XXV Congrés de la Societat Catalana de Digestologia

28 al 30 de gener de 2016

firaReus, Centre de Fires i Convencions

Reus (Tarragona)

ALCANZAR LA RVS AHORA PUEDE SER SIMPLE: EXPERIENCIA EN VIDA REAL

Manejo del paciente pre-tratado, experiencia clínica

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29 de gener de 2016

CONFLICTO DE INTERESES

Participación en reuniones y ponencias:

Janssen
Gilead
AbbVie
Bristol-Myers Squibb
MSD

AASLD/IDSA Guidance for GT1 HCV: Treatment-Experienced Pts

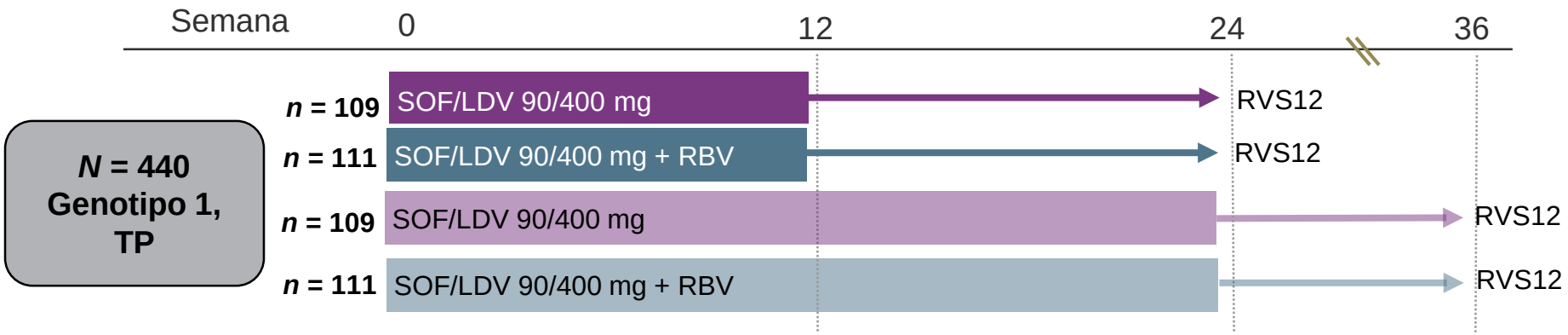
Previous Treatment, Cirrhosis Status	SMV + SOF	LDV/SOF	OMV/PTV/RTV + DSV	DCV + SOF
PegIFN/RBV, no cirrhosis	12 wks	12 wks	12 wks + RBV (1a) 12 wks (1b)	12 wks
PegIFN/RBV, cirrhosis	24 wks ± RBV (GT1a w/out Q80K or GT1b)*	24 wks or 12 wks + RBV	24 wks + RBV (1a) 12 wks (1b)	24 wks ± RBV
SOF + RBV, no cirrhosis	Not recommended	12 wks + RBV	Not recommended	Not recommended
SOF + RBV, cirrhosis	Not recommended	24 wks + RBV	Not recommended	Not recommended
HCV PI, + PegIFN/RBV, no cirrhosis	Not recommended	12 wks	Not recommended	12 wks
HCV PI + PegIFN/RBV, cirrhosis	Not recommended	24 wks or 12 wks + RBV	Not recommended	24 wks ± RBV
SMV + SOF, no cirrhosis	Not recommended	12 wks + RBV	Not recommended	12 wks
SMV + SOF, cirrhosis	Not recommended	24 wks + RBV	Not recommended	24 wks ± RBV

*Not recommended if both GT1a and positive for Q80K.

AASLD/IDSA. HCV guidelines. 2015

ION-2: SOF/LDV ± RBV en pacientes con VHC genotipo 1 con tratamiento previo[1]

Estudio en fase III, aleatorizado, abierto, realizado en EE. UU., estratificado según el genotipo genotipo 1a/1b de VHC, la presencia o no de cirrosis y con fracaso previo a la terapia.[1]



RBV 1000-1200 mg/día
ARN del VHC analizado mediante el test de VHC COBAS® TaqMan® v2.0 HPS, con LIC: 25 UI/mL

- Variable principal: RVS12[1]
- Seguridad:
  - Efectos adversos y discontinuaciones
  - Anomalías de laboratorio
- Criterios de inclusión ampliados: inclusión de fracasos previos del IP (52%), pacientes con cirrosis (20%), sin límite superior de edad o IMC, plaquetas ≥50 000 cél/mm^3 [1,2]

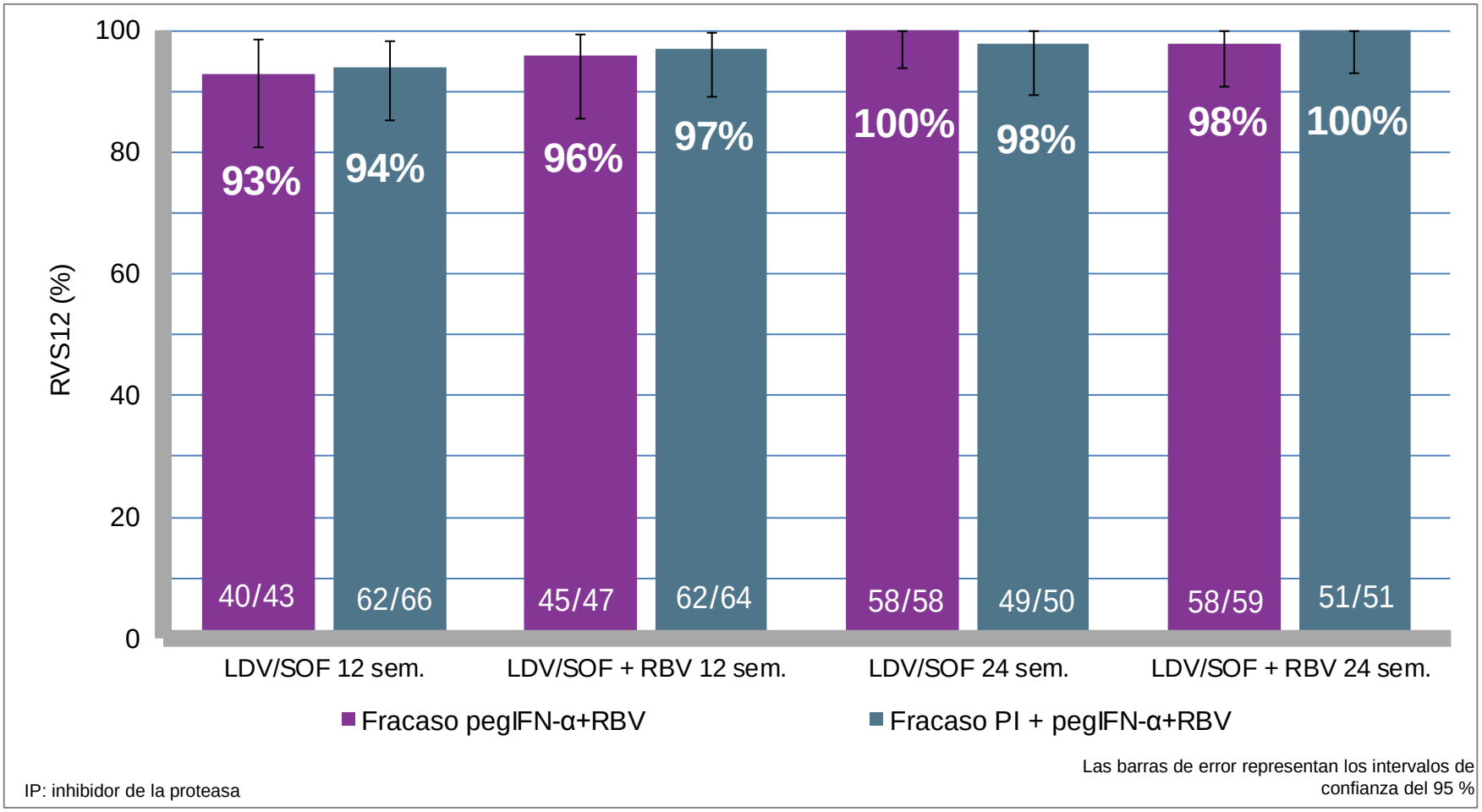
1. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

ION-2: características demográficas basales[1]

Característica	12 semanas		24 semanas	
	SOF/LDV *n* = 109	SOF/LDV+RBV *n* = 111	SOF/LDV *n* = 109	SOF/LDV+RBV *n* = 111
Media de edad, años (intervalo)	56 (24-67)	57 (27–75)	56 (25-68)	55 (28-70)
Hombres, *n* (%)	74 (68)	71 (64)	74 (68)	68 (61)
Raza negra, *n* (%)	24 (22)	16 (14)	17 (16)	20 (18)
Hispanos, *n* (%)	7 (6)	12 (11)	11 (10)	11 (10)
IMC medio, kg/m^2 (intervalo)	29 (19-47)	28 (19-45)	28 (19-41)	28 (19-50)
IL28B CC, *n* (%)	10 (9)	11 (10)	16 (15)	18 (16)
Genotipo 1a, *n* (%)	86 (79)	88 (79)	85 (78)	88 (79)
Nivel medio de ARN del VHC, $\log_{10}$ UI/mL (intervalo)	6,5 (5,0-7,5)	6,4 (4,6-7,3)	6,4 (4,7-7,4)	6,5 (3,1-7,4)
ARN del VHC ≥800 000 UI/mL[2]	103 (95)	98 (88)	93 (85)	96 (87)
Pacientes sin respuesta previa, *n* (%)	49 (45)	46 (41)	49 (45)	51 (46)
Fracasos previos con inhibidores de la proteasa, *n* (%)	66 (61)	64 (58)	50 (46)	51 (46)
Cirrosis, *n* (%)	22 (20)	22 (20)	22 (20)	22 (20)

1. Afdhal N, et al. N, et al. N Engl J Med. 2014;370:1483-1493.

ION-2: RVS12 en función de la exposición previa a tratamiento[1]

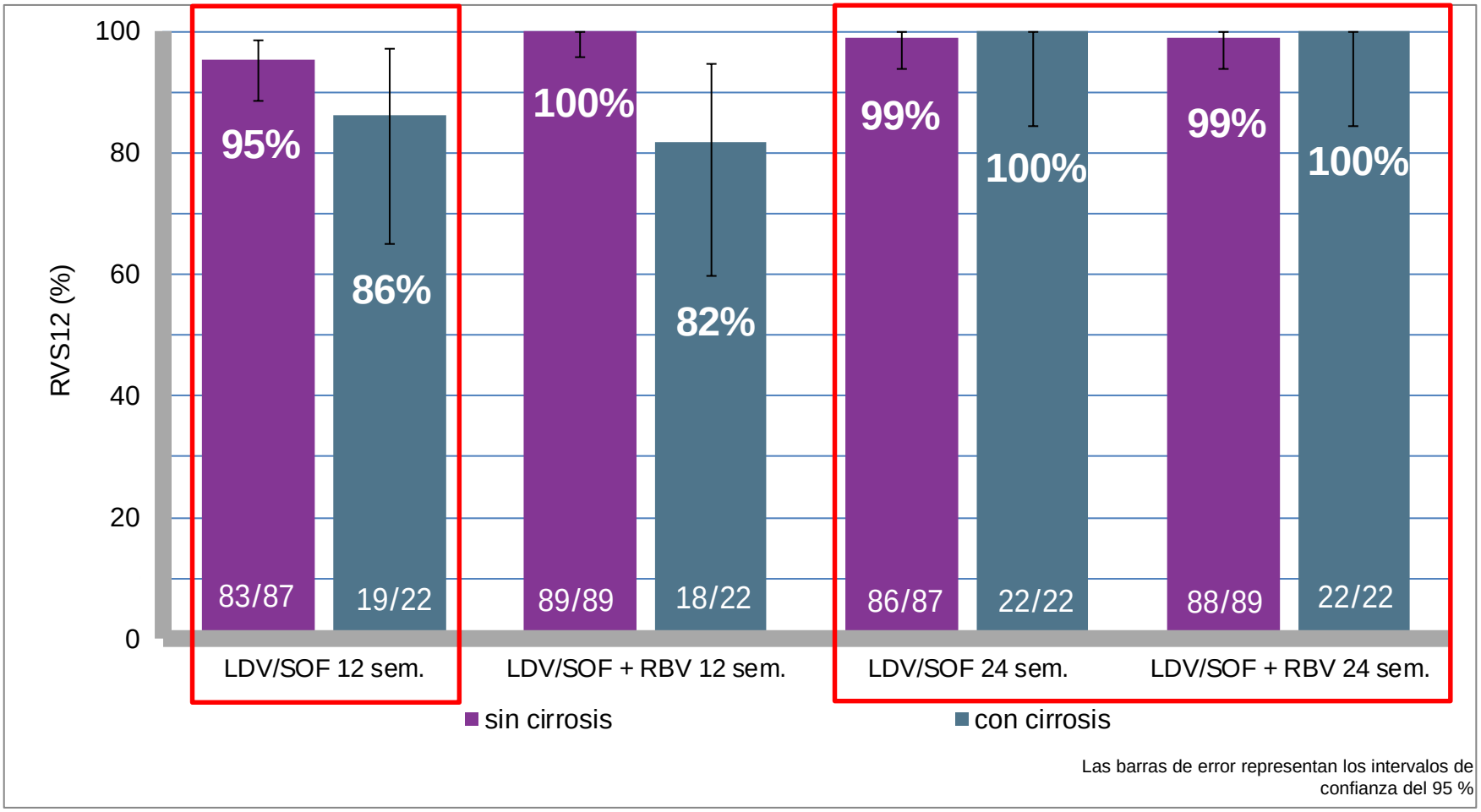


IP: inhibidor de la proteasa

Las barras de error representan los intervalos de confianza del 95 %

1. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

ION-2: RVS12 en función de la presencia de cirrosis[1]



1. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

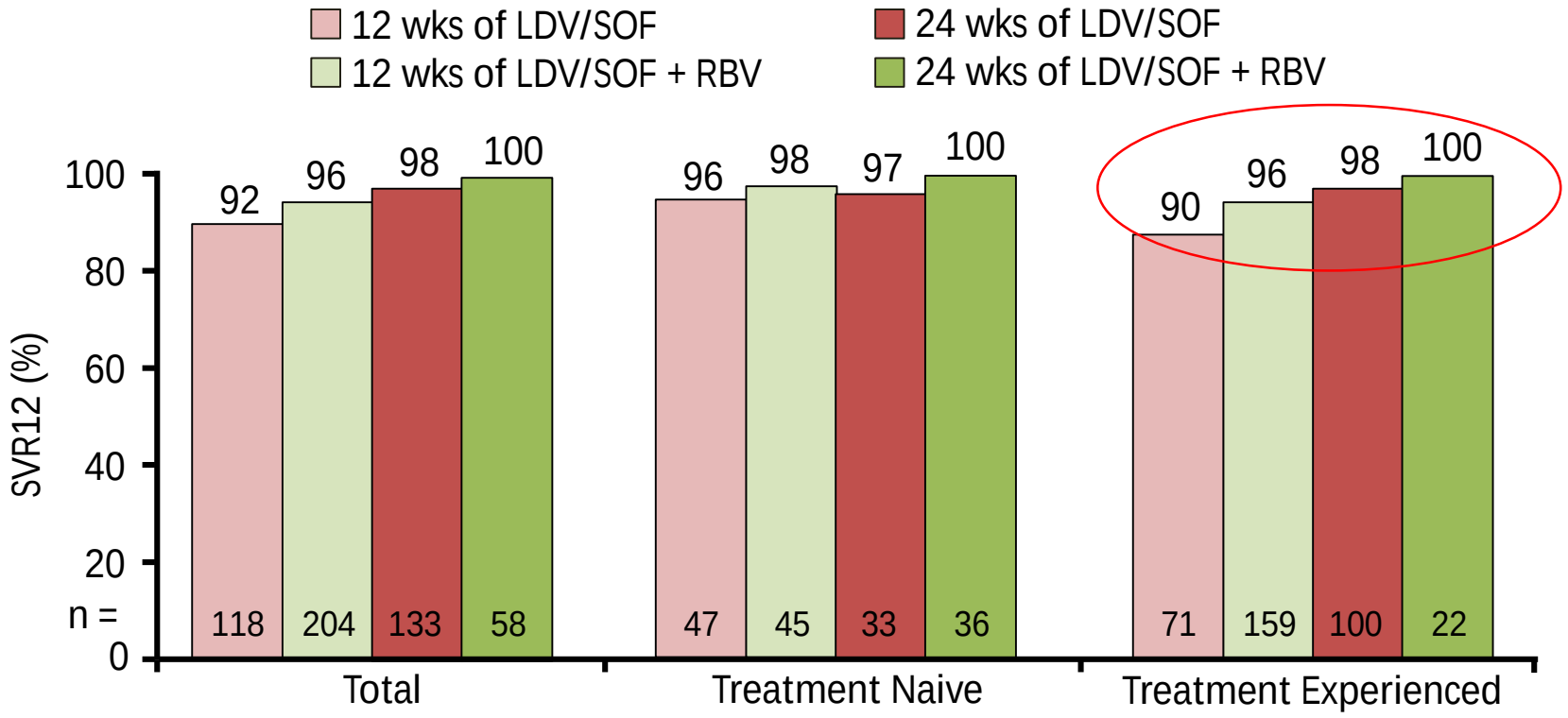
ION-2: Resumen de la seguridad de SOF/LDV ± RBV[1]

Pacientes, n (%)	12 semanas		24 semanas	
	SOF/LDV *n* = 109	SOF/LDV+RBV *n* = 111	SOF/LDV *n* = 109	SOF/LDV+RBV *n* = 111
AA	73 (67)	96 (86)	88 (81)	100 (90)
AA de grado 3-4	2 (2)	3 (3)	10 (9)	8 (7)
AA graves	0	0	6 (6)	3 (3)
Interrupción del tratamiento debido a los AA	0	0	0	0
Muerte	0	0	0	0
Alteraciones analíticas de grado 3-4	5 (5)	15 (14)	9 (8)	27 (24)
Hemoglobina <10 g/dL	0	2 (2)	0	9 (8)
Hemoglobina <8,5 g/dL	0	0	0	2 (2)

1. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

Impact of Tx Duration and RBV in Cirrhotic GT1 Pts (LDV/SOF)

- Pooled data (LONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, SIRIUS)
- No difference in SVR rate by HCV subtype



Reddy KR, et al. Hepatology. 2015;62:79-86.

Is Ribavirin Required for Pts With Cirrhosis and NS5A RAVs?

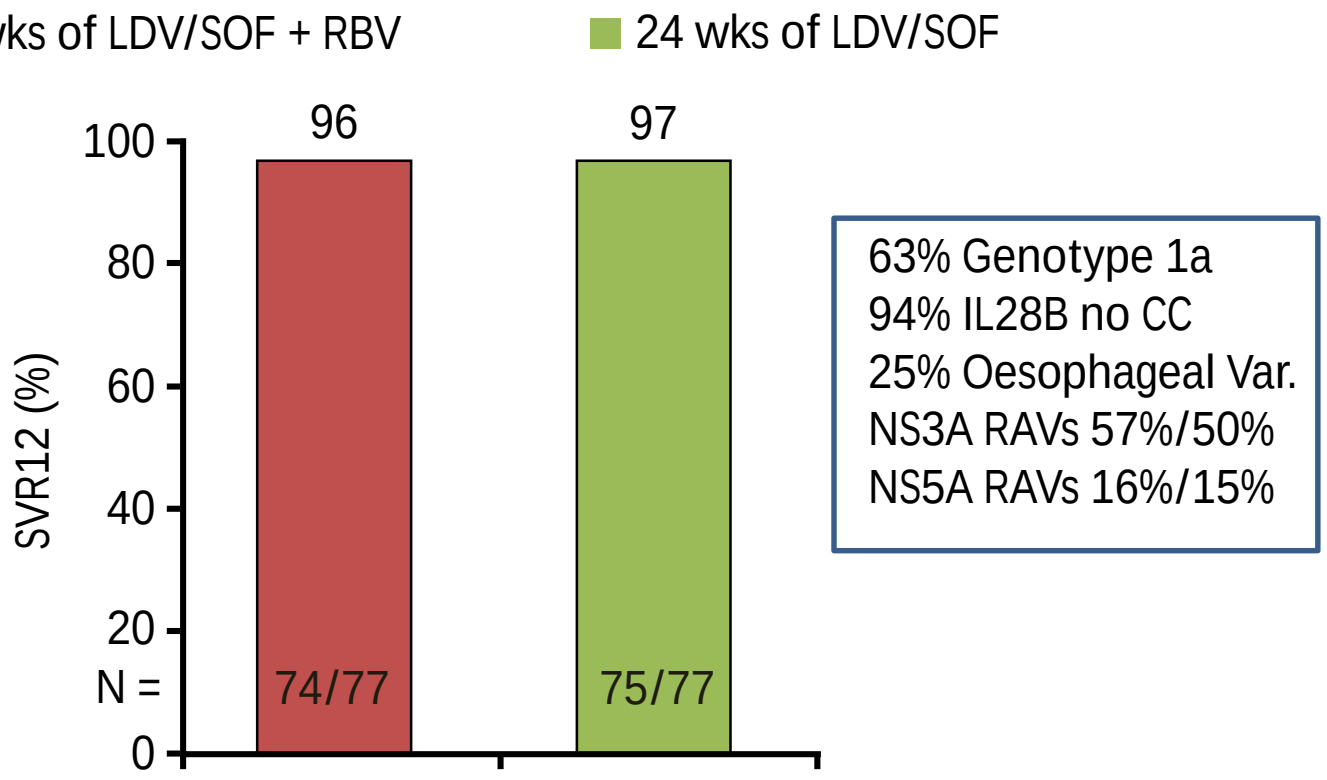
- Integrated analysis of > 500 pts with cirrhosis treated with LDV/SOF ± RBV
- 353 Treatment experienced patients. 68% had previously received HCV PI

(RAVs in 18% pts.)

SVR12, % (n/N)18	With NS5A RAVs	Without NS5A RAVs
Overall	91 (86/94)	98 (407/417)
12 wks without RBV	88 (23/26)	95 (86/91)
12 wks with RBV	94 (32/34)	97 (164/169)
24 wks without RBV	85 (17/20)	100 (113/113)
24 wks with RBV	100 (14/14)	100 (44/44)

Reddy KR, et al. Hepatology. 2015;62:79-86.

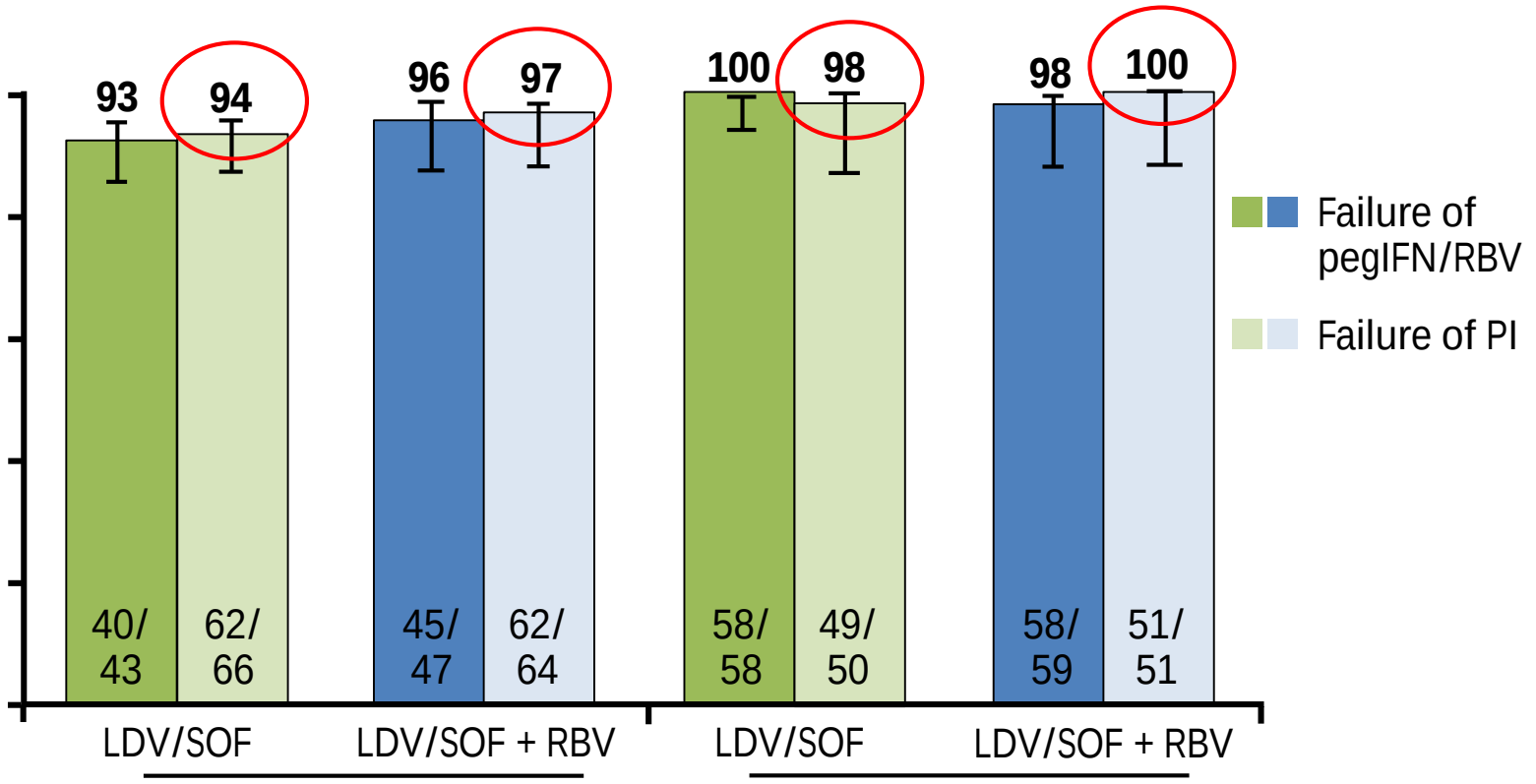
SIRIUS: Impact of Tx Duration and RBV in Cirrhotic, PI-Exp'd, GT1 Pts (LDV/SOF)



- 154 Pts with previous boceprevir, telaprevir, simeprevir, or faldaprevir

Bourlière M, et al. Lancet Infect Dis. 2015;15:397-404.

ION-2: DAAs Effective Against NS3 RAVs After Boceprevir or Telaprevir



- Virologic failure: 1 breakthrough in 24-wk LDV/SOF + RBV due to nonadherence; 11 relapses (7 in 12-wk LDV/SOF, 4 in 12-wk LDV/SOF + RBV)
- **14% of pts had NS5A RAVs at baseline; 89% of these achieved SVR12**
- **71% of pts had NS3 RAVs at baseline; 98% of these achieved SVR12**

Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

Treatment Outcomes with LDV/SOF for 8, 12, and 24 Weeks

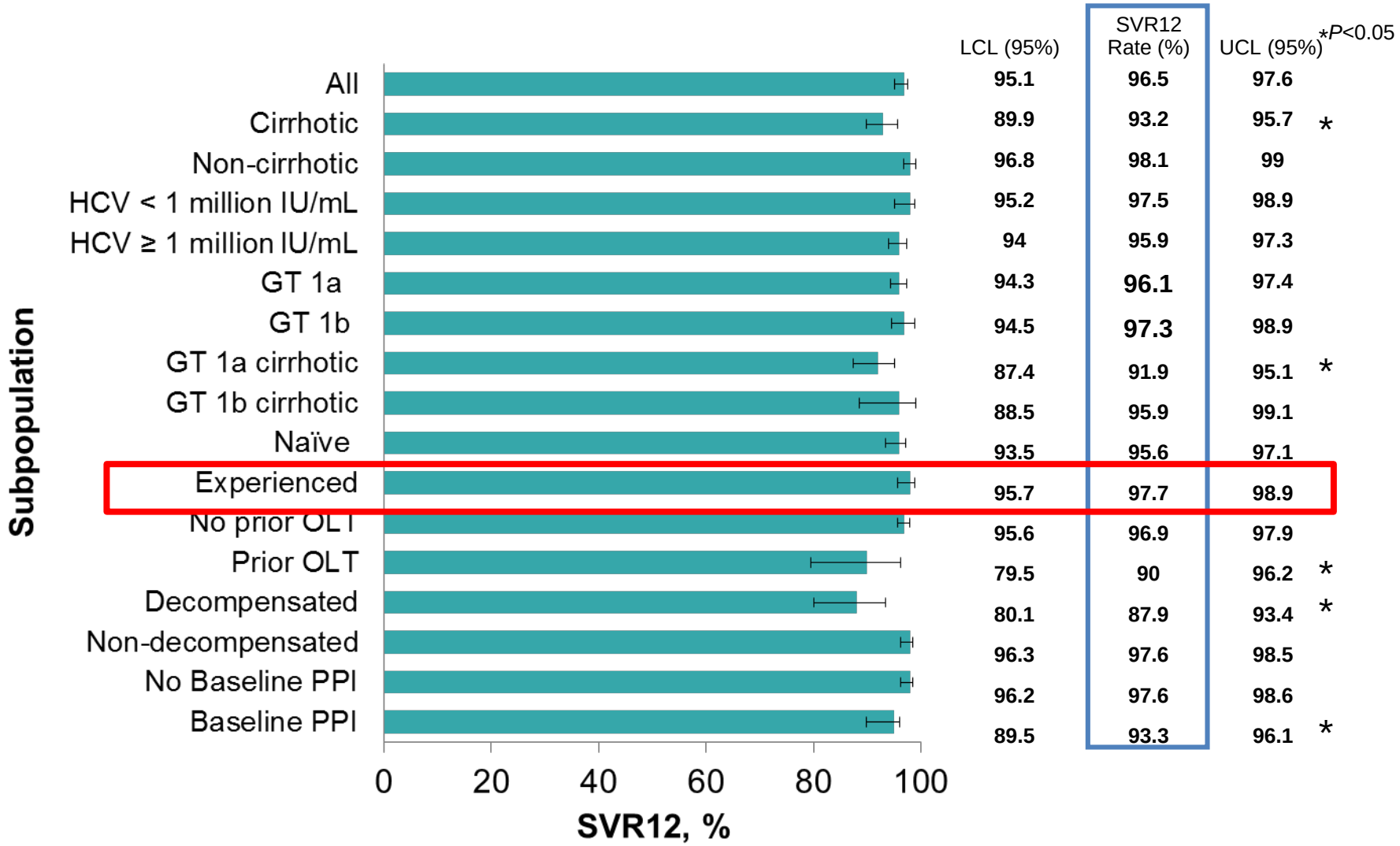
Analysis of 1,270 patients who received LDV/SOF±RBV in HCV-TARGET, a multicenter, prospective, observational, real-world cohort study

	LDV/SOF N=1139	LDV/SOF+RBV N=131
Male, n (%)	647 (57)	90 (69)
Age, yr, median, range	60 (19-87)	61 (31-78)
Caucasian, n (%)	814 (72)	108 (82)
Black, n (%)	245 (22)	12 (9)
Treatment Status, n (%)		
Naïve	634 (56)	40 (31)
Experienced	505 (44)	91 (69)
DAA Experienced	143 (13)	24 (18)
Genotype, n (%)		
1a	751 (66)	79 (60)
1b	302 (27)	40 (31)
Cirrhosis, n (%)	396 (35)	83 (63)
Decompensated, n (%)	142 (13)	28 (21)
Liver transplant, n (%)	71 (6)	58 (44)
HIV, n (%)	35 (3)	4 (3)
Baseline PPI Use, n (%)	305 (27)	47 (36)

Terrault, AASLD, 2015, 94

HCV-TARGET Real-World Cohort: Treatment Outcomes with LDV/SOF for 8, 12, and 24 Weeks

SVR12 with LDV/SOF by Subgroups



Adaptado de Terrault, AASLD, 2015, 94

Safety

	LDV/SOF N=1435	LDV/SOF + RBV N=213
Any AE, n (%)	900 (63)	178 (84)
Fatigue	320 (22)	75 (35)
Headache	307 (21)	50 (24)
Anemia	8 (1)	53 (25)
Nausea	109 (8)	25 (12)
Diarrhea	86 (6)	22 (10)
Rash	30 (2)	21 (10)
Pruritus	27 (2)	21 (10)
Insomnia	89 (6)	19 (9)
Influenza like illness	65 (5)	15 (7)
Dyspnea	44 (3)	20 (9)
Decreased appetite	26 (2)	18 (8)
Dizziness	46 (3)	15 (7)
Cough	37 (3)	13 (6)
Irritability	17 (1)	13 (6)
Dyspnea exertional	5 (0.4)	13 (6)

Terrault, AASLD, 2015, 94

LDV/SOF±RBV for 12 or 24 Weeks in Treatment-Experienced, Cirrhotic GT 1 HCV

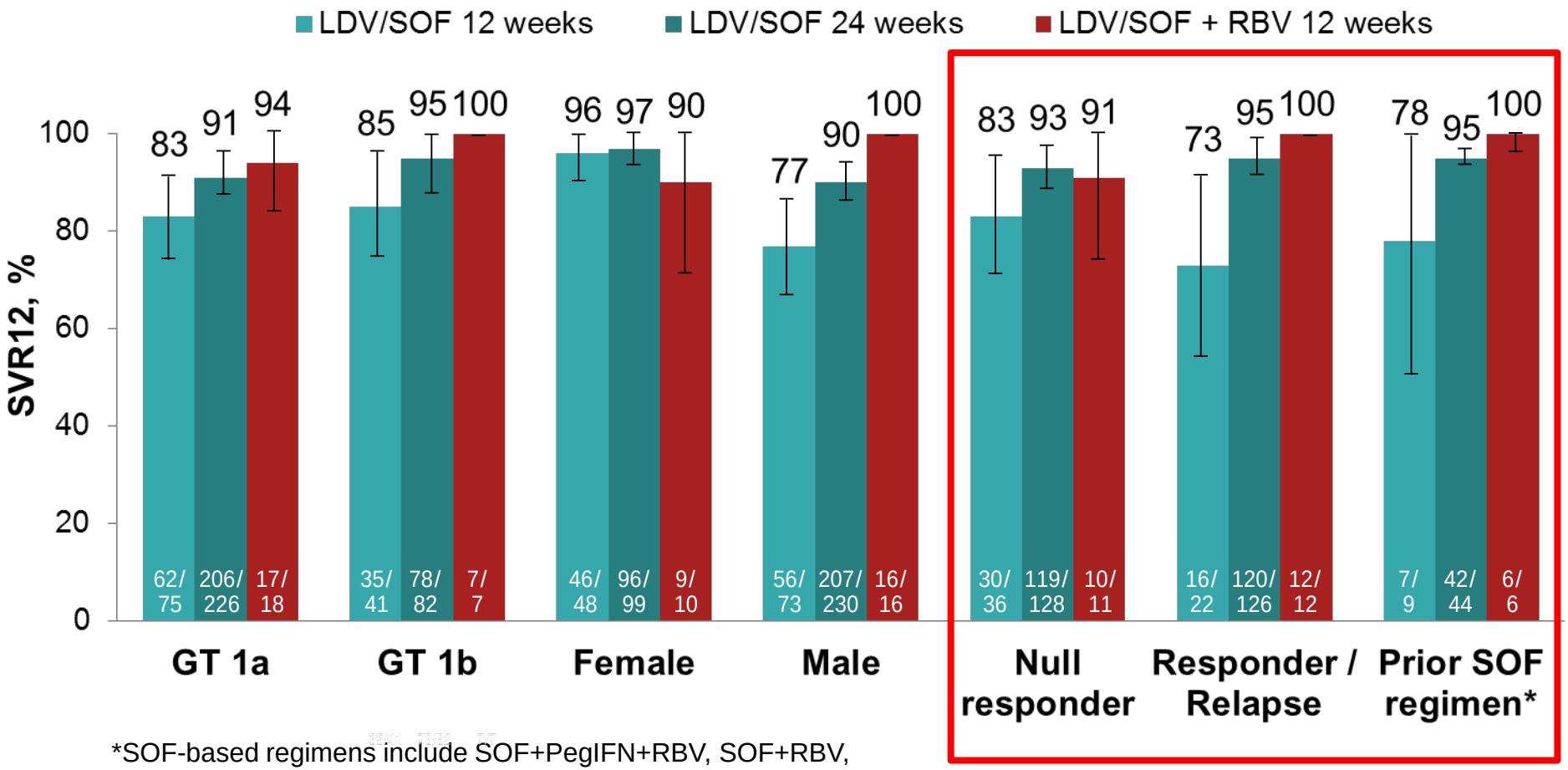
Real-world observational study of 476 patients tre*ated with LDV/SOF±RBV*

	LDV/SOF 12 Week n=121	LDV/SOF* 24 Week n=329	LDV/SOF+RBV 12 Week n=26
Academic practice, n (%)	50 (41)	189 (57)	21 (81)
Mean age, years (range)	61 (29–88)	61 (26–84)	58 (40–71)
Male, n (%)	73 (60)	230 (70)	16 (62)
Black, n (%)	17 (14)	28 (8)	1 (4)
ALT, mean (SD)	69 (61)	86 (59)	92 (59)
AST, mean (SD)	72 (52)	86 (53)	92 (52)
HCV RNA ≥ 6 million IU/mL, n (%)	21 (17)	41 (12)	5 (19)
GT 1a, n (%)	75 (62)	226 (69)	18 (69)
Platelets < 100 K/mL, n (%)	26 (25)	129 (41)	5 (21)
Prior null responder, n (%)	36 (30)	128 (39)	11 (42)
Prior Responder / Relapse, n (%)	22 (18)	126 (38)	12 (46)
Prior therapy, n (%)			
SMV+SOF+RBV	0 (0)	3 (1)	0 (0)
SMV+SOF	2 (3)	27 (8)	3 (12)
SOF+PegIFN+RBV	2 (3)	8 (3)	0 (0)
SOF+RBV	5 (6)	6 (2)	3 (12)
LDV/SOF	1 (1)	0 (0)	0 (0)

Curry, AASLD, 2015, 1108

*8/329 were treated with LDV/SOF+RBV for 24 weeks.

Efficacy by Subgroup



*SOF-based regimens include SOF+PegIFN+RBV, SOF+RBV, SMV+SOF, SMV+SOF+RBV

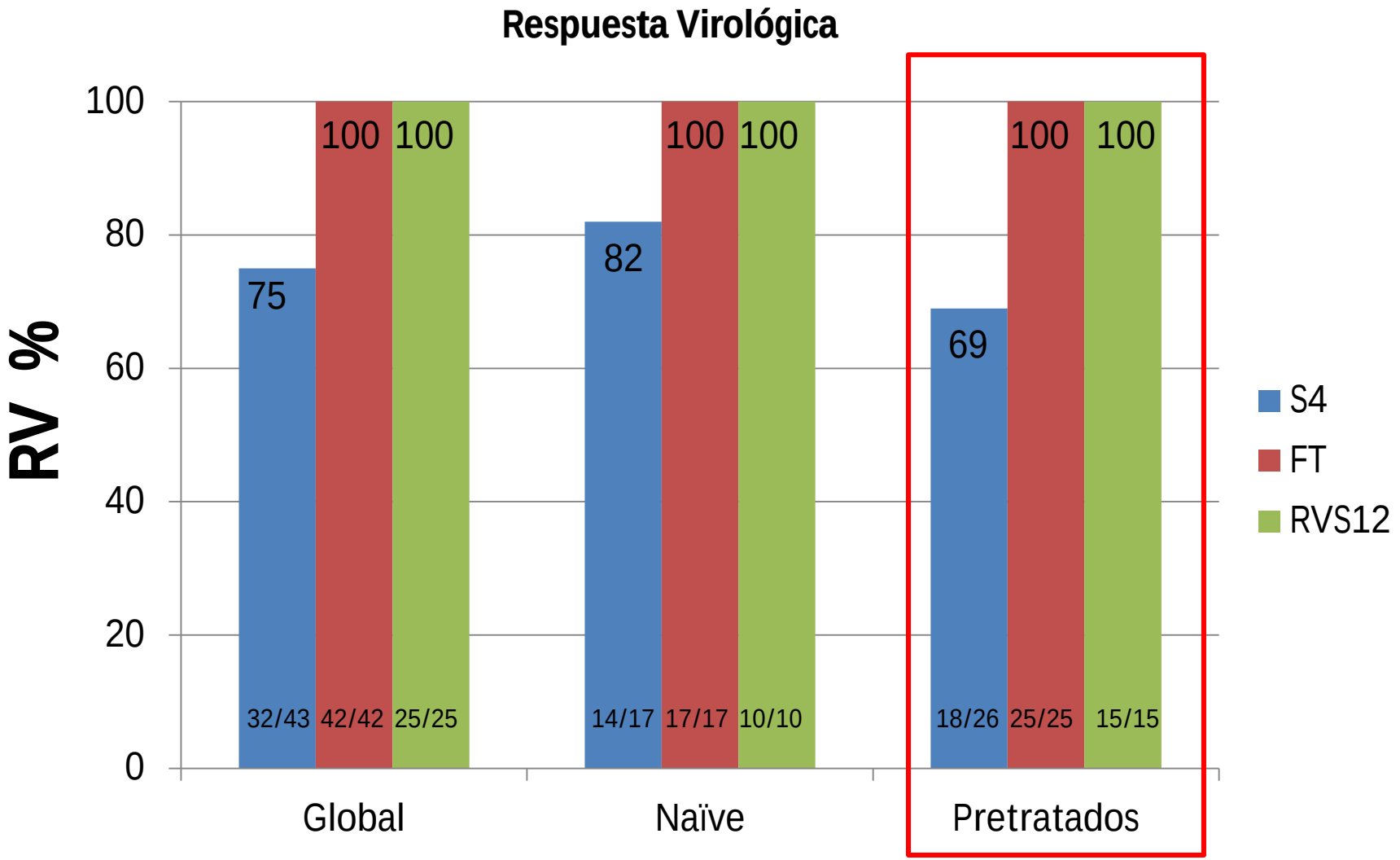
Curry, AASLD, 2015, 1108

LDV/SOF ± RBV durante 12-24 semanas en pacientes GT 1 . Experiencia en Tarragona

Datos basales y demográficos

Pacientes	n=43
Sexo H, n (%)	25 (63)
Edad media, años (rango)	58 (44–66)
GT 1a, n (%)	15 (34)
Cirrosis compensada, n (%)	20 (49)
Cirrosis descompensada, n (%)	1 (1)
Naïves, n (%)	17(40)
Pretratados, n (%): -Fracaso PR, n tot (rec/nresp) -Fracaso triple terapia, n -Fracaso SOF/SIM/RBV, n	26(60) 15(7/8) 10 1
Duración Tratamiento, 12/24 sem.	32/11
Ribavirina, n (%)	32 (79)
Plaquetas (10x3) (Media±DE)	162±74,9
Albúmina (g/dl) (Media±DE)	4,04±0,41

LDV/SOF ± RBV durante 12-24 semanas en pacientes GT 1 . Experiencia en Tarragona



LDV/SOF + RBV in GT 1 HCV Pts With Previous Failure on Sofosbuvir Regimens

- Phase II trial

*25 pts (49%) were previously treated with SOF + pegIFN/RBV, 21 (41%) with SOF ± RBV, 5 (10%) with SOF placebo plus pegIFN/RBV or GS-0938 monotherapy, 1 (2%) with SOF monotherapy.
†1 pt who relapsed found to have GT3a HCV infection and enrolled in error.

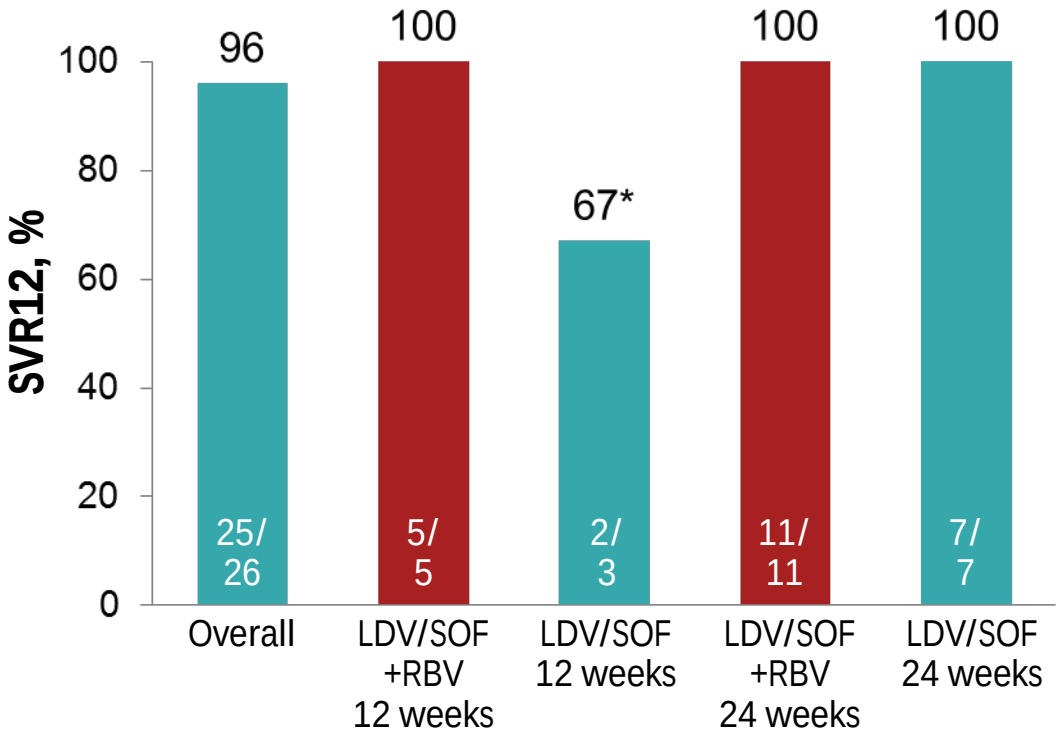
Wyles DL, et al. Hepatology. 2015;61:1793-1797.

LDV/SOF ± RBV in GT 1 Relapsers after SMV+SOF ± RBV: Multicenter Experience from Mayo Clinic: Interim Analysis

Baseline Demographics

Patients	n=34
Average age, years (range)	59 (49–76)
Male, n (%)	28 (82)
Non-white, n (%)	5 (15)
GT 1a, n (%)	24 (71)
IL28B CT/TT, n (%)	21 (88)
Metavir F3–F4, n (%)	27 (79)
CTP Class B/C, n (%)	11 (32)
Post-liver transplant, n (%)	10 (29)
Median time since last dose of SMV+SOF, weeks (range)	23 (7–55)

Virologic Response

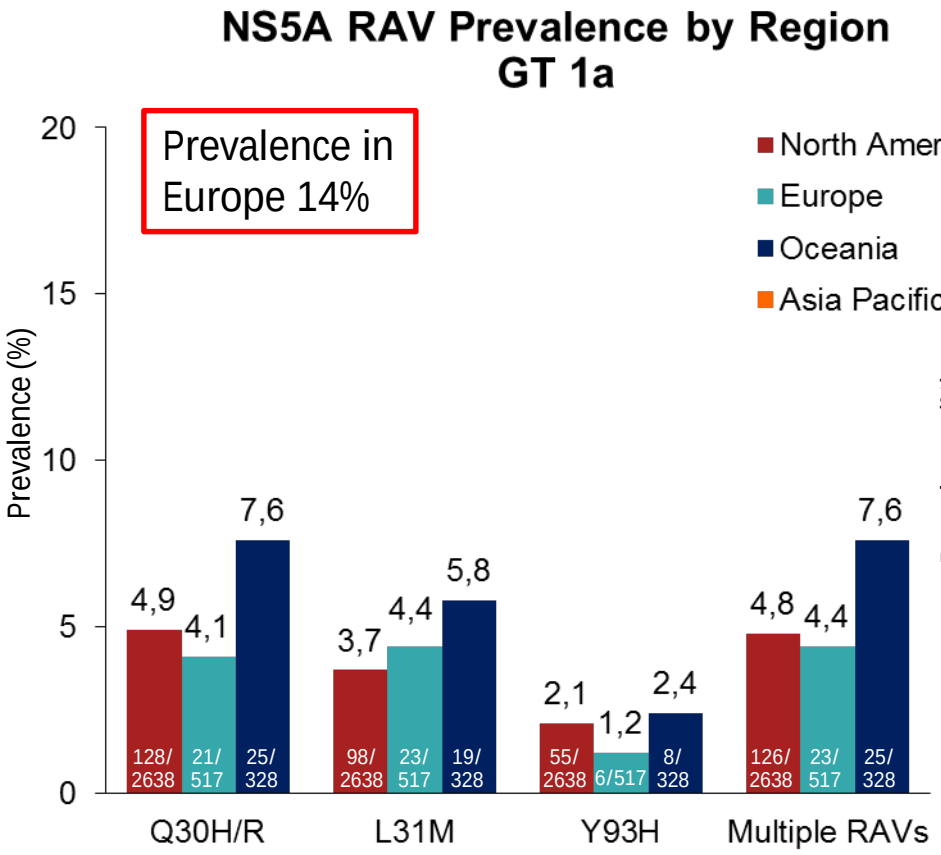


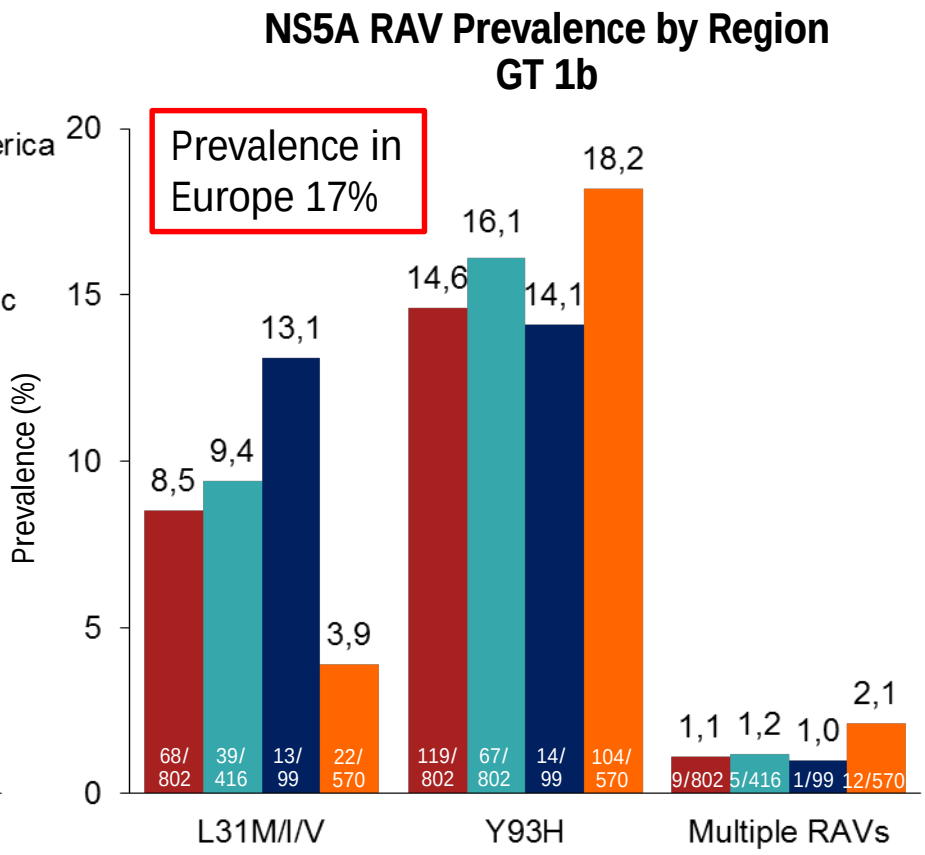
*Only failure was a post-transplant CTP B, MELD 16 patient who was only treated for 12 weeks of LDV/SOF because of insurance issues

Pungpapong, AASLD, 2015, 1038

Prevalence of Pre-Treatment NS5A RAVs in GT 1 and Effect on Treatment Outcome with LDV/SOF

NS5A deep sequencing analysis (1% cut-off) on 5397 patients





Q30H/R, L31M and Y93H RAVs confer >100 fold shift to LDV.

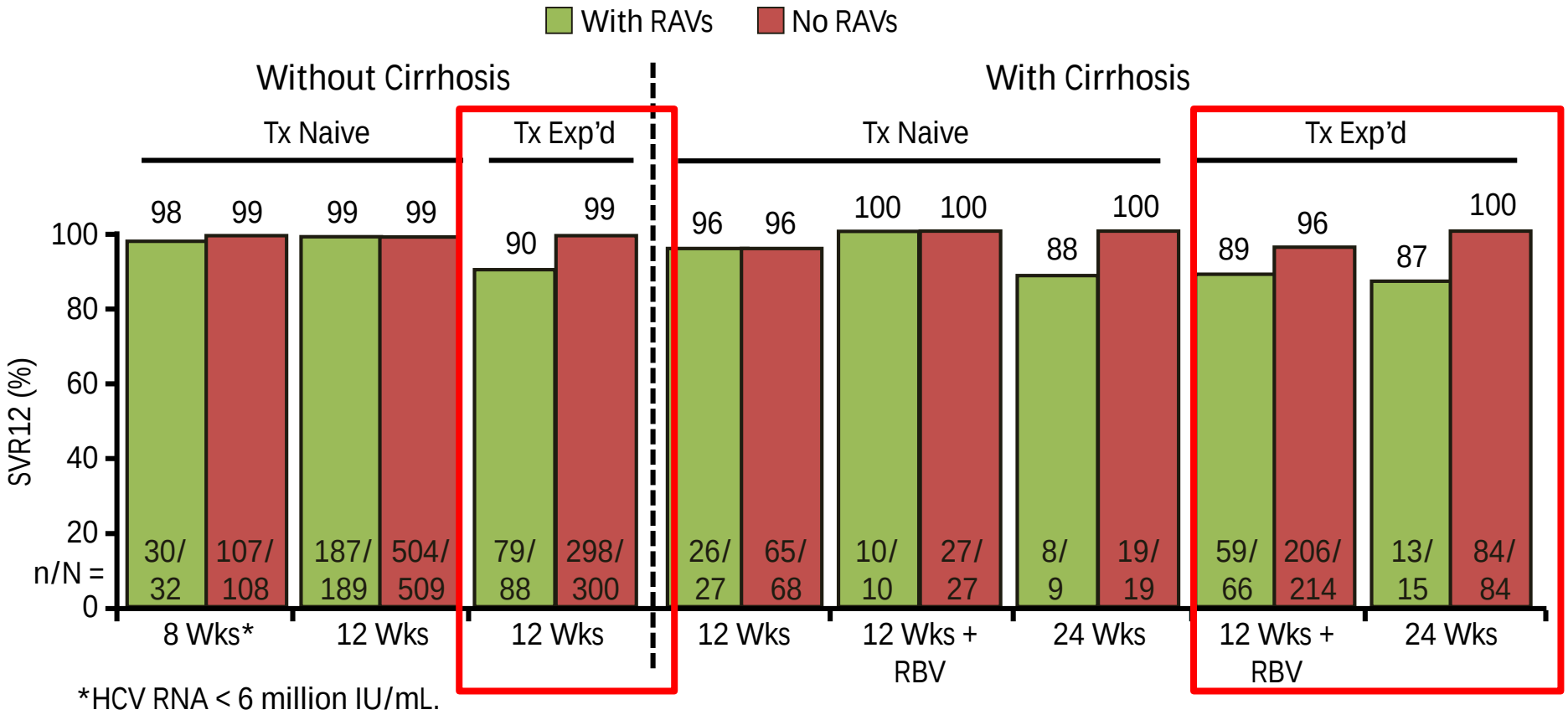
Asia Pacific not included due to low number of patients with GT1a (n=27)

L31M/I/V confer 3-43 fold shift to LDV; Y93H confers >100 fold shift to LDV

Zeuzem, AASLD, 2015, 91

Effect of BL NS5A RAVs on Ledipasvir/ Sofosbuvir Efficacy in GT1 HCV

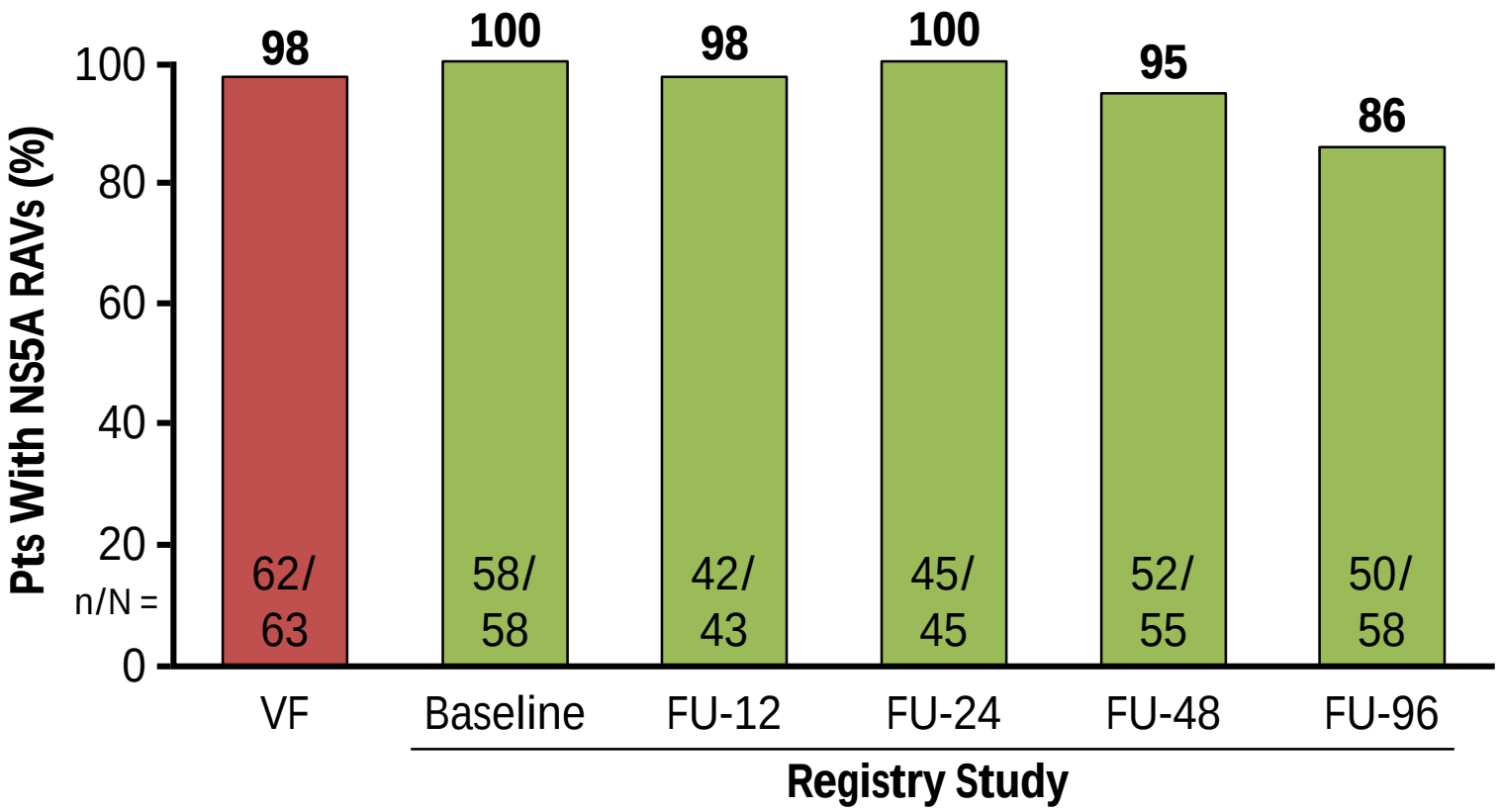
Deep sequencing of baseline samples obtained from 1566 pts treated with guideline-based LDV/SOF regimens in clinical trials



Adaptado de Zeuzem S, et al. AASLD 2015, abstract 91

Durability of Treatment-Emergent NS5A RAVs After Virologic Failure

- Study of pts not achieving SVR after receiving LDV without SOF



- **NS5A RAVs persisted in majority of pts for 96 wks**

Dvory-Sobol H, et al. EASL 2015. Abstract O059.

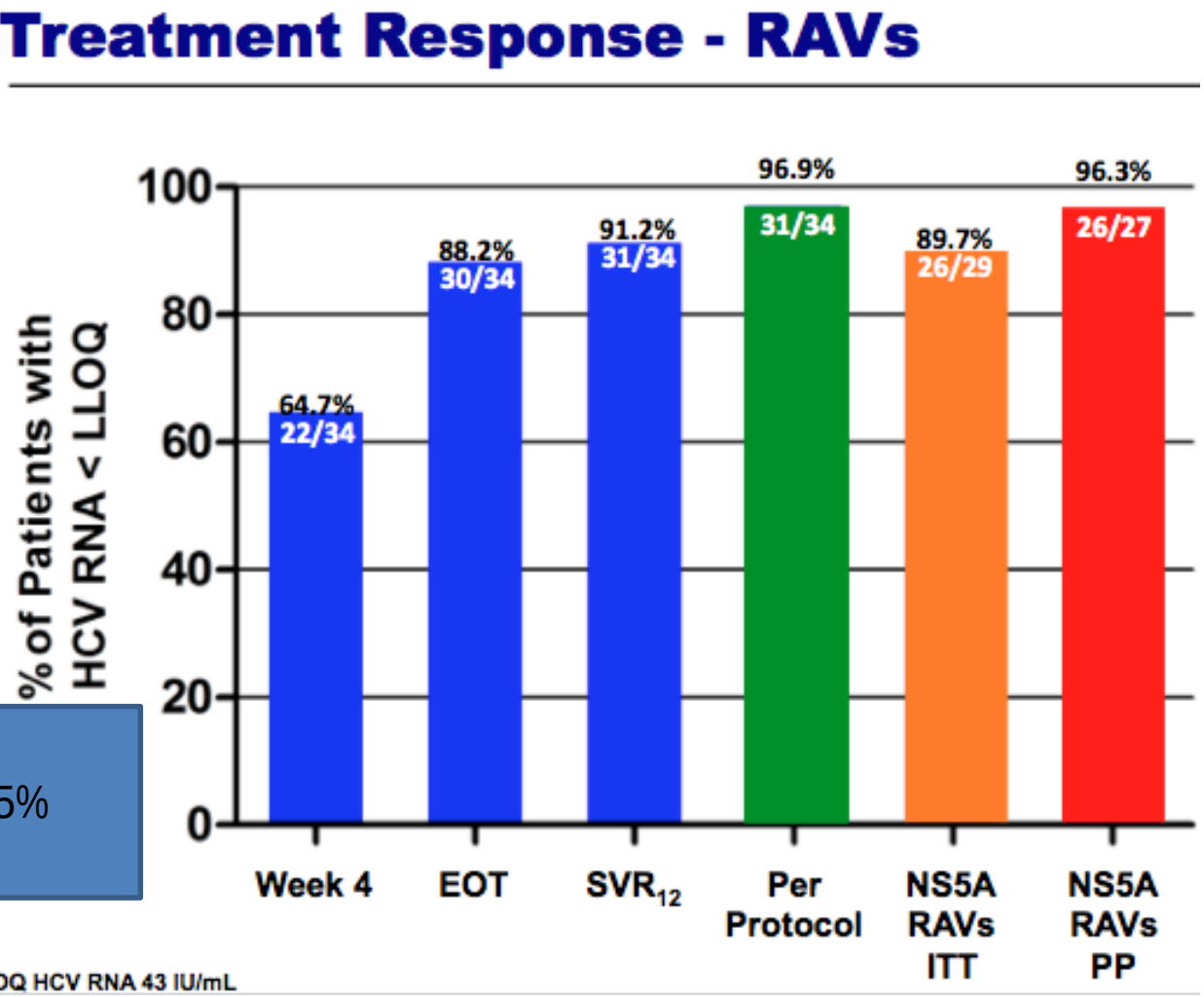
SYNERGY: LDV/SOF for GT1 HCV After Failure of 4-6 Wks' LDV/SOF-Based Tx

- Current analysis includes **noncirrhotic pts** with GT1 HCV who experienced failure (all viral relapse) of first-line therapy on any of 3 other trial arms:
  - LDV/SOF + GS-9669 for 6 wks, LDV/SOF + GS-9451 for 4 wks, or LDV/SOF + GS-9451 + GS-9669 for 4 wks

SVR12 in Pts With NS5A RAVs, % (n/N)	Pts (N = 34)
ITT	90 (26/29)
Per protocol	96 (26/27)

Wilson E, et al. AASLD 2015. Abstract 92

Retreatment with LDV/SOF in HCV Genotype 1 patients who failed shhort-course DAA regimens – The NIH SYNERGY trial

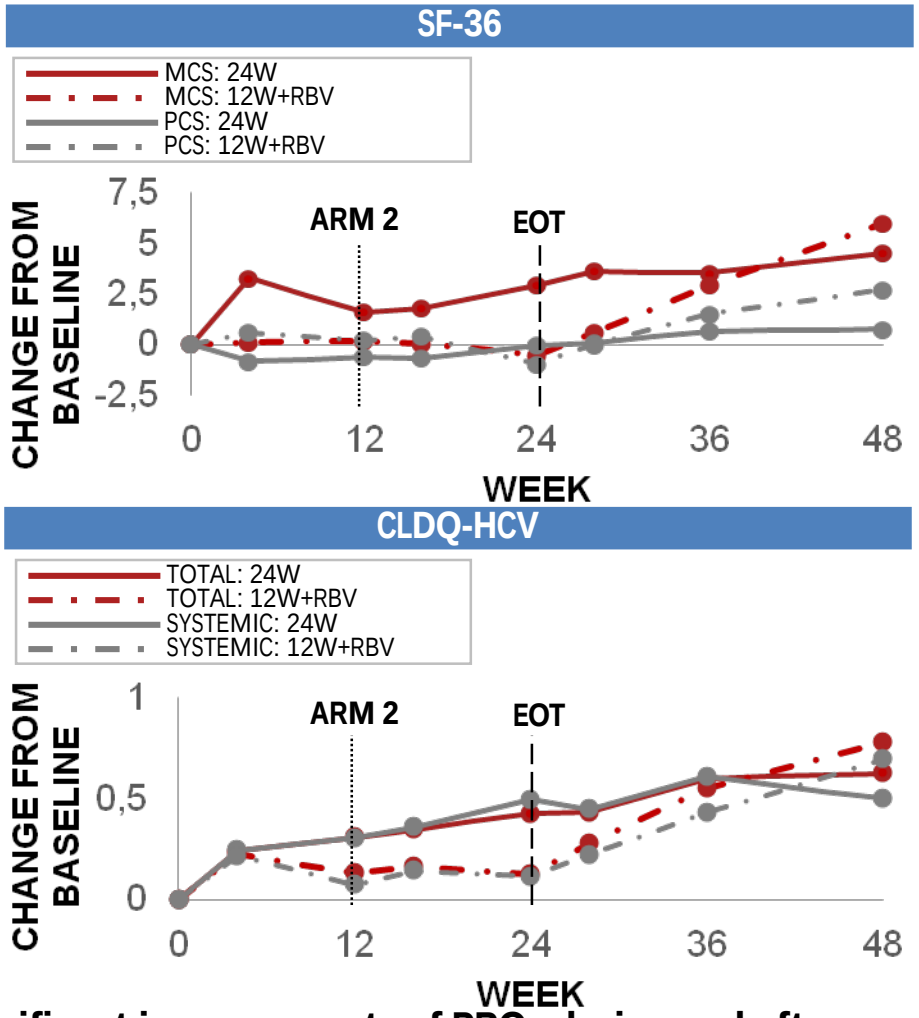


RAVS NS5A 85%

Wilson E, et al. AASLD 2015. Abstract 92

Impact of LDV/SOF on HRQL and PROs

- As **early as 4 weeks after beginning treatment, patients on LDV/SOF showed improvements** in MCS of SF-36, total CLDQ-HCV, emotional well-being of FACIT-F and activity of WPAI:SHP (all p<0.05)
- Patients on RBV-free regimen showed improvements in PROs over the 12 week treatment period
- No significant changes in PROs were noted during the placebo phase (all p>0.05)
- **Multivariate analysis showed that receiving RBV was independently associated with greater PRO impairment** (beta up to -10.5%, p<0.05)



Treatment with IFN/RBV-free regimens showed significant improvements of PROs during and after treatment in difficult-to-treat TE, CC patients

Younossi ZM, Liver Int. 2016; 36:42-48

MCS = mental component summary; PCS = physical component summary; EOT = end of treatment; ACTIVE 2 = Active treatment in Arm 2 begins; TE = treatment-experienced; CC = compensated cirrhosis

CONCLUSIONES (1)

El tratamiento con SOF/LDV durante12 semanas consigue unas tasas de curación del 93-94% en los pacientes con fracaso a un tratamiento previo (PR ;IP+PR), con una tolerabilidad excelente.

En pacientes cirróticos pretratados, añadir RBV o prolongar la duración del tratamiento con SOF/LDV a 24 semanas consigue aumentar sensiblemente la tasa de respuesta.

Estos resultados de los estudios de registro se reproducen en la práctica clínica habitual.

CONCLUSIONES (2)

En nuestro medio, un 16-18% de los pacientes G1 tienen RAVs basales a NS5A. Estas son más frecuentes en G1b.

Este hallazgo parece tener escasa repercusión cuando los pacientes son tratados con SOF/LDV, excepto en pacientes con fracaso a un tratamiento previo en fase de cirrosis.

En estos pacientes, la adición de RBV y la prolongación de la terapia a 24 semanas aumenta las tasas de curación.

CONCLUSIONES (3)

La mayoría de pacientes con fracaso terapéutico a una combinación de AAD desarrollan RAVs relacionadas con los fármacos utilizados. En el caso de NS5A afecta al 60-90% de los pacientes

Las RAVs relacionadas con NS3-4A tienden a desaparecer con rapidez tras la finalización del tratamiento, pero las relacionadas con NS5A persisten durante mucho tiempo, condicionando la posible respuesta a una terapia de rescate.

En un futuro inminente el estudio de resistencias adquirirá un papel importante en el manejo de los paciente con HCC.