Hepatitis C - results in real life

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MERCK
Be well

Disclosures

Advisor and/or speaker for:

AbbVie, Bristol-MyersSquibb, Gilead, Janssen, Merck, Novartis, Roche

LDV/SOF±RBV effectiveness in real-world studies

Reference	Country	Number of patients, n	Cirrhosis, n	SVR 12 in all patients, n (%)	SVR 12 in cirrhosis, n (%)
Terrault et al.	USA	1044		1008 (96)	
Afdhal et al.	USA	1979	679	1936 (98)	654 (96)
Buggisch et al.	Germany	1956		1923 (98)	
Crespo et al.	Spain	1504	814	1436 (95)	779 (96)
Latt et al.	USA	1053		983 (93)	
Qureshi et	U			3 (98	
Flisiak et al	Po d	86		8 (9	37 (86)
Fuchs et al.	USA	27	167	24 (97)	16 (96)
Backus et a	USA	5390	1641[a]	491 (91)	4 (88)[a]
Cheung et al.	UK	162	162	147 (91)	147 (91)
Aghemo et al.	Italy	73		68 (93)	
Overall		13	3	1	2 (9

[a]Patients with FIB-4>3.5.

LDV/SOF±RBV N=13 858

SVR=94%

cirrhosis: n=3 506, SVR=92%

Terrault N, et al. *Hepatology. 2015;62:94*
Afdhal N, et al. *J Hepatol.* 2016;64(Suppl. 2):S222.
Buggisch P, et al. *J Hepatol. 2016;64(Suppl. 2):S810.*
Crespo J, et al. *J Hepatol. 2016;64(Suppl. 2):S217-218.*
Latt NL, et al. *J Hepatol. 2016;64(Suppl. 2):S802-803.*
Qureshi K, et al. *J Hepatol. 2016;64(Suppl. 2):S786.*

OBV/PTV/r±DSV±RBV effectiveness in real-world studies

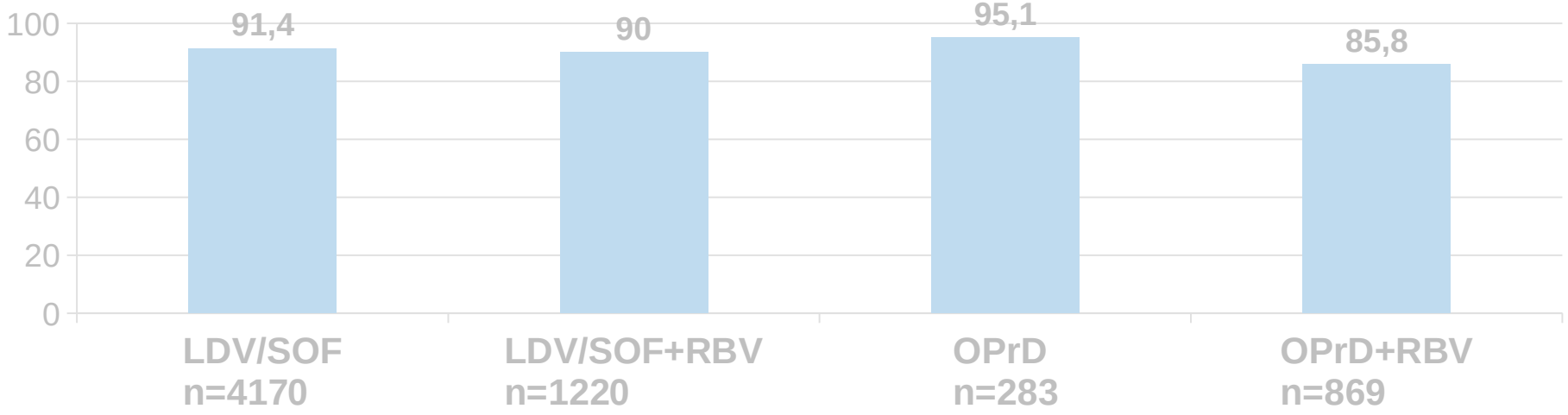
Reference	Country	Number of patients, n	Cirrhosis, n	SVR 12 in all patients, n (%)	SVR 12 in cirrhosis, n (%)
Aghemo et al.	Italy	42	2	41 (98)	41 (98)
Calleja et al.	Spain	1422	732	1376 (97)	710 (97)
Christensen et al.	Germany	8		83 (95)	
Derbala et al.	Qatar	42	4	41 (98)	24 (100)
Flisiak et al.	Poland	209	119	207 (99)	117 (98)
Gómez et al.	Spain	31		31 (100)	
Hinrichsen et al.	Germany			9 ( )	129 (95)
Hunyady et al.	Hungary	61		60 ( )	
Lubel et al.	Australia	167		167 (92)	(91)
McCombs et al.	USA	012		945 (93)	329 (94)
Ouzan et al.	France	20		20 (100)	
Teti et al.	Italy	193		188 (97)	
Zuckerman et al.	Israel	426	253	1 (99)	25 (00)
Overall		4260	1647	4111 (97)	1601 (97)

OBV/PTV/r±DSV±RBV
N=4 260
SVR=97%
cirrhosis: n=1 647, SVR=97%

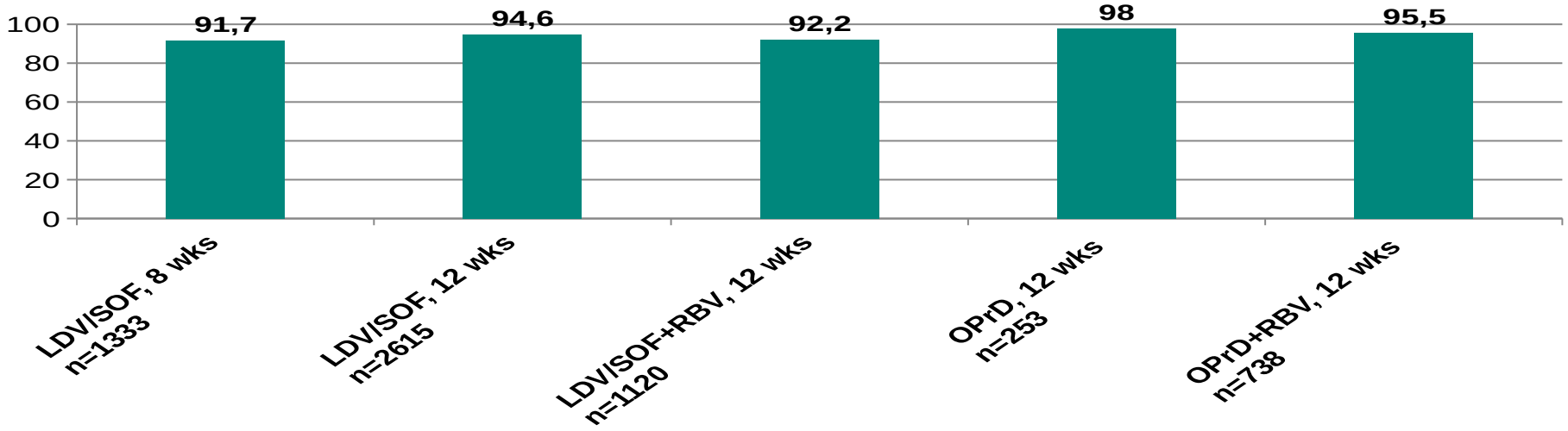
Aghemo A, et al. *J Hepatol. 2016;64(Suppl. 2):S213.*
Calleja J, *J Hepatol. 2016;64(Suppl. 2):S218-219.*
Christensen S, *J Hepatol. 2016;64 (Suppl.* 2): S821.
Derbala M, et al. *J Hepatol.* 2016;64(Suppl. 2):S799-800.
Flisiak R, et al. *Aliment Pharmacol Ther. 2016;44:946–956.*
Gómez R, et al. *J Hepatol. 2016;64(Suppl.* 2):S813.
Hinrichsen H, et al. *J Hepatol. 2016;64(Suppl.* 2):S159.

Comparative effectiveness of LDV/SOF±RBV vs. OBV/PRV/r+DSV±RBV in 6 961 GT1 patients treated in routine medical practice (VA database)

treatment durations of 12 weeks or less

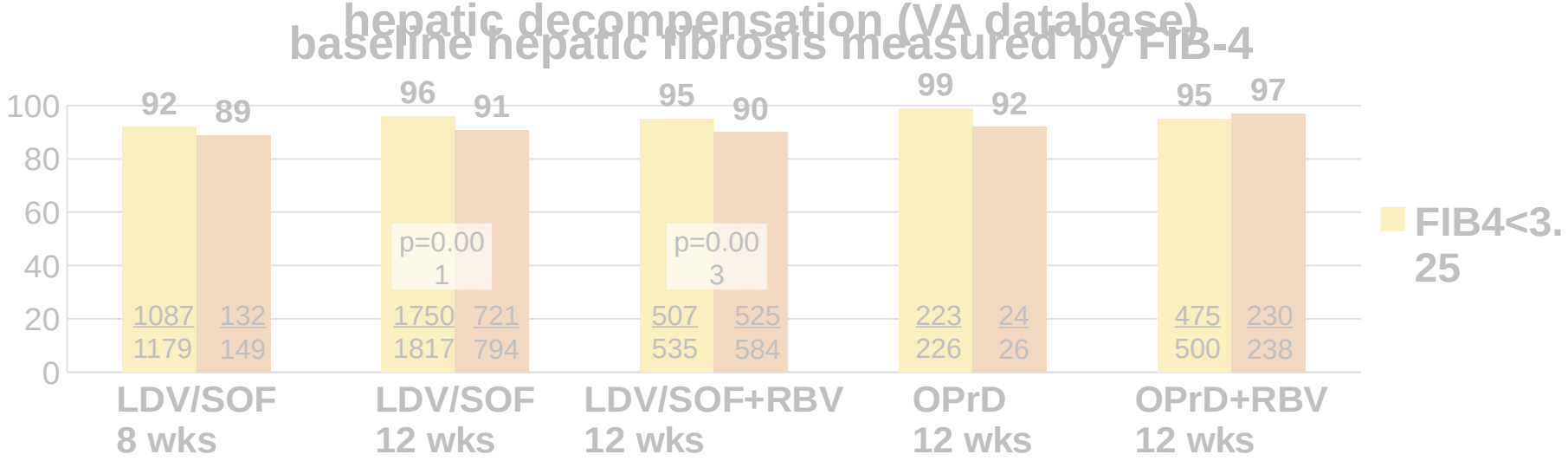


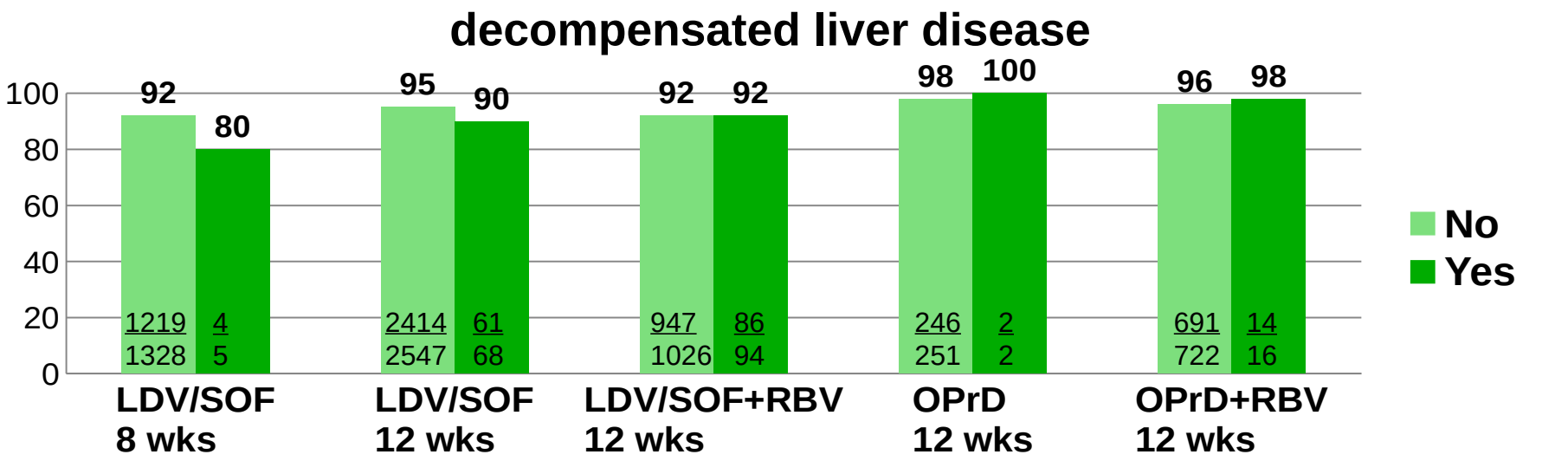
8 or 12 weeks of LDV/SOF and 12 weeks of all other regimens



Backus LI et al. Aliment Pharmacol Ther. 2016;44(4):400-410

Comparative effectiveness of LDV/SOF±RBV vs. OBV/PRV/r+DSV±RBV in GT1 patients with advanced fibrosis and hepatic decompensation (VA database)



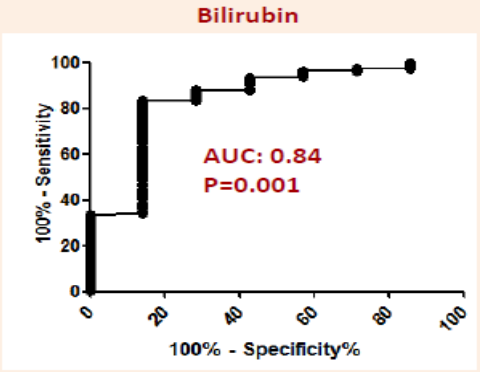


Backus LI et al. Aliment Pharmacol Ther. 2016;44(4):400-410

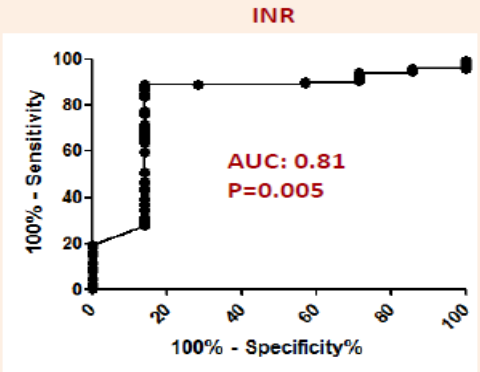
during OBV/PRV/r±DSV±RBV treatment (n=7/209; 3.3%), AMBER study

Age	31	57	56	60	64	54	57
Gender	m	m	f	f	m	f	M
Genotype	1b	1b	1b	1b	1b	1b	1b
HE history		+	+		+		
Ascites history	+	+	+	+	+		+
Therapy discontinuation					+		
Decomp. related to therapy						+	+
Baseline PLT, x1000/mcL	91	125	62	54	87	94	132
Albumins, g/dL	3,57	2,78	3,12	3,9	3,6	2,76	3,0
INR	1,41	1,29	1,33	1,30	1,00	1,30	1,50
MELD score	13	13	17	12	12	13	13
Child-Pugh score	6	8	8	6	6	8	6
Post OLTx			+	+	+		

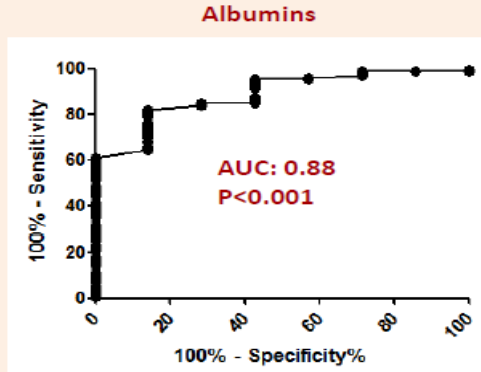
The ROC analysis showed high discriminatory power of bilirubin, INR and albumins to predict on-treatment decompensation



Bilirubin >1.65 mg/dL
Likelihood Ratio=5.83



INR>1.28
Likelihood Ratio=6.22



Albumins<3.6 mg/dL
Likelihood Ratio=5.73

History of decompensation and baseline laboratory signs of hepatic function impairment, are crucial risk factor for on treatment decompensation during anti-HCV therapy.

Flisiak R. et al. Aliment Pharm Ther 2016; 44: 946–

Other SOF containing regimens in real-world studies

SMV+SOF±RBV or DCV+SOF±RBV

SMV+SOF±RBV

N=4 631

SVR=83%

cirrhosis: n=1 822, SVR=79%

Reference	Country	Number of patients, n	Cirrhosis, n	SVR12 in all patients, n (%)	SVR12 in cirrhosis, n (%)
SMV+SOF±RBV					
Fox DS. et al.	USA	3263	1708a	2714 (83)	1335 (78)
Reddy KR et al	USA	131	7b	4 (72)	13 (76)
Sulkowski et al.	USA	802		675 (84)	
Mauss S et al.	Germany	284		245 (86)	
Brown JR et al.	USA	151c	97	133 (88)	83 (86)
Overall		4631	1822	3861 (83)	1431 (79)
DCV+SOF±RBV					
Pol S et al.	France	768	563	729 (95)	528 (94)

a – FIB4>3.25
b – MELD>16
c – posttransplant patients

Sulkowski MS, et al. Gastroenterology 2016;150(2):419-29.
Mauss S, et al. *J Hepatol. 2016;64(Suppl. 2):S820.*
Pol S, et al. *J Hepatol* 2017; 66: 39–47
Brown JR et al. *Liver Transplantation* 2016; 22: 24-33

Safety data of interferon-free regimens in real-world experience

Regimen	Reference	Discontinued due to adverse events (%)	Serious Adverse Events (%)
LDV/SOF±RBV	Crespo et al.	1.7	5.6
	Latt et al.[--]	0.8	0.8
	Flisiak et al.[--]	2.2	0
	Reddy et al.[---]	0.8	9.4
	Colombo et al.[----]	0.9	11
OBV/PTV/ r±DSV±RBV	Calleja et al.[28]	1.7	5.9
	Flisiak et al.[29]	2.4	3.8
	Hinrichsen et al.[52]	1.4	2.6
	Hunyady et al.[31]	0	4.9
	Lubel et al.[32]	1.7	5.4
	Zuckerman et al [30]	3	3.8
SMV+SOF±RBV	Sulkowski et al.[24]	3	5

1-2% **0-11%**

0-3% **2-6%**

Crespo J, et al. *J Hepatol. 2016;64(Suppl. 2):S217-218.*
Latt NL, et al. *J Hepatol. 2016;64(Suppl. 2):S802-803.*
Flisiak R, et al. *Clin Exp Hepatol. 2016;2:80.*
Reddy KR, et al. *Hepatol. 2016;64(Suppl.* 2):S783-784.
Colombo M. et al. *J Hepatol. 2016;64(Suppl. 2):S183.*
Calleja J, *J Hepatol. 2016;64(Suppl. 2):S218-219.*

Adverse events are related mostly to RBV administration

OBV/PTV/r ±DSV therapy in the AMBER study

	With RBV (n = 156)	Without RBV (n = 53)	All (n = 209)
Any adverse events, n (%)	120 (76.9)	31 (58.5)	151 (72.2)
Serious adverse events	8 (5.1)	0 (0.0)	8 (3.8)
Hepatic decompensation	3 (1.9)	0 (0.0)	3 (1.4)
Anaemia	2 (1.3)	0 (0.0)	2 (1.0)
Diarrhoea	1 (0.6)	0 (0.0)	1 (0.5)
Hepatotoxicity	1 (0.6)	0 (0.0)	1 (0.5)
Renal insufficiency	1 (0.6)	0 (0.0)	1 (0.5)
Adverse events leading to treatment discontinuation	4 (2.6)	1 (1.9)	5 (2.4)
Most common adverse events*			
Asthenia	38 (24.4)	6 (11.3)	44 (21.1)
Fatigue	35 (22.4)	3 (5.7)	38 (18.2)
Nausea	21 (13.5)	3 (5.7)	24 (11.5)
Headache	19 (12.2)	10 (18.9)	29 (13.9)
Pruritus	15 (9.6)	2 (3.8)	17 (8.1)
Jaundice	15 (9.6)	2 (3.8)	17 (8.1)
Rash	14 (9.0)	1 (1.9)	15 (7.2)
Insomnia	10 (6.4)	2 (3.8)	12 (5.7)
Peripheral oedema	6 (3.8)	6 (11.3)	12 (5.7)
Pain in the limbs/arthralgia	6 (3.8)	7 (13.2)	13 (6.2)
Laboratory findings			
ALT grade 3 or 4 (>5 × ULN)	4 (2.6)	1 (1.9)	5 (2.4)
Bilirubin grade 3 or 4 (>3 × ULN)	28 (17.9)	0 (0.0)	28 (13.4)
Haemoglobin grade 2 (8–10 g/dL)	12 (7.8)	1 (1.9)	13 (6.2)
Haemoglobin grade 3 or 4 (<8 g/dL)	3 (1.9)	1 (1.9)	4 (1.9)

Flisiak R. et al. Aliment Pharm Ther 2016; 44: 946–

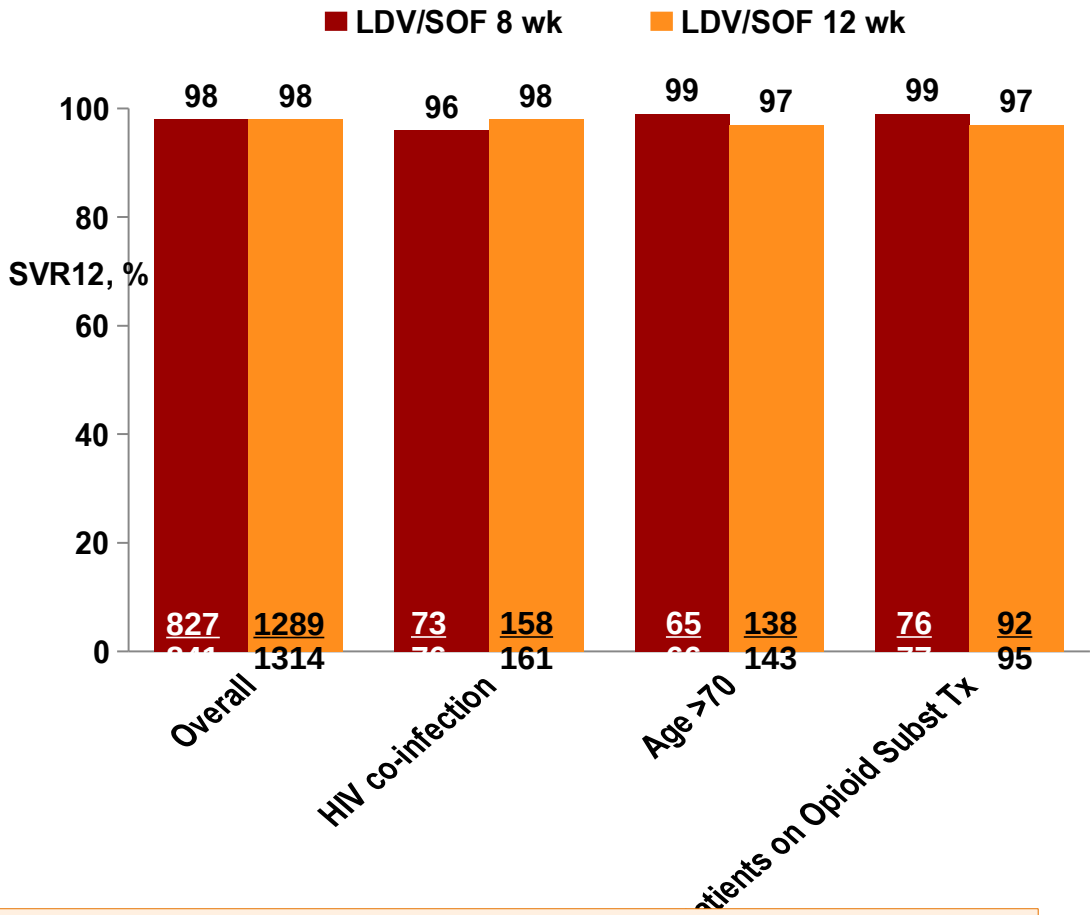
Effectiveness of LDV/SOF therapy shortened to 8 weeks

N=2,485 HCV GT1 patients, German Hepatitis C-Registry (DHC-R)

Baseline Demographics

Patients	LDV/SOF 8 weeks n=976	LDV/SOF 12 weeks n=1,509
Male, n (%)	466 (48)	874 (58)
Mean age, years	50	54
Age >70 years, %	7.3	10.6
Treatment-naïve, %	92	41.3
Fibroscan, mean (kPa)	6.5	9.3
Cirrhosis, %	2.4	13.9
HCV VL>6 million, %	3.0	14.2
HIV/HCV, n (%)	91 (9.3)	187 (12.4)

SVR12 (PP)

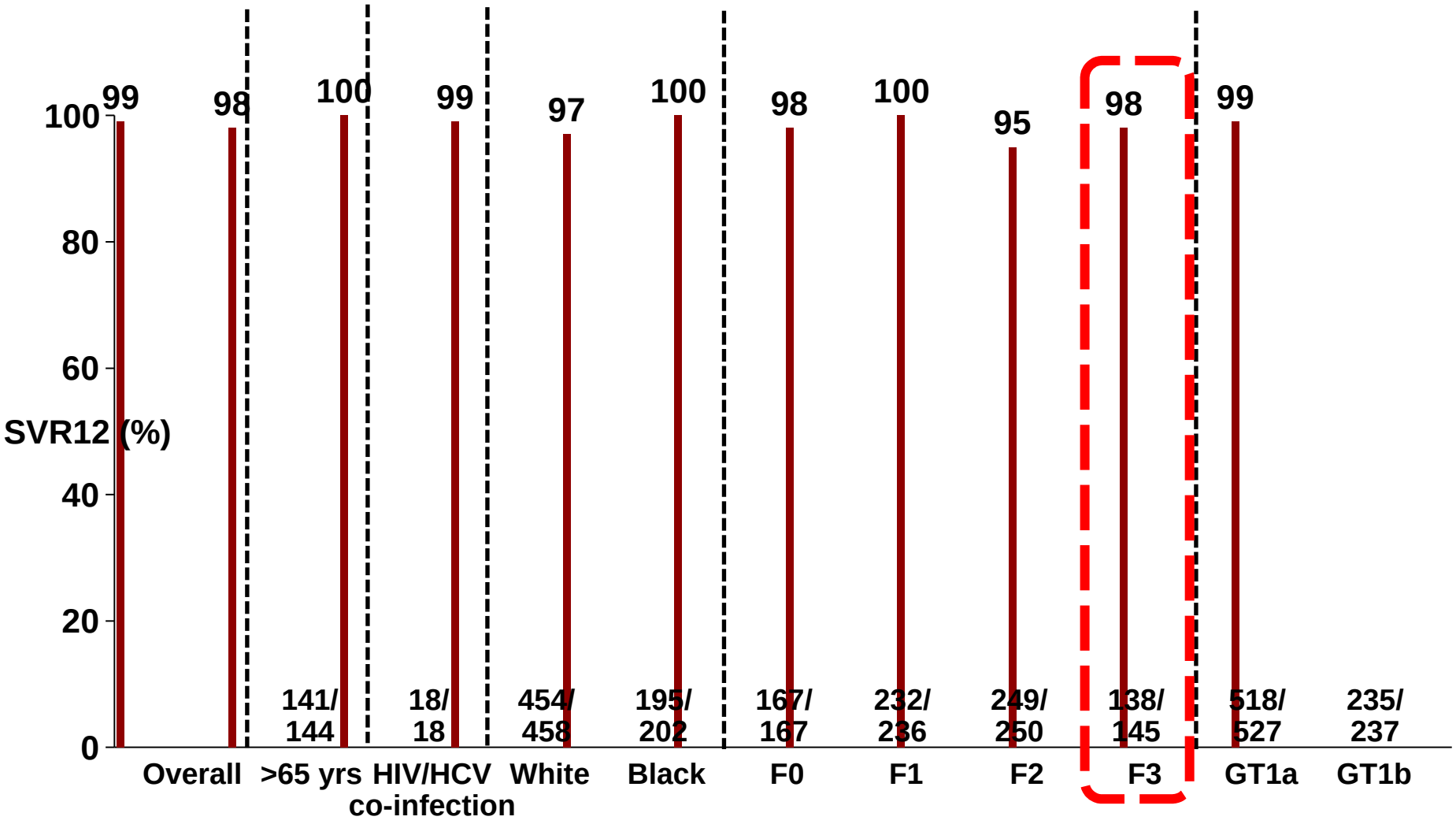


LDV/SOF for 8 weeks achieves comparable SVR rates to 12 week treatment in patients with less advanced fibrosis and lower viral load

Buggisch P, et al. AASLD 2016, Poster 883

Efficacy of LDV/SOF therapy shortened to 8 weeks

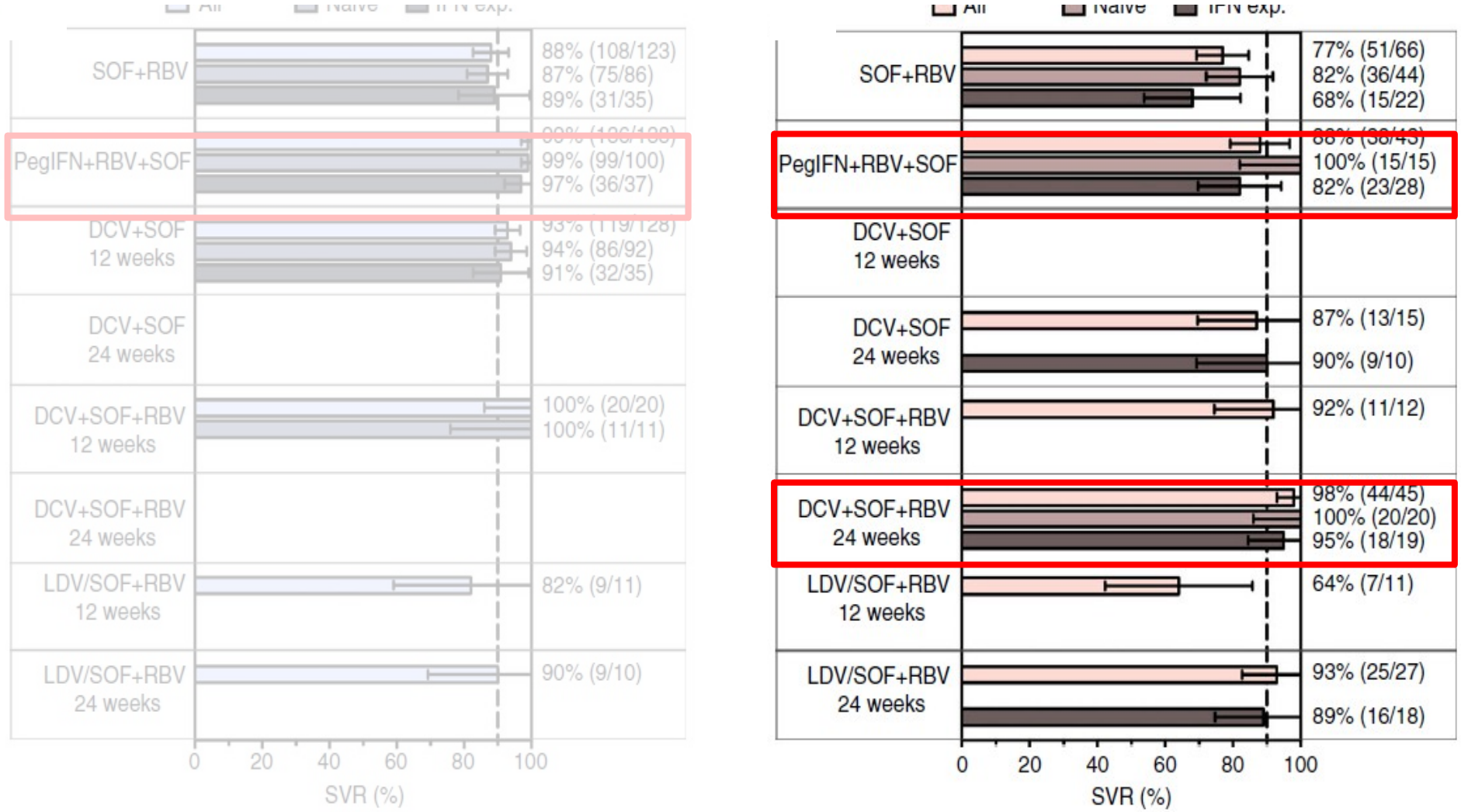
GT1, treatment naive, non-cirrhotic patients from HCV-TRIO study



Efficacy of LDV/SOF for 8 weeks in GT1 infected patients is high and stable irrespective of age, HIV coinfection, race, and subgenotype but <u>is lower in patients with fibrosis >F2</u>

Effectiveness of different treatment strategies for GT3

German Hepatitis C-Registry, non-cirrhosis vs cirrhosis



figures include arms containing at least 10 patients

Cornberg M et al. Aliment Pharmacol Ther ,online : 12 JAN 2017, DOI: 10.1111/apt.13925

Safety of different treatment strategies for GT3

German Hepatitis C-Registry, n=1111

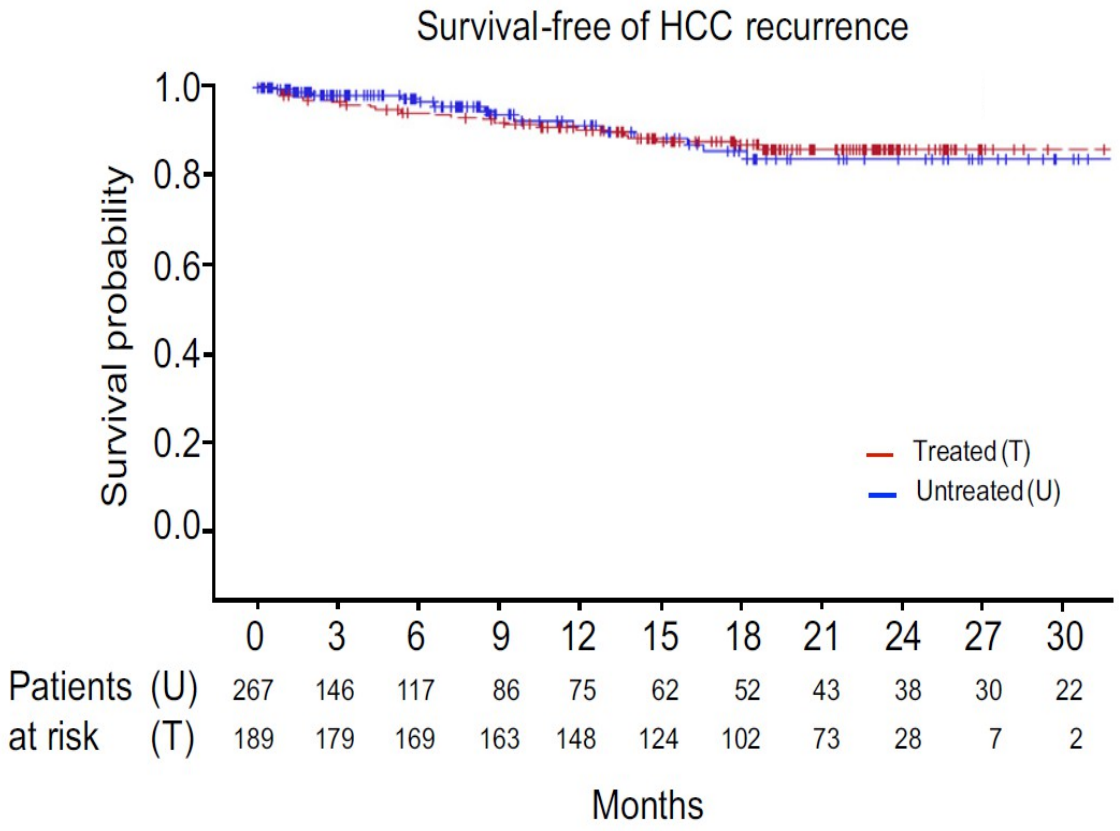
Regimen	AE *n* (%)	SAE *n* (%)
PegIFN+RBV (*n* = 91)	62 (68.1)	3 (3.3)
SOF+RBV 24 weeks (*n* = 308)	218 (70.8)	14 (4.5)
PegIFN+SOF+RBV 12 weeks (*n* = 213)	149 (70.0)	7 (3.3)
DCV+SOF 12 weeks (*n* = 168)	81 (48.2)	2 (1.2)
DCV+SOF 24 weeks (*n* = 19)	16 (84.2)	2 (10.5)
DCV+SOF+RBV 12 weeks (*n* = 33)	24 (72.7)	1 (3.0)
DCV+SOF+RBV 24 weeks (*n* = 60)	51 (85.0)	9 (15.0)
LDV/SOF 12 weeks (*n* = 12)	5 (41.7)	–
LDV/SOF 24 weeks (*n* = 6)	3 (50.0)	1 (16.7)
LDV/SOF+RBV 12 weeks (*n* = 26)	17 (65.4)	1 (3.8)
LDV/SOF+RBV 24 weeks (*n* = 46)	33 (71.7)	2 (4.3)
Total (all regimen, *n* = 1111)	721 (64.9)	48 (4.3)

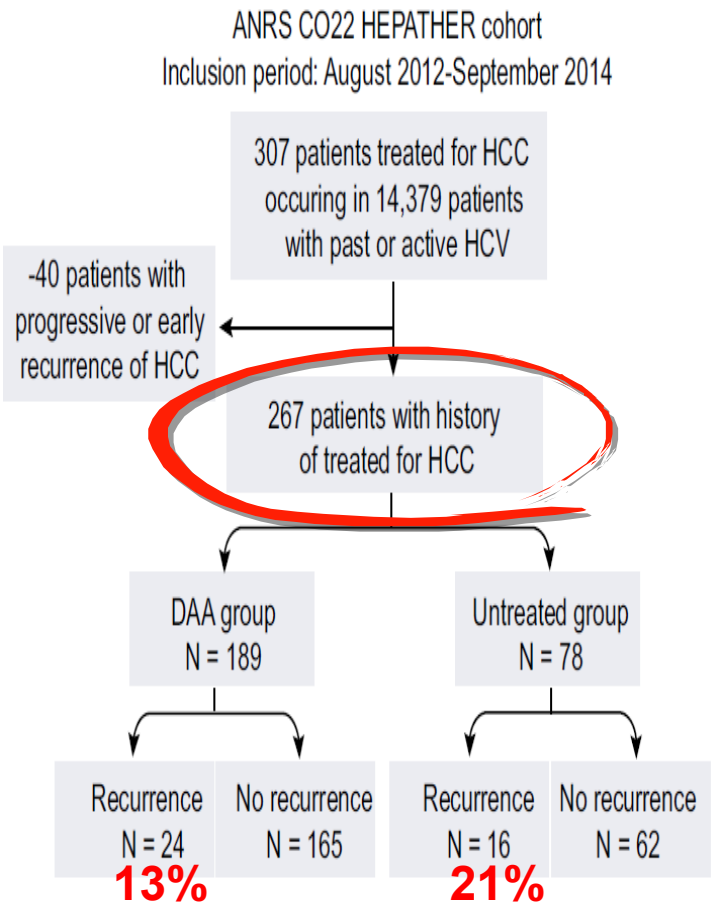
Safety profile of PegIFN+SOF+RBV regimen is similar to IFN-free, 12-weeks, RBV containing therapies

Cornberg M et al. Aliment Pharmacol Ther ,online : 12 JAN 2017, DOI: 10.1111/apt.13925

Recurrence of HCC after DAA treatment

ANRS CO22 HEPATHER cohort



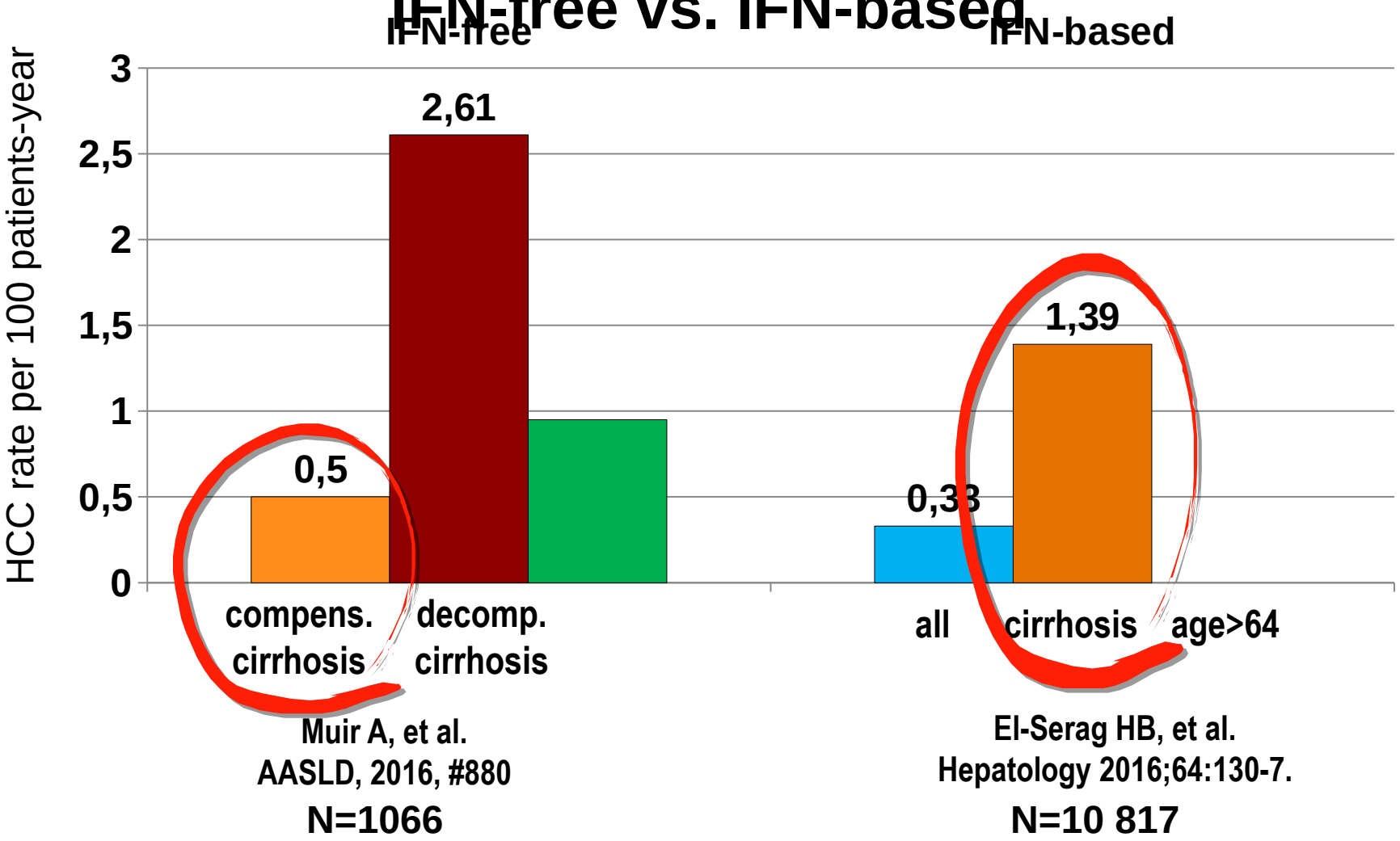


There is no increased risk of HCC recurrence after DAA treatment even in patients with history of HCC treatment

ANRS collaborative study group. J Hepatol 2016;65: 734–740

Risk of HCC in patients with cirrhosis who achieved SVR

IFN-free vs. IFN-based



Muir A, et al.
AASLD, 2016, #880
N=1066

El-Serag HB, et al.
Hepatology 2016;64:130-7.
N=10 817

Risk of HCC development is not related to DAA but to advanced hepatic disease

Risk of HBV reactivation due to DAA therapy

FDA reported cases (22 Nov 2013–15 Oct 2016)

Descriptive Characteristics	Data
Reported cases/geography	• **29 cases** (5 in US, **19 Japan**, 5 in other)
Timing	• occurred within **4-8 weeks of DAA** therapy (mean time to HBV reactivation was 53 days)
Baseline HBV viral parameters	• HBsAg+ (n=13) (**n=12 not reported**); HBcAb+ (n=6) (**n=23 not reported**); HBV DNA undetectable/detectable (**n=16/9**)
Outcome	• **Death (n=2)** (due to decompensated liver failure); transplant (n=1); hospitalization (n=6); other (n=20)
Specific DAAs used	• SOF-based (n=16); DCV+ASV (n=11); PI-based (n=2)
HBV treatment	• 16 patients received HBV treatment, in 7 patients **treatment was delayed** (one died) and possibly

- **HBV reactivation during DAA treatment is possible, but risk is low.**
- **All patients should be tested for HBV (at least HBsAg) before DAA therapy.**
- **If positive should be carefully monitored and treated for HBV immediately if reactivation happen**

Bersoff-Matcha, AASLD 2016, Poster

Conclusions

1. Effectiveness and safety of „new era” HCV regimens in RWE is similar to achieved in clinical trials.
   - for GT1 SOF/LDV, OPrD and SOF+DCV is superior to SOF+SMV
2. Shortening of treatment to 8 weeks is reasonable in patients with fibrosis <F3.
3. Risk of on-treatment hepatic decompensation is related first of all to decompensation history and baseline liver function.
4. For GT3 infected patients PegIFN+SOF+RBV regimen for 12 weeks still seems to be the most effective.
5. Risk of HCC recurrence after IFN-free regimens is similar to IFN-based and related mostly to the disease advancement.
6. To avoid problems - test for HBV before HCV treatment (particularly in HBV high prevalence regions) and do not delay HBV treatment.