Optimizing HCV treatment

Challenging G3 patient

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Disclosures

BMS : Speaker symposium, board , soutien recherche

MSD : speaker symposium , board

Gilead : speaker symposium, board

Janssen : speaker symposium, board

Abbvie : speaker symposium, board

Intercept : board

Patient case : hepatitis C without comorbidity

Age / Gender	58-years / male
HCV diagnosed	2014
Route of transmission	Injectable drugs
Alcohol	0 (30g/d in the past)
Genotype	3a
HCV RNA	5.2 log IU/ml
Fibrosis	Cirrhosis (Fibroscan = 24 kPa)
Complications	Child-Pugh A5
Endoscopy	No varices
Ultrasound	Normal

Antiviral treatment

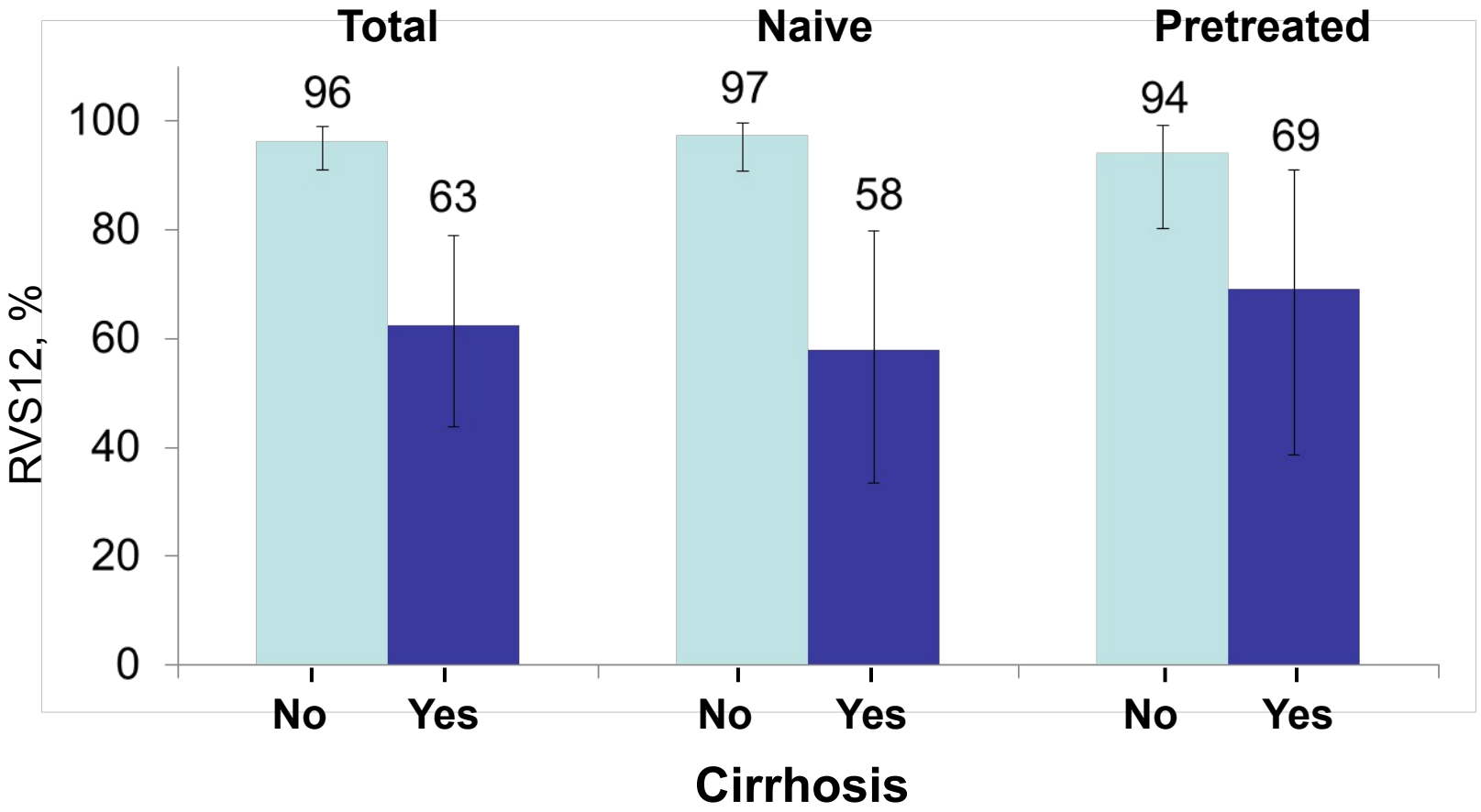
SOF + DCV + RBV 12 weeks

	W0	W4	W12	FU12
ALT (IU/L)	52	24	22	65
HCV RNA (IU/ml)	>5M	< 36	< 12	>5M
GFR (ml/min)	78	73	72	75
Platelets	152	166	167	153
LS (kPa)	24	-	-	27
US	Normal			Nod 3 cm

How could you explain this treatment failure?

1. Suboptimal treatment regimen
2. Presence of cirrhosis
3. Presence of RAS at baseline
4. Insufficient adherance to treatment

Sofosbuvir + daclatasvir 12 weeks : ALLY-3

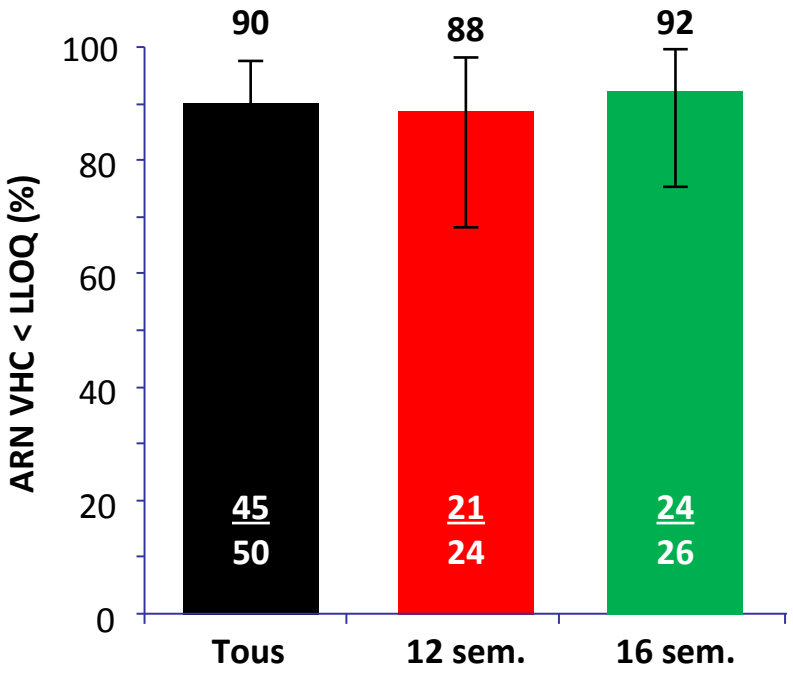


Nelson DR, Etats-Unis, Hepatology 2015

G3 : ALLY-3+ : sofosbuvir + daclatasvir (F3F4)

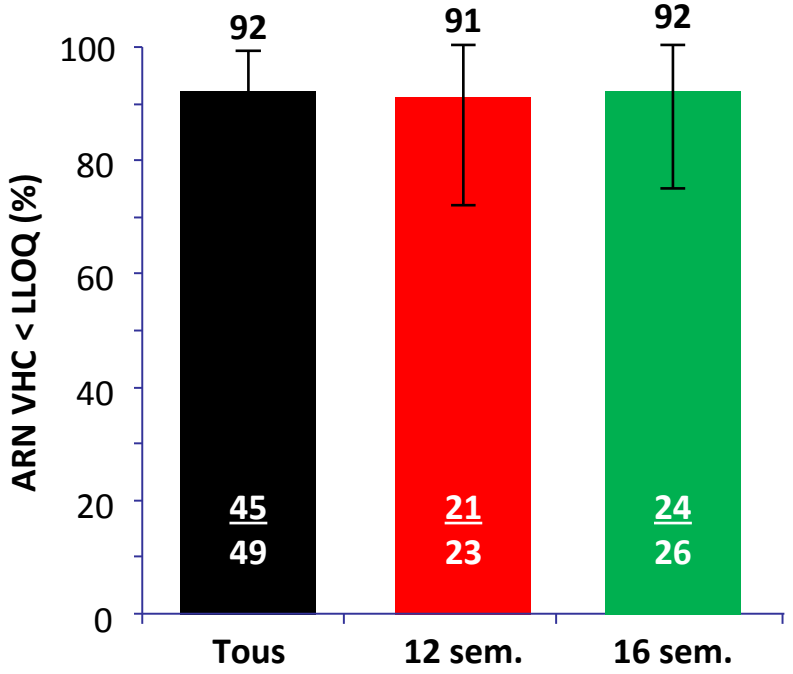
SVR

ITT



Breakthrough	0	0	0
Relapses	4	2	2
Dead	1	1	0

mITT

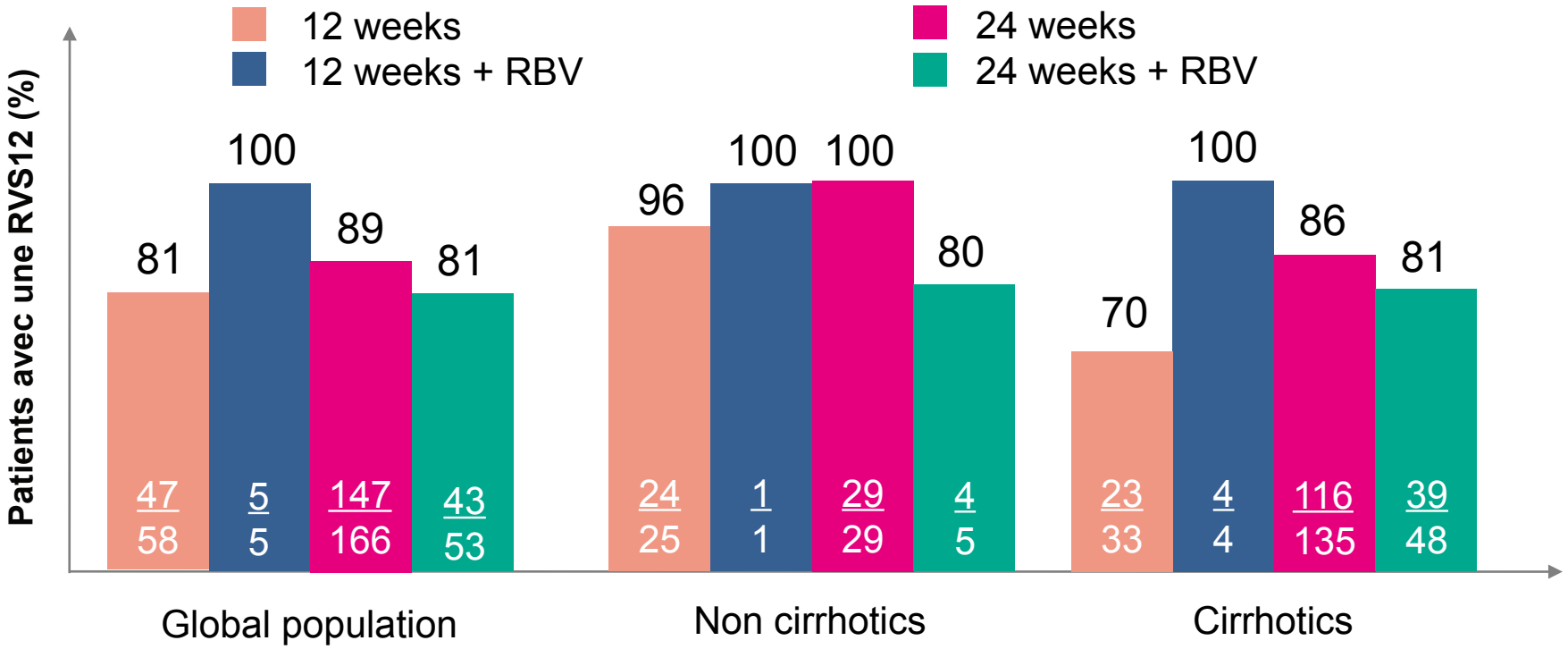


Breakthrough	0	0	0
Relapses	4	2	2

Leroy et al, Hepatology 2016

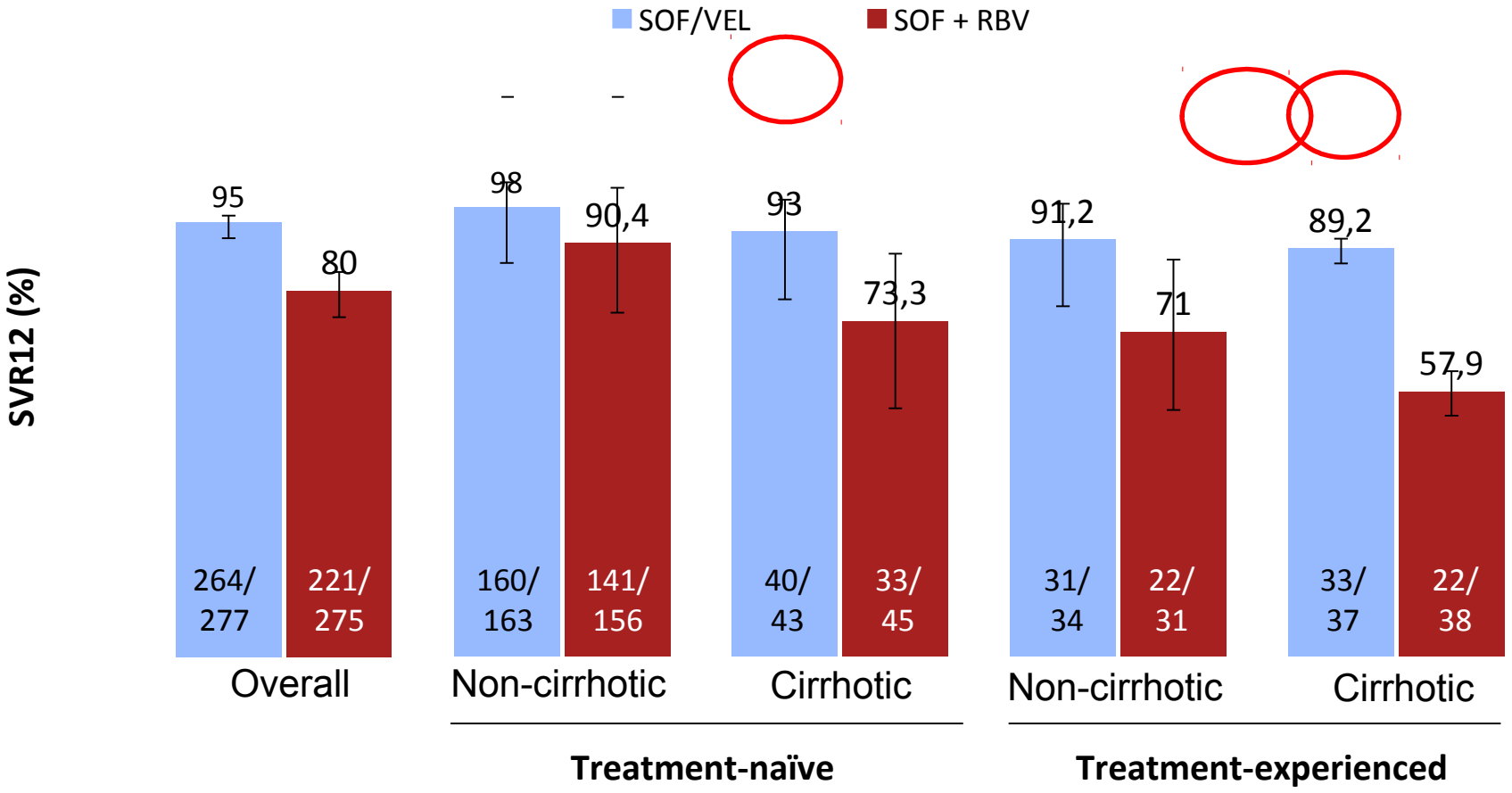
French early access program

➜ *284 patients treated by SOF/DCV 12 - 24 weeks ± RBV (cirrhosis:79%)*



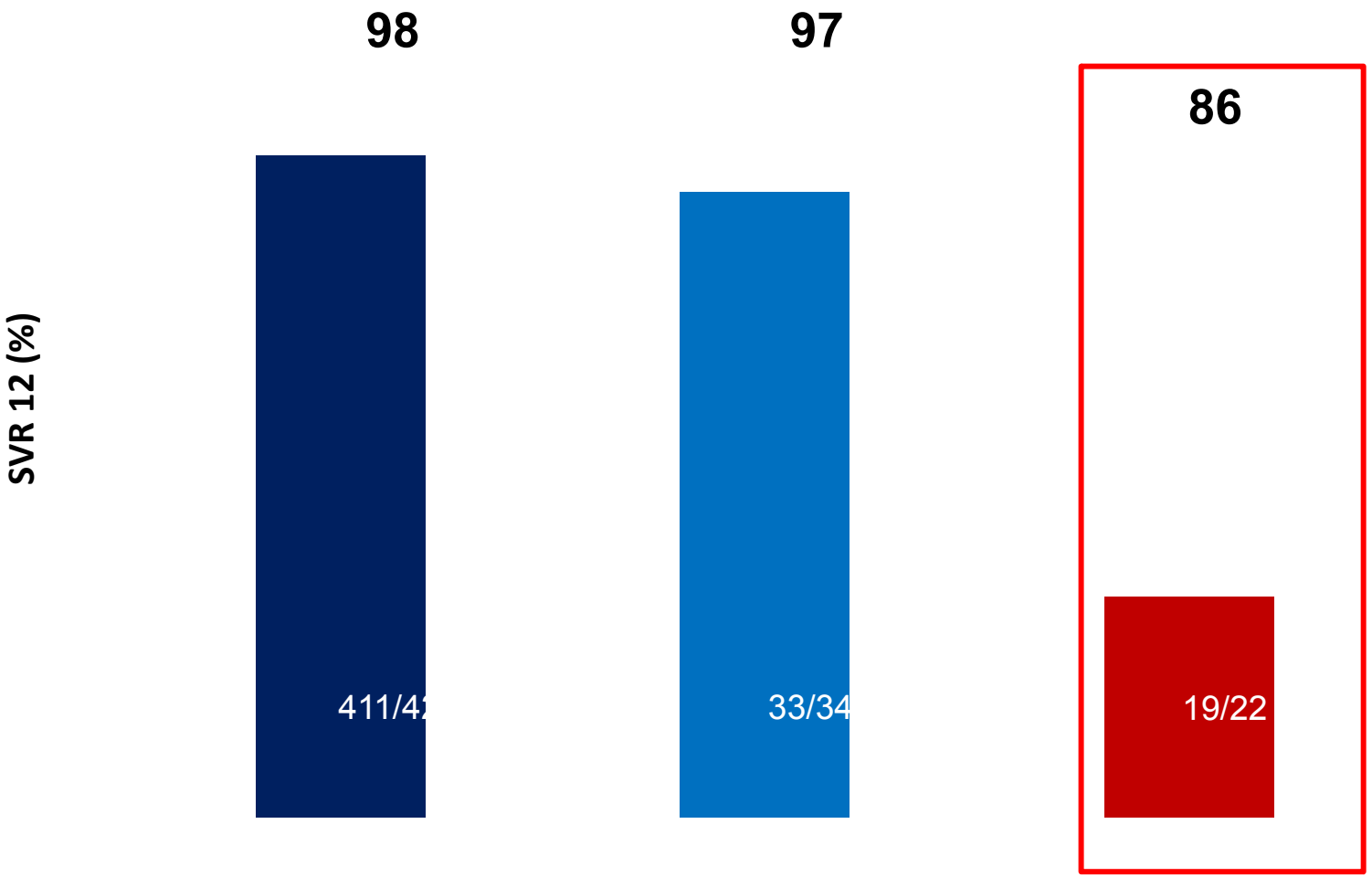
Hezode et al, Liver Int 2017

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



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

ASTRAL/POLARIS studies: SOF/VEL for 12 weeks in GT3 patients
Impact of NS5A RASs (LOD>15%) on SVR

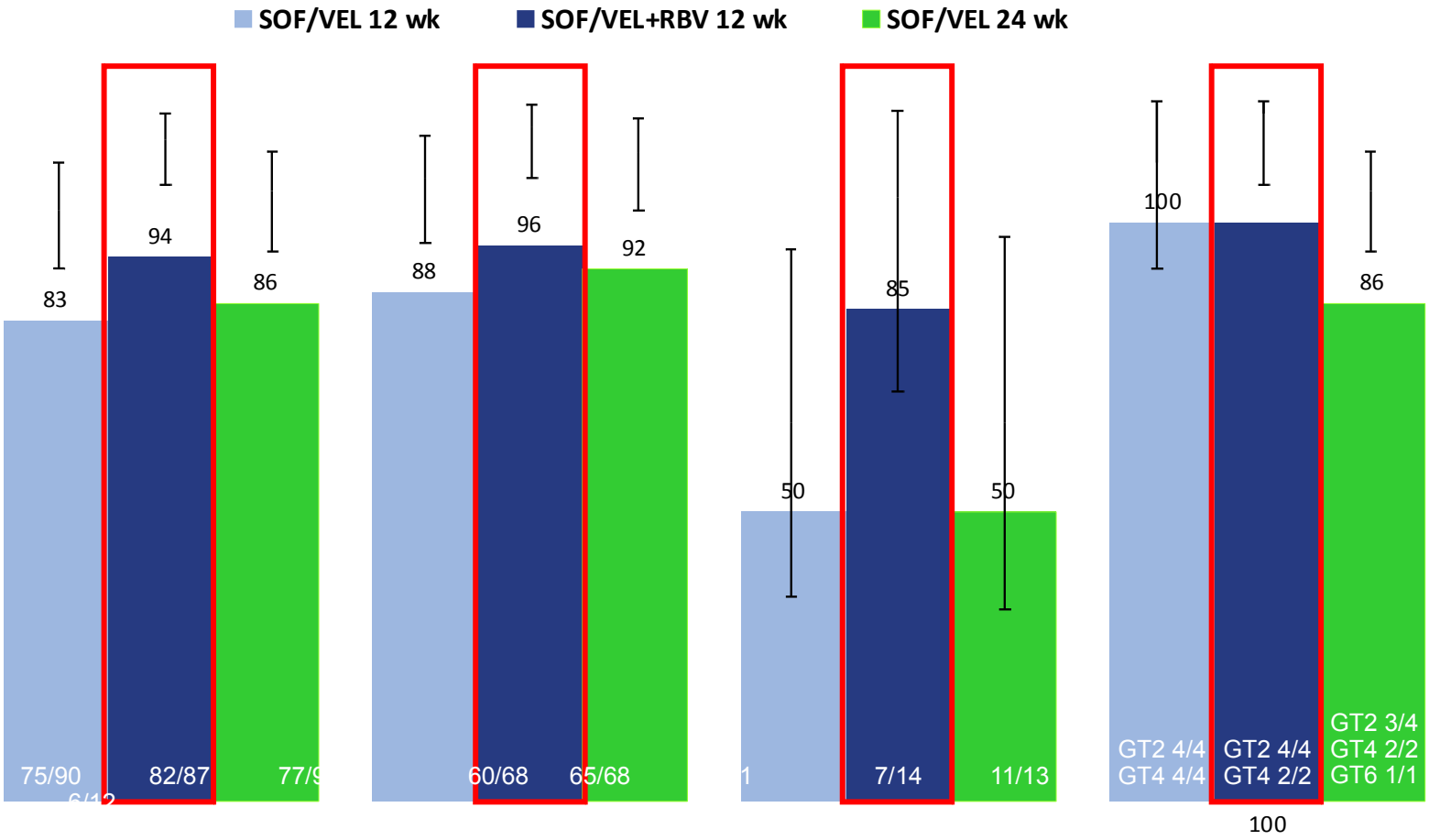


Hézode C et al, J Hepatol accepted

EASL guidelines

- Patients infected with HCV genotype 3 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily, with or without ribavirin (**A1**).
- Treatment-naïve patients without cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).
- If no NS5A resistance testing is performed, treatment-experienced patients without cirrhosis, as well as treatment-naïve and treatment-experienced patients with compensated cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**A1**).
- If reliable NS5A resistance testing is performed, treatment-experienced patients without cirrhosis, as well as treatment-naïve and treatment-experienced patients with compensated cirrhosis, with the NS5A RAS Y93H detectable at baseline should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients without the NS5A RAS Y93H at baseline should receive the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).
- NS5A resistance testing for HCV genotype 3 may be technically challenging, so that a reliable result is not guaranteed in all cases (**B2**).
- Patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the combination of sofosbuvir and velpatasvir for 24 weeks without ribavirin (**C1**).

ASTRAL-4: SOF/VEL in patients with decompensated cirrhosis

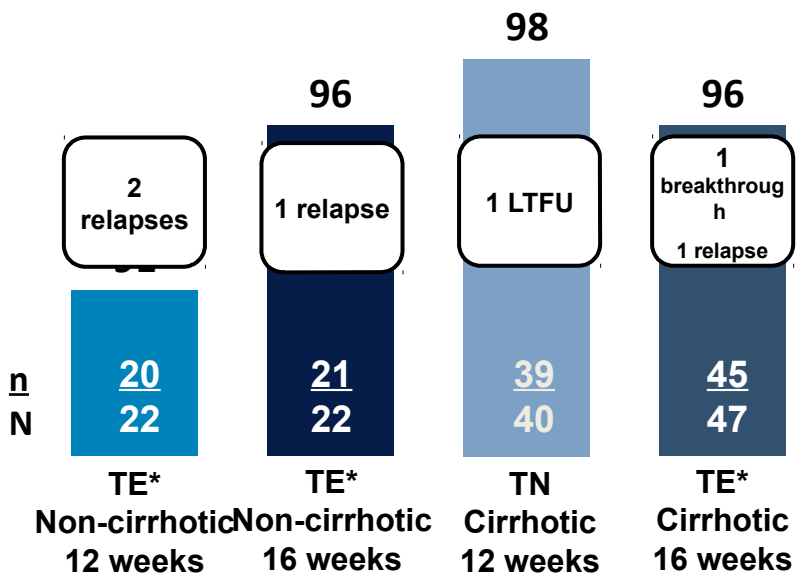


SOF/VEL + RBV resulted in highest SVR12 in patients with decompensated liver disease

Curry MP, et al. N Engl J Med 2015;373:2618–28

SURVEYOR-II, Part 3: G/P for 12 or 16 weeks in GT3 patients with prior treatment failure and/or cirrhosis

Efficacy

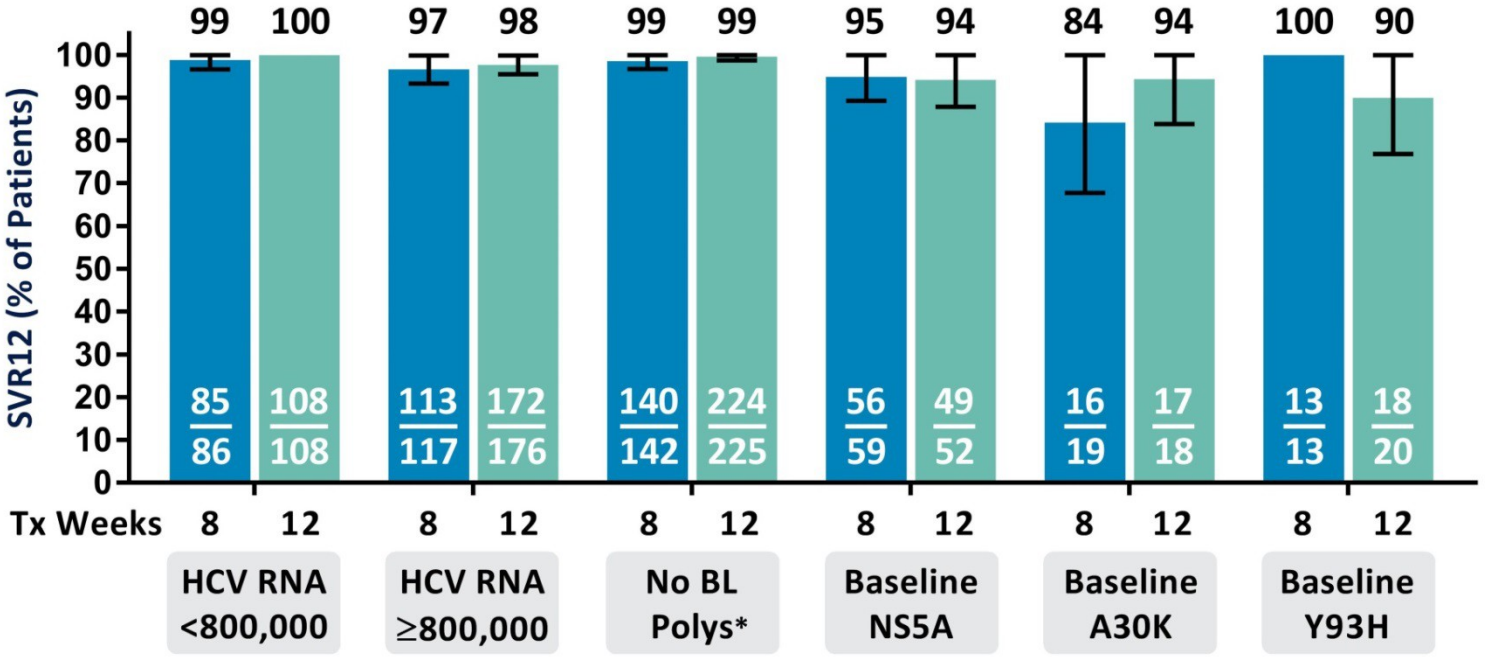


Safety

Safety summary Patients, n	TE Non-cirrhotic 12 Weeks n=22	TE Non-cirrhotic 16 Weeks n=22	TN Cirrhotic 12 Weeks n=40	TE Cirrhotic 16 Weeks n=47
Any AE	12 (55)	17 (77)	32 (80)	34 (72)
Serious AE†	1 (5)	1 (5)	1 (3)	3 (7)
AEs leading to discontinuation	0	0	0	0
Grade 3 lab abnormalities	3 (14)	0	0	1 (2)

*Includes SOF-experienced patients

mITT SVR12 by Viral Characteristics Subgroups: Treatment-naïve patients without cirrhosis, 8 vs 12 weeks



No statistically significant difference in SVR12 rates (8 vs 12 weeks) for any subgroup

* Baseline polymorphisms (BL Polys) at amino acid positions: **NS3**: 155, 156, 168; **NS5A**: 24, 28, 30, 31, 58, 92, 93

Flamm S, Etats-Unis, AASLD 2017, Abs. 62 actualisé

Patient management

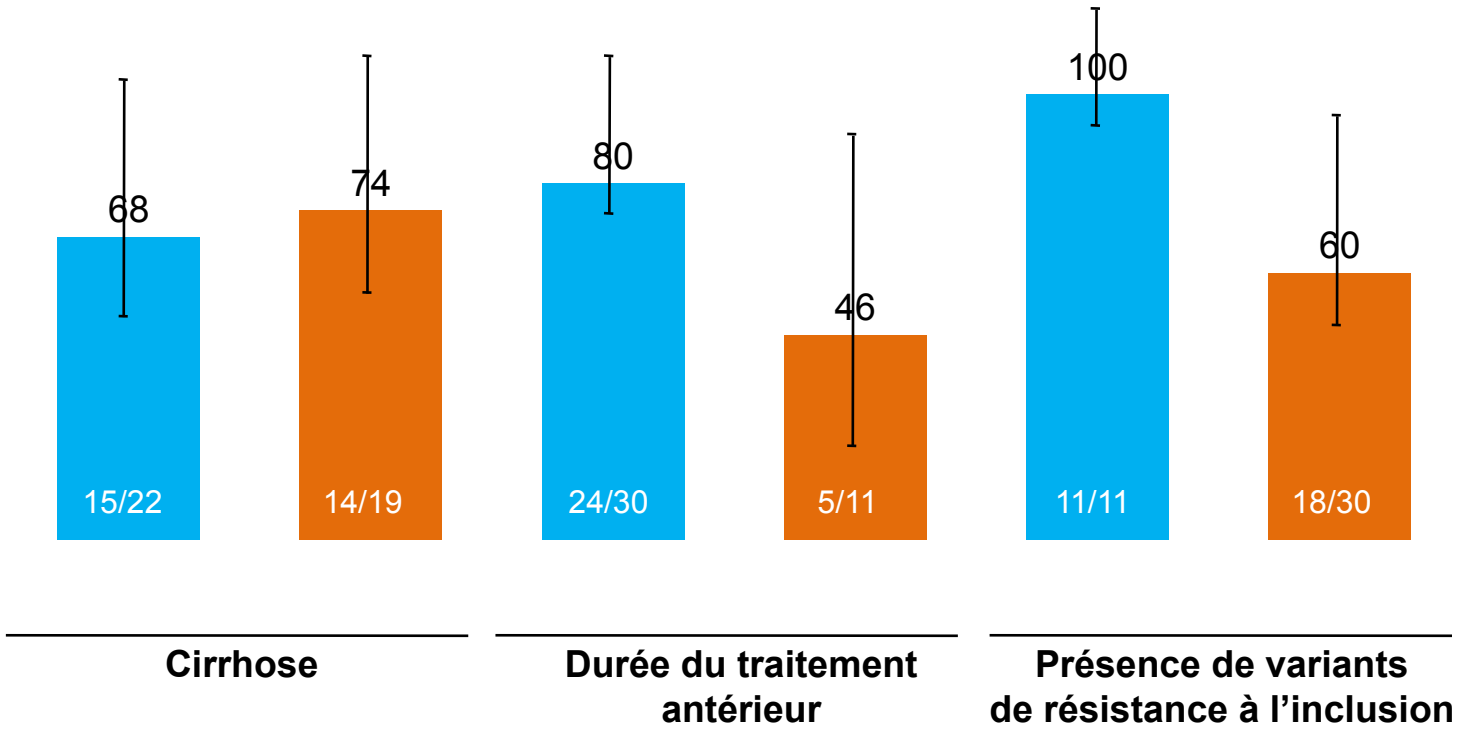
Sequencing	No mutation
Biopsy	HCC (well differentiated)
Treatment	Liver resection (HVBG < 12 mmHg)
Outcome	Decompensation (ascites)
Decision	Liver transplantation
Outcome at 6 months	CT scan : no HCC recurrence
Child/meld	A5 / 9
Fibroscan	32 kPa
Endoscopy	No varices

What is your therapeutic strategy?

1. No antiviral treatment (wait for LT)
2. Sofosbuvir + Velpatasvir
3. Sofosbuvir + Velpatasvir + Voxilaprevir
4. Glecaprevir + Pibrentasvir

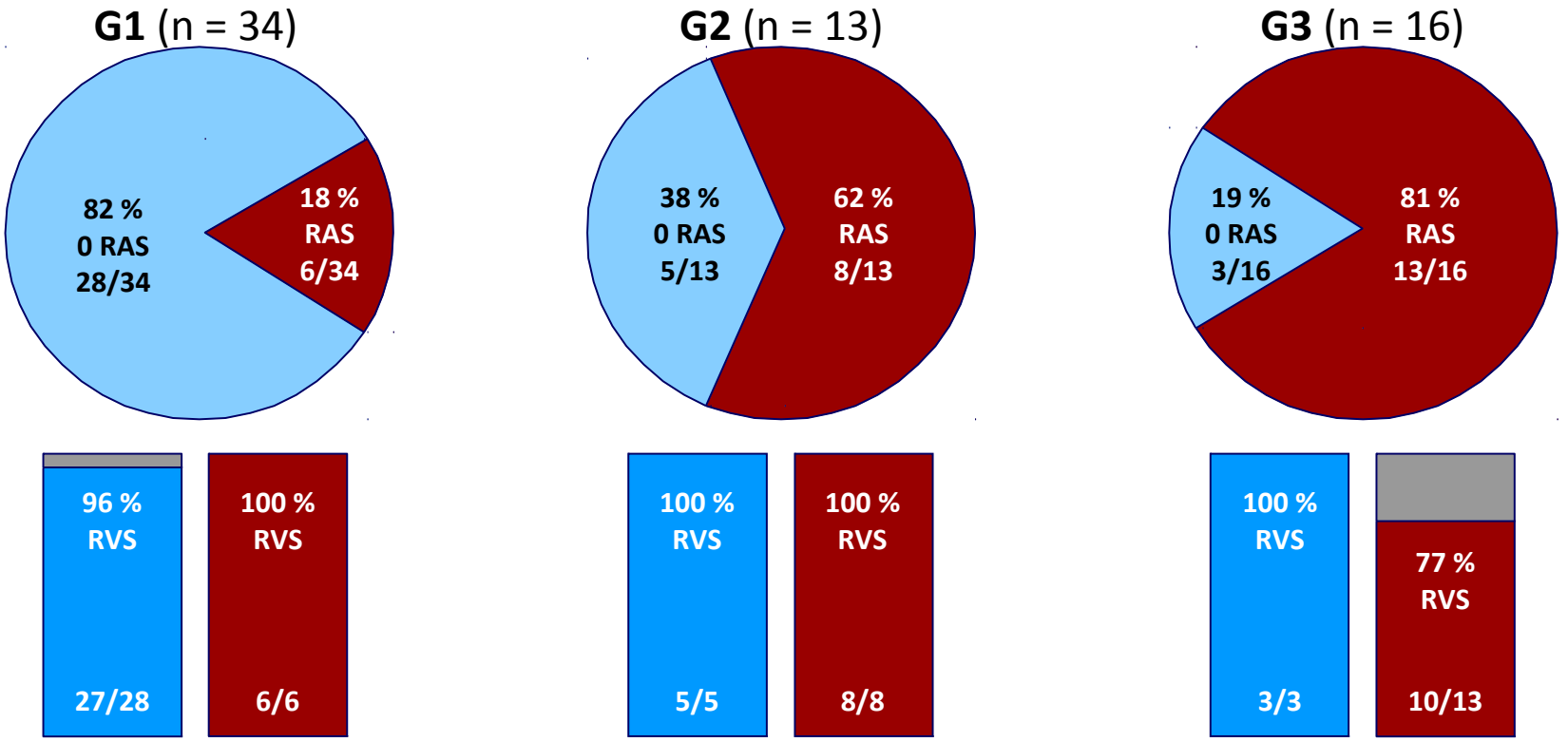
SOF + anti-NS5a in patients who failed SOF + anti-NS5a

- 41 patients who failed SOF + LDV 8-12 weeks
- Retreated by SOF + LDV 24 weeks



Lawitz E et al, EASL 2015, abstr. O005

SOF/VEL + RBV 24 weeks in anti-NS5a failure patients



Gane EJ, Nouvelle-Zélande, EASL 2016, Abs. PS024 actualisé

Antiviral treatment

SOF + VEL + RBV 24 weeks

	W0	W12	W24	FU12
ALT (IU/L)	52	24	22	65
HCV RNA (IU/ml)	>5M	< 12	< 12	>5M
AFP	7	6	6	8
Platelets	152	146	167	160
LS (kPa)	33	-	-	36
CT scan	Normal			Normal

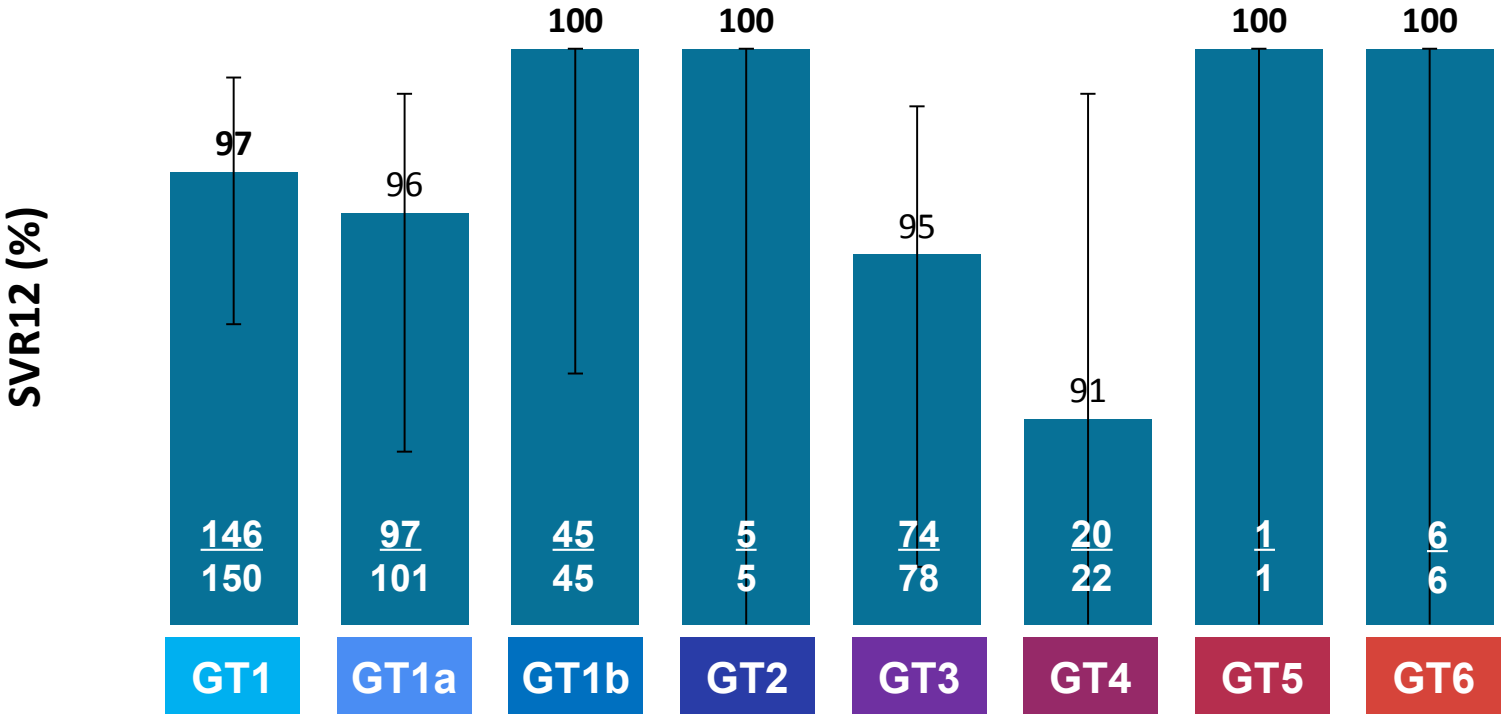
Sequencing :Y93N mutation

What is your therapeutic strategy?

1. **Sofosbuvir maintenance until LT**
2. **Sofosbuvir + Velpatasvir + Voxilaprevir**
3. **Glecaprevir + Pibrentasvir**
4. **Sofosbuvir + Glecaprevir + Pibrentasvir**

POLARIS-1: Sofosbuvir/velpastasvir/voxilaprevir for 12 weeks in experienced patients with NS5A inhibitor

SVR12 according to genotype



➔ **6 patients with relapse (1 GT1a, 4 GT3 et 1 GT4)**

Bourlière M, et al. N Engl J Med 2017;376/2134-46

Impact of mutations on antiviral efficacy (in vitro)

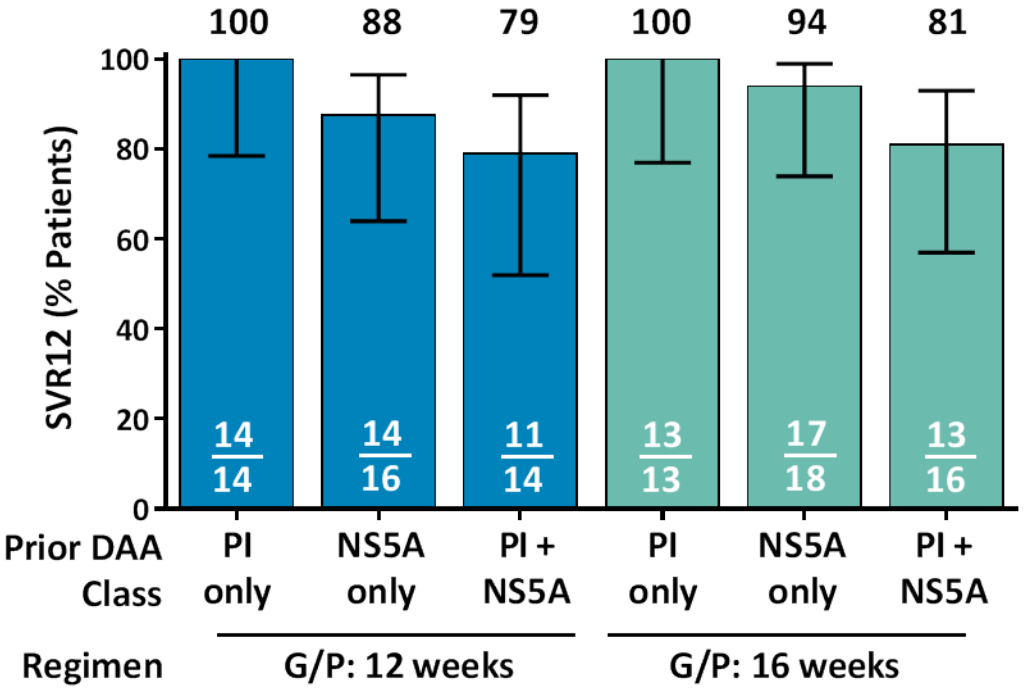
Pibrentasvir is highly active against common GT1a and GT3 NS5A resistance-associated variants

NS5A inhibitor	Fold change EC50						
	GT1a NS5A Variants				GT3 NS5A Variants		
	Q30E	L31M/V	H58D	Y93H/N	M28T	A30K	Y93H
Pibrentasvir1, 2	**2.4**	**1.1–1.3**	**1.1**	**6.7–7.1**	**0.4**	**1.1**	**2.5**
Velpatasvir6,7	37	2.1–9	N/A	81–609	N/A	10–100	>100
Ledipasvir3–5	3279	393–2787	>1000	4918	N/A	>1000	>1000
Daclatasvir8,9	25,205	341–3386	500	5432–47,477	46	56–62	2738–2752
Elbasvir7,10	50	125	N/A	600–2000	N/A	50	486
Ombitasvir11	1326	2	243	41,383–66,740	423	N/A	6728
Odalasvir3,7	71	1–2.4	8	5083	N/A	N/A	N/A
MK-8408	N/A	N/A	N/A	N/A	N/A	N/A	N/A

1. Poordad F, *et al.* EASL 2016 (oral #GS11); 2. Muir A, *et al.* EASL 2016 (oral #PS098); 3. Patel D, *et al.* EASL 2015;
4. Microbiology & Virology Review. Available at:
http://www.accessdata.fda.gov/DRUGSATFDA_DOCS/NDA/2014/205834Orig1s000MicroR.pdf (accessed Sep 2016);
5. Hernandez D, *et al. J Clin Virol* 2013; 6. Doehle BP, *et al.* EASL 2015;
7. Gao M, *et al. Curr Opin Virol*; **3:**514–520; 8. Fridell RA, *et al. Hepatology* 2011; **54:**1924–1935;
9. Wang C, *et al.* AAC 2013; **57:**611–613; 10. Gane E, *et al.* EASL 2015; 11. Krishnan P, *et al.* AAC 2015.

Glecaprevir + Pibrentasvir in DAA-failure patients

SVR12 by DAA Class in Prior Therapy



Overall SVR12:

12-week: 89% (39/44)
- 1 OTVF; 4 relapse

16-week: 91% (43/47)
- 4 OTVF; 0 relapse

Prior Treatment History
PI: TVR, SMV, BOC
NS5A: LDV, DCV
NS5A+PI: OBV and PTV, or other combinations

OTVF, on-treatment virologic failure

Conclusion

- G3 cirrhotic patients may remain difficult to treat
- Individual strategy based on:
  - Liver function and prognosis (HCC)
  - Virology profile
  - Multidisciplinary approach