Engl J Med* 2013; **368**:1878–1887; Zeuzem S, et al. *Hepatology* 2013; **58**(Suppl 1):733A; AbbVie press release 2014 [Accessed 25-02-14]; Gilead press release 2013 [Accessed 25-02-14]; Sulkowski MS, et al. *N Engl J Med* 2014; **370**:211–221.

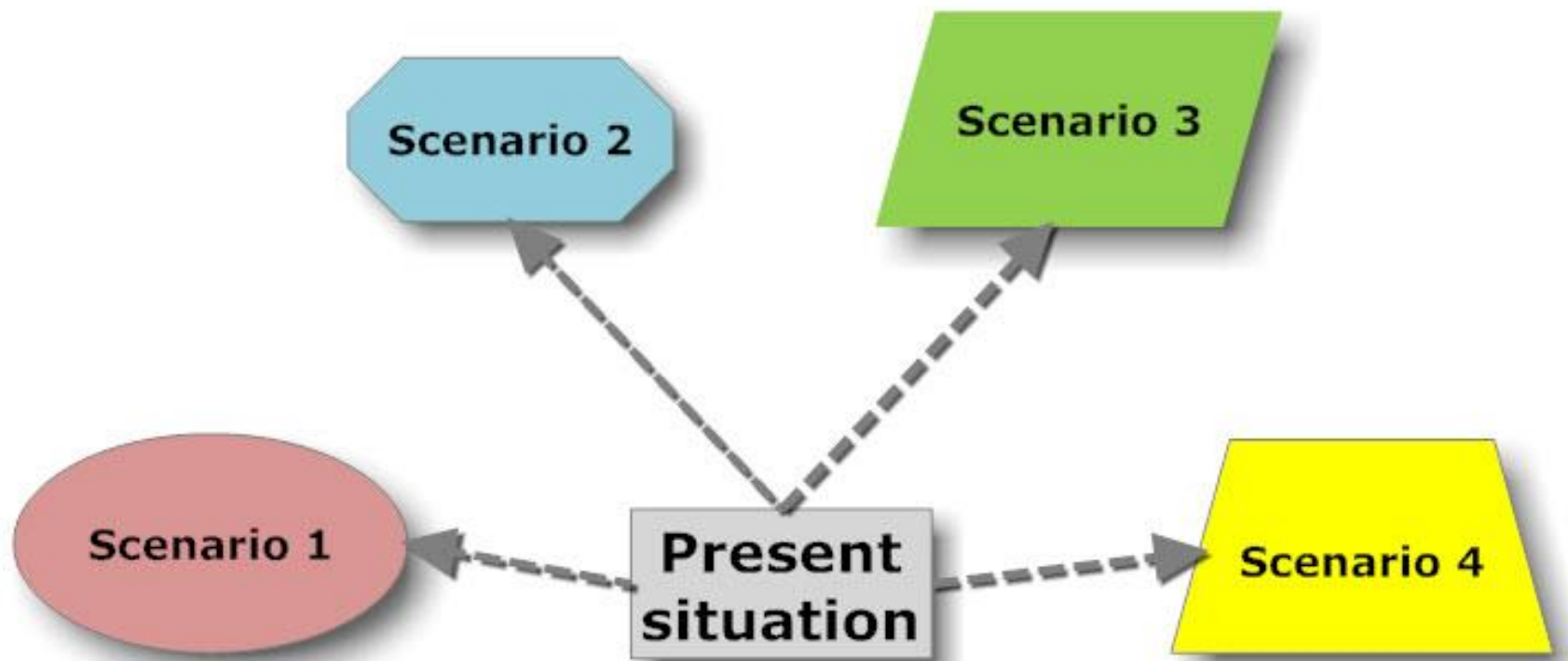


# Different classes of DAA and non-DAA for HCV infection



NS3	NS5A	NS5B	Cyclophilin A
The NS3/4A serine protease	Multifunctional phosphoprotein, component of the HCV-RNA replication complex	RNA-dependent RNA polymerase	Host protein interacting with NS5A and the NS5B
<b>Boceprevir</b> <b>Telaprevir</b> ABT-450/r, ACH-1625 Asunaprevir, TMC-435 (Simeprevir), BI-201335 Danoprevir/r, GS-9451 MK-5172	Daclatasvir GS-5885 ABT-267 PPI-668 MK	<u>Nucleos(t)ide analogue</u> GS-7977 (Sofosbuvir), Mericitabine, IDX-184 <u>Non-nucleoside analogue</u> BI-207127, ABT-333 ABT-072, BMS-791325 Tegobuvir, Setrobuvir VX-222, Filibuvir	Alisporivir  SCY-635











## **EASL Clinical Practice Guidelines: Management of hepatitis C virus infection**

European Association for the Study of the Liver\*

- **All treatment-naïve** patients with compensated disease due to HCV should be **considered for therapy** (recommendation A1)
- •Treatment should be **scheduled, not deferred**, for patients with significant fibrosis (METAVIR score **F3 to F4**) (recommendation A1)
- In patients with **less severe disease**, the indication for and timing of therapy can be **individualized** (recommendation B1)



- AASLD/IDSA guidance emphasizes the potential benefits of—and recommends treatment for—all pts with HCV infection
- **Urgent treatment initiation recommended for:**
  - Advanced fibrosis (Metavir F3)
  - Compensated cirrhosis (Metavir F4)
  - Liver transplantation
  - Severe extrahepatic HCV

- AASLD/IDSA guidance emphasizes the potential benefits of—and recommends treatment for—all pts with HCV infection
- **Urgent treatment initiation recommended for:**
  - Advanced fibrosis (Metavir F3)
  - Compensated cirrhosis (Metavir F4)
  - Liver transplantation
  - Severe extrahepatic HCV
- **Reduced HCV transmission expected with treatment of:**
  - Women wishing to become pregnant
  - Long-term hemodialysis pts
  - MSM with high-risk sexual practices
  - **Injection drug users**
  - **Incarcerated persons**

# EASL 2015 HCV\*: IFN-free therapy in Tx-Naive or PR-Exp'd, GT1, 4, 5, or 6, without cirrhosis

Regimen	HCV Genotype			
	1a	1b	4	5 or 6
LDV/SOF	8-12 wks, <sup>†</sup> no RBV		12 wks, no RBV	12 wks, no RBV
OBV/PTV/RTV + DSV	12 wks + RBV	12 wks, no RBV	Not recommended	Not recommended
OBV/PTV/RTV	Not recommended		12 wks + RBV	Not recommended
SOF + SMV	12 wks, no RBV		12 wks, no RBV	Not recommended
SOF + DCV	12 wks, no RBV		12 wks, no RBV	12 wks, no RBV

\*Recommendations the same for HCV-monoinfected and HCV/HIV-coinfected pts. <sup>†</sup>8 wks may be used in treatment-naïve pts without cirrhosis if baseline HCV RNA < 6 million IU/mL, but should be done with caution, especially in pts with F3 fibrosis.



# EASL 2015 HCV\*: IFN-free therapy in Tx-Naive or PR-Exp'd, GT1, 4, 5, or 6, compensated cirrhosis

Regimen	HCV Genotype			
	1a	1b	4	5 or 6
LDV/SOF	12 wks + RBV or 24 wks, no RBV or 24 wks + RBV if negative predictors	12 wks + RBV or 24 wks, no RBV or 24 wks + RBV if negative predictors	12 wks + RBV or 24 wks, no RBV or 24 wks + RBV if negative predictors	12 wks + RBV or 24 wks, no RBV or 24 wks + RBV if negative predictors
OBV/PTV/RTV + DSV	24 wks + RBV	12 wks + RBV	Not recommended	Not recommended
OBV/PTV/RTV	Not recommended	Not recommended	24 wks + RBV	Not recommended
SOF + SMV	12 wks + RBV or 24 wks, no RBV	12 wks + RBV or 24 wks, no RBV	12 wks + RBV or 24 wks, no RBV	Not recommended
SOF + DCV	12 wks + RBV or 24 wks, no RBV	12 wks + RBV or 24 wks, no RBV	12 wks + RBV or 24 wks, no RBV	12 wks + RBV or 24 wks, no RBV

\*Recommendations the same for HCV-monoinfected and HCV/HIV-coinfected pts.

**EASL HCV Guidelines. April 2015.**

# EASL 2015 HCV\*: IFN-free therapy in Tx-Naive & PR-Exp'd, GT2 or 3

Regimen	No Cirrhosis		Compensated Cirrhosis (Child-Pugh A)	
	GT2	GT3	GT2	GT3
<b>SOF + RBV<sup>†</sup></b>	12 wks	24 wks	16-20 wks	Not recommended
<b>SOF + DCV</b>	12 wks, no RBV	12 wks, no RBV	12 wks, no RBV	24 wks + RBV

\*Recommendations the same for HCV-monoinfected and HCV/HIV-coinfected pts.

<sup>†</sup>Best first-line option for genotype 2 HCV; other options may be useful in pts with GT 2 HCV who experience tx failure on sofosbuvir plus ribavirin. Suboptimal for genotype 3 HCV, particularly in pts with cirrhosis and previous failure of PR.

# “Harder-to-Treat” Populations

- **Cirrhosis status**
  - Compensated
  - Decompensated and post-OLT
- **Genotype 3 HCV infection**
- **DAA treatment experience**
- **Future issues**
  - new drugs

# **Management of HCV in Pts With Compensated Cirrhosis**



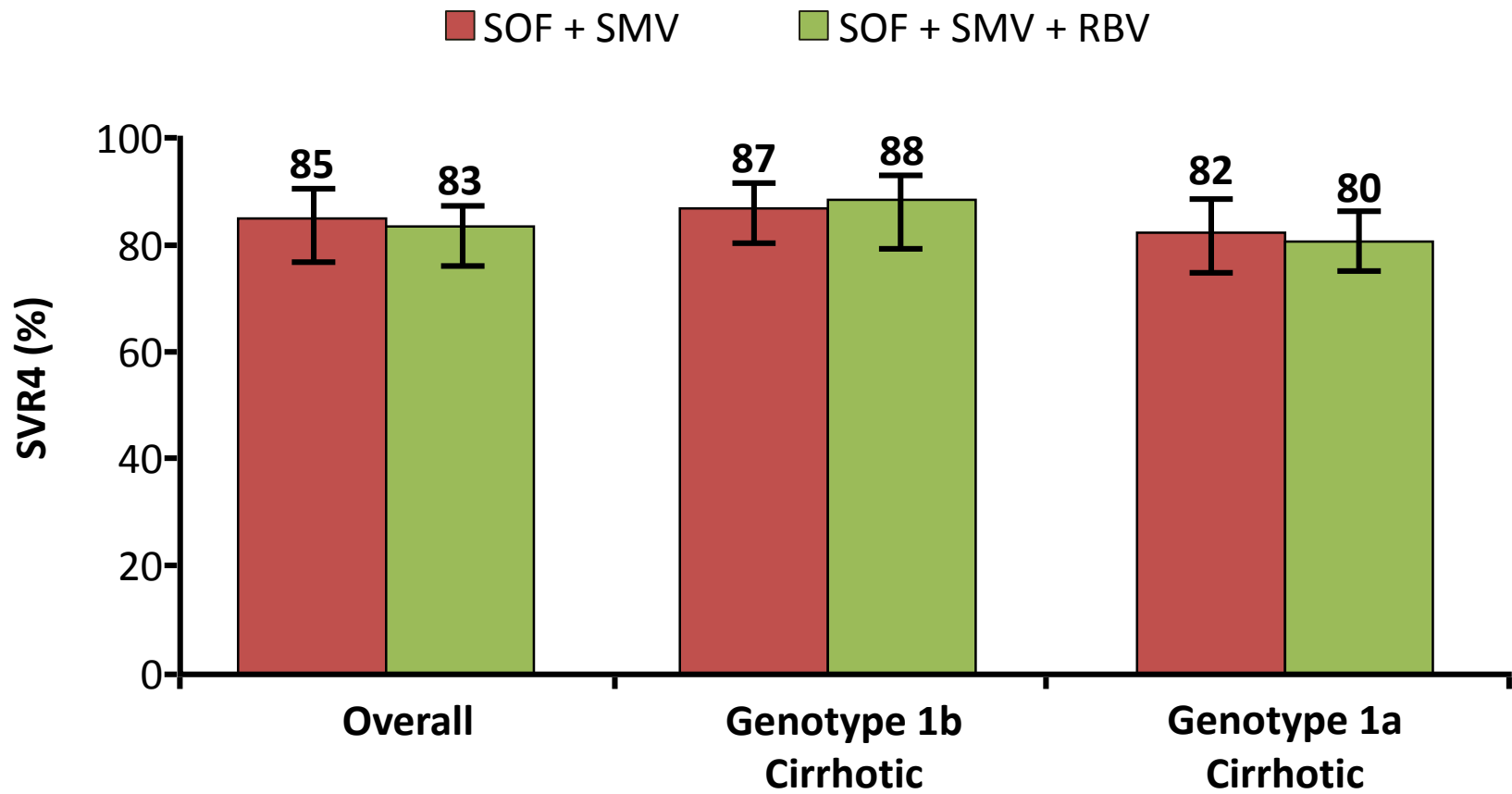
# OPTIMIST-2: SMV + SOF for 12 Wks in Cirrhotic Tx-Naive and Tx-Expd GT1 Pts

SVR12 Rate	12 Wks of Simeprevir + Sofosbuvir (n = 103)	
	% (n/N)	95% CI
Treatment history		
▪ Naive	<b>88 (44/50)</b>	78.0-98.0
▪ Experienced	<b>79 (42/53)</b>	67.4-91.1
HCV subgenotype		
▪ 1a	83 (60/72)	74.0-92.6
▪ 1a with Q80K	74 (25/34)	57.2-89.8
▪ 1a without Q80K	92 (35/38)	82.2-100
▪ 1b	84 (26/31)	69.3-98.4
IL28B genotype		
▪ CC	86 (25/29)	71.9-100
▪ CT	85 (46/54)	74.8-95.6
▪ TT	79 (15/19)	58.0-99.9

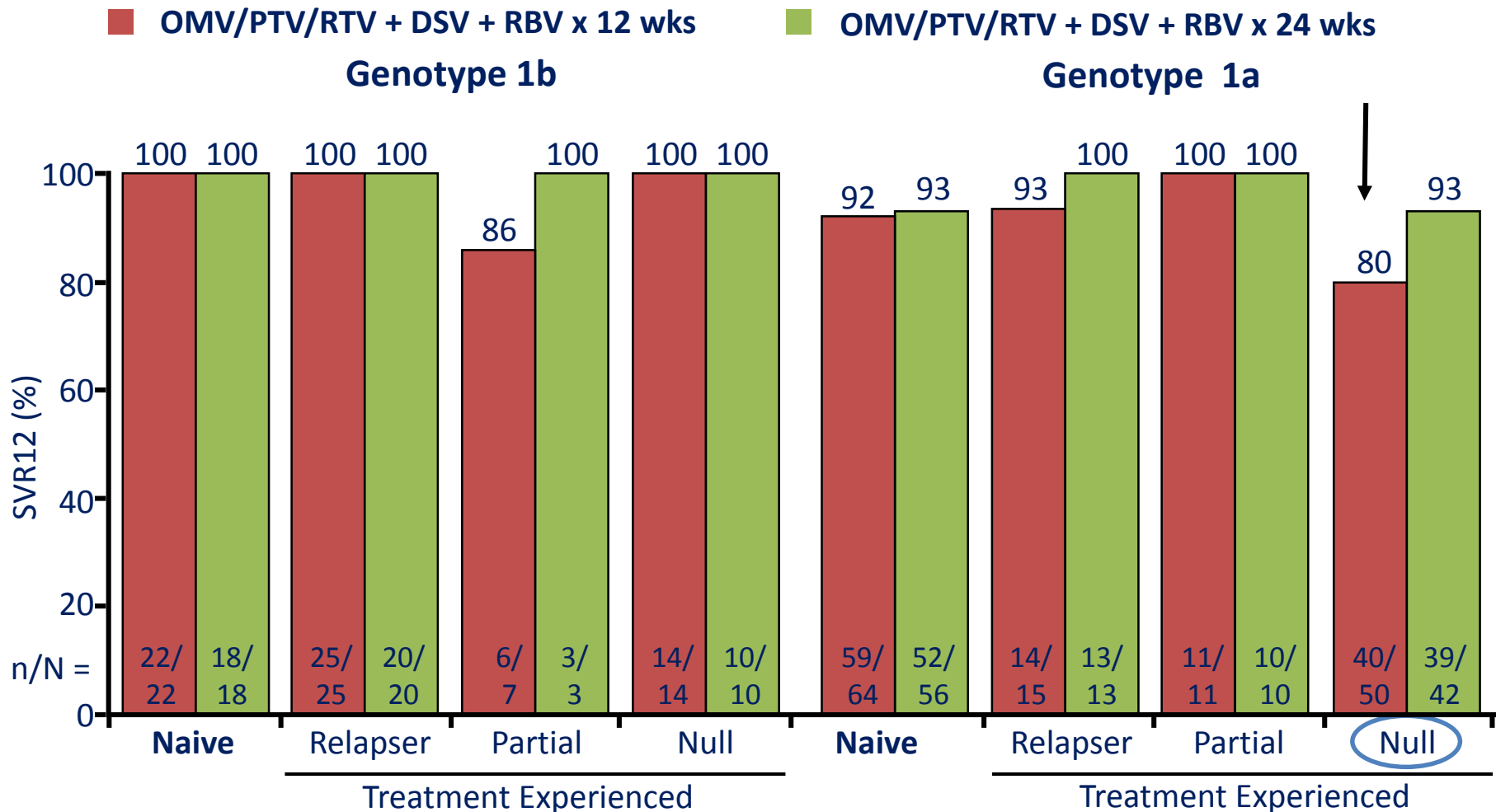
SVR12 Rate	12 Wks of Simeprevir + Sofosbuvir (n = 103)	
	% (n/N)	95% CI
Platelet count		
▪ < 90,000/mm <sup>3</sup>	68 (13/19)	44.9-92.0
▪ ≥ 90,000/mm <sup>3</sup>	87 (73/84)	79.1-94.7
FibroScan score		
▪ > 20 kPa	80 (12/15)	56.4-100
▪ > 12.5 to 20 kPa	100 (11/11)	95.5-100

- Low rate of grade ≥ 3 AEs: 6%
- Majority of laboratory abnormalities low grade
  - Asymptomatic, transient increases in bilirubin, amylase, and lipase

# HCV-TARGET: Real-World Use of SOF + SMV in Cirrhotic Genotype 1 Pts



# TURQUOISE II: Impact of Tx Duration in Cirrhotic GT1 Pts (OMV/PTV/RTV + DSV)



# **Management of HCV infection in decompensated cirrhosis**

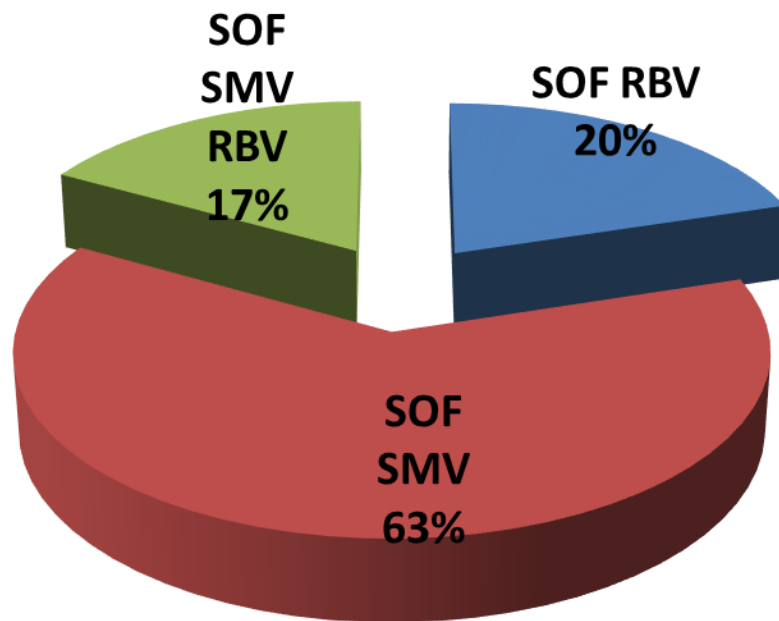


# All Oral HCV Therapy is Safe and Effective in Patients with Decompensated Cirrhosis: Report from HCV-TARGET

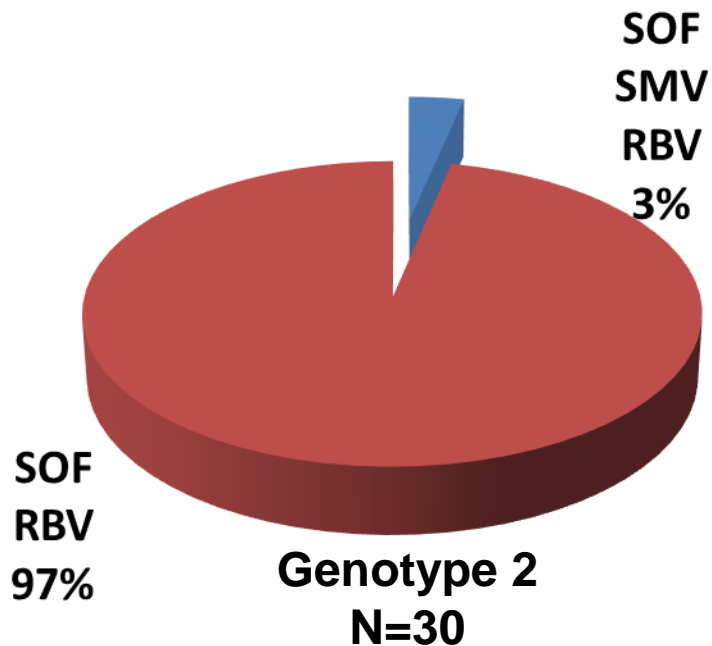
- HCV-TARGET is a **consortium** of academic (n=39) and community (n=13) medical centers in the U.S., Germany, Israel and Canada conducting a longitudinal, observational study
- HCV treatment is administered according to **local standard** of care, and regimen selection is made by the patient's health care provider



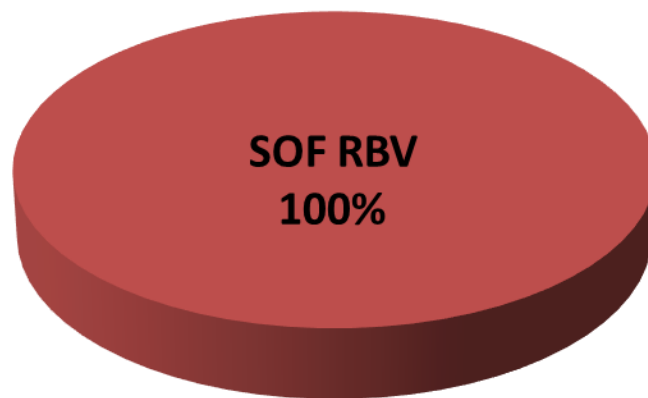
# Distribution of HCV Treatment Regimens by Genotype



**Genotype 1**  
**N=183**

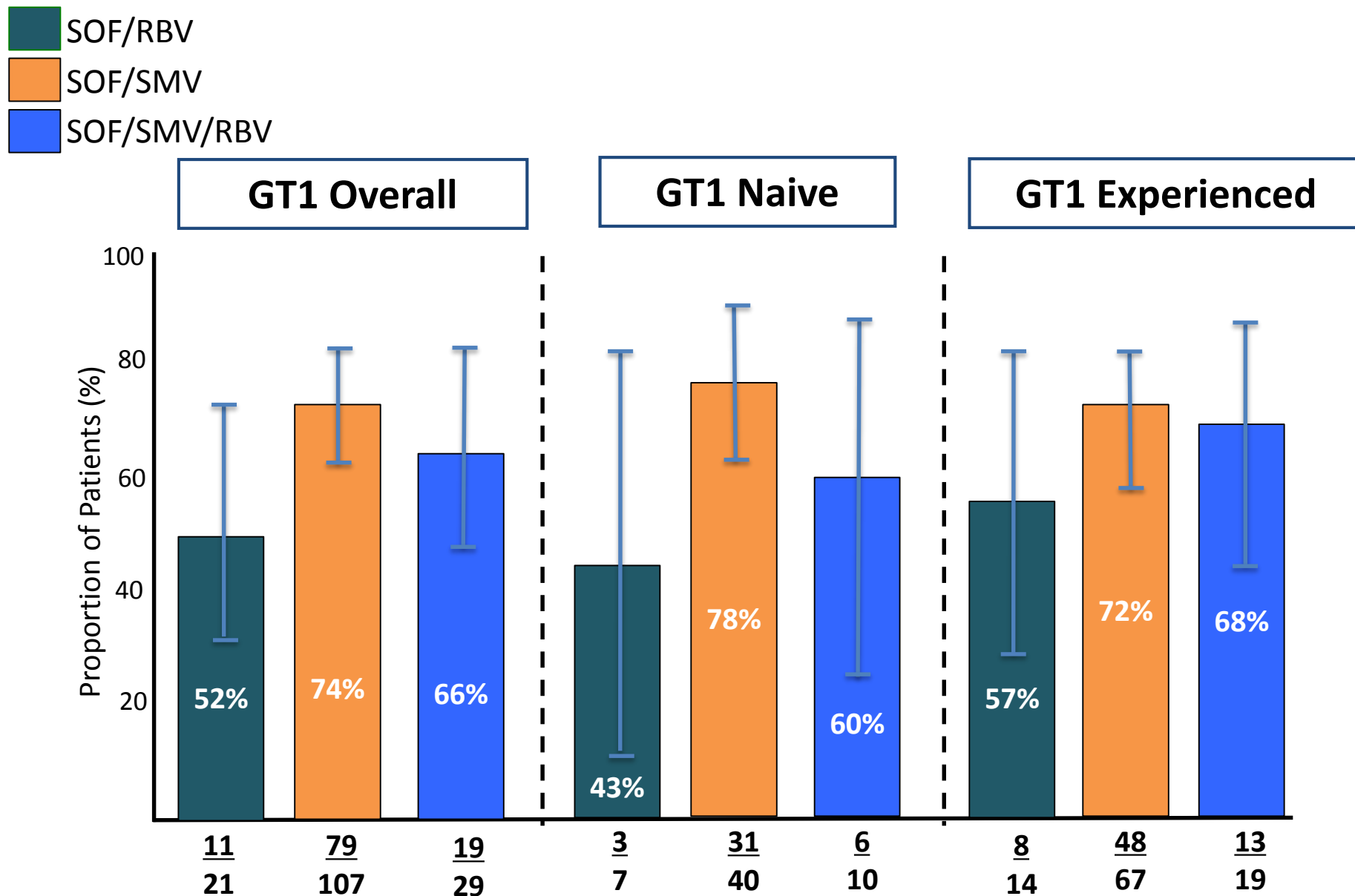


**Genotype 2**  
**N=30**



**Genotype 3**  
**N=33**

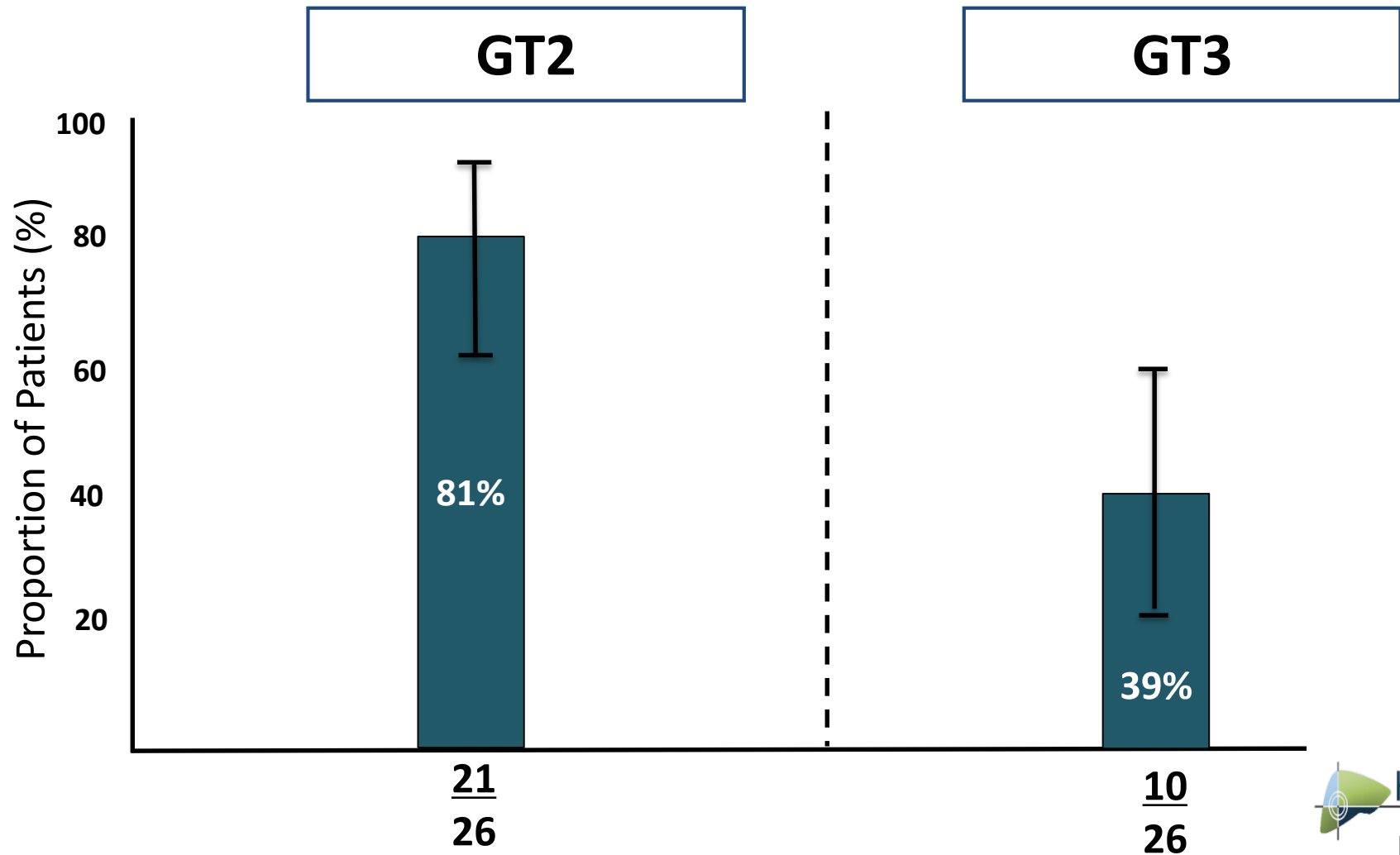
# SVR12: GT1



\*Crude SVR12 in patients with available outcome

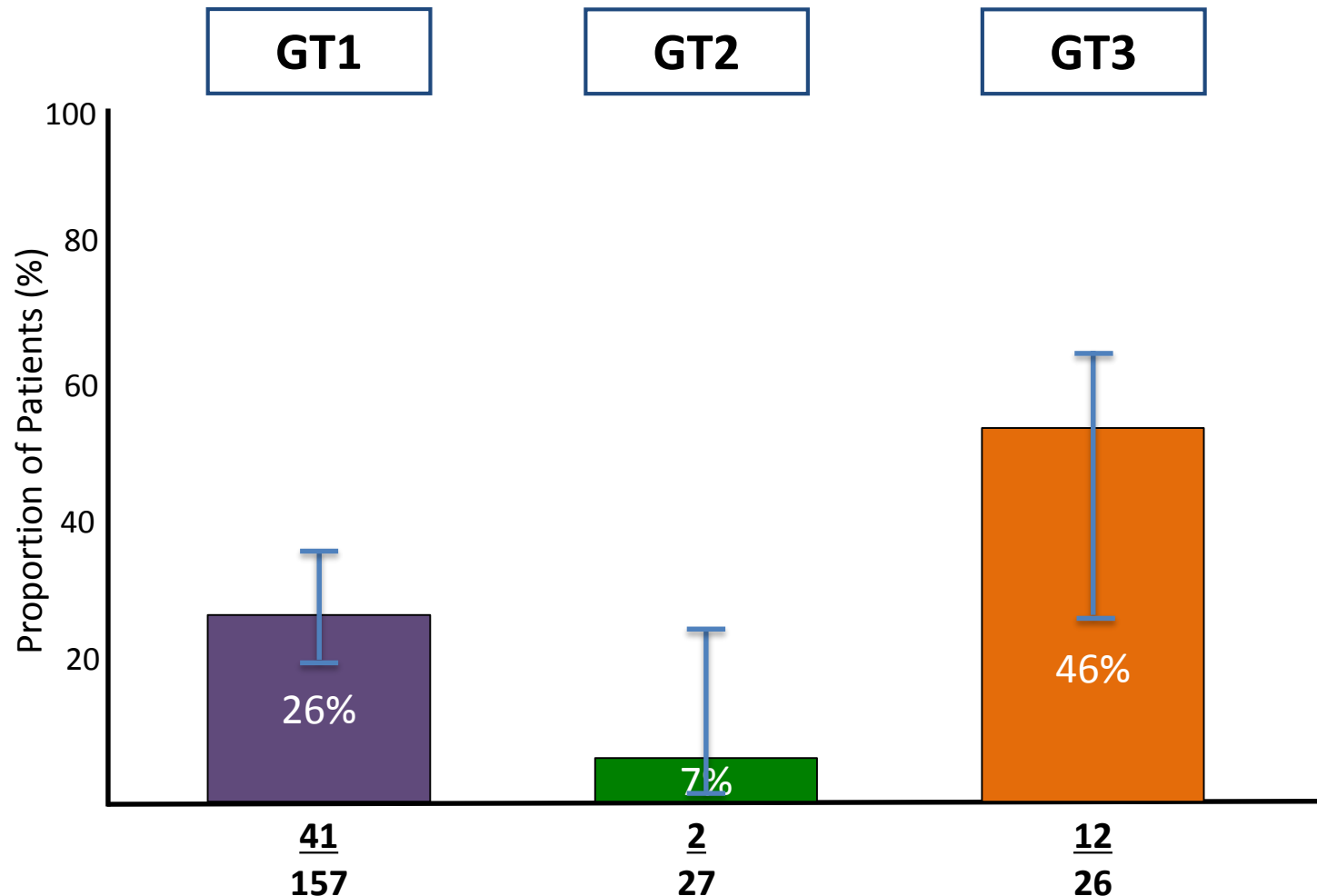
# SVR12: Genotype 2 and 3

SOFOSBUVIR and RIBAVIRIN



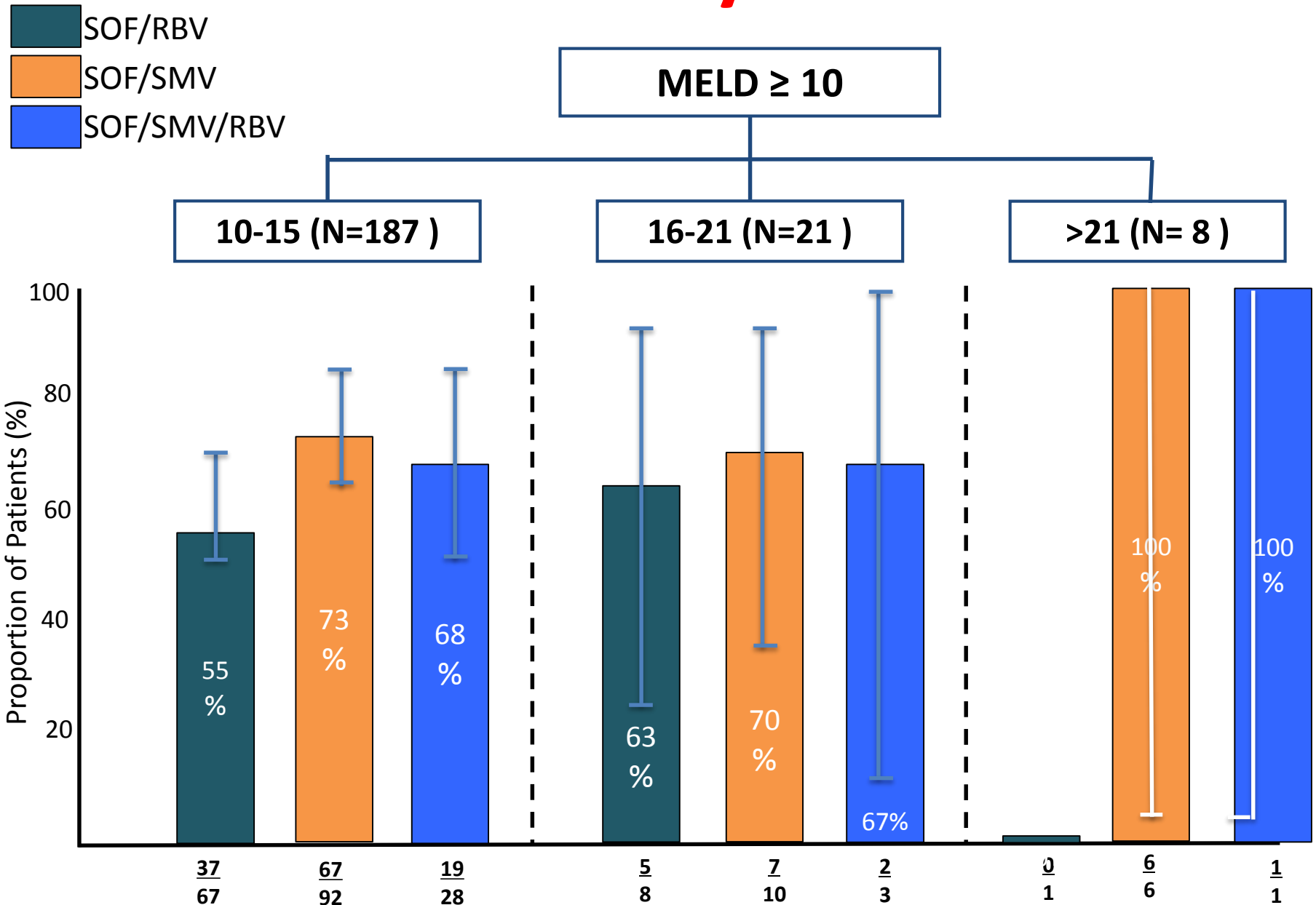


# Relapse rates : Genotype 1, 2 and 3



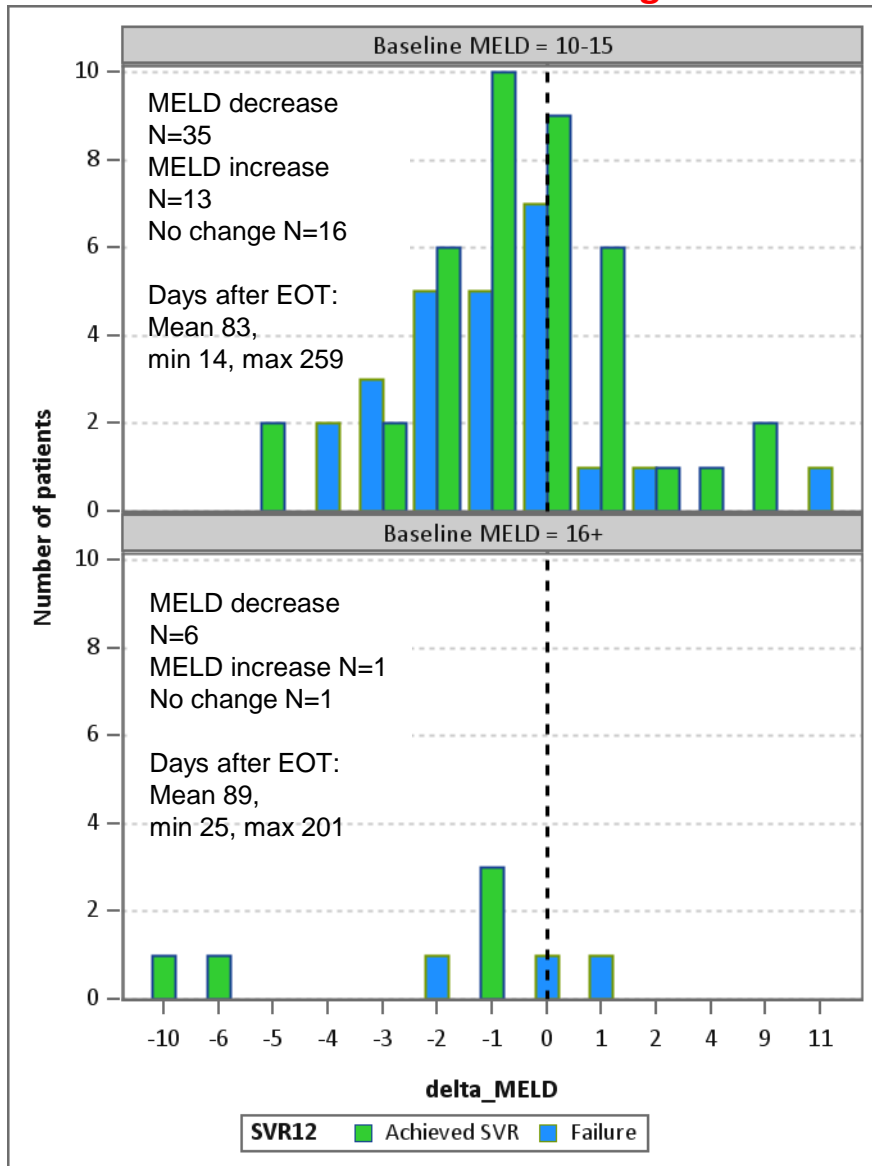
\*Relapse rates in patients with available outcome

# SVR12 by MELD

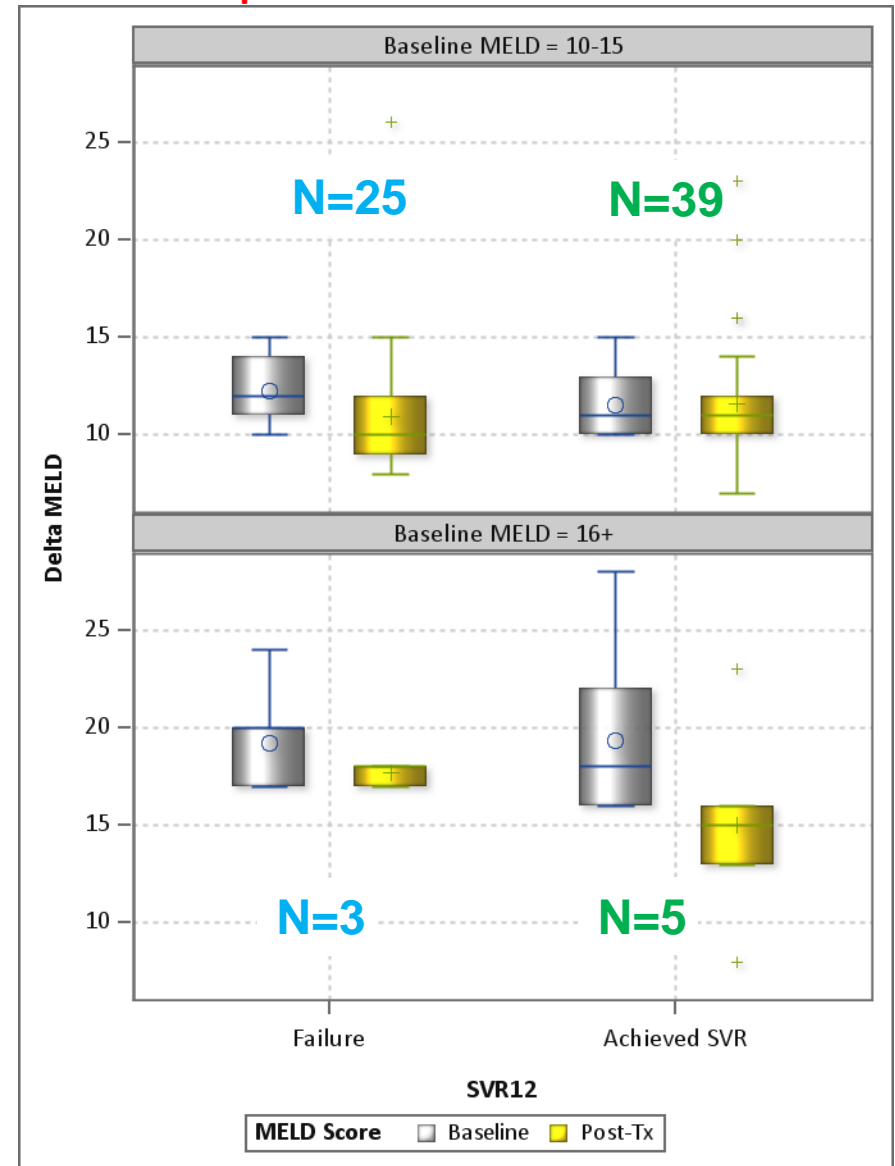


# Change in MELD score

Change from Baseline to Follow up week 2 or later



Pre-treatment to post-treatment value change among individual patients

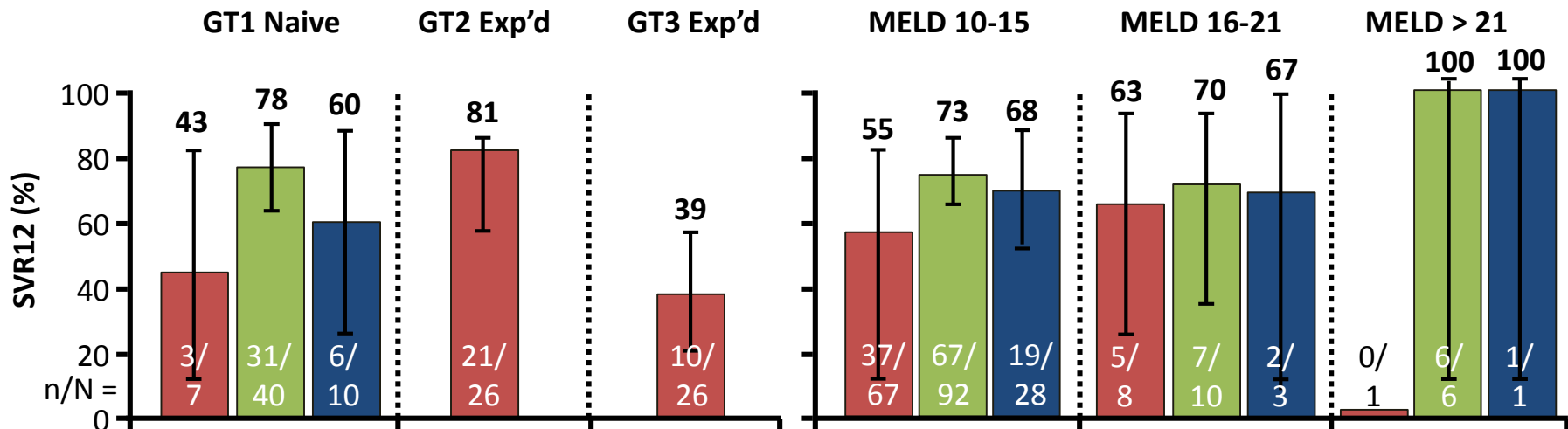


Change from pre-treatment to post-treatment value by treatment outcome

# HCV TARGET: Real-World Sofosbuvir Use in Pts With MELD > 10

39 academic centers and 13 community centers in US, Germany, Israel, Canada

Baseline Characteristic	All Pts (N = 253)	SOF + RBV (n = 102)	SOF + SMV (n = 117)	SOF + SMV + RBV (n = 34)
Mean age, yrs (range)	59 (38-80)	59 (40-80)	60 (41-74)	60 (38-72)
Previous treatment, %	59	56	60	68
Hx of decompensation, %	73	75	73	71
Liver cancer, %	17	23	10	21



# HCV TARGET: Safety of Sofosbuvir Regimens in Pts With MELD > 10

Outcome	All Pts (N = 234)	SOF + RBV (n = 88)	SOF + SMV (n = 114)	SOF + SMV + RBV (n = 32)
Any serious AE, n (%)	44 (17.4)	27 (26.5)	8 (6.8)	9 (26.5)
▪ Hepatic decompensation*	16 (6.3)	10 (19.6)	2 (1.7)	4 (11.8)
▪ Infections	10 (4.0)	7 (7.1)	2 (1.7)	1 (2.9)
Death, n (%)	3 (1.2)	0	2 (1.7)	1 (2.9)
Liver transplantation performed on treatment, n (%)	12 (5.1)	4 (4.6)	3 (2.6)	5 (15.6)

\*Defined as HE, variceal bleeding, hepatic failure, hepatic hydrothorax, bacterial peritonitis.

- Observed AEs in line with known SOF-associated AEs
- Multivariate analysis: higher albumin positive predictor of response ( $P = .026$ )
- Negative predictors of response included elevated total bilirubin ( $P = .002$ ) and genotype 1a HCV ( $P = .069$ )

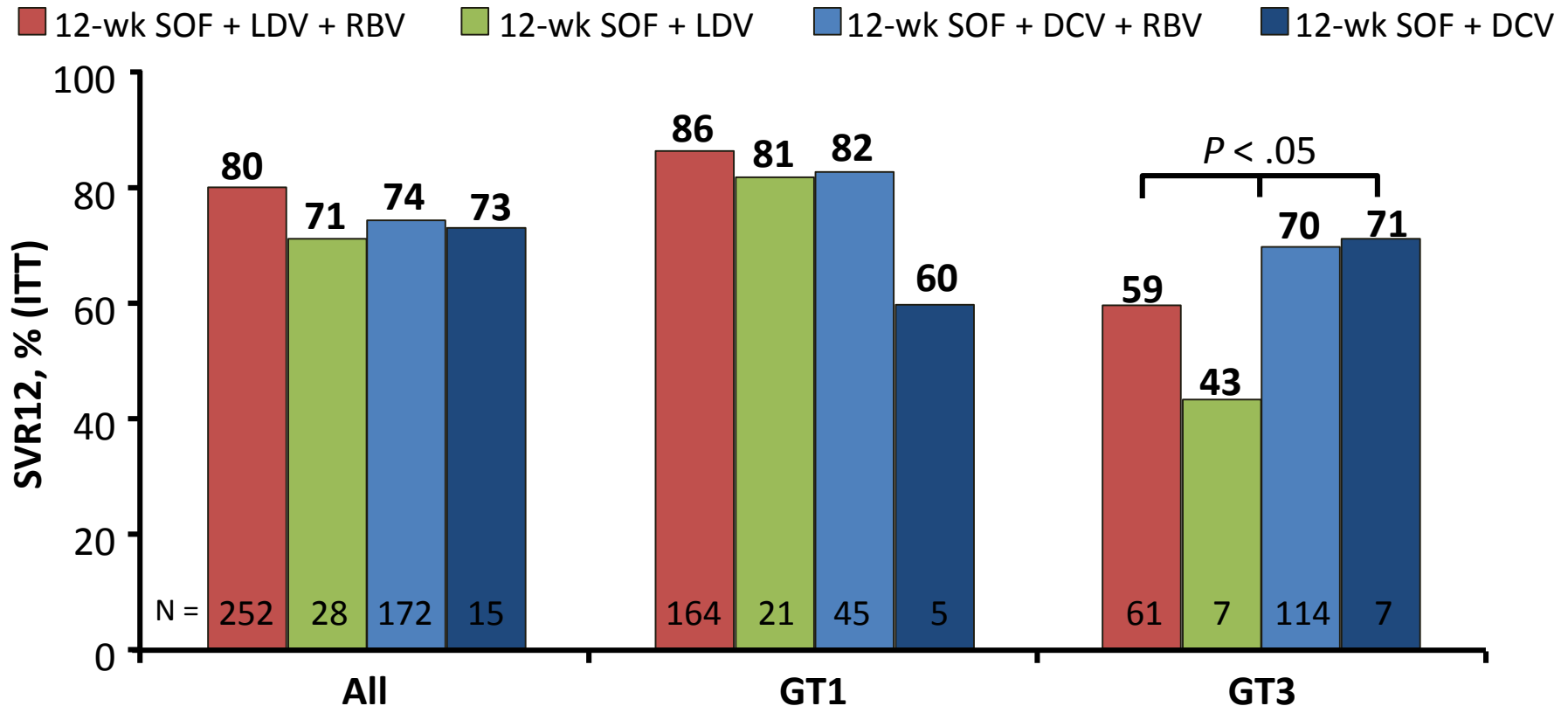
**Reddy RK, et al. EASL 2015. Abstract O007.**

# SOF + NS5A Inhibitors ± RBV in Pts With GT1/3 HCV and Decompensated Cirrhosis

- Observational cohort study of National Health Service of England (N = 467)
- At physician's discretion, pts received 12 wks SOF + LDV or DCV ± RBV

Baseline Characteristic	All Pts (N = 467)	Genotype 1 (n = 235)	Genotype 3 (n = 189)	Other Genotypes (n = 43)
CTP B, %	66.2	68.5	64.0	62.8
CTP C, %	9.9	8.1	12.7	7.0
Mean MELD score (range)	11.9 (6-36)	11.3 (6-24)	12.6 (6-36)	11.9 (6-22)
Regimen, % of total population				
SOF + LDV + RBV	54.0	35.1	13.1	5.8
SOF + DCV + RBV	36.8	9.6	24.4	2.8
RBV-free regimen	9.2	5.6	3.0	0.6

# SOF + NS5A Inhibitors ± RBV in Pts With Decompensated Cirrhosis: Efficacy

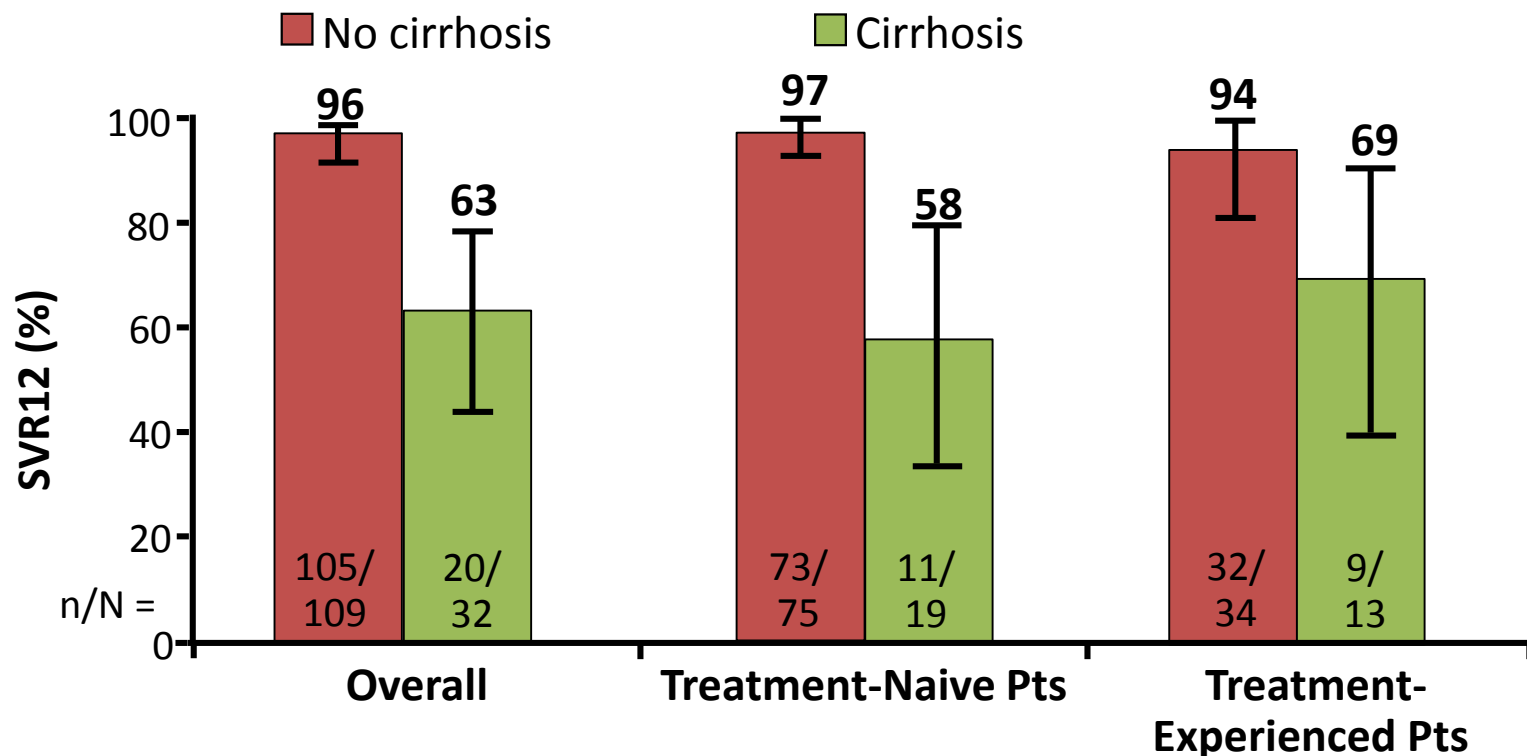


SVR12 among pts with other HCV GTs: 89% (n = 27) with SOF + LDV + RBV; 85% (n = 13) with SOF + DCV + RBV; 100% (n = 3) SOF + DCV



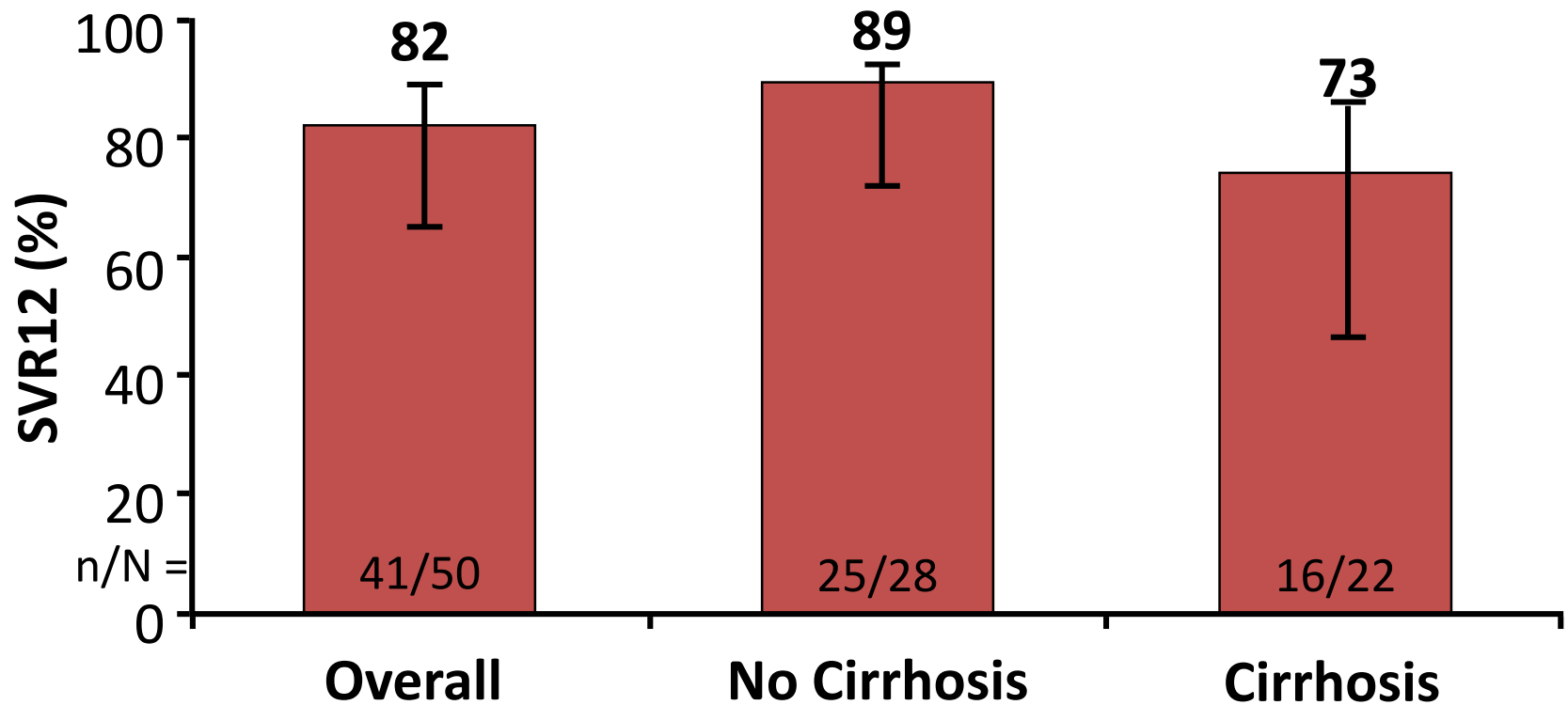
# Management of Genotype 3

# ALLY-3: SOF + DCV for 12 Wks in Pts With GT 3 HCV Infection



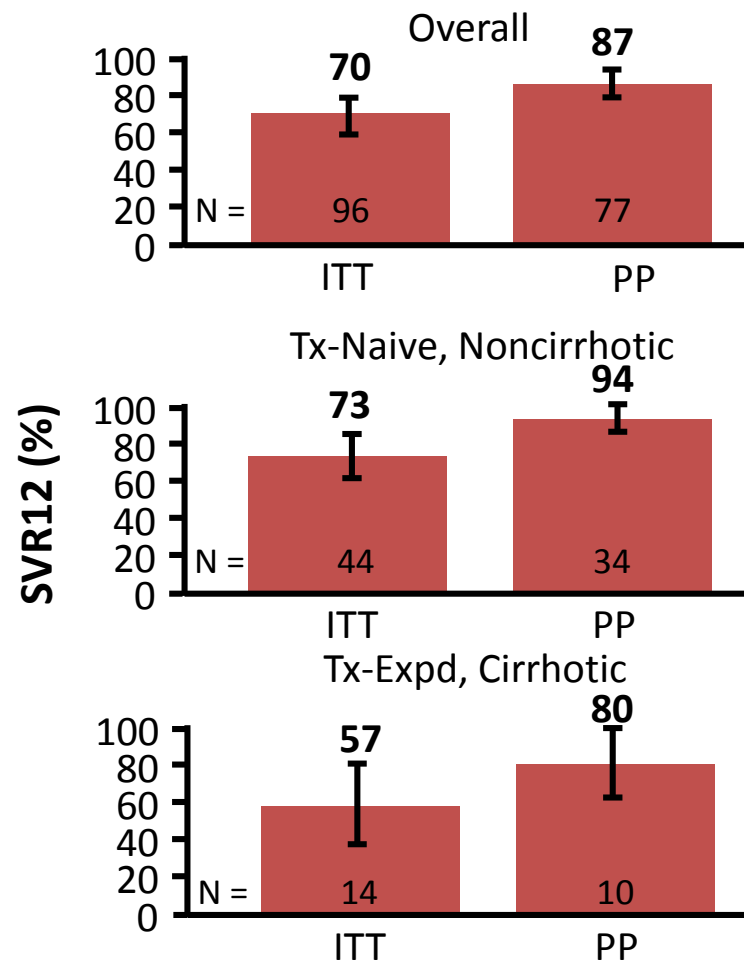
- Of 16 pts with relapse, 11 had cirrhosis
- 1 of 16 relapses occurred between posttreatment Wks 4 and 12

# LDV/SOF + RBV for 12 Wks in Tx-Experienced Pts With Genotype 3 HCV



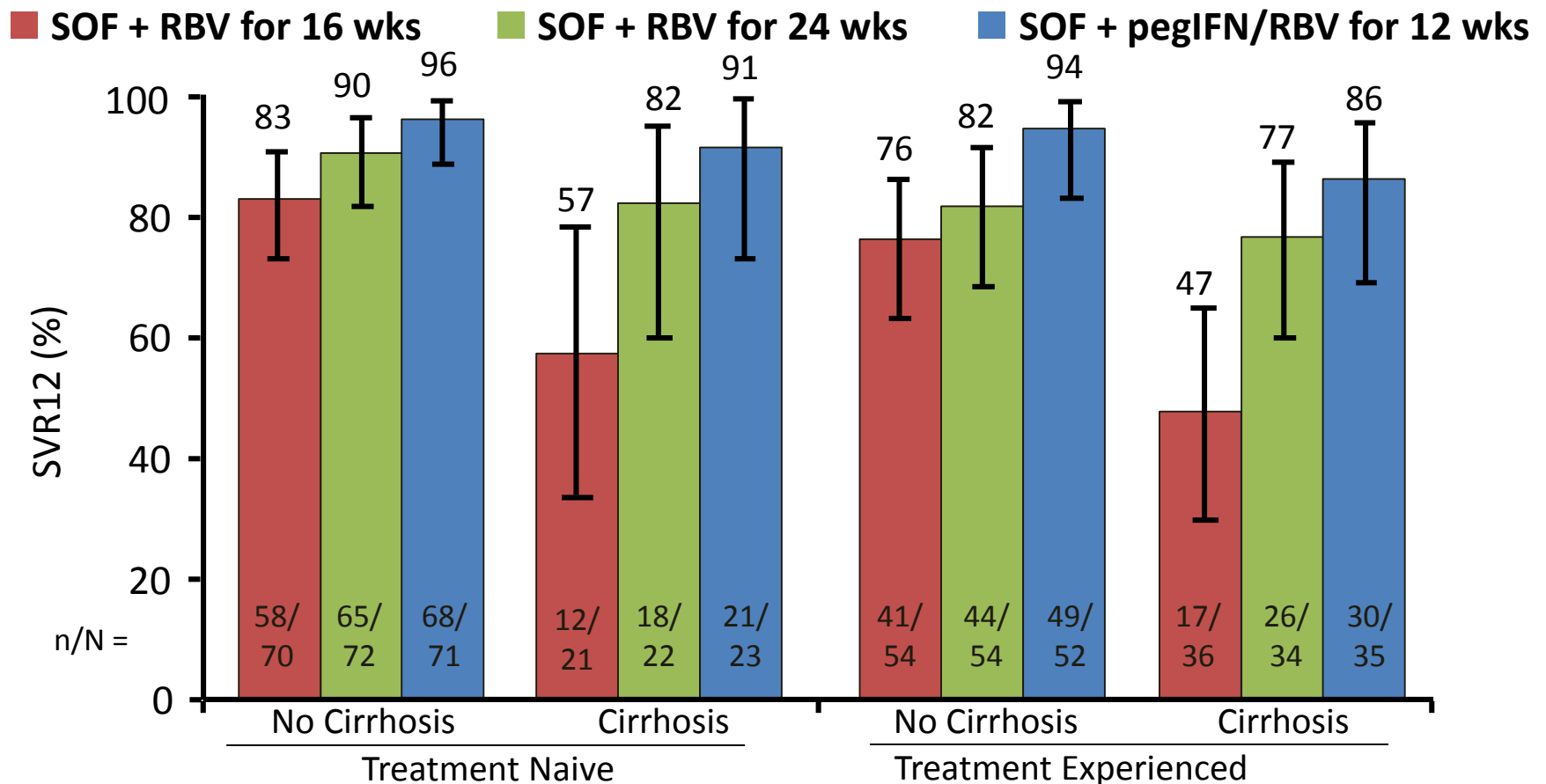
# TRIO: Outcomes With 24 Wks SOF + RBV for GT3 HCV in Real-World Settings

- 18 academic and 17 community practices in US TRIO network
  - 24 wks sofosbuvir + RBV (N = 96)
- ITT population: n = 96; PP population (completed therapy with SVR12 data): n = 77
- Key baseline characteristics
  - Male: 56%
  - HCV RNA >  $6 \times 10^6$  IU/mL: 15%
  - Cirrhosis: 30%
  - Previously treated: 39%
- 2/96 pts died from causes not related to treatment



# BOSON: SVR12 in GT3 by Tx History and Cirrhosis Status

- Multicenter, randomized, open-label study*



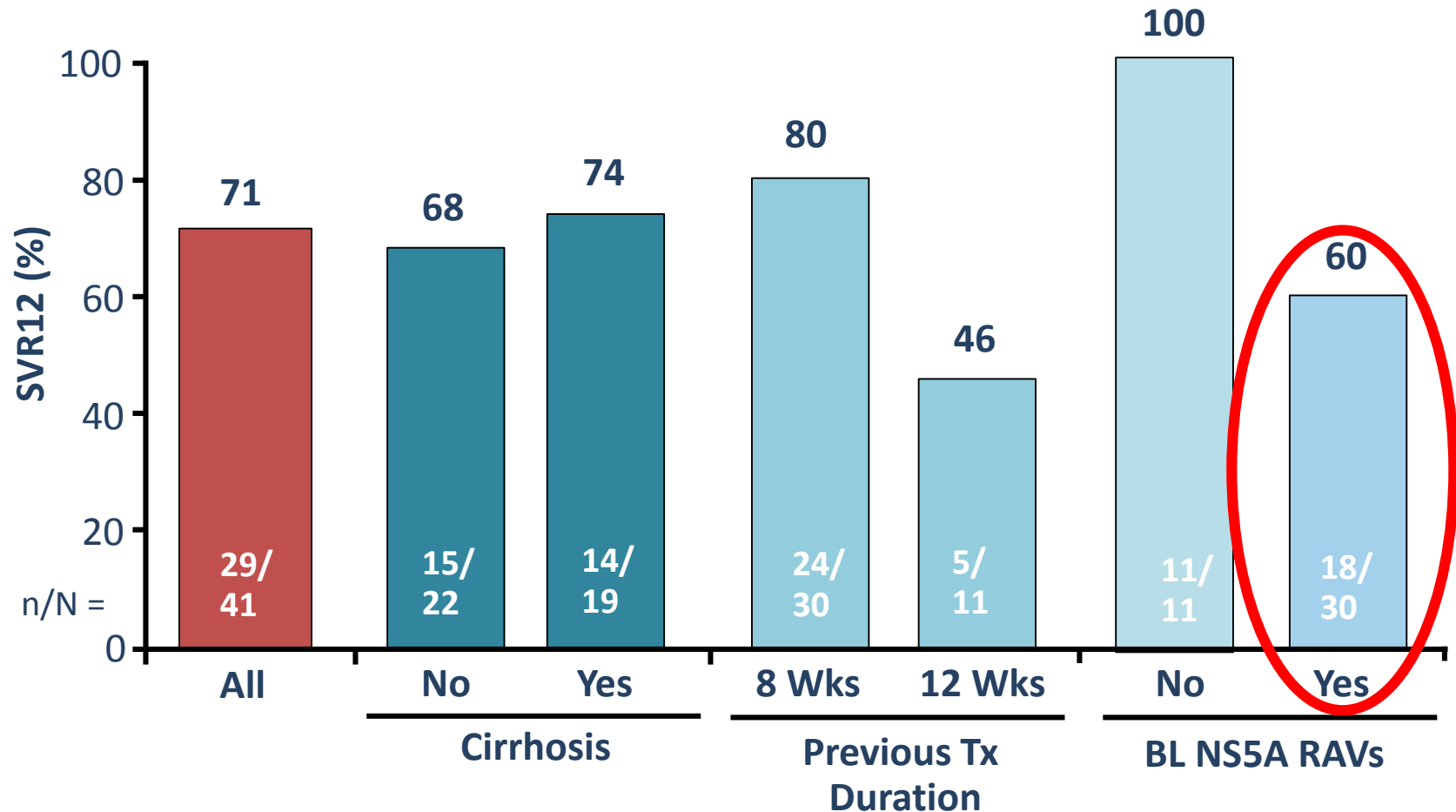
# Take-Home Points: Treatment for Genotype 3 HCV Infection

- SOF + pegIFN/RBV for 12 wks may be best current option in treatment-experienced pts with GT3 HCV infection
  - Addition of pegIFN to SOF + RBV for 12 wks associated with highest rate of SVR12 in treatment-experienced pts with GT3, particularly those with cirrhosis
- To achieve high SVR rates with SOF in GT3, an additional active drug may be needed
  - Studies of combinations of novel DAAs with increased activity against GT3 are under way

# **Management of DAA- experienced patients**



# 24 Wks LDV/SOF After Failure of 8-12 Wks LDV/SOF-Based Therapy: SVR12



# Retreatment of patients who failed to achieve an SVR on prior antiviral therapy containing one or several DAA(s)

Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
PegIFN- $\alpha$ , RBV and either telaprevir or boceprevir	Genotype 1	12 wk with RBV	No	No	No	12 wk with RBV
Sofosbuvir alone, in combination with RBV or in combination with PegIFN- $\alpha$ and RBV	Genotype 1	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 2 or 3	No	No	No	No	12 weeks with RBV or 24 weeks with RBV if F3 or cirrhosis
	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
PegIFN- $\alpha$ , RBV and simeprevir	Genotype 1 or 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
PegIFN- $\alpha$ , RBV and daclatasvir	Genotype 1	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 2 or 3	No	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 4	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Sofosbuvir and simeprevir	Genotype 1 or 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis

# Retreatment of patients who failed to achieve an SVR on prior antiviral therapy containing one or several DAA(s)

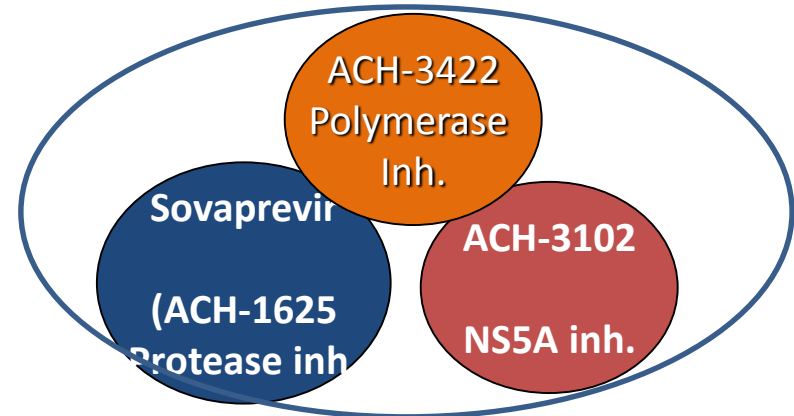
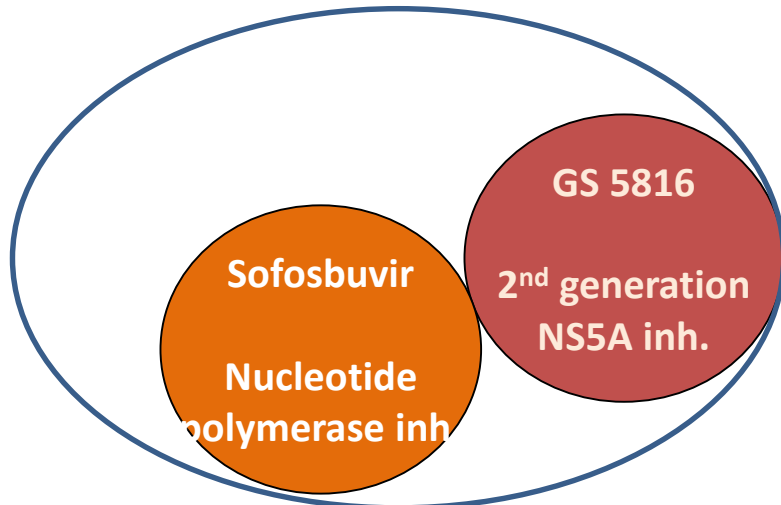
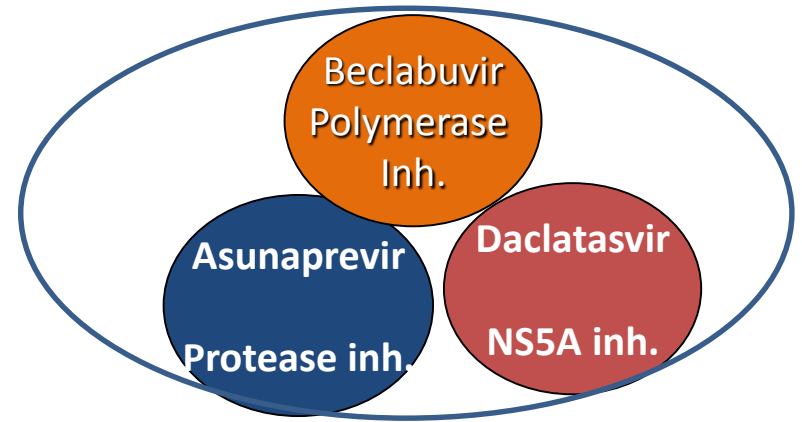
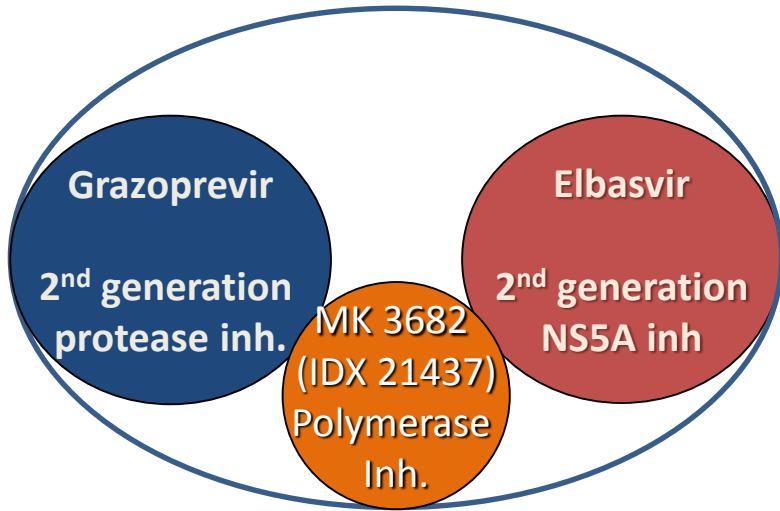
Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Sofosbuvir and daclatasvir or Sofosbuvir and ledipasvir	Genotype 1	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 2 or 3	No	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 4	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Genotype 1	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir and ombitasvir	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis

# Issues for the Future

- new drugs

# DAA combos reaching the clinic by 2016-7

Pangenotypic, fixed dose combination of two or three DAAs, no RBV





**THANK YOU**  
for your  
**ATTENTION!**

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