SCSG 2015 POST-AASLD SYMPOSIUM

SOUTHERN CALIFORNIA SOCIETY OF GASTROENTEROLOGY

Jointly provided by the Annenberg Center for Health Sciences at Eisenhower and the Southern California Society of Gastroenterology.

This activity is supported by grants from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc., and Salix Pharmaceuticals, Inc.

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER

Update: Hepatitis C Abstracts from AASLD

Paul Pockros, MD
Director Liver Disease Center Scripps Clinic
Clinical Director of Research,
Scripps Translational Science Institute

Disclosures

- Grants and/or research support from AbbVie Inc., Bristol-Myers Squibb, Gilead Sciences Inc., Janssen, and Merck & Co., Inc.
- Consultant and/or speaker for AbbVie Inc., Bristol-Myers Squibb, Gilead Sciences Inc., Janssen, and Merck & Co., Inc.
- Advisory Board member for AbbVie Inc., Bristol-Myers Squibb, Gilead Sciences Inc., Janssen, and Merck & Co., Inc.
- Presentation includes “off label” discussion on elbasvir and grazoprevir for HCV/HIV, ESRD. Parataprevir/ombitasvir/ dasabuvir for ESRD. ABT-493 and ABT-530 for TN and TE HCV. Sofosbuvir + velpatasvir for GT 1-6 HCV and Child's B cirrhosis and SOF+VEL+GS9857 for GT 1 and 3.

New Information From AASLD 2015 for HCV

- GT 3 CIRRHOSIS
- POST-OLTX
- HIV CO-INFECTION
- ESRD
- RELEVANCE OF RAVS
- 2nd GENERATION NS5A REGIMENS
- BARRIERS TO TREATMENT FROM PAYERS
- BENEFITS OF SVR

ALLY-3+ Study

Plus Ribavirin for 12 or 16 Weeks in HCV Genotype 3-Infected Patients With Advanced Fibrosis or Cirrhosis: The ALLY-3+ Phase 3 Study

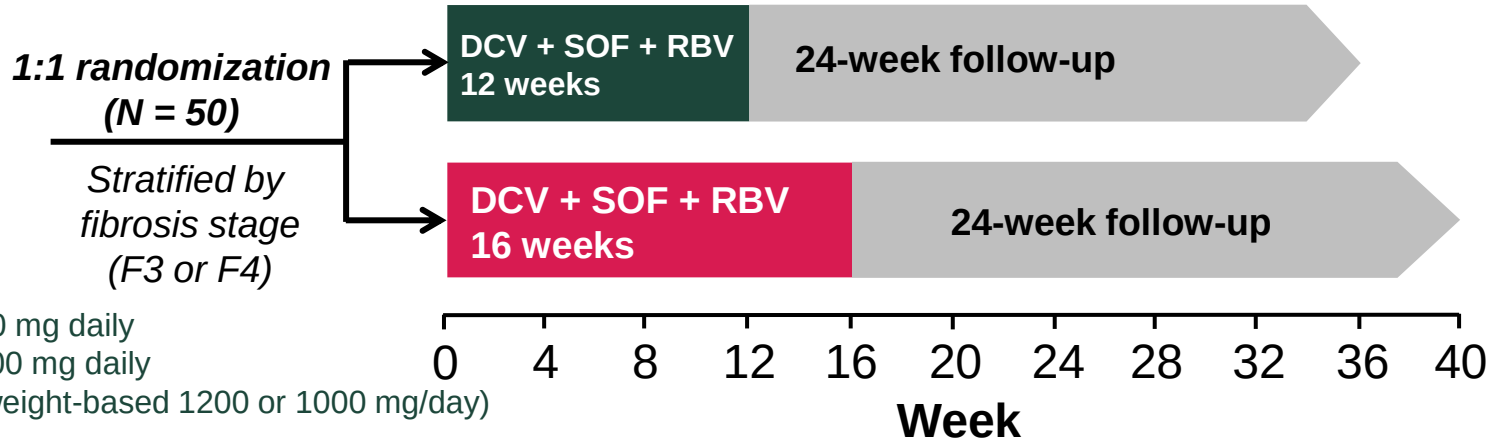
Leroy V,[1] Angus P,[2] Bronowicki JP,[3] Dore G,[4] Hézode C,[5] Pianko S,[6] Pol S,[7] Stuart K,[8] Tse E,[9] McPhee F,[10] Bhore R,[11] Jimenez-Exposito MJ,[11] Thompson A[4]

[1]CHU de Grenoble, La Tronche, France; [2]Austin Hospital, Heidelberg, Australia; [3]CHU Nancy & Lorraine University, Nancy, France; [4]St. Vincent's Hospital and Kirby Institute, Sydney, Australia; [5]CHU Henri Mondor, Créteil, France; [6]Monash Medical Centre, Clayton, Australia; [7]Hôpital Cochin, Paris, France; [8]Gallipoli Medical Research Foundation, Greenslopes, Australia; [9]Royal Adelaide Hospital, Adelaide, Australia; [10]Bristol-Myers Squibb Research & Development, Wallingford, CT; [11]Bristol-Myers Squibb Research & Development, Princeton, NJ.

The Liver Meeting 2015®

ALLY-3+ Study Design

Phase 3b, open-label, randomized study



DCV 60 mg daily
SOF 400 mg daily
RBV (weight-based 1200 or 1000 mg/day)

Primary efficacy endpoint: SVR12

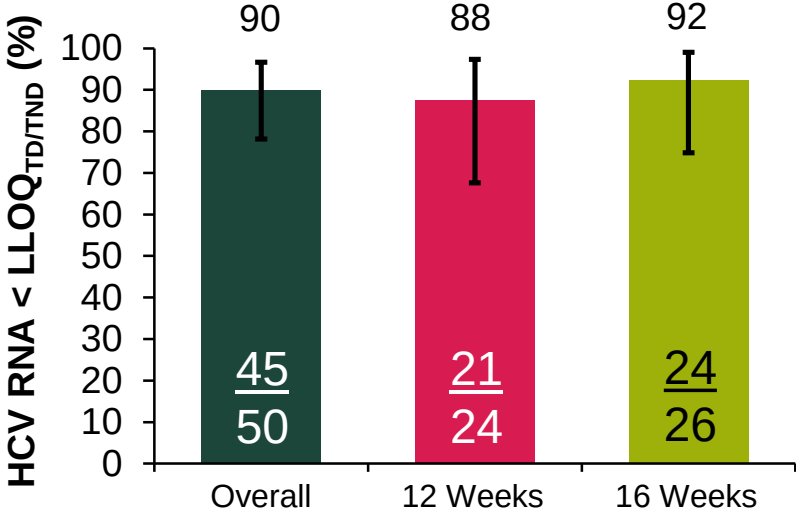
- HCV RNA <$LLOQ_{TD/TND}$ (next observation carried backward) by Roche COBAS TaqMan v2.0 assay (LLOQ 25 IU/mL)

Safety endpoints

- Frequencies of serious AEs, discontinuations due to AEs, grade 3/4 AEs, and laboratory abnormalities

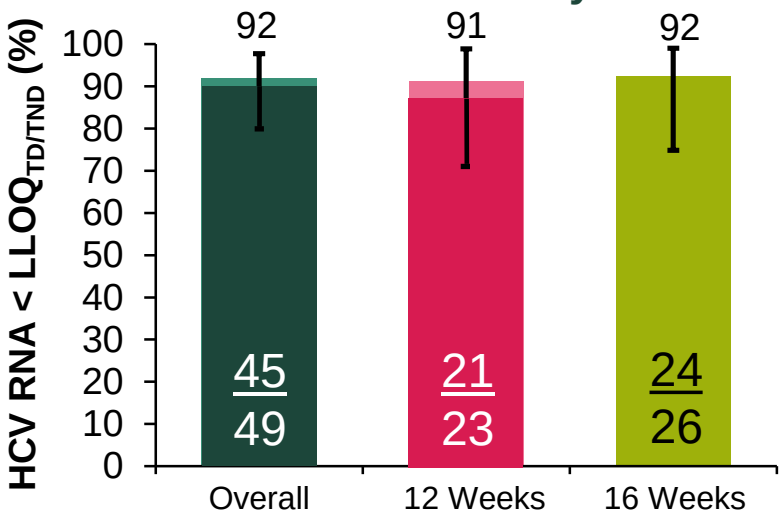
SVR12: All Treated Patients

ITT Analysis (Primary Endpoint)



	Overall	12 Weeks	16 Weeks
VBT[a]	**0**	**0**	**0**
Relapse[b]	**4**	**2**	**2**
Death[c]	**1**	**1**	**0**

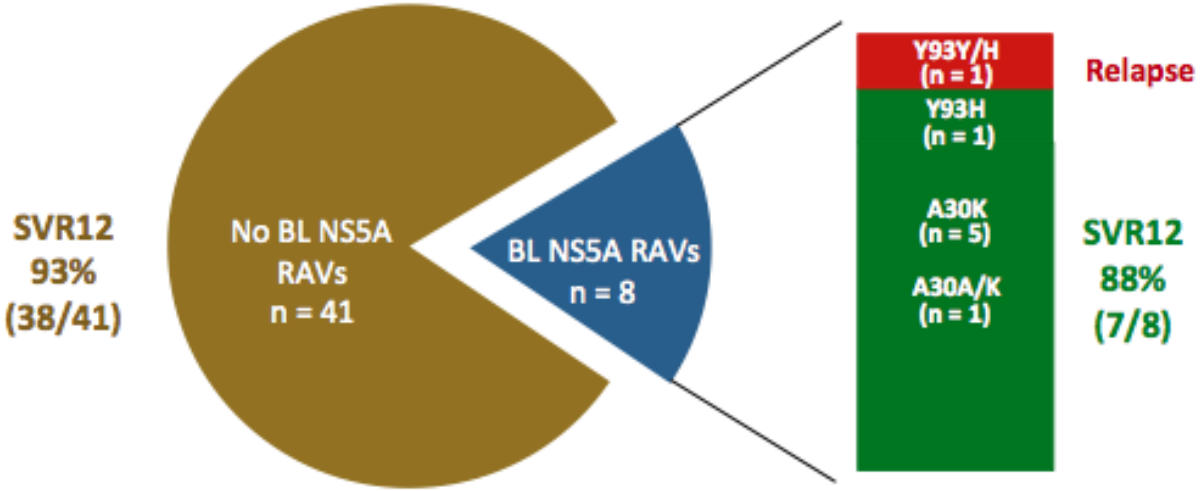
Observed Analysis



	Overall	12 Weeks	16 Weeks
VBT[a]	**0**	**0**	**0**
Relapse[b]	**4**	**2**	**2**

[a]**VBT** (virologic breakthrough}: confirmed HCV RNA ≥ 1 $\log_{10}$ IU/mL above nadir, or ≥ LLOQ if previously < LLOQ TD or TND;
[b]**Relapse:** confirmed HCV RNA ≥ LLOQ at any posttreatment visit following < $LLOQ_{TND}$ at end of treatment;
[c]Dilated cardiomyopathy on Day 72, not related to treatment.

Effect of NS5A RAVS



- At failure, all 4 patients who relapsed had NS5A-Y93H
- No SOF-associated RAVs in NS5B were observed at baseline or relapse (sensitivity ≥ 1%)

Summary

- Overall, 90% SVR12 was achieved in HCV GT 3-infected patients with advanced fibrosis or compensated cirrhosis treated with DCV + SOF + RBV
  - SVR12 was comparable for the 12-week (88%) and 16-week (92%) groups
  - No on-treatment virologic failures; two relapses in each treatment arm
- 86% in 12 week arm and 92% in 16 week arm
- 100% SVR12 in advanced fibrosis
- 88% SVR12 in cirrhosis; 89% excluding death
- Safety; good profile, no grade 4 labs
- Nothing notable in common AE profile

Daclatasvir and Sofosbuvir in Patients with Recurrent HCV Following Liver Transplantation with Advanced Fibrosis or Cirrhosis: United States Multicenter Treatment Protocol

Kwo P,[1] Fried MW,[2] Reddy R,[3] Soldevila-Pico C,[4] Khemichian S,[5] Darling J,[2] Napoli A,[6] Anduze-Faris B,[6] Brown RS Jr[7]

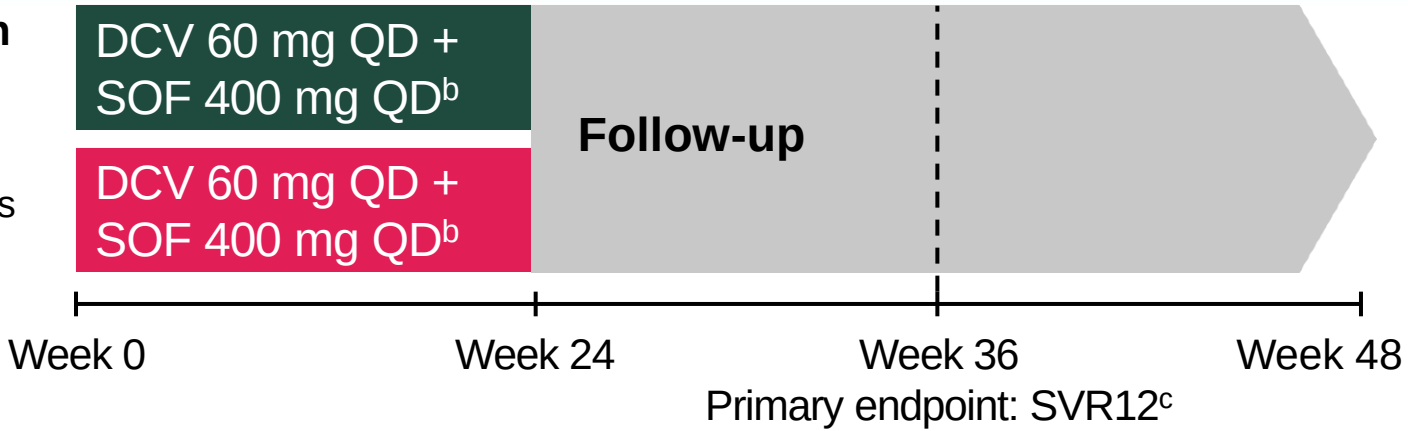
[1]Indiana University, Indianapolis, IN; [2]University of North Carolina, Chapel Hill, NC; [3]Department of Medicine, University of Pennsylvania, Philadelphia, PA; [4]Department of Medicine, University of Florida, Gainesville, FL; [5]Keck School of Medicine, University of Southern California, Los Angeles, CA; [6]Bristol-Myers Squibb, Plainsboro, NJ;[7]Department of Medicine, Columbia University College of Physicians & Surgeons, New York, NY

The Liver Meeting 2015®
San Francisco, CA, 13–17 November 2015

U.S. Expanded Access Protocol Design

Post-transplant with advancing fibrosis (F3/4 or FCH)

Decompensated cirrhosis (Child-Pugh C)[a]

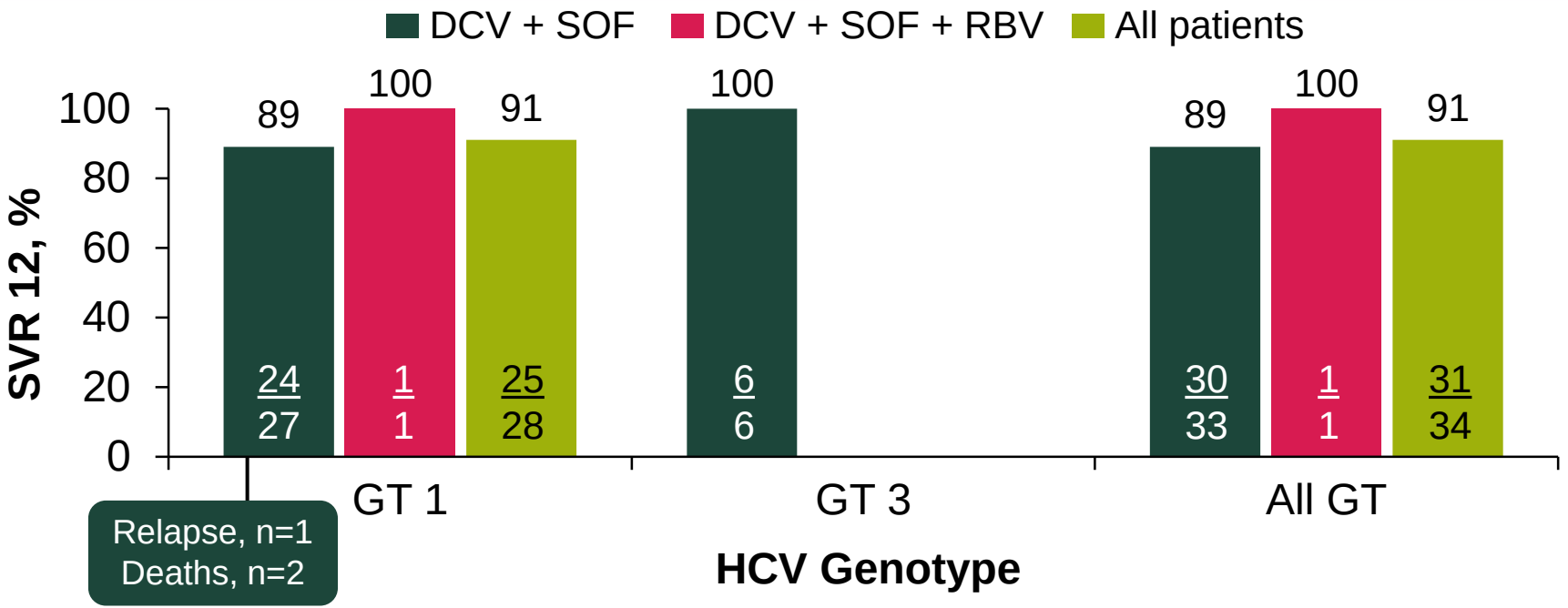


Post-transplant cohort inclusion criteria

- Liver transplant recipients with post-transplant HCV recurrence (any genotype) and advanced fibrosis (F3/4 or FCH)
- Creatinine clearance > 30 mL/min
- Treatment naive or experienced

[a] Cohort added by protocol amendment (Nov 2014); treatment is ongoing, data to be presented at later date.
[b] RBV could be added at physician's discretion following consult with BMS medical monitor.
[c] HCV RNA < lower limit of assay quantitation (LLOQ) at posttreatment Week 12.

Interim SVR12 Results
Post-transplant Cohort



- SVR12 data available for 34 of 36 patients who completed treatment
- NS5A sequencing (population-based) in relapse patient identified Y93S RAV

Summary

- DCV + SOF ± RBV for 24 weeks achieved high rates of SVR12 in patients with severe recurrent post-transplant HCV infection
  - GT 1 infection: 91% (25 of 28)
  - GT 3 infection: 100% (6 of 6)
  - FCH: 100% (4 of 4)
  - Dual liver/kidney transplant: 100% (4 of 4)
- Therapy was generally safe and well tolerated; no events of graft rejection
- HCV regimen allowed a broad range of immunosuppressive regimens
- Program enrollment closed 13 November; final data for post-transplant and decompensated cohorts will be presented at a later date

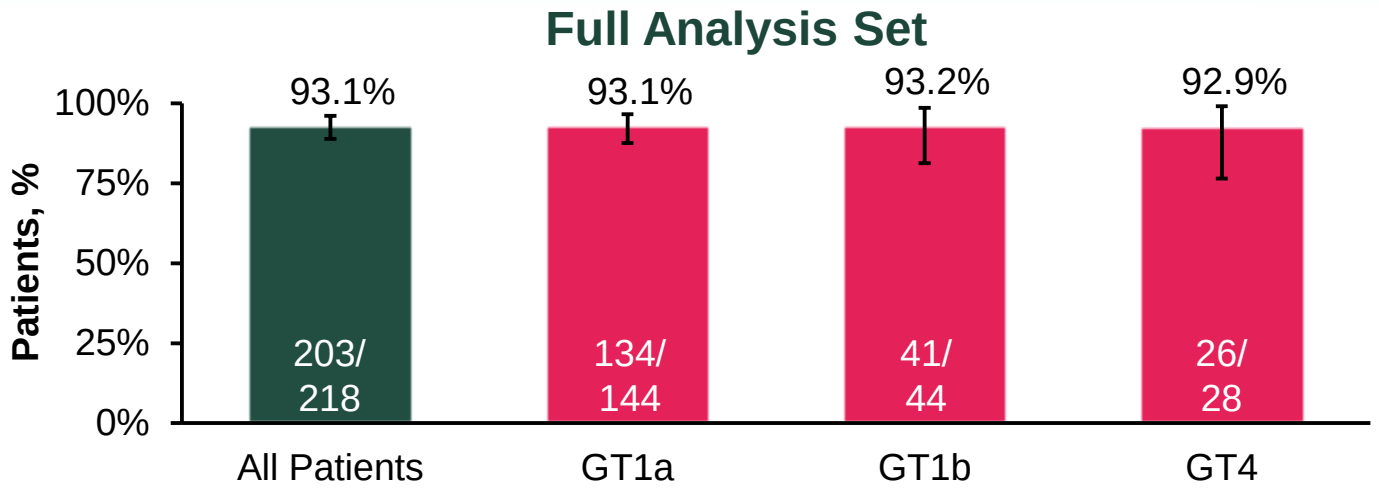
HIV/HCV Coinfection

- An open-label, single-arm, multicenter study across Europe, United States and Australia
- Treatment-naive patients with HCV GT1, 4 or 6 infection with or without cirrhosis
- Co-infected with HIV-1:
  - Naive to ART with CD4+ >500 cells/mm^3 and HIV RNA <50,000 copies/mL
  - On stable on ART† for ≥8 weeks and CD4+ >200 cells/mm^3 and undetectable HIV RNA

† Stable antiretroviral therapy (ART) included tenofovir or abacavir, and either emtricitabine or lamivudine plus raltegravir, dolutegravir, or rilpivirine

Rockstroh J, et al. AASLD 2015;abstract 210.

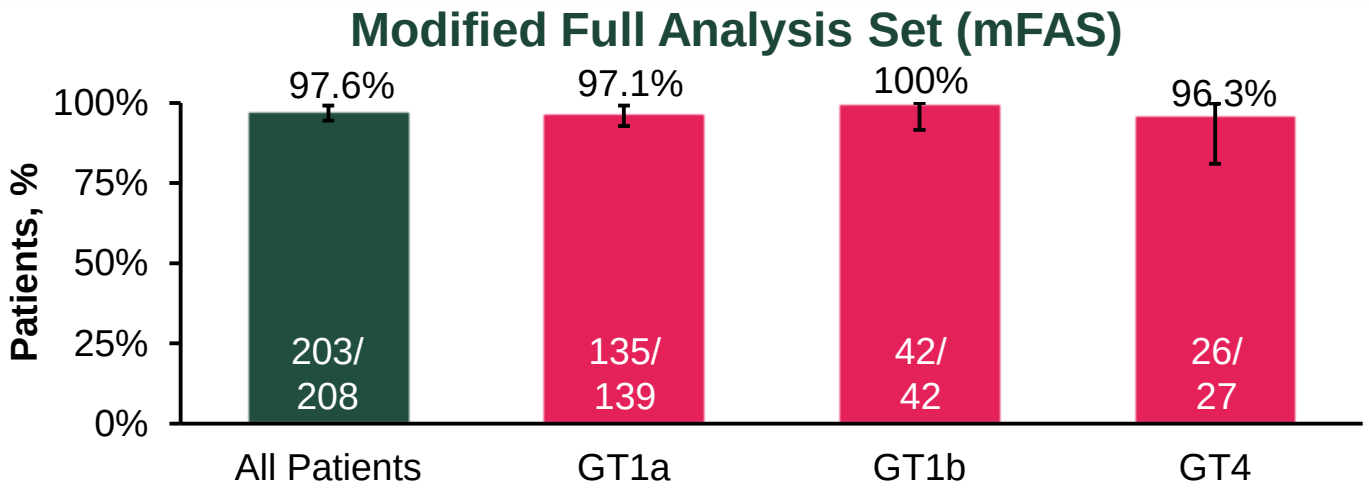
SVR24: Full Analysis Set



	All GT	GT1a	GT1b	GT4
Relapse, n (%)	5 (2.4)	4 (2.8)	0 (0)	1 (3.6)
Other Failure Criteria, n (%)	10 (4.6)	6 (4.2)	3 (6.8)	1 (3.6)
Reinfection, n	2	1	1	0
LTFU or discontinued unrelated to VF, n	8	5	2	1

*2 patients with GT6 infection were also included; both patients achieved SVR12.
GT = genotype; LTFU = lost-to-follow-up

SVR24:
Modified Full Analysis Set (mFAS)

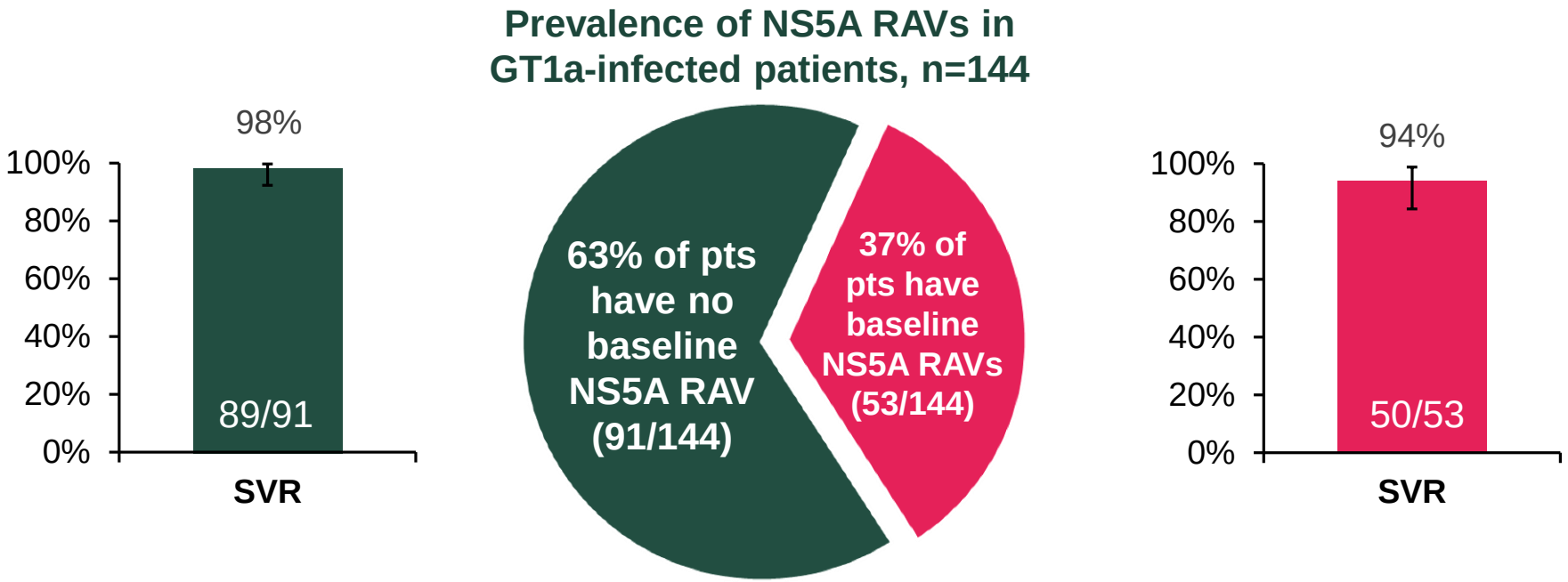


	All GT	GT1a	GT1b	GT4
Relapse, n (%)	5 (2.4)	4 (2.9)	0 (0)	1 (3.7)
Excluded				
Reinfection, n	2	1	1	0
LTFU or discontinued unrelated to VF, n	8	5	2	1

*2 patients with GT6 infection were also included; both patients achieved SVR12.
mFAS = modified Full Analysis Set; GT = genotype; LTFU = lost-to-follow-up

Impact of Baseline NS5A RAVs†

Resistance Analysis Population*



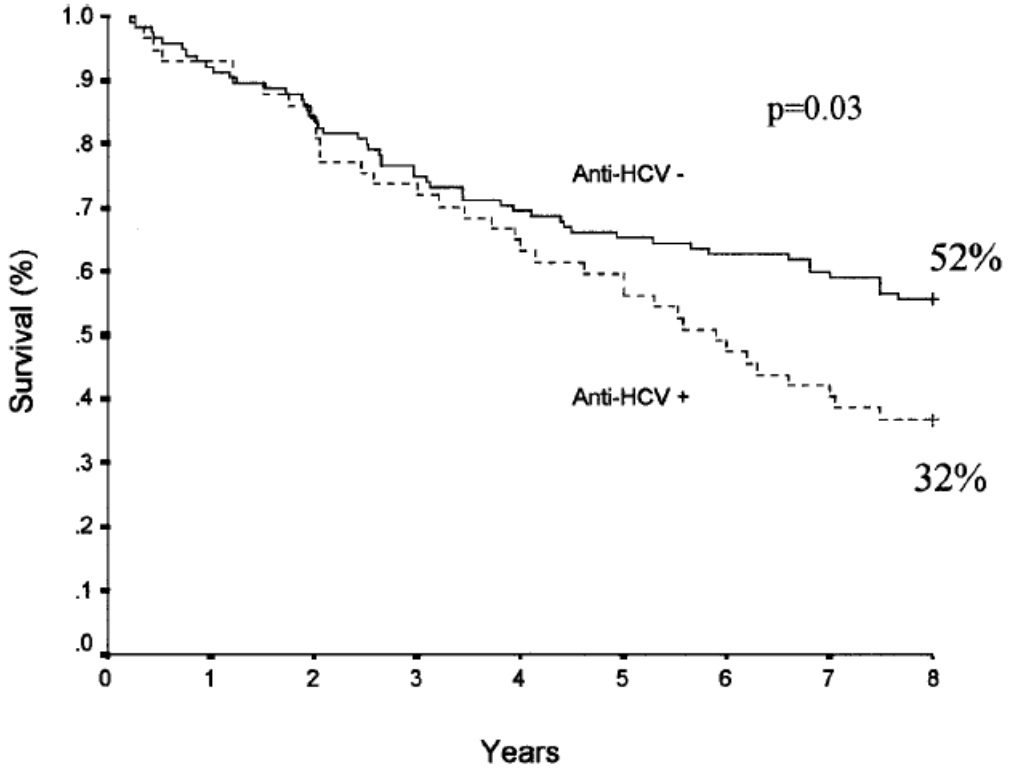
*RAP = Resistance Analysis Population: excludes non-virologic failures or missing baseline sequence data
†NS5A RAVs: any change from reference at NS5A amino acid positions 24, 28, 30, 31, 32, 38, 58, 92 and 93 Next Generation Sequencing with 1% sensitivity threshold with population sequencing when not available
SVR=primary efficacy endpoint of SVR12

Epidemiology of HCV in Patients on Hemodialysis (HD)

- In US, estimated HCV prevalence of **8%**
  - (At the end of 2009, **398,861** ESRD patients were being treated with some form of dialysis; 172,553 ESRD patients had a working transplanted kidney.)
- HCV prevalence 5X greater in HD patients than in general US population
- Risk factors for HCV infection among hemodialysis patients:
  - Number of years on dialysis
  - Number of blood product transfusions
  - Injection drug use
  - History of organ transplantation

Source: Finelli L, et al. *Semi Dial*. 2005;18:52-61.

HCV and Risk of Death in Long-Term Hemodialysis Patients



Espinosa. *Nephrol Dial Transplant*. 2001.

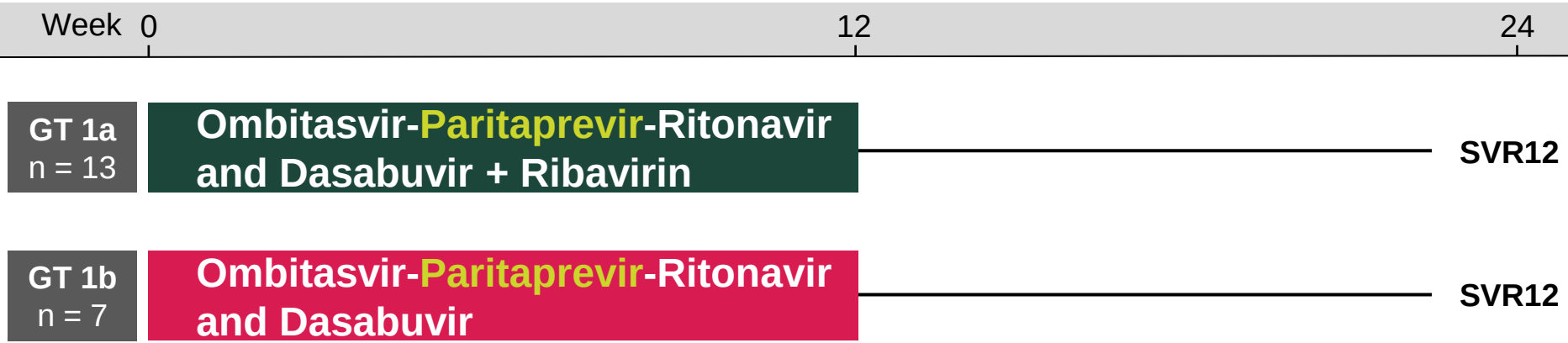
RUBY-I: Study Design

RUBY-I: Features

- **Design**: Phase 3b, randomized, open-label trial evaluating safety and efficacy of 3D (ombitasvir-paritaprevir-ritonavir and dasabuvir) with or without ribavirin for 12 weeks in treatment-naïve patients with chronic HCV GT1 and advanced kidney disease
- **Setting**: 9 sites in United States
- **Entry Criteria**
  - Adults with chronic HCV genotype 1 infection
  - Chronic kidney disease stage 4 or 5 (eGFR <30 mL/min/1.73 m^2) +/- HD
  - Plasma HCV RNA greater than 1,000 IU/mL
  - Absence of cirrhosis
  - Absence of coinfection with HBV or HIV
  - Baseline Hb ≥10 g/dL
- **Primary End-Point**: SVR12

Source: Pockros PJ, et al. 50th EASL. 2015; Abstract L01.

RUBY-I: Regimens



Drug Dosing

Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

Ribavirin for patients not on hemodialysis: 200 mg once daily

Ribavirin for patients on hemodialysis: 200 mg given 4 hours before each hemodialysis session

Source: Pockros PJ, et al. 50th EASL. 2015; Abstract L01.

RUBY-I: Cohort 1 Efficacy

(Data as of 26Aug15)

Subject	1001	1002	1202	1206	1207	1209	1210	1211	1301	1302	1304	1501	1502	1601	1602	1701	1603	1503	1604	1102
GT1a or 1b	1a	1a	1a	1a	1b	1a	1a	1a	1a	1a	1b	1a	1a	1a	1b	1b	1b	1b	1b	1a
Renal Stage 4?	Yes	Yes	No	No	No	No	No	Yes	No	No	No	No	Yes	Yes	No	Yes	No	No	No	No
AGE	56	56	62	60	64	70	63	52	58	60	64	61	49	66	55	65	62	63	58	49
Gender	Male	Female	Male	Male	Male	Male	Male	Male	Female	Male	Male	Male	Female	Male	Male	Male	Male	Male	Male	Male
IL28B	T/T	C/T	C/C	C/C	C/T	C/T	T/T	C/C	C/T	T/T	T/T	C/C	C/C	C/C	C/T	C/T	C/T	C/T	C/T	C/T
Race	- Black or African American	- Black or African American	- White	- White	- Black or African American	- White	- Black or African American	- White	- Black or African American	- Black or African American	- Black or African American	- White	- White	- Black or African American	- Black or African American	- Black or African American	- Black or African American	- Black or African American	- Black or African American	- Black or African American
Ethnicity	None	None	- Hispanic or Latino	- Hispanic or Latino	None	- Hispanic or Latino	None	None	None	None	None	None	None	None	None	None	None	None	None	None
BASE	746000	25300000	17100000	3520000	2980000	429000	1730000	43300000	12600000	6670000	9820000	292000	6980000	2570000	3680000	383000	1230000	6500000	1850000	4210000
W1	25	2310	129	25	152	25	0	311	414	0	625	0	138	25	61	25	25	1090	38	94
W2	0	261	25	0	42	0	25	25	25	25	399	25	25	25	0	0	0	175	0	40
W4	0	25	0	0	0	0	0	0	0	0	25	0	0	0	0	0	0	59	0	0
W8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W12EOT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PTW4	0	0	0	0	0	0	0	0	0	death	0	0	0	0	0	0	0	0	0	146000
PTW12	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	
PTW24	0	0	0	0	0	0			0											

HCV RNA quantifiable

HCV RNA <25 target detected

HCV RNA <25 target not detected

Pockros PJ, et al. *AASLD* 2015; Abstract #1039.

RUBY-I Safety

Cohort 1

- 9 Treatment-emergent SAEs in 4 subjects
  - 1 Death (1302: LV systolic dysfunction/cardiac arrest)
  - 0 DAA drug-related SAEs in 0 subjects
- Grade 3+ ALT elevations: 0
- Discontinuation of DAAs due to AE: 0

Cohort 2

- 0 SAEs in 0 subjects
  - 0 Deaths
  - 0 DAA drug-related SAEs in 0 subjects
- Grade 3+ ALT elevations: 0
- Discontinuation of DAAs due to AE: 0

Pockros PJ, et al. *AASLD* 2015; Abstract #1039.

NS5A Resistance

The HCV Lifecycle Favors Resistance Development…But Not Persistence

Favors Resistance

1. High viral turnover rate
   - 10^{12} virions/day
2. Error-prone RNA polymerase
   - ~1 error per 10,000 bases
   - Involved twice in replication
3. No overlapping reading frames
4. Moderate rate of infected hepatocyte turnover

Lack of Persistence

1. No DNA intermediate
   - Contrast to integrated HIV
   - Contrast to HBV cccDNA
2. No long-lived cellular reservoir known
   - Contrast latently infected HIV + CD4 cells
   - Contrast to transfer of HBV cccDNA in dividing cells
3. There are exceptions!

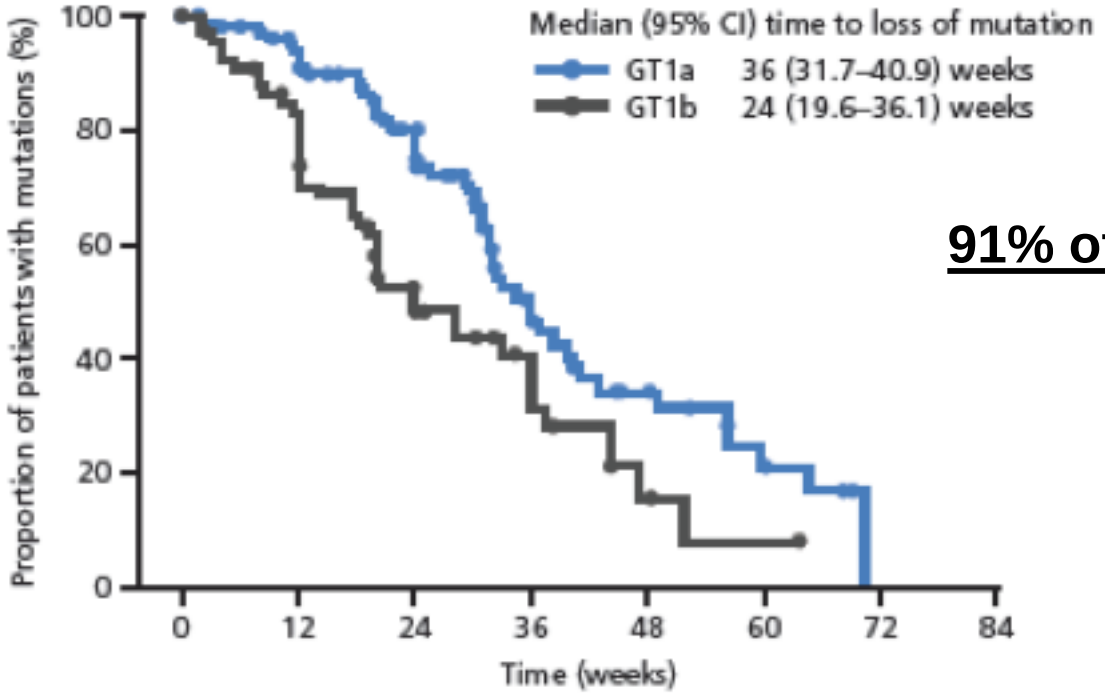
Resistant variants pre-exist in all patients

Available Resistance Testing (US)

- Ultra-deep (or NGS) vs population (Sanger)
  - What is available:
  1. LabCorp/Monogram Biosciences
     - NGS with 10% detection level reported
  2. Quest Diagnostics
     - RT-PCR with DNA sequencing
  - What matters in the clinic?
    - *Jacobson IM. LB-22 AASLD 2015.*

http://www.monogrambio.com/content/hcv-ns5a-testing
http://www.questdiagnostics.com/testcenter/testguide.action?dc=TS_HCV_NS5A_Genotype&tabview=true

The Saving Grace with PI Resistance?



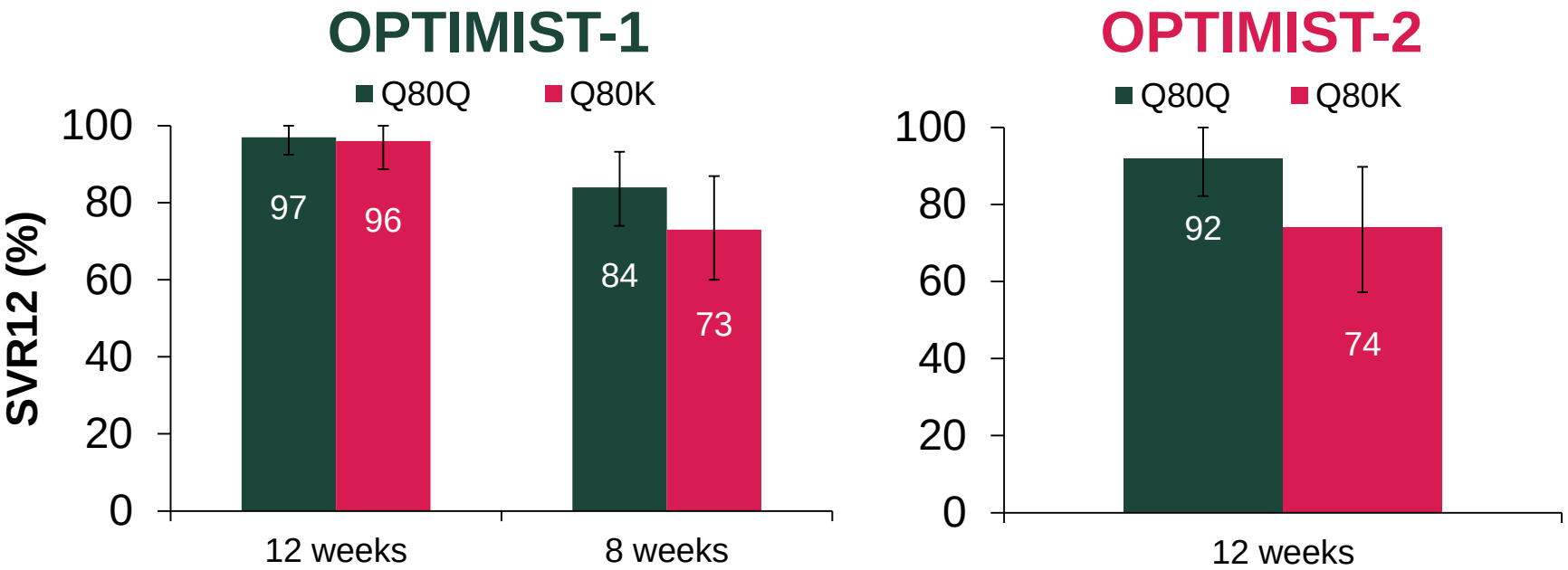
<u>91% of nonSVR with resistance</u>

1a: R155K +/- Q80K

1b: D168V

Lenz O. *EASL.* 2014.

Lack of Q80K Impact with the "Appropriate" Duration of Therapy

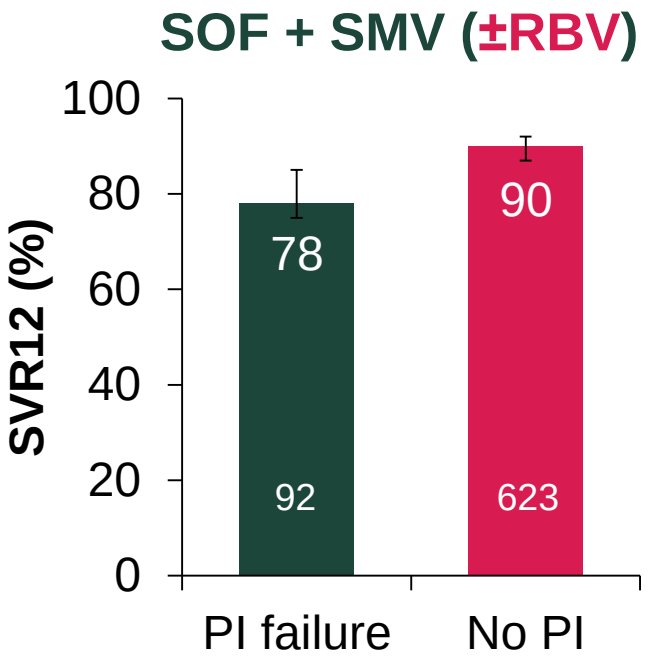


Data are lacking with 24 weeks of SOF/SMV therapy.

Kwo P. #14 EASL. 2015; Lawitz E. #LP04 EASL. 2015.

Real World Data: Impact of Prior PI Therapy?

- PI failure= PEG/RBV + PI
- Resistance testing results not available
  - Majority did not have baseline testing
- Prior PI failure was associated with a decreased SVR rate
  - OR: 0.4 (0.2-0.9)



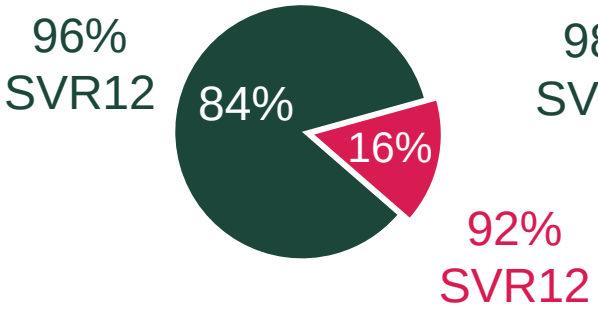
Nelson D. ISVHLD 2015. Jensen D. #45 AASLD 2014.

Baseline NS5A Resistance and SOF/LDV

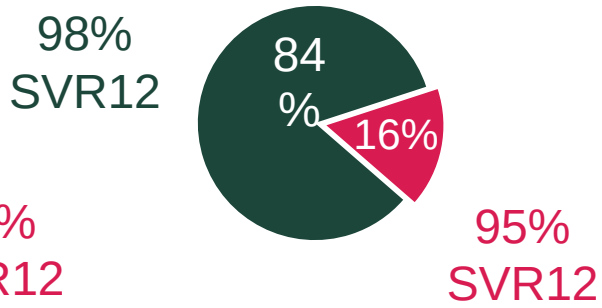
- Deep sequencing analysis of baseline samples (n=1904) in phase 2/3 SOF/LDV studies
  - ELECTRON, LONESTAR and ION studies

GT1 (n=2137)

GT 1a (n=1602)



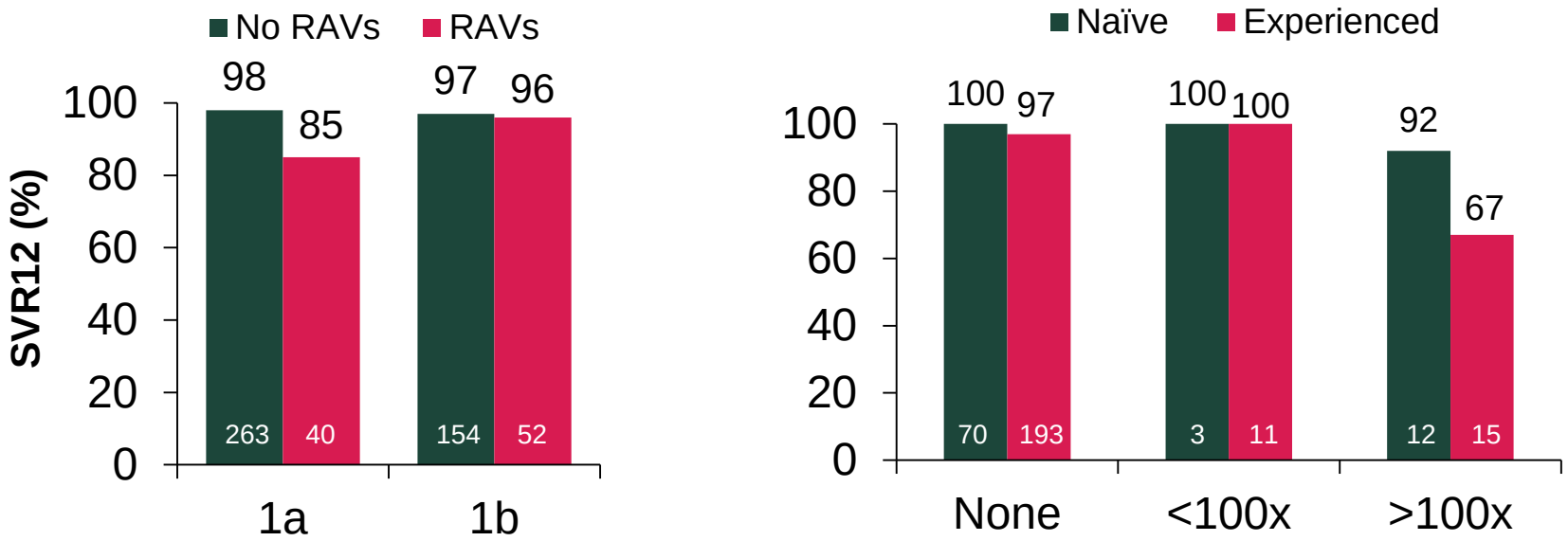
GT 1b (n= 529)



Sarrazin C. #1926 AASLD 2014.

Impact of Baseline NS5A RAVs in Patients with Cirrhosis Treated with SOF/LDV

Impact of Subtype and Fold-Change

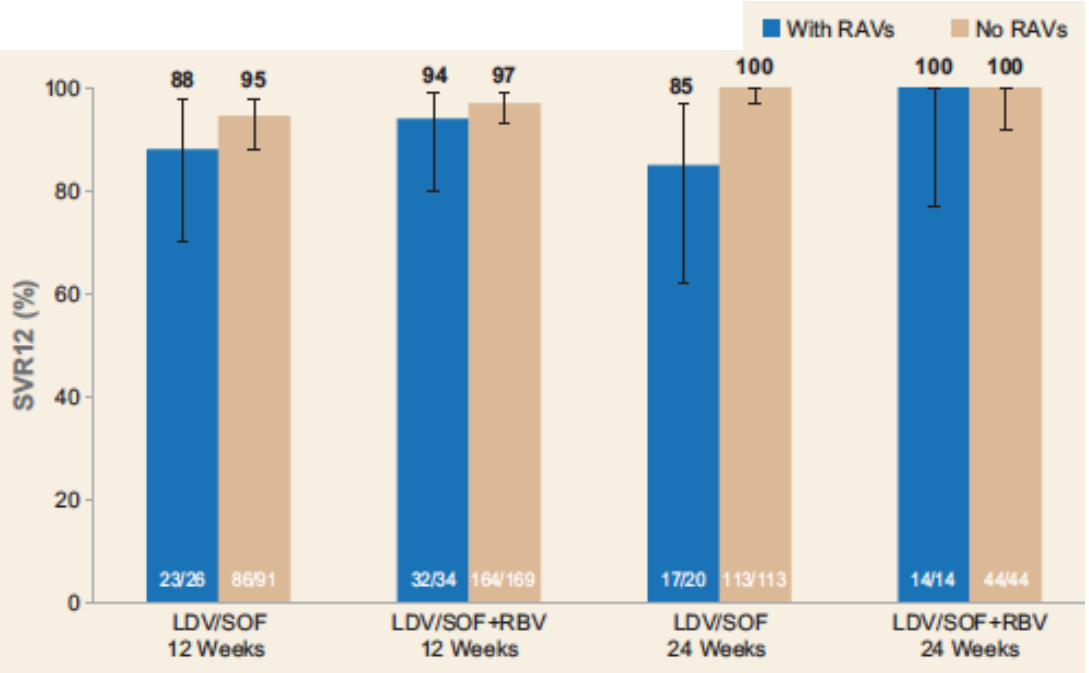


SVR12 combined: 98% no RAVs vs 89% RAVs [@15% level]

Sarrazin C. #P0773. EASL 2015.

Impact of Baseline NS5A RAVs in Patients with Cirrhosis Treated with SOF/LDV

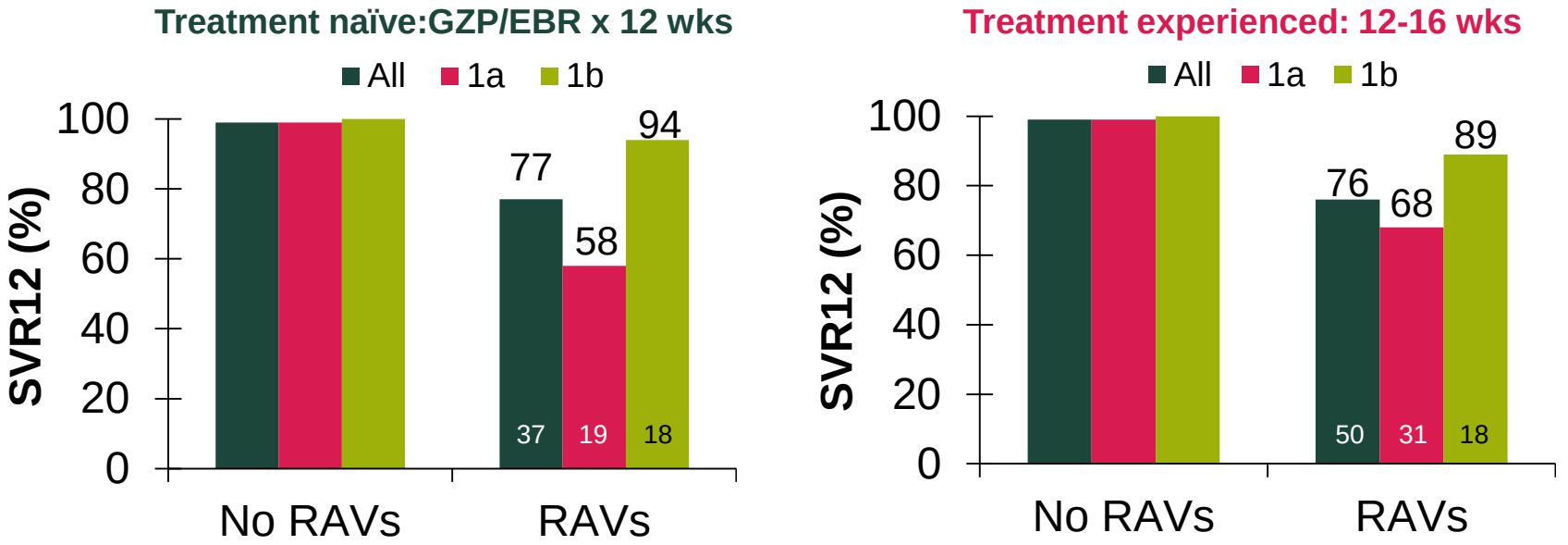
Impact of Duration and RBV



Sarrazin C. #P0773. EASL 2015.

Impact of NS5A RAVs on PI/NS5A

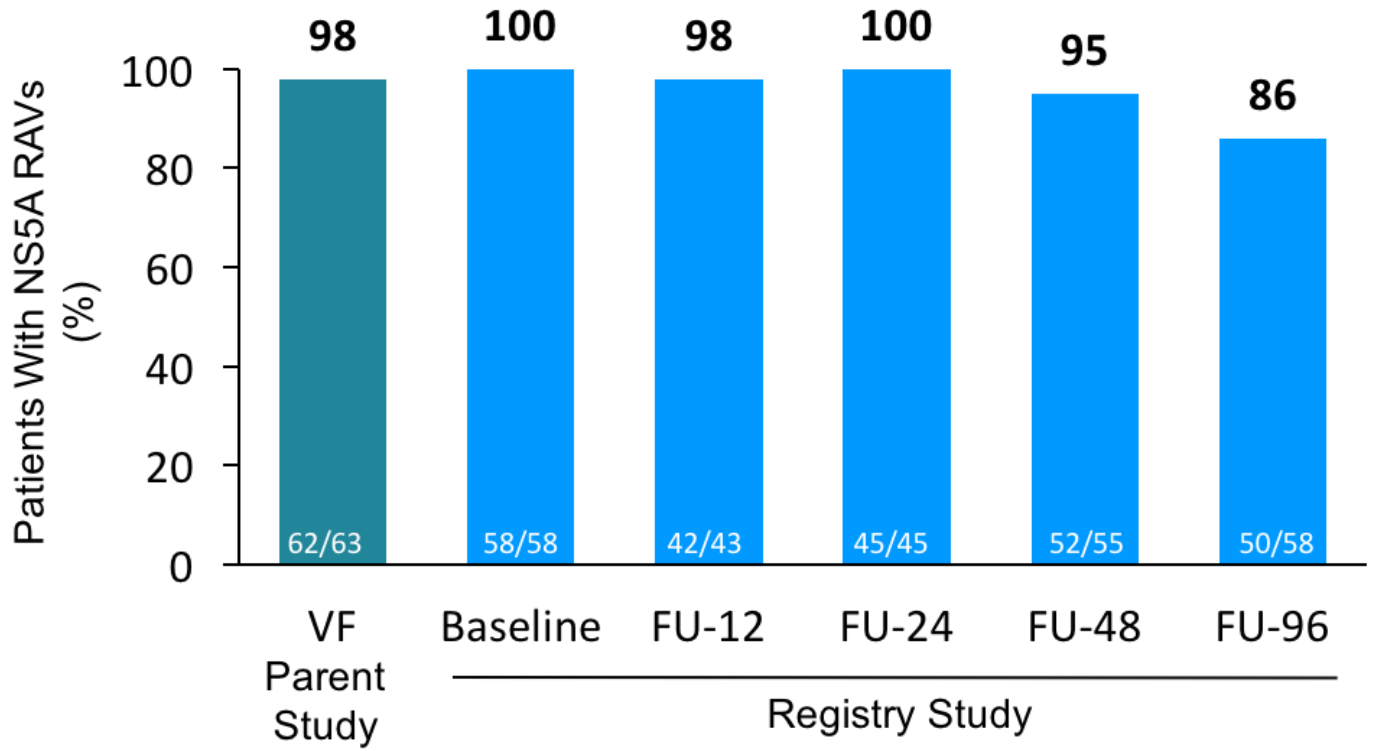
Grazoprevir/Elbasvir



Integrated phase 2/3 analysis: Baseline NS5A RAVs (>5xEC50) predictive of non-SVR with 12 weeks of treatment.

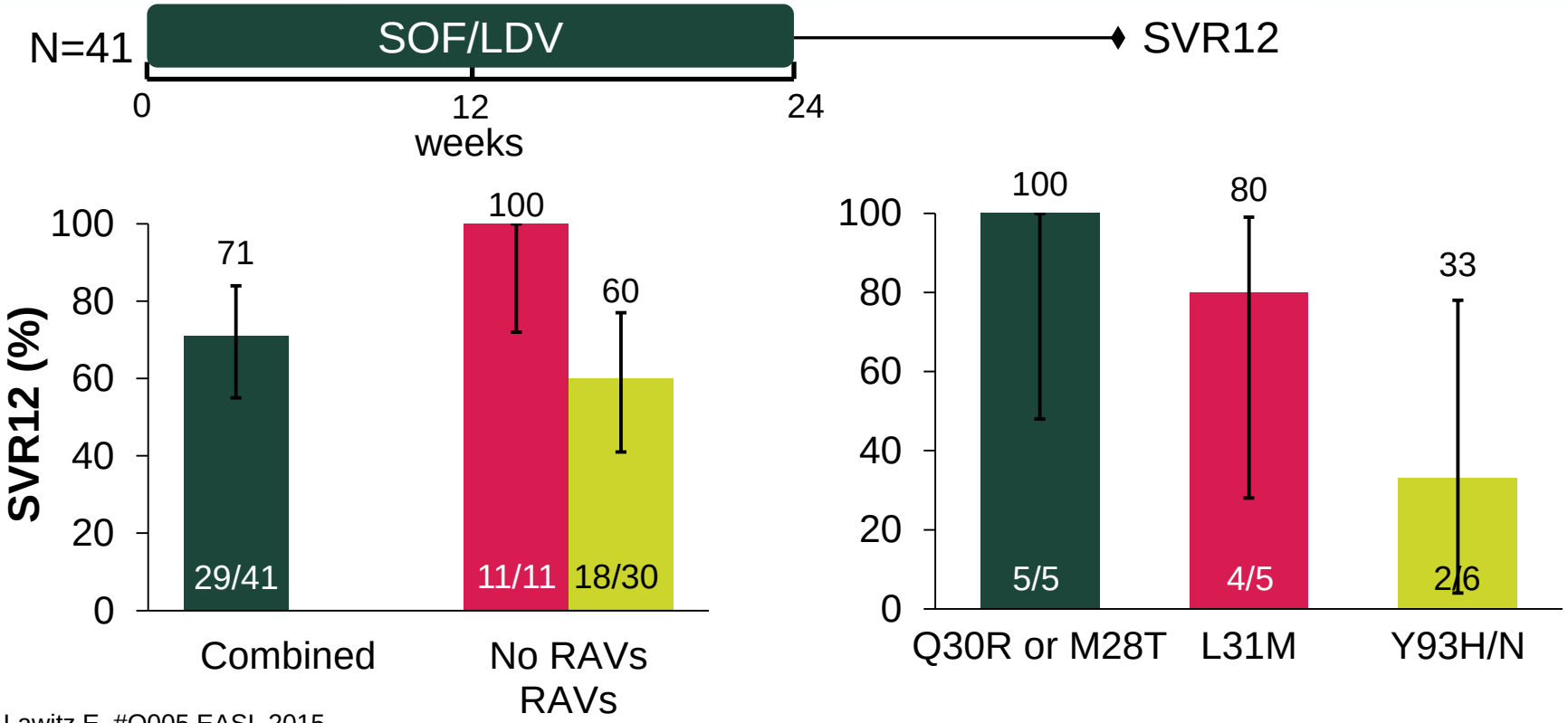
Zeuzem S. #700. AASLD 2015; Zeuzem S. *Annals Intern Med*. 2015; Kwo P. #P0886 EASL 2015.

Durability of Treatment Emergent NS5A RAVs

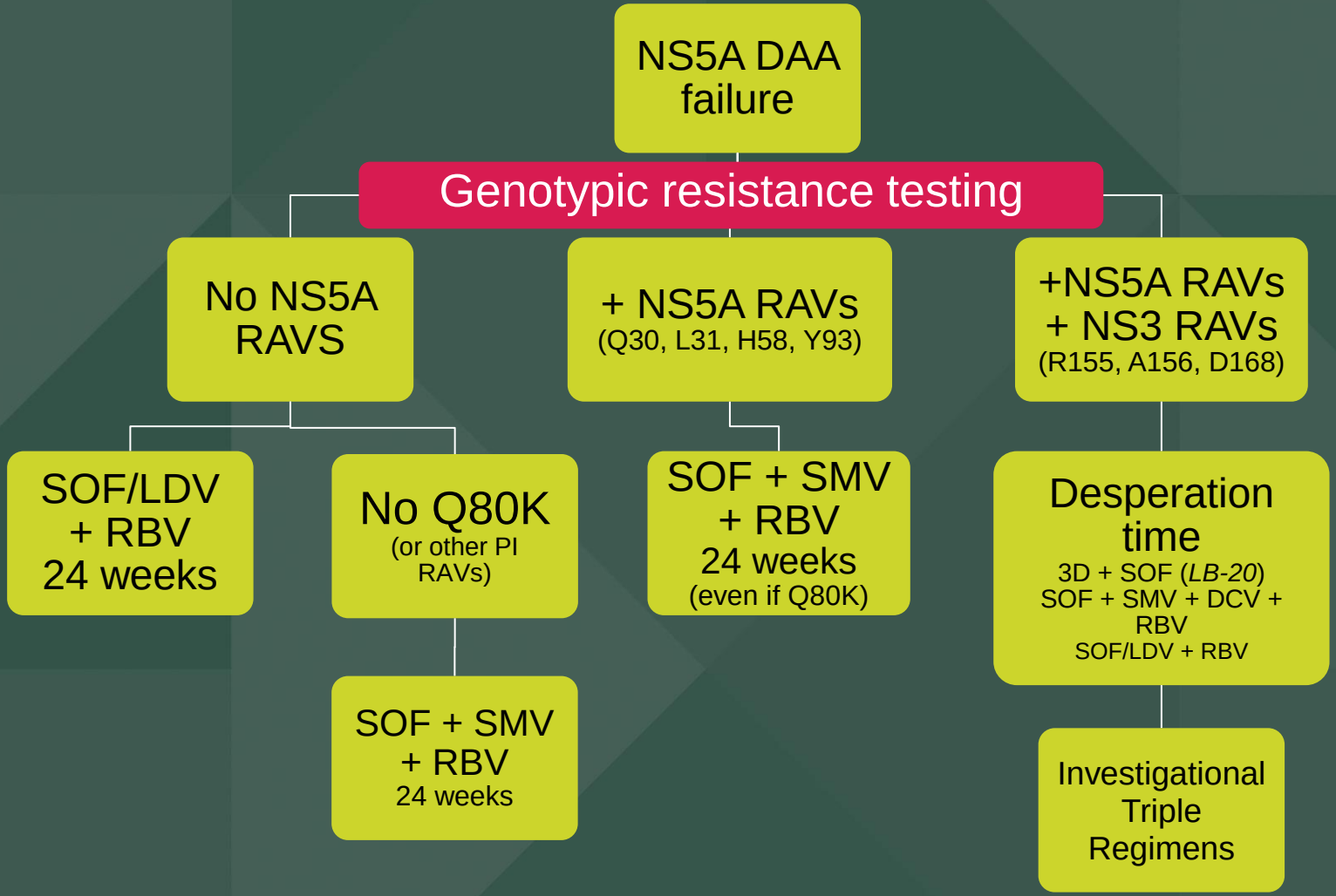


Wyles D, Dvory-Sobol H. EASL 2015.

NS5A RAVs are Associated with Retreatment Failure



Lawitz E. #O005 EASL 2015.


NS5A DAA failure
Genotypic resistance testing
No NS5A RAVS
+ NS5A RAVs (Q30, L31, H58, Y93)
+NS5A RAVs + NS3 RAVs (R155, A156, D168)
SOF/LDV + RBV 24 weeks
No Q80K (or other PI RAVs)
SOF + SMV + RBV 24 weeks (even if Q80K)
Desperation time
3D + SOF (LB-20)
SOF + SMV + DCV + RBV
SOF/LDV + RBV
SOF + SMV + RBV 24 weeks
Investigational Triple Regimens

SURVEYOR-II: High SVR4 Rates Achieved With the Next Generation NS3/4A Protease Inhibitor ABT-493 and NS5A Inhibitor ABT-530 in Non-Cirrhotic Treatment-Naïve and Treatment-Experienced Patients With HCV Genotype 3 Infection

Paul Kwo,[1] Michael Bennett,[2] Stanley Wang,[3] Hugo E. Vargas,[4] David Wyles,[5] J. Scott Overcash,[6] Peter Ruane,[7] Benedict Maliakkal,[8] Asma Siddique,[9] Bal Raj Bhandari,[10] Fred Poordad,[11] Ran Liu,[3] Chih-Wei Lin,[3] Teresa I. Ng,[3] Federico J. Mensa,[3] Jens Kort[3]

[1]Indiana University School of Medicine, Indianapolis, IN, USA; [2]San Diego Digestive Disease Consultants, Inc., and Medical Associates Research Group, Inc., San Diego, CA, USA; [3]AbbVie Inc., North Chicago, IL, USA; [4]Mayo Clinic, Phoenix, AZ, USA; [5]University of California San Diego, La Jolla, CA, USA; [6]eStudySite, San Diego, CA, USA; [7]Ruane Medical & Liver Health Institute, Los Angeles, CA, USA; [8]University of Rochester Medical Center, Rochester, NY, USA; [9]Virginia Mason Hospital and Medical Center, Seattle, WA, USA; [10]Gastroenterology & Nutritional Medical Services, Bastrop, LA, USA; [11]Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, USA

66th Annual Meeting of the American Association for the Study of Liver Diseases
• San Francisco, CA •
17 November 2015

abbvie

Next Generation Direct-Acting Antivirals: ABT-493

ABT-493 demonstrates potent activity against major HCV genotypes *in vitro*

Protease Inhibitor	Stable HCV Replicon EC_{50} (nM)					
	GT1a	GT1b	GT2a	GT3a	GT4a	GT6a
ABT-493	**0.85**	**0.94**	**2.7[a]**	**1.6**	**2.8**	**0.86**
Paritaprevir	1.0	0.21	5.3[a]	19	0.09	0.68
Simeprevir[1,2]	13	9.4	15	472	NA	NA
Asunaprevir[3]	4.0	1.2	230	1162	NA	NA
Grazoprevir	0.38	0.87	1.3	36	1.2	0.89
GS-9451[4]	13	5.4	316	NA	NA	NA
GS-9857[5]	3.9	3.3	3.7	6.1	2.9	1.5

[a]Study conducted at Southern Research Institute.
NA, not available.

1. Simeprevir prescribing information; 2. Chase R, et al. IAPAC, 2013; 3. McPhee F, et al. AAC, 2012; 4. Yang H, et al. AAC, 2014; 5. Taylor J, et al. EASL, 2015

Next Generation Direct-Acting Antivirals: ABT-530

ABT-530 demonstrates potent pangenotypic activity against HCV *in vitro*

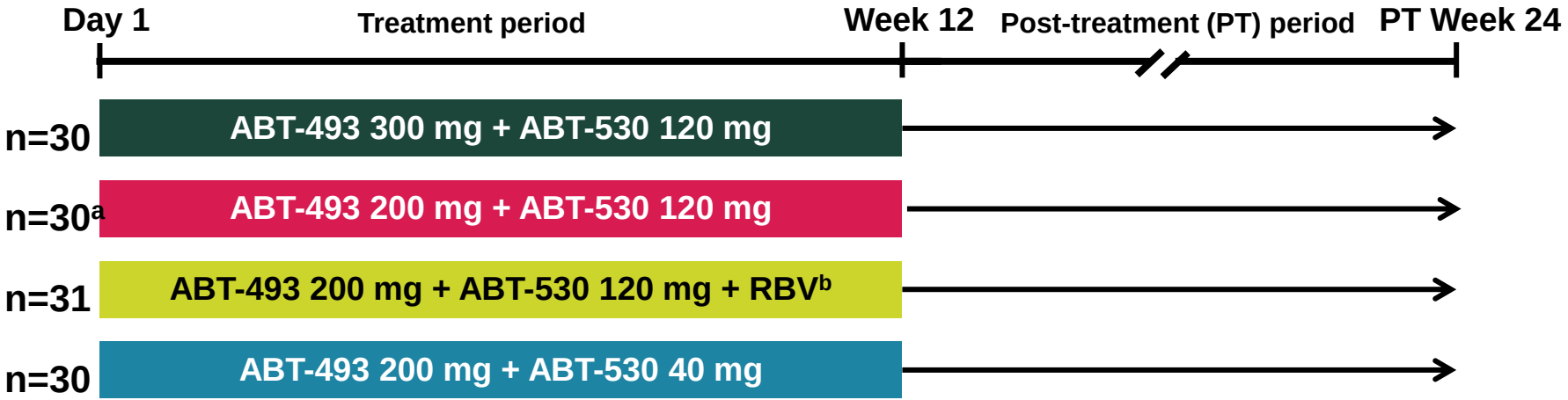
NS5A Inhibitor	Stable HCV Replicon EC_{50} (pM)							
	GT1a	GT1b	GT2a	GT2b	GT3a	GT4a	GT5a	GT6a
ABT-530	**2**	**4**	**2[a]**	**2**	**2**	**2**	**1**	**3**
Ombitasvir	14	5	12	4	19	2	3	366
Daclatasvir[1]	22	3	13,000	NA	530	13	5	74
Ledipasvir[2]	31	4	21,000	16,000	168,000	390	150	1100
Velpatasvir[3]	12	15	9	8	12	9	75	6
Elbasvir[4]	4	3	3	3000	20	3	1	3
MK-8408[5]	1	2	1	4	2	2	1	4
ACH-3102[6]	26	5	21	~150	NA	NA	NA	NA
IDX719[7]	8	3	24	NA	17	2	37	NA

[a]Study conducted at Southern Research Institute.
NA, not available.

1. Wang C, et al. AAC, 2014.; 2. Cheng G, et al. EASL, 2012.; Harvoni prescribing information; 3. Cheng G, et al. EASL, 2013;
4. Liu R, et al. EASL, 2012.; 5. Asante-Appiah E, AASLD, 2014.; 6. Zhao Y, et al. EASL, 2012.; 7. Dousson C, et al. EASL, 2011.

SURVEYOR-II Part 1 (GT3): Study Design

- SURVEYOR-II is an open-label, multicenter phase 2 trial evaluating the safety and efficacy of co-administered ABT-493 and ABT-530, at varying doses, ± ribavirin (RBV), in patients with HCV GT2 or GT3 infection

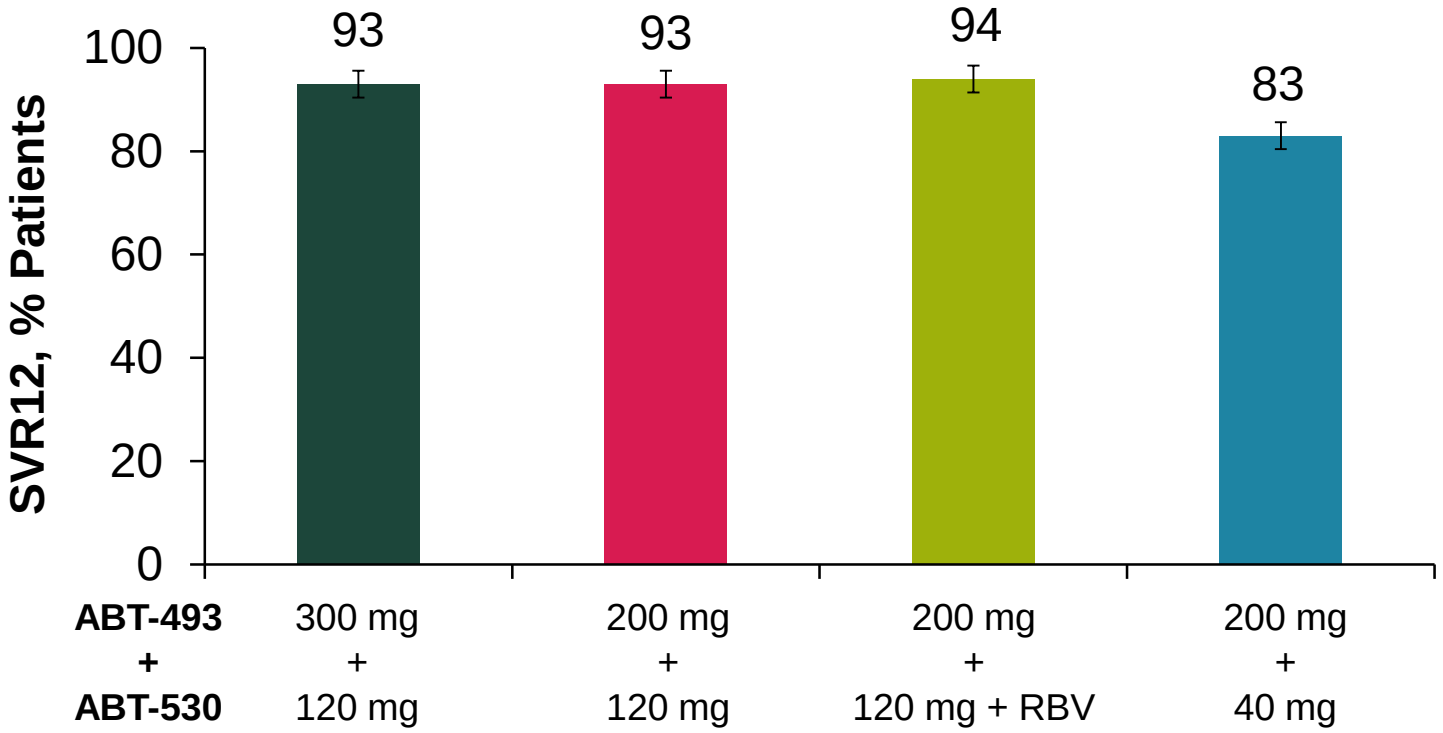


ClinicalTrials.gov: NCT02243293.; N=121.

[a]Includes one patient who was incorrectly assigned to treatment in the GT2 cohort.

[b]Daily dose of 1000 mg or 1200 mg RBV dosed BID based on patient body weight being <75 kg or ≥75 kg.

SURVEYOR-II Part 1 (GT3): ITT SVR12 Rates by Treatment



SURVEYOR-II Part 1 (GT3): Reasons for SVR12 Non-Response

	ABT-493 300 mg + ABT-530 120 mg (n = 30)	ABT-493 200 mg + ABT-530 120 mg (n = 29)	ABT-493 200 mg + ABT-530 120 mg + RBV (n = 31)	ABT-493 200 mg + ABT-530 40 mg (n = 30)
SVR12, n/N (%)	28/30 (93)	28/30 (93)	29/31 (94)	25/30 (83)
Non-SVR12, n				
Virologic failure, n	1	2	1	3
On-treatment breakthrough	0	0	1	1
Relapse	1	2	0	2
Non-virologic failure, n				
Early study drug discontinuation	0	0	1	1
Missing SVR12 data	1	0	0	1

ABT-493 300 mg + ABT-530 120 mg prevented breakthroughs

SURVEYOR-II Part 1 (GT3): Laboratory Abnormalities

Event, n (%)	ABT-493 300 mg + ABT-530 120 mg (n = 30)	ABT-493 200 mg + ABT-530 120 mg (n = 29)	ABT-493 200 mg + ABT-530 120 mg + RBV (n = 31)	ABT-493 200 mg + ABT-530 40 mg (n = 30)
ALT Grade 3+ (>5 × ULN)	0	0	0	0
AST Grade 3+ (>5 × ULN)	0	1 (3)	0	0
Alkaline phosphatase Grade 3+ (>5 × ULN)	0	0	0	0
Total bilirubin Grade 3+(>3 × ULN)	0	0	0	0
Hemoglobin				
Grade 2 (<10-8 g/dL)	0	0	3 (10)	0
Grade 3 (<8 g/dL)	0	0	0	0

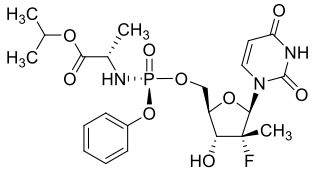
In all patients with baseline ALT elevations, ALT levels normalized with DAA treatment and there were no on-treatment ALT elevations above baseline

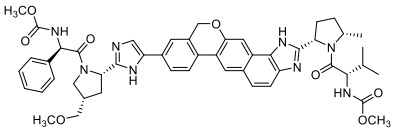
SURVEYOR-II : Summary

- Non-cirrhotic GT3-infected patients treated with ABT-493 300 mg + ABT-530 120 mg for 12 weeks achieved a high SVR12 rate
- Based on these results and data in other genotypes, the selected doses moving forward are:
  - ABT-493: 300 mg QD
  - ABT-530: 120 mg QD
- This combination demonstrated a favorable safety profile
  - AEs were mostly mild in severity
  - No dose-dependent increases in the frequency of AEs
  - Study drug discontinuation due to AEs was low (n = 1)

Background

SOF
Nucleotide polymerase inhibitor





VEL
NS5A inhibitor

SOF | **VEL**

- **Sofosbuvir (SOF)[1,2]**
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet
- **Velpatasvir (VEL; GS-5816)[3-5]**
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile
- **SOF/VEL FDC**
  - Once daily, oral, FDC (400/100 mg)

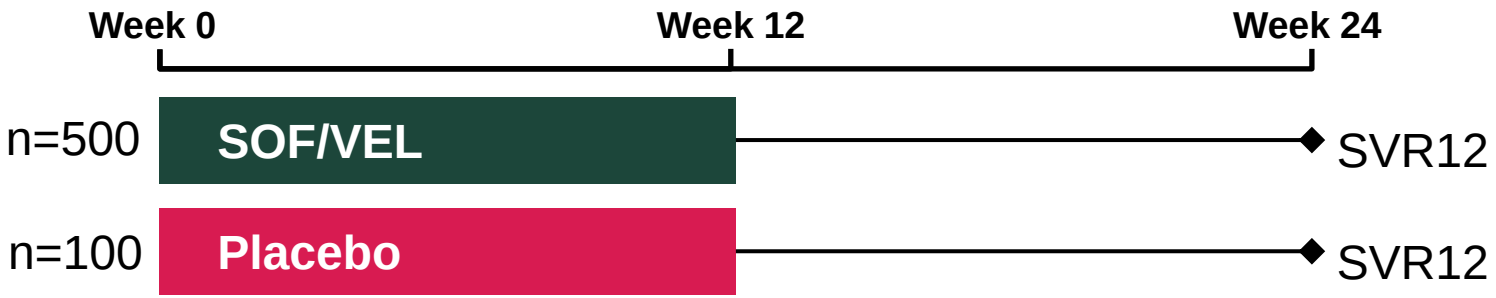
1. Jacobson IM, et al. *N Engl J Med.* 2013;368:1867-77; 2. Lawitz E, et al. *N Engl J Med.* 2013;368:1878-87;
3. Cheng G, et al. EASL 2013, poster 1191; 4. German P, et al. EASL 2013, poster 1195; 5. Lawitz E, et al. EASL 2013, poster 1082.

The ASTRAL Program

SOF/VEL (400 mg/100 mg) 12 Weeks

ASTRAL-1	ASTRAL-2	ASTRAL-3	ASTRAL-4
GT 1, 2, 4–6	GT 2	GT 3	GT 1–6 CPT-B Cirrhosis

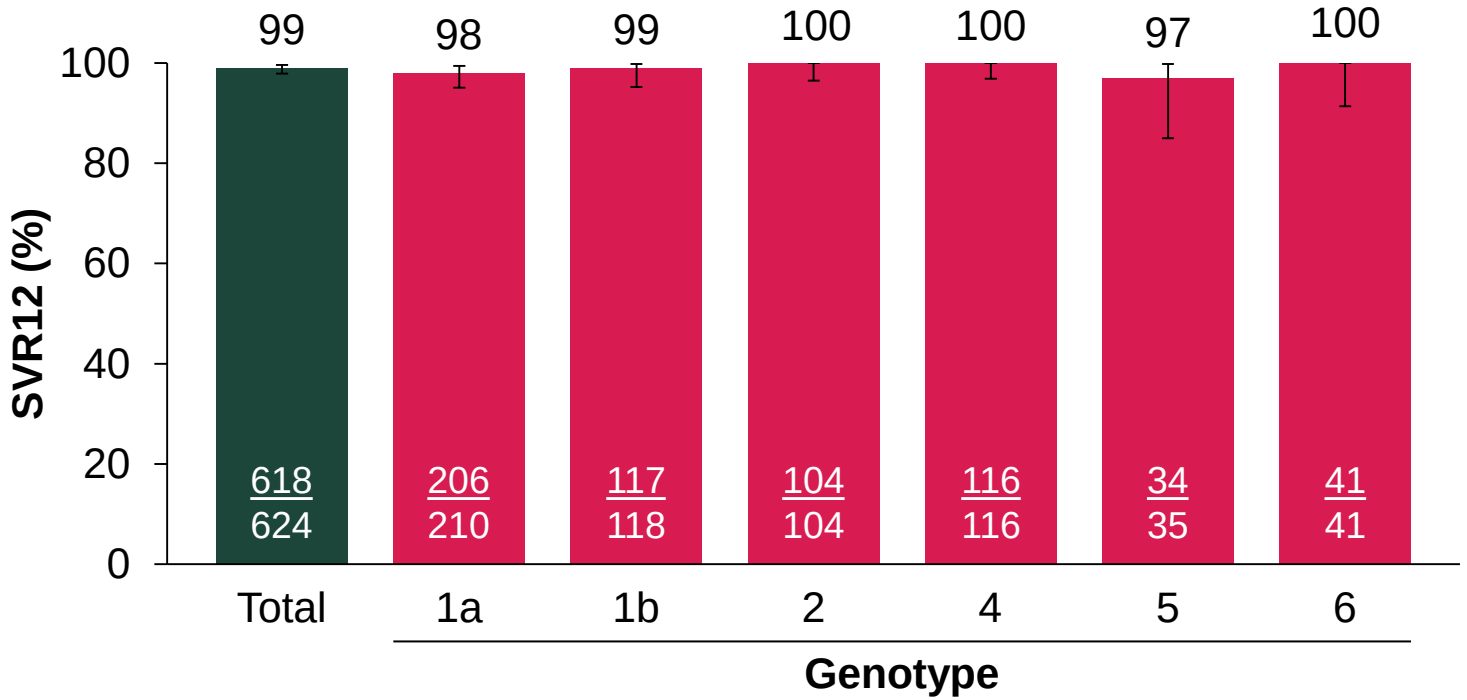
Study Design
ASTRAL-1



- Double blind, placebo controlled
- Broad inclusion criteria
- 5:1 randomization to SOF/VEL or placebo
  - Stratified by HCV genotype and cirrhosis (presence/absence)
  - GT 5 patients not randomized
- Conducted at 81 sites in US, Canada, UK, Germany, France, Italy, Belgium, and Hong Kong

Results: SVR12 by Genotype

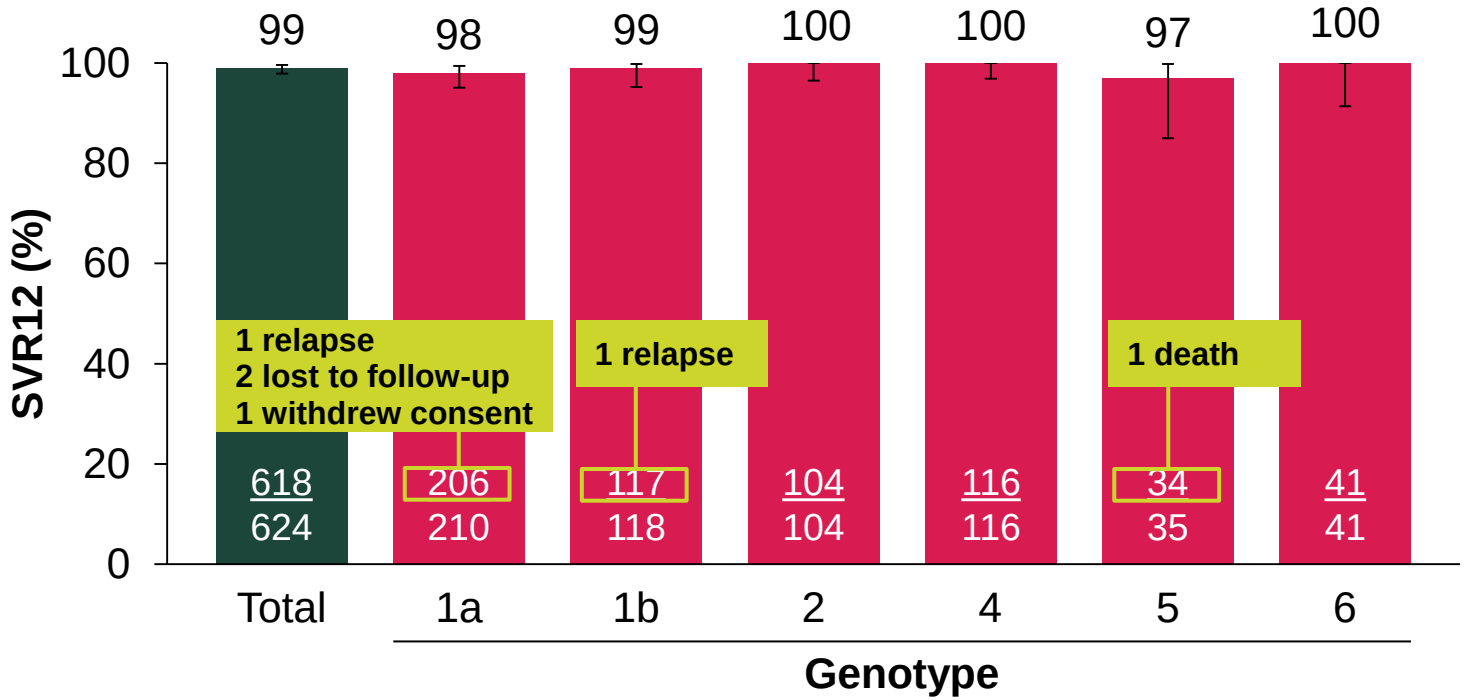
ASTRAL-1, SOF/VEL



Error bars represent 95% confidence intervals.

Results: SVR12 by Genotype

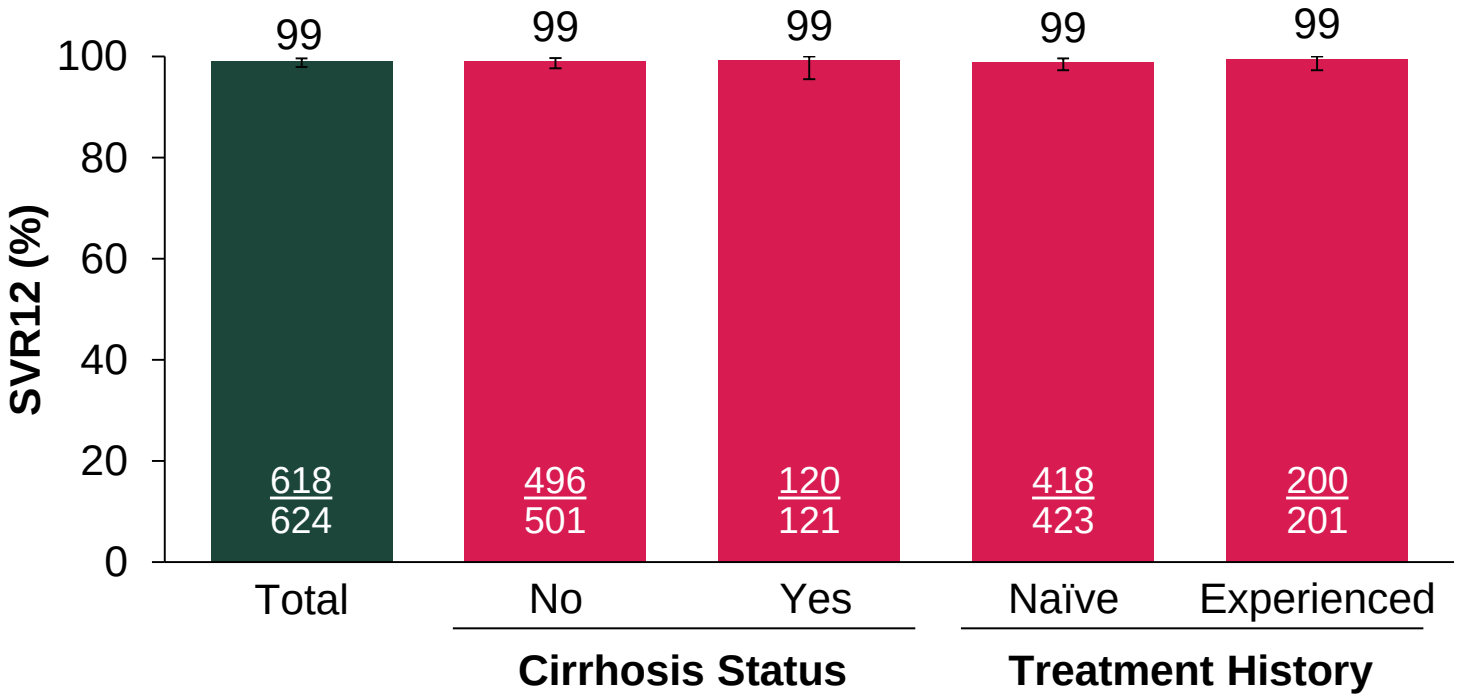
ASTRAL-1, SOF/VEL



Error bars represent 95% confidence intervals.

Results: SVR12 by Cirrhosis or Prior Treatment

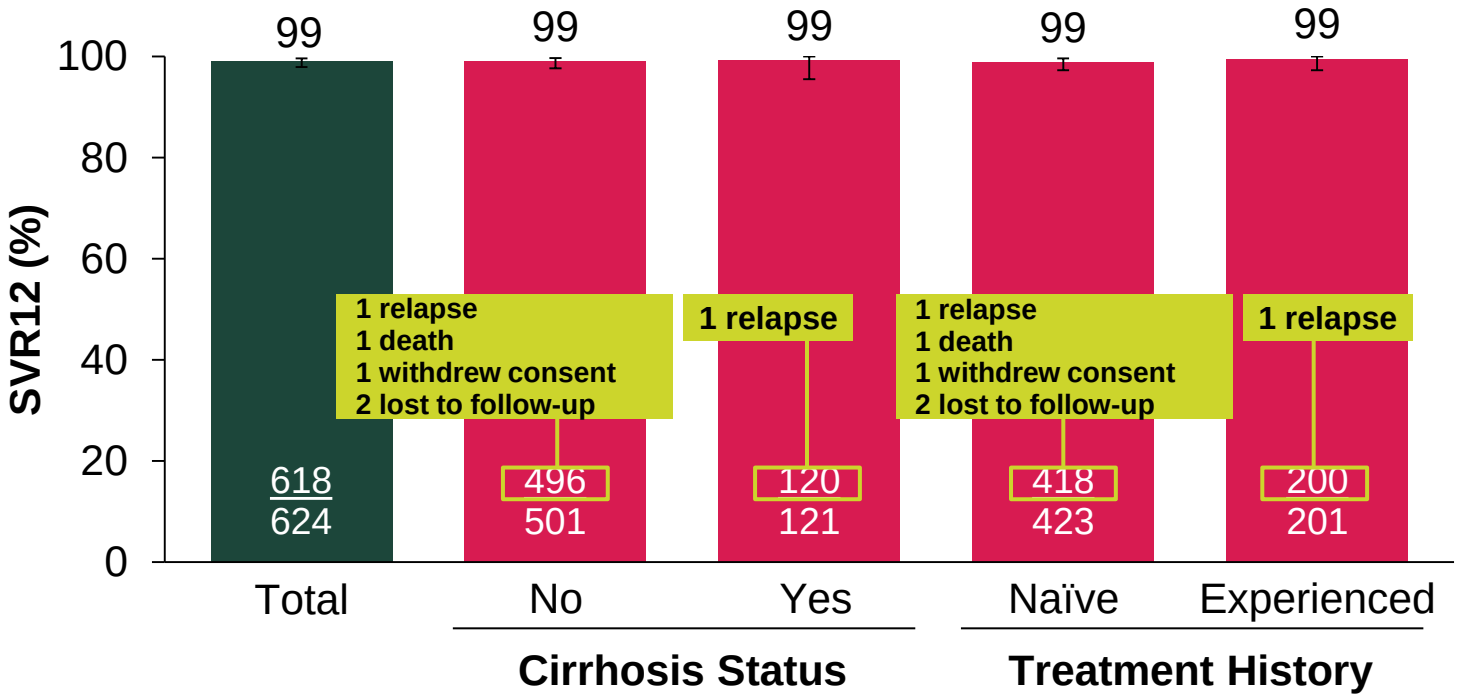
ASTRAL-1, SOF/VEL



Error bars represent 95% confidence intervals.

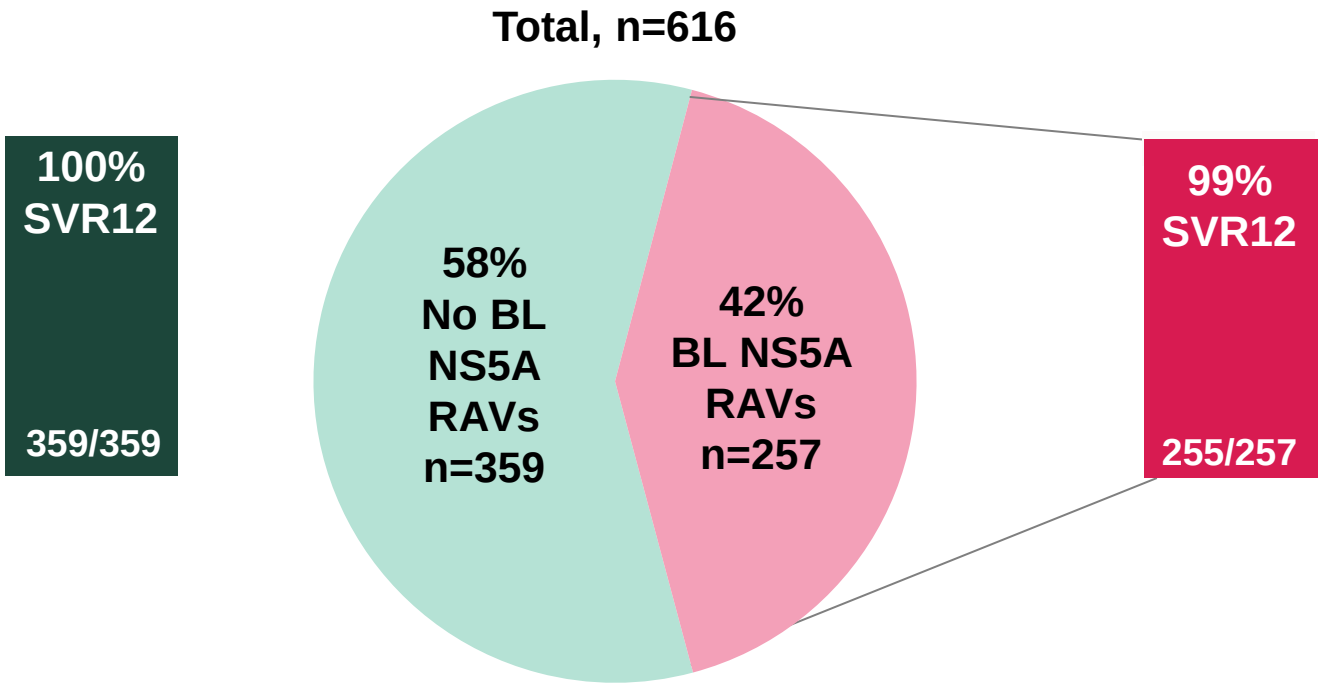
Results: SVR12 by Cirrhosis or Prior Treatment

ASTRAL-1, SOF/VEL



Error bars represent 95% confidence intervals.

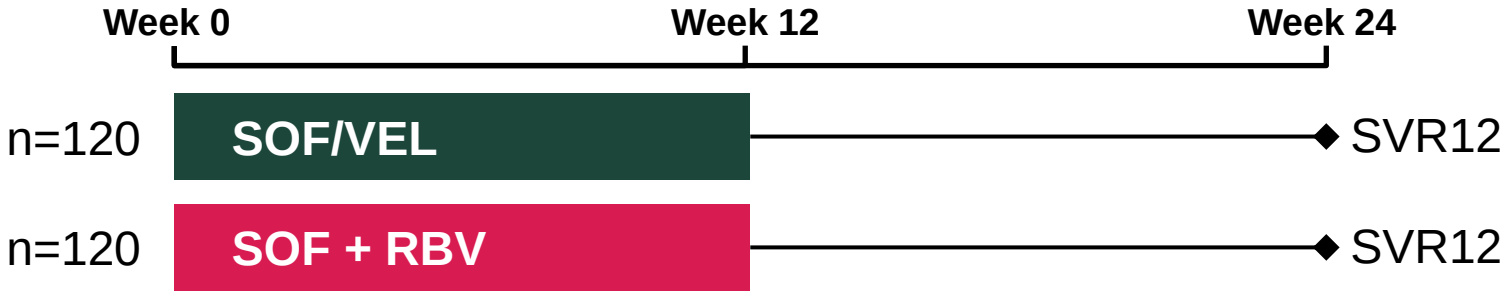
Results: Resistance Analysis (1% cut-off)
ASTRAL-1, SOF/VEL



Results: Adverse Events in ≥10%
ASTRAL-1

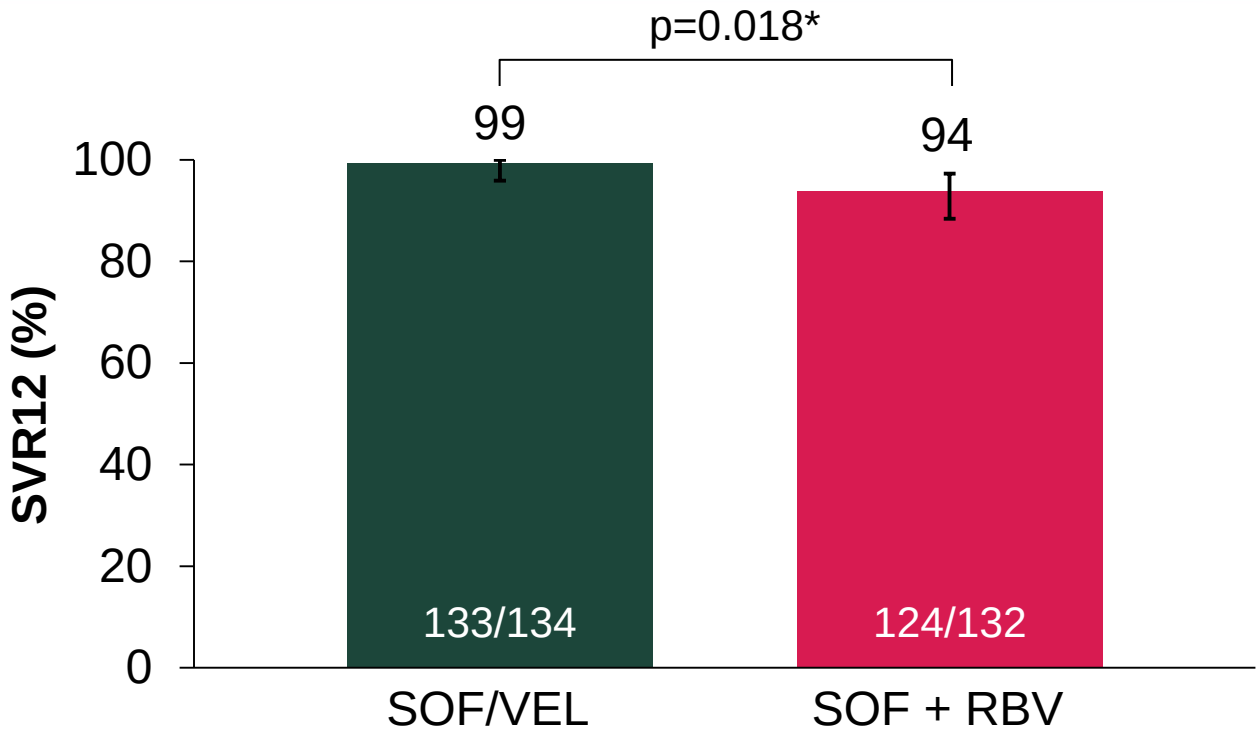
Adverse Event, n (%)	Placebo n=116	SOF/VEL n=624
Headache	33 (28)	182 (29)
Fatigue	23 (20)	126 (20)
Nasopharyngitis	12 (10)	79 (13)
Nausea	13 (11)	75 (12)

Study Design
ASTRAL-2



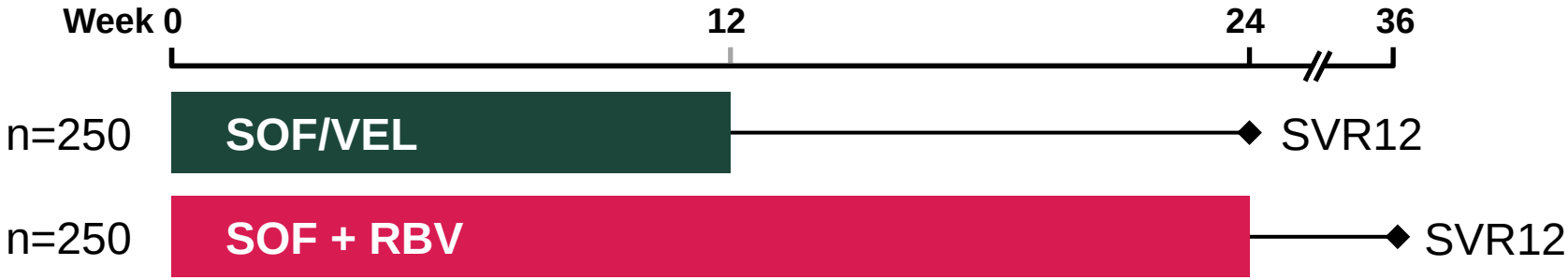
- Open-label, active-comparator trial
- Broad Inclusion criteria
- 1:1 randomization to SOF/VEL or SOF + RBV
- Stratified by prior treatment (TN/TE) and cirrhosis (presence/absence)
- Conducted at 51 sites in US

Results: SVR12
ASTRAL-2



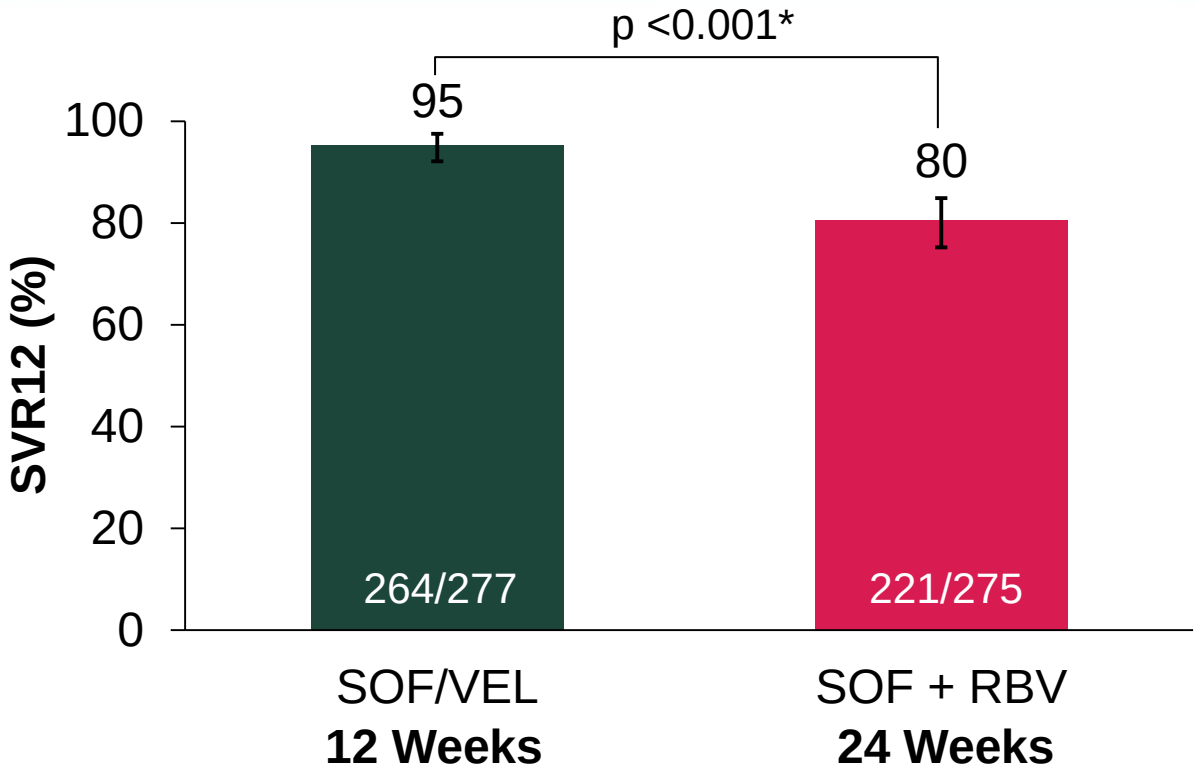
* P-value for superiority of SOF/VEL compared with SOF+RBV
Error bars represent 95% confidence intervals.

Study Design
ASTRAL-3



- Open-label, active-comparator trial
- Broad inclusion criteria
- 1:1 randomization to SOF/VEL or SOF + RBV
  - Stratified by prior treatment (TN/TE) and cirrhosis (presence/absence)
- Conducted at 76 sites in US, Canada, UK, Germany, France, Italy, Australia, and New Zealand

Results: SVR12
ASTRAL-3

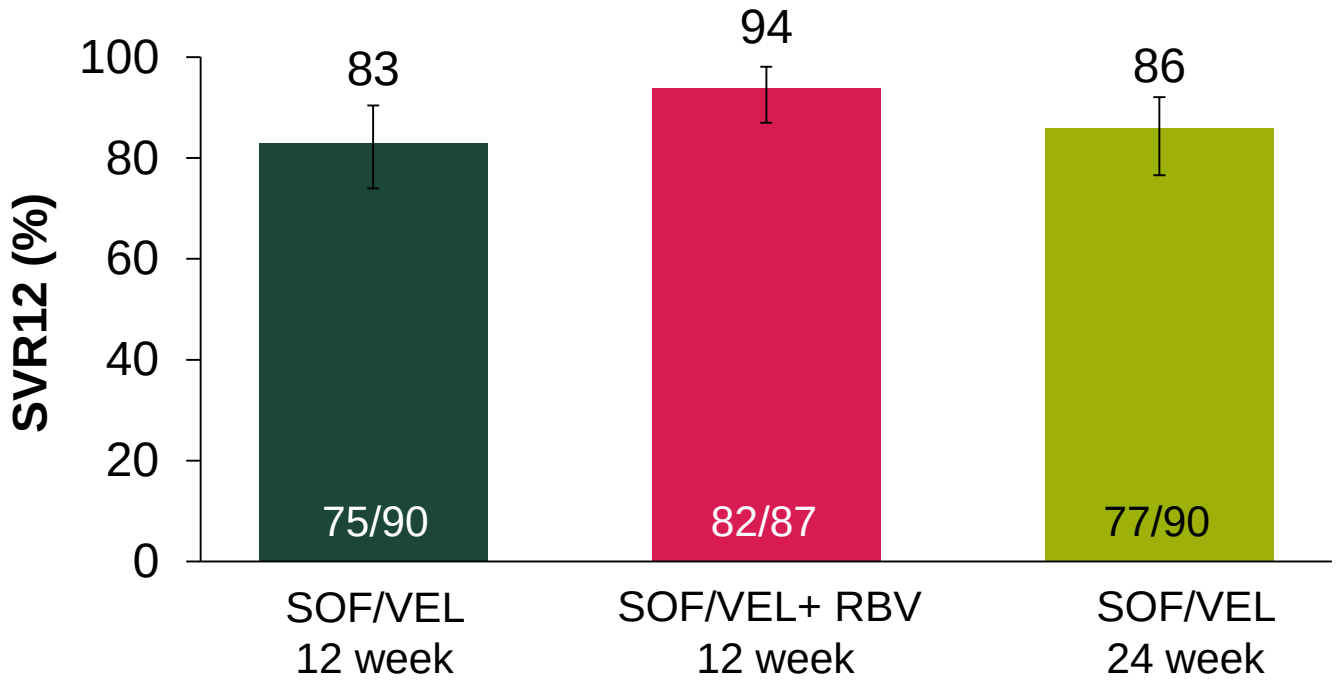


* P-value for superiority of SOF/VEL compared with SOF+RBV. Error bars represent 95% confidence intervals.

Study Design
ASTRAL-4

- Open-label, randomized (1:1:1) US study
- GT 1-6 treatment-naïve or -experienced patients with CPT B cirrhosis
- Eligibility criteria: CrCL >50 mL/min, platelets >30,000 x 103/μL; no HCC or liver transplant
- Weight-based RBV dosing (1000 or 1200 mg/day)

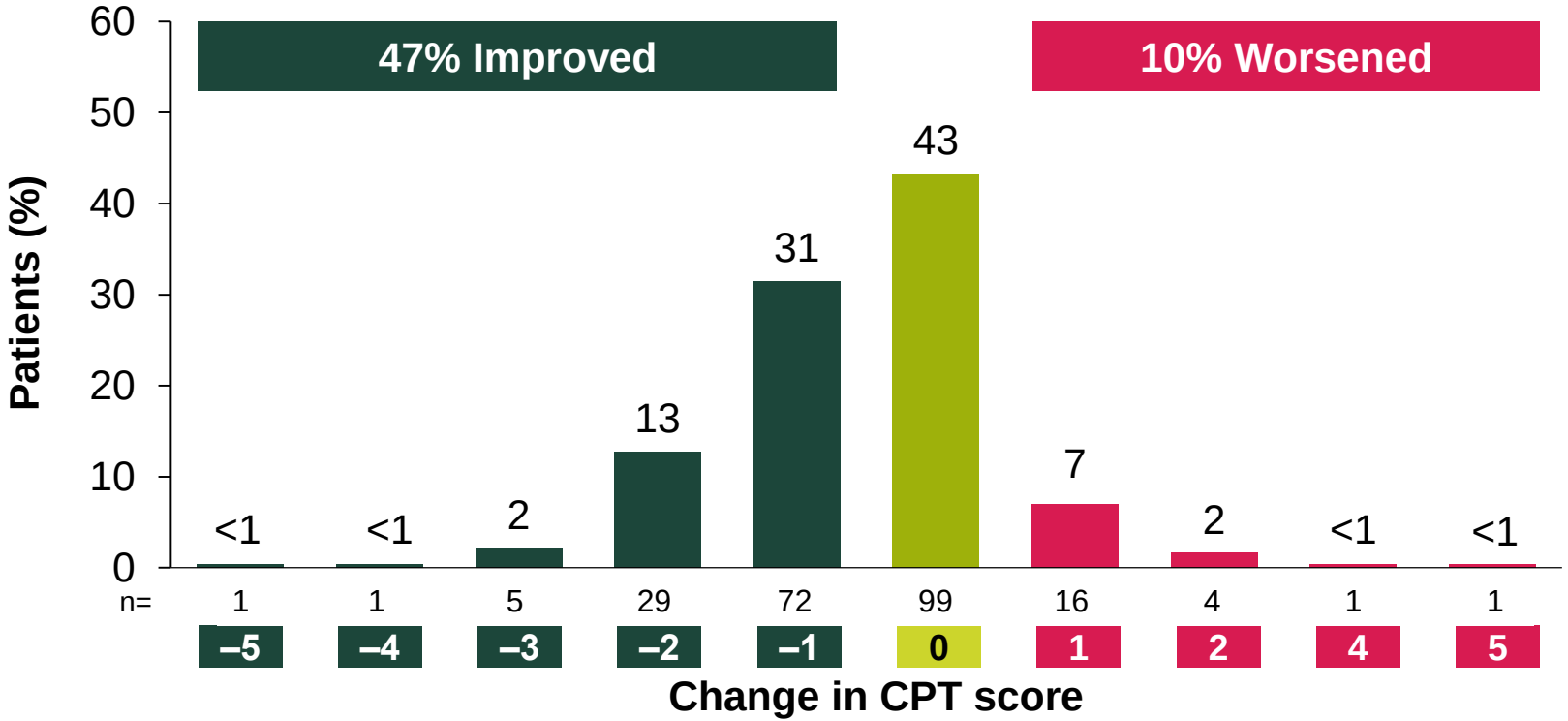
Results: Overall SVR12
ASTRAL-4



P-value < 0.001 for comparison of SVR12 rate to 1% for each treatment group

Results: CPT Score Change From Baseline

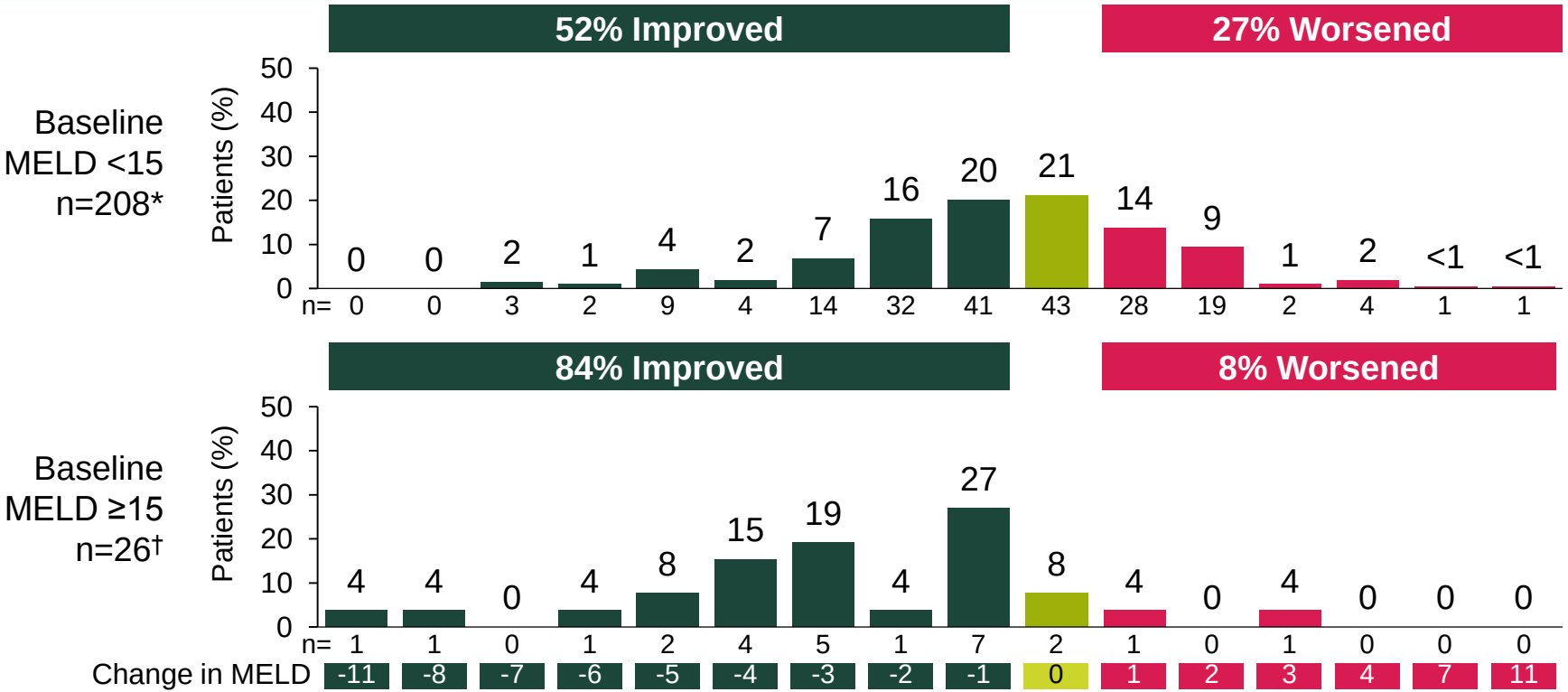
ASTRAL-4: Subjects with SVR12, Overall



Total n=234; 5 patients had no follow-up Week 12 assessment.

Results: MELD Change (Baseline to FU12)

ASTRAL-4: Subjects with SVR12, Overall



No follow-up Week 12 assessment for *5 patients, †0 patients.

Results: Overall Safety Summary
ASTRAL-4

Patients, n (%)	SOF/VEL 12 Weeks n=90	SOF/VEL + RBV 12 Weeks n=87	SOF/VEL 24 Weeks n=90
Any AE	73 (81)	79 (91)	73 (81)
Grade 3 or 4 AE	16 (18)	11 (13)	17 (19)
SAE	17 (19)	14 (16)	16 (18)
Treatment-related SAE	0	1 (1)	1 (1)
AE leading to D/C	1 (1)	4 (5)	4 (4)
Transplant	0	0	1 (1)
Death	3 (3)	3 (3)	3 (3)

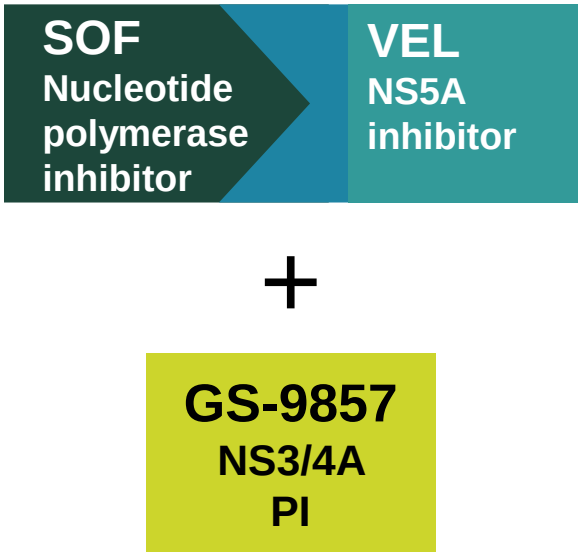
- SAEs assessed as related included dyspnea (SOF/VEL +RBV 12 Weeks) and hepatorenal syndrome peritonitis, sepsis, hypotension (SOF/VEL 24 weeks)
- Deaths: sepsis/septic shock/MOF (n=4); liver failure (n=2); cardiopulmonary arrest (n=1); respiratory failure (n=1); myocardial infarction (n=1)
- None considered treatment related

Sofosbuvir/Velpatasvir + GS-9857 for 6 or 8 Weeks in Genotype 1 or 3 HCV-Infected Patients

Edward J. Gane[1], Robert H. Hyland[2], Yin Yang[2], Evguenia S. Svarovskaia[2], Luisa M. Stamm[2], Diana M. Brainard[2], John G. McHutchison[2], Catherine A. Stedman[3]

[1]Auckland Clinical Studies Ltd, Auckland, New Zealand; [2]Gilead Sciences, Inc., Foster City, CA; [3]Christchurch Clinical Studies Trust, Christchurch, New Zealand

Background

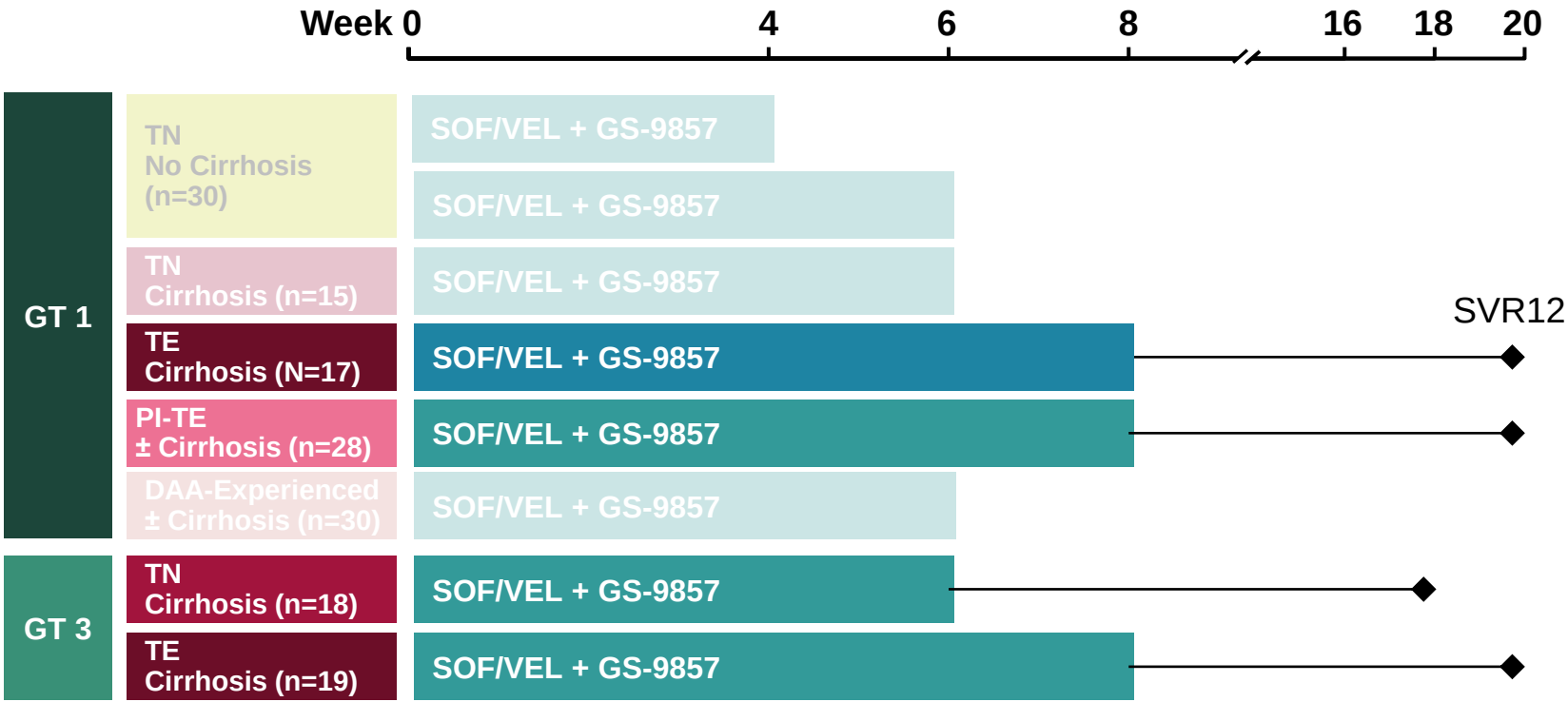


- **Sofosbuvir (SOF)/Velpatasvir (VEL; GS-5816)**
  - Once-daily, oral, FDC (400/100 mg)
  - Potent antiviral activity against HCV GT 1–6
- **GS-9857**
  - Pangenotypic HCV NS3/4A PI with potent antiviral activity against HCV GT 1–6[1, 2]
  - 100 mg monotherapy for 3 days resulted in maximal viral load reductions of >3 log10 IU/mL in patients infected with HCV GT 1–4[2]
  - Improved resistance profile compared with first generation HCV PIs[1, 3]

FDC, fixed dose combination; PI, protease inhibitor

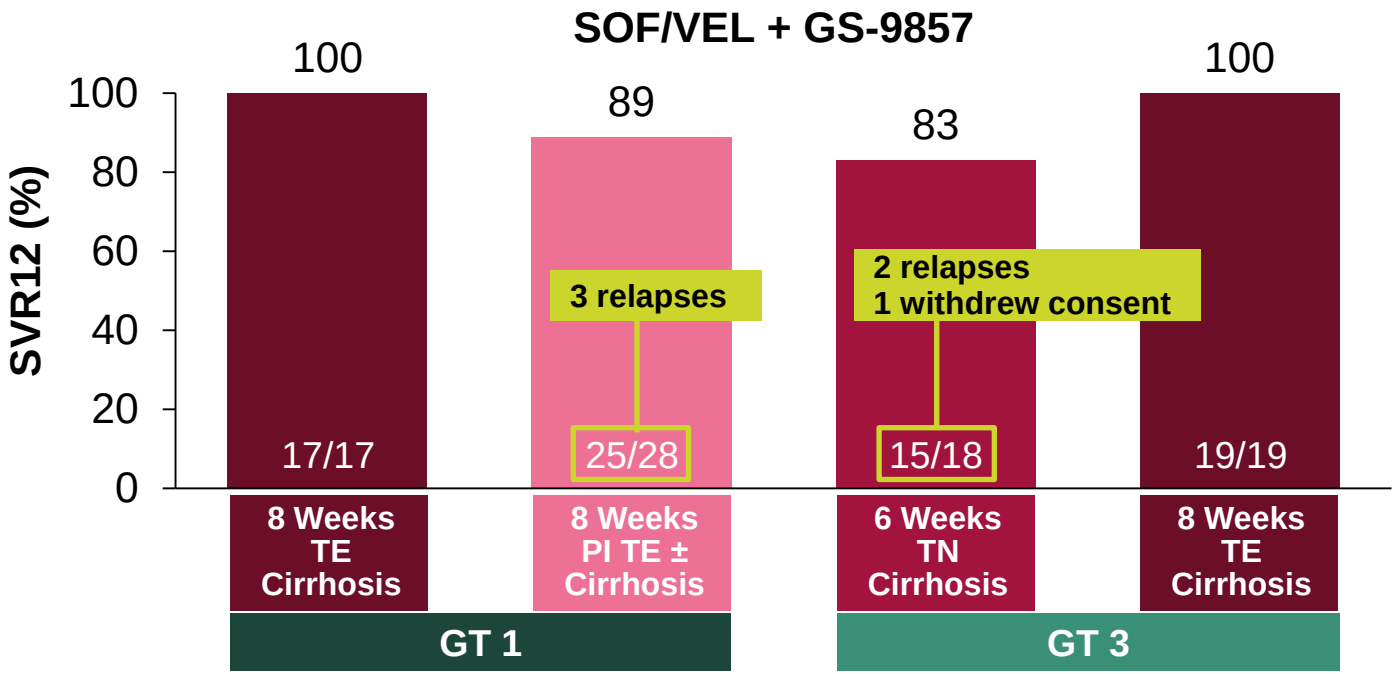
1. Taylor JG, et al. EASL 2015, Poster 899; 2. Rodriguez-Torres, M, et al. EASL 2015, Poster 901; 3. Lawitz E, et al. AASLD 2015, Poster 718.

Study Design



DAA, direct-acting antiviral; PI, protease inhibitor; TE, PEG+RBV treatment experienced; TN, treatment naïve.

Results: SVR12 Rates

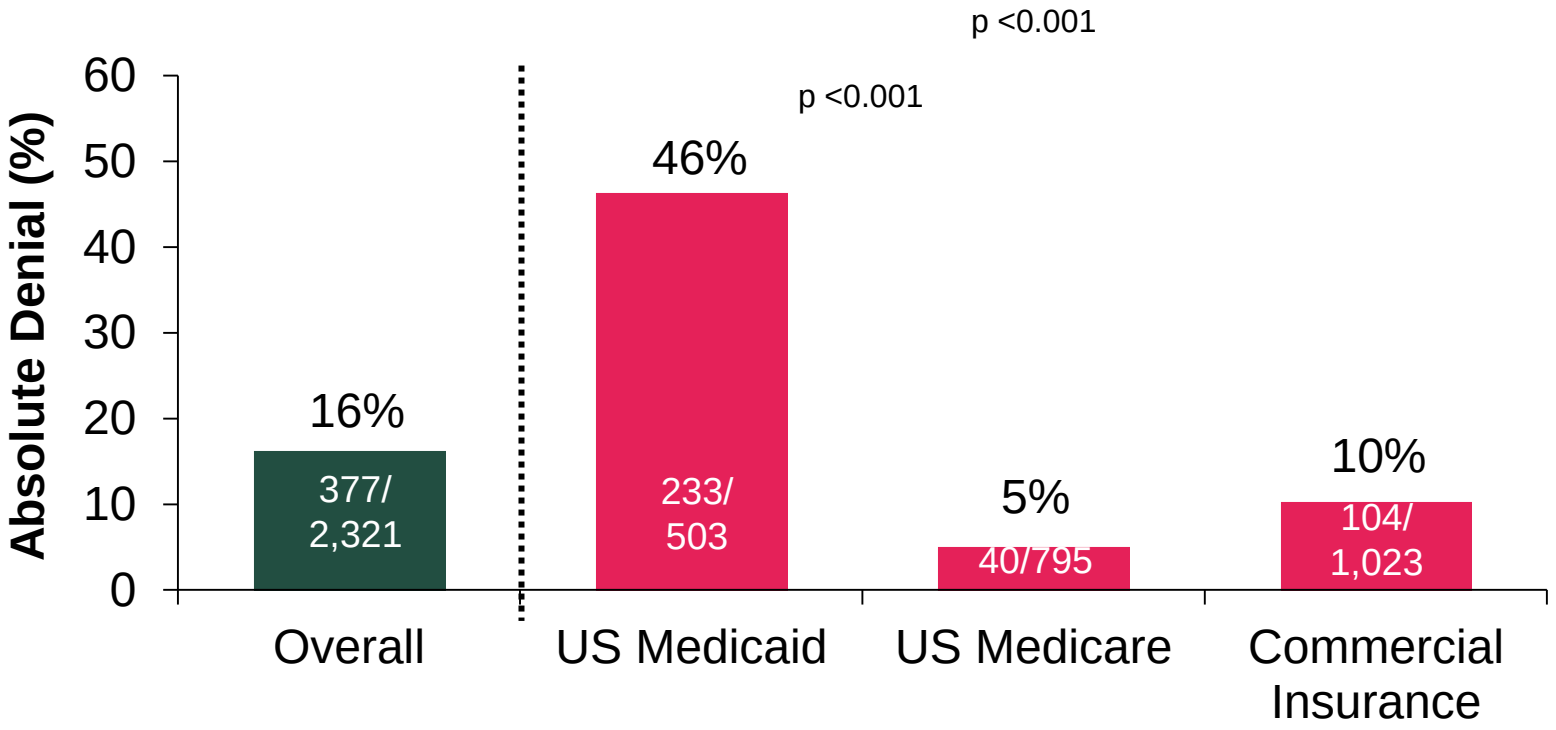


TE, PEG + RBV treatment experienced; PI TE, protease inhibitor treatment experienced; TN, treatment naïve.

Conclusions

- SOF/VEL + GS-9857 for 8 weeks resulted in high SVR12 rates in difficult-to-cure, treatment-experienced populations
  - 100% (36/36) in cirrhotic PEG/RBV-experienced GT 1 and 3
  - 89% (25/28) in PI-experienced GT 1
- Baseline RAVs reduced SVR rates among PI-experienced patients treated with SOF/VEL + GS-9857 for 8 weeks; treatment-emergent RAVs were uncommon
- SOF/VEL + GS-9857 was safe and well tolerated

Incidence of Absolute Denial of DAA Therapy, By Insurance (n=2,321*)



*Excludes 21 patients with incomplete prior authorization after 60 days

The Association of Sustained Virological Response and Mortality After Interferon-based Therapy for Chronic Hepatitis C (HCV) in a Large U.S. Community-based Health Care Delivery System

Lisa M. Nyberg[1], Xia Li[2], Su-Jau Yang[2], Kevin Chiang[3], T. Craig Cheetham[2], Susan Caparosa[2], Jose Pio[2], Zobair M. Younossi [4], Anders H. Nyberg[1]

1. Hepatology Research, Kaiser Permanente, San Diego, CA, United States.
2. Department of Research and Evaluation, Kaiser Permanente, Pasadena, CA, United States.
3. Pharmacy Analytical Services, Kaiser Permanente, Downey, CA, United States.
4. Inova Fairfax Hospital, Falls Church, VA, United States.

Table 1: The Association of SVR and All-Cause Mortality With and Without Cirrhosis

	HCV cases received treatment (n=4,990)	Ever Cirrhosis (n=2,842)		Never cirrhosis (n=2,148)	
		SVR	No SVR	SVR	No SVR
N (%)		1,099 (38.7%)	1743 (61.3%)	1212 (56.4%)	936 (43.6%)
Mortality	577 (11.6%)	89 (8.1%)	413 (23.7%)	25 (2.1%)	50 (5.3%)
		P<0.0001		P<0.0001	

Table 2: The Association of SVR and Liver-Related Mortality With and Without Cirrhosis

	HCV cases received treatment	Ever Cirrhosis (n=2,842)			Never cirrhosis (n=2,148)		
		SVR	No SVR		SVR	No SVR	
N (%)	4,990	1,099 (38.7%)	1743 (61.3%)		1212 (56.4%)	936 (43.6%)	
Liver related mortality	201 (34.8%)	22 (24.7%)	173 (41.9%)	P<0.0001	0	6 (12.0%)	P=0.0178

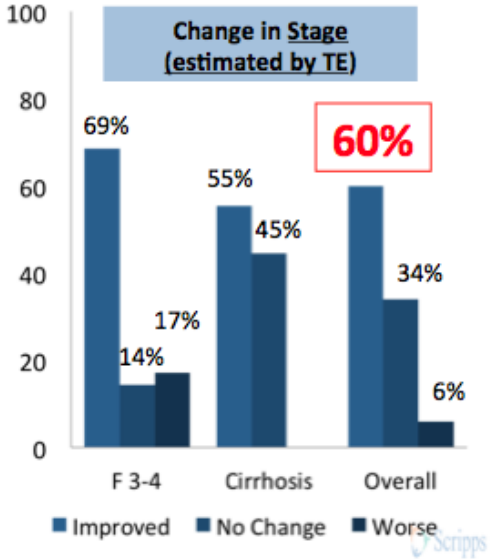
Discussion

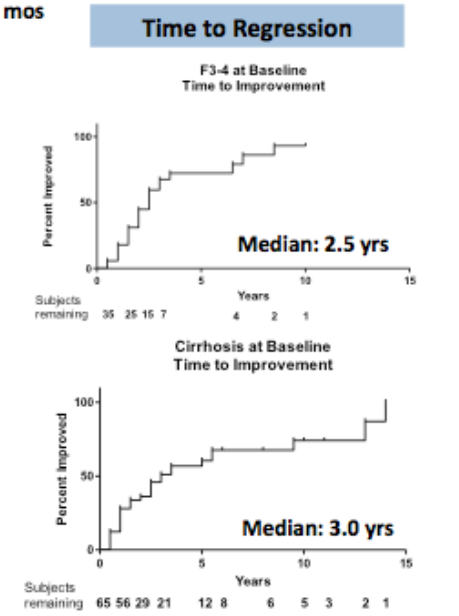
- 4,990 patients were treated for HCV
  - Achieving SVR was associated with significant reductions in mortality in all groups
  - This holds for both cirrhotics and non-cirrhotics
  - Applies to both liver related mortality and non-liver related mortality
  - Notably, “never” cirrhotics who achieve SVR have zero liver related mortality
  - Supports the concept of HCV as a systemic disease

Benefits of an SVR With DAA Therapies

Fibrosis Regression Among Patients Achieving SVR with DAA Therapy*

N=100, followed prospectively with Fibroscan® every 6 mos





*82% DAA; 45% SOF-based therapy

Crissien AM, AASLD Abstract 108

New Information From AASLD 2015 for HCV

- GT 3 Cirrhosis: DCV+SOF+RBVX 12-16 Wks
- Post-OLTX: DCV+SOFX 24 WKS
- HIV Co-Infection: EBR+GZRX 12 Wks
- ESRD: 3D+RBV (GT1a)-RBV(GT1b) X12 Wks
- Relevance of RAVS: Test NS5A Failures
- 2nd Generation NS5A Regimens: Great!
- Barriers To Treatment Payers: 16%
- Benefits of SVR: Reversal of Cirrhosis