Post-EASL
Neues zur Hepatitis C

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HCV

Direkt antivirale Substanzen

Proteaseinhibitor	NS5A-Inhibitor	Nukleotidischer Polymeraseinhibitor	Nicht-nukleotidischer Polymeraseinhibitor
Simeprevir		Sofosbuvir	
	Daclatasvir	Sofosbuvir	
	Ledipasvir	Sofosbuvir	
Paritaprevir	Ombitasvir		Dasabuvir
	Velpatasvir	Sofosbuvir	
Grazoprevir	Elbasvir		
Glecaprevir	Pibrentasvir		2017
Voxilaprevir	Velpatasvir	Sofosbuvir	
Grazoprevir	Ruzasvir	Uprifosbuvir	2018

HCV – welche Probleme bleiben?

- „One size fits all“ oder individuelle Therapie?
- Lohnt die Behandlung bei fortgeschrittener Zirrhose?
- Beeinflusst die Therapie das HCC Risiko?
- Was tun bei Resistenzen?
- Was tun bei Niereninsuffizienz?

HCV – Neue Besen

Integrierte Analyse – Keine Zirrhose
Glecaprevir/Pibrentasvir

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A
protease inhibitor

Collectively: G/P

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A
inhibitor

In vitro:[8]
- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, and 168) and NS5A polymorphisms (eg, positions 28, 30, 31, and 93)
- Synergistic antiviral activity

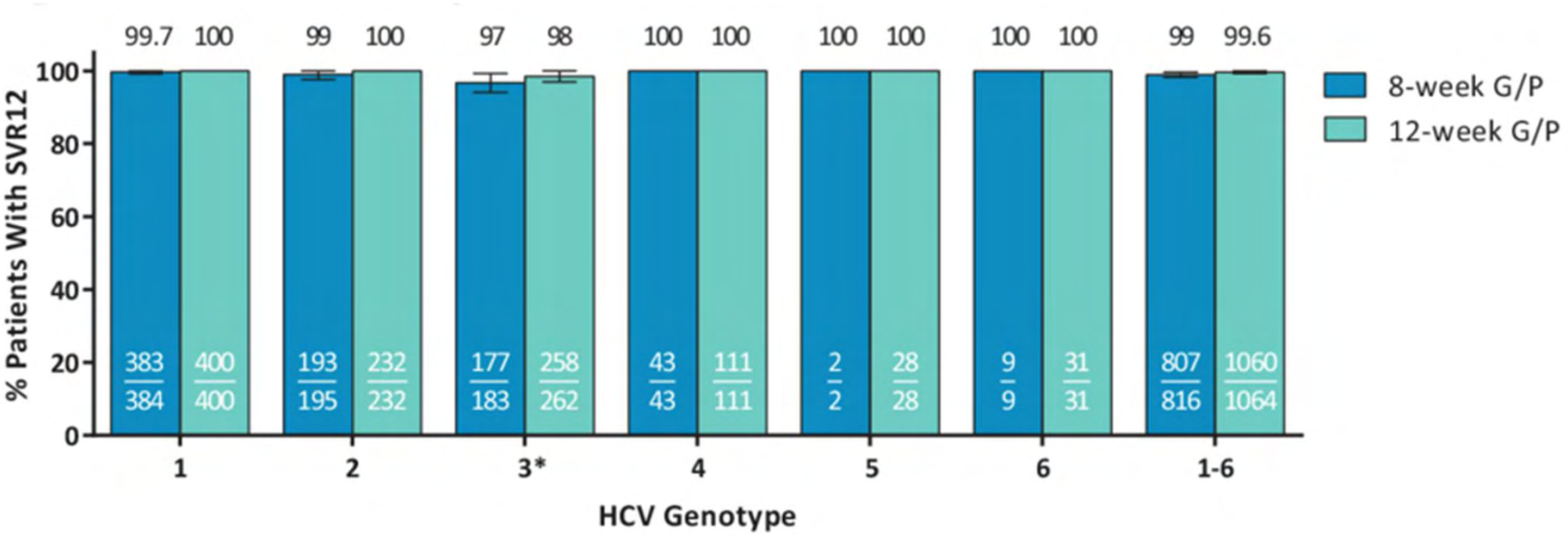
Clinical PK & metabolism:
- Oral dosing of 3 pills once-daily
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg.
Glecaprevir was identified by AbbVie and Enanta.

Gane E et al., SAT-233, EASL 2017

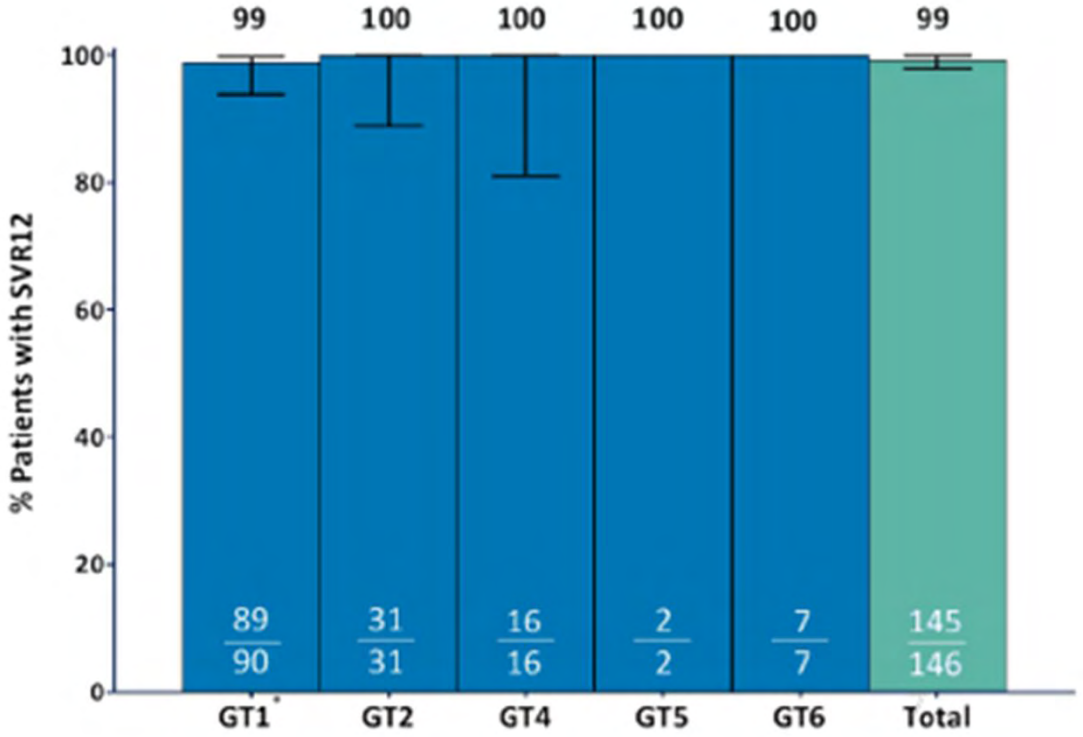
Integrierte Analyse – Keine Zirrhose

Glecaprevir/Pibrentasvir



Gane E et al., SAT-233, EASL 2017

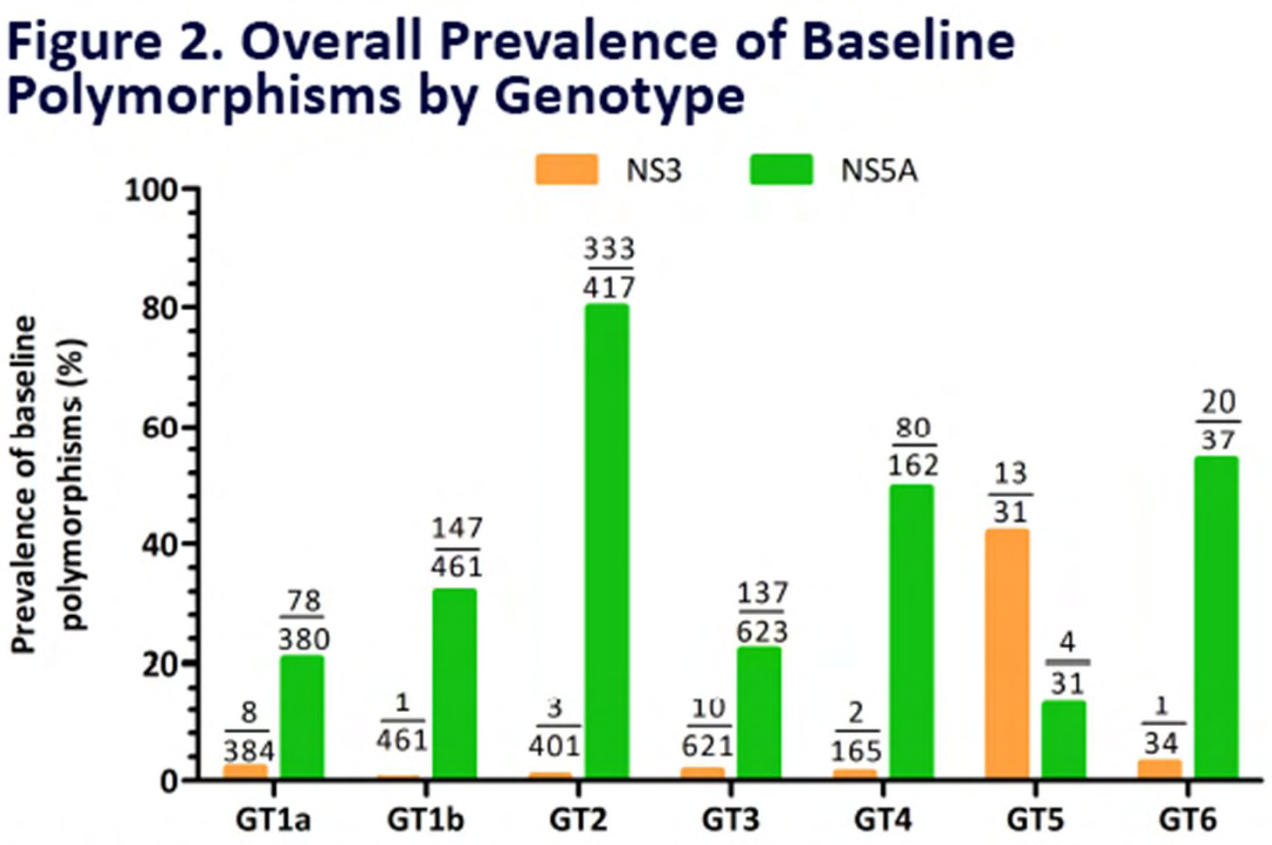
Expedition 1 – kompensierte Zirrhose
Glecaprevir/Pibrentasvir



Forns X et al., EASL 2017

Resistenzen

Glecaprevir/Pibrentasvir – NS3/NS5A-naïve Patienten



Krishnan P et al., EASL 2017, Fri-205

Resistenzen

Glecaprevir/Pibrentasvir – NS3/NS5A-naïve Patienten

Table 3. Description of Virologic Failures in Pooled Analysis of Phase 2 and 3 Studies

GT	Duration (Weeks)	Prior Treatment Experience	Cirrhosis (Y/N)	Number of Virologic Failures and Outcomes
1a	8	TE-PRS	N	1 OTVF
1a	12	TE-PRS	Y	1 Relapse
2a	8	TE-PRS	N	2 Relapse
3a	8	TN	N	1 OTVF, 5 Relapse
3a	12	TN	N	1 OTVF, 1 Relapse
3b	12	TN	N	1 Relapse
3a	12	TE-PRS	N	1 OTVF, 4 Relapse
3a	16	TE-PRS	Y	1 OTVF, 2 Relapse
3a	16	TE-PRS	N	1 Relapse

GT = HCV subtype by phylogenetic analysis; OTVF = on treatment virologic failure; TN = treatment-naïve; TE-PRS = treatment-experienced to pegIFN + RBV ± SOF; Y/N = yes/no.

Krishnan P et al., EASL 2017, Fri-205

Resistenzen

Glecaprevir/Pibrentasvir – NS3/NS5A-naïve Patienten

Table 5A. In Vitro Activity of GLE Against Amino Acid Substitutions in NS3

	NS3 Amino Acid Substitutions	GLE, Fold EC_{50} change
GT1a	A156V	NA
GT3a	Y56H	NA
	Q80R	21
	A156G	1654
	S166A	NA
	S166T	4.7
	Q168L	13
	Q168R	54
	Y56H + Q168R	1387

NA = not available due to poor replication capacity of the variant.

Table 5B. In Vitro Activity of PIB Against Amino Acid Substitutions in NS5A

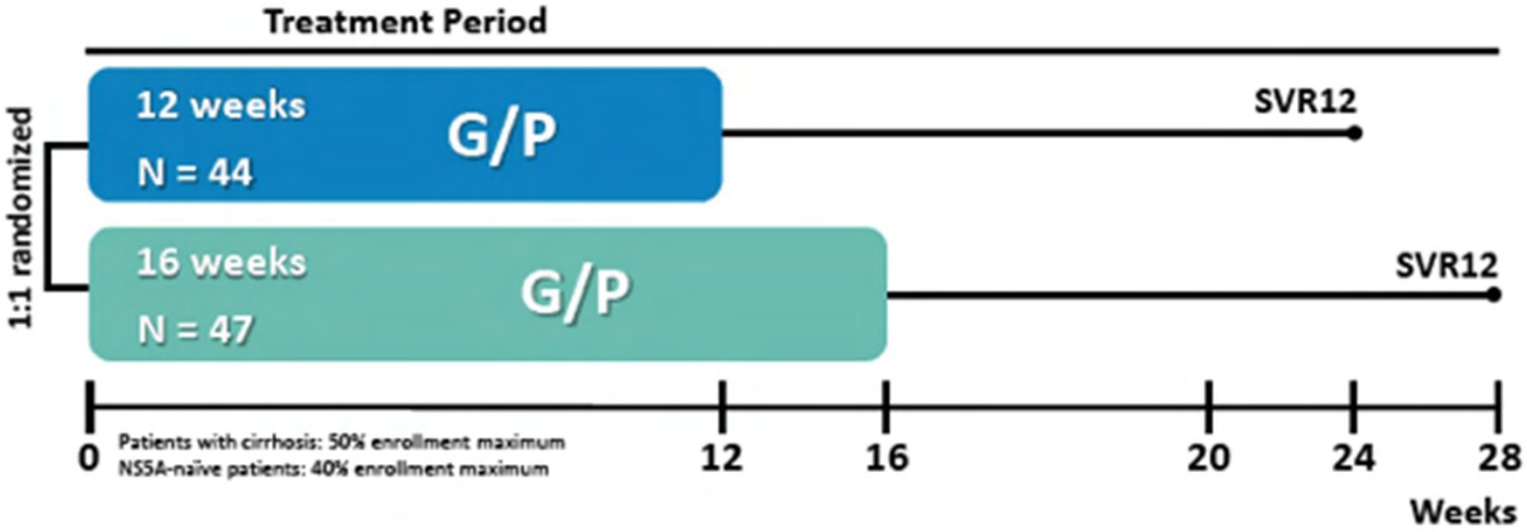
	NS5A Amino Acid Substitutions	PIB, Fold EC_{50} change
GT1a	Q30R	1.7
	L31M	1.1
	H58D	1.1
	Y93N	7
	Q30R + L31M	3
	Q30R + Y93N	131
	L31M + H58D	23
	Q30R + L31M + H58D	1704
GT3a	M28G	NA
	A30K	1.1
	L31F	NA
	Y93H	2.3
	A30K + Y93H	69
	L31F + Y93H	NA

NA = not available due to poor replication capacity of the variant.

Krishnan P et al., EASL 2017, Fri-205

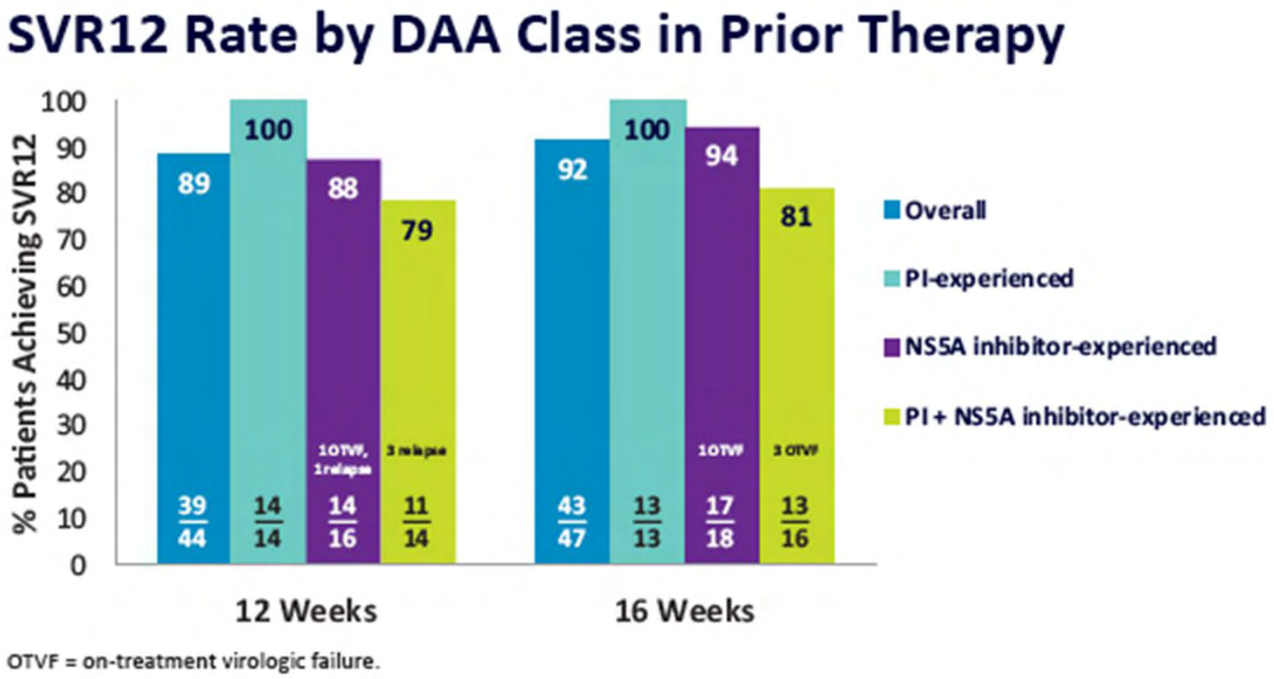
Therapie von DAA Versagern

Glecaprevir/Pibrentasvir



Poordad F et al., EASL 2017

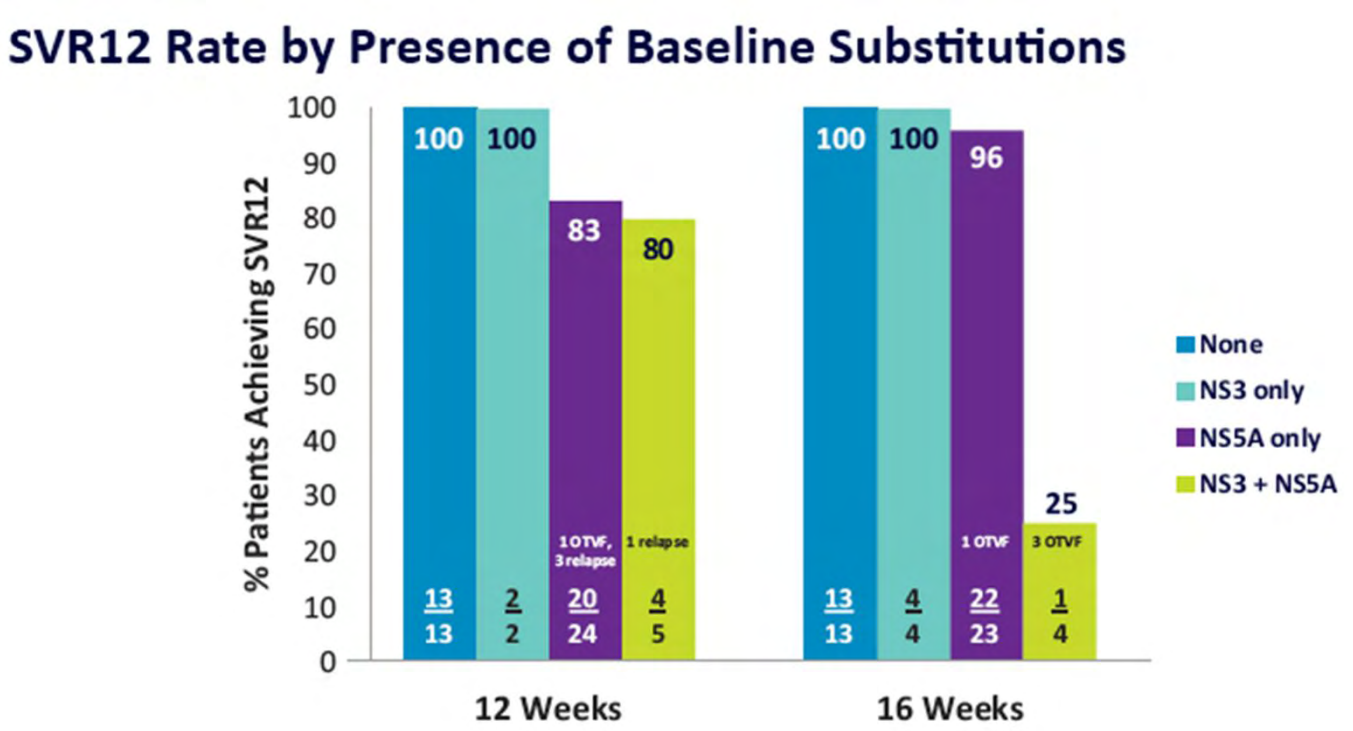
Resistenzen
Glecaprevir/Pibrentasvir – DAA-erfahrene Patienten



OTVF = on-treatment virologic failure.

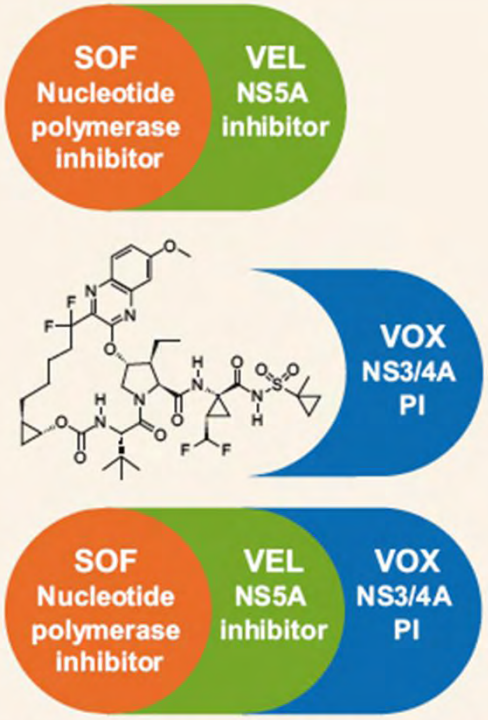
Pilot-Matias T et al., EASL 2017, SAT-204

Resistenzen
Glecaprevir/Pibrentasvir – DAA-erfahrene Patienten



Pilot-Matias T et al., EASL 2017, SAT-204

Integrierte Analyse
Sofosbuvir/Velpatasvir/Voxilaprevir



Sofosbuvir (SOF)/Velpatasvir (VEL)

- **SOF:** nucleotide polymerase inhibitor with activity against HCV GT 1–6
- **VEL:** 2nd-generation NS5A inhibitor with picomolar potency against GT 1–6
- Approved for use in treatment-naïve, and PEG/RBV- and PI + PEG/RBV-experienced patients

Voxilaprevir (VOX)

- HCV NS3/4A PI with potent antiviral activity against GT 1–6
- Favorable resistance profile

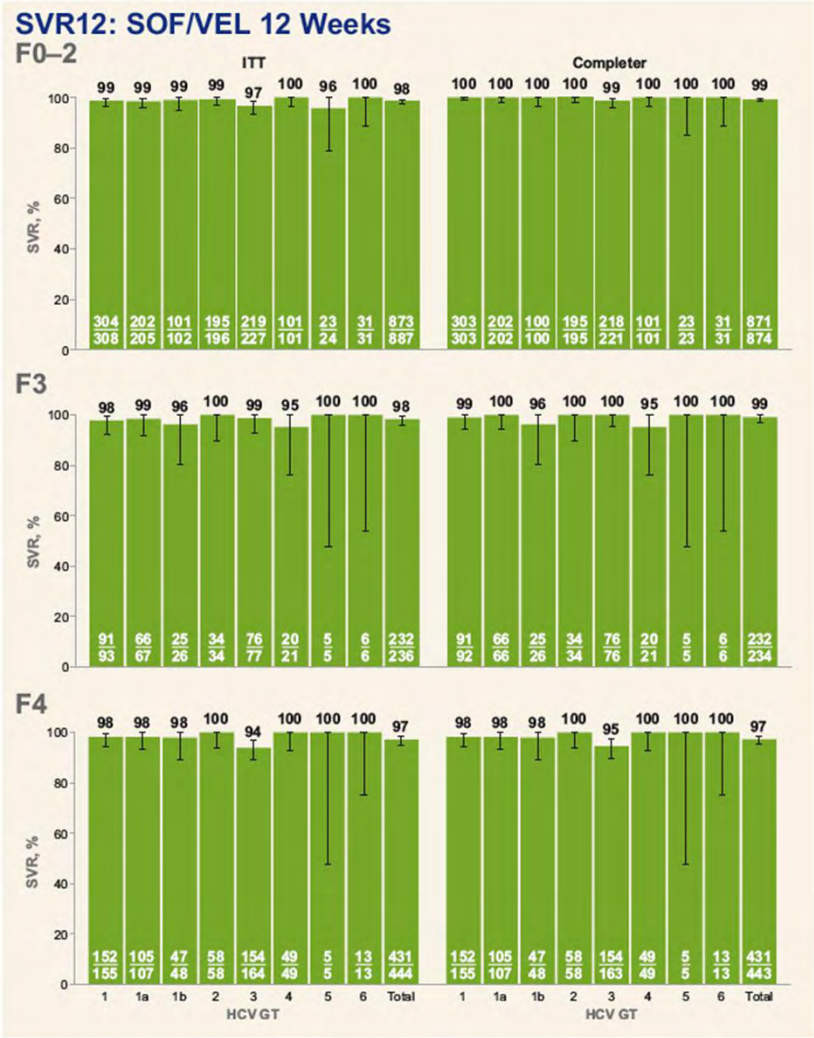
SOF/VEL/VOX

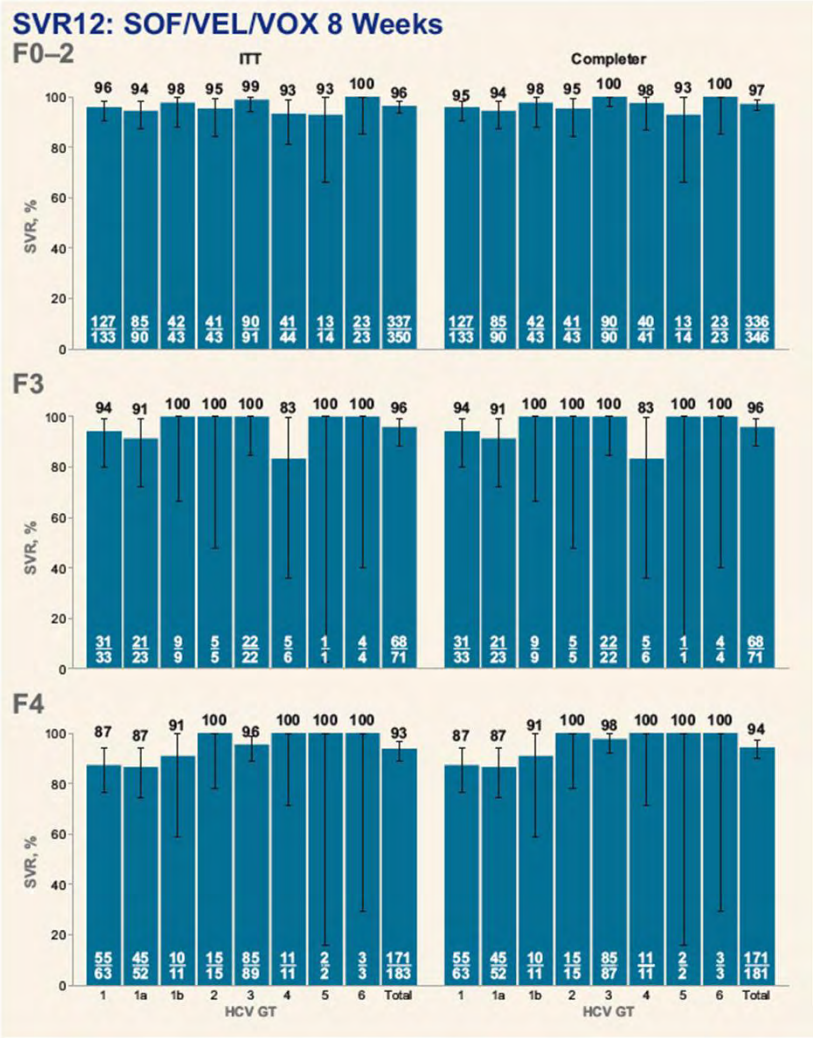
- Once-daily, oral, fixed-dose combination (400/100/100 mg) for GT 1–6

GT, genotype; HCV, hepatitis C virus; PEG, peginterferon; PI, protease inhibitor; RBV, ribavirin.

Lawitz E et al., EASL 2017, SAT-273

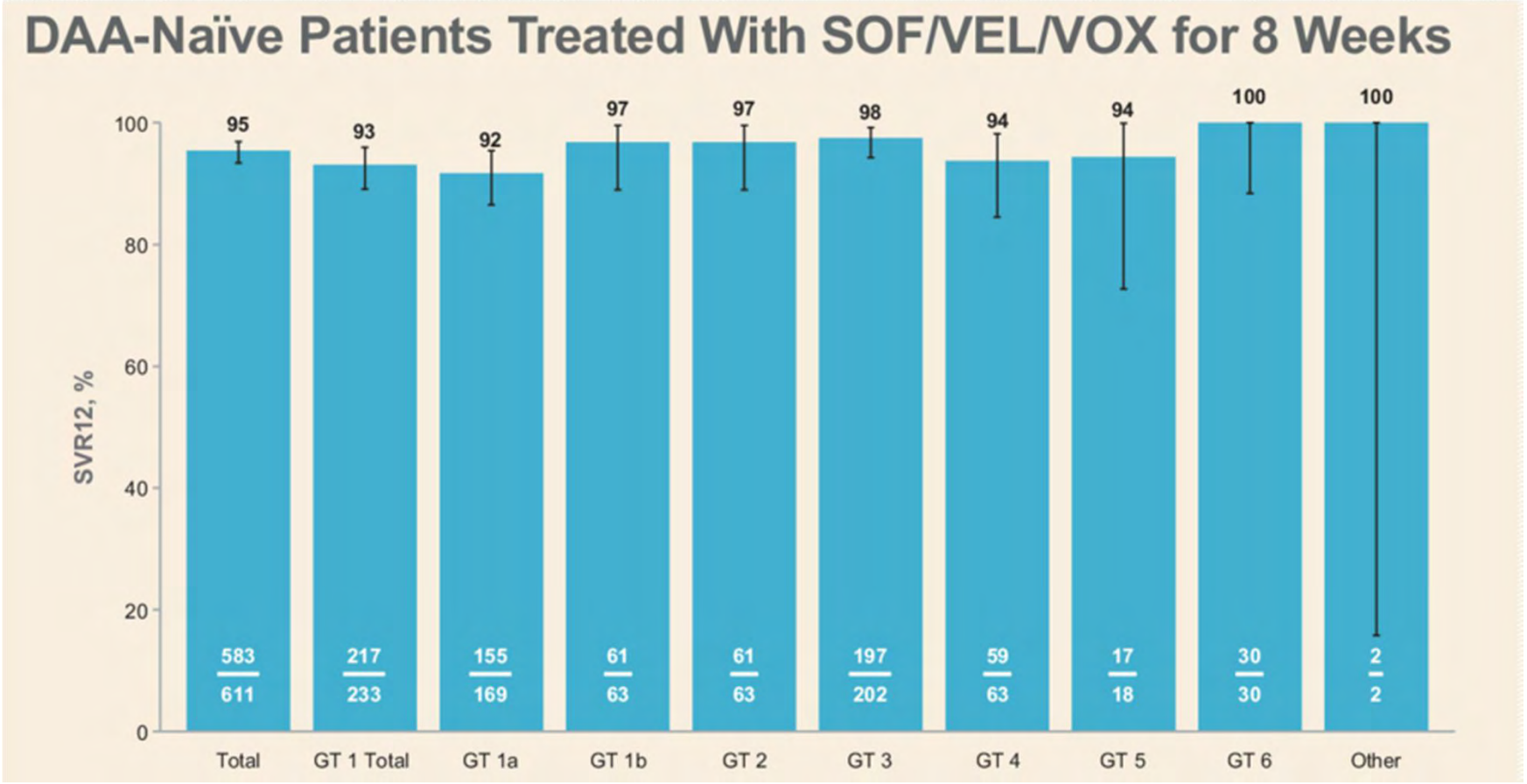
Integrierte Analyse
Sofosbuvir/Velpatasvir/Voxilaprevir





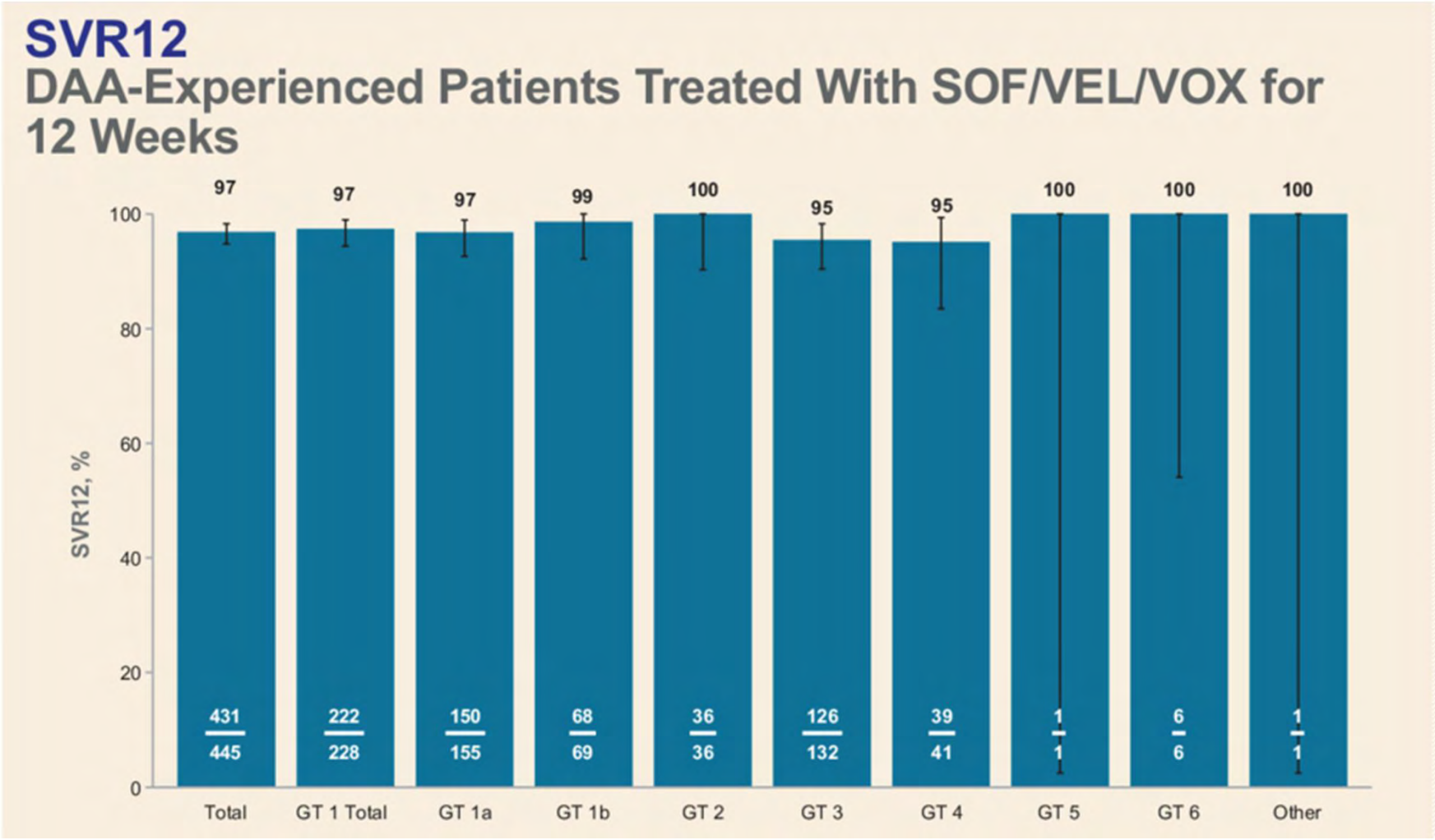
Lawitz E et al., EASL 2017, SAT-273

Integrierte Analyse
Sofosbuvir/Velpatasvir/Voxilaprevir



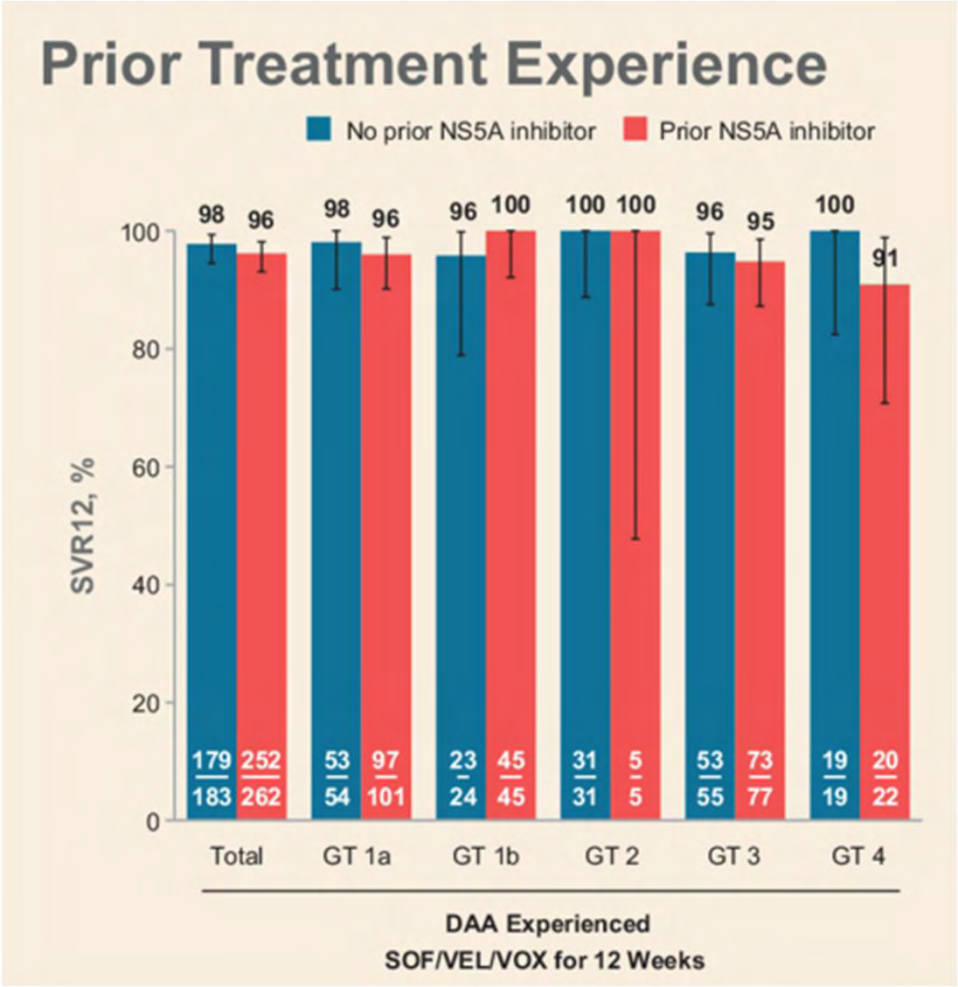
Roberts SK et al., SAT-280, EASI 2017

Integrierte Analyse
Sofosbuvir/Velpatasvir/Voxilaprevir



Roberts SK et al., SAT-280, EASI 2017

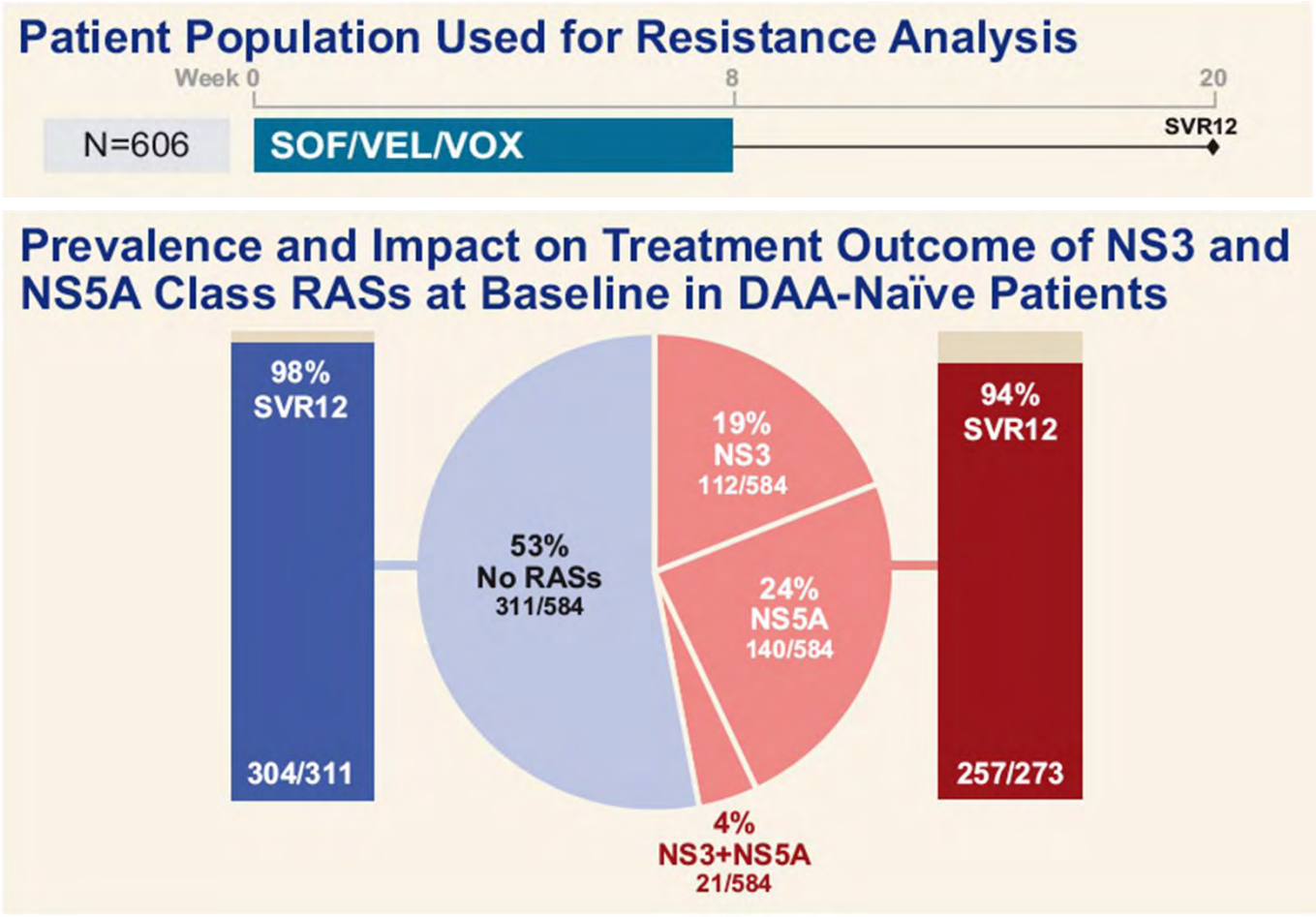
Integrierte Analyse
Sofosbuvir/Velpatasvir/Voxilaprevir



Roberts SK et al., SAT-280, EASI 2017

Resistenzen

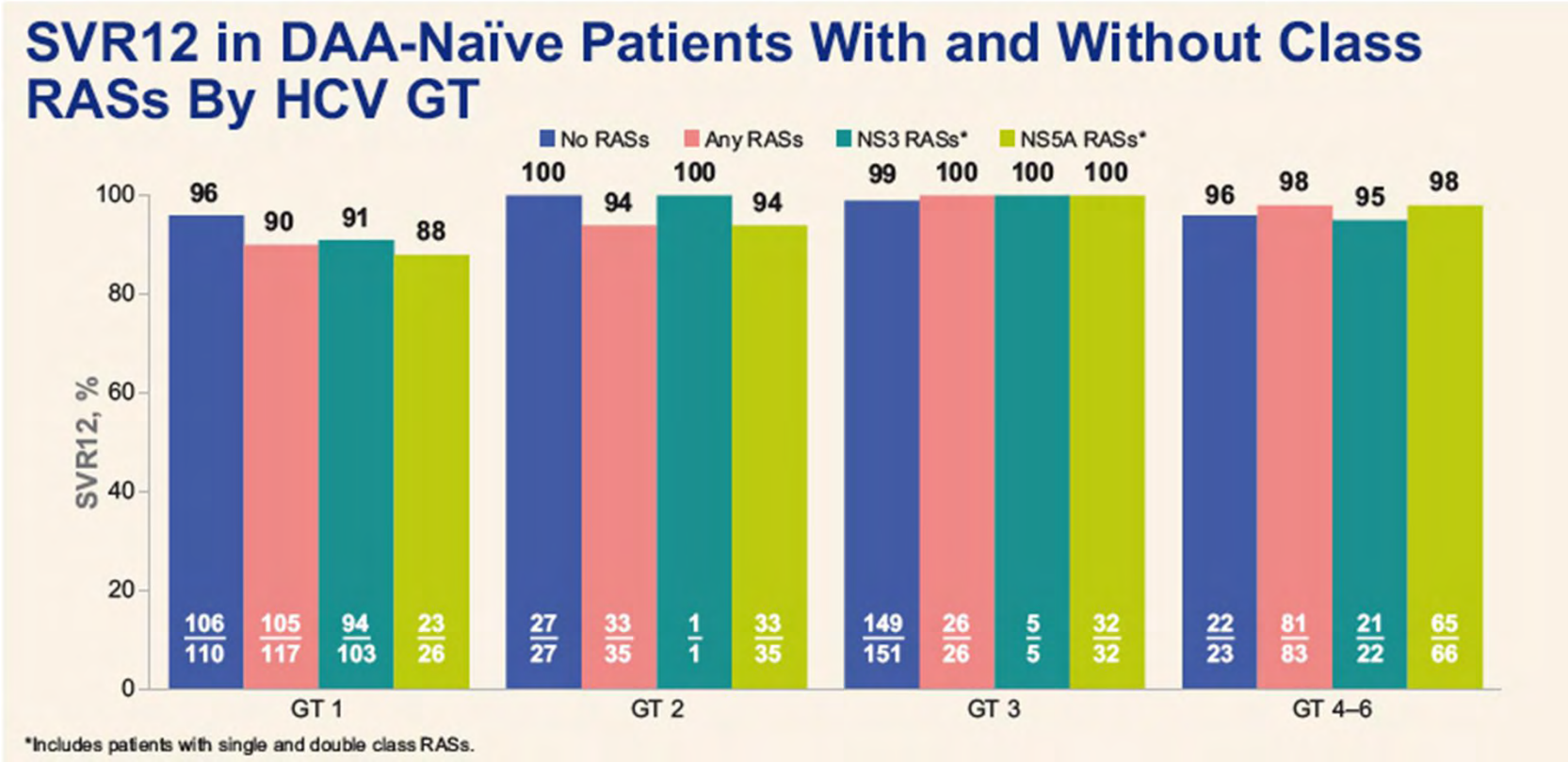
Sofosbuvir/Velpatasvir/Voxilaprevir – DAA-naive Patienten



Whyles D. et al., EASL 2017, Thu-257

Resistenzen

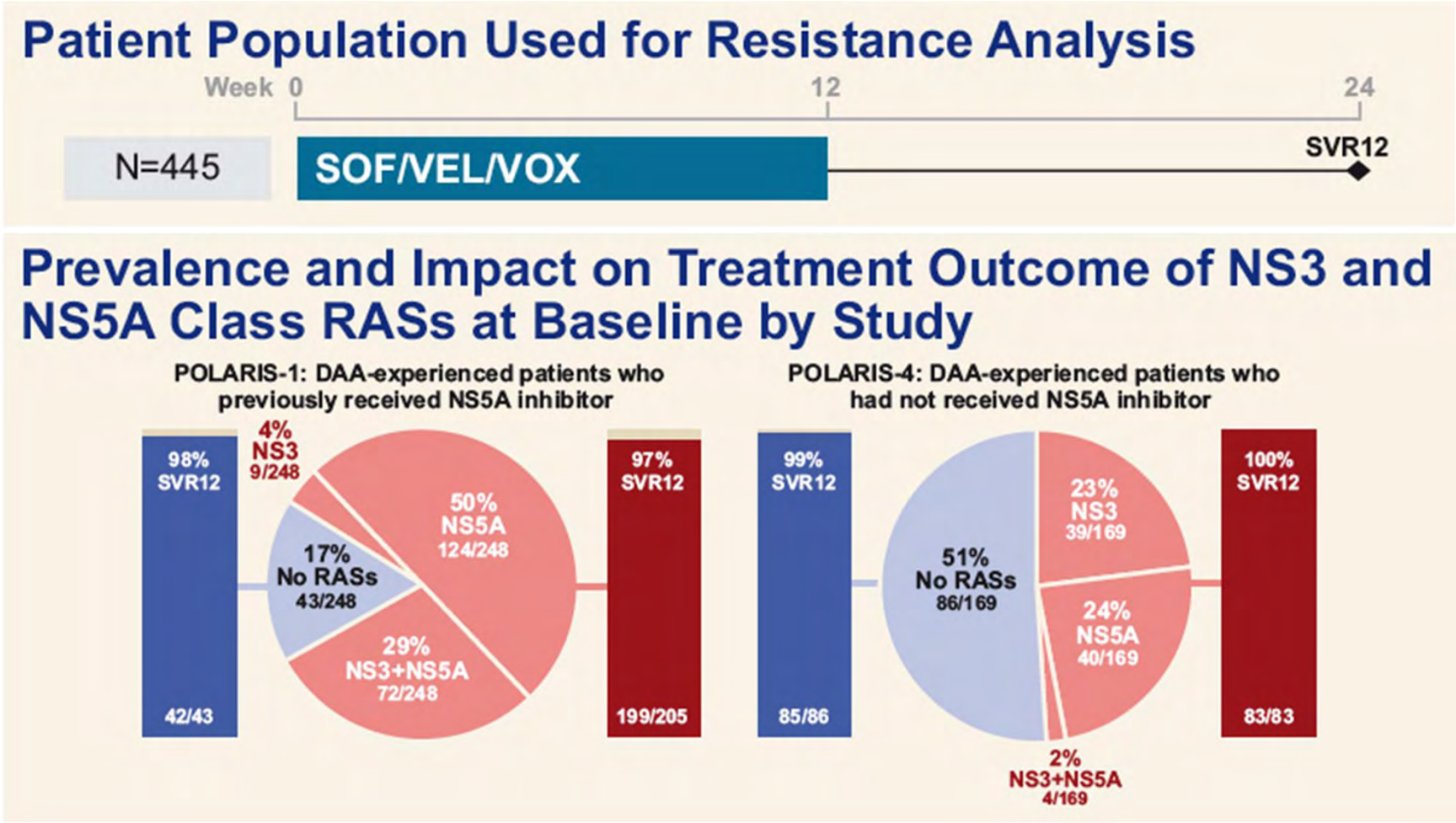
Sofosbuvir/Velpatasvir/Voxilaprevir – DAA-naive Patienten



Whyles D. et al., EASL 2017, Thu-257

Resistenzen

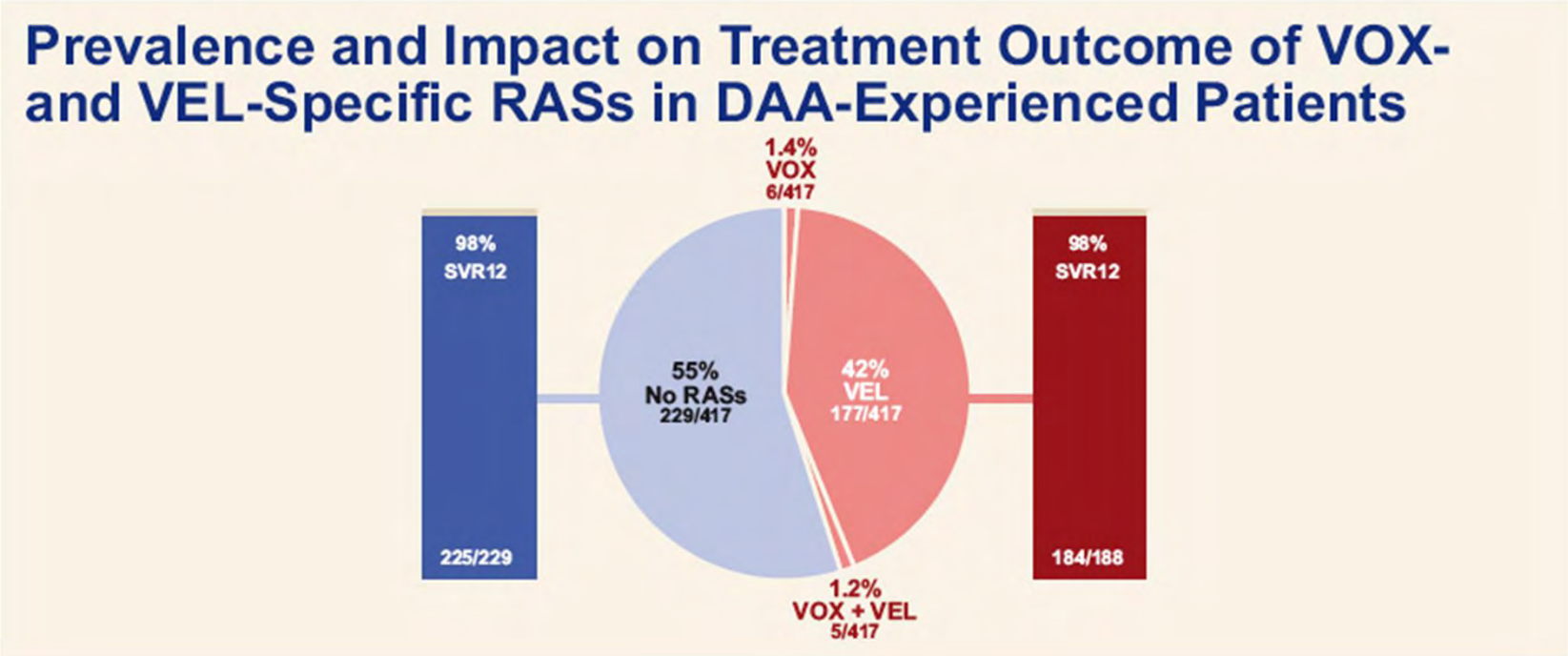
Sofosbuvir/Velpatasvir/Voxilaprevir – DAA-erfahrene Patienten



Sarrazin C et al., EASL 2017, Thu-248

Resistenzen

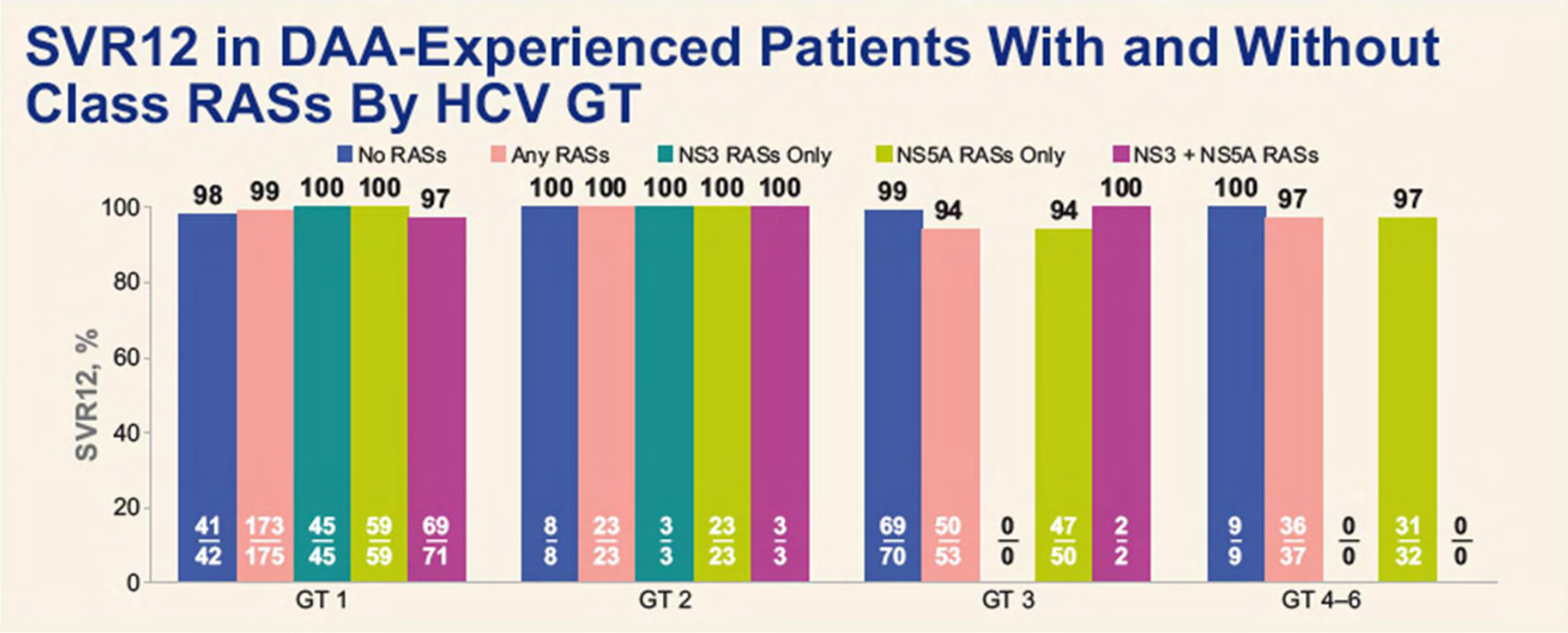
Sofosbuvir/Velpatasvir/Voxilaprevir – DAA-erfahrene Patienten



Sarrazin C et al., EASL 2017, Thu-248

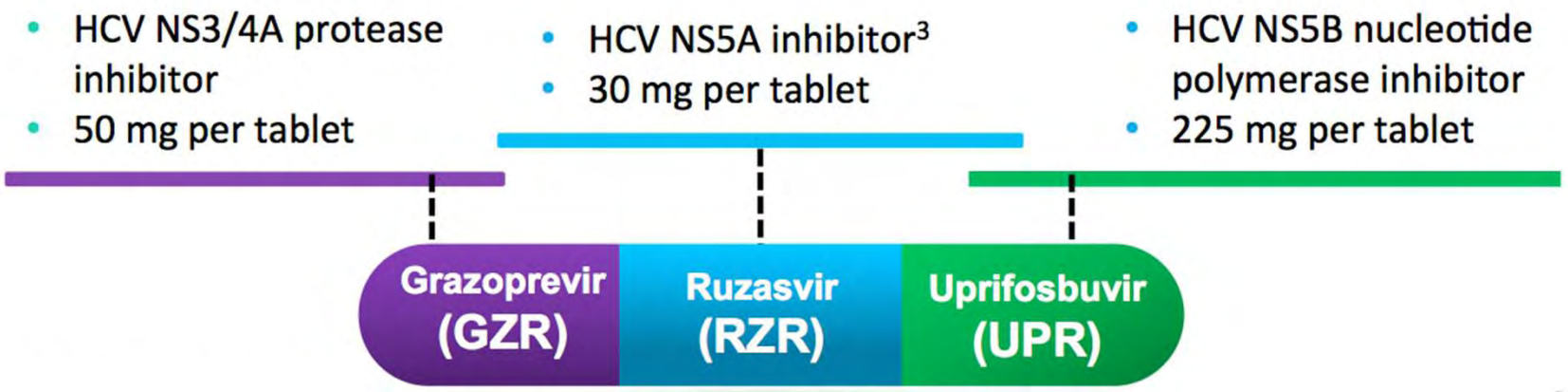
Resistenzen

Sofosbuvir/Velpatasvir/Voxilaprevir – DAA-erfahrene Patienten



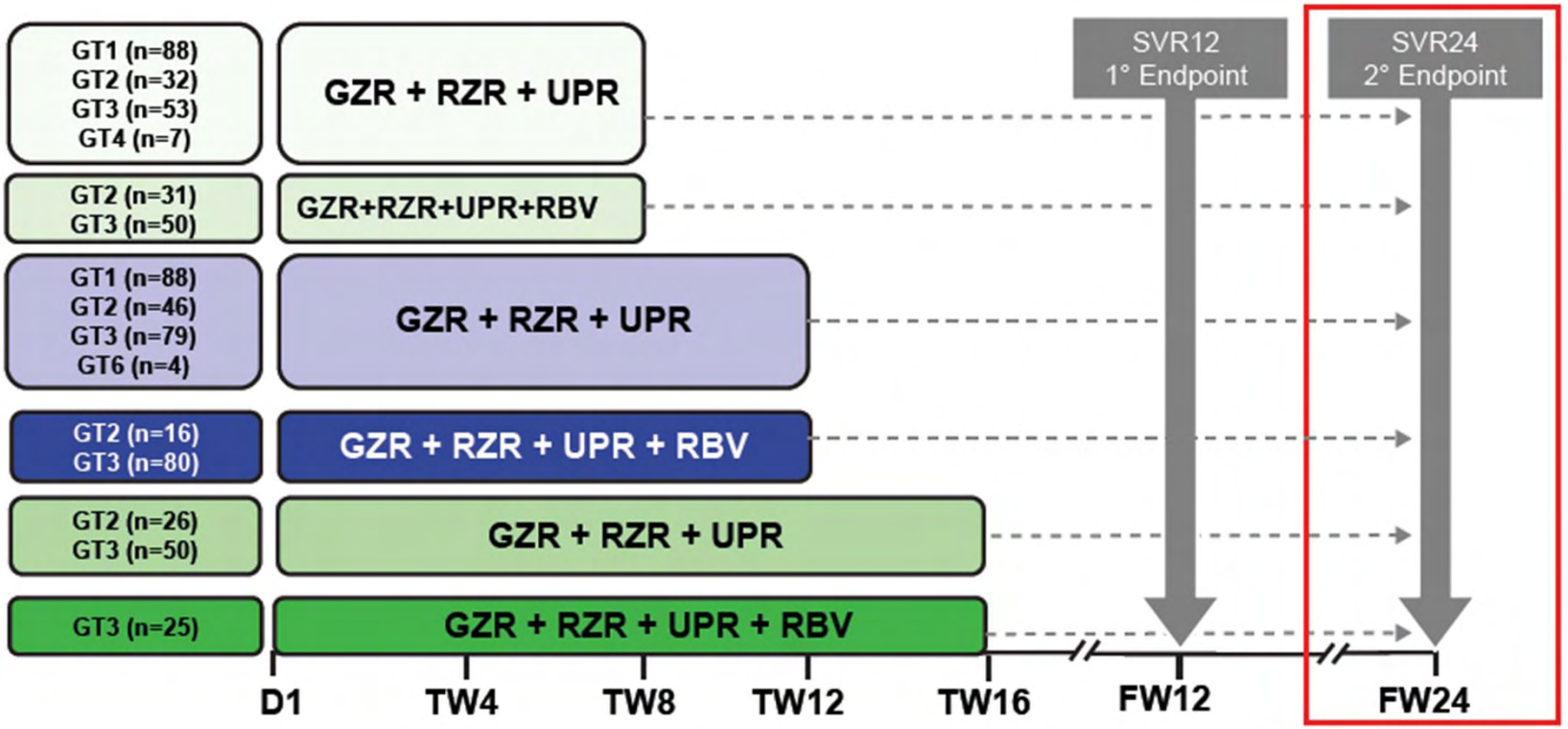
Sarrazin C et al., EASL 2017, Thu-248

Therapie-naïve Patienten
Grazoprevir/Ruzasvir/Uprifosbuvir



Lawitz E et al., EASL 2017, Thu-285

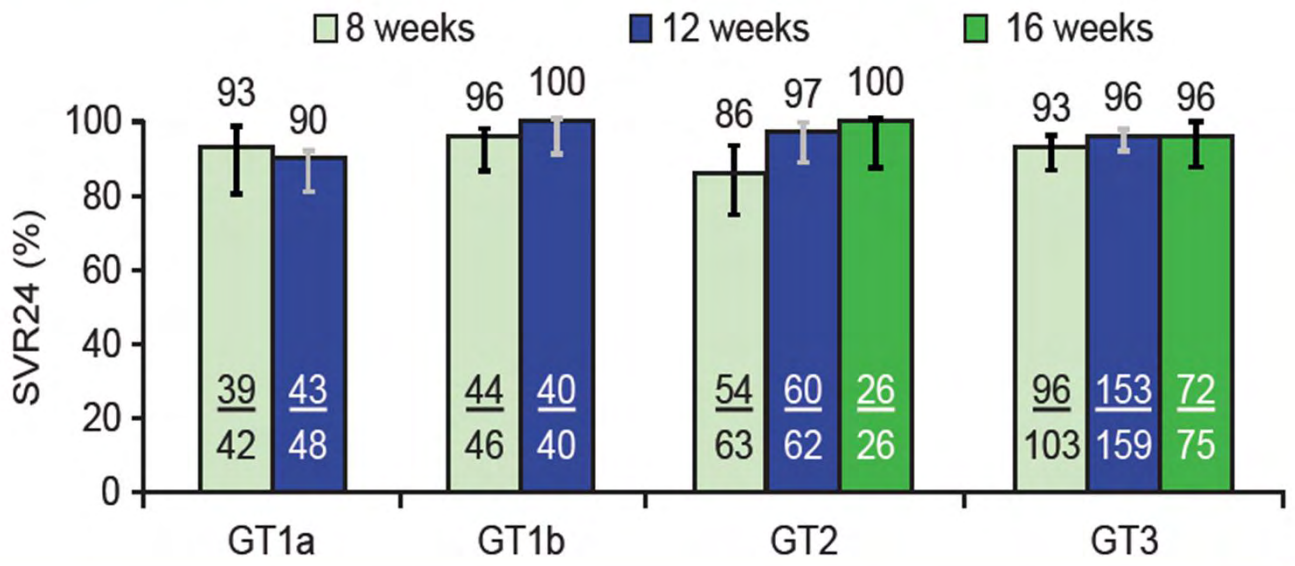
Therapie-naïve Patienten
Grazoprevir/Ruzasvir/Uprifosbuvir



Lawitz E et al., EASL 2017, Thu-285

Therapie-naïve Patienten
Grazoprevir/Ruzasvir/Uprifosbuvir

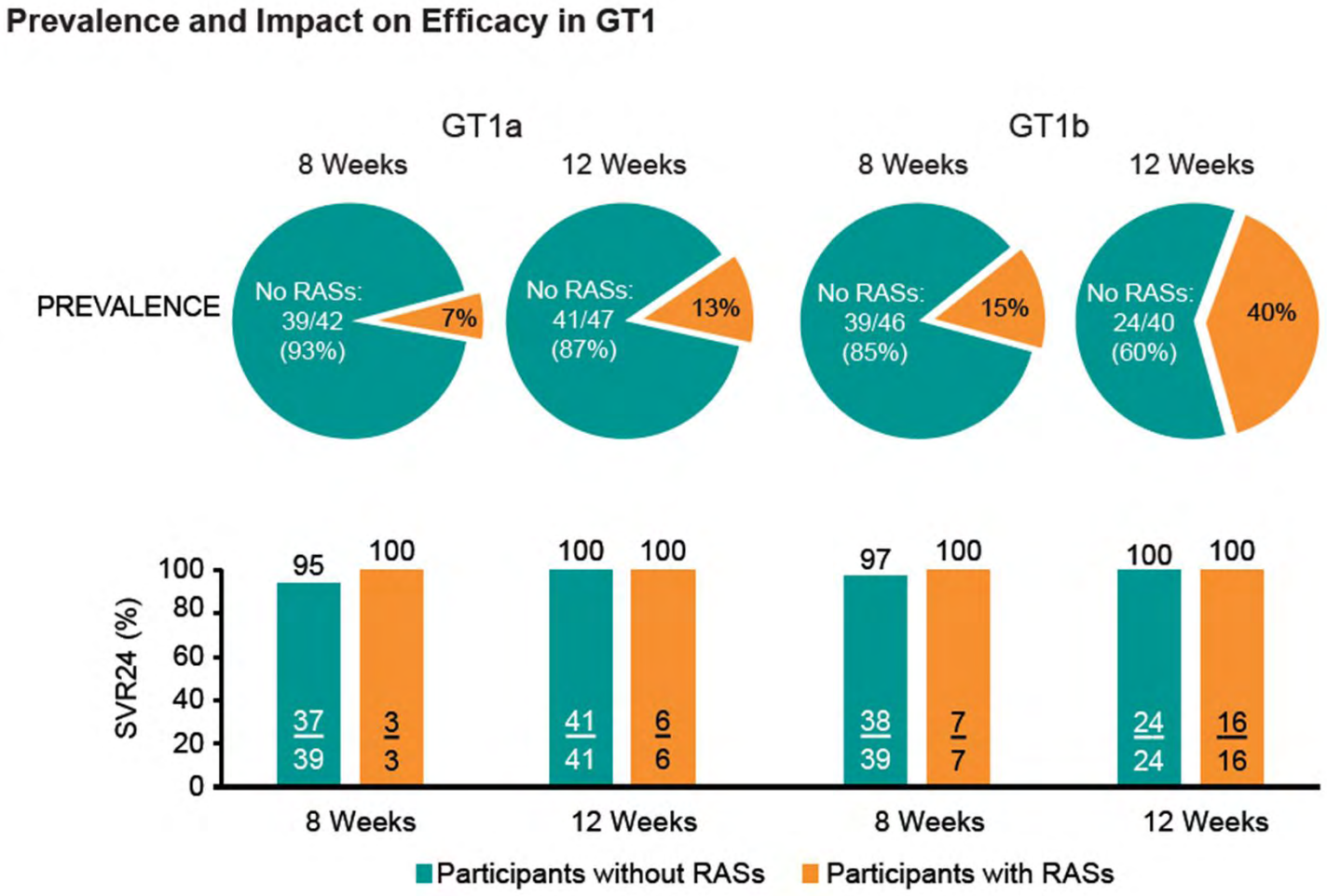
SVR24 (Full Analysis Set) GT1–3: 8, 12, or 16 Weeks



Relapse before FW12*	2	0	1	0	7	0	0	4	3	2
Discontinuation (DR-AE)	0	0	0	0	1	0	0	0	0	0
Reinfection	1	0	0	0	0	0	0	0	0	0
LTFU before FW12	0	1†	0	0	1	1	0	1	1	1
LTFU betw. FW12 & FW24	0	4	1	0	0	1	0	2	2	0

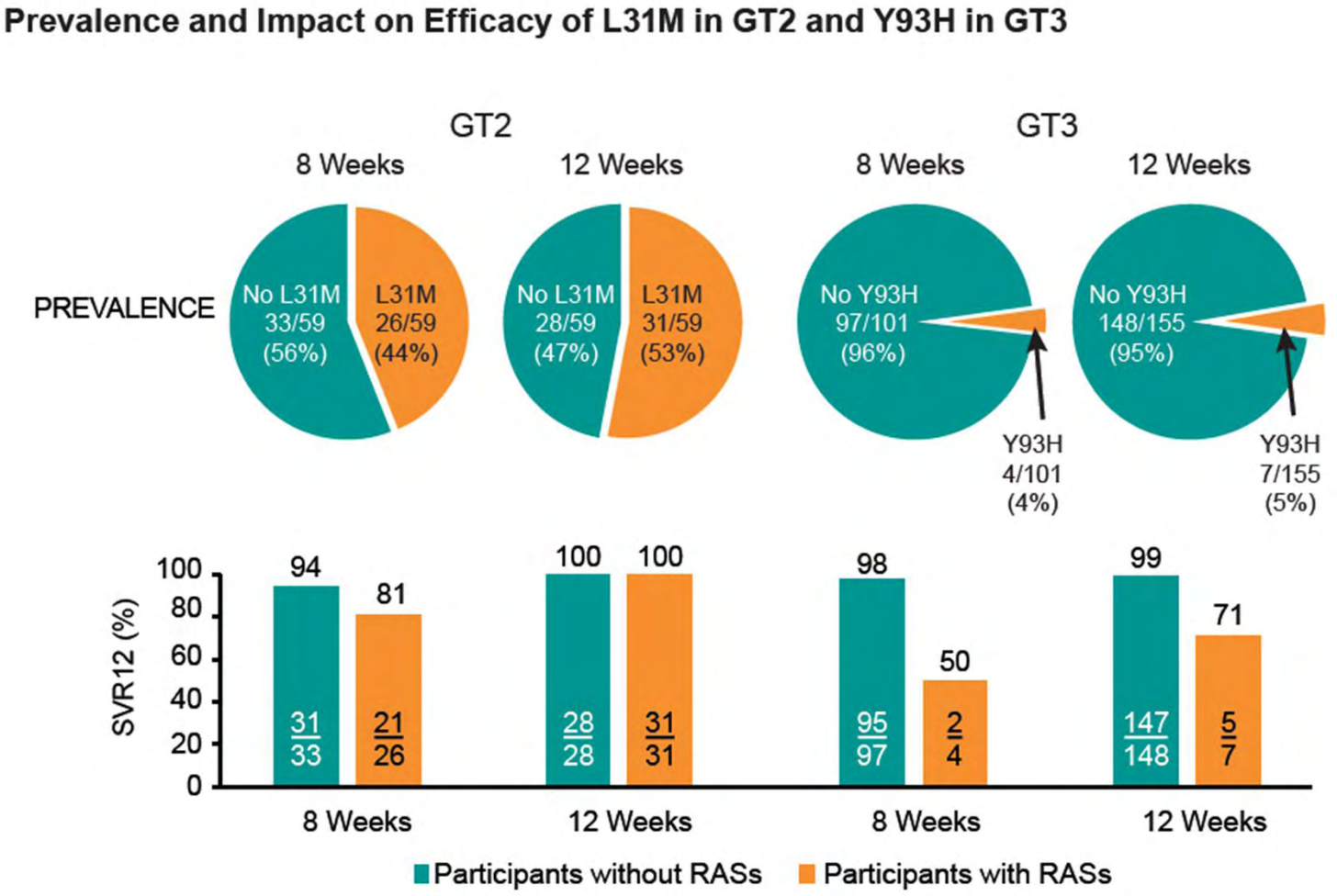
Lawitz E et al., EASL 2017, Thu-285

Therapie-naïve Patienten
Grazoprevir/Ruzasvir/Uprifosbuvir



Lawitz E et al., EASL 2017, Thu-285

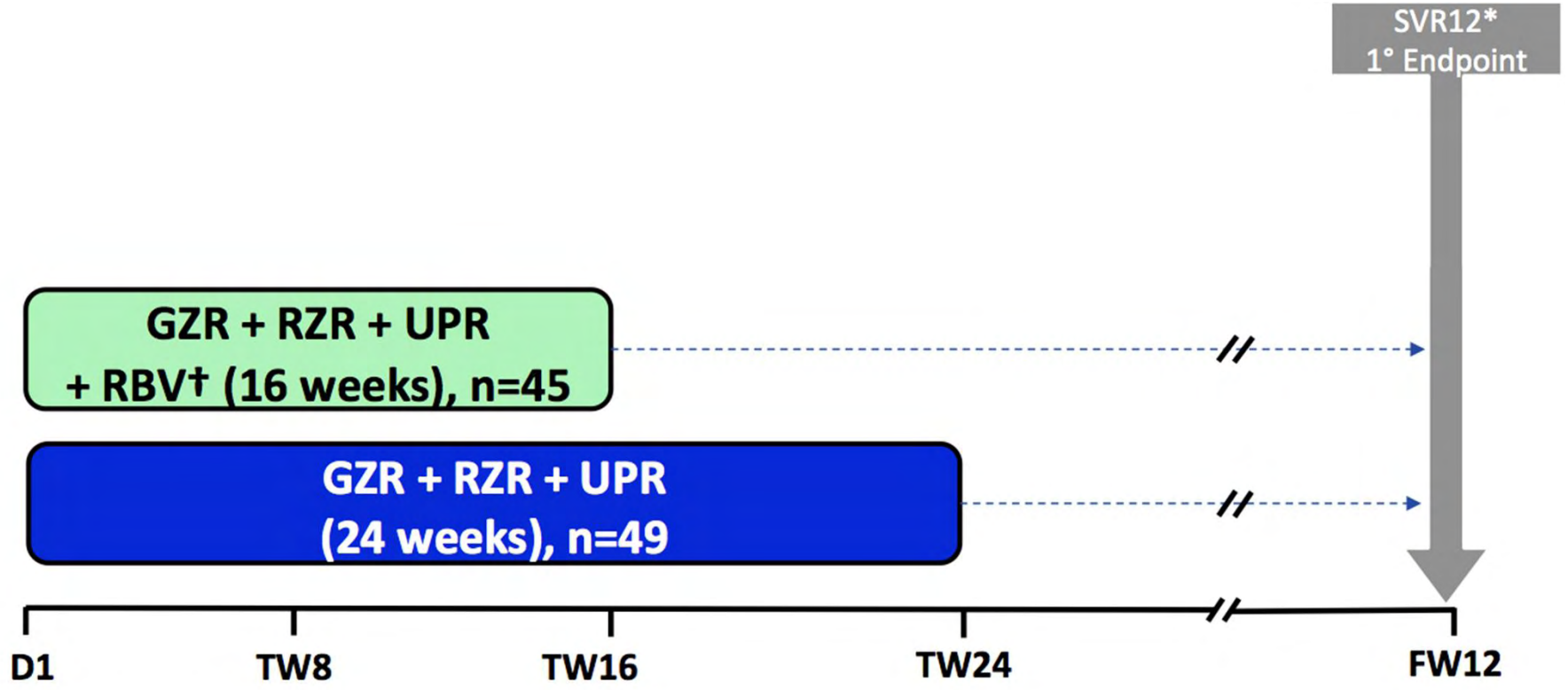
Therapie-naïve Patienten
Grazoprevir/Ruzasvir/Uprifosbuvir



Lawitz E et al., EASL 2017, Thu-285

Re-Therapie von DAA Versagern

Grazoprevir/Ruzasvir/Uprifosbuvir



Wedemeyer H et al., EASL 2017

Re-Therapie von DAA Versagern

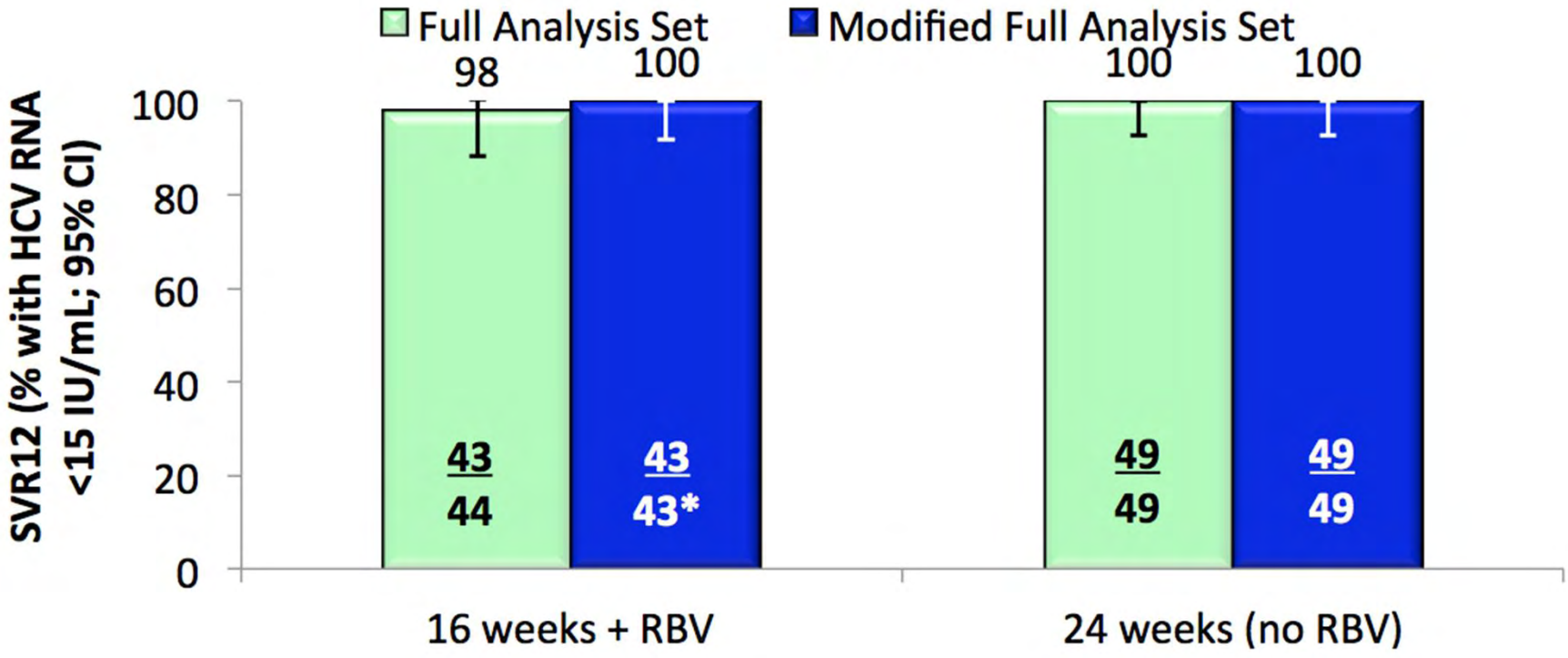
Grazoprevir/Ruzasvir/Uprifosbuvir

Demographics	16 Weeks + RBV, n=44*	24 Weeks without RBV, n=49	Overall GT1 N=93*
Male, n (%)	37 (84)	43 (88)	80 (86)
Age, median years, (range)	61.0 (33 to 70)	60.0 (25 to 71)	60.0 (25 to 71)
Race, White, n (%)	31 (71)	37 (76)	68 (73)
HCV Genotype 1a, n (%)	40 (91)	40 (82)	80 (86)
Non-cirrhotic, n (%)	25 (57)	27 (55)	52 (56)
Cirrhotic, n (%)	19 (43)	21 (43)†	40 (43)
NS5A RASs at baseline, n (%)‡	32 (79)	46 (94)	78 (84)
NS3 RASs at baseline, n (%)‡	25 (57)	35 (71)	60 (65)
Baseline HCV RNA >2,000,000 IU/mL, n (%)	29 (66)	33 (67)	62 (67)
Median baseline HCV RNA (log_{10} IU/mL)	6.5	6.4	6.5
Previously failed:			
12 - 24 weeks of LDV/SOF	26 (59)	31 (63)	57 (61)
8 weeks of LDV/SOF	9 (20)	5 (10)	14 (15)
12 weeks of EBR/GZR	9 (20)	13 (27)	22 (24)

Wedemeyer H et al., EASL 2017

Re-Therapie von DAA Versagern

Grazoprevir/Ruzasvir/Uprifosbuvir



Wedemeyer H et al., EASL 2017

HCV – Alte Hüte

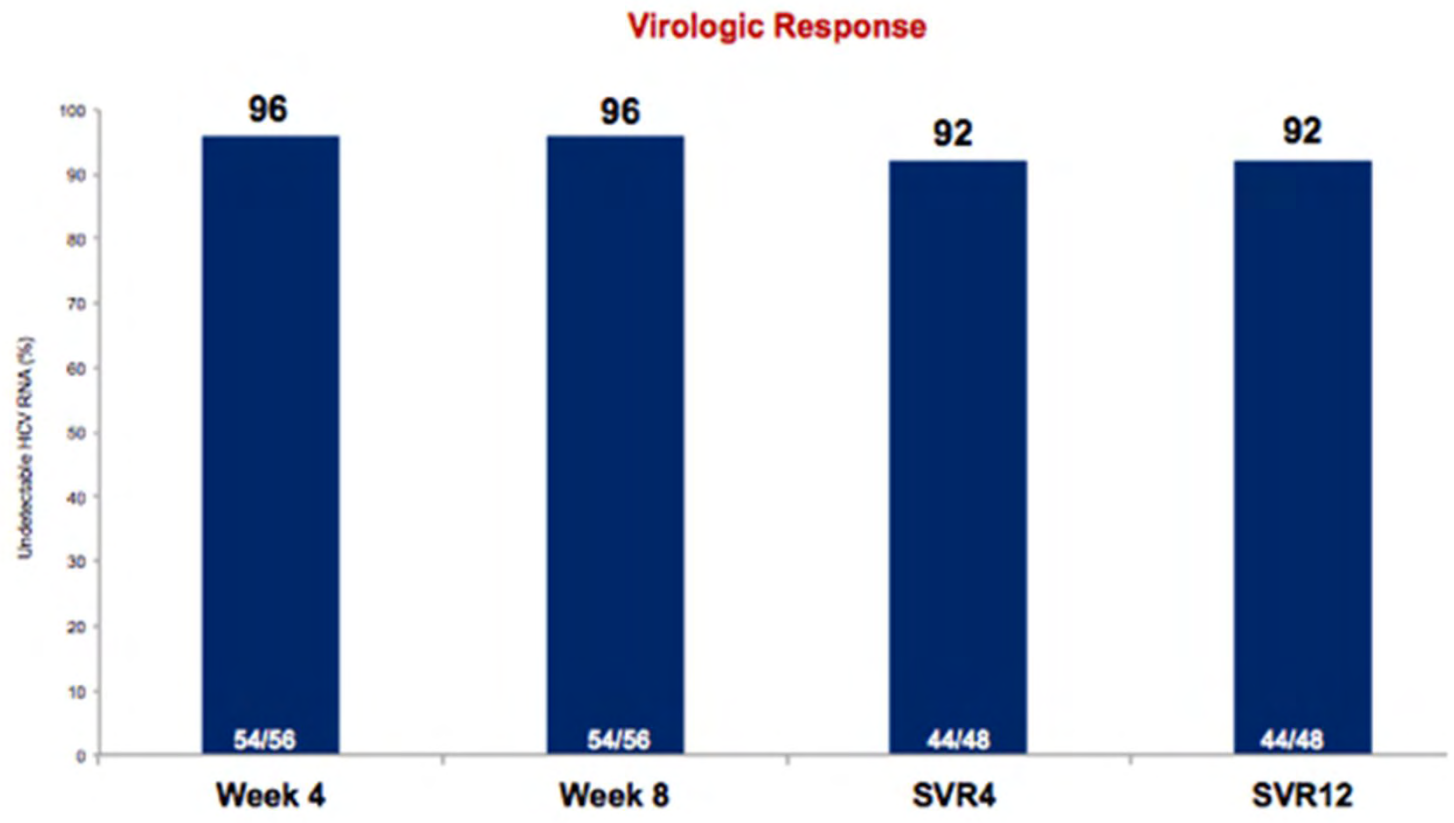
Genotyp 3
8 Wochen SOF/DCV

Demographics and baseline characteristics of the patients

Parameters	Patients (n=56)
Male, n (%)	42 (75)
Mean Age, years (±SD)	48 (11.1)
Mean BMI, Kg/m^2 (±SD)	24.5 (4.6)
Genotype 3	56 (100)
Naïve patients	56 (100)
Median Fibroscan, kPa	7.3
FS <7kPa, n (%)	23 (41)
FS >7 and ≤9.5 kPa, n (%)	28 (50)
FS >9,5 and <12.5kPa, n (%)	5 (9)
Mean HCV RNA, Log_{10} IU/mL	5.65
No NS5A RAS, n (%)* NS5A RAS, n (%)*	26 (93) 2 (7) A30V (n=1); S62L/Y93H (n=1)

Hezode C et al., EASL 2017

Genotyp 3
8 Wochen SOF/DCV



Hezode C et al., EASL 2017

Genotyp 3
8 Wochen SOF/DCV

Patients who failed (relapse in all cases)

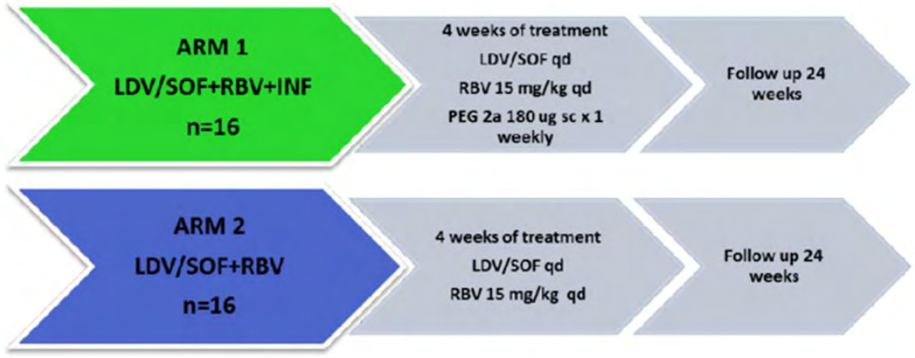
Patients	Age (years)	Gender	Fibroscan (kPa)	HCV RNA (Log_{10} IU/mL)	NS5A RAS Baseline	NSAA RAS Failure
1*	24	M	5.8	6.56	None	NA
2	55	F	8.4	5.95	S62L/Y93H	NA
3	52	M	8.8	6.20	None	A30K, Y93H
4	53	M	9.2	6.25	NA	NA

NA: Not available
*Poor compliance

Hezode C et al., EASL 2017

Genotyp 1-3
4 Wochen SOF/LDV/RBV +/- pegIFN

Randomized controlled trial # open label



All study procedures performed at Odense Drug Treatment Center

Inclusion criteria

- Persons followed in a drug treatment center in the trial
- Chronic hepatitis C
- Age 18-49
- LSM <8 kPa or a liver biopsy with F0 or F1 (Metavir score)
- All HCV genotypes accepted
- Viral load <2.000.000 IU/ml*
- Weight <100 kg or BMI <30
- Compliant as judged by center and study team
- Naïve to all hepatitis C treatment

Exclusion criteria

- Risk of noncompliance
- Insufficient venous access
- Clinical signs of cirrhosis (liver biopsy not required), or cirrhosis suspected by blood tests.
- Contraindication to treatment with study drugs; Autoimmune liver disease
- Unable to understand Danish
- Co-infection with Hepatitis B or HIV
- Any other significant clinical illness deemed to interfere with response to treatment

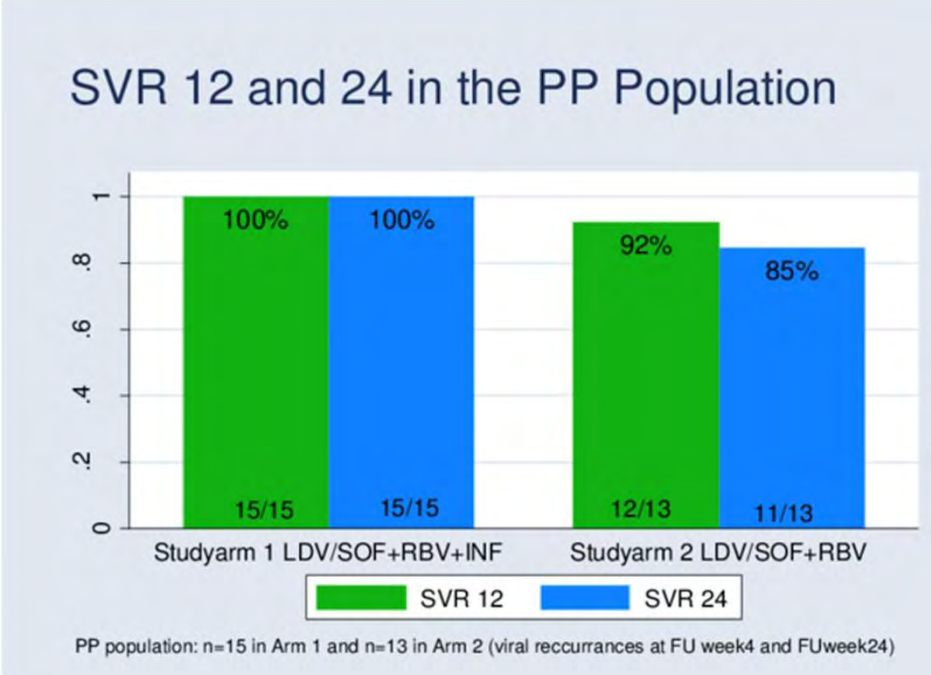
Oevrehus ALH et al., EASL 2017, Thu-225

Genotyp 1-3
4 Wochen SOF/LDV/RBV +/- pegIFN

Baseline values and demographics		Arm 1 LDV/SOF/RBV +PEG 2a n= 16	Arm 2 LDV/SOF/RBV n= 16	p
Age, mean (95% CI)		39.0 (35.8- 42.2)	38.5 (36.1- 40.9)	0.77
Sex	Male	14	11	0.37
	Female	2	5	
Genotype	1a	2	6	0.05
	1b	2	3	for
	2	0	1	genotype
	3	12	6	1 vs 3
Weight in kilograms, mean(95% CI)		76 (66,5-82,5)	76 (68,5-86,5)	0.77
BMI mean kg/m^2(95% CI)		23.4 (21.5- 25.3)	24.5 (22.7- 26.3)	0.43
IL28b subtype	CC	3	6	0.24
	CT/TT	13	10	
Viral load (x10^3 IU/ml) at screen, mean(95% CI)		169.5 (7.54-1140)	149.5 (7.05-1730)	0.57
Fibroscan in kPa, Median(range)		5.3 (3.5-7.9)	5.1 (3.6-7.9)	0.90
Baseline blood tests	Hemoglobin mmol/L	9. 5 (7.1-10.7)	8.9 (6.4-9.8)	0.07
Median(range)	Neutrophils x 10^9/L	4.4 (2.2- 12.2)	5.6 (1.8-11.2)	0.26
	Platelets x 10^9/L	237 (152- 332)	256 (167-364)	0.14
	ALT IU/L	68 (26 -205)	50 (31-183)	0.41
	Bilirubin umol/L	8.5 (5 -22)	6.5 (3-18)	0.08
	Albumin g/L	43 (39-49)	42.0 (39-46)	0.13

Oevrehus ALH et al., EASL 2017, Thu-225

Genotyp 1-3
4 Wochen SOF/LDV/RBV +/- pegIFN



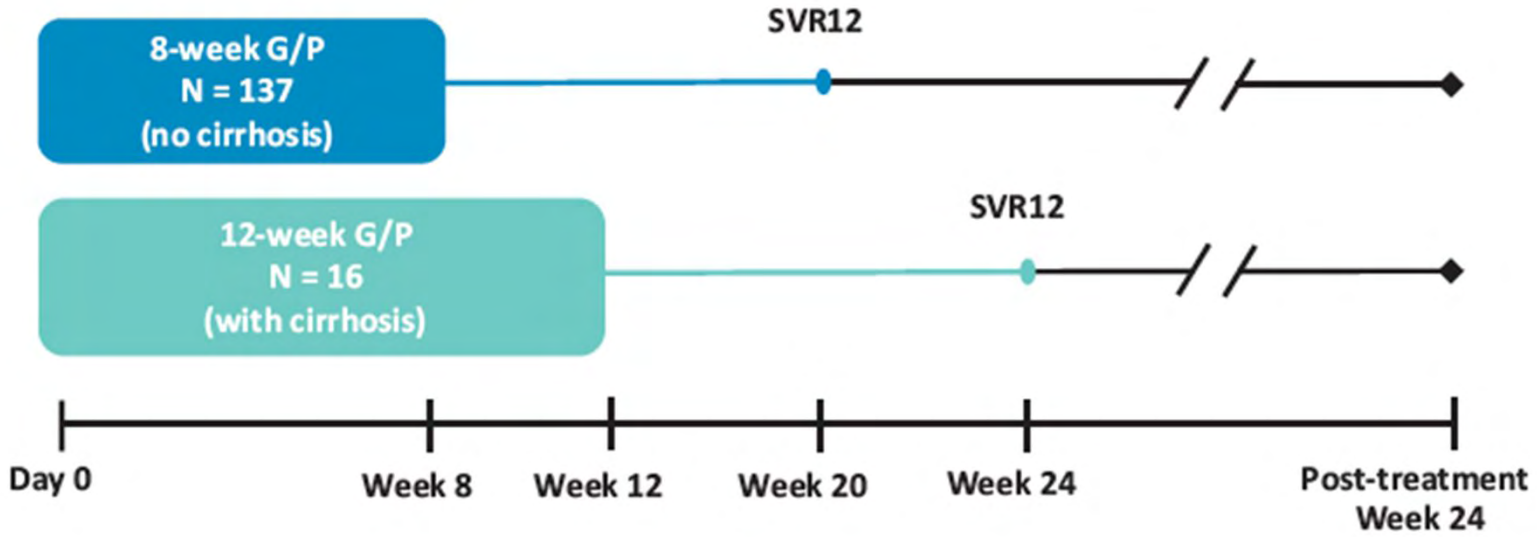
Pt no	Age, year	Sex	Genotype at Baseline	Genotype at Recurrence	Treatment	Doses received LDV/SOF	Recurrence	Adherent to protocol	NS5A RAS at baseline/ follow-up	Reinfection likely
1	42	M	2a/2b	2a	LDV/SOF+RBV	28	FU week 4	Yes	L31M/L31M	No
2	27	M	3a	3a	LDV/SOF+RBV+INF	27+3 INF	FU week 64	No	None/None	Yes
3	40	F	3a	3a	LDV/SOF+RBV	21	FU week 6	No	None/None	No
4	37	M	1a	1a	LDV/SOF+RBV	28	FU week 24	Yes	None/None	Yes
5	41	M	3	-	LDV/SOF+RBV	21	SVR 4 –LTFU	No	NA	-
6	34	F	3	.	LDV/SOF+RBV	1	Died day 10	No	NA	-

* Was genotype 2a/2b at baseline and 2a at recurrence – probably selection

Oevrehus ALH et al., EASL 2017, Thu-225

HCV – Koinfektion

HIV-Ko-Infektion
Glecaprevir/Pibrentasvir



Rockstroh J. et al., EASL 2017, LBP-522

HIV-Ko-Infektion
Glecaprevir/Pibrentasvir

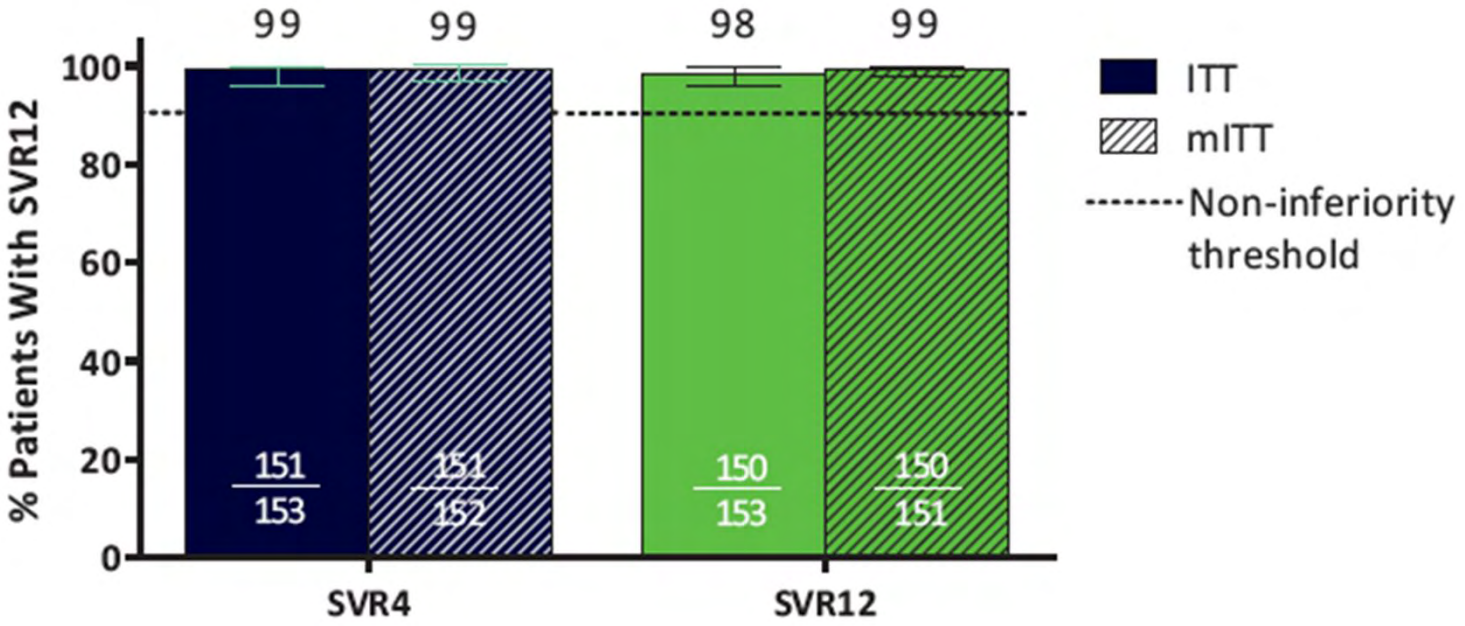
- Antiretroviral therapy (ART) naïve with CD4+ count ≥500 cells/mm^3 or ≥29% *or*
- On a stable ART regimen for at least 8 weeks prior to screening, with CD4+ count ≥200 cells/mm^3 or ≥14%, and plasma HIV-1 RNA <LLOQ:

Allowed ART Anchor Agents (all patients)	Raltegravir (RAL) BID
	Dolutegravir (DTG) QD or BID
	Rilpivirine (RPV) QD
	Elvitegravir/cobicistat (EVG/COBI) QD
Allowed ART Regimens (patients without cirrhosis)	Darunavir (DRV) + ritonavir (r) QD
	DRV/COBI QD
	Lopinavir/r BID
Allowed N(t)RTI Backbone (all patients)	Tenofovir disoproxil fumarate (TDF)
	Tenofovir alafenamide (TAF)
	Abacavir (ABC)
	Emtricitabine (FTC)
	Lamivudine (3TC)

ART, antiretroviral therapy; BID, twice-daily; QD, once-daily; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor.

Rockstroh J. et al., EASL 2017, LBP-522

HIV-Ko-Infektion
Glecaprevir/Pibrentasvir



	SVR4	SVR12
Breakthrough	1	1
Relapse	0	0
Missing Data	0	1*
Discontinued	1	1

Rockstroh J. et al., EASL 2017, LBP-522

HIV-Ko-Infektion

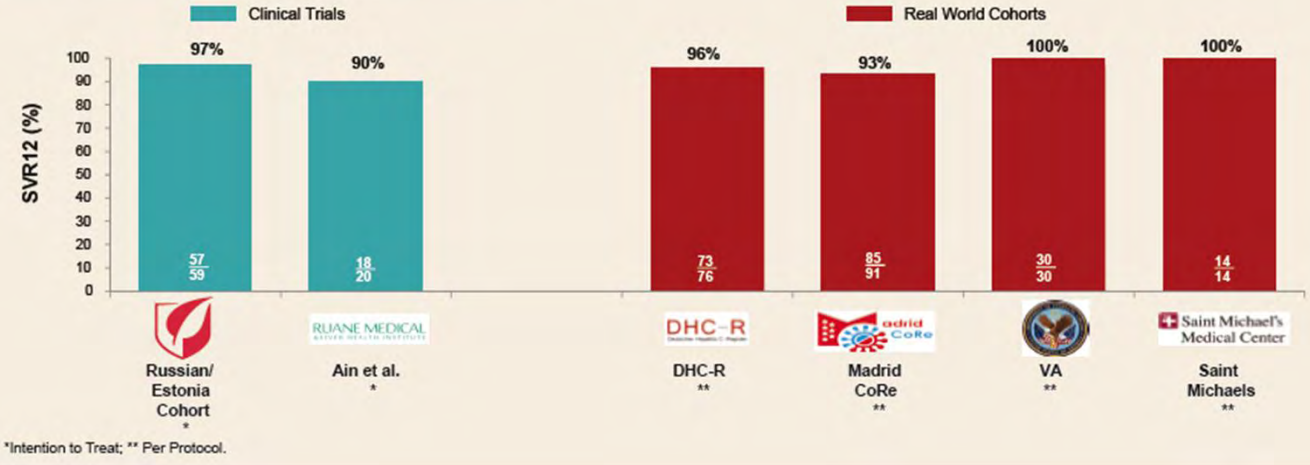
Sofosbuvir/Ledipasvir – 8 Wochen

Baseline Demographics

Characteristic	Russian/Estonia Cohort N=59	Ruane Medical N=20	DHC-R N=76	Madrid-CoRe N=93	VA N=31	Saint Michaels N=15
Mean age, years (range)	34 (23-58)	52 (35-66)	43 (24-67)	49 (45-53)	61 (49-73)	61 (41-77)
Male, n (%)	34 (58)	18 (90)	67 (88)	70 (75)	31 (100)	12 (80)
Race, n (%)						
White	59 (100)	11 (55)	73 (96)	93 (100)	9 (2)	1 (7)
Non-White	0	9 (45)	3 (4)	0	22 (71)	14 (93)
Tx Experienced, n (%)	0	0	58 (76)	0	0	0
Cirrhosis, n (%)	0	0	3 (4)	0	7 (23)	0
Mean HCV RNA $\log_{10}$ IU/mL	6.1	6.0	5.6*	5.9	6.1	1.4
Median CD4 count (range)	531 (417-1006)	514 (106-1038)	400 (200-400)**	N/A	553 (186-1131)	578 (226-1318)
On HIV ARVs, n (%)	49 (83)	19 (95)	69 (91)	89 (95)	30 (97)	14 (93)
TDF-containing regimen, n (%)	21 (36)	15 (75)	49 (64)	N/A	22 (71)	3 (20)
GT 1a, n (%)	15 (25)	17 (85)	64 (84)	67 (72)	21 (68)	9 (60)
GT 1b, n (%)	44 (75)	3 (15)	7 (9)	20 (22)	8 (26)	6 (40)
Unspecified GT 1/ Other, n (%)	0	0	3 (4) / 2 (3)	6 (6)	2 (6)	0

* Data available for 75 patients; ** Data available for 60 patients

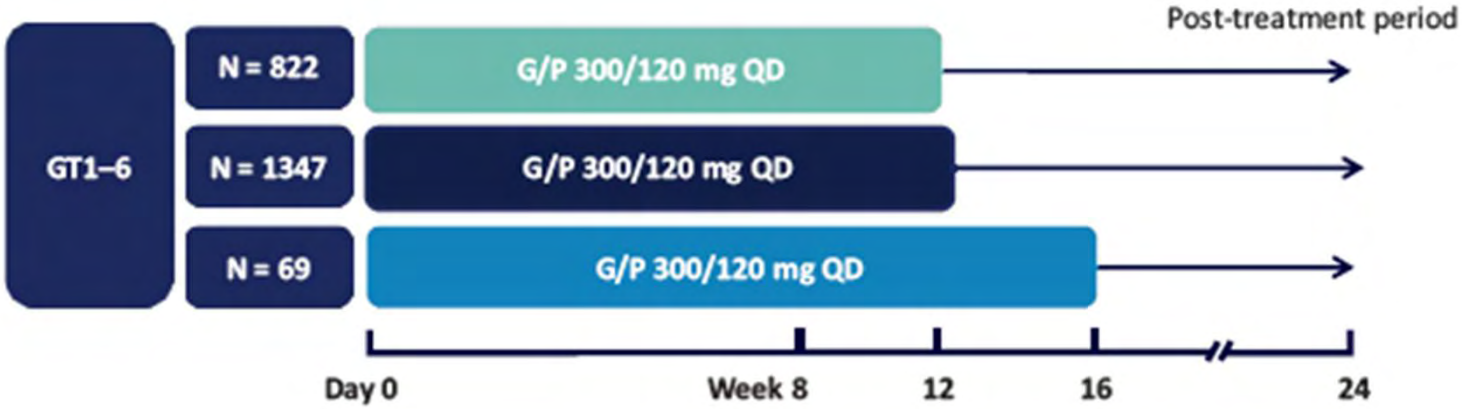
SVR12 in HIV/HCV GT 1 Coinfected Patients Treated with LDV/SOF for 8 weeks: Clinical Trials Compared to Real-World Cohorts



Buggisch P. et al., EASL 2017, SAT-253

HCV – Niereninsuffizienz

Niereninsuffizienz
Glecaprevir/Pibrentasvir



Pol S et al., EASL 2017, SAT-273

Niereninsuffizienz
Glecaprevir/Pibrentasvir

Characteristic, n (%)	CKD 1 n = 1054	CKD 2 n = 1045	CKD 3 n = 36	CKD 4–5 n = 103	Total N = 2238
Baseline HCV RNA level					
≥6 000 000 IU/mL	207/220 (94)	238/248 (96)	12/12 (100)	8/8 (100)	465/488 (95)
<6 000 000 IU/mL	821/834 (98)	786/797 (99)	23/24 (96)	93/95 (98)	1723/1750 (99)
Treatment duration					
8 weeks	378/392 (96)	407/413 (99)	16/17 (94)	0	801/822 (97)
12 weeks	622/633 (98)	581/593 (98)	18/18 (100)	101/103 (98)	1322/1347 (98)
16 weeks	28/29 (97)	36/39 (92)	1/1 (100)	0	65/69 (94)
Treatment-naive, n (%)	764/786 (97)	746/757 (99)	24/25 (96)	58/60 (97)	1592/1628 (98)
Treatment-experienced, n (%)	264/268 (99)	278/288 (97)	11/11 (100)	43/43 (100)	596/610 (98)
Cirrhosis status					
Yes	127/129 (98)	112/115 (97)	8/8 (100)	18/20 (90)	265/272 (97)
No	901/925 (97)	912/930 (98)	27/28 (96)	83/83 (100)	1923/1966 (98)
IL28B					
CC	361/372 (97)	325/332 (98)	15/15 (100)	24/24 (100)	725/743 (98)
non-CC	666/681 (98)	699/713 (98)	20/21 (95)	77/79 (98)	1462/1494 (98)
Missing	1/1 (100)	N/A	N/A	N/A	1/1 (100)
Presence of polymorphisms					
NS5A	176/183 (96)	177/184 (96)	5/5 (100)	17/17 (100)	375/389 (96)
NS3	15/17 (88)	17/17 (100)	1/1 (100)	1/1 (100)	34/36 (94)
Haemodialysis					
Yes	N/A	N/A	N/A	83/85 (98)	83/85 (98)
No	1028/1054 (98)	1024/1045 (98)	35/36 (97)	18/18 (100)	2105/2153 (98)

Pol S et al., EASL 2017, SAT-273

Niereninsuffizienz
Glecaprevir/Pibrentasvir

Event	CKD 1 n = 1054	CKD 2 n = 1045	CKD 3 n = 36	CKD 4–5 n = 103	Total N = 2238
Any AE, n (%)	712 (68)	698 (67)	23 (64)	74 (72)	1507 (67)
AEs occurring in ≥10% of patients, n (%)					
Nausea	111 (11)	78 (8)	7 (19)	12 (12)	208 (9)
Fatigue	154 (15)	158 (15)	4 (11)	15 (15)	331 (15)
Headache	204 (19)	174 (17)	4 (11)	9 (9)	391 (18)
Nasopharyngitis	58 (6)	39 (4)	4 (11)	2 (2)	103 (5)
Vomiting	20 (2)	21 (2)	4 (11)	7 (7)	52 (2)
Pruritus	35 (3)	61 (6)	2 (6)	21 (20)	119 (5)
Any SAE	25 (2)	17 (2)	3 (8)	25 (24)	70 (3)
DAA-related SAE	0	1 (<0.1)	0	0	1 (<0.1)
Any AE leading to discontinuation of study drug	4 (0.4)	3 (0.3)	1 (3)	4 (4)	12 (0.5)
Any fatal AE	1 (<0.1)	0	1 (3)	1 (1)	3 (0.1)
Death*†	3 (0.3)	1 (<0.1)	1 (3)	1 (1)	6 (0.3)

Pol S et al., EASL 2017, SAT-273

Niereninsuffizienz
Glecaprevir/Pibrentasvir

Event	CKD 1 n = 920	CKD 2 n = 905	CKD 3 n = 31	CKD 4–5 n = 18	Total N = 1874
Mean change in eGFR (mL/min/1.73m²) from baseline to final post-treatment visit	-6.02 ± 14.13	0.62 ± 10.21	7.73 ± 9.49	-0.82 ± 2.29	-2.54 ± 12.74

		GLE $AUC_{24,ss}$ ng*h/mL		PIB $AUC_{24,ss}$ ng*h/mL	
CKD Stage	N*	Geometric Mean (Mean, %CV)	Central Value Ratio (90% Confidence Interval) vs CKD Stage 1	Geometric Mean (Mean, %CV)	Central Value Ratio (90% Confidence Interval) vs CKD Stage 1
1	1050	5120 (9040, 189)	—	1390 (1590, 58)	—
2	1042	5490 (9290, 158)	1.07 (1.00 to 1.15)	1510 (1720, 56)	1.08 (1.04 to 1.12)
3–4	48	8320 (16600, 156)	1.63 (1.29 to 2.06)	1540 (1870, 65)	1.11 (0.98 to 1.25)
5	91	9490 (18200, 175)	1.85 (1.56 to 2.20)	2090 (2580, 76)	1.50 (1.37 to 1.65)

Pol S et al., EASL 2017, SAT-273

HCV

Direkt antivirale Substanzen

Pangenotypische Wirksamkeit

Proteaseinhibitor	NS5A-Inhibitor	Nukleotidischer Polymeraseinhibitor	Nicht-nukleotidischer Polymeraseinhibitor
Simeprevir		Sofosbuvir	
	Daclatasvir	Sofosbuvir	
	Ledipasvir	Sofosbuvir	
Paritaprevir	Ombitasvir		Dasabuvir
	Velpatasvir	Sofosbuvir	
Grazoprevir	Elbasvir		
Glecaprevir	Pibrentasvir		2017
Voxilaprevir	Velpatasvir	Sofosbuvir	
Grazoprevir	Ruzasvir	Uprifosbuvir	2018

HCV

Direkt antivirale Substanzen

Einsetzbar bei Niereninsuffizienz

Proteaseinhibitor	NS5A-Inhibitor	Nukleotidischer Polymeraseinhibitor	Nicht-nukleotidischer Polymeraseinhibitor
Simeprevir		Sofosbuvir	
	Daclatasvir	Sofosbuvir	
	Ledipasvir	Sofosbuvir	
Paritaprevir	Ombitasvir		Dasabuvir
	Velpatasvir	Sofosbuvir	
Grazoprevir	Elbasvir		
Glecaprevir	Pibrentasvir		2017
Voxilaprevir	Velpatasvir	Sofosbuvir	
Grazoprevir	Ruzasvir	Uprifosbuvir	2018

HCV

Direkt antivirale Substanzen

Einsetzbar bei Resistenzen

Proteaseinhibitor	NS5A-Inhibitor	Nukleotidischer Polymeraseinhibitor	Nicht-nukleotidischer Polymeraseinhibitor
Simeprevir		Sofosbuvir	
	Daclatasvir	Sofosbuvir	
	Ledipasvir	Sofosbuvir	
Paritaprevir	Ombitasvir		Dasabuvir
	Velpatasvir	Sofosbuvir	
Grazoprevir	Elbasvir		
Glecaprevir	Pibrentasvir		2017
Voxilaprevir	Velpatasvir	Sofosbuvir	
Grazoprevir	Ruzasvir	Uprifosbuvir	2018

HCV – HBV-Reaktivierung

HBV-Reaktivierung

FDA Sammlung der post-Marketing Fälle

- N=24 Fälle mit Re-Aktivierung
- N=2 mit letalem Ausgang
- N=1 musste transplantiert werden

Zur Baseline:

- N=7 mit messbarer Viruslast
- N=4 HBsAg positiv
- N=3 HBsAg negativ
- Für die übrigen liegen keine Daten vor

Bersoff-Matcha SJ et al., AASLD 2016, #LB17

HBV-Reaktivierung

- 242 patients exposed to HCV treatment had evidence of chronic/inactive HBV infection prior to HCV treatment start
  - Diagnosis of chronic HBV infection or HBV carrier status: N=115
  - Lab evidence of HBcAb positivity with concomitant HBsAg negativity: N=127

Table 1: Observed rates of HBV re-activation (per 100 PY) during exposure to HCV treatment

HCV treatment exposure	N patients[a]	Follow-up time (PY)[a]	N events	Event rate per 100 PY (95% CI)
SOF containing - total	144	22.75	2	8.8 (1.1-31.8)
SOF without IFN	135	21.52	2	9.3 (1.1-33.6)
SOF w IFN	10	1.23	0	0 (-)
Non-SOF - total	105	17.54	8	45.6 (19.7-89.9)
Non-SOF IFN-free DAA[b]	13	1.60	1	62.7 (1.6-349.1)
Non-SOF 1st gen DAA (w IFN)[c]	21	3.54	0	0 (-)
IFN/RBV without SOF or other DAAs[d]	80	12.40	7	56.4 (22.7-116.3)

a. Subgroup N's may not add up to total N's because analysis was done on a treatment-era level basis (using PY of exposure) rather than on a patient-level basis. For example, a patient with exposure to Sovaldi ® with IFN, followed by exposure to Harvoni ® without IFN, will have person time in both the "SOF without IFN" and "SOF with IFN" rows, and be counted in the patient count of each row.
b. Includes non-SOF-based HCV regimens containing second-generation DAA products such as Viekira Pak ®, Technivie ®, and Zepatier ®. Of note: all person time observed in this stratum occurred without concomitant IFN.
c. Includes non-SOF-based HCV regimens containing IFN with first-generation DAAs telaprevir and/or boceprevir.
d. Includes IFN/RBV-based regimens without SOF or other DAAs (first or second generation)

Chokkalingam AP et al., EASL 2017, Thu-218

HBV-Reaktivierung

- 242 patients exposed to HCV treatment had evidence of chronic/inactive HBV infection prior to HCV treatment start
  - Diagnosis of chronic HBV infection or HBV carrier status: N=115
  - Lab evidence of HBcAb positivity with concomitant HBsAg negativity: N=127

Table 2: Incidence rate ratios estimating risk of HBV reactivation associated with exposure to SOF-containing HCV treatment

Exposure	IRR		P-value
	IRR	(95% CI)	
Exposure to total SOF-containing HCV treatment	0.19	(0.04-0.93)	0.0399
Exposure to total non-SOF containing HCV treatment	1.00	(ref)	
Exposure to IFN-free SOF-containing HCV treatment	0.16	(0.03-0.77)	0.0225
Exposure to non-SOF, non-DAA based HCV treatment exposure (IFN/RBV-based)	1.00	(ref)	

Chokkalingam AP et al., EASL 2017, Thu-218

HBV-Reaktivierung

		LDV/SOF 12 weeks N=111
HCV	Mean age, y (range)	55 (32–76)
	Male, n (%)	42 (38)
	Mean BMI, kg/m^2 (range)	25 (17–34)
	IL28B CC, n (%)	85 (77)
	GT 1 / GT 2, n (%)	68 (61) / 43 (39)
	HCV treatment experienced, n (%)	37 (33)
	Mean baseline HCV RNA, $\log_{10}$ IU/mL (range)	5.9 (3.8–7.1)
	Cirrhosis, n (%)	18 (16)
	Mean ALT, U/L (range)	68 (17–281)
HBV	HBsAg positive, n (%)	110* (99)
	HBeAg positive, n (%)	1 (<1)
	GT B/ GT C n (%)	37 (33) / 5 (5)
	GT Missing†	69 (62)
	HBV treatment experienced, n (%)	5 (4)
	Mean baseline HBV DNA, $\log_{10}$ IU/mL (range)	2.1 (1.3–5.8)
	Baseline HBV DNA <LLOQ, n (%)	37 (33)

*1 patient changed HBsAg status between screening and baseline; †HBV genotype could not be determined if HBV DNA <5000 IU/mL.

Liu CJ et al., EASL 2017

HBV-Reaktivierung

n, %	Overall N=111	BL HBV DNA <LLOQ n=37	BL HBV DNA ≥LLOQ n=74
Increase to ≥LLOQ	31 (28)	31 (84)	—
+ ALT >2x ULN	0	0	—
Increase >1 – <2 $\log_{10}$ IU/mL	37 (33)	11 (30)	26 (35)
+ ALT >2x ULN	1 (<1)	0	1 (1)
Increase ≥2 $\log_{10}$ IU/mL (any visit)	24 (22)	11 (30)	13 (18)
+ ALT >2x ULN	4 (4)	0	4 (5)

- No patient had AEs of jaundice, liver decompensation, liver failure or liver transplant

Liu CJ et al., EASL 2017

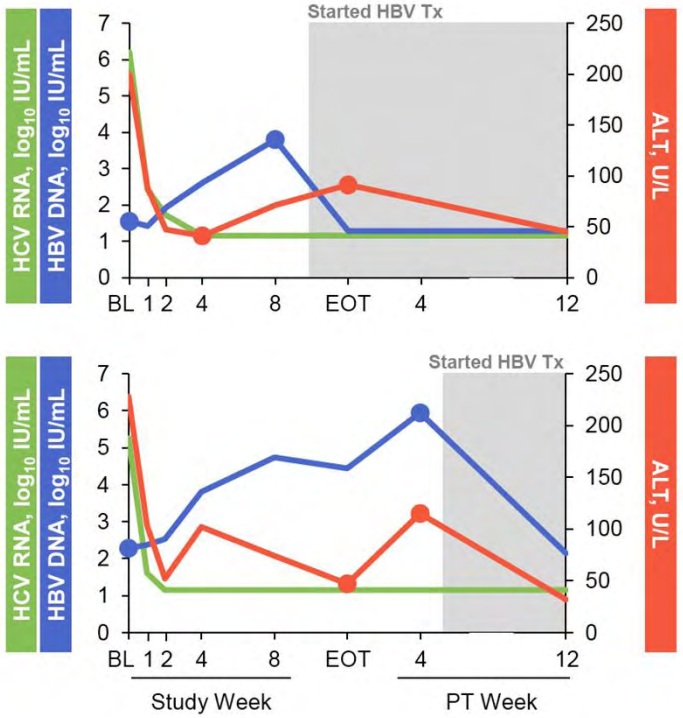
HBV-Reaktivierung

60-year-old female, HCV GT 1b, HBeAg negative, with cirrhosis

- HBV DNA increased from 1.54log$_{10}$ IU/mL (BL) to 3.8log$_{10}$ IU/mL at Day 57 (Week 8)
- Associated with ALT increase from nadir value of 41 to 71 IU/mL
- Started HBV treatment on study Day 71

61-year-old male, HCV GT 2, HBeAg negative, without cirrhosis

- HBV DNA increased from 2.28log$_{10}$ IU/mL (BL) to 5.95log$_{10}$ IU/mL 30 days post last dose (post-treatment Week 4)
- Associated with ALT increase from nadir value of 47 to 115 IU/mL
- Started HBV treatment during post-treatment follow-up Week 5



Liu CJ et al., EASL 2017

HBV-Reaktivierung

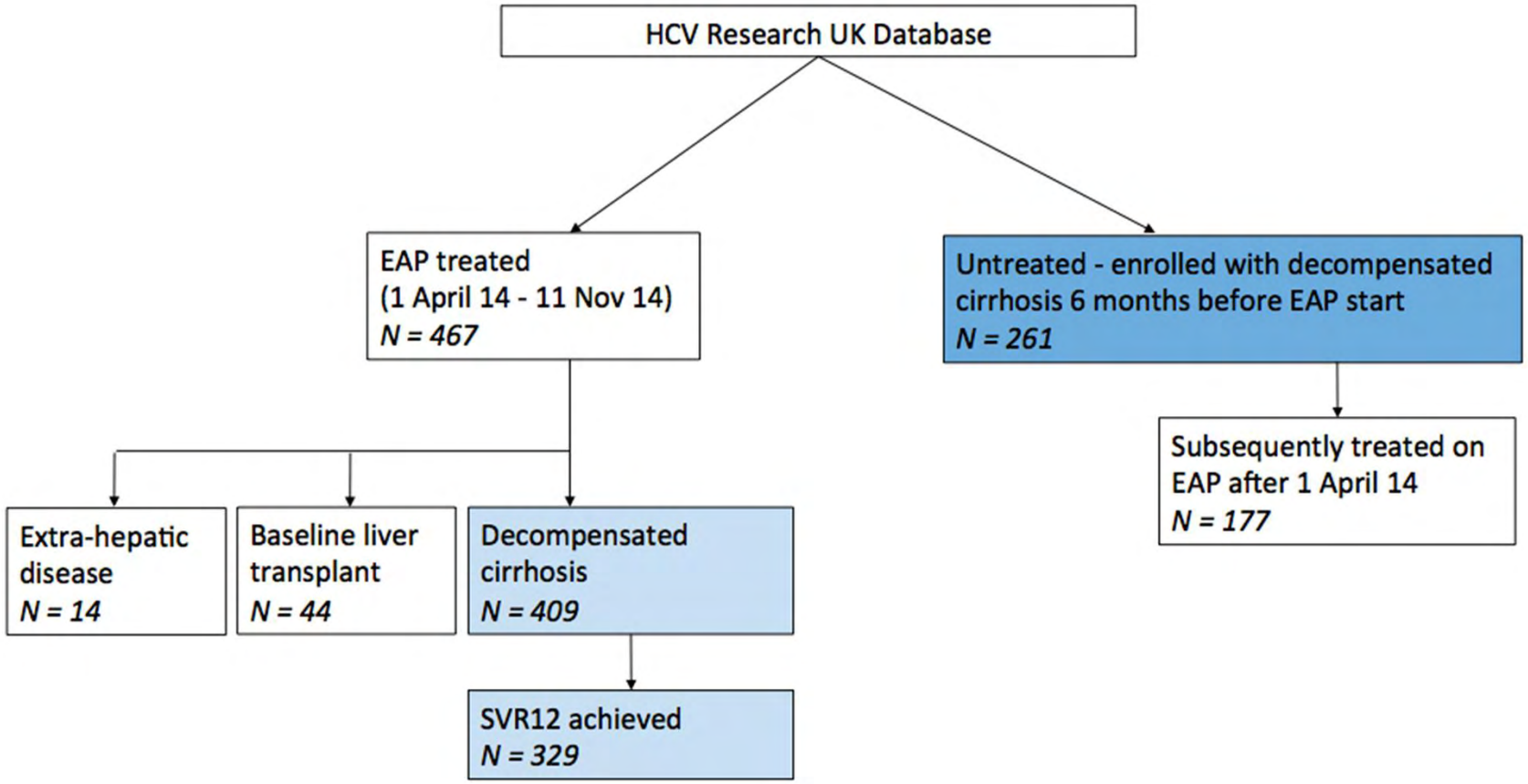
Factors Associated with HBV DNA Increase >1log$_{10}$ IU/mL and ALT >2x ULN

HBV Reactivation	No n=106	Yes n=5	p-Value
Mean baseline ALT, U/L (range)	64 (17–281)	149 (40–228)	0.0032
Mean baseline HBV DNA, log$_{10}$ IU/mL (range)	2.05 (1.28–5.83)	2.97 (1.54–5.46)	0.0188

Liu CJ et al., EASL 2017

HCV – Dekompensation

Wann bringt die Behandlung nichts (mehr)?



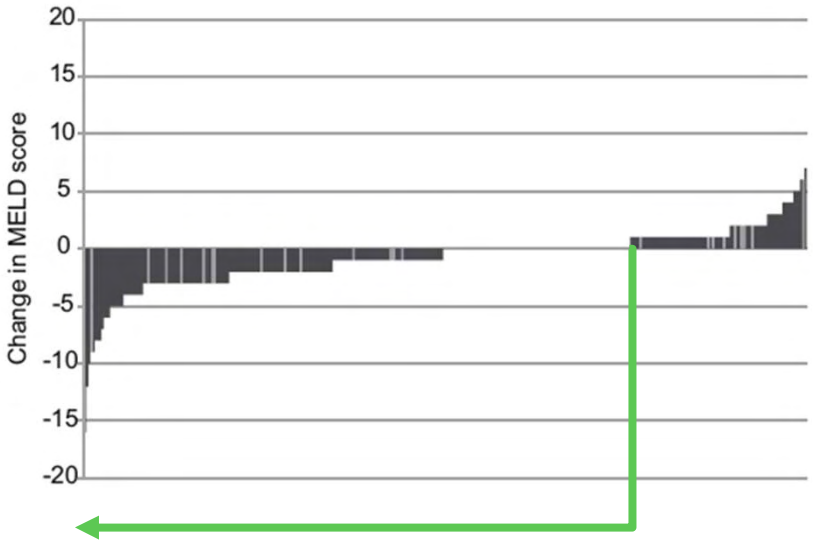
Cheung M et al., EASL 2016 PS097

Wann bringt die Behandlung nichts (mehr)?

Änderung des MELD Scores

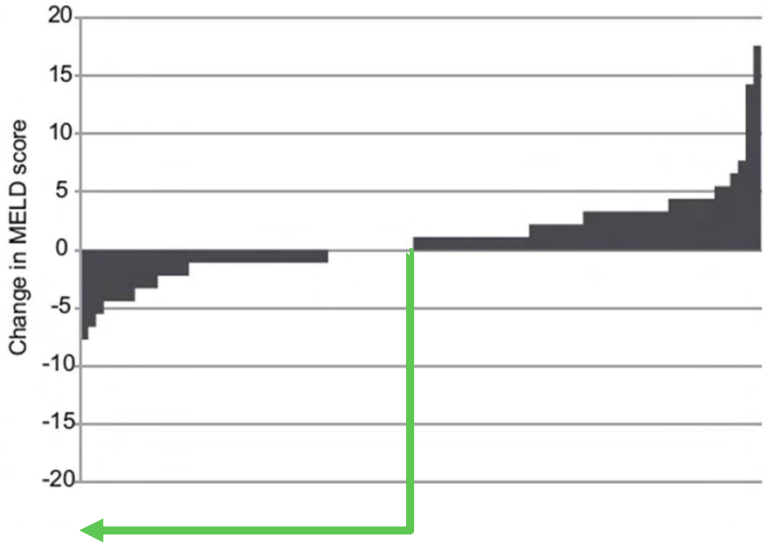
6 Monate

behandelt



≈ 75%

unbehandelt

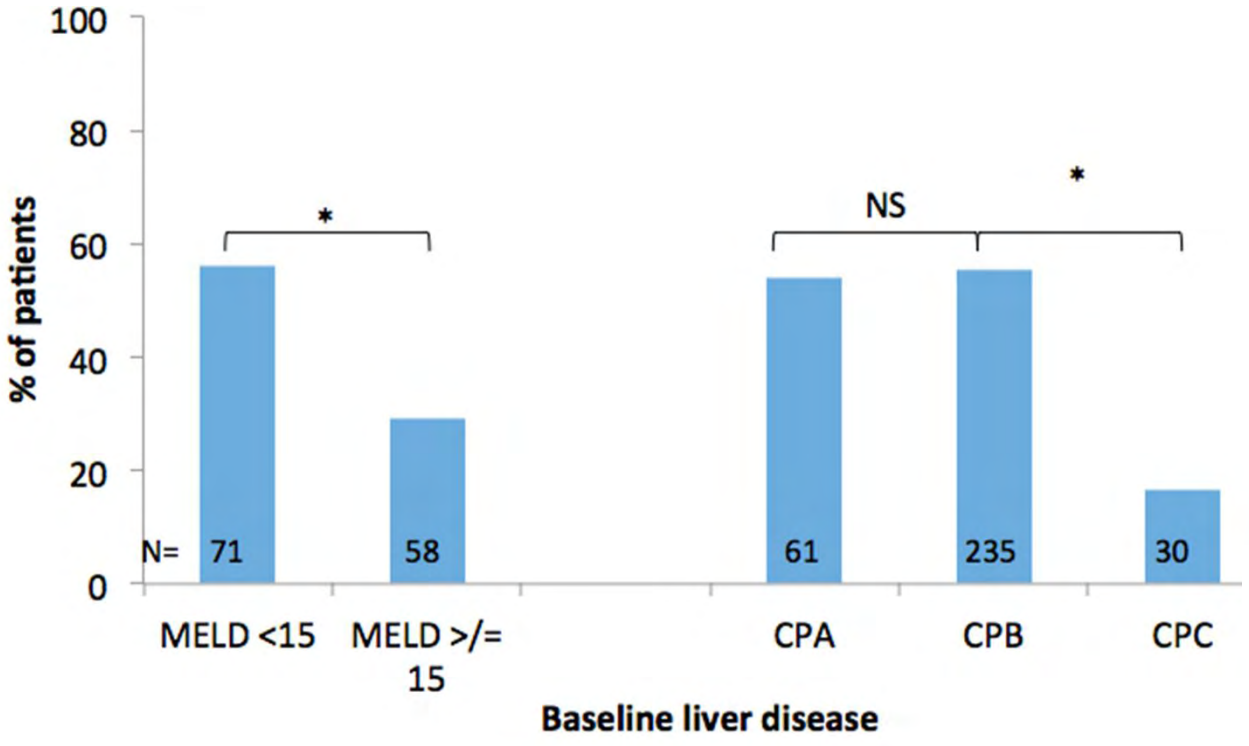


≈ 50%

Foster GR et al., J Hepatol 2016

Wann bringt die Behandlung nichts (mehr)?

Überleben ohne „Adverse outcome“
15 Monate

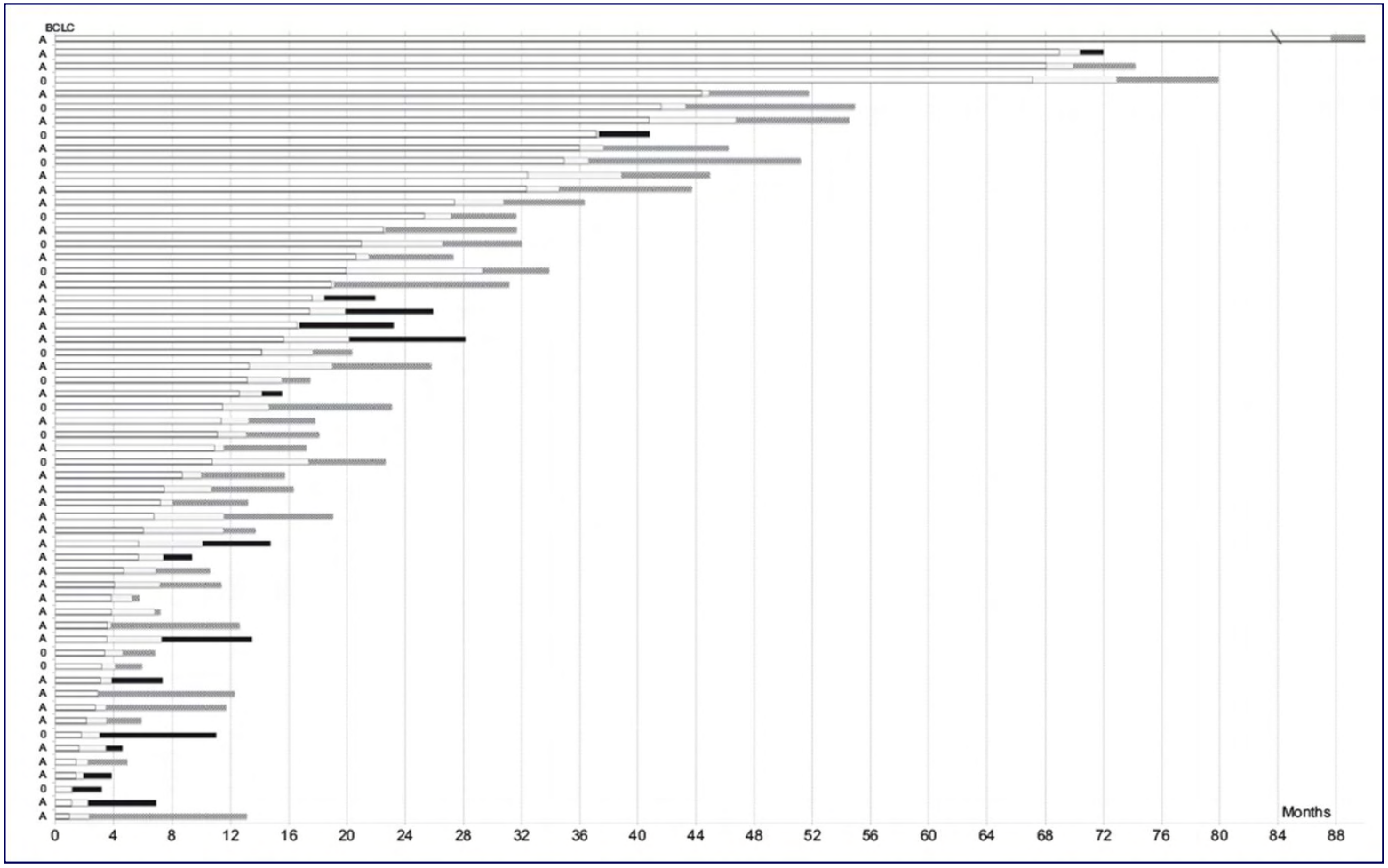


* p< 0.05

Cheung M et al., EASL 2016 PS097

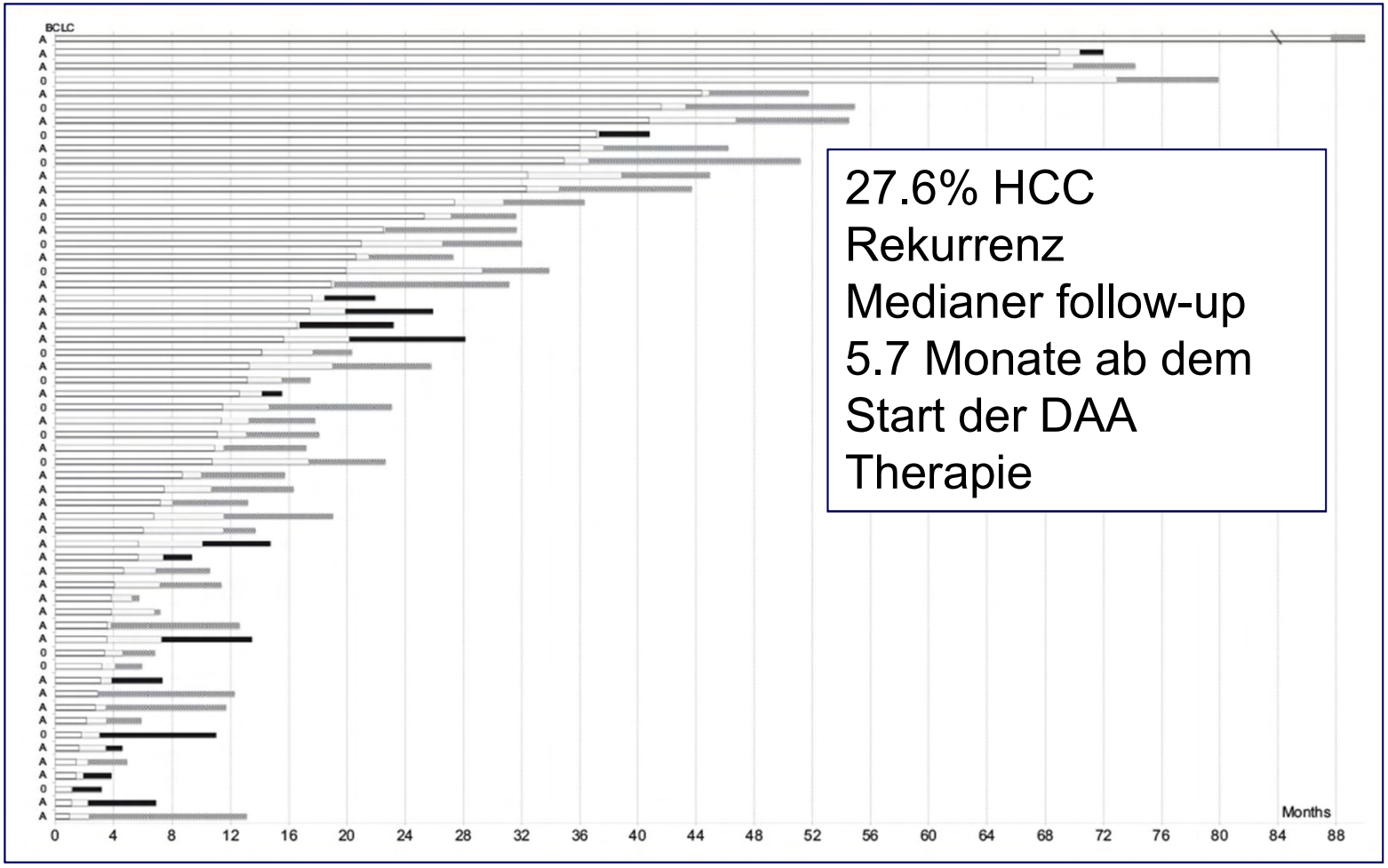
HCV – HCC Risiko

Führt die Behandlung zum HCC?



Reig M et al., J Hepatol 2016

Führt die Behandlung zum HCC?

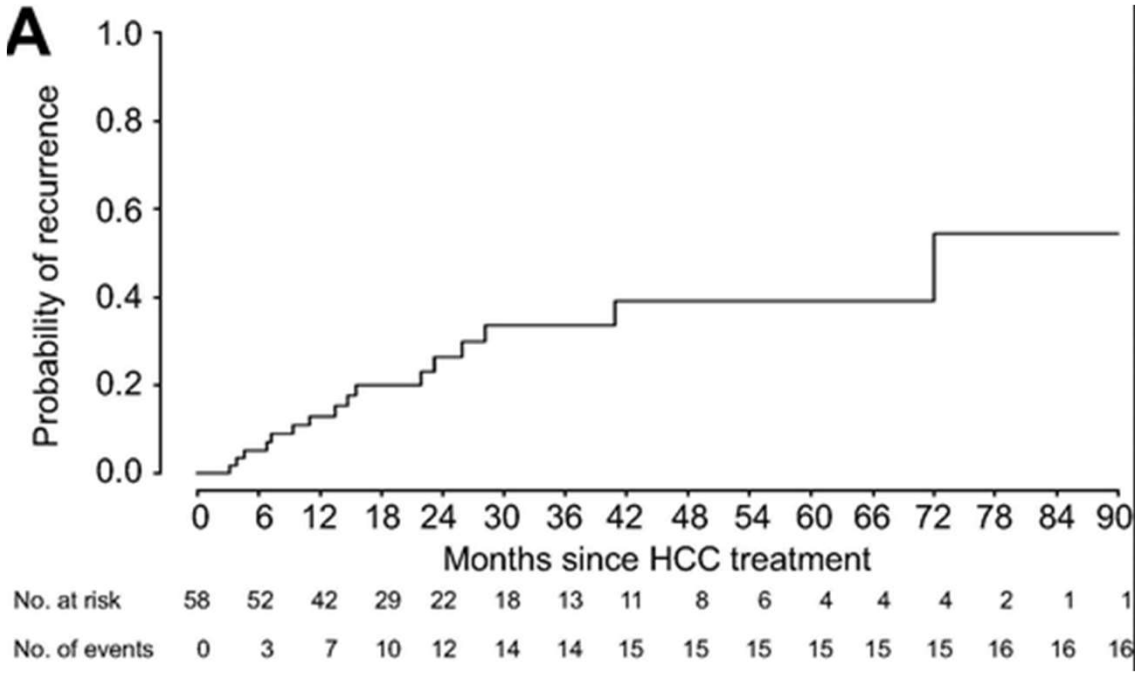


Reig M et al., J Hepatol 2016

Führt die Behandlung zum HCC?

JOURNAL OF HEPATOLOGY

Direct antiviral agents and risk for HCC early recurrence: Much ado about nothing



Camma and Craxi et al., J Hepatol 2016

HCC Risiko nach DAA Therapie

HCC occurrence

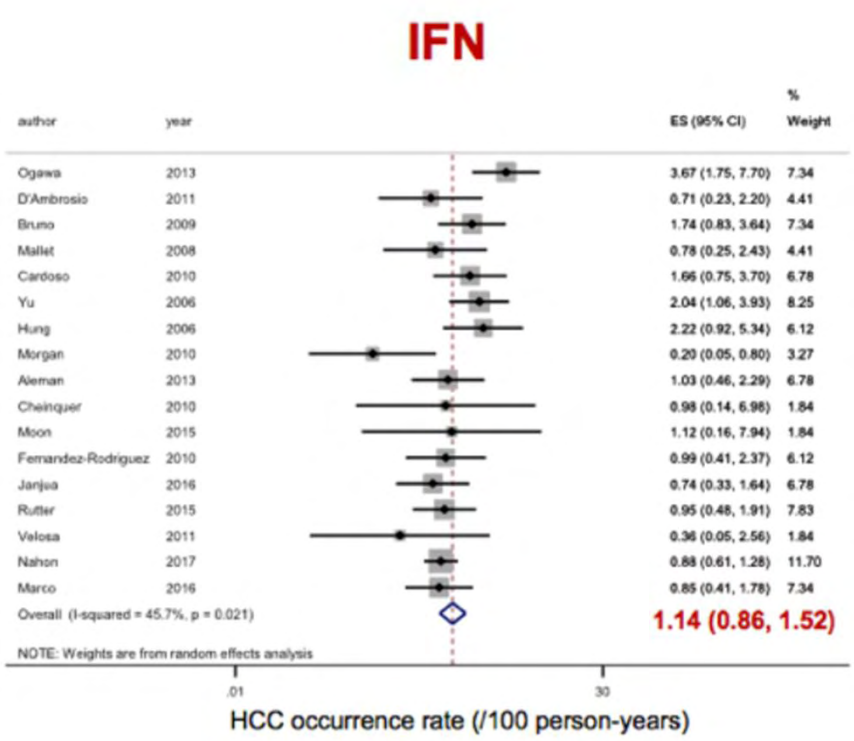
Characteristic	DAA	IFN
Age (years)	60	52
Male (%)	57	62
Genotype 1 (%)	77	39
Cirrhosis (%)	90	87
Child-Pugh A (%)	66	100
Follow-up (years)	1.0	5.5

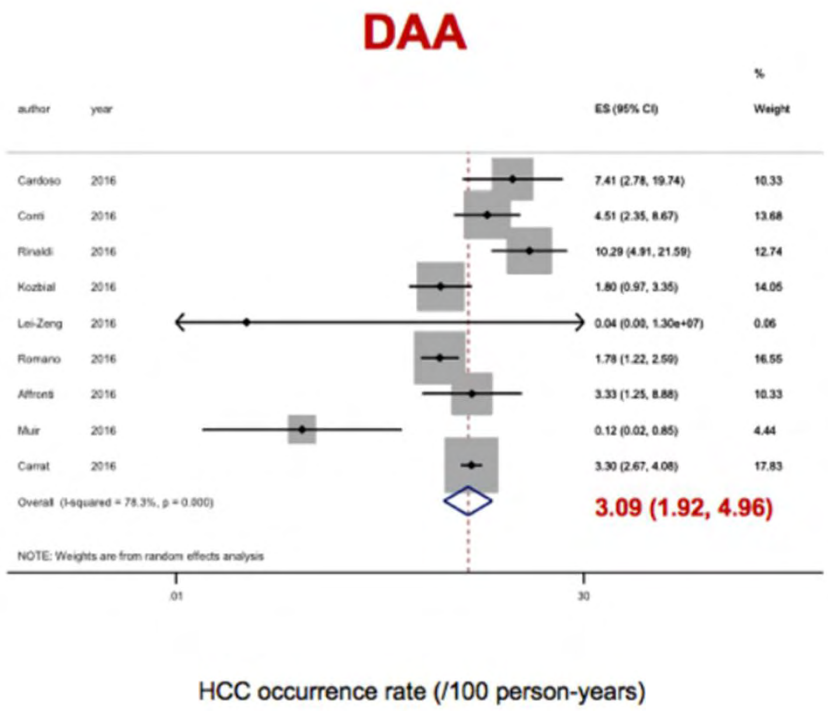
HCC recurrence

Characteristic	DAA	IFN
Age (years)	64	66
Male (%)	67	82
Genotype 1 (%)	80	54
AFP ng/ml	22	14
Curative HCC treatment (%)	96	100
Follow-up (years)	1.3	5.0

Waziry Ret al., EASL 2017

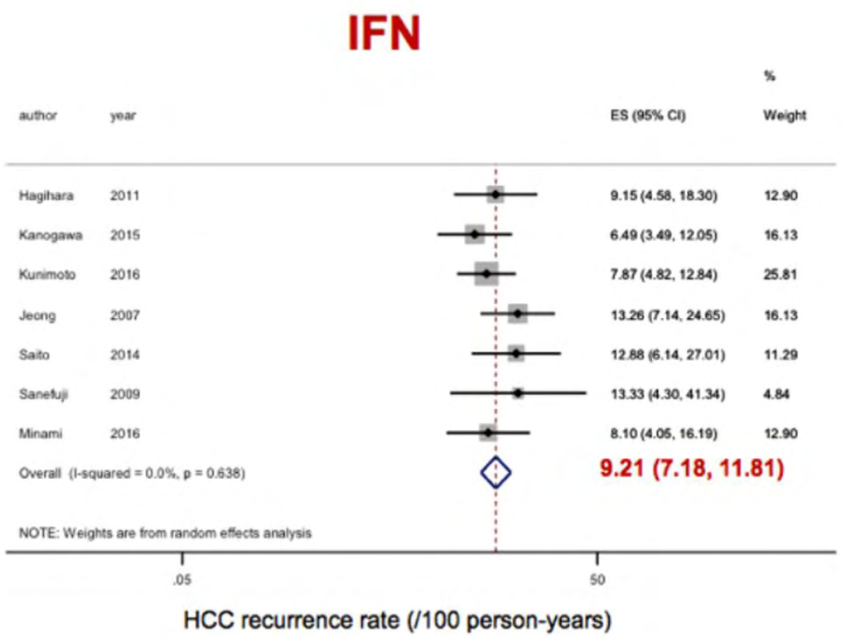
HCC Risiko nach DAA Therapie

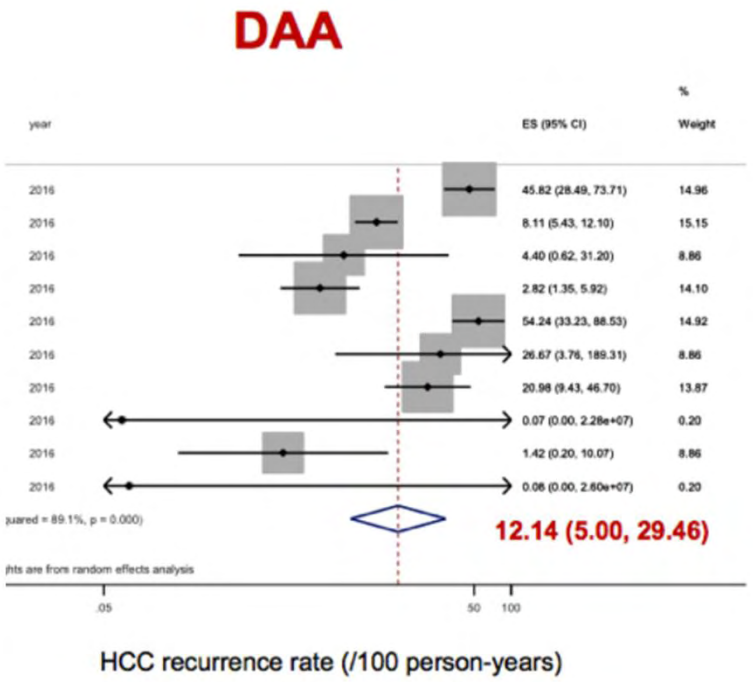




Waziry Ret al., EASL 2017

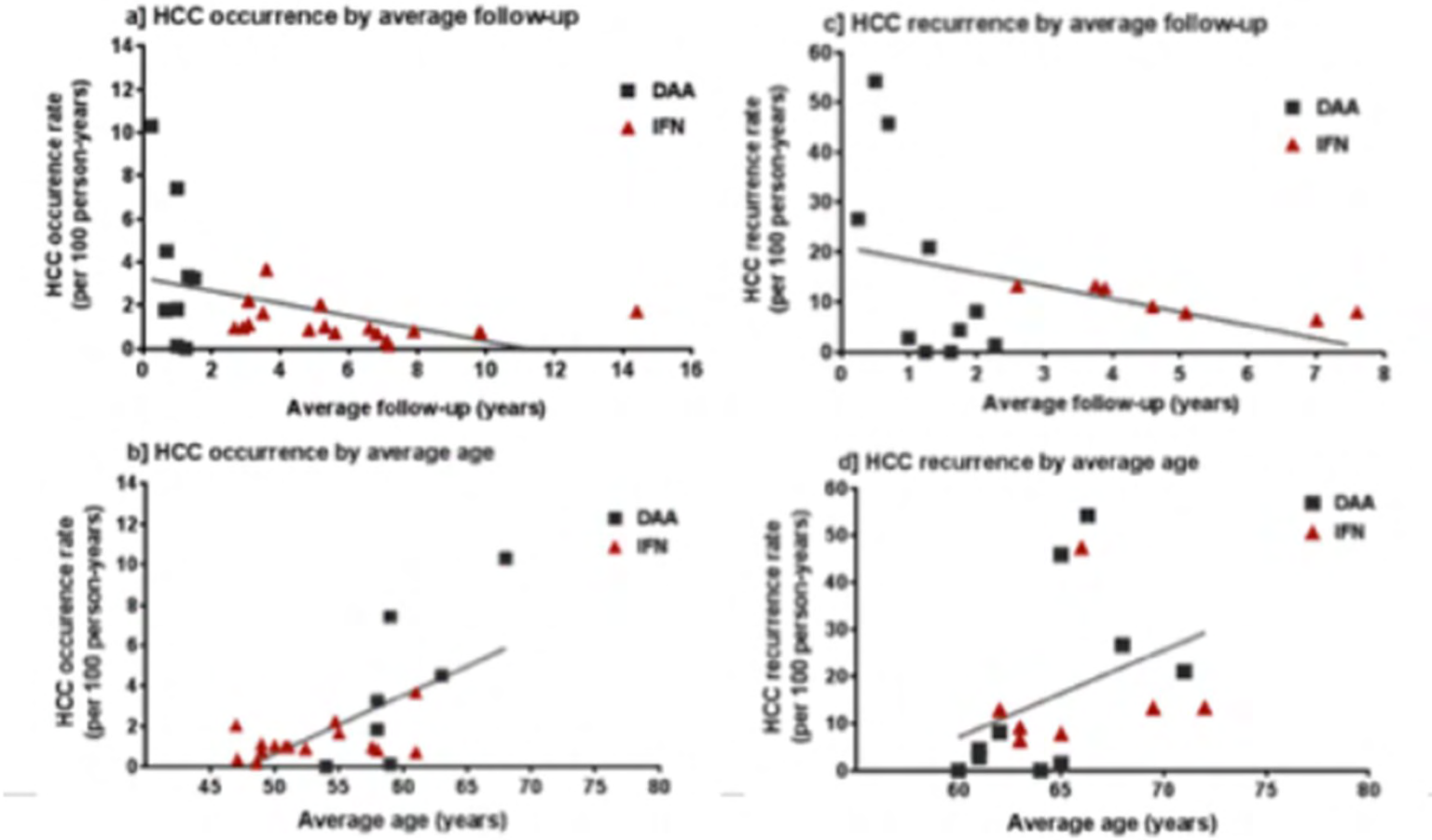
HCC Risiko nach DAA Therapie





Waziry Ret al., EASL 2017

HCC Risiko nach DAA Therapie



Waziry Ret al., EASL 2017

HCC Risiko nach DAA Therapie

HCC occurrence

	Unadjusted RR	Adjusted RR	95% CI	P value
Average follow-up	0.88	0.77	0.62, 0.97	0.03
Average age	1.11	1.06	0.99, 1.14	0.08
Treatment	2.77	0.75	0.22, 2.52	0.62

HCC recurrence

	Unadjusted RR	Adjusted RR	95% CI	P value
Average follow-up	0.86	0.79	0.55, 1.15	0.19
Average age	1.11	1.11	0.96, 1.27	0.14
Treatment	1.36	0.62	0.11, 3.45	0.56

Waziry Ret al., EASL 2017

HCC Risiko nach DAA Therapie

Study population
N=1253

Main Characteristics	N
Mean age, years (±SD)	57.2 (±10.6)
Gender, males (%)	781 (62%)
Past excessive alcohol intake	375 (31%)
HCC occurrence during study period, N(%)	179 (14%)
SVR at baseline, N(%)	249 (20%)
SVR during study period, N(%)	637 (52%)
with DAA-free regimens	468 (38%)
with DAA-based regimens	169 (14%)
Median follow-up, months (IQR)	55 (32-77)
Median post-SVR follow-up, months (IQR)	31 (12-63)
with DAA-free regimens	44 (25-72)
with DAA-based regimens	8 (5-12)

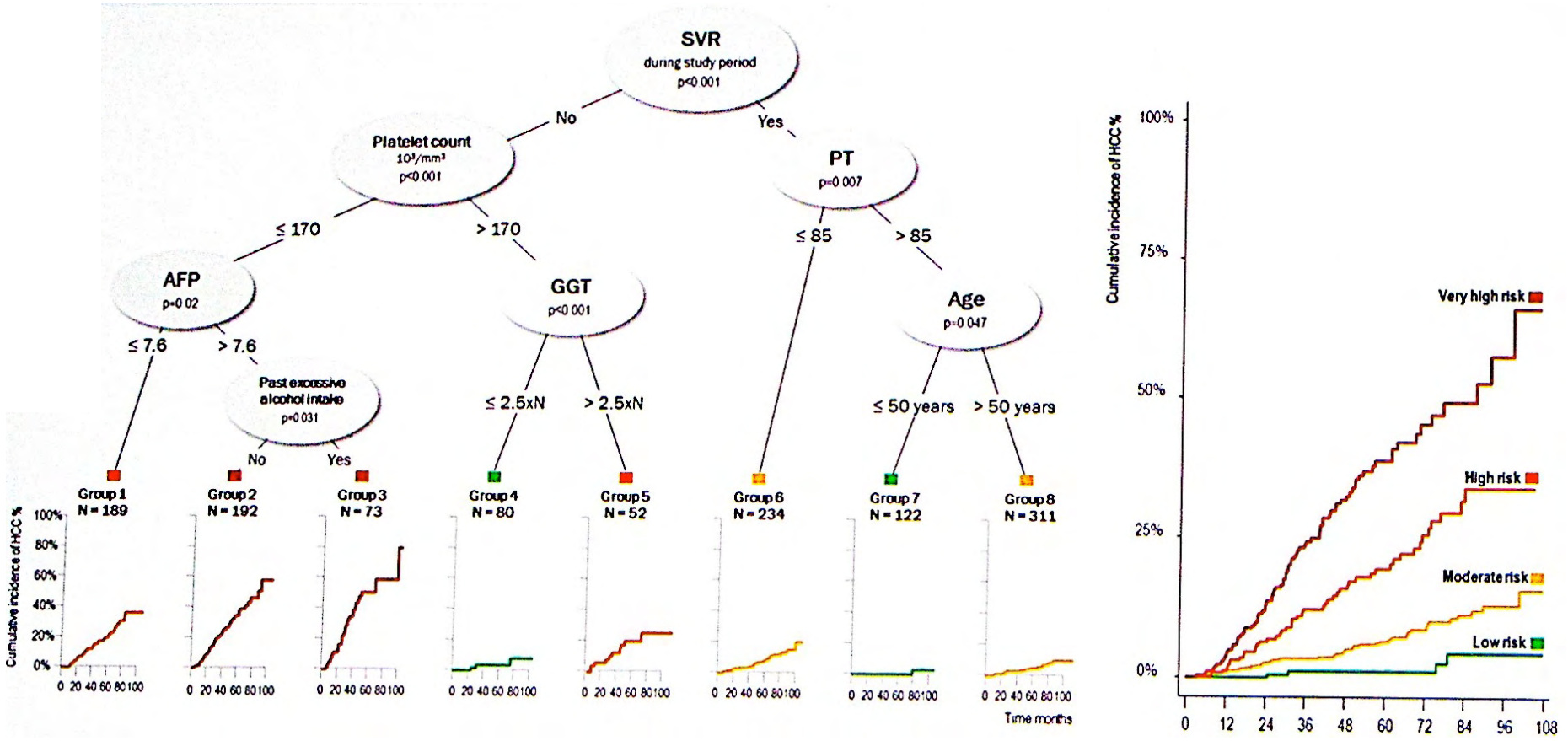
Audureau E et al., EASL 2017

HCC Risiko nach DAA Therapie

BASELINE FEATURES		HR	CI95%	p-value
Age > 50 years		1.86	[1.25-2.77]	0.002
Past excessive alcohol intake		1.68	[1.21-2.33]	0.002
Prothrombin Time ≤ 85%		1.54	[1.13-2.11]	0.007
Alpha-fetoprotein (AFP) ≥ 6 ng/mL		1.45	[1.02-2.05]	0.037
Platelet count ≤ 170k /mm^3		1.99	[1.28-3.09]	0.002
Gamma-Glutamyl Transpeptidase (GGT) ≥ N		1.93	[1.21-3.08]	0.006
SVR during study period	*No SVR*	1 (ref)		<0.001
	SVR (DAA-free regimens)	0.31	[0.20-0.17]	
	SVR (DAA-based regimens)	0.18	[0.10-0.34]	

Audureau E et al., EASL 2017

HCC Risiko nach DAA Therapie



Audureau E et al., EASL 2017

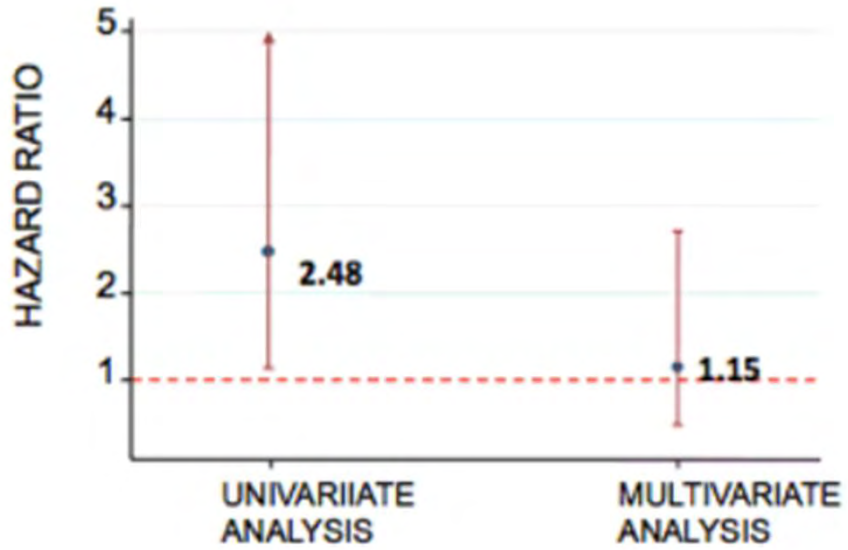
HCC Risiko nach DAA Therapie

Characteristic		% of cohort (N=857)
Demographics	Average age	Mean: 49 years (sd: 8)
	White ethnicity	92%
	Male gender	75%
Health behaviours	History of heavy alcohol use	44%
	Current tobacco smoker	73%
	History of intravenous drug use	70%
Clinical	Thrombocytopenia (<100/ 10^9/L)	28%
	Child Pugh B/C	15%
	Diabetes	9%
Treatment	Treatment experienced	35%
	IFN-free regimen	32%

Innes H et al., EASL 2017

HCC Risiko nach DAA Therapie

Vergleich zwischen IFN-basierter und DAA Therapie
857 Patienten, 272 erhielten DAA Therapie



* Die multivariate Analyse berücksichtigt Alter, Geschlecht, Ethnizität, Child score, Thrombopenie, AFP, Genotyp, Therapieerfahrung, Ort der Klinik

Innes H et al., EASL 2017

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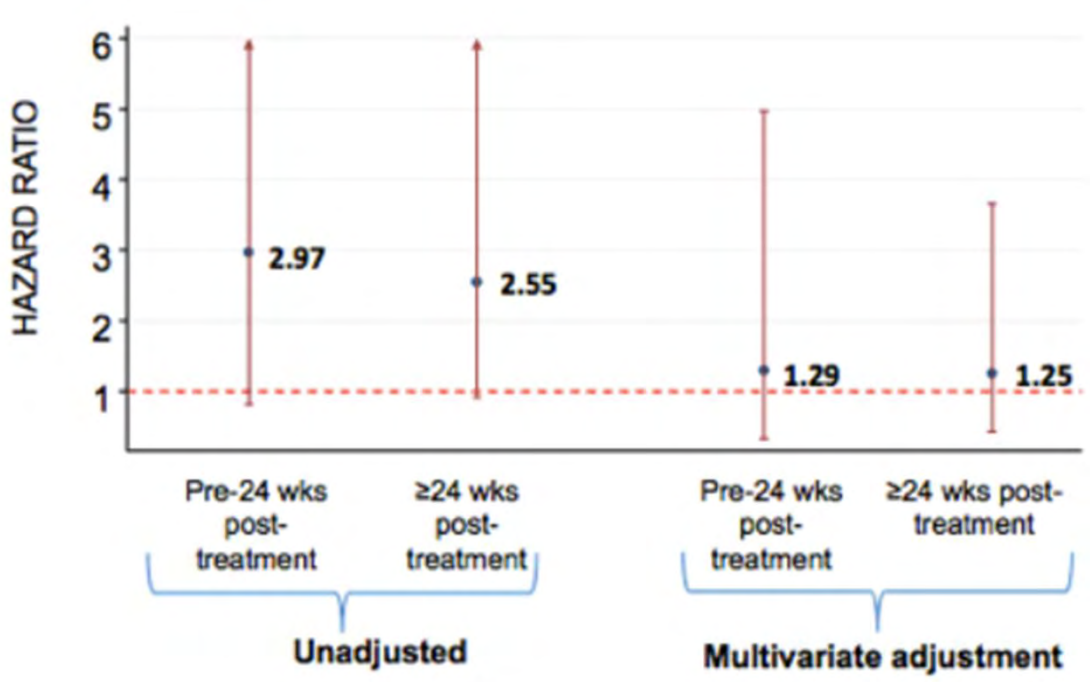

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Innes H et al., EASL 2017

HCV – welche Probleme bleiben?

- „One size fits all“ oder individuelle Therapie?
- Lohnt die Behandlung bei fortgeschrittener Zirrhose?
- Beeinflusst die Therapie das HCC Risiko?
- Was tun bei Resistenzen?
- Was tun bei Niereninsuffizienz?