UPEC
UNIVERSITÉ PARIS-EST CRÉTEIL
FACULTÉ
DE MÉDECINE

GROUPE HOSPITALIER
HENRI MONDOR
ALBERT CHENEVIER - GEORGES CLEMENCEAU
JOFFRE-DUPUYTREN - EMILE ROUX

How to optimize treatment in G3 patients

Pr Christophe Hézode, Hôpital Henri Mondor, Université Paris-Est, Créteil, France

Paris Hepatology Conference, January 30th 2017

Links of interest

Adviser, speaker, investigator for:

Abbvie, BMS, Gilead, Janssen, MSD

Patient case

Age/gender	54 years / male
HCV diagnosed	2010
Route of transmission	Injectable drugs
Genotype	3a
Fibrosis	Cirrhosis (Fibroscan = 21.8 kPa)
Complications	Child-Pugh A6
Concomitant diseases	Diabetes Grade 2, esophageal varices
Associated treatment	Metformin / Propranolol
HCV RNA	6.36 log10 IU/mL
Previous treatment	PR Treatment-experienced
Platelets / Albumin	89,000 µL / 34g/L

How will you treat?

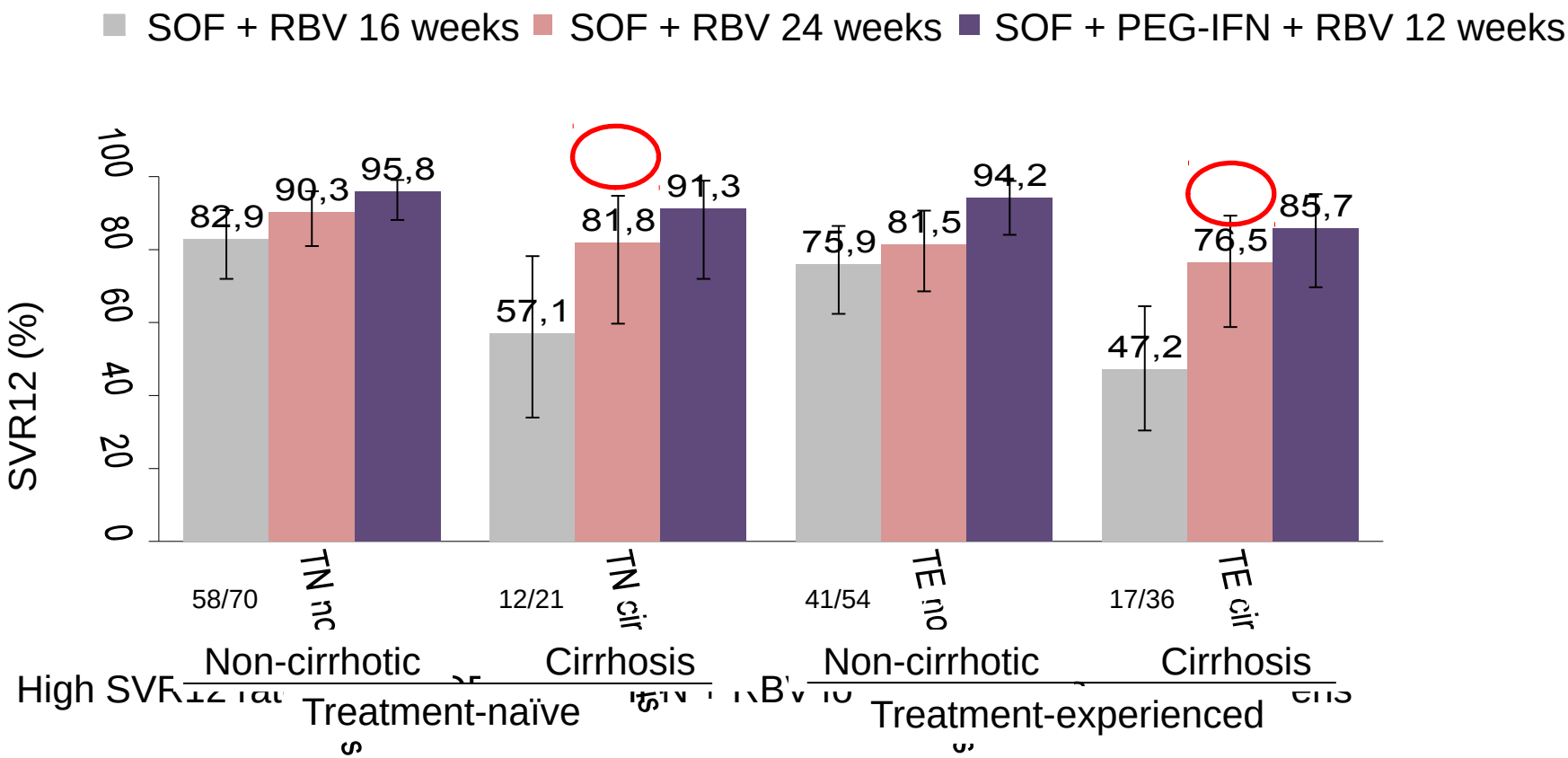
1. Sofosbuvir + Daclatasvir + RBV for 12 weeks

2. Peg-IFN + RBV + SOF for 12 weeks

3. Sofosbuvir + Daclatasvir + RBV 24 weeks

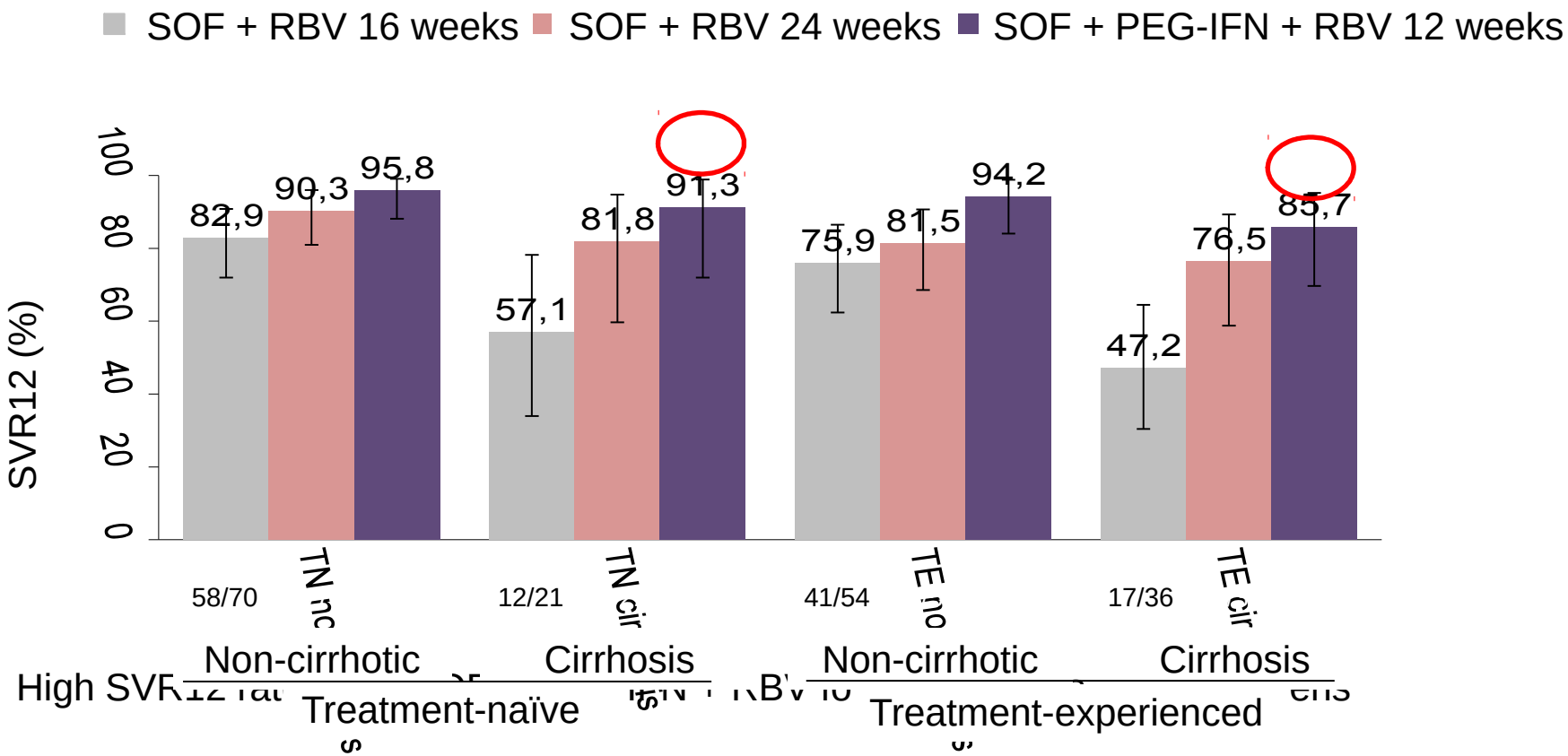
4. Sofosbuvir + RBV for 24 weeks

BOSON: Efficacy of SOF + RBV ± Peg-FN by treatment history and cirrhosis status in GT-3 patients



Foster G, et al. Gastroenterology 2015;149:1462-70

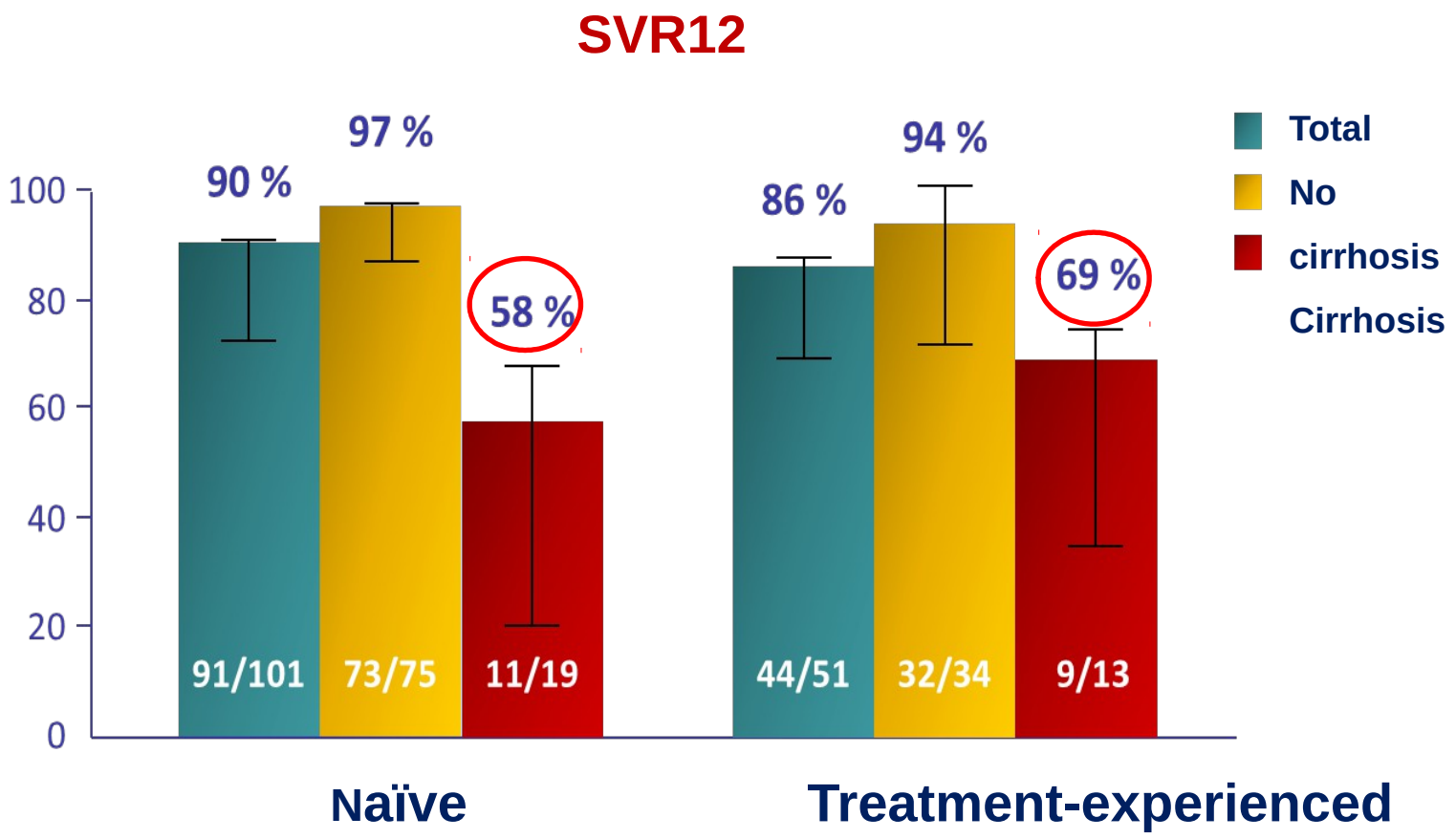
BOSON: Efficacy of SOF + RBV ± Peg-FN by treatment history and cirrhosis status in GT 3 patients



Foster G, et al. Gastroenterology 2015;149:1462-70

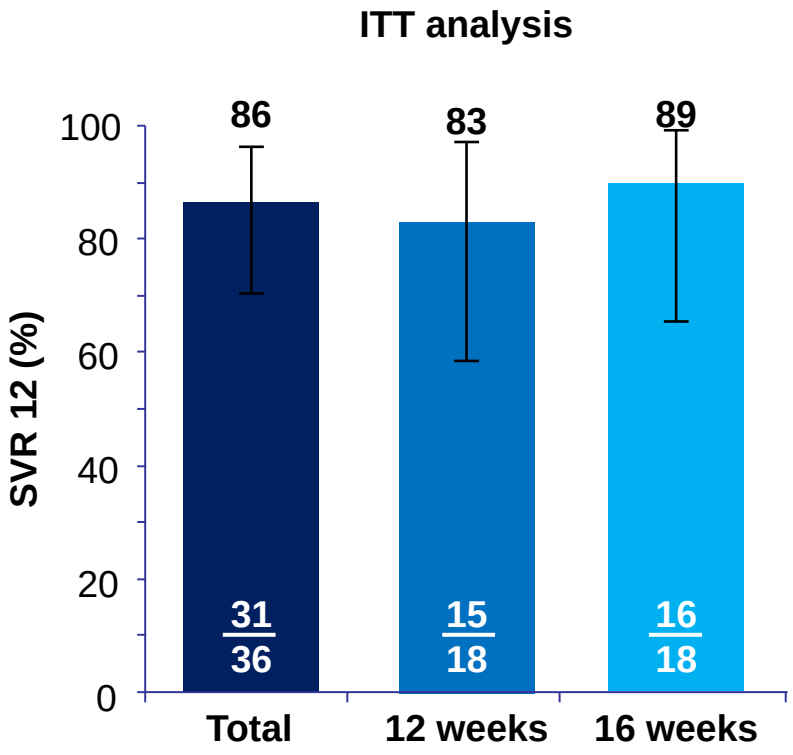
ALLY-3: SOF + DCV for 12 weeks in GT-3 patients

- Phase III: 152 naïve or P/R treatment-experienced GT-3 patients

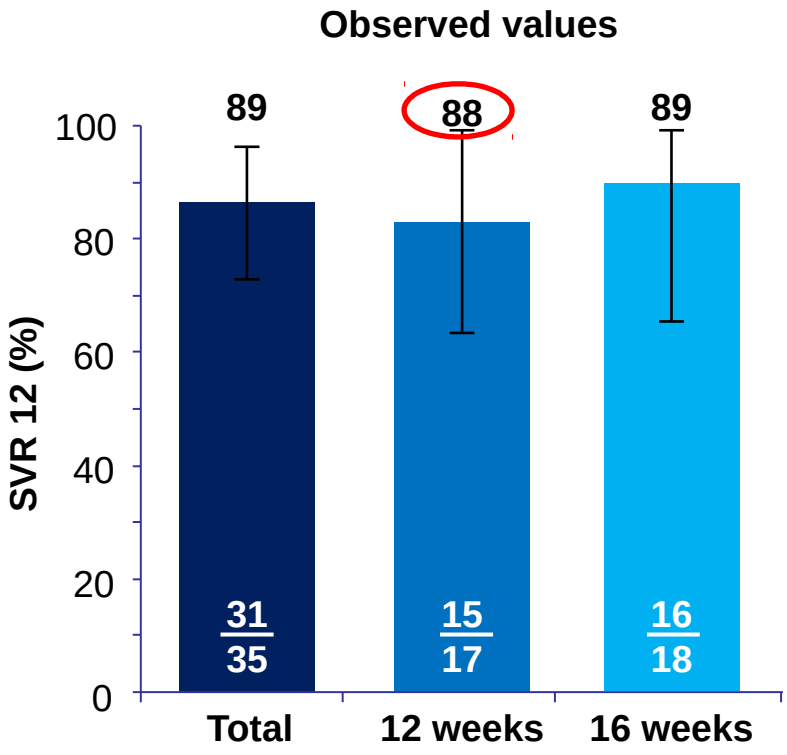


Nelson DR, et al. Hepatology 2015;61:1127-35

ALLY-3+: SOF + DCV + RBV for 12 to 16 weeks in GT-3 patients with compensated cirrhosis



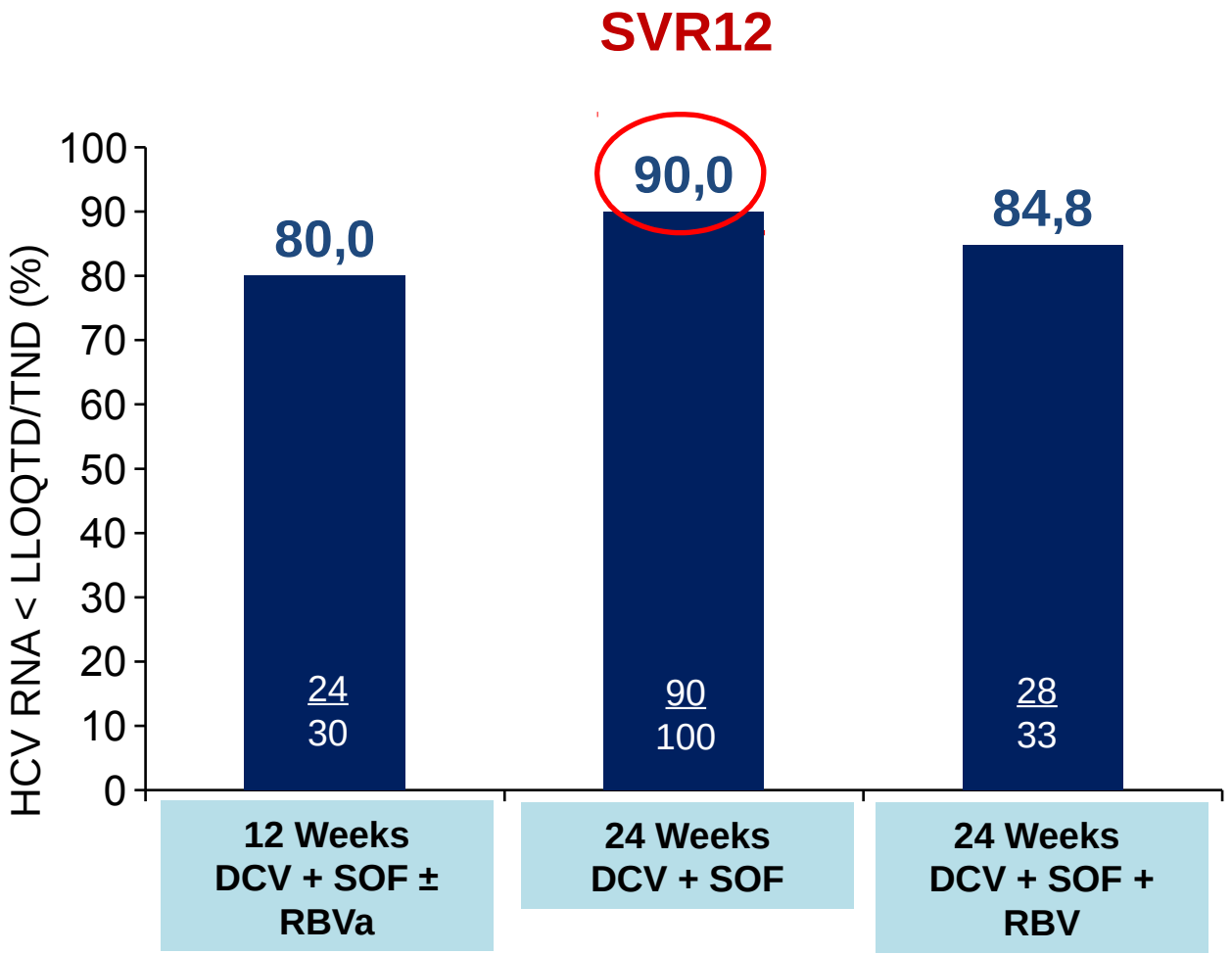
	Total	12 weeks	16 weeks
Breakthrough	0	0	0
Relapse	4	2	2
Death	1	1	0



	Total	12 weeks	16 weeks
Breakthrough	0	0	0
Relapse	4	2	2

Leroy V, et al. Hepatology 2016;63:1430-41

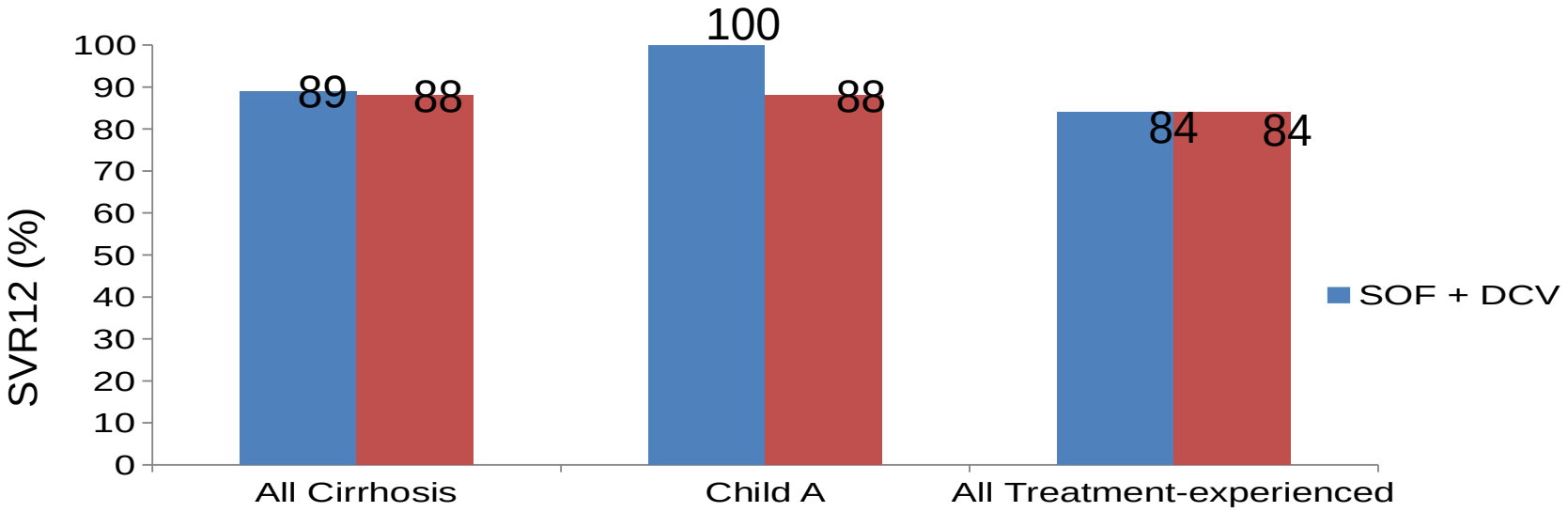
French compassionate use programme: SOF + DCV ± RBV in GT-3 patients with Child-Pugh A cirrhosis



Hézode C, et al. Liver Int 2017, in revision

a 4 patients received RBV for 12 weeks, all were Child–Pugh A, and all achieved SVR12

European compassionate use programme: SOF + DCV ± RBV in GT-3 patients with cirrhosis or treatment-experienced



Welzel TM, et al. Gut 2016;65:1861-70

Recommended therapies for GT 3 patients with cirrhosis: SOF + DCV

EASL	Regimen	Dosing	Duration
Patients without contraindications to the use of RBV			
C1	SOF + DCV + RBV	Daily SOF + DCV + WBD RBV (400mg/60mg)	24 weeks
Patients with contraindications to the use of RBV			
C1	SOF + DCV	Daily SOF + DCV (400mg/60mg)	24 weeks

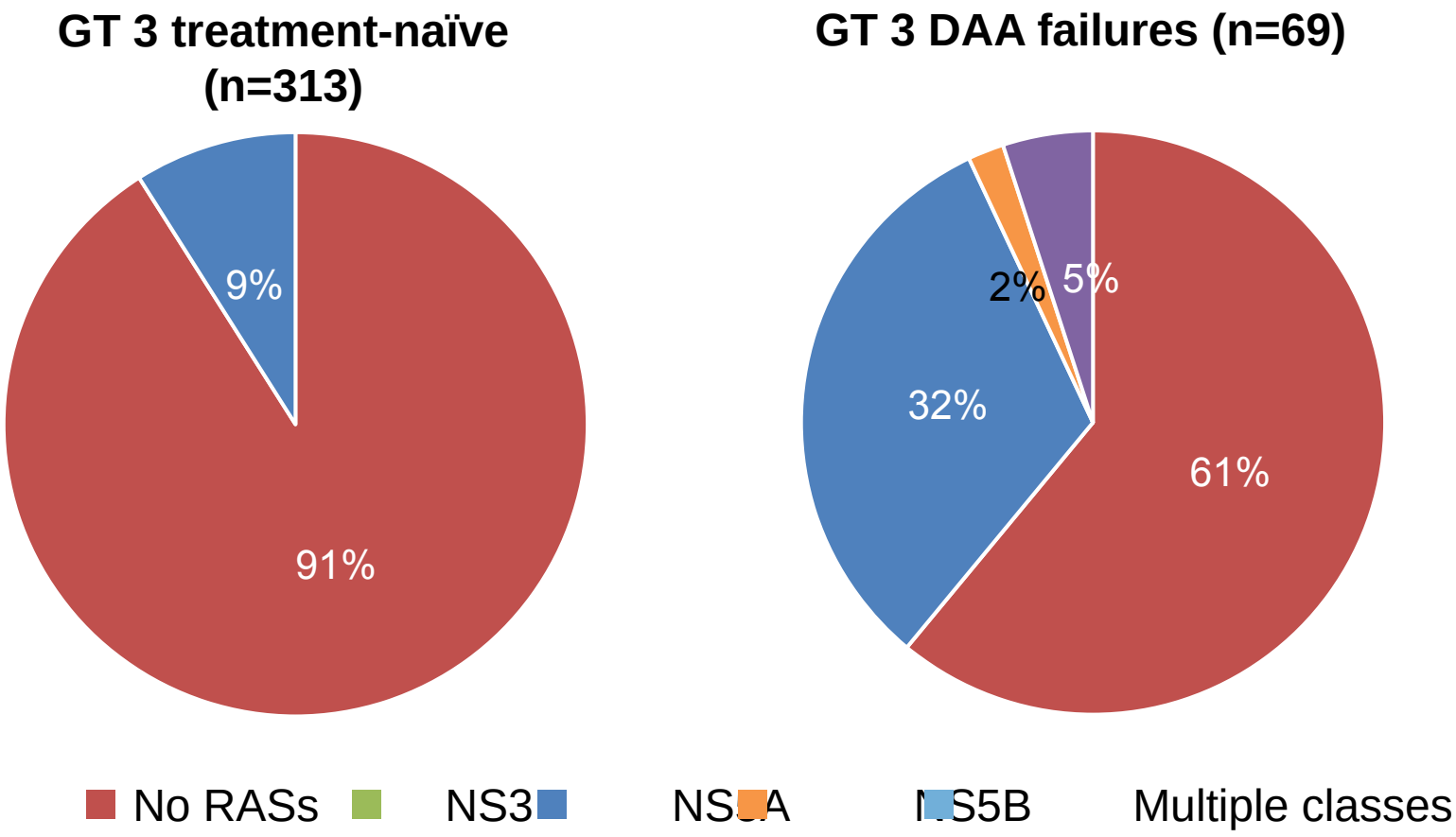
EASL Recommendations on treatment of hepatitis C. Available at: http://www.easl.eu/medias/cpg/HCV2016

Do you think that resistance testing is useful before starting SOF/DCV-based regimen in GT3 patients with cirrhosis?

1. Yes

2. No

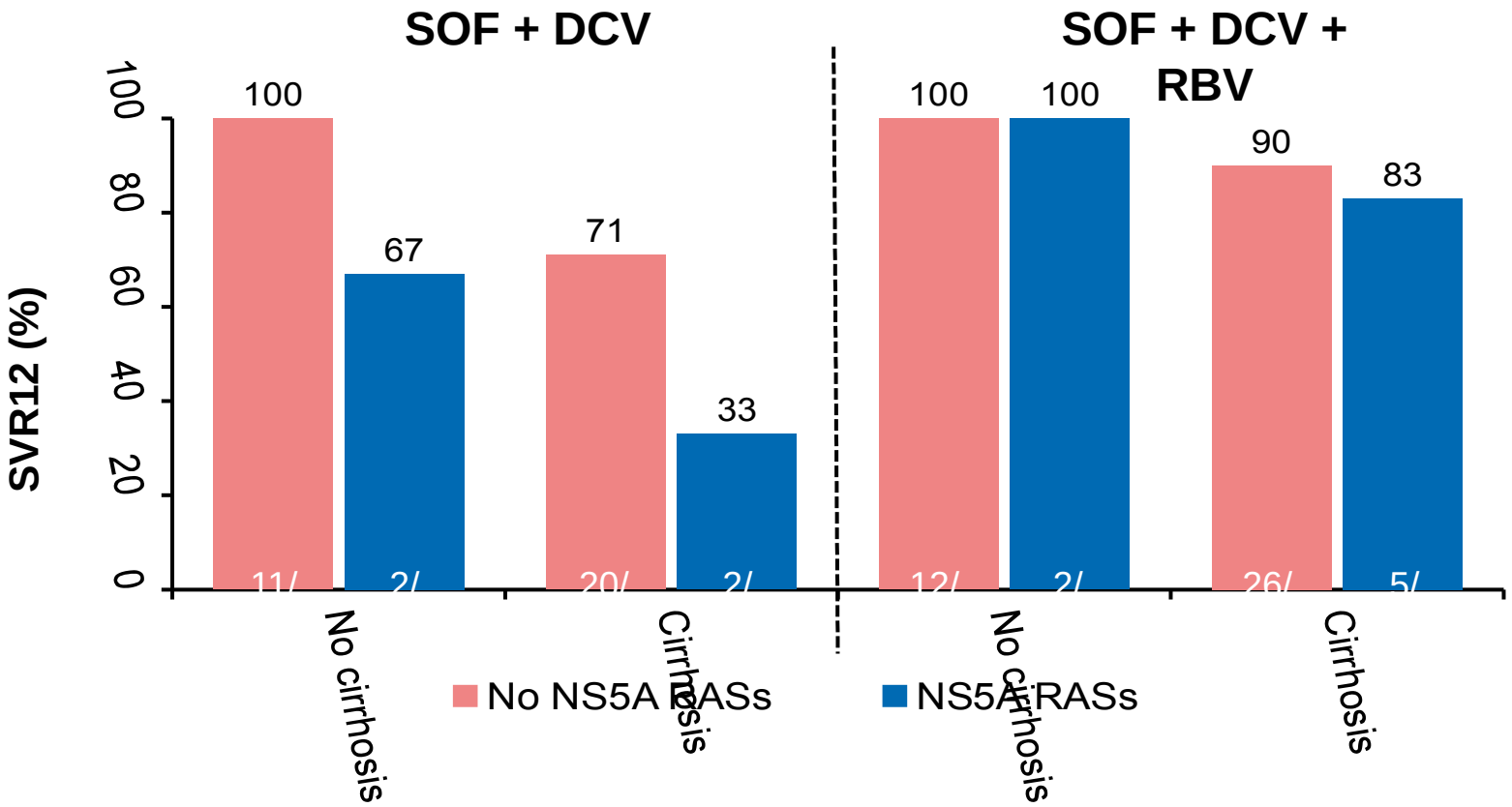
The frequency of RASs in GT 3 patients



Vermehren J, et al. EASL 2016; Oral #PS-103

Additional baseline factors may potentiate the effect of RASs – cirrhosis

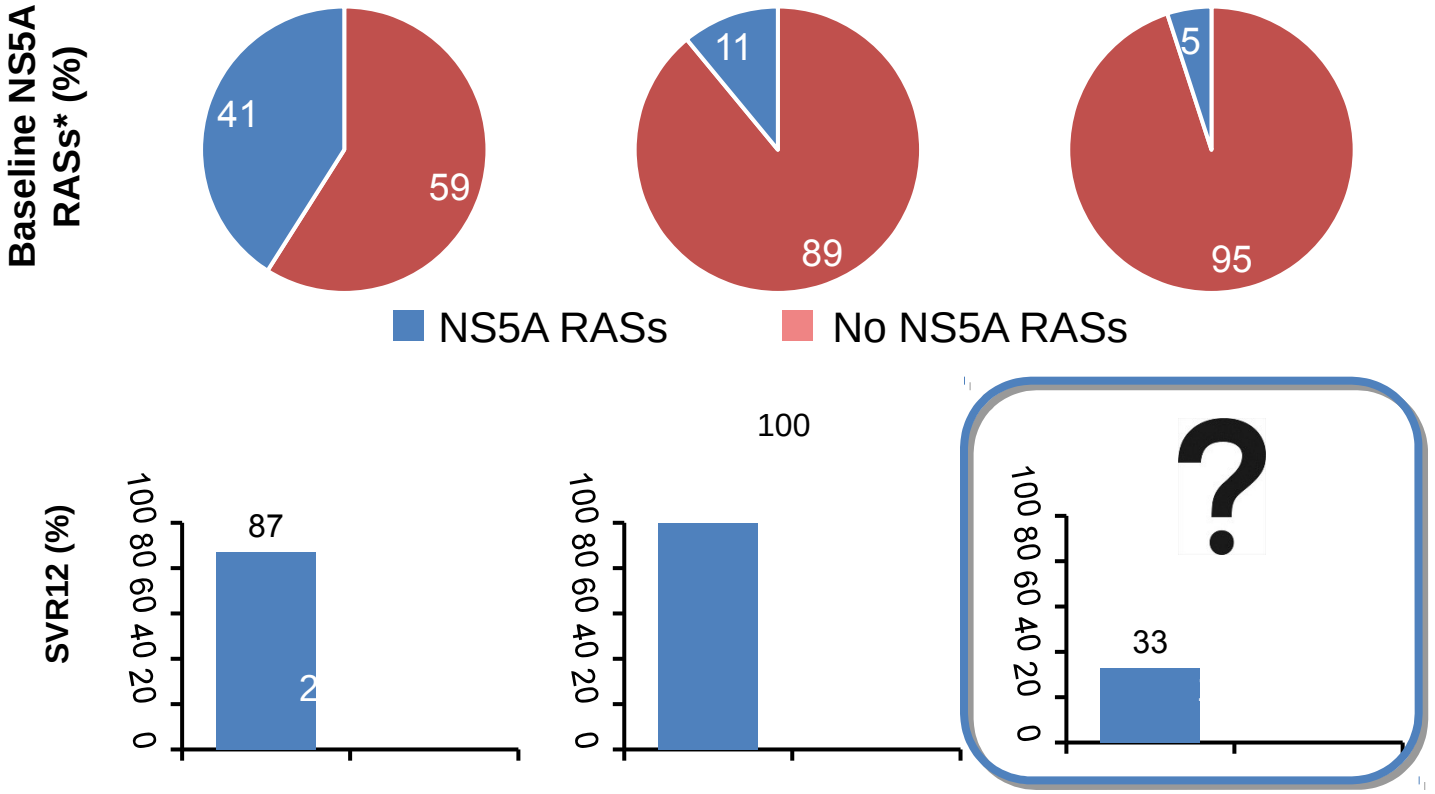
Pooled analysis of GT 3 patients who received SOF + DCV ± RBV for 12 weeks in the ALLY-3 and ALLY-3+ studies



Kowdley KV, et al. EASL 2016; Oral #SAT-199

What little data there are suggest the presence of Y93H NS5A may impact SVR in GT 3

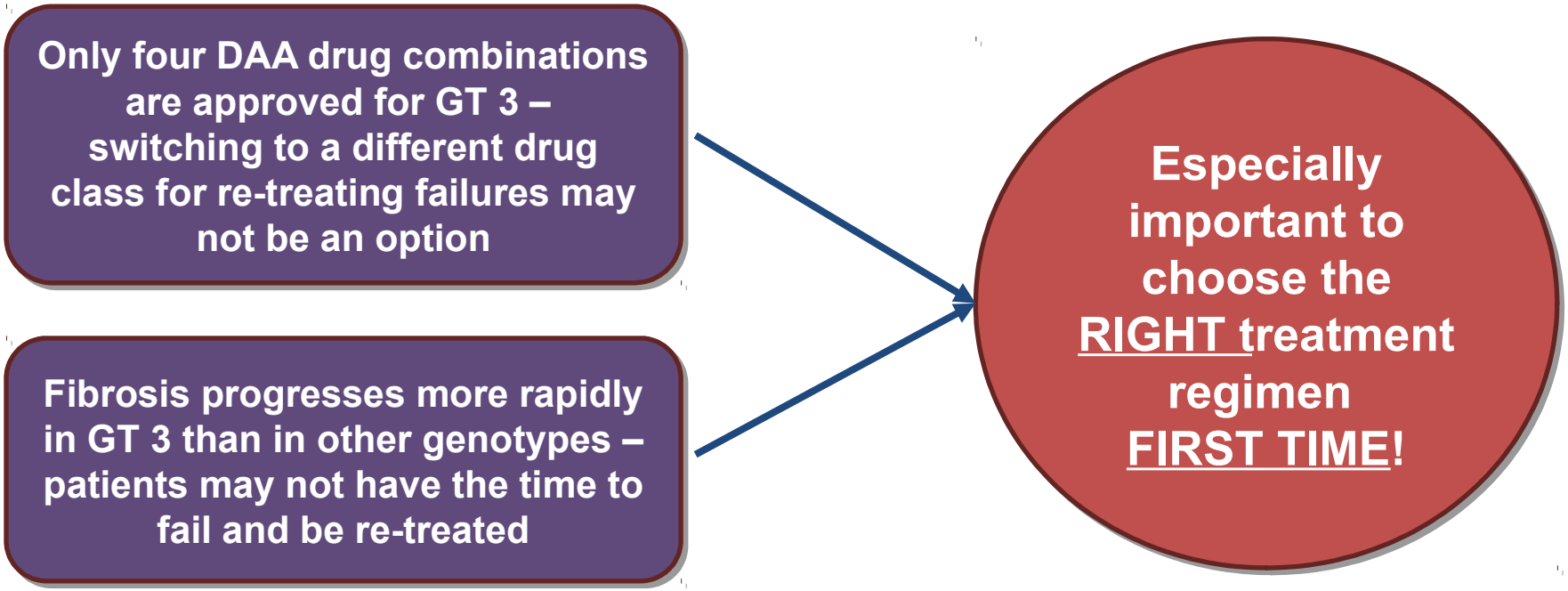
Pooled analysis of GT 3 patients who received SOF + DCV for 12 weeks in the ALLY-1–3+ studies



*≥10% cut-off; Pooled data from ALLY-1–3+

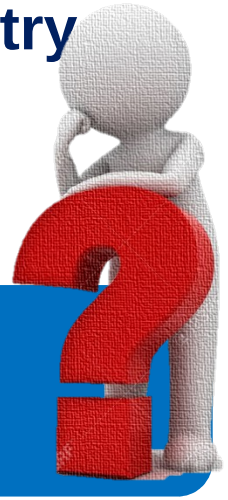
McPhee F, et al. EASL 2016; Oral #171

Genotype 3 – a special genotype?



Bristol-Myers Squibb Pharma EEIG. DAKLINZA▼ (daclatasvir) SmPC, July 2016;
Gilead Sciences Europe Ltd. EPCLUSA▼ (sofosbuvir/ velpatasvir) SmPC, July 2016;
Gilead Sciences Europe Ltd. SOVALDI▼ (sofosbuvir) SmPC, September 2016;
Gilead Sciences Europe Ltd. HARVONI▼ (ledipasvir/sofosbuvir) SmPC, July 2016;
Bochud P-Y, et al. J Hepatol 2009;51:655–63;

SOF/VEL-based regimens are available in your country
How will you treat?



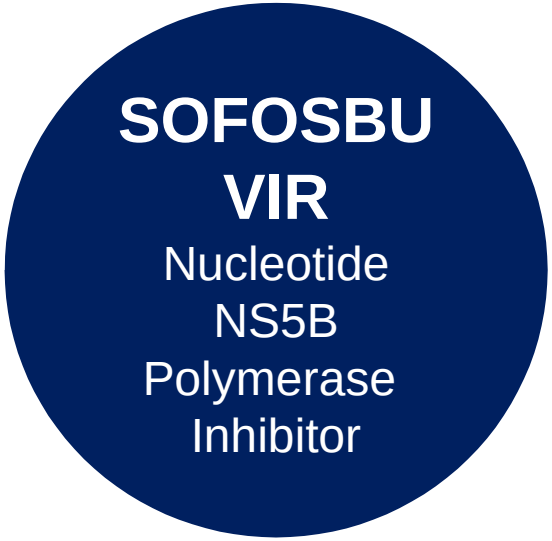
1. Sofosbuvir + Velpatasvir for 12 weeks

2. Sofosbuvir + Velpatasvir + RBV for 12 weeks

3. Sofosbuvir + Velpatasvir + Voxilaprevir for 8 weeks

4. Resistance test prior to treating

SOF/VEL-based regimens



Pangenotypic antiviral activity

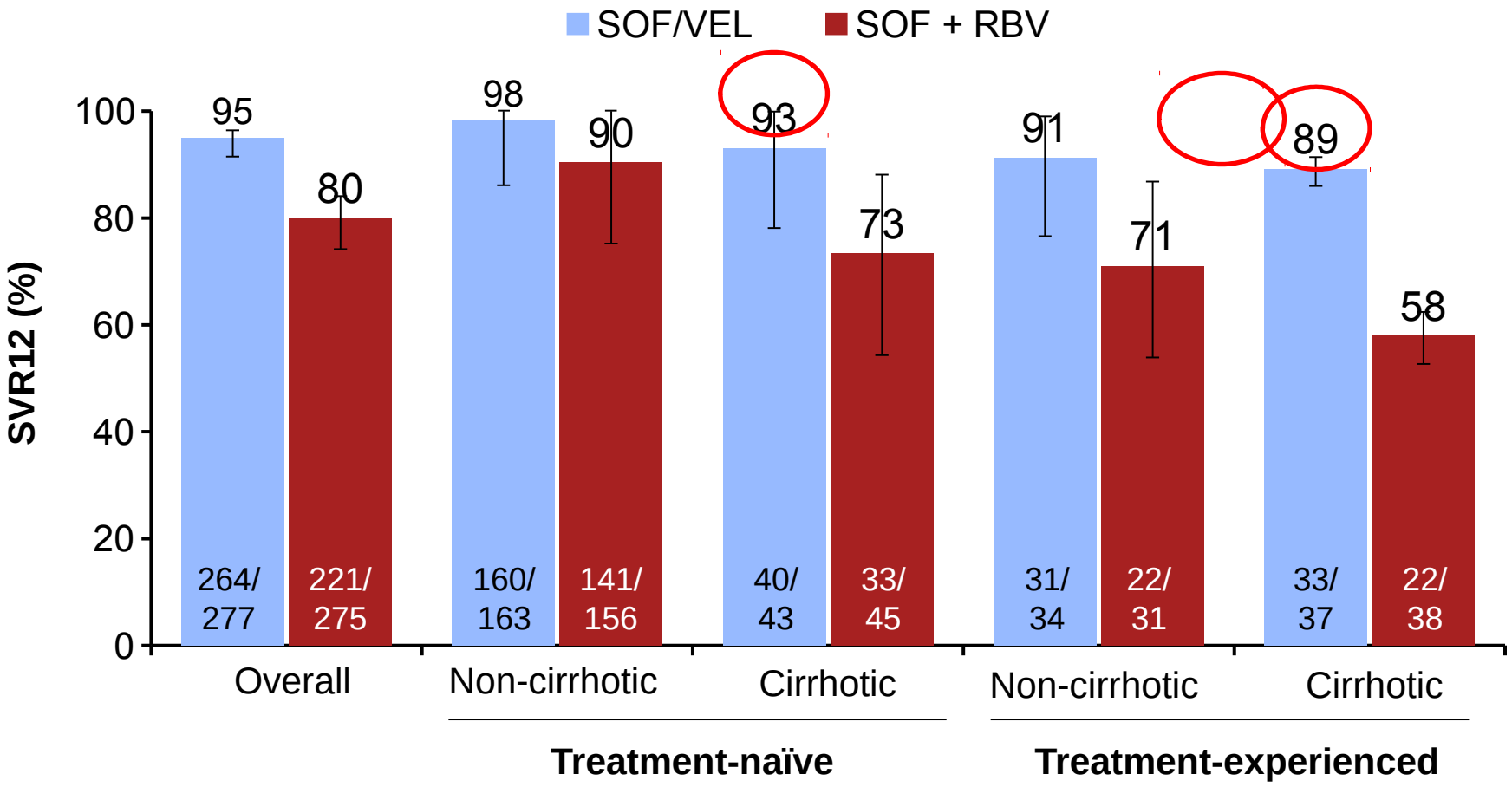
High barrier to resistance

Pangenotypic antiviral activity including most RASs

Pangenotypic antiviral activity including most RASs

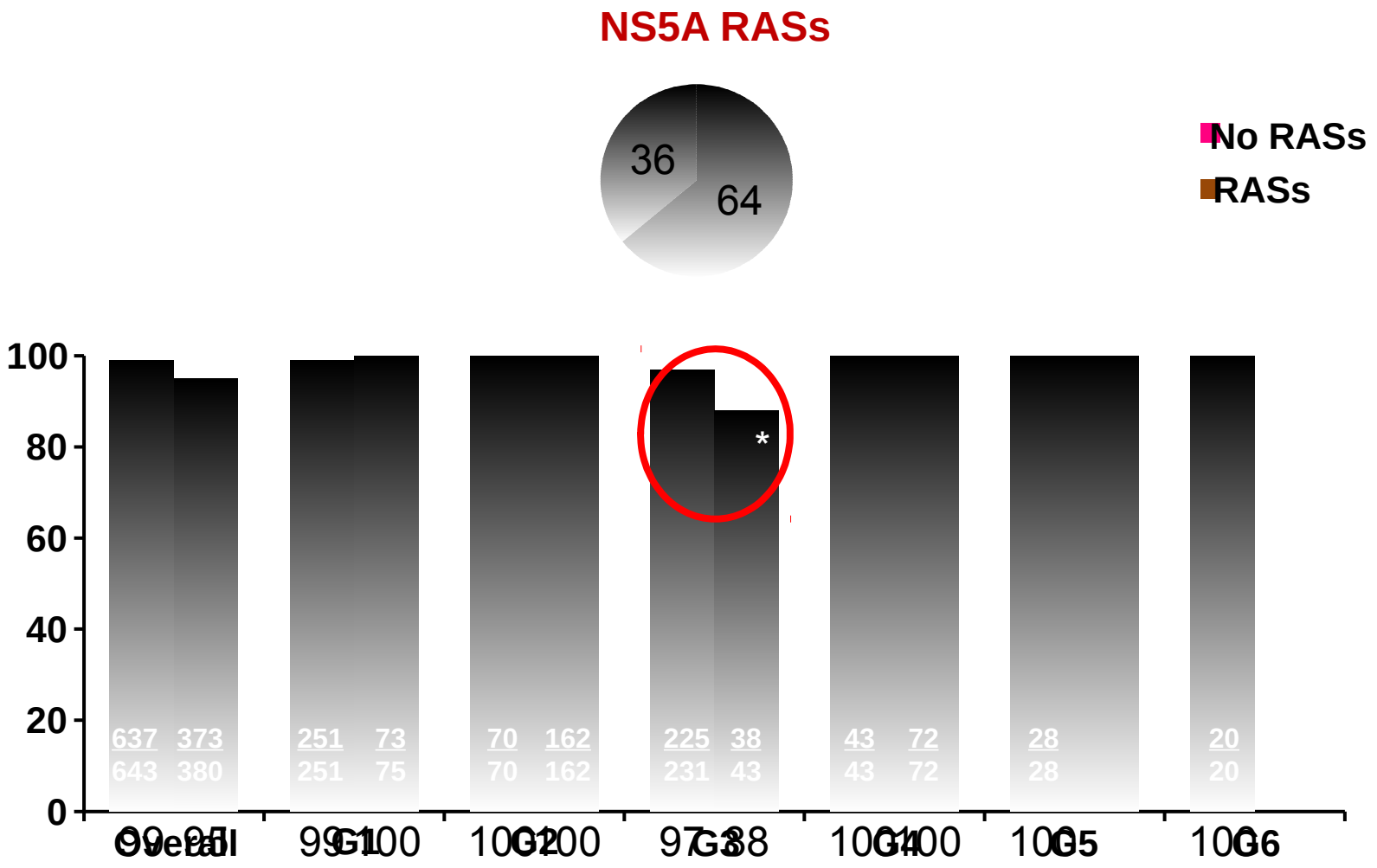
Once-daily, oral fixed-dose (400/100/100 mg) combination tablet

ASTRAL-3: SOF/VEL for 12 weeks in Genotype 3 patients



Foster GR, et al. N Engl J Med 2015;373:2608–17

ASTRAL studies: SOF/VEL for 12 weeks
Impact of NS5A RASs (LOD≥1%) on SVR

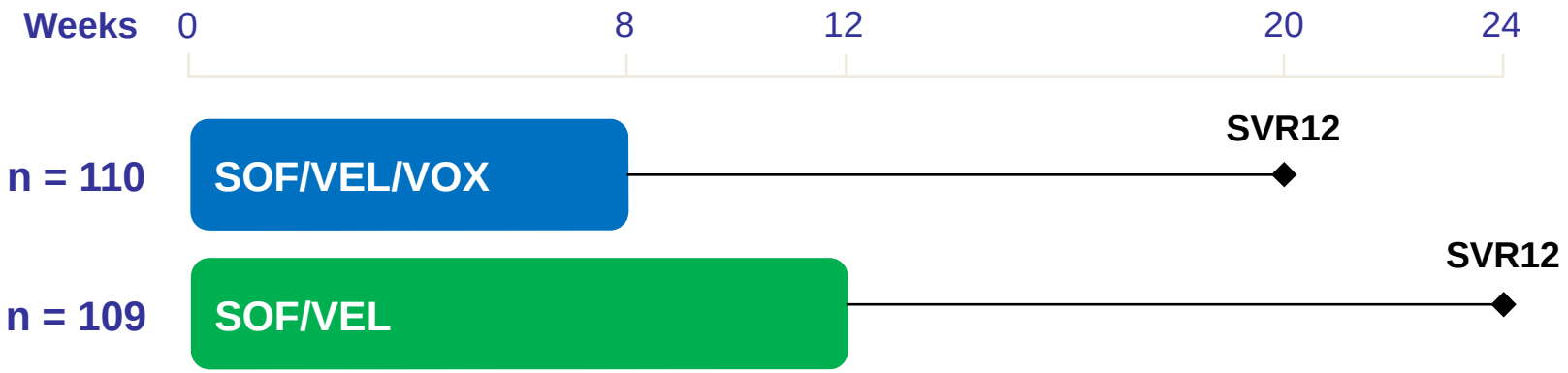


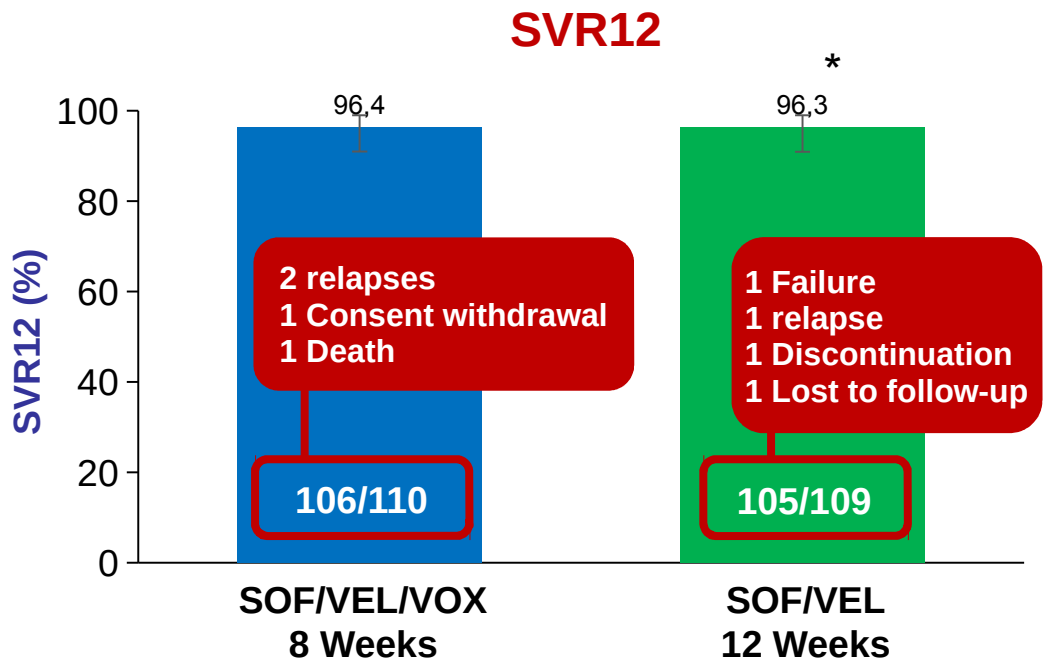
*SVR12 was 84% (21/25) in patients with Y93H

Foster GR, et al. N Engl J Med 2015;373:2608–17

Hézode C et al, EASL 2016;Abs 216

POLARIS-3: SOF/VEL/VOX for 8 weeks in G3 DAA naïve patients with cirrhosis





*19 patients with NS5A RAS, SVR=100%

Foster GR, et al. AASLD 2016, Abstract 258

Recommended therapies for GT 3 patients with compensated cirrhosis: SOF + VEL

EASL	Regimen	Dosing	Duration
NS5A Resistance Testing and No Baseline RAS (Y93H)			
A1	SOF/VEL	Daily SOF/VEL (400mg/100 mg)	12 weeks
No NS5A resistance testing or baseline RAS (Y93H)			
A1	SOF/VEL + RBV	Daily SOF/VEL+ WBD RBV (400mg/100 mg)	12 weeks

EASL Recommendations on treatment of hepatitis C. Available at: http://www.easl.eu/medias/cpg/HCV2016

Do you think that alternative options could be effective in GT 3 patients with cirrhosis?

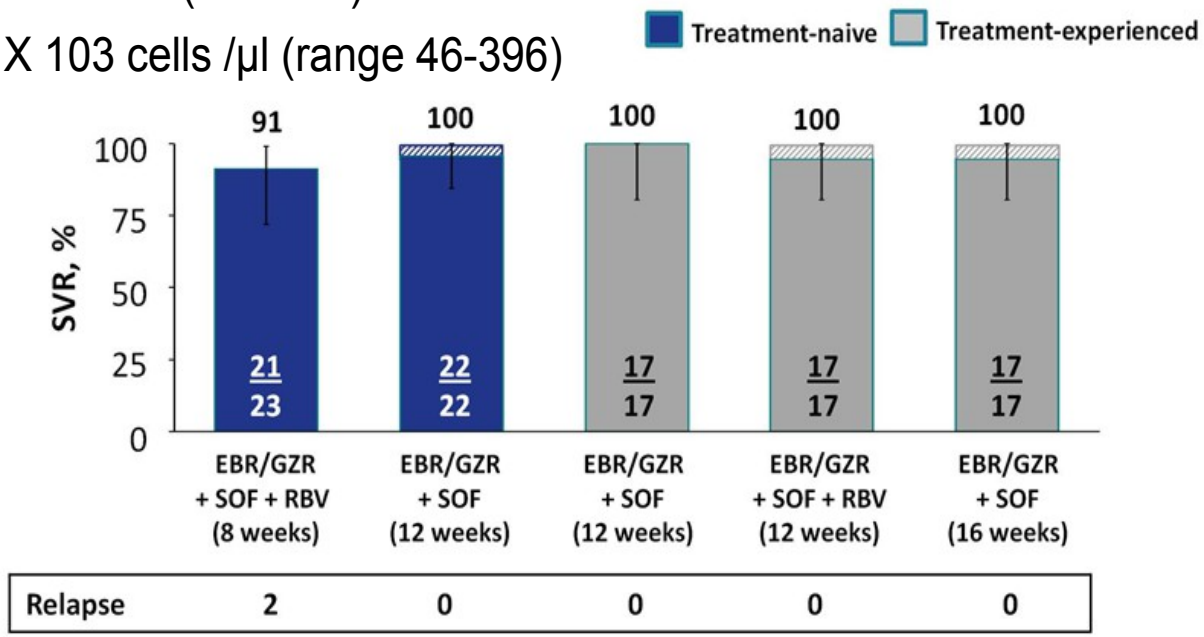
1. Yes

2. No

Grazoprevir/Elbasvir-based regimens

C-ISLE: Grazoprevir + elbasvir + sofosbuvir in genotype 3 patients with compensated cirrhosis*

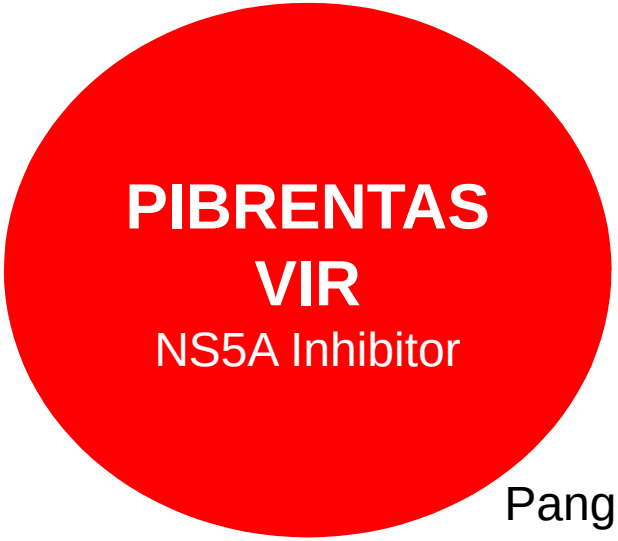
- Randomized, open label
- 100 patients with compensated cirrhosis
- Treatment naive or PR treatment experienced
- Mean Fibroscan® score 25.4 kPa (SD 12.1)
- Mean platelet count 148 X 103 cells /µl (range 46-396)

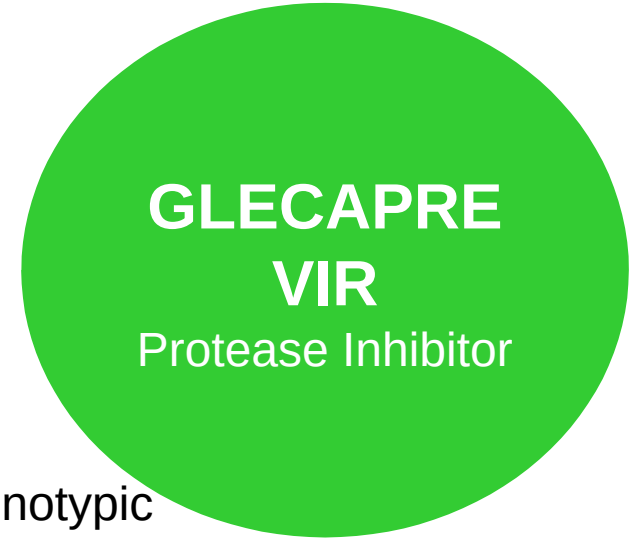


*mFAS: excluded patients who discontinued treatment for reasons unrelated to study medication

Foster GR, et al. AASLD 2016, Abstract 74

Glecaprevir/Pibrentasvir-based regimens





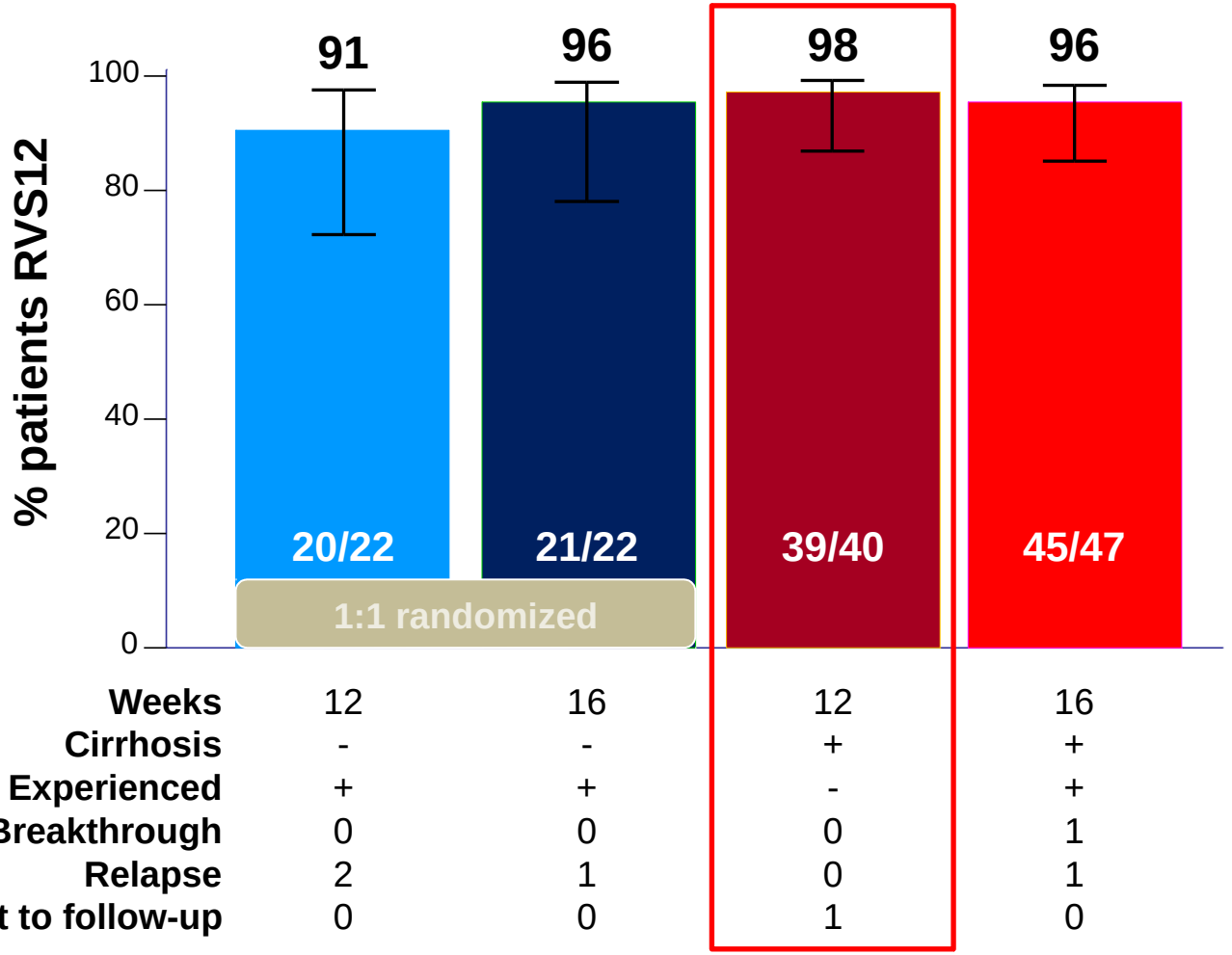
Pangenotypic antiviral activity including most RASs

High barrier to resistance

Negligible renal elimination

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg

SURVEYOR-II (part 3): Glecaprevir/pibrentasvir (G/P) in G3 patients



Weeks	12	16	12	16
Cirrhosis	-	-	+	+
Experienced	+	+	-	+
Breakthrough	0	0	0	1
Relapse	2	1	0	1
Lost to follow-up	0	0	1	0

Wyles DL, et al. AASLD 2016, Abstract

Patient case

NS5B NUC Inhibitor

NS5A Inhibitor

Resistance testing: No NS5A RAS

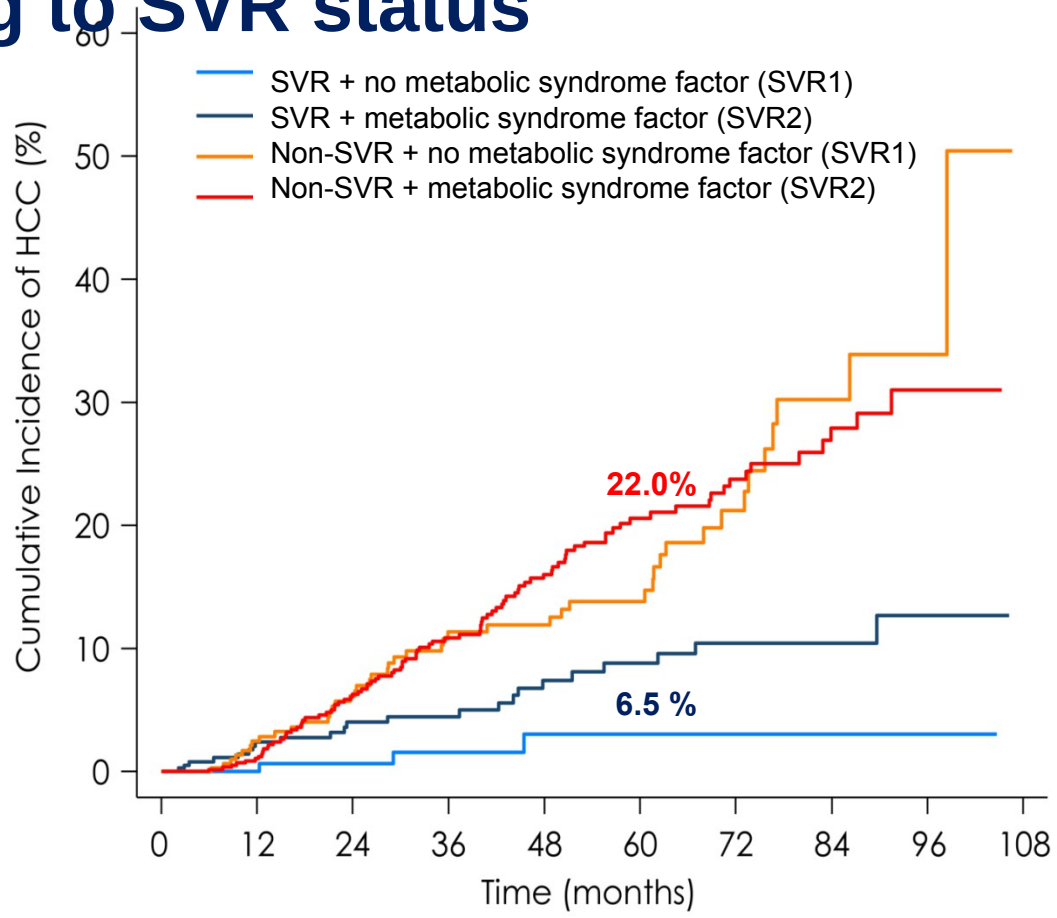
SOF + DCV for 24 weeks

HCV viral load outcome	
Day 0	6.36 log10 IU/mL
Week 4	<12 IU/mL detected
Week 24 (EOT)	<12 IU/mL not detected
Follow-up week 12	<12 IU/mL not detected

NOTE: SOF + DCV for 12 weeks is not approved by the EMA in compensated cirrhosis.
EOT: end of treatment

Patient case

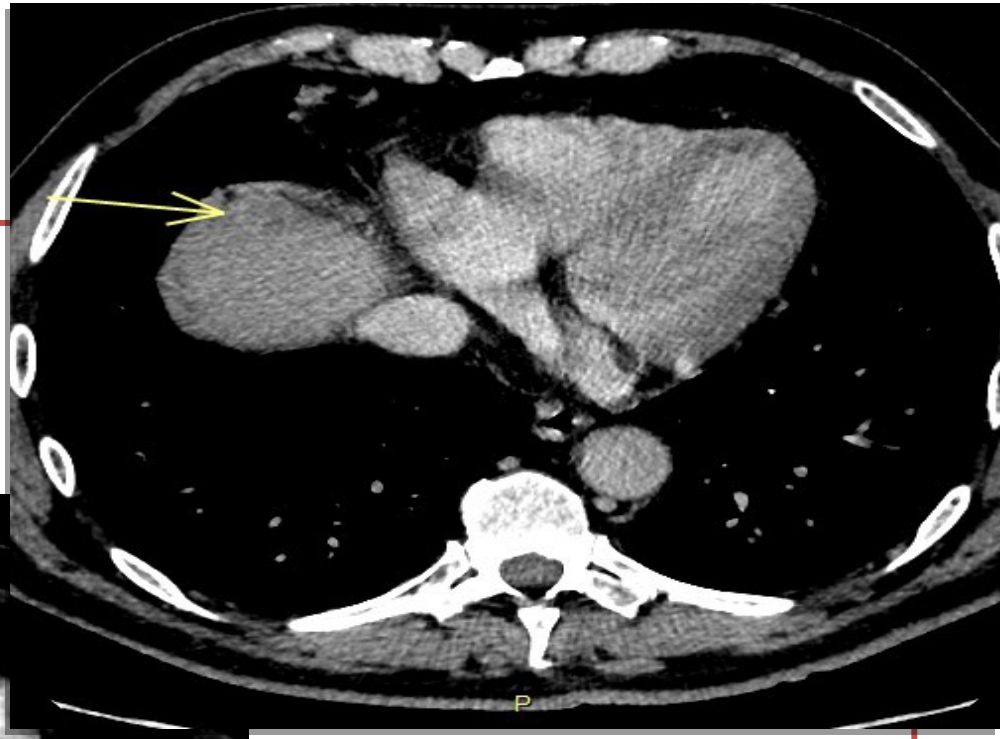
CIRVIR cohort: Influence of metabolic syndrome on the development of HCC according to SVR status

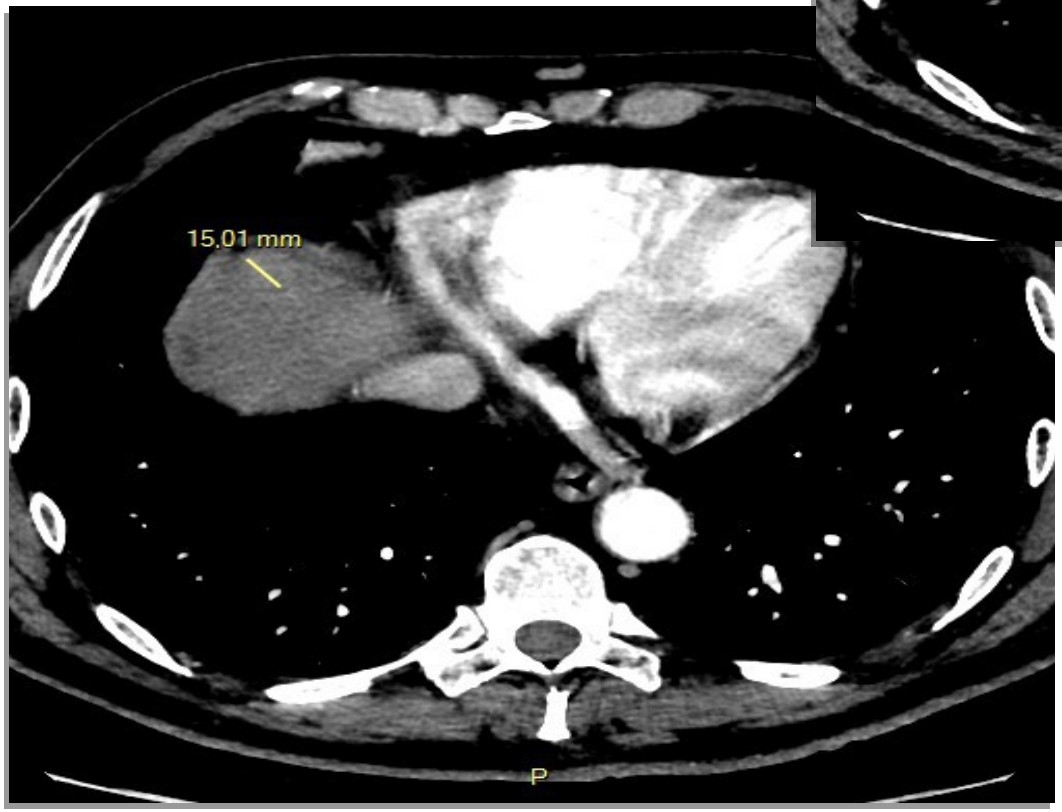


	Number at risk (events)																					
SVR1	208	(0)	152	(1)	118	(1)	89	(1)	59	(0)	40	(0)	25	(0)	15	(0)	8	(0)	2
SVR2	378	(8)	289	(4)	230	(1)	186	(5)	147	(2)	121	(2)	91	(0)	56	(1)	22	(0)	1
Non-SVR1	316	(7)	264	(9)	214	(11)	172	(1)	142	(3)	100	(7)	53	(5)	22	(1)	5	(1)	0
Non-SVR2	624	(6)	524	(25)	447	(21)	342	(18)	272	(13)	187	(6)	126	(5)	71	(2)	20	(0)	2

Nahon P, et al, Gastroenterology 2016, Sep 15

Outcome





Courtesy of Pr Alain Luciani