10th International Workshop on Hepatitis C
– Resistance & New Compounds –
Barcelona 4th June 2015

Future Treatment Strategies for Hepatitis C

Stefan Zeuzem, MD
University of Frankfurt
Germany

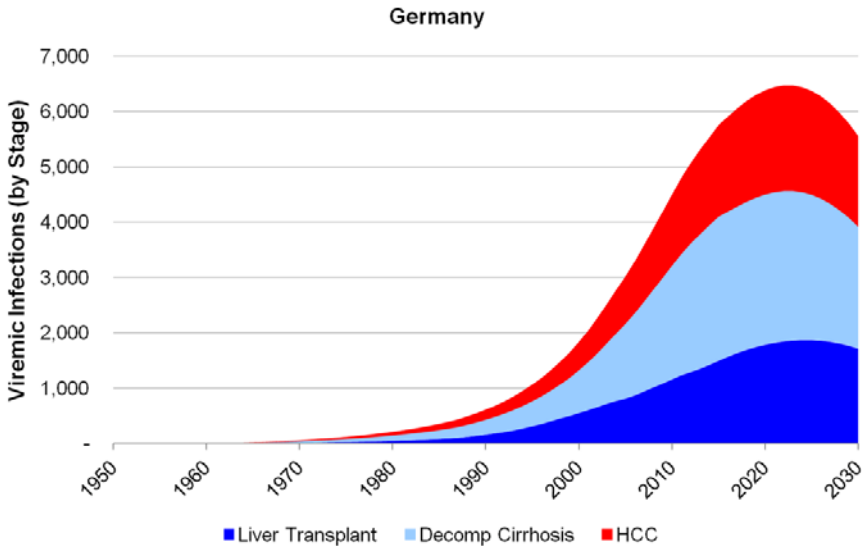
MEDIZINISCHE KLINIK 1

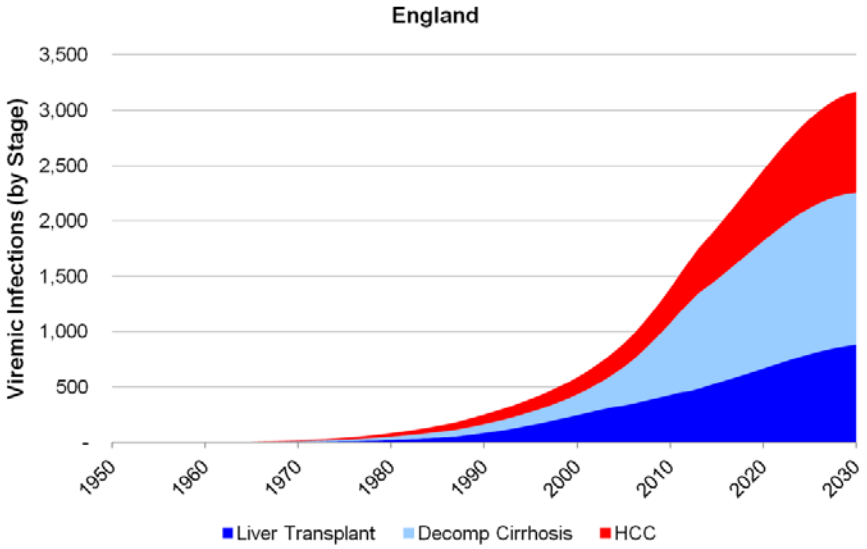
Disclosures

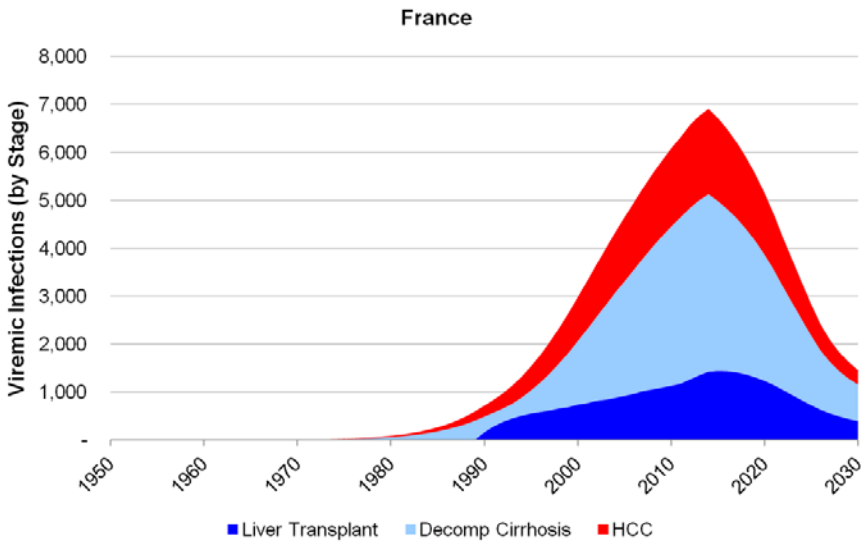
- Consultancies: Abbvie, BMS, Gilead, Janssen, and MSD/Merck.
- Honoraria for lectures: Abbvie, BMS, Gilead, Janssen, and MSD/Merck.

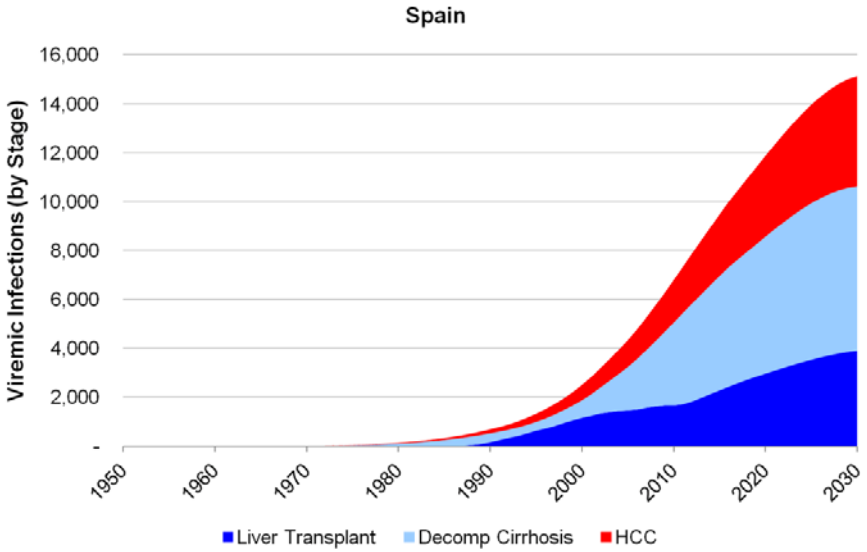
Natural Course of Disease and Impact of Treatment

HCC, decompensated cirrhosis and transplant, 1950-2030



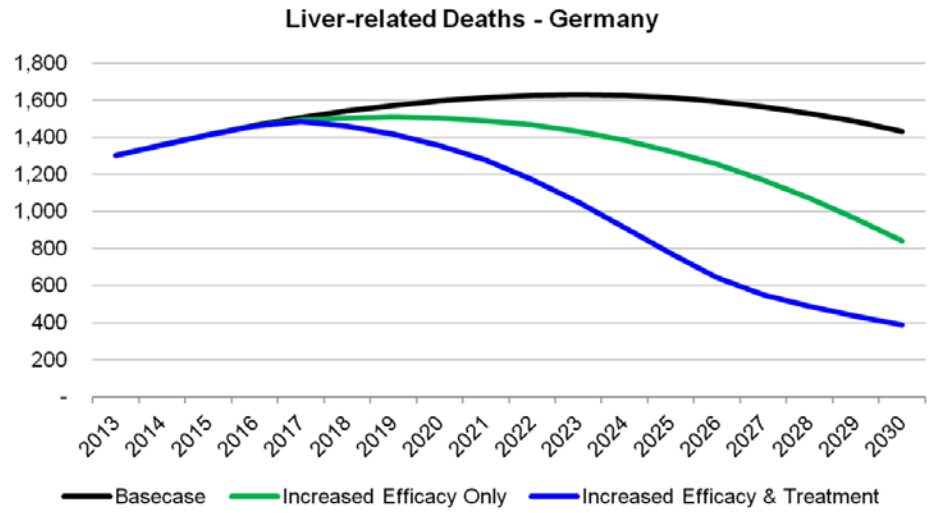


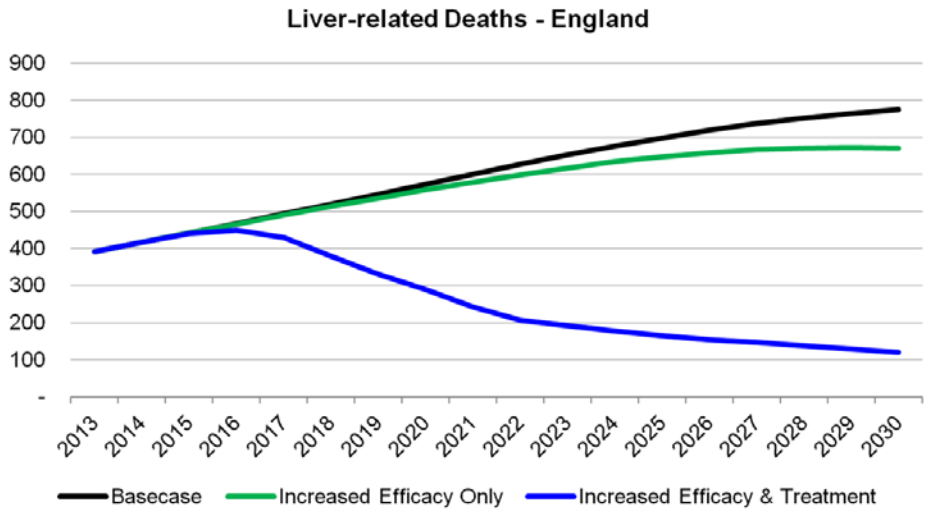


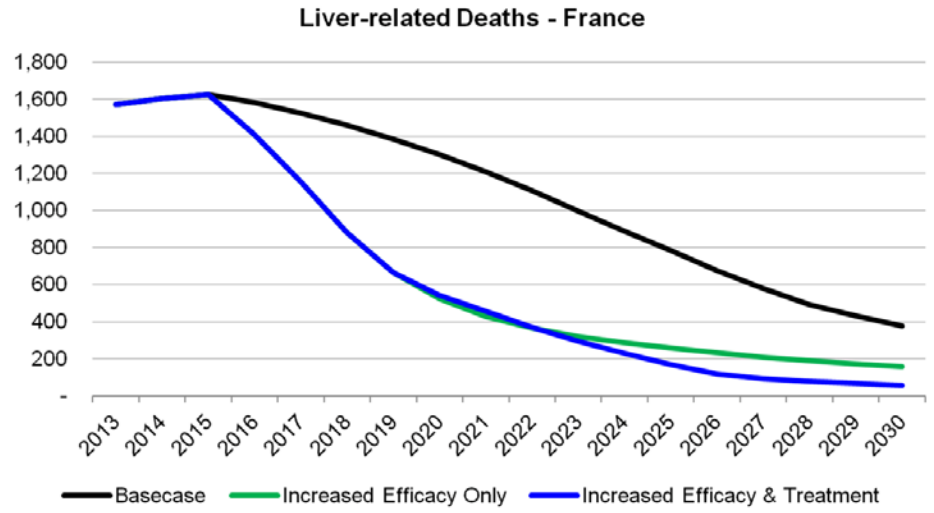


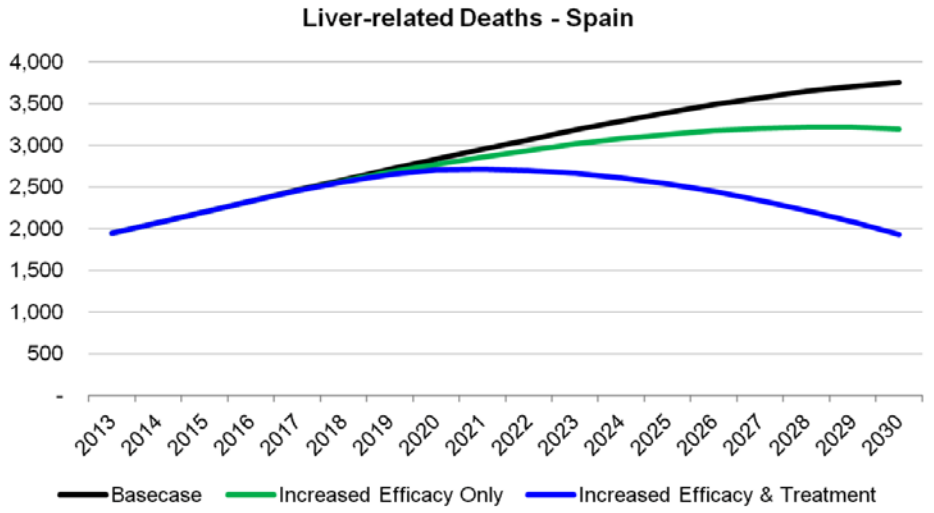
Razavi H, Waked I, Sarrazin C, Myers RP, Idilman R, Calinas F, et al. J Viral Hepat 2014;21 Suppl 1:34-59.

Liver-related deaths, 2013-2030
Germany, England, France and Spain









Germany: Basecase: 12.700 therapies/yr at 55% SVR;
Increased efficacy to 90% SVR; 22.100 tx at 90% SVR

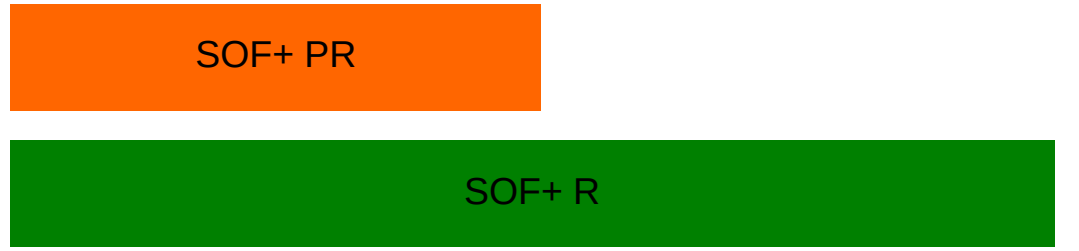
Wedemeyer H, Duberg AS, Buti M, et al. J Viral Hepat 2014; 21 Suppl 1: 60-89.

Treatment of Hepatitis C (approved regimen)

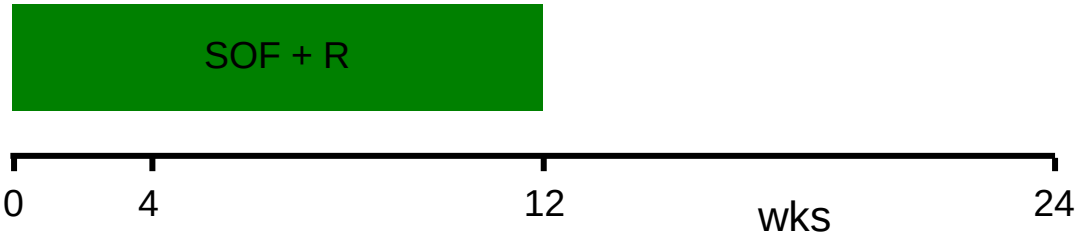
Sofosbuvir in Patients with CHC

- 400 mg (one tablet) qd with food

Patients with GT 1, 3, 4, 5, 6 infection



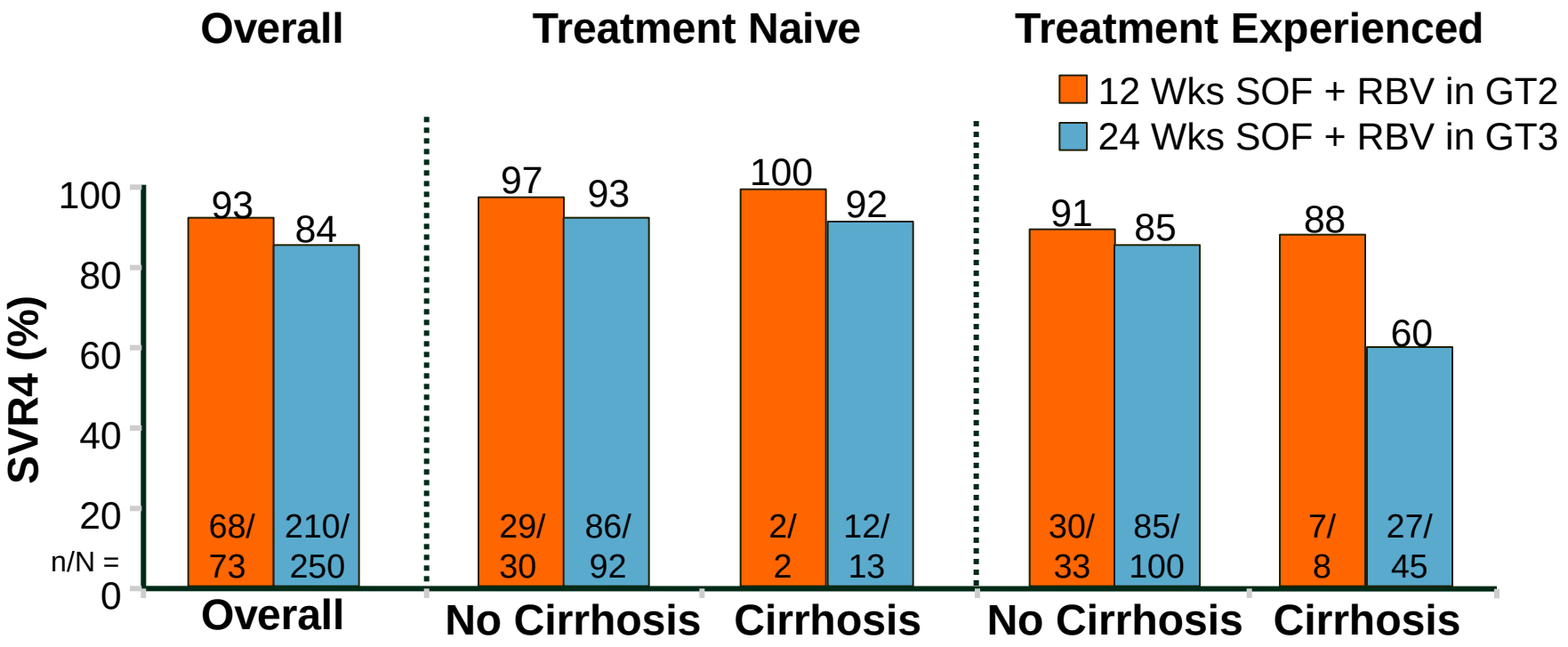
Patients with GT 2 infection



- In patients with (multiple) negative predictive factors (cirrhosis, high BL viral load, IL28B-non-CC genotype, previous null-response to PR) tx duration might be extended for up to 24 wks
- Pts waiting for liver transplantation should be treated with SOF + RBV until transplantation
- No dose adjustment in patients with hepatic impairment (Child-Pugh Class A, B or C) and in patients with mild or moderate renal impairment (no data for eGFR < 30 mL/min/1.73m^2)

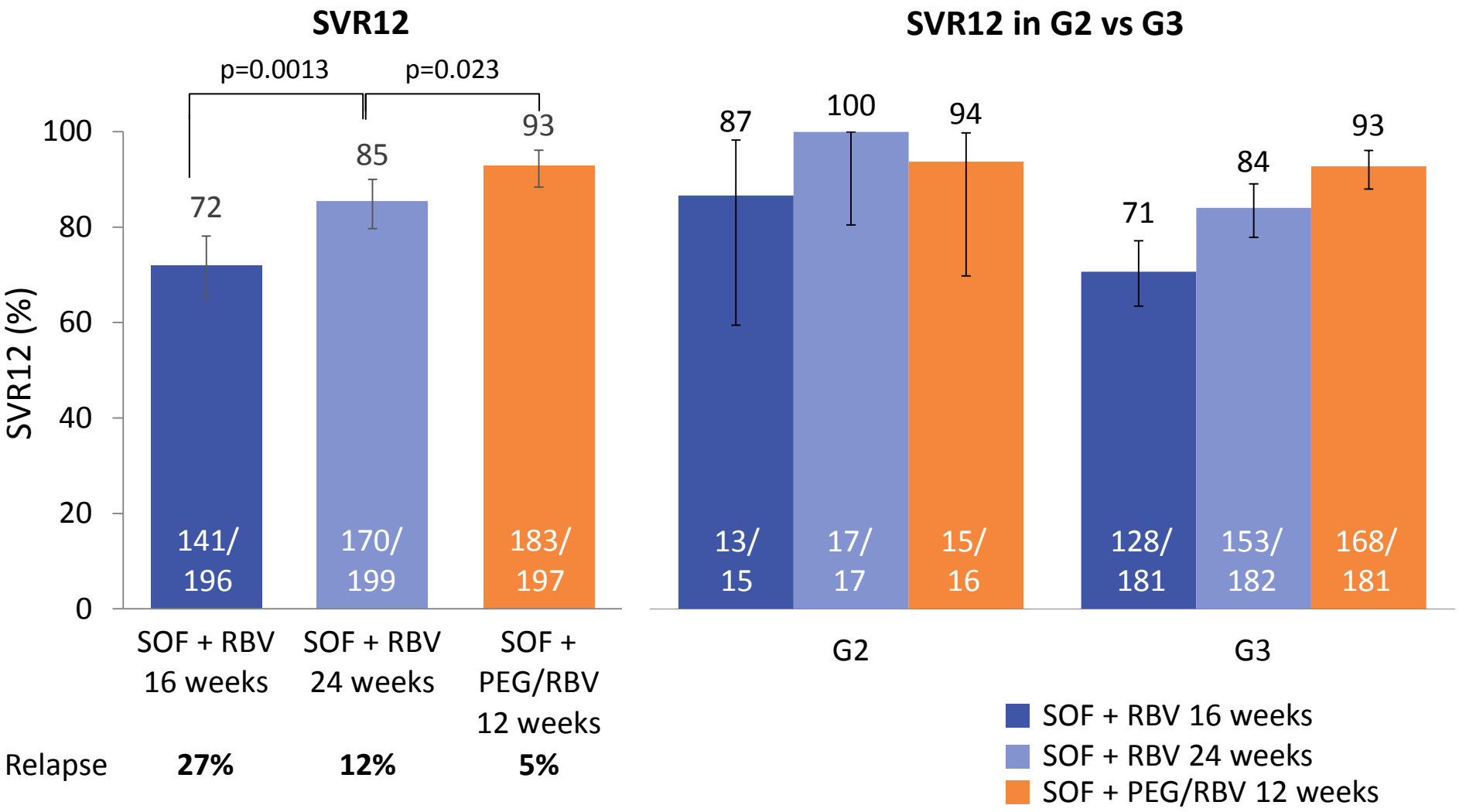
EMA. Sofosbuvir [package insert] 2014

VALENCE Efficacy : SVR12 in GT-2 and -3



Zeuzem S, et al., NEJM 2014

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 patients with G2 HCV

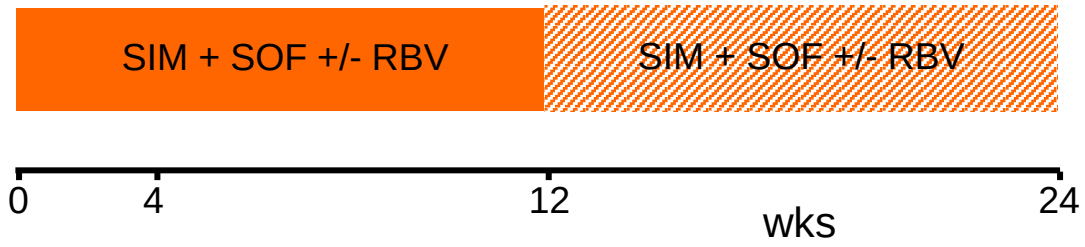


Foster G.R, et al. EASL 2015, Vienna. #LO5

Simeprevir plus Sofosbuvir in Pts with CHC

- 150 mg Simeprevir (one tablet) qd with food
- 400 mg Sofosbuvir (one tablet) qd with food

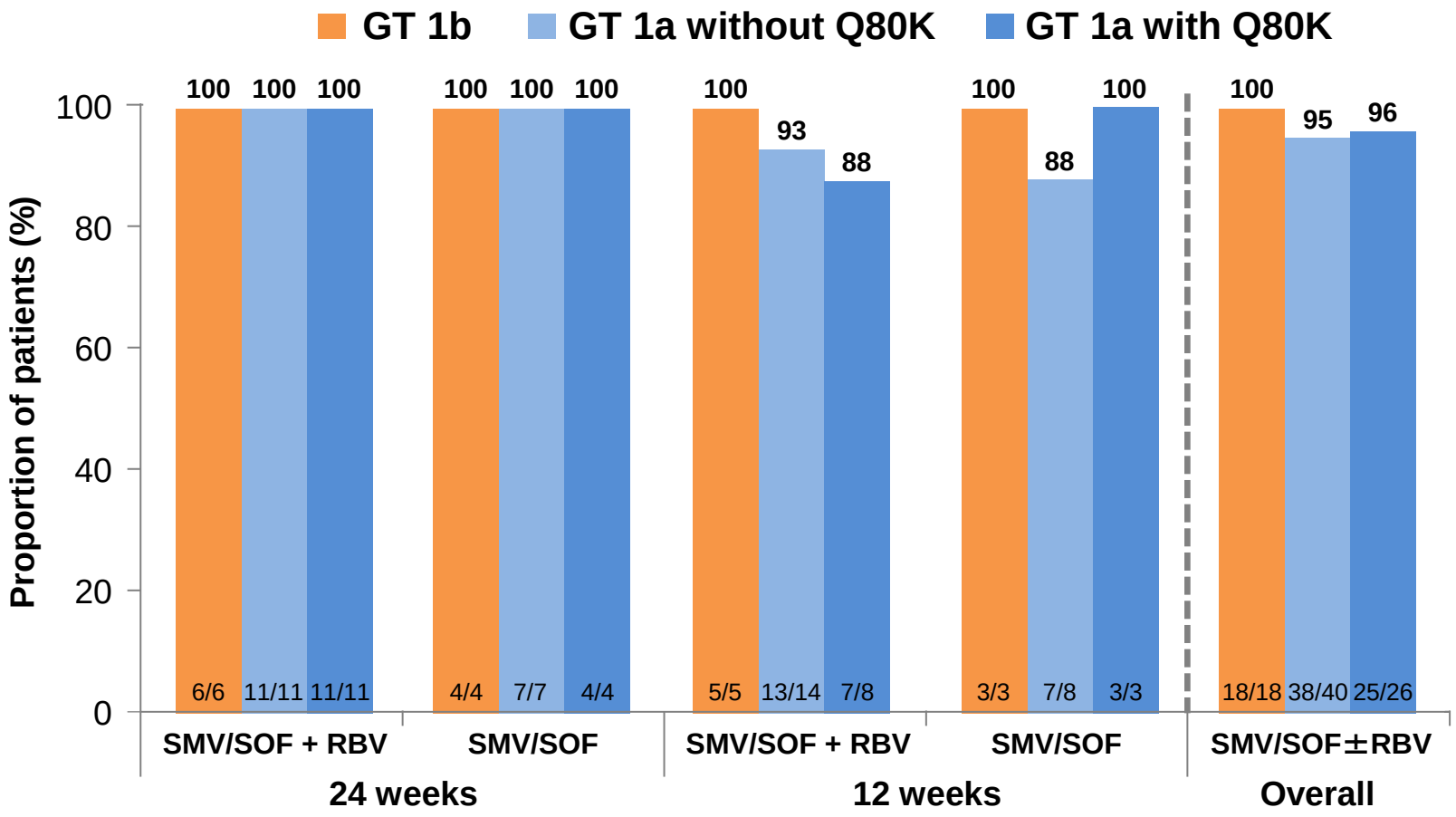
Patients with GT 1 or 4 infection +/- cirrhosis



- Includes treatment-naive patients or patients who failed prior treatment with peginterferon alfa and ribavirin with or without cirrhosis.
- Simeprevir with sofosbuvir should only be used in patients who are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment. Ribavirin could be added based on a clinical assessment of each individual patient.
- The recommended treatment duration is 12 weeks. A longer treatment duration (up to 24 weeks) of simeprevir with sofosbuvir (with or without ribavirin) could be considered based on an individual basis.
- Interferon-free regimens with simeprevir have not been investigated in phase 3 studies. The optimal regimen and treatment duration have not been established

EMA. Simeprevir [package insert] 2014

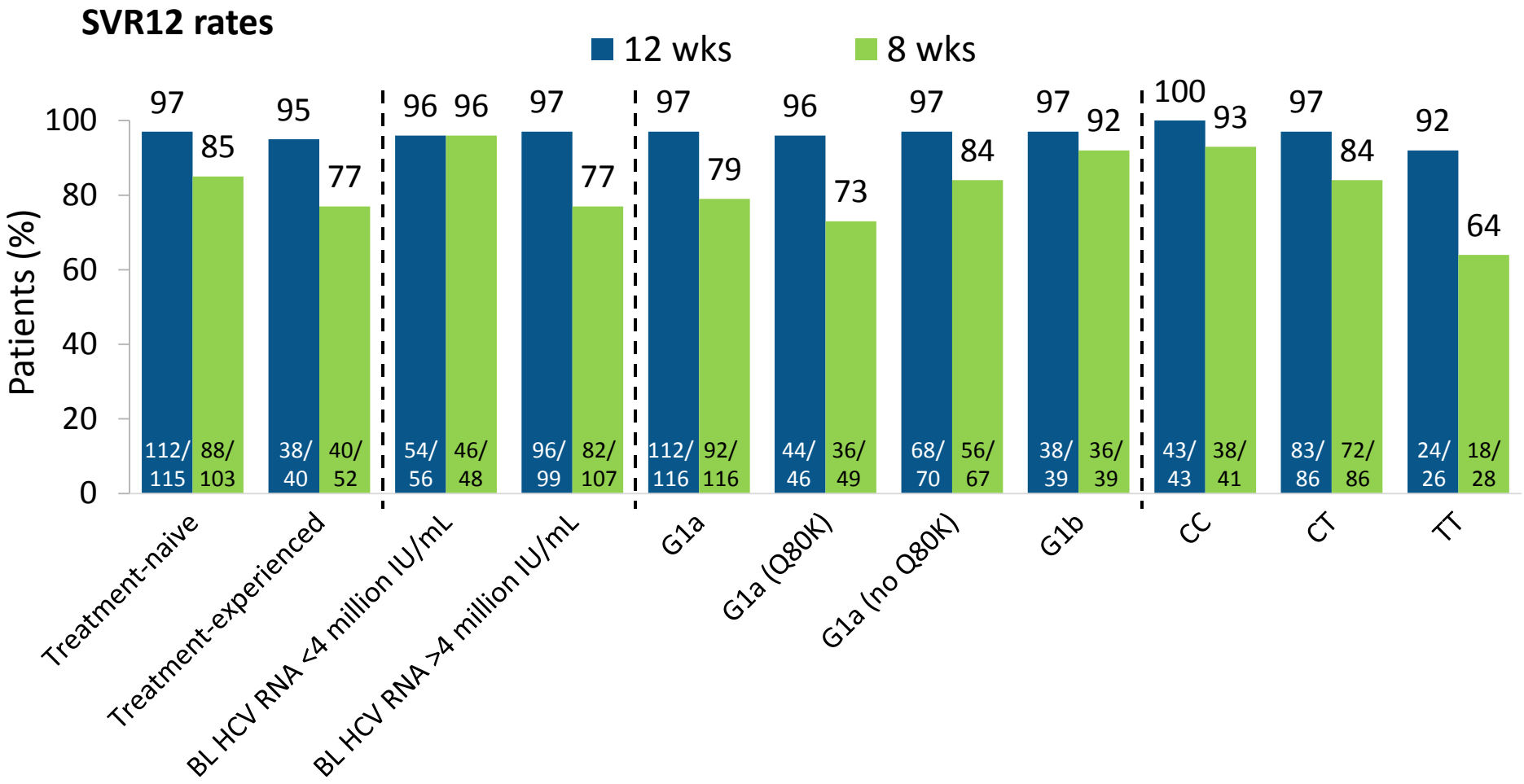
COSMOS Cohort 2: SVR12 by GT 1 subtype and baseline NS3 Q80K polymorphism*



*Excluding patients who discontinued for non-virological reasons

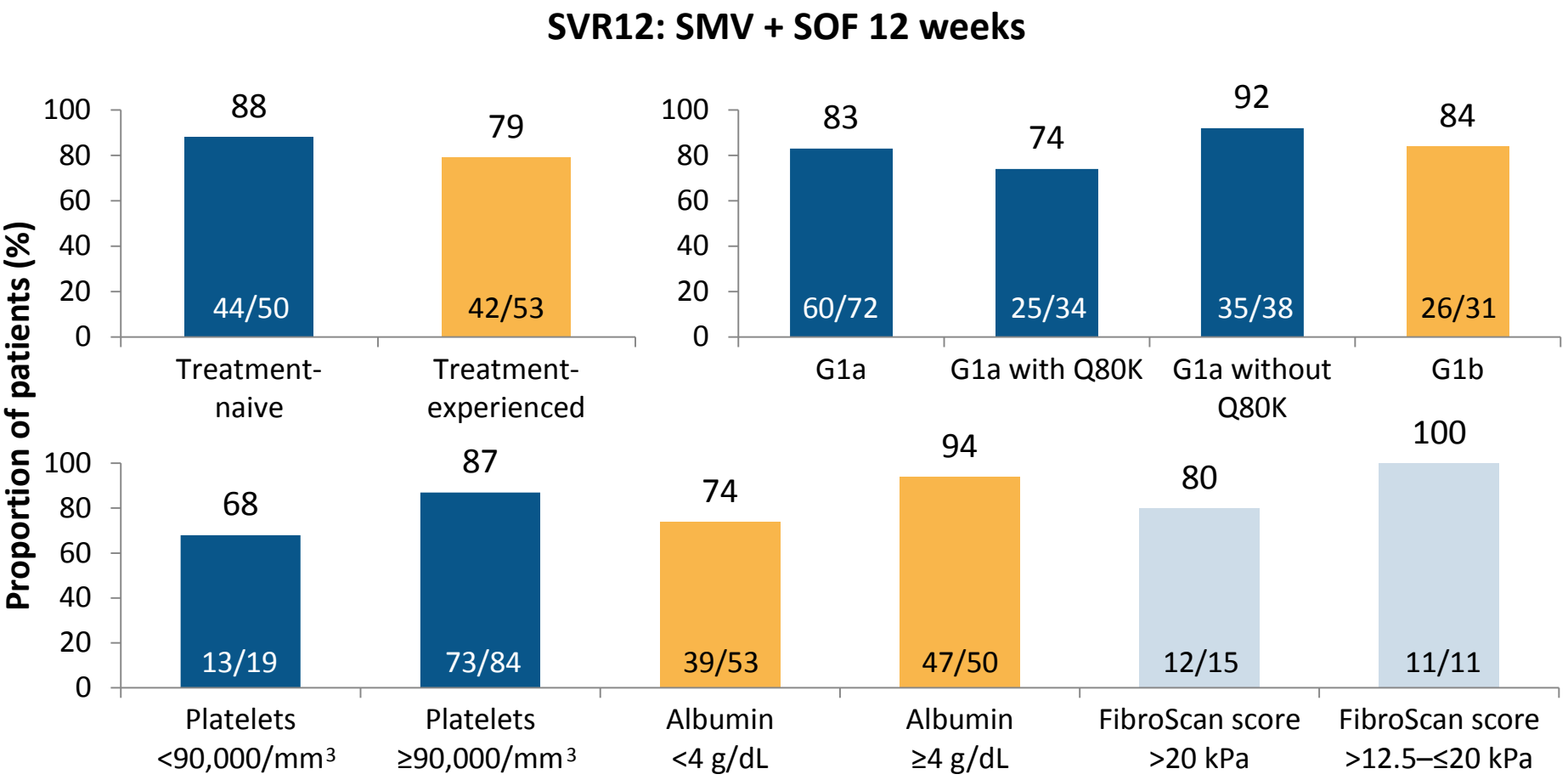
Lawitz E, et al. Lancet 2014

8 or 12-week regimen of SMV + SOF in treatment-naive and -experienced G1 patients without cirrhosis: OPTIMIST-1



Kwo P, et al. EASL 2015, Vienna. #LP14

OPTIMIST-2: A Phase 3, open-label, single-arm study to evaluate the efficacy and safety of 12 weeks of SMV + SOF in treatment-naive or -experienced G1 cirrhotic patients



Lawitz E, et al. EASL 2015, Vienna. #LP04

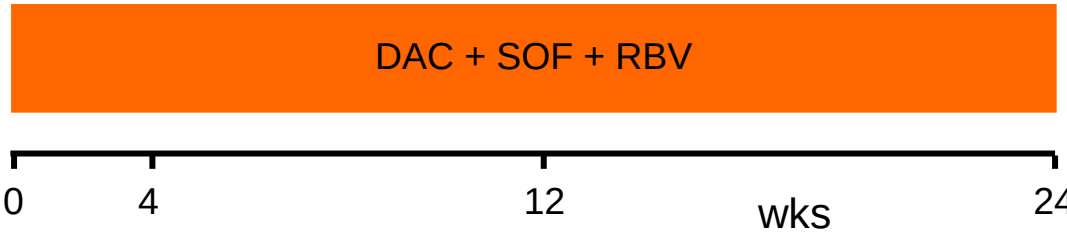
Daclatasvir plus Sofosbuvir in Pts with CHC

- 60 mg (one tablet) qd with or without food
  (30 mg with strong CYP3A4 inhibitors and 90 mg with moderate CYP3A4 inducers)

Patients with GT 1 or 4 infection without cirrhosis

Patients with GT 1 or 4 infection and compensated cirrhosis

- In pre-treated pts (including a PI) consider 24 wks of treatment.
- In untreated patients with cirrhosis and positive predictors consider 12 wks of treatment.
- In pts with advanced disease and other negative predictors consider the addition of RBV.

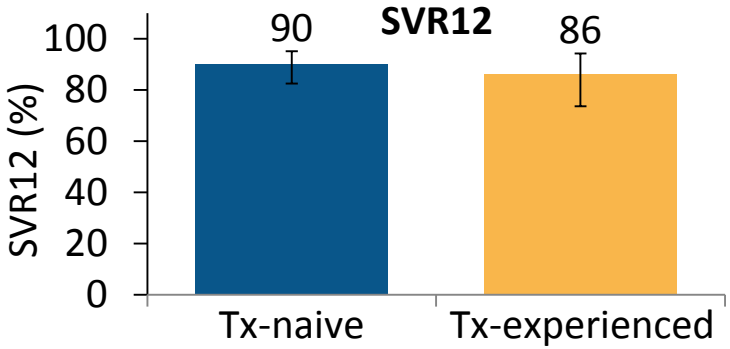


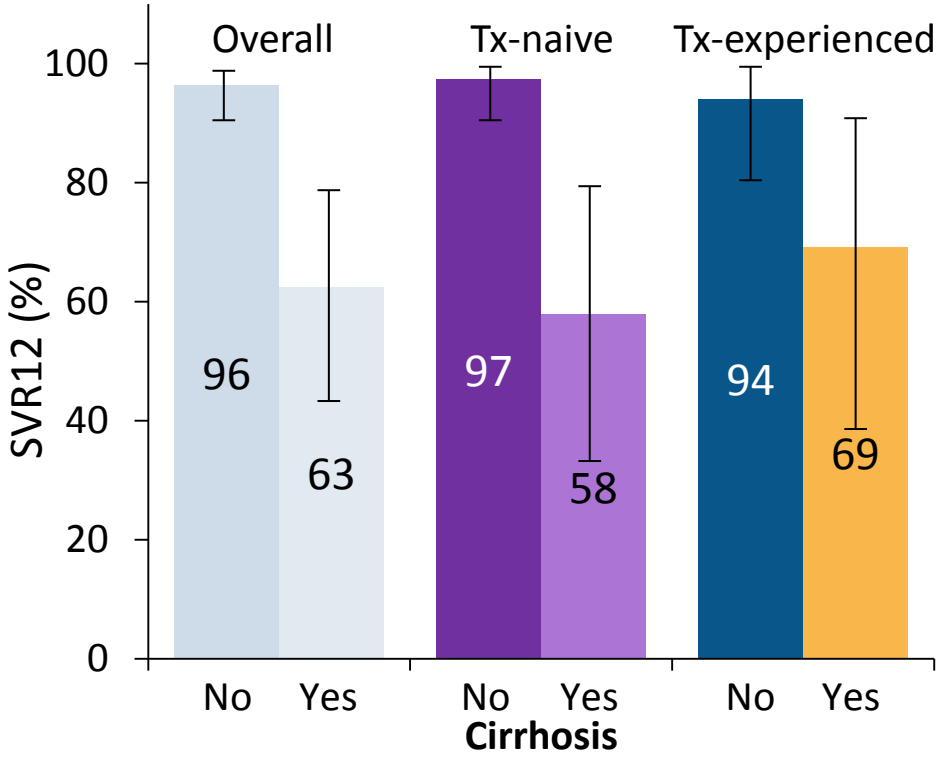
Patients with GT 3 infection and compensated cirrhosis and/or treatment-experienced

- Data for DAC + SOF x 12 wks only for HCV-1 treatment-naive pts available.
- Data for DAC + SOF +/- RBV only for pts without cirrhosis available.
- Recommendation for DAC + SOF in HCV-4 extrapolated from HCV-1 pts.

EMA. Daclatasvir [package insert] 2014

ALLY-3 Phase 3 Study: 12-week combination treatment with DCV + SOF in patients with HCV G3





- DCV + SOF for 12 wk duration in G3 may be the treatment of choice in non-cirrhotic patients with 96% SVR
- 63% overall SVR in cirrhosis disappointing
- Safety profile excellent

Nelson DR, et al. AASLD 2014, Boston. #LB-3

Phase III Trials of IFN-free Regimens: Genotype 1

- **Sofosbuvir + Ledipasvir ± RBV**
- **Ion-1**: TN ± cirrhosis; 12 vs. 24 wks
- **Ion-2**: TE (incl. PI-failure), ± cirrhosis; 12 vs. 24 wks
- **Ion-3**: TN w/o cirrhosis; 8 vs. 12 wks
- **Paritaprevir/r + Ombitasvir + Dasabuvir ± RBV**
- **Sapphire-I**: TN w/o cirrhosis; 12 wks
- **Sapphire-II**: TE w/o cirrhosis; 12 wks
- **Turquoise-II**: TN and TE + cirrhosis; 12 vs. 24 wks
- **Pearl-II, -III, IV**: ± RBV

ION-1: Reasons for Not Achieving SVR

Patients, n (%)	12 Weeks		24 Weeks	
	LDV/SOF n=214	LDV/SOF+RBV n=217	LDV/SOF n=217	LDV/SOF+RBV n=217
SVR12	211 (99)	211 (97)	212 (98)	215 (99)
Breakthrough	0	0	1 (<1)	0
Relapse	1 (<1)	0	1 (<1)	0
Lost to Follow-Up	2 (<1)	4 (2)	2 (<1)	2 (<1)
Withdrew Consent	0	2 (<1)	1 (<1)	0

- Single on-treatment breakthrough was due to non-adherence
- Two of 865 subjects (0.23%) had post-treatment relapse
  - Both had NS5A-resistant variants at baseline and at relapse
- 16% of all subjects had NS5A RAVs at baseline, with 96% achieving SVR

Afdhal N, *et al.* N Engl J Med. 2014;370:1889-98

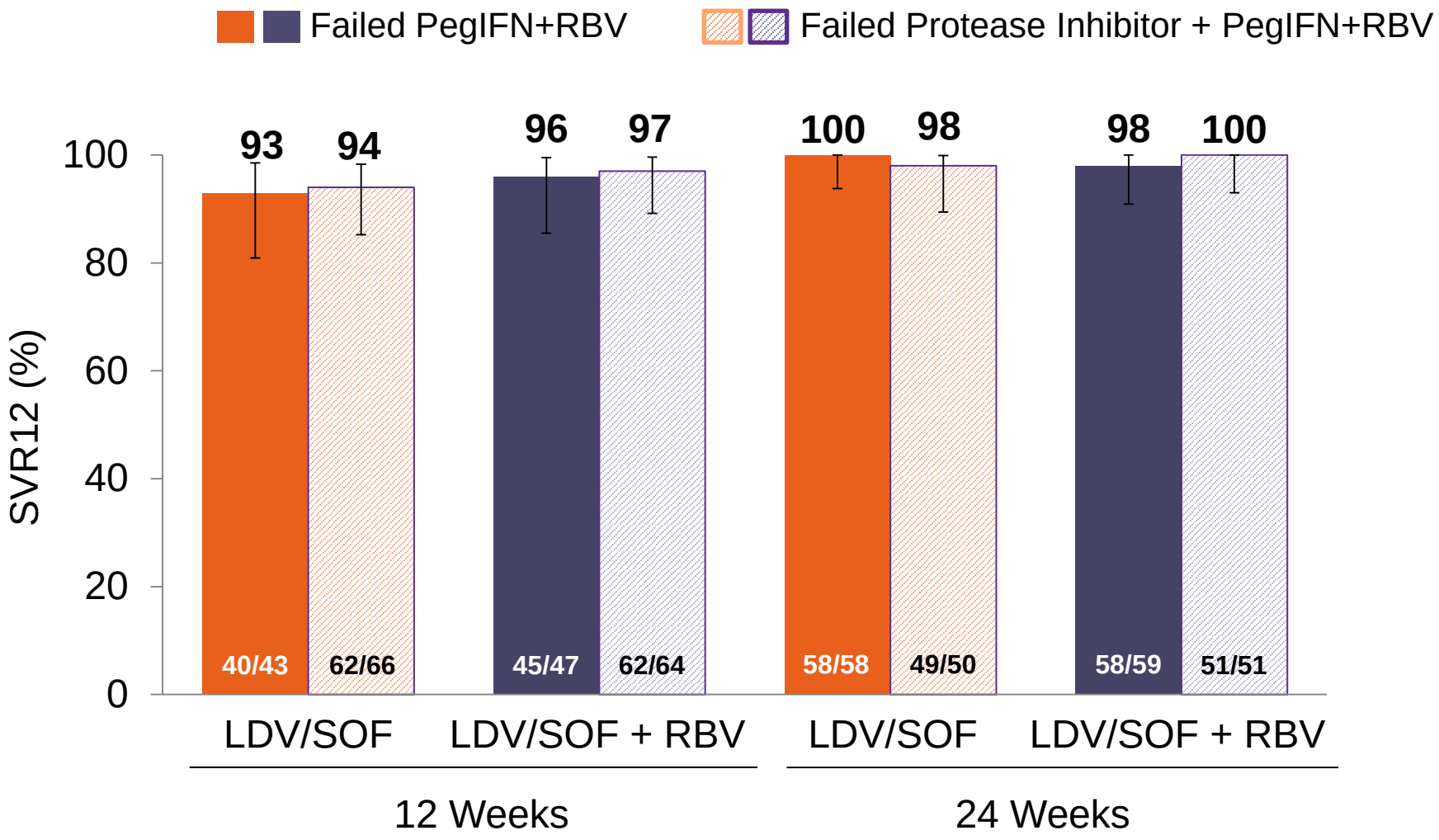
ION-3: Reasons for Not Achieving SVR

Patients, n (%)	8 Weeks		12 Weeks
	LDV/SOF n=215	LDV/SOF + RBV n=216	LDV/SOF n=216
SVR12	202 (94)	201 (93)	206 (95)
Breakthrough	0	0	0
Relapse	11 (5)	9 (4)	3 (1)
Lost to Follow-Up	1 (<1)	5 (2)	7 (3)
Withdrew Consent	1 (<1)	1 (<1)	0

- All virologic failures were due to relapse (n=23)
  - 9 subjects had baseline RAVs, 8 subjects with no RAVs, 6 subjects with new RAVs
- 18% of subjects had baseline NS5A RAVs, and 90% achieved SVR12

Kowdley KV, *et al.* N Engl J Med. 2014;370:1879-88

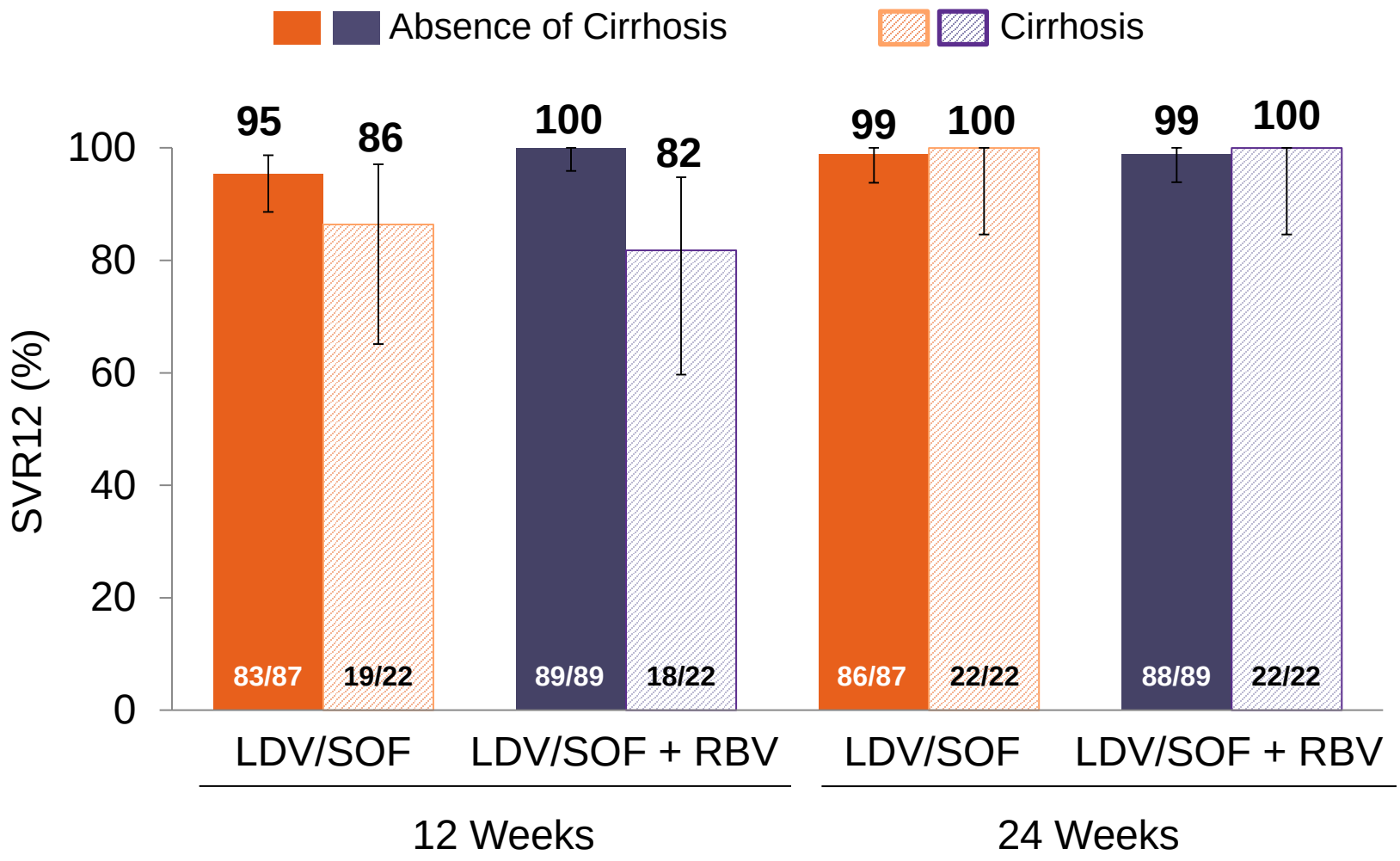
ION-2: SVR12 in PegIFN+RBV vs. PI+PegIFN+RBV Failures



Error bars represent 95% confidence intervals

Afdhal N, *et al.* N Engl J Med. 2014;370:1483-93

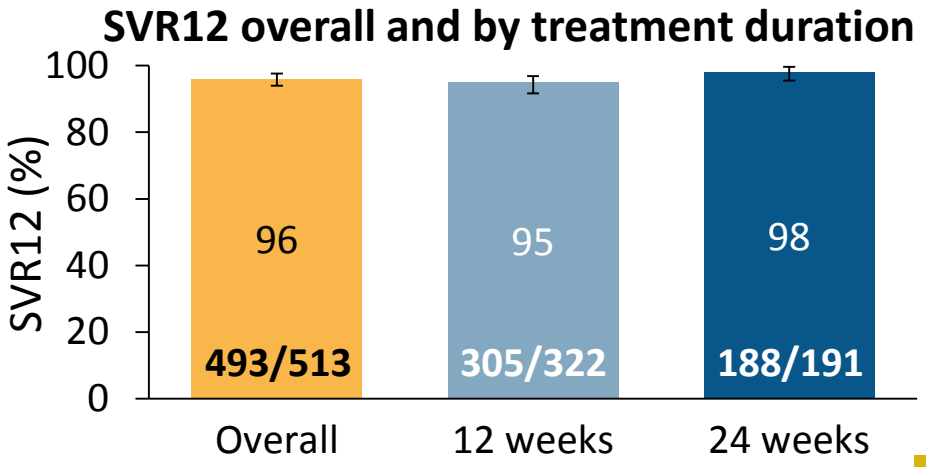
ION-2: SVR12 - Absence of Cirrhosis vs. Cirrhosis



Error bars represent 95% confidence intervals

Afdhal N, *et al.* N Engl J Med. 2014;370:1483-93

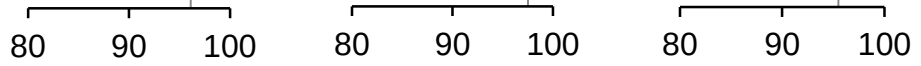
An integrated safety and efficacy analysis of >500 patients with compensated cirrhosis treated with LDV/SOF ± RBV



- 20 of 513 patients failed to achieve SVR12
  - 18 relapsed
  - 1 LTFU, 1 death (presumed infection)

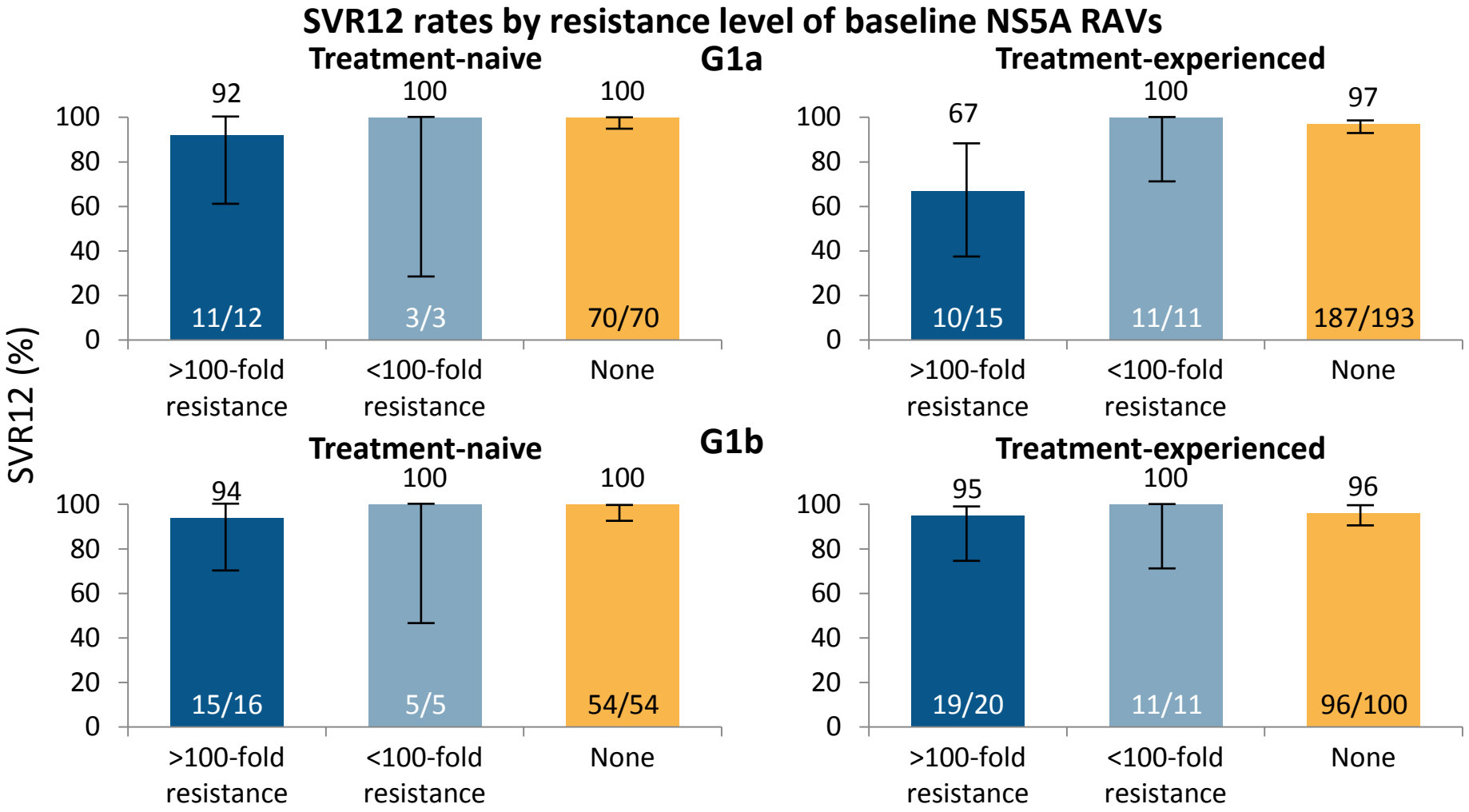
SVR12 by treatment regimen

		Total	Treatment-naive	Treatment-experienced
Overall SVR12		96%	98%	95%
Duration	12 wk	95%	97%	94%
	24 wk	98%	99%	98%
Regimen	LDV/SOF	95%	96%	95%
	LDV/SOF + RBV	97%	99%	96%
Duration/ ± RBV	LDV/SOF 12 wk	92%	96%	90%
	LDV/SOF + RBV 12 wk	96%	98%	96%
	LDV/SOF 24 wk	98%	97%	98%
	LDV/SOF + RBV 24 wk	100%	100%	100%



Bourlière M, et al. AASLD 2014, Boston. #82

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

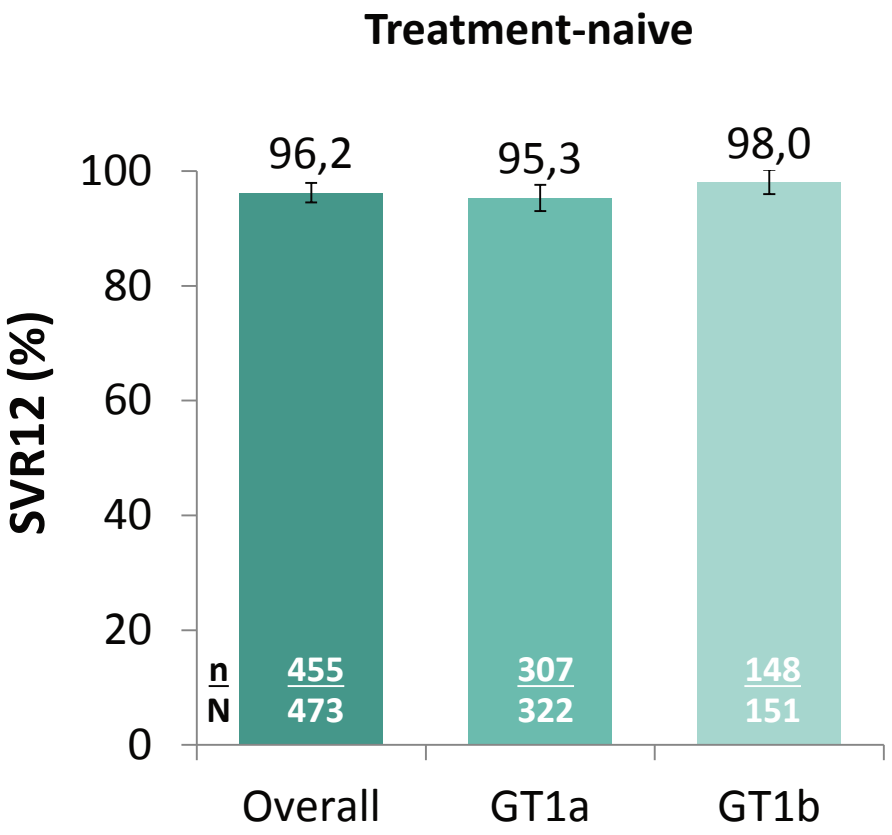
Sarrazin C, et al. EASL 2015, Vienna. #P0773

Phase III Trials of IFN-free Regimens: Genotype 1

- **Sofosbuvir + Ledipasvir ± RBV**
- **Ion-1**: TN ± cirrhosis; 12 vs. 24 wks
- **Ion-2**: TE (incl. PI-failure), ± cirrhosis; 12 vs. 24 wks
- **Ion-3**: TN w/o cirrhosis; 8 vs. 12 wks

- **Paritaprevir/r + Ombitasvir + Dasabuvir ± RBV**
- **Sapphire-I**: TN w/o cirrhosis; 12 wks
- **Sapphire-II**: TE w/o cirrhosis; 12 wks
- **Turquoise-II**: TN and TE ± cirrhosis; 12 vs. 24 wks
- **Pearl-II, -III, IV**: ± RBV

SAPPHIRE-I: HCV GT1 treatment-naive patients



3D + RBV x 12 wks

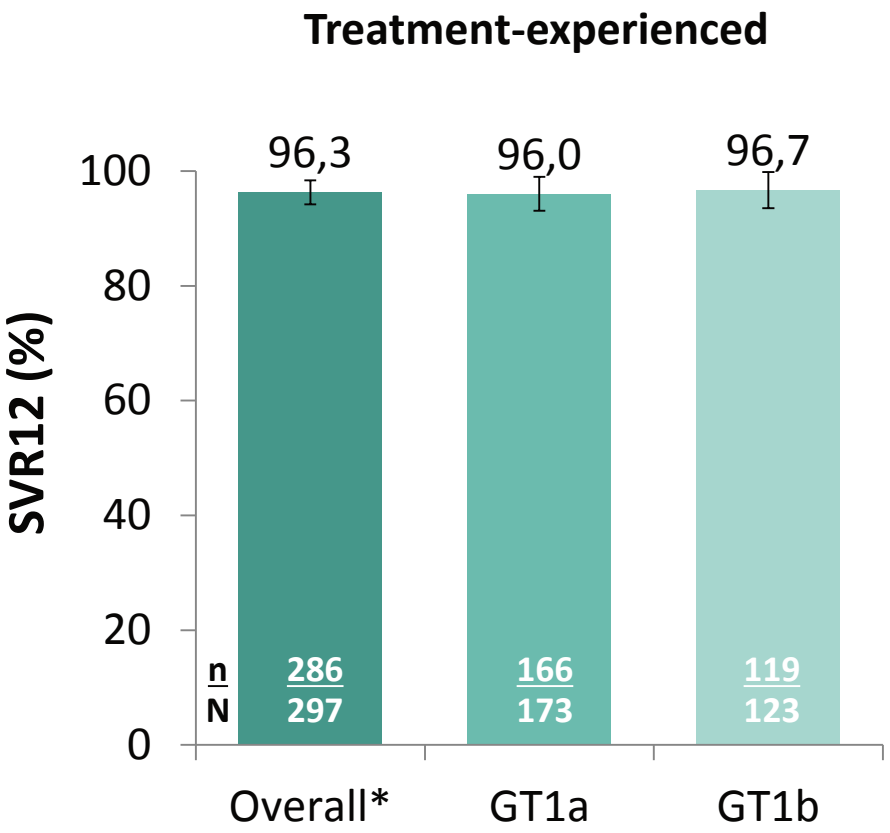
3D:
co-formulated Paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

Error bars: 95% CI.

Feld JJ, *et al.* N Engl J Med. 2014;370:1594-603

SAPPHIRE-II: HCV GT1 tx-experienced patients



3D + RBV x 12 wks

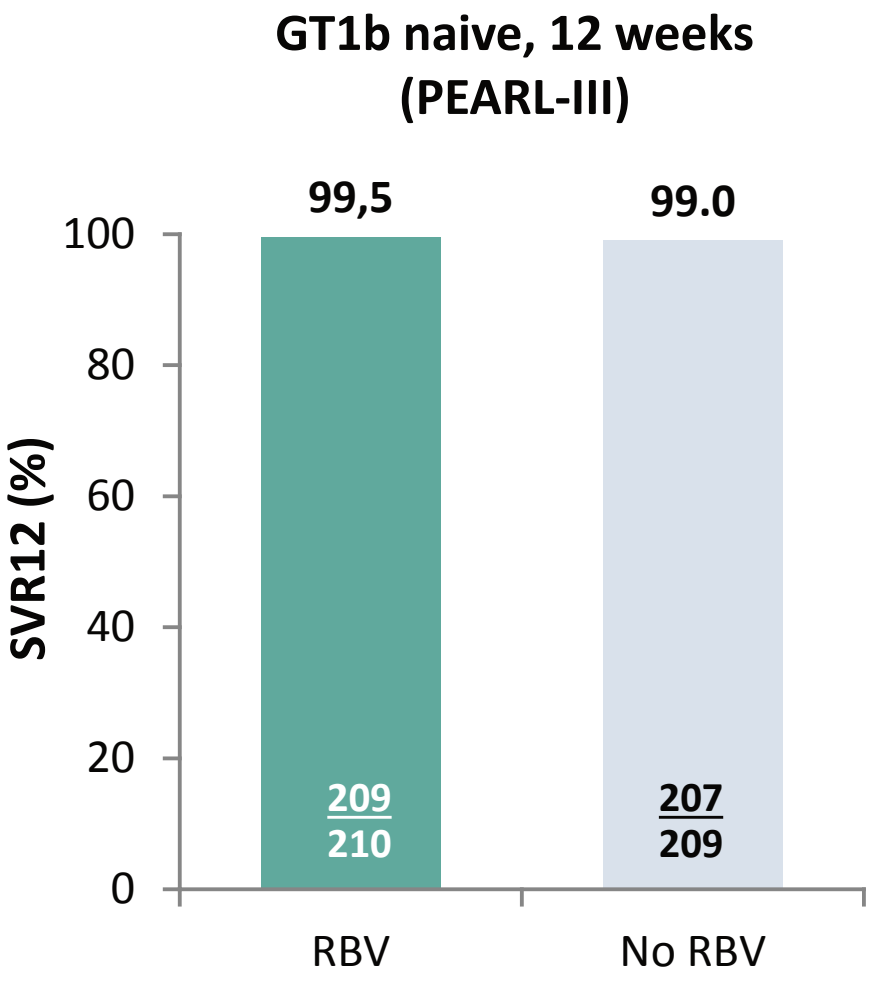
3D:
co-formulated Paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

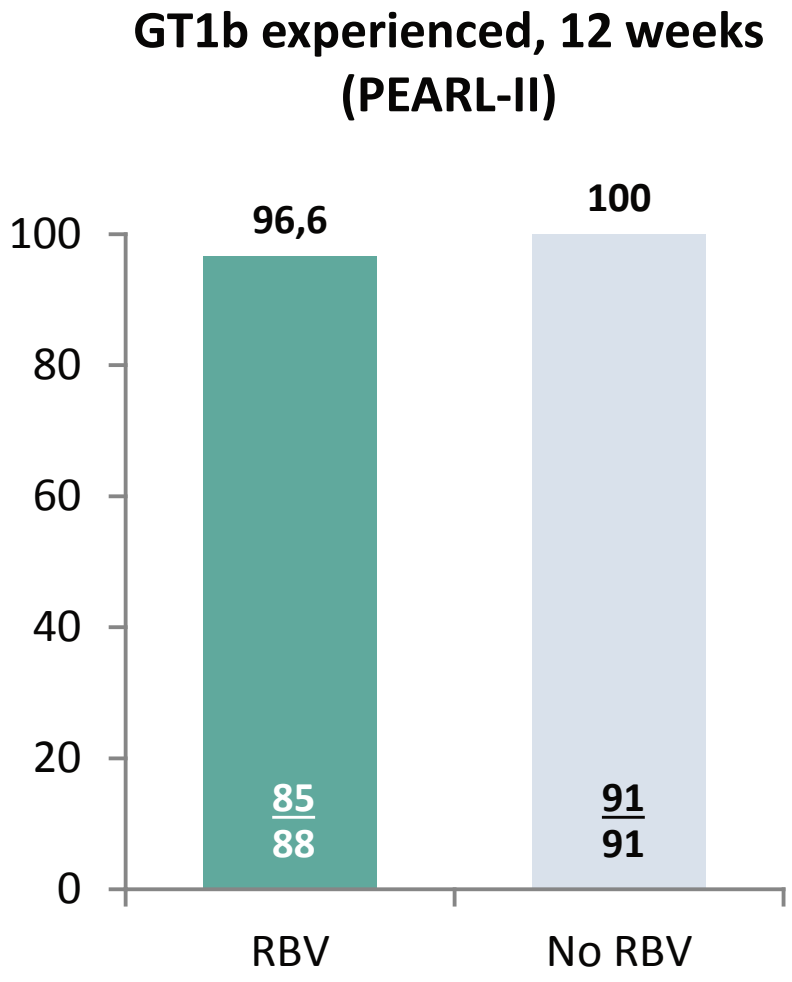
RBV: 1000-1200 mg/d

* One patient achieved SVR12, but was unable to be subgenotyped.
Error bars: 95% CI.

Zeuzem S, *et al.* N Engl J Med. 2014;370:1604-141

PEARL-II and -III: Paritaprevir/r + Ombitasvir + Dasabuvir ± RBV

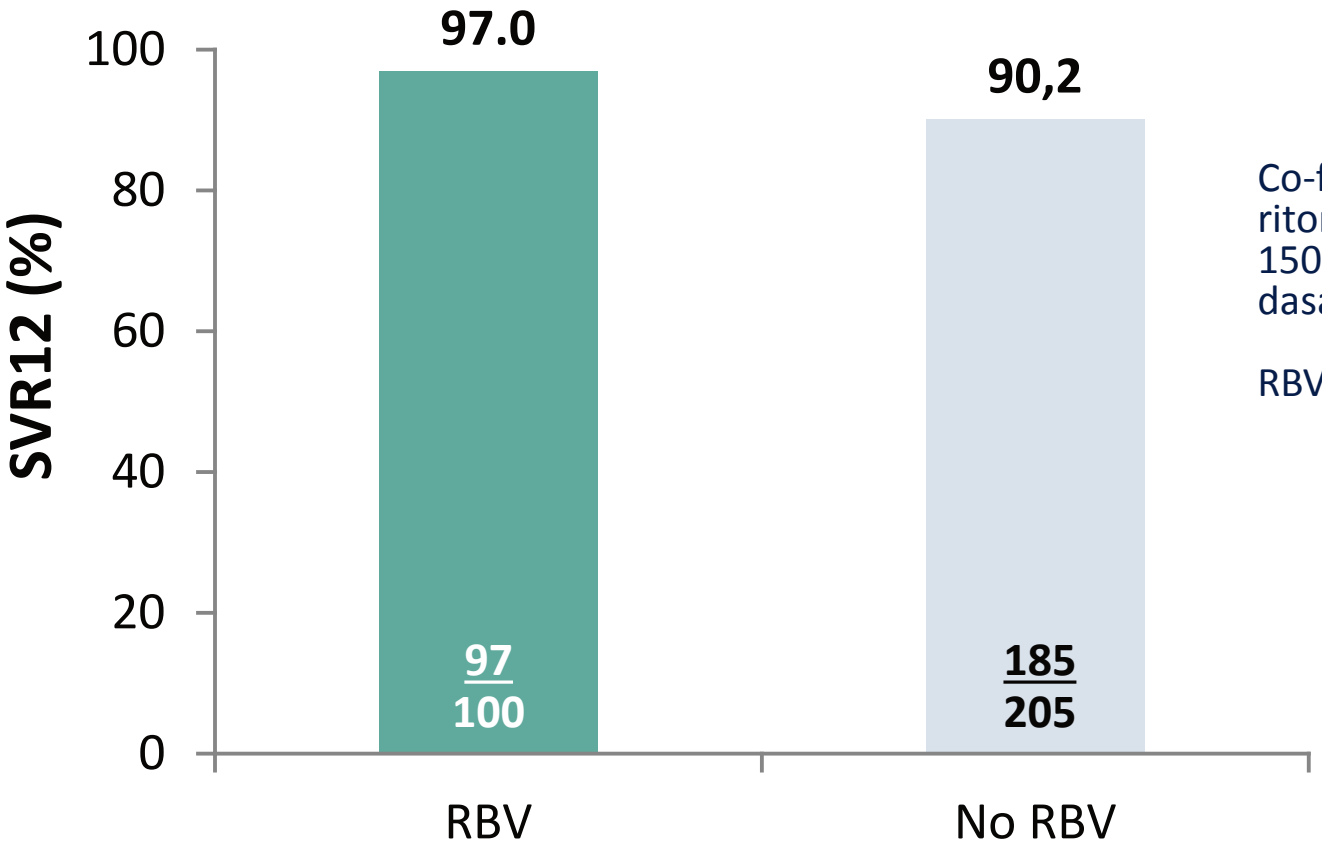




Co-formulated paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid
RBV: 1000-1200 mg/d

Ferenci P, *et al.* N Engl J Med. 2014;370:1983-92
Andreone P, *et al*. Gastroenterology. 2014;147:359-365

PEARL-IV: Paritaprevir/r + Ombitasvir + Dasabuvir ± RBV for 12 weeks in GT1a treatment-naive patients

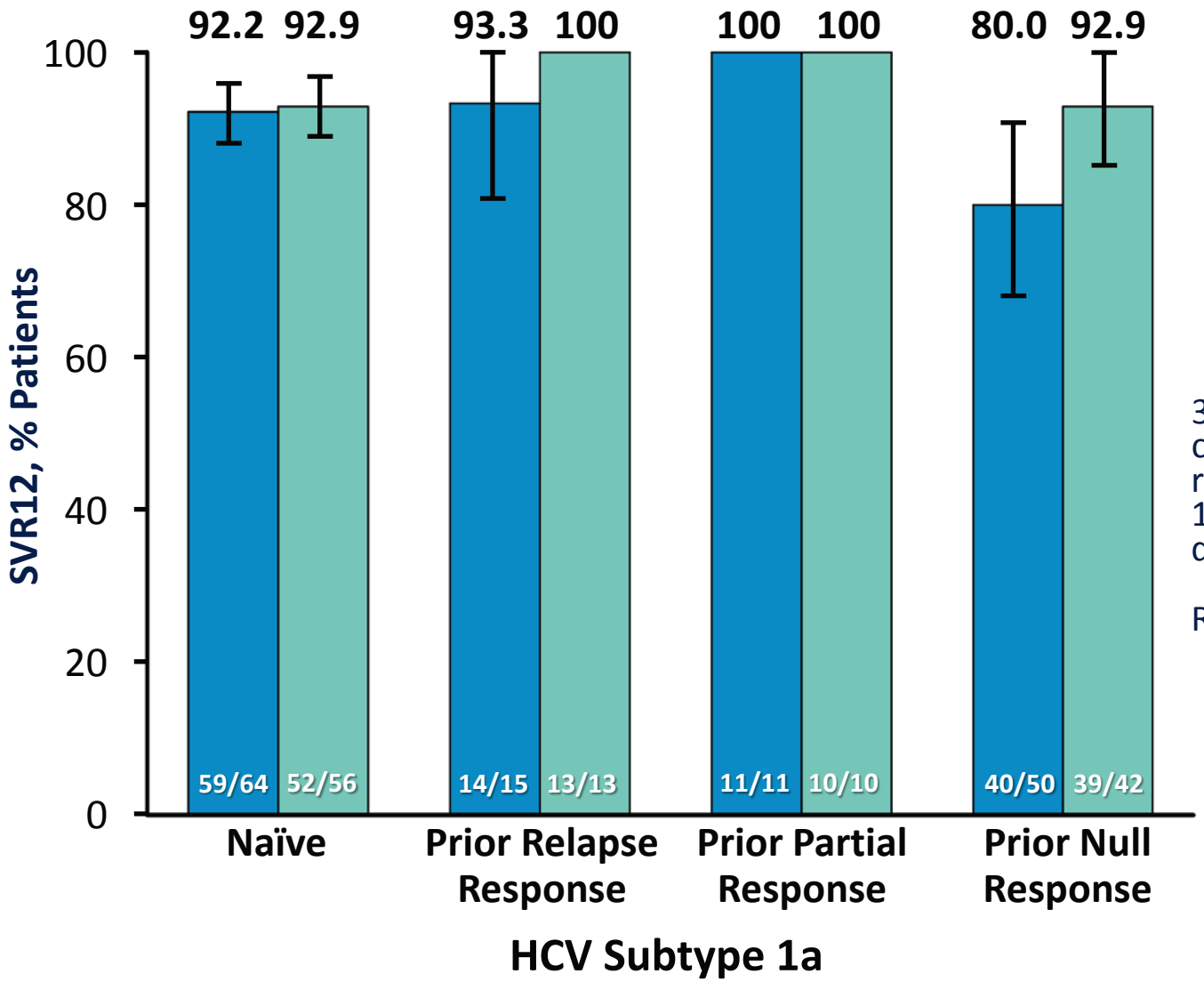


Co-formulated paritaprevir/ ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

Ferenci P, *et al*. N Engl J Med. 2014;370:1983-92

TURQUOISE-II: SVR12 Rates by Prior Treatment Response in HCV Subtype 1a

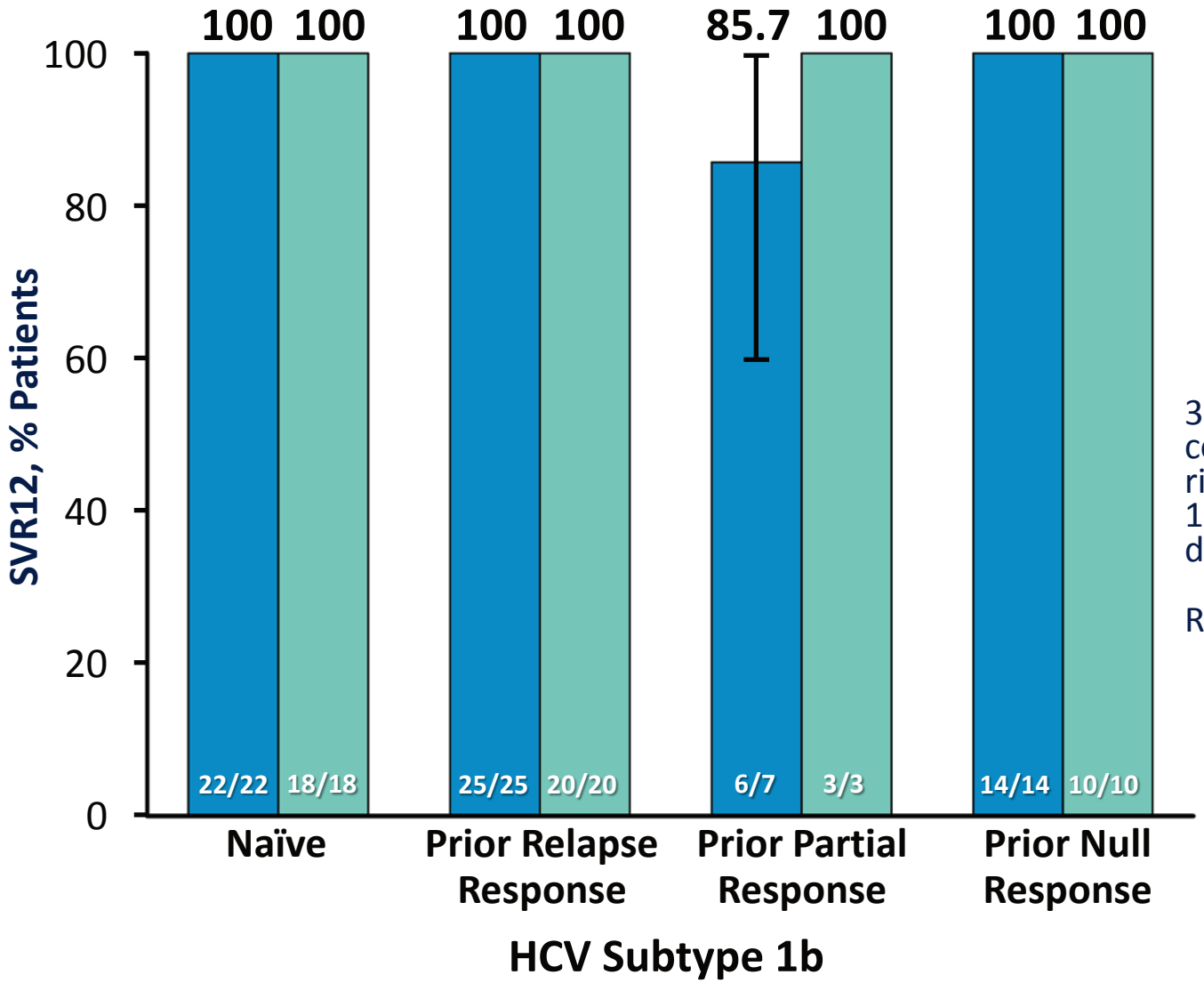


3D:
co-formulated paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

Poordad F, *et al.* N Engl J Med. 2014;370:1973-82

TURQUOISE-II: SVR12 Rates by Prior Treatment Response in HCV Subtype 1b



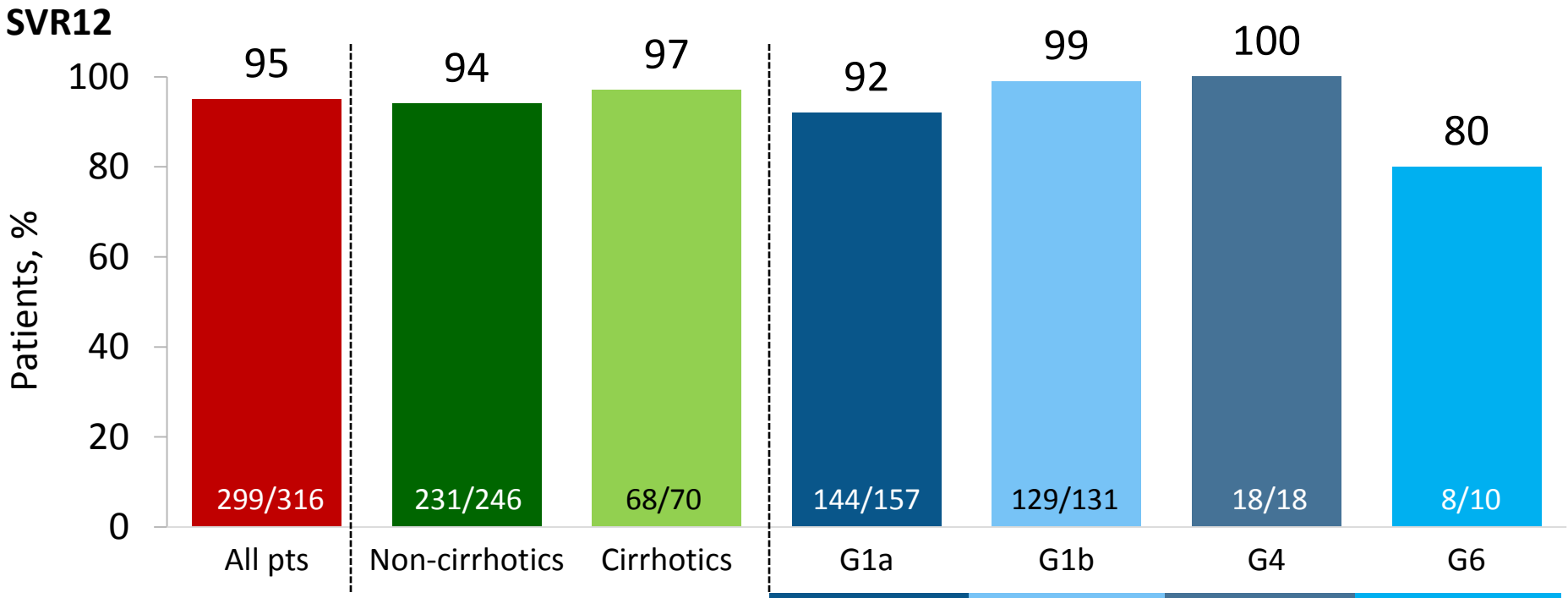
3D:
co-formulated paritaprevir/ritonavir/ombitasvir, 150 mg/100 mg/25 mg qd; dasabuvir, 250 mg bid

RBV: 1000-1200 mg/d

Poordad F, *et al.* N Engl J Med. 2014;370:1973-82

Treatment of Hepatitis C (Phase 3 data available, but not yet approved)

C-EDGE treatment-naive study: 12-week regimen of GZR/EBR in G1/4/6 patients



	G1a	G1b	G4	G6
Non-VF	3	1	0	0
Breakthrough	1	0	0	0
Relapse	9	1	0	2

- Good safety and tolerability profile: No drug-related SAE; 2 deaths unrelated to drug
- Lab: No concurrent ALT/Bili increase

Zeuzem S, et al. EASL 2015, Vienna. #G07

C-EDGE treatment-naive study: 12-week regimen of grazoprevir/elbasvir (GZR/EBR) in G1/4/6 patients

NS3 RAVs	RAV status in pts with BL sequence % (n/m)	SVR12 All pts % (N/n)	SVR12 NS3 RAVs ≤5-fold potency loss	SVR12 NS3 RAVs >5-fold potency loss
G1a RAVs				
BL NS3 RAVs	57 (86/151)	97 (83/86)	97 (83/86)	0 (0/0)
No BL NS3 RAVs	43 (65/151)	89 (58/65)	—	—
G1b RAVs				
BL NS3 RAVs	19 (25/129)	96 (24/25)	95 (21/22)	100 (3/3)
No BL NS3 RAVs	81 (104/129)	100 (104/104)	—	—

NS5A RAVs	RAV status in pts with BL sequence % (n/m)	SVR12 All pts % (N/n)	SVR12 NS5A RAVs ≤5-fold potency loss	SVR12 NS5A RAVs >5-fold potency loss
G1a RAVs				
BL NS5A RAVs	12 (19/154)	58 (11/19)	90 (9/10)	22 (2/9)
No BL NS5A RAVs	88 (135/154)	99 (133/135)	—	—
G1b RAVs				
BL NS5A RAVs	14 (18/130)	94 (17/18)	100 (1/1)	94 (16/17)
No BL NS5A RAVs	86 (112/130)	100 (112/112)	—	—

m: pts with evaluable BL sequence; n: number of pts with/without BL RAVS; N: pts who achieved SVR

- All pts with virologic failure had BL HCV RNA of >800,000 IU/mL

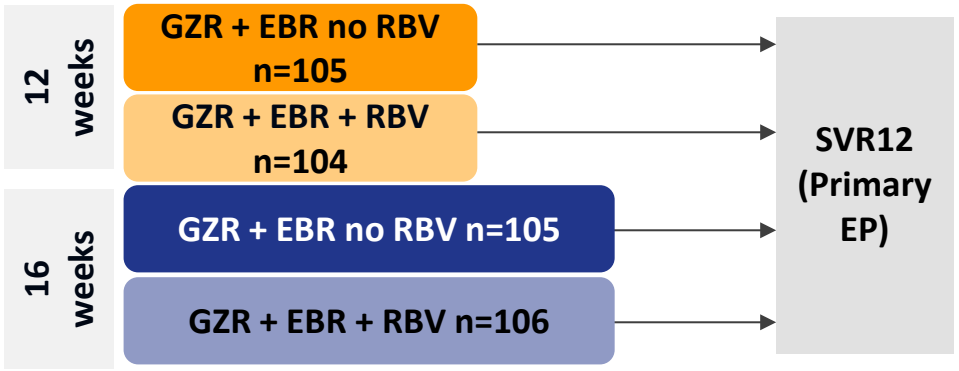
- SVR was achieved by 95% of pts
- Lower SVR in G1a accounted for by high-level (>5x fold) NS5A RAVs in G1a
- Although such RAVs uncommon (6% of G1a), BL NS5A testing with high BL VL might be needed to identify need for RBV, longer duration, or selection of a different regimen
- Well tolerated, with similar safety profile and similar efficacy in cirrhotic and non-cirrhotic patients

Zeuzem S, et al. EASL 2015, Vienna. #G07

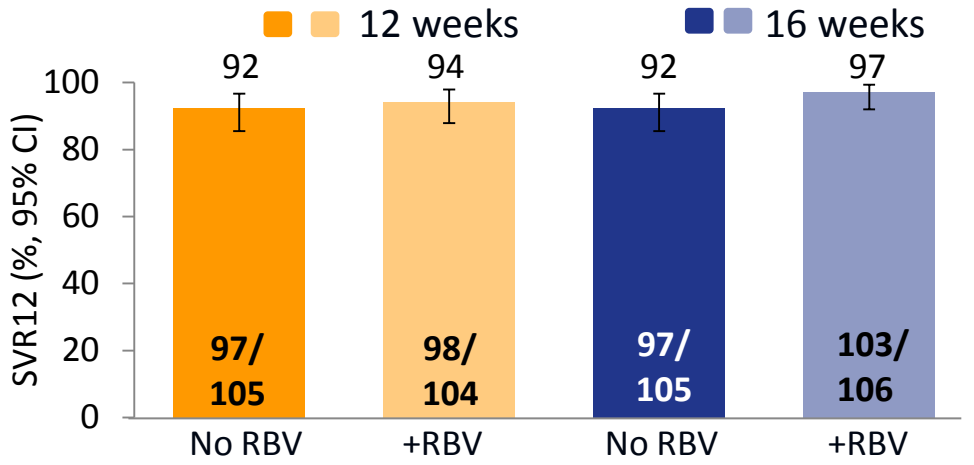
GZR/EBR ± RBV for 12 weeks in G1/4 patients who previously failed PegIFN/RBV: C-EDGE tx-experienced trial

- Phase 3 study of GZR (100 mg QD) and EBR (50 mg QD) in G1/4/6 PR failures
  - Includes cirrhotics and HIV+
  - Randomized to 12 vs 16 wks; ± RBV

%	12 wks no RBV n=105	12 wks + RBV n=104	16 wks no RBV n=105	16 wks + RBV n=106
Black	22	23	9	14
G1a G1b G4 G6	58 33 9 0	58 28 14 0	46 46 5 4	55 36 8 2
HIV+	6	5	6	4
Cirrhosis	35	34	36	35
Nulls Partials Relapser	47 20 33	42 21 37	44 20 36	41 22 38



Results: SVR12 ITT



Breakthrough	0	0	1	0
Rebound	0	0	2	0
Relapse	6	6	4	0
LTFU/early d/c	2	0	1	3

Kwo P, et al. EASL 2015, Vienna. #P0886

Treatment of Hepatitis C (in earlier development)

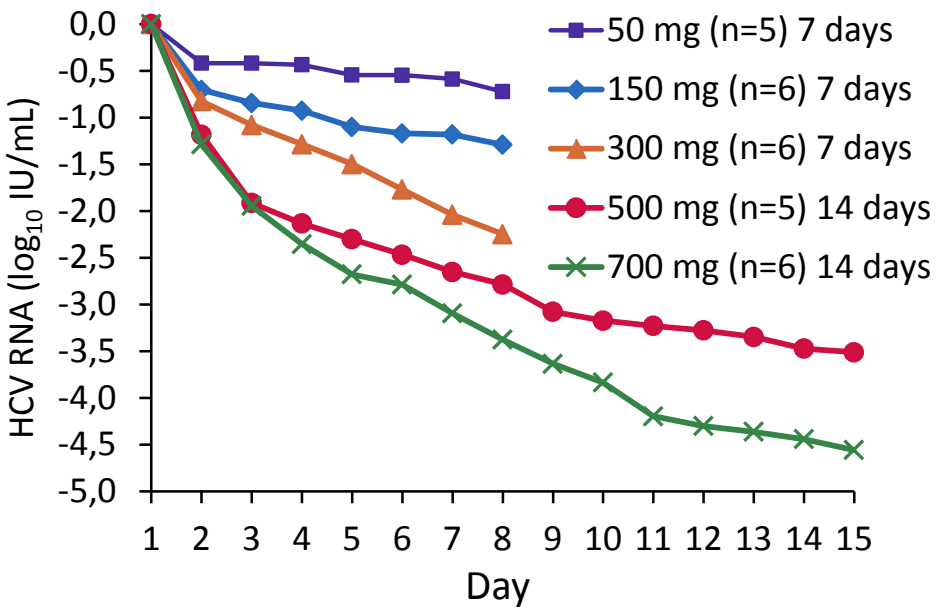
2nd Generation DAAs in Early Clinical Development

	Protease-Inhibitor	NS5A-Inhibitor	Nucleosidic Polymerase-Inh.	Non-Nucleosidic Polymerase-Inh.
Abbvie	+	+	?	
BMS				
Gilead	+	+		
Janssen/Achillion		+	+	
Merck	+	+	+	

- Higher genetic barrier
- Active against common baseline polymorphisms associated with lower sensitivities to first generation DAAs
- Active against RAVs selected by first generation DAAs

ACH-3422, a novel nucleotide prodrug inhibitor of HCV NS5B polymerase

Mean HCV RNA reduction from baseline



Mean maximum change (min, max)

	50 mg	150 mg	300 mg	500 mg	700 mg
7 days	**-0.7** (-1.1, -0.5)	**-1.3** (-1.6, -1.1)	**-2.3** (-4.4, -1.0)	**-2.8** (-3.7, -1.6)	**-3.4** (-4.9, -2.1)
10 days	--	--	--	**-3.2** (-4. 7, -1.9)	**-4.2** (-5.5, -3.2)
14 days	--	--	--	**-3.5** (-5.3, -2.3)	**-4.6*** (-6.5, -3.3)

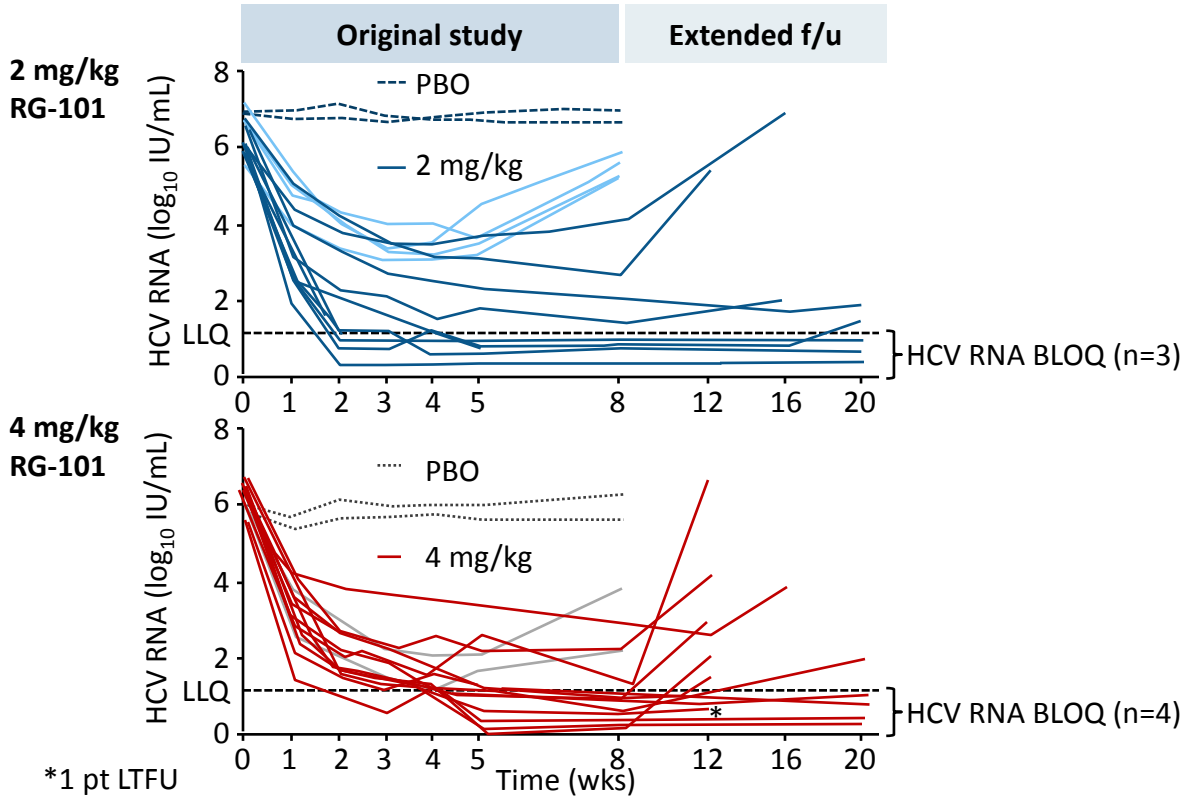
*3/6 patients were TND at D14

- ACH-3422 achieved dose-related virologic responses in G1 patients
- After 700 mg QD for 14 days, mean maximal reduction from baseline was 4.6 $\log_{10}$
- ACH-3422 up to 700 mg was safe and well-tolerated with no SAEs, treatment-related discontinuations, or clinically significant laboratory or ECG abnormalities
- Phase 2 studies of ACH-3422 + NS5A inhibitor ACH-3102, ± NS3/4A protease inhibitor sovaprevir, for short duration therapy in different patient populations

Gane E, et al. EASL 2015, Vienna. #LP27

Single SC dose of 2 mg/kg or 4 mg/kg of RG-101, a GalNac-conjugated oligonucleotide with antagonist activity against MiR-122, results in significant viral load reductions in HCV patients

- RG-101: Oligonucleotide inhibitor of MiR-122
- Single SC dose of 2 or 4 mg/kg and followed to 20 wks
  - Oligo linked to GalNac carbohydrate to enhance hepatic concentration results in 20-fold increase in potency vs non-conjugated oligo
  - Long biologic activity
- 32 non-cirrhotic pts, G 1,3,4 (14 active/2 PBO per dose)
- **Safety**:
  - Injection site reaction 16%



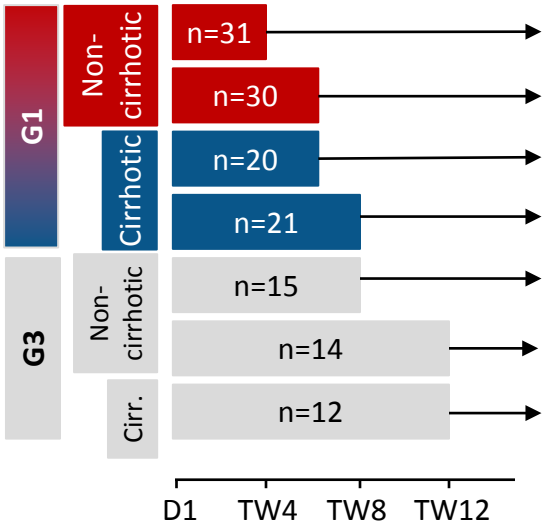
- MiR-122 inhibitor without any primary non-responders which is encouraging for future development
- One dose suppressed 7 pts <LLQ to 20 wks
- Novel HTA that could be used to shorten DAA course or treat failures with multiclass resistance

Van Der Ree M, et al. EASL 2015, Vienna. #LO7

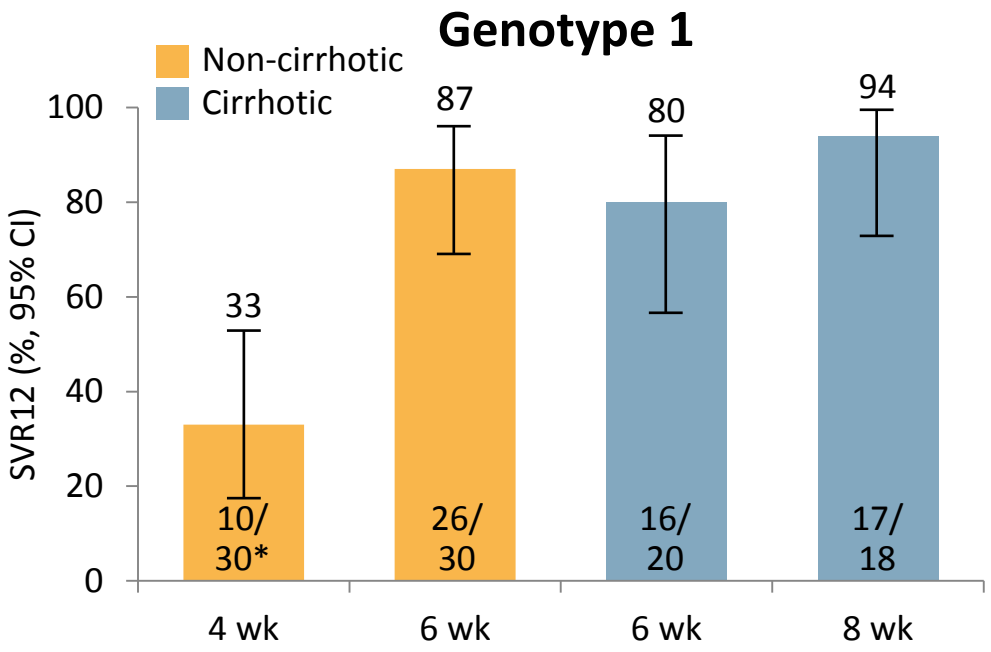
Shorter Durations of HCV Treatment

C-SWIFT: GZR/EBR + SOF in cirrhotic and noncirrhotic, treatment-naive G1/3 patients

- 143 G1 ± cirrhosis treated with GZR 100 mg/EBR 50 mg FDC QD + SOF 400 mg QD



Primary endpoint: SVR12



Breakthrough	0	0	0	0
Relapse	20	4	4	1
Early discon.*	1	0	0	3†

*mITT excluded patients who discontinued early due to reasons other than VF

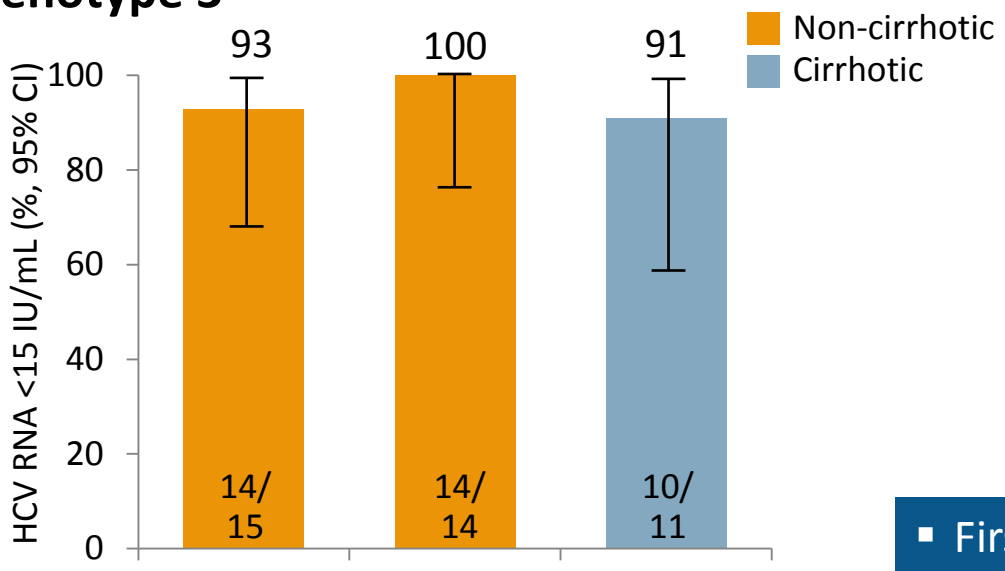
†One of the 3 pts who discontinued early had G2 at discontinuation

- G1a 76–87%

Poordad F, et al. EASL 2015, Vienna. #O006

C-SWIFT: GZR/EBR + SOF in cirrhotic and noncirrhotic, treatment-naive G1/3 patients

Genotype 3



Tx duration:	8-wk	12-wk	12-wk
Breakthrough	0	0	0
Relapse	1	0	1
Early discon.	0	0	1*

*mITT excluded pts who discontinued early due to reasons other than VF

- First trial to cure patients with designed 4-week duration but reaches limits of biologic plausibility with current generation of antivirals
- 8-week duration plausible goal for 3 antivirals for all patients
- Combination DAA therapy may make G3 easier to treat in future

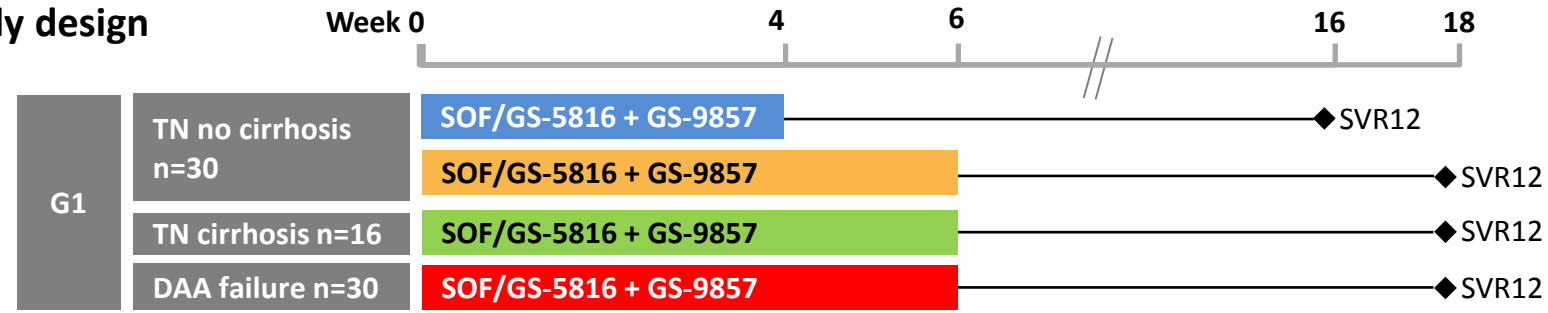
Poordad F, et al. EASL 2015, Vienna. #O006

Short-duration treatment with GS-9857 + SOF/GS-5816 in treatment-naive and DAA-experienced G1 patients with and without cirrhosis

Aim

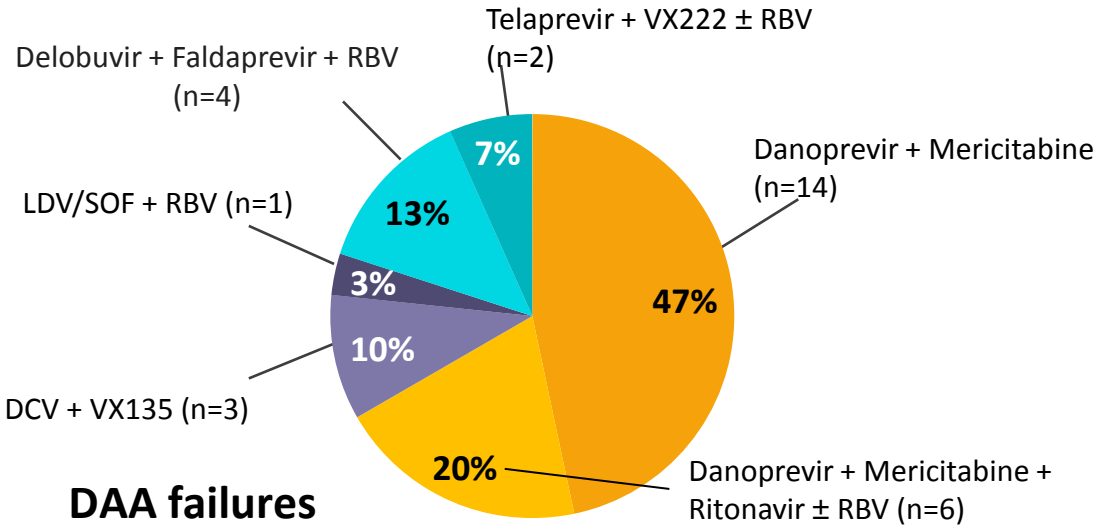
- Triple therapy with SOF plus 2nd gen NS5A inhibitor (GS-5816) and NS3/4A (GS-9857) could reduce treatment duration across patient populations

Study design



Inclusion criteria

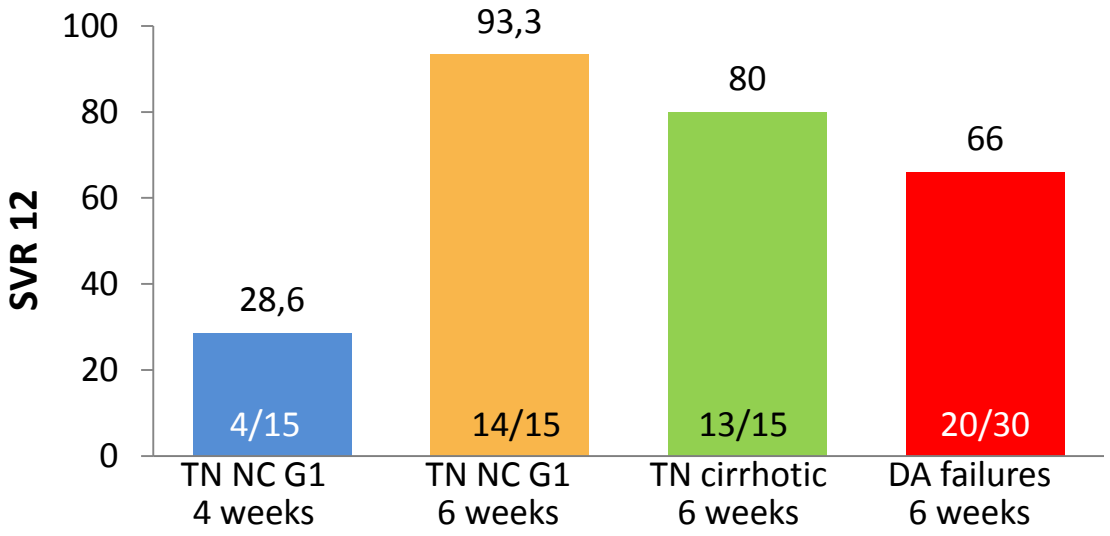
- No upper age limit
- Platelets >50,000
- Methadone allowed
- TE received 2 classes of DAAs ± RBV



DAA failures

Gane E, et al. EASL 2015, Vienna. #LP03

Short-duration treatment with GS-9857 + SOF/GS-5816 in treatment-naive and DAA-experienced G1 patients with and without cirrhosis



RAVs at virologic failure (relapse)

NS3	0	0	1	0*
NS5A	0	0	0	0*
NS5B	0	0	0	0*

*Only 3/10 subjects have been sequenced

Gane E, et al. EASL 2015, Vienna. #LP03

Conclusions

- Response to IFN-based therapy is irrelevant
- Baseline HCV RNA, **NS5A RAVs**, and cirrhosis remain baseline predictors for SVR
- Shortest treatment options 6-8 weeks
- Main differentiation between regimens
  - SVR and safety in patients with advanced disease
  - Requirement for ribavirin and drug-drug interactions
- Treatment for decompensated cirrhotic pts, pts with renal impairment, those infected with GT3 and pts who failed DAAs need further refinement
- Increase of diagnosis and treatment rates required