Neues vom EASL 2013
-Hepatitis-

Arbeitskreis AIDS, KV Berlin, 09.05.2013

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Hepatitis B – was gibt es Neues?

Arbeitskreis AIDS, KV Berlin, 09.05.2013

+ Isolierung des Rezeptors für Hepatitis B und Hepatitis D

+ Regression von Fibrose und Zirrhose bei optimaler Therapie aber HCC Risiko ?

+ Therapie immuntoleranter Patienten

+ Subquantifizierung von HBsAg in der zukünftigen Therapie

+ Therapieende vor HBsAg Verlust

+ Pipeline HBV

+ Impfrealität und neuer Impfstoff

Paper of the year 2012 for Hepatitis B (vermutlich)

eLIFE
elife.elifesciences.org

RESEARCH ARTICLE

Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus

Huan Yan[1,2†], Guocai Zhong[2†], Guangwei Xu[2], Wenhui He[2,3], Zhiyi Jing[2], Zhenchao Gao[1,2], Yi Huang[2,3], Yonghe Qi[2], Bo Peng[2], Haimin Wang[2], Liran Fu[2,3], Mei Song[2,3], Pan Chen[2,3], Wenqing Gao[2], Bijie Ren[2], Yinyan Sun[2], Tao Cai[2], Xiaofeng Feng[2], Jianhua Sui[2], Wenhui Li[2]*

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Published: 13 November 2012

INFECTIOUS DISEASES

Getting to grips with hepatitis

The receptor that allows hepatitis B and hepatitis D viruses to enter human liver cells has been identified as a protein that transports bile acids in the liver.

ZHIJIAN J CHEN AND JIN YE

+ Isolierung des Rezeptors

+ Knockdown des Rezeptors verhindert Infektion

+ Austausch von 9AS macht Affenhepatozyten permissiv für HBV und HDV

+ Huh7 und HepG2 Zellen werden durch Rezeptorexpression permissiv für HBV und HDV

- Neutralisierende Ak gegen NTCP blockiert HBV/HDV Infektion – fehlt noch

JVI Accepts, published online ahead of print on 17 April 2013
J. Virol. doi:10.1128/JVI.03533-12
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1 # Sodium taurocholate cotransporting polypeptide mediates woolly monkey
2 # hepatitis B virus infection of *Tupaia* hepatocytes

3

4 **Running title:** Receptor for WMHBV infection of *Tupaia* hepatocytes

5 **Authors:** Guocai Zhong [1], Huan Yan [1,2], Haiming Wang [1], Wenhui He [1,3], Zhiyi Jing [1], Yonghe Qi [1,4], Liran Fu [1,3],
6 Zhenchao Gao [1,2], Yi Huang [1,3], Guangwei Xu [1], Xiaofeng Feng [1], Jianhua Sui [1], Wenhui Li [1 *]

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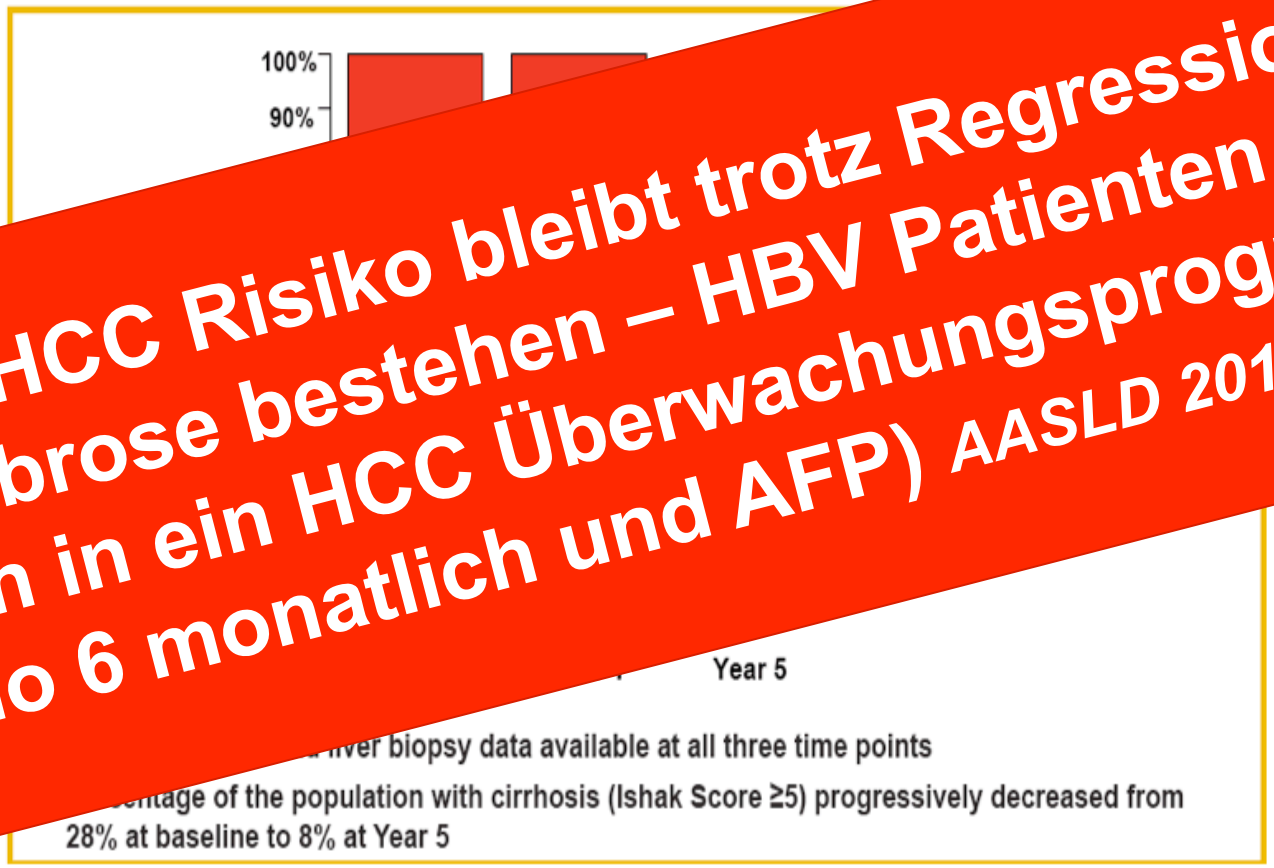
Fünf Jahre Tenofovirtherapie: Suffiziente HBV DNA Suppression und signifikante Fibroseregression

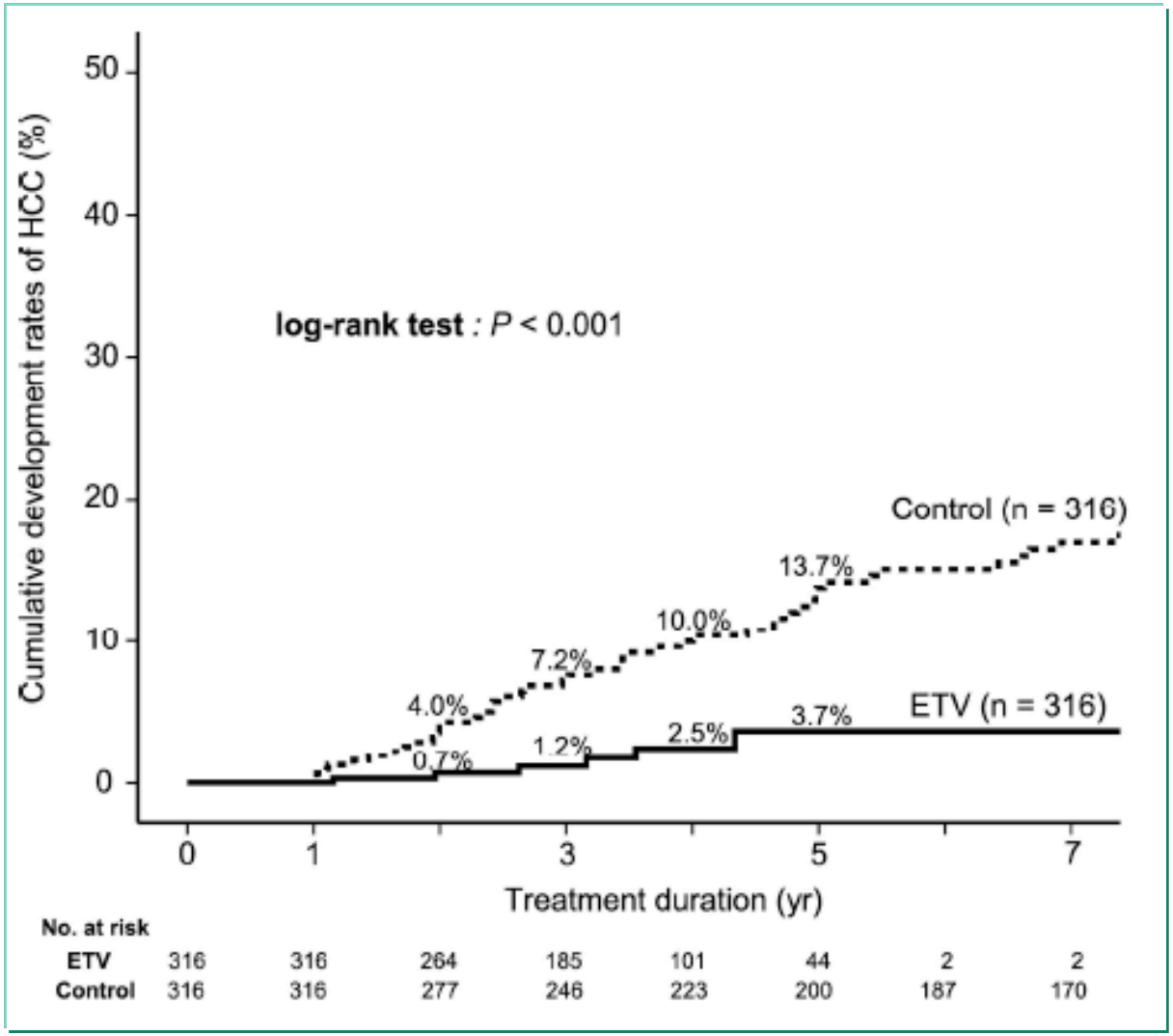
Figure 3b. Distribution of Ishak Fibrosis Scores at Baseline, Year 1, and Ye



Aber: HCC Risiko bleibt trotz Regression der Fibrose bestehen – HBV Patienten sollen in ein HCC Überwachungsprogramm (Sono 6 monatlich und AFP) *AASLD 2012*

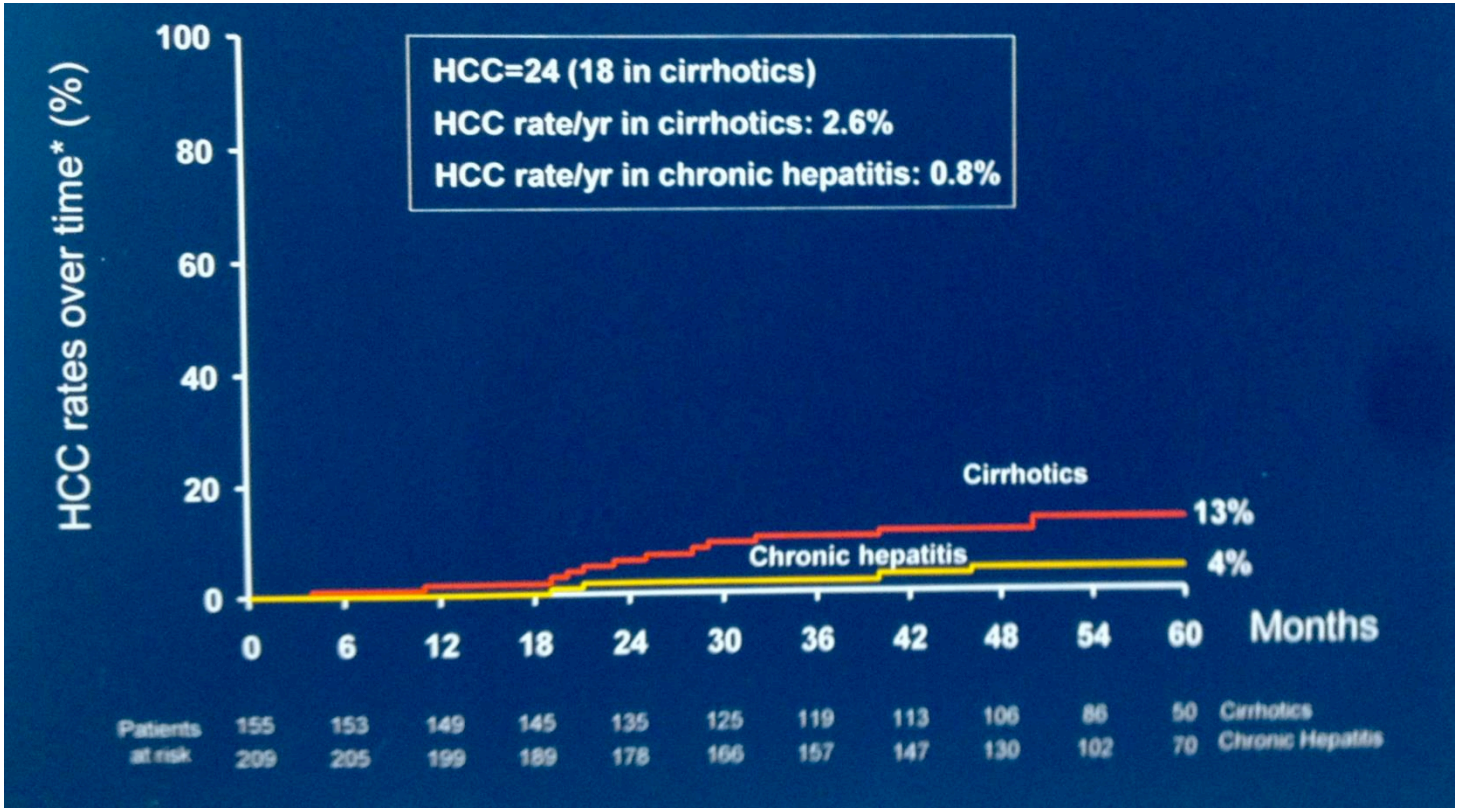
P. Marcellin, Lancet 2013

Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection



Hosaka et al. Hepatology 2012

5-Jahres Risiko für HCC bei Patienten mit chronischer Hepatitis B und Entecavir Therapie



Lampertico EASL 2012, AASLD 2012, EASL 2013

Baseline factors associated with HCC

(n=1531 HBV Patienten, 3,1% HCC nach 42 Mona

Univariate analy						
Factors	HR					
Male gender						
Age ≥50						
			<0.001	3.2	1.5-6.4	0.002
D ≥	.4	0.2-0.7	0.01	0.3	0.1-0.6	0.007

"Improvement in risk scores after entecavir treatment is associated with reduced but not zero risk of HCC"

Wong et al., EASL 2013; Gastroenterology 2013 in press

Wong et al., EASL 2013

Take Home Message

- Trotz HBV DNA Suppression sollte weiterhin ein HCC Screening erfolgen
- Alle 3-12 Monate je nach Risikoprofil (Albumin, Fibroscan. Sonographie)
- Scores könnten sinnvoll sein, die Überwachungsintervalle neu zu definieren.

Beispiel

- 24 jähriger Patient, gebürtig aus Vietnam

- HBeAg positiv
- HBV DNA >110 Mio. IU/ml
- qHBsAg 35.000 IU/ml *
- ALT 17 IU/ml, AST 14 IU/ml

- Großvater hatte „Gelbsucht“ und ist daran verstorben

*HBsAg ≥ 25,000 IU/mL was independently associated with fibrosis score ≤ 1 (Seto et al., PloS One 2013)

Low risk of fibrosis or fibrosis progression in immune tolerant patients

- Mild fibrosis (F1) detected in 50% of immune tolerant patients; no fibrosis in remainder[1]
- No change in fibrosis score in 42 of 48 patients who remained in the immune tolerant phase for 5 years[2]

Stage	Initial biopsy, n	Final biopsy, n	p value
F0	15	16	0.58
F1	33	31	
F2	0	1	

[1]Andreani T et al. Clin Gastroenterol Hepatol 2007;5:636–641;
[2]Hui CK et al. Hepatology 2007;46:395–401.

Therapie: PRO & CONTRA

- Hohes Transmissionsrisiko
- HCC Risiko?
  (HBV-DNA ist assoziiert mit HCC)
- Leitlinienempfehlung EASL >30 Jahre

- keine Entzündung / Fibrose
- IFN nicht effektiv
- Bislang keine Daten zu NA
  → vermutlich lebenslange Therapie
- Keine Daten zum HCC Risiko bei Patienten <30 Jahre
- Leitlinienempfehlung <30 Jahre

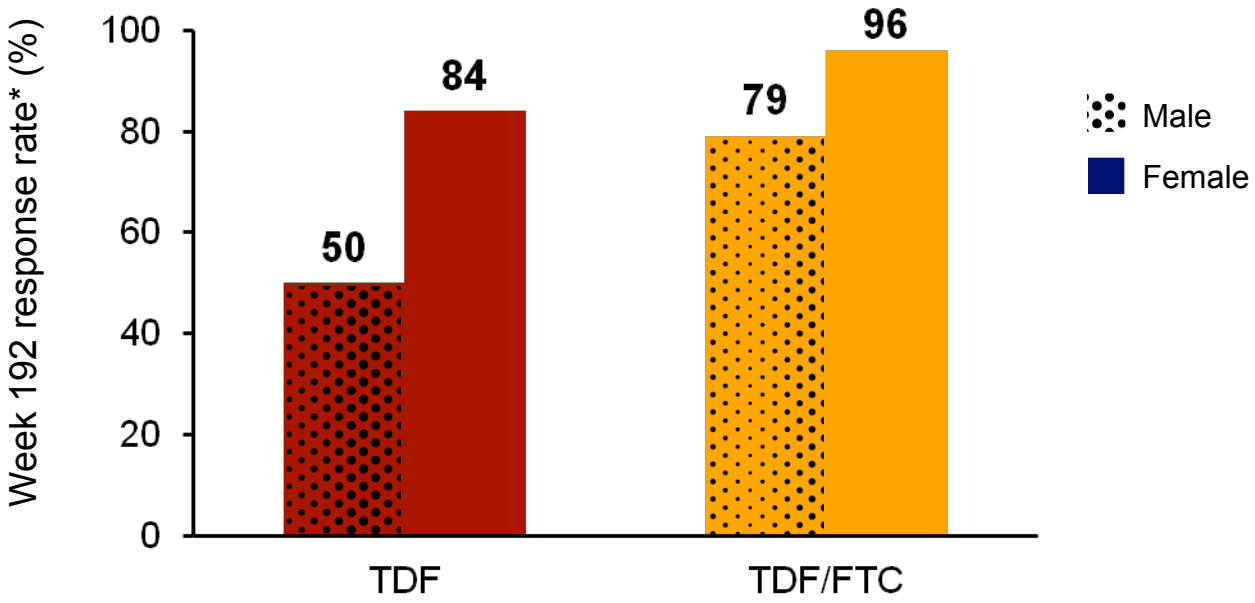
Therapie mit Tenofovir oder Truvada bei "immuntoleranten" Patienten (192 Wochen, 4J)

	TDF n=64	TDF/FTC n=62	p-value*
Primary endpoint, n/N (%)			
HBV DNA <69 IU/mL	35/64 (55)	47/62 (76)	0.016
Secondary endpoints, n/N (%)			
HBeAg loss	4/63 (6)	1/62 (2)	0.365
HBeAg seroconversion	3/63 (5)	0/62 (0)	0.244
HBsAg loss	0	0	
HBsAg seroconversion	0	0	

Missing data = failure.
*p-values derived using Fisher exact test.

Chan HL et al. EASL 2013; Oral 101.

Multivariate analysis of treatment response

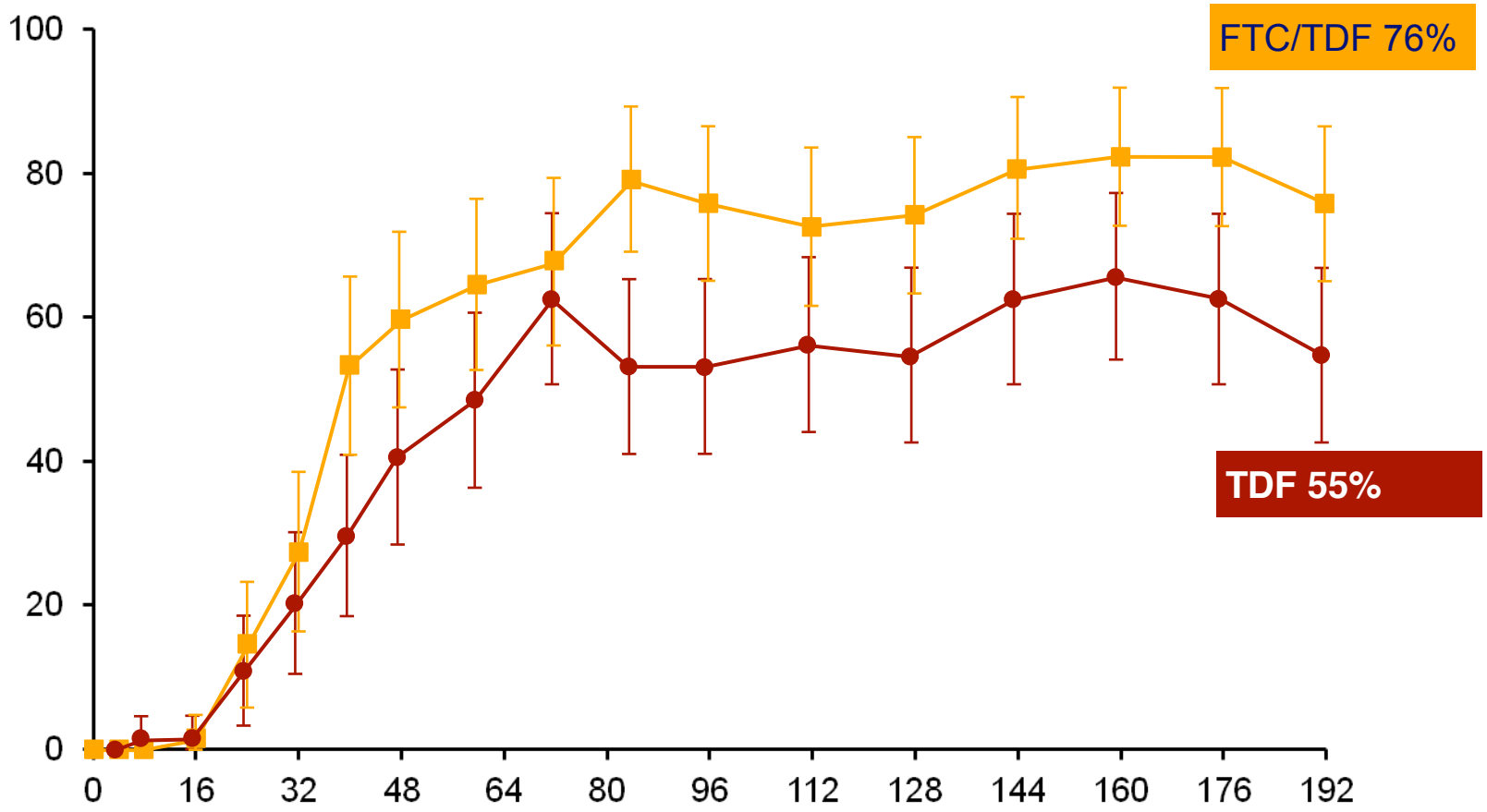


	Odds ratio†	CI
Female	6.0	1.9–18.2
TDF/FTC treatment	3.9	1.4–11.1

*Proportion of patients with HBV DNA <69 IU/mL at Wk 192 among those with Wk 192 visit.
†Multivariate logistic regression performed using forward selection model.

Chan HL et al. EASL 2013; Oral 101.

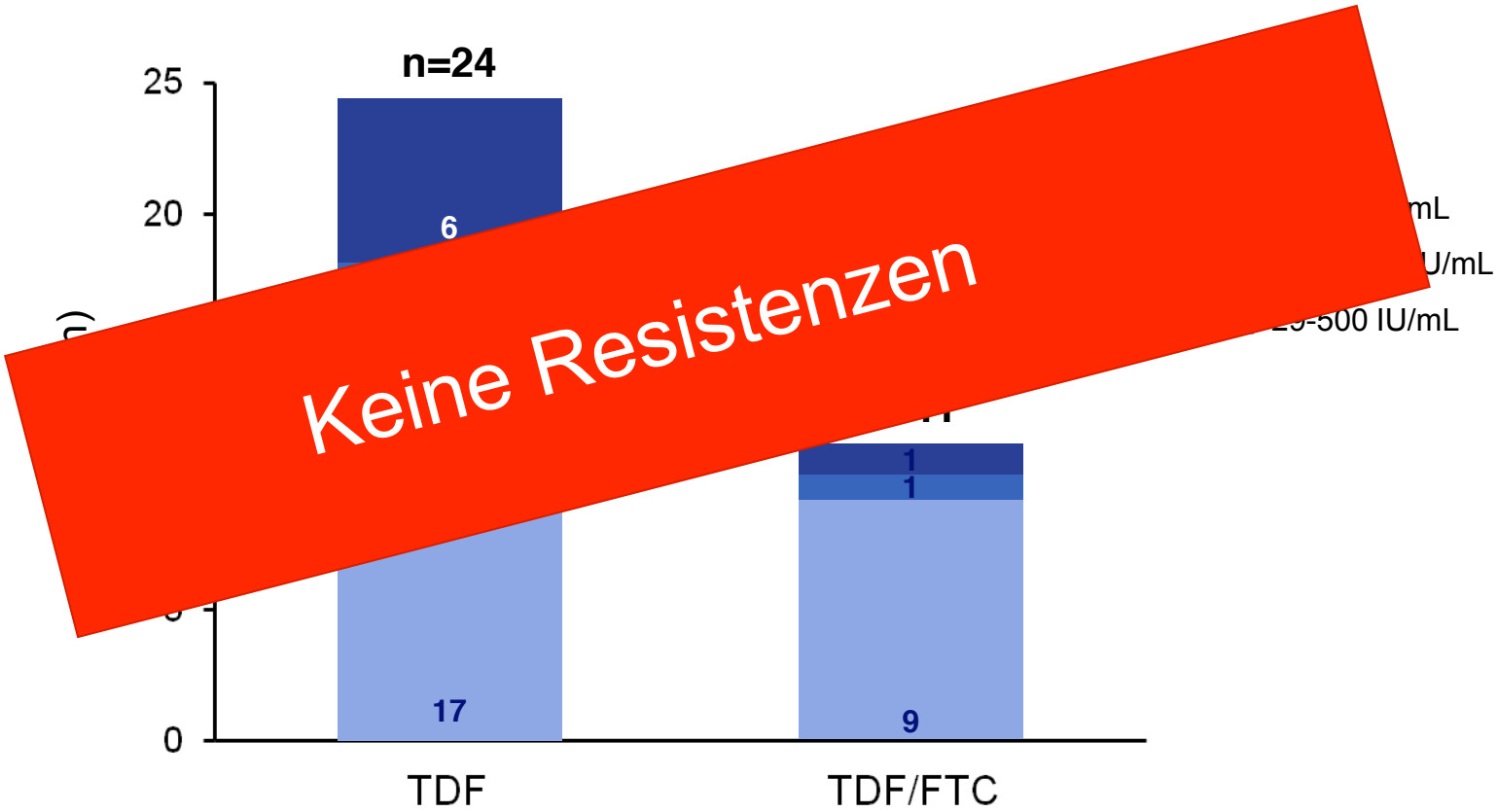
Proportion of Patients With HBV DNA <69 IU/mL at Week 192*



Chan HL et al. EASL 2013; Oral 101.

Week 192 patient viral load levels

- Majority of patients with detectable virus at Week 192 had low viral loads (<500 IU/mL)

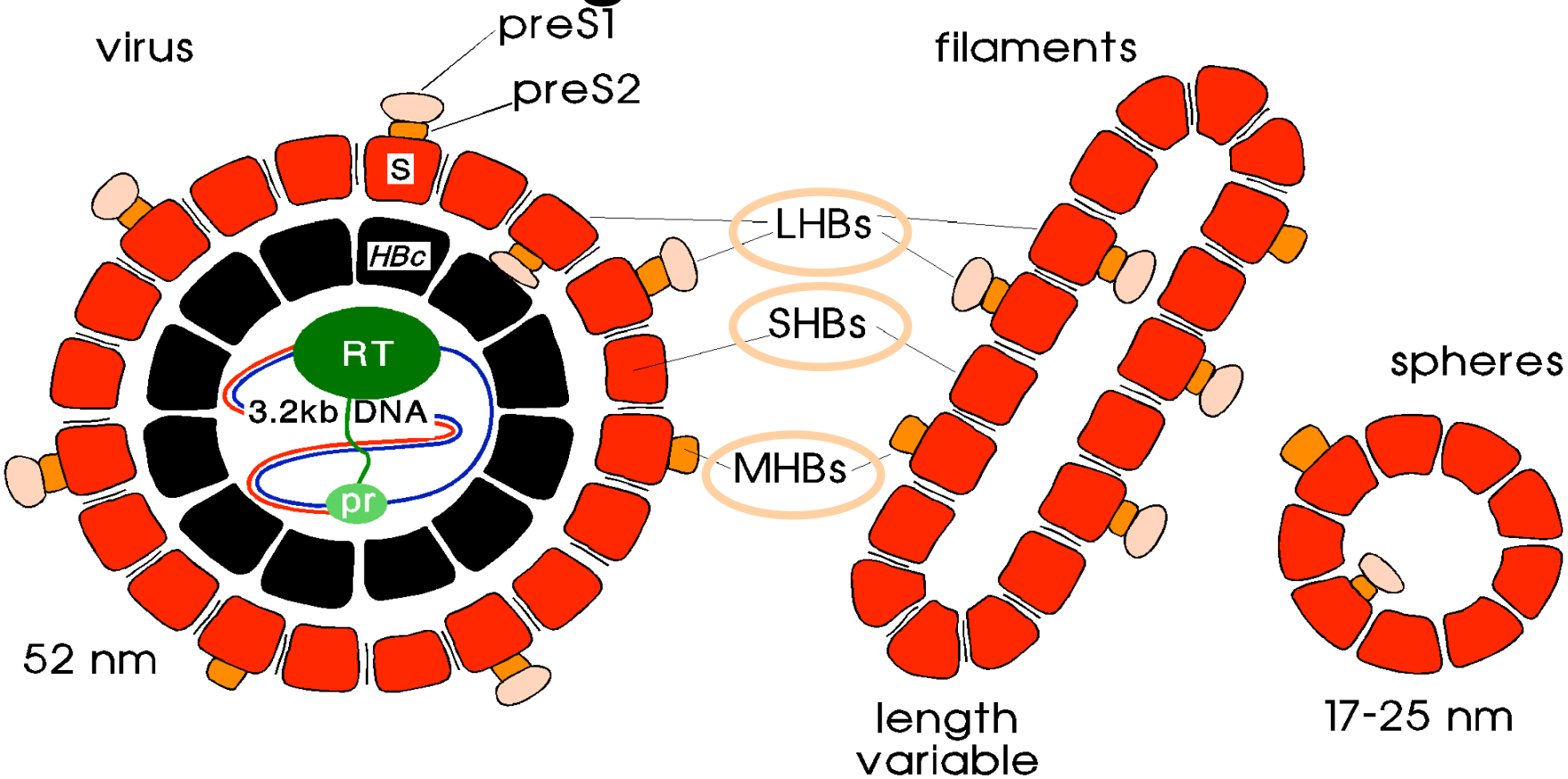


Chan HL et al. EASL 2013; Oral 101.

Schlussfolgerung

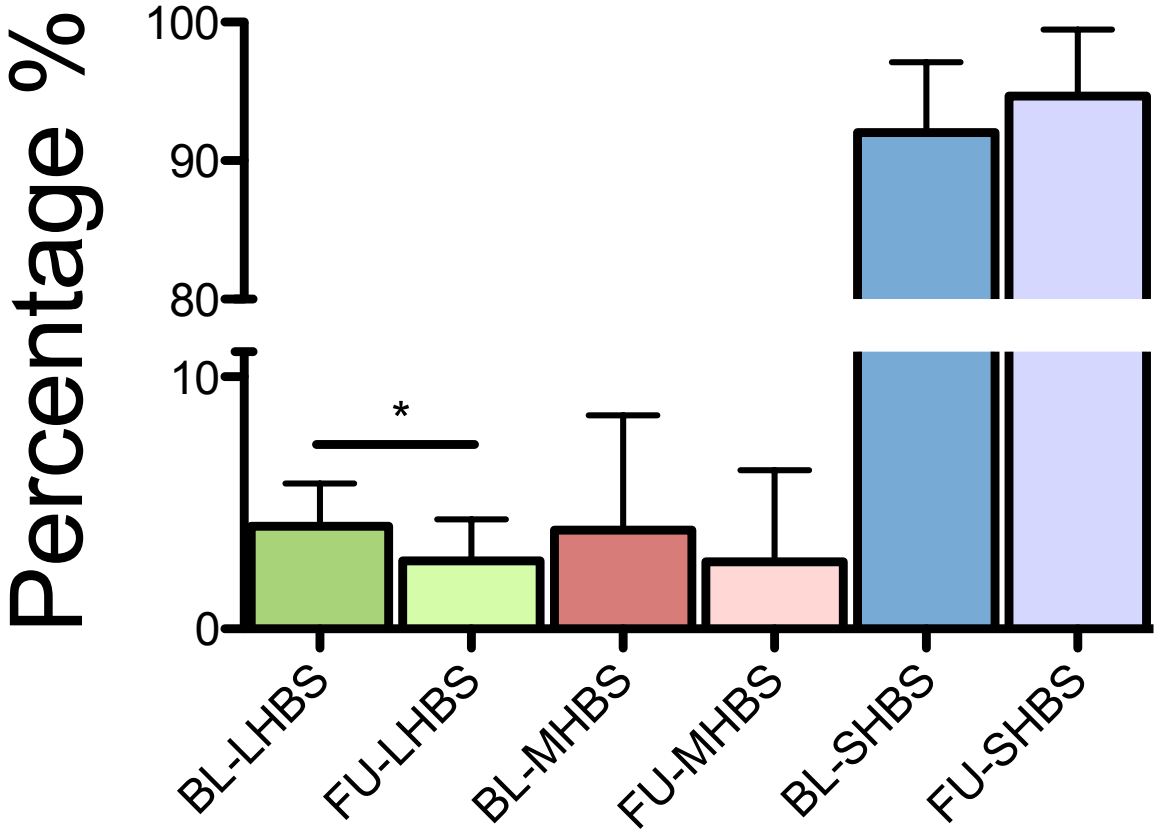
- Die Therapie „immuntoleranter“ Patienten mit TDF ist sicher und führt (bislang, 4 Jahre) nicht zu Resistenzen
- Frauen sprechen besser an (Schwangerschaft !!)
- Anti-HBe Serokonversionsrate ist allerdings sehr gering, kein HBs Ag Verlust
- Die Leitlinie wird sich aufgrund dieser Daten nicht ändern

HBsAg Subfraktionen



Glebe (DZIF Project 2012)

Schneller Abfall des LHBs bei Patienten mit akuter Hepatitis B



Mean with SD, t-test unpaired with Welch's correction
*p<0.05

Wiegand, Glebe, Cornberg EASL 2013

Ist ein Therapieauslass vor Erreichen des HBsAg Verlust möglich?

Patient	Previous therapy	Duration of therapy (months)	qHBsAg at stopping point (IU/ml)	Last HBsAg level available (IU/ml) after stopping therapy
1	Lamivudine	74	930	726
2	Lamivudine	62	140	HBsAg seroconversion
3	Lamivudine	80	453	479
4	Adefovir	64	18	HBsAg loss (<0.05)
5	Adefovir	52	49	not available
6	Telbivudine	54	not available	HBsAg loss (<0.05)
7	Entecavir 0.5	37	not available	357
8	Entecavir 0.5	42	432	280
9	Entecavir 1.0	48	121	HBsAg seroconversion

Petersen et al., AASLD 2011; Abstract 1417
5 Deutsche Zentren (Hamburg, Kiel, Düsseldorf, Leipzig, Hannover)

Langzeitverlauf nach Therapieende

Results III: qHBsAg (IU/ml), anti-HBs (IU/ml), viremia and ALT in patients without relapse after stopping NUC therapy

Patient #	Previous therapy /months	qHBsAg therapy stop	qHBsAg month 6	qHBsAg month 12	qHBsAg month 18	qHBsAg month 24	qHBsAg month 30	qHBsAg month 36	qHBsAg month 42	HBV-DNA (IU) and ALT month 42
1	Lamivudine / 74	930	1028	854	659	726	901	788	946	6900 / ALT nl
2	Lamivudine / 62	140	n.a.	HBsAg- Anti-HBs-	HBsAg- Anti-HBs (+)	HBsAg- Anti-HBs + (19)	HBsAg- Anti-HBs + (65)	HBsAg- Anti-HBs + (45)	HBsAg- Anti-HBs + (105)	<20 / ALT nl
3	Lamivudine / 80	453	632	390	705	479	399	486	536	350 / ALT 68 U
4	Adefovir / 64	18	qHBsAg <0.05 Anti-HBs-	qHBsAg 7 Anti-HBs-	qHBsAg<0.05 Anti-HBs-	HBsAg <0.05 Anti-HBs-	HBsAg- Anti-HBs+ (137)	HBsAg- Anti-HBs+ (129)	HBsAg- Anti-HBs+ (177)	<20 / ALT nl
5	Adefovir / 52	49	35	19	HBsAg- Anti-HBs-	n.a.	HBsAg- Anti-HBs-	HBsAg- Anti-HBs-	HBsAg- Anti-HBs-	<20 / ALT 73 U NASH
6	Telbivudine / 54	n.a.	1024	379	15	12	qHBsAg<0.05 Anti-HBs-	HBsAg- Anti-HBs-	HBsAg- Anti-HBs-	<20 / ALT nl
7	Entecavir 0.5 / 37	n.a.	669	458	577	357	567	876	398	<20 / ALT nl
8	Entecavir 0.5 / 42	432	377	330	78	HBsAg- Anti-HBs-	HBsAg- Anti-HBs-	HBsAg- Anti-HBs-	HBsAg- Anti-HBs-	<20 / ALT nl
9	Entecavir 1.0 / 48	121	15	HBsAg- Anti-HBs-	HBsAg- Anti-HBs + (46)	HBsAg- Anti-HBs+ (105)	n.a.	HBsAg- Anti-HBs + (187)	HBsAg- Anti-HBs + (78)	<20 / ALT nl

Andere Studien: Hohe Relapse Raten >100 IU/ml HBsAg

Petersen J et al., EASL 2013

Pipeline HBV

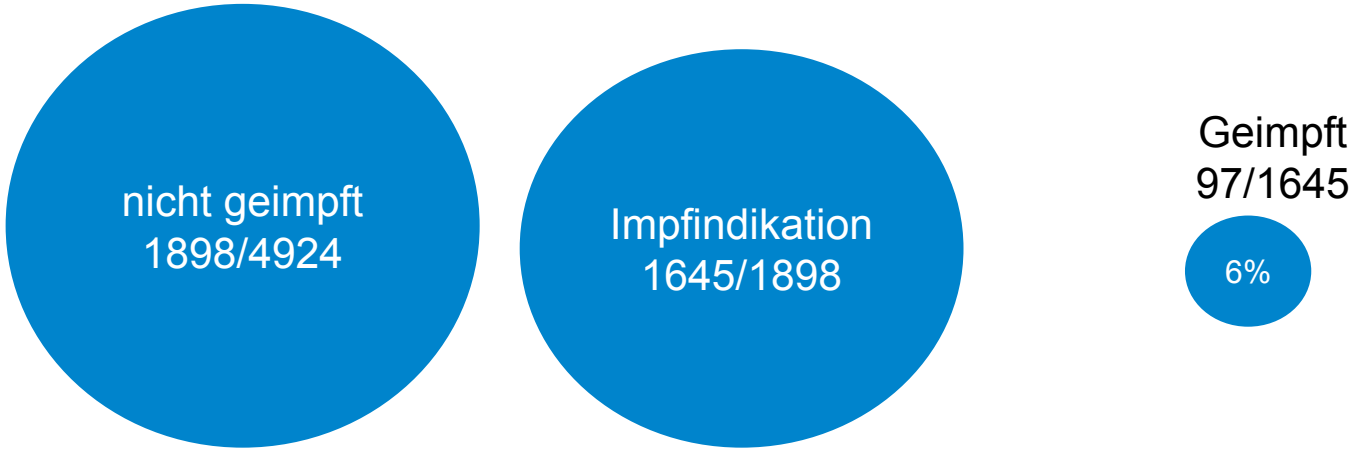
PEG-IFN lambda	Phase II-Daten AASLD 2012
Myrcludex (Entry Inhibitor)	Phase Iia Studie in Russland (bis 5mg i.v. / 0.8 mg s.c.)[1]
TLR 7 Agonist (Innate Immune-Response)	Phase 1b Studien begonnen oder geplant (Gilead[2], Roche[3])
Therapeutische Impfungen (Yeast expressing HBV proteins X,S,C)	In vitro, Mausmodelle[5] (Globeimmune, Gilead[4])
Epigenetische Kontrolle der cccDNA Small molecules gegen Chromatin modifizierende Enzyme, Capsid Inhibitoren	In-vitro Daten[6,7]

1 Haefeli, Urban A 369, 2 EASL 2012 3 www.roche.com, 4 Kemmler et al., A 372, 5 Jäger et al., EASL 2013, 6 Belloni et al., EASL 2013; 7 Palumbo et al., EASL 2013

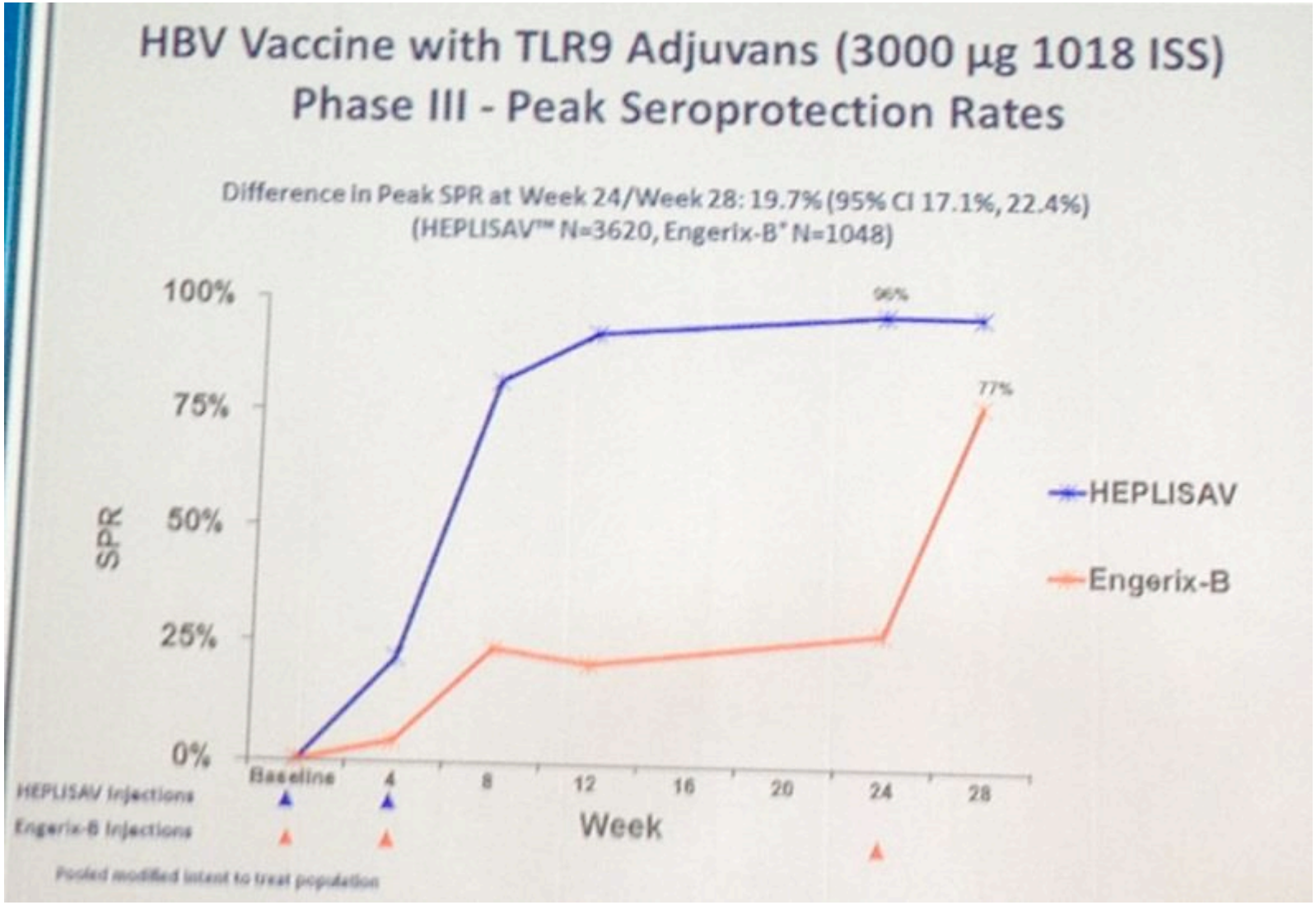
HBV Impfrealität 2013 (Beispiel Frankreich)

2500 Neuinfektionen pro Jahr

Screening von 4924 Personen auf HBV



Bottero et al, #47, EASL 2013



Janssen R et al Late Breaker #1426, EASL 2013

Hepatitis C – was gibt es Neues?

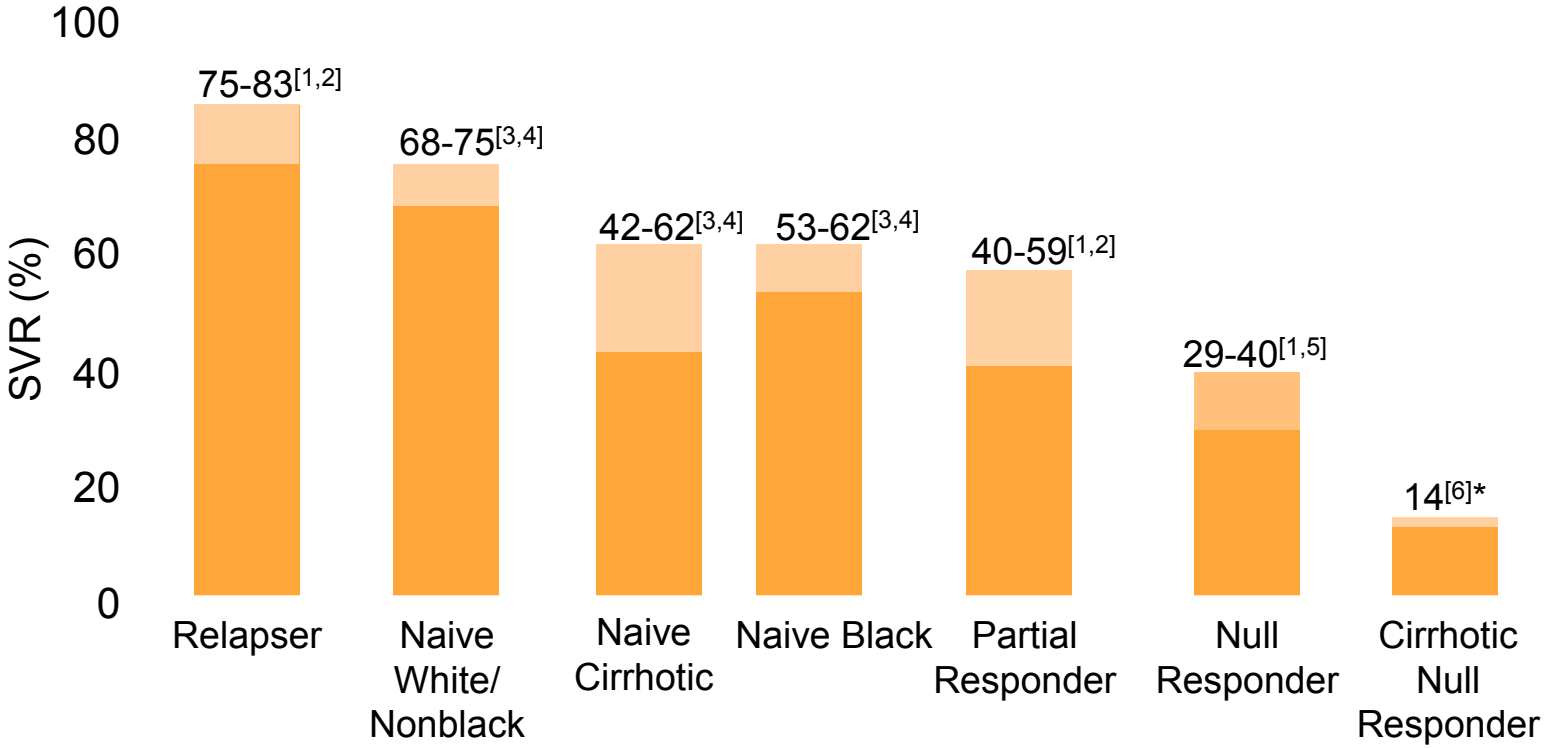
Arbeitskreis AIDS, KV Berlin, 09.05.2013

+ Triple Therapie mit BOC und TVR – real world

+ HCV / HIV Koinfektion

+ Pipeline HCV

Room for improvement in all patient groups with Telaprevir and Boceprevir



*Pooled TVR arms of REALIZE trial.

1. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.
3. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 4. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
5. Bronowicki J, et al. EASL 2012. Abstract 11. 6. Zeuzem S, et al. EASL 2011. Abstract 5.

Clin Gastroenterol Hepatol. 2013 Apr 16 [Epub ahead of print]

A Small Percentage of Patients with Hepatitis C Receive Triple Therapy with Boceprevir or Telaprevir.

Chen EY, Sclair SN, Czul F, Apica B, Dubin P, Martin P, Lee WM.

Department of Internal Medicine, Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center and Parkland Health and Hospital System, Dallas, TX; Department of Medicine, Division of Hepatology, University of Miami Miller School of Medicine, Miami, FL.

CONCLUSION:
Only 18.7% of patients with HCV genotype 1 infection received triple therapy in the 12 months following FDA approval of boceprevir and telaprevir.

This low percentage might result from concerns of side effects and recognition that more effective medications could be available in the future.

Real life cohorts, compassionate use, early access programmes, genotype 1, EASL 2013

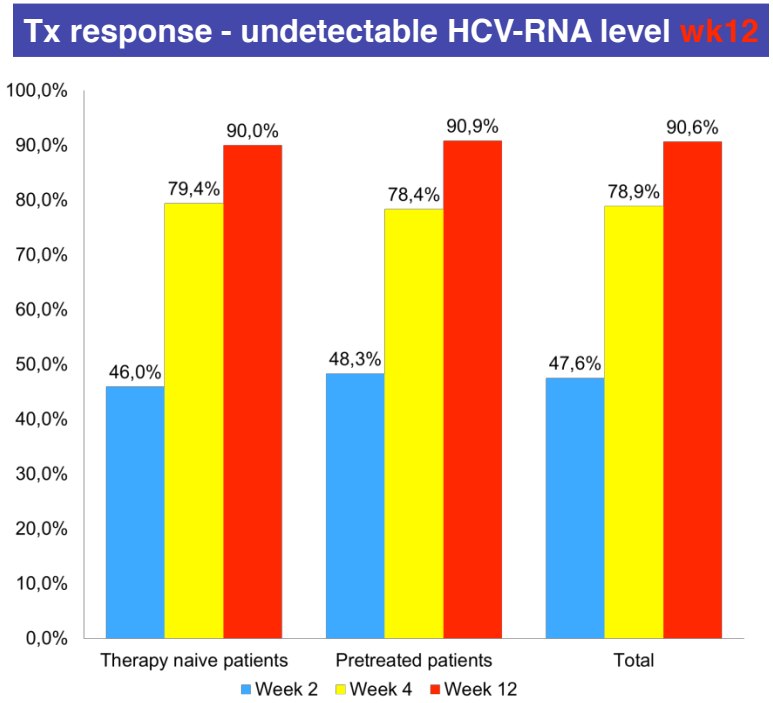
# 65	SAFETY OF TRIPLE THERAPY WITH TELAPREVIR OR BOCEPREVIR IN HEPATITIS C PATIENTS WITH ADVANCED LIVER DISEASE – PREDICTIVE FACTORS FOR SEPSIS
# 793	REAL-LIFE DATA OF TELAPREVIR-BASED TRIPLE-THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C GT1 IN GERMANY - AN INTERIM ANALYSIS
# 799	EFFICACY AND SAFETY OF TRIPLE-THERAPY WITH PEGINTERFERON-RIBAVIRIN, AND BOCEPREVIR AS COMPASSIONATE-USE IN SPANISH PATIENTS WITH HEPATITIS C GENOTYPE 1 WITH SEVERE FIBROSIS:INTERIM-ANALYSIS AT 12 WEEKS
# 805	WEEK 4 AND 12 EFFICACY OF TELAPREVIR (TVR) IN COMBINATION WITH PEGINTERFERON ALFA 2A/RIBAVIRIN (P/R) IN TREATMENT EXPERIENCED PATIENTS WITH GT-1 UNDER REAL LIFE CONDITIONS
# 806	MANAGEMENT AND OUTCOMES OF ANEMIA IN THE INTERNATIONAL TELAPREVIR EARLY ACCESS PROGRAM, FOR PATIENTS WITH HEPATITIS C GENOTYPE 1 INFECTION
# 853	ANEMIA IN A COHORT OF PATIENTS WITH CHRONIC HEPATITIS C ON TRIPLE THERAPY (BOC and TVR)
# 857	TRIPLE THERAPY FOR HEPATITIS C VIRUS (HCV) INFECTION IN PATIENTS WITH COMPENSATED LIVER CIRRHOSIS: LESSONS LEARNED FROM THE FIRST REAL-WORLD EXPERIENCE (BOC and TVR)
# 871	REAL-WORLD EFFICACY AND SAFETY OF TELAPREVIR IN COMBINATION WITH PEGINTERFERON ALFA-2A AND RIBAVIRIN: INTERIM ANALYSIS FROM THE GERMAN NON-INTERVENTIONAL PAN STUDY
# 872	SUBSTANTIAL RENAL IMPAIRMENT IS NOT INFREQUENT IN HCV PATIENTS UNDER TRIPLE THERAPY WITH TELAPREVIR OR BOCEPREVIR
# 875	REAL-WORLD EFFICACY AND SAFETY OF BOCEPREVIR IN COMBINATION WITH PEGINTERFERON ALFA-2A AND RIBAVIRIN IN TREATMENT-NAIVE PATIENTS: INTERIM ANALYSIS FROM THE GERMAN NON-INTERVENTIONAL PAN STUDY
# 884	LOW TREATMENT RATES AND SUBOPTIMAL TREATMENT COMPLETION RATES TO HEPATITIS C VIRUS (HCV) THERAPY: A REAL-WORLD ANALYSIS OF A LARGE US COHORT (BOC and TVR)
# 891	REAL WORD EXPERIENCE WITH TRIPLE THERAPY FOR HCV GT1 PATIENTS IN DIFFICULT TO TREAT PATIENTS: SEVERE ADVERSE EVENTS AND HIGH RATES OF VIROLOGICAL BREAK-THROUGH (BOC and TVR)
# 908	REAL-WORLD EFFICACY OF BOCEPREVIR IN COMBINATION WITH PEGINTERFERON ALFA-2A AND RIBAVIRIN IN TREATMENT-EXPERIENCED PATIENTS: INTERIM ANALYSIS FROM THE GERMAN NON-INTERVENTIONAL PAN STUDY
# 915	WORSE TOLERABILITY OF TRIPLE THERAPY IN SPECIAL POPULATIONS: CIRRHOTICS AND LIVER TRANSPLANT RECIPIENTS (BOC and TVR)

- Patients without negative predictors for treatment

REAL-LIFE DATA OF TELAPREVIR-BASED TRIPLE-THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C GT1 IN GERMANY - AN INTERIM ANALYSIS

- eRVR rates of more than 70% in tx-naïve and pretreated patients
- As observed in clinical trials, adverse events were reported frequently, including anemia and rash.

	Total Population (N=400)
Age [years ± SD] at baseline	49.9 ± 10.9
Males	62.3%
BMI [kg/m² ± SD]	26.4 ± 6.5
Cirrhosis at baseline	16.0%
HCV subtype	
1a	37.8%
1b	51.0%
Subtype unknown	12.0%
IL-28B genotype	
CC	7.3%
CT	20.0%
TT	6.0%
IL-28B genotype unknown	66.8%



Berg, T et al. EASL 2013. Abstract 793

WEEK 4 AND 12 EFFICACY OF TELAPREVIR (TVR) IN COMBINATION WITH PEGINTERFERON ALFA 2A/RIBAVIRIN (P/R) IN TREATMENT EXPERIENCED PATIENTS WITH GT-1 UNDER REAL LIFE CONDITIONS

- Viral response data seem to be consistent with phase III studies

Table 1: Baseline data

		Parameter
Patients, n		537
Age >40 years, n (%)		457 (85.1%)
Male, n (%)		340 (63.3%)
Caucasian race, n (%)		526 (98.0%)
Body mass index (kg/m²), mean ± SD		26.7 ± 4.3
Diagnosis of cirrhosis*, n (%)		113 (21.0%)
Platelets (x10⁹/L), mean ± SD		197 ± 72
ALT (>3x ULN**), n (%)		107 (21.5%)
HCV RNA (log_{10} IU/mL), mean ± SD		6.0 ± 0.8
HCV RNA (>400,000 IU/mL), n (%)		389/511 (76.1%)
Genotype, n (%)	1a	132 (24.6%)
	1b	287 (53.4%)
Genotype 1 subtype:	other/unknown	118 (22.0%)
IL28B genotype	CC	23 (4.3%)
	CT	74 (13.8%)
	TT	27 (5.0%)
	Unknown	413 (76.9%)

* ≥1 result concluding cirhosis: biopsy, clinical appearance, sonography, elastography
** ULN = upper limit of normal

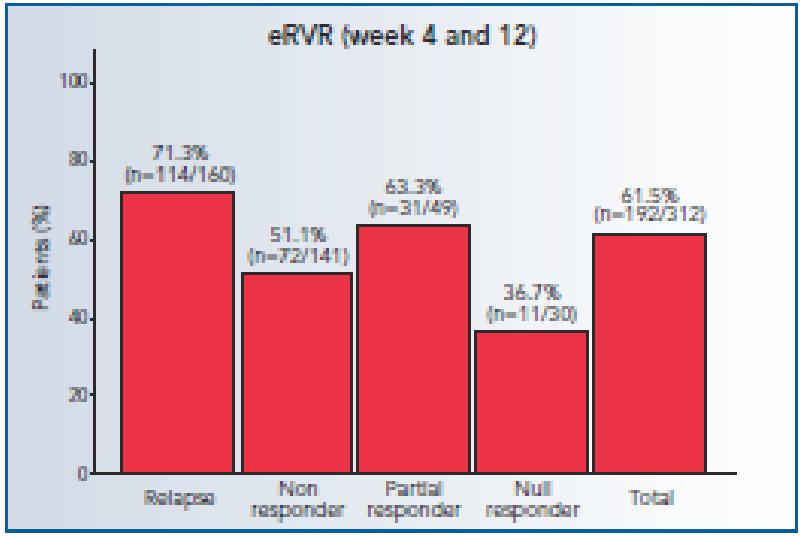


Fig 4. Patients with HCV RNA at weeks 4 and 12

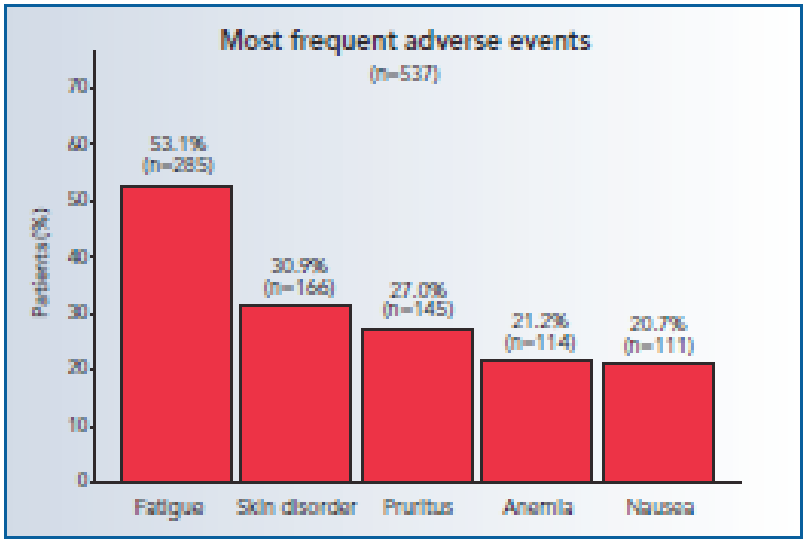


Fig 6. Adverse events

Christensen S, et al. EASL 2013. Abstract 805

REAL-WORLD EFFICACY OF BOCEPREVIR WITH PEGIFN ALFA-2A AND RIBAVIRIN IN TREATMENT-EXPERIENCED PATIENTS: INTERIM ANALYSIS FROM THE GERMAN NON-INTERVENTIONAL PAN STUDY

- Interim analysis week 12
- 52% relapse, NR 45%

Table 1: Baseline data

		Parameter
Patients, n		108
Age >40 years, n (%)		97 (89.8%)
Male, n (%)		58 (53.7%)
Caucasian race, n (%)		105 (97.2%)
Body mass index (kg/m²), mean ± SD		27.2 ± 4.3
Diagnosis of cirrhosis*, n (%)		15 (13.9%)
Platelets (x10⁹/L), mean ± SD		206 ± 72
ALT (>3x ULN**), n (%)		13 (13.7%)
HCV RNA (log_{10} IU/mL), mean ± SD		6.0 ± 1.0
HCV RNA (>400,000 IU/mL), n (%)		75/102 (73.5%)
Genotype, n (%)	1a	25 (23.1%)
	1b	67 (62.0%)
Genotype 1 subtype:	other/unknown	16 (14.8%)
IL28B genotype	CC	6 (5.6%)
	CT	17 (15.7%)
	TT	5 (4.6%)
	Unknown	80 (74.1%)

* ≥1 result concluding cirhosis: biopsy, clinical appearance, sonography, elastography
** ULN = upper limit of normal

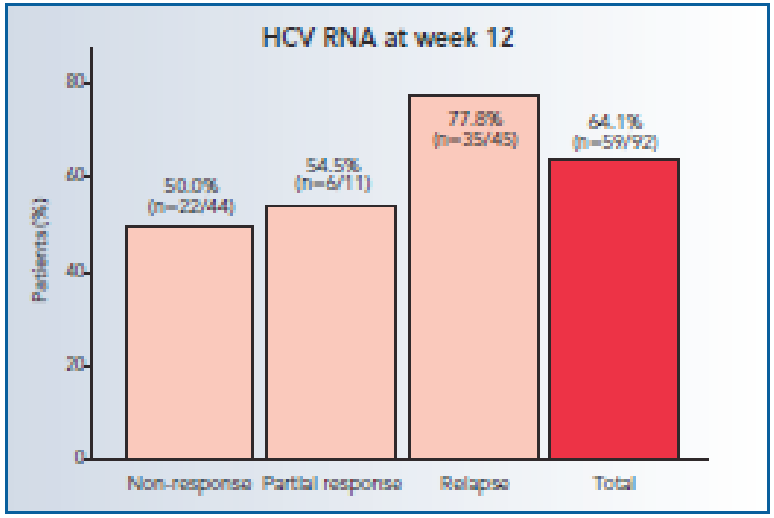


Fig 5. HCV RNA at week 12

CONCLUSIONS

- Early virological responses among treatment experienced patients treated with BOC plus PegIFN alfa-2a/RBV in Germany are generally consistent with the results of published phase 3 trials.
- A high proportion of patient did not have a week 8 value for HCV RNA which may reflect the BOC European prescribing information for patients with previous treatment failure who are required to undergo a full 48 weeks course of re-treatment irrespective of the HCV RNA result at week 8.

Spengler U et al. EASL 2013. Abstract 908

- Side affects – anemia and renal impairment

MANAGEMENT AND OUTCOMES OF ANEMIA IN THE INTERNATIONAL TELAPREVIR EARLY ACCESS PROGRAM, FOR PATIENTS WITH HEPATITIS C GENOTYPE 1 INFECTION

- Grade 3 or grade 4 anemia was reported in 31%, discontinuation for anemia only 3%. EPO and blood tx as therapeutic options
- 16 week interim analysis (ITT), 45% F3, 55% F4 patients

Outcome	F3 patients (n=273)	F4 patients (n=335)	Total (n=609)
Grade 3 anemia SSC event	55 (20%)	100 (30%)	155 (26%)
Grade 4 anemia SSC event	13 (5%)	20 (6%)	33 (5%)
Discontinuation for anemia	3 (1%)	16 (5%)	19 (3%)
Anemia as Serious AE	11 (4%)	22 (7%)	33 (5%)
RBV dose reduction	80 (29%)	126 (38%)	206 (34%)
EPO use	53 (19%)	93 (28%)	146 (24%)
Blood transfusion	26 (10%)	44 (13%)	70 (11%)

Colombo M, et al. EASL 2013. Abstract 806

Renal impairment due to PI treatment ? Reversible?

SUBSTANTIAL RENAL IMPAIRMENT IS NOT INFREQUENT IN HCV PATIENTS UNDER TRIPLE THERAPY WITH TELAPREVIR OR BOCEPREVIR,EASL 2013, #872, Mauss et al

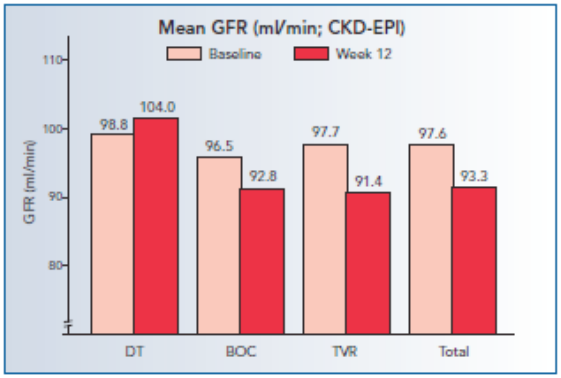


Fig 2. GFR data at baseline and week 12

risk factors: age
hypertension
diabetes
triple therapy

- Ozeki et al. AASLD 2012, Abstract 1818:

Renal dysfunction = eGFR < 50 ml/min/m^2

age	< 50	50 - 64	65 - 70
%	0	50 %	71 %

- Crismale et al. AASLD 2012, Abstract 1756

- Karino et al. AASLD 2012, Abstrct 1754

reduction in GFR associated with TVR-dose per kg body weight

- Patients with advanced liver disease

CUPIC SVR12 rates and safety in 221 cirrhotic NR patients (ANRS CO20-CUPIC) - EASL 2013

- CUPIC trial: early access program with telaprevir and boceprevir from France enrolling treatment-experienced patients with cirrhosis, NR
- Wk 60 subgroup analysis of 221 patients with cirrhosis Child Pugh A:
- High rate of serious adverse events: 57% (TVR) and 40% (BOC)

Undetectable HCV RNA (ITT) n (%)	BOC n = 114	TVR n = 107
Week 12	52 (46)	79 (74)
Week 24	58 (51)	65 (61)
Week 48 (EOT)	44 (39)	45 (42)
SVR_{12} (Total)	44 (39)	49 (46)
SVR_{12} in relapsers	24/46 (52)	32/45 (71)
SVR_{12} in partial responders	20/64 (31)	17/58 (29)
SVR_{12} in null responders	0/2 (0)	0/3 (0)
SAE	40.4%	57%
Death	0.9%	2.8%
Infections	4.4%	6.5%
Hepatic decompensation	1.8%	0.9%
Anemia <8g/dl or blood tx	8.7%	17.8%

Fontaine H, et al. EASL 2013. Abstract 60

Risk of occurrence of death or severe complications during triple therapy (%)

Albumin level at baseline	Platelet count at baseline	
	≥ 100,000/nL	< 100,000/nL
≥ 35 g/dL	3.4%	4.3%
< 35 g/dL	7.1%	44.1%

Hezode C et al. J Hepatol 2013, in p

TRIPLE THERAPY FOR HEPATITIS C VIRUS (HCV) INFECTION IN PATIENTS WITH COMPENSATED LIVER CIRRHOSIS: LESSONS LEARNED FROM THE FIRST REAL-WORLD EXPERIENCE

- n=48 cirrhotic pts, 31% naïve, platelets 144/nl
- 50% anemia <10g/dl, 27<8.5g/dl, dose reduction in 50%
- TVR 33 (69%), BOC 15 (31%)

	Group A Platelets <110/nl and Child-Pugh Score >5 n=7	Group B Platelets <110/nl or Child-Pugh Score >5 n=16	Group C Platelets ≥110/nl and Child-Pugh Score 5 n=20#
Treatment Failure	100% (n=7/7)	69% (n=11/16)	30% (n=6/14)
SAE	57% (n=4/7)	63% (n=10/16)	25% (n=5/20)
Either SAE or Treatment Failure	100%	94%	50%

➢Almost every patient (96%; n=22/23) with a Child-Pugh Score >5 and/or baseline platelets <110/nl (Group A/B) experienced either a treatment failure and or at least one SAE until EOT

Massoumy B, et al. EASL 2013. Abstract 857

SAFETY OF TRIPLE THERAPY WITH TELAPREVIR OR BOCEPREVIR IN HEPATITIS C PATIENTS WITH ADVANCED LIVER DISEASE – PREDICTIVE FACTORS FOR SEPSIS

- Poor outcome and high rate of SAE
- 3 deaths out of n=110 treated patients
- Platelet count < 100.000/ul , Albumin <35g/l, and Hepatovenous Pressure Gradient (HVPG) >10mm Hg were predictive markers for severe septic events.

Rutter K et al. EASL 2013. Abstract 65

REAL WORD EXPERIENCE WITH TRIPLE THERAPY FOR HCV GT1 PATIENTS IN DIFFICULT TO TREAT PATIENTS: SEVERE ADVERSE EVENTS AND HIGH RATES OF VIROLOGICAL BREAK-THROUGH

- High rates of serious adverse events: 64% (BOC) and 53% (TVR)
- Severe anemia (<9g/dl) occurred in 65%, blood tx 38%
- All pts > 60 yrs and all cirrhotic patients received blood tx
- Discontinuation rate 33% (BOC) and 31% (TVR)

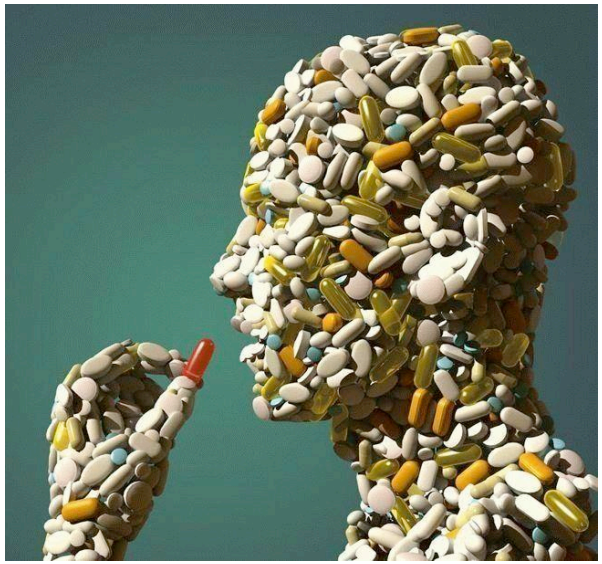
Baseline characteristics	n = 143
Median age	55yrs 30% > 60a
male	67%
Caucasian	90%
Genotype 1a / 1b	39% / 60%
Advanced fibrosis >F3	48%
F4 and platelets < 120/nl	23%
Tx naïve / pretreated	26% /74%
Non responder	50%
Tx BOC / TVR	69 / 74

Patients at risk for development of SAE and treatment failure	n = 83	
Platelets <100.000 /ul and albumine <39g/l	n=17	100% treatment failure and 100% SAE

Petersen J et al. EASL 2013. Abstract 891

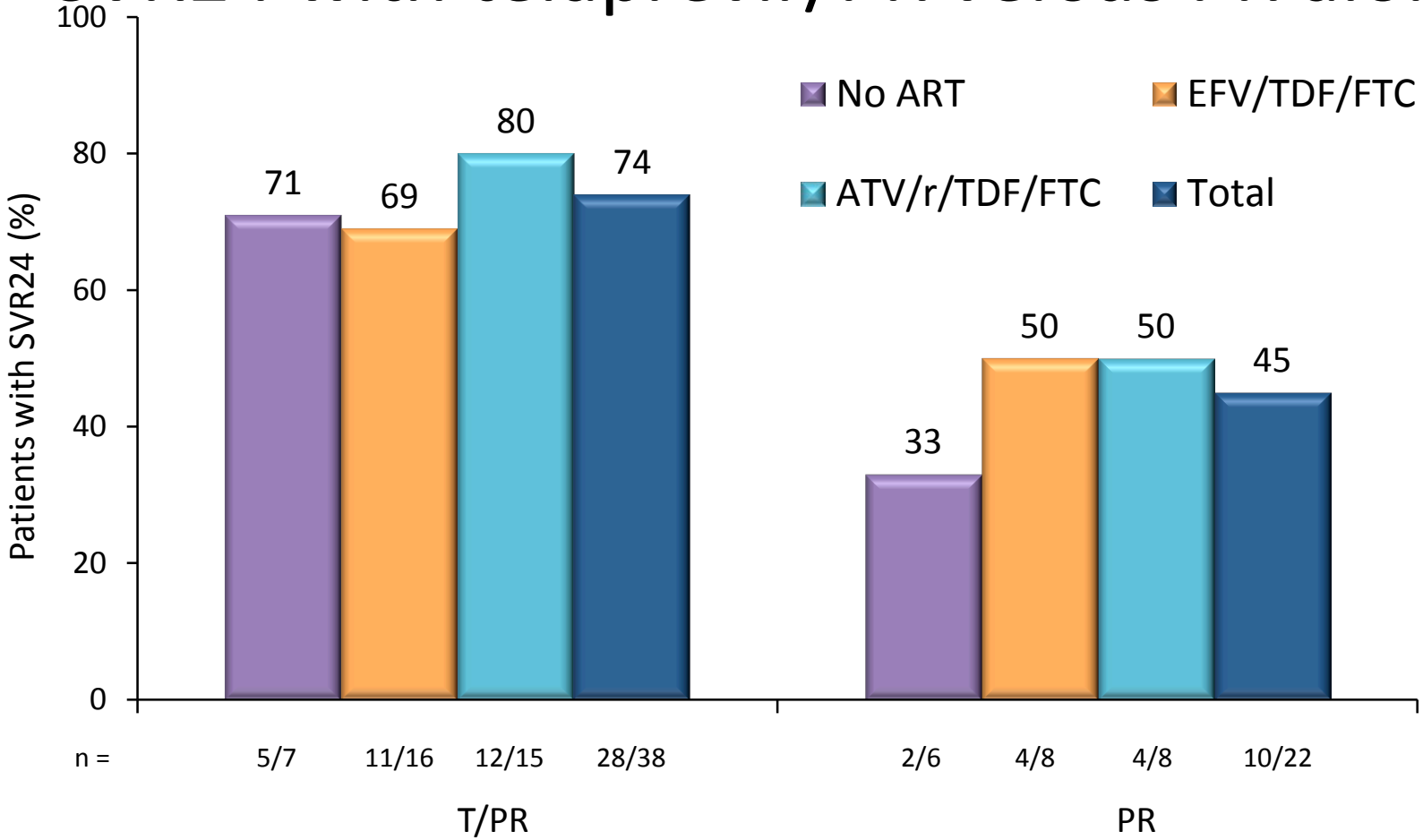
Therapeutic implications of HCV-HIV co-infection

- In patients with HIV, liver disease is a major cause of death and this is mostly (>75%) related to HCV
- The presence of HIV infection can accelerate HCV-related liver damage, hastening development of cirrhosis
- Considerations when treating HIV-HCV co-infected patients include over-lapping side effects, pill burden and drug-drug interactions



Andreoni et al. Eur Rev Med Pharmacol Sci 2012;16:1473–83.
Image sourced from http://www.picvalley.net/u/103/25524_775.JPG

HCV/HIV co-infection: SVR24 with telaprevir/PR versus PR alone



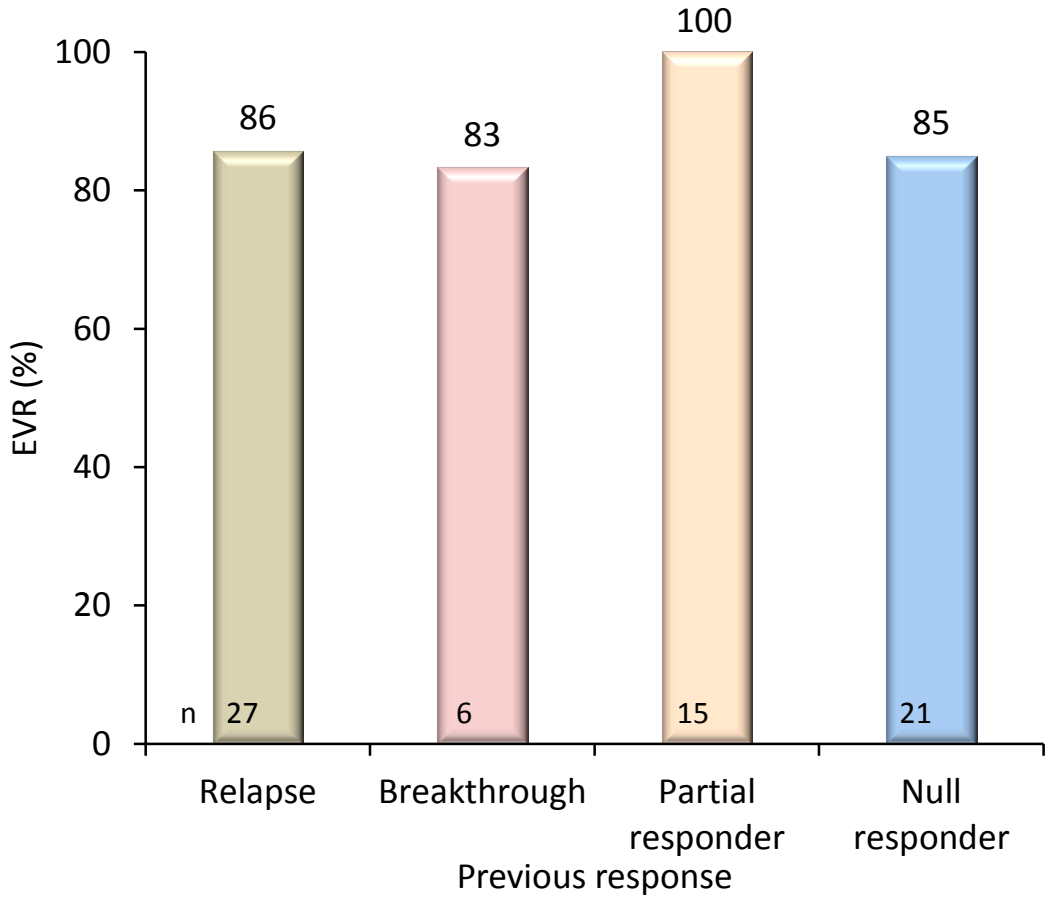
Prior to Week 24 visit, 1 patient in this cohort was lost to follow up. SVR24 was imputed based on SVR12 for this patient

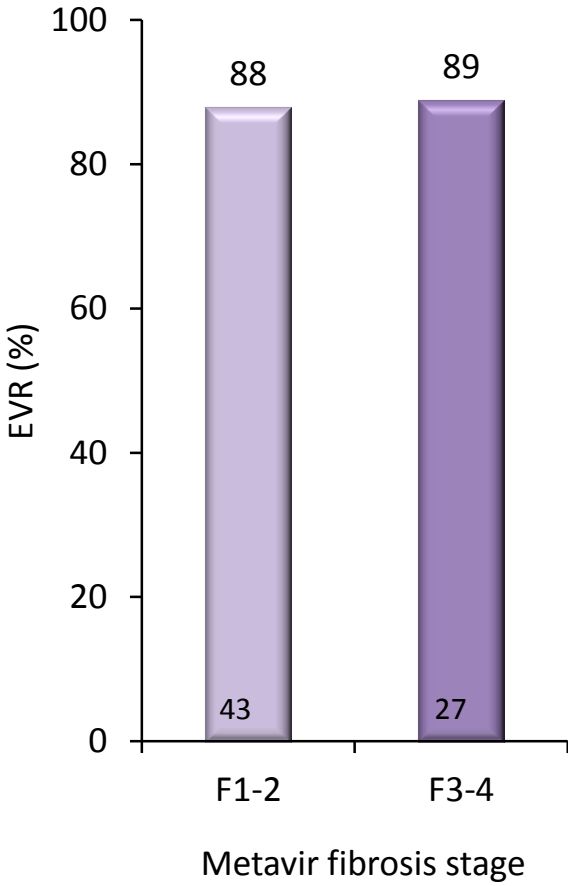
T/PR, telaprevir + peginterferon and ribavirin; ART, antiretroviral therapy; EFV, efavirenz; TDF, tenofovir; FTC, emtricitabine

Sulkowski et al. AASLD 2012, abstract 54.

HCV/HIV co-infection: EVR (W16) with single-arm telaprevir/pIFN/RBV in experienced HCV/HIV (ANRS HC26)

- Single-arm study
- 70 patients were enrolled, and 69 started treatment
- Median age 50 years, 80% male, 86% white, 55% IDU, 68% HCV GT1





Early virological response (EVR) was defined as HCV RNA <15 UI/mL at week 16.

Cotte et al. CROI 2013, abstract 36.

HCV/HIV co-infection: Numerous trials with novel DAAs ongoing or planned

Faldaprevir (PI) once-daily + PegIFN/RBV
(phase III, open-label, GT1)[4]

Sofosbuvir (NS5B) once-daily + RBV
(phase III, open-label, GT 1, 2 and 3)[2]

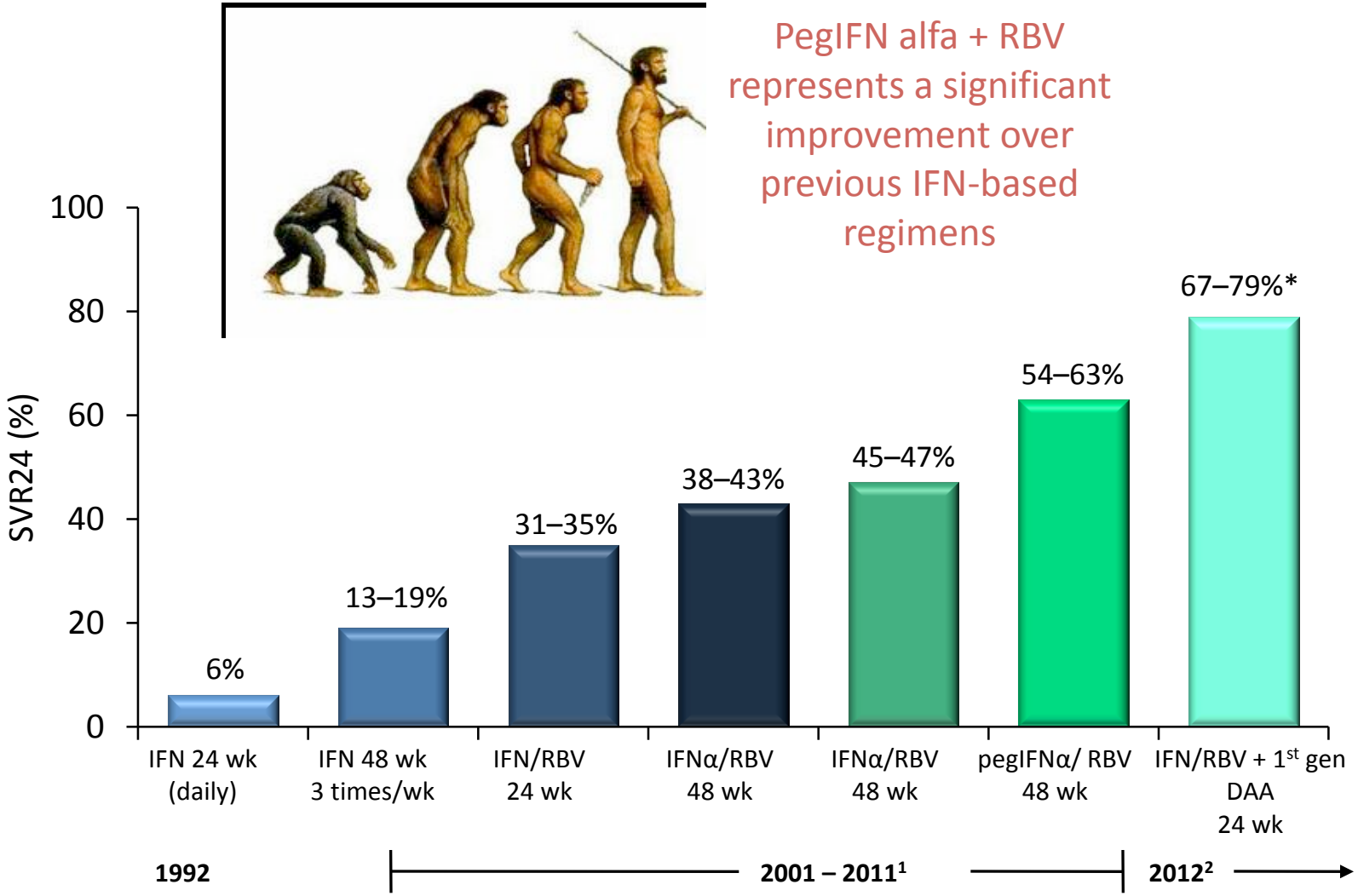
Simeprevir (PI) once-daily + PegIFN/RBV
(phase III, open-label, GT1)[1]

Daclatasvir (NS5A) once-daily + PegIFN/RBV[3]
COMMAND-HIV is a phase 3, open-label, safety and efficacy study of daclatasvir with pegIFN alfa-2a and RBV ongoing in ~300 genotype 1 treatment-naive patients

- Co-infection studies must take account of potential drug-drug interactions with antiretroviral therapy for HIV
- Clinical needs not met by current trials include:
  - Treatment regimens for co-infected patients with cirrhosis
  - All-oral treatment regimens

1. http://clinicaltrials.gov/ct2/show/NCT01479868
2. http://clinicaltrials.gov/ct2/show/NCT01667731
3. http://clinicaltrials.gov/show/NCT01471574
4. http://clinicaltrials.gov/ct2/show/NCT01399619

Evolution of HCV therapy



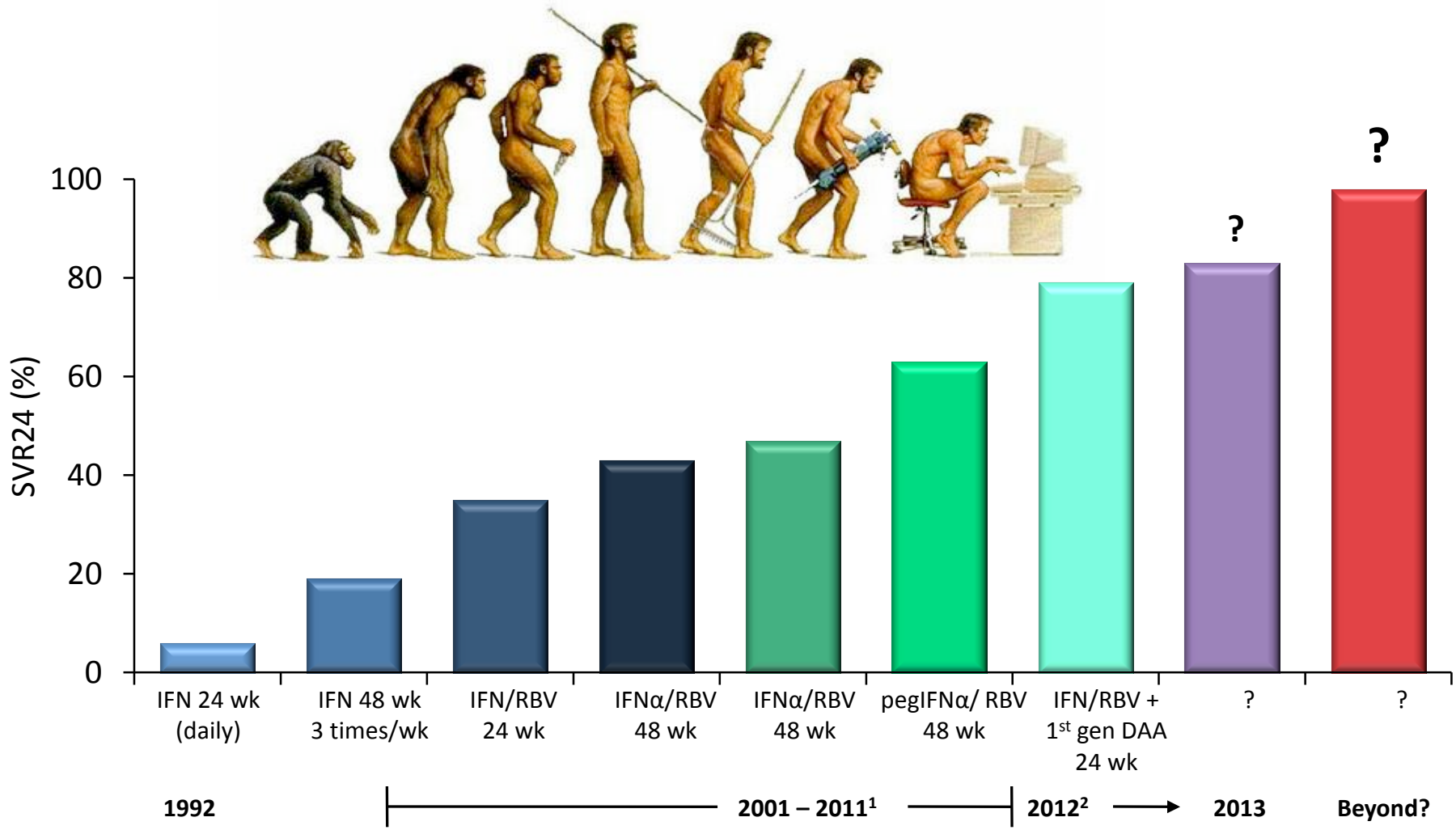
* in patients with HCV genotype 1

DAA, direct-acting antiviral; IFN, interferon; RBV, ribavirin; SVR24, sustained virologic response

1. Adapted from Manns MP et al. Gut 2006;55:1350-1359. 2. Tran. Am J Manag Care 2012;18 (14 Suppl):S340–9.

http://www.metrolic.com/human-evolution-102891/

But what does the future hold?

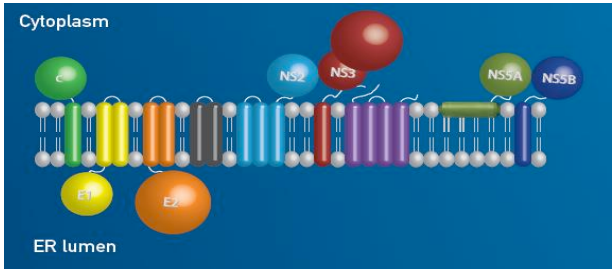


DAA, direct-acting antiviral; IFN, interferon; RBV, ribavirin; SVR24, sustained virologic response

1. Adapted from Manns MP et al. Gut 2006;55:1350-1359. 2. Tran. Am J Manag Care 2012;18 (14 Suppl):S340–9.

http://www.metrolic.com/human-evolution-102891/

Several potential innovative drug targets in HCV



NS3/4A	NS5A	NS5B	
A serine protease, essential for post-translational processing of HCV polyproteins	Multifunctional membrane-associated phosphoprotein, essential component of the HCV-RNA replication complex	An HCV-specific, RNA-dependent RNA polymerase	
Boceprevir[1] Telaprevir[1] ABT-450/r[2] Sovaprevir[3] Asunaprevir[11] Simeprevir[9] Faldaprevir[12] Danoprevir[12] GS-9451[13] MK-5172[14] ACH-806/GS-9132[1]	Daclatasvir[4] Ledipasvir[4] ABT-267[2] PPI-668[6] AZ-689[4] BMS-824393[4] PPI-461[4]	<u>Nucleos(t)ide analogue</u> Sofosbuvir[10] Mericitabine[15]	<u>Non-nucleoside analogue</u> BI-207127[16] ABT-333[2] ABT-072[17] BMS-791325[18] Tegobuvir[12] Setrobuvir[12] VX-222[19] Filibuvir[12]

IFN-lambda
A type III interferon with a restricted distribution of receptors contributing to a favourable adverse event profile[7]
BMS-914143[8]
Cyclophilin A
Host protein involved in HCV replication through interaction with NS5A and the HCV polymerase
Alisporivir[5,**] SCY-635[1]

*Voluntary clinical hold, BMS press release;
**On clinical hold, Novartis press release

1. Rehman et al. Genetic Vaccines and Therapy 2011, 9:11 2.http://clinicaltrials.gov/ct2/show/NCT01464827 3. http://ir.achillion.com/releasedetail.cfm?releaseid=6989383. 4.Gish R & Meanwell NA Clin Liver Dis. 2011;15:627–39. 5. Coelmont L et al. PLoS One 2010;5:e13678. 6.http://clinicaltrials.gov/ct2/show/NCT01448200 7. Miller DM et al. Ann N Y Acad Sci 2009;1182:807. 8. http://clinicaltrials.gov/show/NCT01309932 9.Poordad et al. AASLD 2012, abstract 83. 10.Gane E, et al. EASL 2012. Poster 1113. 11. http://clinicaltrials.gov/ct2/show/NCT01030432 12 . Delang et al.Viruses 2010, 2, 826-866. 13. http://www.gilead.com/research 14. http://clinicaltrials.gov/ct2/show/NCT01353911 15. Wedemeyer et al. Hepatology. 2013 Jan 24. doi: 10.1002/hep.26274. 16. http://www.pipelinereport.org/browse/hcv-treatment/bi-207127 17.http://www.pipelinereport.org/browse/hcv-treatment/abt-072 18.http://clinicaltrials.gov/show/NCT01193361. 19. http://www.vrtx.com/research-development/pipeline

Each class appears to have some characteristic features

NS3/4A Protease Inhibitors	• Poor/no activity against GT31 • Low-to-medium barrier to resistance[1] • Extensive cross-resistance[1]	• QD, BID or TID dosing • Potential for CYP-mediated DDIs[2,3] • Some may require RTV
NS5A Replication Complex Inhibitor	• General picomolar activity against multiple GTs in vitro[4,5] • Low-to-medium barrier to resistance[1]	• QD dosing[6,7] • Potential for CYP-mediated DDIs[7]
NS5B Nucleos(t)ide Inhibitors	• Broad GT coverage[1] • High barrier to resistance[1] • QD or BID dosing[9]	• Limited potential for CYP-mediated DDIs
NS5B Non-nucleos(t)ide Inhibitors	• Most are GT/subtype specific[1] • Low barrier to resistance[1] • QD or BID dosing[9]	• Limited potential for CYP-mediated DDIs[10]
Cyclophilin Inhibitors (HTA)	• Broad GT coverage *in vitro*[1] • Limited resistance data available	• BID/QD dosing[11] • Potential for CYP-mediated DDIs[10,12]
Pegylated interferon lambda	• More limited receptor expression may lead to fewer adverse events[13]	• No evidence of hematologic toxicity[13]

DDI=drug-drug interactions; HTA,=host-targeted antiviral; GT=genotype

Created from 1.Sarrazin C, et al. *J Hepatol*. 2012;56:S88–S100; 2. Eley T, et al. AASLD 2011. Poster 381; 3. Sekar V, et al. EASL 2010, Poster 1076; 4. Gao M, et al. *Nature* 2010;465:96–100; 5. Belda et al. Virus Res. 2012;170:1-14. 6. Pol S, et al. ICAAC 2011. Oral Presentation HI-376; 7. Lawitz EJ, et al. *J Hepatol*. 2012;Feb 4 [epub]; 8. Bifano M, et al. CROI 2012. Poster 618; 9. Poordad F, et al. *Am J Manag Care* 2011;17:S123–S130; 10. Seden K, et al. *J Antimicrob Chemother*. 2010;65:1079–1085; 11. Flisiak R, et al. EASL 2011. Oral 4; 12. Park S, et al. AASLD 2011. Abstract 364; 13. Miller DM et al. Ann N Y Acad Sci 2009;1182:80.

Many studies have looked at different ways of combining these compounds

In different patient types

- Different genotypes
- Treatment-naive
- Non-responders to prior therapy
- Intolerant to previous therapy

Future HCV treatment strategies

Treatment-naive

Peg-IFNα-containing regimens

2nd Gen. PI Triple — Phase III HCV type 1 naive

Faldaprvir, Simeprevir

NUC Triple — Phase III HCV type 1 and 4-6 naive

Sofosbuvir

2013 | 2014 | 2015 | 2016 | 2017

Interferon-free regimens

NUC + RBV — 3 Phase III HCV type 2 and 3 in tx naive/experienced pts

Sofosbuvir

PI = Protease Inhibitor, NUC = nucleosidic Polymerase (NS5B) Inhibitor

Phase III second generation PIs
HCV type 1 treatment naive patients

Protease-Inhibitor (PI)	N (% Ci)	Treatment duration
[1] Faldaprevir (120 vs. 240 mg)	652 (17% >=F3)	12-24 W RGT (24-48 W) SVR 79-80% vs 52%
[2] Simeprevir QUEST-2 Peg-IFNa-2a or-2b backbone	391 (7%)	12W RGT (24-48W) SVR 81% vs 50%
[3] Simeprevir QUEST-1 only Peg-IFNa2a backbone	394 (12% F4, 18% F3)	12W RGT (24-48W) SVR 80% vs 50%

Ferenci LB #1416, Manns LB #1413, EASL 2013, Jacobson LB #1425

Phase III second generation PIs
HCV type 1 treatment naive patients
Response-guided concept

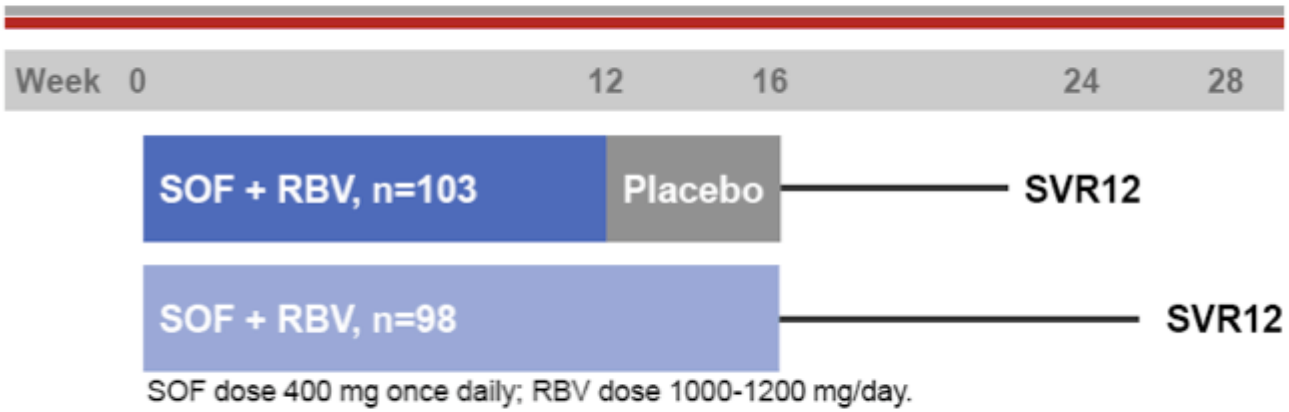
Faldaprevir Triple	eRVR 89%	SVR 86-89%
Simeprevir Triple	eRVR 91%	eRVR 86%

24 weeks treatment duration in most patients
Less side effects as compared to first generation PI Triple
Once a day dosing

Ferenci LB 1416, Manns LB 1413, EASL 2013

All Oral Therapy With Sofosbuvir + Ribavirin for 12 or 16 Weeks in Treatment-Experienced Genotype 2/3 HCV-Infected Patients: Results of the Phase 3 FUSION Trial

Study Design



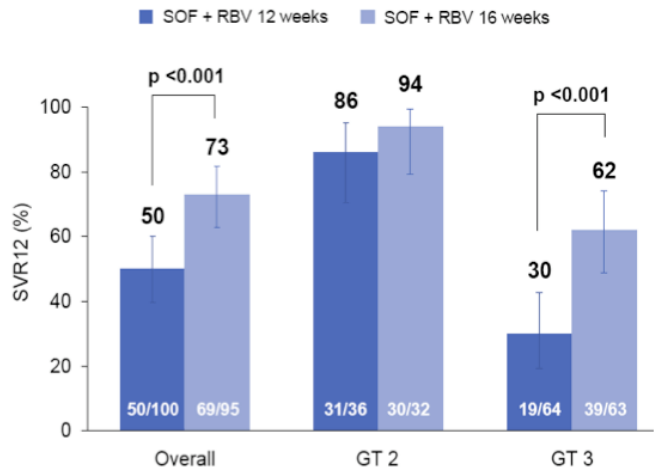
SOF dose 400 mg once daily; RBV dose 1000-1200 mg/day.

- Genotype 2 or 3 HCV-infected patients who had failed prior interferon-based treatment
- Expanded inclusion criteria
  - Targeted 30% enrollment of patients with cirrhosis
  - No upper limit to age or BMI
  - Platelet count ≥50,000/mm^3, no neutrophil minimum
- Randomized (1:1), double blind, placebo controlled
- Stratified by cirrhosis and genotype

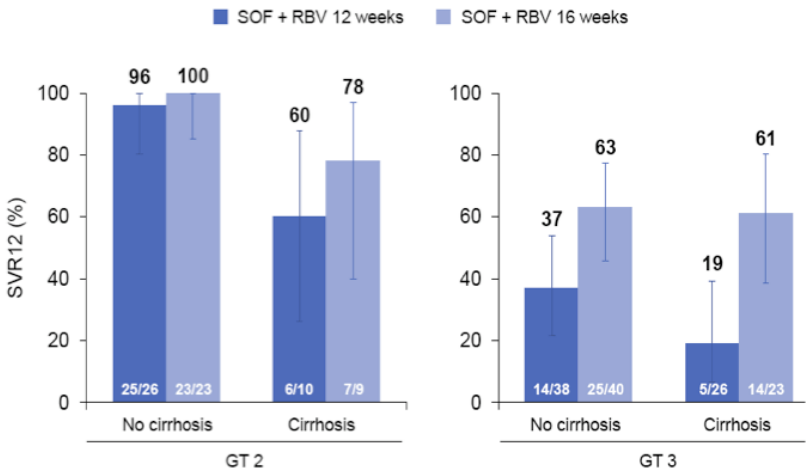
Nelson et al, #6, EASL 2013

All Oral Therapy With Sofosbuvir + Ribavirin for 12 or 16 Weeks in Treatment-Experienced Genotype 2/3 HCV-Infected Patients: Results of the Phase 3 FUSION Trial

Results: SVR12 by HCV Genotype



Results: SVR12 by HCV Genotype/Cirrhosis



Nelson et al, #6, EASL 2013

Future HCV treatment strategies

Peg-IFNa-containing regimens

Phase III
Treatment-naive

- 2nd Gen. PI Triple
  - Faldaprvir, Simeprevir
- NUC Triple
  - Sofosbuvir
  - HCV type 1 and 4-6

Next wave of triple/quadruple regimens

- Asunaprevir (PI)
- MK5172 (PI)
- MK7009 (PI)
- Daclatasvir (NS5A)
- GS8558 (NS5A)
- Daclatasvir + Asunaprevir
- GS5885 + GS9451

2013 | 2014 | 2015 | 2016 | 2017

Interferon-free regimens

Phase III

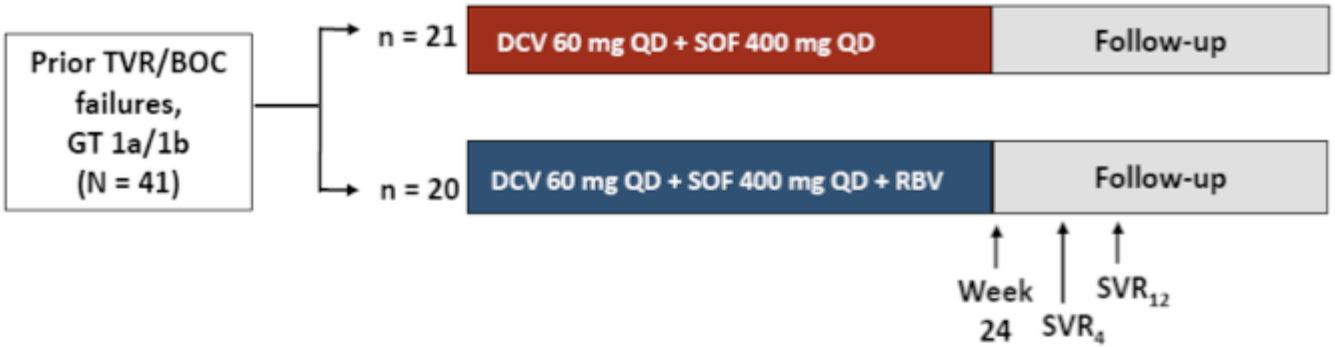
- NUC + RBV
  - Sofosbuvir
  - HCV type 2 and 3

Next wave of all-oral regimens

- ABT-450/r (PI/r)+ABT-267 (NS5A)+ABT-333 (NNUC)+RBV
- Faldaprevir + BI 207127 (NNUC) + RBV
- Daclatasvir (NS5A) + Sofosbuvir (NUC) ± RBV
- GS5885 (NS5A) + Sofosbuvir (NUC) + RBV
- GS9669 (Non-NUC) + Sofosbuvir (NUC) RBV
- Asunaprevir (PI) + Daclatasvir (NS5A) + BMS791325

Sustained Virologic Response With Daclatasvir Plus Sofosbuvir ± Ribavirin in Chronic HCV Genotype (GT) 1-Infected Patients Who Previously Failed Telaprevir or Boceprevir

Sulkowski et al, #1417, EASL 2013



Methods

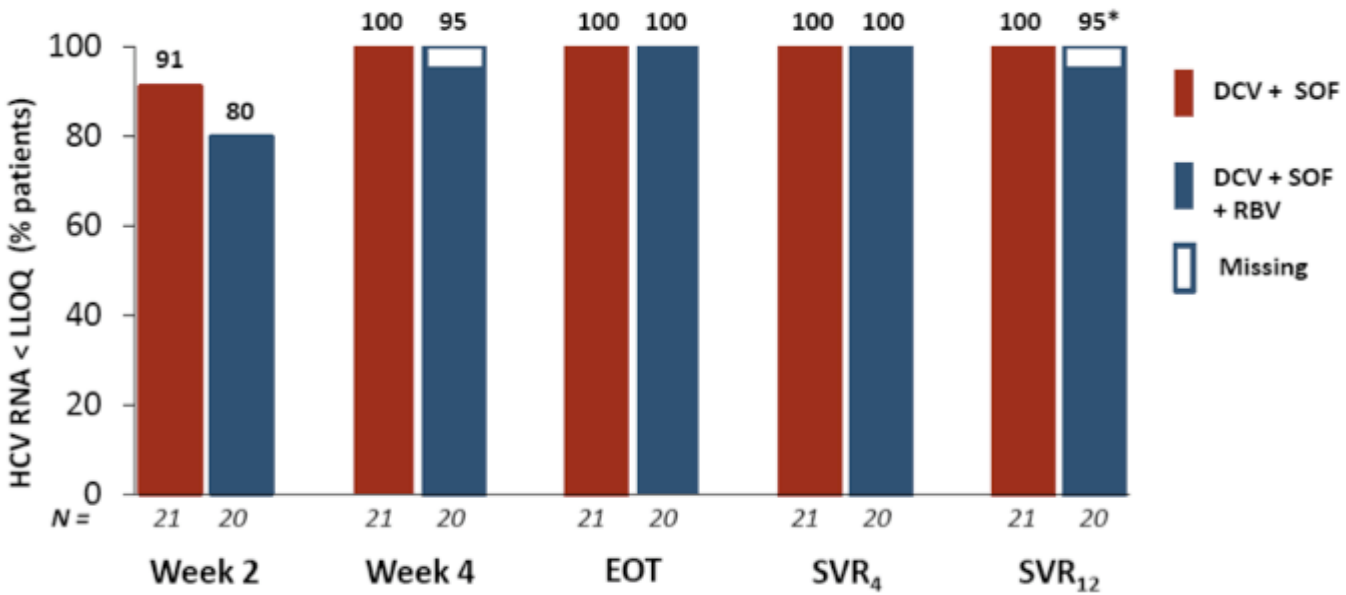
- Chronic HCV infection, GT 1 (1a/1b), HCV RNA ≥ 10^5 IU/mL
- Non-cirrhotic
- Prior nonresponse, relapse, or breakthrough during treatment with pegIFN-alfa/RBV plus TVR (750 mg TID) or BOC (800 mg TID)
  - **Nonresponse**: HCV RNA detectable at end of treatment
  - **Relapse**: HCV RNA undetectable at end of treatment, then ≥ lower limit of quantitation (LLOQ) during 24-week follow-up
  - **Breakthrough**: confirmed > 1 log increase from nadir in HCV RNA or confirmed HCV RNA ≥ LLOQ after HCV RNA undetectable on treatment

Sustained Virologic Response With Daclatasvir Plus Sofosbuvir ± Ribavirin in Chronic HCV Genotype (GT) 1-Infected Patients Who Previously Failed Telaprevir or Boceprevir

Sulkowski et al, #1417, EASL 2013

- No virologic breakthrough or treatment discontinuations through EOT

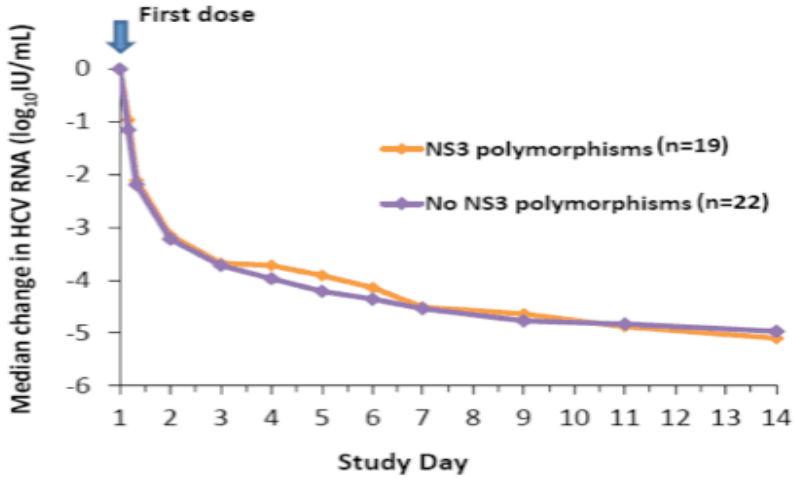
Virologic Response During and After Treatment (mITT)



* 1 patient missing at post-treatment (PT) Week 12: HCV RNA was undetectable at PT Week 4 and at PT Week 24 (preliminary)

- 21/41 patients have reached PT Week 24; all have achieved SVR_{24}

Patients with NS3 polymorphisms, n	
V36M-R155K	6
R155K	3
V36L-R155K	1
T54S-R155K	1
T54S-V55I-R155K	1
V36M	1
V36M-V55I	1
V36M-V55A-R155K	1
V36M-R155K-I170T	1
V36A	1
V55A	1
V170T	1



Safety On-Treatment

Patients with event, n (%)		DCV + SOF (n = 21)	DCV + SOF + RBV (n = 20)
Safety parameters	Grade 3/4 AEs	0	1 (5)
	Discontinuations due to AEs	0	0
	SAEs[a,b]	0	1 (5)
	Hgb < 9 g/dL (grade 3/4)	0	0

SAE, serious adverse event.
[a]One event of overdose (extra study dose of medication), classified as an SAE, is not included in the table.
[b]The SAE and grade 3/4 AE represent a single patient with hypokalemia.

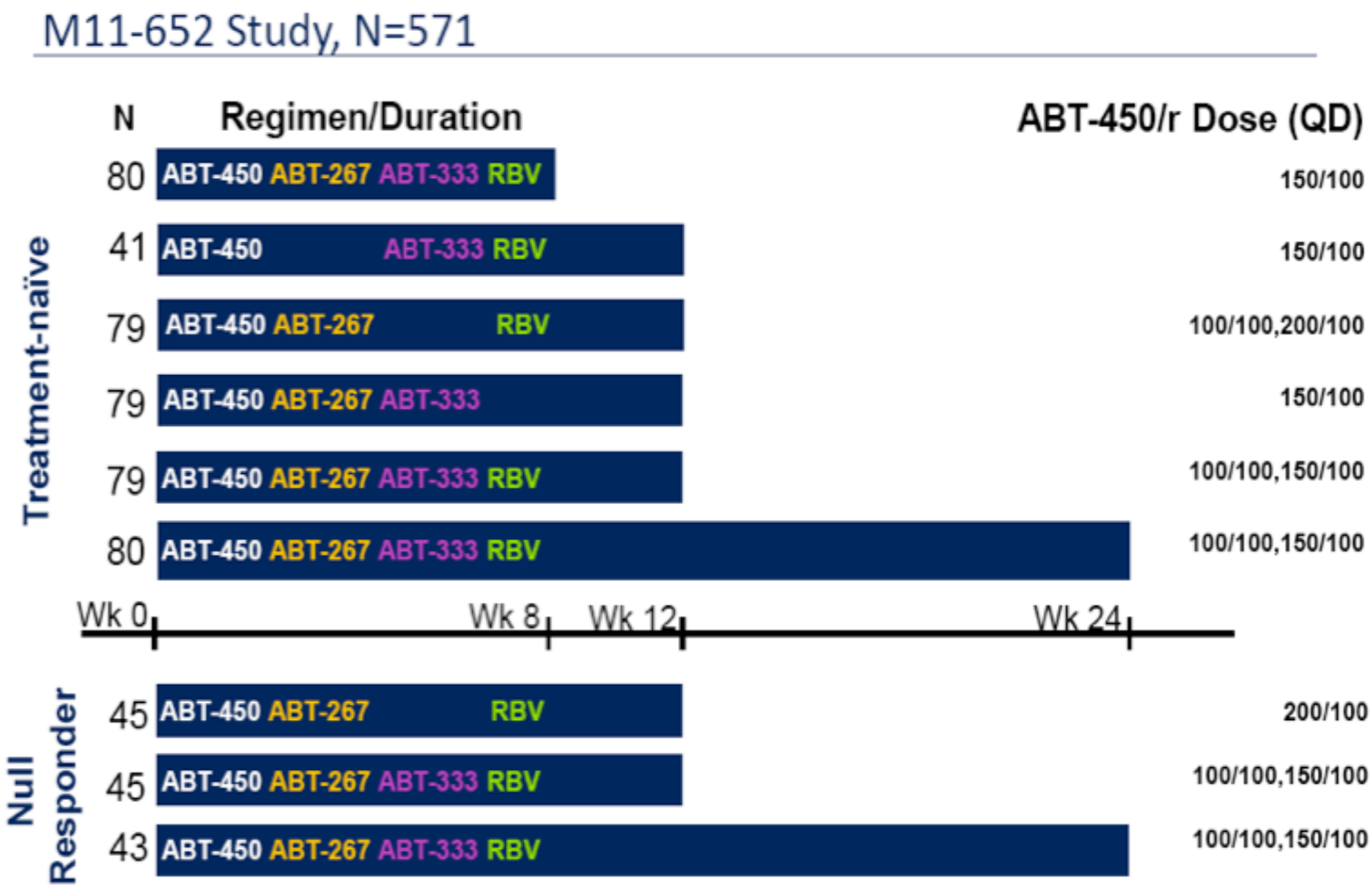
- No grade 3/4 elevations of ALT, AST, or total bilirubin

Sulkowski et al, EASL 2013

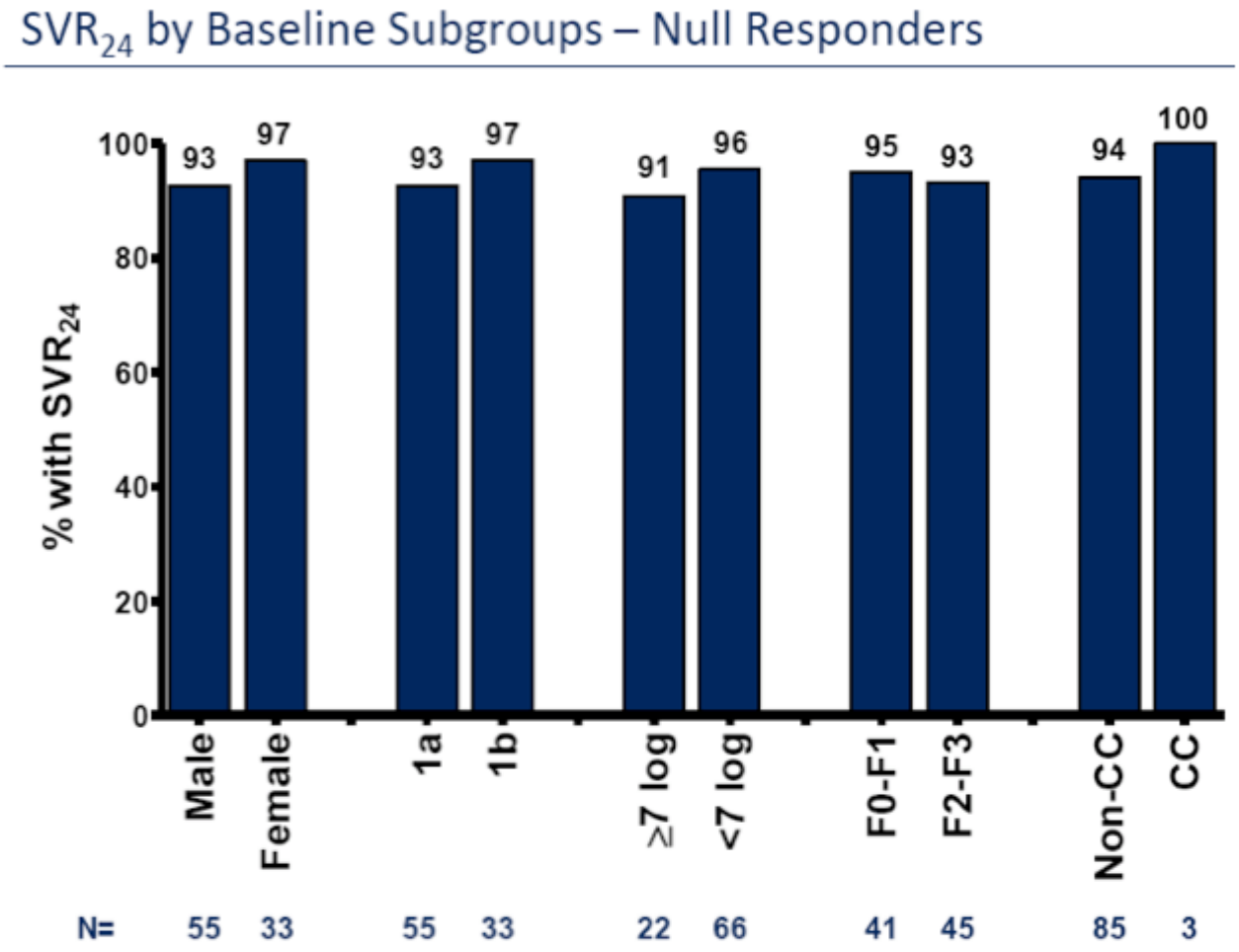
ALT, alanine aminotransferase, AST, aspartate aminotransferase

SAFETY AND EFFICACY OF INTERFERON-FREE REGIMENS OF ABT-450/r, ABT-267, ABT-333 +/- RIBAVIRIN IN PATIENTS WITH CHRONIC HCV GT1 INFECTION: RESULTS FROM THE AVIATOR STUDY

Kowdley et al, #3, EASL 2013



ABT-267 25mg QD; ABT-333 400mg BID; RBV weight-based 1000-1200 mg daily dose divided BID
All patients to be followed through 48 weeks post-treatment

SAFETY AND EFFICACY OF INTERFERON-FREE REGIMENS OF ABT-450/r, ABT-267, ABT-333 +/- RIBAVIRIN IN PATIENTS WITH CHRONIC HCV GT1 INFECTION: RESULTS FROM THE AVIATOR STUDY

Kowdley et al, #3, EASL 2013