German Hepatitis C Resistance Registry

5th HCV Therapy Advances Workshop
Virology Education, Amsterdam, 05 December 2015

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Disclosures

Consultancies / Advisory boards:

Abbott, Abbvie, BMS, Gilead, Janssen, Merck/MSD, Roche

Research support:

Abbott, Gilead, Janssen, Qiagen, Roche, Siemens

Speaker:

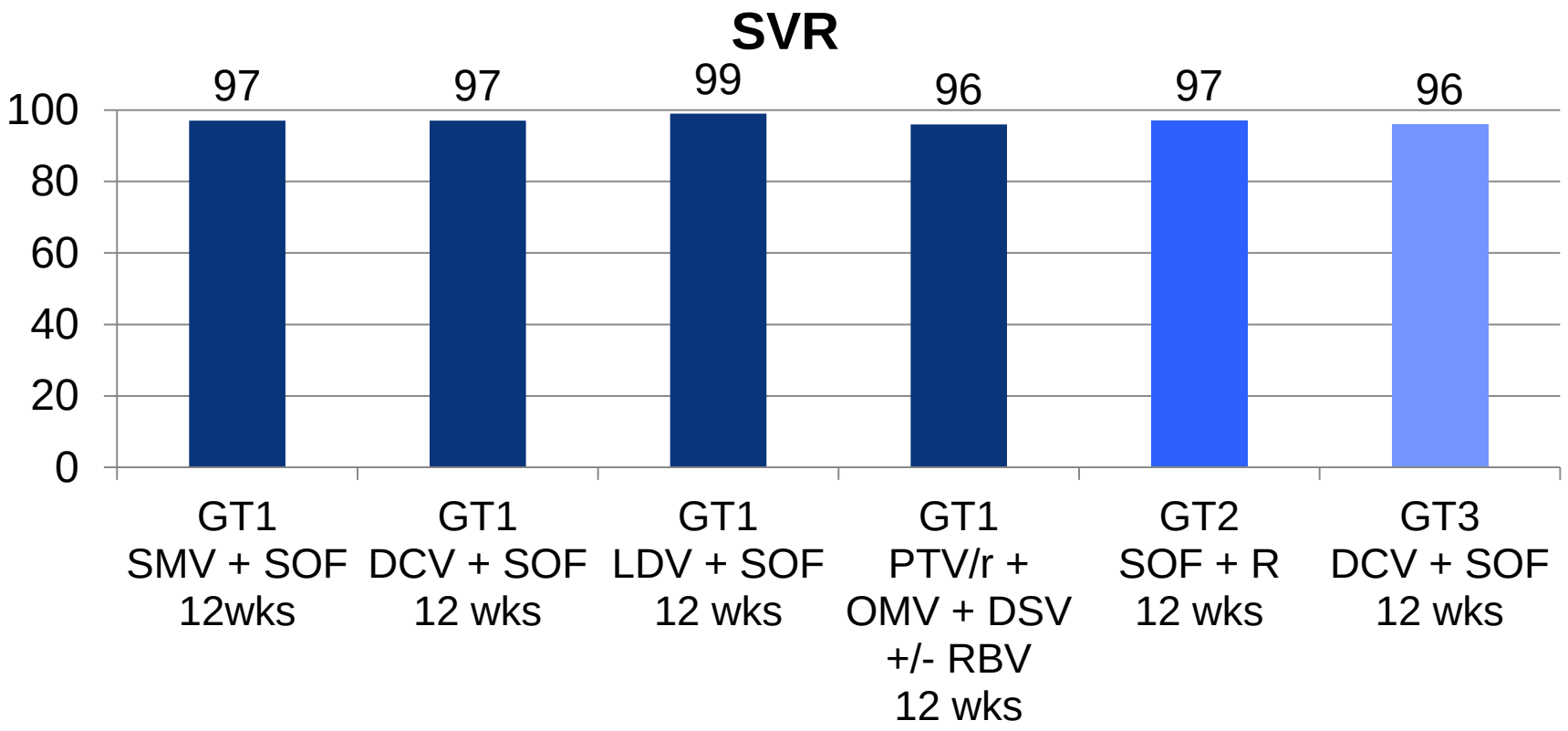
Abbott, Abbvie, Achillion, BMS, Gilead, Janssen, Merck/MSD, Qiagen, Roche, Siemens

Overview

- Efficacy of DAA combination therapies
- Naturally pre-existing resistance
- Importance of RAVs after BOC and TVR
- Importance of RAVs after SOF/R +/- PEG
- Importance of RAVs after DAA combination therapies

Antiviral efficacy of DAA therapies

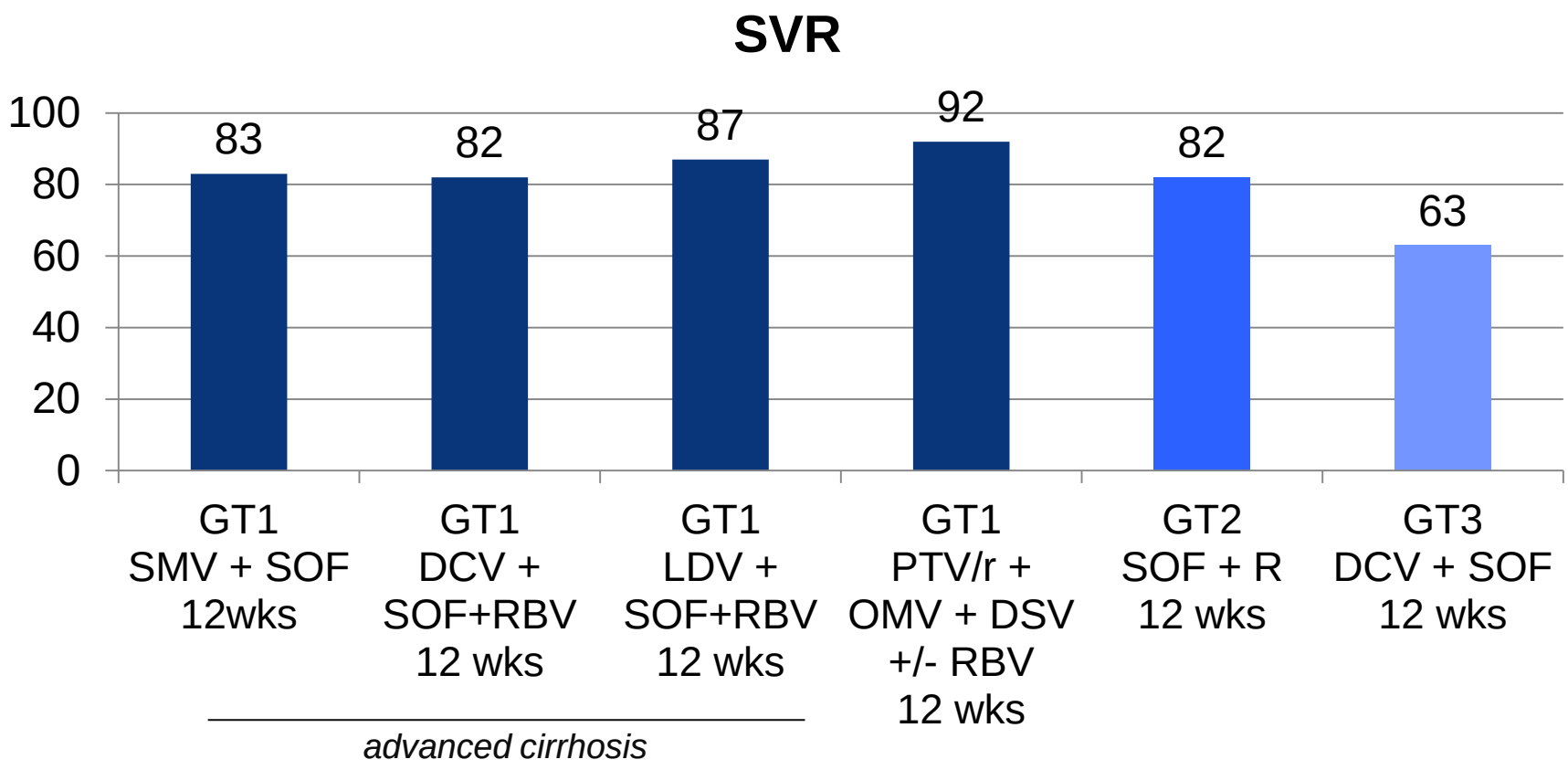
SVR Rates in HCV patients without cirrhosis
(no head-to-head studies)



Kwo et al., EASL 2015, LB04; Wyles et al., ESL 2015, LP01; Afdhal et al., NEJM 2014; Feld et al., NEJM 2014; Zeuzem et al., NEJM 2014
Gane et al., NEJM 2013. Nelson et al., Hepatology 2015

Antiviral efficacy of DAA therapies

SVR Rates in HCV patients with (advanced) cirrhosis
(no head-to-head studies)



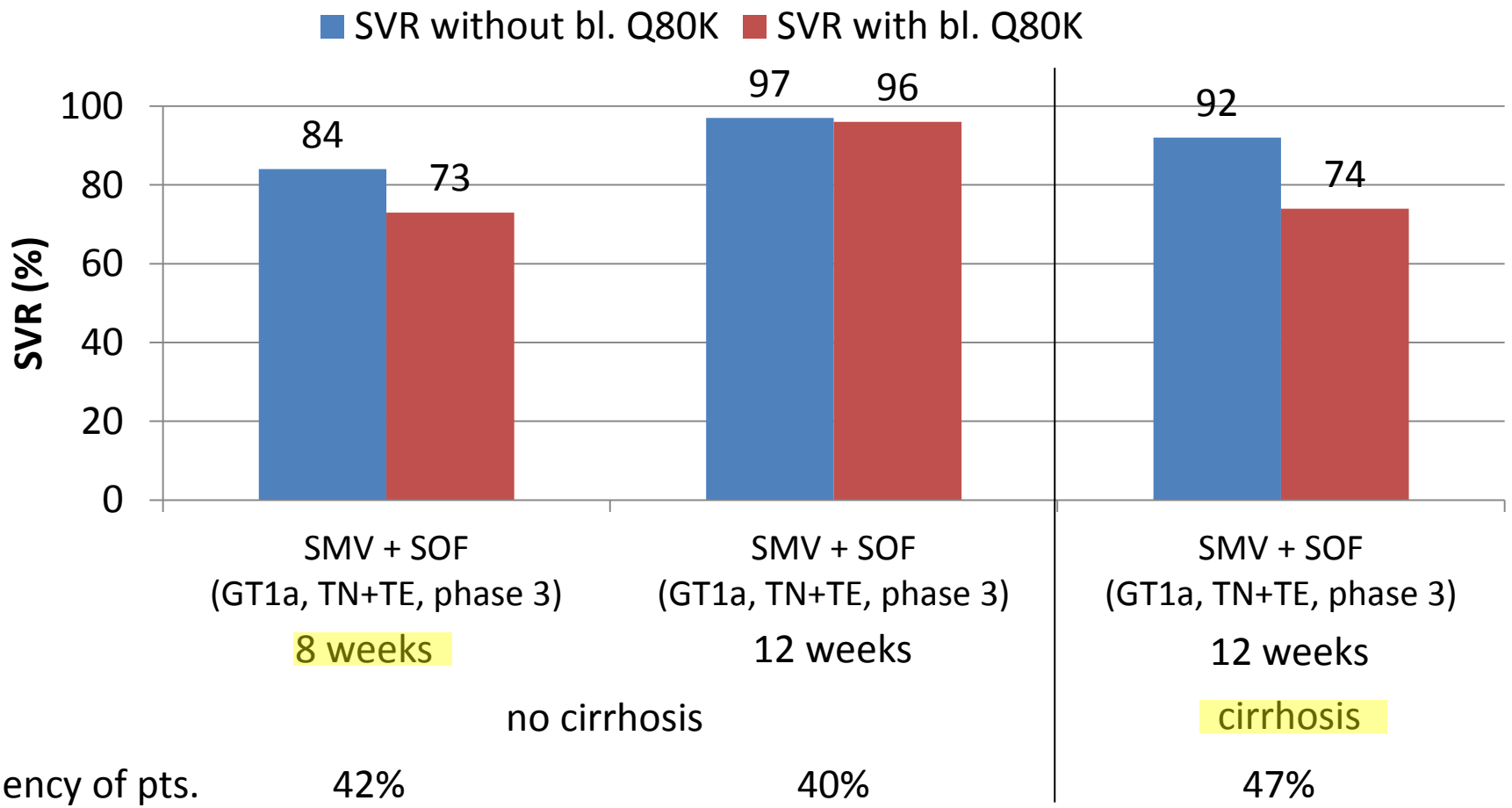
Lawitz et al., EASL 2015, LB04; Wyles et al., ESL 2015, LP01; Afdhal et al., NEJM 2014; Feld et al., NEJM 2014; Zeuzem et al., NEJM 2014
Gane et al., NEJM 2013. Nelson et al., Hepatology 2015; Gane et al., AASLD 2015, 1049

Importance of resistance associated variants

DAA combination treatment naïve patients (GT1)

NS3 protease plus NS5B NUC

no head to head studies, different resistance analysis



Sarrazin; J Hepatol 2015 epub

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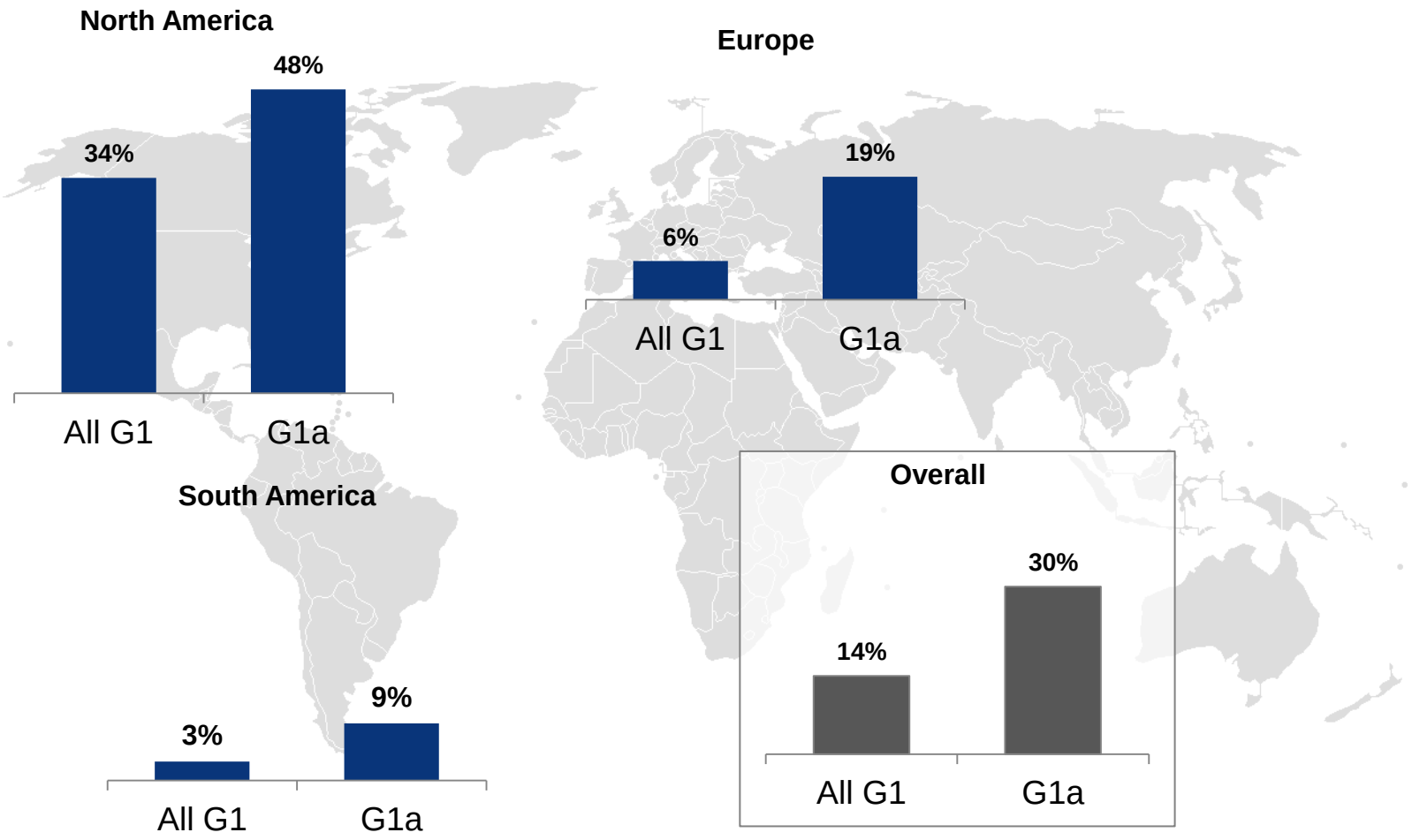
Rate and frequency of DAA failures

		Tx status [n=]	total RAVs detected [n=]	special RAVs detected [n=]		(re-)Tx w/o RAVs possible in
Treatment-naïve		968	365 (38%)	365 (38%)	NS3 (57%), NS5A (38%), NS5B (5%)	99%

Tx-treatment; RAVs-resistance associated variants; w/o-without; TVR-telaprevir; BOC-boceprevir; SOF-sofosbuvir; RBV-ribavirin; PEG-pegylated interferon-alfa; SMV-simeprevir; DCV-daclatasvir; LDV-ledispasvir; PTV-paritaprevir; OMB-ombitasvir; DSV-dasabuvir

Overall prevalence of Q80K in G1 across different regions



Q80K in G1b was seen with an overall prevalence of 0.5% (0.3% in Europe; 0% in North and South America)

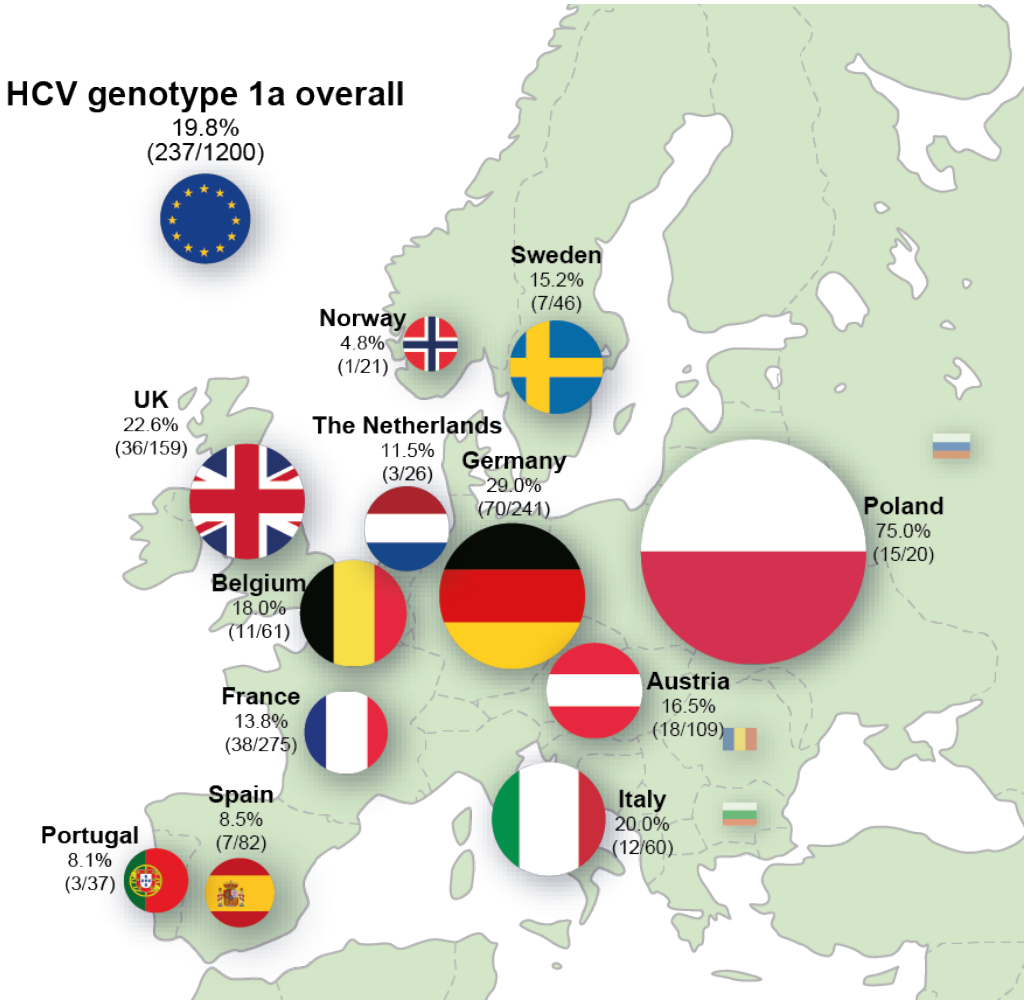
Includes 15 patients with non-1a/b genotype.

Sarrazin et al., Antiviral Res 2015
Lenz et al. J Hepatol 2014

Q80K prevalence in European GT1a patients

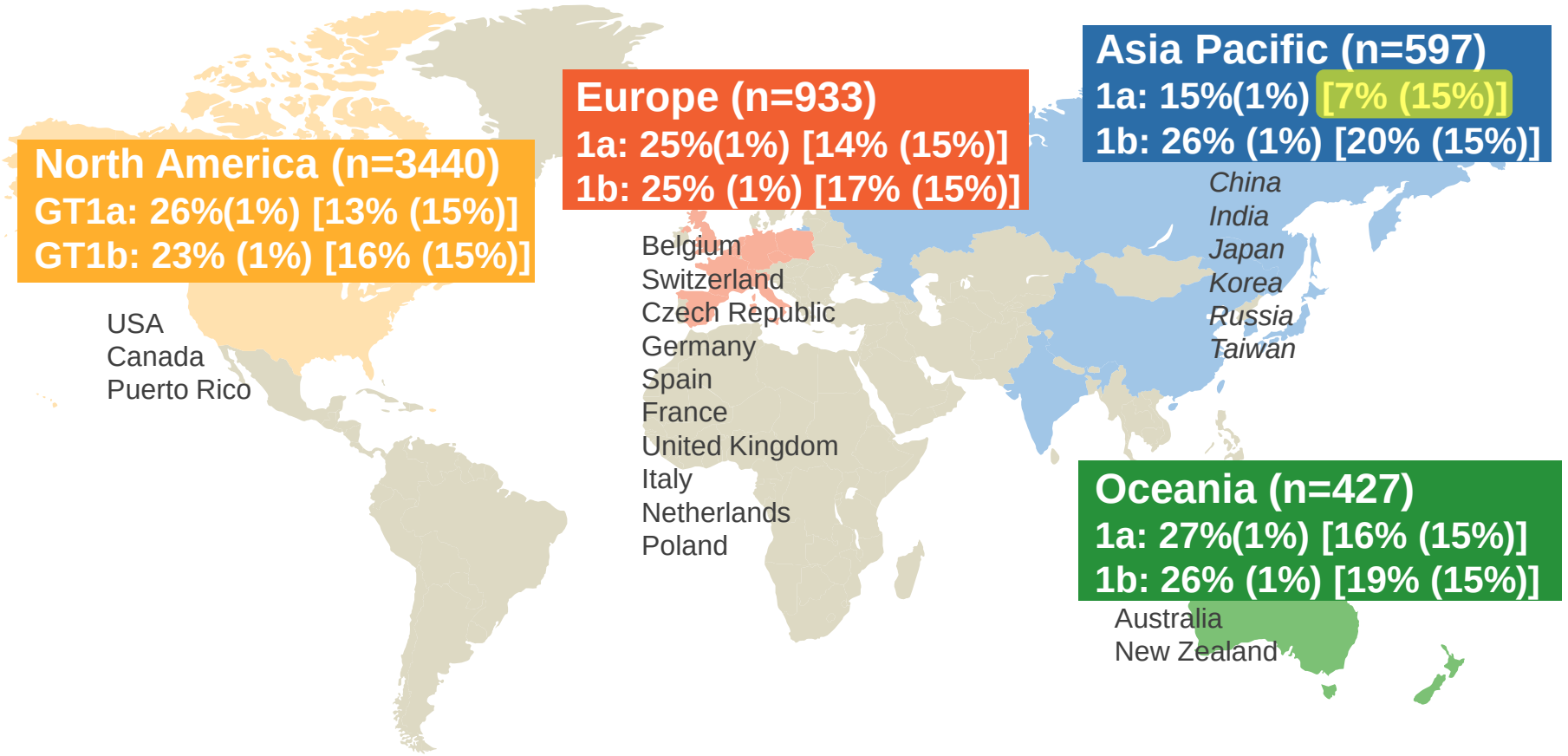
Country	GT1a prevalence within GT1 population (%)
Austria	53.4
Belgium	28.9
Bulgaria	28.6
France	52.8
Germany	41.1
Italy	28.6
The Netherlands	63.4
Norway	80.8
Poland	4.3
Portugal	80.4
Romania	0
Russia	3.3
Spain	31.2
Sweden	78.0
UK	80.3

Q80K prevalence within GT1a population



Sarrazin C, et al. Antiviral Research 2015. Antiviral Res. 2015;116:10–16

Overall prevalence of NS5A resistance across different regions (GT1; n=5397)



GT1a: mainly Q30H/R and L31M (≈ 13%), Y93H (≈2%)
GT1b: mainly Y93H (≈15%) and L31M/I/V (≈10%)

GT1a NS5A RAVs: K24G/N/R, K26E, M28A/G/T/V, Q30C/E/G/H/I/L/K/R/S/T/Y, L31I/F/M/V, P32L, S38F, H58D/L, A92K/T, Y93C/F/H/L/N/R/S/T/W

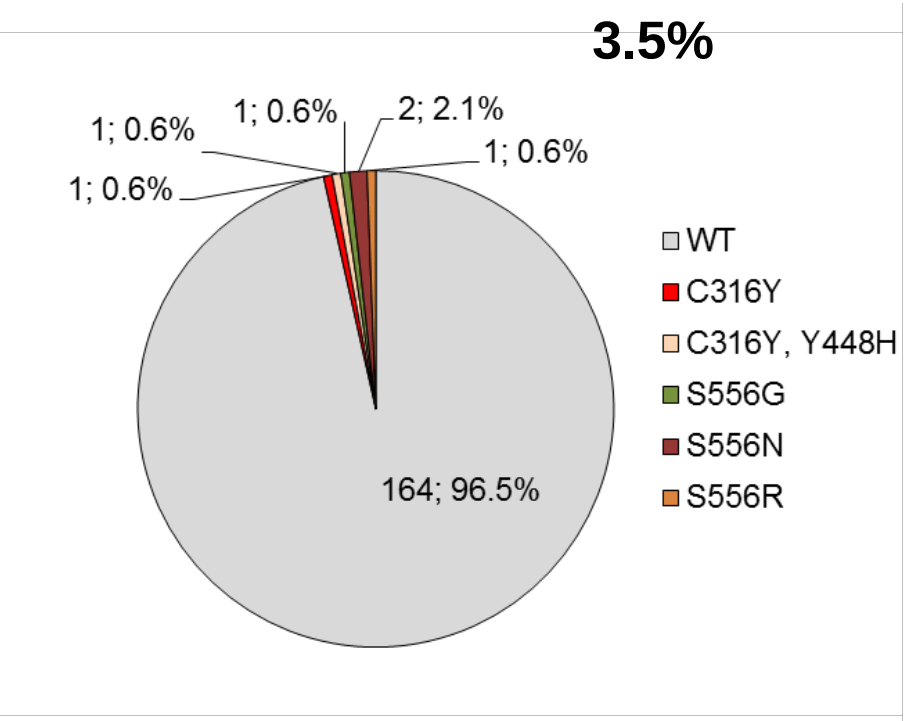
Zeuzem et al., AASLD 2015, #91

Natural frequency of resistance

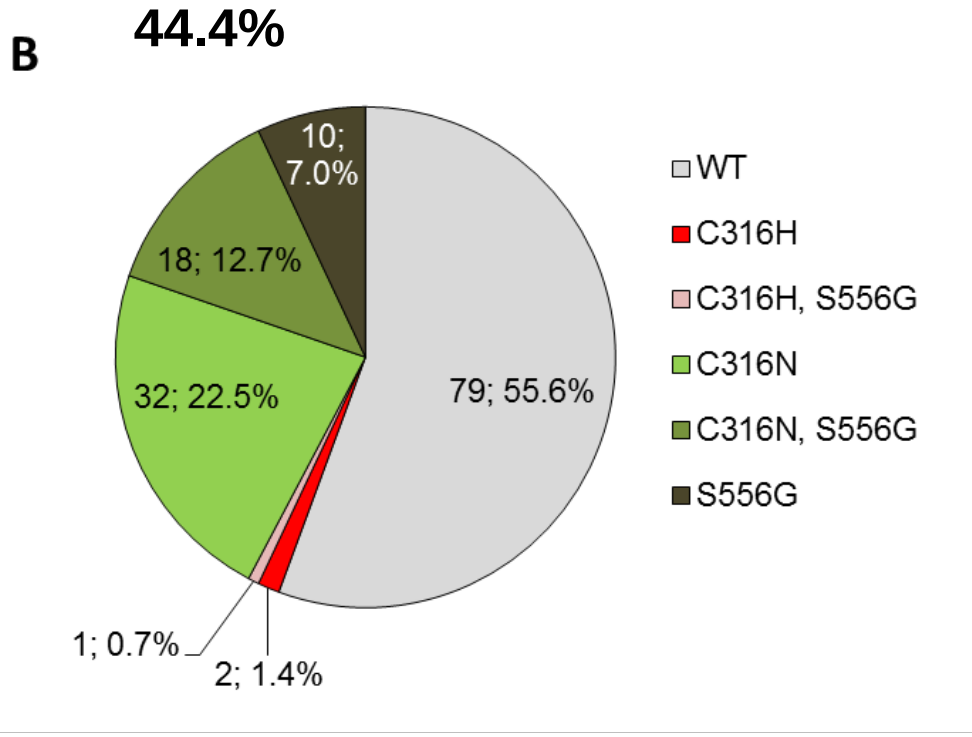
Differences for targets and between HCV geno- and subtypes

NS5B gene (palm I and NUC)

Genotype 1a



Genotype 1b



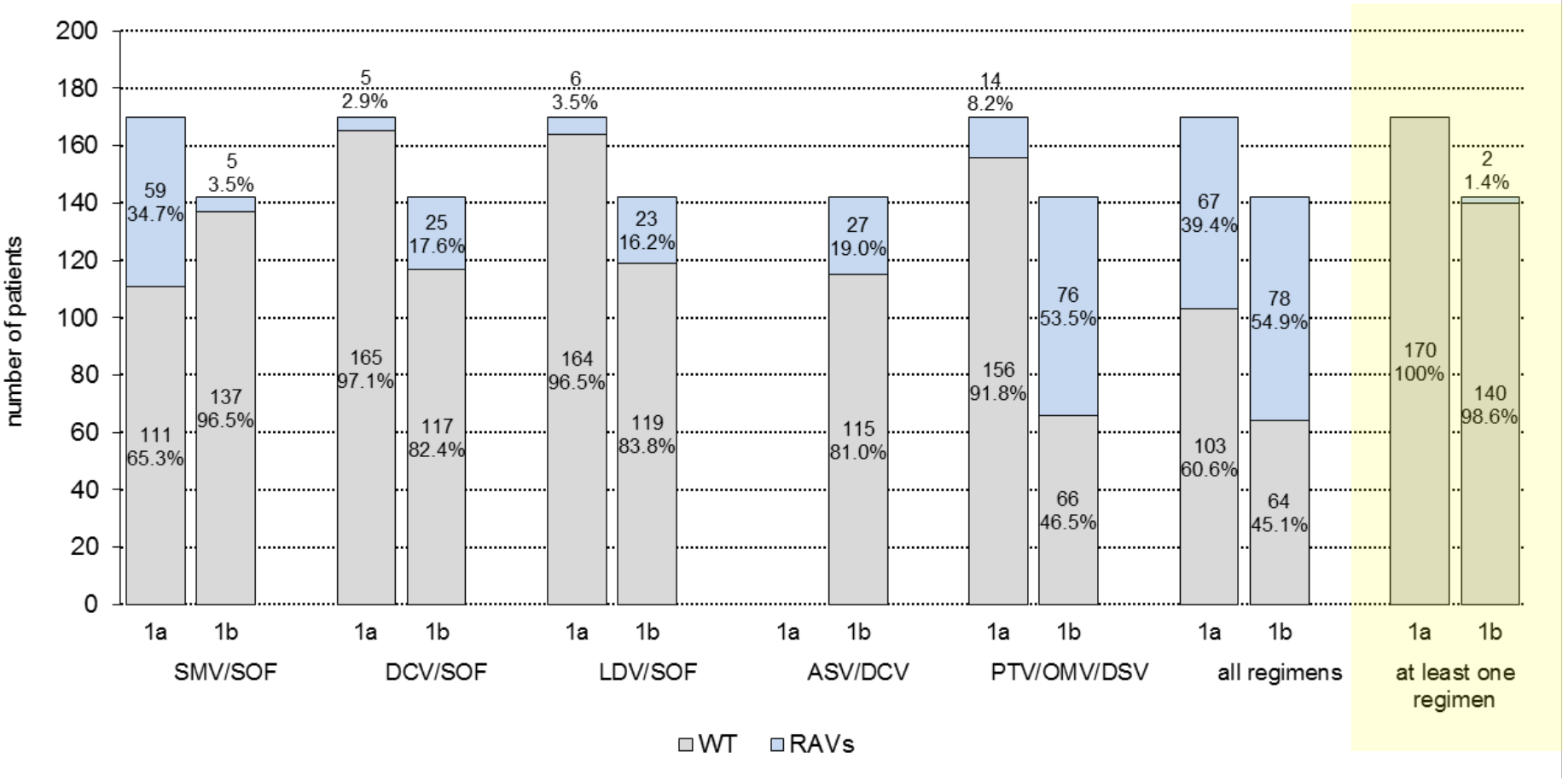
no pre-existence of S282T variants

Dietz et al., PlosOne 2015

Natural frequeny of resistance

Selection of DAA regimens without baseline resistance

Availability of an IFN-free DAA combination regimen without baseline RAVs according to European GT1 patients



Dietz et al., PlosOne 2015

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- Importance of RAVs after DAA combination therapies

Rate and frequency of DAA failures

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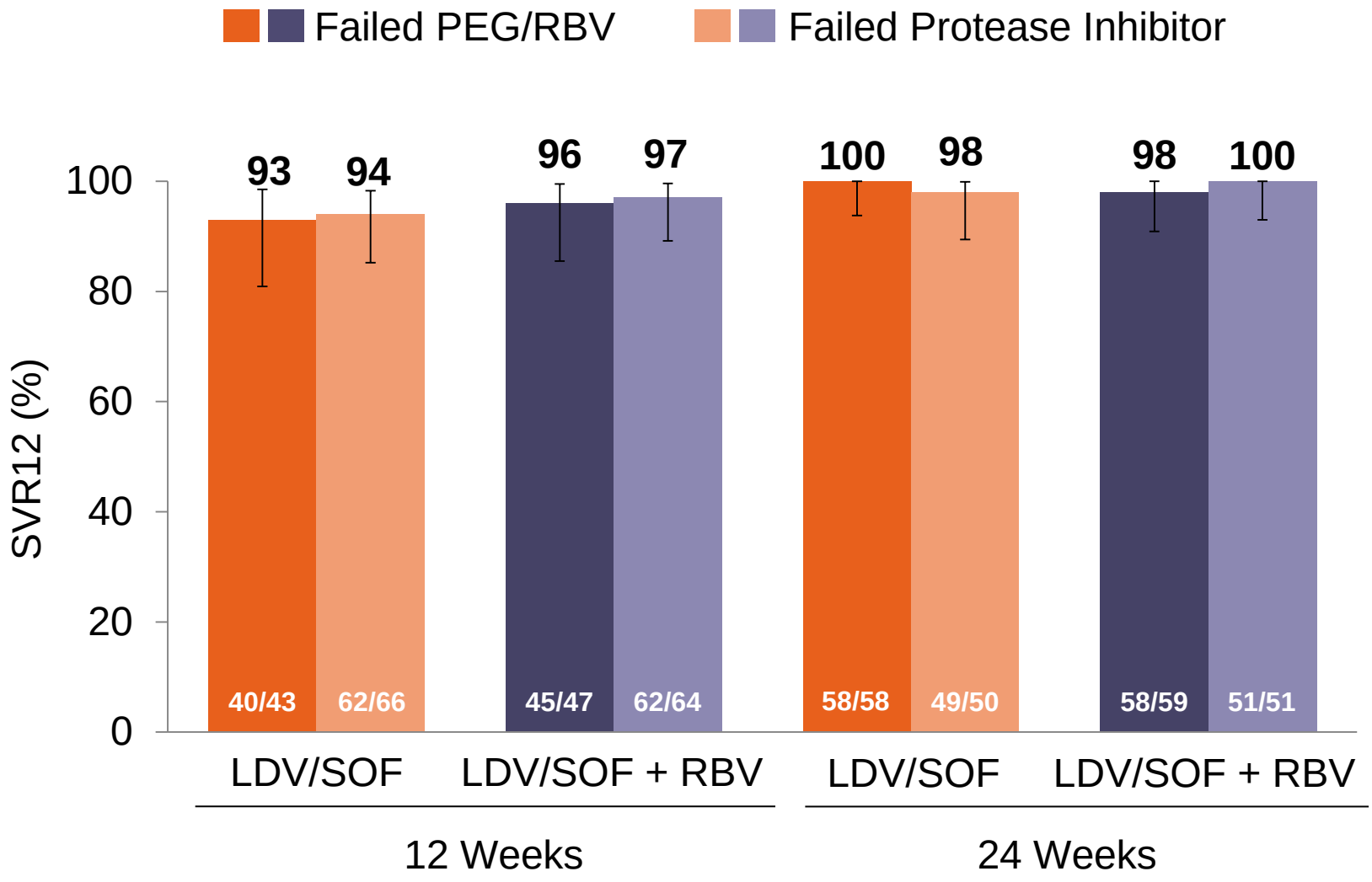
Treatment-naïve	968	365 (38%)	365 (38%)	NS3 (57%), NS5A (38%), NS5B (5%)	99%
Pre-treatment:					
PEG/RBV	797	275 (34%)	275 (34%)	NS3, NS5A/B	98%
TVR	201	90 (45%)	72 (36%)	NS3	96%
BOC	132	48 (36%)	34 (26%)	NS3	95%

Tx-treatment; RAVs-resistance associated variants; w/o-without; TVR-telaprevir; BOC-boceprevir; SOF-sofosbuvir; RBV-ribavirin; PEG-pegylated interferon-alfa; SMV-simeprevir; DCV-daclatasvir; LDV-ledispasvir; PTV-paritaprevir; OMB-ombitasvir; DSV-dasabuvir

SOF/LDV: Re-treatment

Genotype 1 (79% 1a), 20% cirrhosis, TE (50% BOC/TVR failure), (ION 2)



Error bars represent 95% confidence intervals.

Afdhal et al., EASL 2014, #O109 und NEJM 2014

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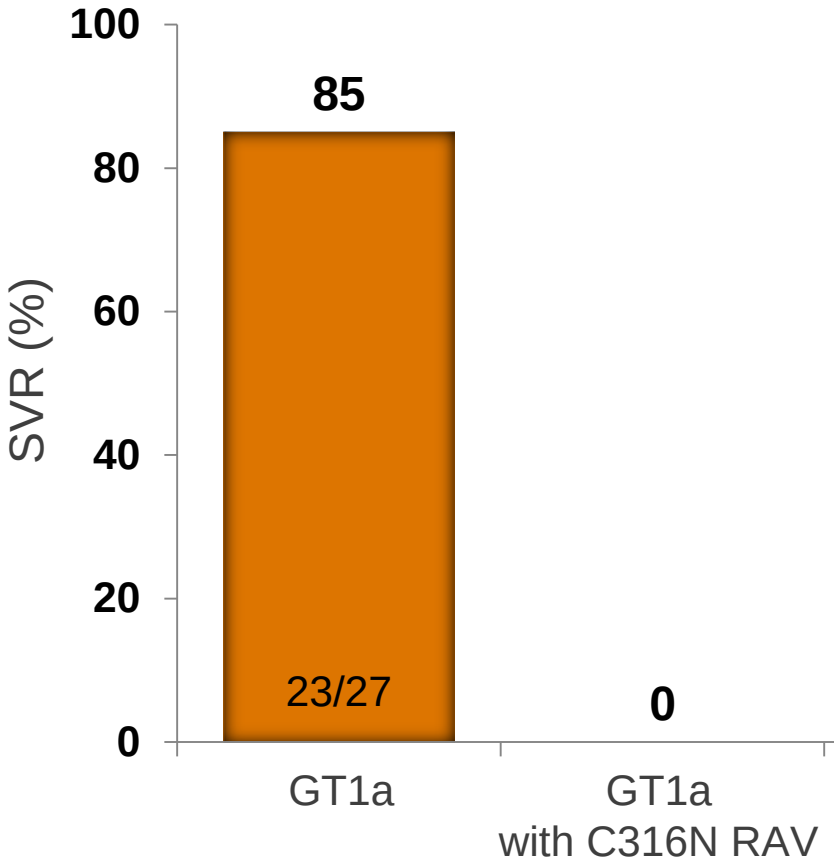
BOC	132	48 (36%)	34 (26%)	NS3	95%
SOF/RBV	89	52 (58%)	0 (0%)	NS5B	83%
SOF/PEG/RBV	39	18 (46%)	0 (0%)	NS5B	90%

Tx-treatment; RAVs-resistance associated variants; w/o-without; TVR-telaprevir; BOC-boceprevir; SOF-sofosbuvir; RBV-ribavirin; PEG-pegylated interferon-alfa; SMV-simeprevir; DCV-daclatasvir; LDV-ledispasvir; PTV-paritaprevir; OMB-ombitasvir; DSV-dasabuvir

Importance of Baseline-Resistance

SOF + (PEG) / RBV

- 71 pts with HCV GT1 infection treated with SOF+RBV or SOF+PEG-IFN+RBV (GT1a n=29, GT1b n=39, GT1 n=3)
- Importance of C316N (L159F always in combination with C316N, no other RAVs as S282T, V321, S368), baseline samples available in 48 pts.



Vermehren et al., AASLD 2015, #1055

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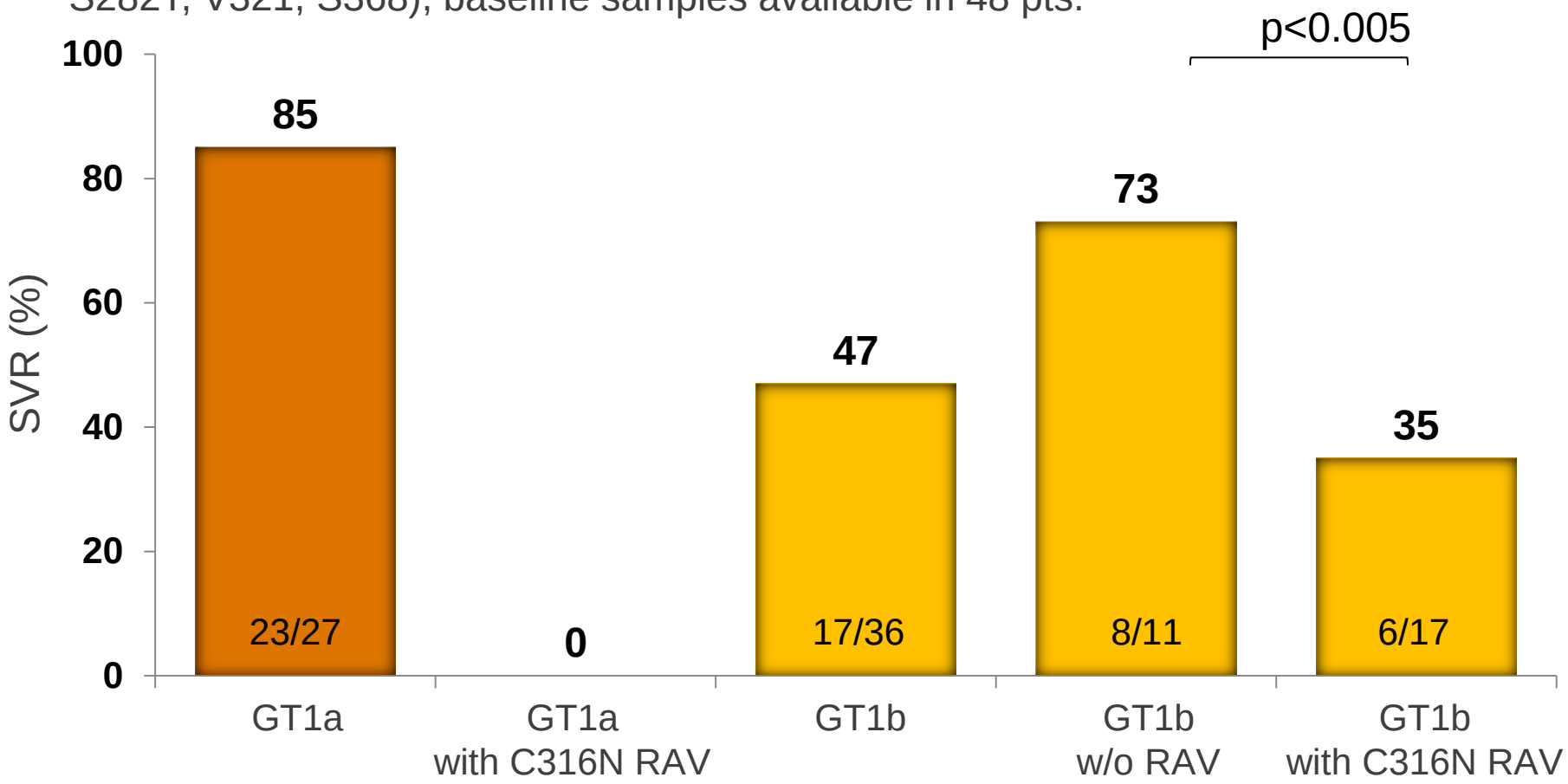
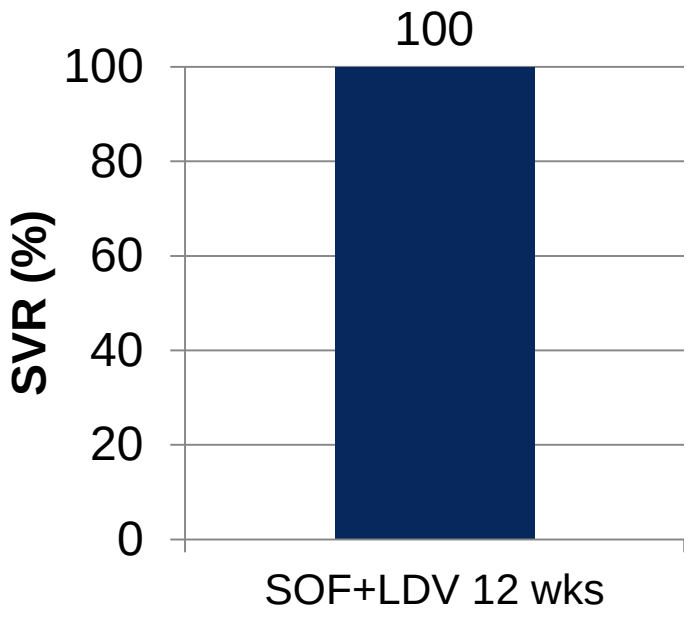


Vermehren et al., AASLD 2015, #1055

Salvage therapy for SOF/RBV +/-PEG Failures

Failure to SOF+RBV HCV genotype 1

N=14 patients with failure to 24 weeks SOF+RBV



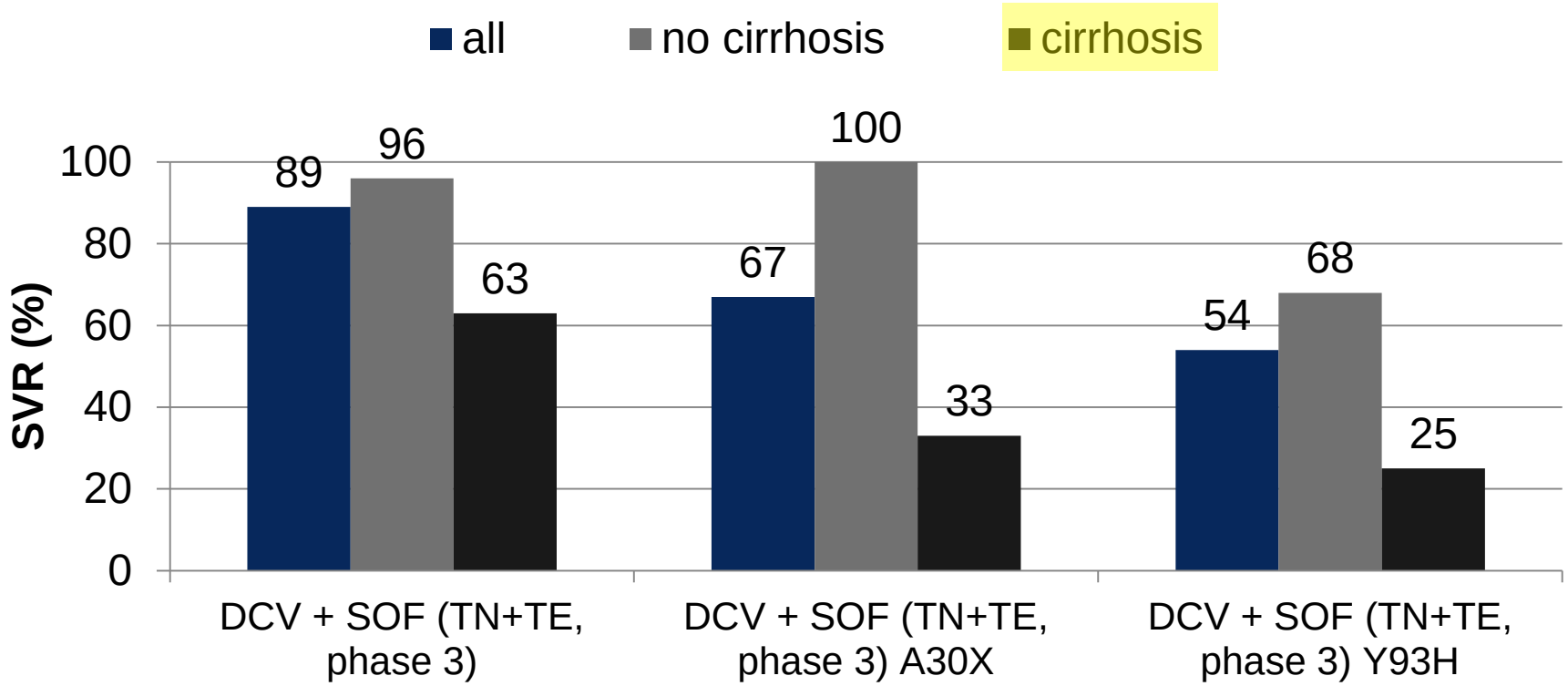
7 patients with F3/4 are included

Osinusi et al., Ann Intern Med 2014

Importance of resistance associated variants

DAA combination treatment naïve patients (GT3)

Genotype 3
NS5A inhibitor plus NS5B NUC



Frequency of pts. with baseline RAVs

10%

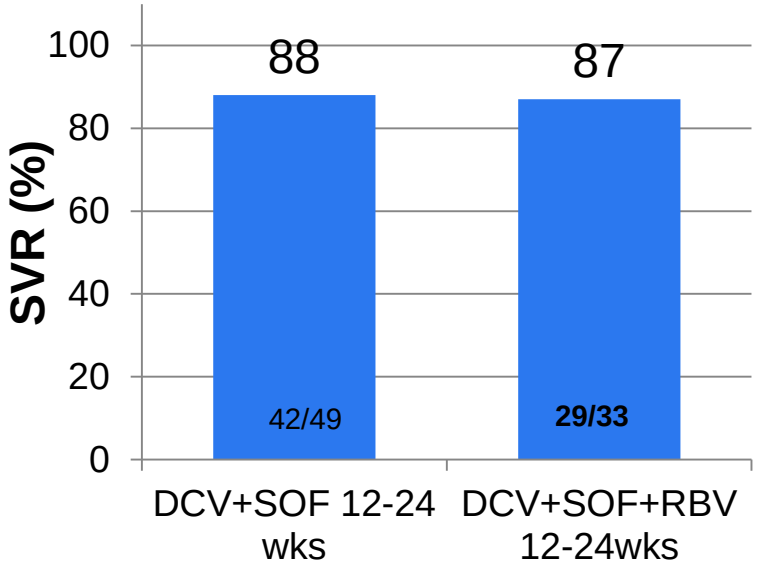
9%

Nelson et al., Hepatology 2015; Sarrazin; J Hepatol 2015 epub

Genotype 3
DCV + SOF and DCV + SOF + RBV

DCV+SOF +/-RBV

EU comp use
TN+TE, 81% cirrhosis, n=82
12 – 24 wks

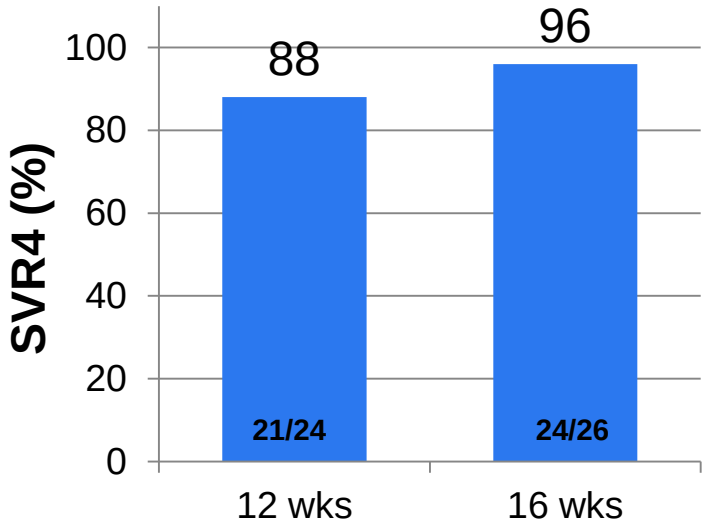


Zirrhose	88% (37/42)	86% (25/29)
12 wks	86% (6/7)	71% (5/7)
24 wks	86% (36/42)	92% (24/26)

Welzel et al., AASLD 2015, O#37

DCV + SOF + RBV

Ally 3+
12 or 16 wks
F3 or F4, n=50



REL n=2 n=2

- 2 pts SOF-exp. relapsed (16wks)
- 1 pat. died (12 wks)
- BL RAV Y93H 50% SVR (1/2)

Leroy et al., AASLD 2015, LB3

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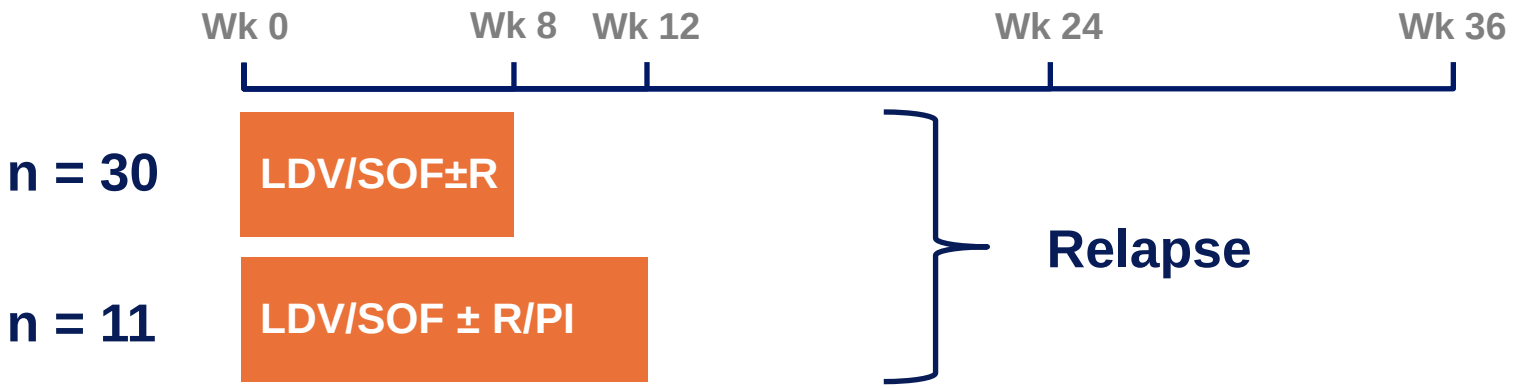
SOF/PEG/RBV	39	18 (46%)	0 (0%)	NS5B	90%
SOF/SMV	44	38 (86%)	28 (64%)	NS3, NS5B	88%
SOF/DCV	43	38 (88%)	36 (84%)	NS5A/B	49%
SOF/LDV	63	48 (76%)	38 (60%)	NS5A/B	62%
PTVr/OMB/DSV	18	18 (100%)	18 (100%)	NS3, NS5A/B	28%

Tx-treatment; RAVs-resistance associated variants; w/o-without; TVR-telaprevir; BOC-boceprevir; SOF-sofosbuvir; RBV-ribavirin; PEG-pegylated interferon-alfa; SMV-simeprevir; DCV-daclatasvir; LDV-ledispasvir; PTV-paritaprevir; OMB-ombitasvir; DSV-dasabuvir

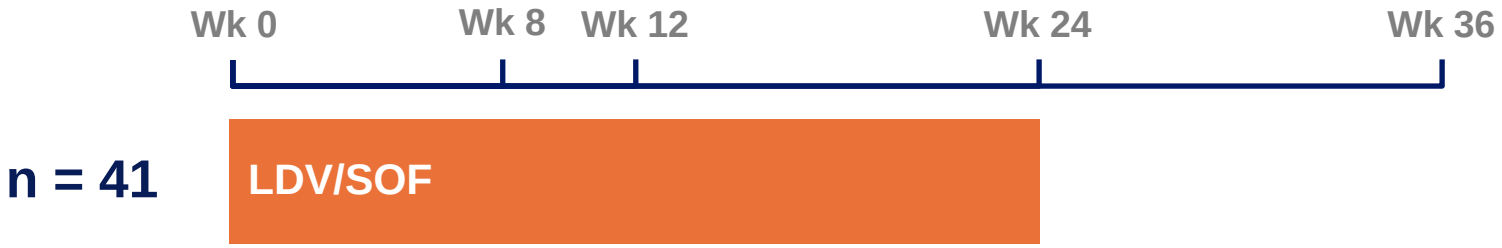
Deutsches Hepatitis C Register, TTU Hepatitis, Europ. HCV Resistenzdatenbank, Frankfurt am Main

Efficacy of salvage therapies after DAA failure (Genotype 1)

Initial therapy (ION-1, ION-2, ION-3, LONESTAR, and TRILOGY-1)



Re-treatment

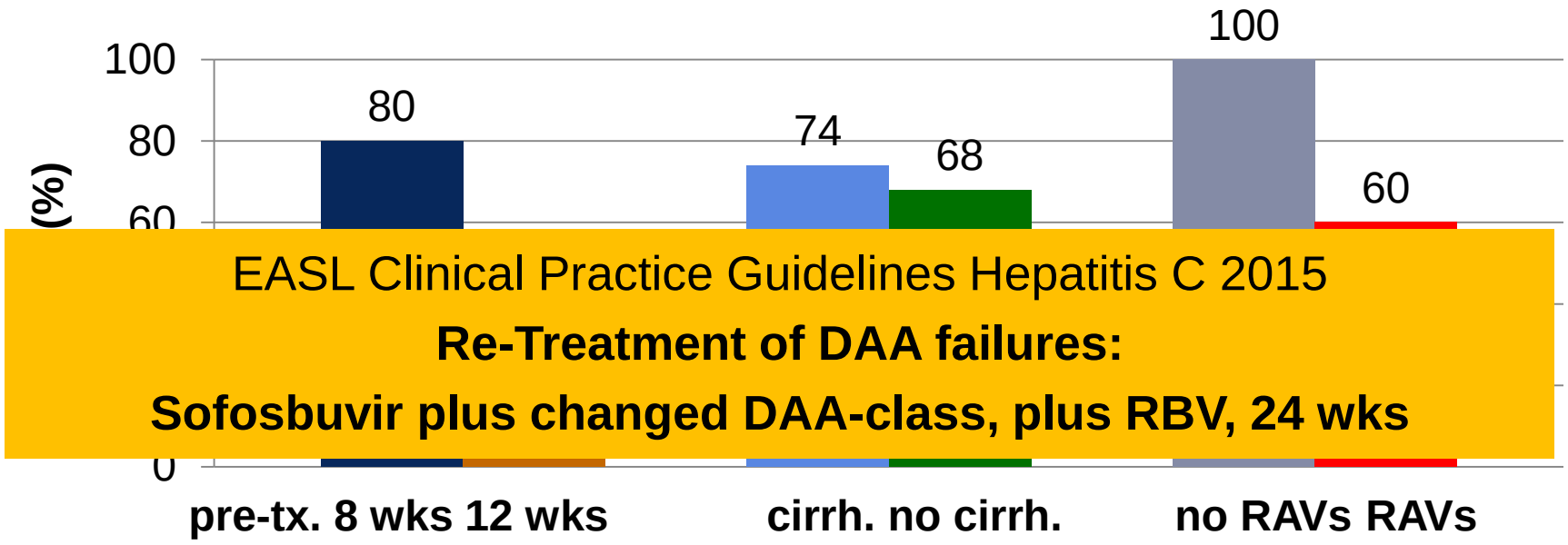


Lawitz et al., EASL 2015

Re-treatment of DAA combination failure patients

24 wks. SOF/LDV after virolog. failure to SOF/LDV +/- RBV

n=41, cirrh. n=19, failure to 8 (n=30) or 12 weeks (n=11)
SOF/LDV +/-RBV



EASL Clinical Practice Guidelines Hepatitis C 2015

Re-Treatment of DAA failures:

Sofosbuvir plus changed DAA-class, plus RBV, 24 wks

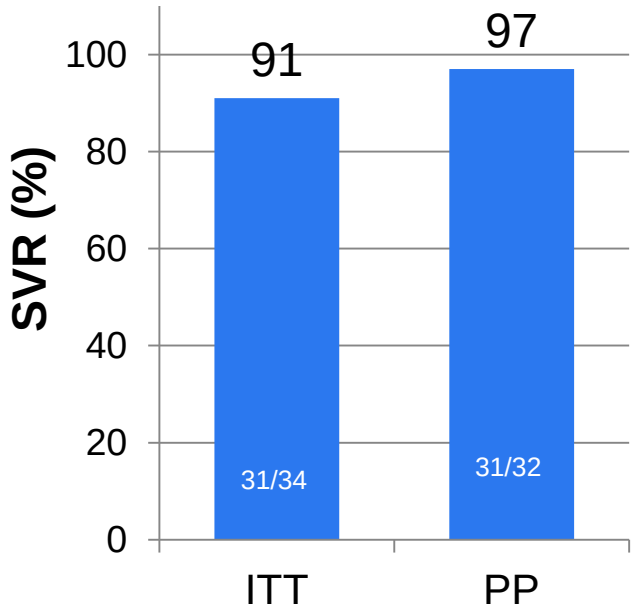
- All 11 patients without NS5A RAVs received 8 weeks of prior treatment

Lawitz et al., EASL 2015, O005

Salvage Therapy

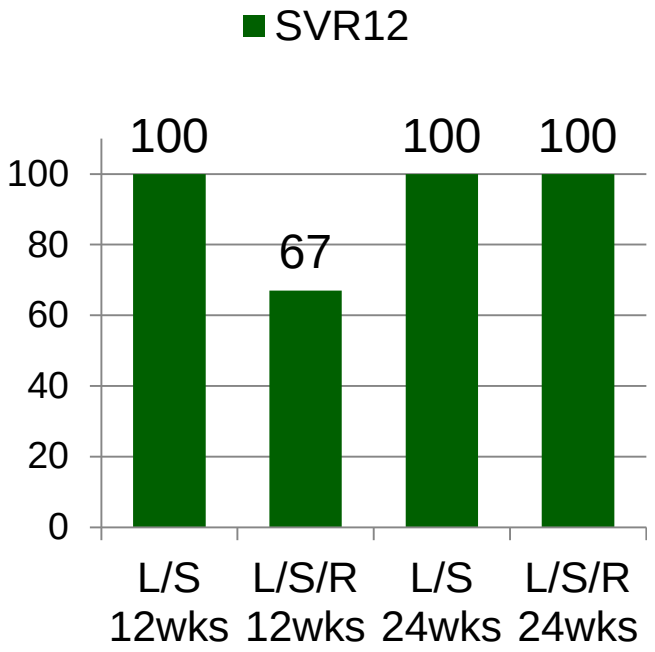
LDV/SOF after DAA triple or SMV/SOF

- n=32, GT1, no cirrhosis, 3-4 DAA (LDV/SOF + **PI**+/- NonNUC) 4-6 wks
- Baseline RAVs in 85% by NGS
- ➢ Treatment LDV/SOF for 12 wks



Wilson et al., AASLD 2015, #O92

- n=46, GT1, relapse to **SMV**/SOF
- Baseline RAVs ?
- ➢ Treatment LDV/SOF +/- RBV for 12 or 24 wks



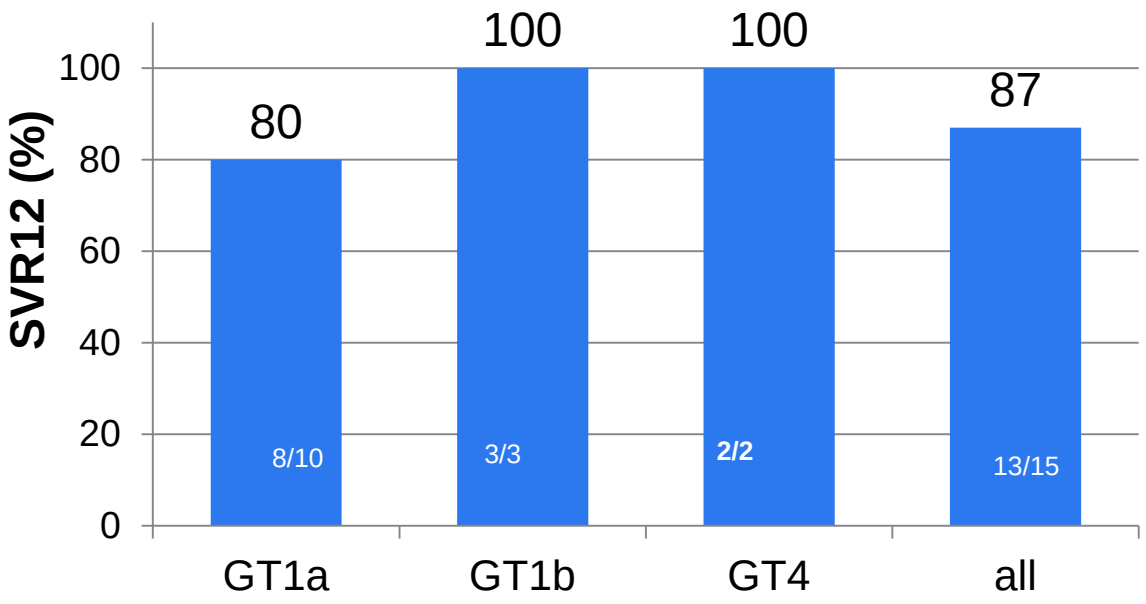
Pungpapong et al., AASLD 2015, #1038

Salvage Therapy

SMV/SOF after NS5A-based DAA Therapy

- n=16, GT1 or GT4 with failure to DCV/PEG/R (n=13), DCV/ASV(PEG/R (n=3)
- 56% cirrhosis

➢ Treatment with SMV/SOF for 12 wks



NS5A RAVs
n=12
Relapse: n=2

NS3 RAVs
n=8
Q80K, R155K, V170L
Relapse: n=2
(ASV exposed!)

1 patient did not reach SVR12 yet

Hezode et al., AASLD 2015, #1123

Salvage Therapy

3D + SOF after DAA failure (Quarz 1)

- n=22, GT1 (n=20 GT1a) with failure to 3D (n=14), 2D (n=2), TVR (n=2), SOF-based (n=3), SMV/SAV (n=1)
- ➢ Treatment with 3D (GT1b) for 12 wks or 3D + RBV for 12 wks (24 wks cirrhosis)

Characteristic	HCV GT1a OBV/PTV/r + DSV + SOF + RBV 12 Weeks (N = 14)	HCV GT1a OBV/PTV/r + DSV + SOF + RBV 24 Weeks (N = 6)	HCV GT1b OBV/PTV/r + DSV + SOF 12 Weeks (N = 2)
Prior DAA experience, n (%)			
Relapse	11 (79)	6 (100)	1 (50)
Breakthrough	3 (21)	0	1 (50)
Prior DAA regimen			
OBV/PTV/r	2 (14)	0	0
OBV/PTV/r + DSV	8 (57)	6 (100)	0
SIM + SOF	0	0	1 (50)
SIM + SAM + RBV	0	0	1 (50)
SOF + RBV	1 (7)	0	0
SOF + PR	1 (7)	0	0
TPV + PR	2 (14)	0	0
Resistance-associated variants			
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 et al., AASLD 2015, #LB20

Salvage Therapy

3D + SOF after DAA failure (Quarz 1)

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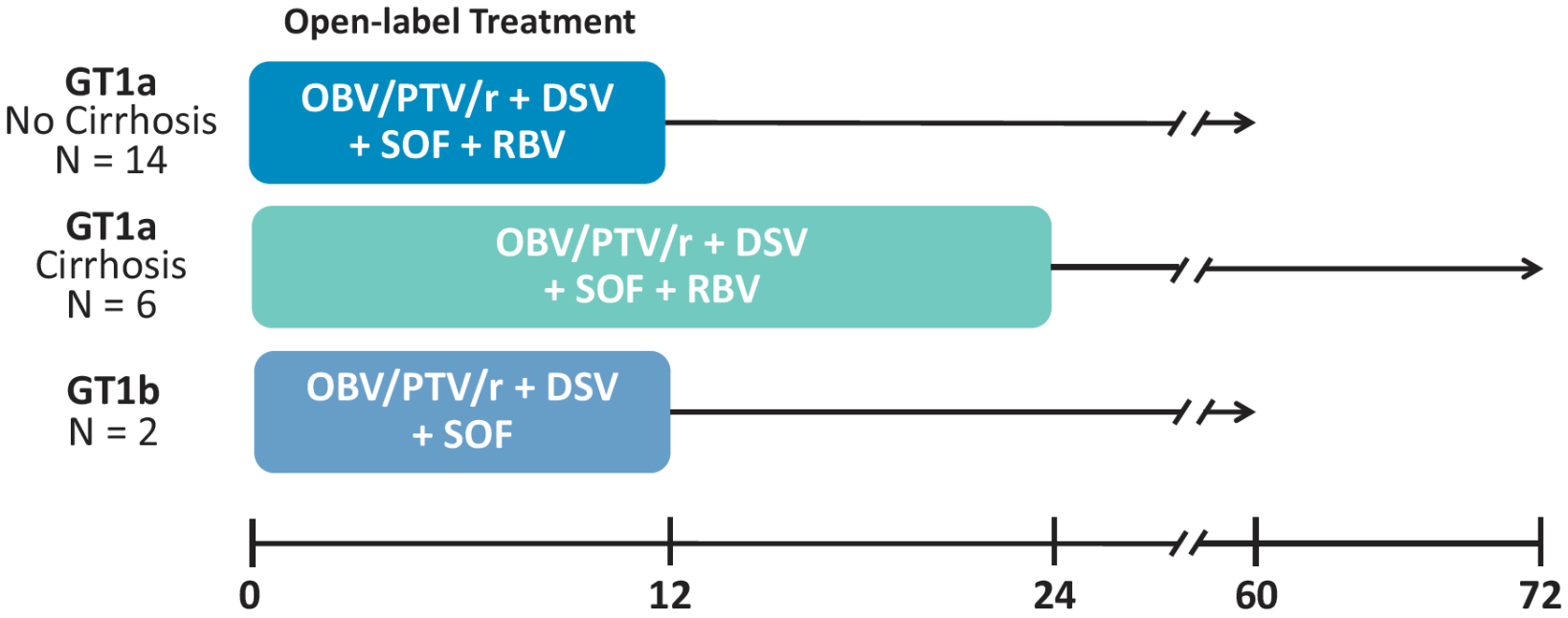
Figure 1. QUARTZ-I: Open-label, Phase 2, Multicenter Study Design



Poordad et al., AASLD 2015, #LB20

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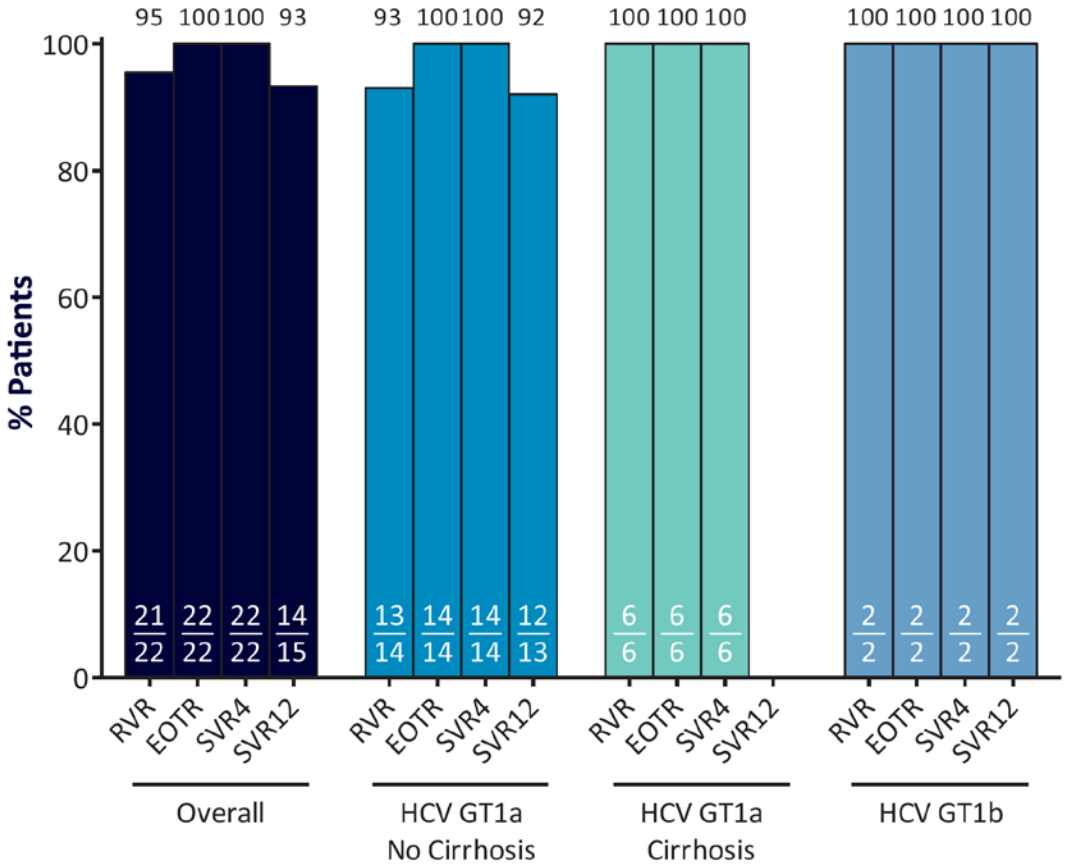
➢ Treatment with 3D (GT1b) for 12 wks or 3D + RBV for 12 wks (24 wks cirrhosis)

Figure 2. Virologic Response During and After Treatment



12 weeks treatment

24 wks pending (currently 6/6 SVR4)

Poordad et al., AASLD 2015, #LB20

Summary

- Importance of pre-existing baseline resistance
  - reduced SVR rates especially in the presence of additional stress factors (high level of resistance, certain HCV subtypes /GT1a, shortened treatment duration / 8 wks., patients with cirrhosis)
- Different frequencies of baseline RAVs according to DAA target, HCV geno-/subtype, geographical region
- German Resistance Registry with >3500 RAVs tests
- RAVs free treatment option
  - TN/TE, DAA+R+/-PEG: 83-99%
  - SMV/SOF failure: 88%
  - DCV or LDV/SOF failure: 49-62%
  - 3D failure: 28%
- Salvage therapy
  - high SVR rates for P/R and DAA+R+/- PEG failures
  - limited experience with failures to DAA combination regimens