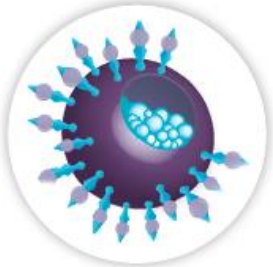
12TH INTERNATIONAL WORKSHOP ON HEPATITIS C: RESISTANCE AND NEW COMPOUNDS

Session 1:

Real-life efficacy of HCV-retreatment after DAA-failure: the role of NS5A-resistance



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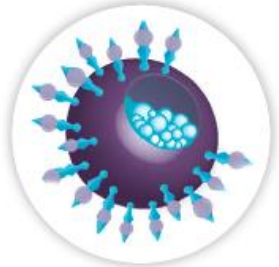
VIRONET C

Disclosures

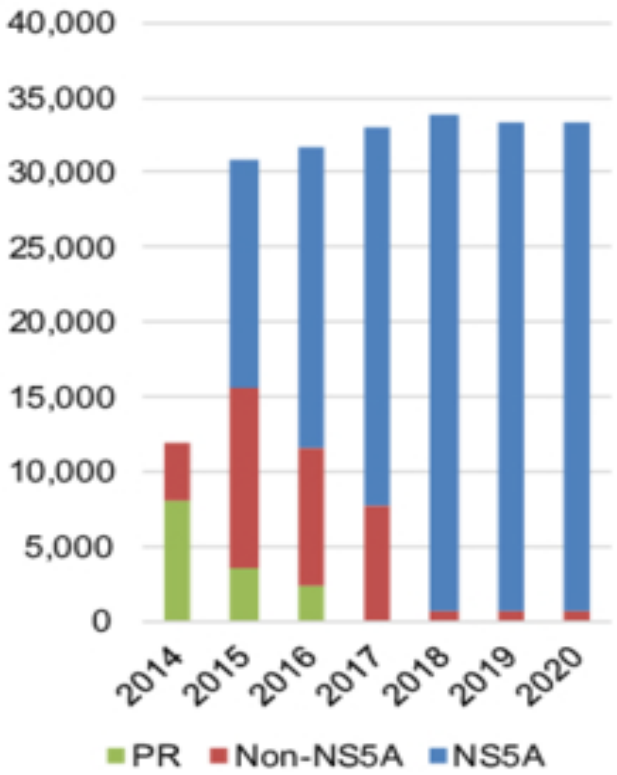


- Advisory Board: Abbvie
- Training: Merck Sharp & Dohme
- Sponsored lectures: Bristol-Myers Squibb, Janssen-Cilag, Abbvie, Merck Sharp & Dohme

Even in the era of DAAs, ~47,000 patients would fail to achieve SVR in Europe

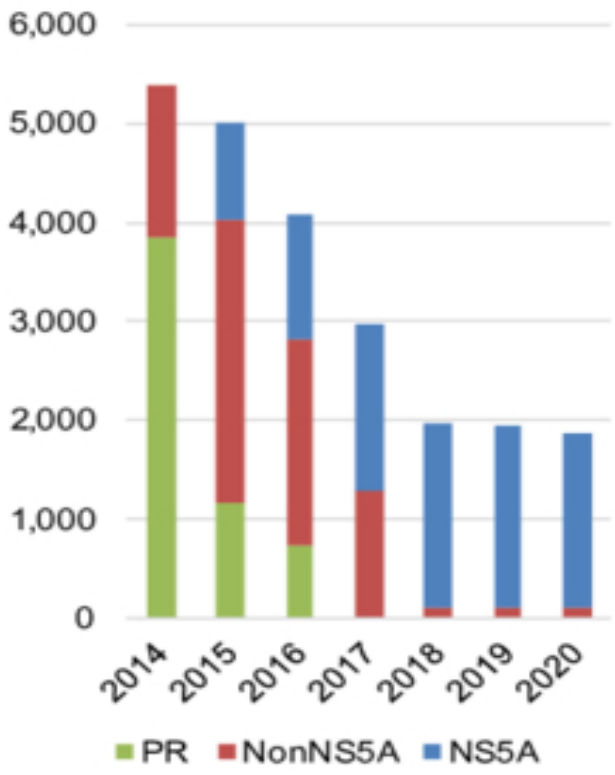
In Italy, **23,224 failures** are expected before 2020, **40.4%** of which will be NS5A-failures.

Number of patients treated between 2014 and 2020



Italy

Number of patients who fail treatment: by nonNS5A/NS5A

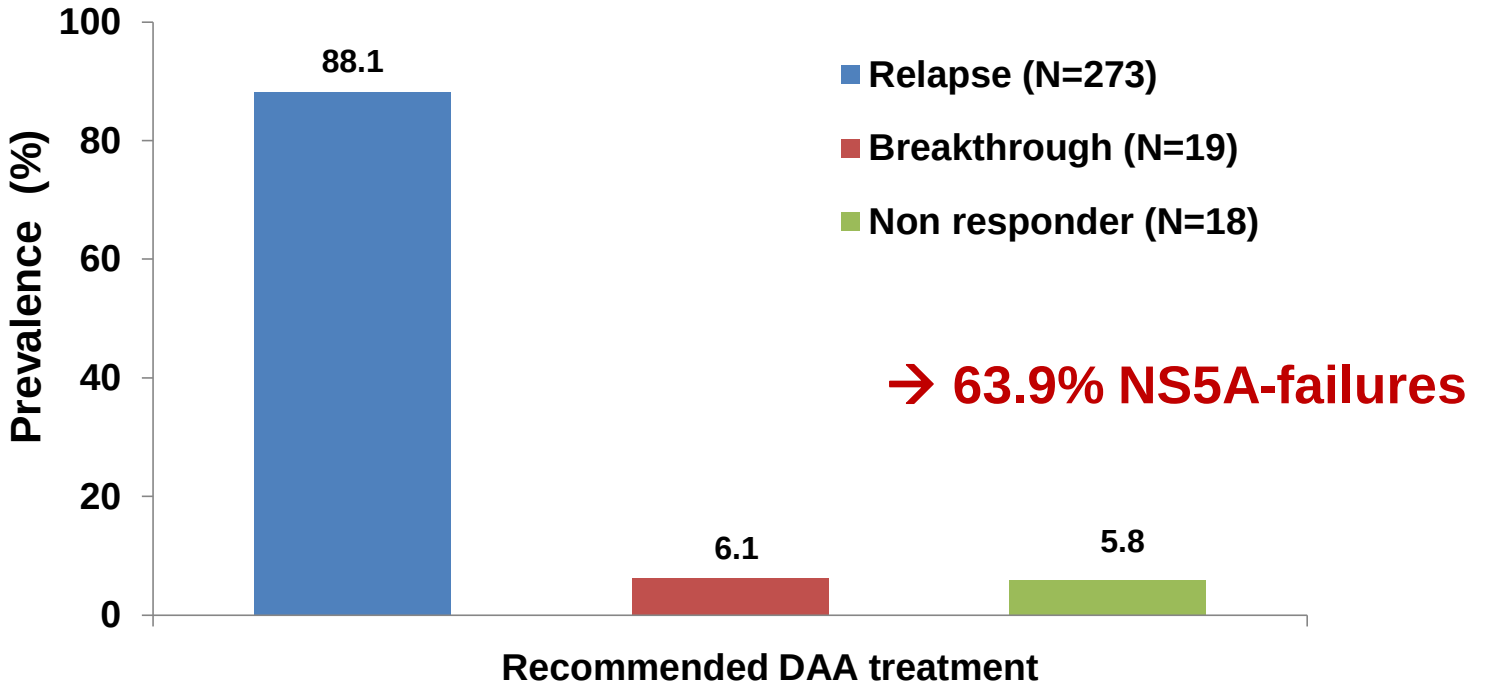


Chhatwal J et al., EASL 2017 poster #FRI-233

We have DAA-experienced patients that need to be retreated

310 HCV-infected patients who failed a <u>currently recommended</u> INF-free DAA regimen were analyzed

→ See Di Maio VC *et al.*, Poster #78



→ 63.9% NS5A-failures

- **SMV+SOF+/-RBV (N=84)**
- **3D+/-RBV (N=47)**
- **2D+/-RBV (N=2)**
- **LDV+SOF+/-RBV (N=91)**
- **DCV+SOF+/-RBV (N=58)**
- **SOF+RBV (N=28, HCV-2)**

AIMS

- Summarise a ‘real world’ experience of retreatment of patients who failed treatment with IFN-free combinations within the Italian HCV resistance network VIRONET C.
- Evaluate the role of baseline resistance on retreatment efficacy.
- Identify possible predictors of virological outcome to 2nd line IFN-free regimens.

Methods

- The choice of treatment was based on the availability of DAAs. The use of ribavirin and the duration of treatment were at the discretion of the investigator.
- Genotypic resistance test of drug-resistance-relevant HCV regions in NS3, NS5A and NS5B was performed for routine clinical purposes or for research (at the discretion of the investigator), by mean of Sanger population sequencing.
  - The sensitivity of population-based sequencing is approximately 15-20% for minority variants.
- Sustained virological response rate was considered as HCV-RNA undetectability (HCV-RNA<LLOD, not detectable) at week-12 of follow-up after treatment discontinuation (SVR_{12}). Only observed success or failure contributed to the efficacy analysis.
- All statistical analyses were performed using the SPSS software package (version 23.0) for Windows (SPSS Inc., Chicago, IL).

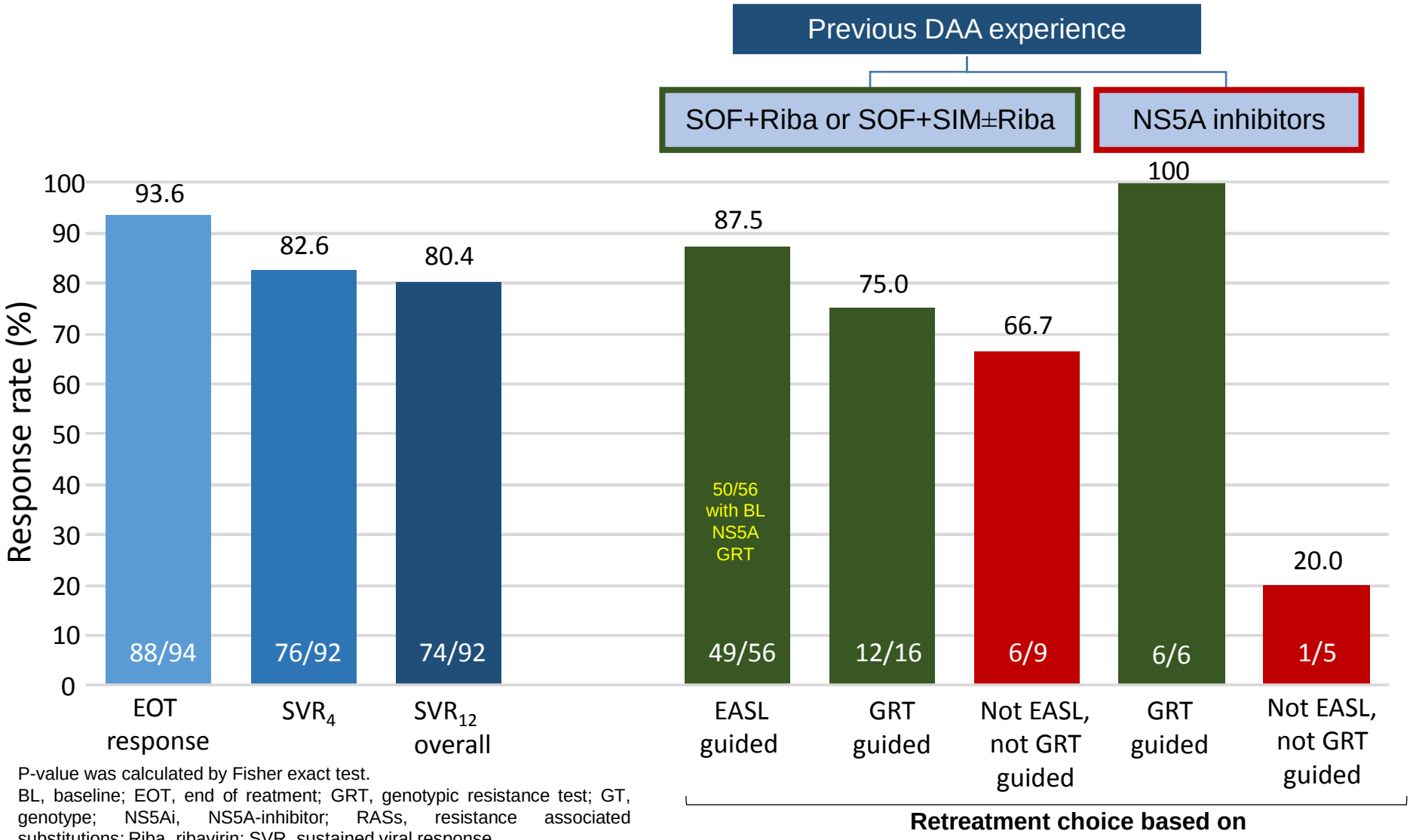
100 IFN-free DAA failures started a 2nd line regimen

Males, N(%)		75 (75.0)
Age (years), Median (IQR)		56 (51-66)
HCV geno/subtype	**1a**	**25 (25.0)**
	1b	**25 (25.0)**
	2a	1 (1.0)
	2c	5 (5.0)
	3a	**33 (33.0)**
	4d	11 (11.0)
Liver Transplant, N (%)		4 (4.0)
HCC, N (%)		10 (10.0)
Cirrhotic patients, N (%)		**85 (85.0)**
Stiffness at baseline (Kpa), Median (IQR)[a]		**21.2 (12.0-32.7)**
Prior DAA experience, N (%)	**3D combination** ± Riba	**1 (1.0)**
	Daclatasvir + PI ± Riba	**5 (5.0)**
	Ledipasvir + Sofosbuvir ± Riba	**8 (8.0)**
	Simeprevir + Sofosbuvir ± Riba	23 (23.0)
	Sofosbuvir[b] + Riba	63 (63.0)
Baseline HCV-RNA (logIU/ml), Median (IQR)		5.7 (5.2-6.2)
Baseline ALT (IU/ml), Median (IQR)		68 (44-133)

[a] Stiffness value was available for 48 patients; [b] 6 patients had previously failed a treatment with telaprevir or boceprevir.

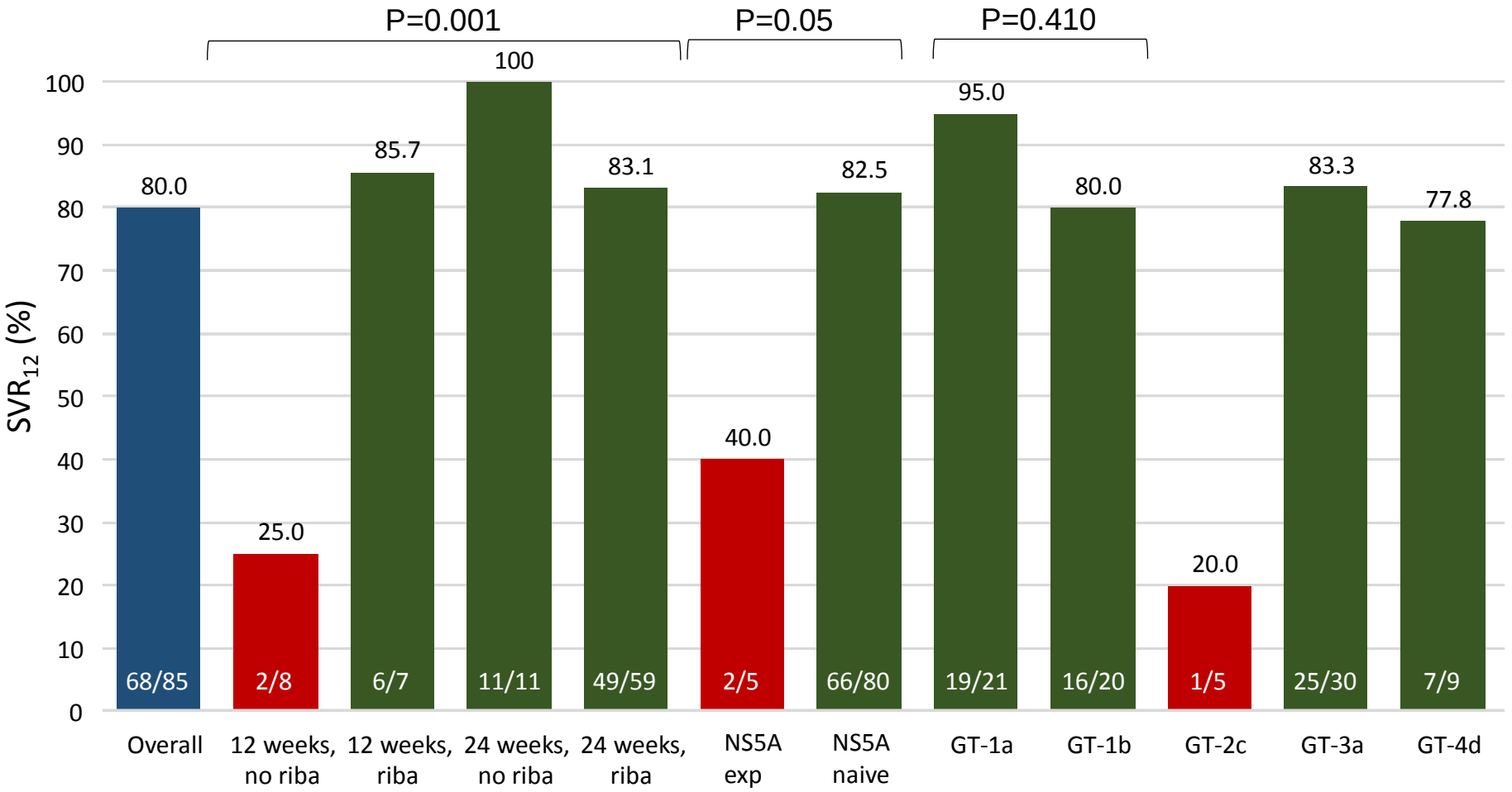
3D, paritaprevir/ritonavir, ombitasvir and dasabuvir; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; IQR, interquartile range; IU, international units; PI, protease inhibitor

80.4% (74/92) of patients achieved SVR_{12} after retreatment



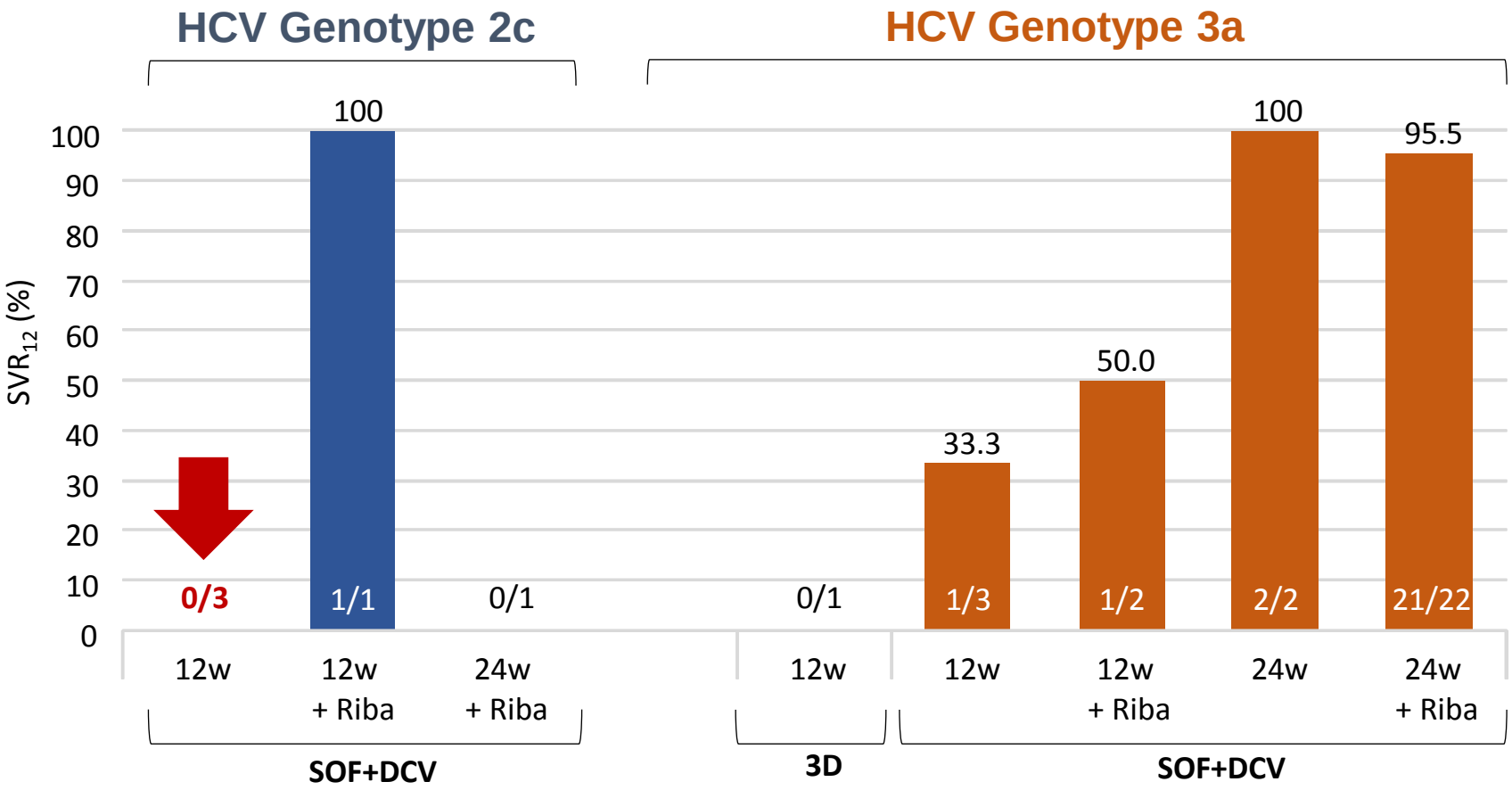
P-value was calculated by Fisher exact test.
BL, baseline; EOT, end of reatment; GRT, genotypic resistance test; GT, genotype; NS5Ai, NS5A-inhibitor; RASs, resistance associated substitutions; Riba, ribavirin; SVR, sustained viral response

The majority of patients were retreated with NS5Ai: overall SVR rate was 80.0%



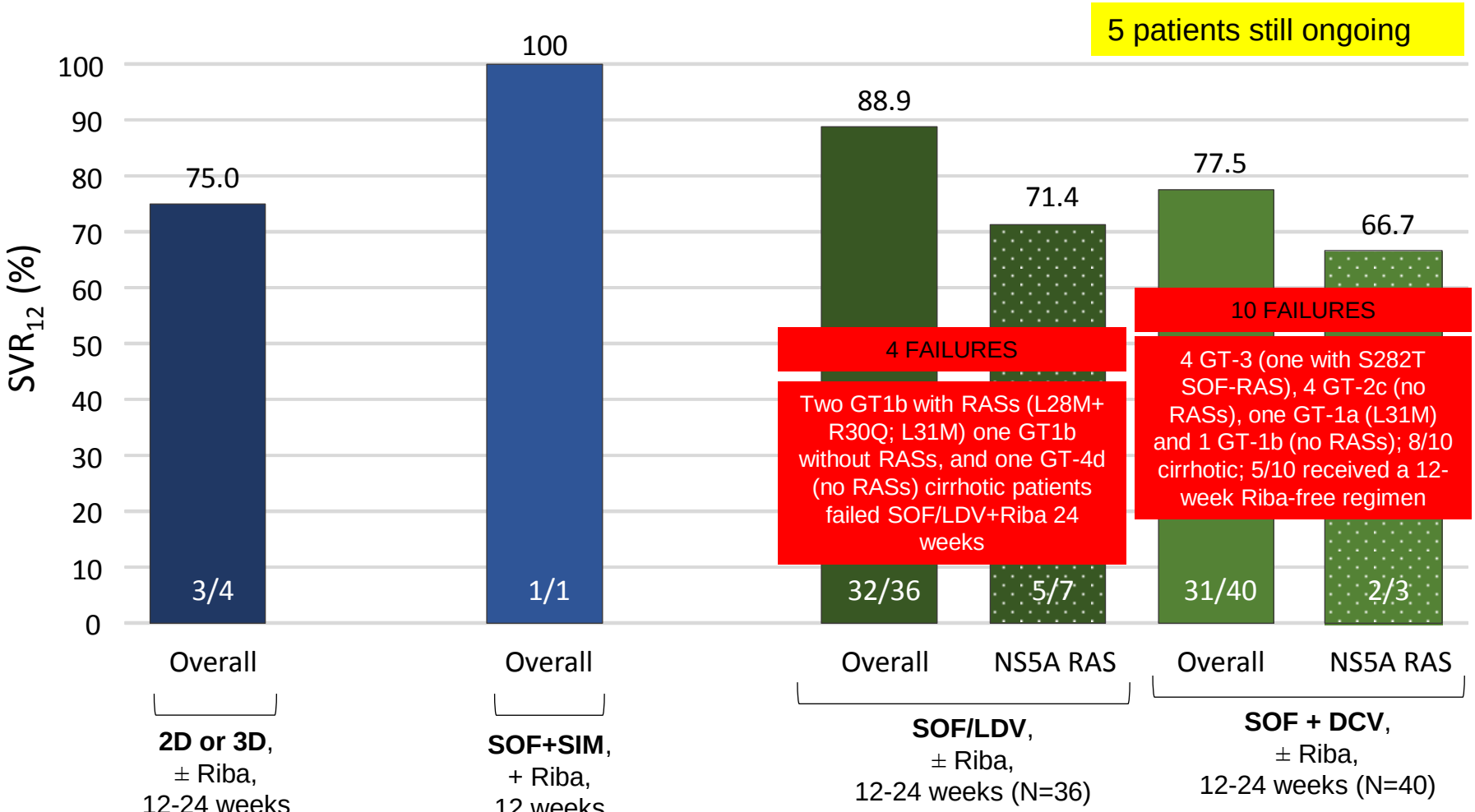
P-value was calculated by Fisher exact test.
GT, genotype; NS5Ai, NS5A inhibitor; Riba, ribavirin; SVR, sustained viral response

NS5Ai-retreatment strategies for GT-2c and GT-3a patients



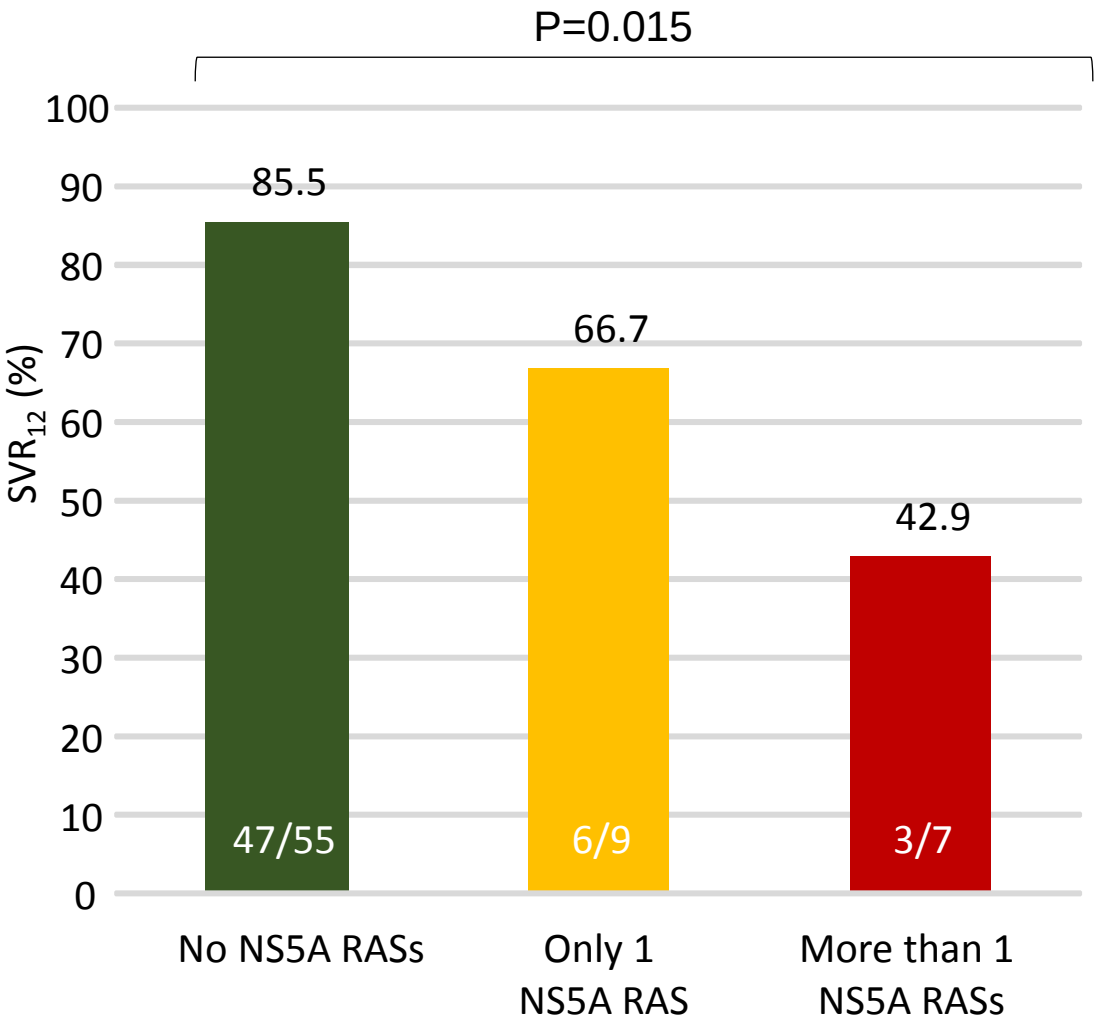
Ad interim results on «easy» retreatment of non-NS5A DAA-experienced patients

23 SOF+SIM-experienced patients, and 63 SOF-experienced patients were retreated …



2D, paritaprevir/ritonavir and ombitasvir; 3D, paritaprevir/ritonavir, ombitasvir and dasabuvir; DCV, daclatasvir; GT, genotype; LDV, ledipasvir; RAS, resistance associated substitution; Riba, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virological response.

Efficacy of NS5A-retreatment is reduced by baseline presence of NS5A-RASs (natural or derived by NS5Ai-exp)



Double NS5A RASs reduced SVR rates to 50% even in GT-1b patients.

Only 3/7 patients with Y93H/C RASs reached SVR.

P-value was calculated by Fisher exact test.
NS5Ai, NS5A inhibitor; RAS, resistance associated substitution; SVR, sustained viral response

Short regimens, and the presence of 1 or more NS5A RASs at baseline of a NS5Ai regimen were independently associated with virological failure

Variable	Univariable		Multivariable	
	OR (95% C.I.)	p-value	OR (95% C.I.)	p-value
Gender (M[a] vs. F)	0.50(0.16-1.58)	0.239	2.07 (0.34-12.62)	0.431
GT-3 infection (0[a] vs. 1)	1.62 (0.52-5.11)	0.689	0.8 (0.17-3.85)	0.783
GT-1 subtype (1a[a] vs. 1b)	2.37 (0.38-14.7)	0.352	0.61 (0.02-23.31)	0.789
Cirrhosis (0[a] vs. 1)	0.61 (0.12-3.06)	0.551	0.27 (0.02-3.46)	0.313
Length of retreatment (24 weeks[a] vs. 12 weeks)	**1.15 (1.04-1.27)**	**0.007**	**1.17 (1.01-1.36)**	**0.039**
Ribavirin use (0[a] vs. 1)	2.31 (0.72-7.39)	0.159	1.38 (0.25-7.74)	0.711
At least 1 BL NS5A RAS (0[a] vs. 1)	**0.22 (0.06-0.76)**	**0.016**	**0.16 (0.03-0.86)**	**0.033**
RVR (0[a] vs. 1)	0.97 (0.32-2.91)	0.953	1.16 (0.25-5.45)	0.854
Baseline HCV-RNA >800,000 IU/ml (0[a] vs. 1)	1.15 (0.39-3.34)	0.802	0.8 (0.17-3.85)	0.783

[a] Reference group (dummy).

BL, baseline; C.I., confidence interval; F, female; GT, genotype; IU, international units; M, male; OR, odds ratio; RAS, resistance associated substitution; RVR, rapid viral response (HCV-RNA undetectable at week 4 of treatment)

19 patients failed retreatment, and all those tested showed NS5A RASs

Patient ID	HCV GT	Metavir	First-line DAA regimen	RASs after first DAA-regimen/retreatment baseline			Second-line DAA regimen	Length (weeks)	Outcome of retreatment	RASs at retreatment failure		
				NS3	NS5A	NS5B				NS3	NS5A	NS5B
1331	1b	F4	SOF+SIM+RBV	D168V	-	L159F+ C316N	**SOF+SIM**	12	Relapse	D168V	**L31M+ Y93H**	L159F+ C316N
2068	3a	F4	SOF+SIM+RBV	Q80K	Y93H	-	**3D**	12	Non-responder	n.a.	n.a.	n.a.
1304	1a	F4	SOF+SIM	S122G+D168V	L31M	-	**SOF+DCV+RBV**	24	Relapse	n.a.	n.a.	n.a.
2098	1b	F4	SOF+RBV	n.a	-	-	**SOF+DCV+RBV**	24	Relapse	n.a.	n.a.	n.a.
1000	1b	F4	DCV+SIM	D168V	L31V+Y93H	-	**SOF+DCV+RBV**	24	Relapse	n.a.	L31V+ Y93H	n.a.
1967	2c	F4	SOF+RBV	-	-	-	**SOF+DCV+RBV**	24	Relapse	n.a.	n.a.	n.a.
2704	2c	F4	SOF+RBV	-	-	-	**SOF+DCV**	12	Relapse	n.a.	n.a.	n.a.
2134	3a	F4	SOF+RBV	-	-	-	**SOF+DCV+RBV**	24	Relapse	n.a.	**Y93H**	n.a.
490	3a	F4	SOF	n.a	n.a	S282T	**SOF+DCV**	11	Breakthrough	-	**Y93H**	-
2131	3a	F3	SOF+RBV	-	-	-	**SOF+DCV**	12	Breakthrough	n.a.	n.a.	n.a.
2184	1a	F4	DCV+SIM	D168E+Q80R	L31M+Y93C	n.a	**SOF/LDV+RBV**	24	Relapse	n.a.	n.a.	n.a.
2183	1b	F4	SOF+SIM	-	-	-	**SOF/LDV+RBV**	24	Relapse	n.a.	n.a.	n.a.
2193	1b	F4	SOF+SIM	D168V	L31M	-	**SOF/LDV+RBV**	24	Relapse	n.a.	L31M+ **Y93H**	n.a.
2238	1b	F4	SOF+SIM	D168V	L28M+R30Q	-	**SOF/LDV+RBV**	24	Relapse	n.a.	n.a.	n.a.
2022	4d	F4	SOF+RBV	-	-	-	**SOF/LDV+RBV**	24	Relapse	-	**Y93H**	-
663	4d	F4	DCV+SIM+RBV	D168V	M31V+Y93H	-	**SOF/LDV+RBV**	24	Relapse	D168V	M31V+ Y93H	n.a.

8/12 tested showed multiple and/or multiclass RASs …

«-» indicates no RASs; n.a., not available

Conclusions

- Real-life retreatment of DAA failing patients following current EASL guidelines and baseline resistance testing leads to good SVR_{12} rates (85.9%).
- The majority of patients received a NS5A-containing 2nd line regimen, whose efficacy was affected by:
  1. Short duration of retreatment (above lack of ribavirin association)
  2. Presence of one or more NS5A RAS
  3. Previous NS5Ai-experience → Beware of reusing the same DAA class!!

Over time, they might increase in number …

- Optimization of retreatment regimens for DAA-failed patients takes advantage of baseline resistance testing.

  In this «fragile» population, regimens longer and with ribavirin (whenever possible) should be preferred (as recommended by current international guidelines).

HCV Virology Italian Resistance Network Study Group: VIRONET-C

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