Post EASL

Arbeitskreis AIDS niedergelassener Ärzte Berlin e. V.
7. Mai 2014

Karsten Wursthorn

Institut für Interdisziplinäre Medizin
An der Asklepios Klinik St. Georg
Hamburg

HIV / HCV Koinfektion
- Inzidenz

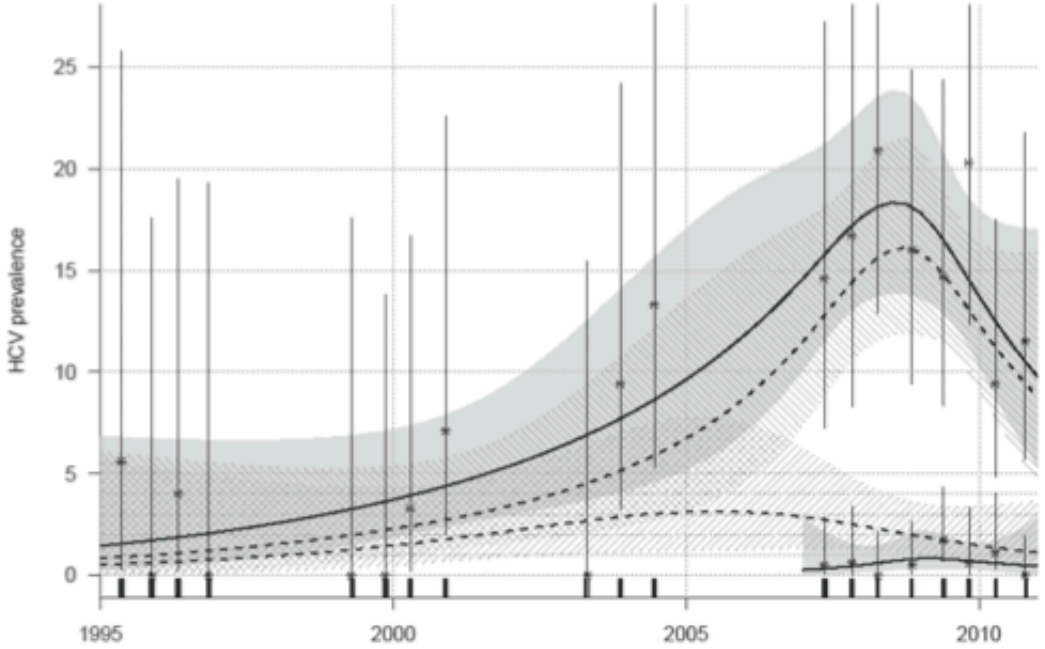
Amsterdam Kohorte

- 2080 MSM, 17‘310 person years
- Follow-Up 7,4 Jahre
- 526 (25,3%) waren HIV positiv, weitere 222 serokonvertierten im Verlauf
- 29 Fälle von Hepatitis C bei 748 HIV-positiven MSM
- 0 Fälle von Hepatitis C bei HIV-negativen MSM

Vanhommerig et al, EASL 2014

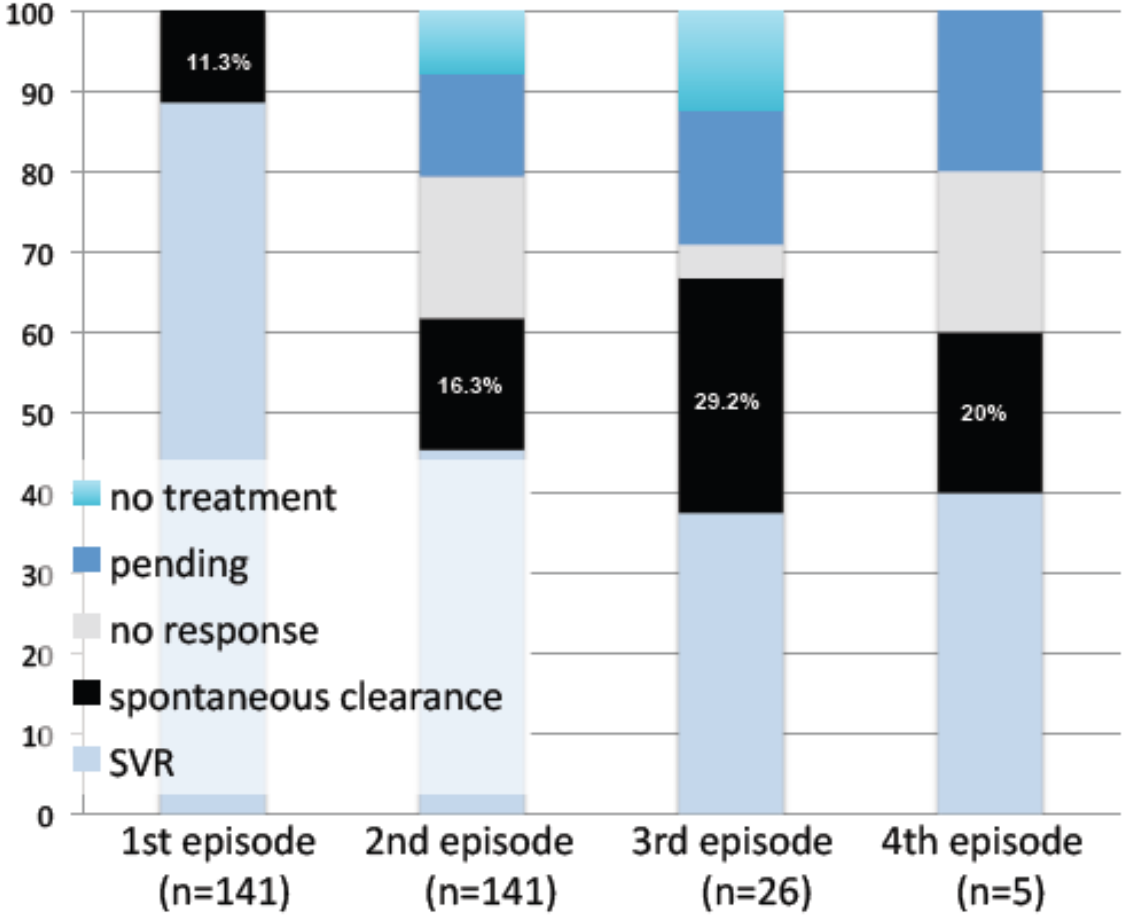
Hepatitis C Inzidenz in der Amsterdam Kohorte leicht rückläufig

Amsterdam STI Clinic; 1995-2010



Urbanus et al, AIDS 2014

Häufigere spontane Ausheilung der Hepatitis C mit zunehmender Reinfektionshäufigkeit



NEAT Kohorte
HIV-positive MSM

Figure 2: Outcome of acute hepatitis C according to episode

Ingiliz et al, EASL 2014

HIV / HCV Koinfektion
- Behandlung

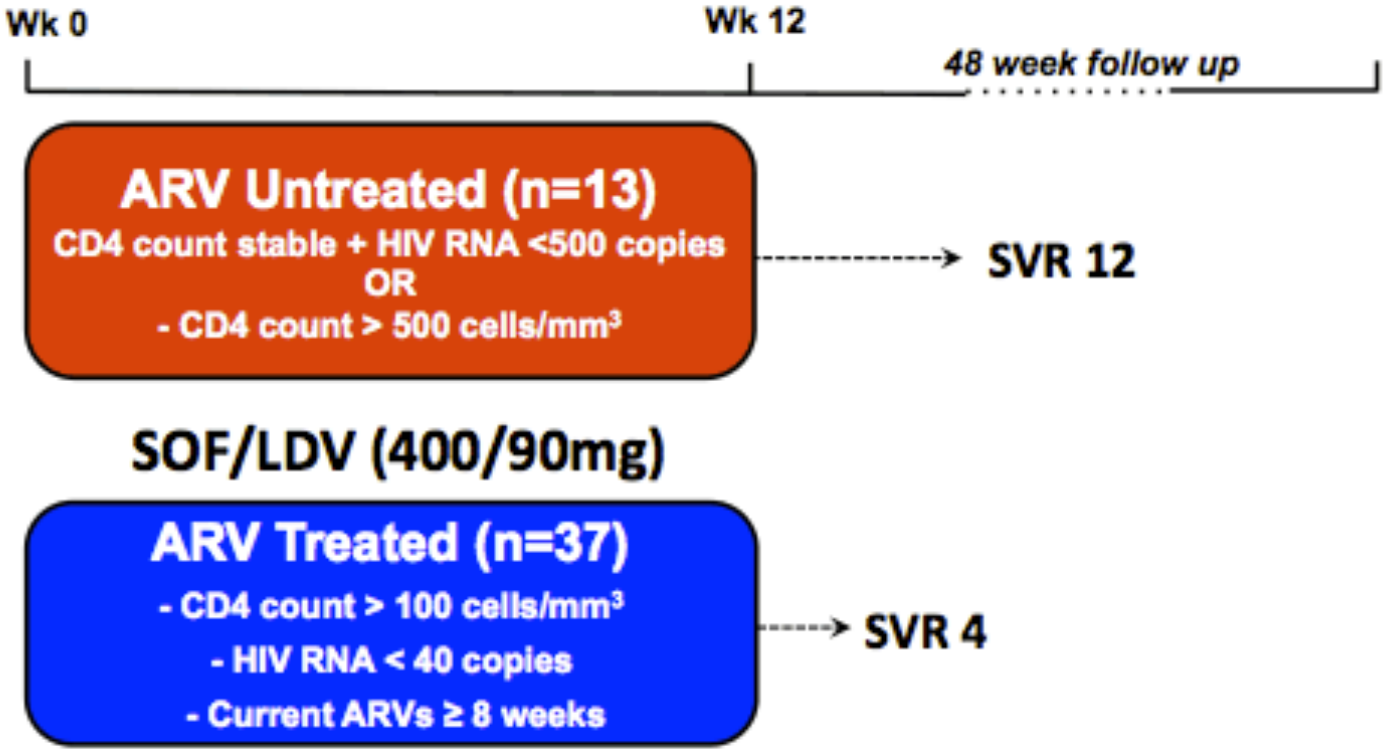
USE OF SOFOSBUVIR/LEDIPASVIR FIXED DOSE COMBINATION FOR TREATMENT OF HCV GENOTYPE-1 INFECTION IN PATIENTS COINFECTED WITH HIV *(Interim results)*

Anu Osinusi[1,2], Kerry Townsend[1], Amy Nelson[1], Anita Kohli[3,4], Eric Meissner[1], Chloe Gross[3], Michael A. Polis[1], Phil S Pang[5], William T. Symonds[5], Mohammed M. Sajadi[1], John Hogan[6], G. Mani Subramanian[5], John G. McHutchison[5], Henry Masur[4], Shyam Kottilil[1] for the NIAID/CC Hepatitis C ERADICATE team[1,3,4]

[1]Laboratory of Immunoregulation, NIAID, NIH, Bethesda, Maryland, [2]Dept of Infectious Diseases, University of Maryland, Baltimore, [3]Leidos /SAIC-Frederick, Frederick National Laboratory for Cancer Research, Frederick, Maryland , [4]Critical Care Medicine Department, NIH, Bethesda, Maryland , [5]Gilead Sciences, Foster City, California, [6]Unity Health Care Inc, Washington DC

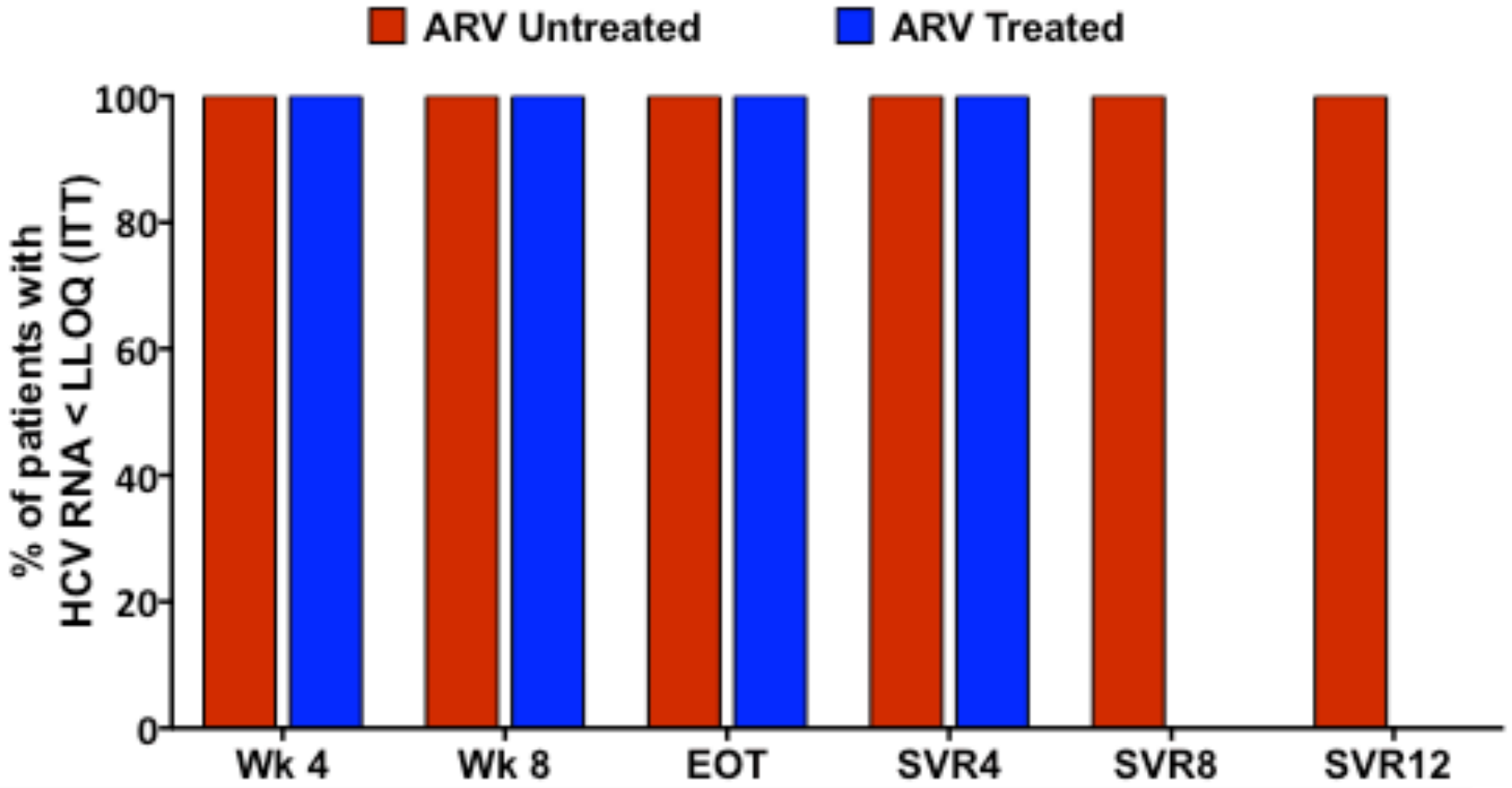
Study Design

- Fifty HIV/HCV genotype 1, treatment-naive subjects
- HAI fibrosis stage 0 – 3



Interim results

Treatment Response *(Observed)*



ARV -	13/ 13	13/13	13/ 13	12/12	10/10	10/10
ARV +	37/37	37/37	30/30	22/22		

EFFICACY AND SAFETY OF THE ALL-ORAL REGIMEN, MK-5172/MK-8742 +/- RBV FOR 12 WEEKS IN GT1 HCV/HIV CO-INFECTED PATIENTS: THE C-WORTHY STUDY

Mark Sulkowski[1], Josep Mallolas[2], Marc Bourliere[3], Jan Gerstoft[4], Oren Shibolet[5], Ronald Nahass[6], Edwin DeJesus[7], Melissa Shaughnessy[8], Peggy Hwang[8], Barbara Haber[8]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Hospital de Dia. Enfermedades Infecciosas, Barcelona, Spain; [3]Service d'hépato-gastroentérologie, Hôpital Saint-Joseph, Marseille, France; [4]Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark; [5]Liver Unit, Department of Gastroenterology, Tel-Aviv Medical Center, Tel-Aviv, Israel; [6]ID Care, Hillsborough, NJ, USA; [7]Orlando Immunology Center, Orlando, Florida; [8]Merck & Co., Inc., Whitehouse Station, NJ, USA.

C-WORTHY

Background

- MK-5172 is a highly potent, HCV-specific NS3/4A protease inhibitor
- MK-8742 is a highly potent, HCV-specific NS5A replication complex inhibitor
- Combination of MK-5172 and MK-8742: high barrier to resistance; activity against common resistance-associated variants
- Part A of C-WORTHy demonstrated an efficacy of 89-100% in treatment naive non-cirrhotic patients with G1 infection and supported expansion to more diverse populations

C-WORTHy: MK-5172/MK-8742 ± RBV in 471 HCV G1-infected patients

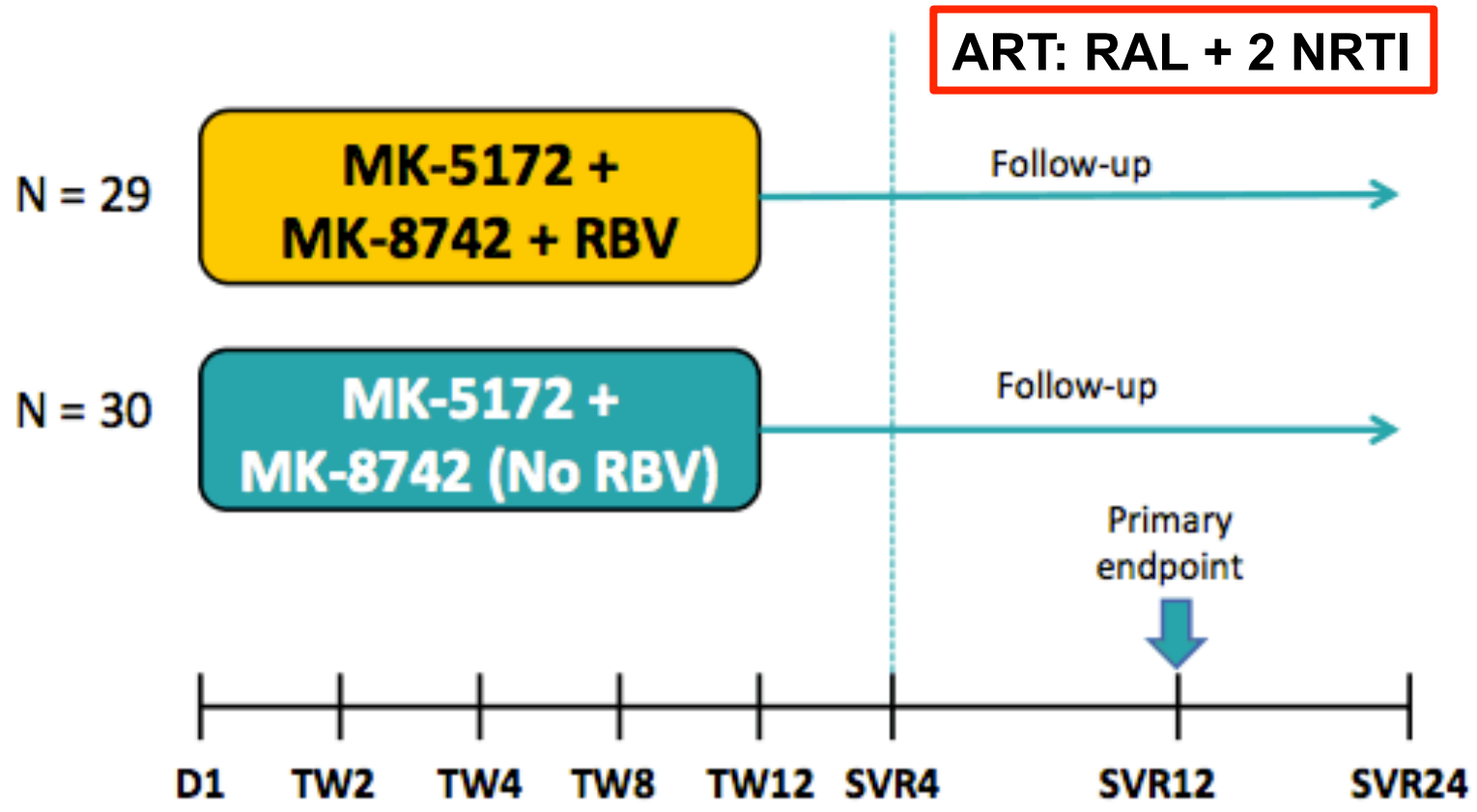
Part A: Treatment-naive, non-cirrhotic
12 weeks ± RBV
(n = 65)

Treatment-naive Non-cirrhotic	Treatment-naive Cirrhotic	Null responders Cirrhotic / Non-cirrhotic	HIV/HCV co-infected Non-cirrhotic
8-12 weeks ± RBV	12-18 weeks ± RBV	12-18 weeks ± RBV	12 weeks ± RBV
(n = 94)	(n = 123)	(n = 130)	(n = 59)

Study Design

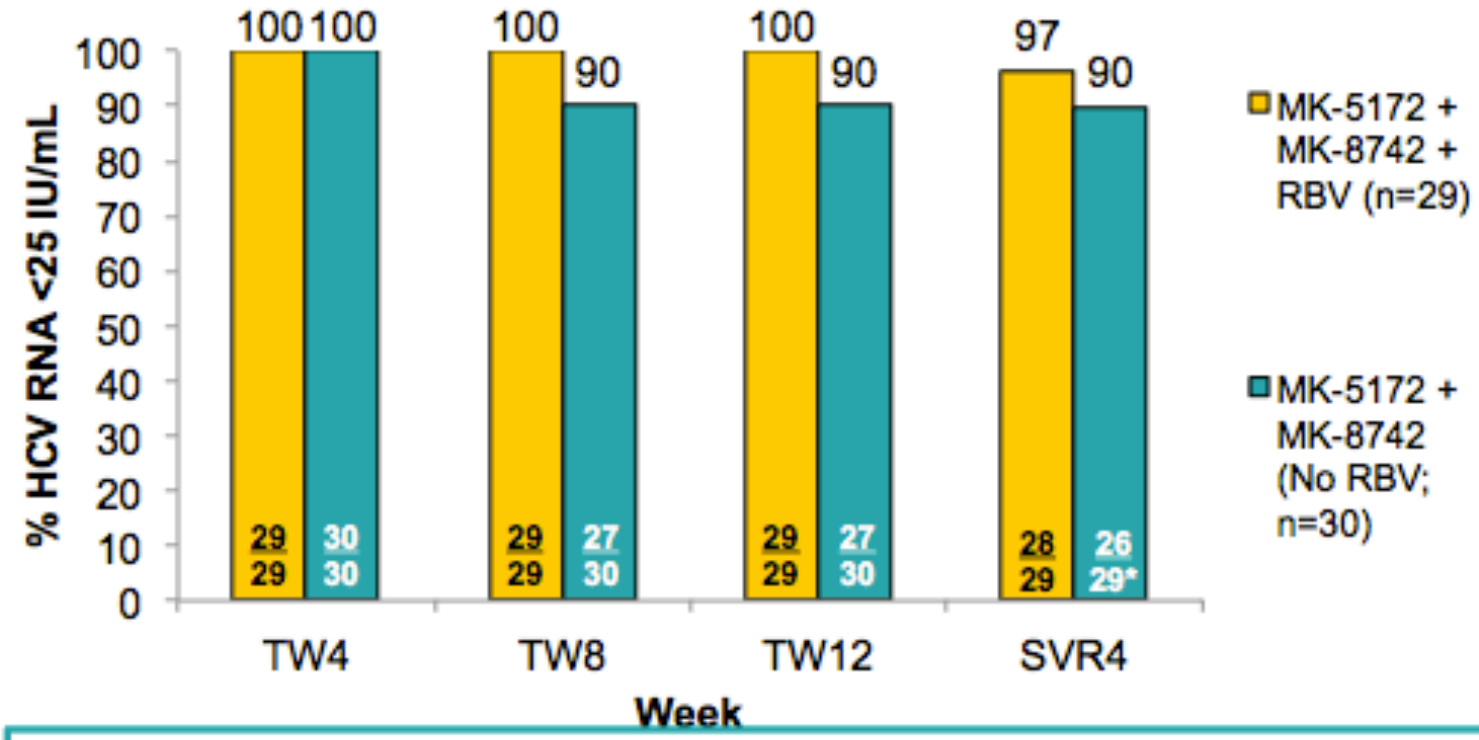
C·WORTHY

HIV/HCV Co-infected Non-cirrhotic Patients



MK-5172 (100 mg QD) + MK-8742 (50 mg QD); 12 weeks

Virologic Responses ITT Population



Virologic Failures: 1 relapse in +RBV arm;
2 breakthrough and 1 lost to follow up in No RBV arm

* One patient has not yet reached FU4

Neue Leitlinien

Praxisempfehlung zur Therapie der chronischen Hepatitis C nach Zulassung des Polymerase-Inhibitors Sofosbuvir

Christoph Sarrazin[1], Peter Buggisch[2], Holger Hinrichsen[3], Dietrich Hüppe[4], Stefan Mauss[5], Jörg Petersen[2], Karl-Georg Simon[6].

Aktuelle Empfehlung der DGVS zur Therapie der chronischen Hepatitis C

Christoph Sarrazin[1], Thomas Berg[2], Heiner Wedemeyer[3], Stefan Mauss[4], Matthias Dollinger[5], Michael Manns[3], Stefan Zeuzem[1]

World Health Organization

GUIDELINES FOR THE SCREENING, CARE AND TREATMENT OF PERSONS WITH HEPATITIS C INFECTION

APRIL 2014

Behandlung der HIV / HCV Koinfektion

Recommendations

- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection **(Recommendation A1)**
- The same treatment regimens can be used in HIV-co-infected patients as in patients without HIV infection, as the virological results of therapy are identical

HIV/HCV Koinfektion Genotyp 1-6:

- *Die antivirale Therapie sollte analog zu den Empfehlungen bei HCV monoinfizierten Patienten durchgeführt werden (Evidenzgrad IIb)*

DGVS Empfehlungen 2014

ritonavir and to 90 mg daily in those receiving efavirenz **(Recommendation B2)**

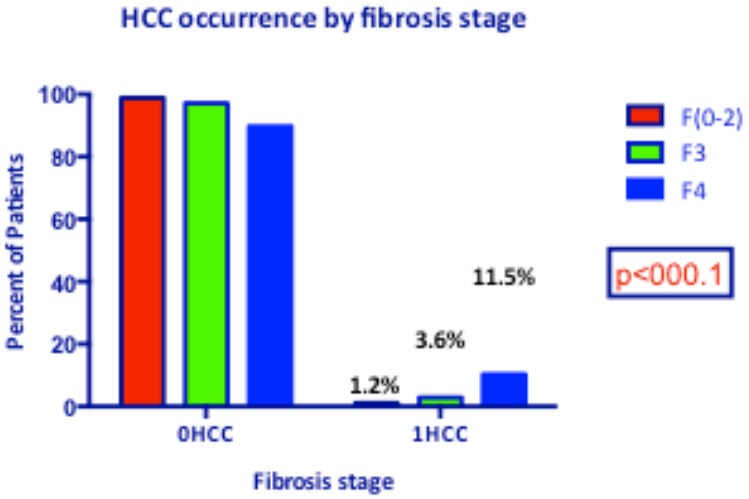
- No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs **(Recommendation A2)**

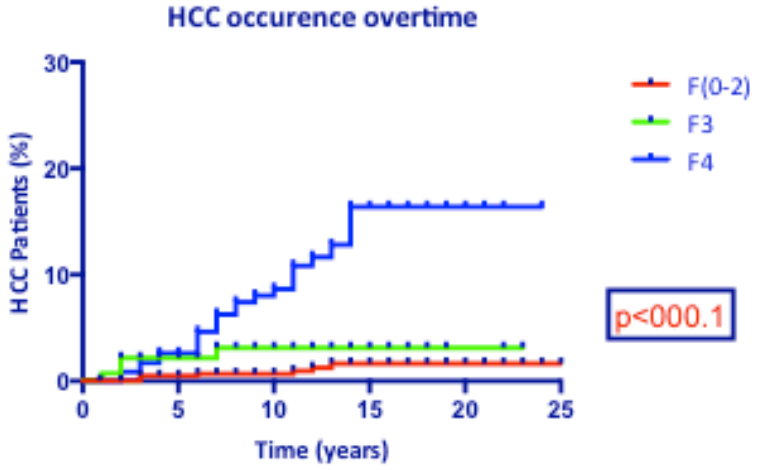
HCV Monoinfektion
- HCC und SVR

HCC Inzidenz bei Hepatitis C ist abhängig vom Fibrosestadium

HCC incidence – Fibrosis stage at baseline

MEDICAL UNIVERSITY OF VIENNA





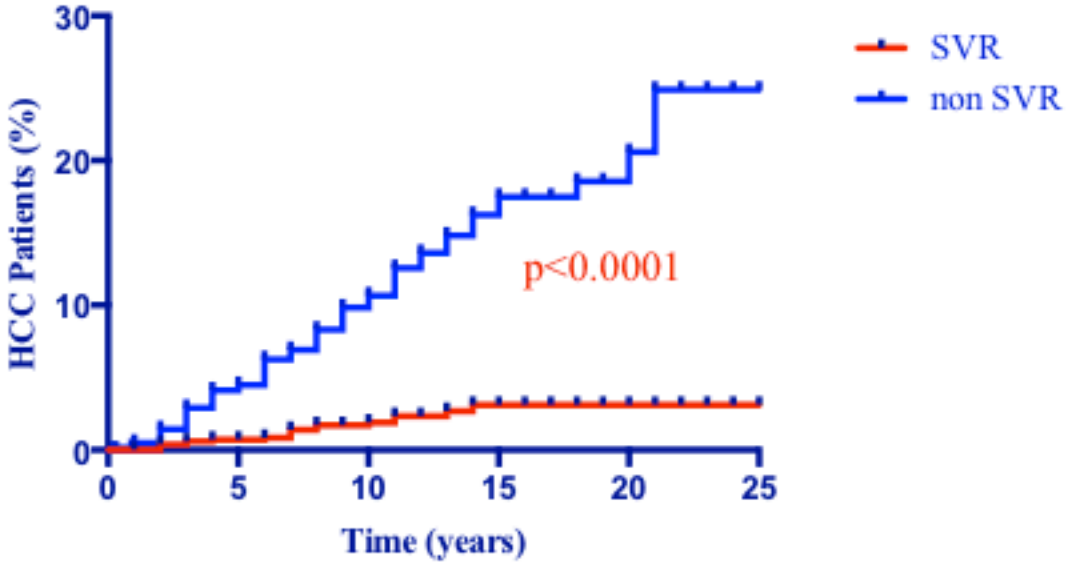
Purevsambuu et al, EASL 2014

… und von der SVR

HCC incidence – SVR /non-SVR

MEDICAL UNIVERSITY OF VIENNA

SVR group = 1.8% vs. Non-SVR = 12.1%, p<0.0001

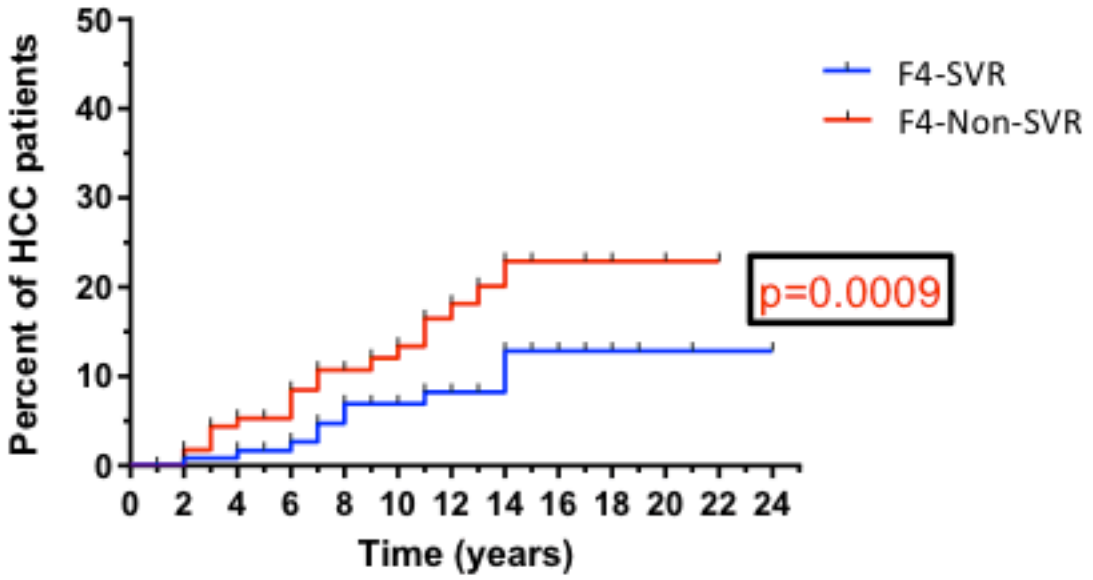


Purevsambuu et al, EASL 2014

HCC incidence overtime in F4 patients according SVR

MEDICAL UNIVERSITY OF VIENNA

HCC-Incidence: SVR 7.7% *vs.* Non-SVR 15.6%



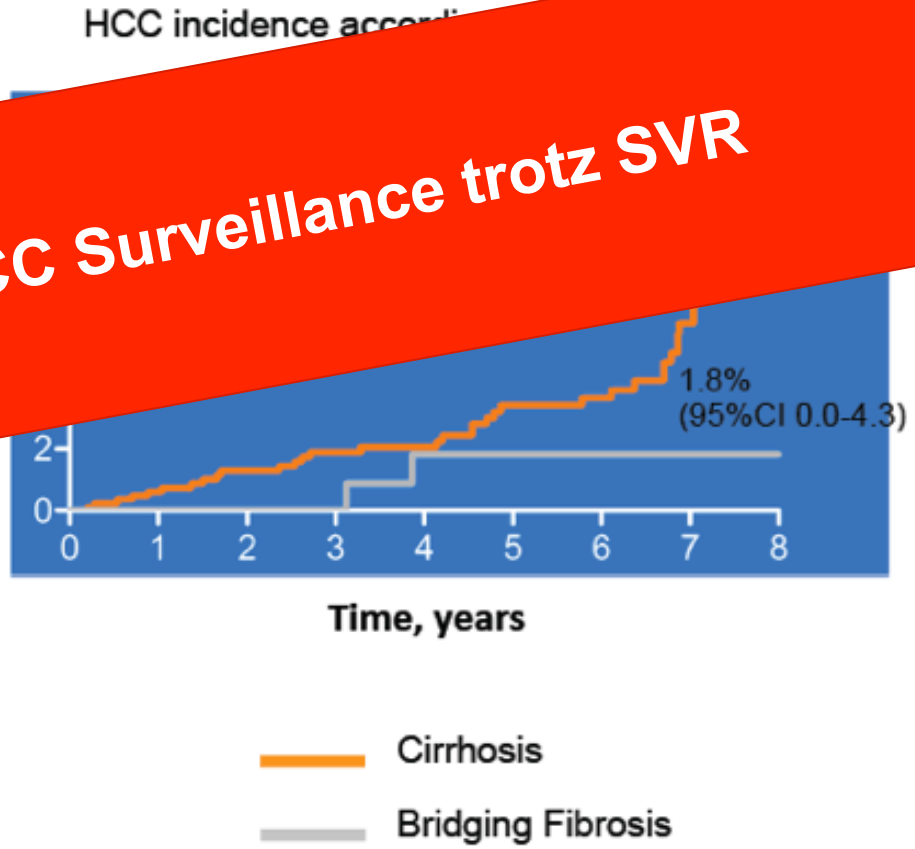
Purevsambuu et al, EASL 2014

HCV geheilt – aber nicht die Leberzirrhose

Hepatocellular carcinoma in HCV-infected patients with advanced hepatic fibrosis following SVR

- 10 cohorts studies with 1000 patients followed for a median of 5.7 years
  - Platelet count < 150 X 10^9/L
  - AST/ALT ratio ≥ 0.90
  - Diabetes mellitus

Regelmäßige HCC Surveillance trotz SVR



van der Meer AJ et al. The Liver Meeting 2013; Abstract 143

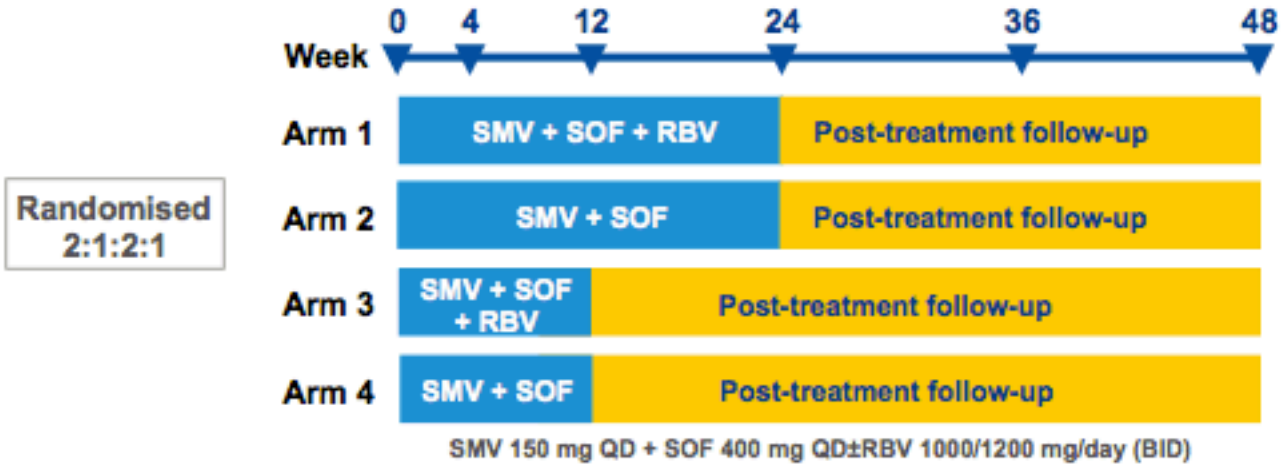
HCV Monoinfektion

- Therapie

2 Konzepte

- Mix & Match
- Aus einer Hand

COSMOS study design: Randomised, multicentre, open-label trial



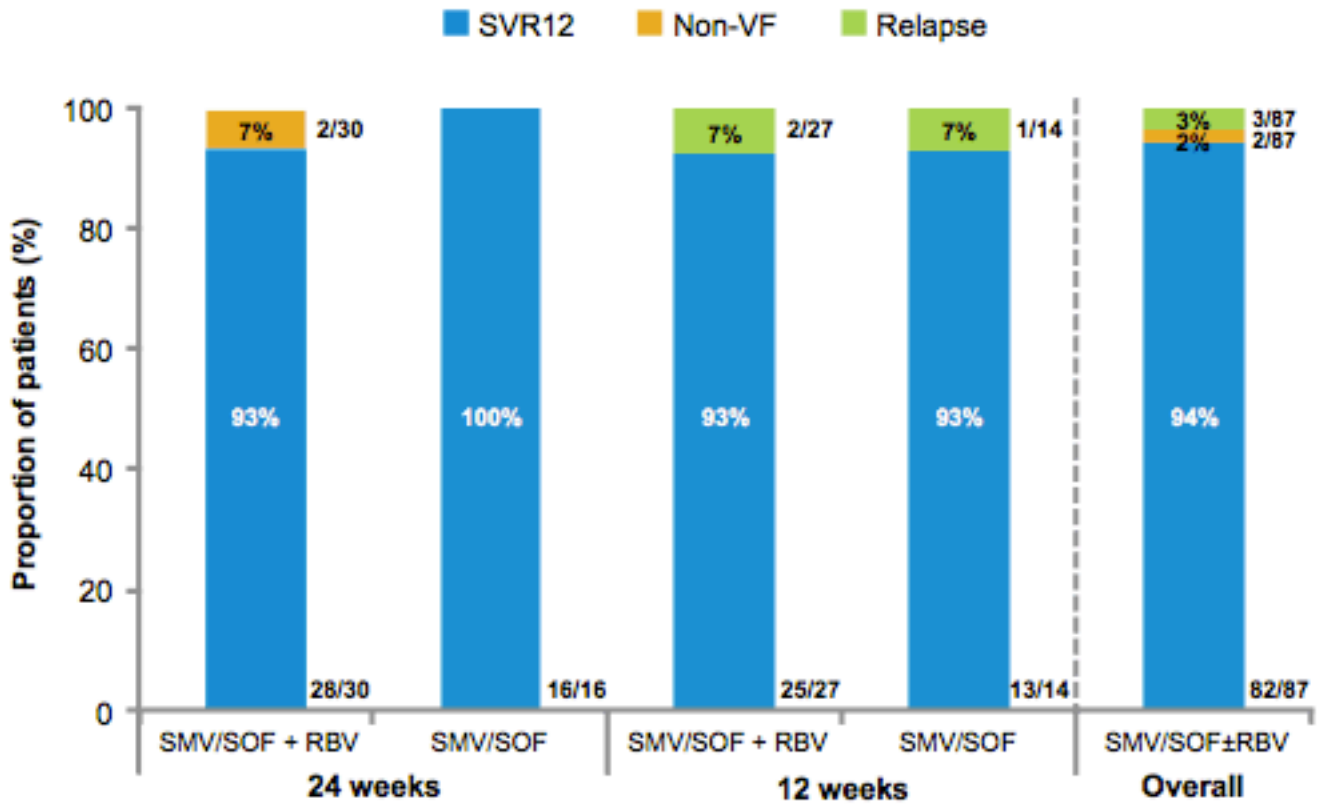
- Cohort 1: METAVIR F0-F2, prior null responders to PR therapy
  - Stratified by *IL28B*, HCV GT 1 subtype
- Cohort 2: METAVIR F3-F4, prior null responders or treatment-naïve
  - Data being presented Dr Eric Lawitz, Saturday 12 April, Late Breaker Session (16.00-16.15)
- Primary endpoint: SVR12
- Secondary endpoints included RVR and relapse rate

BID, twice daily; QD, once daily; RBV, ribavirin;

SMV, simeprevir; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after planned end of treatment

Sulkowski et al, EASL 2014

COSMOS Cohort 2: SVR12 – Primary endpoint
(ITT population)



Non-VF, patients who did not achieve SVR12 for reasons other than virologic failure

ITT, intent-to-treat; Non-VF, Non-virologic failure; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after planned treatment end

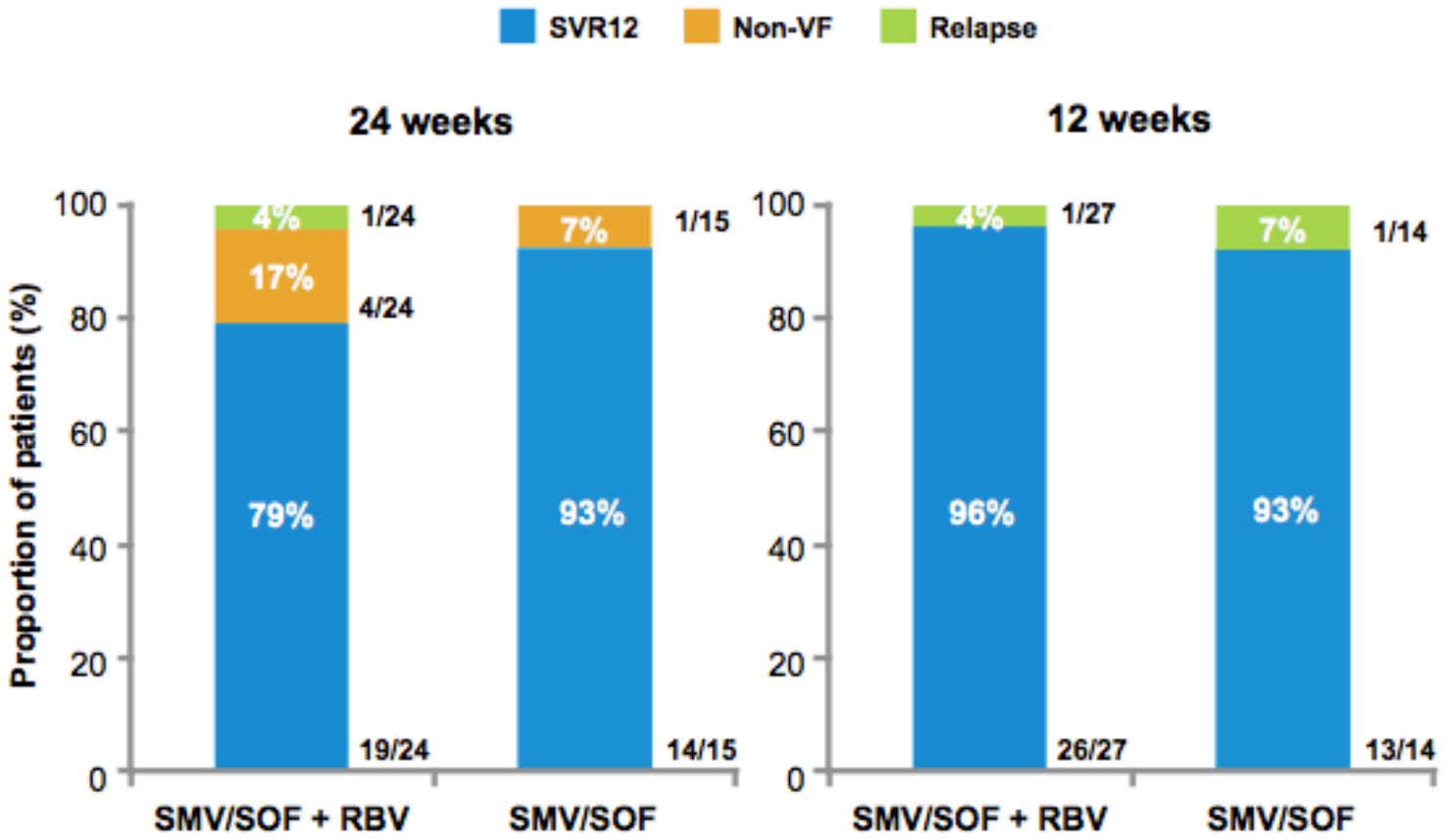
Lawitz et al, EASL 2014

Once-daily simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype-1 prior null responders with METAVIR F0-2: COSMOS study subgroup analysis

Mark S Sulkowski,[1] Ira M Jacobson,[2] Reem Ghalib,[3] Maribel Rodriguez-Torres,[4] Zobair Younossi,[5] Ana Corregidor,[6] Bart Fevery,[7] Katleen Callewaert,[8] William Symonds,[9] Guy De La Rosa,[10] Gaston Picchio,[11] Sivi Ouwerkerk-Mahadevan,[7] Tom Lambrecht,[12] Eric Lawitz[13]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Weill Cornell Medical College, New York, NY, USA; [3]Texas Clinical Research Institute, Arlington, Texas, USA; [4]Fundación de Investigación, San Juan, Puerto Rico, USA; [5]Department of Internal Medicine, Inova Fairfax Hospital, Falls Church, VA, USA; [6]Borland-Groover Clinic, Jacksonville, FL, USA; [7]Janssen Research & Development, Janssen Infectious Diseases BVBA, Beerse, Belgium; [8]Janssen Research & Development, Beerse, Belgium; [9]Gilead Sciences, Inc. Foster City, CA, USA; [10]Janssen Global Services, Titusville, NJ, USA; [11]Janssen Research & Development LLC, Titusville, NJ, USA; [12]Novellas Healthcare, Zelik, Belgium; [13]The Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, USA

COSMOS Cohort 1: SVR12 – Primary endpoint
(ITT population)



Sulkowski et al, EASL 2014

ITT, intent-to-treat;

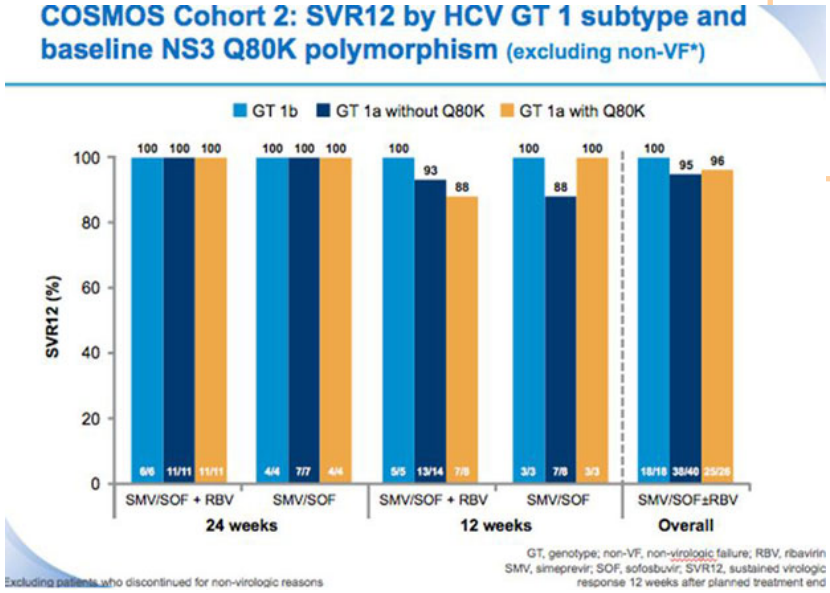
Non-VF, Non-virologic failure, patients who did not achieve SVR12 for reasons other than virologic failure

Sofosbuvir plus Simeprevir (GT-1) COSMOS, Phase II

Kohorte 1:
N=41
Nullresponder / keine Zirrhose

95% SVR_{12}

Simeprevir
Sofosbuvir
mit oder ohne Ribavirin



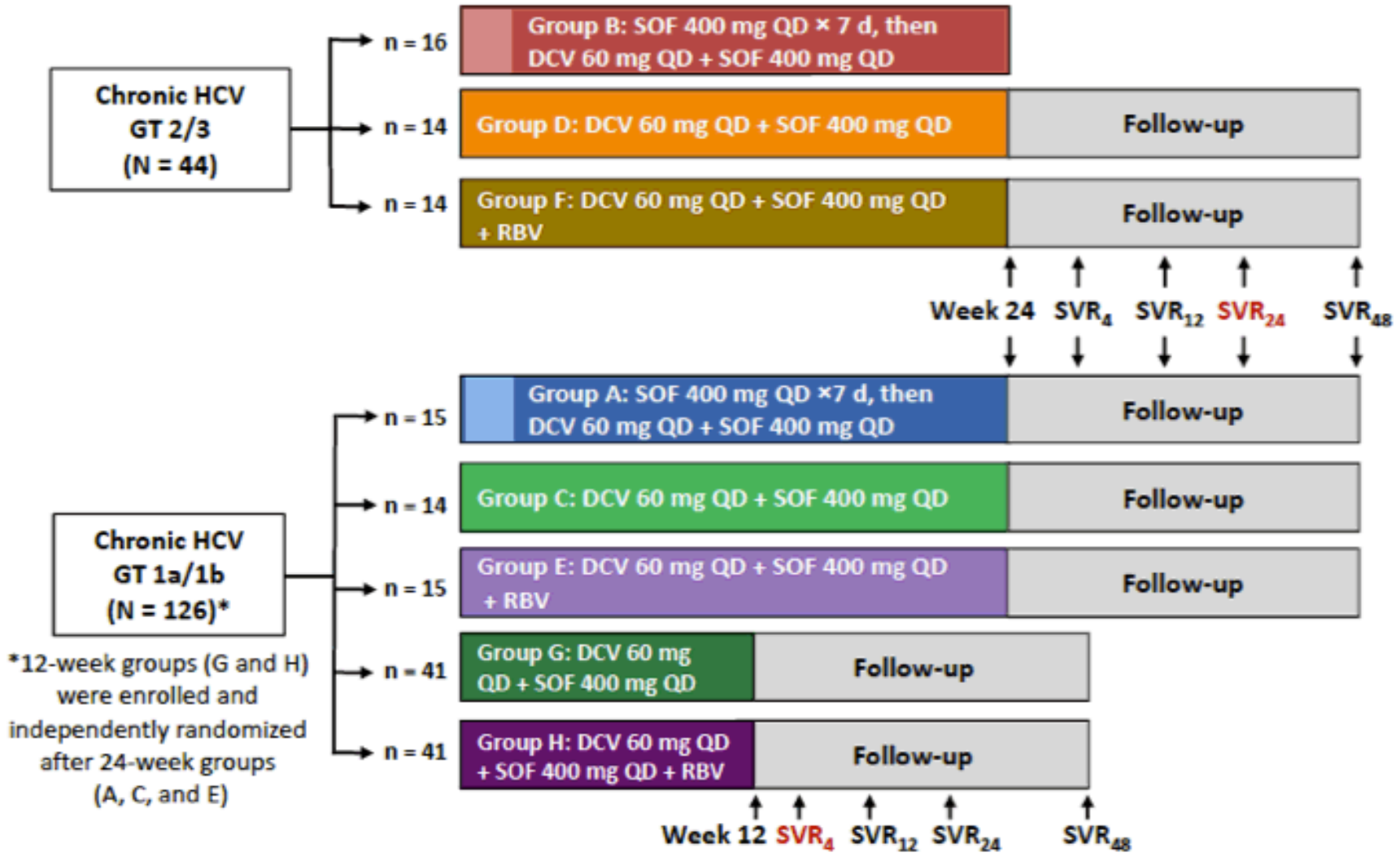
Kohorte 2:
N=41 Naive oder Nullresponder **mit F3/F4**

95% SVR_{12}
3 Patienten mit Relapse
(1x Q80K)

Genotyp 1 a versus 1 b (Q80K) wenn PEG/Riba
IFN intolerant / ineligible
Lücke GT3
Preis /IQWIG/AMNOG/GBA

Jacobson et al, AASLD 2013
Sulkowski et al, EASL 2014
Lawitz et al, EASL 2014

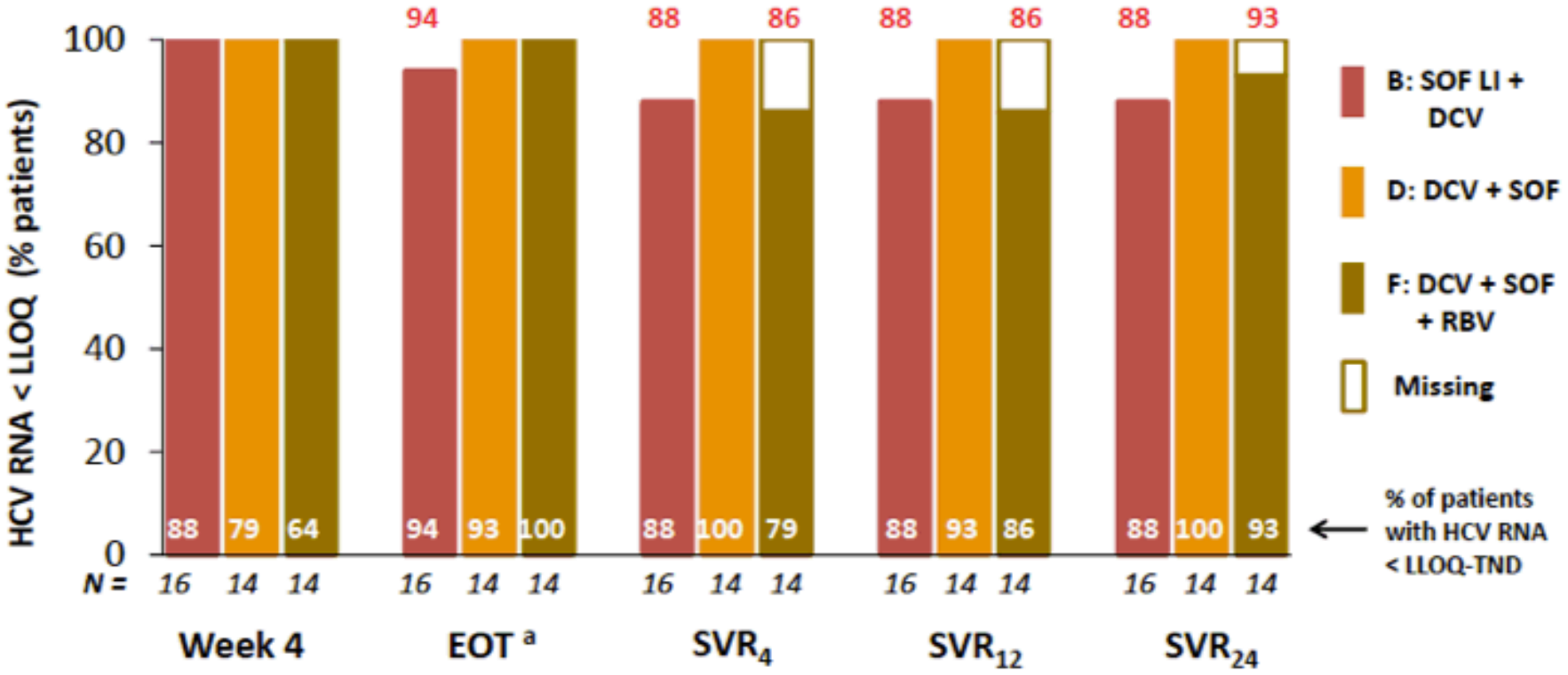
Randomized, Open-label, 2-Stage, Parallel-Group Phase 2a Study: AI444-040



RBV: 1000-1200 mg/d, weight-based (GT 1); 800 mg/d (GT 2/3).

Sulkowski et al., AASLD 2012

Genotype 2/3: Virologic Response During and After Treatment (mITT)



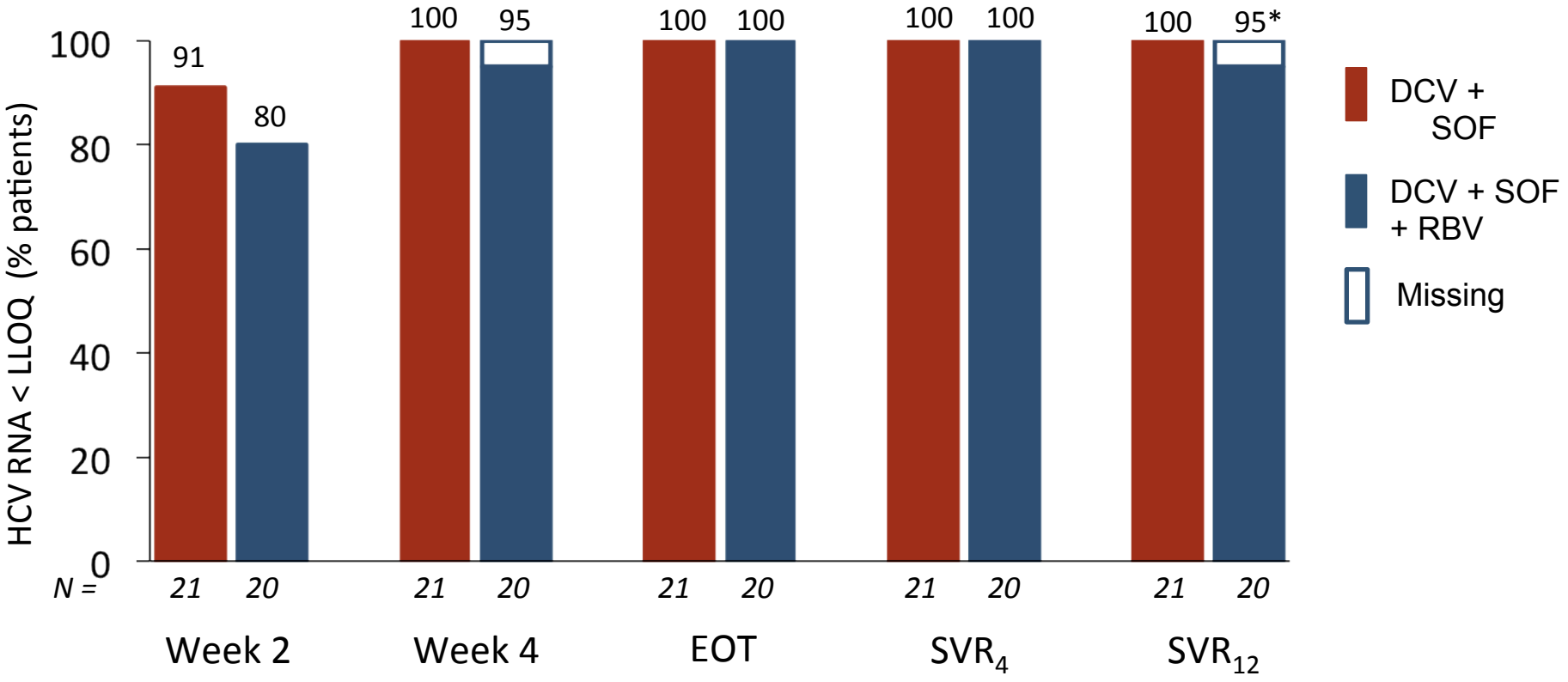
- **Group B**: 1 patient (GT3) relapsed; NS5A-A30K polymorphism (associated with DCV resistance) detected at baseline and PT Week 4. 1 patient (GT3) met protocol definition of virologic breakthrough; added pegIFN alfa/RBV – achieved SVR_{24}
- **Group F**: 2 lost to follow-up after EOT; 1 returned at PT Week 24 with HCV RNA < LLOQ-TND

[a] End-of-treatment (EOT) includes patients who discontinued early, with last visit considered EOT; TD, target detected; TND, target not detected.

Sulkowski et al., AASLD 2012

Sofosbuvir und Daclatasvir bei P/R/Telaprevir Nonrespondern (GT-1)

Sulkowski et al., New England Journal of Medicine 2014



IFN intolerant / ineligible
keine Zulassung GT4
Compassionate Use Program Start 05/2014

Sofosbuvir und Daclatasvir – Phase IIII

Phase III Daclatasvir, Sofosbuvir, and Ribavirin in Cirrhotic Subjects and Subjects Post-liver Transplant (ALLY 1)

This study is currently recruiting participants.

Verified March 2014 by Bristol-Myers Squibb

Sponsor:
Bristol-Myers Squibb

Information provided by (Responsible Party):
Bristol-Myers Squibb

ClinicalTrials.gov Identifier:
NCT02032875

First received: January 9, 2014
Last updated: March 18, 2014
Last verified: March 2014
History of Changes

Phase III HIV/HCV Co-Infection Daclatasvir (DCV)+ Sofosbuvir (SOF) (ALLY 2)

This study is currently recruiting participants.

Verified March 2014 by Bristol-Myers Squibb

Sponsor:
Bristol-Myers Squibb

Information provided by (Responsible Party):
Bristol-Myers Squibb

ClinicalTrials.gov Identifier:
NCT02032888

First received: January 9, 2014
Last updated: March 10, 2014
Last verified: March 2014
History of Changes

Phase III Daclatasvir and Sofosbuvir for Genotype 3 Chronic HCV (ALLY 3)

This study is ongoing, but not recruiting participants.

Sponsor:
Bristol-Myers Squibb

Information provided by (Responsible Party):
Bristol-Myers Squibb

ClinicalTrials.gov Identifier:
NCT02032901

First received: January 9, 2014
Last updated: April 24, 2014
Last verified: April 2014
History of Changes

A Multicenter Compassionate Use Protocol of Daclatasvir (BMS-790052) in Combination With Sofosbuvir With or Without Ribavirin for the Treatment of Subjects With Chronic Hepatitis C

Expanded access is currently available for this treatment.

Verified April 2014 by Bristol-Myers Squibb

Sponsor:
Bristol-Myers Squibb

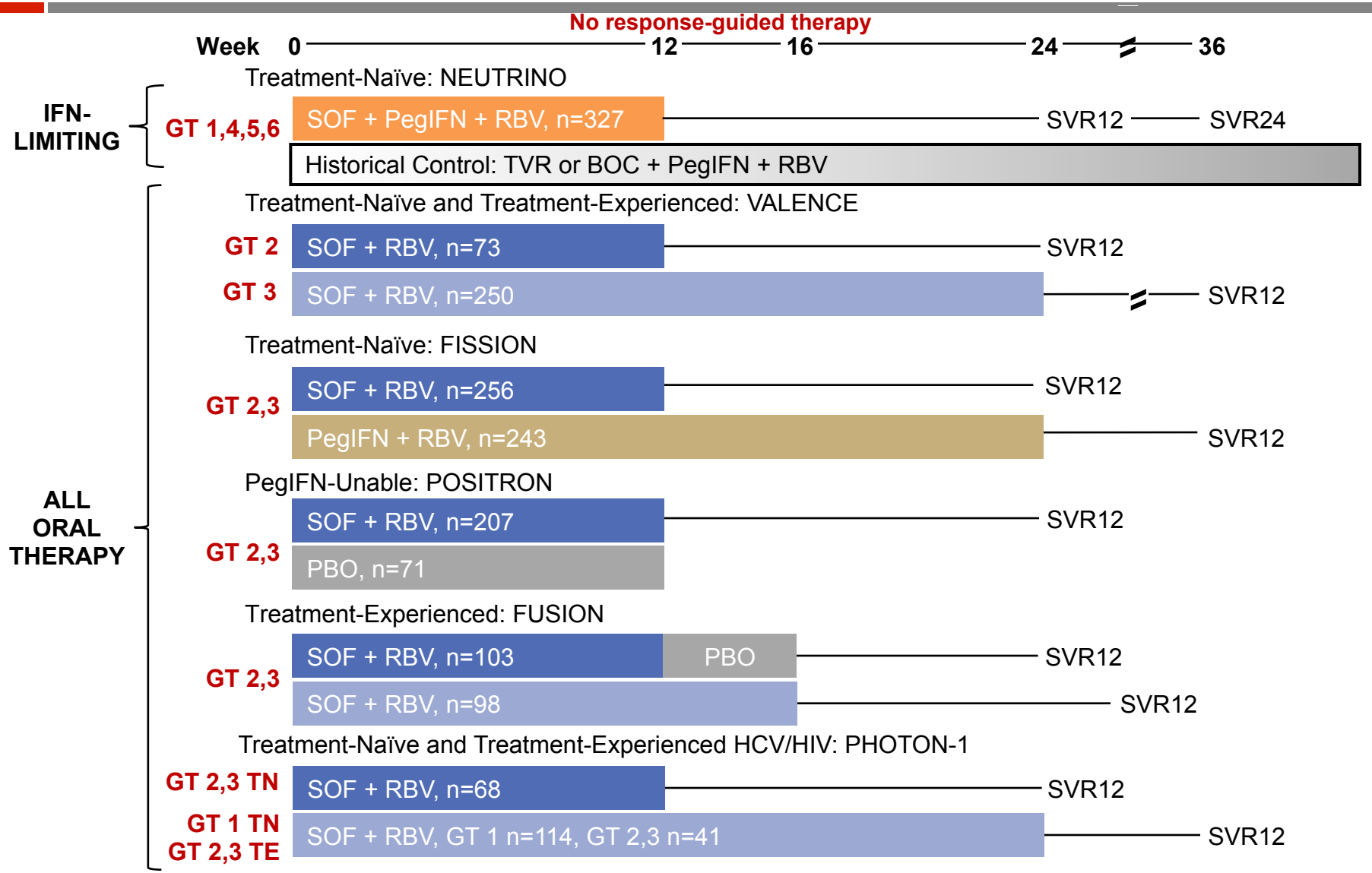
Information provided by (Responsible Party):

ClinicalTrials.gov Identifier:
NCT02097966

First received: March 25, 2014
Last updated: April 16, 2014
Last verified: April 2014
History of Changes

Sofosbuvir

Sofosbuvir Phase 3 Study Designs

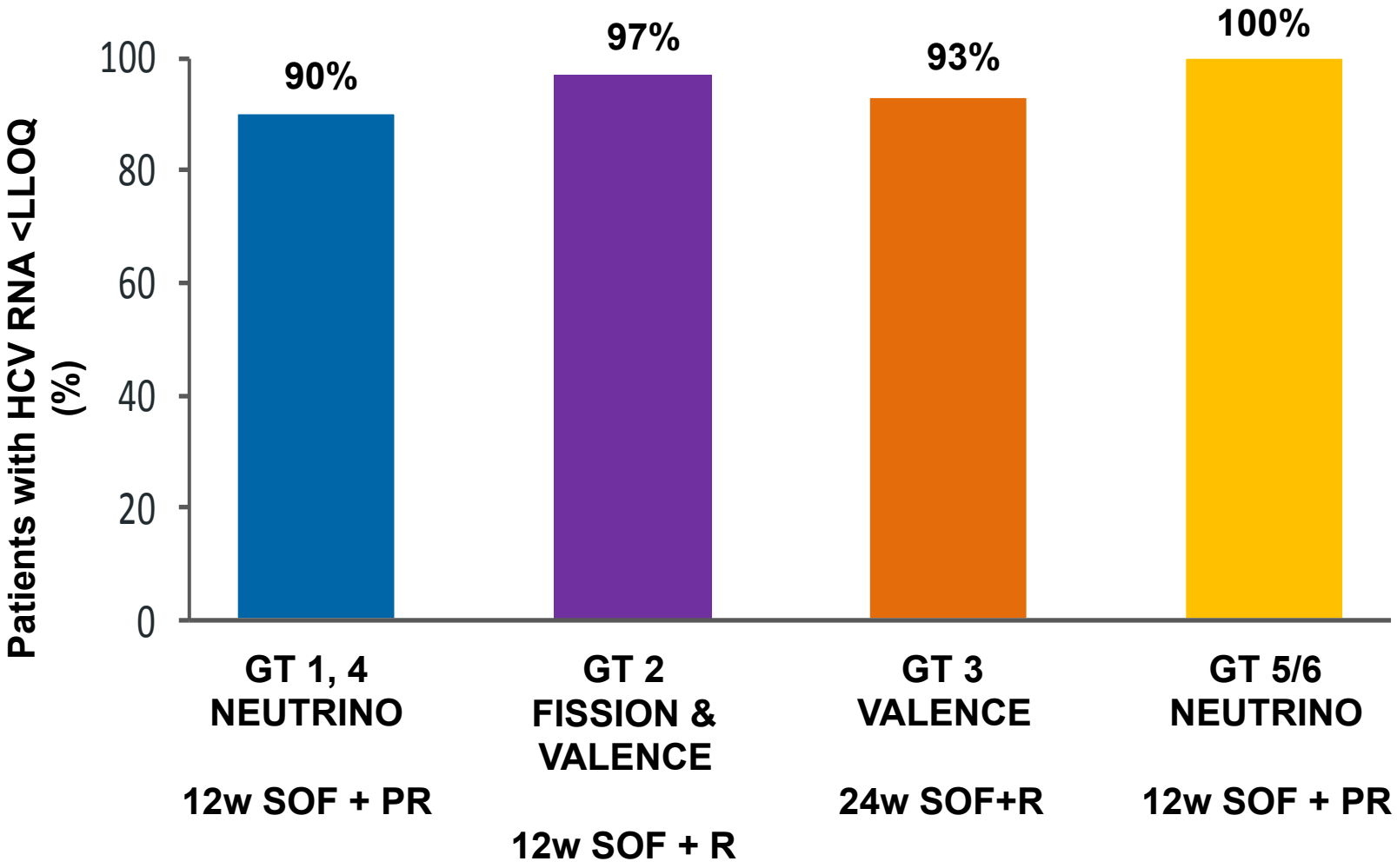


SOF 400 mg/d; PegIFN 180 µg/wk; RBV 1000-1200 mg/d for SOF+RBV arms and **800 mg/d for PegIFN+RBV arm**

Sofosbuvir Phase 3 Studies

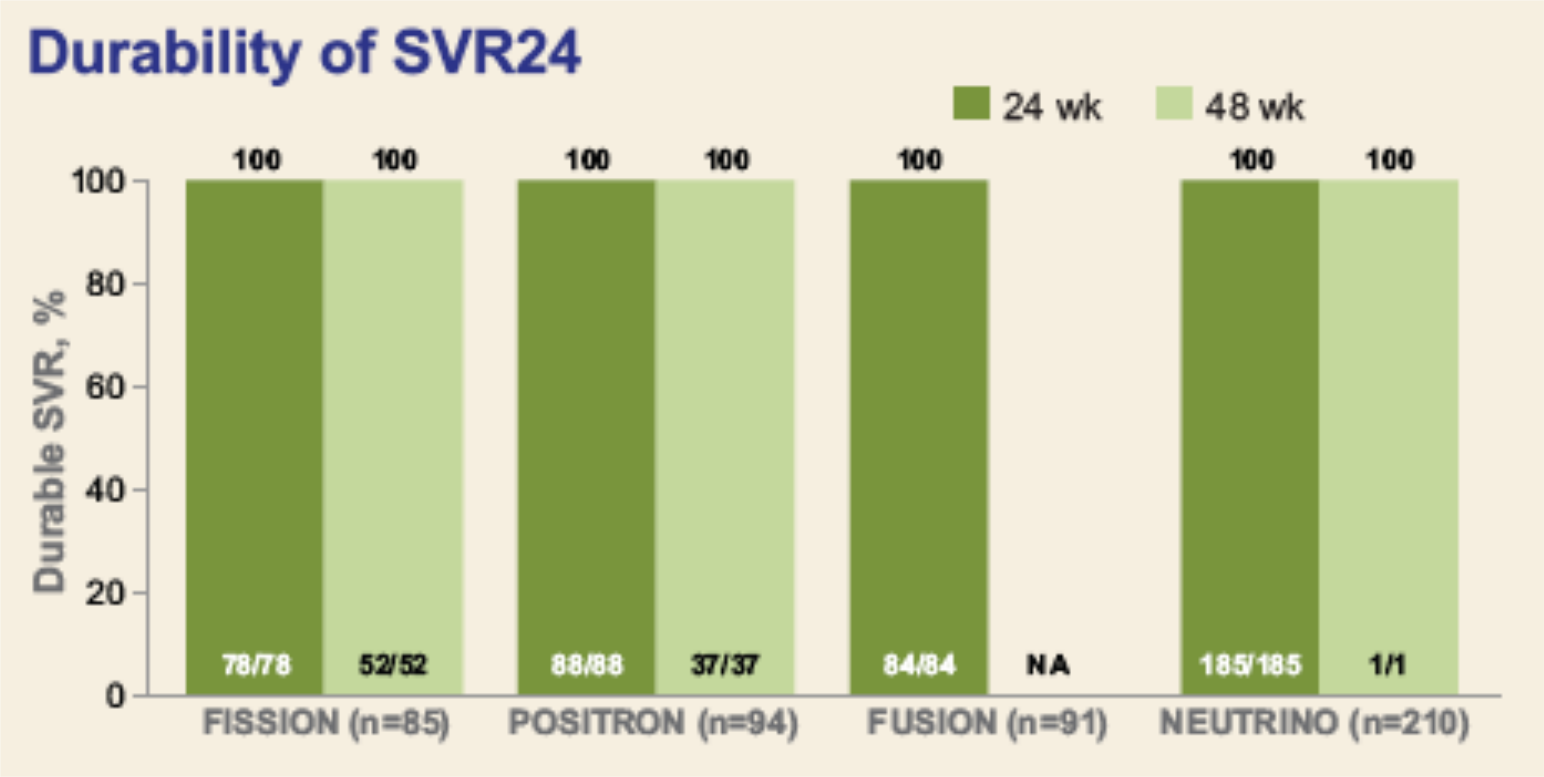
Study	Population	Total Patients	Percentage with Cirrhosis	Lower Limit of Platelets
NEUTRINO	GT 1,4,5,6 Treatment Naïve	327	17%	≥ 90,000/mm^3
VALENCE	GT 2,3 Treatment-Naïve & Treatment-Experienced	323	21%	≥ 50,000/mm^3
FISSION	GT 2,3 Treatment Naïve	499	20%	≥ 75,000/mm^3
POSITRON	GT 2,3 IFN Unable	278	16%	No Lower Limit
FUSION	GT 2,3 Treatment-Experienced	201	34%	≥ 50,000/mm^3
PHOTON-1	GT 1,2,3 Treatment-Naïve GT 1,2,3 and Treatment-Experienced GT 2,3 with HCV/HIV co-infection	223	10%	No Lower Limit
Total		1,851	19%	

≥ 90% SVR 12 Across Treatment-Naïve Genotypes 1, 2, 3, 4, 5, 6



Lawitz E, et al. *N Engl J Med.* 2013 May 16
Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02
Zeuzem S, et al. AASLD 2013. Washington, DC. #1085

Ansprechen unter Sofosbuvir dauerhaft



- Of 480 patients with SVR24 from the Phase 3 trials, 435 (91%) and 90 (19%) had available Week 24 and 48 data, respectively
- SVR24 was durable in 100% of these patients

Cheng et al, EASL 2014

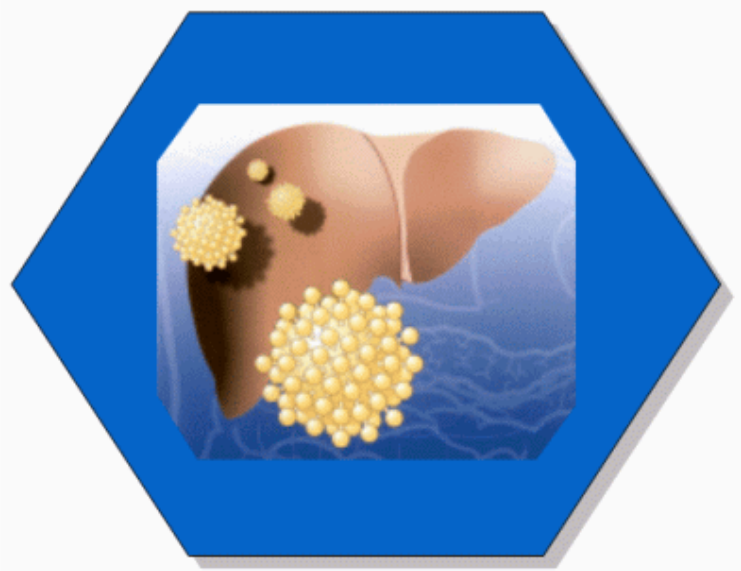
Fall

- 76-jähriger Mann
- HCV GT2, 127000 IU/ml
- ALT 2x ULN
- ARFI Fibrose F2-F3
- Vorerkrankungen
  - KHK, Z. n. Bypass OP, Aortenbioklappenersatz, Bauchaortenaneurysma, pAVK, Eisenmangelanämie, M. Parkinson, Depression, Osteoporose, Wirbelkörperfrakturen

HepData

ein Expertenratsystem zur

Optimierung von Therapieentscheidungen bei viraler Hepatitis
Dokumentation und Analyse von Krankheitsverläufen viraler Hepatitis



- Allgemeine Informationen
- Registrierung
- Mitgliederbereich
- english version

Bitte melden Sie alle Verdachtsfälle von unerwünschten Arzneimittelwirkungen an den entsprechenden Zulassungsinhaber oder an die entsprechende Bundesoberbehörde.

Sponsoren

- Abbott GmbH & Co KG
- Boehringer Ingelheim GmbH
- Bristol-Myers Sqibb GmbH
- Gilead Sciences GmbH
- Janssen-Cilag GmbH
- MSD Sharp & Dohme GmbH

Fall – Hepdata Expertenmeingungen

Experte 1

- Abwarten, bis Sofosbuvir/RBV zur Verfügung steht.

Experte 2

- Anfang nächsten Jahres wird vermutlich die Kombination von Sofosbuvir mit Ribavirin für Genotyp 2 Patienten in Deutschland zugelassen. Hier würde ich jetzt abwarten.

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

02.05.2014

Sofosbuvir: Für bestimmte Patienten Hinweis auf Zusatznutzen

Besseres virologisches Ansprechen bei chronischer Hepatitis C vom Genotyp 2 / Ausmaß des Zusatznutzens aber unklar / Für andere Virustypen fehlen geeignete Daten

Für die meisten Virustypen keine angemessenen Analysen

Für die Infektionen mit Viren vom Typ 1 sowie Typ 3 bis 6 und für die HIV-Koinfektion legt der Hersteller keine angemessenen Analysen vor. Zwar hat er Ergebnisse aus Studien ausgewertet, in denen in mindestens einem Studienarm die jeweilige Vergleichstherapie untersucht wurde, und diese in einem „historischen" Vergleich gegenüber gestellt.

Nuklearphysik und Edelsteine

The NEW ENGLAND JOURNAL of MEDICINE

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Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection

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Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis

Kris V. Kowdley, M.D., Stuart C. Gordon, M.D., K. Rajender Reddy, M.D., Lorenzo Rossaro, M.D., David E. Bernstein, M.D., Eric Lawitz, M.D.,

ORIGINAL ARTICLE

Retreatment of HCV with ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin

Stefan Zeuzem, M.D., Ira M. Jacobson, M.D., Tolga Baykal, M.D., Rui T. Marinho, M.D., Ph.D., Fred Poordad, M.D., Marc Bourlière, M.D., Mark S. Sulkowski, M.D., Heiner Wedemeyer, M.D., Edward Tam, M.D.,

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Treatment of HCV with ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin

Jordan J. Feld, M.D., M.P.H., Kris V. Kowdley, M.D., Eoin Coakley, M.D., Samuel Sigal, M.D., David R. Nelson, M.D., Darrell Crawford, M.D.,

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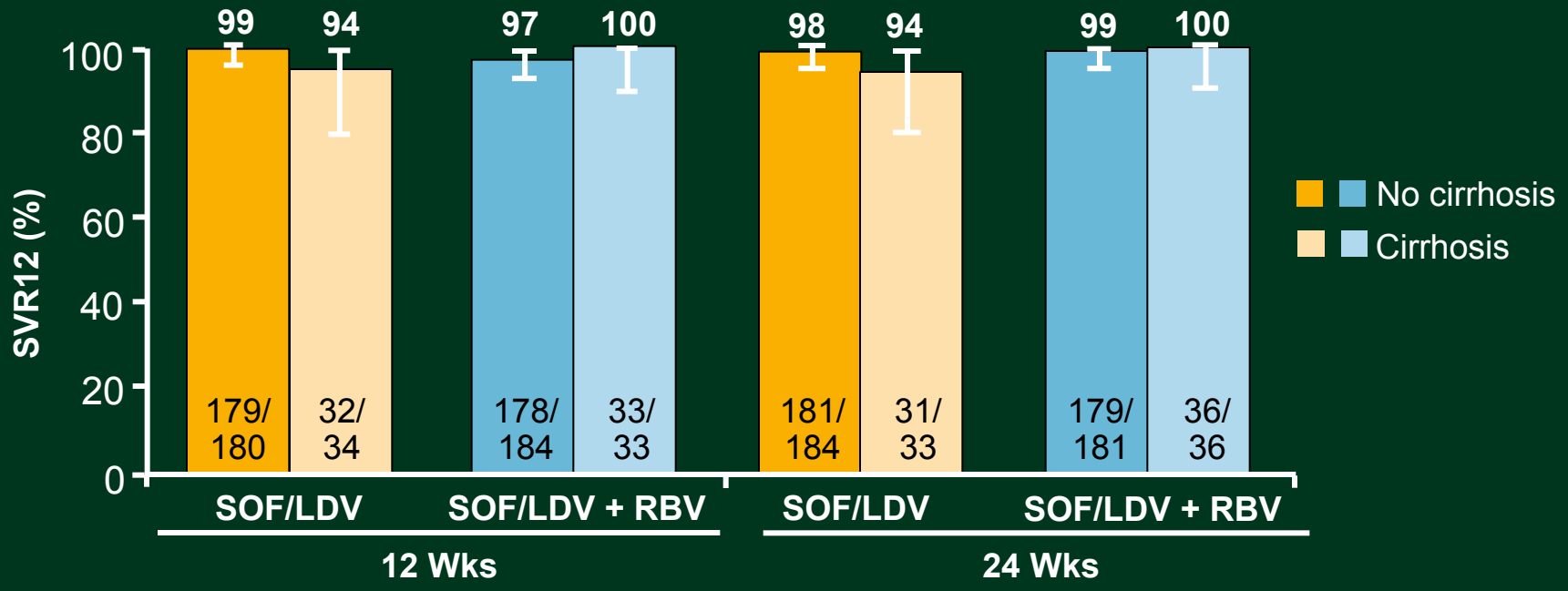
ORIGINAL ARTICLE

ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis

Fred Poordad, M.D., Christophe Hezode, M.D., Roger Trinh, M.D., M.P.H., Kris V. Kowdley, M.D., Stefan Zeuzem, M.D., Kosh Agarwal, M.D., Mitchell L. Shiffman, M.D., Heiner Wedemeyer, M.D., Thomas Berg, M.D.,

ION 1: SVR12 With 12 or 24 Wks SOF/LDV ± RBV in Tx-Naive Pts by Cirrhosis Status



- SVR12 rates did not differ by GT1a vs GT1b in any treatment arm
- Virologic failure: 1 breakthrough in 24-wk SOF/LDV; 2 relapses (1 in 12-wk SOF/LDV, 1 in 24-wk SOF/LDV)
- 16% of patients had NS5A resistance-associated variants at baseline; 96% of these achieved SVR12

Mangia A, et al. EASL 2014. Abstract O164. Reproduced with permission. Afdhal N, et al. N Engl J Med. 2014;[Epub ahead of print].

All Oral Fixed-Dose Combination Ledipasvir/Sofosbuvir With or Without Ribavirin for 12 or 24 Weeks in Treatment-Experienced Genotype 1 HCV-Infected Patients: The Phase 3 ION-2 Study

Nezam Afdhal[1], Rajender K. Reddy[2], Paul Pockros[3], Adrian M. Di Bisceglie[4], Sanjeev Arora[5], Jenny C. Yang[6], Hadas Dvory-Sobol[6], Yanni Zhu[6], Phil S. Pang[6], William T. Symonds[6], John G. McHutchison[6], Mark Sukowski[7], Paul Kwo[8]

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Results: Demographics

GT 1 Treatment-Experienced (ION-2)

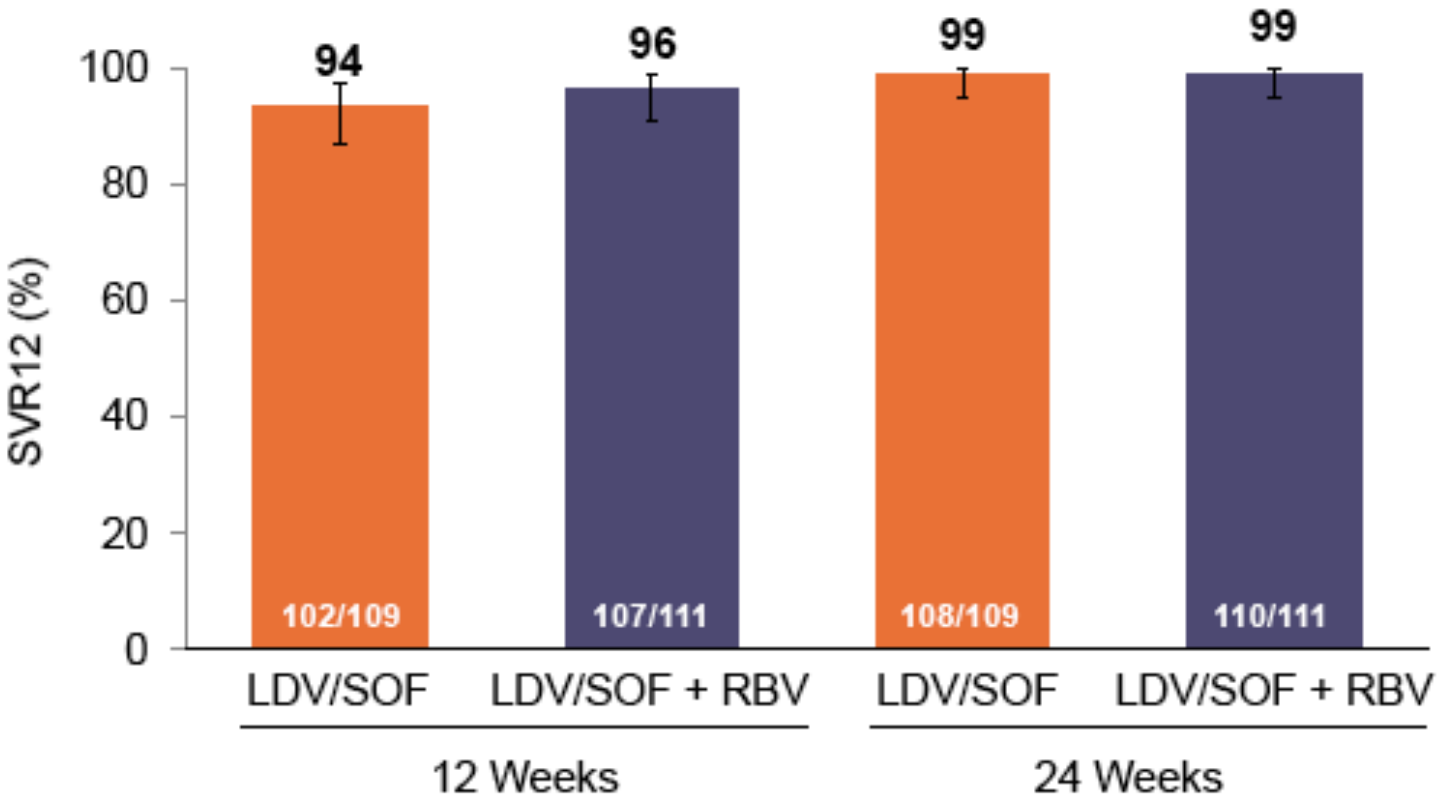
	12 Weeks		24 Weeks	
	LDV/SOF n=109	LDV/SOF+RBV n=111	LDV/SOF n=109	LDV/SOF+RBV n=111
Mean age, y (range)	56 (24–67)	57 (27–75)	56 (25–68)	55 (28–70)
Male, n (%)	74 (68)	71 (64)	74 (68)	68 (61)
Black, n (%)	24 (22)	16 (14)	17 (16)	20 (18)
Hispanic, n (%)	7 (6)	12 (11)	11 (10)	11 (10)
Mean BMI, kg/m^2 (range)	29 (19–47)	28 (19–45)	28 (19–41)	28 (19–50)
IL28B CC, n (%)	10 (9)	11 (10)	16 (15)	18 (16)
GT 1a, n (%)	86 (79)	88 (79)	85 (78)	88 (79)
Mean HCV RNA, log_{10} IU/mL (range)	6.5 (5.0–7.5)	6.4 (4.6–7.3)	6.4 (4.7–7.4)	6.5 (3.1–7.4)
HCV RNA ≥800,000 IU/mL	103 (95)	98 (88)	93 (85)	96 (87)
Prior non-responders, n (%)	49 (45)	46 (41)	49 (45)	51 (46)
Prior protease inhibitor failures, n (%)	66 (61)	64 (58)	50 (46)	51 (46)
Cirrhosis, n (%)	22 (20)	22 (20)	22 (20)	22 (20)

- Arms were balanced with respect to demographics and baseline characteristics

Afdhal et al, EASL 2014

Results: SVR12

GT 1 Treatment-Experienced (ION-2)



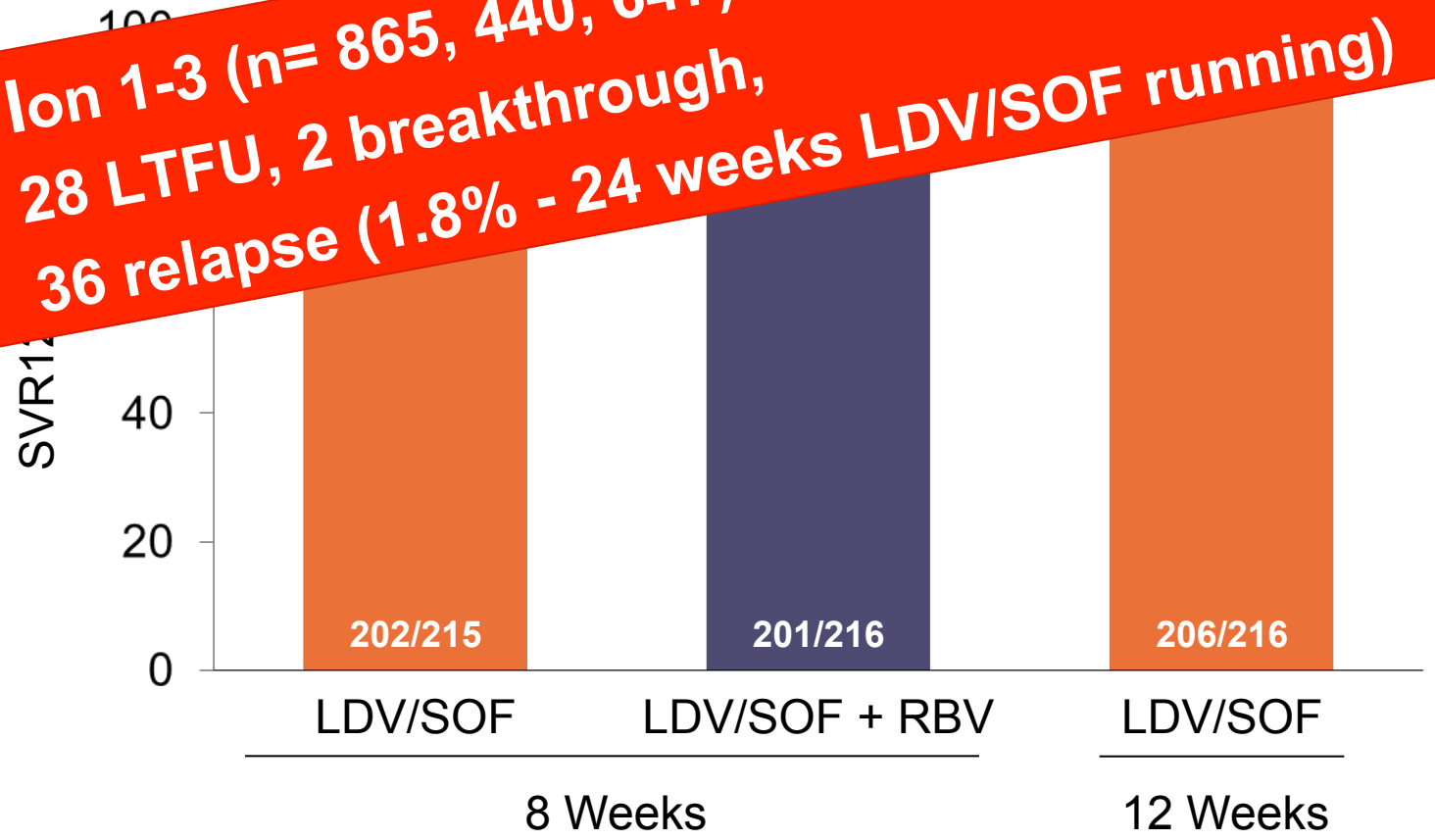
Error bars represent 95% confidence intervals.

Afdhal et al, EASL 2014

Results: SVR12

GT 1 Treatment-Naïve (ION-3)

- Ion 1-3 (n= 865, 440, 647): 66/1952 not cured:
- 28 LTFU, 2 breakthrough,
- 36 relapse (1.8% - 24 weeks LDV/SOF running)



Error bars represent 95% confidence intervals.

Noch kürzer: 6 Wochen Triple – SYNERGY Trial

Genotyp 1
Therapienaiv
Phase 2

Study Design

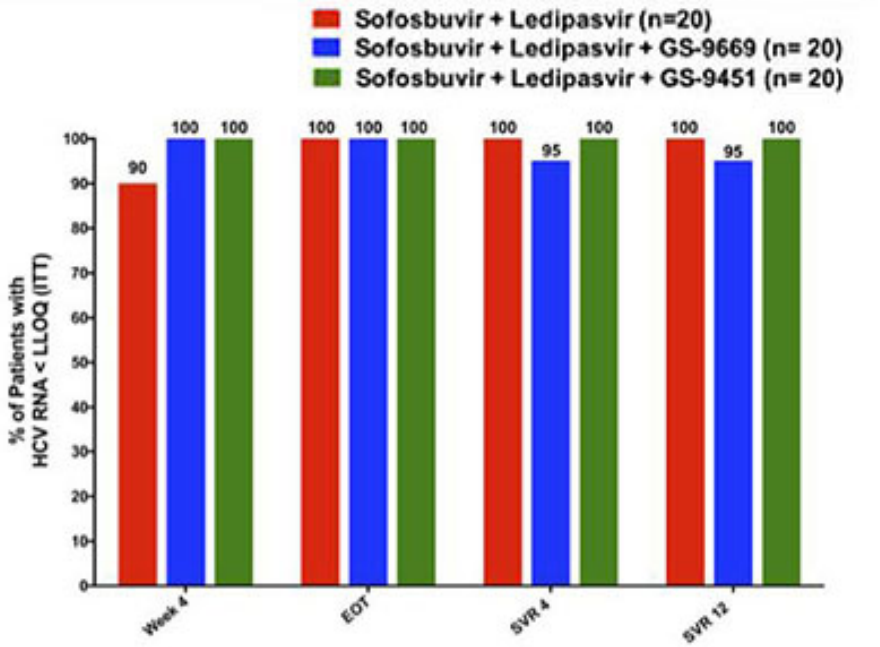
- Sofosbuvir (nucleotide NS5B inhibitor) 400 mg / ledipasvir (NS5A inhibitor) 90 mg once daily
- GS-9669 (non-nucleoside NS5B inhibitor) 500 mg once daily
- GS-9451 (a protease/ NS3/4 inhibitor) 80 mg once daily

Week	0	6	12	
Treatment naïve All stages fibrosis	Sofosbuvir + Ledipasvir (n=20)			SVR12
Treatment naïve Cirrhosis excluded	Sofosbuvir + Ledipasvir + GS-9669 (n=20)			SVR12
Treatment naïve Cirrhosis excluded	Sofosbuvir + Ledipasvir + GS-9451 (n=20)			SVR12

Non NUC

PI

Treatment Response (ITT)



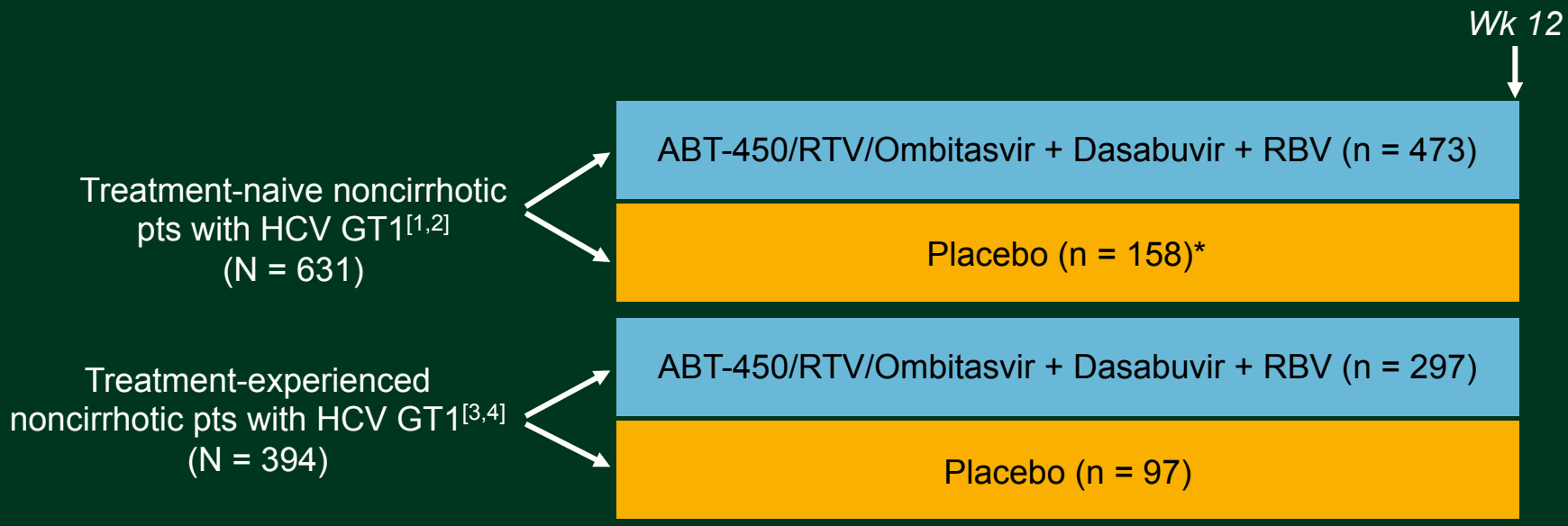
Kohli A, Sims Z, Nelson A, et al.
Combination Oral Hepatitis C Antiviral Therapy for 6 or 12 Weeks: Final Results of the SYNERGY Trial.
21st Conference on Retroviruses and Opportunistic Infections (CROI 2014). Boston, March 3-6, 2014. Abstract 27LB.

Summary of Direct-Acting Antivirals Abbvie Substanzen in rot

Class	Drug	Dosing
NS3/4A protease inhibitor	ABT-450/RTV	150/100 mg
NS3 protease inhibitor	Asunaprevir	100 mg BID
NS3/4A protease inhibitor	MK-5172	100 mg QD
NS3/4A protease inhibitor	Simeprevir	150 mg QD
NS5B nonnucleoside polymerase inhibitor	Dasabuvir	250 mg BID
NS5B nucleotide polymerase inhibitor	Sofosbuvir	400 mg QD
NS5A inhibitor	Daclatasvir	60 mg QD
NS5A inhibitor	GS-5816	25 or 100 mg QD
NS5A inhibitor	Ledipasvir	90 mg QD
NS5A inhibitor	MK-8742	20 or 50 mg QD
NS5A inhibitor	Ombitasvir	25 mg QD

SAPPHIRE I & II: ABT-450/RTV/Ombitasvir + Dasabuvir + RBV in Noncirrhotic GT1 Pts

- Double-blind, placebo-controlled phase III trials in treatment-naive (SAPPHIRE I) and treatment-experienced (SAPPHIRE II) GT1 HCV pts

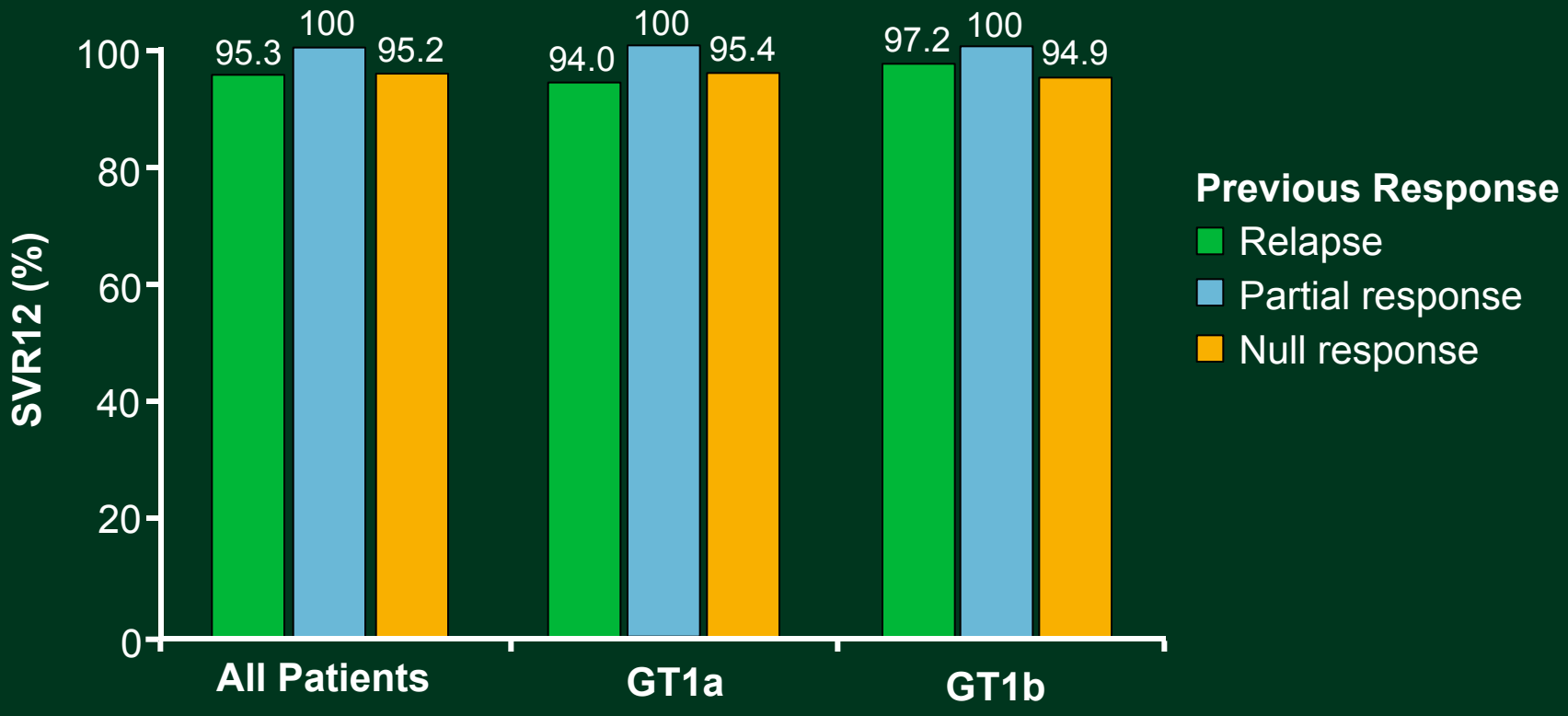


ABT-450/RTV/ombitasvir 150/100/25 mg once daily; dasabuvir 250 mg twice daily; RBV 1000-1200 mg/day.
*Placebo recipients crossed over to active treatment regimen at Wk 12.

1. Feld JJ, et al. EASL 2014. Abstract O60. Reproduced with permission. 2. Feld JJ, et al. N Engl J Med. 2014;370:1594-1603. 3. Zeuzem S, et al. EASL 2014. Abstract O1. 4. Zeuzem S, et al. N Engl J Med. 2014;370:1604-1614.

SAPPHIRE II: SVR12 in Treatment-Exp Pts by HCV Subtype and Previous Treatment

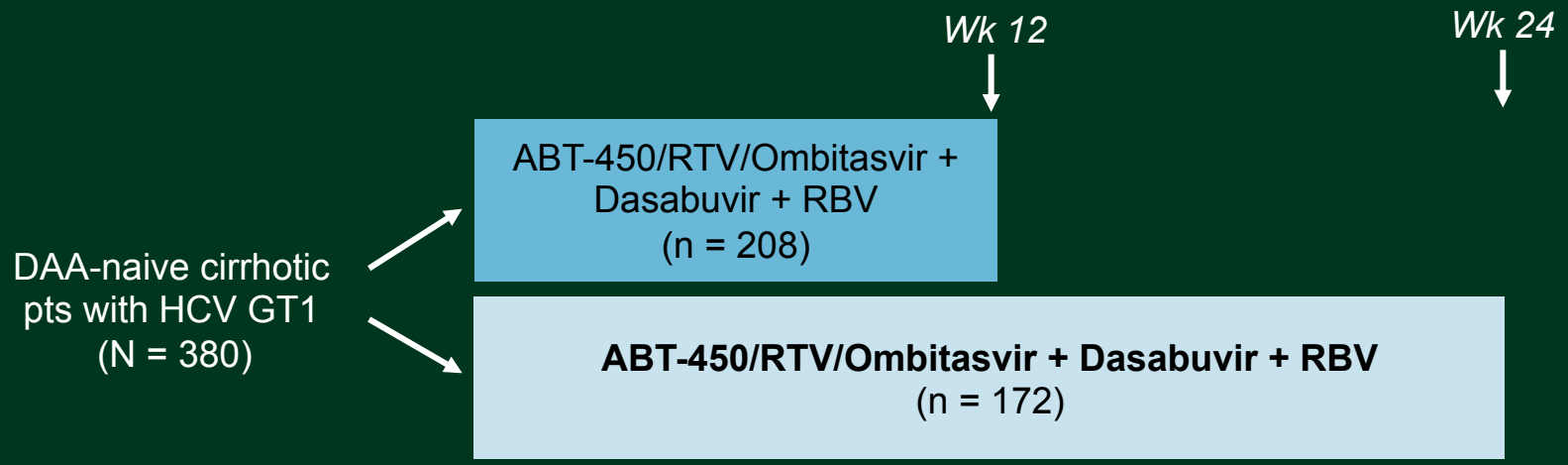
- High response rates in treatment-experienced patients, across subgenotypes, and regardless of previous response to peginterferon/ribavirin



Zeuzem S, et al. EASL 2014. Abstract O1. Zeuzem S, et al. N Engl J Med. 2014;370:1604-1614.

TURQUOISE II: ABT-450/RTV/Ombitasvir + Dasabuvir + RBV in Cirrhotic GT1 Pts

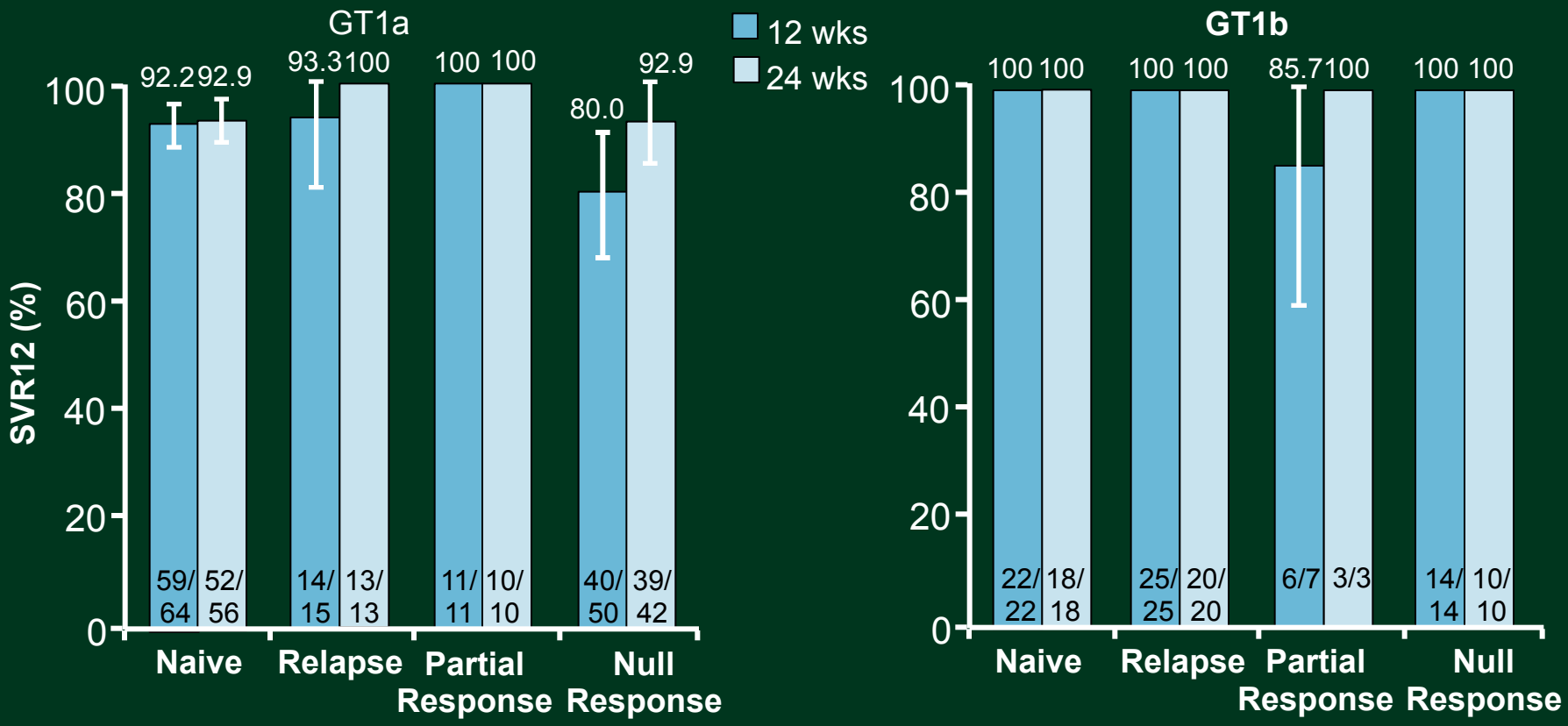
- Open-label phase III trial
- Inclusion criteria: GT1, compensated cirrhosis (Child-Pugh A), DAA naive, radiographic ascites and varices permitted, serum albumin ≥ 2.8 g/dL, total bilirubin < 3 mg/dL, serum AFP ≤ 100 ng/mL, INR ≤ 2.3, platelets ≥ 60,000 cells/mL



ABT-450/RTV/ombitasvir 150/100/25 mg once daily; dasabuvir 250 mg twice daily; RBV 1000-1200 mg/day.

Poordad F, et al. EASL 2014. Abstract O163. Reproduced with permission.

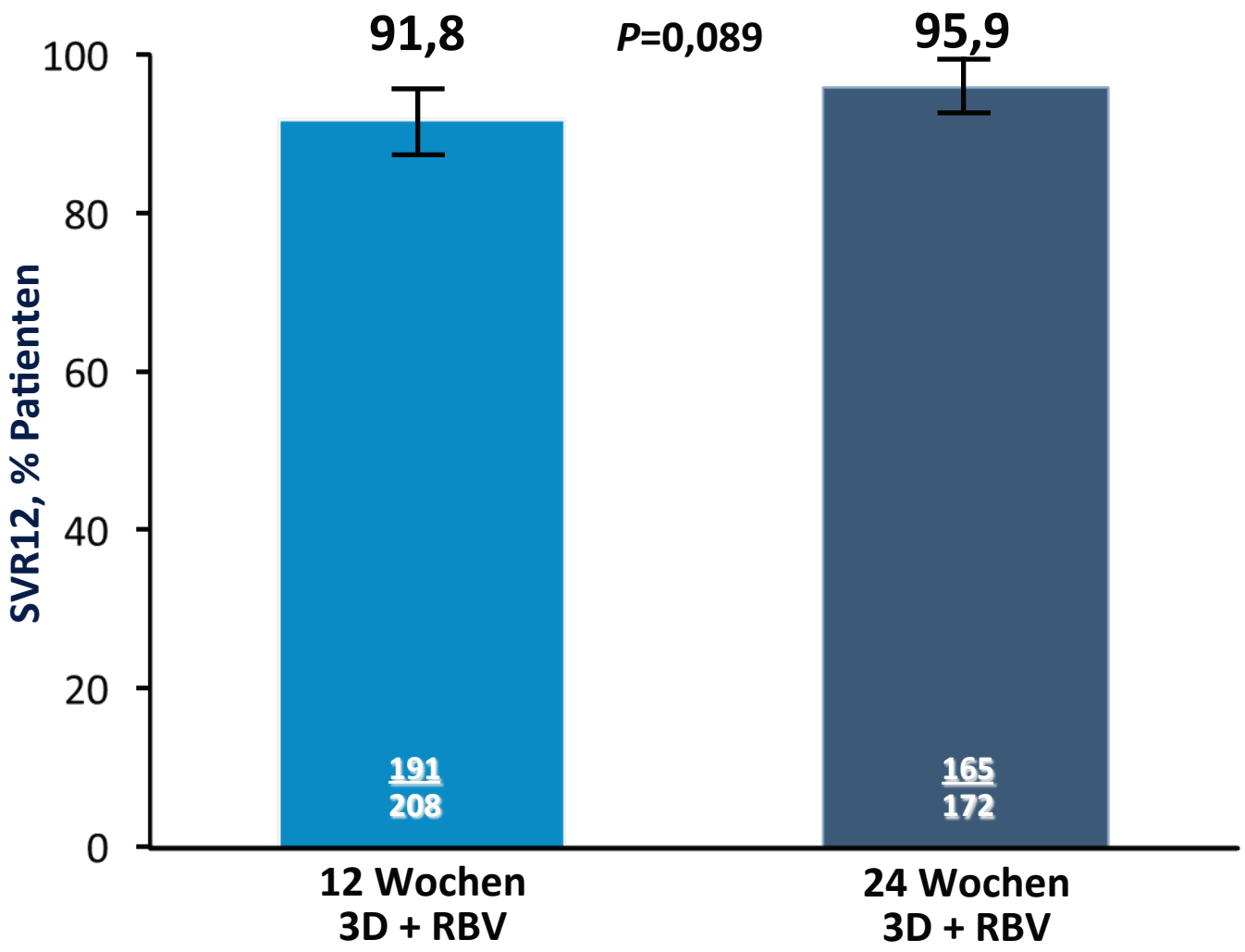
TURQUOISE II: SVR12 With 3 DAAs + RBV in Cirrhotic Pts by HCV Subtype



- Virologic failure in 17/380 pts (4.5%); relapse more frequent with 12-wk vs 24-wk treatment (12 vs 1 pt), 7/12 relapsers by posttreatment Wk 12 were GT1a null responders

Poordad F, et al. EASL 2014. Abstract O163. Reproduced with permission.

TURQUOISE-II: Behandlungsnaive und vorbehandelte GT1-Patienten mit Leberzirrhose – SVR_{12}-Raten



Poordad F, *et al. N Engl J Med* 2014. Online DOI:10.1056/NEJMoa1402869.

In der Praxis 2014 wichtig:
Wann noch Interferon, wann Interferon-frei ?

„ ***Counting down the final days of Interferon*** “ (AASLD 2013)

- **2014**: **Übergangsphase**

  noch IFN-Triple-Therapie für GT1 Patienten, im Verlauf des Jahres erste IFN freie Therapiemöglichkeiten für GT1

Erwartete DAA-Zulassungen 2014:

- Sofosbuvir 18.01.2014: SOF + PEG / RBV für 12 Wochen
- Simeprevir etwa Anfang Juni 2014
- Daclatasvir etwa Ende August 2014
- Ledipasvir + Sofosbuvir: etwa Ende November 2014
- 2015: AbbVie: Q1 2015
- 2015: MSD 5172 + 8742
- 2015: BMS

Vorschriften des Sozialgesetzbuches (SGB) Paragraph 12 des SGB V; dort steht nach wie vor:

“Die Leistungen müssen ausreichend, zweckmäßig und wirtschaftlich sein; sie dürfen das Maß des Notwendigen nicht überschreiten. Leistungen, die nicht notwendig oder unwirtschaftlich sind, können Versicherte nicht beanspruchen, dürfen die Leistungserbringer nicht bewirken und die Krankenkassen nicht bewilligen.”

Zusammenfassung

- HIV / HCV Koinfektion wird genauso zu behandeln sein wie HCV Monoinfektion
- SVR verringert die HCC Inzidenz (bei Nicht-Zirrhotikern) weniger bei Zirrhotikern
  - Heilung (von HCV) ist nicht gleich Heilung (von der Lebererkrankung)
- SVR >90% auch bei schwierig zu behandelnden Patienten
- Frage der Wirtschaftlichkeit noch unbeantwortet