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I fallimenti al primo trattamento con DAA: quali possibilità terapeutiche

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- Quanti e perchè
- RAVs, RASs, RAPs or RATs
- Caratteristiche dei pazienti con fallimento a DAA IFN free in Italia
- Schemi di ritrattamento:
  - Terapie attuali
  - Terapie future

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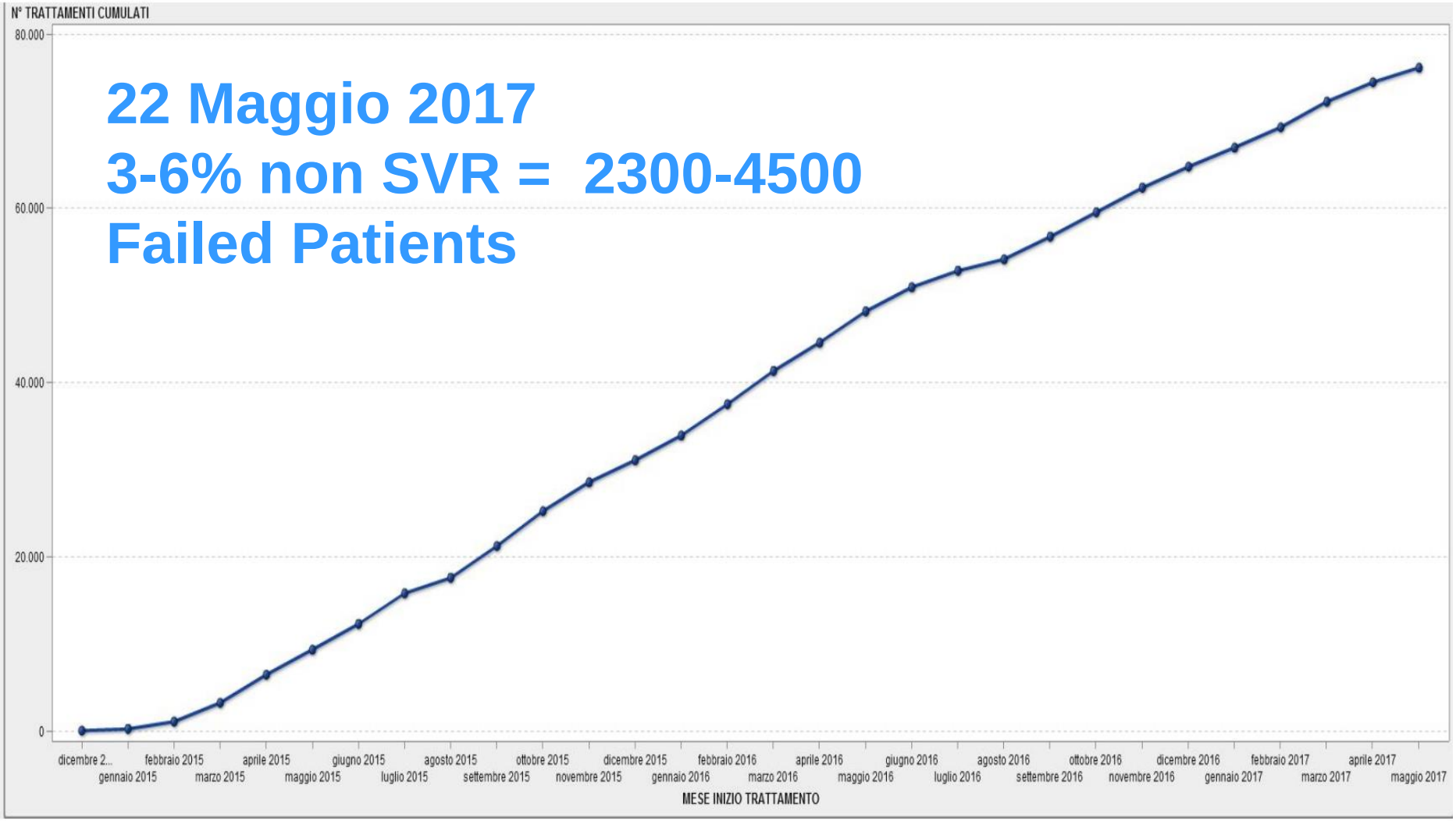
Trend cumulativo dei trattamenti avviati



22 Maggio 2017
3-6% non SVR = 2300-4500
Failed Patients

Agenzia Italiana del Farmaco
AIFA

76.140 «avviati» sono i trattamenti (solo pazienti eleggibili) con almeno una scheda di Dispensazione farmaco

Failure & Susceptibility to antiviral therapy.

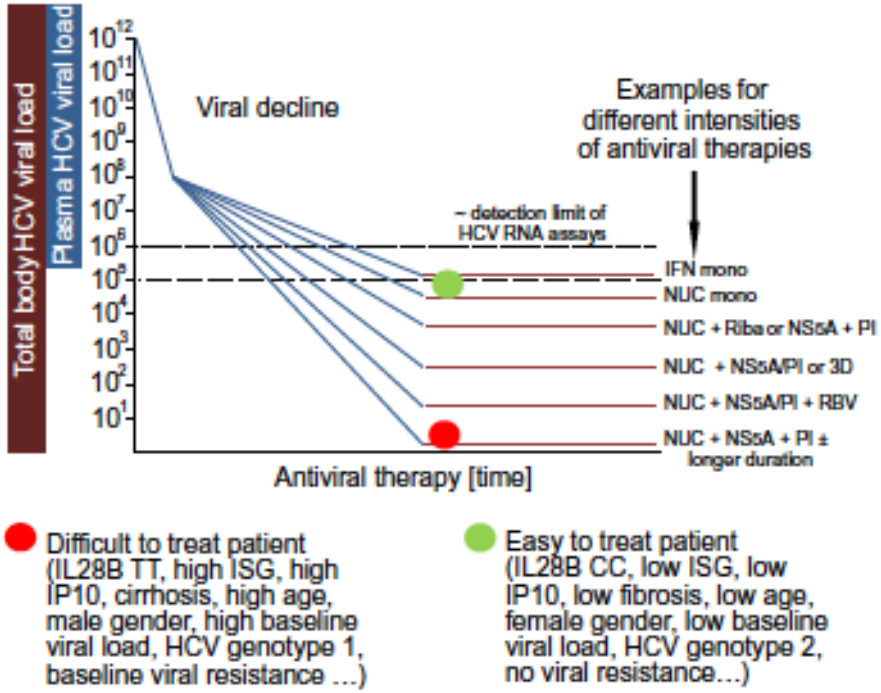
Different levels of suppression of HCV RNA are required for final eradication of the virus by the immune system

Depending on:

- the **used antiviral agents**,
- **duration of treatment & RBV use**
- viral- related factors:
  - **HCV Genotypes**
  - **RASs**
  - **Viremia**
- host-related factors:
  - **IL28b, IP-10, ISG**
  - **Fibrosis**
  - **Age & gender**

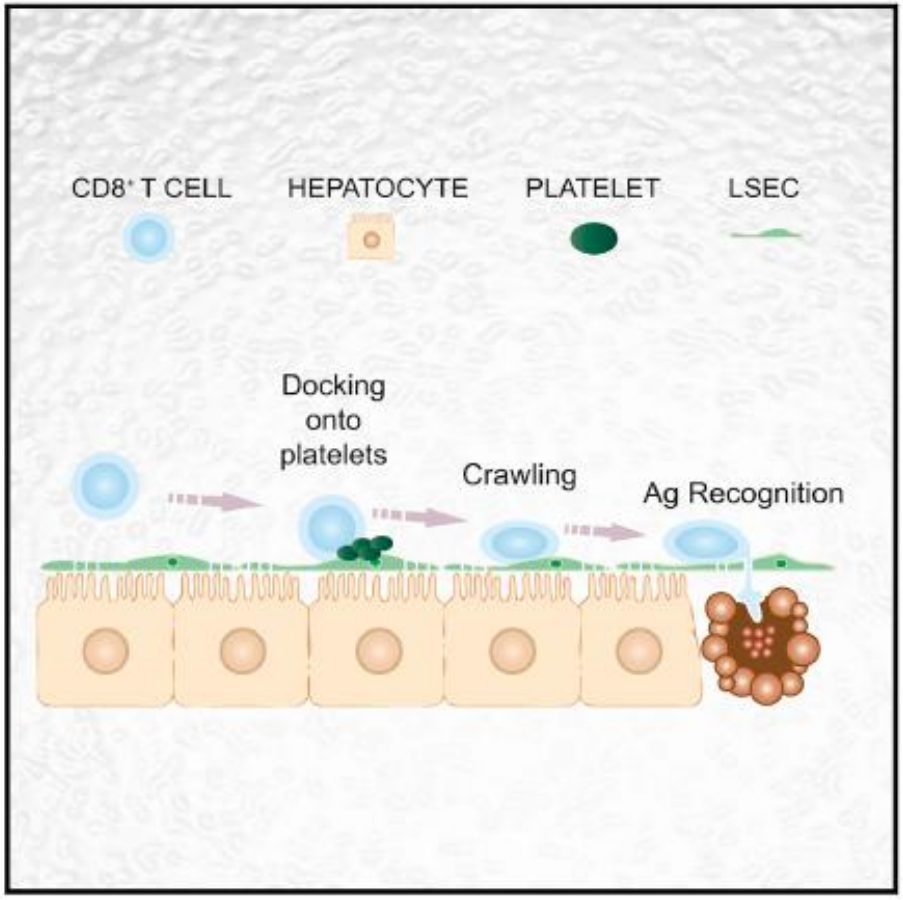
.

Failure:
- **Breakthrough**
- **Relapse**



Immunosurveillance of the Liver by Intravascular Effector CD8+ T Cells

- Circulating effector cytotoxic T cells recognize antigen and kill virus-infected hepatocytes without need to migrate into the tissue. Rather, they arrest within liver sinusoids, docking onto platelets, from where they probe hepatocytes for the presence of antigens, a process that is inhibited during liver fibrosis.



Guidotti et al., 2015, Cell 161, 486–500

Several factors are involved in DAA treatment failure

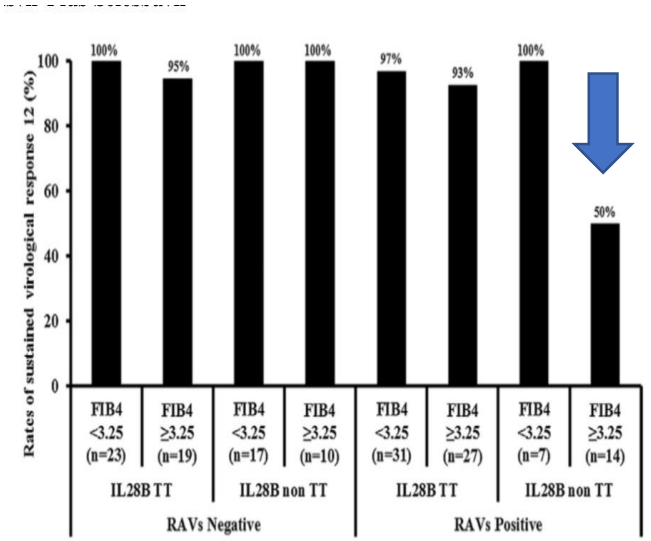
Viral factors
(e.g. HCV genotype, subtype, and baseline RAS)

Socioeconomic factors
(e.g. lifestyle)

Host factors
(e.g. cirrhosis status and other comorbidities)

Regimen-related factors
(e.g. DDIs, adherence, DAA barrier-to-resistance)

SVR12 rates by combination of three factors (NS3 and/or NS5A resistance-associated variants (RAVs), IL28B rs8099917 genotype, and



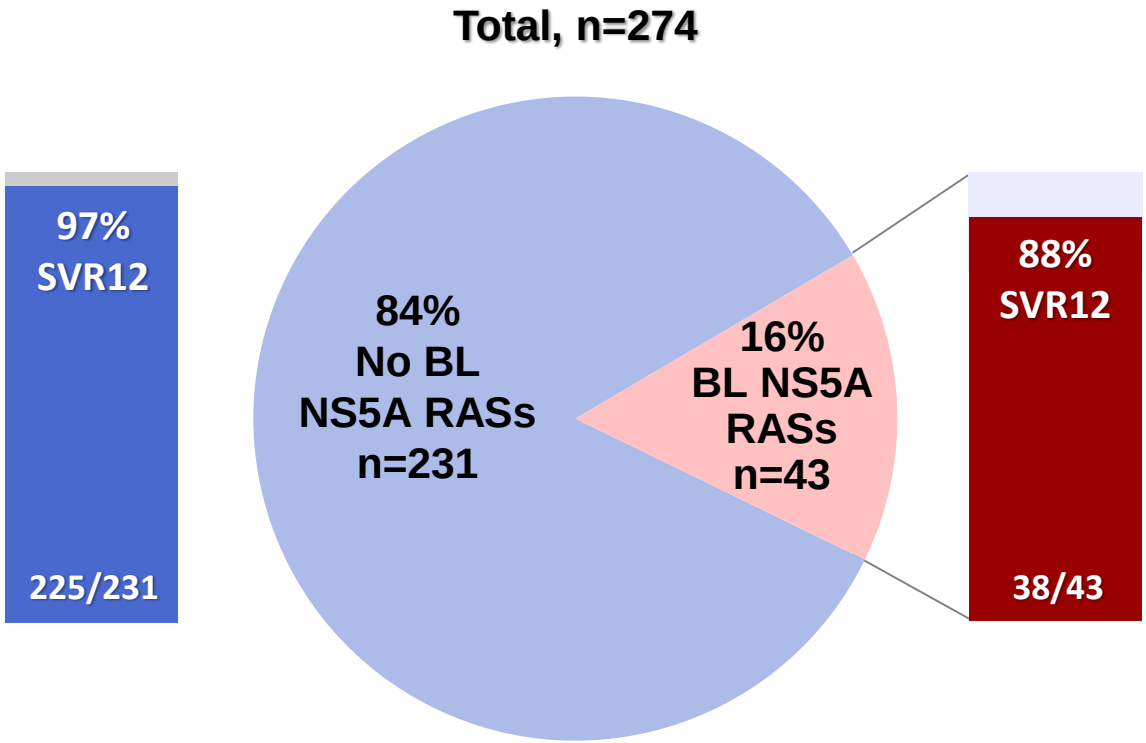
Buti M, et al. Clin Mol Hepatol 2016; 22:432-438;
Soriano V, et al. Expert Opin Pharmacother 2016; 17:217–229.

Akuta N et al. J Med Virol 2017; 89:284–290

Sofosbuvir + Velpatasvir

ASTRAL-3– Phase III, TN and TE (26%), Gt 3, 30% cirrhosis, 12 weeks

Resistance analysis (1% cutoff, deep sequencing)



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

(Foster et al., N Engl J Med 2015;373:2608-17)

Sofosbuvir + Velpatasavir
Integrated Efficacy: SVR12 by Number of Negative Predictive Factors

Patients, n/N (%)	GT1 n=328	GT2 n=238	GT3 n=277	GT4 n=116	GT5 n=35	GT6 n=41	
Overall							35
0 factor							9
1 factor	148/151 (98)	80/81 (99)	108/111 (97)	31/31 (100)	21/21 (100)	17/17 (100)	405/412 (98)
2 factors							342/347 (99)
3 factors	44/45 (98)	30/30 (100)	29/34 (85)	25/25 (100)	4/4 (100)	4/4 (100)	136/142 (96)
4 factors	2/2 (100)	3/3 (100)	0/1 (0)	9/9 (100)	0	0	14/15 (93)

4 predictors of treatment failure. High HCVRNA, advanced fibrosis, NS5A RASs, previous failure of PEGIFN + R

In HCV GT 3 > 2 factors vs ≤2 factors p< 0.001

Baseline factors analysed included presence of NS5A RAVs, presence of cirrhosis, baseline HCV RNA ≥800 IU/mL, and prior HCV treatment.

High SVR12 rates with SOF/VEL for 12 weeks were achieved by patients with multiple factors historically associated with virologic failure

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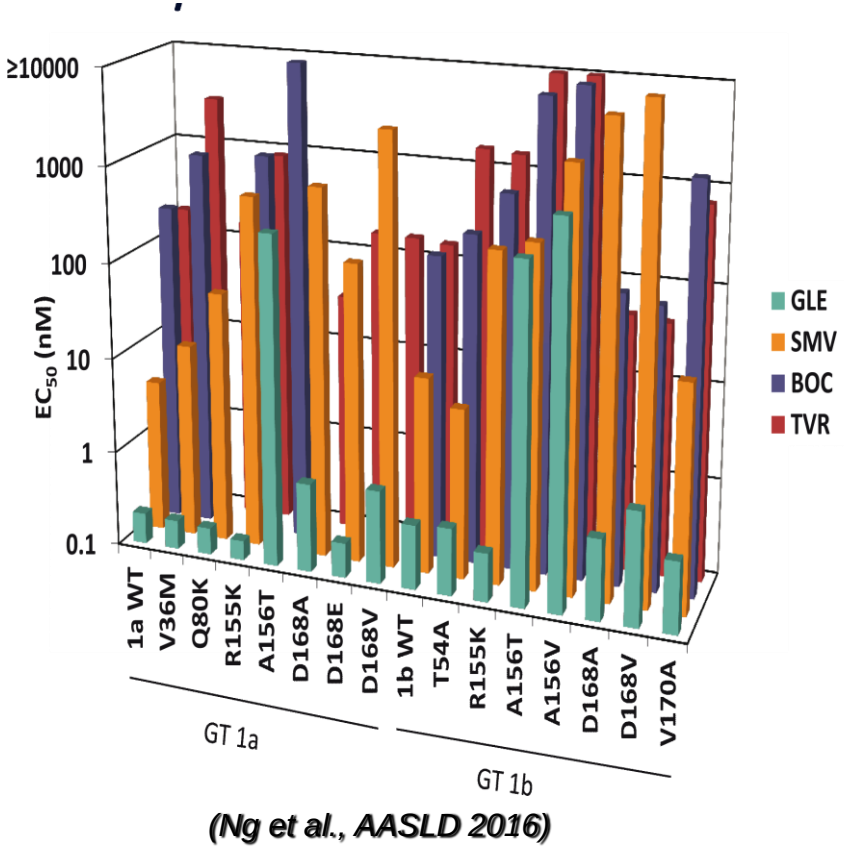
Conditions for a broad use of HCV resistance testing in clinical practice

- A **standardized assay** should be available as a **purchasable kit**, **externally validated** for its performance and **easy to routinely used** in any virology laboratory with experience in molecular biology. Whatever the technology used, the assay should be able to reliably report the presence of RASs with **a validated and repeatable sensitivity of 15%** equivalent to population sequencing. (ii)
- **Interpretation and reporting** of HCV resistance data should be **homogenized and standardized** through **recommendations by an international organization.**
- **Clinically relevant RASs** should be **clearly identified**, and only these RASs should be reported and used for treatment decisions.
- **Guidelines** should be provided by international societies to guide **treatment decisions based on resistance testing results**, on the basis of data from **clinical trials and real-life studies** reporting strong predictive values of the different RAS profiles.

Pawlotsky JM Gastroenterology 2016

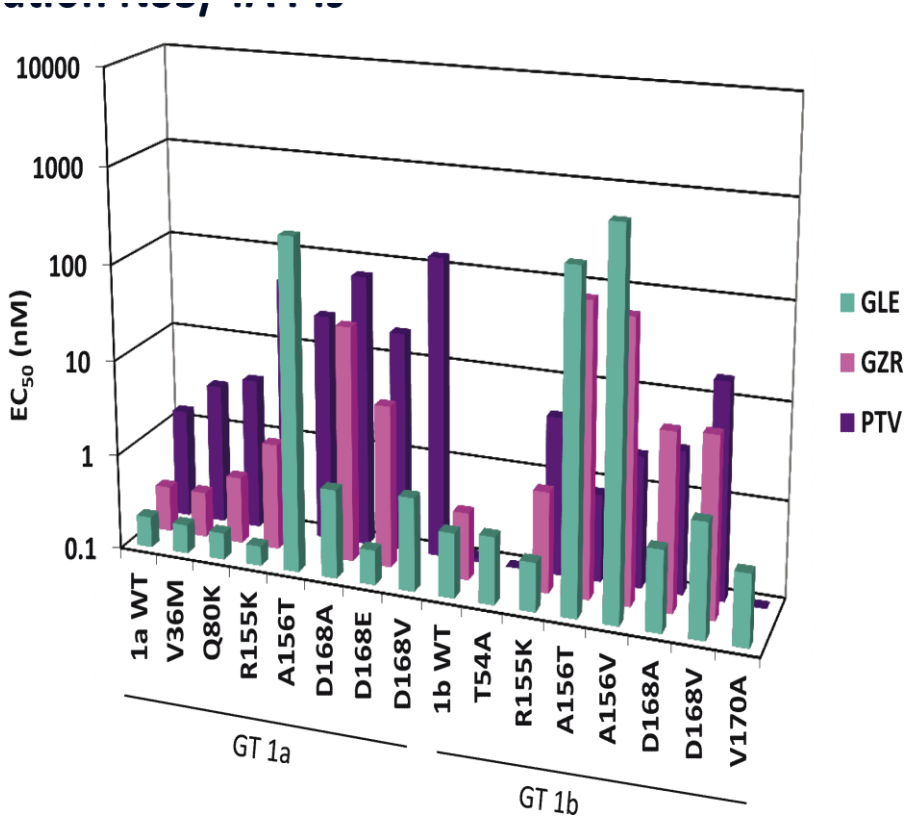
Protease Inhibitor Resistance Profile

GLE vs 1st-wave PIs



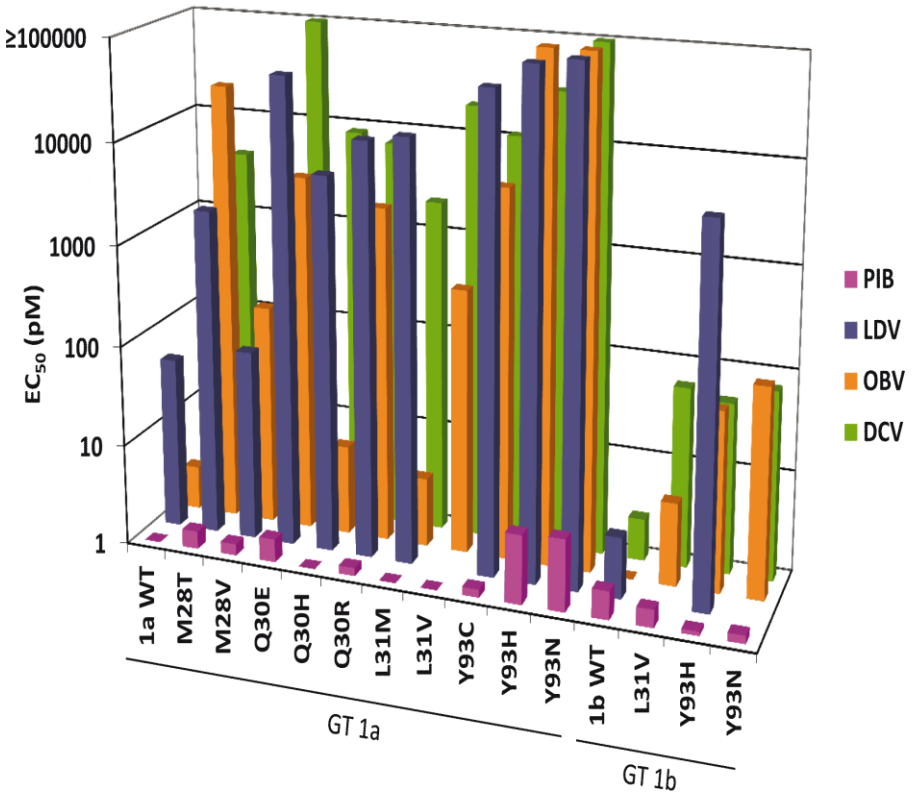
(Ng et al., AASLD 2016)

GLE vs 2nd-wave PIs

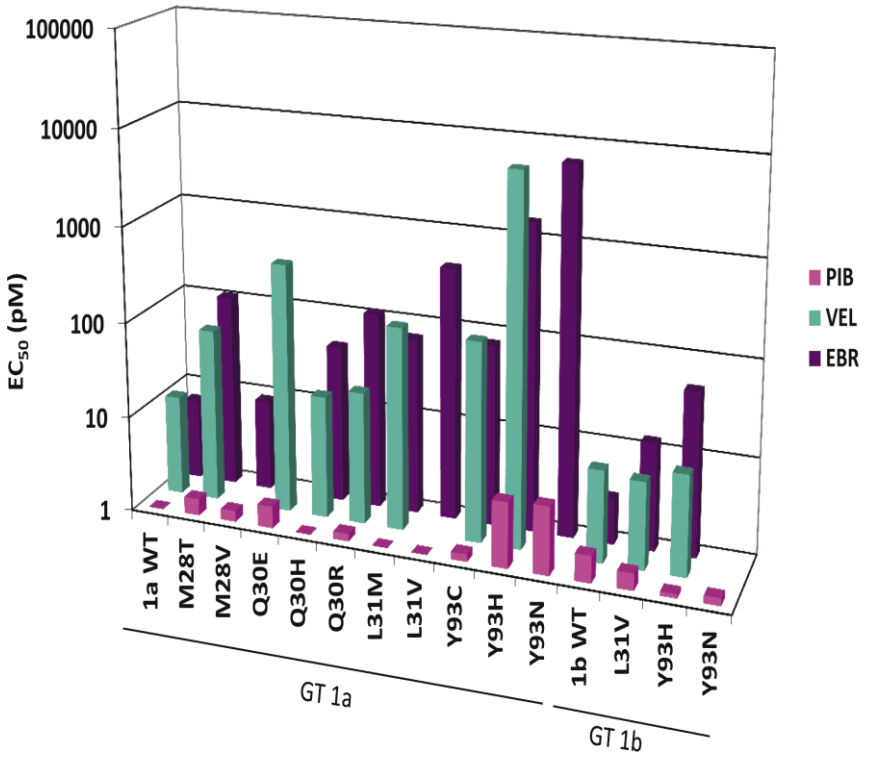


NS5A Inhibitor Resistance Profile

PIB vs 1st-gen NS5A inhibitors



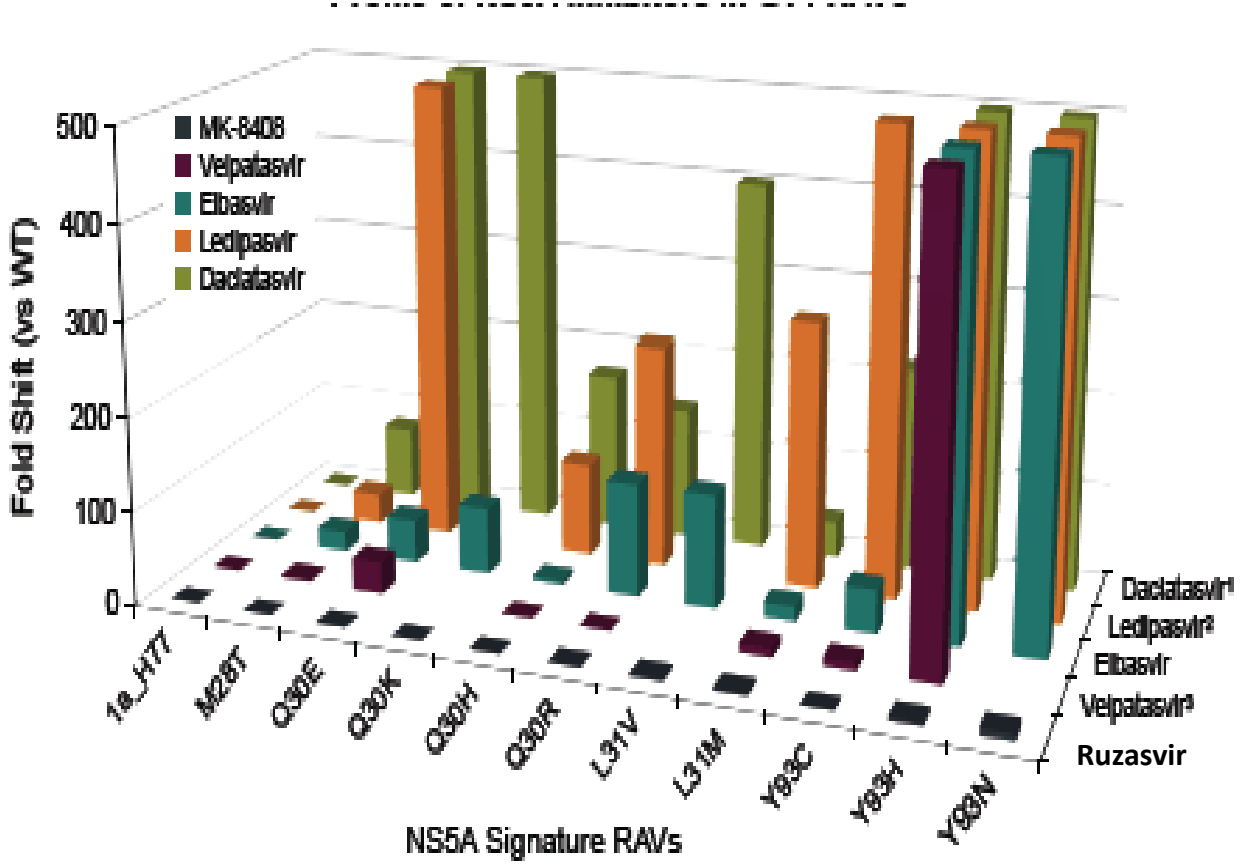
PIB vs 2nd-gen NS5A inhibitors



(Ng et al., AASLD 2016)

Ruzasvir Resistance Profile

In vitro activity against resistant variants



NB: Residues 32 and 38 behind molecule

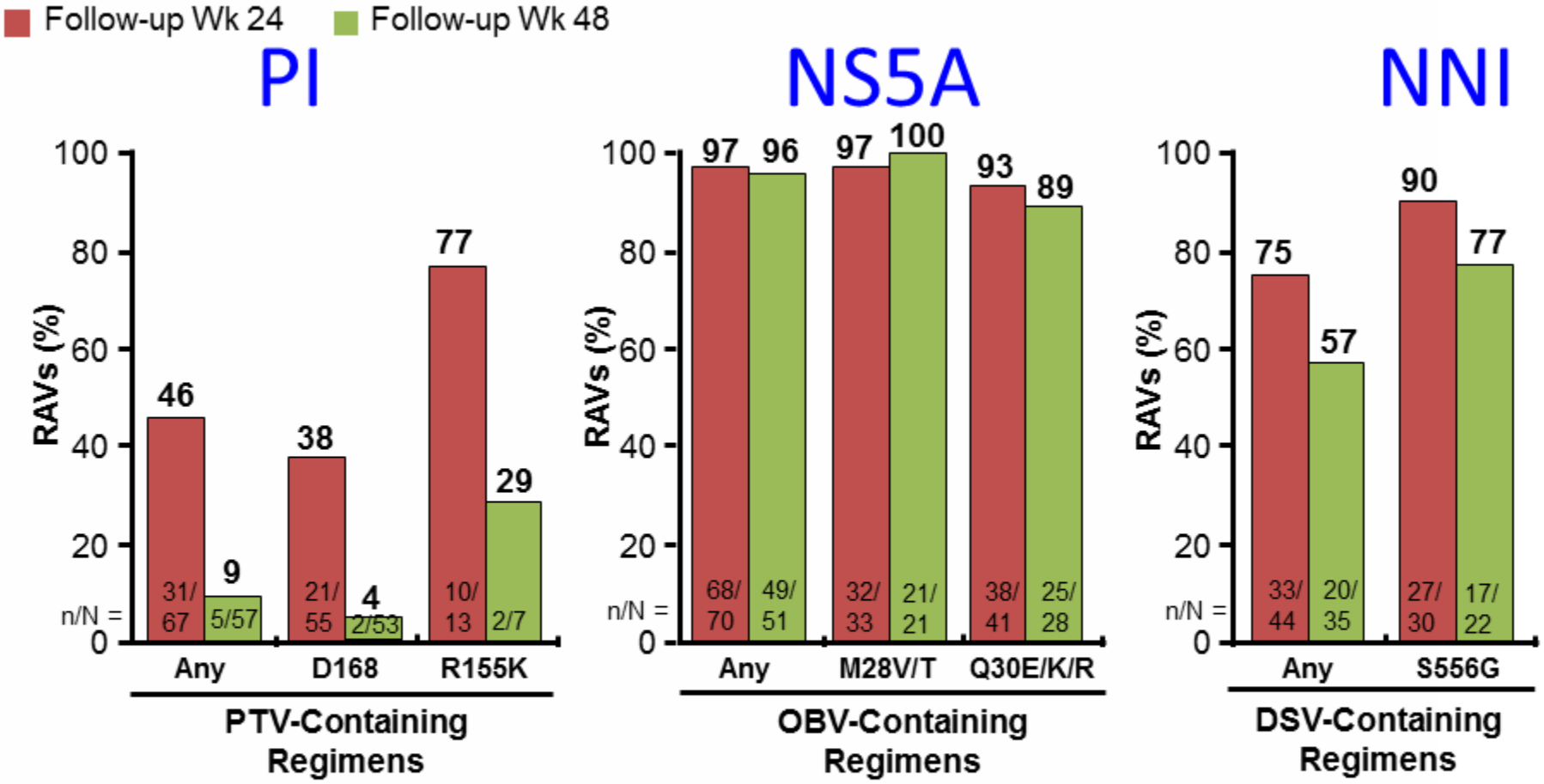
(Asante-Appiah et al., AASLD 2015)

NS5A inhibitors Activity Against Common GT1a and GT3 Single-Position NS5A Substitutions

NS5A inhibitor	Fold change EC_{50}						
	GT1a NS5A Variants				GT3 NS5A Variants		
	Q30E	L31M/V	H58D	Y93H/N	M28T	A30K	Y93H
Pibrentasvir[1,2]	**2.4**	**1.1–1.3**	**1.1**	**6.7–7.1**	**0.4**	**1.1**	**2.5**
Velpatasvir[6,7]	37	2.1–9	N/A	81–609	N/A	10–100	>100
Ledipasvir[3–5]	3279	393–2787	>1000	4918	N/A	>1000	>1000
Daclatasvir[8,9]	25,205	341–3386	500	5432–47,477	46	56–62	2738–2752
Elbasvir[7,10]	50	125	N/A	600–2000	N/A	50	486
Ombitasvir[11]	1326	2	243	41,383–66,740	423	N/A	6728

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.

Not all RAS are created equal



RAS Persistence aka fitness: **NS5A>NNI>>PI>>>>Nuc**

Evaluation of IFN Free treatment failure

- Patients' characteristics
  - Fibrosis stage & disease stage
  - IL28b SNP
  - Previous history of treatment failure
- Virological data
  - RASs pre treatment
  - RASs at failure and post treatment
  - Baseline HCVRNA
  - HCV Genotype and subtype
- Treatment data
  - Drugs: class and specific drug
  - Ribavirin use
  - Duration

Resistance testing/ Evaluation of RASs

- Method Next Gen sequencing or Population sequencing (15% quasispecies) → Vironet quality control
- Evaluation of RASs pattern:
  - HCV genotype-subtype by sequencing
  - RASs in NS5A, NS3, NS5B
  - Drug specific RASs

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PS-154

Multiclass HCV resistance to direct acting antivirals in real life interferon-free regimens failures advocates for tailored second-line therapies

V.C. Di Maio, V. Cento, I. Lenci, M. Aragri, S. Barbaliscia, S. Francioso, S. Paolucci, M. Melis, G. Verucchi, N. Coppola, C.F. Magni, V. Micheli, T. Pollicino, T. Ruggiero, F. Santopaolo, S. Landonio, A. Mancon, M. Starace, A. Bertoli, F.P. Antonucci, C. D'Ambrosio, V. Calvaruso, F. Morisco, C. Pasquazzi, I. Maida, A. Picciotto, A. Di Biagio, B. Bruzzone, L. Sticchi, V. Ghisetti, R. Cozzolongo, D. Romagnoli, V. Boccaccio, A. Grieco, J. Vecchiet, G. D'Ettorre, M. Merli, G.B. Gaeta, A. Ciancio, L. Marinaro, P. Andreone, G. Barbarini, R. Gulminetti, V. Pace Palitti, P. Tarquini, M. Puoti, V. Sangiovanni, G. De Stefano, A. Giorgini, M. Paoloni, N. Caporaso, S. Babudieri, G. Gubertini, S. Bruno, M. Andreoni, A. Pellicelli, G. Parruti, G. Raimondo, F. Baldanti, A. Craxì, M. Angelico, C.F. Perno, F. Ceccherini-Silberstein
on behalf of HCV Virology Italian Resistance Network Group (VIRONET-C)

Baseline characteristics of 310 HCV failures included in the analysis

Patients, N		310
Males, N (%)		240 (77.4)
Age (years), Median (IQR)		58 (52-69)
Liver Transplant, N (%)[a]		7 (3.4)
Hepatocellular carcinoma, N (%)[a]		28 (12.1)
Cirrhotic patients, N (%)		251 (81.0)
Stiffness at baseline (kPa), Median (IQR)		17.9 (12.5-25.9)
HIV coinfection, N (%)[a]		14 (6.2)
Naïve patients, N (%)[a]		47 (34.1)
Treatment experienced, N (%)[a]		91 (65.9)
	Breakthrough	7 (7.7)
	Non-responder	35 (38.5)
	Relapse	29 (31.9)
	Other	20 (21.9)
	DAA experienced[a]	22 (15.9)
Unknown previous treatment		172 (55.5)
Baseline HCV-RNA (logIU/ml), Median (IQR)[a]		6.0 (5.4-6.5)
Baseline ALT (IU/ml), Median (IQR)[a]		76 (52-131)
HCV genotype/subtype	1a	70 (22.6)
	1b	119 (38.4)
	2 (a-b-c)	33 (10.6)
	3 (a-h)	52 (16.8)
	4 (a-d-n-v)	36 (11.6)

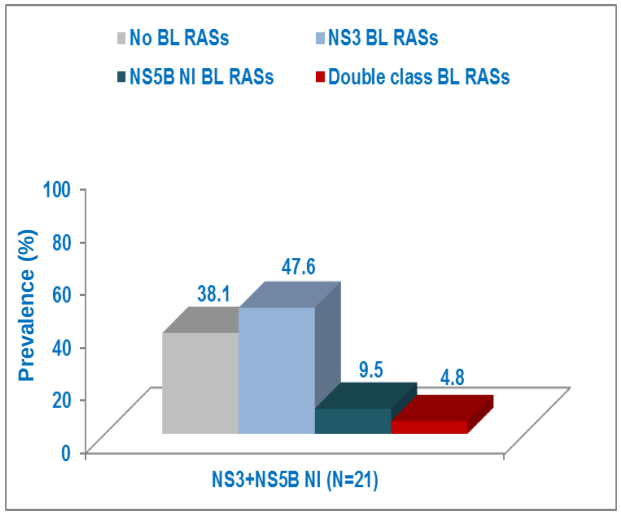
15/310 (4.8%) patients were found infected with a different HCV genotype at failure

Notably, 10 patients previously classified as infected with HCV-1 were actually infected with HCV-2 and HCV-3, 9/10 failed a 3D±RBV regimen and all presented RASs at failure

ID Patient	Pre-therapy genotype by commercial assay	Genotype by sequencing at failure	DAA regimen	DAA response	Failure RASs		
					NS3	NS5A	NS5B
1497	**1a**	**3a**	3D+RBV	Non-responder		**Y93H**	
2150	**1a**	**3a**	3D+RBV	Breakthrough	**Q80K**	**Y93H**	
2068	**1b**	**3a**	3D	Non-responder	**Q80K**	**Y93H**	
1424	**1b**	**3a**	3D+RBV	Non-responder		**Y93H**	
2140	**1b**	**3a**	3D+RBV	Non-responder		**A30K**	
2353	**1**	**3a**	3D	Non-responder		**Y93H**	
1823	**1b**	**2c**	3D+RBV	Non-responder	**D168V**		
2020	**1b**	**2c**	3D	Non-responder	**D168V**	**F28C**	
2623	**1b**	**2c**	3D	Relapse		**F28C**	
2890	**1b**	**2c**	SMV+SOF	Relapse		**L31M**	
2204	2	1b	LDV+SOF+RBV	Relapse		R30Q+L31I+Y93H	C316N
2886	2	1b	SOF+RBV	Relapse	Y56F		C316N
2153	2	3a	SOF+RBV	Relapse		A30K+L31F	
1111	4	1a	2D+RBV	Breakthrough	V36M+Y56H	M28T	
45	4	3a	SMV+SOF	Relapse	D168K		

29/48 (60.4%) patients showed at least one baseline RAS specific for the treatment used

NS3+NS5B

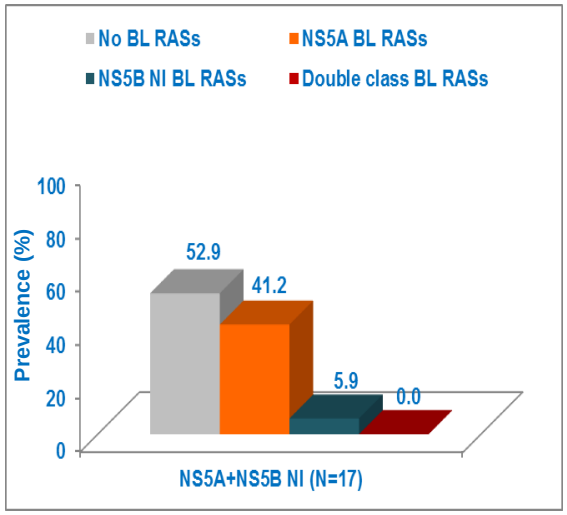


(HCV-1a N=11, HCV-1b N=8, HCV-4d N=2)

Q80K: 36.4% in HCV-1a
R155K: 18.2% HCV-1a

L159F+C316N: 37.5% HCV-1b

NS5A+NS5B

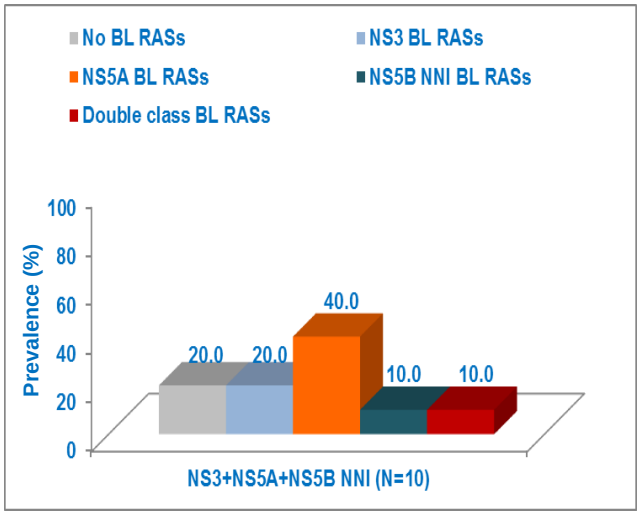


(HCV-1a N=5, HCV-1b N=5, HCV-3a N=5, HCV-4a/d N=2)

Y93H: 20.0% HCV-1b
Y93H: 40.0% HCV-3a
Y93H: 50.0% HCV-4a/d

L159F+C316N: 20.0% HCV-1b

NS3+NS5A+NS5B



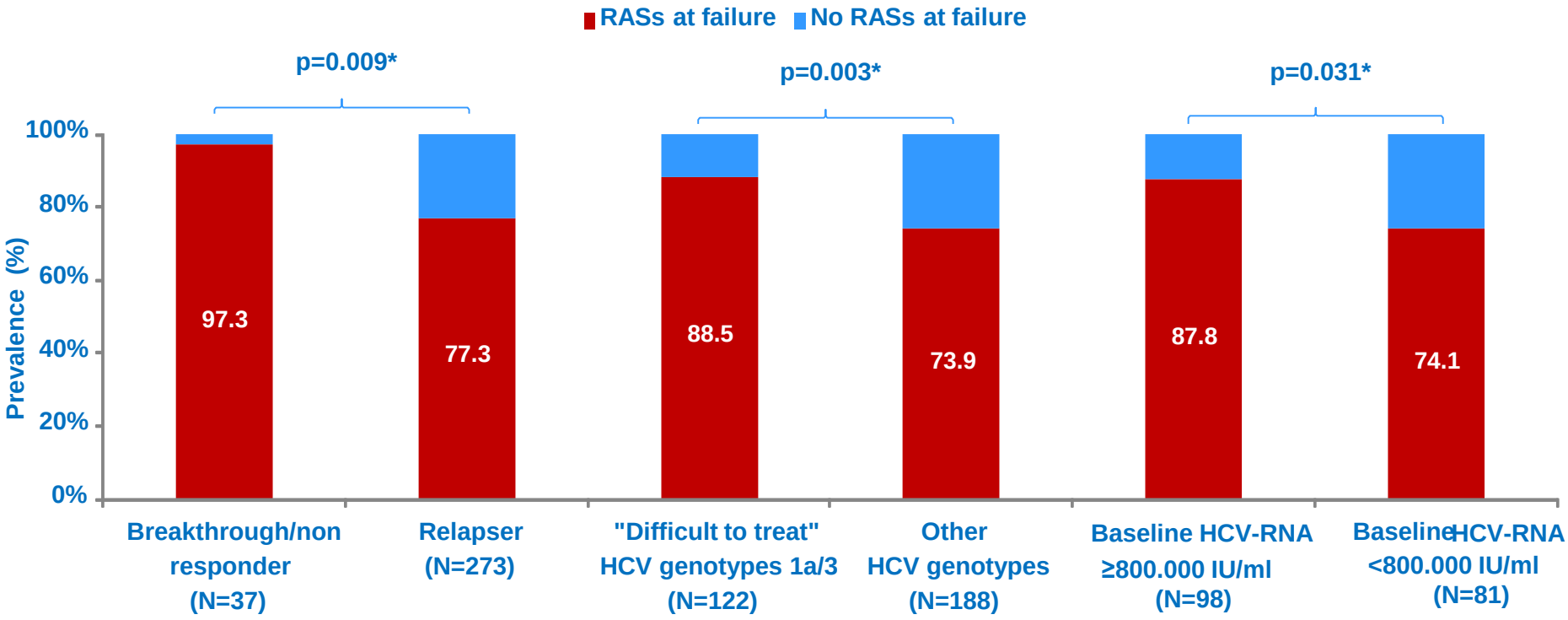
(HCV-1a N=4, HCV-1b N=6)

Q80K: 25.0% HCV-1a
R155K: 25.0% HCV-1a

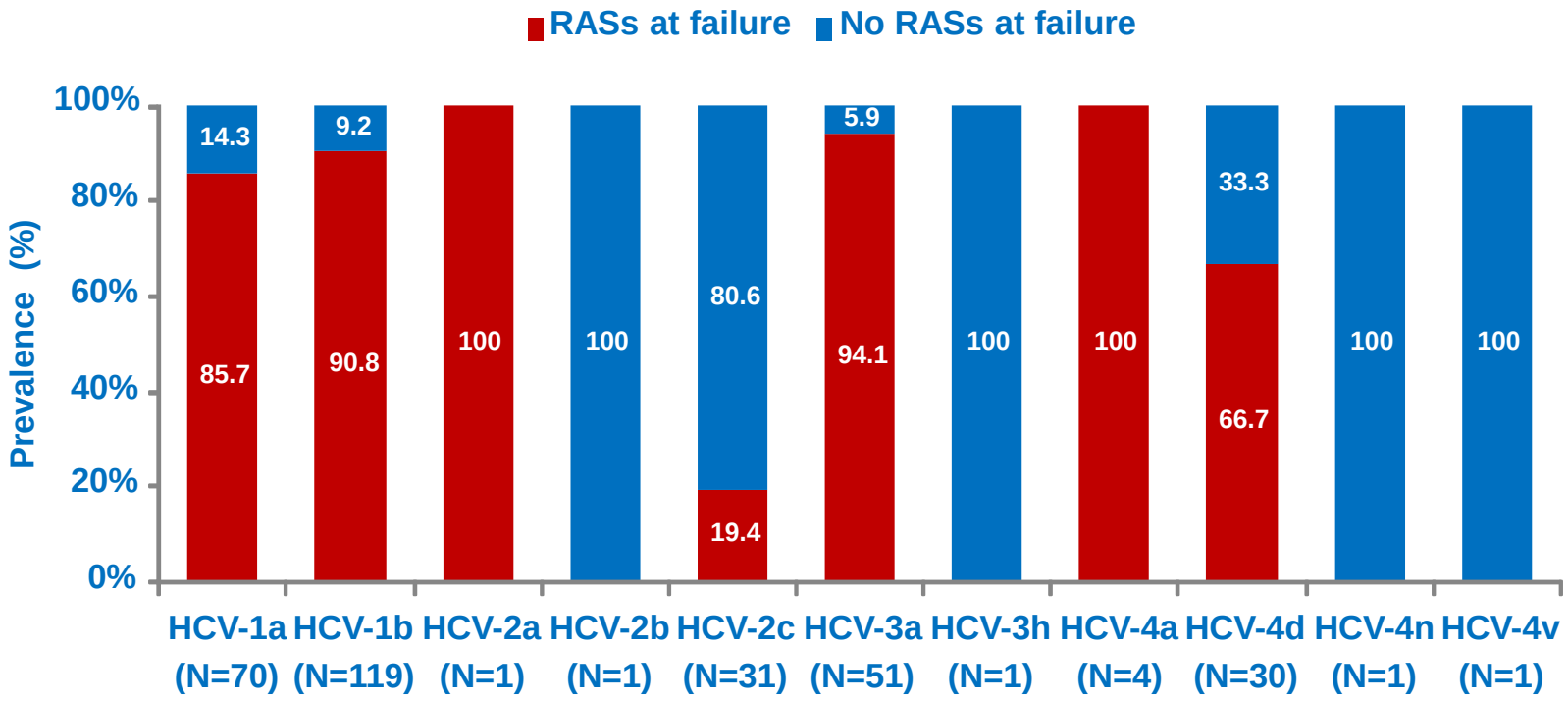
Y93H: 50.0% HCV-1b

Overall, 247/310 patients (79.7%) showed at least one RAS related to the DAA-regimen at failure

RASs prevalence was significantly higher in breakthrough/non-responders (97.3%) than in relapsers (77.3%) and in patients infected with “difficult to treat” HCV genotypes 1a/3 (88.5%) compared to other HCV genotypes (73.9%).



RASs prevalence at failure was high in almost all HCV genotypes/subtypes



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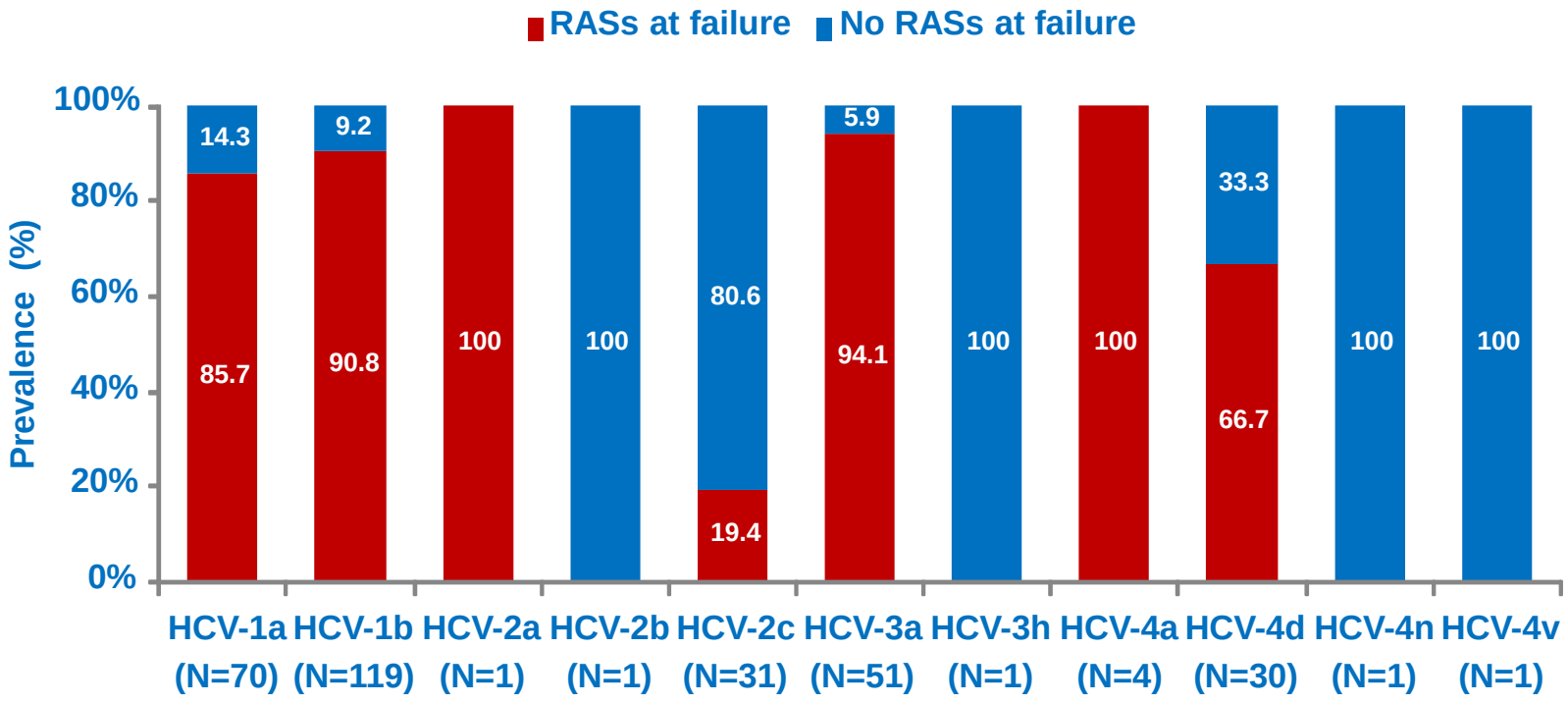
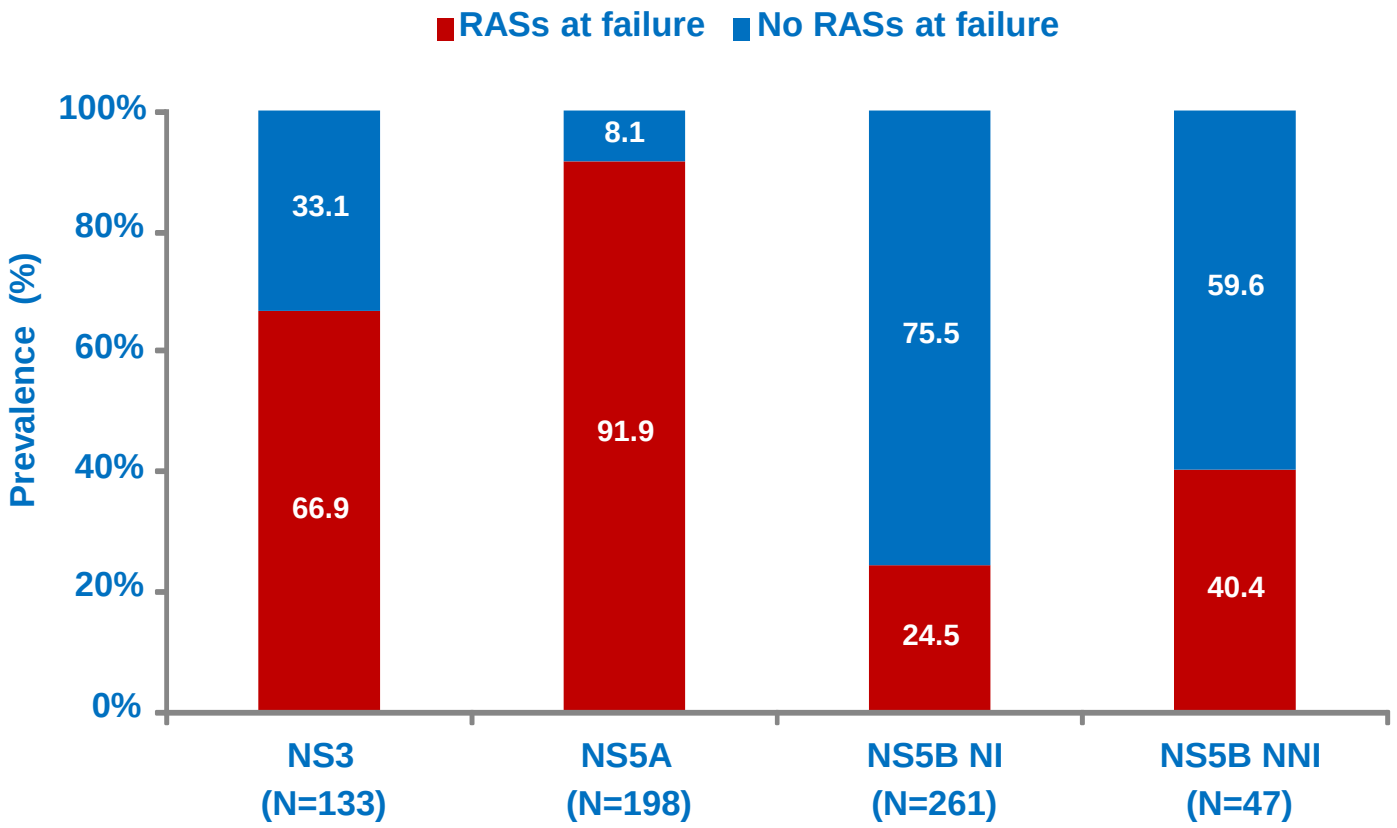
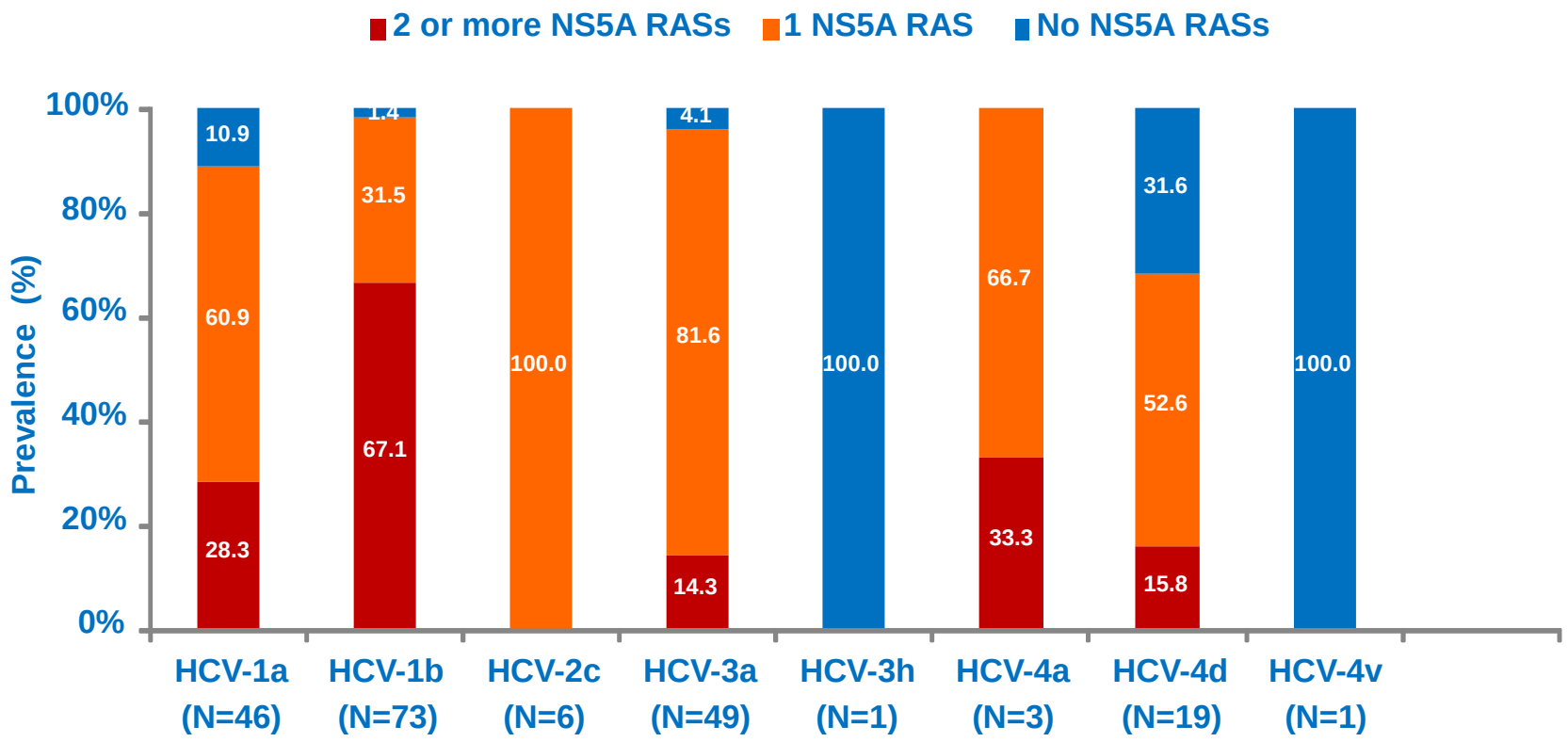


And…..

RASs prevalence was found in all genes tested: NS5A very frequent, NS3 frequent, NS5B less common



73/198 (36.9%) of NS5A-failing patients presented ≥2 NS5A-RASs



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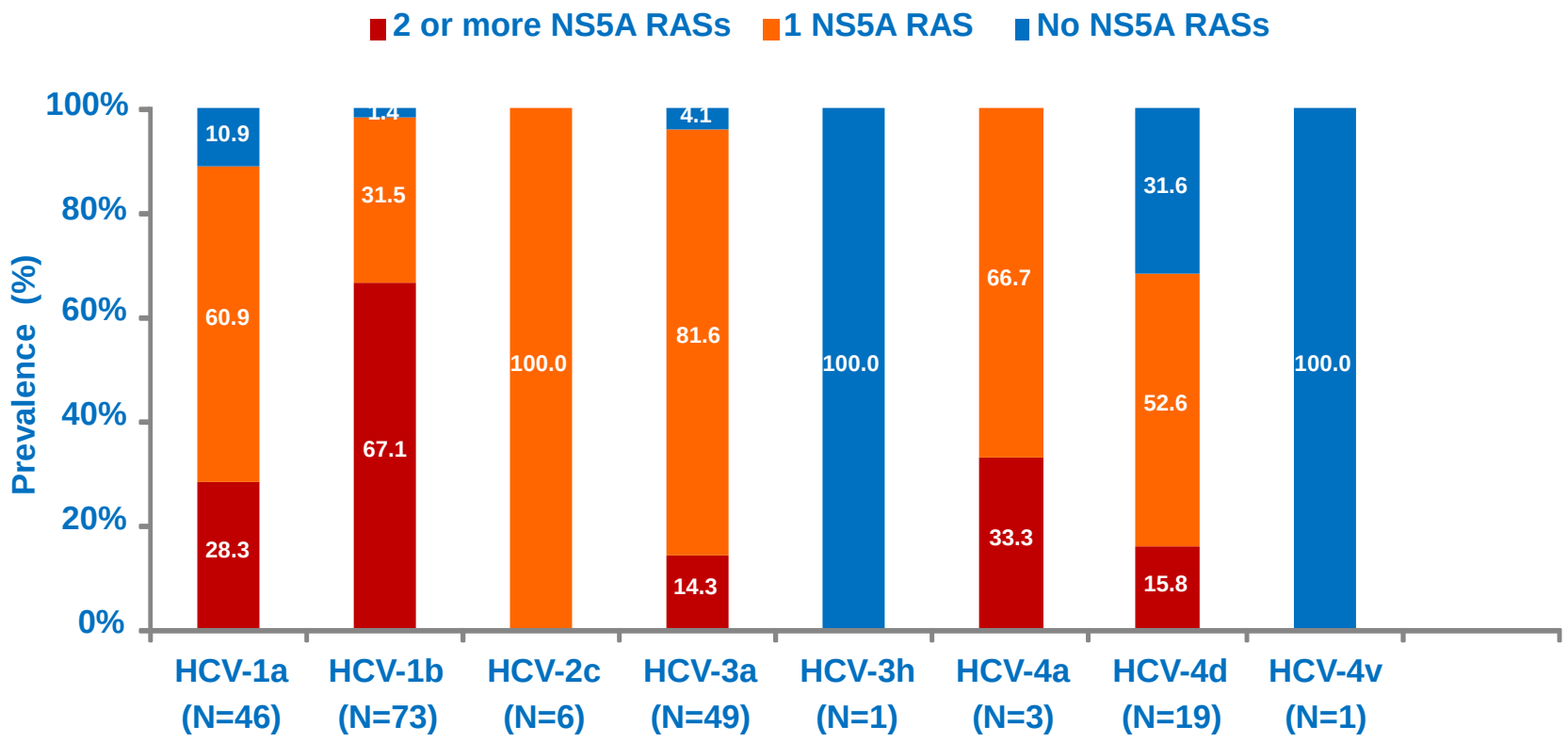
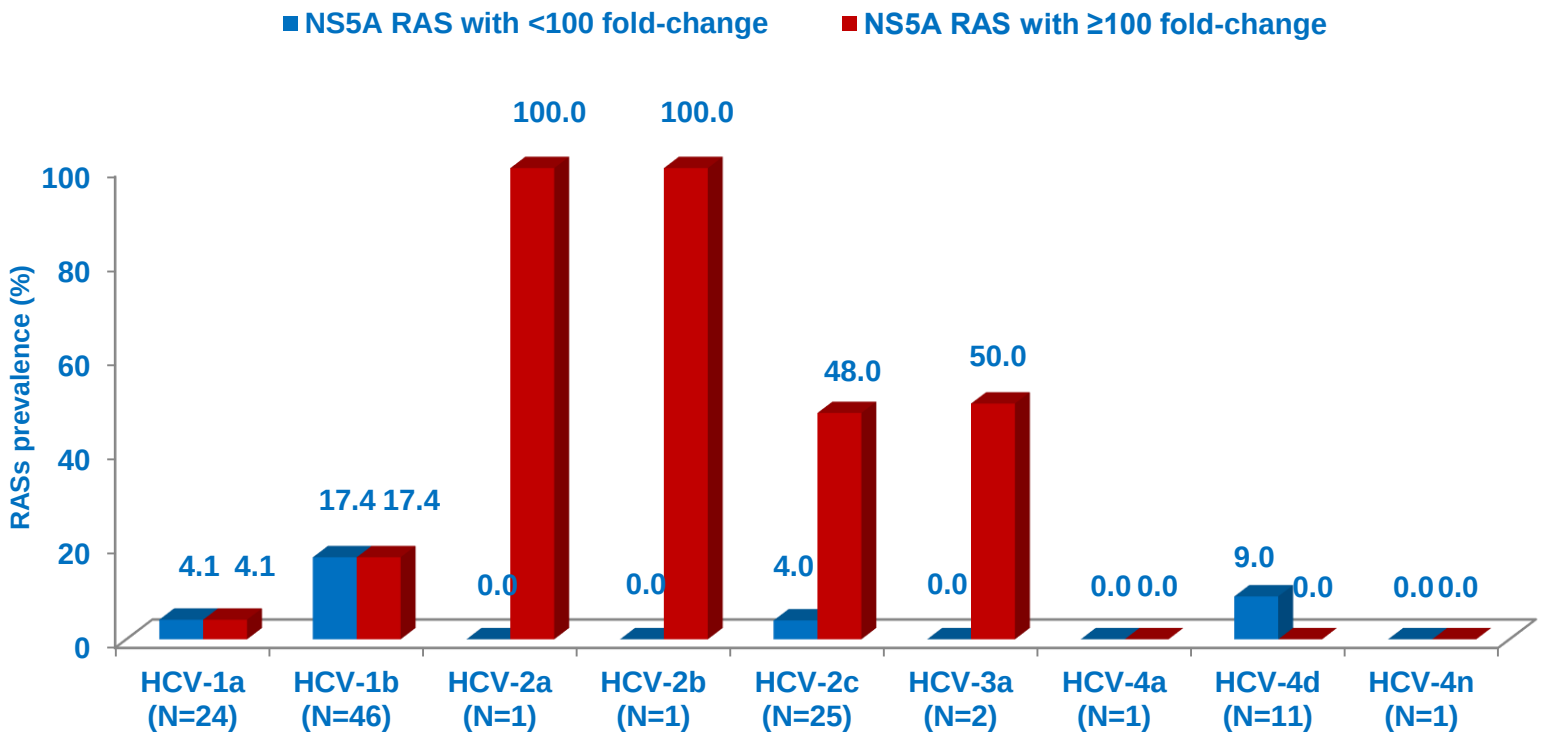
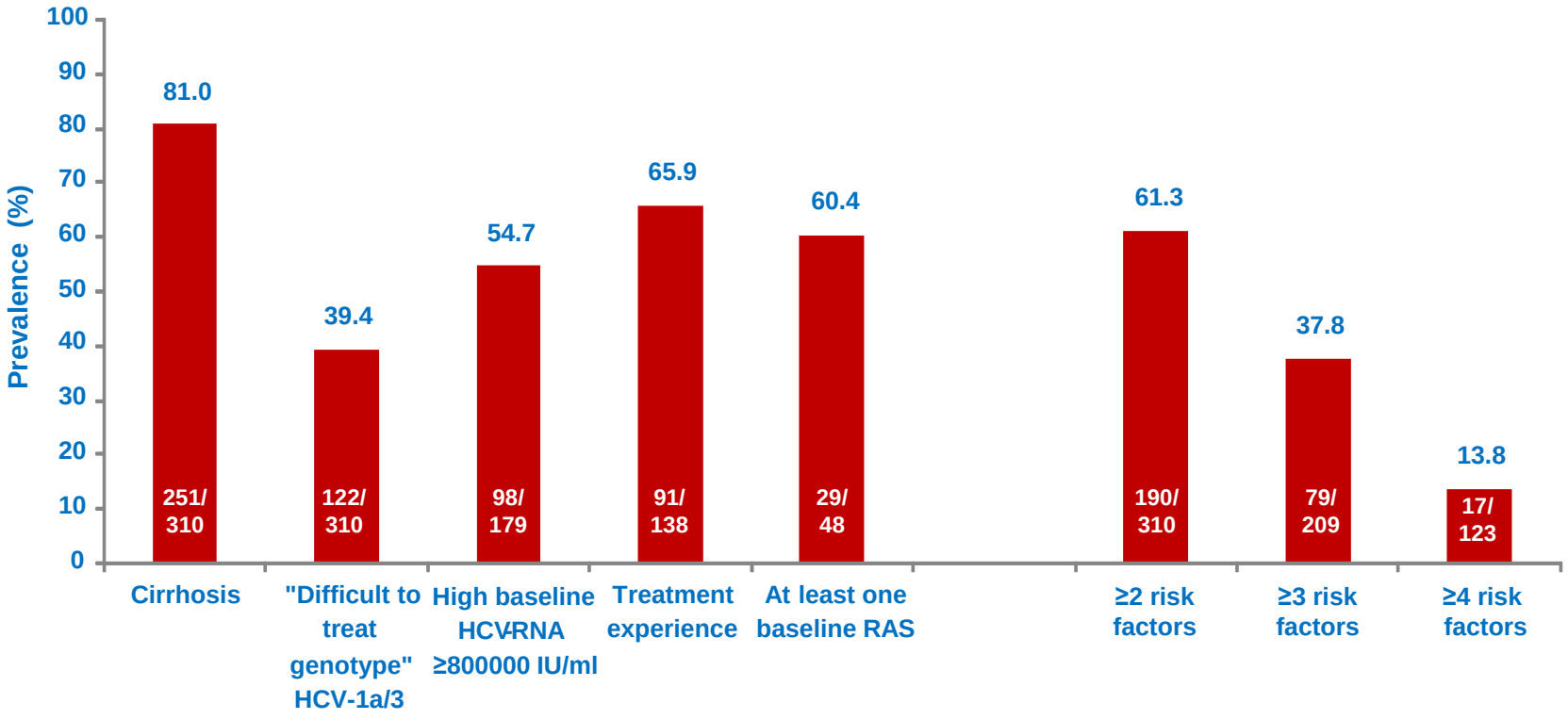


Among 112 patients treated without NS5A-inhibitors, 31.2% showed also extra-target NS5A-RASs, more frequently in HCV-1b (34.8%) and HCV-2a/b/c (55.5%)



Y93H was detected in 8/46 HCV-1b (17.4%)

2 or more failure risk factors were present at baseline in the majority of failing patients



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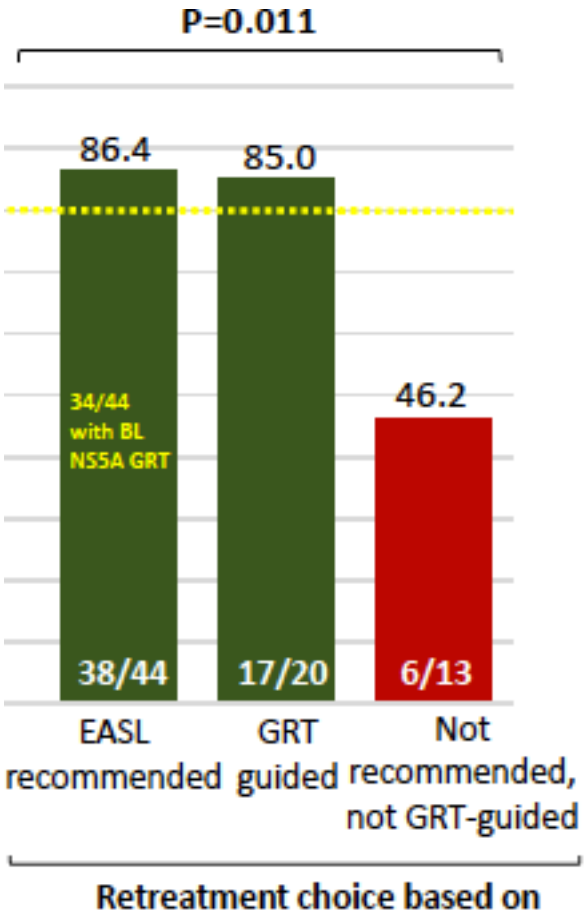
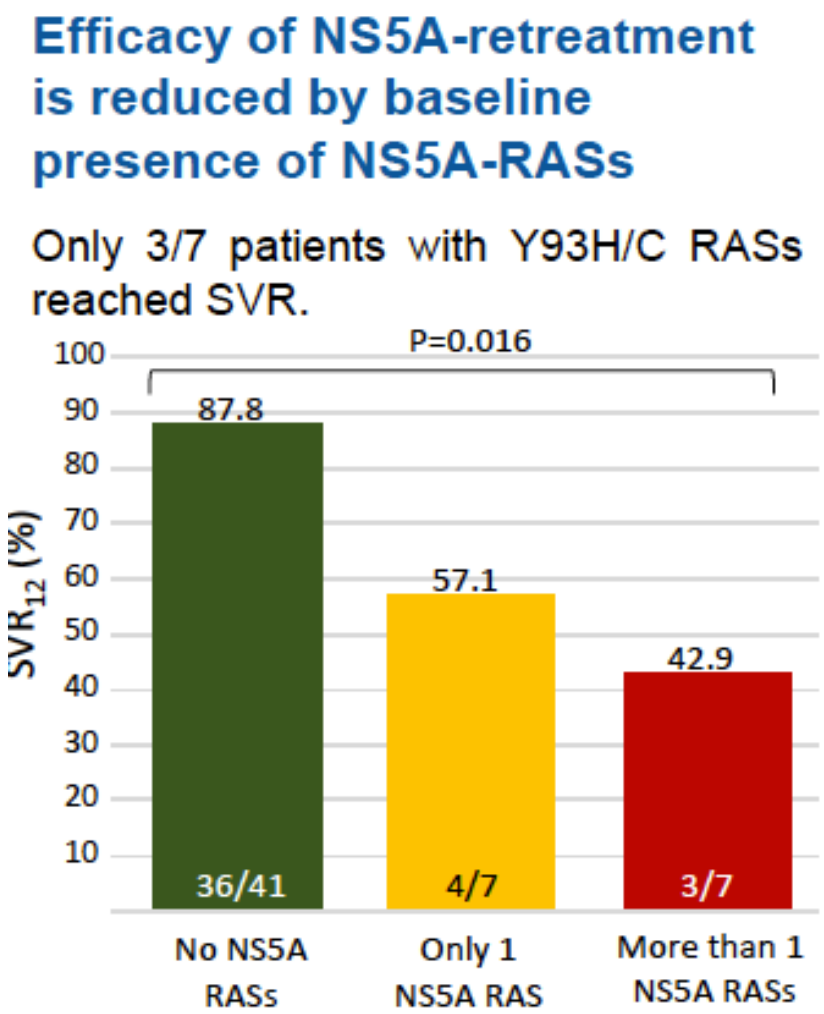
The challenge of HCV-retreatment after DAA-failure: retreatment of 98 DAA failures

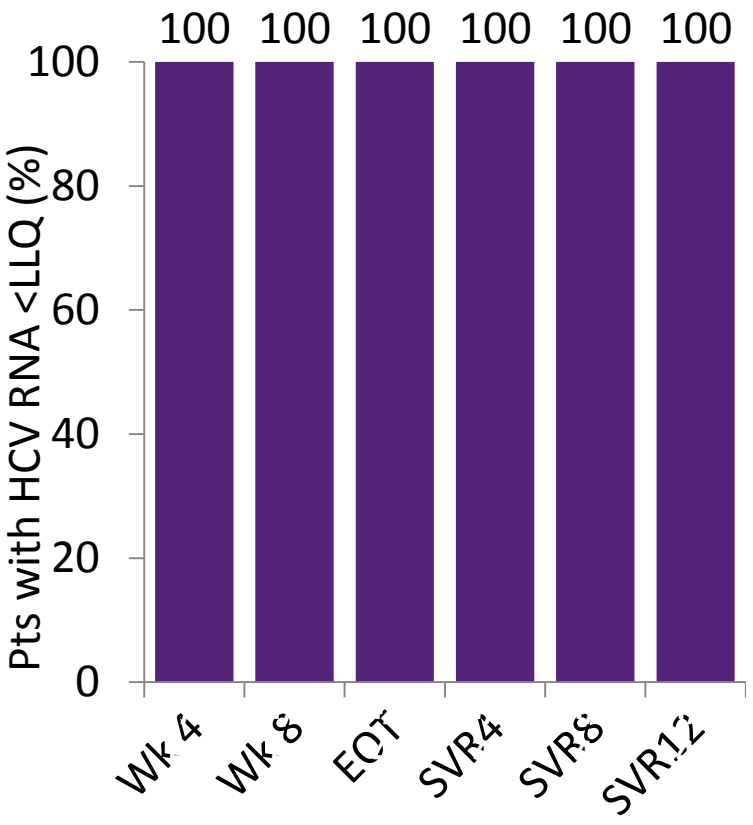




Cento V EASL 2017

Retreatment of relapsers to SOF/RBV with SOF/LDV

- SPARE trial evaluated SOF + RBV 24 wks in Tx-naive G1 pts, with SVR in 68% w/RBV 1000–1200 mg and 48% w/RBV 600 mg
- SOF/LDV studied in relapsers from SPARE trial (14/17 relapsers participated)
  - SOF 400 mg/LDV 90 mg QD 12 wks
  - 57% G1a, 93% AA, 86% non-CC
  - 50% advanced liver disease (F3–4)
  - One pt with prior S282T
    - Safety: 2 × Grade 3 hypophosphatemia, no AE leading to d/c, no SAEs



Osinusi A, et al. EASL 2014, London, O11

Retreatment of patients who failed prior SOF-based regimens with all oral FDC LDV/SOF + RBV for 12 weeks

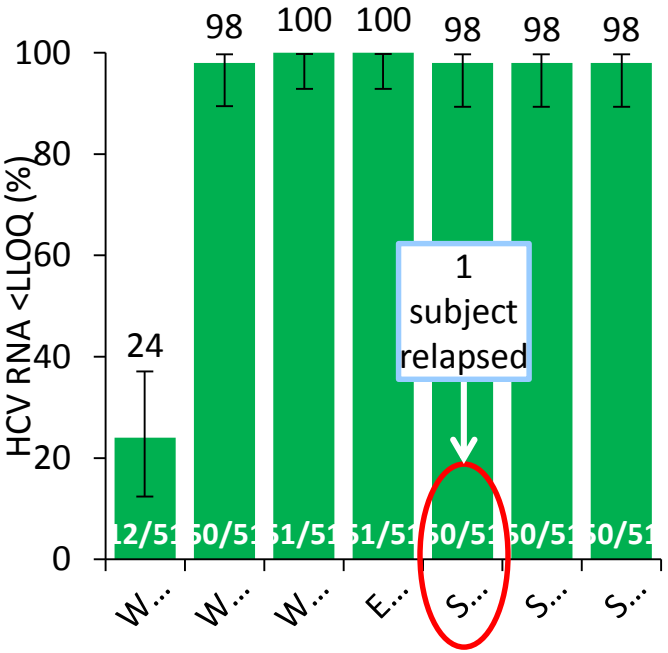
- 51 G1 SOF failures treated with 12 weeks SOF/LDV/RBV
- G1a 59%
- Non-CC 92%
- Cirrhosis 29%
- Failed regimen
  - SOF/PEG/RBV 49%
  - SOF/RBV 41%
  - SOF 10%

Baseline resistance

- NS5B: No S282T; L159F in 2 pts both had SVR
- NS5A: 12% RAV; 6/6 achieved SVR

Safety

- 1 early d/c due to AE (bipolar)
- HB <10 g/dL in 10% (0% <8.5 g/dL)
- Fatigue (26%); HA (22%); diarrhea (14%); rash (12%)



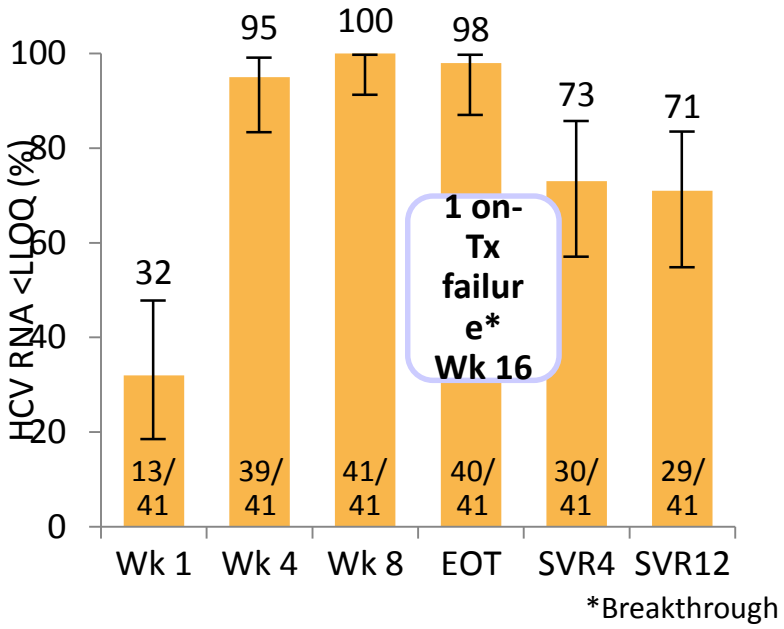
1 relapser was incorrectly genotyped as G1a by LIPA but on sequencing was confirmed as G3a

- SOF/LDV/RBV for 12 weeks highly effective in previous SOF/RBV or SOF/P/R failures
- No impact of baseline NS5A RAV

Wyles DL, et al. AASLD 2014, Boston. #235

Retreatment of patients who failed 8 or 12 weeks of LDV/SOF-based regimens with LDV/SOF for 24 weeks

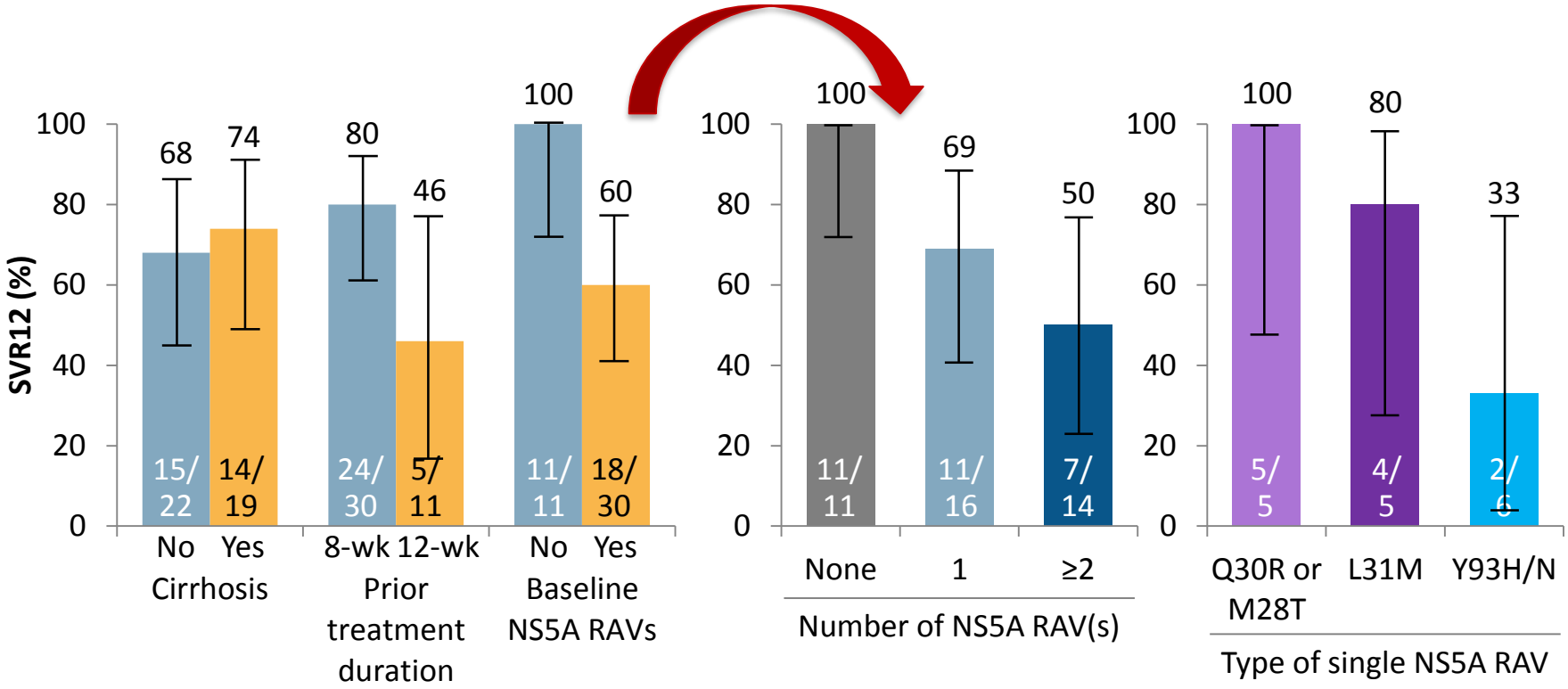
- 41 patients who failed LDV/SOF retreated for 24 weeks LDV/SOF
  - Prior Tx
    - LDV/SOF ± RBV; n=33 (80%)
    - LDV/SOF + GS-9669; n=8 (20%)
  - Tx durations
    - 8-wk Tx; n=30
    - 12-wk Tx; n=11
  - Cirrhosis; n=19 (46%)
- Safety
  - No d/c due to AE
    - HA (15%); fatigue (10%)
    - Grade 3 AE (7%) and SAE (5%)
  - None related to Tx



- Baseline resistance
  - 8-wk Tx; n=30
    - NS5A resistance; n=19 (63%)
    - No NS5B resistance
  - 12-wk Tx; n=11
    - NS5A resistance; n=11 (100%)
    - No NS5B resistance
- Post-Tx resistance
  - NS5B; n/N = 4/12 (33%)
    - S282T (n=2)
    - L159F (n=1)
    - Double-mutant S282T + L159F (n=1)

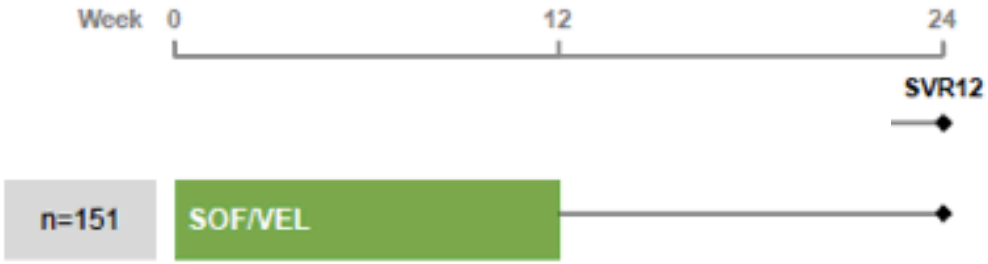
Lawitz E, et al. EASL 2015, Vienna, #O005

Retreatment of patients who failed 8 or 12 weeks of LDV/SOF-based regimens with LDV/SOF for 24 weeks



Lawitz E, et al. EASL 2015, Vienna. #O005

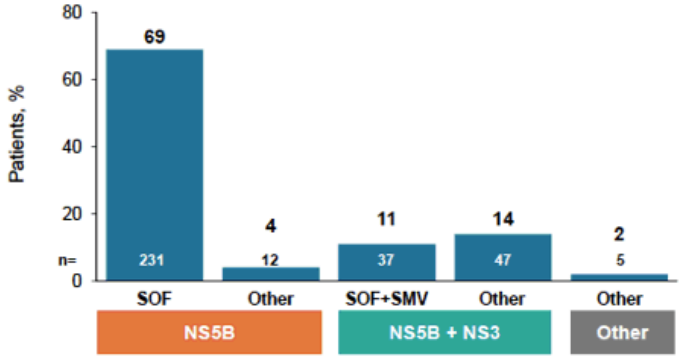
POLARIS 4: SOF/VEL in DAA Experienced



- Open-label, randomized, active-comparator trial in DAA-experienced GT 1–6 patients without prior NS5A inhibitor experience conducted at 102 sites (USA, Canada, France, Germany, UK, Australia, New Zealand)

- Patients with HCV GT 1, 2, and 3 at screening were randomized equally to SOF/VEL/VOX or SOF/VEL (all other GTs assigned to SOF/VEL/VOX)
  - Stratified by GT and presence of cirrhosis

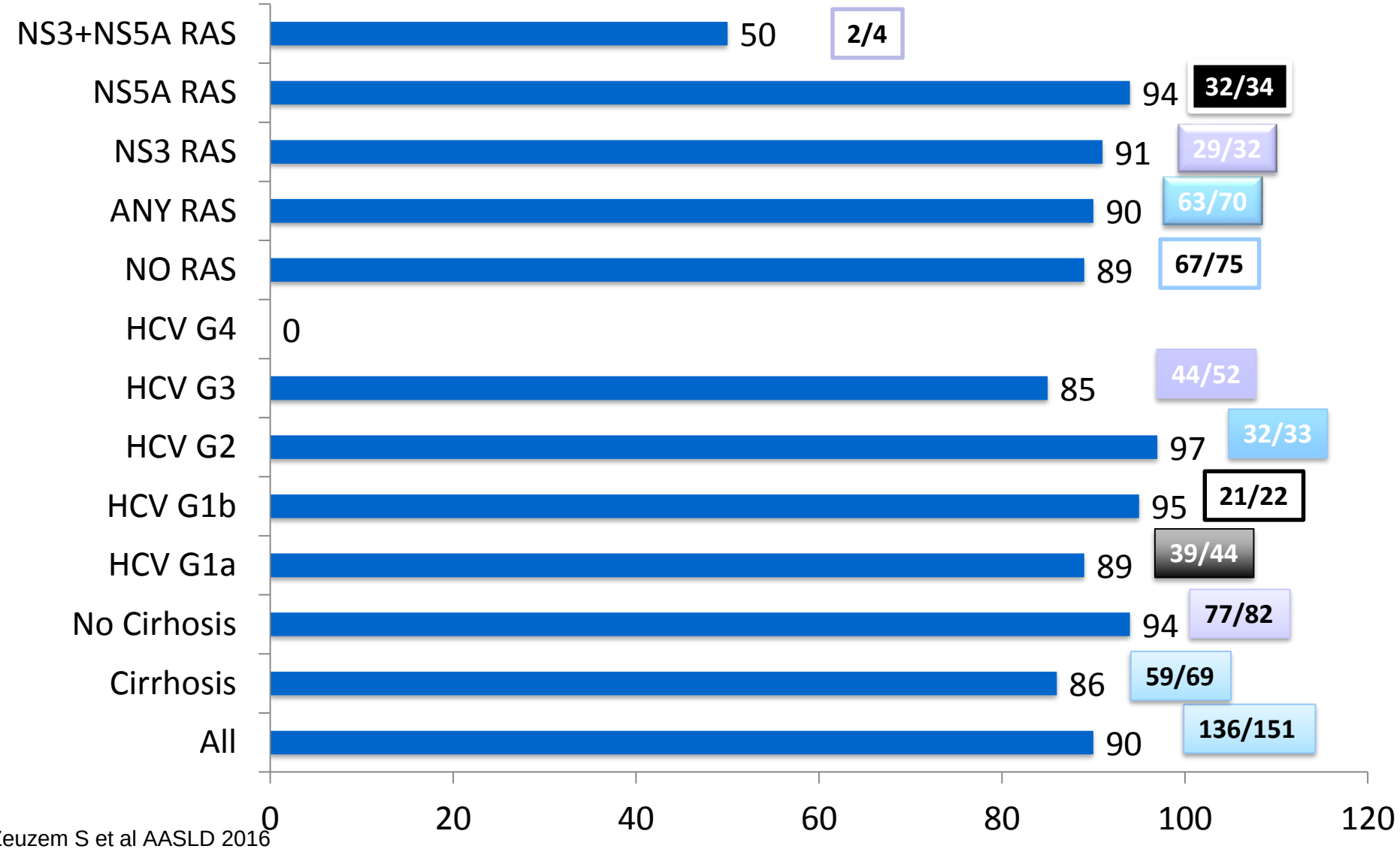
		SOF/VEL 12 weeks n=151
Mean age, y (range)		57 (24–80)
Male, n (%)		114 (75)
White, n (%)		131 (87)
Mean BMI, kg/m² (range)		29 (18–53)
Cirrhosis, n (%)		69 (46)
Genotype, n (%)	1a / 1b	44 (29) / 22 (14)
	2	33 (22)
	3	52 (34)
	4	–
IL28B CC*, n (%)		29 (19)
Mean HCV RNA, log_{10} IU/mL (range)		6.3 (3.6–7.3)



Other NS5B included mericitabine (n=7); other NS5B+NS3 included deleobuvir+faldaprevir (n=14), mericitabine+danoprevir (n=8), and SOF+telaprevir (n=6); one patient without prior DAA exposure is excluded; SMV, simeprevir; SOF, sofosbuvir.

Zeuzem S et al AASLD 2016

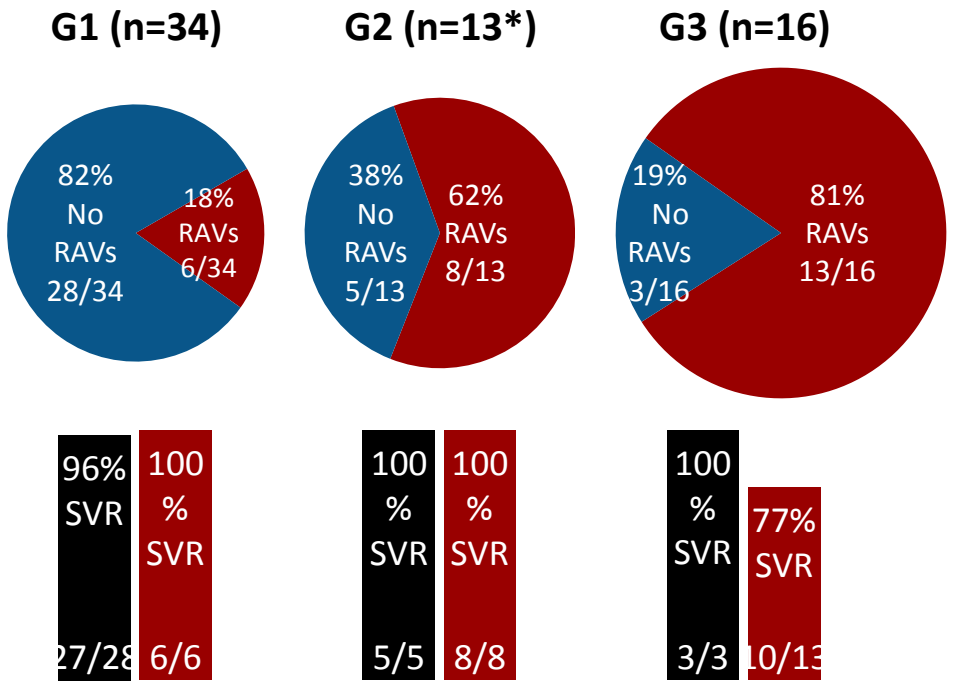
Polaris 4 SOF VEL 12 w in IFN-FREE treatment failure not exposed to DAA inhibitors



Zeuzem S et al AASLD 2016

SOF/VEL + RBV for 24 weeks is an effective retreatment for patients who failed prior NS5A containing DAA regimens

Impact of RAVs (1% deep sequencing cut-off)

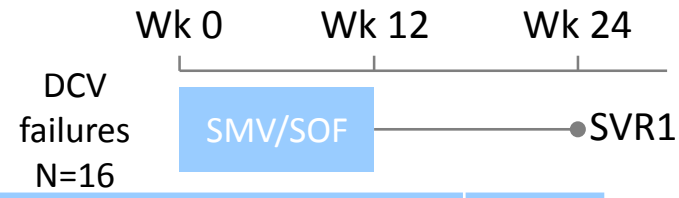


- 11/13 G3 patients with RAVs had Y93H: 9/11 achieved SVR12
- 5 patients had 2 RAVs: 5/5 achieved SVR12
- 3 patients had NS3 RAVs: 3/3 achieved SVR12

*1 pt could not be sequenced; 1 pt who withdrew consent was excluded.
**1 pt d/c'ed SOF/VEL and RBV due to irritability (Day 21)

Gane EJ, et al. EASL 2016, Barcelona. #PS024

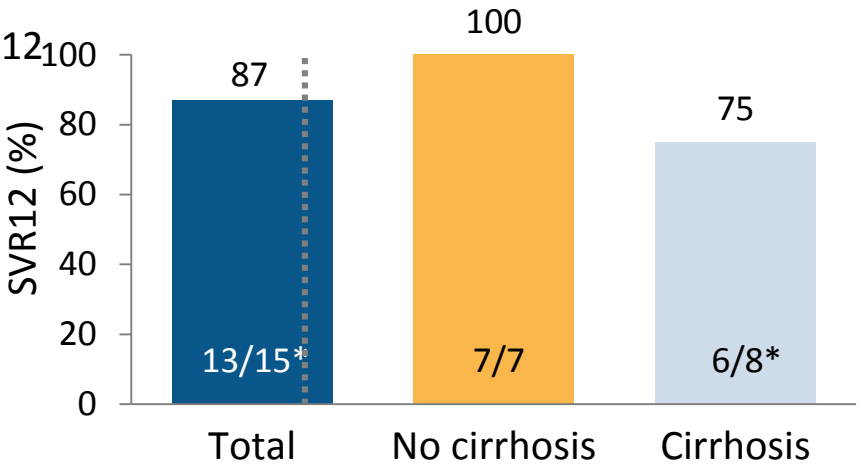
Retreatment with SOF/SMV in patients who previously failed on an HCV NS5A inhibitor–containing regimen



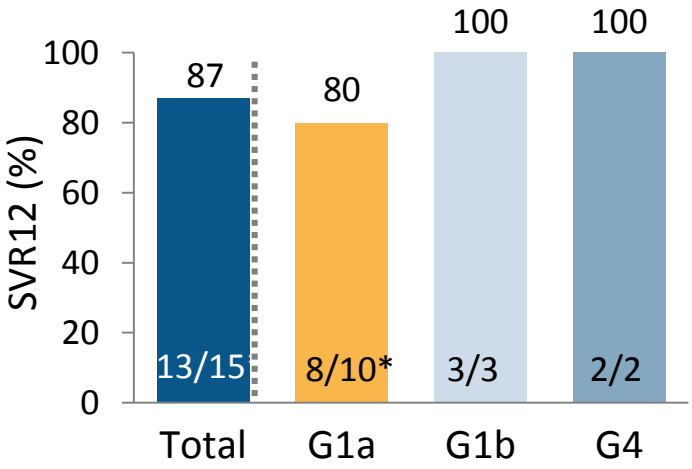
Baseline characteristics	N=16
Mean age, y (range)	54 (43–73)
Male, n (%)	13 (81)
G1a, n (%)	11 (69)
G1b, n (%)	3 (23)
G4, n (%)	2 (13)
Median HCV RNA, 10^6 IU/mL	1.38
HCV RNA >800,000, IU/mL, n (%)	14 (88)
Severe fibrosis (FS 9.6–12.5 kPa), n (%)	7 (44)
Cirrhosis (FS>12.5 kPa), n (%)	9 (56)
Median time between DCV-based regimen and SMV/SOF, months (range)	32 (16–53)
Presence of NS5A RAVs	13 (81)
Presence of NS3 RAVs	8 (57)*
Prior HCV treatment, n (%) DCV/PR DCV/ASV/PR	13 (81) 3 (19)

*Available in 14 patients

SVR12 according to fibrosis stage



SVR12 according to genotype

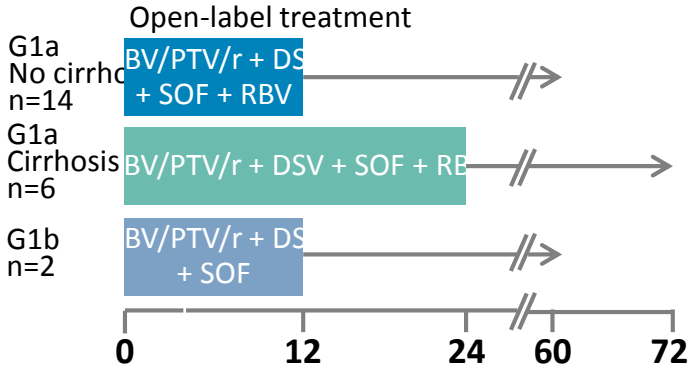


*1 patient did not reach Week 12 follow-up visit

Hezode C, et al. Hepatology 2016

QUARTZ-I: Retreatment of HCV G1 DAA-failures with OBV/PTV/r, DSV + SOF ± RBV

- Phase 2, multicenter study

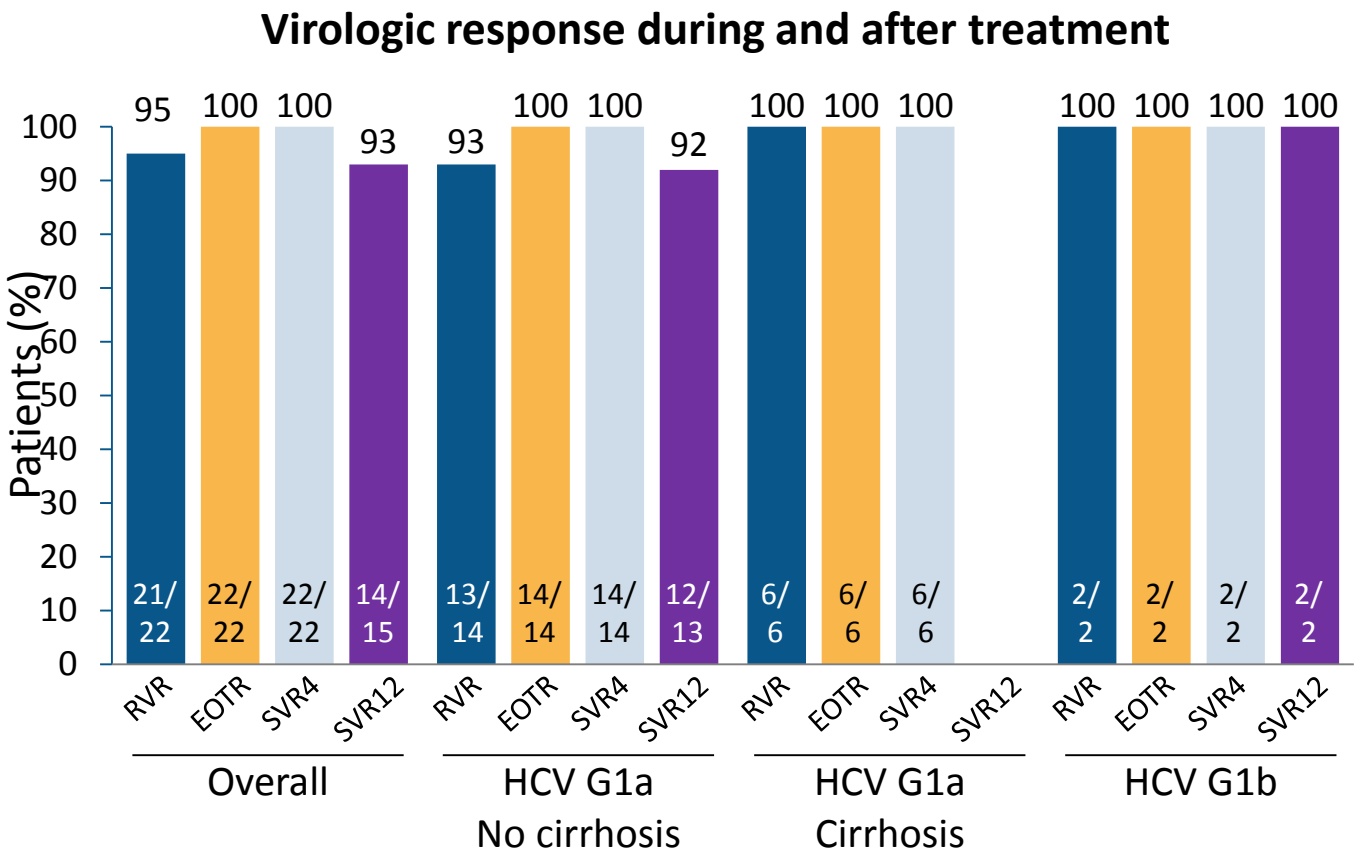


- 22 DAA-experienced G1 patients
  - 20 G1a and 7 cirrhotics
- Baseline: 17 pts had ≥1 RAV in 1 DAA target, 7 pts had RAVs in 2 DAA targets, and 2 pts had RAVs in all 3 targets

Baseline characteristics		OBV/PTV/r + DSV + SOF + RBV G1a 12 wks, n=14	OBV/PTV/r + DSV + SOF + RBV G1a 24 wks, n=6	OBV/PTV/r + DSV + SOF G1b 12 wks, n=2
Prior DAA regimen	OBV/PTV/r	2 (14)	0	0
	OBV/PTV/r + DSV	8 (57)	6 (100)	0
	SMV + SOF	0	0	1 (50)
	SMV + SAM + RBV	0	0	1 (50)
	SOF + RBV	1 (7)	0	0
	SOF + PR	1 (7)	0	0
	TVR + PR	2 (14)	0	0
RAVs	NS3-Q80K	9 (64)	5 (83)	0
	NS3-D168E/V	2 (14)	1 (17)	0
	NS5A-M28T/V	8 (57)	0	0
	NS5A-Q30E/H/R	7 (50)	2 (33)	0
	NS5A-L31M	0	0	1 (50)
	NS5A-H58D	0	1 (17)	0
	NS5A-Y93C/F/H	2 (14)	0	1 (50)
	NS5B-S556G	4 (29)	2 (33)	1 (50)
	NS5B-M414I/T	2 (14)	0	0
	NS5B-Y448H	1 (7)	0	0

Poordad F, et al. AASLD 2015, San Francisco. #LB-20

QUARTZ-I: Retreatment of HCV G1 DAA-failures with OBV/PTV/r, DSV + SOF ± RBV



Poordad F, et al. AASLD 2015, San Francisco. #LB-20

C-ISLE: A RANDOMIZED, OPEN-LABEL, UK-BASED CLINICAL TRIAL IN GT3-INFECTED CIRRHOTICS

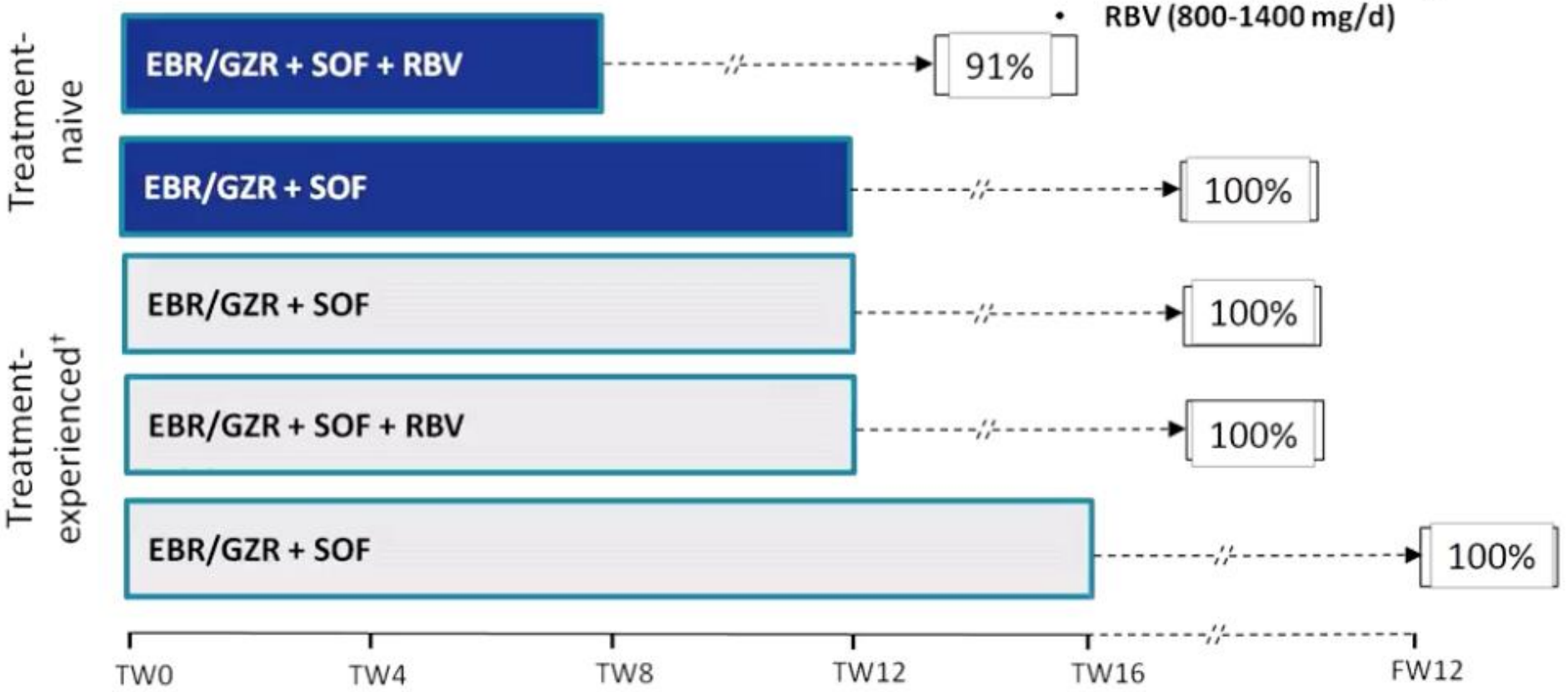
Sofosbuvir

Elbasvir (MK-8742) Grazoprevir (MK-5172)

HCV Genotype 3

Target enrollment was 25 patients per arm

Dosing
- EBR/GZR FDC (50 mg/100 mg/d)
- SOF (400 mg/d as per PI)
- RBV (800-1400 mg/d)

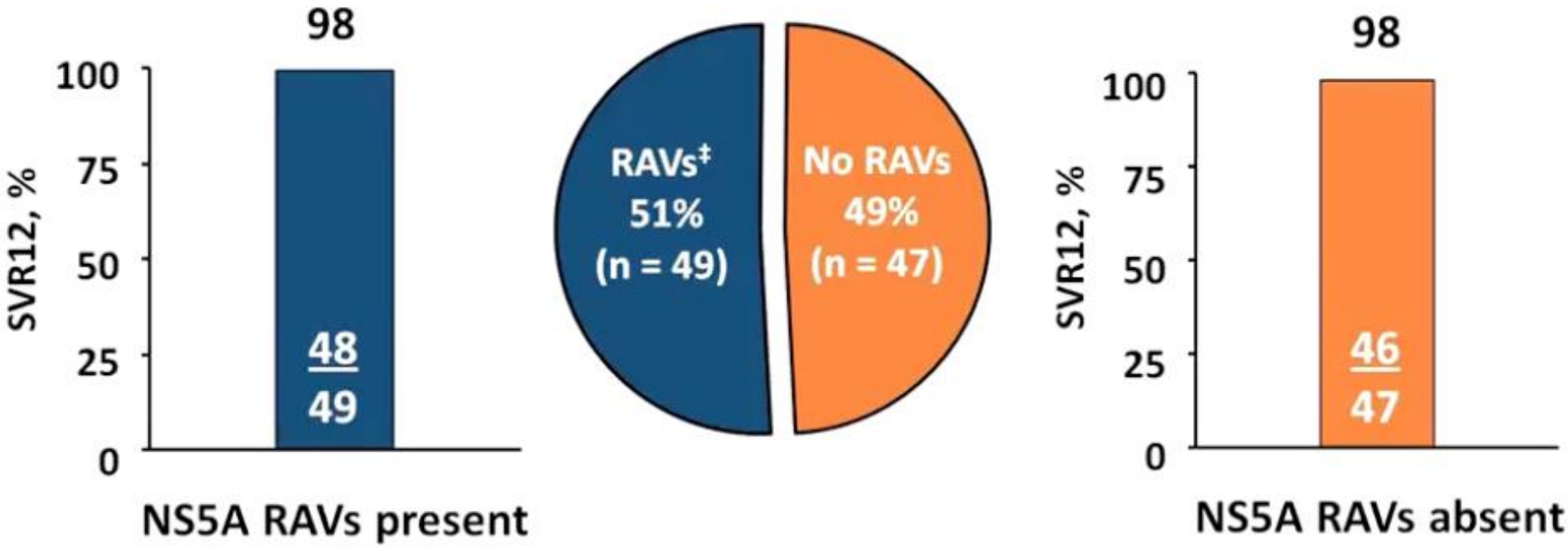


FDC, fixed-dose combination; FW, follow-up week; TW, treatment week.

GT3 NS5A RAVs: PREVALENCE AND IMPACT ON SVR12

Sofosbuvir
Elbasvir (MK-8742) Grazoprevir (MK-5172)
HCV Genotype 3

Prevalence of NS5A RAVs†



EASL recommendations 2016
"Easy-to-Retreat" Patients
Never exposed to NS5A inhibitors

- Peg-IFN + RBV failures

  => General recommendations for "treatment-experienced" patients

- Peg-IFN + RBV + protease inhibitor failures

  => Sofosbuvir + NS5A inhibitor, 12 weeks, with RBV

- SOF, SOF + RBV or Peg-IFN + RBV + SOF failures

  => General recommendations, 12-24 weeks, with RBV

- SOF + SIM failures

  => Sofosbuvir + NS5A inhibitor, 12-24 weeks, with RBV

EASL Recommendations 2016
"Difficult-to-Retreat" Patients
NS5A inhibitor-containing regimen failures

- The retreatment regimen should contain
  - Sofosbuvir because of the high barrier to resistance
  - 2 to 3 other DAA(s), if possible with no cross-resistance with the DAA(s) already administered
  - Ribavirin

- Treatment duration should be 12 or 24 weeks (24 weeks recommended in F3-F4)

- Close monitoring is required, as these regimens are off-label combinations with very limited safety data

EASL recommenadtions 2016
"Difficult-to-Retreat" Patients
NS5A inhibitor-containing regimen failures

- Genotype 1 or 4
  - Sofosbuvir + ombitasvir/paritaprevir/r ± dasabuvir + RBV
  - Sofosbuvir + grazoprevir/elbasvir + RBV
  - Sofosbuvir + daclatasvir + simeprevir + RBV

  NB: With caution in F3 and compensated cirrhosis

- Genotype 2, 3, 5 or 6
  - Sofosbuvir + velpatasvir + RBV, 24 weeks

- Alternatively, wait until alternative therapeutic options become available
- Utility of HCV resistance testing unknown. If reliable resistance testing → retreatment can be guided by resistance testing by a multidisciplinary team

What do the guidelines say after DAA failure?

AASLD/IDSA

- Stress deferral unless urgent treatment needed
- PI/PR → SOF/NS5A as PR
- DAA → RAS testing for all
  - **No RAS**: SOF/NS5A/RBV x 24w
  - **NS3**: SOF/NS5A/RBV x 24w
  - **NS5A**: SOF/SMV/RBV x 24w
  - **NS3 + NS5A**:
    - SOF + ELB/GZV/RBV x 12w
    - SOF + PrOD/RBV x 12w 1b/24w 1a
    - SOF/VEL + RBV x 24w
- **G3**:
  - **SOF/RBV**: SOF/DCV/RBV x 12w or SOF/VEL/RBV x 12w
  - **SOF/DCV**: SOF/VEL/RBV x 24w

EASL

- Brief mention of treatment deferral as alternative
- PI/PR → SOF/NS5A + RBV
- DAA → consider RAS testing
  - **All**: F0-2 + RBV & F3/4 24w + RBV
  - **SOF/SIM**: SOF/NS5A
  - **SOF/NS5A**:
    - SOF + ELB/GZV + RBV
    - SOF + PrOD + RBV
    - SOF + SMV + DCV + RBV
  - **G2,3,5,6**: SOF/VEL + RBV x 24w

I fallimenti al primo trattamento con DAA: quali possibilità terapeutiche

- Quanti e perchè
- RAVs, RASs, RAPs or RATs
- Caratteristiche dei pazienti con fallimento a DAA IFN free in Italia
- Schemi di ritrattamento:
  - Terapie attuali
  - Terapie future

Upcoming treatment options in HCV

Combo	NS5A	NS3/NS4	NUC	Activity on genotypes
Glecaprevir (ABT 493) + Pibrentasvir (ABT 530) G/P				All
Sofosbuvir + Velpatasvir + Voxilaprevir (GS5897)				All
Grazoprevir + Ruzasvir (MK 8408) + Uprifosbuvir				All

In Vitro and Clinical PK Characteristics of ABT-493/ABT-530

Glecaprevir

ABT-493

Pangenotypic NS3/4A protease inhibitor

Pibrentasvir

ABT-530

Pangenotypic NS5A inhibitor

In vitro:[1,2]

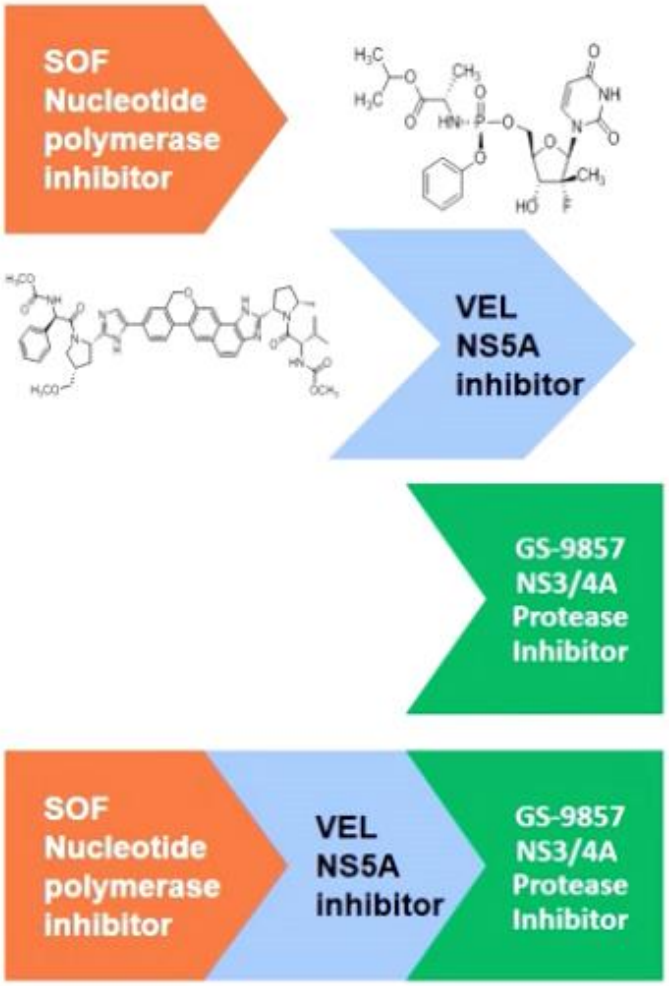
- High barrier to resistance
- Potent against common NS3 polymorphisms (eg., positions 80, 155, 168) and NS5A polymorphisms (eg., positions 28, 30, 31 and 93)
- Additive/synergistic antiviral activity

Clinical PK & metabolism:

- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

ABT-493 identified by AbbVie and Enanta

SOF/VEL/VOX



- **Sofosbuvir (SOF)[1,2]**
  - Potent antiviral activity against HCV GT 1–6
- **Velpatasvir (GS-5816; VEL)[3-5]**
  - Picomolar potency against HCV GT 1–6
  - 2nd-generation NS5A inhibitor with improved resistance profile
- **GS-9857[6,7]**
  - HCV NS3/4A protease inhibitor with potent antiviral activity against HCV GT 1–6
  - Improved resistance profile compared with other HCV protease inhibitors
- **SOF/VEL/GS-9857**
  - SOF/VEL/GS-9857 FDC (400/100/100 mg) tablet is taken orally, once daily

FDC, fixed-dose combination

SOF/VEL/VOX SAFETY SUMMARY

Adverse Events in ≥10% of Patients

Patients, n (%)	SOF/VEL/VOX 8 Weeks n=611	SOF/VEL/VOX 12 Weeks n=445	SOF/VEL 12 Weeks n=700	Placebo 12 Weeks n=152
Headache	161 (26)	116 (26)	174 (25)	26 (17)
Fatigue	134 (22)	99 (22)	164 (23)	30 (20)
Diarrhea	105 (17)	83 (19)	44 (6)	19 (13)
Nausea	103 (17)	59 (13)	62 (9)	12 (8)

Graded Gastrointestinal Adverse Events

Patients, n (%)	SOF/VEL/VOX 8 Weeks n=611	SOF/VEL/VOX 12 Weeks n=445*	SOF/VEL 12 Weeks n=700†	Placebo 12 Weeks n=152
Diarrhea	**105 (17)**	**83 (19)**	**44 (6)**	**19 (13)**
Grade 1	100 (16)	74 (17)	38 (5)	15 (10)
Grade 2	5 (<1)	9 (2)	6 (<1)	4 (3)
Nausea	**103 (17)**	**59 (13)**	**62 (9)**	**12 (8)**
Grade 1	98 (16)	56 (13)	58 (8)	12 (8)
Grade 2	5 (<1)	3 (<1)	4 (<1)	0

*n=444 evaluated; †n=698 evaluated.

Manns M et al EASL 2017

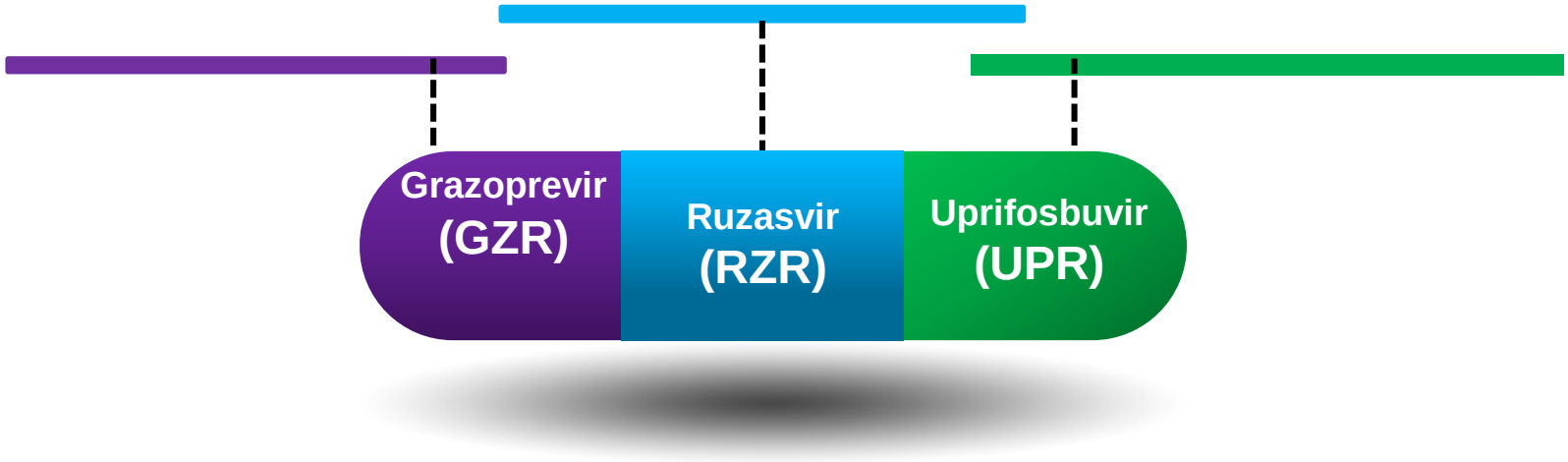
Grazoprevir + Ruzasvir + Uprifosbuvir

- Co-formulated as a fixed-dose combination tablet; administered as 2 tablets once-daily for a total daily dose of 100 mg grazoprevir (GZR), 60 mg ruzasvir (RZR), and 450 mg of uprifosbuvir (UPR; MK-3682).

- HCV NS3/4A protease inhibitor
- 50 mg per tablet

- HCV NS5A inhibitor[3]
- 30 mg per tablet

- HCV NS5B nucleotide polymerase inhibitor
- 225 mg per tablet

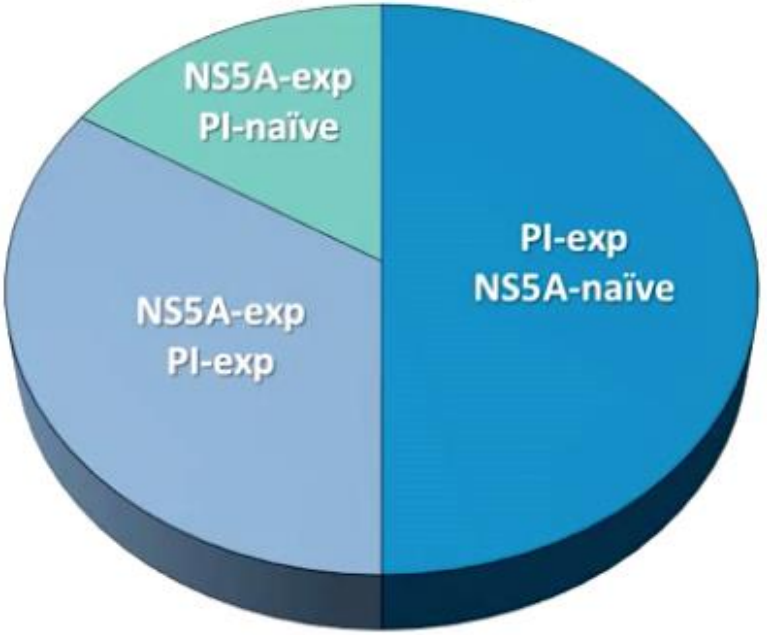


MAGELLAN-1 Study: DAA failure retreatment
12 weeks ABT-493/ABT-530 +/- RBV

Prior regimen	n
LDV/SOF	8
SMV + SOF ± RBV	8
OBV/PTV/r + DSV ± RBV	4
DBV + FDV + RDV ± RBV	4
SAM + SMV	2
TVR + PR	8
BOC + PR	10
DCV ± PR	2
Other	9

4 patients were treated more than once with DAA-containing regimens.

Treatment experience by DAA class:

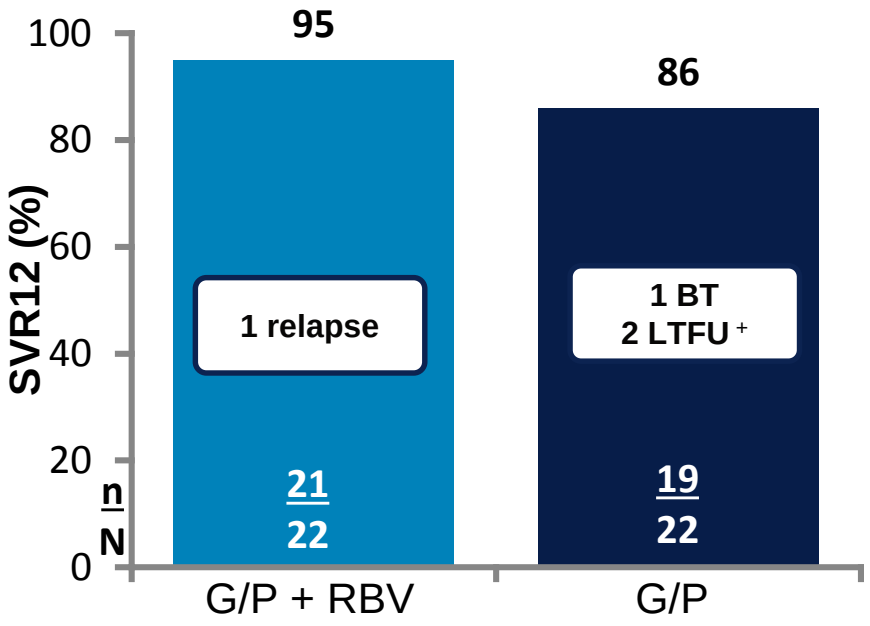


25 (50%) NS5A-experienced
42 (84%) PI-experienced

Overall mITT SVR12= 96% (45/47)

MAGELLAN-I Part 1: G/P ± RBV for 12 Weeks in GT1-Infected Patients with Prior DAA Experience

Efficacy



Safety

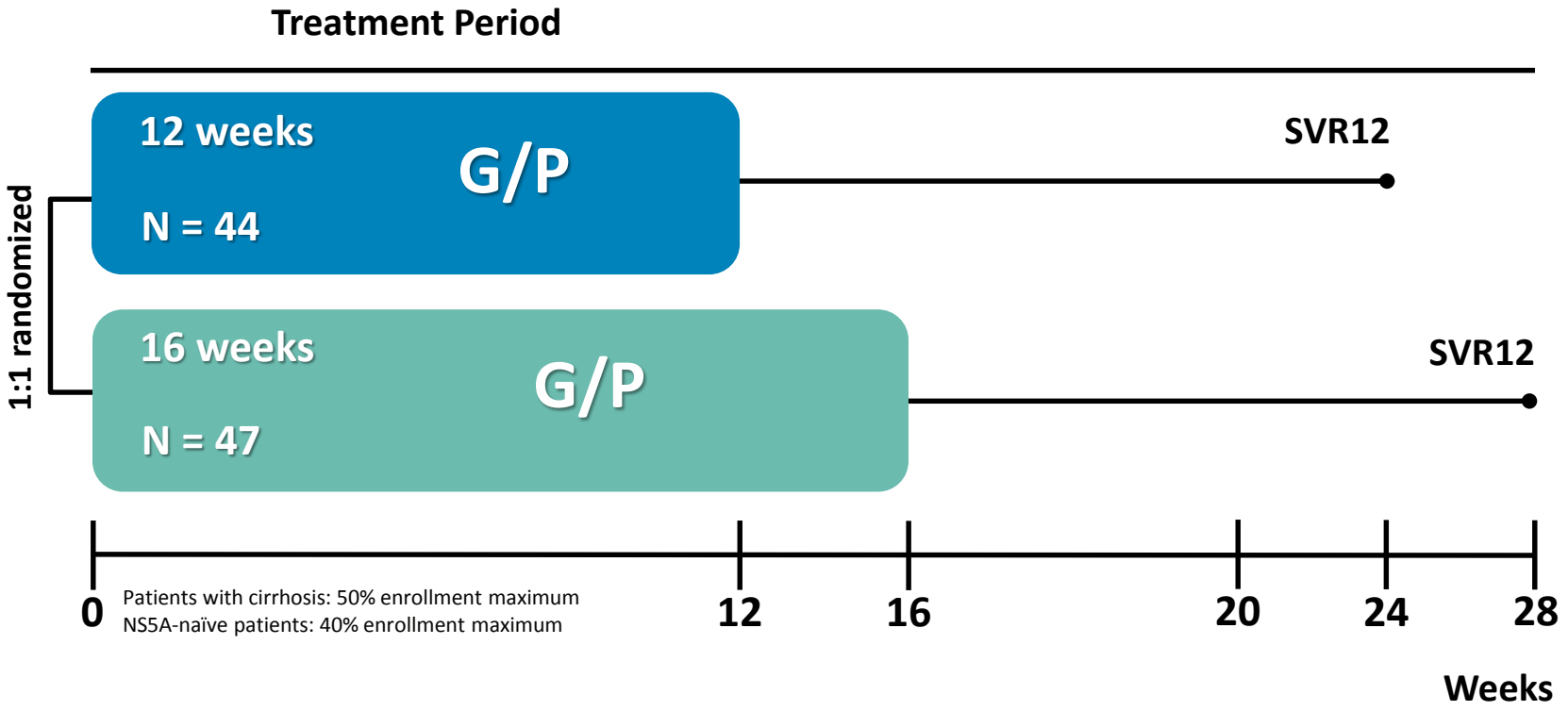
Safety summary Patients, n (%)	G/P + RBV	G/P
Any AE	19 (86)	17 (77)
SAE	0	0
D/c due to AE	0	0
Grade 3–4 lab abnormalities	0	0

Baseline NS3A or NS5A RASs – 14% had none,
30% had 1, 56% had 2 or more, 6 has 4 or more*

- BT, Breakthrough; LTFU, lost to follow up.
- * Percentages include 6 patients treated with G/P 200/80 mg
- + Two GT1a patients were LTFU; both had undetectable HCV RNA at post-treatment week 8

Ng T, *et al. Hepatology* 2016; **64**(Suppl 1):417A–418A (poster presentation, 849);
Poordad F, *et al. Hepatology* 2016; **64**(Suppl 2):S160–161 (oral presentation, GS11).

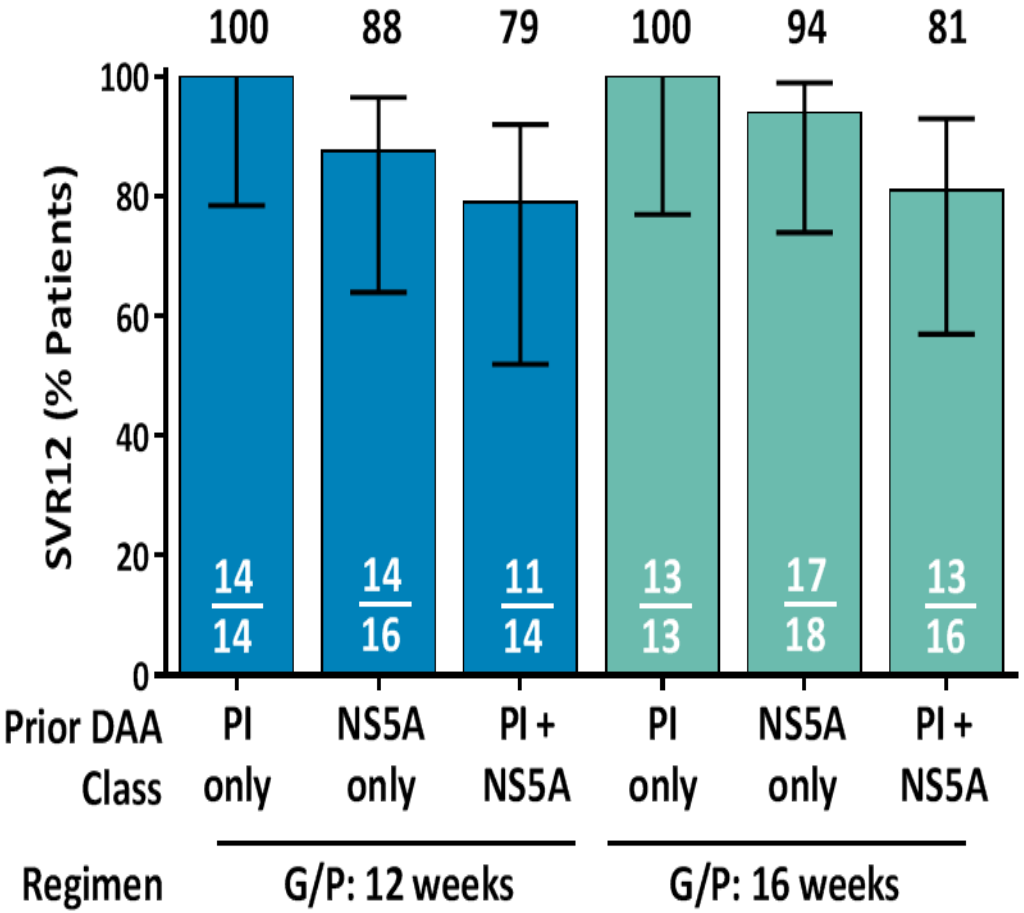
MAGELLAN 1 PART 2: DAA-Failure Study: Objective and Study Design



Objective

- Determine the efficacy and safety of G/P for 12 or 16 weeks in patients with chronic HCV GT1, 4, 5 or 6 infection and prior DAA failure, including those with compensated cirrhosis

MAGELLAN 1 PART 2 :
SVR12 by DAA Class in Prior Therapy



Overall SVR12:

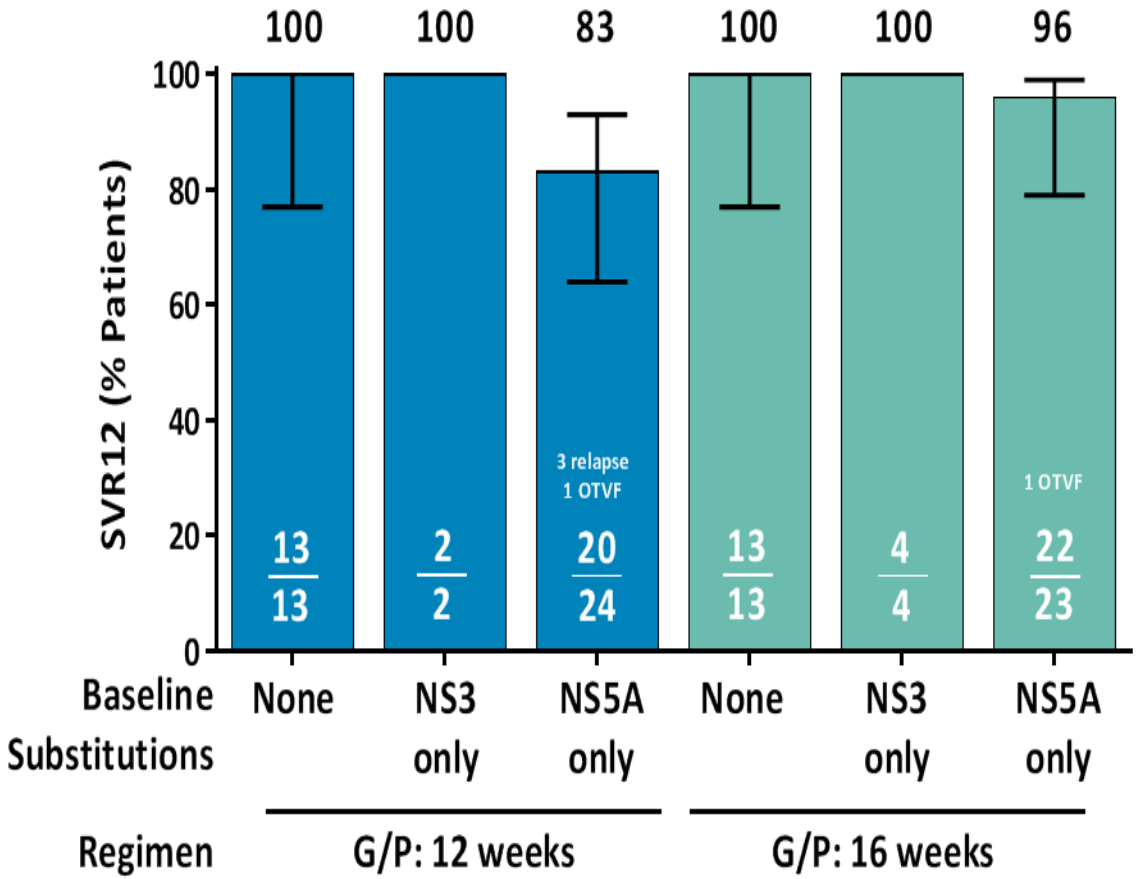
12-week: 89% (39/44)
- 1 OTVF; 4 relapse

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

MAGELLAN 1 PART 2:
SVR12 by Key NS3 and NS5A Baseline Substitutions



Key baseline NS3 **and** NS5A substitutions were only present in patients with prior failure to both PI and NS5A inhibitors

5/9 of these patients achieved SVR12

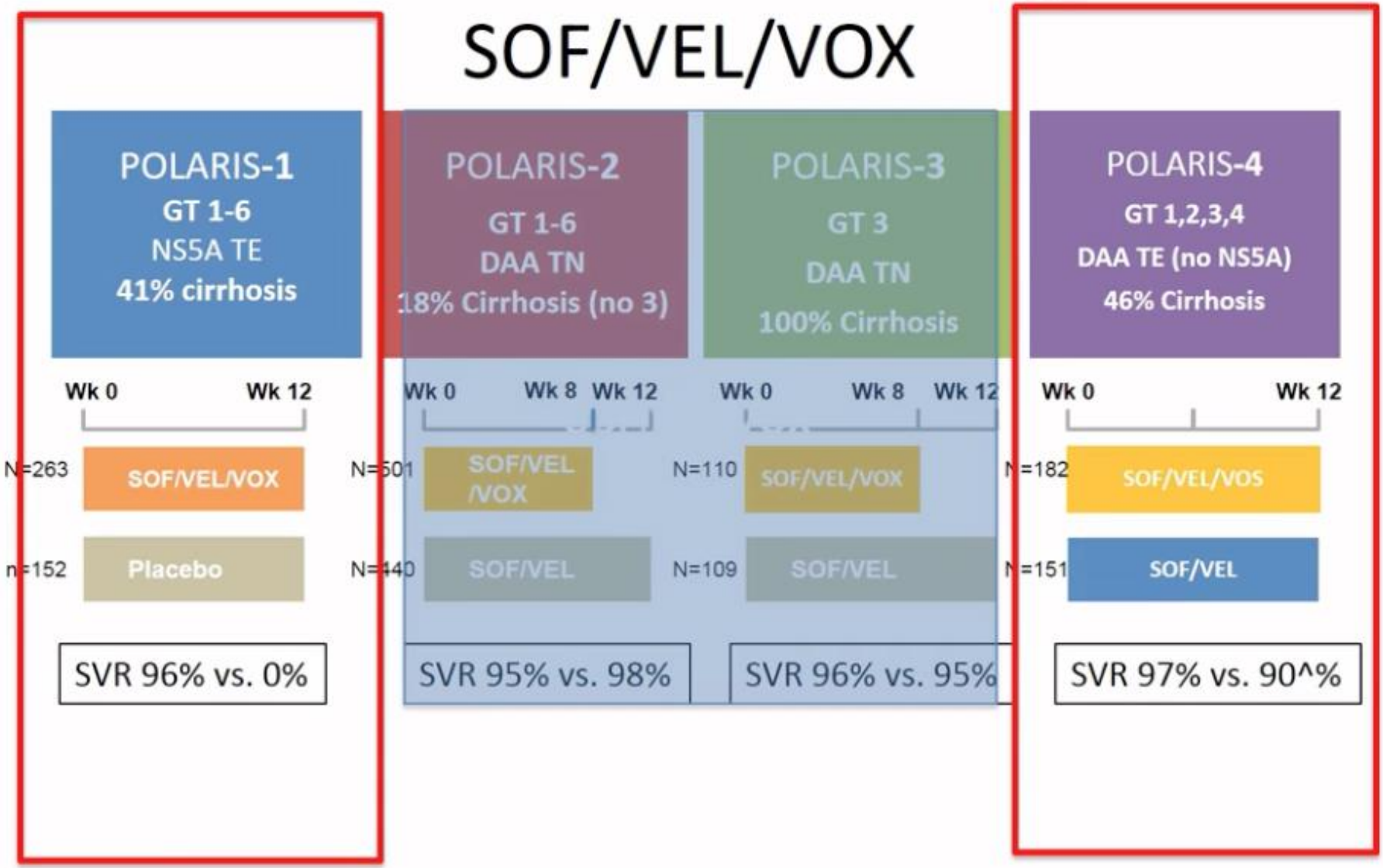
Key NS3 positions: 155, 156, 168
Key NS5A positions: 24, 28, 30, 31, 58, 92, 93
OTVF: on-treatment virologic failure

Y93H/N at baseline: 100% (13/13) SVR12 in patients with NS5A inhibitor experience (PI-naïve)

Conclusions: MAGELLAN-1, Part 2

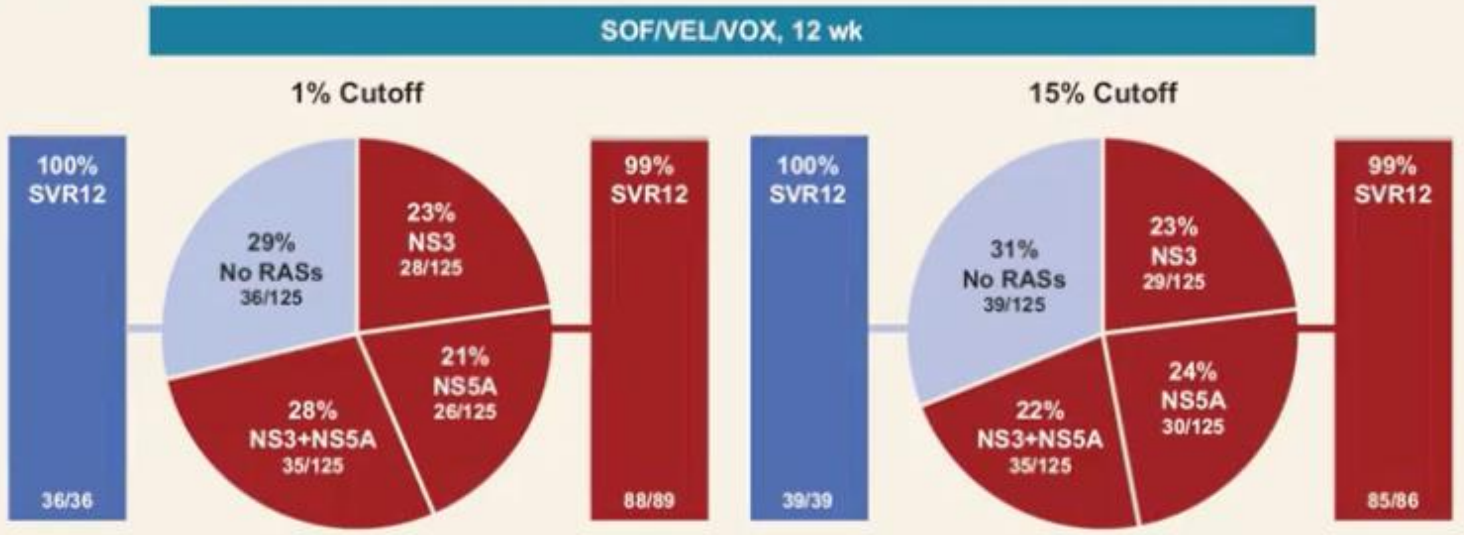
- Patients with prior failure to PI containing regimens (NS5A inhibitor-naïve):
  - 100% SVR12 with 12 or 16 weeks of G/P treatment
- Patients with prior failure to both PI- and NS5A inhibitor-containing regimens had lower SVR12 rates
- Patients with prior failure to NS5A inhibitors (i.e., LDV or DCV); NS3/4A PI-naïve:
  - 94% SVR12 with 16 weeks of G/P treatment with no relapse
  - No impact of baseline NS5A substitutions on SVR12
- G/P for 12 or 16 weeks was well tolerated; Grade 3 lab abnormalities were rare, with no discontinuations due to AEs, and no DAA-related serious AEs

The POLARIS Phase 3 Program
SOF/VEL/VOX



Integrated Resistance Analyses TN/TE Treated With SOF/VEL/VOX for 8 and 12 Weeks From Phase 2 Studies

Prevalence and Impact on Treatment Outcome of NS3 and NS5A Class RASs at Baseline in DAA-Experienced Patients



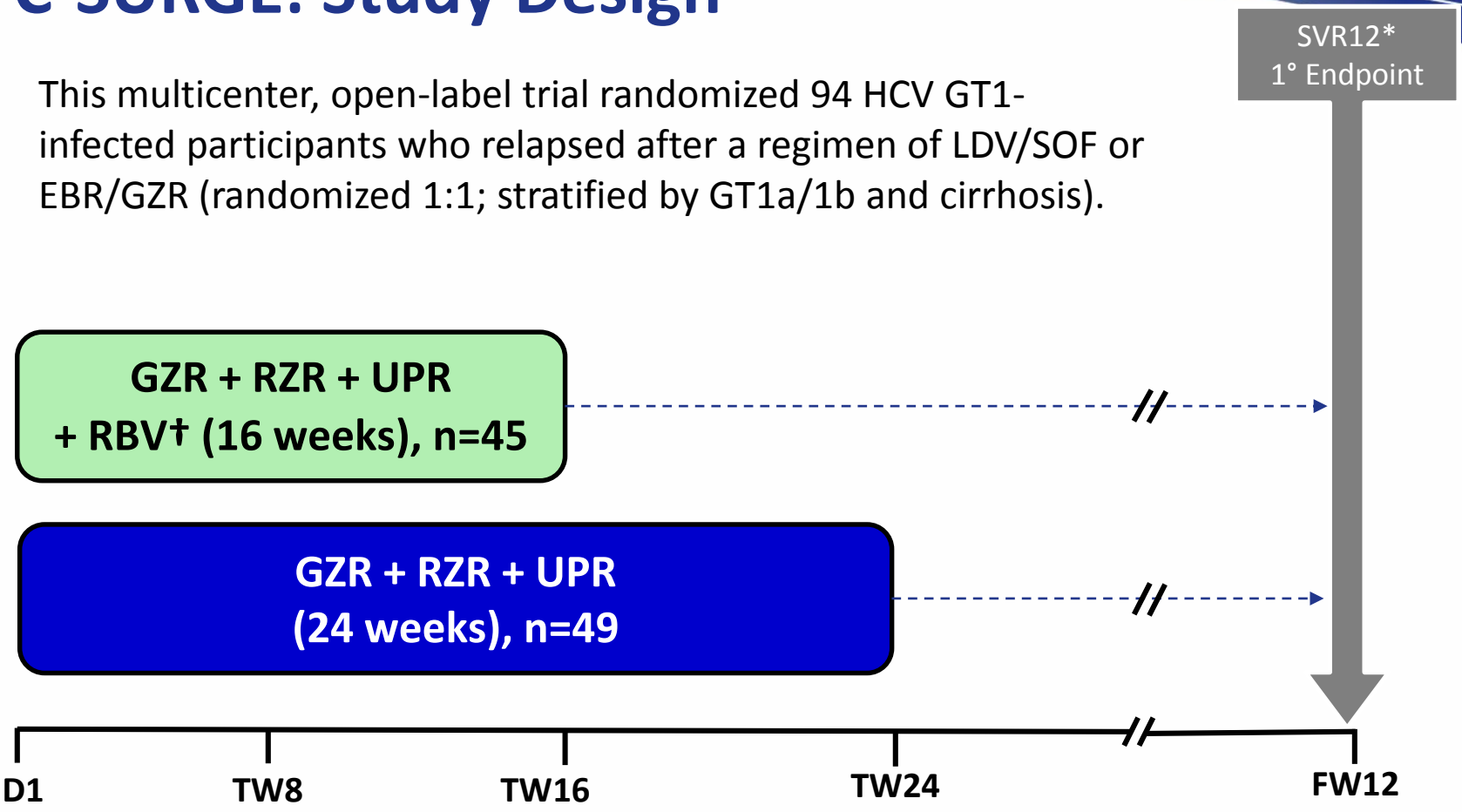
- Among DAA-experienced patients, 71% and 69% had NS3 or NS5A class RASs at baseline with 1% and 15% cutoffs, respectively

Among DAA-experienced patients NS3 or NS5A class RASs at baseline had no effect on SVR12

GZR RZR UPR

C-SURGE: Study Design

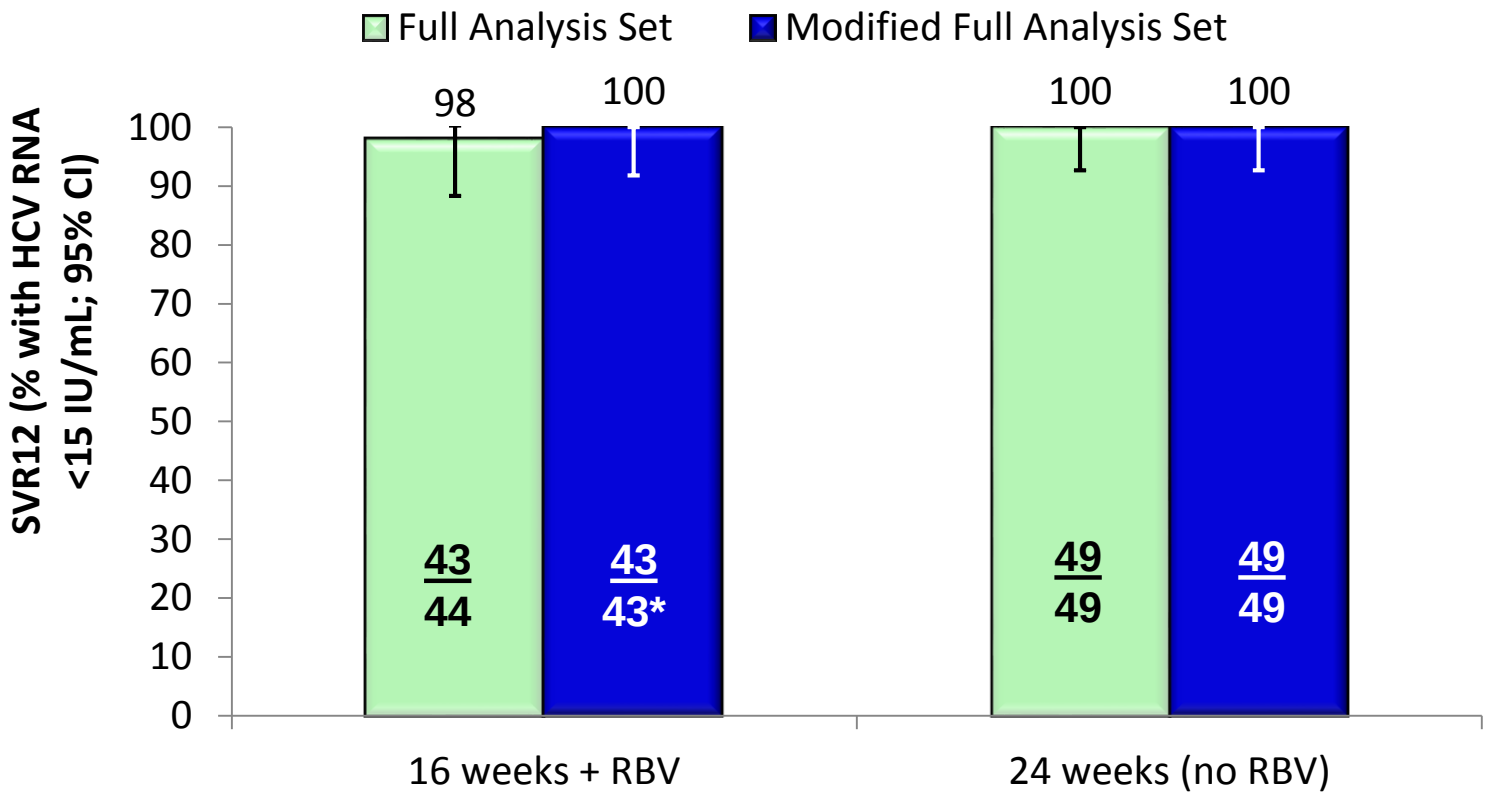
- This multicenter, open-label trial randomized 94 HCV GT1-infected participants who relapsed after a regimen of LDV/SOF or EBR/GZR (randomized 1:1; stratified by GT1a/1b and cirrhosis).



GZR: 100 mg once-daily; RZR: 60 mg once-daily; UPR: 450 mg once-daily; TW= treatment week; FW=follow-up week; LDV=ledipasvir; SOF=sofosbuvir.
*SVR12 = HCV RNA <15 IU/mL at 12 weeks after end of treatment (COBAS™ AmpliPrep/COBAS™ Taqman™ HCV Test, v2.0®).
†RBV dose based on body weight (<65 kg=800 mg/d; 65-85 kg=1000 mg/d; >85-105 kg=1200 mg/d; >105 kg=1400 mg/d).
Individuals could be compensated cirrhotic (platelet cutoff=75,000/µL; excluded Child-Pugh B & C) or non-cirrhotic individuals.

C-SURGE 1

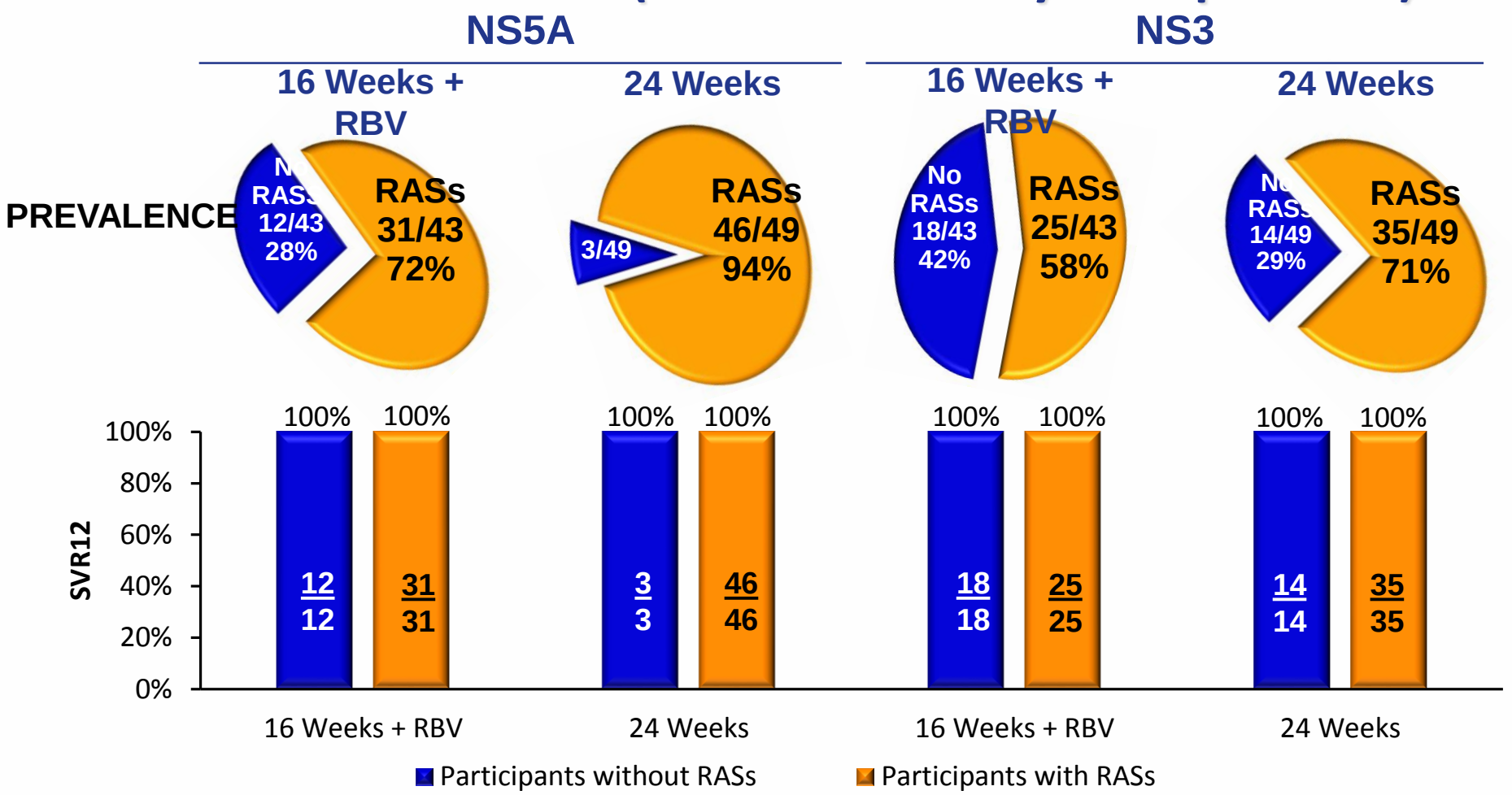
C-SURGE: MK3 Efficacy in LDV/SOF or EBR/GZR experienced (SVR12; Full Analysis Set; Modified Full Analysis Set*)



SVR12 = % of participants with HCV RNA <15 IU/mL at 12 weeks after end of treatment.
Full analysis set = all patients who received at least one dose of study medication;
*Modified full analysis set excluded one participant from the 16-week + RBV arm who withdrew from the study after taking 3 doses of study medication.

GZR RZR UPR

No Impact of Baseline NS5A or NS3 RASs on SVR12 (Resistance Analysis Population)

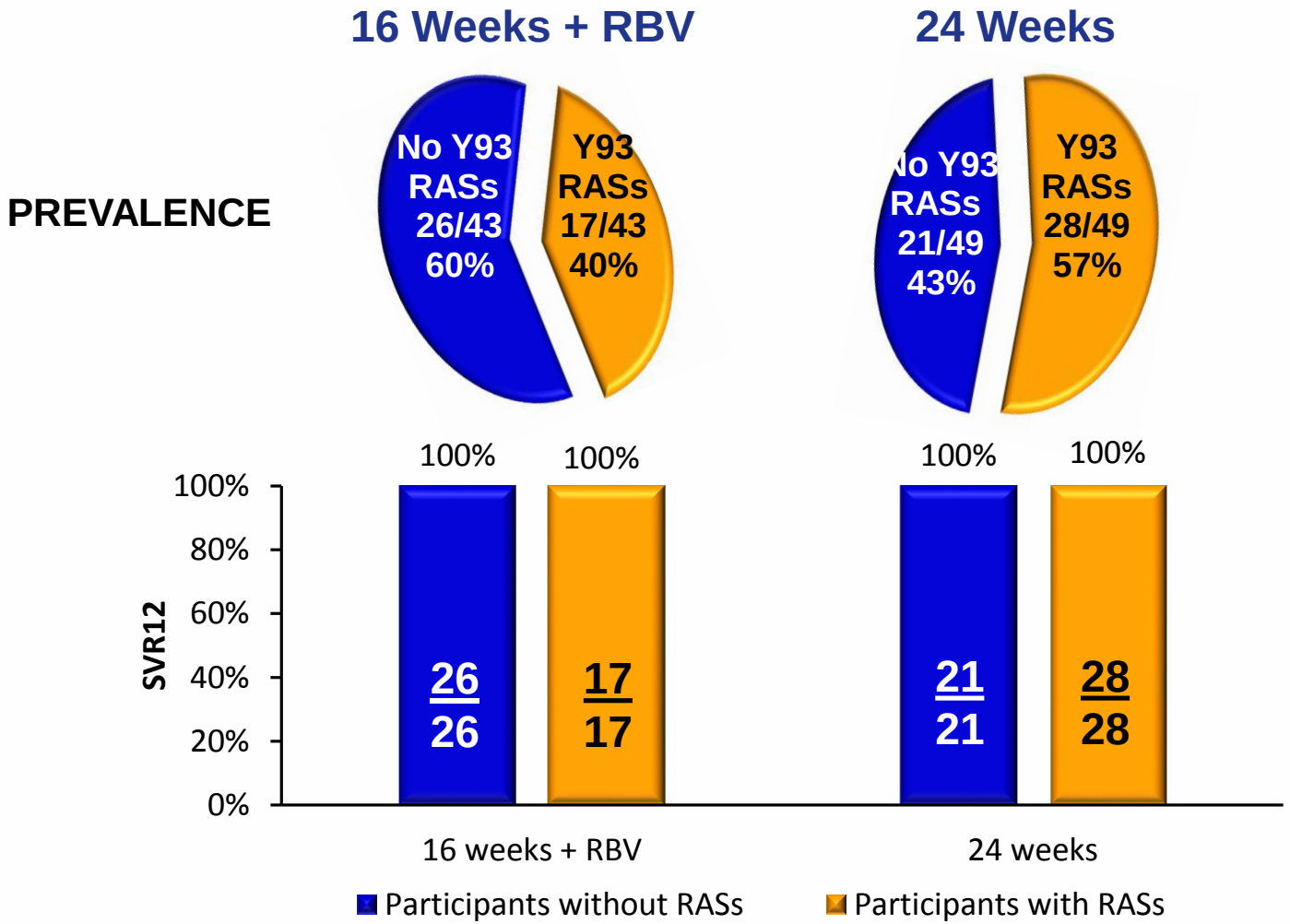


SVR12=proportion of participants with HCV RNA <15 IU/mL at 12 weeks after end of treatment.
*RASs detected by next-generation sequencing with 15% sensitivity; NS5A RAS: any change from wild-type at 4 positions (28, 30, 31, or 93); NS3 RASs = any change from wild-type at 14 positions (36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175).
†Excluded 1 participant from the 16-week group who withdrew after receiving 3 doses of study medication; Includes 38 of 49 participants who have reached follow-up week 4.

C-SURGE 1

GZR RZR UPR

No Impact of Baseline Y93 RASs in NS5A on SVR12 (Resistance Analysis Population)



SVR12=proportion of participants with HCV RNA <15 IU/mL at 12 weeks after end of treatment.
*RASs detected by next-generation sequencing with 15% sensitivity.
†Excludes 1 participant from the 16-week group who withdrew after receiving 3 doses of study medication.

C-SURGE 1

I fallimenti al primo trattamento con DAA: quali possibilità terapeutiche

- **Quanti:** 3-4% dei pazienti trattati: in Italia 2100-3000
- **Perchè**: Fallimento multifattoriale non solo RASs
- **Ruolo dei tests molecolari:** mandatorio, sui tre geni target, modalità: NGS o PS con cut off 15% associando genotipizzazione basata sulla sequenza
- Caratteristiche dei pazienti con fallimento a DAA IFN free in Italia:
  - Il diavolo è nei dettagli
- Schemi di ritrattamento:
  - Terapie attuali:
    - Cirrosi scompensata SOF VEL RBV 24 settimane
    - Cirrosi compensata: Sof + 3D o G/E HCV G1 e G4 attesa vigile HCV G2 e G3
  - Terapie future: tre è meglio di 2