Need to Assess HCV Resistance to DAAs: Is it Useful and When?

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Patient Case

Age/gender	54 years, male
HCV diagnosed	2013
Route of transmission	Injectable drugs
Genotype	1a (VERSANT HCV Genotype 2.0)
Fibrosis stage	Cirrhosis (Fibroscan 27 kPa)
Complications	Child-Pugh A5
Concomitant diseases	Obesity (BMI 30.2 kg/m2)
Associated treatment	None
HCV RNA levels	5.4 Log IU/mL (Abbott RealTi*me* HCV)
Previous HCV treatment	pegIFN/RBV (relapse)

Will you Prescribe an HCV Resistance Testing Prior to Treatment?

1. Yes

2. No

Systematic Resistance Testing Prior to First-Line Therapy is NOT Recommended

Pawlotsky JM., Gastroenterology 2016;151:70-86; EASL recommendations on treatment of hepatitis C 2016., J Hepatol 2016, in press.

No need to Perform Systematic HCV Resistance Testing at Baseline

Clinical reasons

- In clinical trials and in the real-world setting, most patients achieve an SVR
- Presence of RASs has limited impact on SVR except in some subgroups of patients (cirrhotic, treatment-experienced and genotypes 1a and 3)
- Patients who failed to a first course of DAA therapy can be successfully retreated following guidelines

Virological reasons

- No commercially standardized methods are available

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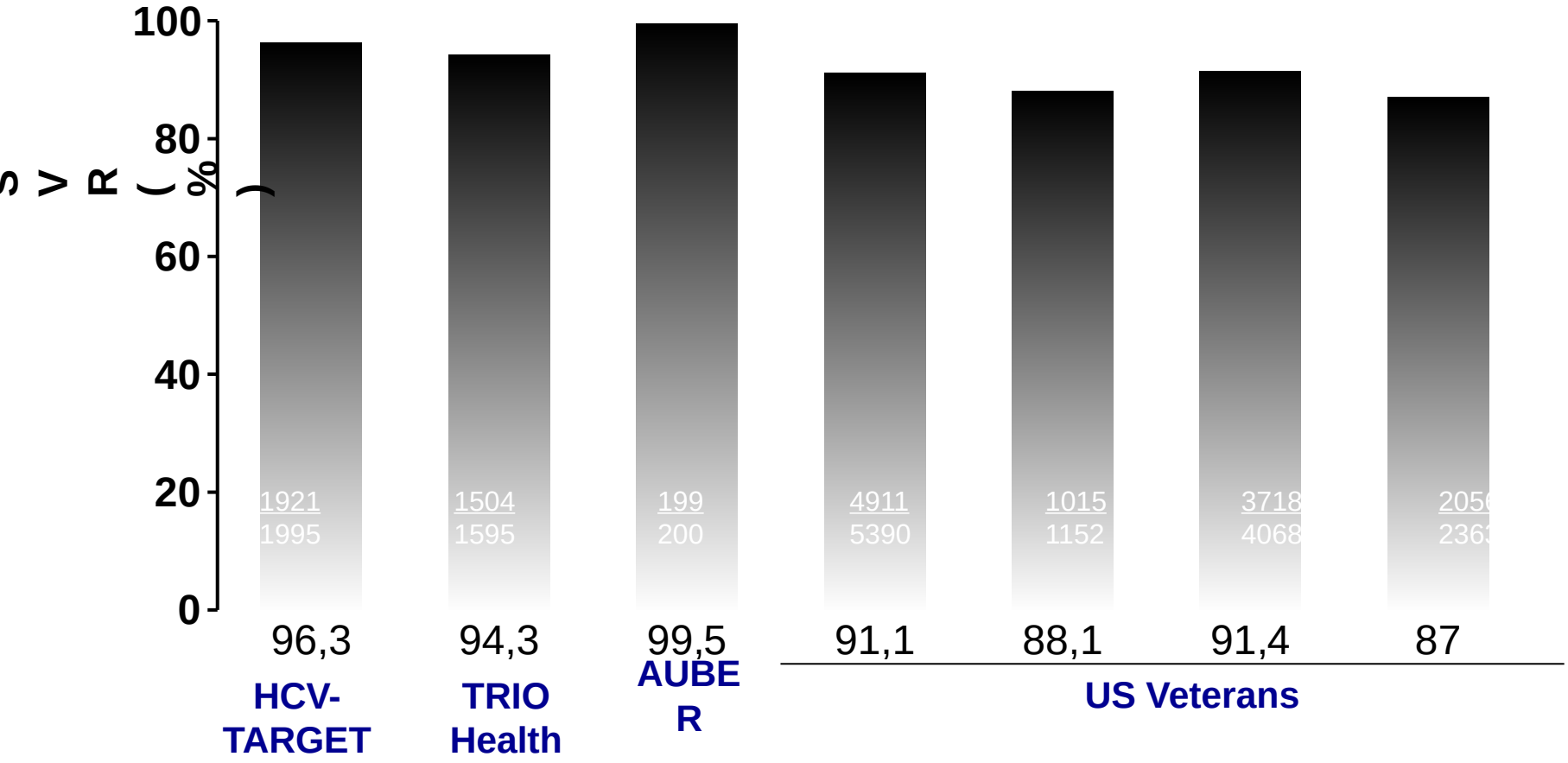
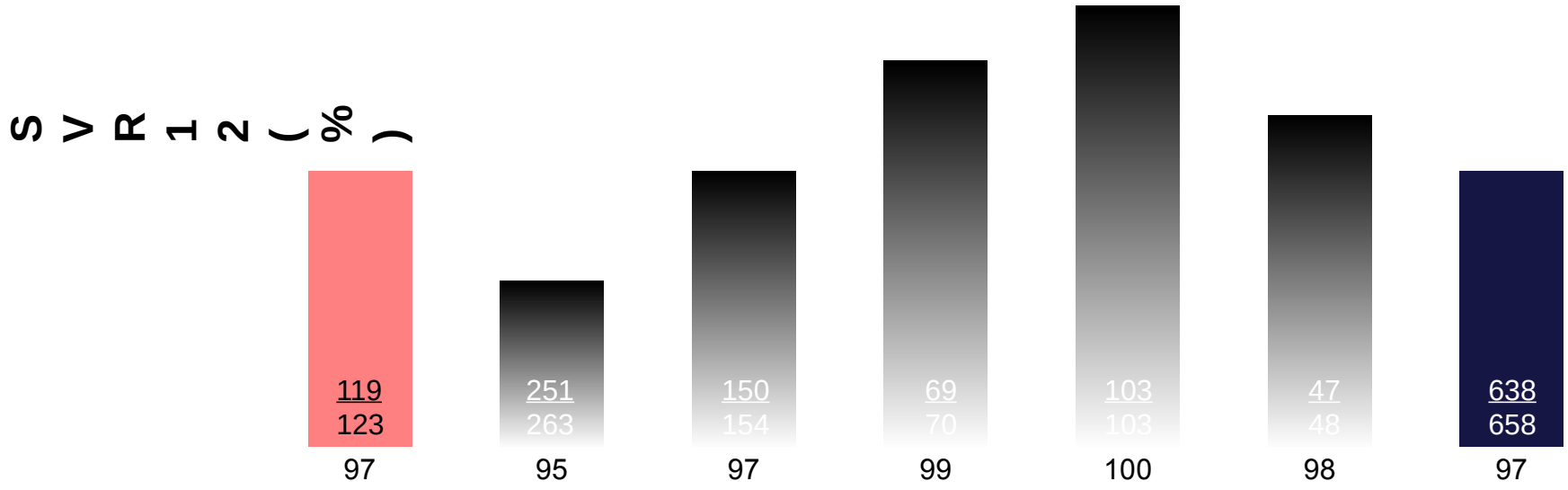
In the Real-World, Most Patients Achieve an SVR

Most Patients Achieve an SVR with All-oral DAAs (Genotype 1)



Terrault et al., Gastroenterology 2016;151(6):1131-1140.Tapper et al., J Viral Hepat 2017;24(1):22-27; Flisiak et al., Aliment Pharmacol Ther 2016;44(9):946-956; Backus et al., Aliment Pharmacol Ther 2016;44(4):400-10; Backus et al., Hepatology 2016;64(2):405-14; McCombs et al., EASL 2016;abstract LB510.

SVR in Genotype 1 Patients Treated with SOF/LDV for 8 Weeks

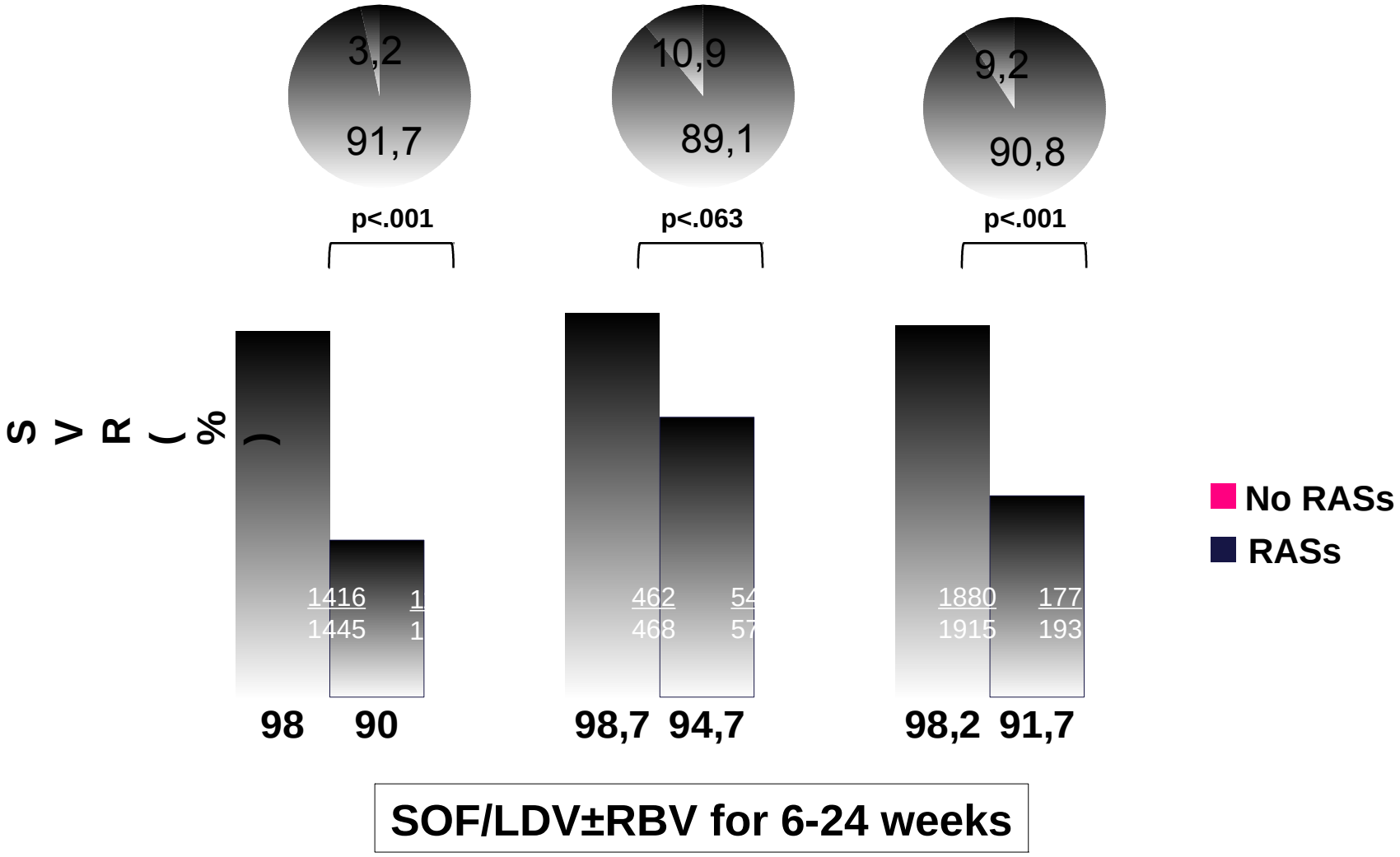


Post hoc analysis: patients qualified = Treatment-naïve, no cirrhosis, HCV RNA ≤ 6 million IU/mL
** Per protocol analysis
*** ITT analysis

Buggisch P, et al. EASL 2016, Abstract. SAT-242.

Presence of RASs Has Limited Impact on Antiviral Response

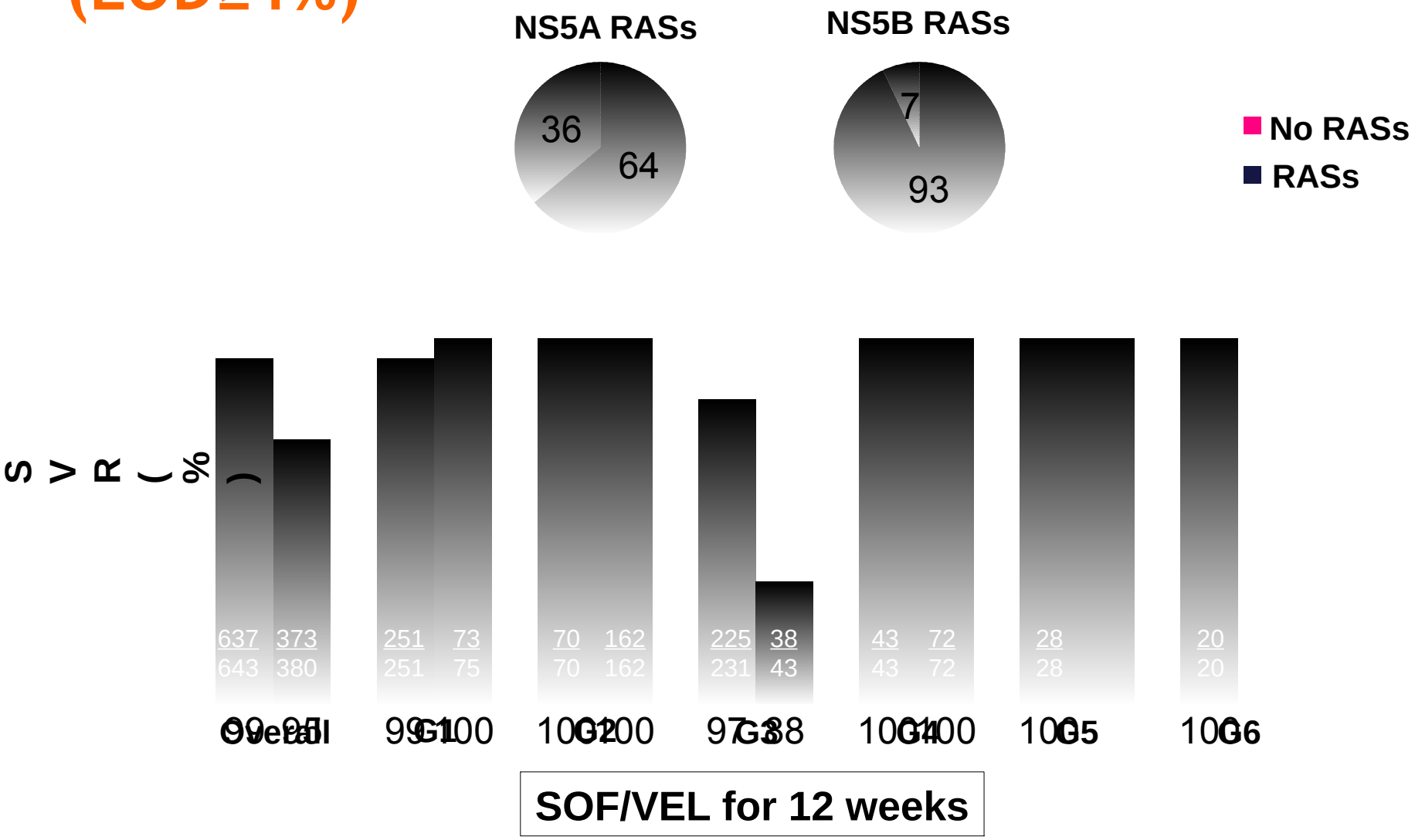
Impact of RASs on Virological Responses (LOD≥15%)



SOF/LDV±RBV for 6-24 weeks

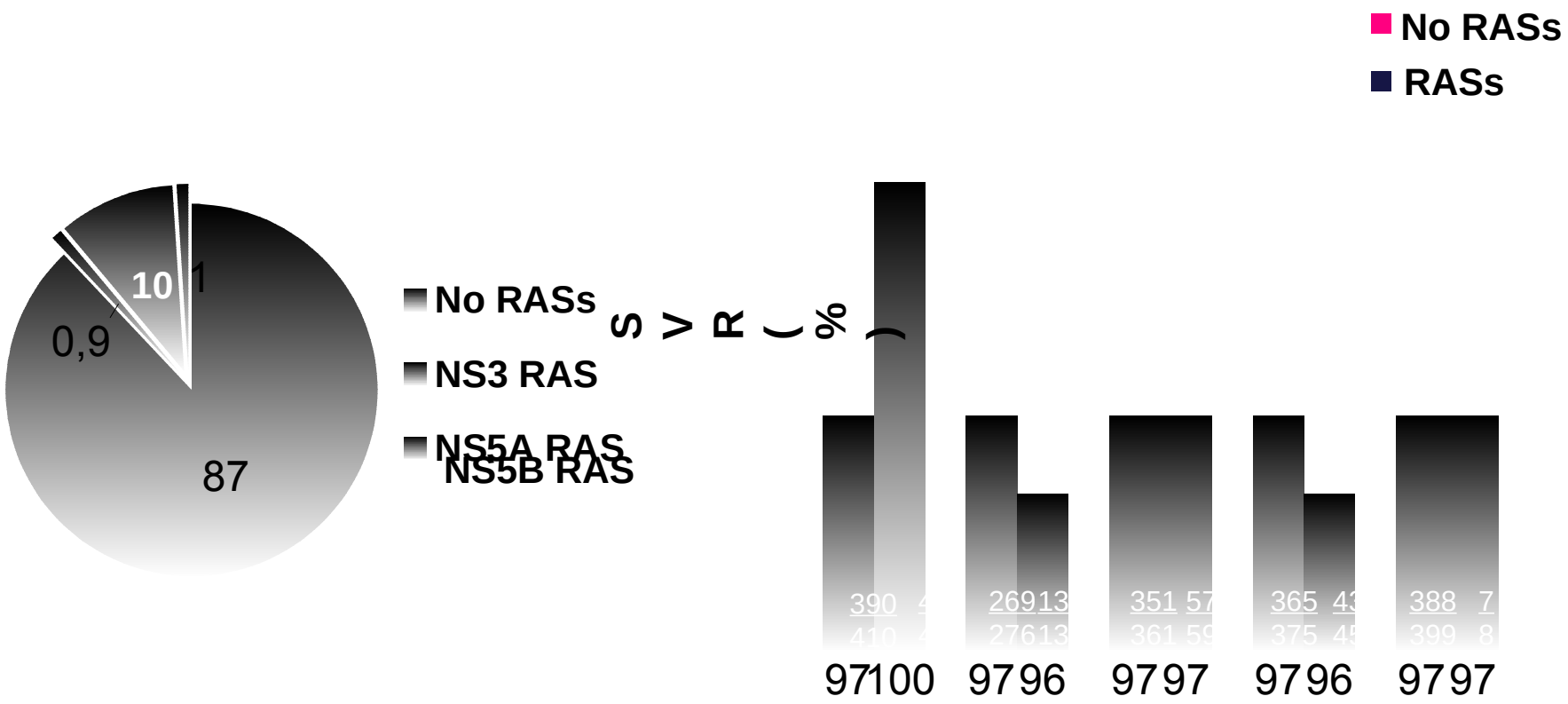
Sarrazin et al., Gastroenterology 2016;151(3):501–512.

Impact of RASs on Virological Responses (LOD≥1%)



Hézode et al., EASL 2016;Abstract 216.

Impact of RASs on Virological Responses (LOD≥15%)



PTV/r+OMB+DSV±RBV for 12-24 weeks

Sarrazin et al., EASL 2016, Abstract LB503.

Methods Available to Determine Resistance Profile

Tests Available in Europe?

No commercially standardized test are available

Except for the detection of NS3 Q80K RAS (Polymorphism kit, Clonit srl, Milan)1

Only homebrew population sequencing based methods for NS3pro, NS5A domain I and NS5B

NGS-based tests are currently in development

Sentosa SQ HCV Genotyping Assay (VELA Diagnostics)2

1Vicenti et al., J Clin Virol. 2016;76:20-3; 2Poon et al., AASLD 2015.

Features

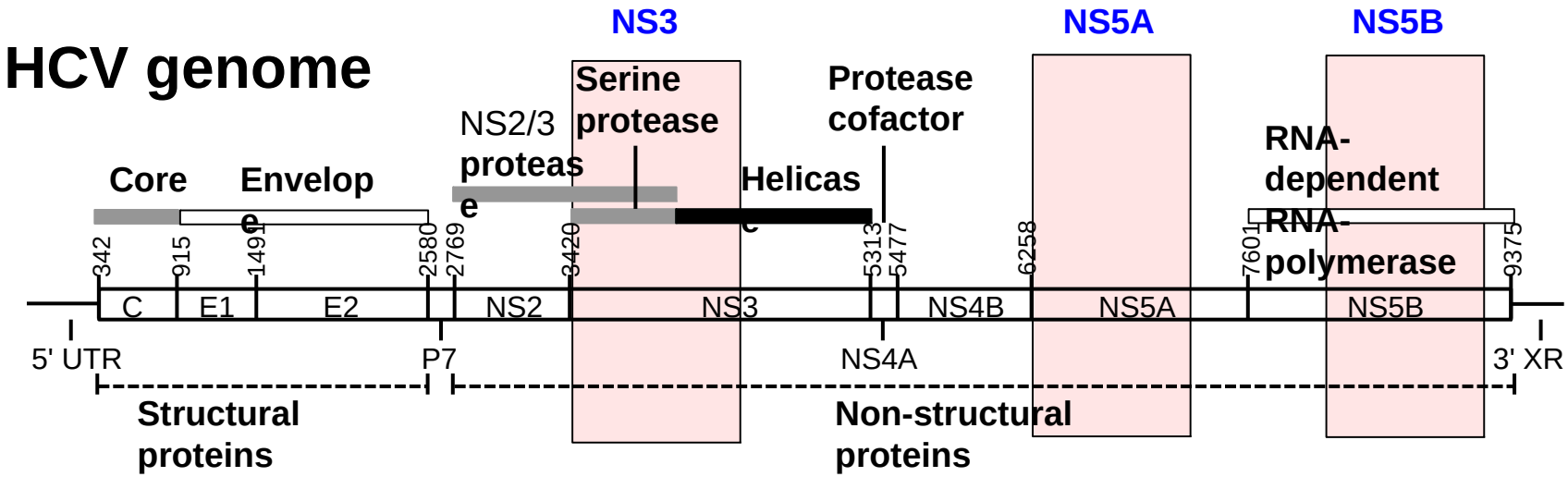
Sentosa SQ HCV Genotyping Assay

HCV RNA level >1000 IU/mL

Serum or plasma specimens accepted

Time to obtain results

48 hours



How Will you Treat?

1. Sofosbuvir + Ledipasvir ± RBV for 12/24 weeks
2. Sofosbuvir + Velpatasvir ± RBV for 12/24 weeks
3. Paritaprevir/r + Ombitasvir + Dasabuvir ± RBV for 12/24 weeks
4. Grazoprevir + Elbasvir ± RBV for 12/16 weeks
5. Sofosbuvir + Daclatasvir ± RBV for 12/24 weeks

EASL recommendations on treatment of hepatitis C 2016., J Hepatol 2016, in press.

Patient Case

First treatment received in May 2014

SOF + DCV for 12 weeks

HCV RNA levels

Day 0	5.4 Log IU/mL
Week 4	1.1 Log IU/mL
Week 8	<1.08 Log UI/mL, Target not detected
Week 12 (EoT)	<1.08 Log UI/mL, Target not detected
Follow-up week 4	5.55 Log IU/mL
Follow up week 12	5.15 Log IU/mL

Patient Case

First treatment received in May 2014

SOF + DCV for 12 weeks

HCV RNA levels

Day 0	5.4 Log IU/mL
Week 4	1.1 Log IU/mL
Week 8	<1.08 Log UI/mL, Target not detected
Week 12 (EoT)	<1.08 Log UI/mL , Target not

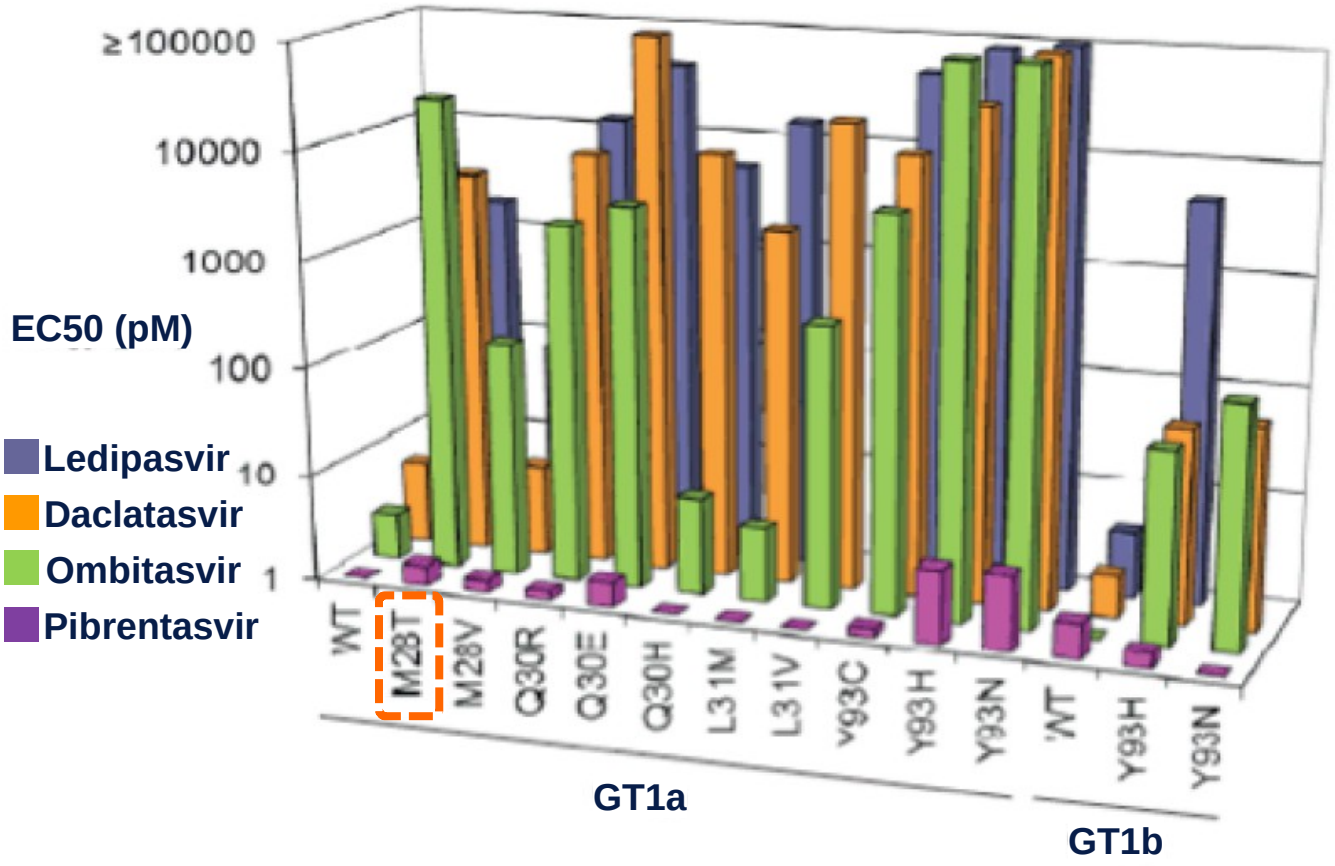
Relapse

Patient Case

RASs post-DAA treatment (population sequencing 20-30%)

NS3	• M28T
NS5 A	• None
NS5 B	• None

M28T RAS Confer a High Level of Resistance to NS5A Inhibitors



Selection of NS5A RAS in Patients Who Fail to Achieve an SVR

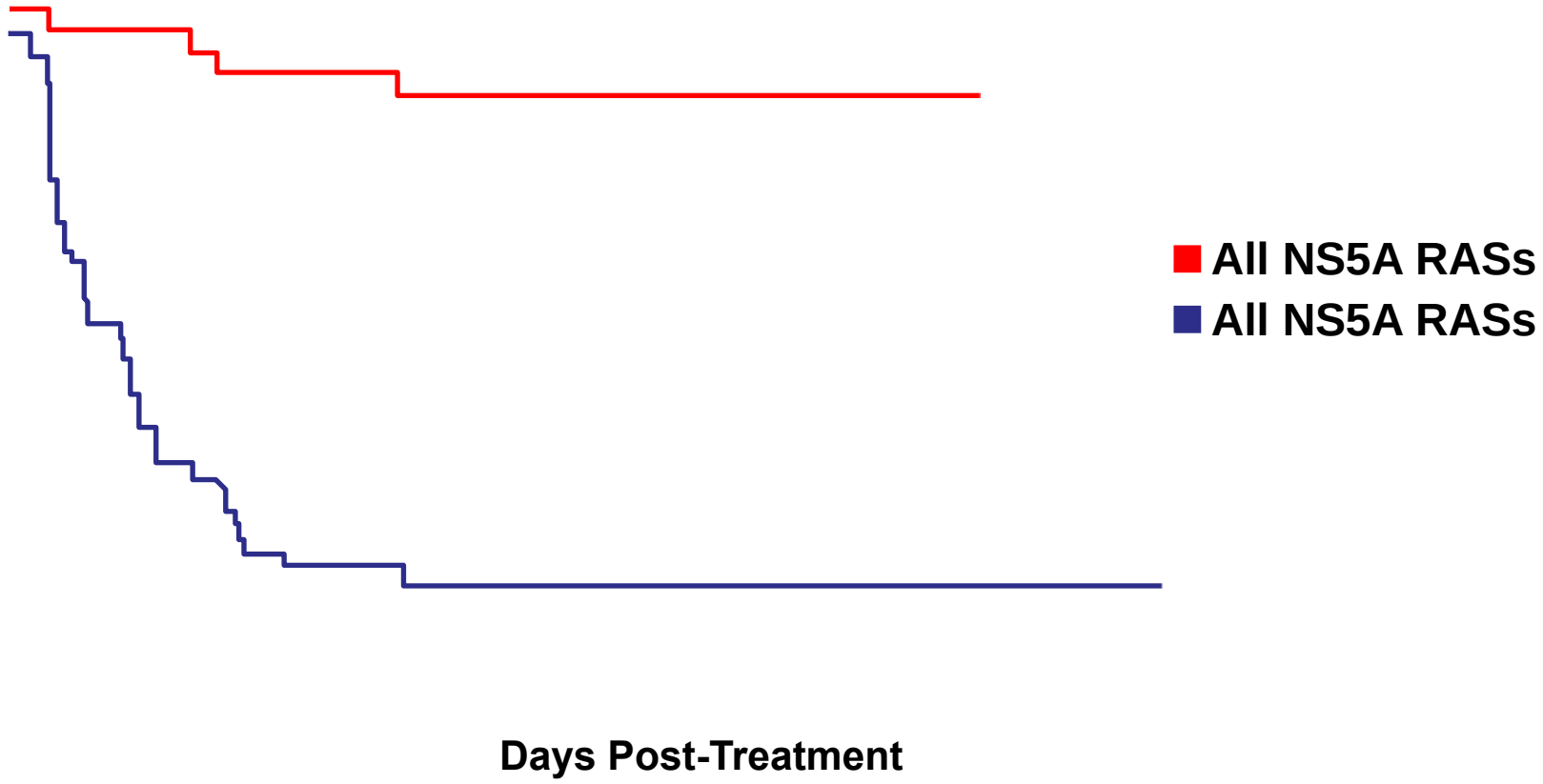
Treatment Failures Were Associated with Selection of RASs

	Populations	Treatment groups	N	Virologic Failure	NS5A RAS at failure
Ledipasvir1	G1 Rx-naïve and -exp.	SOF/LDV±RBV 8, 12 or 24 Wks	1952	37 (1.9%)	29 (78%)
Ombitasvir2	G1/4 Rx-naïve and -exp. G2 Rx-exp.	2D or 3D±RBV 8, 12 or 24 Wks	2652	82 (3.1%)	73 (89%)
Elbasvir3	G1/4/6 Rx-naïve and -exp.	GZR/ELB±RBV 12 Wks	1492	47 (3.1%)	42 (89%)
Velpatasvir4	G1/2/3/4/5/6 Rx-naïve and -exp	SOF/VEL±RBV 12 or 24 Wks	1623	35 (2.1%)	29 (83%)
Daclatasvir5	G1/2/3/4 Rx-naïve and -exp	SOF+DCV±RBV 8, 12, 16 or 24 Wks	616	33 (5.4%)	24 (73%)
Pibrentasvir 4	G1/2/3/4 Rx-naïve and -exp	GLE/PIB 8, 12 Wks	843	5 (0.6%)	

1ION-1, -2, -3
2PEARL-I, -II, -III, -IV, AVIATOR, TURQUOISE-I, SAPPHIRE-II
3C-SUFFER, C-EDGE, C-SALVAGE, C-WORTHY
4ASTRAL-1, -2, -3, -4
5ALLY-2, -3, AI4444040
4ENDURANCE-1, -2, -3, -4

Persistence of NS5A RASs in Patients Who Fail to Achieve an SVR

Long-term Persistence of NS5A RASs In G1-Patients who Failed to GZR-containing Regimens



Lahser et al., AASLD 2016;Abstract 61.

Will you Retreat this Patient?

1. Yes

2. No

What is Recommended for Patients Who Fail DAA Therapy?

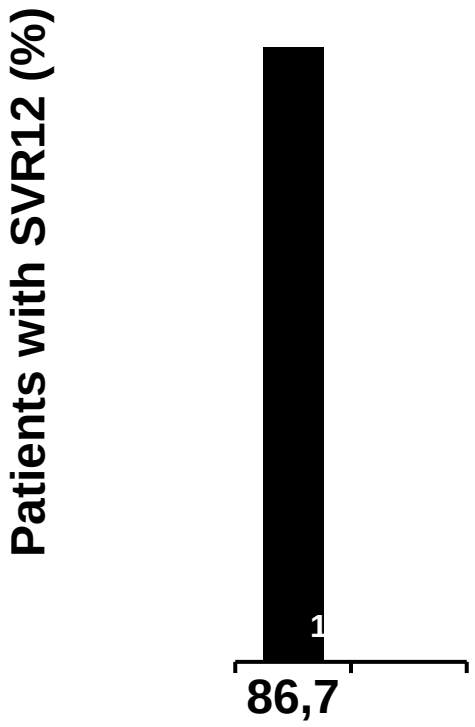
For patients who failed IFN-free DAA combination therapies, EASL and AASLD guidelines recommend the following:

AASLD/IDSA HCV Guidance Panel., Hepatology 2015;62(3):932-54; EASL Recommendations on Treatment of Hepatitis C J Hepatol 2016; Sep 12. pii: S0168-8278(16)30489-5. doi: 10.1016/j.jhep.2016.09.001.

How Will you Retreat?

1. Sofosbuvir + Ledipasvir + RBV for 24 weeks
2. Sofosbuvir + Velpatasvir + RBV for 24 weeks
3. Sofosbuvir + Paritaprevir/r + Ombitasvir + Dasabuvir + RBV for 24 weeks
4. Sofosbuvir + Grazoprevir + Elbasvir + RBV for 16/24 weeks
5. Sofosbuvir + Simeprevir + RBV for 24 weeks

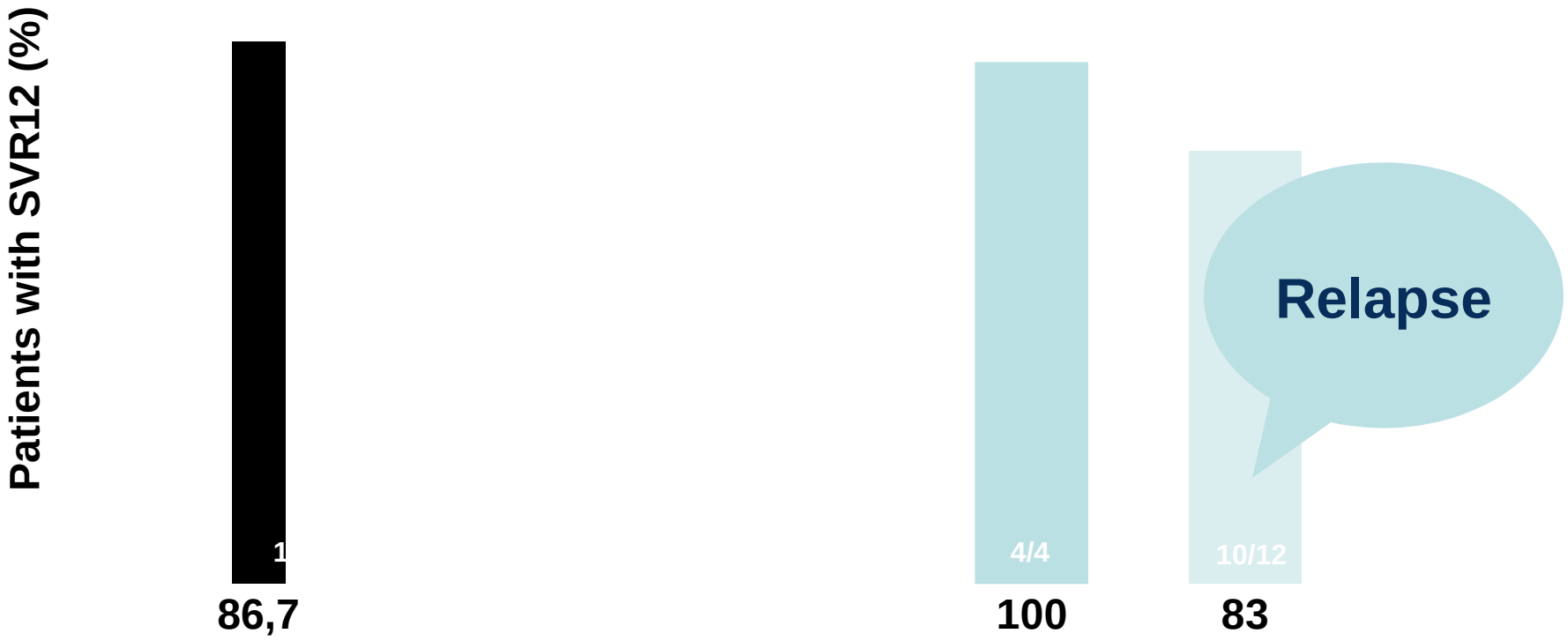
SOF/SMV for 12 weeks in Patients Who Failed Prior DCV-based Therapy



➥ **2 patients relapsed**

Hézode et al., Hepatology 2016;63(6):1809-16.

SOF/SMV for 12 weeks in Patients Who Failed Prior DCV-based Therapy



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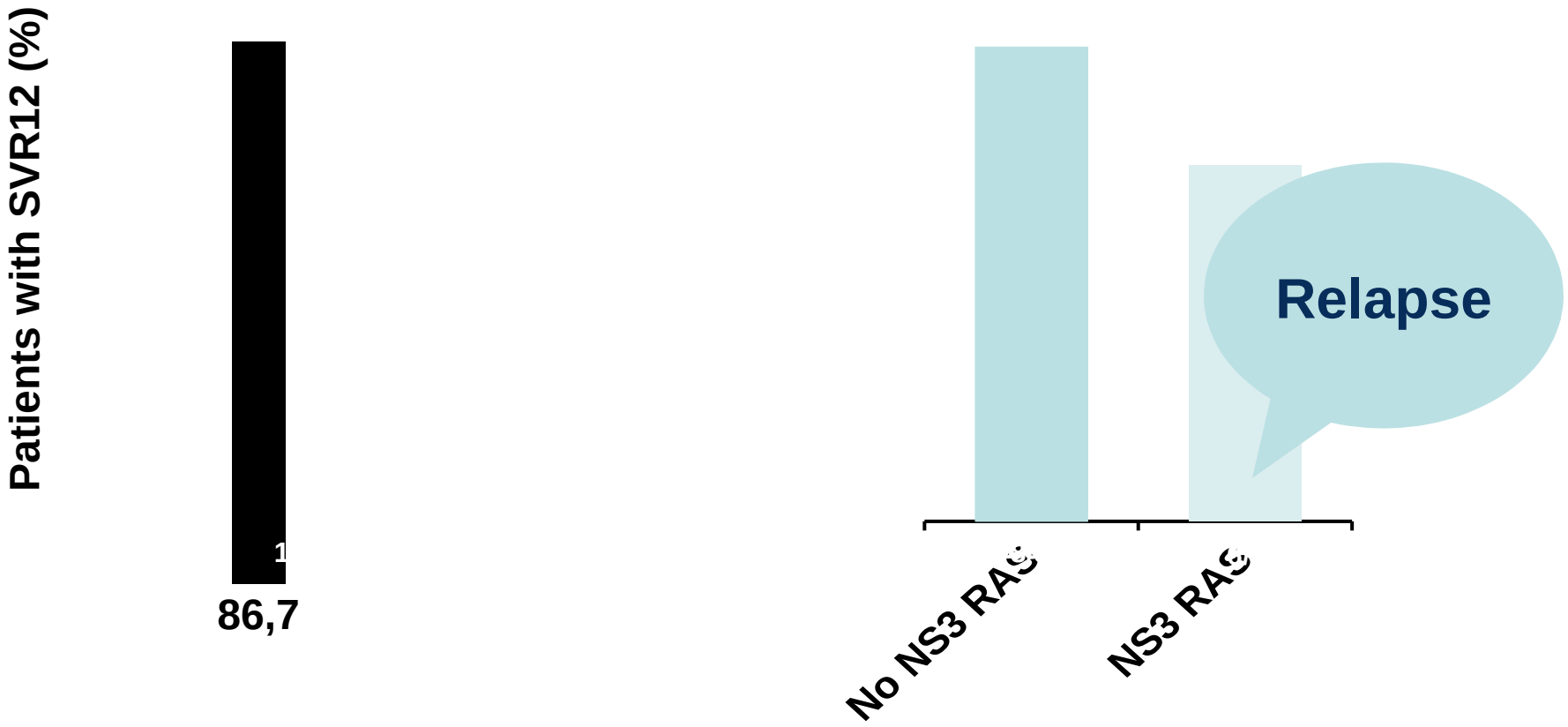
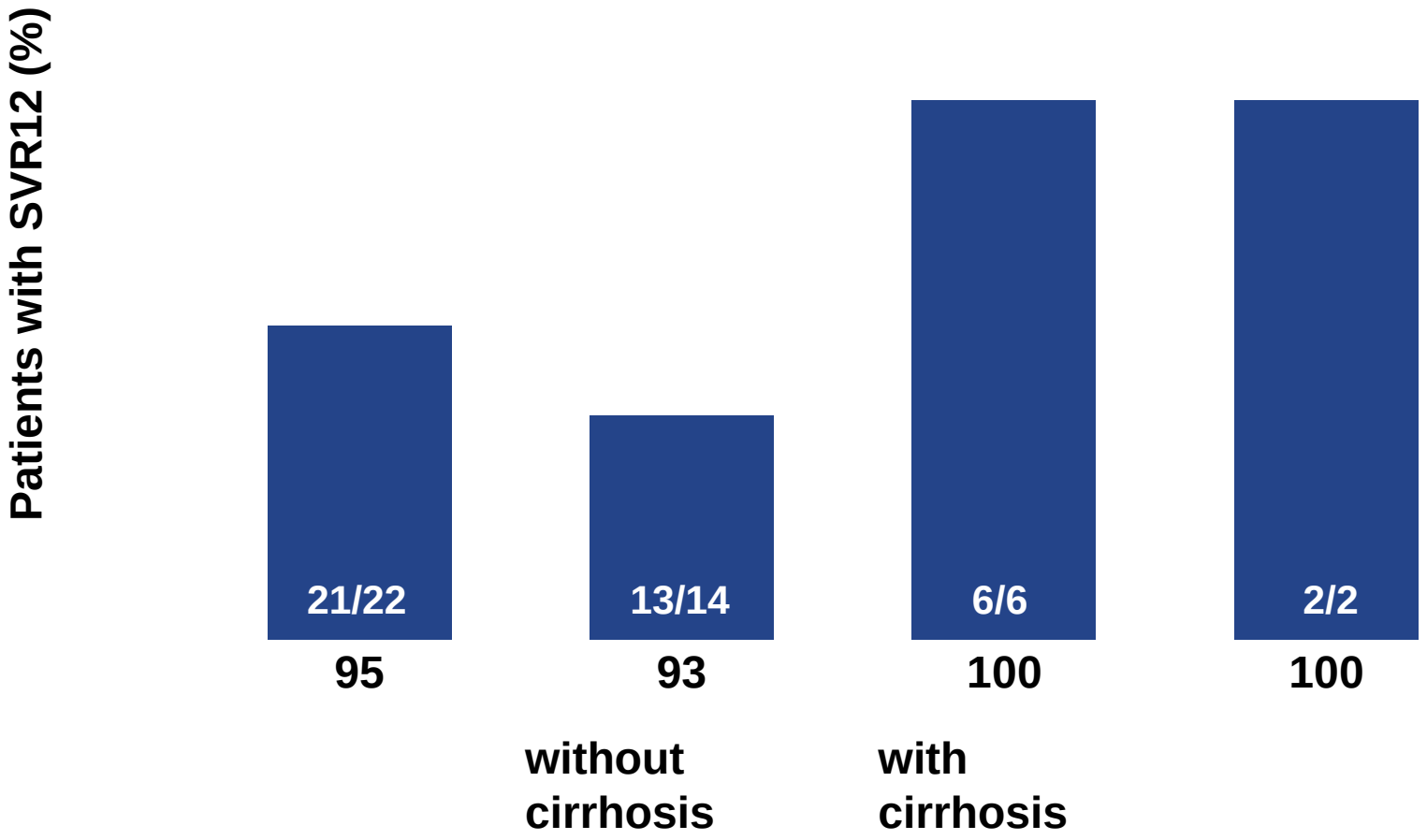


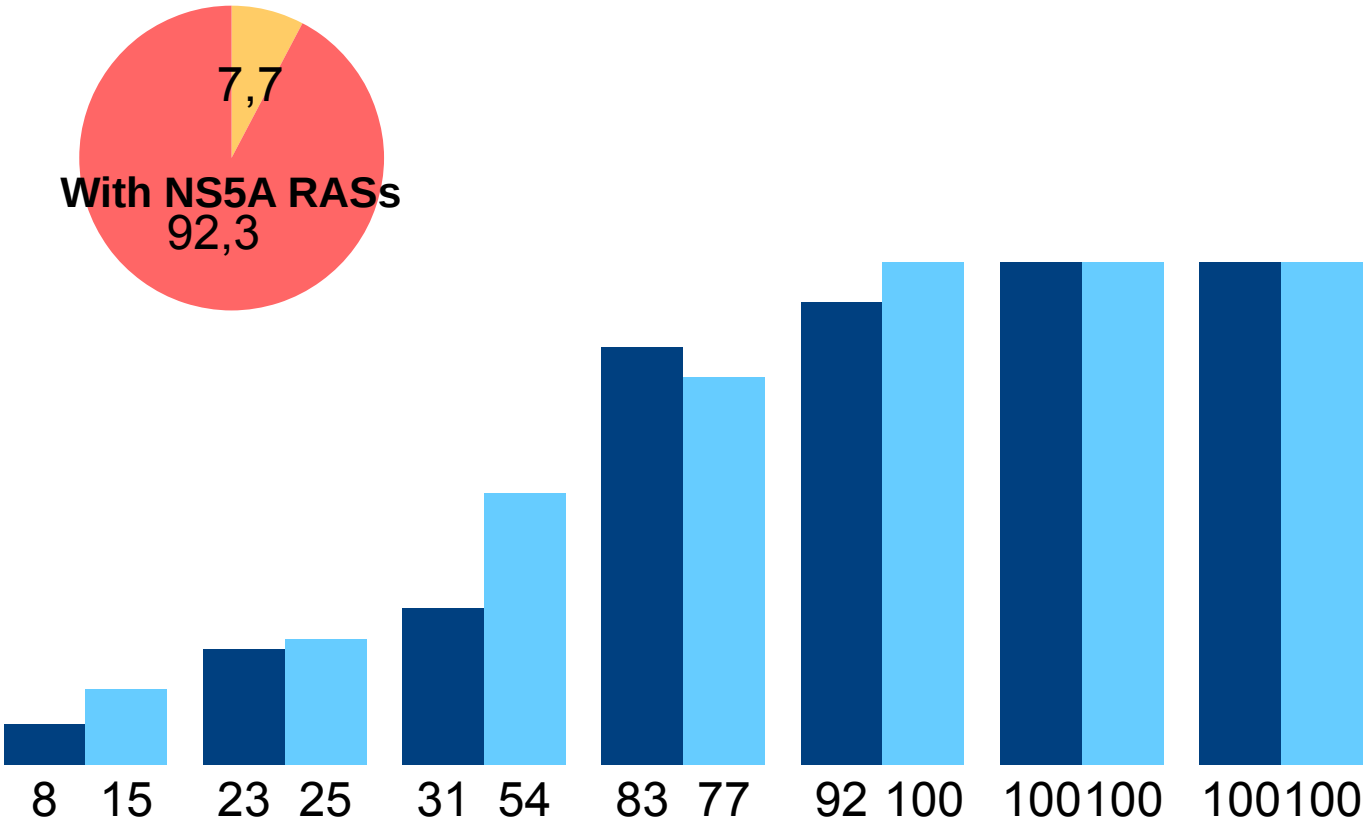
Hézode et al., Hepatology 2016;63(6):1809-16.

3D Combination plus SOF for 12-24 Weeks in Patients who Failed Prior DAA Regimen



Poordad et al,. EASL 2016;Abstract 156.

GZR/ELB plus SOF and RBV for 16-24 Weeks in Patients who Failed Prior DAA Regimen



N=26 Pts (20 G1 & 6 G4)

de Ledinghehn et al., AASLD 2016; Abst. LB-18

Patient Case

Second treatment received in <u>January 2015</u>

SOF + SMV + RBV for 24 weeks

In September 2015, SVR12 achieved

Patient is cured!

Conclusions

Systematic HCV resistance testing prior to first-line treatment is NOT recommended

SVR rates are >90%, however some relapses can occur, especially when treatment is suboptimal

- **Patients who failed to a first course of DAA therapy can be successfully retreated following guidelines**

- **Cure of infection does not mean cure of disease (cirrhotics), and these patients must be closely monitored for HCC**