Zentrum für Infektiologie
Berlin/Prenzlauer Berg

THE INTERNATIONAL LIVER CONGRESS™ 2016

APRIL 13-17, BARCELONA, SPAIN

Post EASL

4. Mai 2016

Patrick Ingiliz, Berlin

Interessenkonflikte

- Vortrags- und/oder Beratungshonorare von abbVie, BMS, Gilead, Janssen, MSD, Roche, ViiV.

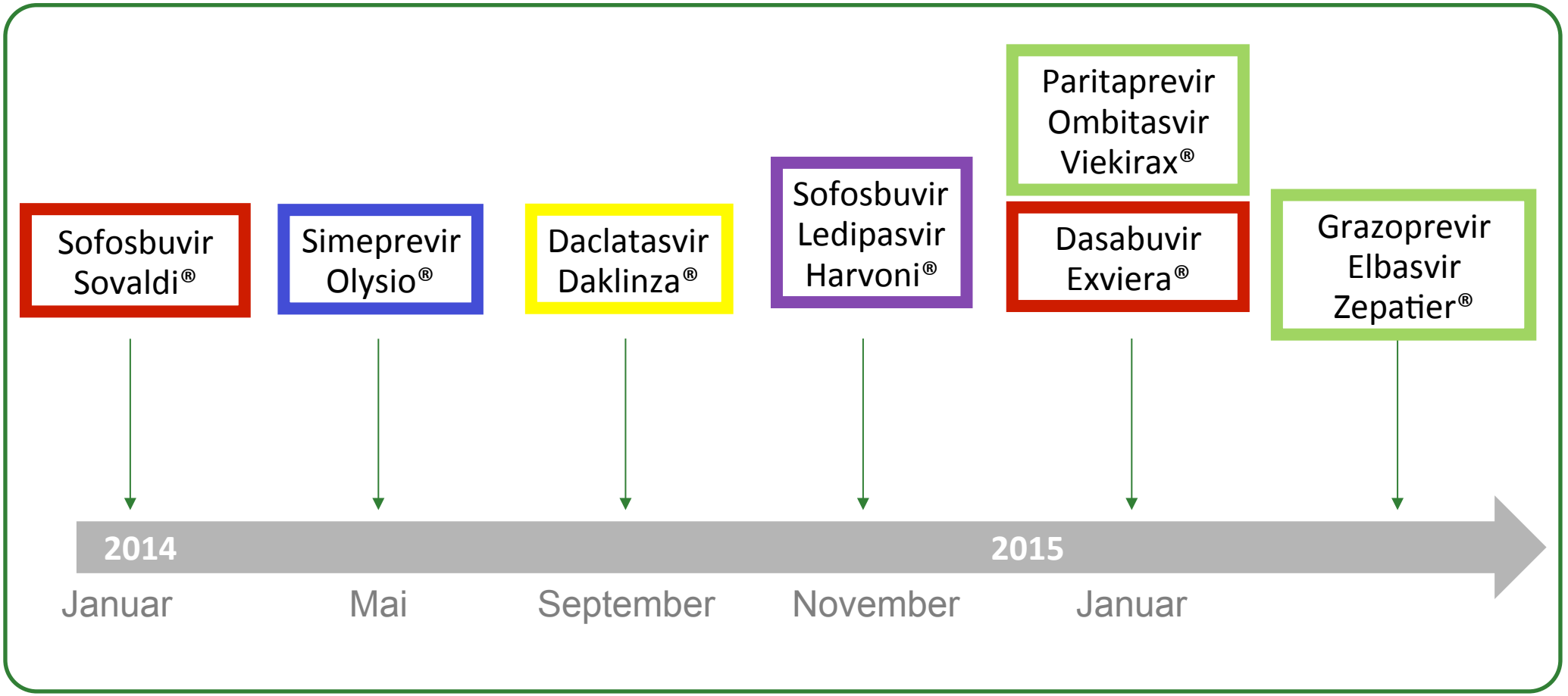
- Klinische Studien für abbVie, Gilead, BMS, ViiV, Hologic, Janssen, MSD, Boehringer-Ingelheim.

Personen, die mir beim Erstellen der Slides geholfen haben...

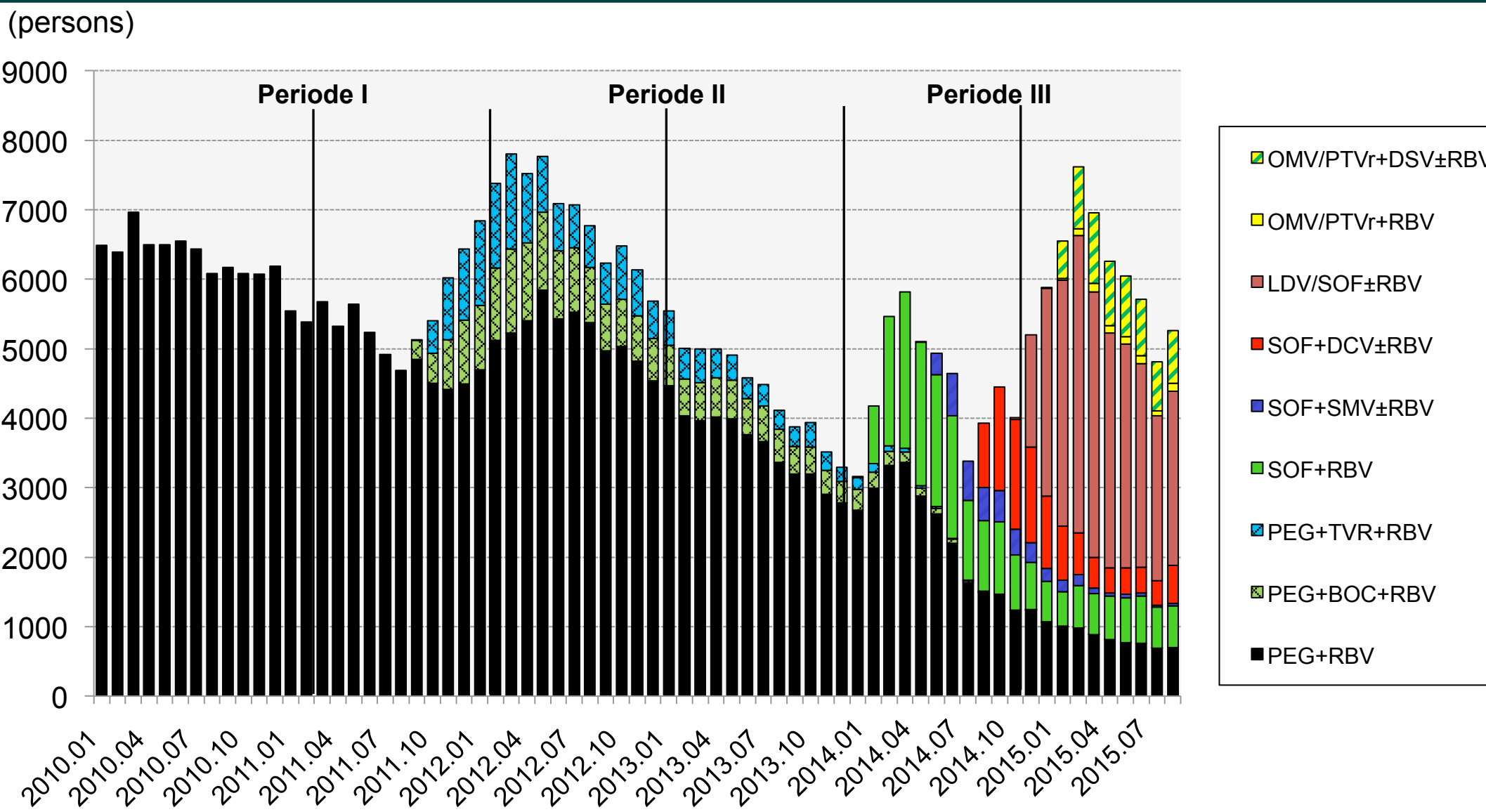
- Markus Cornberg, Hannover
- Julian Schulze zur Wiesch, Hamburg
- Maud Lemoine, London
- Marc Bourlière, Marseille
- Axel Baumgarten, Berlin
- Ivanka Krznaric, Berlin
- Frank Tacke, Aachen

HCV-Therapie aktuell

Medikamente die aktuell (bald) in Deutschland zur Verfügung stehen



Die Behandlungsrealität in Deutschland



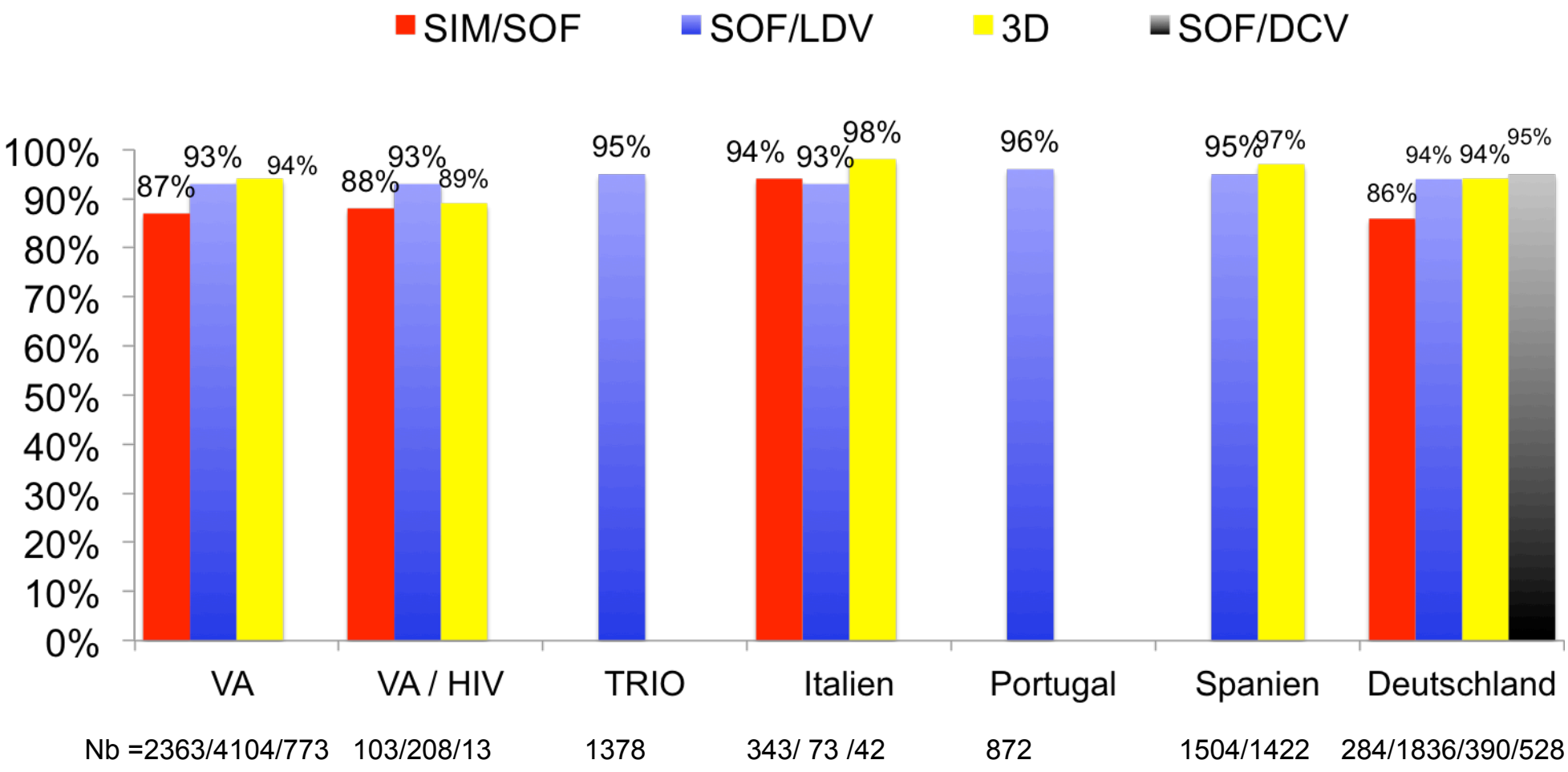
Kollan C et al., EASL 2016, FRI-428

Die Behandlungsrealität in Deutschland

- In Periode III: 72.900 Behandlungsmonate mit DAA-Regimen
- Bei durchschnittlicher Behandlungsdauer von 12 Wochen: 24.300 Person
- Bei einer SVR-Rate von 90% → 21.900 Heilungen
- In 2015: 5000 Personen/Monat unter DAA-Behandlung

Heilungsrate in Deutschland aktuell: 18.000/Jahr

Große Real-Life-Kohorten bestätigen die Ergebnisse klinischer Studien:16236 GT-1 Patienten



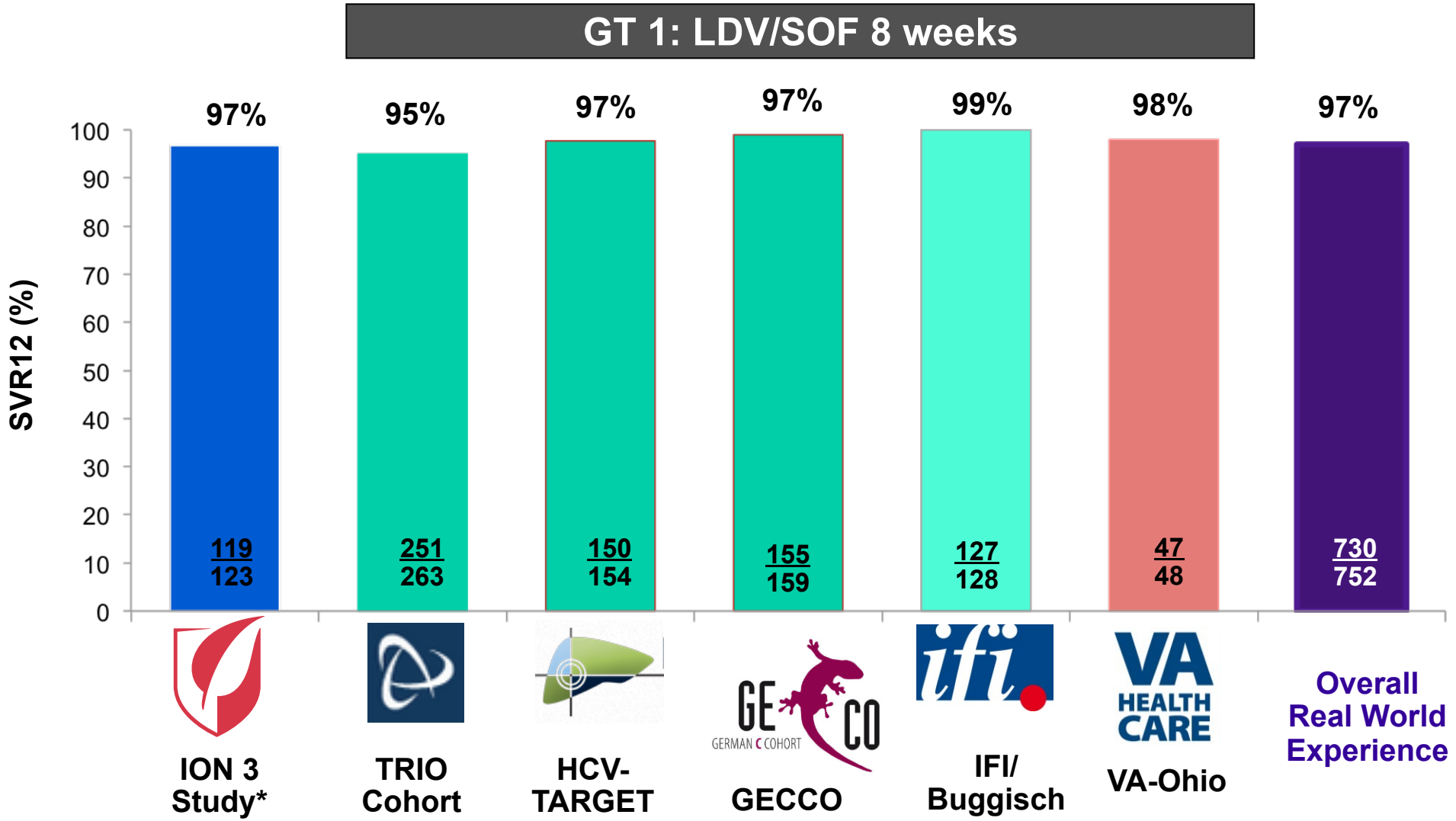
Kein Einfluß von HIV, HBV, Diabetes oder Adipositas auf SVR

Beachtung EASL Guidelines (93% vs 87%)

Hypo Alb <35g/l negativer Prädiktor für SVR

McCombs J et al: LBP-510,McGinnis J et al: LBP-514, Afdhal N et al: LBP-519, Aghemo A et al: LBP-500, Marinho T et al: LBP-523, Crespo, J et al: LBP-511, Calleja JL et al: LBP-512, Mauss. S et al: SAT-263

8 Wochen Sofosbuvir/Ledipasvir RWE vs ION-3



*Post hoc analysis

Kowdley KV, et al. N Engl J Med 2014;370:1879-88; Curry M, et al AASLD 2015; Terrault N, et al AASLD 2015; Buggisch P, et al. EASL 2016; Christensen, et al. CROI 2016; Marshall et al. AASLD 2015

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

2D/3D: Real-life-Ergebnisse aus dem deutschen HCV-Register

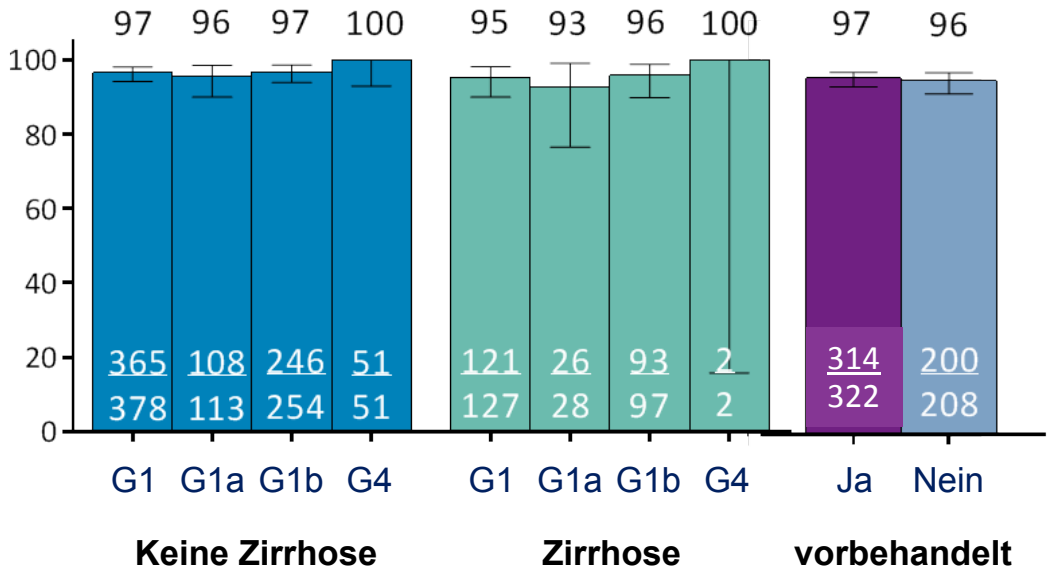
Patientencharakteristika (n = 1 017)

G1a	261 (26 %)
G1b	614 (60 %)
Genotyp nicht spezifziert, gemischt oder anderer G1	17 (2 %)
G4	125 (12 %)
Zirrhose	228 (22 %)
Vorbehandelt	598 (59 %)

Verträglichkeit (n = 1 017)

Ereignis, n (%)	Keine Zirrhose		Zirrhose	
	2D/3D (n = 436)	2D/3D + RBV (n = 353)	2D/3D (n = 44)	2D/3D + RBV (n = 184)
AE	185 (42)	201 (57)	20 (45)	119 (65)
SAE	5 (1)	8 (2)	0	8 (4)
Abbruch wegen AE	2 (0,5)	4 (1)	0	9 (5)

SVR12/24 (n = 558)



Spielen Baseline-RAVs eine Rolle?

Häufigkeit NS5A-RAVs (15%-threshold): GT 1a: 11%, GT1b: 19%

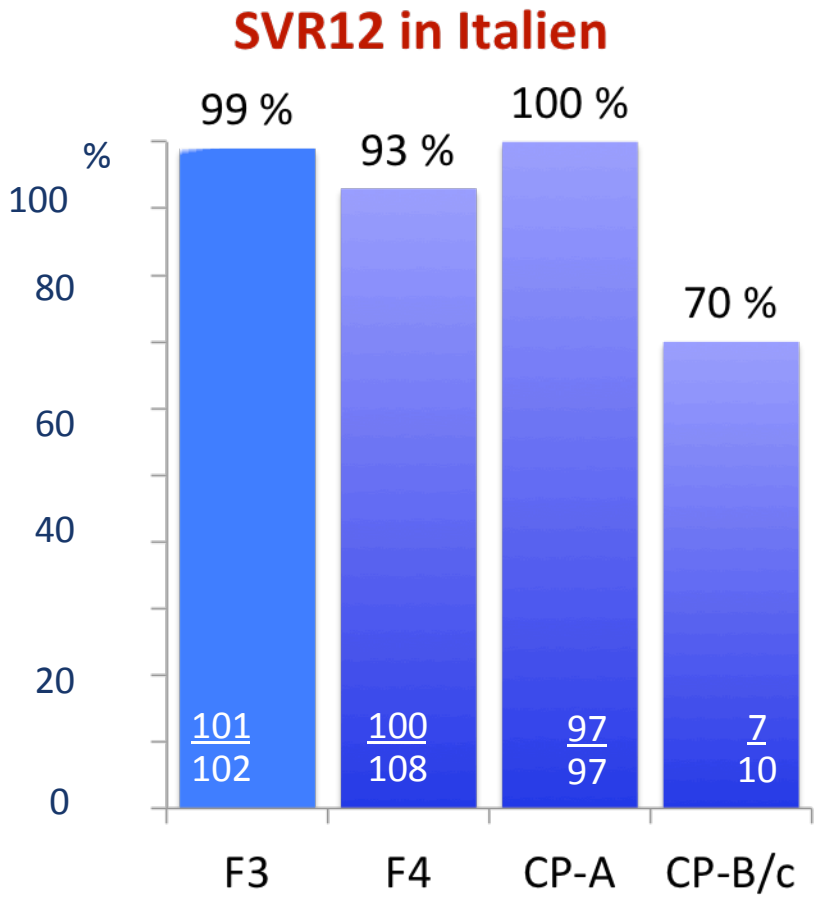
Ansprechen je NS5A-RAV:

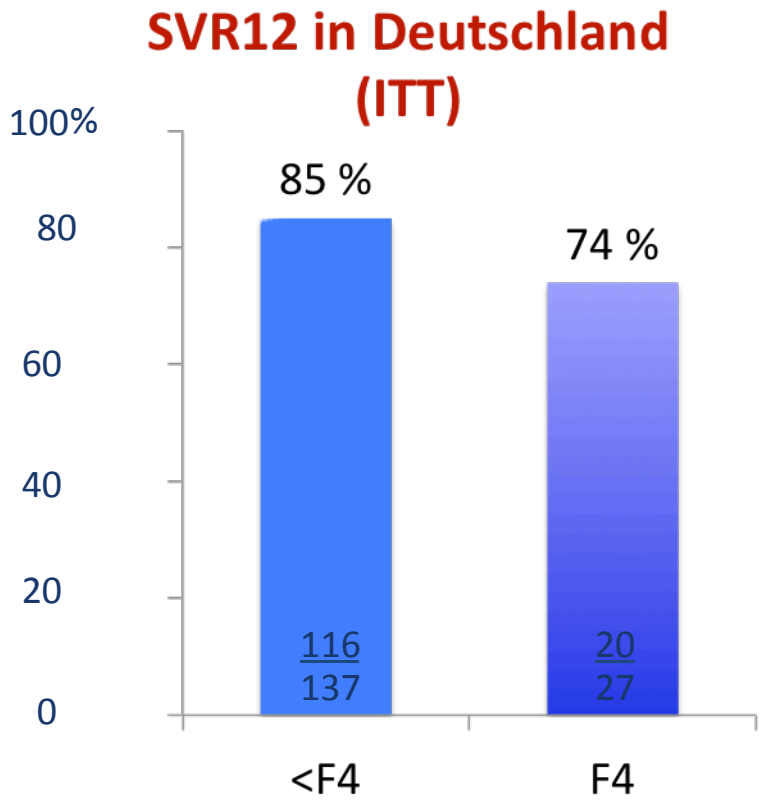
Study[a]	Genotype	Description	Drugs	Duration	Number of Patients Enrolled	Number of Patients Analyzed[b]
SAPPHIRE-II	1a	Double-blind; P/R experienced; no cirrhosis	OBV/PTV/r + DSV + RBV	12 weeks	220	214
TURQUOISE-II	1a	Open-label; P/R experienced and treatment-naive; with compensated cirrhosis		24 weeks	121	118
PEARL-IV	1a	Double-blind; treatment-naive; no cirrhosis		12 weeks	100	90
PEARL-II	1b	Open-label; P/R experienced; no cirrhosis	OBV/PTV/r + DSV	12 weeks	91	89
TURQUOISE-III	1b	Open-label; P/R experienced and treatment-naive; with compensated cirrhosis			60	59

Sarrazin C et al., EASL 2016, LBP503

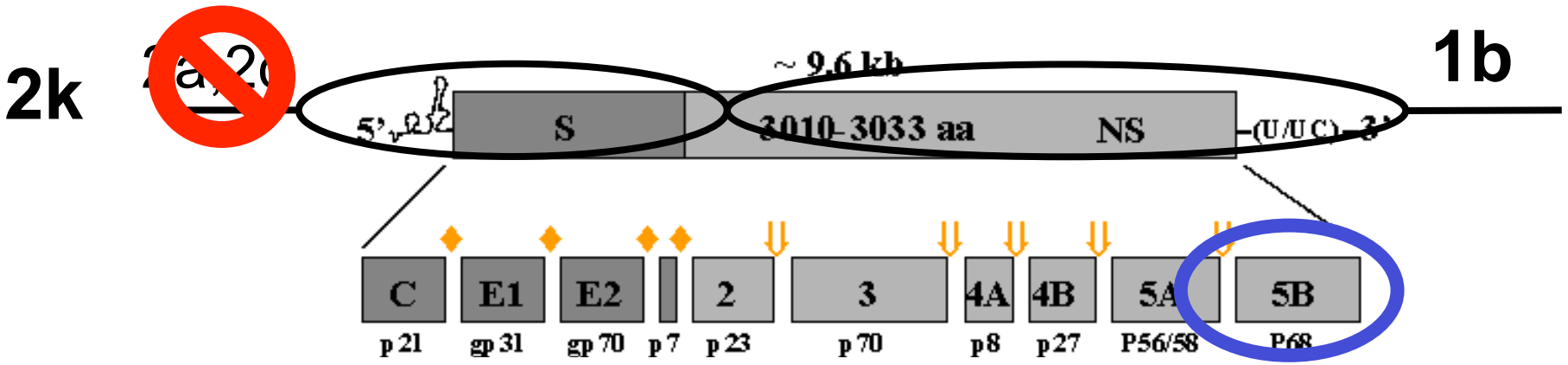
SOF-RBV bei Genotyp 2: widersprüchliche Ergebnisse aus Italien und Deutschland

- Italien : 102 F3 12w., 108 F4 ≤ 20w
- Deutschland : 88 % aller Patienten 12w





VERSANT HCV Genotype 2.0 Assay

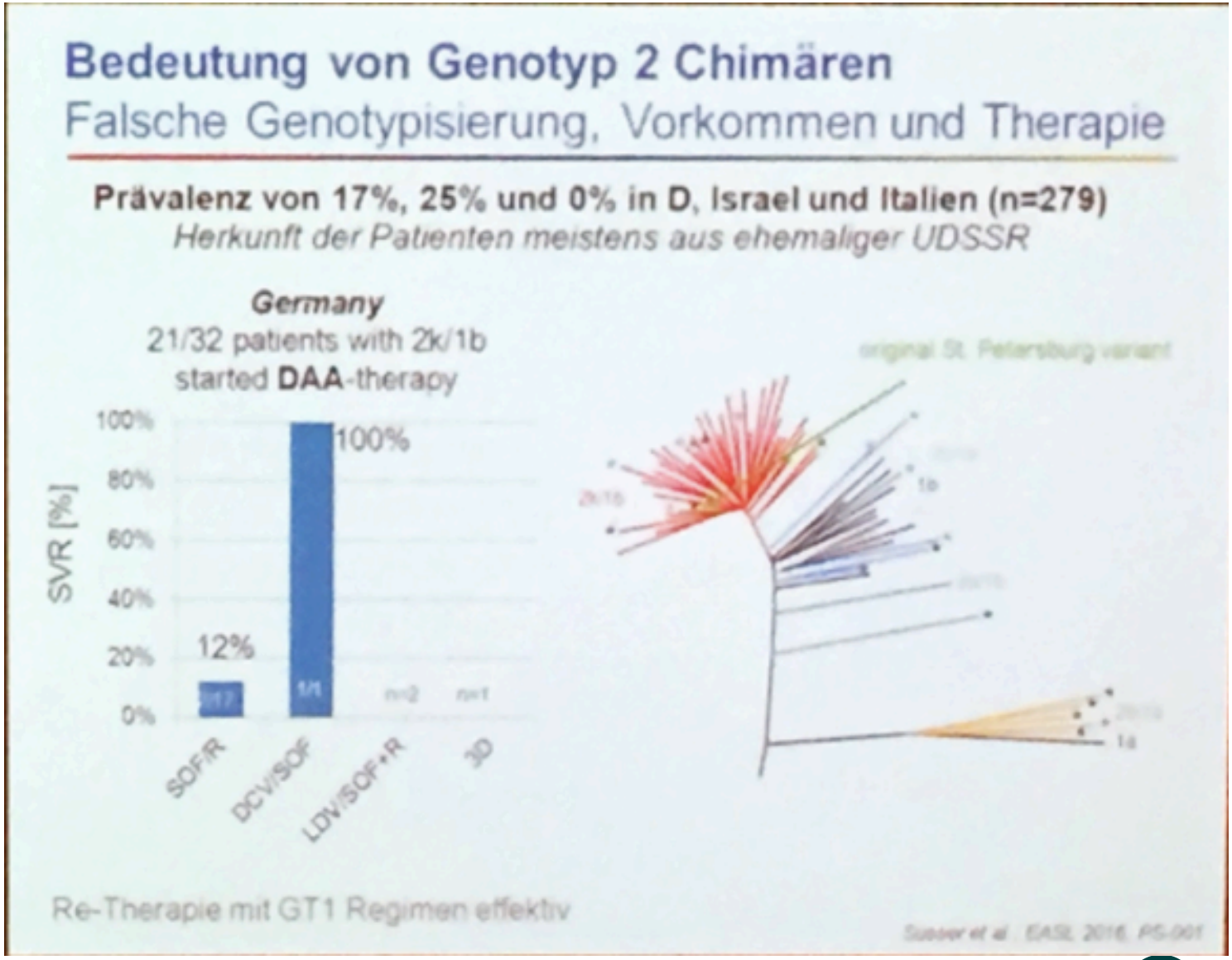


NS5B sequencing proves the presence of 1b genotype

St. Petersburg recombinant form 2k1b

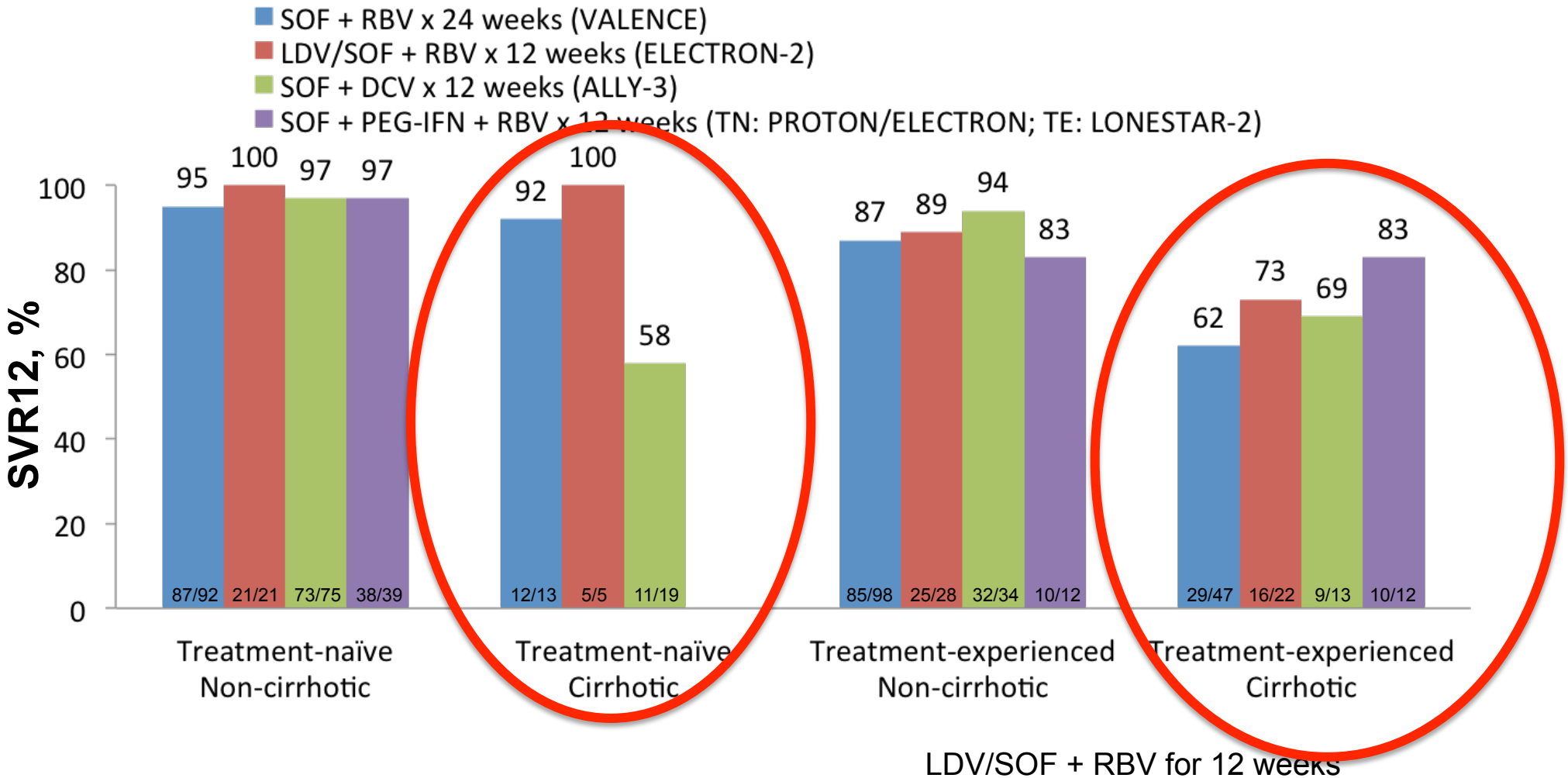
Kalinina et al., J Virol 2002

Mögliche Ursache: „falsche Genotypisierung“



Susser et al., EASL 2016

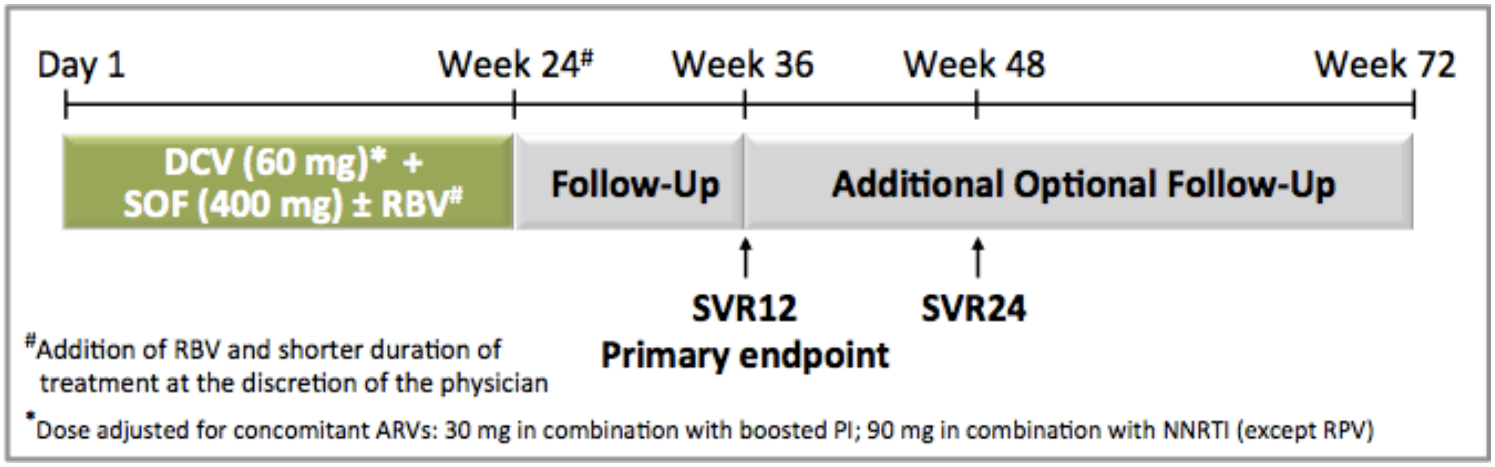
Was ist die beste Therapie für Patienten mit Genotyp-3-Infektion

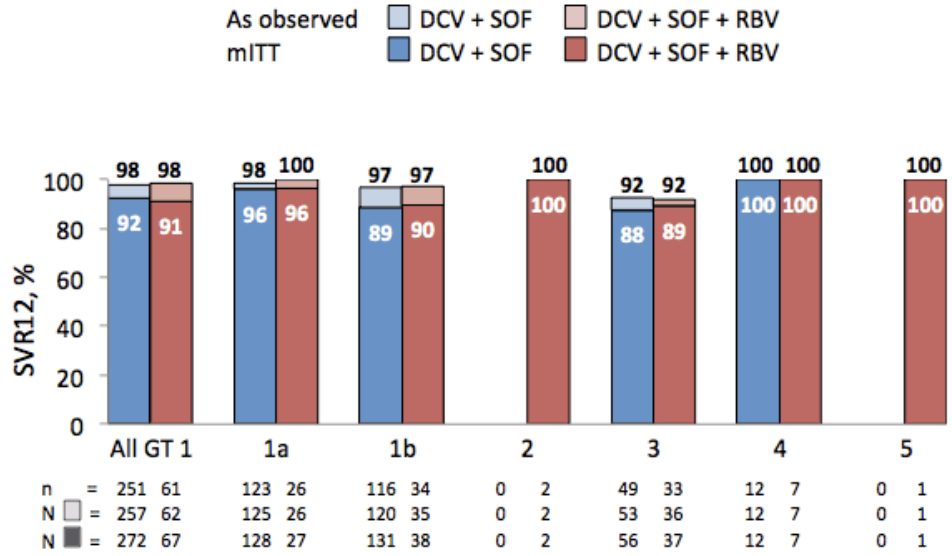


LDV/SOF + RBV for 12 weeks
not EMA-recommended treatment regimen for GT 3

Zeuzem S, et al. N Engl J Med 2014;370:1604-14; Gane E, et al. EASL 2014; Oral #6; Gane E et al. NEJM 2013;368:34–44; Lawitz E et al. Lancet Infect Dis 2013;13:401–408; Gane E et al. AASLD 2014, Poster #LB-11; Lawitz E et al. AASLD 2013, Oral #LB-4; Nelson M et al. AASLD 2014, Oral #LB-3

Europäisches Compassionate Use Programm





- GT 1 subtype other/unknown, n = 15 (13 SVR12, 2 deaths)
- Mixed GT, n = 3 (1 SVR12, 2 deaths)
- Unknown GT, n = 3 (2 SVR12, 1 discontinuation due to AE)

Welzel TM *et al.*, EASL 2016; poster SAT-275

Genotyp 3

Genotyp 3 im Deutschen Hepatitis C Register

Table 1. Overview of SVR in different treatment groups

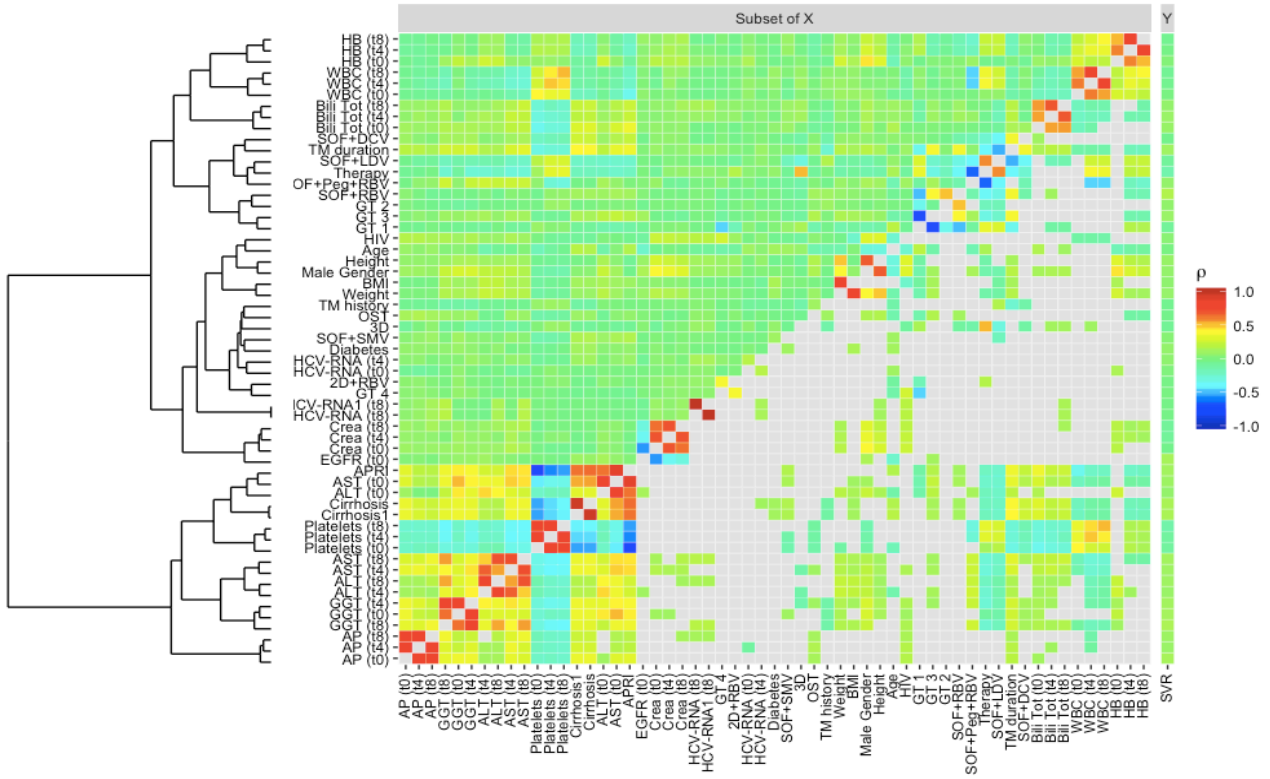
Regimens	pts who started treatment n=	% of all treatments	% cirrhosis in treatment group *	% early termination of therapy * #	SVR12 ITT	SVR12 ITT ×	SVR12 PP	SVR12 PP×
					n/total	%	n/total	%
PegIFN + RBV	92	10.6	1.5	19.7	33/58	56.9	32/41	78.0
PegIFN + RBV + SOF	202	23.4	21.8	4.3	164/182	90.1	160/167	95.8
SOF + RBV	245	28.4	28.1	8.4	115/156	73.7	112/133	84.2
SOF + DCV ± RBV	201	23.3	43.6	6.1	121/135	89.6	119/127	93.7
SOF/LDV ± RBV	115	13.3	64.0	5.3	40/53	75.5	40/47	85.1
Other	9	1.0	14.3	0	7/7	100.0	7/7	100.0
Total	864	100	31.4	7.4	480/591	81.2	470/522	90.0

Cornberg M et al., EASL 2016, SAT-208

Assoziation mit Relapse in GECCO

GERMAN C COHORT

N=1353, 21% HIV-HCV-koinfiziert
Relapse-Rate: 4.6%

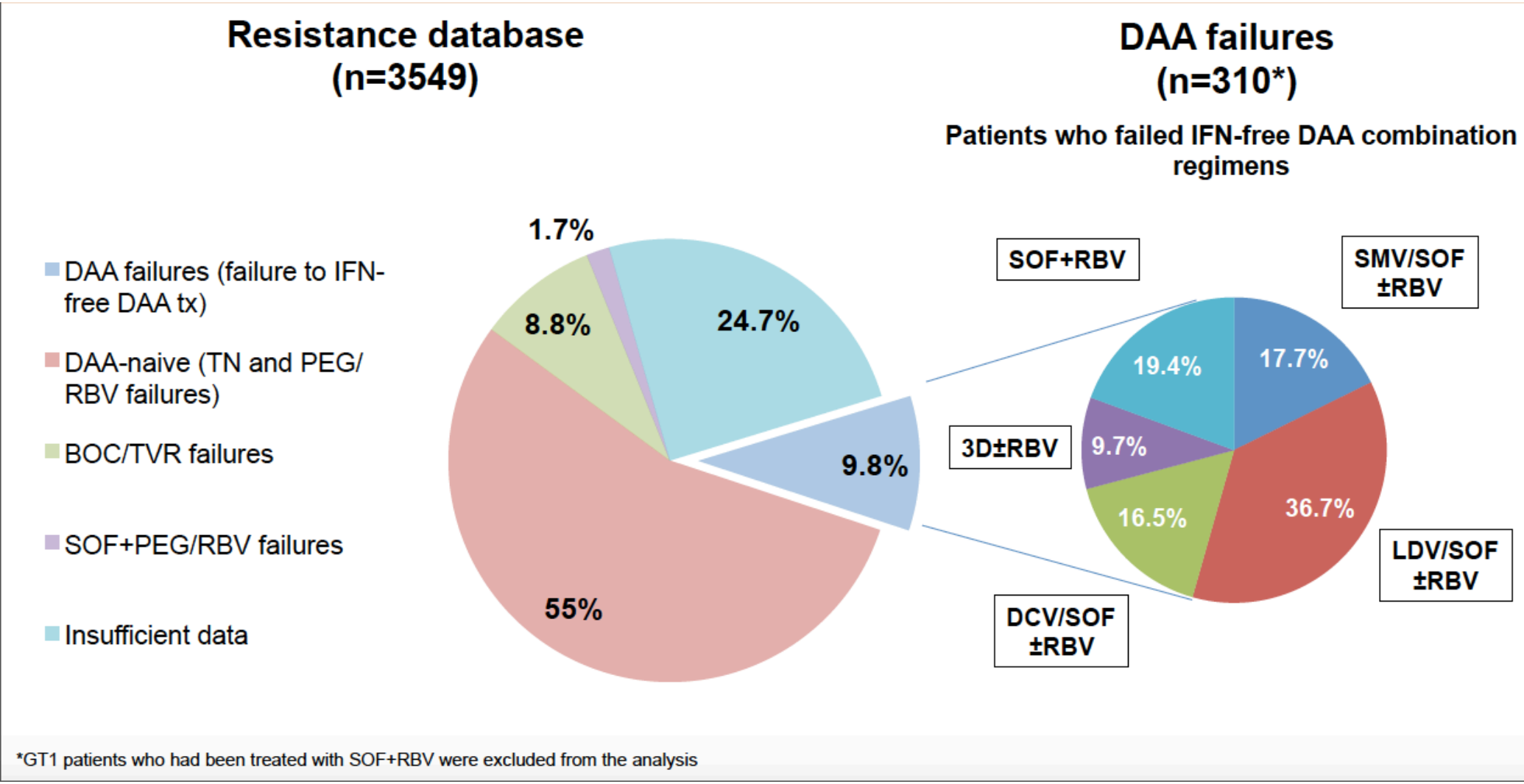


In a linear discriminant context, the following factors were associated with SVR/ relapse:

- **APRI (coefficient=0.12, p value=0.00023)**
- **Baseline leucocytes (coefficient=0.04, p value=0.08333)**
- **Baseline creatinine coefficient=0.68, p value=0.03747)**
- **Baseline eGFR (coefficient=0.006, p value=0.02064)**
- **Genotype 3 (coefficient=-0.19, p value=0.09892)**

Ingiliz P et al., EASL 2016, SAT-238

Was tun im Falle von DAA-Versagen?

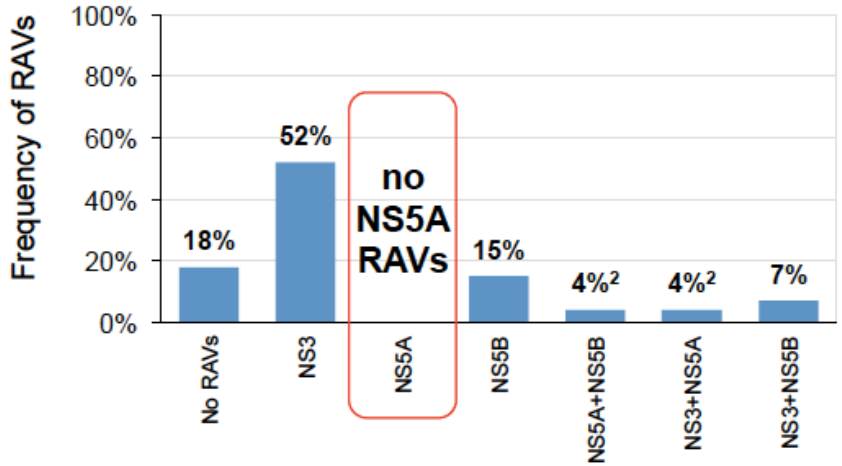


*GT1 patients who had been treated with SOF+RBV were excluded from the analysis

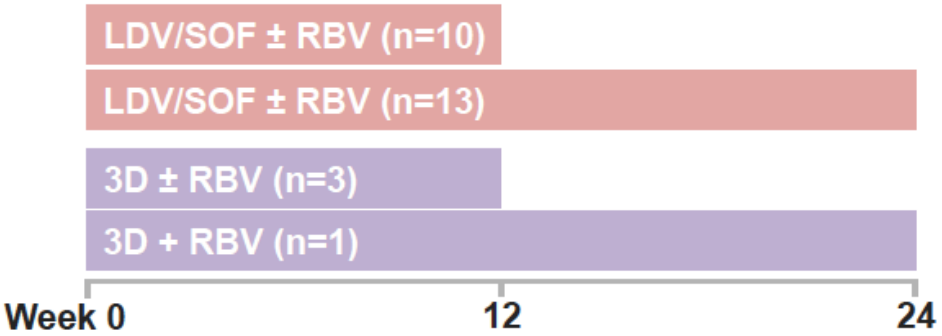
Retreatment in Genotype 1

PI Failure → Retreatment with NS5A-Containing Regimens

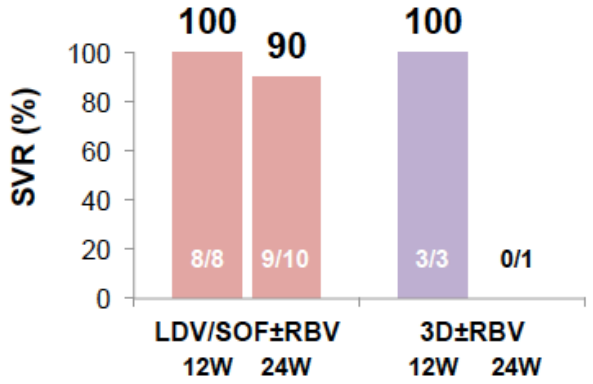
SMV/SOF Failures
n=27/49 (55%)[1]



Retreatment with NS5A Inhibitor-containing regimen



Interim analysis: SVR12 91% (n=20/22)



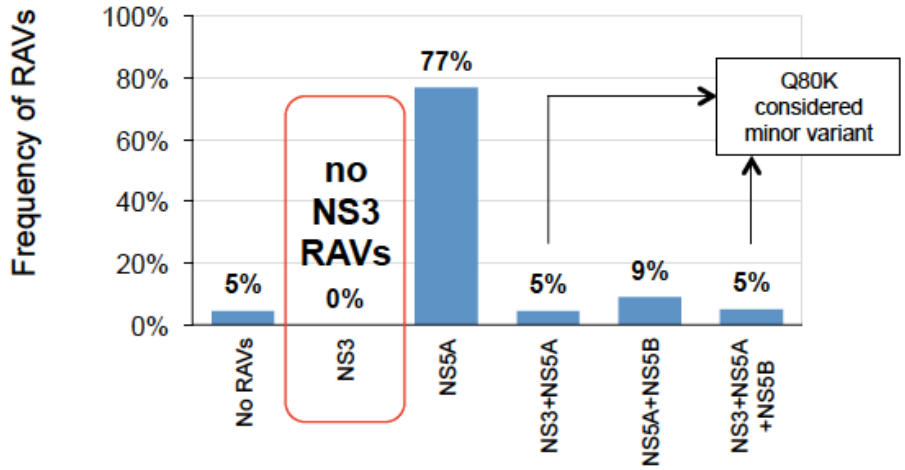
[1] Resistance analysis failed in two pts. due to low volume/failed sequence analysis
[2] One GT1b pt. with L31M as minor variant and one GT1b pt. with L31M+Y93H were retreated with LDV/SOF+RBV for 24 weeks

Retreatment in Genotype 1

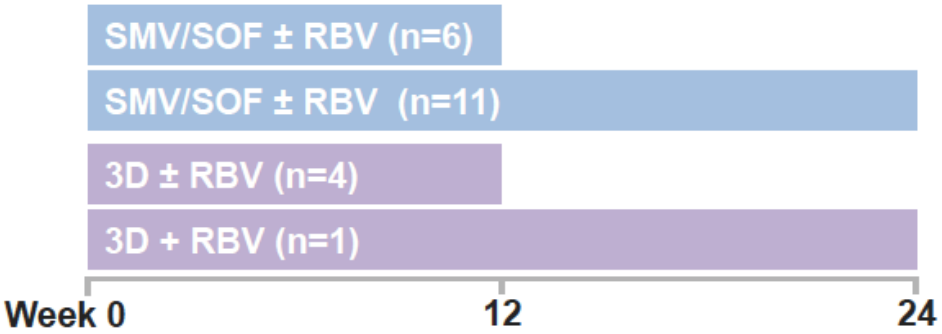
NS5A Failure → Retreatment with PI-Containing Regimens

LDV/SOF Failures
n=11/90 (12%)[1]

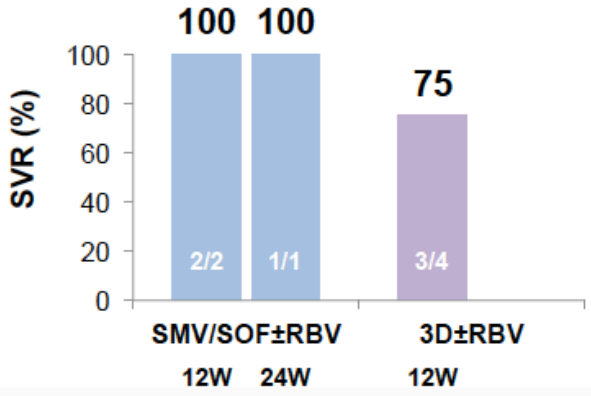
DCV/SOF Failures
n=11/29 (38%)



Retreatment with PI Inhibitor-containing regimen



Interim analysis: SVR12 86% (n=6/7)



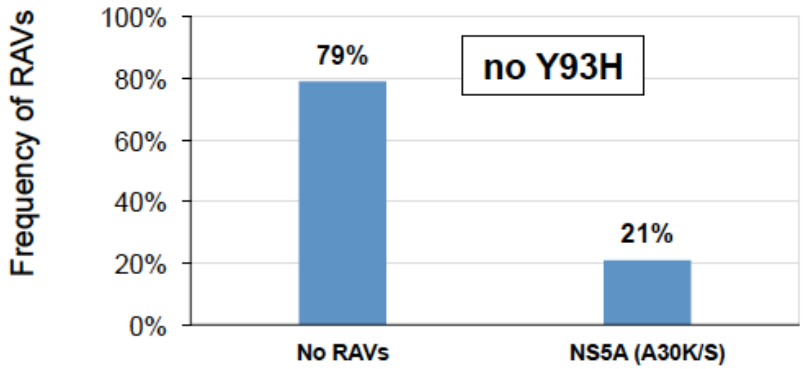
pts. were re-treated with LDV/SOF+RBV for 24 wks., one of whom has achieved SVR12 so far

38,7 x 190,5 mm

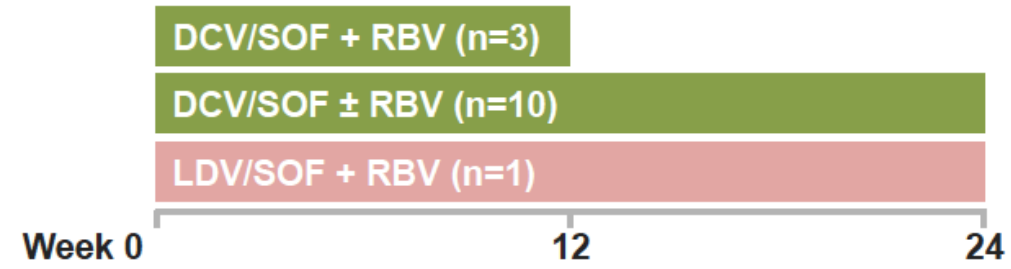
Retreatment in Genotype 3

SOF/RBV Failure → Retreatment with NS5A-Containing Regimens

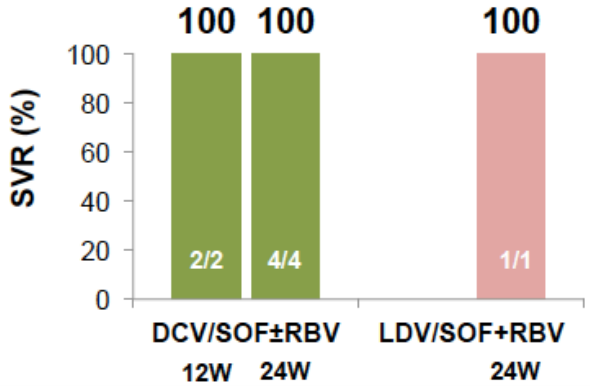
SOF/RBV Failures
n=14/33 (42%)[1]



Retreatment with NS5A Inhibitor-Containing Regimen



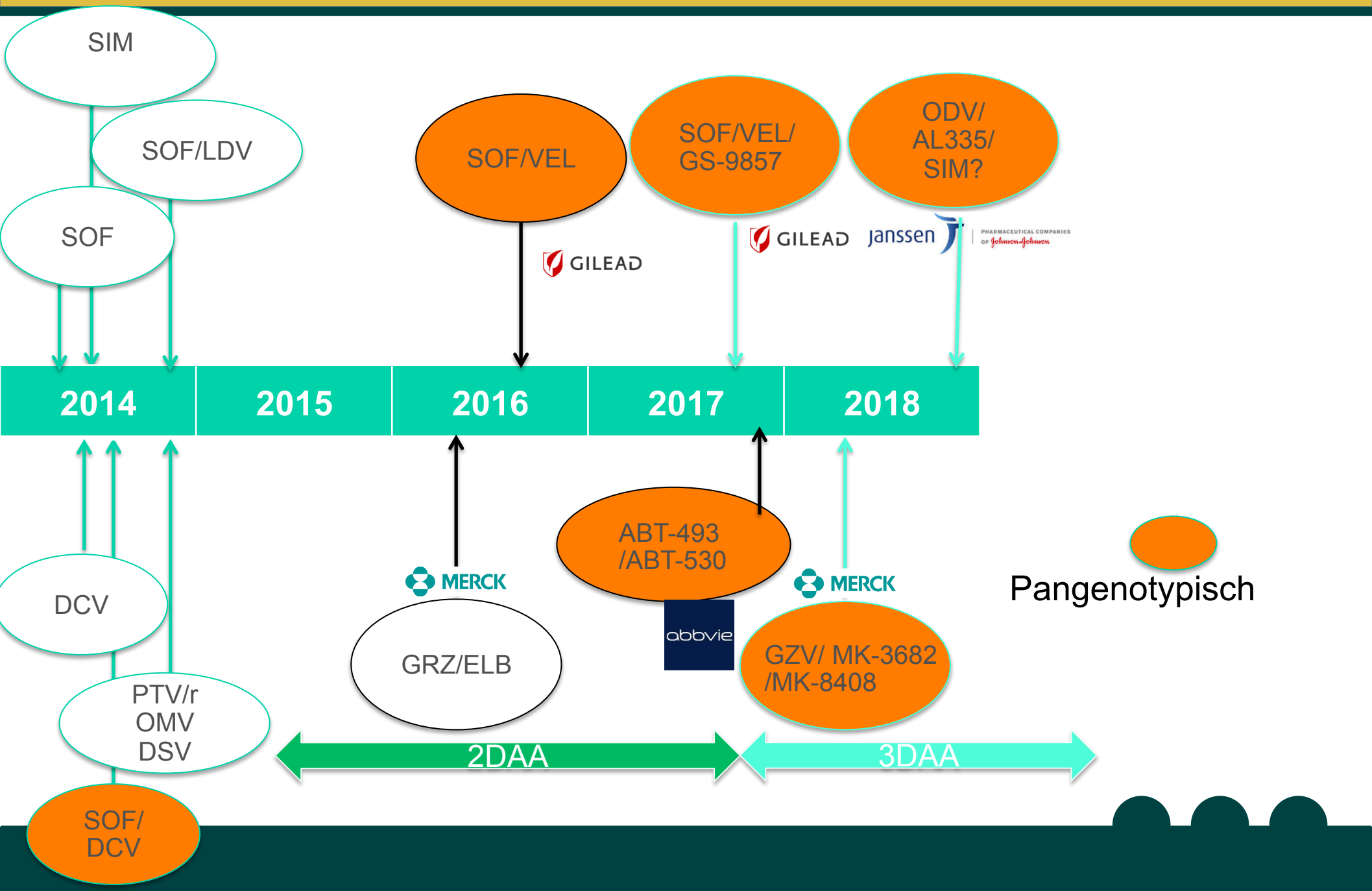
Interim analysis: SVR12 100% (n=7/7)



8,7 x 190,5 mm

l patients with failure to DCV/SOF are currently re-treated with DCV/SOF+RBV for 24 weeks

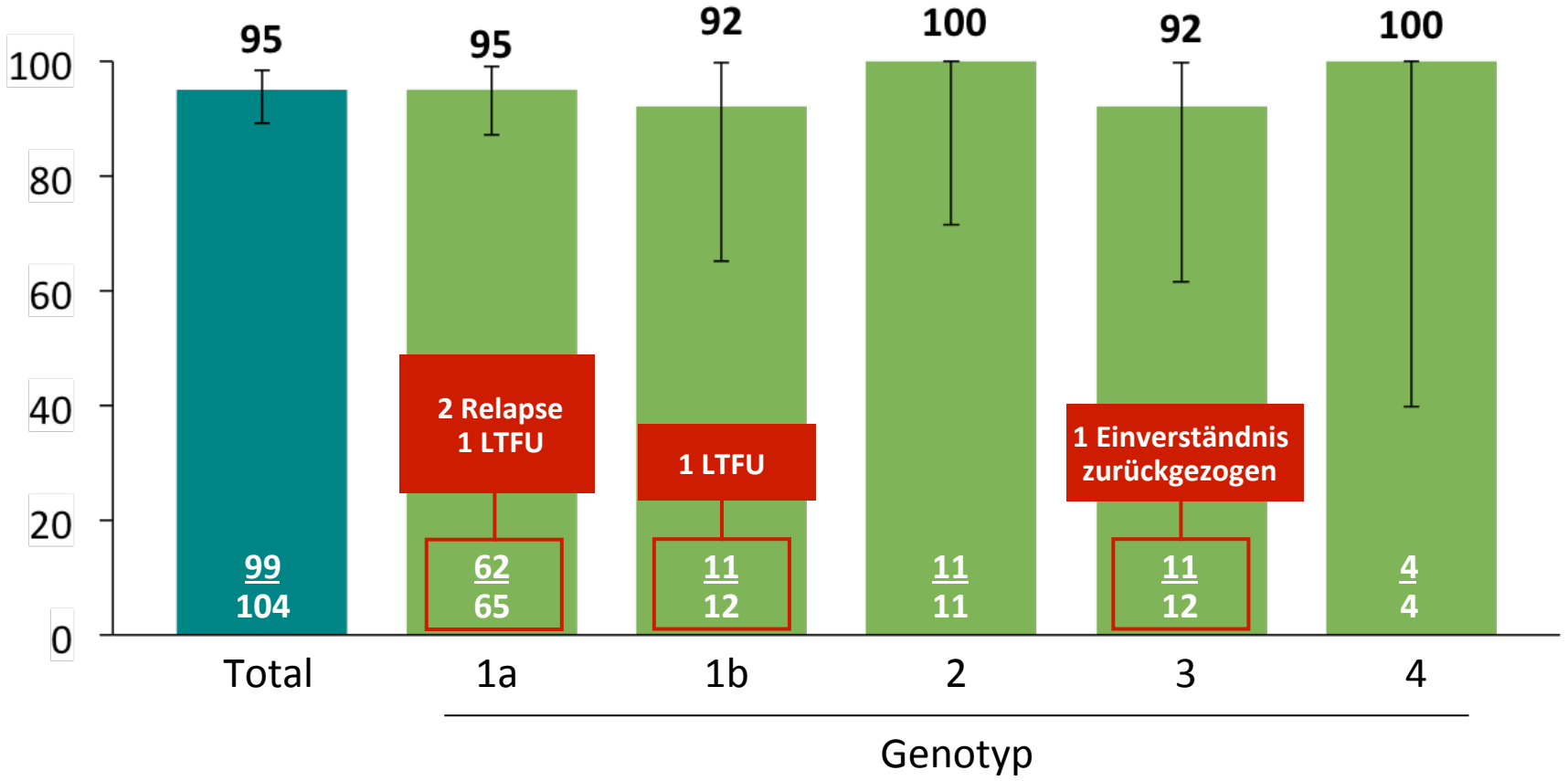
Zukünftige DAA-Kombinationen



HCV-Therapie morgen

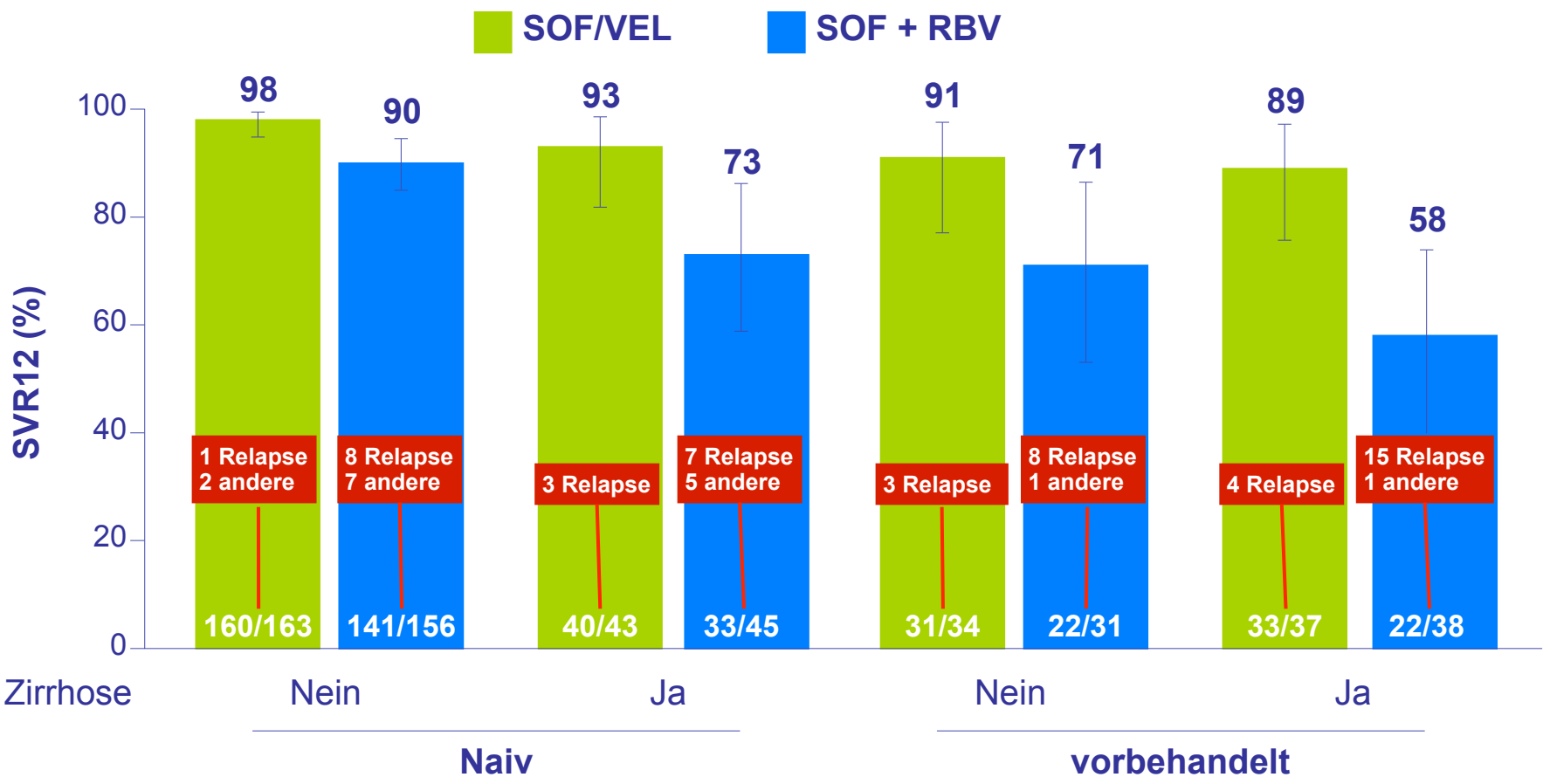
ASTRAL-5 : SOF/VEL 12 Wochen bei HIV-HCV-Koinfizierten

SVR12 nach Genotyp



Sofosbuvir/Velpatasvir bei HCV-Mono-Patienten mit Genotyp 3: ASTRAL-3

SVR-Raten nach Zirrhosstatus und Vortherapiestatus



➔ **89 % SVR bei vorbehandelten Zirrhotikern**

Mangia A, AASLD 2015, Abs. 249

Interaktionen mit HIV-Medikamenten

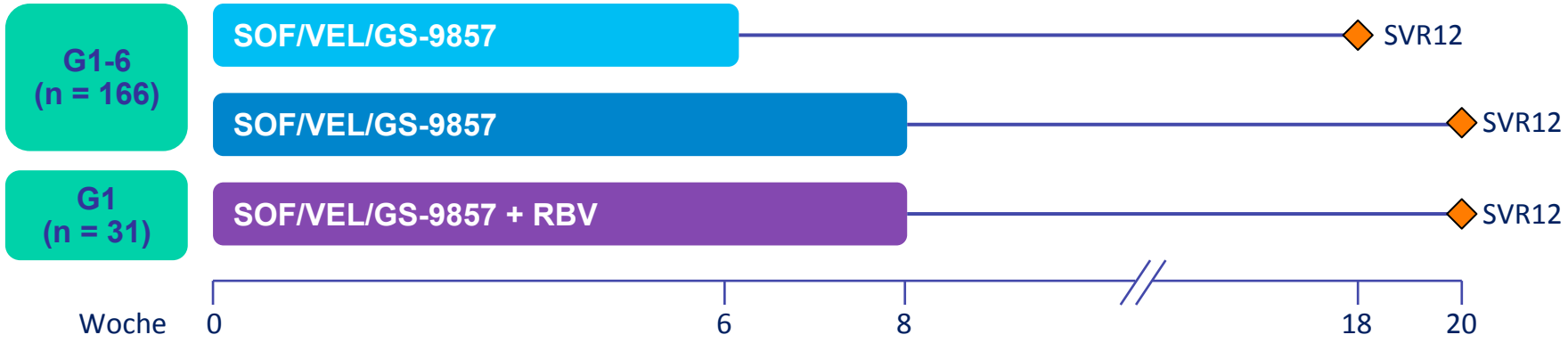
	Simeprevir	Sofosbuvir	Ledipasvir	Daclatasvir	AbbVie 3D	Grazoprevir/Elbasvir	Velpatasvir
ATV/r	No data	ATV ↔ SOF ↔	ATV↑, LDV↔	DCV ↑*	ATV ↔; ABT450 ↑		VEL↑
DRV/r	SIM ↑; DRV ↔	SOF ↑; DRV ↔	DRV↔, LDV↔	DCV (↑)	DRV ↓; 3D ↓		
LPV/r	No data	No data	No data	DCV↔	LPV ↔; ABT450 ↑		
TPV/r	No data	No data	No data	No data	No data		
EFV	SIM ↓; EFV ↔	SOF ↔; EFV ↔	LDV ↓; EFV ↓	DCV ↓*	No PK data**		VEL ↓
RPV	SIM ↔; RPV ↔	SOF ↔; RPV ↔	LDV ↔; RPV ↔	No data	ABT450 ↑; RPV ↑		
ETV	No data	No data	No data	No data	No data		
RAL	SIM ↔; RAL ↔	SOF ↔; RAL ↔	LDV ↔; RAL ↔	No data	3D ↔; ↑ RAL		
ELV/ cobi	No data	No data	No data	No data	No data		
DTG	No data	No data	No data	No data	No data		
MVC	No data	No data	No data	No data	No data		
TDF	SIM ↔; TDF ↔	SOF ↔; TDF ↔	LDV ↔; ↑TDF***	DCV ↔; TDF ↔	3D ↔; TDF ↔		↑TDF**

- Decrease DCV dose to 30mg QD, Increase DCV dose to 90mg QD, ** 3D + EFV led to premature study discontinuation due to toxicities

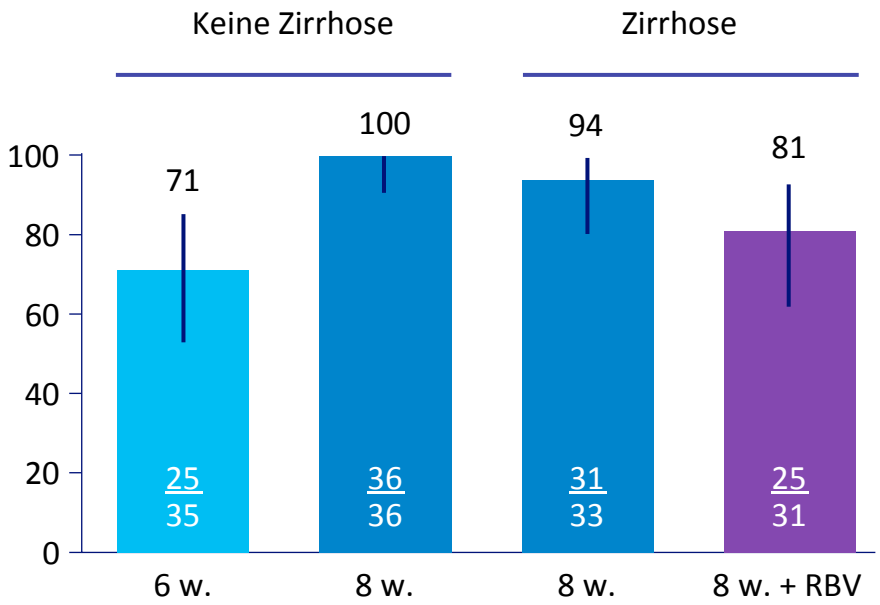
***when TDF is administered with a boosted HIV-PI and LDV significantly higher TDF levels can be expected warranting closer renal monitoring

HCV-Therapie übermorgen

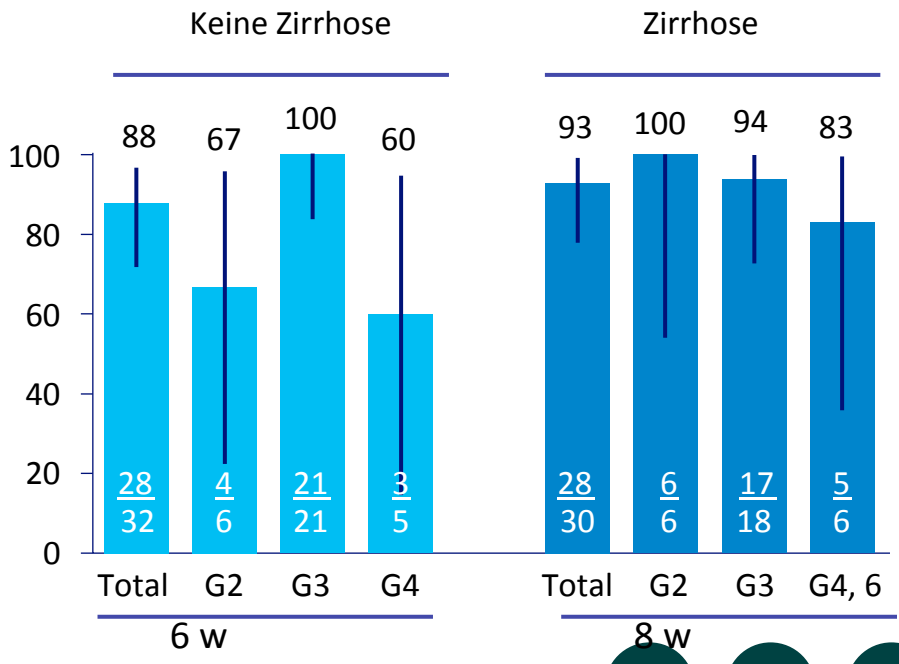
Sofosbuvir/Velpatasvir/GS-9857 bei Patienten mit G1 bis G6 mit und ohne Zirrhose



SVR12 bei G1-Patienten

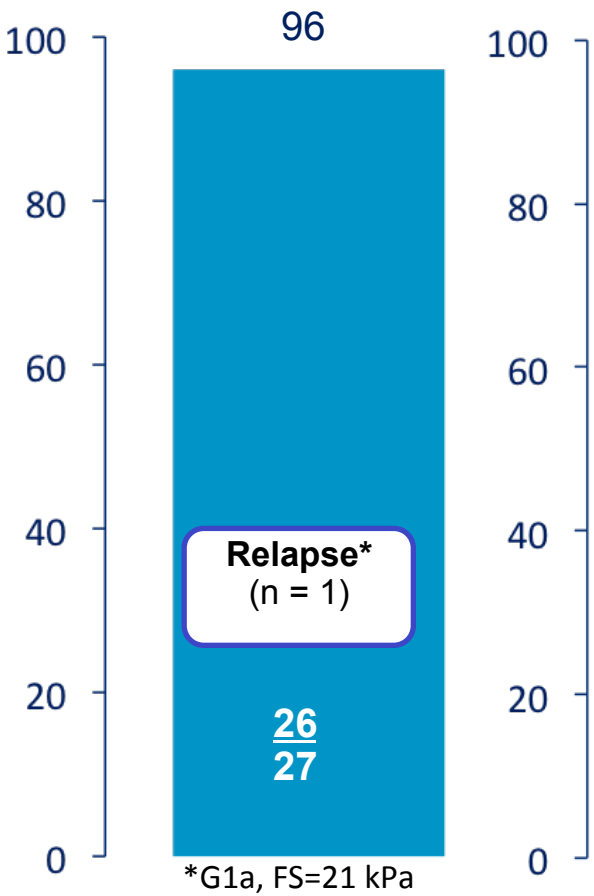


SVR12 bei G2, 3, 4 und 6



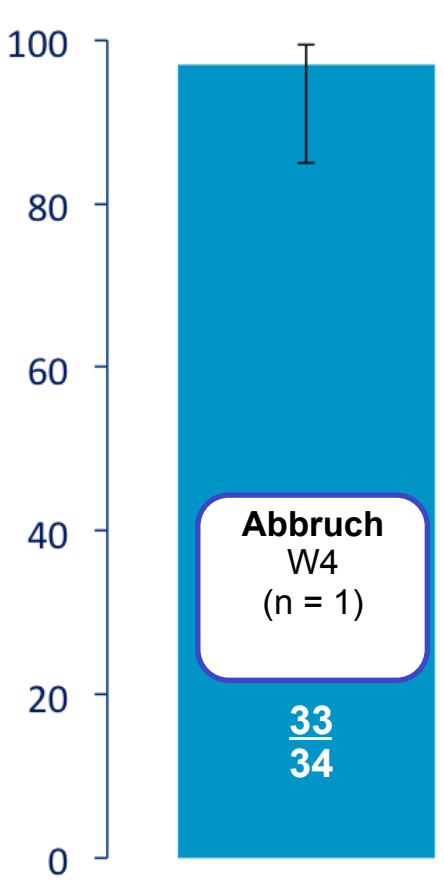
ABT-493+ABT-530 bei HCV GT 1,2,4, 5 und 6

SVR12
12 Wochen
G1
Komp. Zirrhose

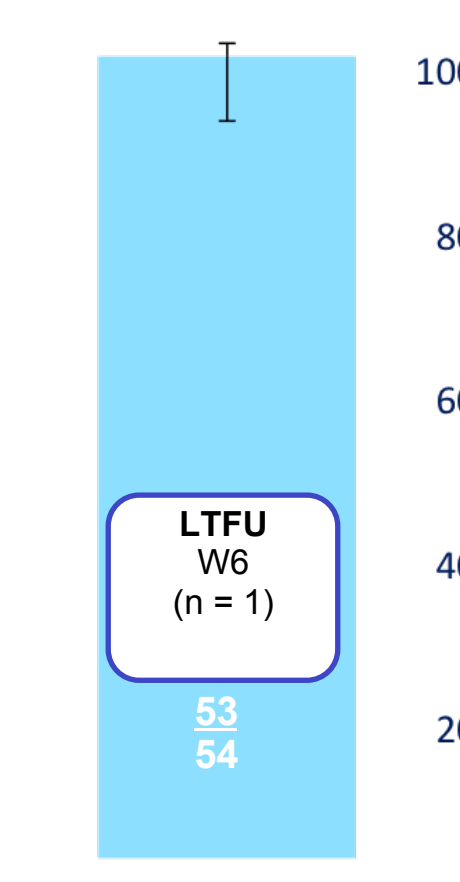


*G1a, FS=21 kPa
RAV Start: I170V, L31M
RAV Relapse: I170V, L31M, Y93N

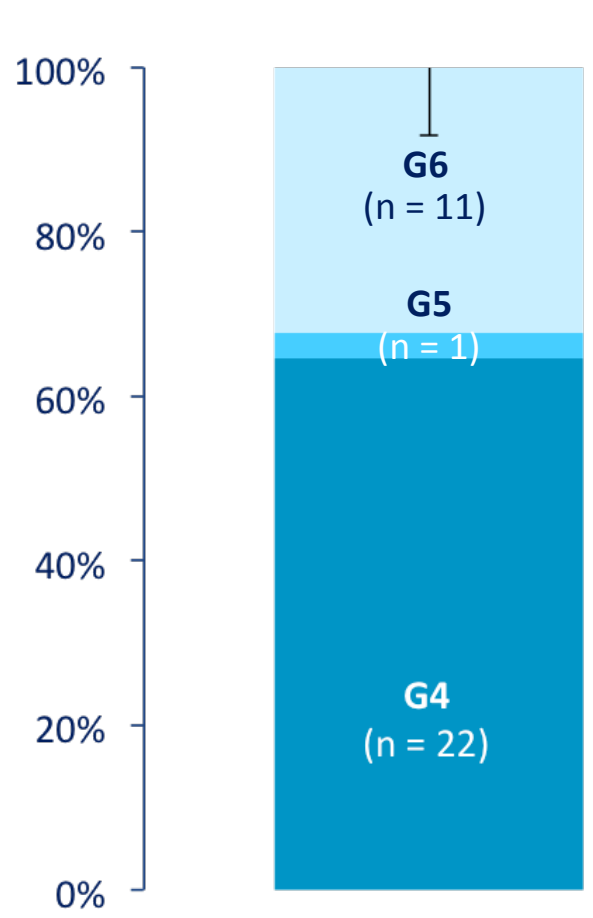
SVR12
8 Wochen
G1
Keine Zirrhose



SVR12
8 Wochen
G2
Keine Zirrhose



SVR12
12 Wochen
G4, 5, 6
Keine Zirrhose

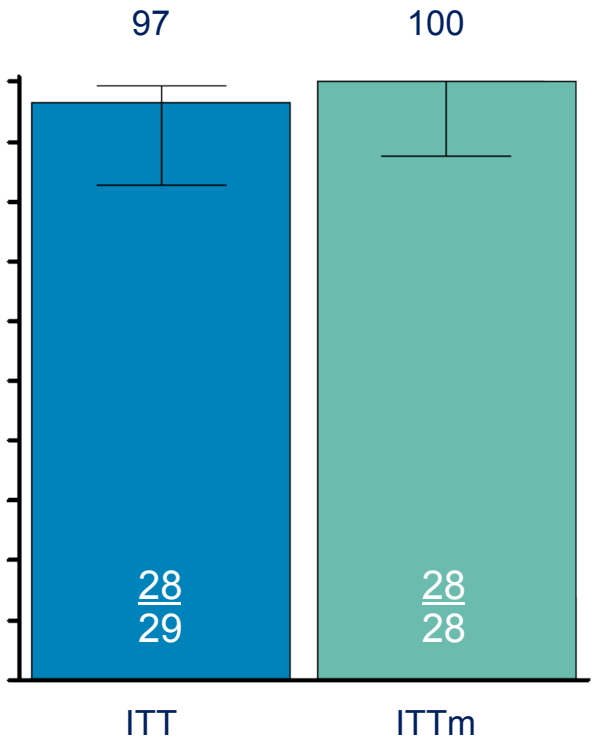


Gane E, EASL 2016, Abs. SAT135, SAT137

Poordad F, EASL 2016, Abs. SAT157

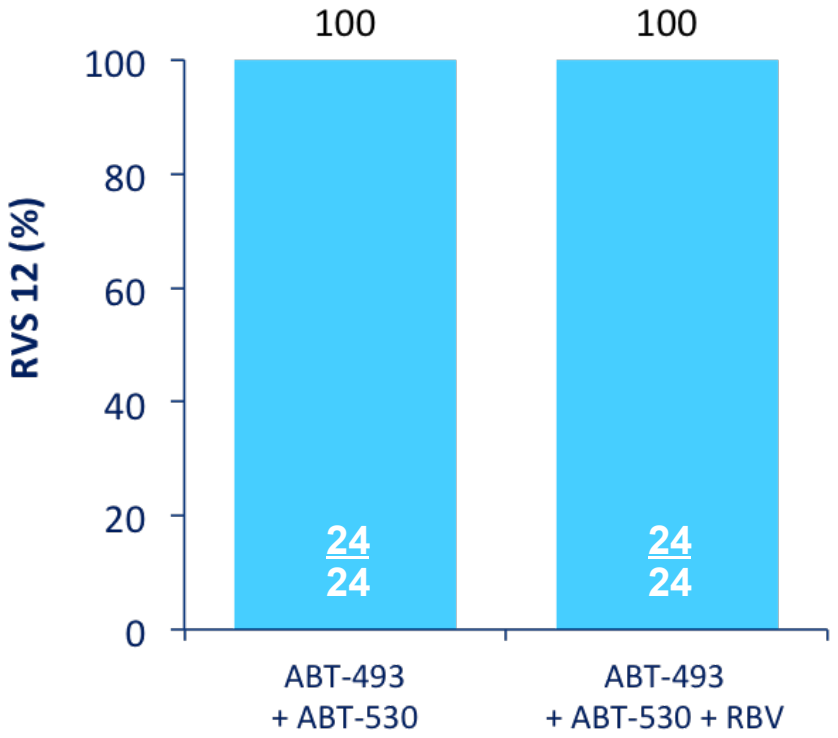
SURVEYOR-II (Part 2) : ABT-493 + ABT-530 bei therapienaiven Genotyp 3-Patienten

ABT-493 + ABT-530
für 8 Wochen
Keine Zirrhose
SVR 12



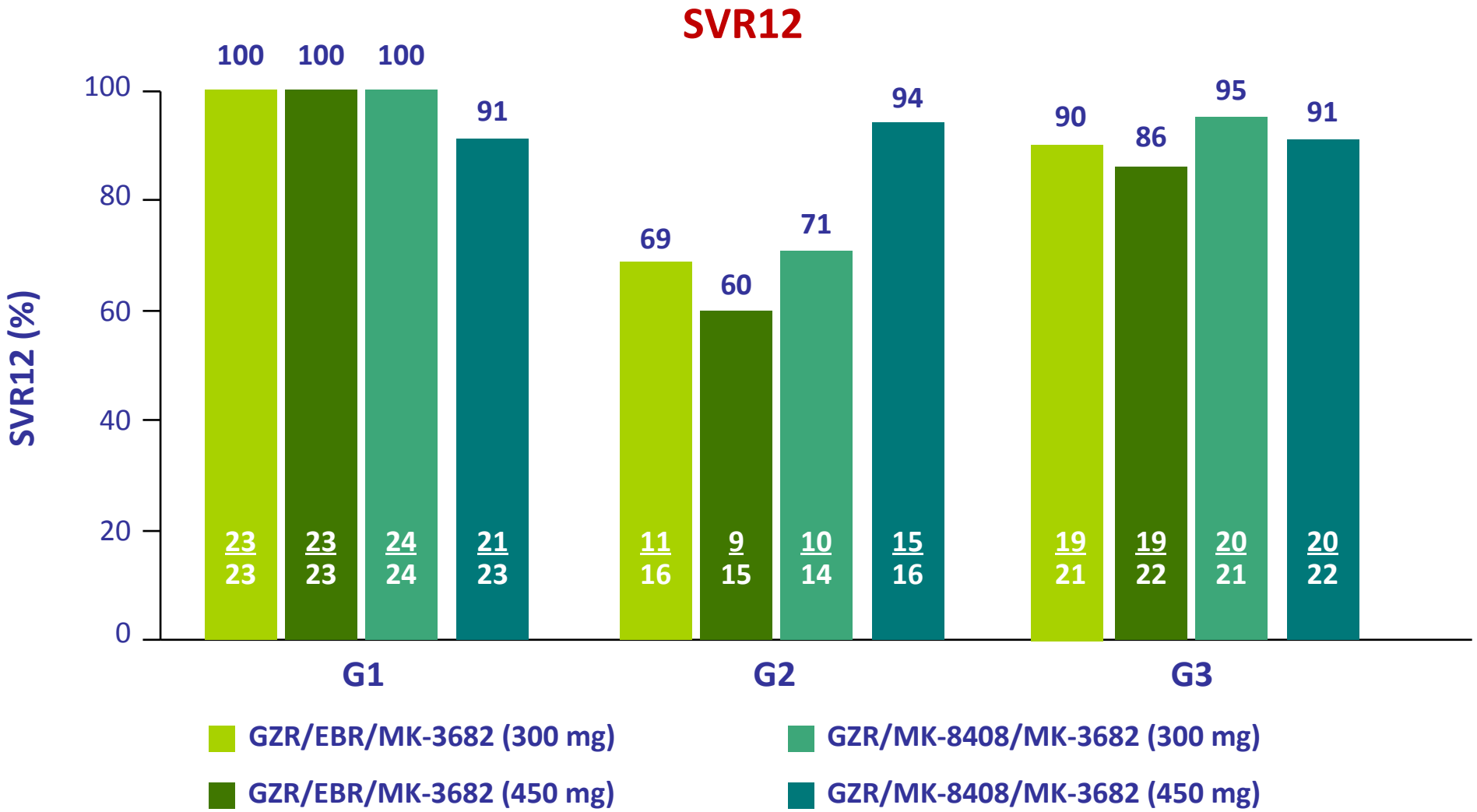
Nicht-virologisches Versagen (n = 1)
Einverständnis zurückgezogen zu W6
HCV RNA nicht nachweisbar

ABT-493 + ABT-530
12 Wochen ± RBV
Zirrhose
SVR 12



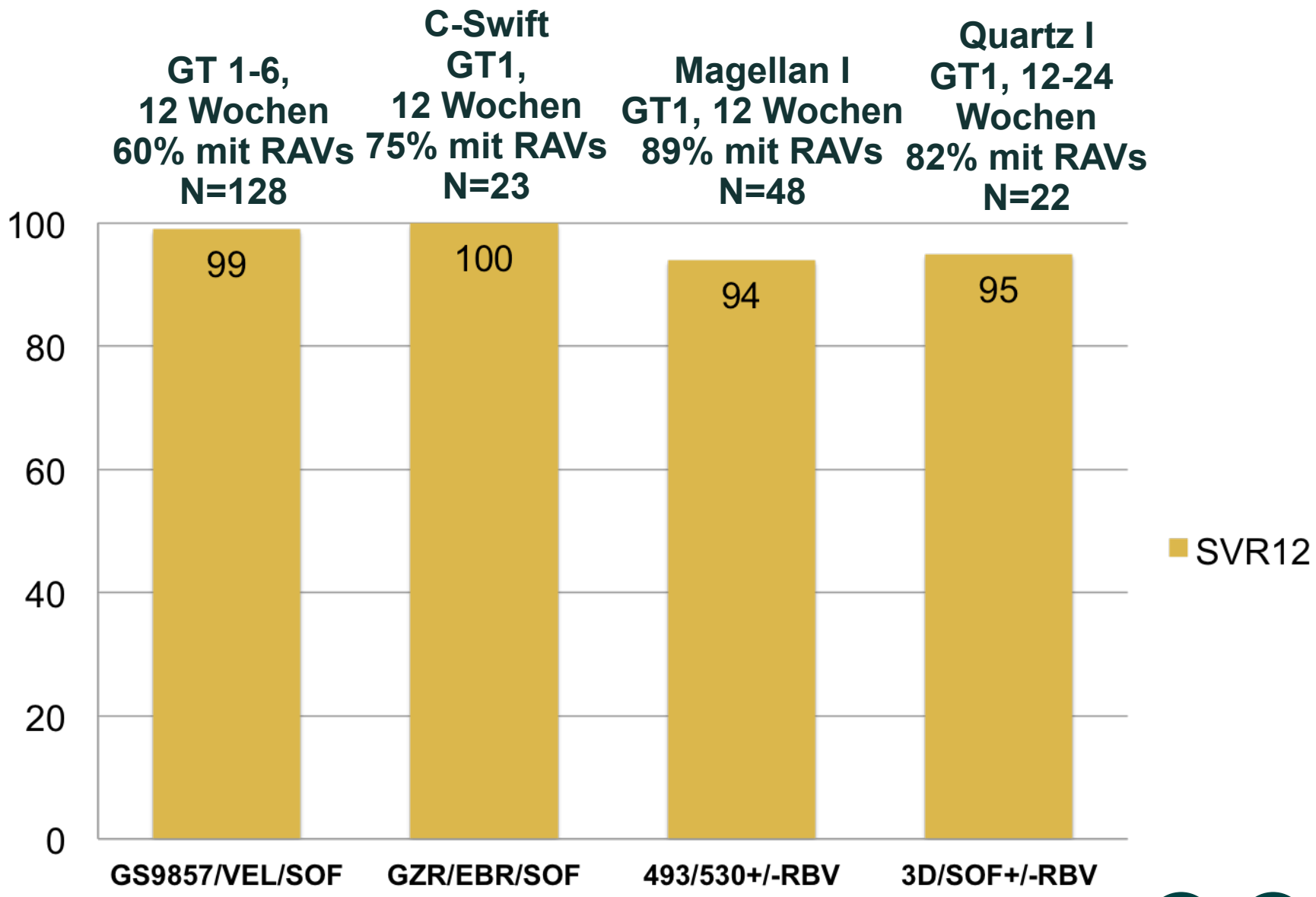
EASL 2016 Muir A, Abs. PS098 ; Kwo P, Abs. LB01

C-CREST 1 und 2: Grazoprevir und MK-3682 (anti-NS5B) + elbasvir oder MK-8408 (anti-NS5A) für 8 Wochen bei G1, 2 und 3



Gane EJ, AASLD 2015, Abs. LB15

Rescue-Therapien bei DAA-Versagen



EASL 2016: Poordad, SAT-156, Poordad, GS11, Lawitz, PS008, Lawitz, SAT-184

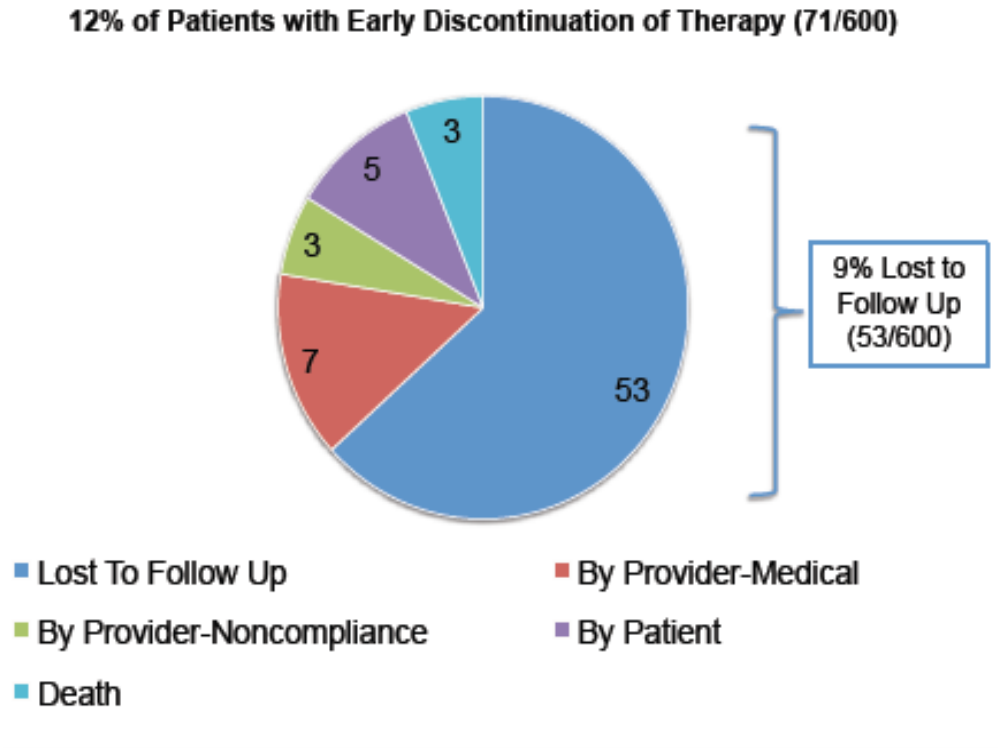
DAA-Behandlung: Spezialist notwendig?

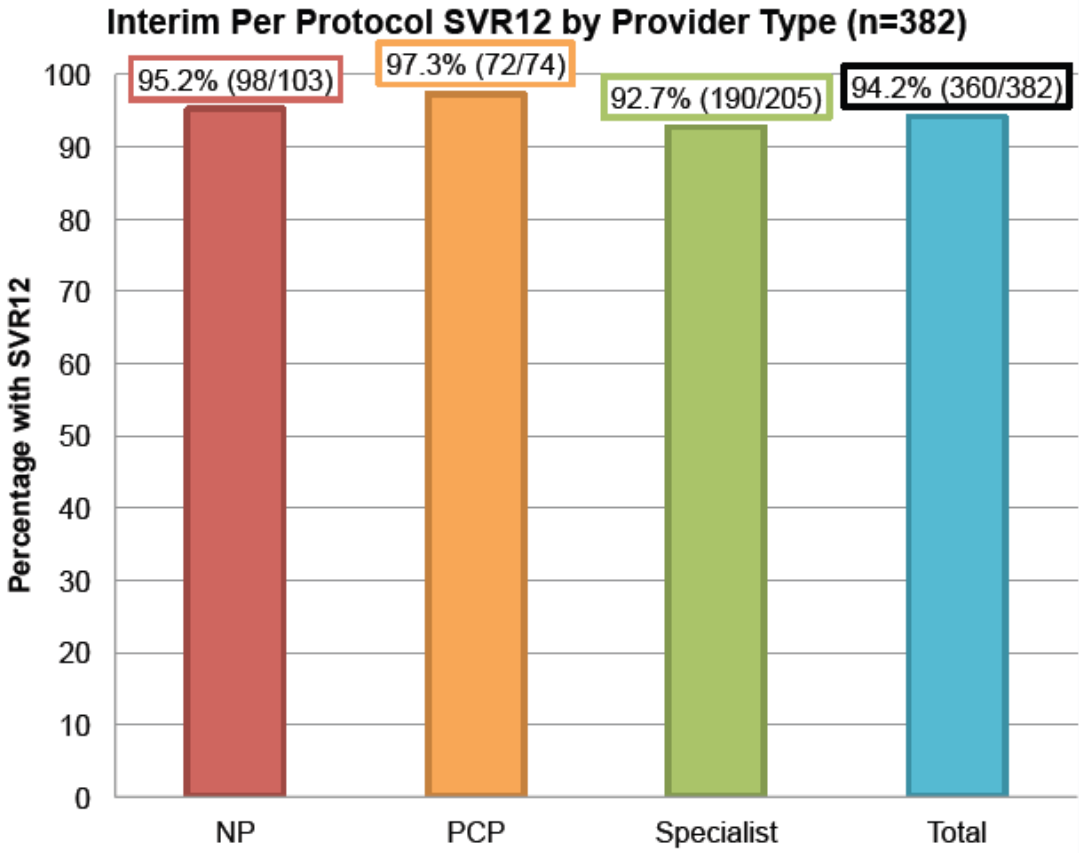
Multi center open label phase IV study (ASCEND) : 600 GT-1 patients treated by

Nurse Practitioner (NP)

Primary Care Physicians (PCP)

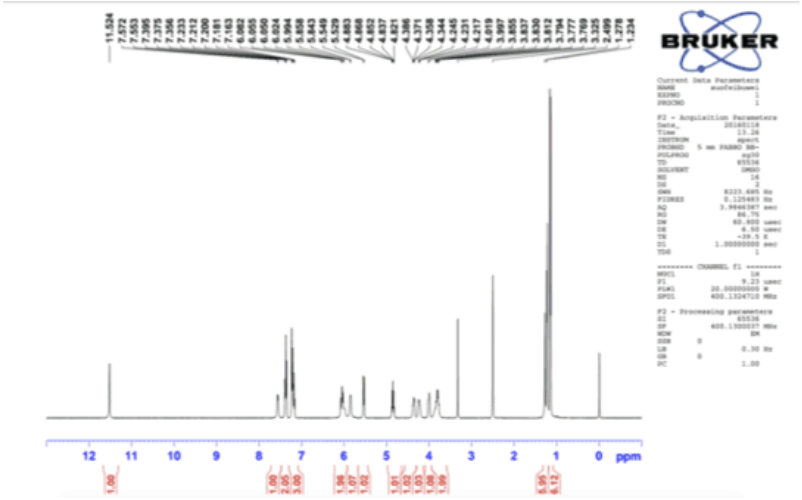
Specialist (BC/BE Infectious Disease or Hepatology)

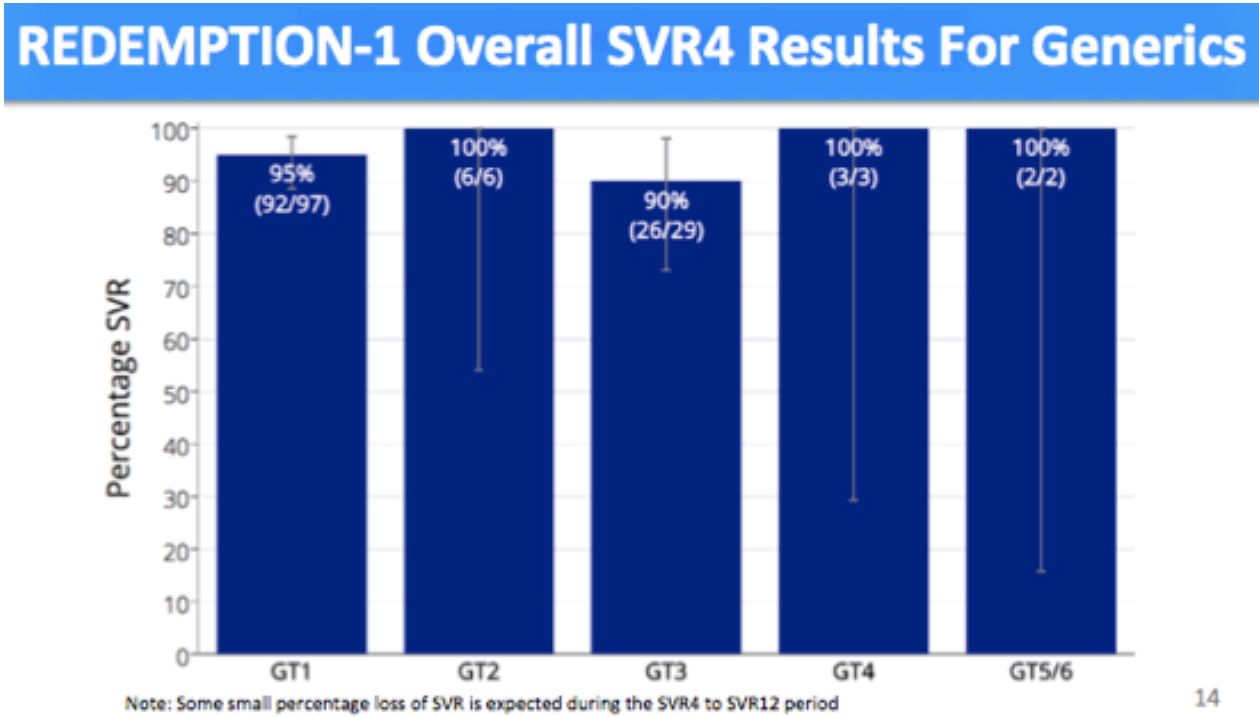




HCV treatment administered independently by PCPs and NPs is safe and equally Effective as care observed with specialist even in HIV co-infected

REDEMPTION: HCV-Generika zeigen gleiche SVR-Rate



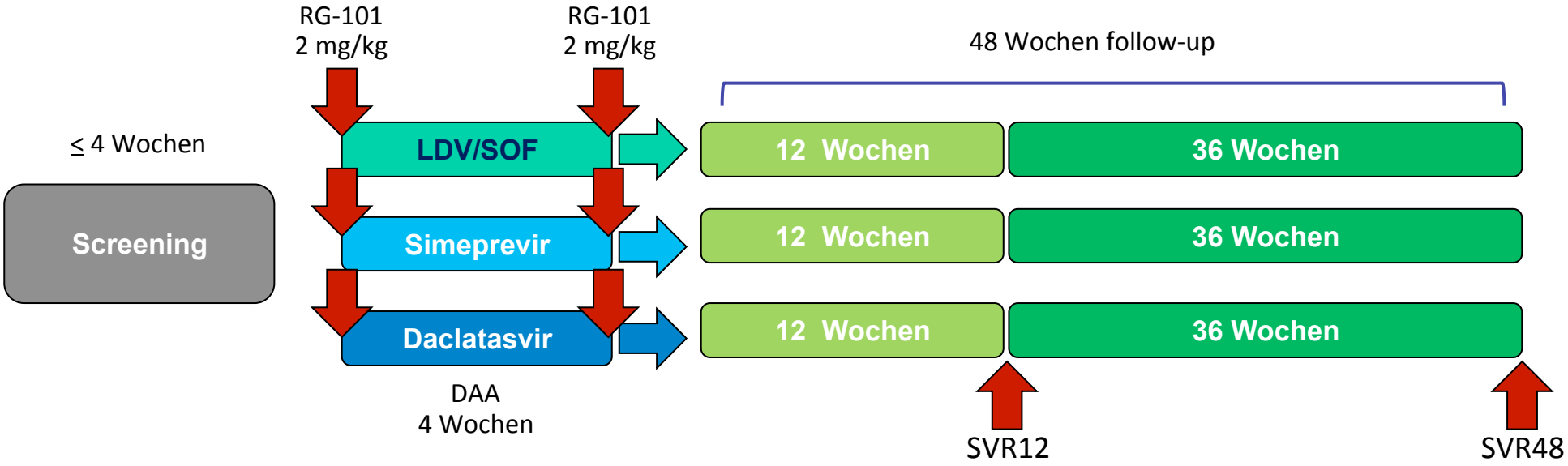


**„Emancipate yourself from mental slavery,
None but ourselves can free our mind!“
(Redemption Song, Bob Marley)**

Freeman J et al., EASL 2016, LB06

RG-101 mit DAA für 4 Wochen

79 Patienten : 77 % GT-1, 23 % GT-4 , keine Zirrhose(89 % F0-F2, 11 % F3)



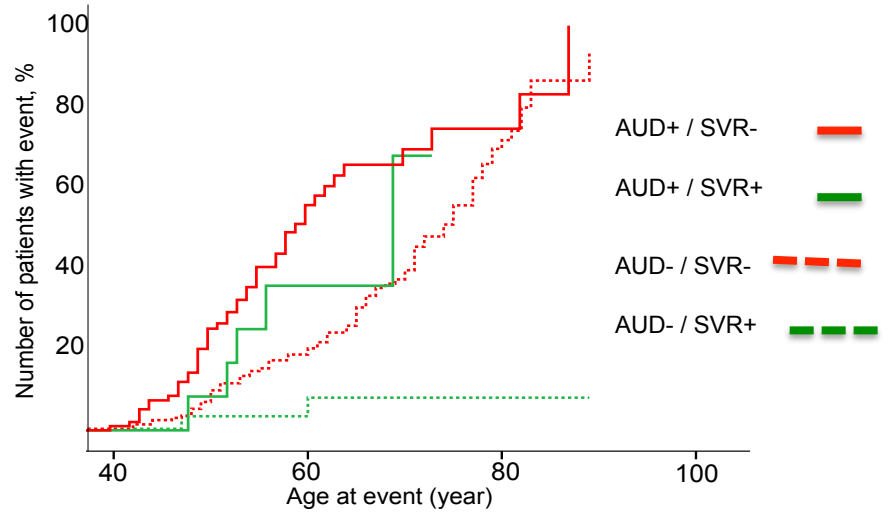
Nachbeobachtung	RG-101+ SOF/LDV	RG-101 + SIM	RG-101 + DCV
SVR8	21/21 (100 %)	21/21 (100 %)	20/22 (91 %)
SVR12	14/14 (100 %)	14/15 (93 %)	12/12 (100 %)
SVR16	9/9 (100 %)	8/9 (89 %)	9/9 (100 %)
SVR20	2/2 (100 %)	2/2(100 %)	2/2 (100 %)
SVR24	1/1	2/2	-/-

- 2xRelapse: einer im DCV-Arm, einer im SMV-Arm

Klinische Outcomes bei DAA-Therapien: geht es nur um SVR?

Sultanik P et al THU-370 :

- 341 cirrhotic patients (2006-2015)
- SVR : 13% (IFN-based)
- Evolution to ESLD/HCC
- SVR slow down ESLD only
  - in those without AUD



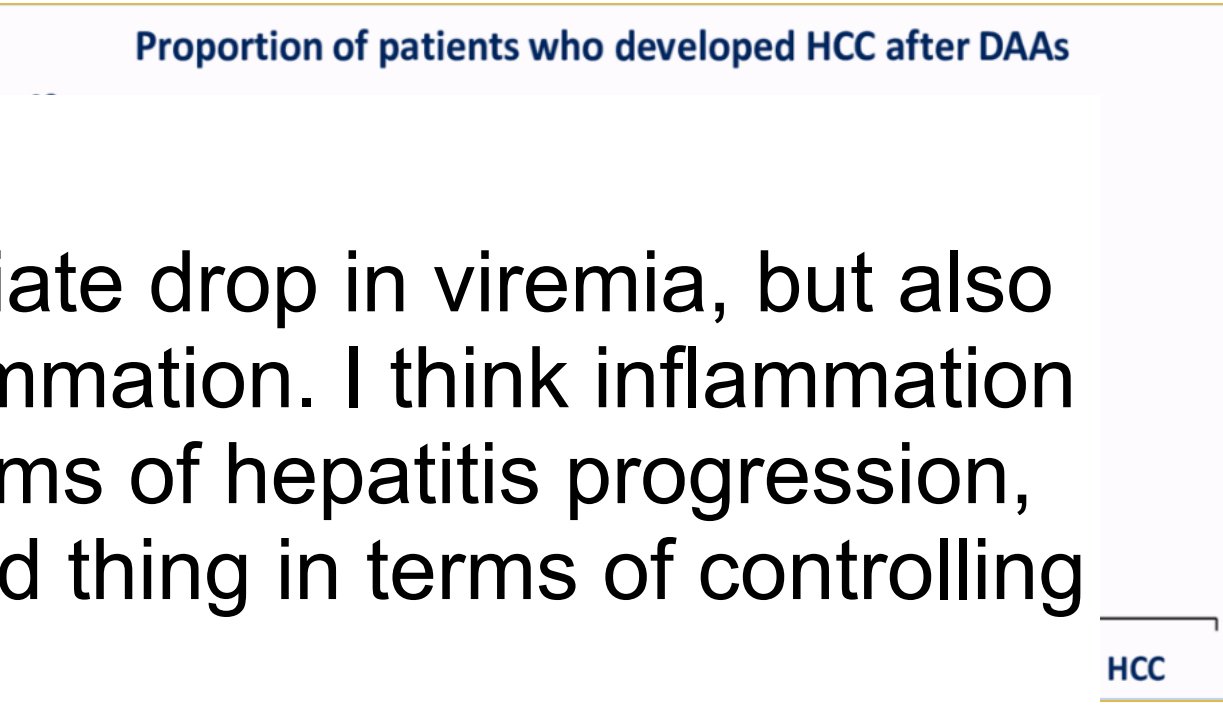
Number of patients at risk

patients SVR-/AUD+	n = 100	97	20	3	0
patients SVR+/AUD+	n = 12	11	60	0	0
patients SVR-/AUD-	n = 196	188	106	13	0
patients SVR+/AUD-	n = 33	31	20	3	0

HCC nach erfolgreicher DAA-Therapie

CHILD A/B, n=344, DAA-Therapie, SVR 89%, follow-up 12-24W

Males, n. (%)	207 (60.2)
Age,	
HCV 1 / 4 2 / 3	
Anti Naiv Expe	
Chil	
Live	
HBs	
Hist	



"You have an immediate drop in viremia, but also attenuation of inflammation. I think inflammation is a bad thing in terms of hepatitis progression, but it may be a good thing in terms of controlling cancer."

J Hepatol. 2016 Apr 12. pii: S0168-8278(16)30113-1. doi: 10.1016/j.jhep.2016.04.008. [Epub ahead of print]

Unexpected early tumor recurrence in patients with hepatitis C virus -related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution.

Reig M[1], Mariño Z[2], Perelló C[3], Iñarrairaegui M[4], Ribeiro A[1], Lens S[2], Díaz A[5], Vilana R[6], Darnell A[6], Varela M[7], Sangro B[4], Calleja JL[3], Forns X[2], Bruix J[8].

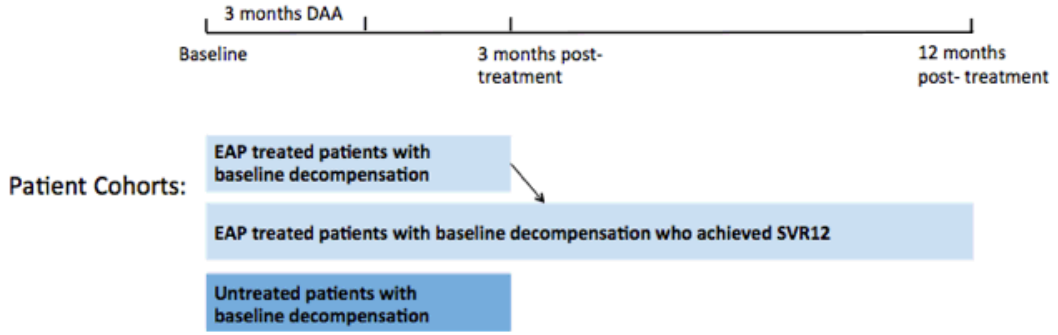
Author information

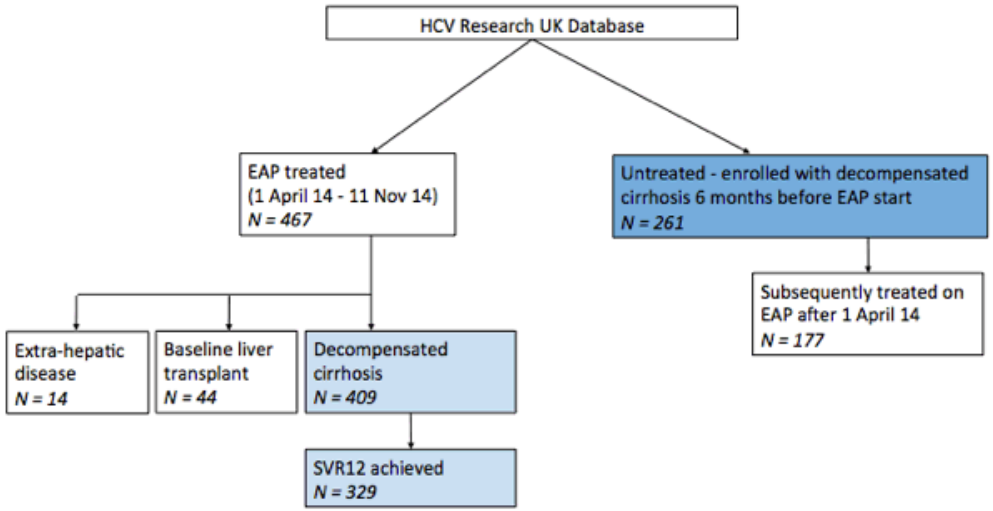
27,6% nach 5.7 Monaten!

Buonfigliogli et al, EASL LBP-506

Wie spät ist zu spät?

Method - Cohort Study

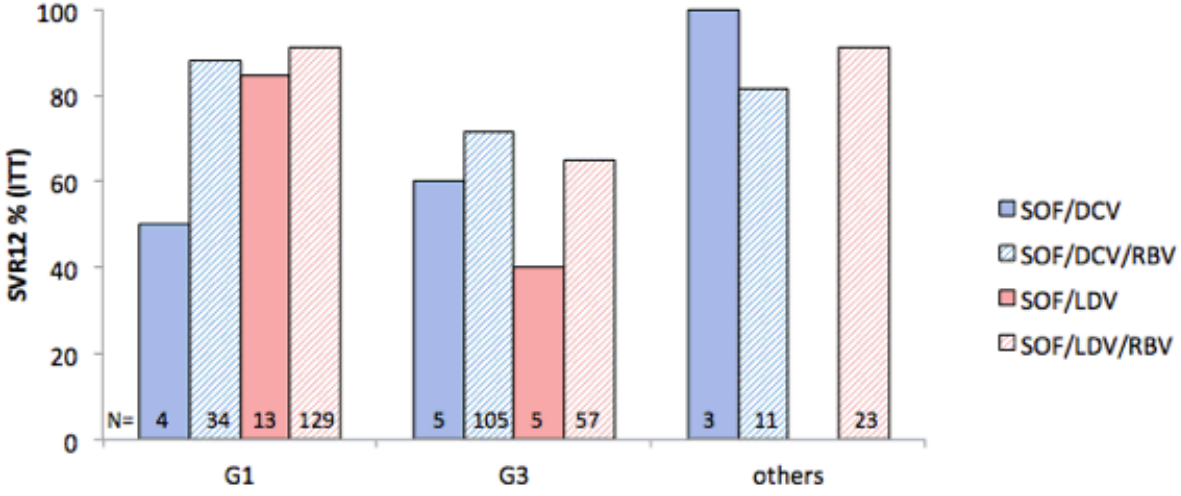




Cheung CM et al, EASL 2016, PS097

Results: Virological Outcomes

For patients with decompensated cirrhosis (N=409) – Overall SVR = 80.4%



esults: Adverse Events – first 6 month (3 months Rx, 3 months post-Rx)

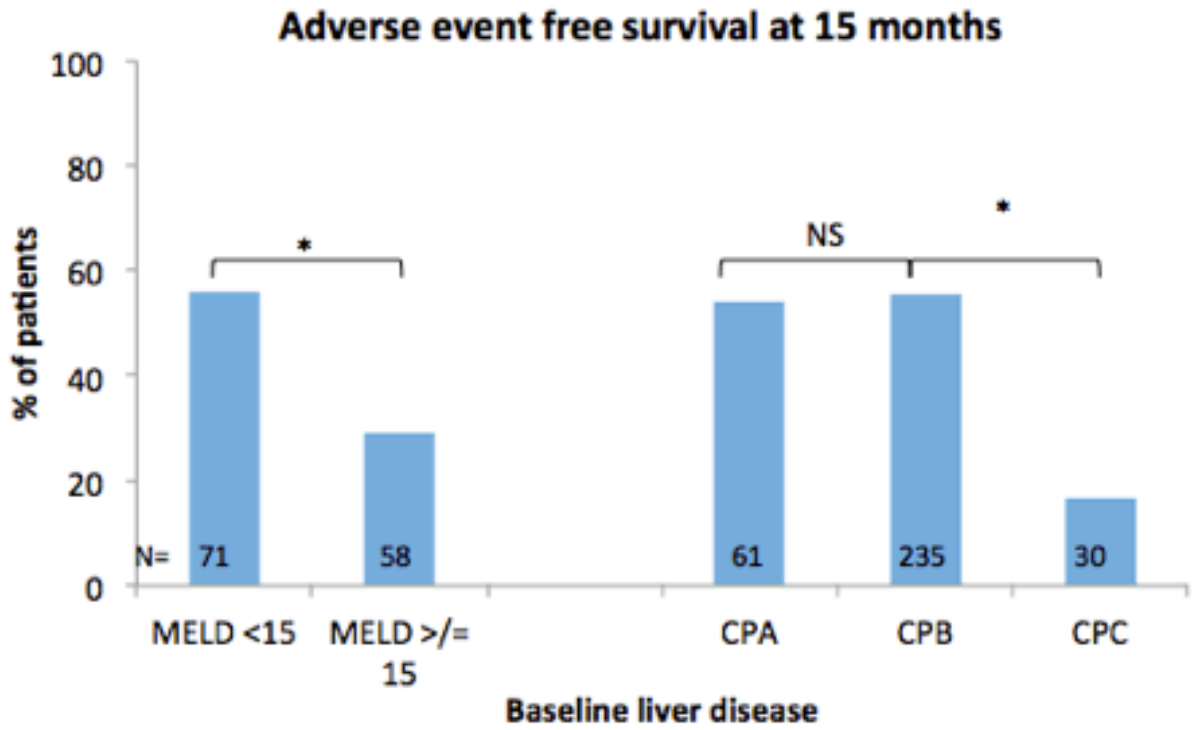
Event	All Treated (n=409)	Untreated (n=261)
Deaths	13 (3.2%)	15 (5.7%)
Decompensation	72 (17.6%)	73 (28.0%)*
New HCC	19 (4.6%)	21 (8.0%)
Sepsis	27 (6.6%)	15 (5.7%)
New OLT	27 (6.6%)	10 (3.8%)
Hospital admissions	133 (32.5%)	83 (31.8%)
MELD worsening >2	94 (23.0%)	99 (37.9%)*
Total adverse outcomes	213 (52.1%)	166 (63.6%)*

* p< 0.05 between treated and u

ng WL et al. J Hepatol 2016 Jan 29

Cheung CM et al, EASL 2016, PS097

Which Patients Benefit from Viral Clearance?



* p< 0.05

Cheung CM et al, EASL 2016, PS097

DAAs bei akuter HCV-Infektion

Study name	Coordinator	DAAs	HCV genotype	Duration (weeks)	HIV status
DAHHS	Erasmus MC	BOC + pegIFN + RBV	1	12	pos
CHAT	UKB	TPV + pegIFN + RBV	1	12	pos
DARE-C I	Kirby Institute	TPV + pegIFN + RBV	1	8–24	neg + pos
DARE-C II	Kirby Institute	SOF + RBV	all	6	neg + pos
SWIFT-C	ACTG	SOF + RBV	all	8 *vs* 12	pos
SOL	UKB	SOF + LDV	1, 4	6	pos
Hep-Net acute HCV	MHH	SOF + LDV	1	6	neg

- pegIFN / RBV + Telaprevir or Boceprevir: 56-84%
- Sofosbuvir + RBV: 21-92%
- Sofosbuvir + Simeprevir: 93%
- Sofosbuvir + Ledipasvir: 100%

Boesecke, Rockstroh, J Viral Hepat 2015

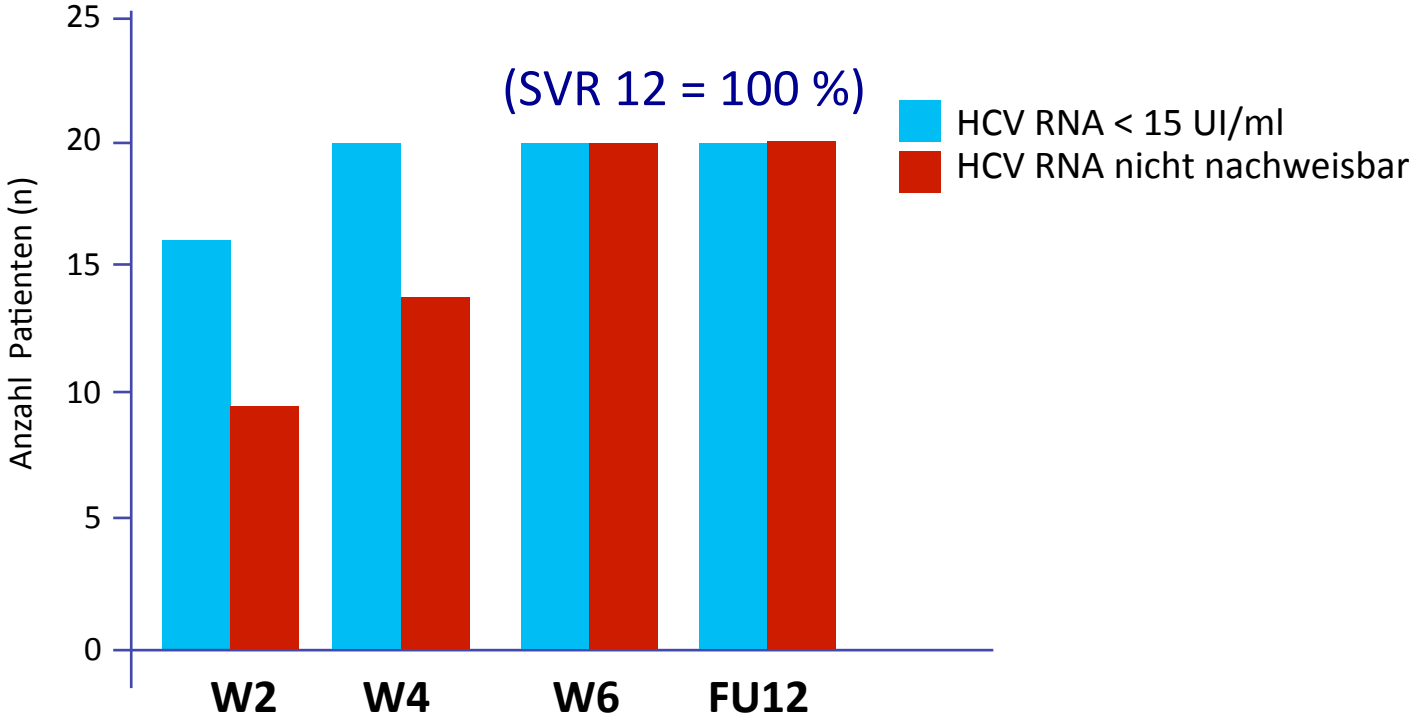
Sofosbuvir und Ledipasvir bei akuter HCV-Infektion

20 Patienten mit akuter HCV-Infektion, G1 Monoinfiziert (11 G1a)

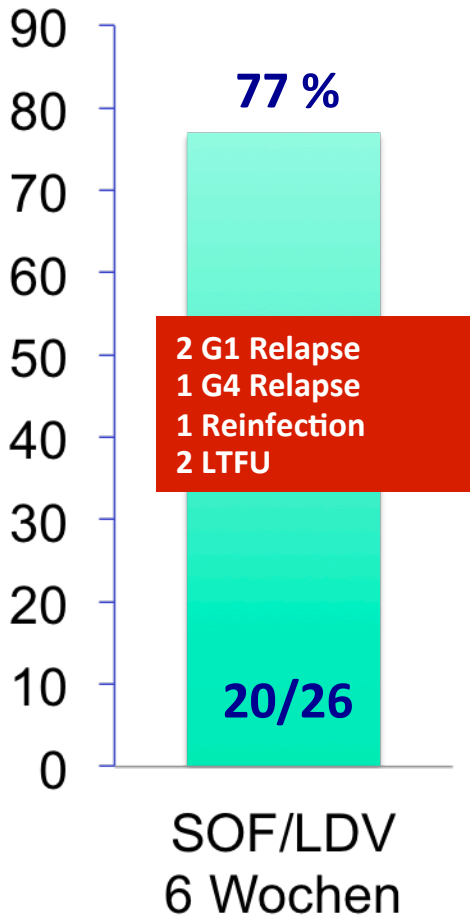
Transmission: sexuell 11, medizinisch 5, Nagelstudio 1, unbekannt 2

SOF/LDV für 6 Wochen

Virologisches Ansprechen nach 6 Wochen SOF/LDV

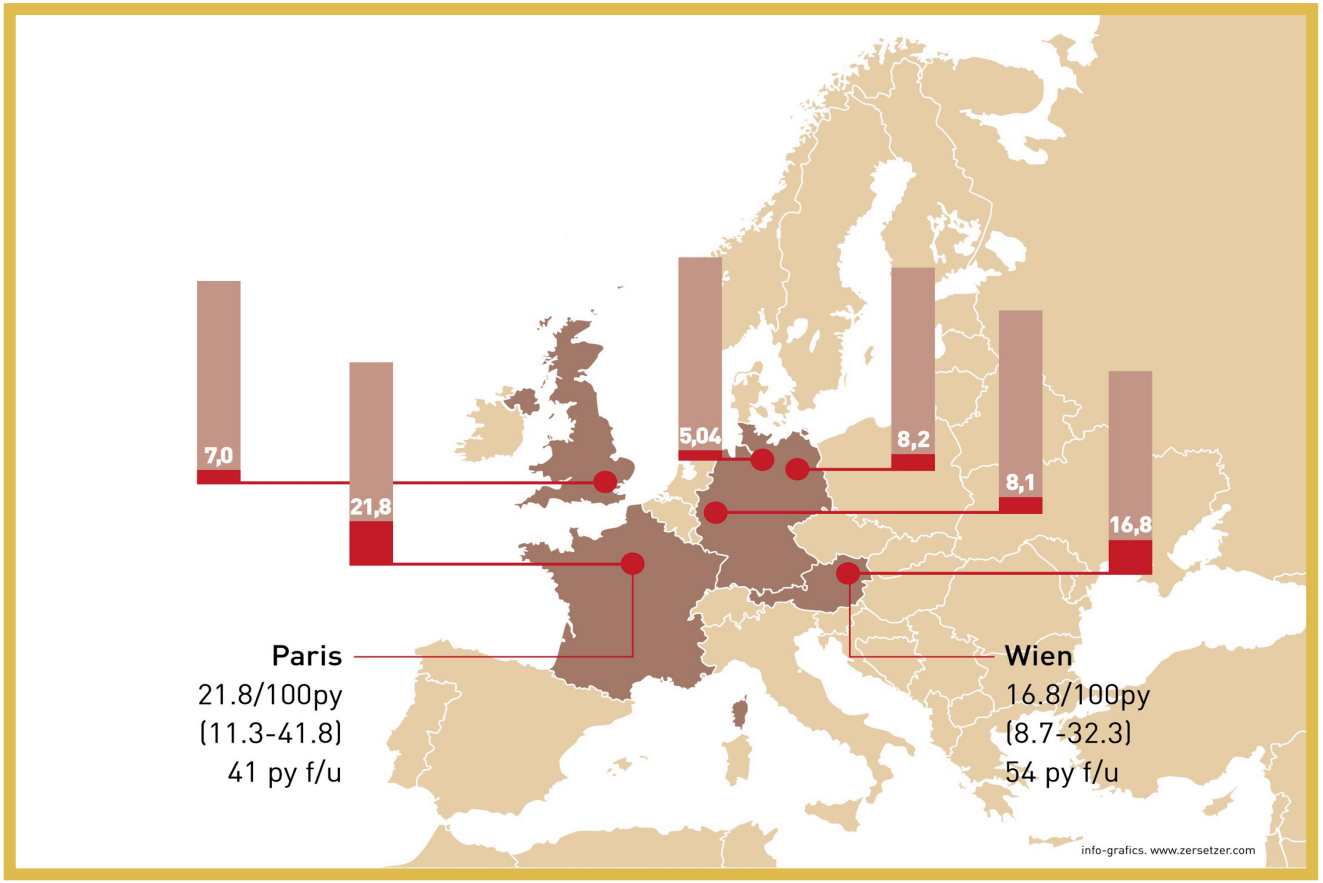


SVR12 bei HIV-HCVG1/4



Deterding K, EASL 2016, Abs. LB08

Inzidenz der HCV-Reinfektion nach Region

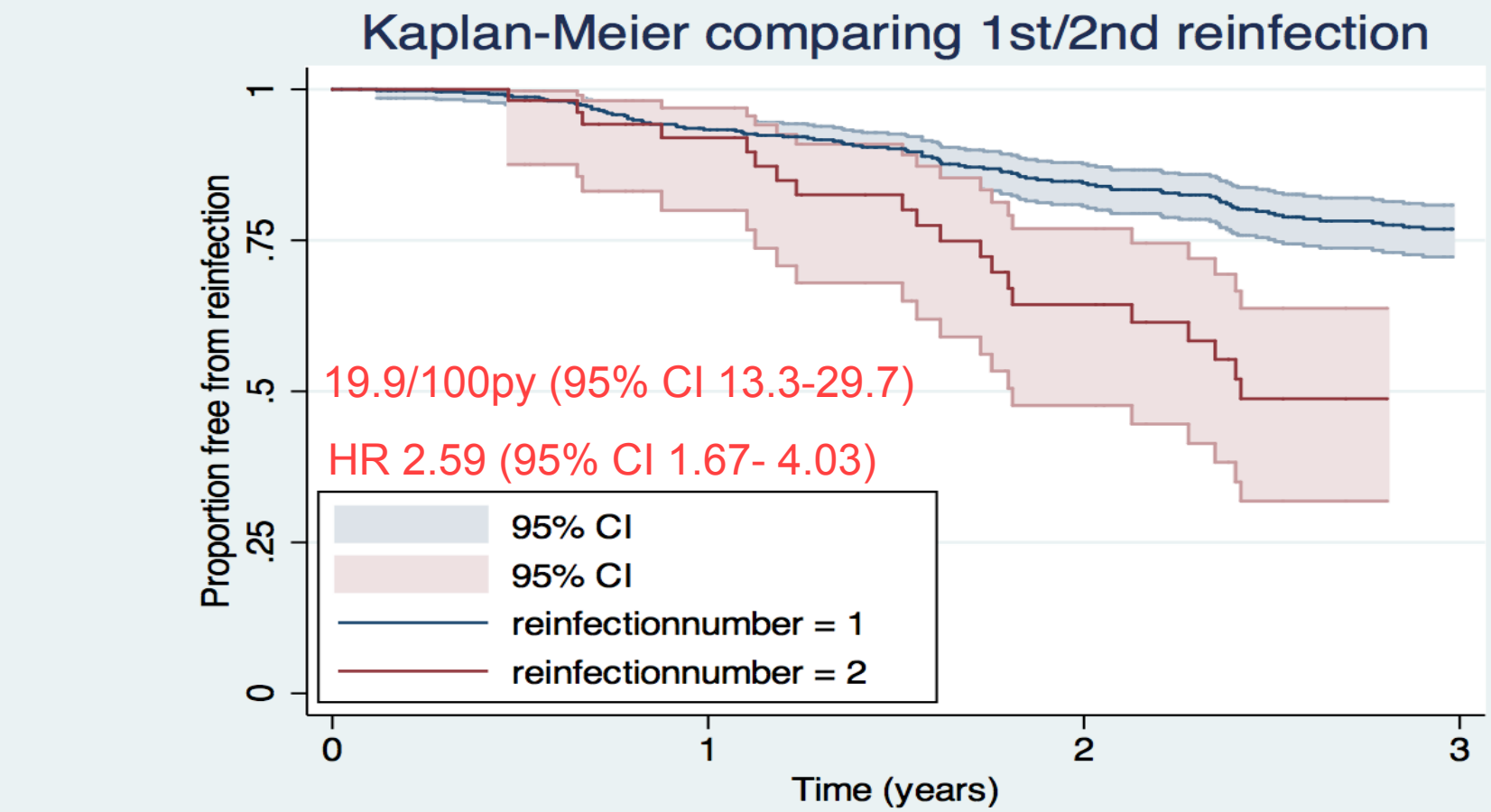


606 HIV+MSM mit akuter HCV-Infektion und Heilung wurden nachbeobachtet:

Reinfektionsrate: 24,6% nach 1.8 Jahren
Retherapie: SVR 87%

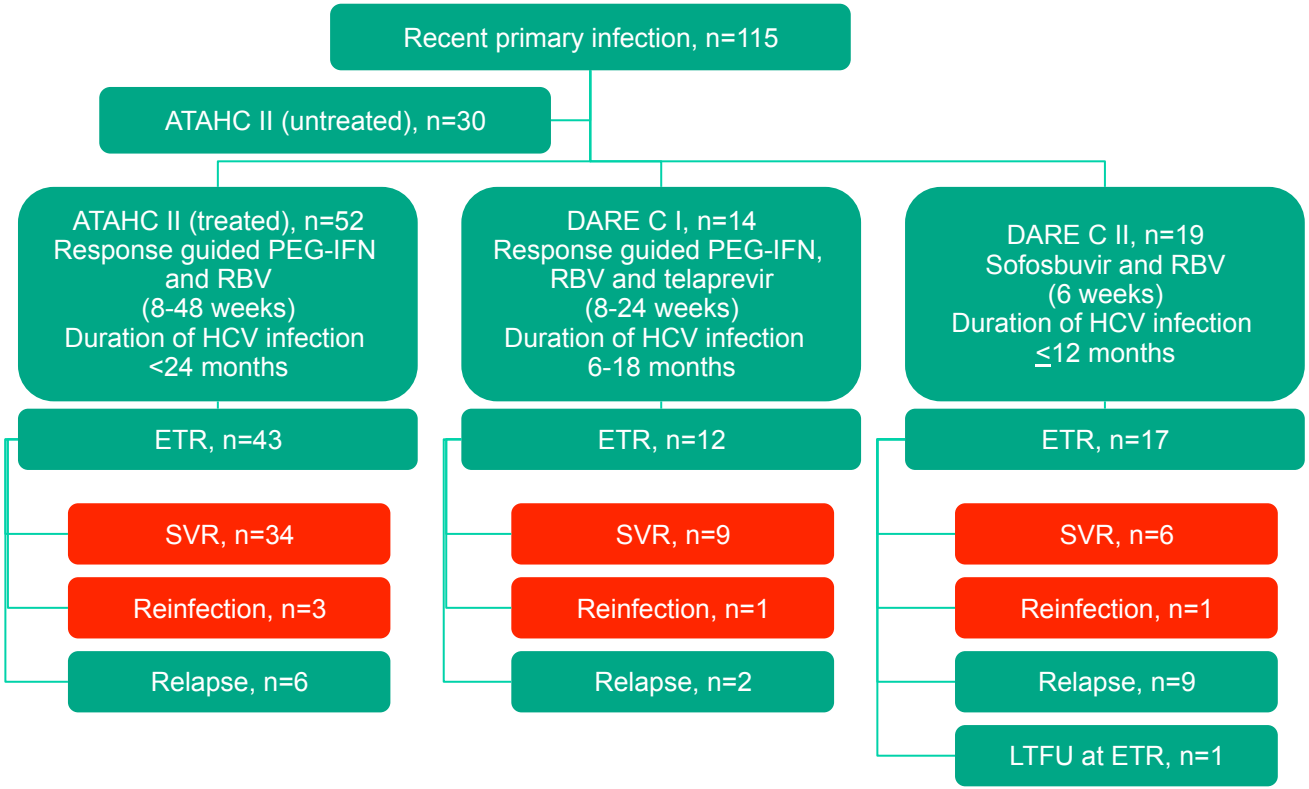
Martin TC, EASL 2016, PS006

Inzidenz der zweiten Reinfektion noch höher!



Martin TC, EASL 2016, PS006

HCV Reinfektion/Australische Kohorte



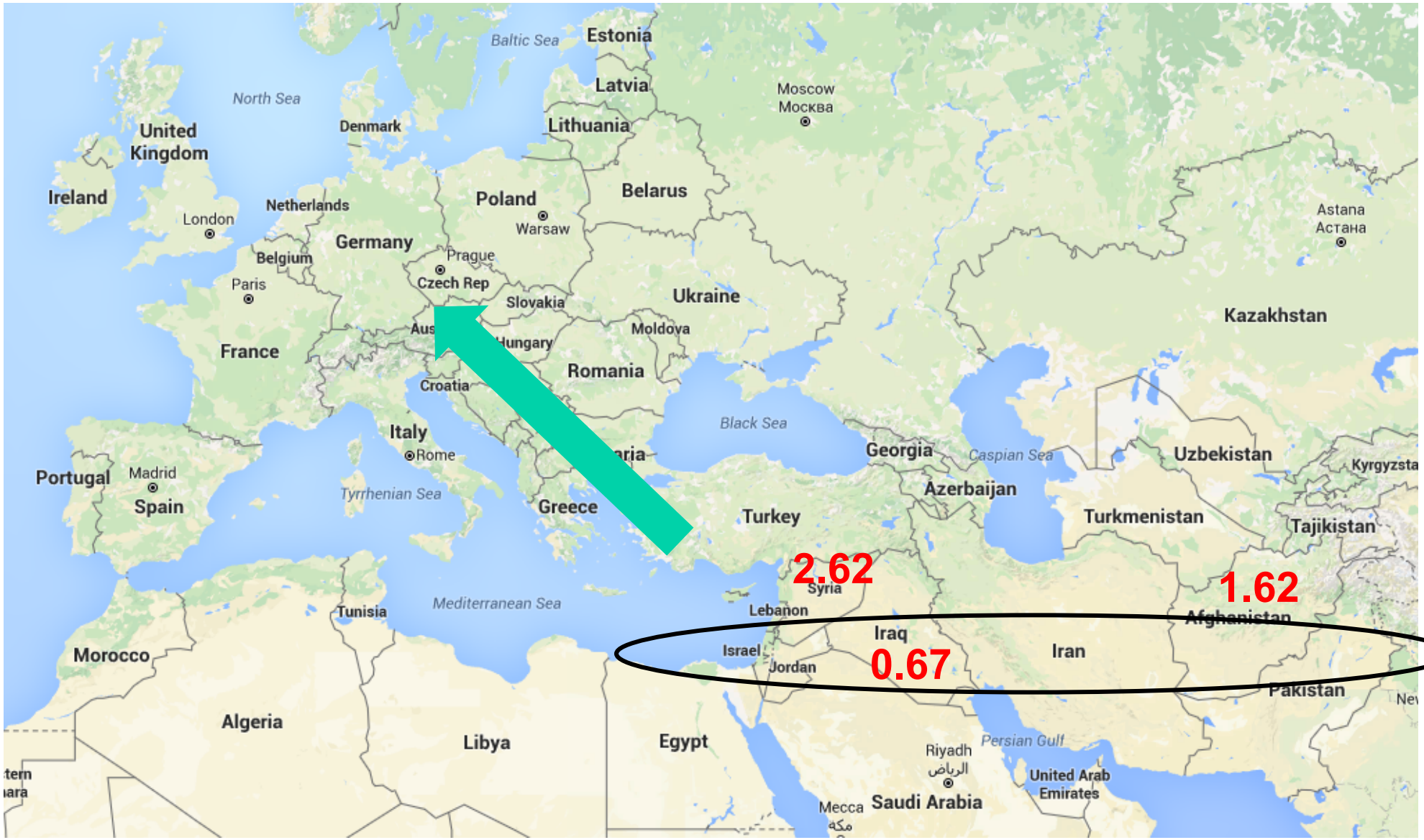
- ✓ All cases of reinfection occurred in HIV+ MSM with IDU reported
- ✓ Need for post treatment surveillance
- ✓ Education and harm minimization strategies are needed

Participants type	Cases of infection	Number at risk	Person years follow up (PYFU)	Incidence per 100 PYFU	95% CI
All	**5**	**54**	**56**	**8,88**	**3.70, 21.34**
HCV mono-infection	**0**	**16**	**16**	**0**	**0. 23,.06***
HIV-HCV co-infection	**5**	**38**	**41**	**12,.30**	**5.12, 29.56**

* One sided, 97.5%

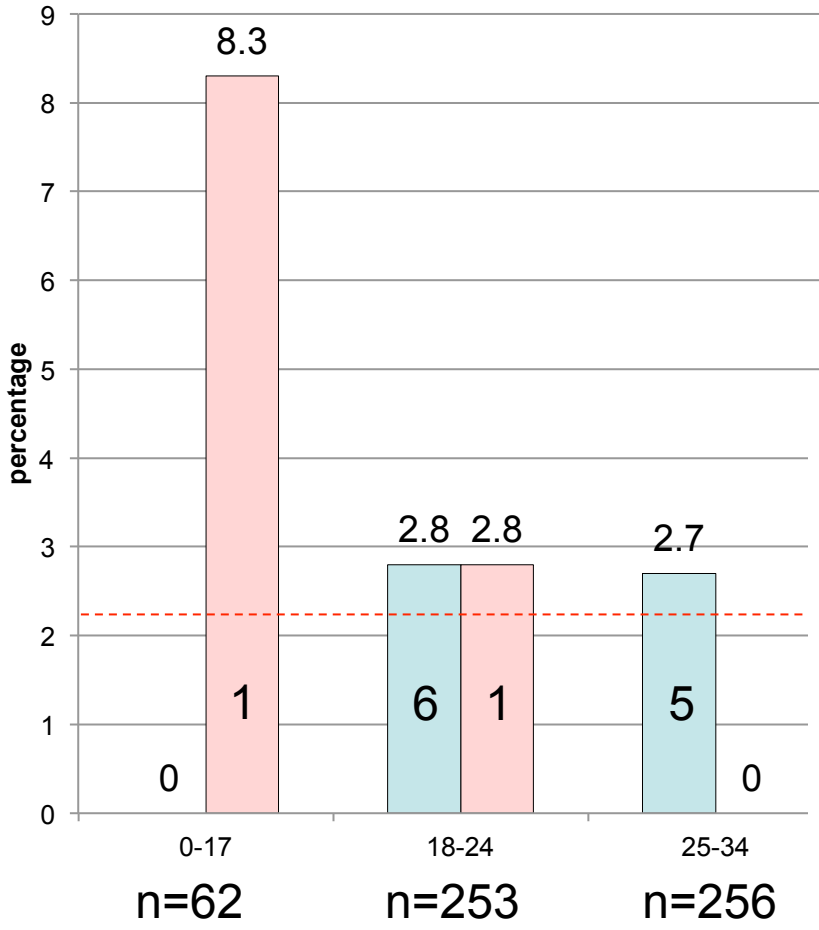
HBV

Seroprevalenz **HBsAg** (%)



Schweitzer A et al. LANCET 2015

Seroprävalenz HBsAg 2.3% (18/793)

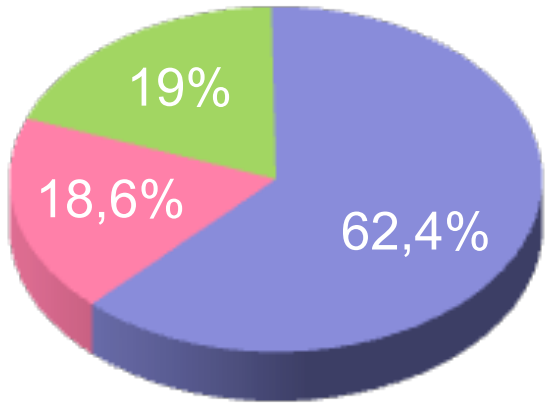


18 HBsAg positive patients

- 0/18 elevated AST
- 2/18 elevated ALT (58 U/l, 107 U/l)

→ PPV 0 for AST and 0.016 for ALT

4.5



anti-HBs and anti-HBc negative

anti-HBs positive

anti-Hbc and/or HBsAg positive

Solbach et al., EASL 2016 (PS137)

HBV – doch alle behandeln?

Antiviral therapy prolongs survival in immune tolerant hepatitis B patients

Nucleos(t)ide analogue treatment reduces risk of developing liver cancer and liver cirrhosis among immune tolerant patients

No/mild Inflammatory Phase

Characteristics (unweighted)

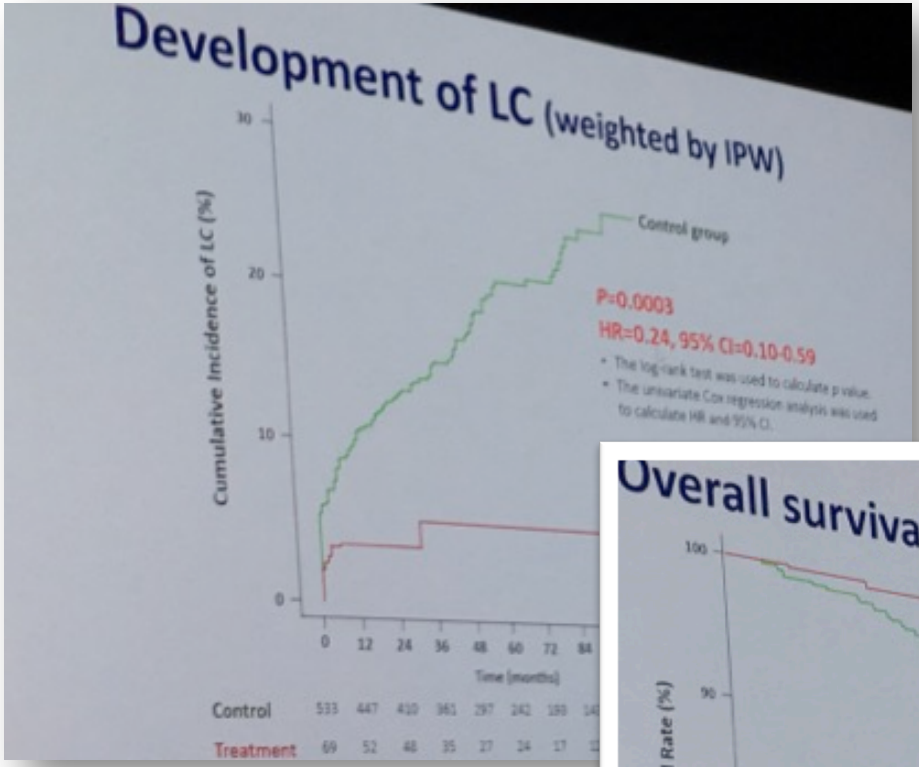
Variables	Control (n = 533)		Treatment (n = 69)		P value
	Mean	SD	Mean	SD	
Age	41.65	11.66	43.74	12.07	0.15
Log (HBV DNA)	16.77	2.53	16.37	2.96	0.83
BUN	13.49	5.57	13.86	5.76	0.91
Creatinine	1.00	0.64	0.96	0.33	0.16
Albumin	4.24	0.36	3.97	0.58	*0.002
Total bilirubin	0.96	0.40	1.64	2.05	0.07
ALP	72.88	30.85	87.20	38.64	*0.002
AST	37.38	18.11	38.14	16.21	0.78
ALT	45.12	23.64	38.75	18.54	*0.02
GGT	36.14	40.90	62.06	69.05	*0.002
PT (INR)	1.05	0.11	1.12	0.17	*0.0009
Platelet	193.25	60.21	192.99	74.96	0.94
APRI	0.59	0.50	0.68	0.70	0.97
FIB-4	1.80	1.67	2.26	2.54	

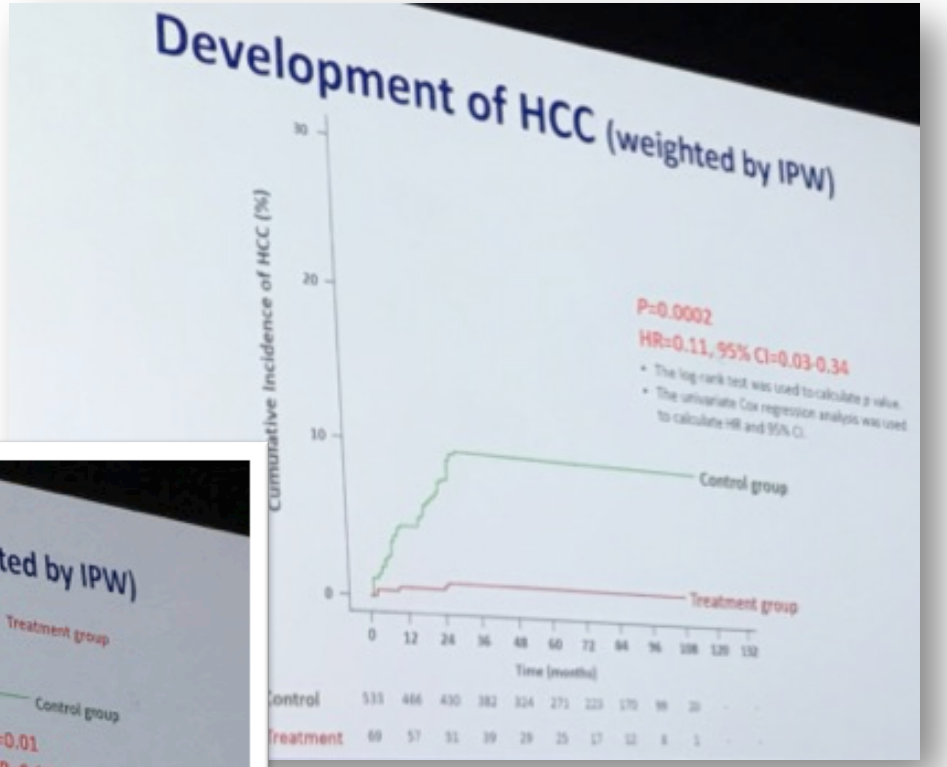
Patienten >40 Jahre...

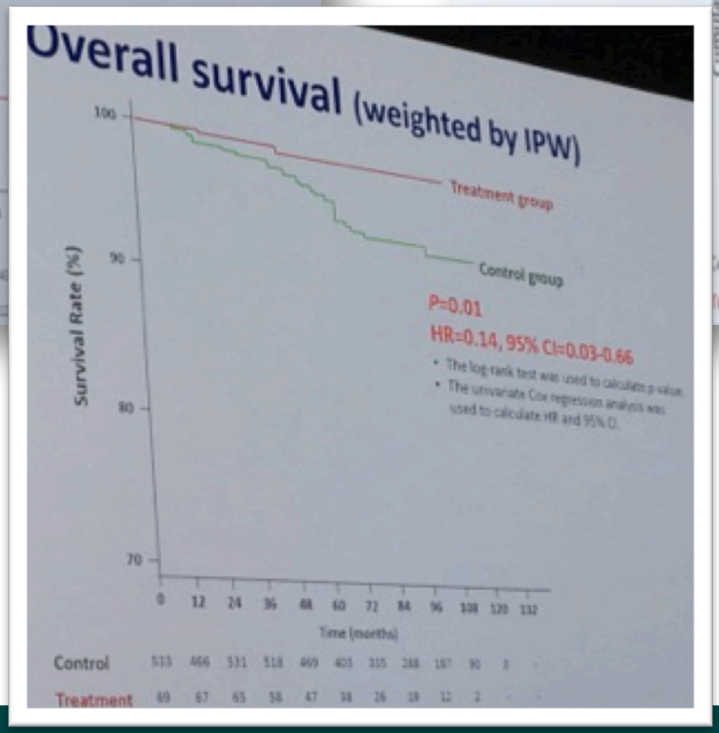
Einschlusskriterium ALT <80 U/L
Ca. 45% hatten normale ALT

Chang et al., EASL 2016, PS049

Therapie der chronischen HBV Infektion (no/mild inflammatory phase) reduziert Zirrhose/HCC Risiko und verbessert Überleben





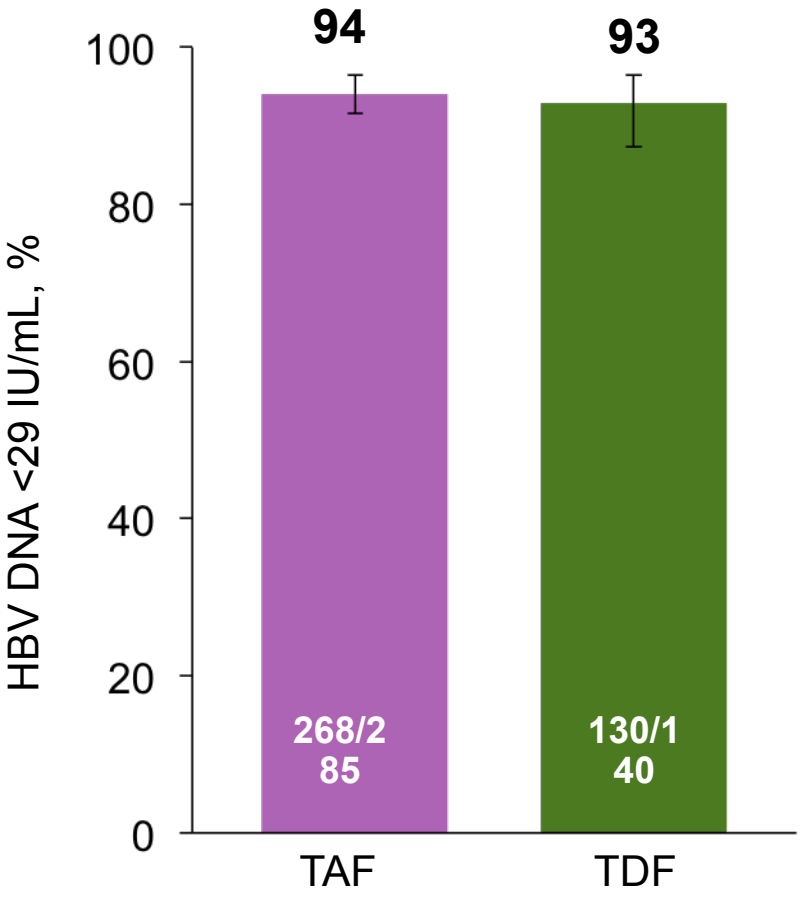


Chang et al., EASL 2016, PS049

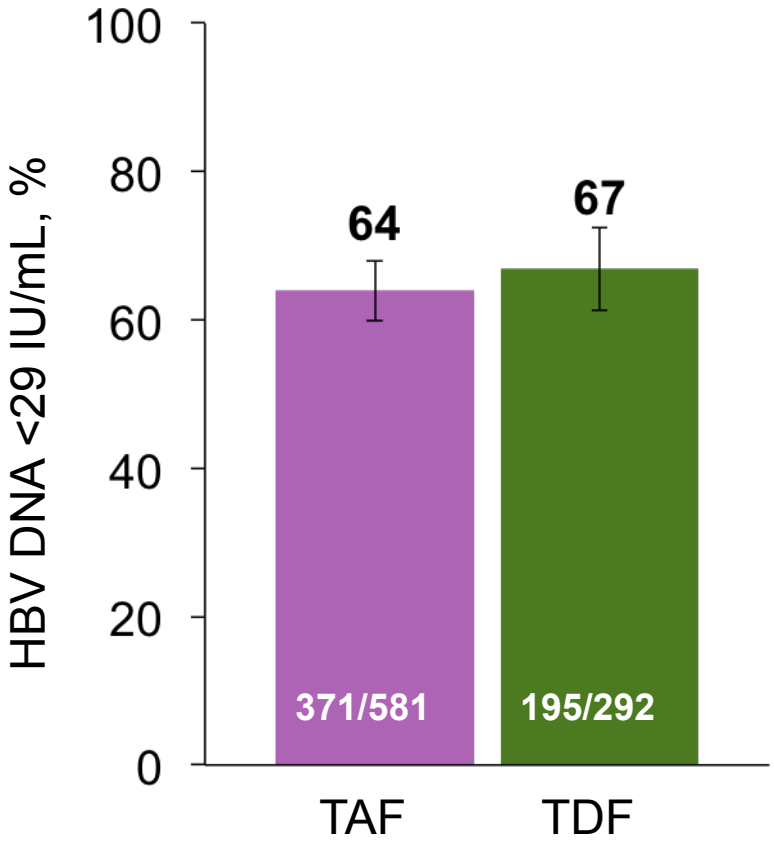
Neues Tenofovir -TAF

Author	Substance (Company)	Class	Phase	Outcome
Buti M et al. (GS06)	Tenofovir alafenamide (Gilead)	NUC	Phase III HBeAg negative	
Chan H Y-L et al. (GS12)	Tenofovir alafenamide (Gilead)	NUC	Phase III HBeAg positive	

TAF Phase III Results: Primary Endpoint (HBV DNA <29 IU/mL) Study 108 and 110



HBeAg negative
Study 108, Buti M et al.

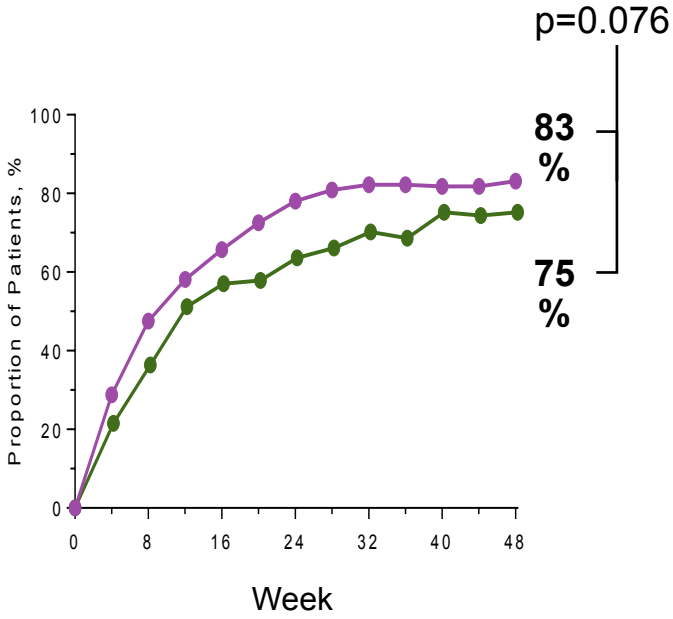


HBeAg positive
Study 110, Chan H Y-L et al.

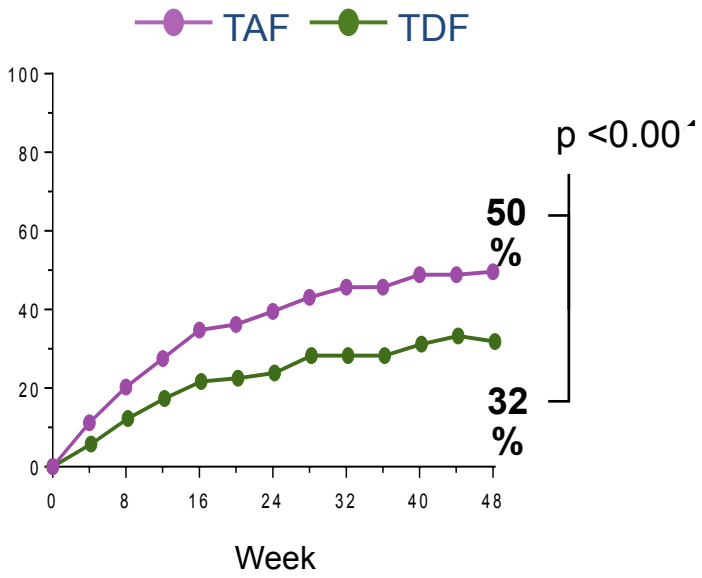
Buti M et al. GS06, and Chan H Y-L et al. GS12

Mehr ALT-Normalisierung unter TAF

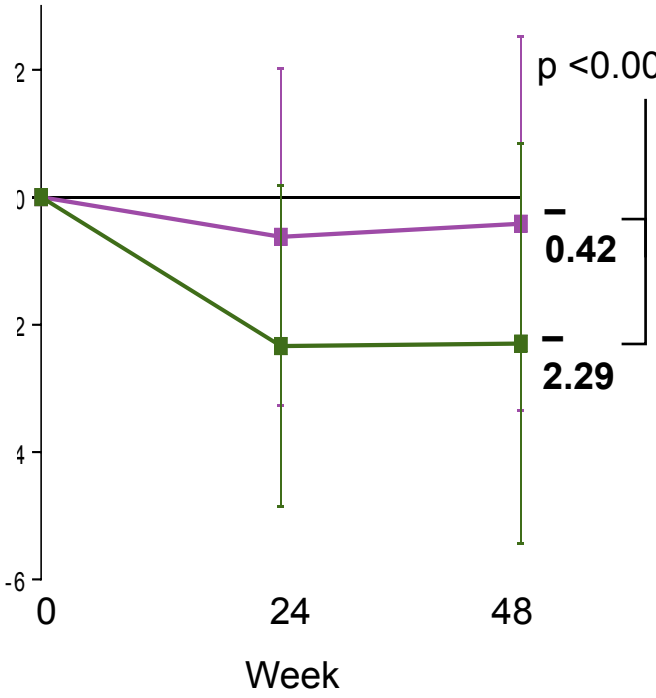
Central Laboratory



AASLD Laboratory Criteria



Spine

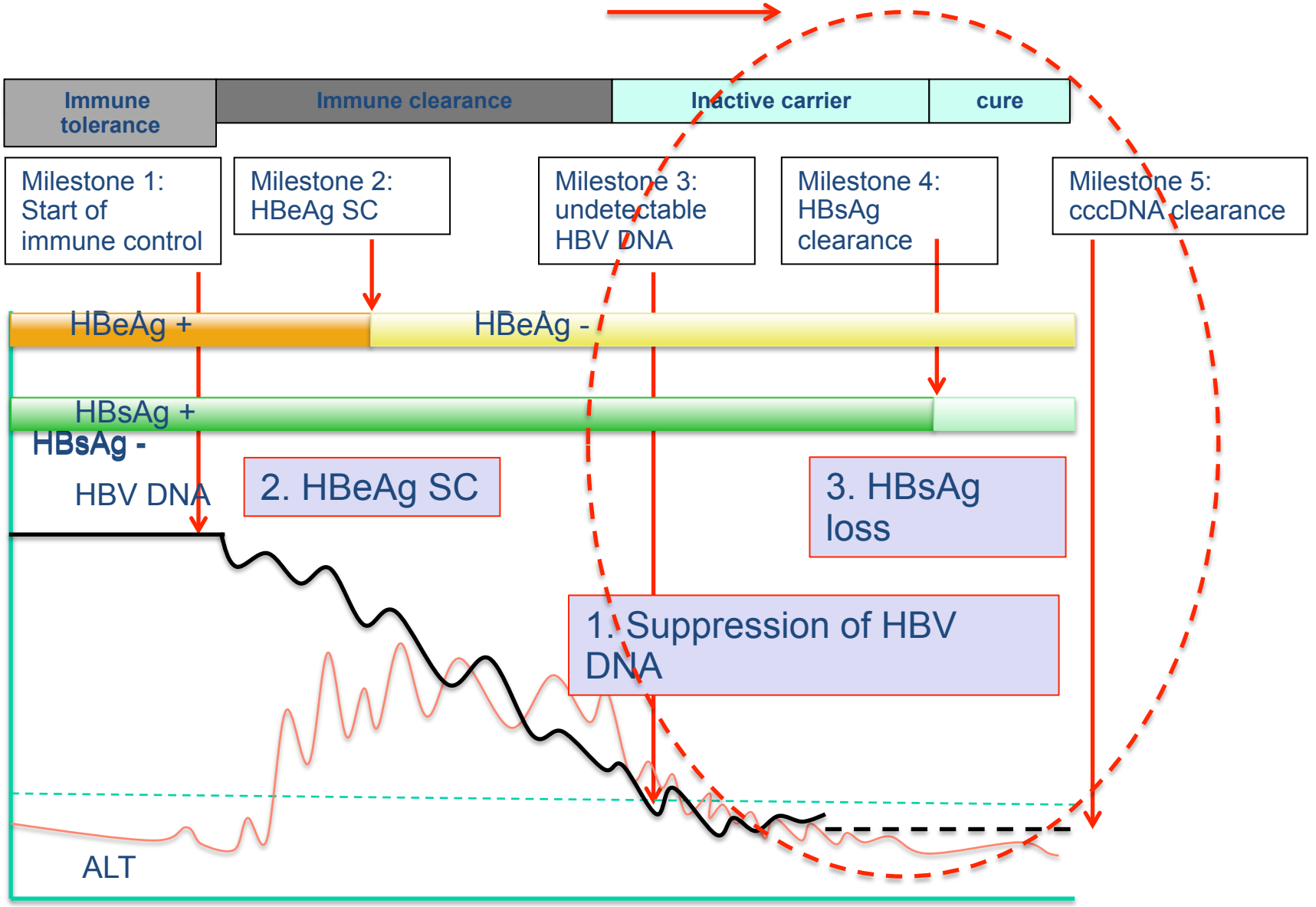


Central lab upper limit of normal (ULN): males ≤43 U/L, females ≤34 U/L (≥69 y, males ≤35 U/L, females ≤32 U/L); AASLD criteria ULN: males ≤30 U/L, females ≤19 U/L.

	TAF n=581	TDF n=292	p-value
sCr change, mg/dL	0.009 (0.124)	0.026 (0.095)	0.020
$eGFR_{CG}$ change, mL/min	-0.3 (14.5)	-4.7 (13.5)	<0.001
No dipstick proteinuria, n/n (%)	419/577 (73)	221/286 (77)	0.21
Confirmed renal events, n (%)			
sCr ≥0.5 mg/dL from baseline	0	0	–
$eGFR_{CG}$ <50 mL/min	0	5 (2)	0.004
PO_4 <2.0 mg/dL	3 (<1)	1 (<1)	1.0

Buti M et al. GS06, and Chan H Y-L et al. GS12

Behandlungsziele HBV

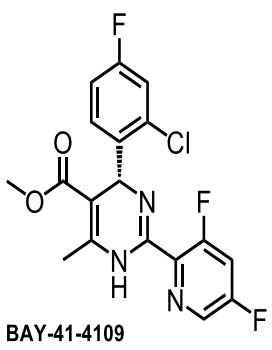


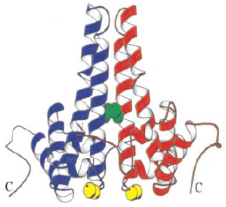
Neue Strategien HBV – experimentell/früh klinisch

Author	Substance (Company)	Class	Phase
Yuen M-F et al. (LB06)	NVR3-778 (Novira Therapeutics)	Core inhibitor	Phase 1b
Mani N et al. (THU-198)	AB-423 (Arbutus Biopharma)	Capsid assembly inhibitor (small molecule)	preclinical (mice)
Li P-C et al. (FRI-136)	CpAMs (Assembly Biosciences)	Core protein assembly modulators	preclinical
Yuen M-F et al. (THU-193)	ARC-520 (Arrowhead Pharmaceuticals)	siRNA	Phase IIa
Xu Z et al. (THU-213)	ARC-520 (Arrowhead Pharmaceuticals)	siRNA	Chimps
Blank A et al. (PS054)	Myrcludex B (Maxwell Biotech)	Entry inhibitor	Phase 0/I

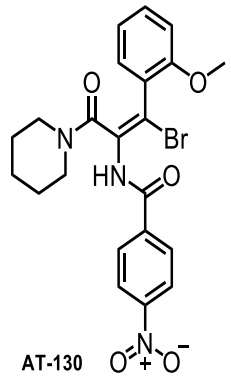
Inhibition of HBV capsid assembly and pgRNA encapsidation are well validated targets

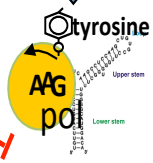
AB-423 a potent small molecule inhibitor of HBV capsid assembly (Mani N et al.)



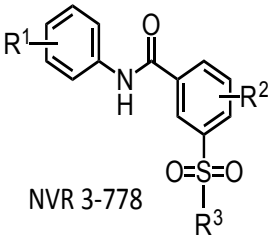


Core + pgRNA





Assembly

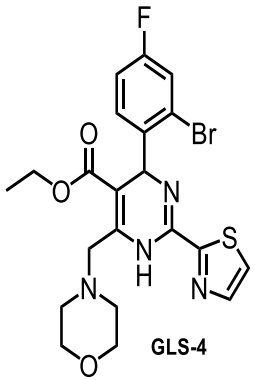


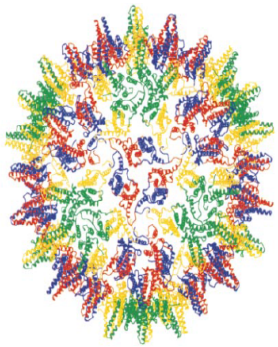
(*cf.* Campagna et al J.Virol. 2013)

NVR-3-778 core inhibitor

HBV DNA decline with highest dose (600mg): 1.72 log, and plus pegIFN: 1.97 log

GLS-4 capsid assembly inhibitor (Bassit L et al. LB050/ EASL_ILC 2016)





Retrotrans
+ DNA rep

1 SAE: Grad 3 Hand-Foot Rash
Kein Effekt auf HBsAg

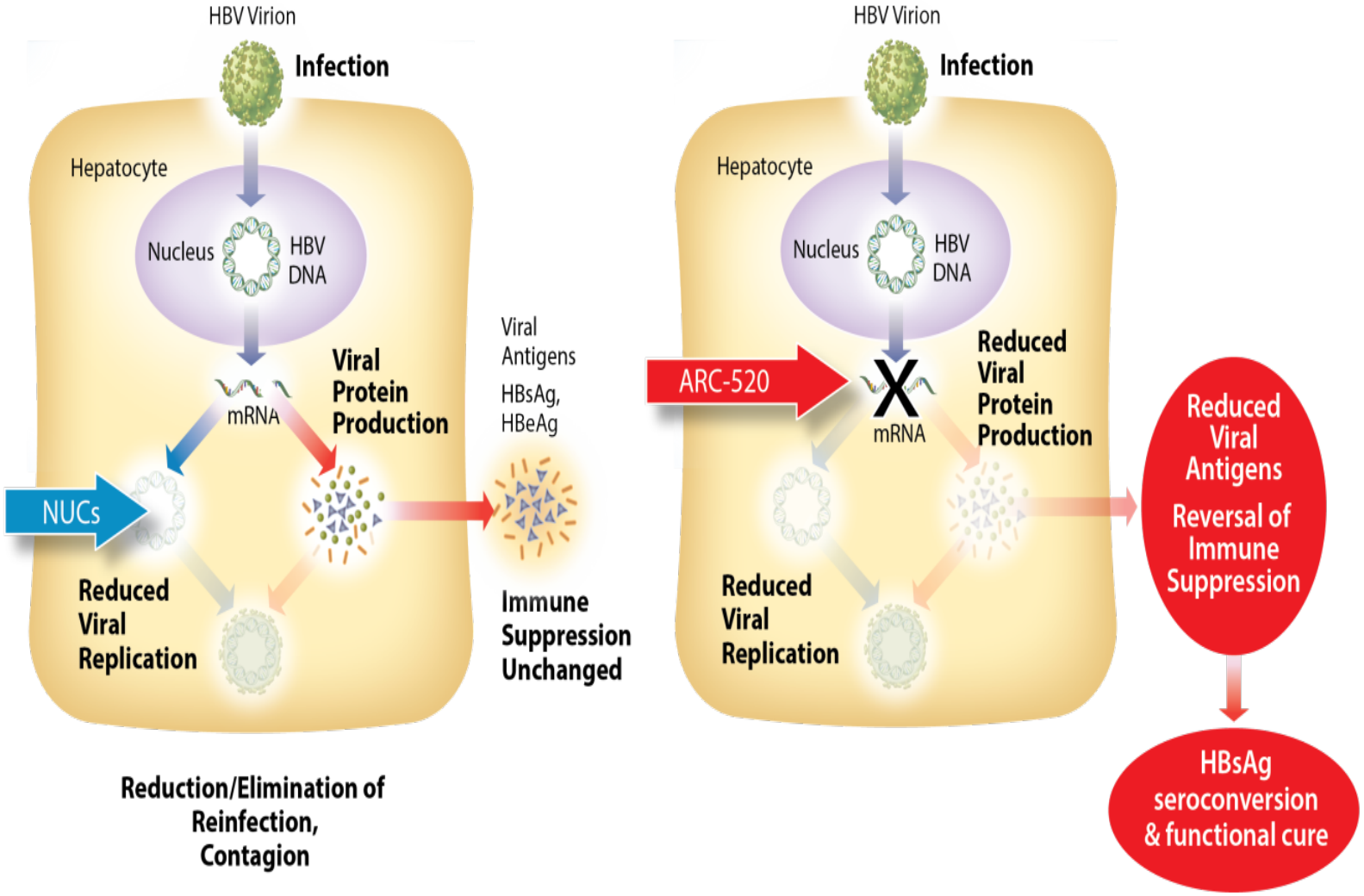
2016)

Hu et al., Ann. Rep. in Med. Chem. 2013

Winne et al, Mol.Cell 1999

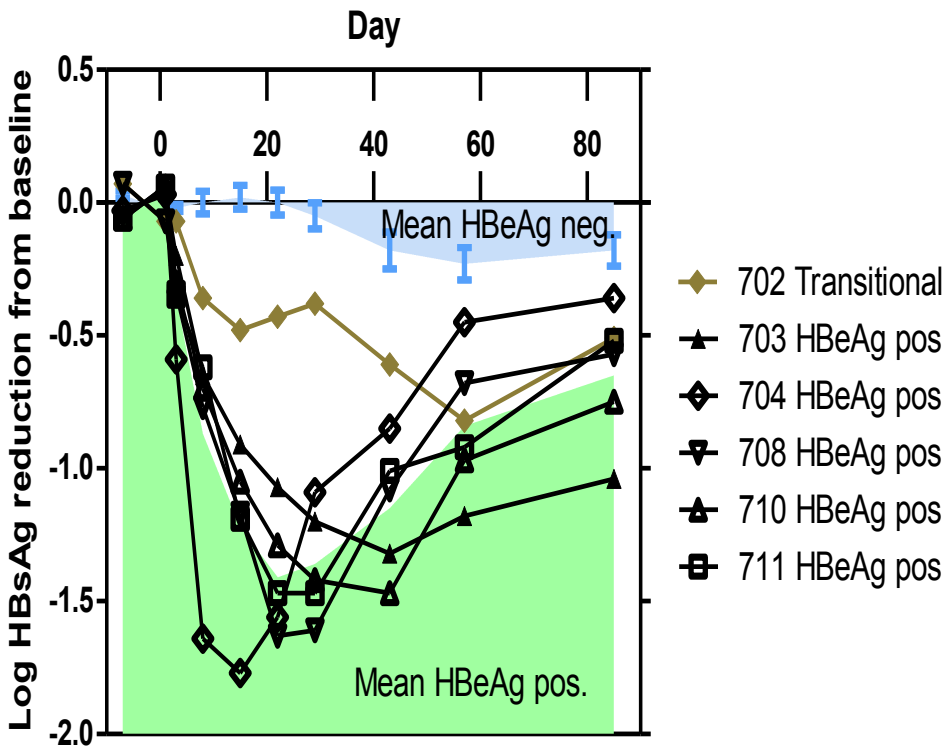
Courtesy Mani N et al. Poster THU-198/EASL_ILC 2016; modified

RNAi therapeutics vs. reverse transcriptase inhibitors (NUCs) for treatment of chronic HBV



Courtesy Xu Z et al. Poster THU-213

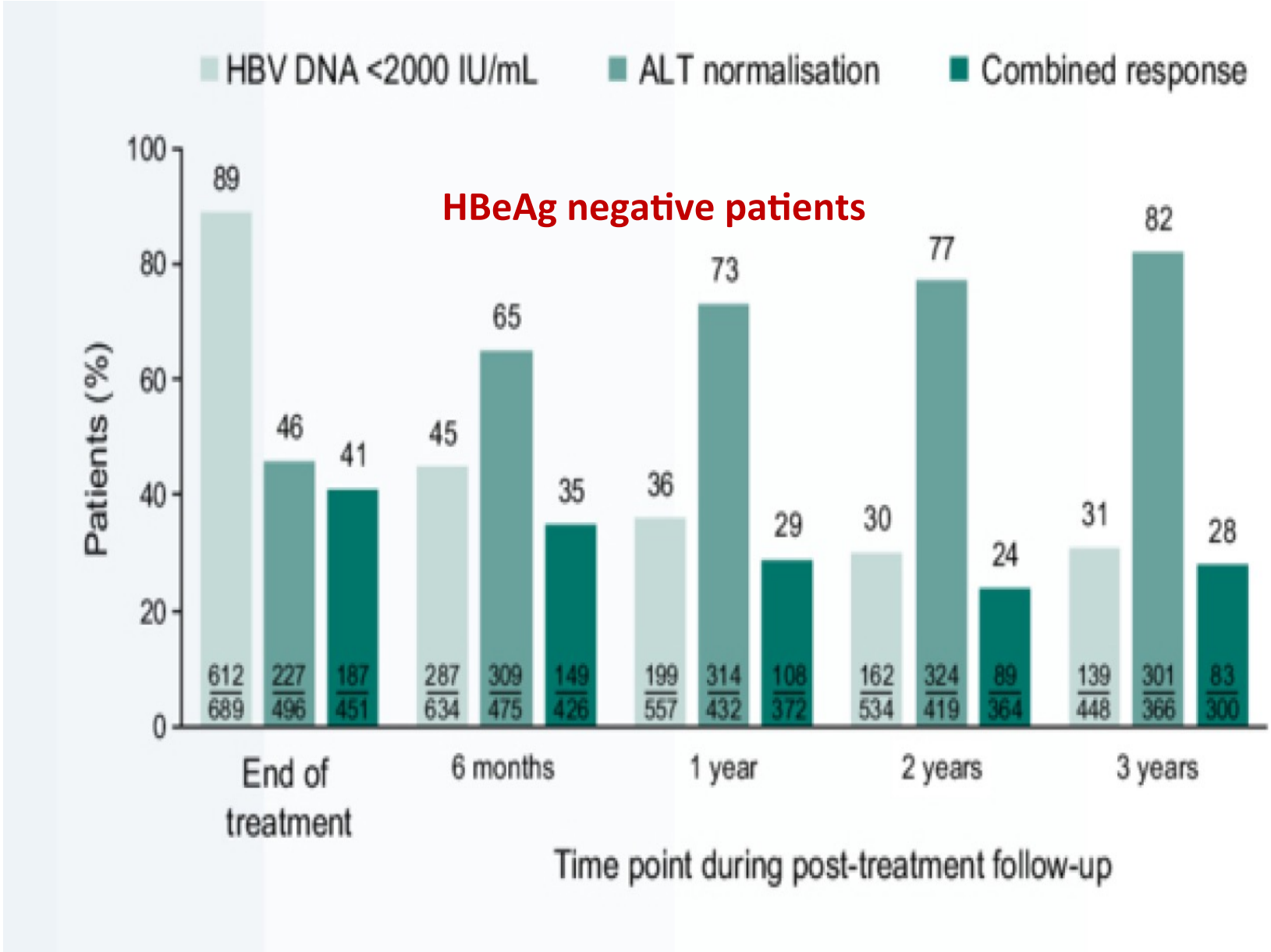
HBsAg reduction in naïve HBeAg positive and negative patients with chronic HBV after RNA interference therapy with ARC-520



Transitional patient was HBeAg-pos. at baseline and HBeAg negative at days 3 to 43

- Two distinct patterns of HBsAg reduction
- HBeAg positive:
  - Immediate antiviral effect
  - Max 1.8 log, mean 1.5 log reduction
  - Still reduced at day 85
- HBeAg negative:
  - Delayed response
  - Max 0.5 log, mean 0.3 log reduction

S-Collate study: Langzeitresultate PEG enttäuschend

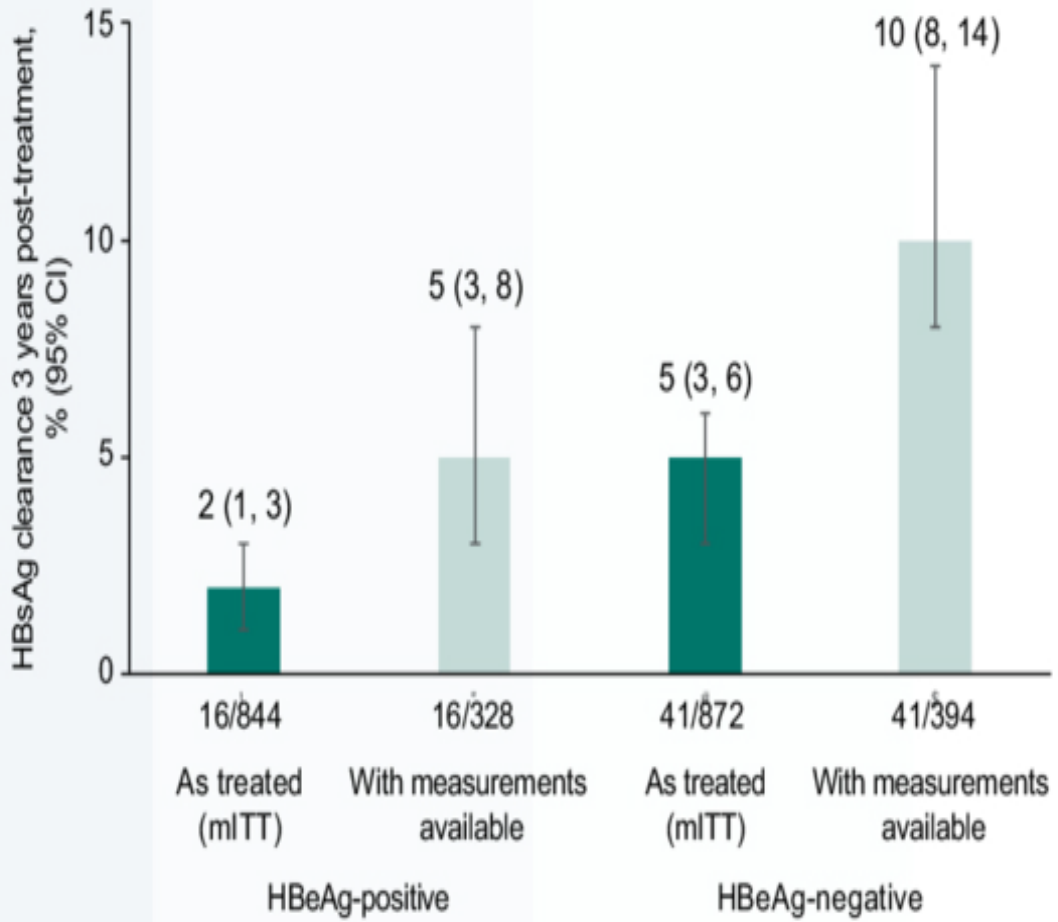


Combined response = ALT normalisation plus HBV DNA < 2000 IU/mL

Marcellin P et al. FRI-137

S-Collate study: Langzeitresultate PEG enttäuschend

Figure 2. HBsAg clearance after 3 years' follow-up

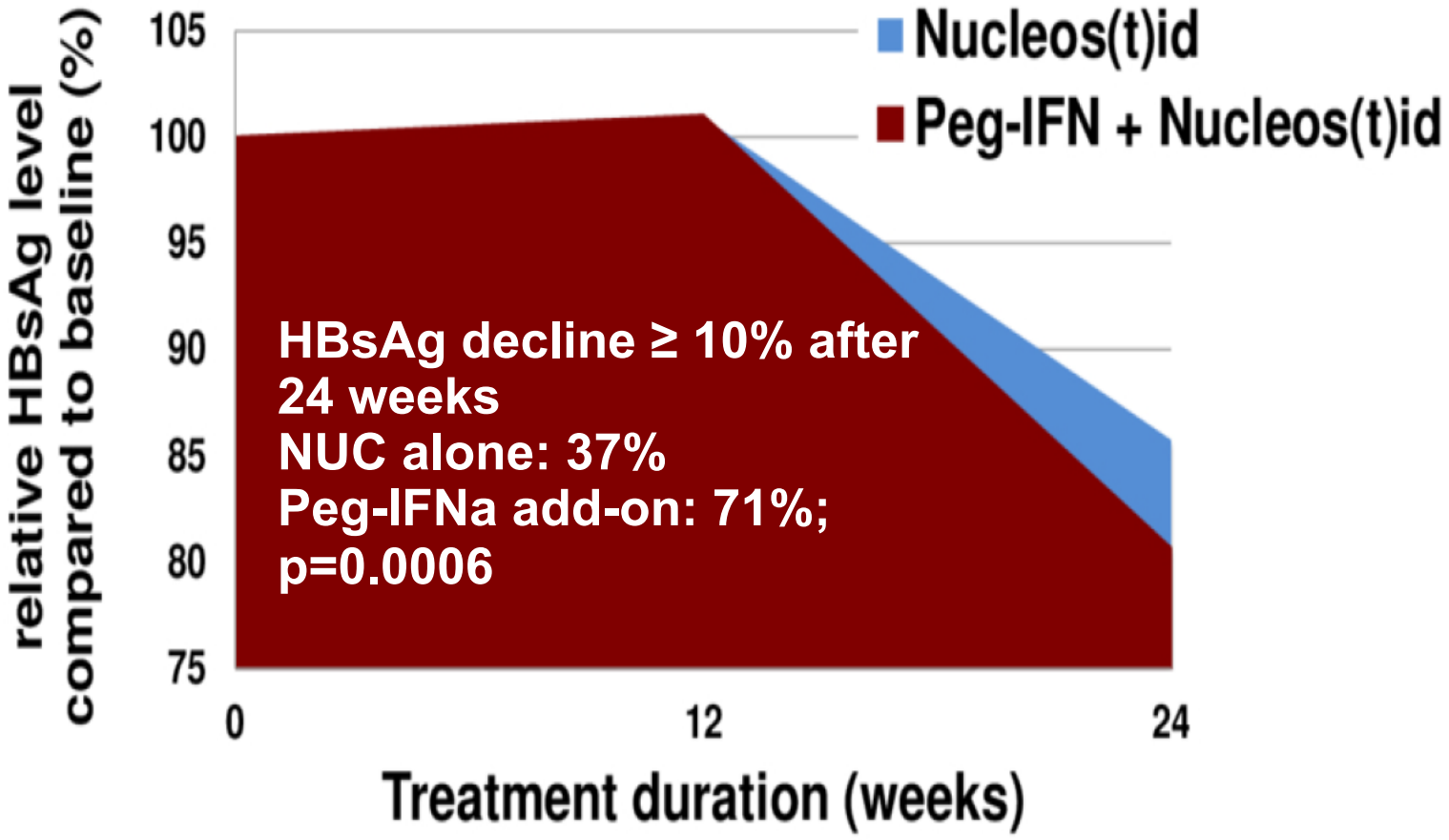


Marcellin P et al. FRI-137

Add-on peg-interferon-alfa-2a bei HBeAg-negativen Patienten

Author	Population	Study design	Follow-up
Lampertico P et al. (LBP521)	HBeAg-negative, HBV type D (n=70)	Prospective, single arm (multicenter) (add-on for 48 weeks)	Week 96
Sprinzl MF et al. (LBP517)	HBeAg negative on NUC (n=137)	RCT (2:1) (add-on for 48 weeks)	Week 24 interim analysis
Yu Y et al. (FRI-151)	HBeAg positive (n=157)	Retrospective, comparing add-on for 48 weeks (n=81) vs. continued ETV (n=116)	Week 48 (higher rate of HBeAg-seoconversion and HBsAg loss

Add-on peg-interferon-alfa-2a bei HBeAg-negativen Patienten



Sprinzl MF et al. LBP517

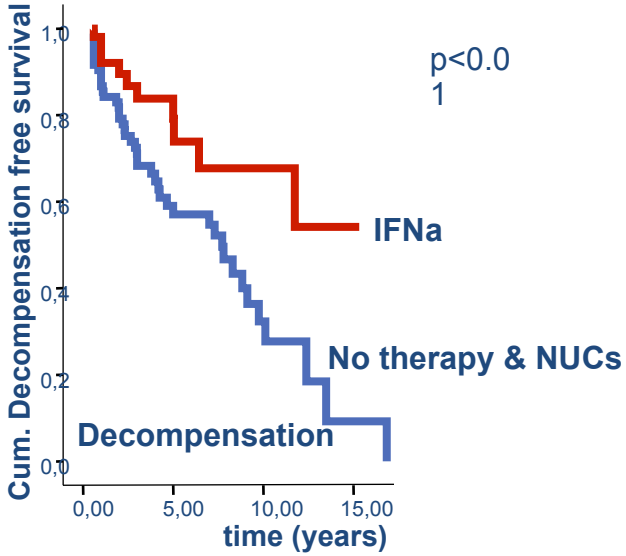
Does antiviral treatment affect the clinical long-term outcome of hepatitis delta?

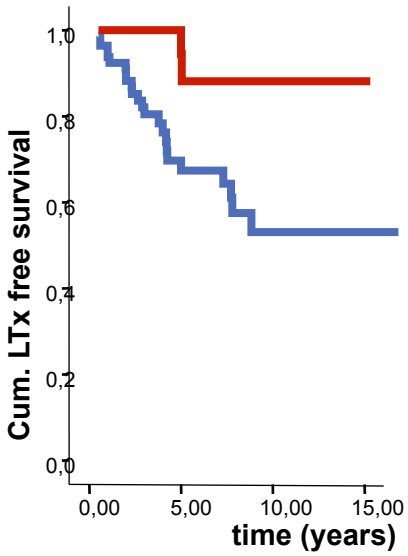
A. Wranke[1],

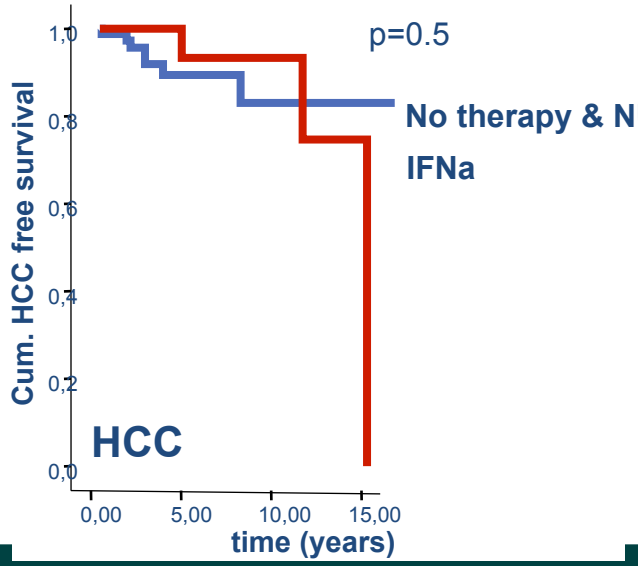
B. Cale Serrano[1], B. Heidrich[1], J. Kirschner[1], B. Bremer[1], S. Hardtke[1], K. Deterding[1], K. Port [1], M. Cornberg[1], M. P. Manns[1], H. Wedemeyer[1, 2,3]

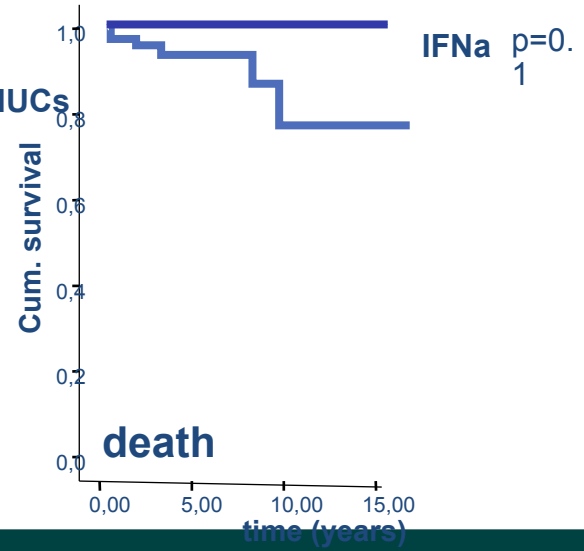
[1]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany,
[2]German Center for Infection Research (DZIF), Partner Side Hannover Medical School, Hannover, Germany,
[3]Integrated Research and Treatment Center Transplantation, Hannover Medical School, Germany.

Interferon bisher das einzige Medikament gg. Delta-Hepatitis





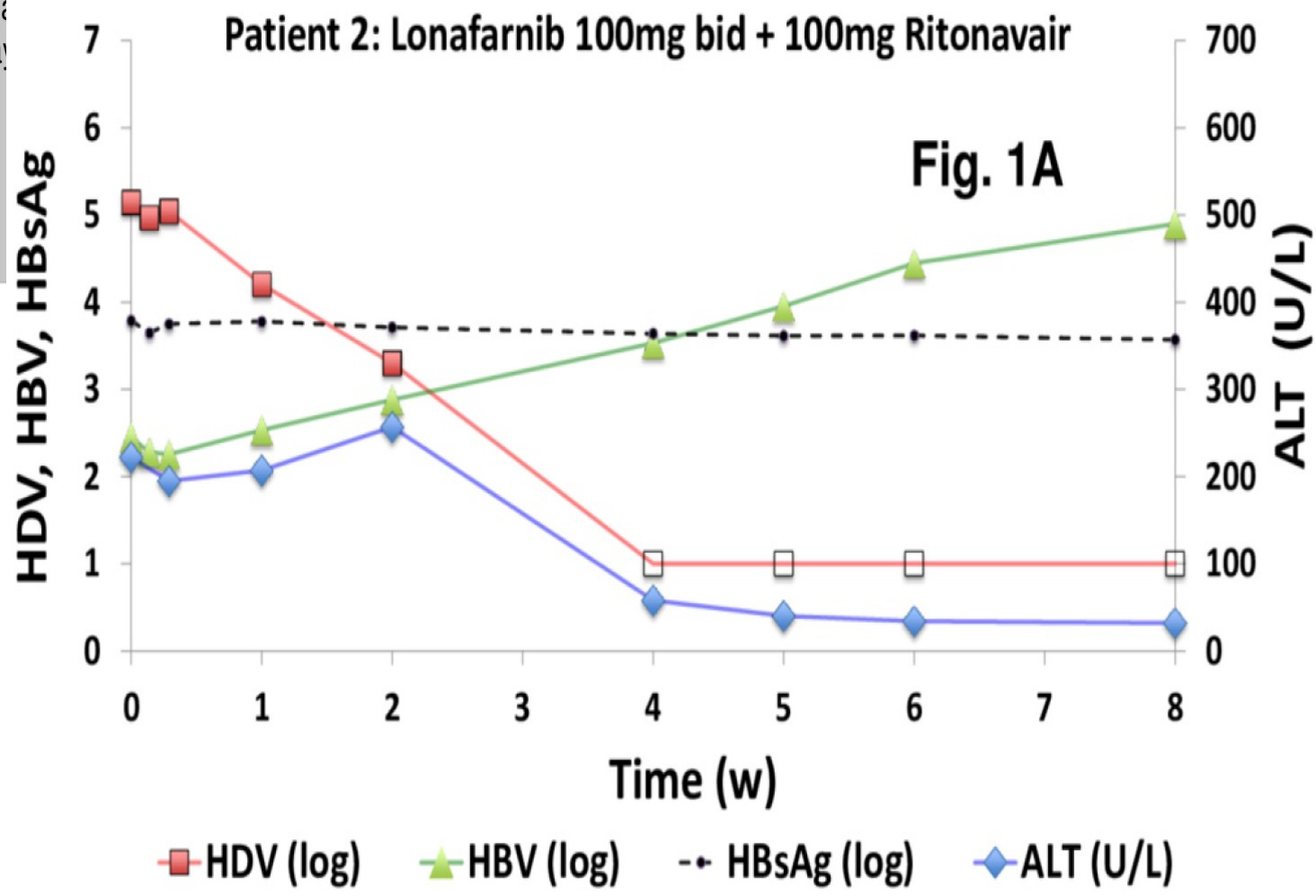




Wranke A et al. PS053

Prenylierungsinhibitoren: neue Substanzklasse gegen HDV

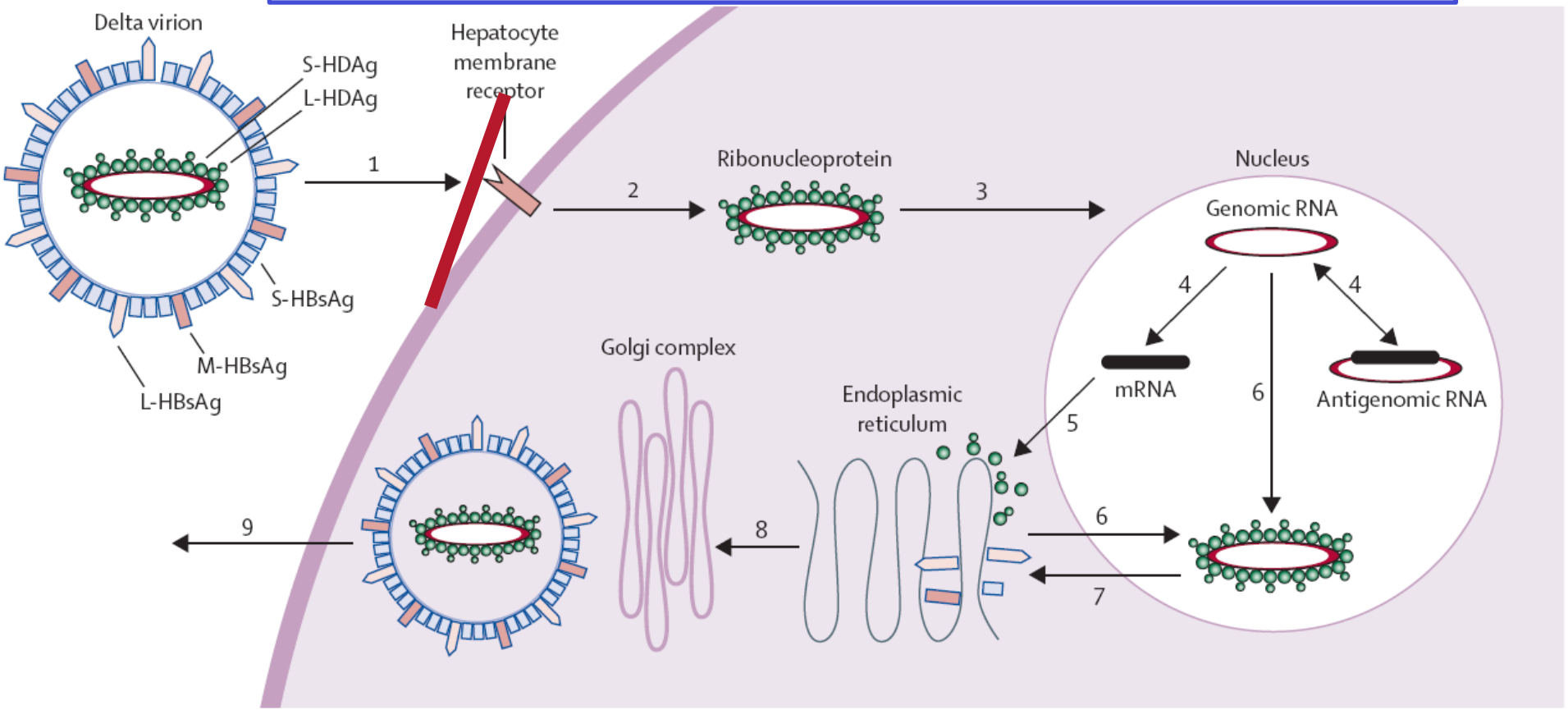
Hepatitis delta virus (HDV) kinetics under the prenylation inhibitor lonafarnib suggest HDV-mediated suppression of HBV replication



Yurdaydin C et al. FRI-111

Neue Therapien bei Hepatitis Delta

Inhibit entry of HDV into hepatocytes (i.e. Myrcludex)*



*S. Urban et al., Gastroenterology. 2014 Jul;147(1):48-64.

Review: Hughes, Wedemeyer, Harrison Lancet 2011

Evaluation des CCR2/5-Inhibitors CVC in Steatohepatitis und Fibrose

MCD diet - progressive steatosis & fibrosis

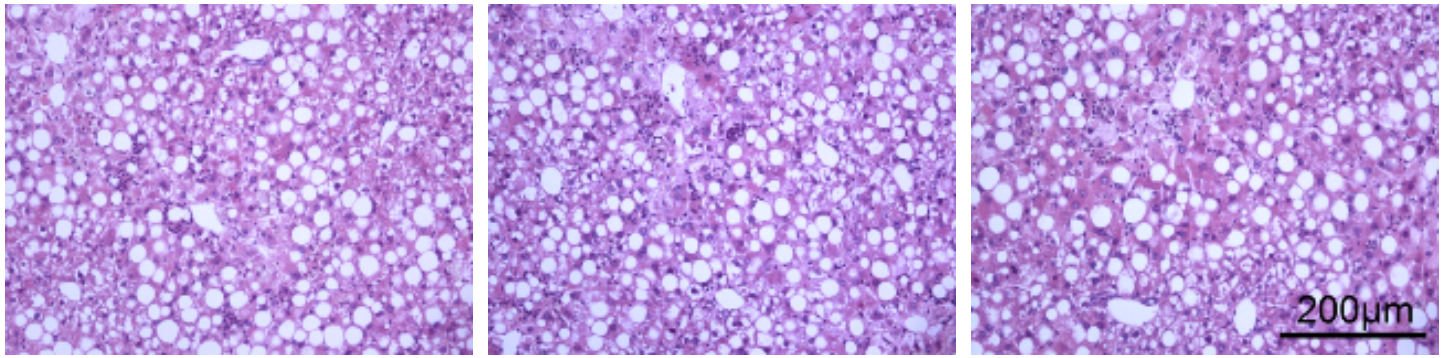
0wks. — n = 8 — **4wks.** — **8wks.**

Vhc. p.o. 1x/d

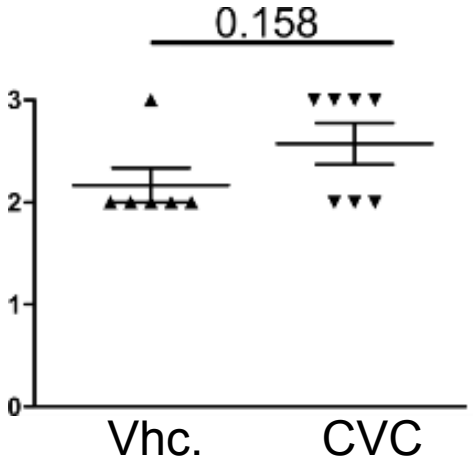
CVC p.o. 1x/d

8wks. **MCD diet**	+4wks. **Vhc.**	+4wks. **CVC**

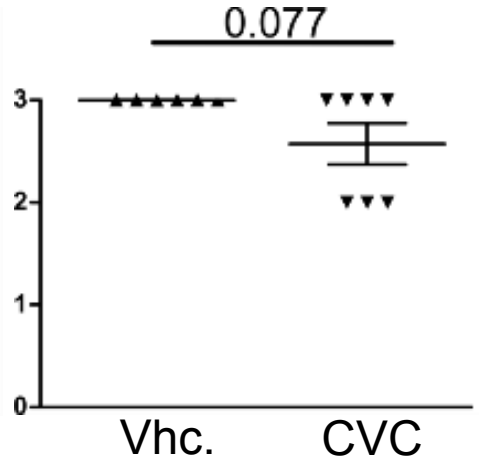
H&E

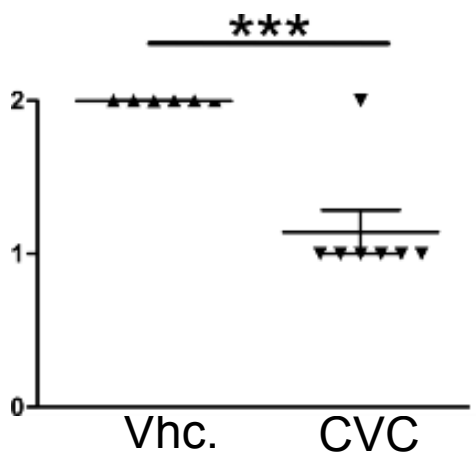


Steatosis

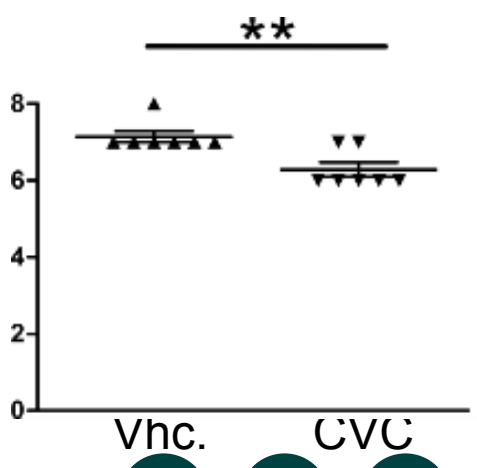


Lobular Inflammation Hepatocyte Ballooning





NAFLD Activity Score



Vielen Dank für die Aufmerksamkeit!

ABT-530 Retains Antiviral Activity Against Common GT1a Single-Position NS5A Variants

NS5A Inhibitor	Fold Change in EC_{50} for GT1a NS5A Variants			
	Q30E	L31M/V	H58D	Y93H/N
ABT-530	**2.4**	**1.1 – 1.3**	**1.1**	**6.7 – 7.1**
Ledipasvir[1,2]	3279	393 – 2787	>1000	4918
Velpatasvir[3,4]	37	2.1 – 9	NA	81 – 609
Daclatasvir[5]	25205	341 – 3386	500	5432 – 47477
Elbasvir[4,6]	50	125	NA	600 – 2000
Ombitasvir[7]	1326	2	243	41383 – 66740
Odalasvir[1,4]	71	1 – 2.4	8	5083
MK-8408	NA	NA	NA	NA

NA, not available

1. Patel D, et al. EASL, 2015. 2. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205834Orig1s000MicroR.pdf
3. Doehle BP, et al. EASL, 2015. 4. Gao M, et al. Curr Opin Virol ; 3:514-20.
5. Fridell RA, et al. Hepatology,54:1924-35. 6. Gane E, et al. EASL, 2015. 7. Krishnan P, et al. AAC, 2015.

ABT-493 and ABT-530 Have Potent Activities Against All Major HCV Genotypes, Including GT3

Stable HCV GT3a Replicon EC_{50}			
NS3/4AProtease Inhibitor	**nM**	**NS5A Inhibitor**	**pM**
ABT-493	**1.6**	**ABT-530**	**2**
Grazoprevir[1]	35	Elbasvir[7]	140
GS-9857[2]	6.1	Velpatasvir[8]	20
Simeprevir[3,4]	472	Ledipasvir[9]	168,000
Paritaprevir	19	Ombitasvir	19
Asunaprevir[5]	1162	Daclatasvir[10]	530
		Odalasvir[11]	48
		MK-8408[12]	2

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2. Taylor J, et al. EASL, 2015.
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8. Cheng G, et al. EASL, 2013.
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11. ACHN R&D/Analyst Day
12. Asante-Appiah E, AASLD, 2014.