What every clinician should now about HCV resistance

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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

- Natural frequency of resistance associated variants
- Resistance associated with differences between HCV genotypes / subtypes
- Importance of RAVs for all oral DAA treatment naïve patients
- Importance of RAVs for DAA combination failure patients
- Frequency and importance of chimera

Natural frequency of resistance

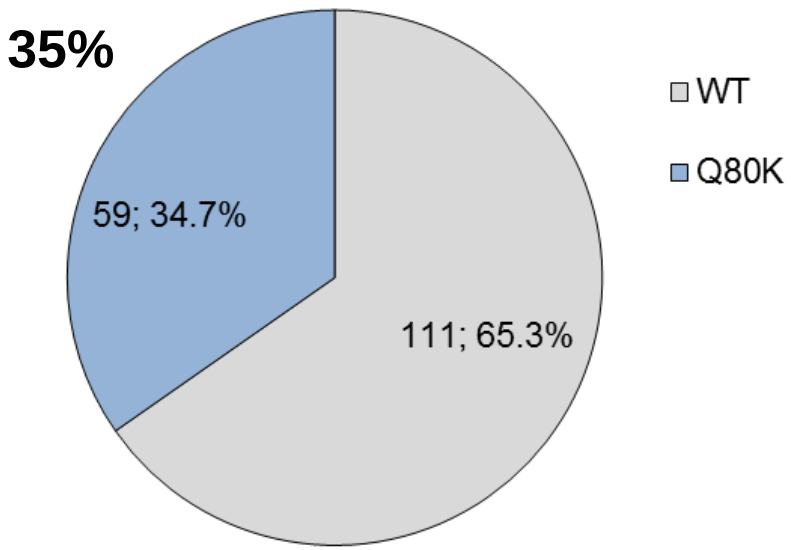
Differences for targets and between HCV geno- and subtypes

NS3 protease

Genotype 1a

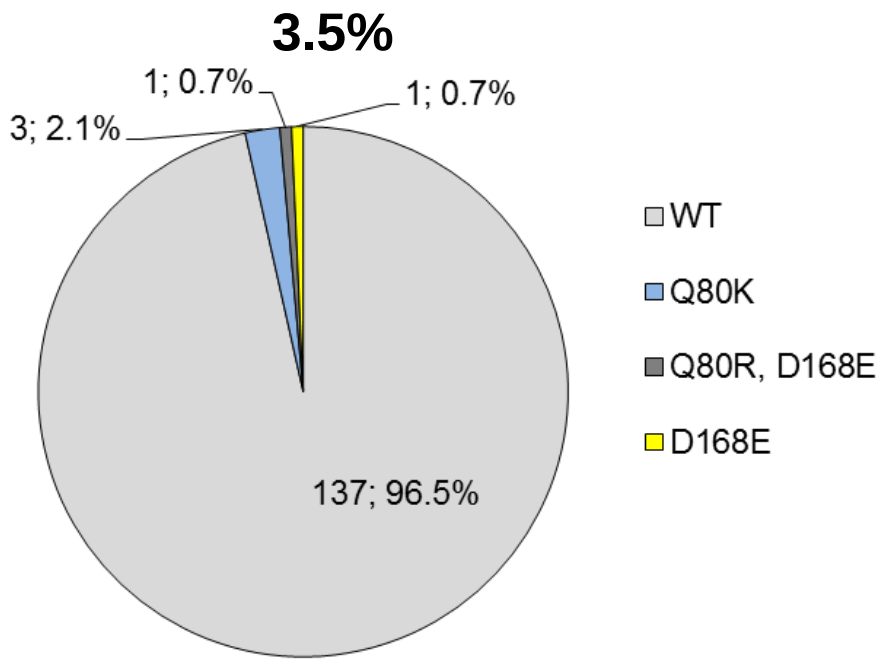
(geographical distribution of Q80K)

A



Genotype 1b

B



Genotype 2: **V36L, Q80G, S122R**
Genotype 3: **V36L, D168Q**

} **as natural variants**

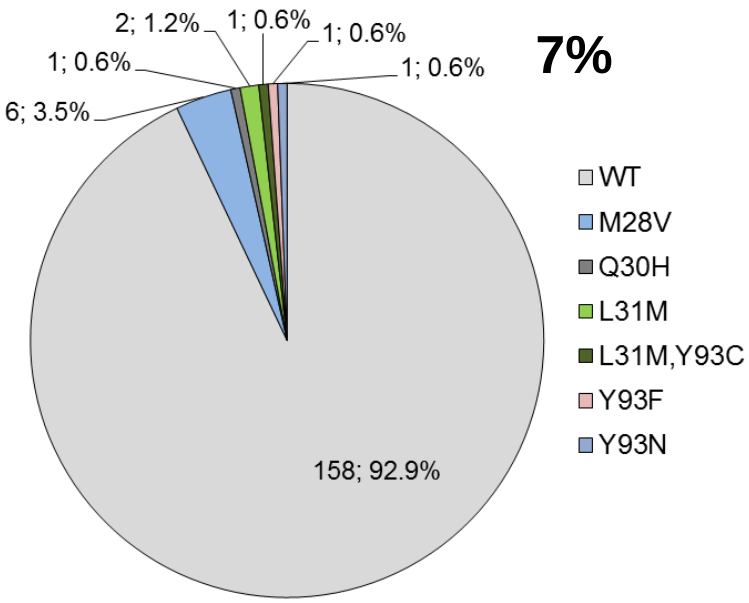
Dietz et al., PlosOne 2015; Lenz et al., J Hepatol 2013

Natural frequency of resistance

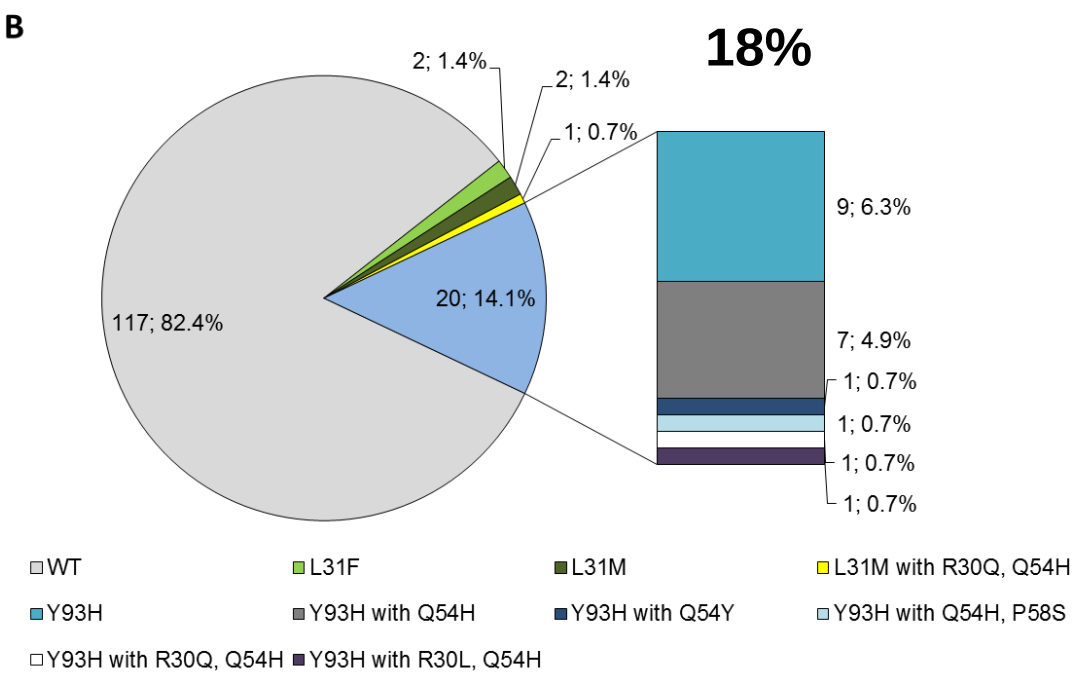
Differences for targets and between HCV geno- and subtypes

NS5A gene

Genotype 1a



Genotype 1b



Genotype 2: **L31M in 48%**
Genotype 3: **A30X in 19% + Y93H in 9%**
Genotype 4r: **M28V/I**

} **as natural variants**

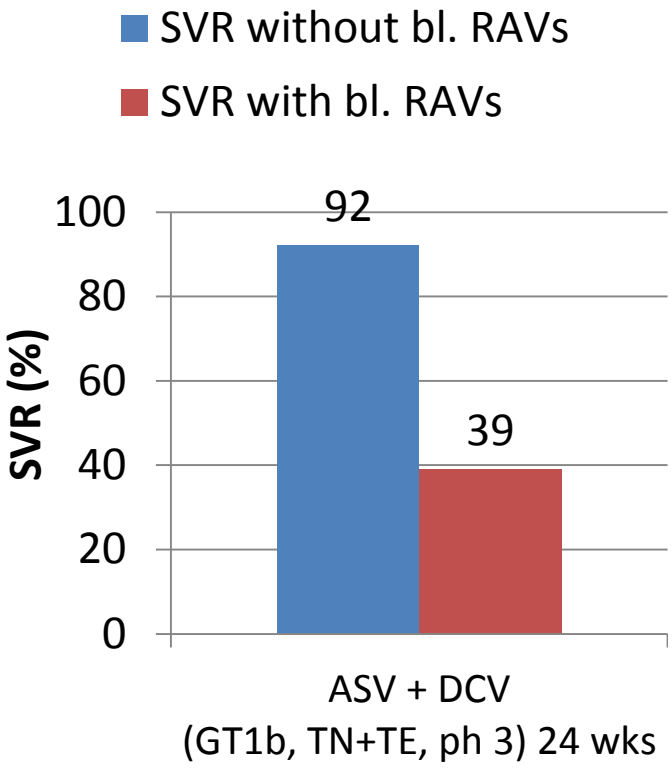
Dietz et al., PlosOne 2015; Doehle et al., AASLD 2014

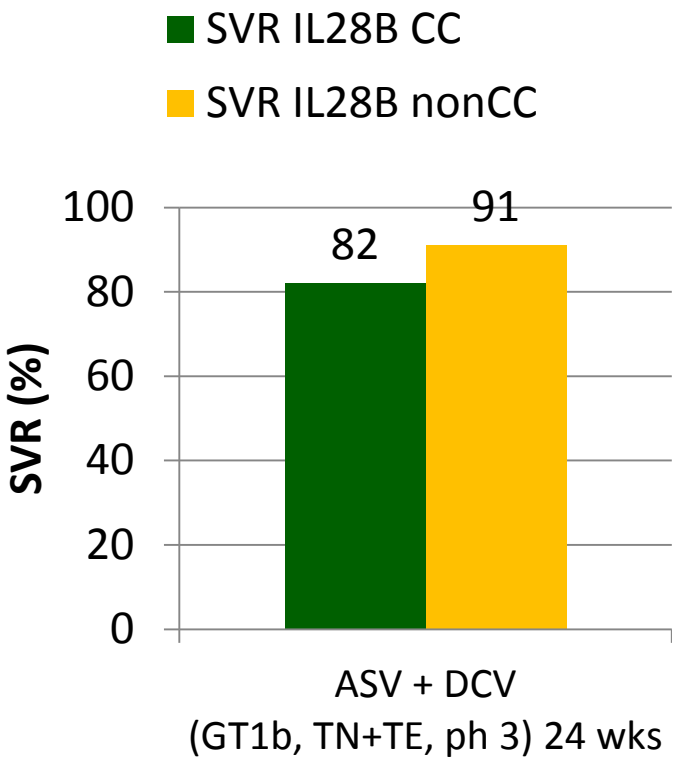
Association of RAVs and IL28B genotype

SVR rates according to NS5A sequence analysis and IL28B

NS3 protease plus NS5A inhibitor

unexpected lower SVR rates in IL28B CC



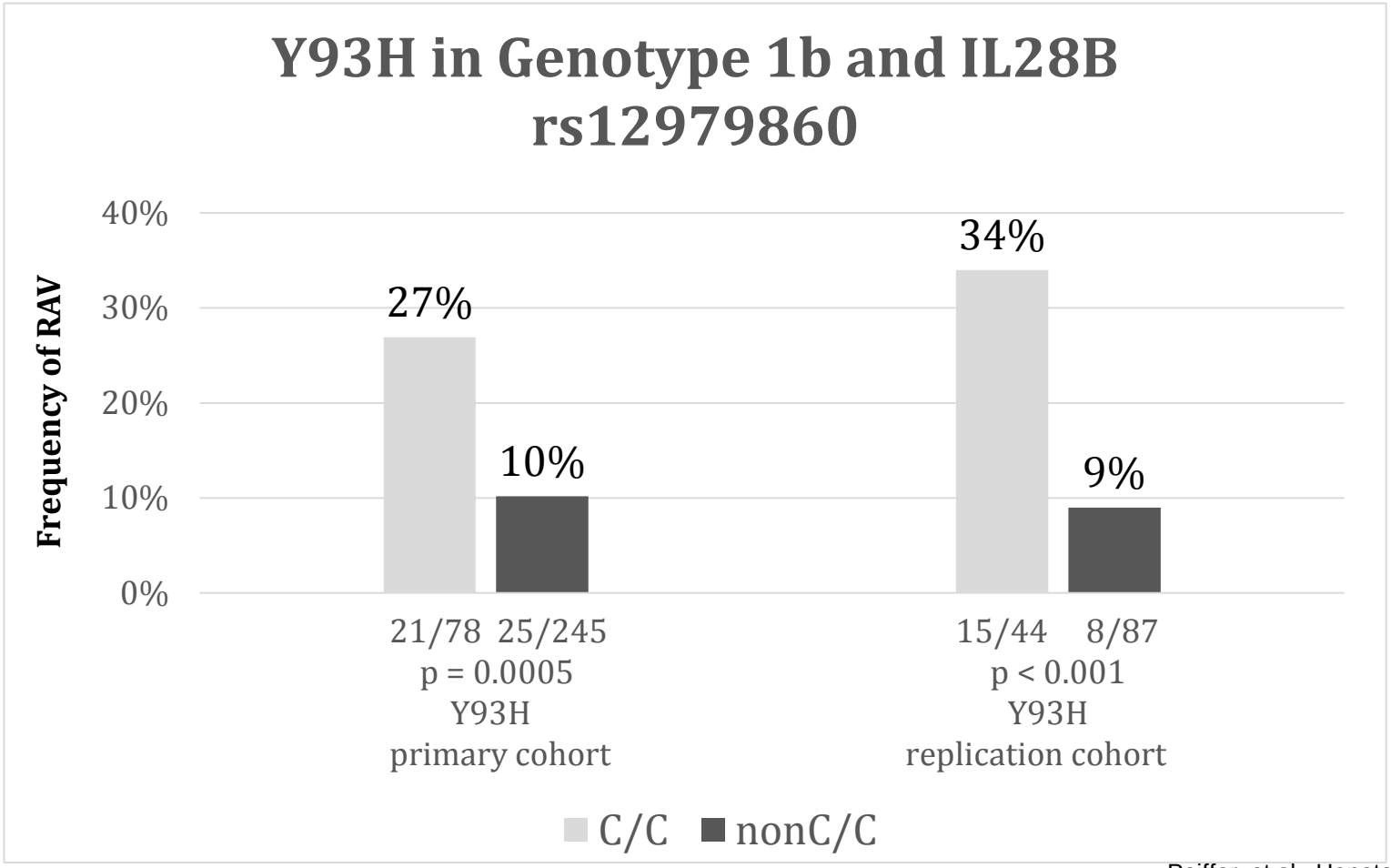


Manns et al., Lancet 2014

Association of RAVs and IL28B genotype

SVR rates according to IL28B and NS5A sequence analysis

Highly significant association of Y93 RAVs with IL28B CC genotype



Peiffer et al., Hepatology 2015 epub

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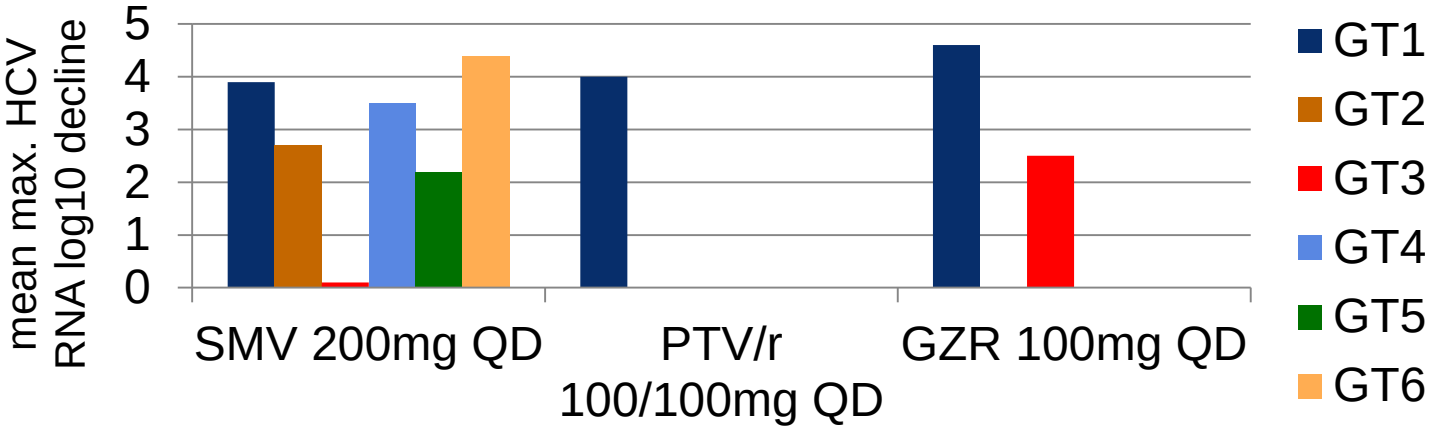
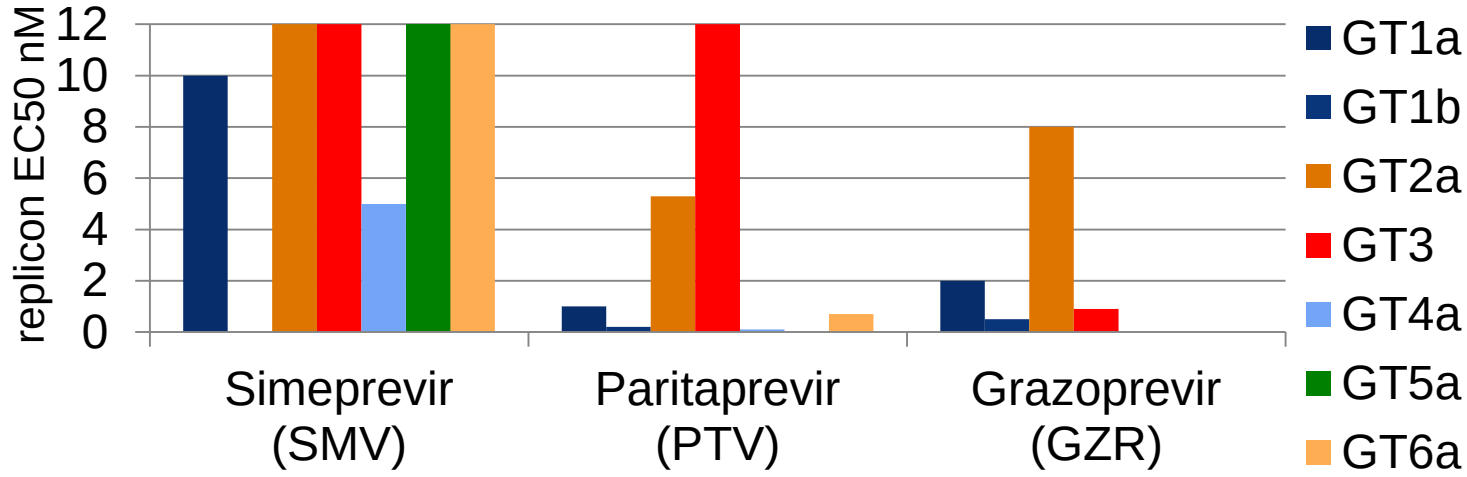
Importance of HCV geno-/subtypes

Antiviral activities in patients and in vitro *(no head-to-head studies)*

NS3-protease inhibitors (patients)



NS3-protease inhibitors *(in vitro)*



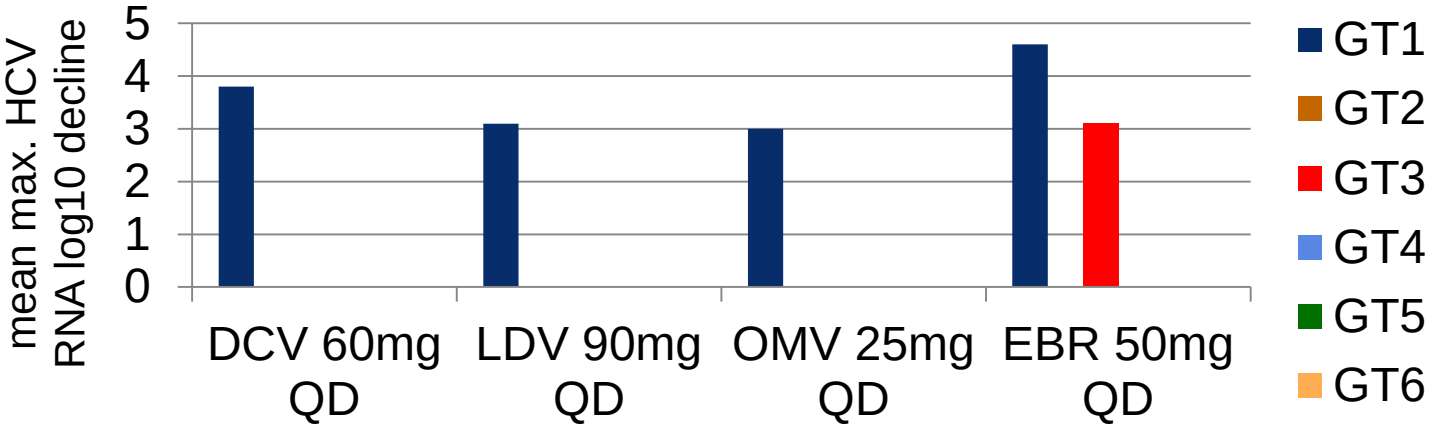
mean max. HCV RNA log10 decline in monotherapy studies;
nM EC50 values from chimeric HCV replicon studies,
no head-to-head comparison

Sarrazin; J Hepatol 2015 in press

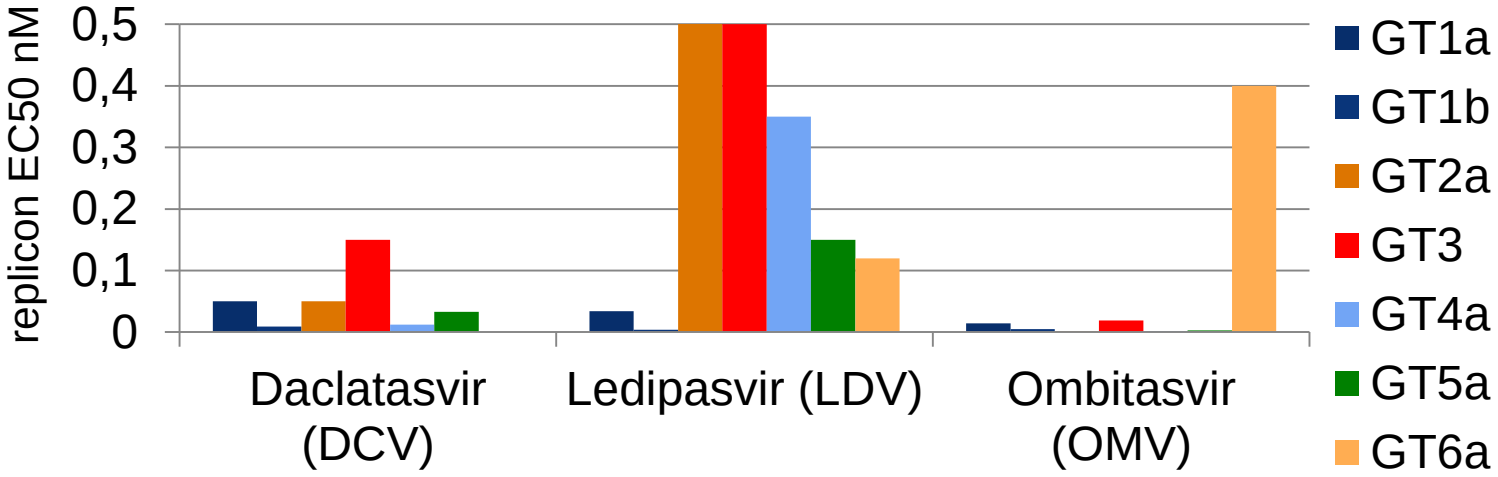
Importance of HCV geno-/subtypes

Antiviral activities in patients and in vitro *(no head-to-head studies)*

NS5A-inhibitors (patients)



NS5A-inhibitors *(in vitro)*



mean max. HCV RNA log10 decline in monotherapy studies;
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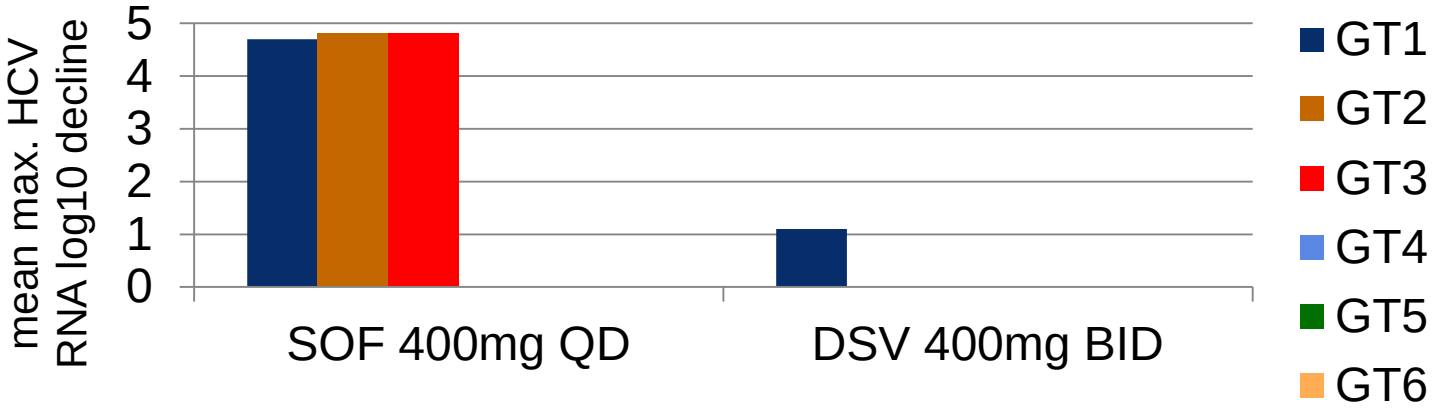
no head-to-head comparison

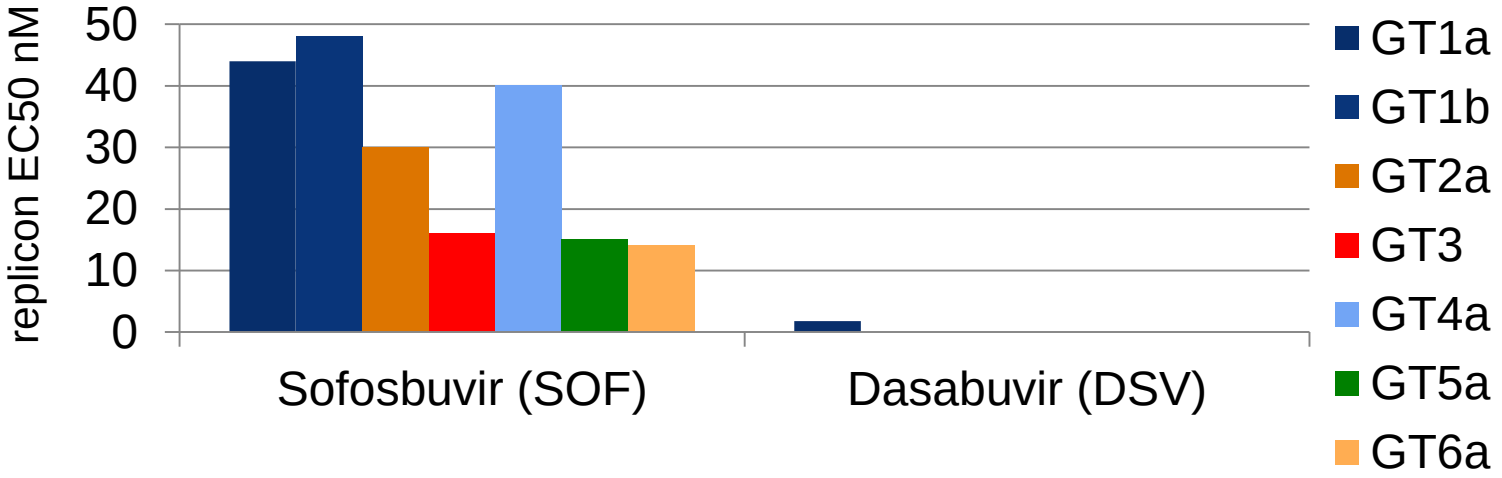
Importance of HCV geno-/subtypes

Antiviral activities in patients and in vitro *(no head-to-head studies)*

NS5B-inhibitors (patients)



NS5B-inhibitors *(in vitro)*



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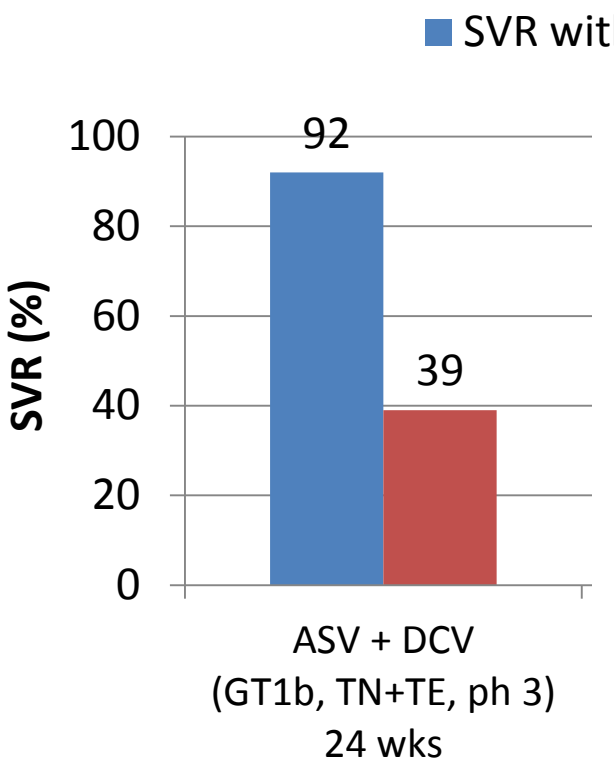
Importance of resistance associated variants

DAA combination treatment naïve patients (GT1)

NS3 protease plus NS5A inhibitor

no head to head studies, different resistance analysis



Frequency of pts. with baseline RAVs: 13%

Manns et al., Lancet 2014; Zeuzem et al., CROI 2014; Zeuzem et al., EASL 2015; Kwo et al., EASL 2015; Sarrazin; J Hepatol 2015 epub

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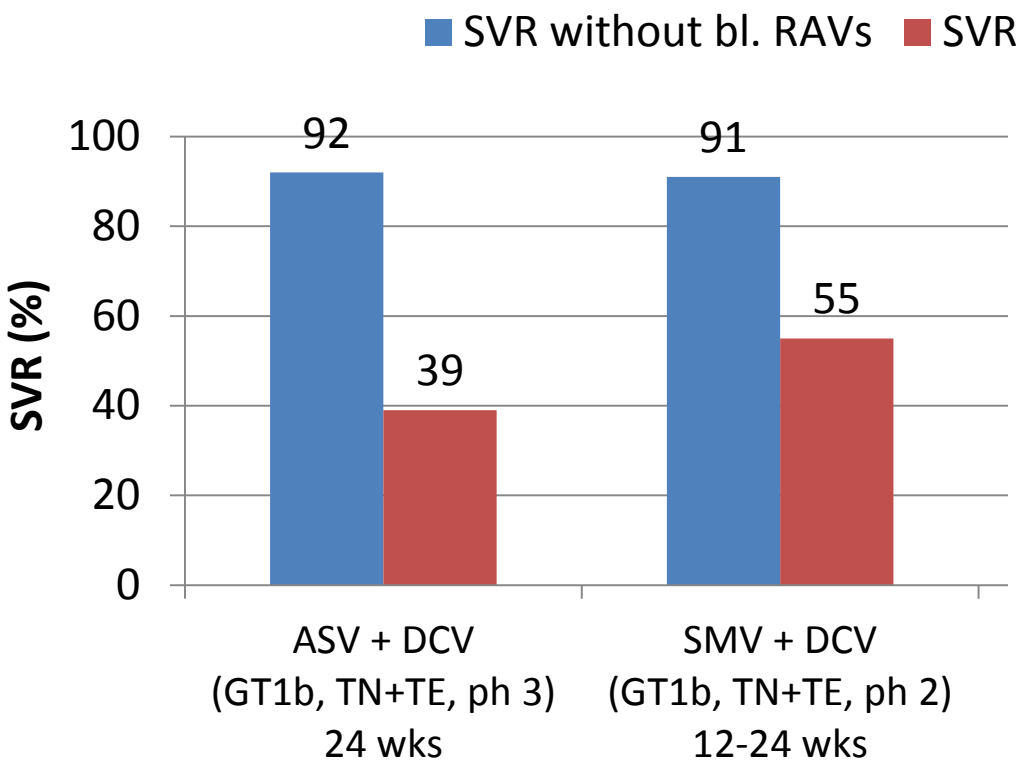

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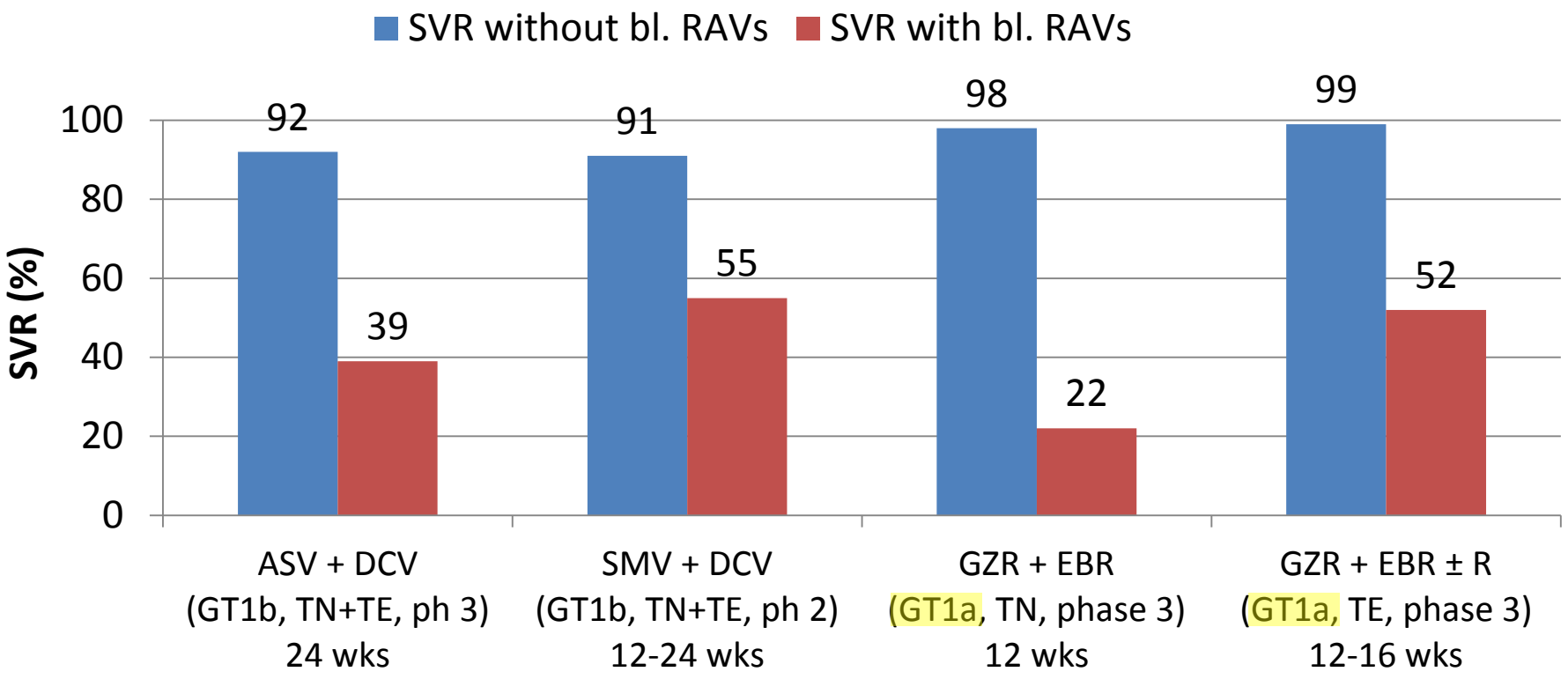


Frequency of pts. with baseline RAVs	13%		6%	10%

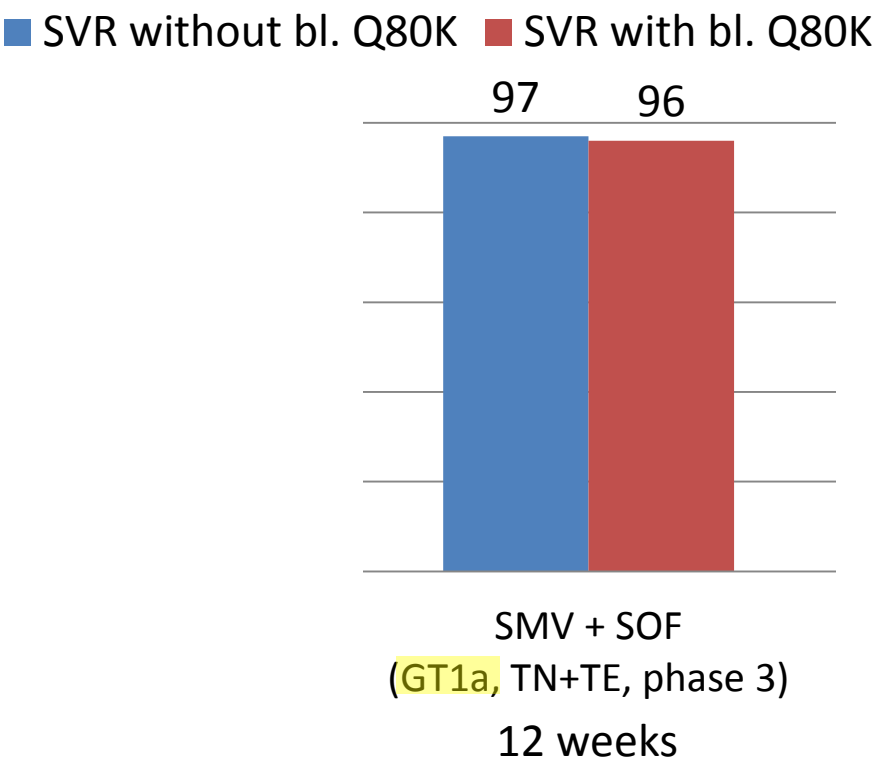
Manns et al., Lancet 2014; Zeuzem et al., CROI 2014; Zeuzem et al., EASL 2015; Kwo et al., EASL 2015; Sarrazin; J Hepatol 2015 epub

Importance of resistance associated variants

DAA combination treatment naïve patients (GT1)

NS3 protease plus NS5B NUC

no head to head studies, different resistance analysis



Frequency of pts. with baseline RAVs

40%

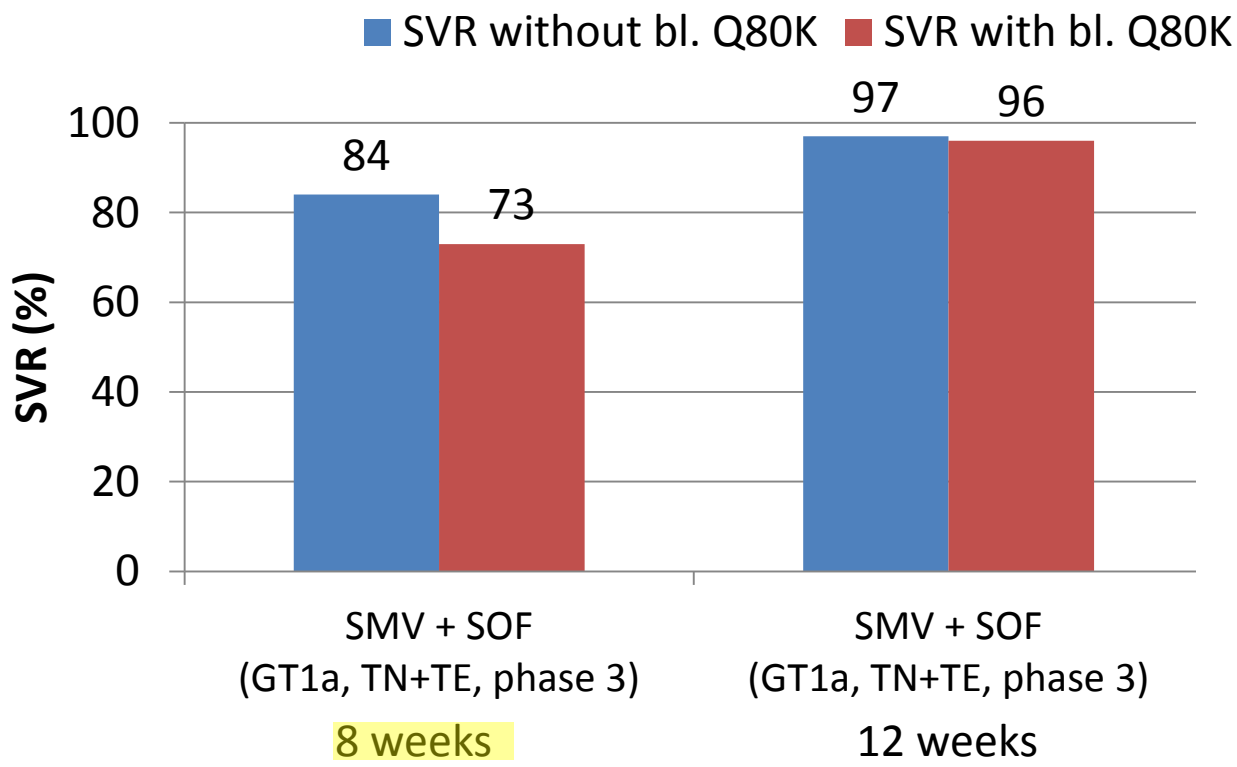
Lawitz et al., EASL 2015; Kwo et al., EASL 2015; Sarrazin; J Hepatol 2015 in press

Importance of resistance associated variants

DAA combination treatment naïve patients (GT1)

NS3 protease plus NS5B NUC

no head to head studies, different resistance analysis



no cirrhosis

Frequency of pts. with baseline RAVs	42%	40%

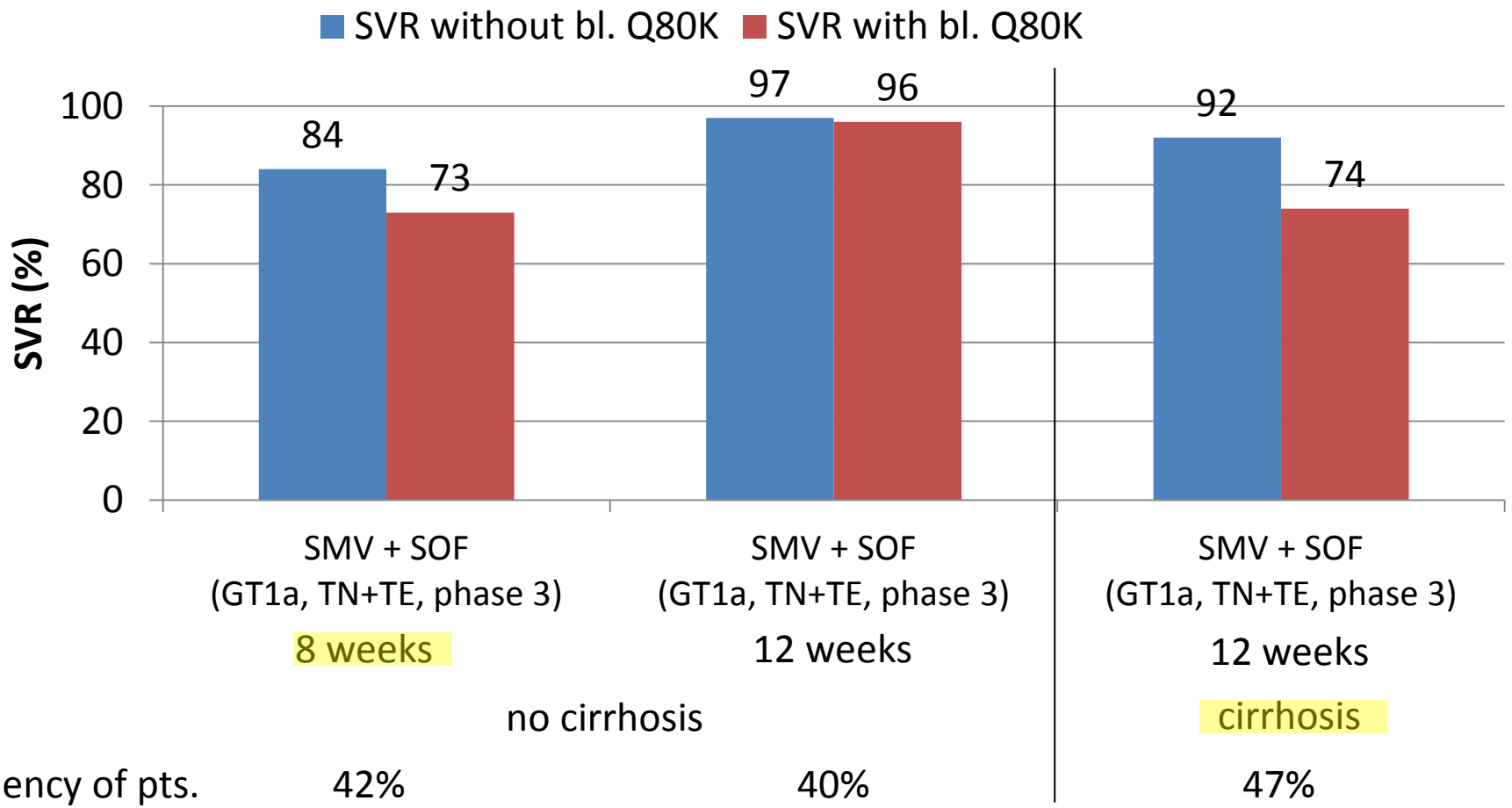
Lawitz et al., EASL 2015; Kwo et al., EASL 2015; Sarrazin; J Hepatol 2015 in press

Importance of resistance associated variants

DAA combination treatment naïve patients (GT1)

NS3 protease plus NS5B NUC

no head to head studies, different resistance analysis



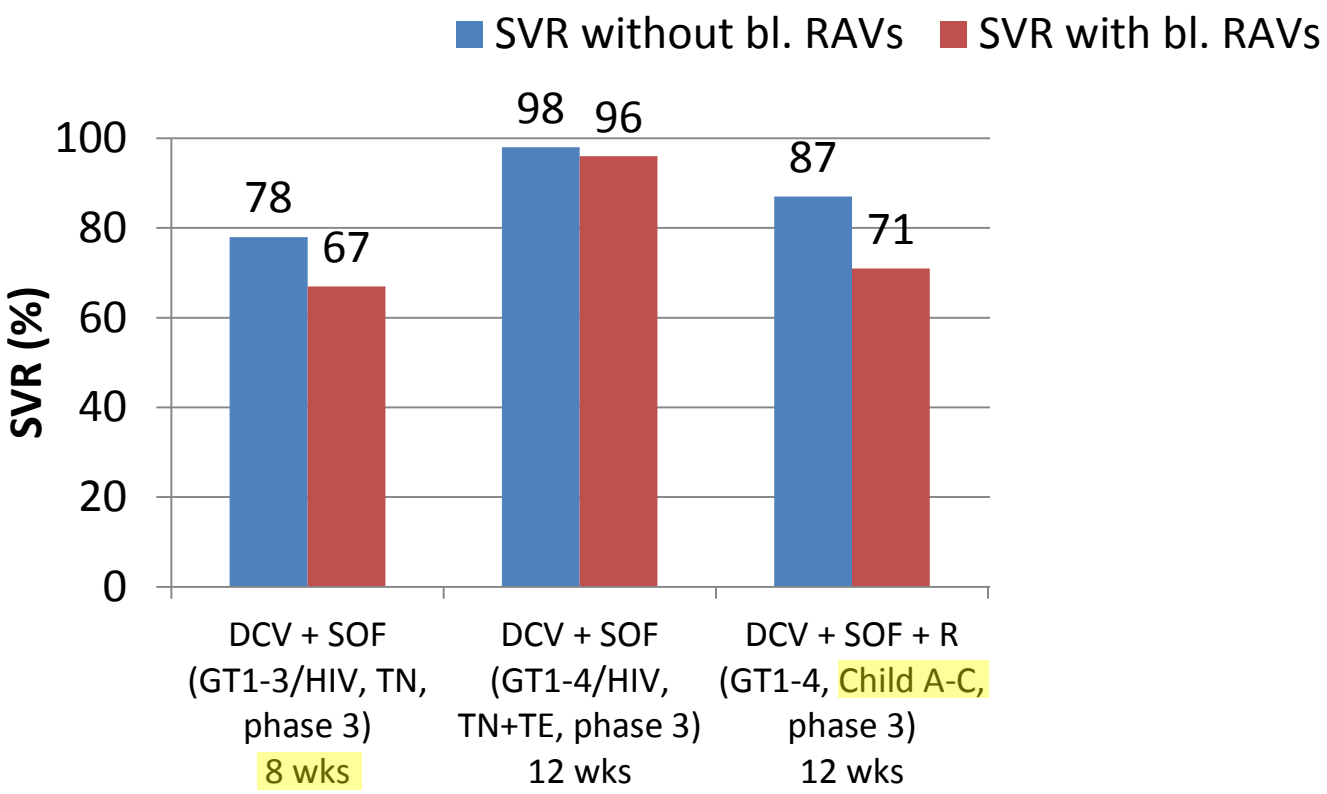
Lawitz et al., EASL 2015; Kwo et al., EASL 2015; Sarrazin; J Hepatol 2015 in press

Importance of resistance associated variants

DAA combination treatment naïve patients (GT1)

NS5A inhibitor plus NS5B NUC

no head to head studies, different resistance analysis



Frequency of pts. with baseline RAVs	18%	16%	24%

Wyles et al., CROI 2015/NEJM 2015; Poordad et al., EASL 2015; Sarrazin et al., AASLD 2014; Sarrazin et al., EASL 2015; Sarrazin; J Hepatol 2015 in press

Importance of resistance associated variants

DAA combination treatment naïve patients (GT1)

NS5A inhibitor plus NS5B NUC

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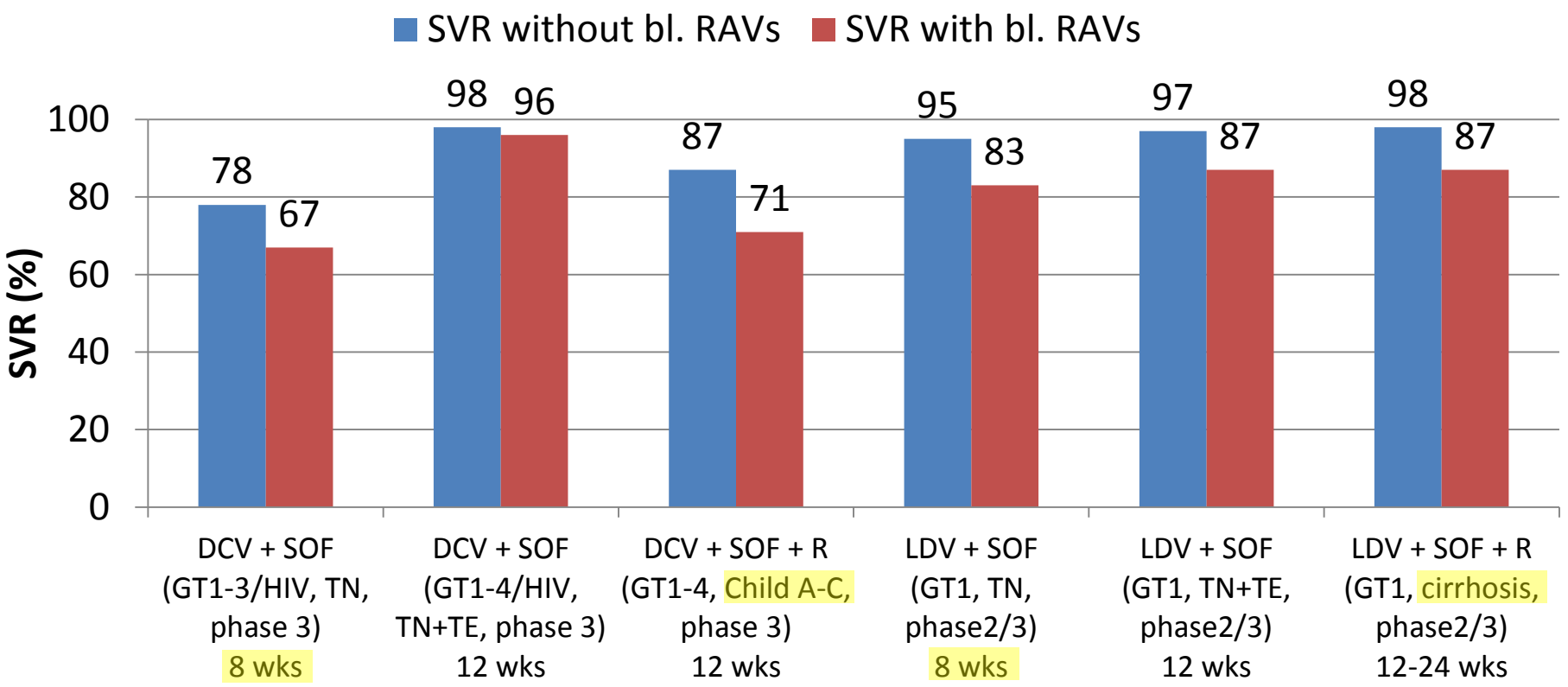


Frequency of pts. with baseline RAVs	18%	16%	24%	12%	12%	12%

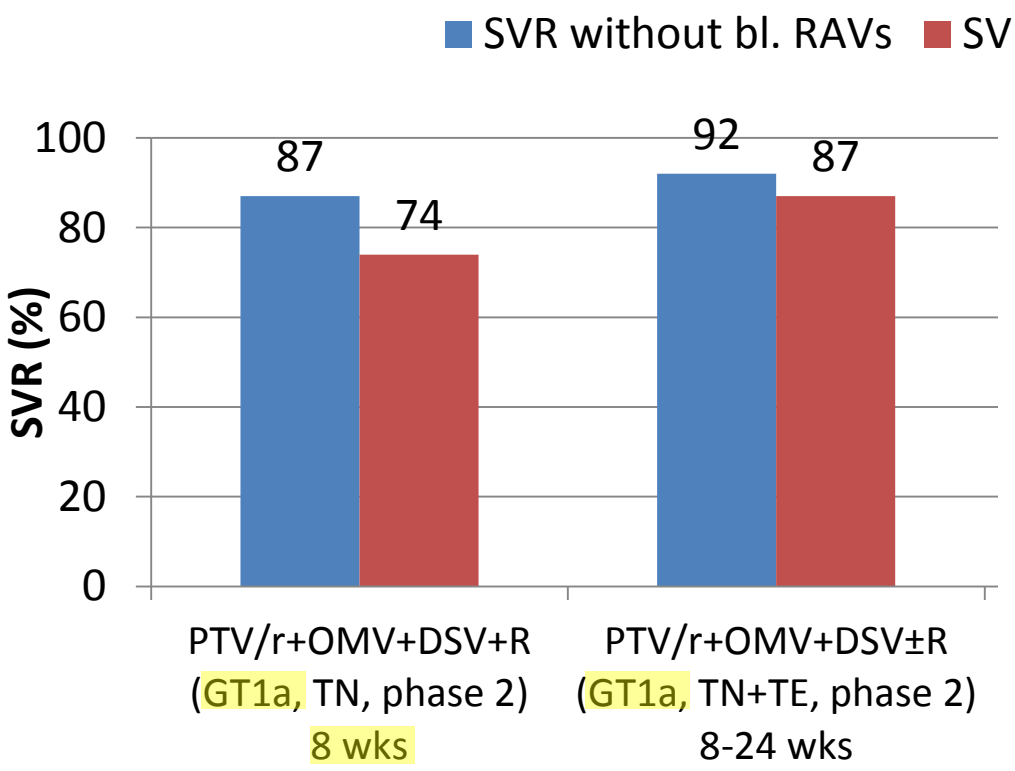
Wyles et al., CROI 2015/NEJM 2015; Poordad et al., EASL 2015; Sarrazin et al., AASLD 2014; Sarrazin et al., EASL 2015; Sarrazin; J Hepatol 2015 in press

Importance of resistance associated variants

DAA combination treatment naïve patients (GT1)

NS3 PI plus NS5A inhibitor plus NS5B NonNUC

no head to head studies, different resistance analysis



Frequency of pts. with baseline RAVs	39%	52%

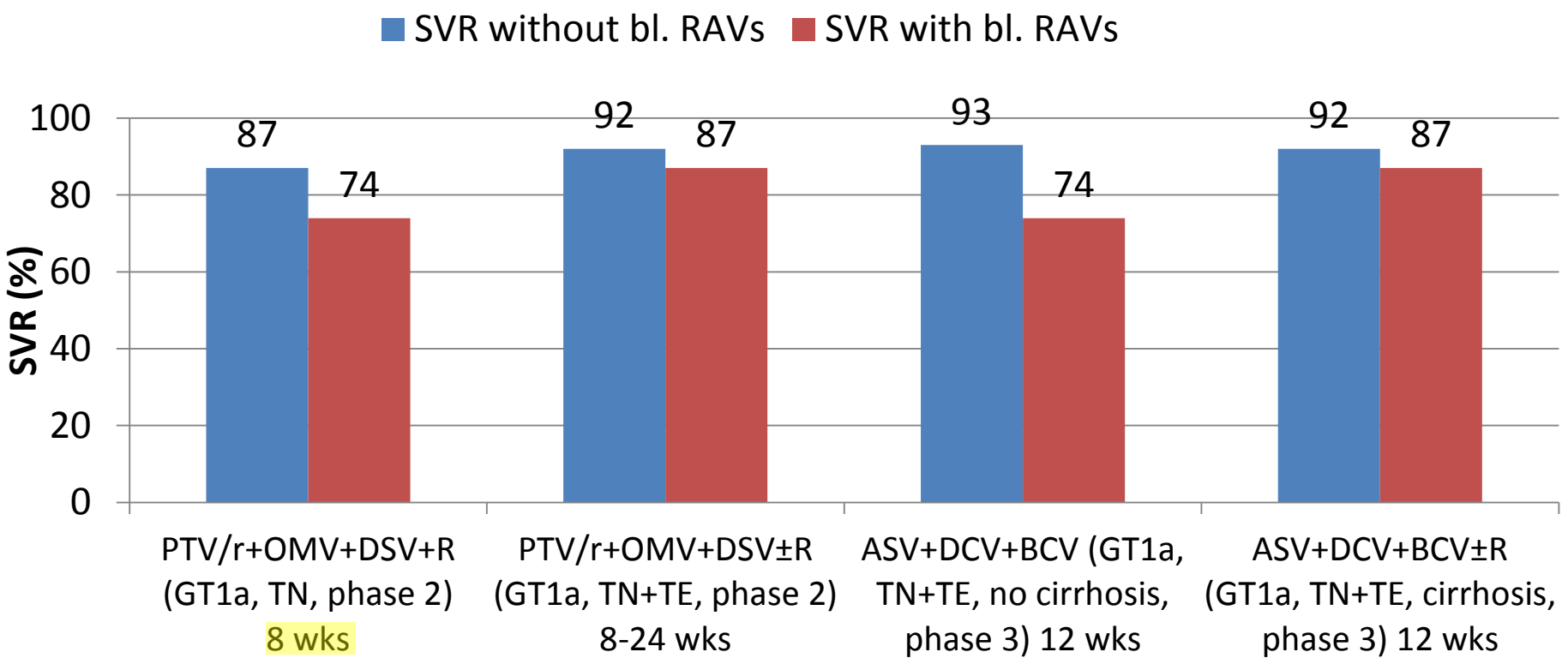
Krishnan et al., AAC 2015; EMA CHMP Assessment Report 20. Nov 2014; Sarrazin; J Hepatol 2015 in press

Importance of resistance associated variants

DAA combination treatment naïve patients (GT1)

NS3 PI plus NS5A inhibitor plus NS5B NonNUC

no head to head studies, different resistance analysis



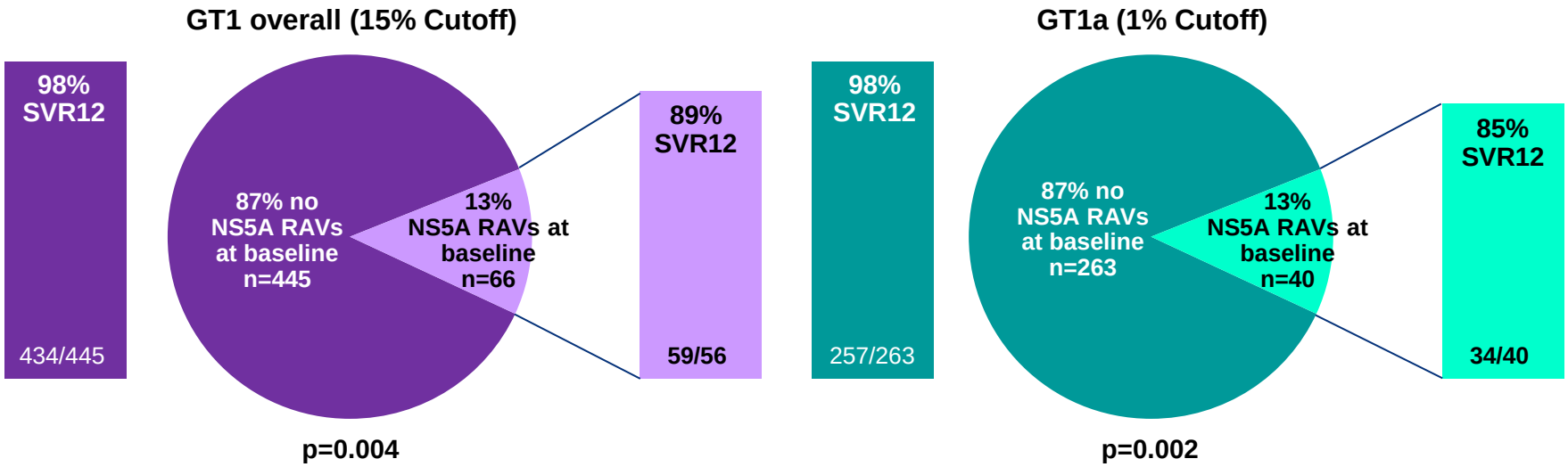
Frequency of pts. with baseline RAVs	39%	52%	11%	10%

Krishnan et al., AAC 2015; EMA CHMP Assessment Report 20. Nov 2014; Sarrazin; J Hepatol 2015 in press

Importance of resistance

Ledipasvir/sofosbuvir (Child A cirrhosis)

n=513 patients with cirrhosis (integrated analysis)



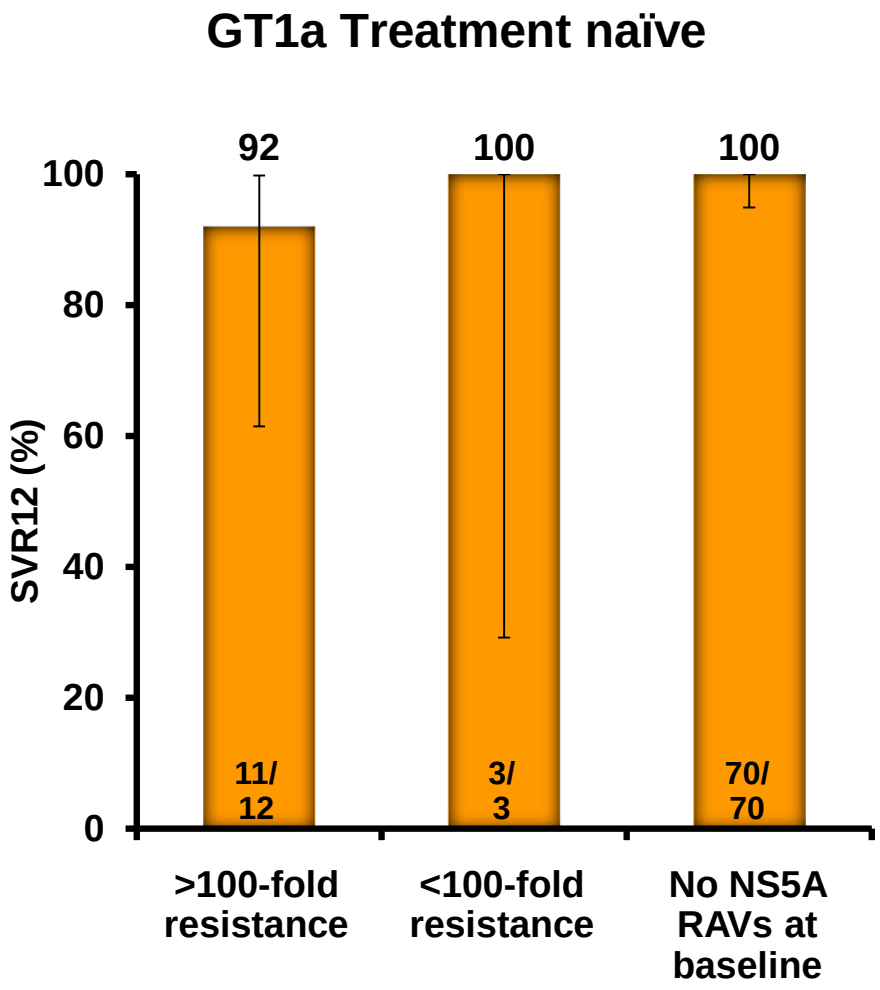
	RAVs	
HCV genotype	**2.5–100-fold resistance**	**>100-fold resistance**
1a	K24R, Q30L, Q30T, K24G, K24N, A92T, Y93F, M28T, S38F	Q30H, Q30G, Q30R, L31I, L31M, L31V, P32L, M28A, M28G, Q30E, Q30K, H58D, Y93C, Y93H, Y93N, Y93S
1b	L31M, P32L, L31I, L31V	P58D, A92K, Y93H

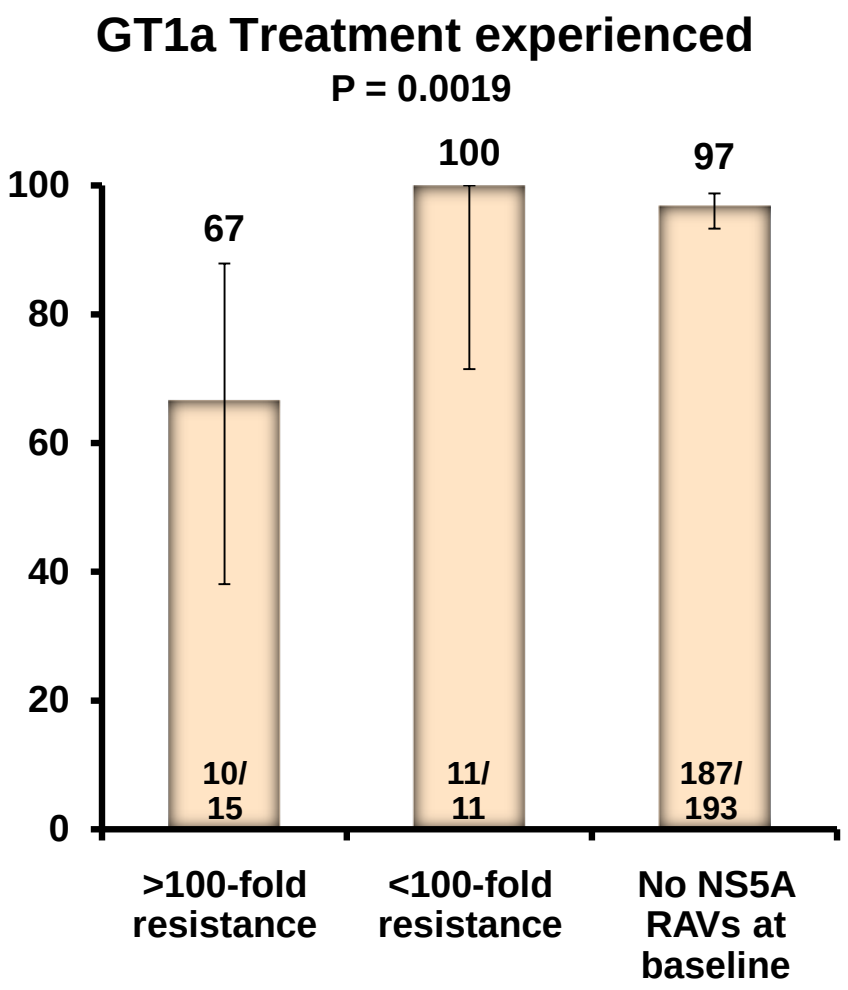
Sarrazin C et al. AASLD 2014. Poster 1926
Sarrazin C et al. EASL 2015, Poster P773

Importance of resistance

Ledipasvir/sofosbuvir (Child Pugh A cirrhosis)

SVR12 rates by resistance level of Baseline NS5A RAVs



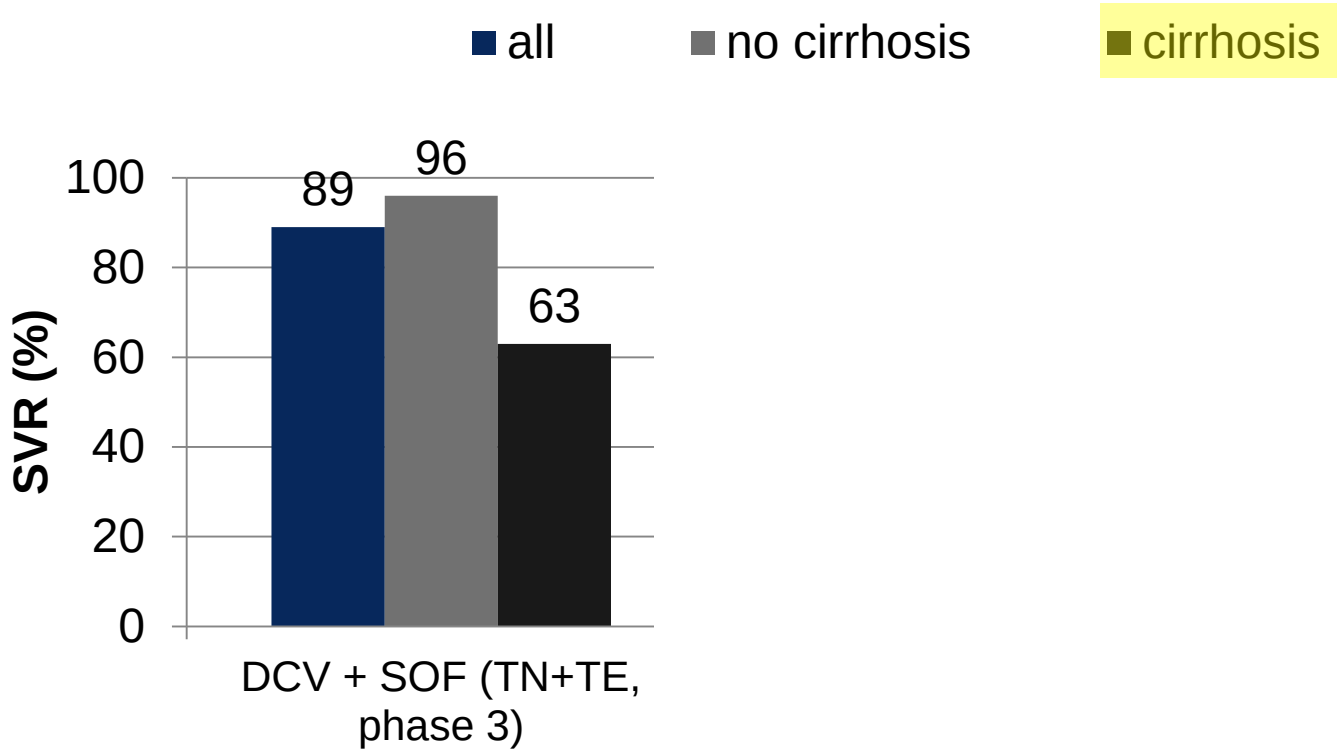


Sarrazin C et al. EASL 2015, Poster P773

Importance of resistance associated variants

DAA combination treatment naïve patients (GT3)

Genotype 3
NS5A inhibitor plus NS5B NUC



Frequency of pts. with baseline RAVs

Nelson et al., Hepatology 2015; Sarrazin; J Hepatol 2015 in press

Importance of resistance associated variants

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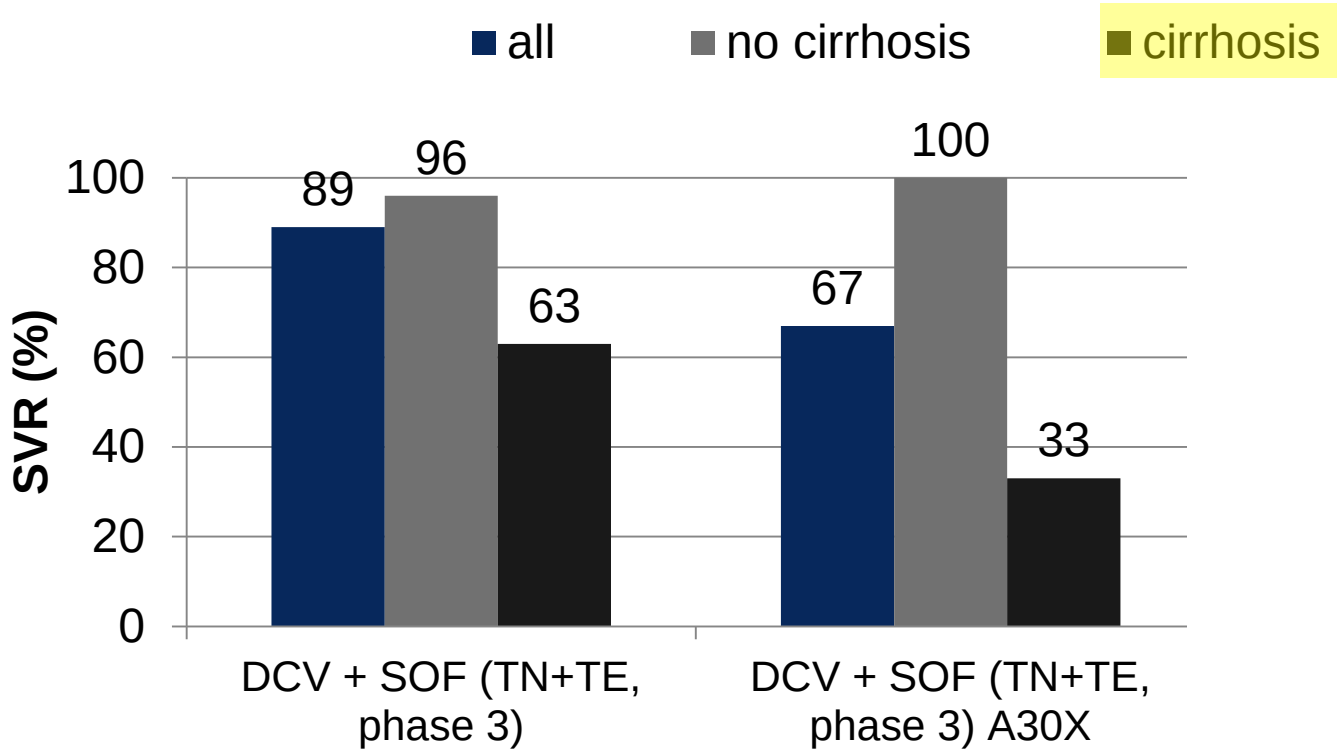

Frequency of pts. with baseline RAVs

10%

Nelson et al., Hepatology 2015; Sarrazin; J Hepatol 2015 in press

Importance of resistance associated variants

DAA combination treatment naïve patients (GT3)

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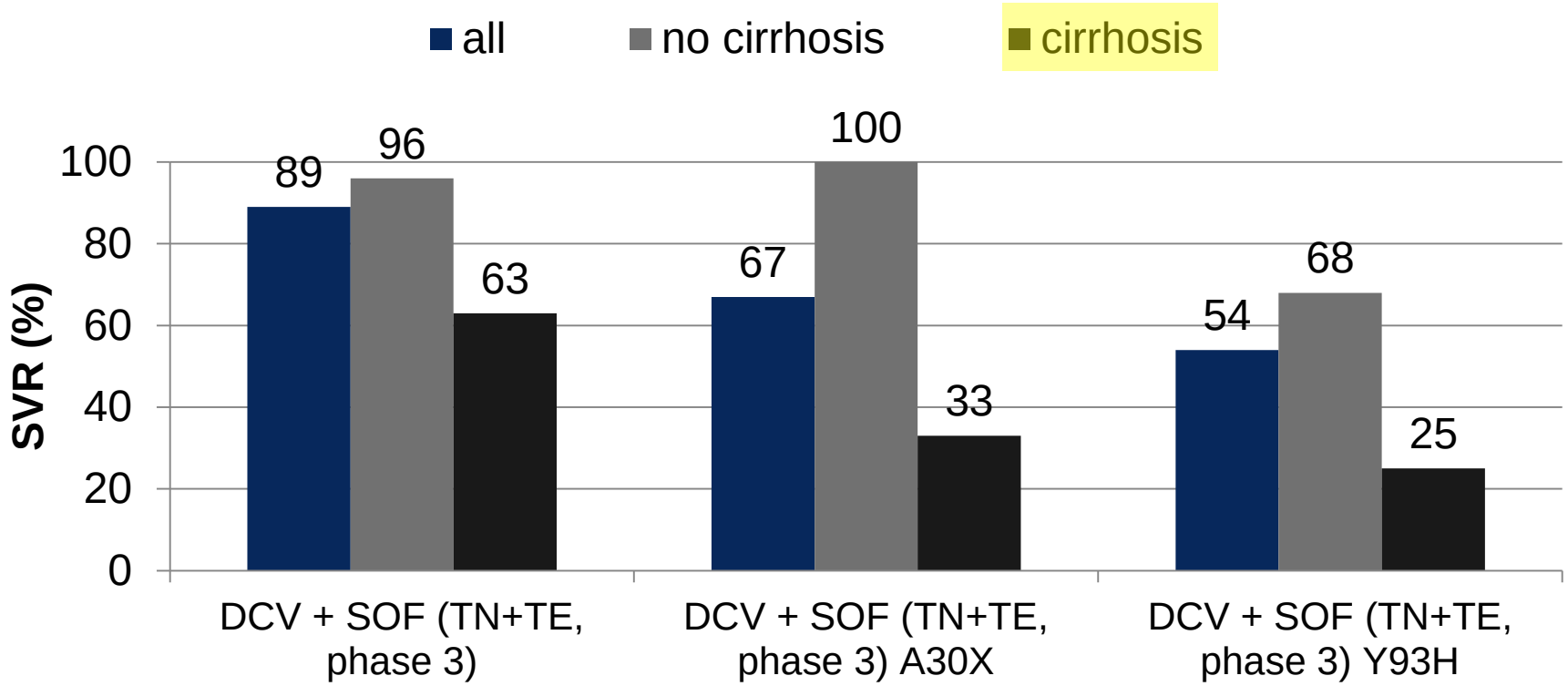

Frequency of pts. with baseline RAVs

10%

9%

Nelson et al., Hepatology 2015; Sarrazin; J Hepatol 2015 in press

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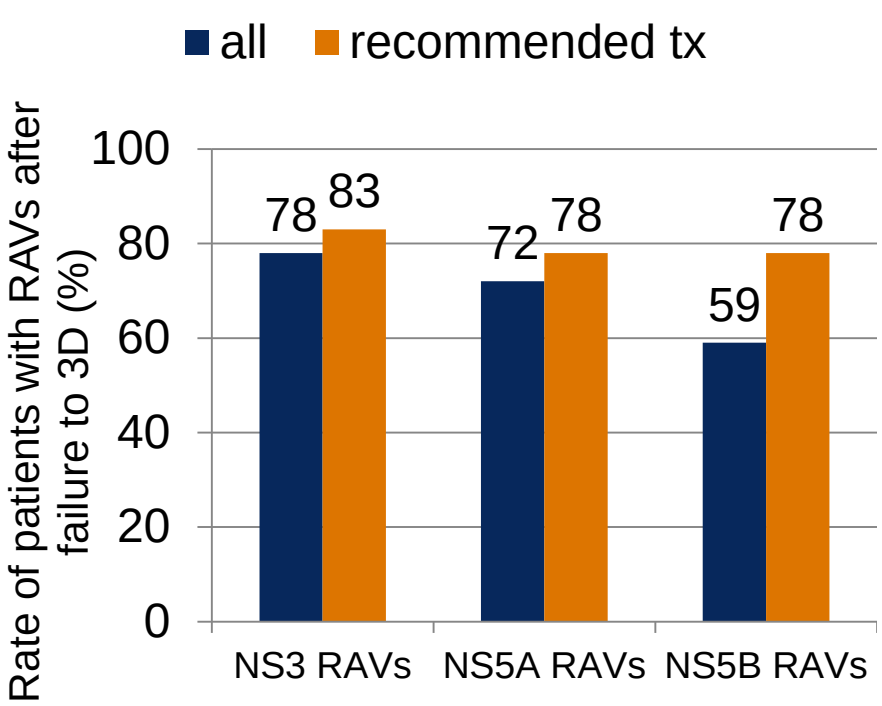
Persistence of resistance associated variants

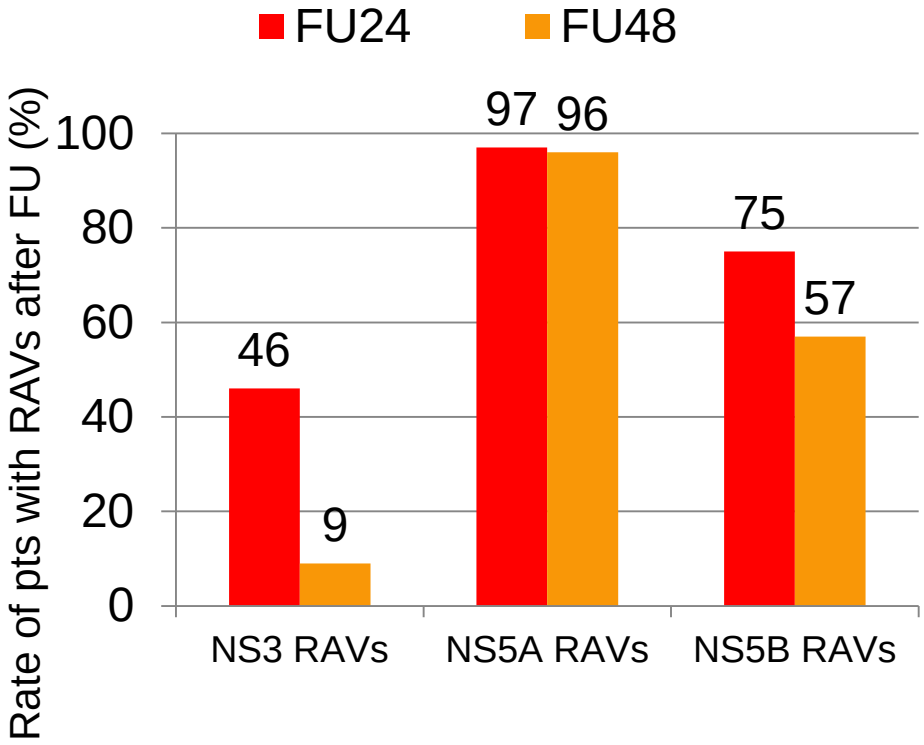
Persistence rates for NS3, NS5A and NS5B variants

Follow up after failure to 3D (n=67 GT1a, n=7 GT1b)
follow-up 24 and 48 wks., pop. based seq. (if no RAVs cloning)

Rate of pat. with RAVs at failure to 3D



Rate of pat. with RAVs at 24 and 48 wks FU

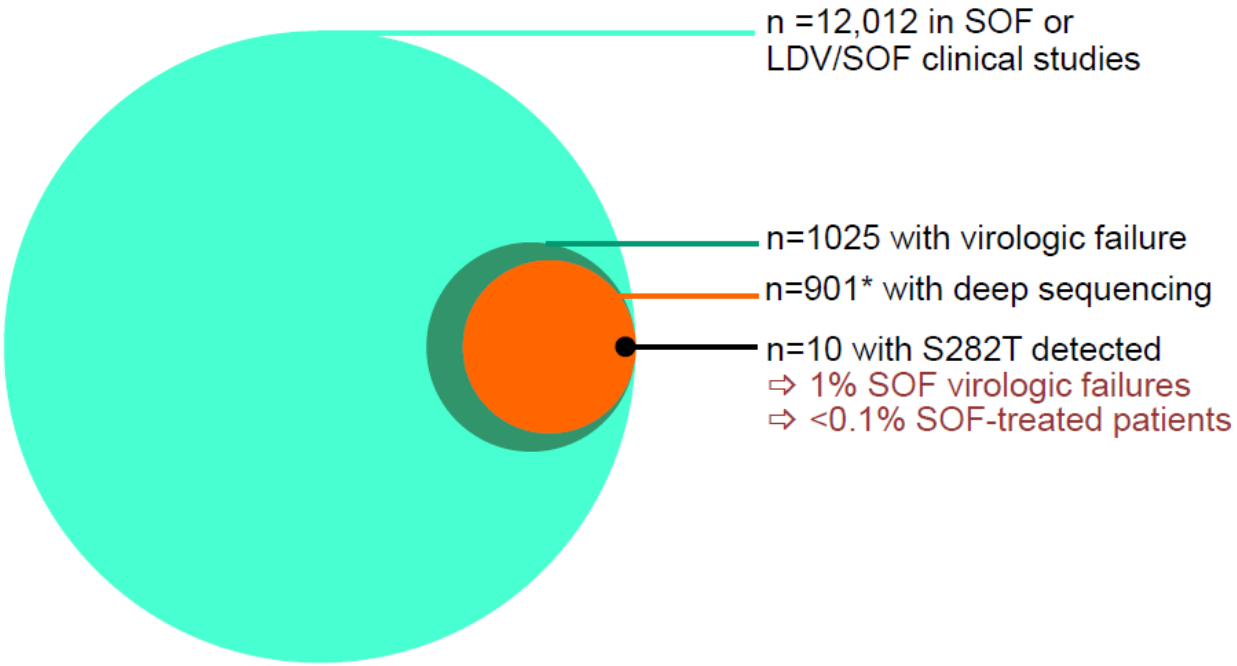


Krishnan et al., EASL 2015, #O057

Persistence of resistance associated variants

S282T resistance for sofosbuvir

- Detection of Treatment-Emergent S282T Variant Is Rare



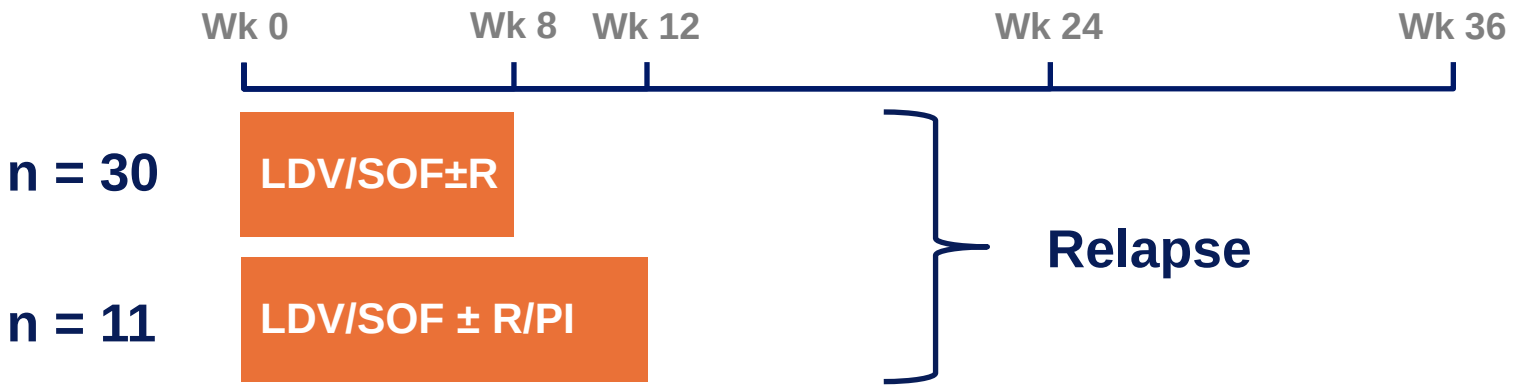
N=10 patients with S282T

- **n=4 GT1a, n=1 GT1b, n=1 GT2, 3, 4, 5, 6**
- **n=5 DAA experienced / n=5 TN/TE**
- **8/9 IL28B non-CC**
- **5/10 cirrhosis**
- **reversion to wild type within several weeks**

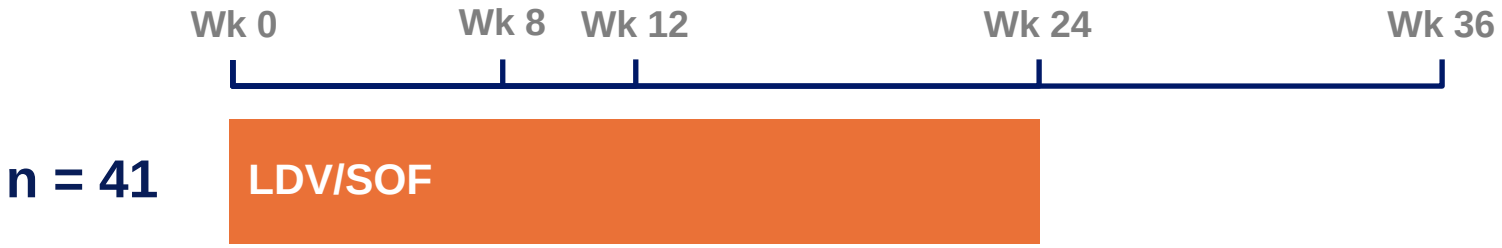
Gane et al., AASLD 2015, #O057

Efficacy of salvage therapies after DAA failure (Genotype 1)

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



Re-treatment

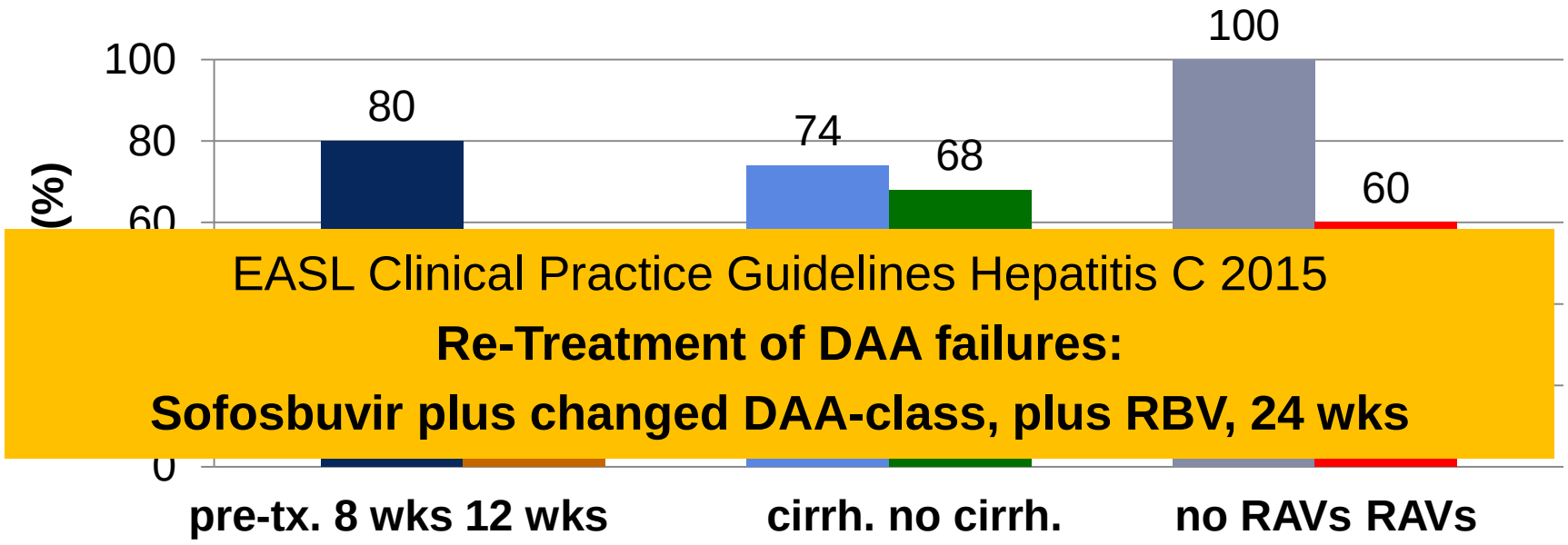


Lawitz et al., EASL 2015

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

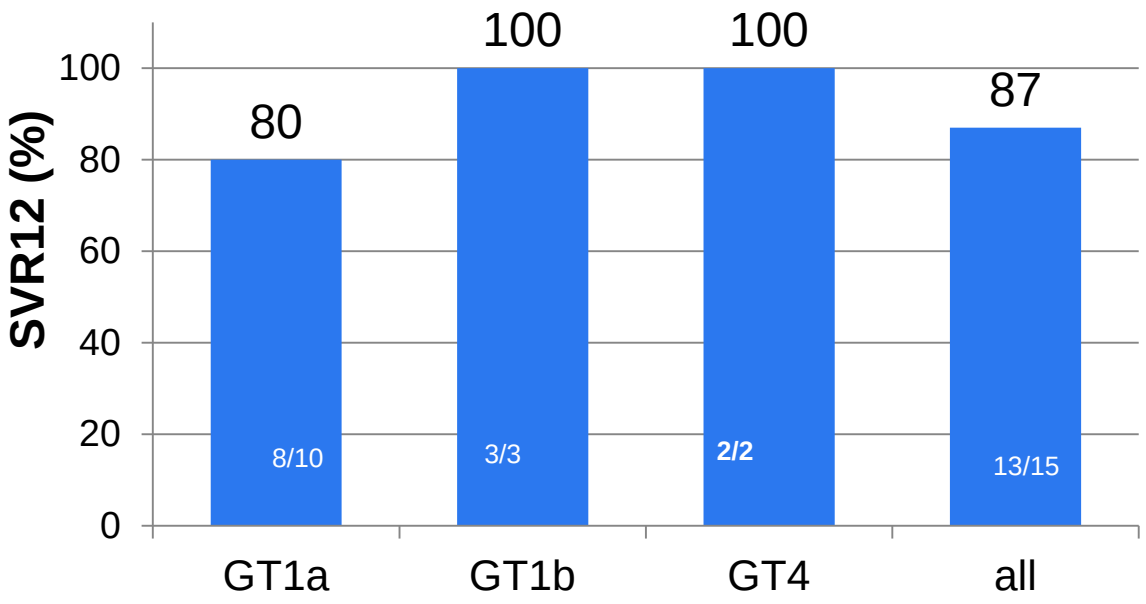
Lawitz et al., EASL 2015, O005

Salvage Therapy

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!)

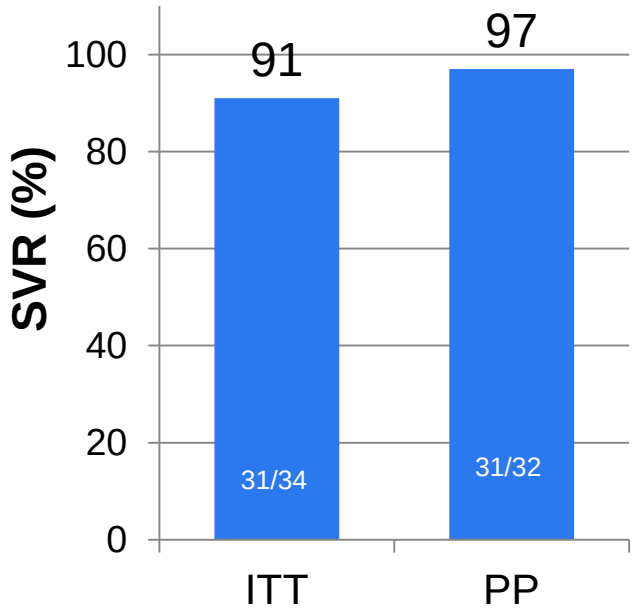
1 patient did not reach SVR12 yet

Hezode et al., AASLD 2015, #1123

Salvage Therapy

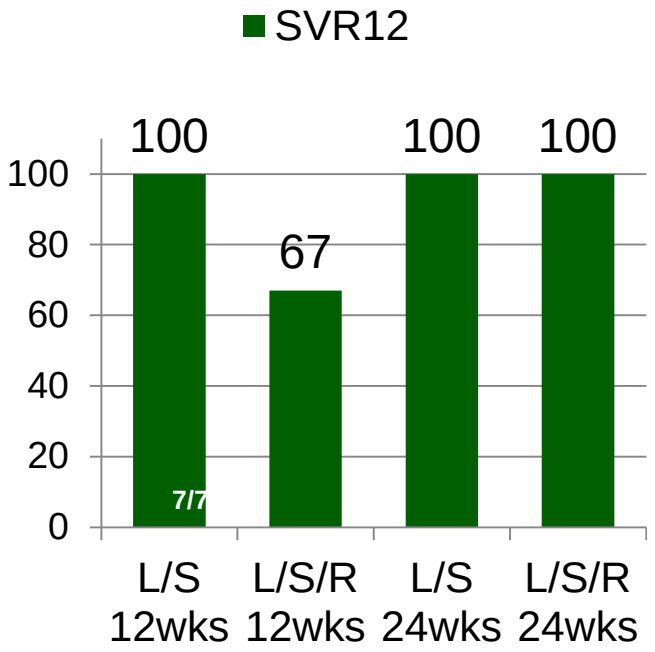
LDV/SOF after DAA triple or SMV/SOF

- 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

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)

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

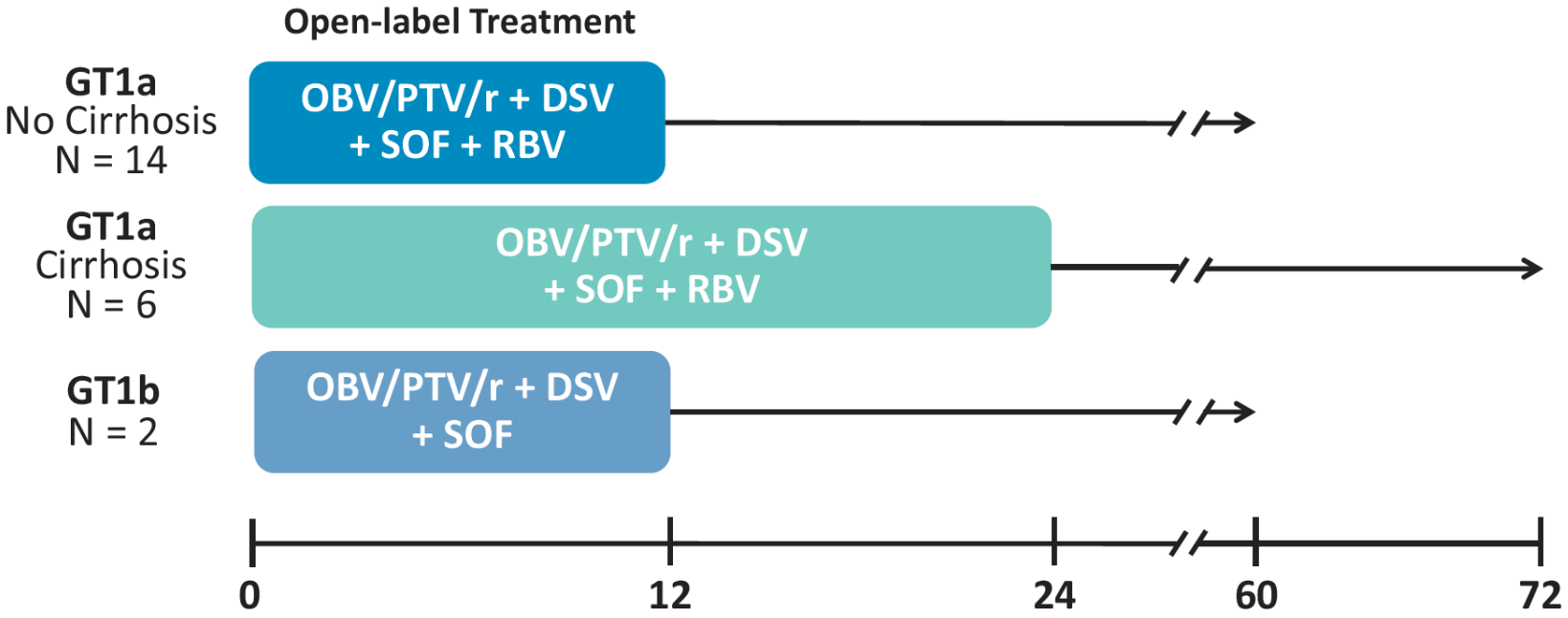
Poordad et al.,
AASLD 2015, #LB20

Salvage Therapy

3D + SOF after DAA failure (Quarz 1)

- 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)

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

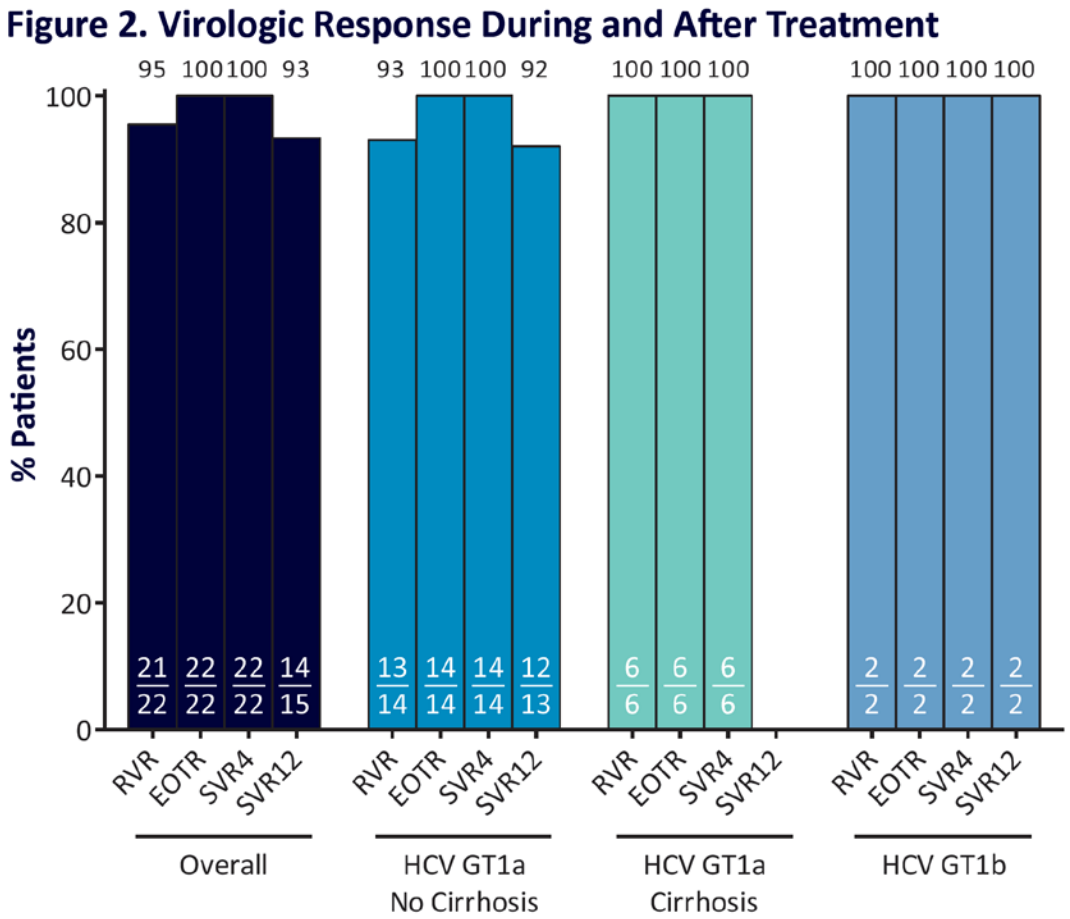


Poordad et al., AASLD 2015, #LB20

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)
- ➢ 3D+SOF (1b) for 12 wks or 3D+SOF+RBV for 12 wks (24 wks cirrhosis) (1a)



12 weeks treatment

24 wks pending (currently 6/6 SVR4)

Poordad et al., AASLD 2015, #LB20

Overview

- Natural frequency of resistance associated variants
- Resistance associated with differences between HCV genotypes / subtypes
- Importance of RAVs for all oral DAA treatment naïve patients
- Importance of RAVs for DAA combination failure patients
- Frequency and importance of chimera

Importance of chimera

HCV viral recombination

LiPA Assay 2.0

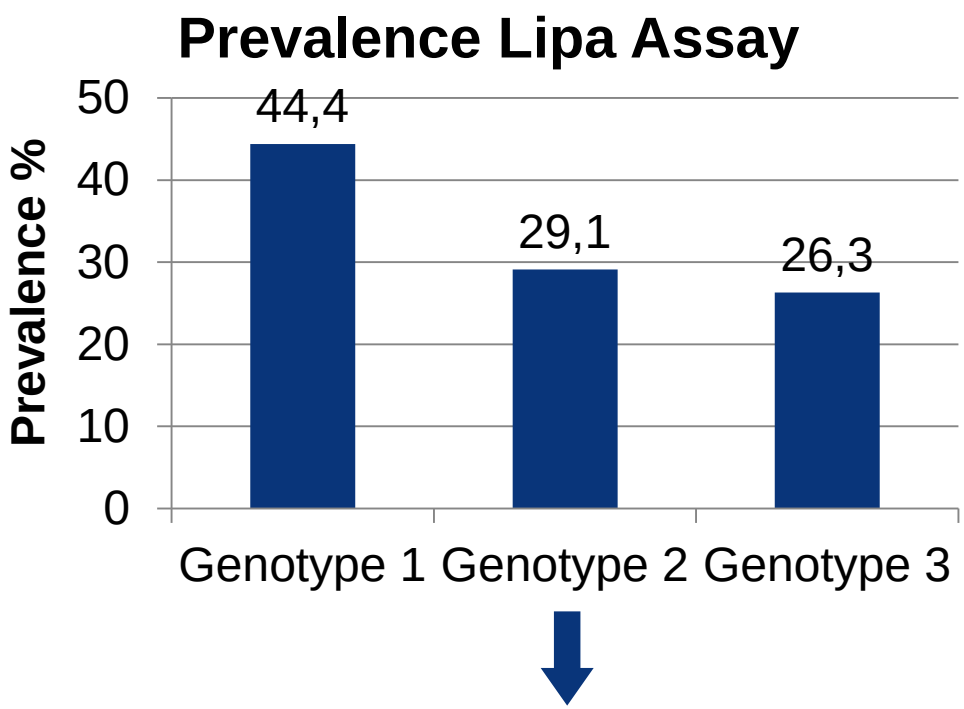
nucleotide polymerase-inhibitor
Sofosbuvir

- **St. Petersburg variant**

Raghwani et al., J Virol 2012; Kalinina et al., J Virol 2002

Prevalence of chimera

- **Georgia**



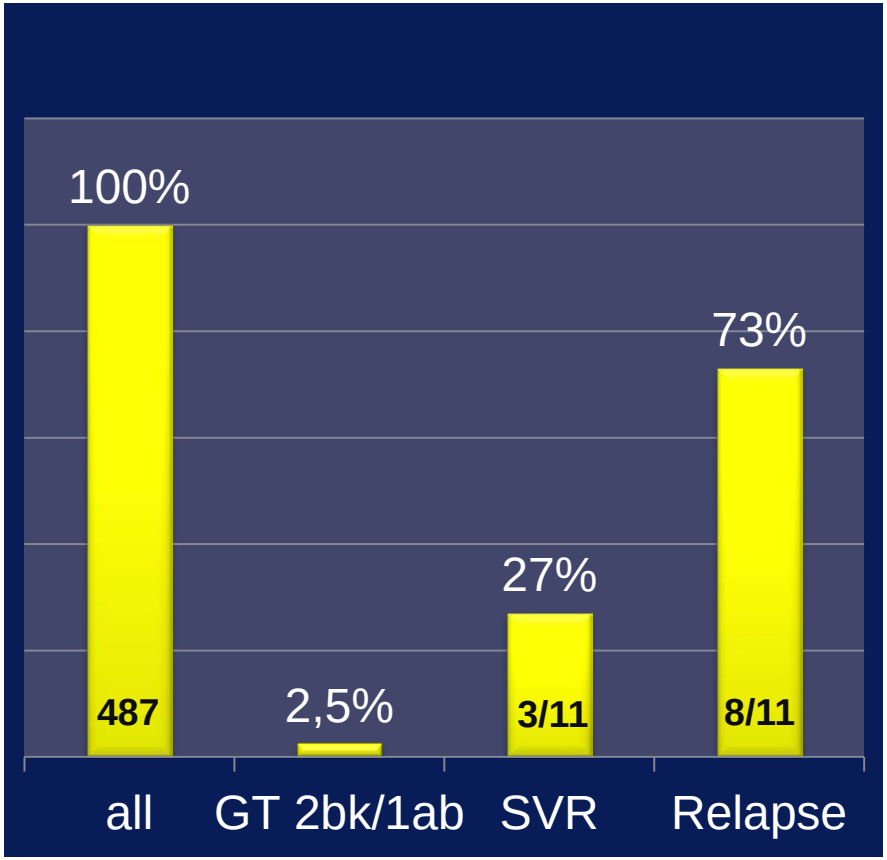
76% of GT2 are GT2k/1b by sequencing

Karchava et al., Hep Research 2015

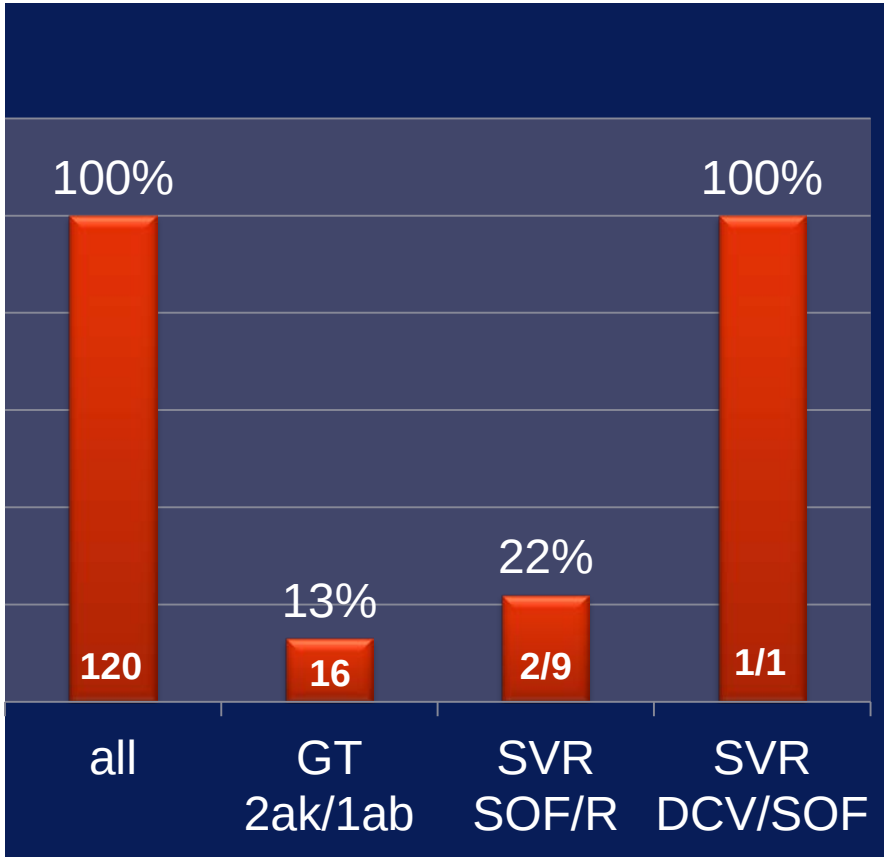
Treatment response in Genotype 2 chimera

Sofosbuvir plus RBV

GT2 patients from SOF/R
12-16 wks. approval studies



Experience
FFM resistance data base



Hedskog C et al., Hepatology 2015; data on file FFM Resistenzdatenbank

Summary

- Different frequencies of baseline RAVs according to DAA target, HCV geno-/subtype, geographical region
- Antiviral activities of DAAs with high variation between HCV geno-/subtypes
- 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)
- DAA failure patients
  - different persistence rates of RAVs (NS3 vs NS5A and nonNUC NS5B)
  - re-treatment with the same regimen seems to be inefficient
  - resistance testing, change of DAA class, extension to 24 wks., add RBV
- Viral chimera
  - mainly HCV genotype 2/1 recombinants / other chimera are rare
  - prevalence between 2 and 70% of GT2 pts. with geographical variation
  - response to sofosbuvir plus RBV significantly reduced