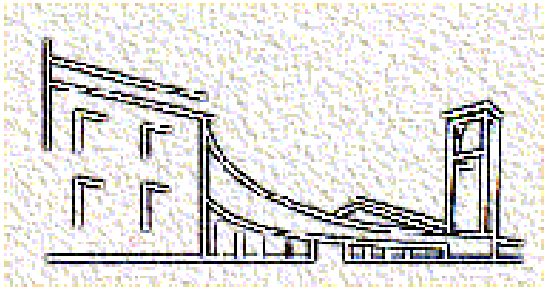
Novedades EASL/CROI 2014. Tto Monoinfectados.



Dr. MIGUEL GARCÍA DELTORO
Hospital General Universitario Valencia
Unidad Enfermedades Infecciosas

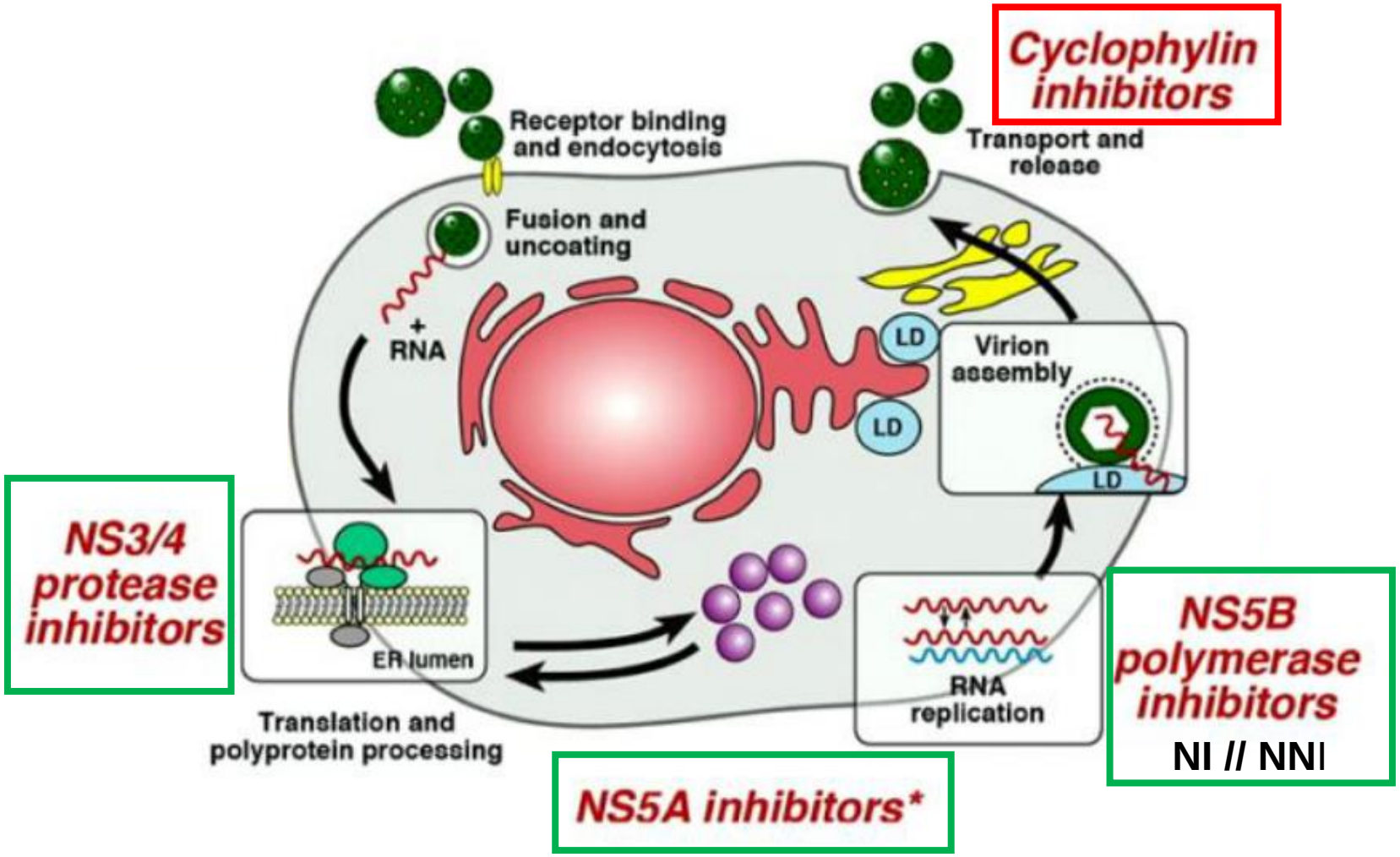
Tto Monoinfectados VHC.

EASL/CROI 2014. Tto Monoinfectados SUMARIO….

- 1.-Múltiples fármacos. Nomenclatura. Excepciones.
- 2.-EASL Guidelines (≠ AASLD).
- 3.-Los grandes estudios Fase III libres de IF.
- 4.-Otros estudios (telegráfico) priorizando SOF, SMP y DCV.
- 5.-Ttos en Cirrosis Avanzada, Trasplante y Retratamientos.

1.-Múltiples Fármacos. Nomenclatura. Excepciones...

DAA VHC: Ya 3 Dianas Terapéuticas ≥ Fase 3.



DAA: ¿Cómo distinguimos La diana?.

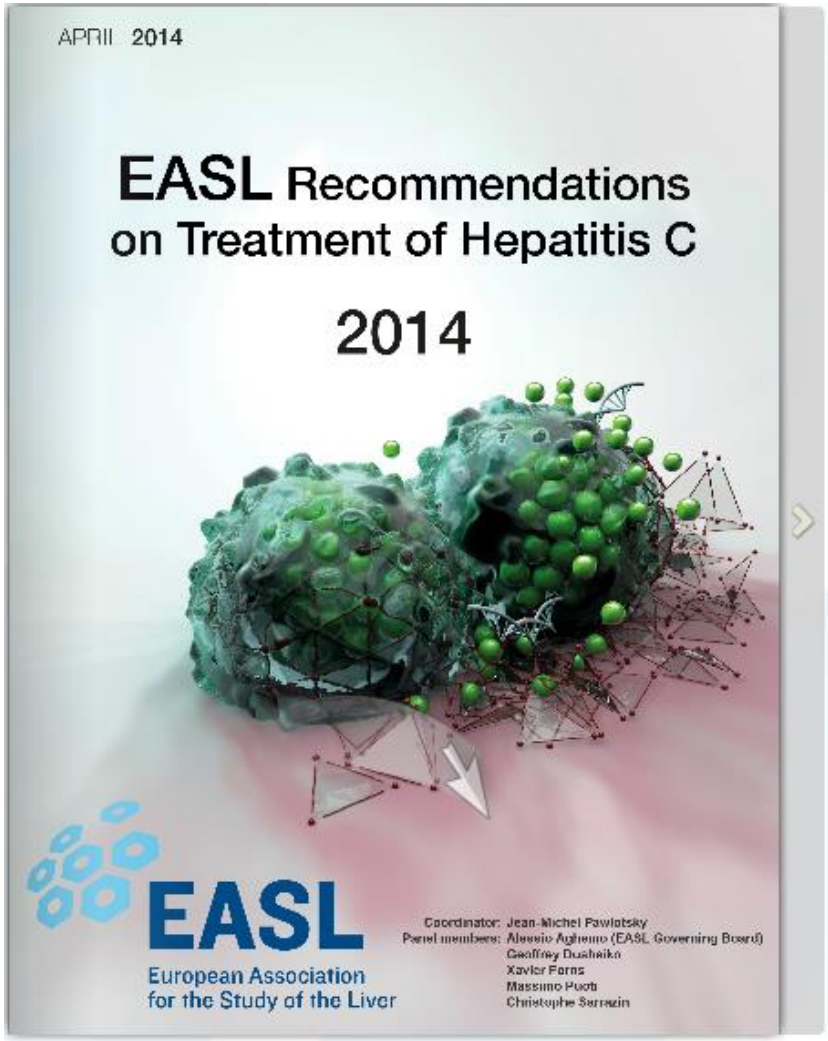
NI y NNI Polimerasa (NS5B): …..buvir

	NI	PI	NS5A	NNI
Nucleos(t)ide analogue-based strategies				
Gilead	Sofosbuvir	GS-9451	Ledipasvir	9669
Vertex/others	VX-135	Simeprevir	Daclatasvir	
Roche	*Mericitabine*	*Danoprevir/r*		*Setrobuvir*
Nucleoside-free triple combo strategies				
Abbvie		ABT-450/r	**Ombitasvir**	**Dasabuvir**
BMS		Asunaprevir	Daclatasvir	BMS791325
BI/Presidio		Faldaprevir	PPI-668	Deleobuvir
Janssen/GSK		Simeprevir	GSK2336805	TMC647055
Nucleoside-free, second-generation double combo strategies				
Merck		MK-5172	MK-8742	
Achillion		ACH-2684	ACH-3102	

NS5A: …..asvir.

PI (NS3/4): …..previr.

2.-EASL Guidelines (≠ AASLD)...



APRIL 2014

EASL Recommendations on Treatment of Hepatitis C

2014

Contents

EASL Office
7 rue Daubin, 1205 Geneva, Switzerland
Tel: (+41) 22 807 03 87
Fax: (+41) 22 850 24 00
e-mail: easloffice@easloffice.eu

Coordinator: Jean-Michel Pawlotsky
Panel members: Alessio Aghemo (EASL governing Board)
Geoffrey Dusheiko
Xavier Forns
Massimo Puoti
Christophe Sarrazin

1. Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide [1]. The long-term impact of HCV infection is highly variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). The number of chronically infected persons worldwide is estimated to be about 150 million, but most are unaware of their infection. The implementation of extended criteria for screening for HCV, such as targeting birth cohorts, is a subject of major debate among different stakeholders. Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, thanks to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention.

These EASL Recommendations on Treatment of Hepatitis C are intended to assist physicians and other healthcare providers, as well as policy makers, by describing the optimal management of patients with acute and chronic HCV infection. These guidelines apply to therapies that will be approved within less than 6 months at the time of their publication.

2. The standard of care up to 2014

The primary goal of HCV therapy is to cure the infection. A sustained virological response (SVR) is defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion. The infection is cured in more than 99% of patients who achieve an SVR. The SVR is generally associated with resolution of liver disease in patients without cirrhosis. Patients with cirrhosis remain at risk of life-threatening complications; however hepatic fibrosis may regress and the risk of complications such as hepatic failure and portal hypertension is reduced. More data is required to ascertain the lifetime residual risk of hepatocellular carcinoma after viral infection has been eradicated.

Until 2011, the combination of pegylated interferon (IFN)-α and ribavirin for 24 or 48 weeks was the approved treatment for chronic hepatitis C [2]. With this regimen, patients infected with HCV genotype 1 had SVR rates of approximately 40% in North America and 50% in Western Europe. Higher SVR rates were achieved in patients infected with HCV genotypes 2, 3, 5, and 6 (up to about 80%, and higher for genotype 2 than for genotypes 3, 5, and 6) and intermediate SVR rates were achieved in those with HCV genotype 4 [3].

In 2011, telaprevir and boceprevir were licensed for use in HCV genotype 1 infection, in combination with pegylated IFN-α and ribavirin (first-wave direct-acting antivirals; DAAs). Both target the HCV NS3/4A serine protease and have been approved as protease inhibitor (PI)-based triple and boceprevir must be administered in combination with pegylated IFN-α and ribavirin. In the phase III trials of boceprevir and telaprevir in HCV genotype 1 treatment-naïve patients, triple therapy regimens achieved higher SVR rates than pegylated IFN-ribavirin dual therapy, of the order of 63% to 75% [4-7]. However, the side effect profiles of these triple combination therapies are not favourable, and the costs per SVR in patients with advanced hepatic fibrosis are such that they should ideally no longer be used in patients infected with HCV genotype 1, as soon as other, more efficacious and better-tolerated options are available.

In addition to pegylated IFN-α and ribavirin, three new HCV DAAs will be licenced in the EU in the first half of 2014, for use as part of combination therapies for HCV infection. Sofosbuvir, a nucleotide analogue inhibitor of HCV RNA-dependent RNA polymerase, has been approved in January 2014. Simeprevir, a second-wave, first-generation NS3/4A protease inhibitor will be approved in May 2014. Daclatasvir, an NS5A inhibitor, is likely to be approved in August or September 2014. Other drugs may be approved later in 2014 or in 2015 and an update of these guidelines will be provided when this is the case.

3. Methodology

These EASL Recommendations have been updated by a panel of experts chosen by the EASL Governing Board. The recommendations were approved by the EASL Governing Board.

The Recommendations have been based as far as possible on evidence from existing publications and presentations at international meetings, and, if evidence was unavailable, the experts' personal experiences and opinion. Where possible, the level of evidence and recommendation are cited. The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated [28]. The quality of the evidence in the GPG has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2) (Table 1). The GPGs thus consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted.

These recommendations are necessarily based on currently licenced drugs. Several major Phase III trials have been completed and filing for licencing has been completed or is imminent. The panel could not recommend treatments with these compounds, but provides a perspective at the end, given the likely importance of these imminent regimens under review. These Recommendations will be updated regularly, following approval of new drug regimens by the European Medicines Agency.

4. Recommendations

4.1. Diagnosis of acute and chronic hepatitis C

The diagnosis of acute and chronic HCV infection is based on the detection of HCV RNA by a sensitive molecular method (lower limit of detection <15 International units [IU]/ml). Anti-HCV antibodies are detectable by enzyme immunoassay (EIA). In the vast majority of patients with HCV infection, but EIA results may be negative in early acute hepatitis C and in profoundly immunocompromised patients. Following spontaneous or treatment-induced viral clearance, anti-HCV antibodies persist in the absence of HCV RNA but may decline and finally disappear in some individuals [8, 9].

The diagnosis of acute hepatitis C can be confidently made only if seroconversion to anti-HCV antibodies can be documented, since there is no serological marker which proves that HCV infection is in the de novo acquired acute phase. Not all patients with acute hepatitis C will be anti-HCV positive at diagnosis. In these cases, acute hepatitis C can be suspected if the clinical signs and symptoms are compatible with acute hepatitis C (alanine

EASL HCV Guidelines 2014: Genotype 1

Genotype	Options for Therapy
Genotype 1*	**PegIFN/ribavirin** + **sofosbuvir**: 12 wks (A1)
	PegIFN/ribavirin + **simeprevir**†: 12 wks, followed by 12 wks of **pegIFN/ribavirin** in previously untreated pts and prior relapsers (A1), or 36 wks of **pegIFN/ribavirin** in previous partial responders and null responders (B1)
	PegIFN/ribavirin + **daclatasvir** (genotype 1b only; B1): 12 wks followed by 12 wks of **pegIFN/ribavirin** alone or a further 12 wks of **pegIFN/ribavirin** + **daclatasvir** (response-guided therapy) (B2)
	Sofosbuvir + **ribavirin**: 24 wks for interferon-intolerant pts only, where no other interferon-free option available (B2)
	Sofosbuvir + **simeprevir**: 12 wks (ribavirin may be added for previous nonresponders & cirrhotics) (B1)
	Sofosbuvir + **daclatasvir**: 12 wks in previously untreated pts; 24 wks in treatment-experienced patients (including TVR/BOC-experienced patients) (ribavirin may be added in previous nonresponders and cirrhotics) (B1)

*In settings where recommended options are not available, treatment with pegIFN/ribavirin + TVR or BOC remains acceptable.

†Not recommended in pts with genotype 1a and detectable Q80K polymorphism.

EASL. J Hepatology. 2014;60:392-420.

EASL HCV Guidelines 2014: Genotype 2-6

Genotype	Options for Therapy
Genotype 2*	**Sofosbuvir** + **ribavirin**: 12 wks (16-20 weeks in cirrhotic patients, especially treatment experienced) (A1) **PegIFN/ribavirin** + **sofosbuvir**: 12 wks for cirrhotic and/or treatment-experienced patients (B1)
Genotype 3*	**Sofosbuvir** + **ribavirin**: 24 wks (unsuitable for treatment-experienced cirrhotics, no specific alternative proposed) (A2) **PegIFN/ribavirin** + **sofosbuvir**: 12 wks (A2) **Sofosbuvir** + **daclatasvir**: 12 wks (24 wks for treatment-experienced patients) (B1)
Genotype 4*	**PegIFN/ribavirin** + **sofosbuvir**: 12 wks (B1). **PegIFN/ribavirin** + **Simeprevir** 12 wks followed by 12 wks of **pegIFN/ribavirin** alone or a further 36 wks of **pegIFN/ribavirin** in prior partial and null responders amd cirrotics (B1) **Sofosbuvir + ribavirin**: 24 wks for interferon-intolerant patients (C2) **Sofosbuvir + simeprevir**: 12 wks (ribavirin may be added in previous nonresponders and cirrhotics) (B2) **PegIFN/ribavirin** + **daclatasvir**: 12 wks followed by 12 wks of **pegIFN/ribavirin** alone or a further 12 wks of **pegIFN/ribavirin** + **daclatasvir** (response-guided therapy) (B1) **Sofosbuvir + daclatasvir**: 12 wks in previously untreated patients; 24 wks in treatment-experienced patients (ribavirin may be added in previous nonresponders and cirrhotics) (B2)
Genotype 5/6*	**PegIFN/ribavirin** + **sofosbuvir** 12 wks (B1) **Sofosbuvir** + **ribavirin**: 24 wks for interferon-intolerant patients (C2)

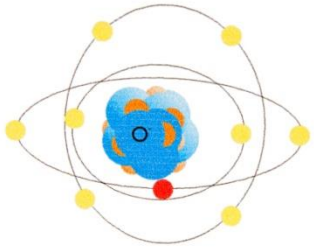
*In settings where recommended options are not available, treatment with pegIFN/ribavirin remains acceptable.

EASL. J Hepatology. 2014;60:392-420

3.-Los grandes estudios Fase III libres IF...

CROI/EASL VHC. Estudios Fase III sin IF.

1.- ION 1-3.



GILEAD

2.- PEARL 3.

3.- SAPPHIRE 1-2.

4.- TURQUOISE 2.

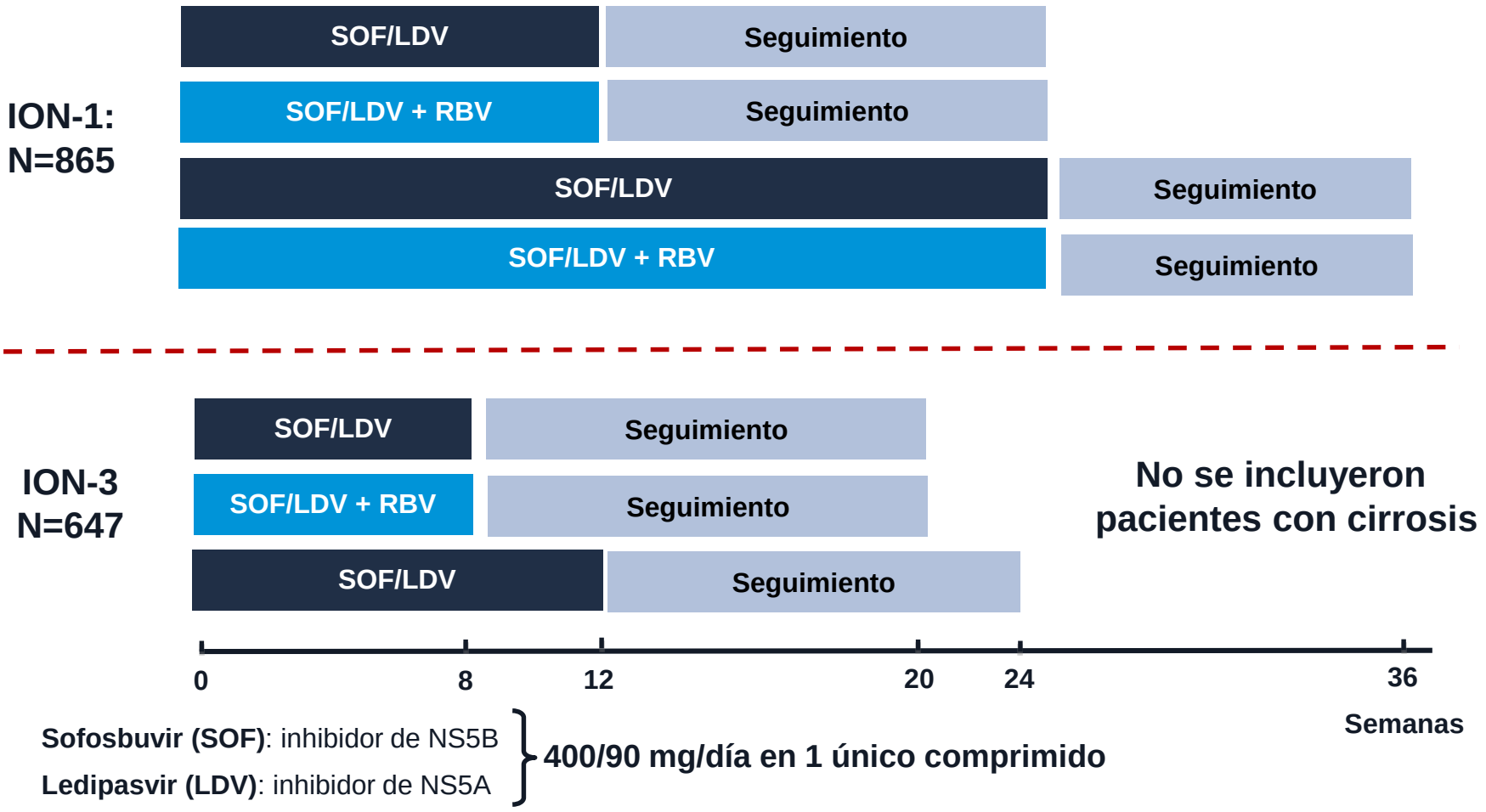
abbvie

5.- HALLMARK-DUAL.

Bristol-Myers Squibb Company

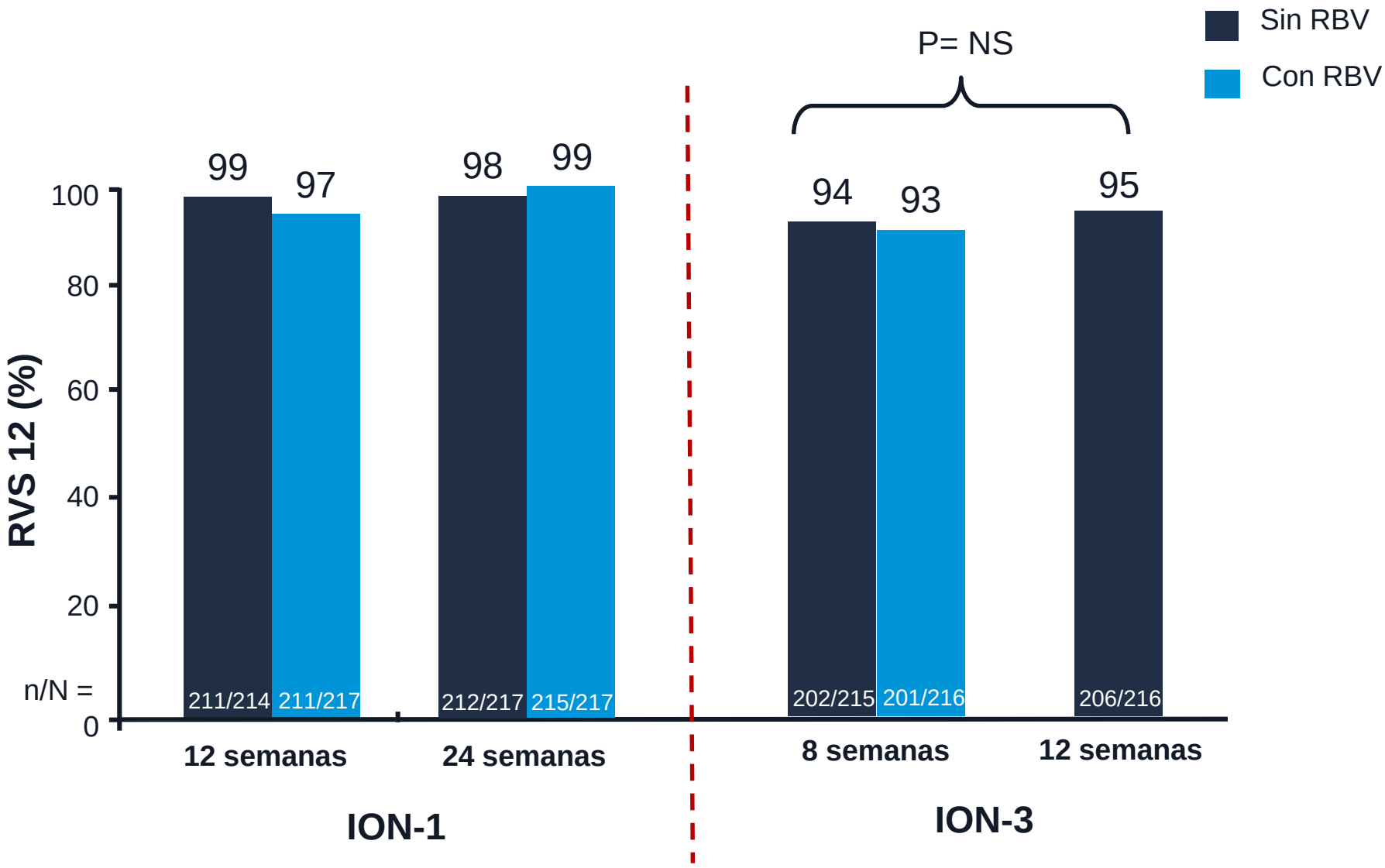
ION-1 e ION-3: duración óptima del tratamiento con Sofosbuvir + Ledipasvir en pacientes genotipo 1 naive (estudios fase III, n= 1.512)

- Aleatorización 1:1:1:1
- Estratificación según: subtipo de genotipo 1 (G1a=80%) y presencia de cirrosis (16%)



Mangia A. EASL 2014 #LB2. Kowdley KV. EASL 2014 #55A. Afdhal N. NEJM 2014 May 15;370:1889-98. Kowdley KV, NEJM 2014 May 15;370:1879-88

Elevada eficacia de Sofosbuvir + Ledipasvir sin RBV durante 8 semanas en pacientes genotipo 1 naive sin cirrosis



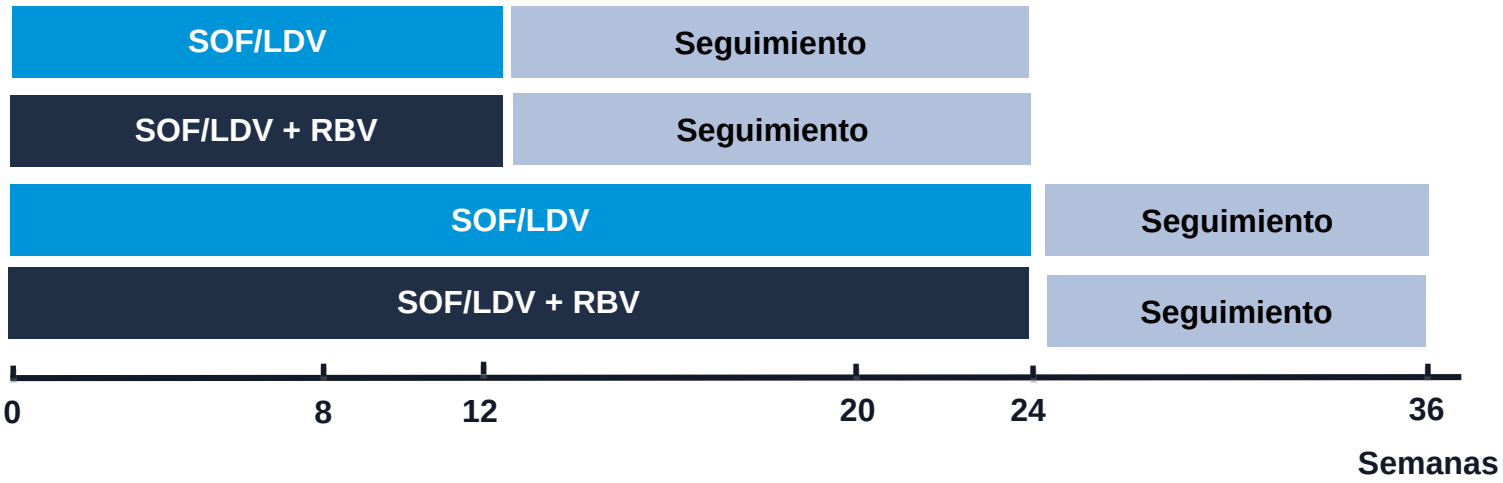
Mangia A. EASL 2014 #LB2. Kowdley KV. EASL 2014 #55A. Afdhal N. NEJM 2014 May 15;370:1889-98. Kowdley KV, NEJM 2014 May 15;370:1879-88

ION-2: eficacia de Sofosbuvir + Ledipasvir ± RBV en pacientes con fracaso a tratamientos previos

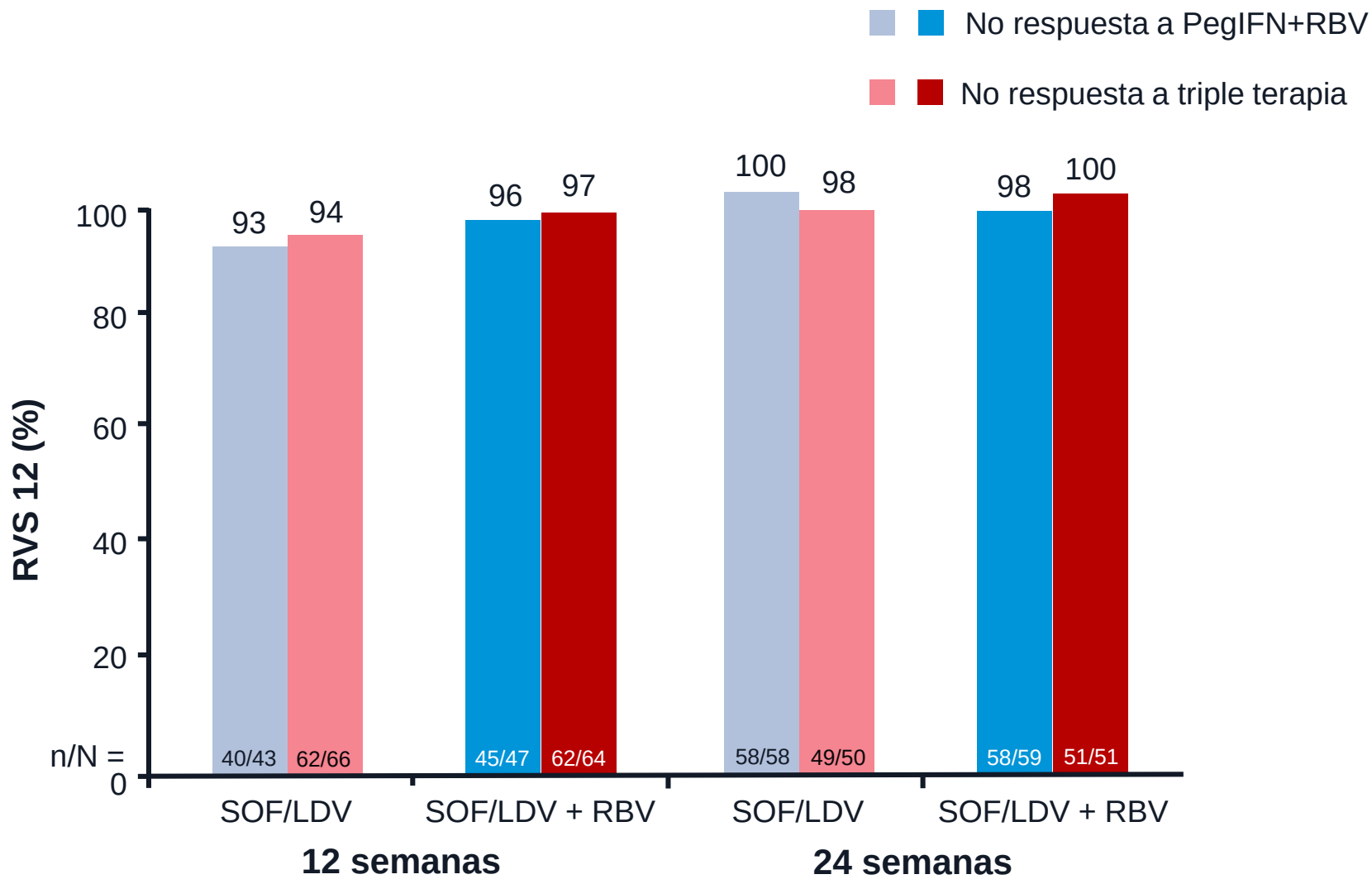
- Aleatorización 1:1:1:1
- Estratificación según: subtipo de genotipo 1, cirrosis y tipo de respuesta previa:
  - Genotipo 1a: 79%
  - Cirrosis: 20%
  - Fracaso a triple terapia previa: 53%

Afdhal N. et al. EASL 2014, Londres 10-12 Abril #109A. Afdhal N, et a. INEJM 2014 Apr 17;370(16):1483-93.

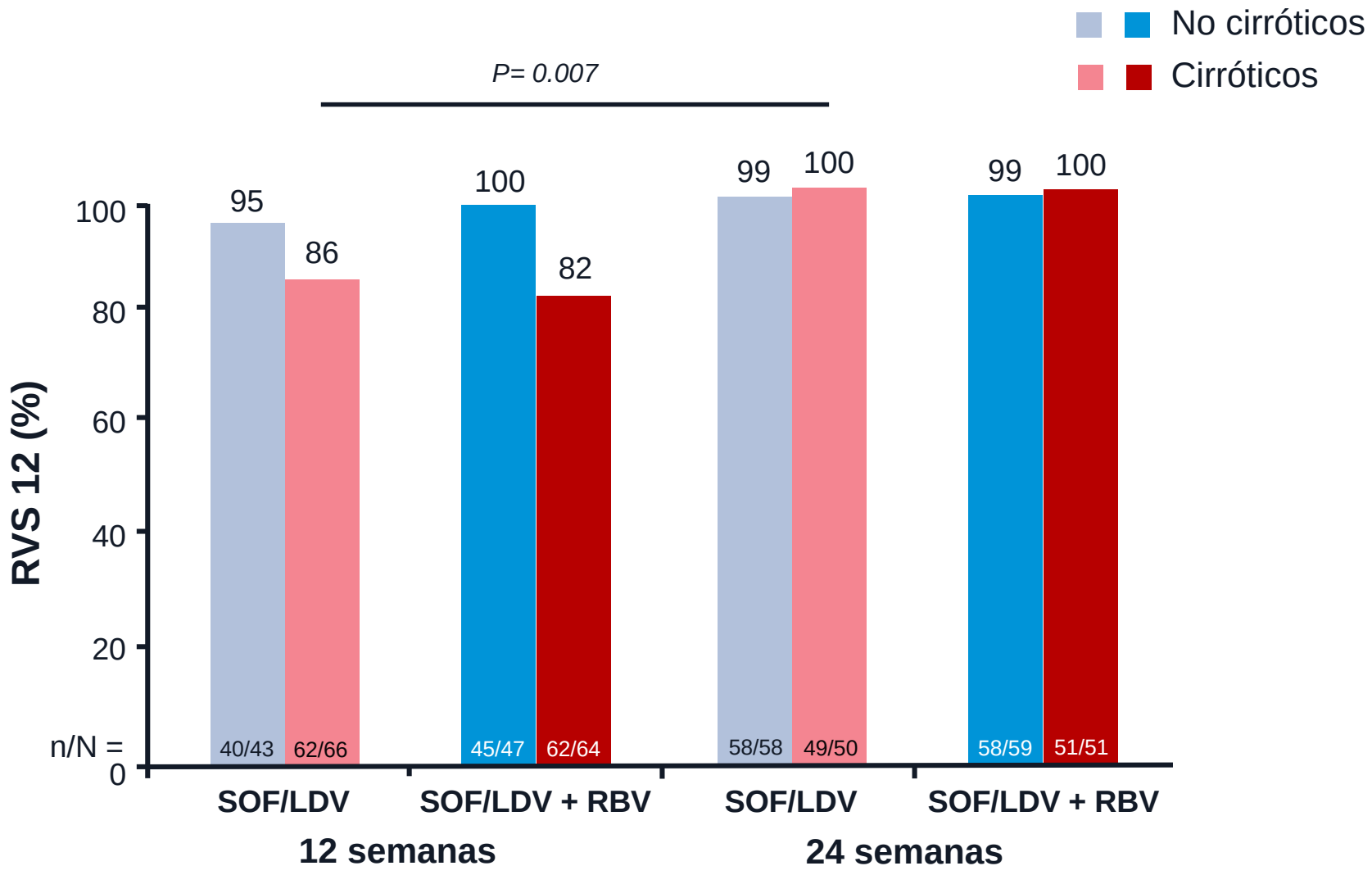
ION-2: N=440



ION-2: Sofosbuvir + Ledipasvir es igualmente eficaz en no respondedores a biterapia o triple terapia



ION-2: el tratamiento durante 12 semanas es inferior a 24 semanas en pacientes con cirrosis hepática



Seguridad de la combinación de Sofosbuvir + Ledipasvir en los estudios ION-1, ION-2 e ION-3

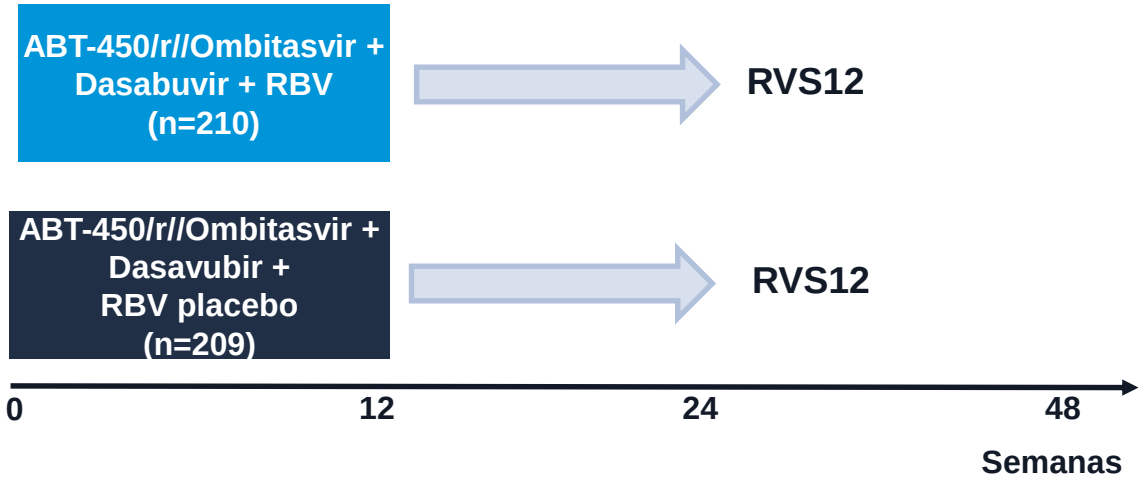
Pacientes, n (%)	8 semanas	12 semanas	24 semanas
EAs* grado 3-4	2 (<1)	13 (2)	31 (10)
EAs* graves	4 (2)	6 (1)	24 (7)
Discontinuación por EAs*	0	2 (0.4)	4 (1)
Cefalea	45 (21)	114 (21)	79 (24)
Náuseas	15 (7)	61 (11)	36 (11)
Insomnio	11 (5)	42 (8)	33 (10)
Artralgias	9 (4)	32 (6)	26 (8)
Diarrea	15 (7)	40 (7)	33 (10)
Rash	3 (1)	23 (4)	22 (7)

**AE: Adverse Effects*

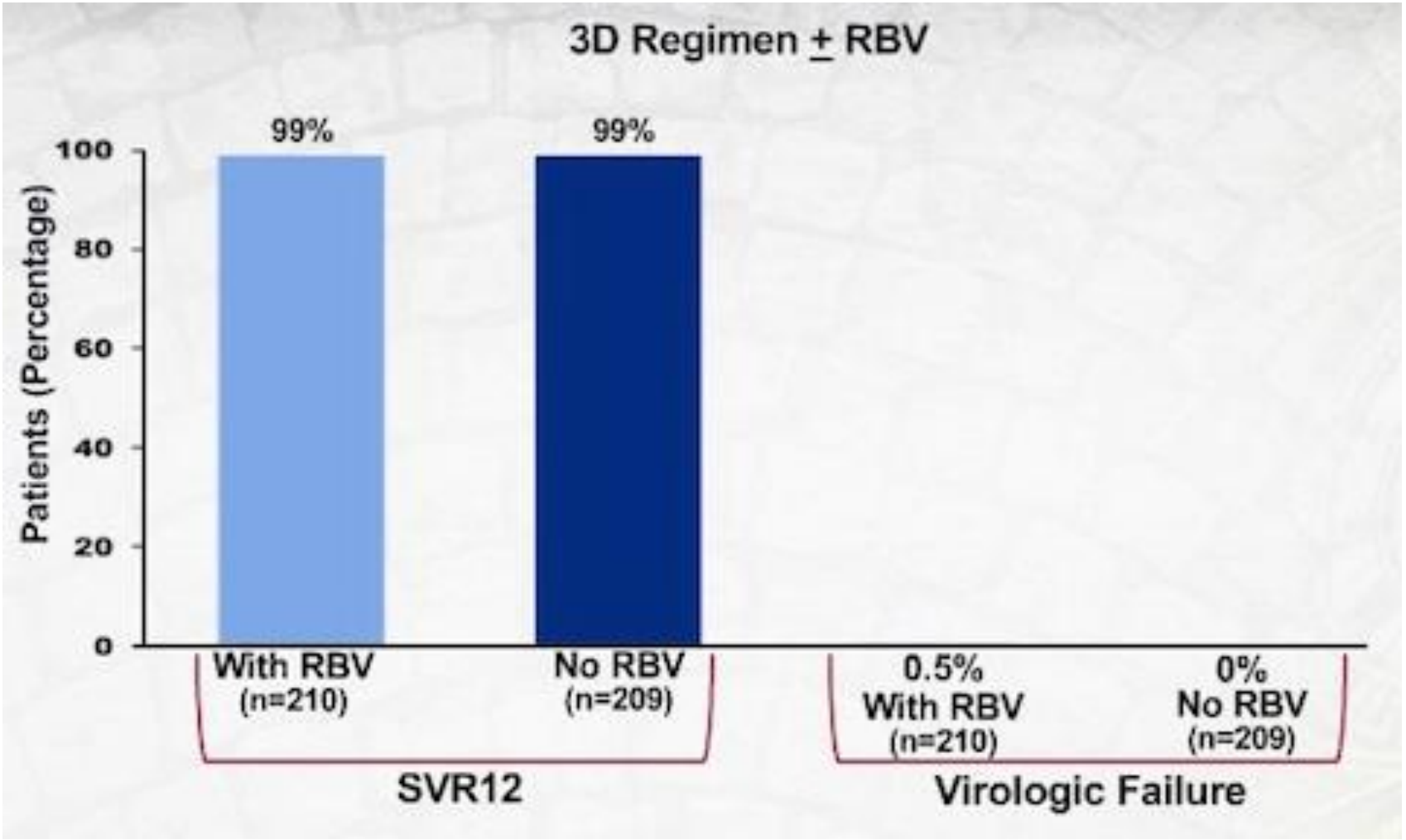
Mangia A. et al. 49th EASL 2014 #LB2; Kowdley KV. et al. 49th EASL 2014 #55A ; Afdhal N. et al. 49th EASL 2014 #109A

PEARL III: elevada eficacia de ABT-450/r + Ombitasvir + Dasabuvir +/- RBV en 419 pacientes naive genotipo 1b.

- Estudio fase III exclusivamente Ptes naive genotipo 1b (el Pearl IV es de 1a) :
  - Doble ciego controlado con placebo RBV.
  - ABT-450/r//Ombitasvir (150/100/25 mg qd) + Dasabuvir (250 mg bid)
  - No cirrosis, ni coinfección VIH, VHB.



PEARL III: elevada eficacia de ABT-450/r + Ombitasvir + Dasabuvir independientemente de +/- RBV.



Ferenci P, et al. 49th EASLD 2014. #129Q. Ferenci P, et al. N Engl J Med. 2014 May 4. [Epub ahead of print]

PEARL III: elevada eficacia de ABT-450/r + Ombitasvir + Dasabuvir y muy buena tolerancia.

Adverse Events (>10% in Either Arm)

	3-DAA + RBV (N = 210)	3-DAA (N = 209)	*P* value
Headache	51 (24.3)	49 (23.4)	
Fatigue	45 (21.4)	48 (23.0)	
Pruritus	25 (11.9)	11 (5.3)	0.022
Nausea	23 (11.0)	9 (4.3)	0.016
Asthenia	22 (10.5)	11 (5.3)	

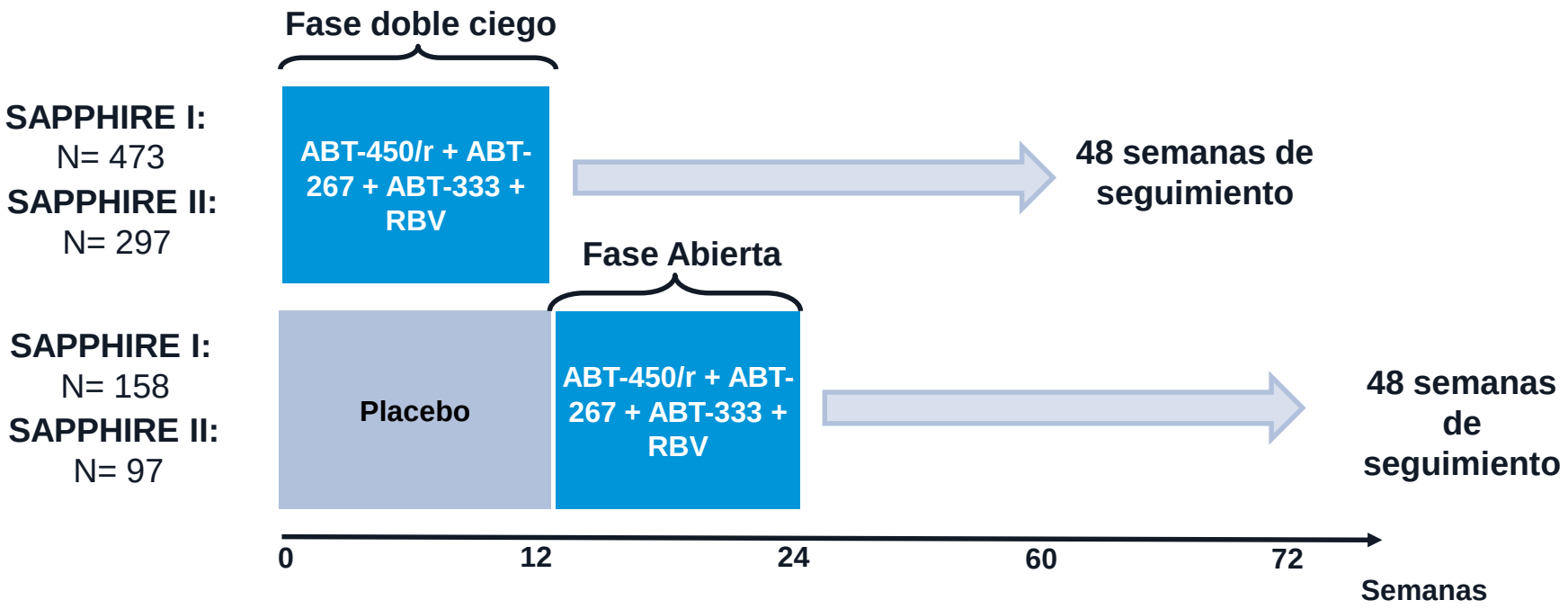
Other adverse events occurring significantly more frequently with 3-DAA + RBV: insomnia (9% vs. 3%), cough (9% vs. 2%), and anemia (7% vs. <1%)

Serious adverse events occurred in 4 patients in each arm

- Only one (arthritis, 3-DAA regimen) was possibly related to study drug

No patient discontinued the study drug due to adverse events

SAPPHIRE I y II: eficacia y seguridad de cuádruple terapia sin interferón en pacientes genotipo 1 naive y no respondedores a tratamientos previos (fases III, n= 1.025)



- Ramdomización 3:1. No incluyó pacientes con cirrosis.
- Genotipo 1a= 58-68%
- SAPPHIRE I Ptes naive // SAPPHIRE II pretratados pero excluidos ptes con fallo triple terapia.

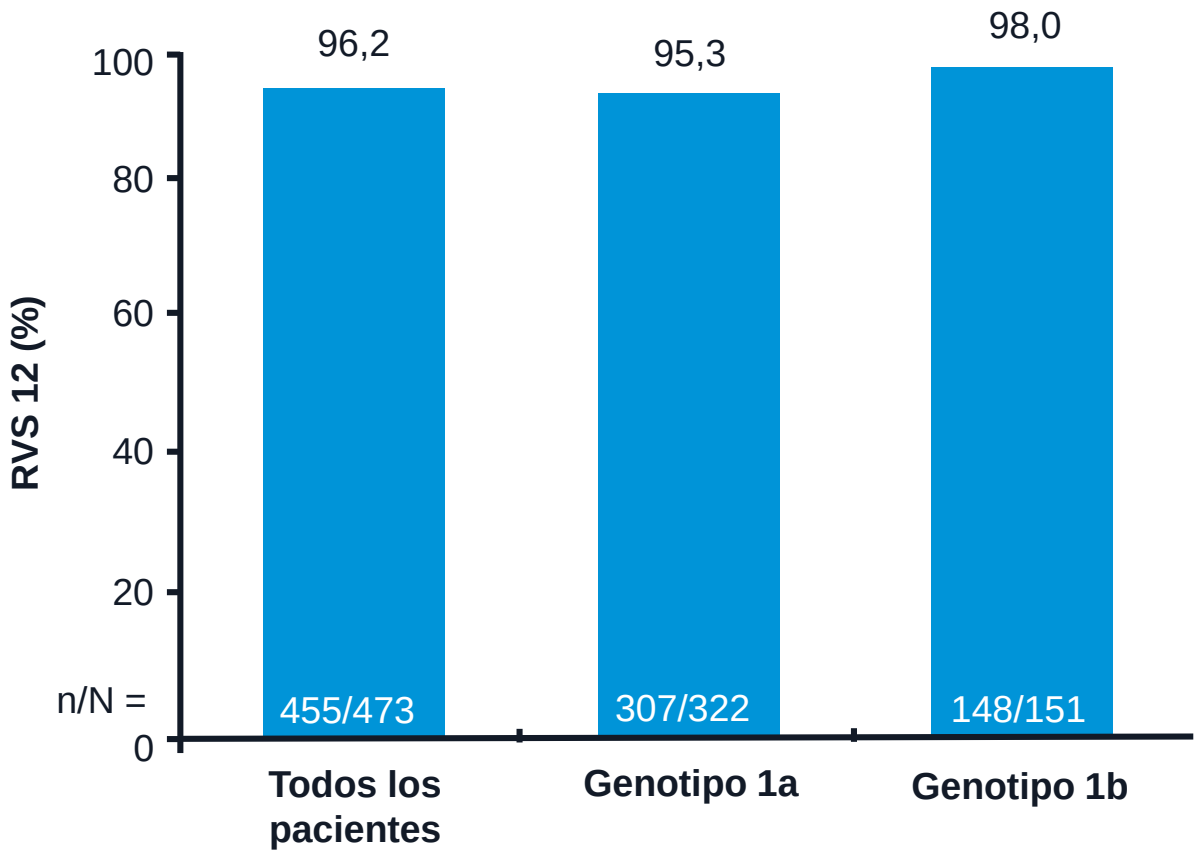
ABT-450: inhibidor NS3/4A

Ombitasvir (ABT-267): inhibidor NS5A } **Co-formulado en 1 comprimido: 150/100/25 mg/d**

Dasabuvir (ABT-333): inhibidor NS5B → **250 mg/12h**

Feld J. EASL 2014 #60A ; Zeuzem S. EASL 2014 #1A. Feld JJ. NEJM 2014 Apr 24;370:1594-603. Zeuzem S. NEJM 2014 Apr 24;370:1604-14.

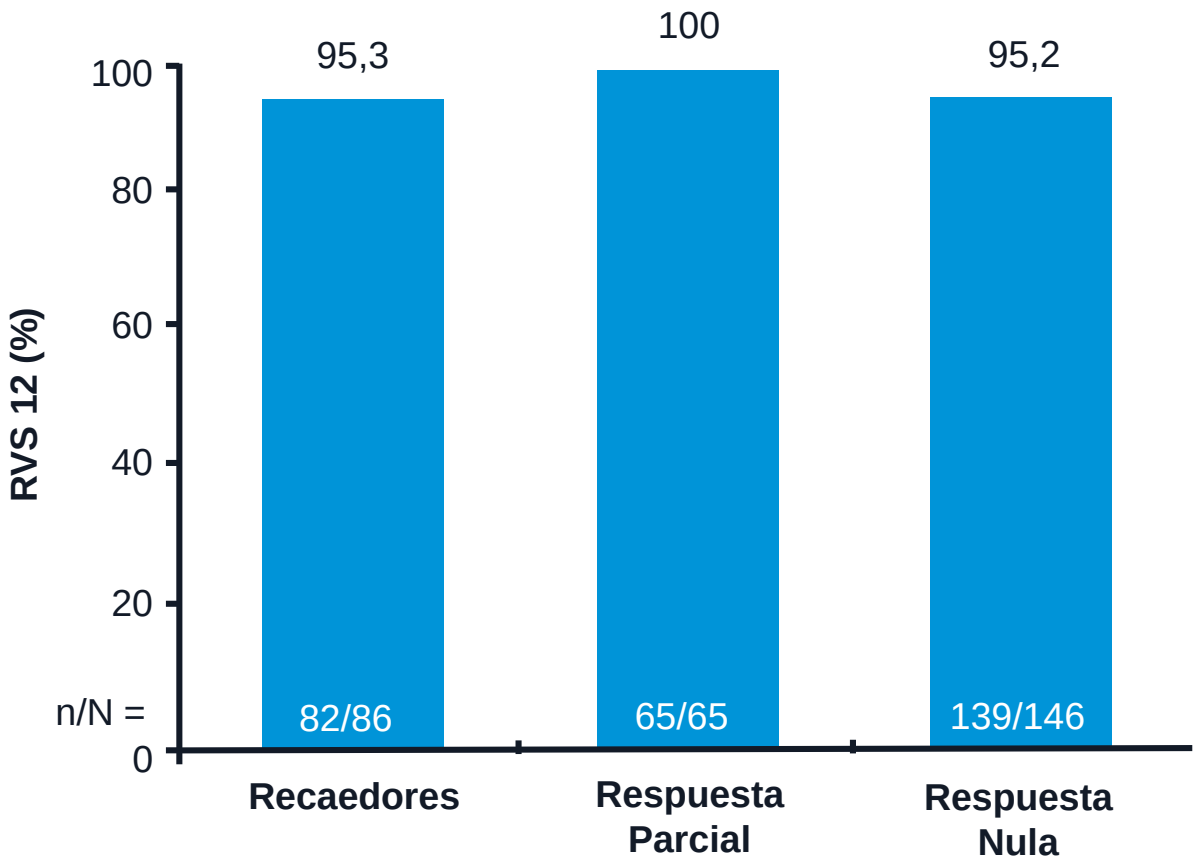
SAPPHIRE I: respuesta viral sostenida a 12 semanas (ITT)



Causas de no respuesta:

- 1 rebrote viral
- 7 recaídas
- 2 suspensiones por AEs
- 8 pérdidas de seguimiento

SAPPHIRE II: excelente eficacia independientemente del tipo de fracaso a un tratamiento previo



Causas de no respuesta:

- 7 recaídas (6 en respuestas nulas).
- 4 pérdidas de seguimiento.

Feld J. EASL 2014 #60A ; Zeuzem S. EASL 2014 #1A. Feld JJ. NEJM 2014 Apr 24;370:1594-603. Zeuzem S. NEJM 2014 Apr 24;370:1604-14.

Seguridad del tratamiento en SAPPHIRE I y II respecto al grupo control (placebo)

Pacientes, n (%)	3 ABTs + RBV (n= 770)	Placebo (n=255)
EAs severos	16 (2)	1 (0.4)
Discontinuación por EAs	6 (0.8)	0
Cefalea	264 (34)	76 (30)
Cansancio	263 (32)	67 (26)
Náuseas	172 (22)	38 (15)
Insomnio	108 (14)	19 (7)
Prurito	92 (12)	14 (5)
Diarrea	104 (14)	23 (9)
Disnea	37 (12)*	10 (10)*
Rash	51 (11)Y	9 (6) Y

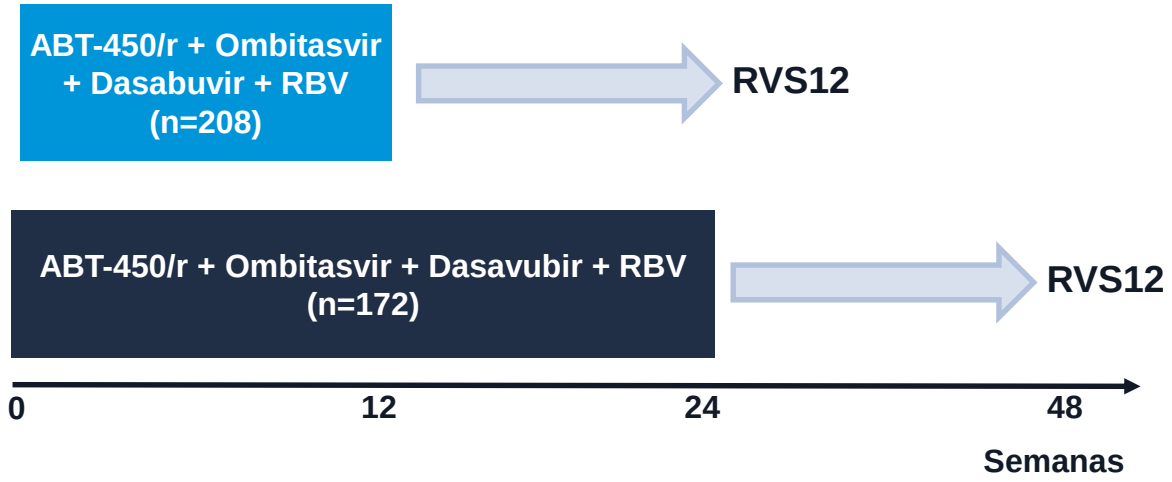
SAPPHIRE II

YSAPPHIRE I

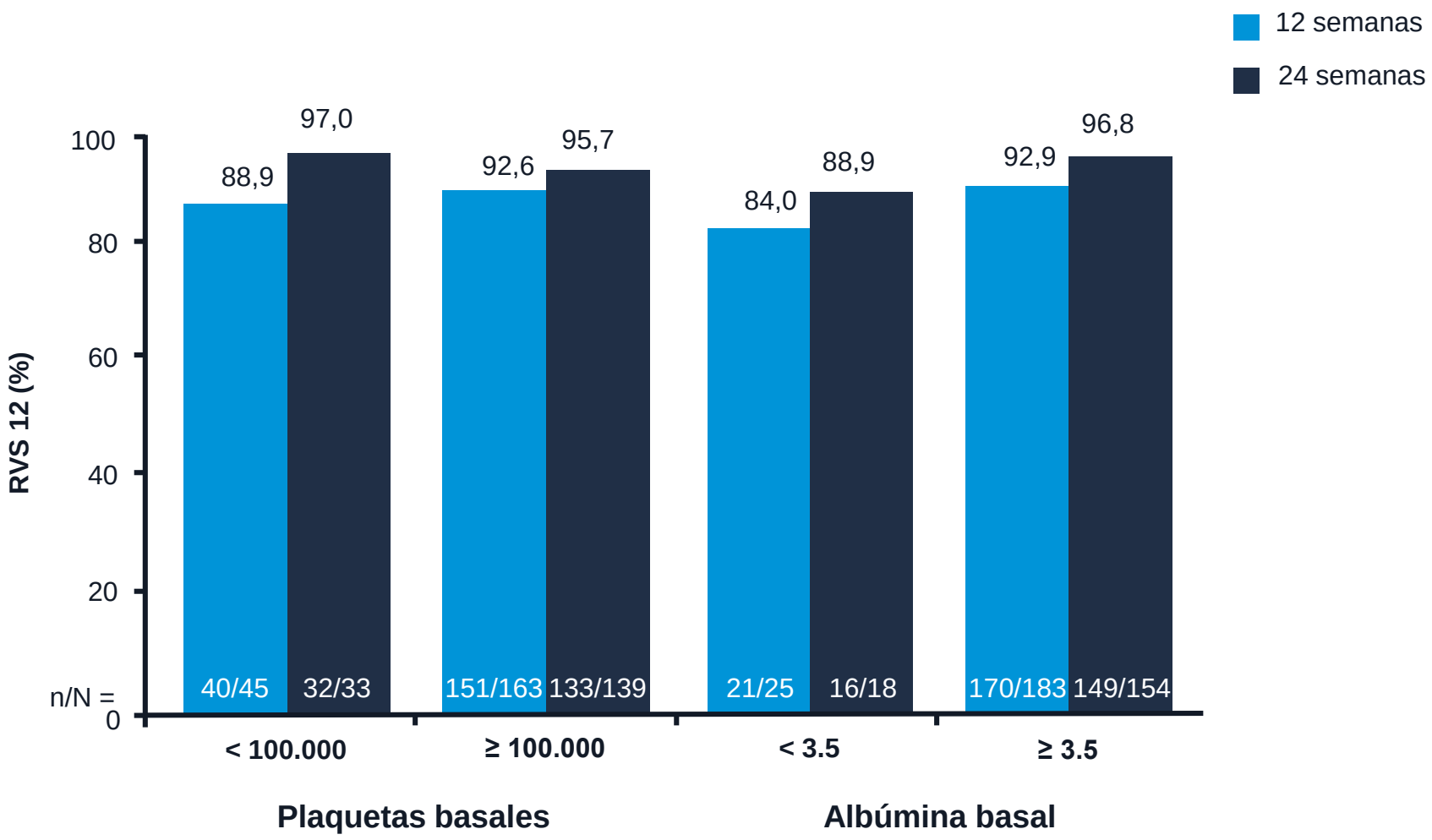
Feld J. EASL 2014 #60A ; Zeuzem S. EASL 2014 #1A. Feld JJ. NEJM 2014 Apr 24;370:1594-603. Zeuzem S. NEJM 2014 Apr 24;370:1604-14.

TURQUOISE-II: elevada eficacia de ABT-450/r + Ombitasvir + Dasabuvir + RBV en 380 pacientes genotipo 1 con cirrosis

- Estudio fase III exclusivamente para pacientes con cirrosis compensada:
  - Naives o fallos a tratamiento con Peg-IFN+RBV
  - Child-Pugh A
  - Plaquetas ≥ 60.000, albúmina ≥ 2,8, Bil.tot. < 3,0, INR ≤ 2,3
- Características basales:
  - Child-Pugh A6: 18%
  - Albúmina < 3,5: 11%
  - Plaquetas < 100.000: 20%

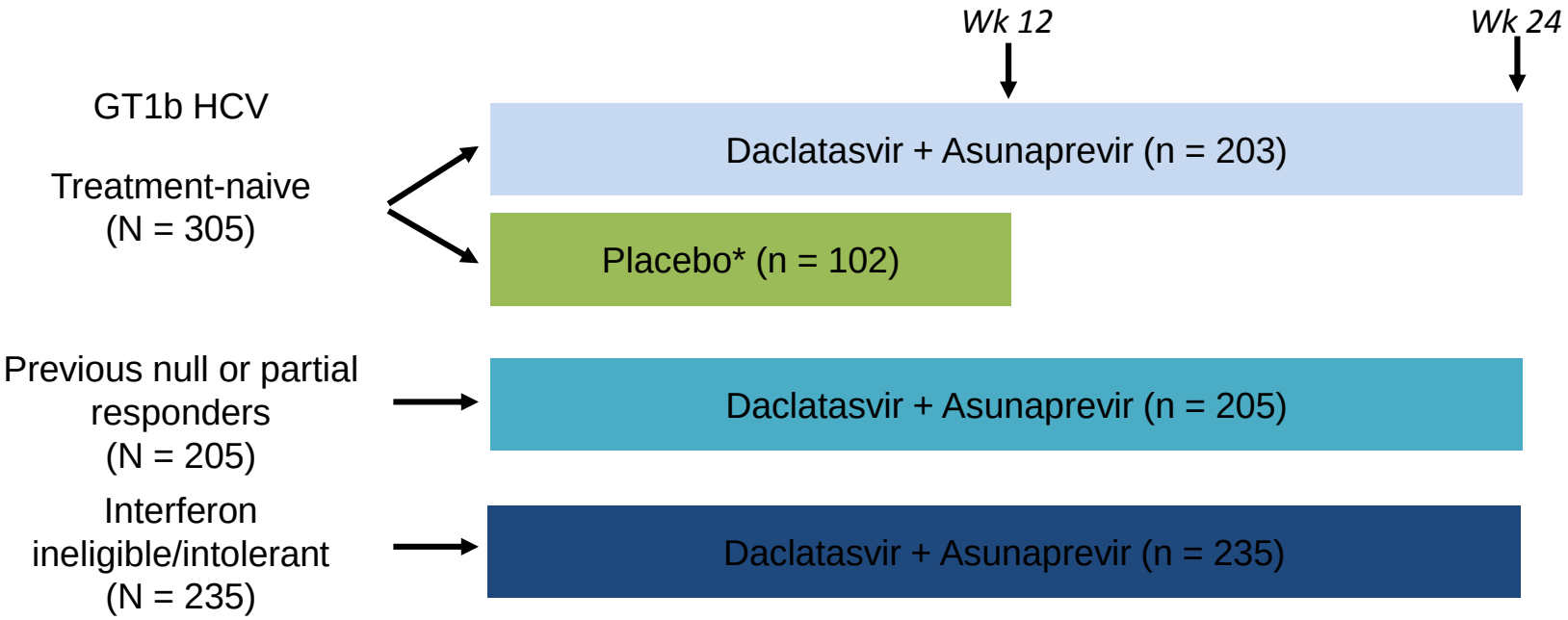


TURQUOISE-II: influencia de la gravedad de la cirrosis y la duración del tratamiento sobre la eficacia



HALLMARK-DUAL: Daclatasvir + Asunaprevir in Patients With GT1b HCV

- AI447-028: double-blinded, placebo-controlled phase III trial

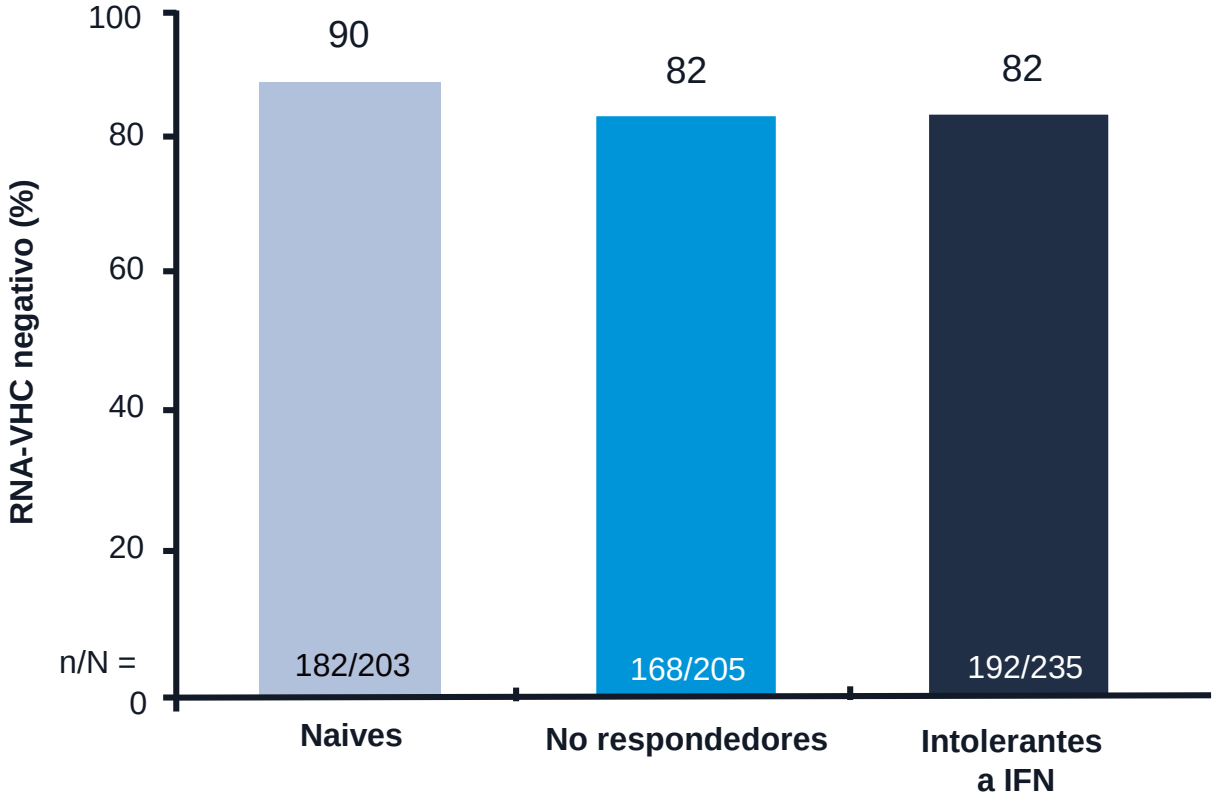


Daclatasvir 60 mg once daily; asunaprevir 100 mg twice daily.

*Patients allocated placebo crossed over into a separate study after 12 wks.

Manns M, et al. EASL 2014. Abstract O166.

HALLMARK-DUAL: Daclatasvir + Asunaprevir en genotipo 1b naive, no respondedores o intolerantes a IFN



Pacientes con cirrosis:

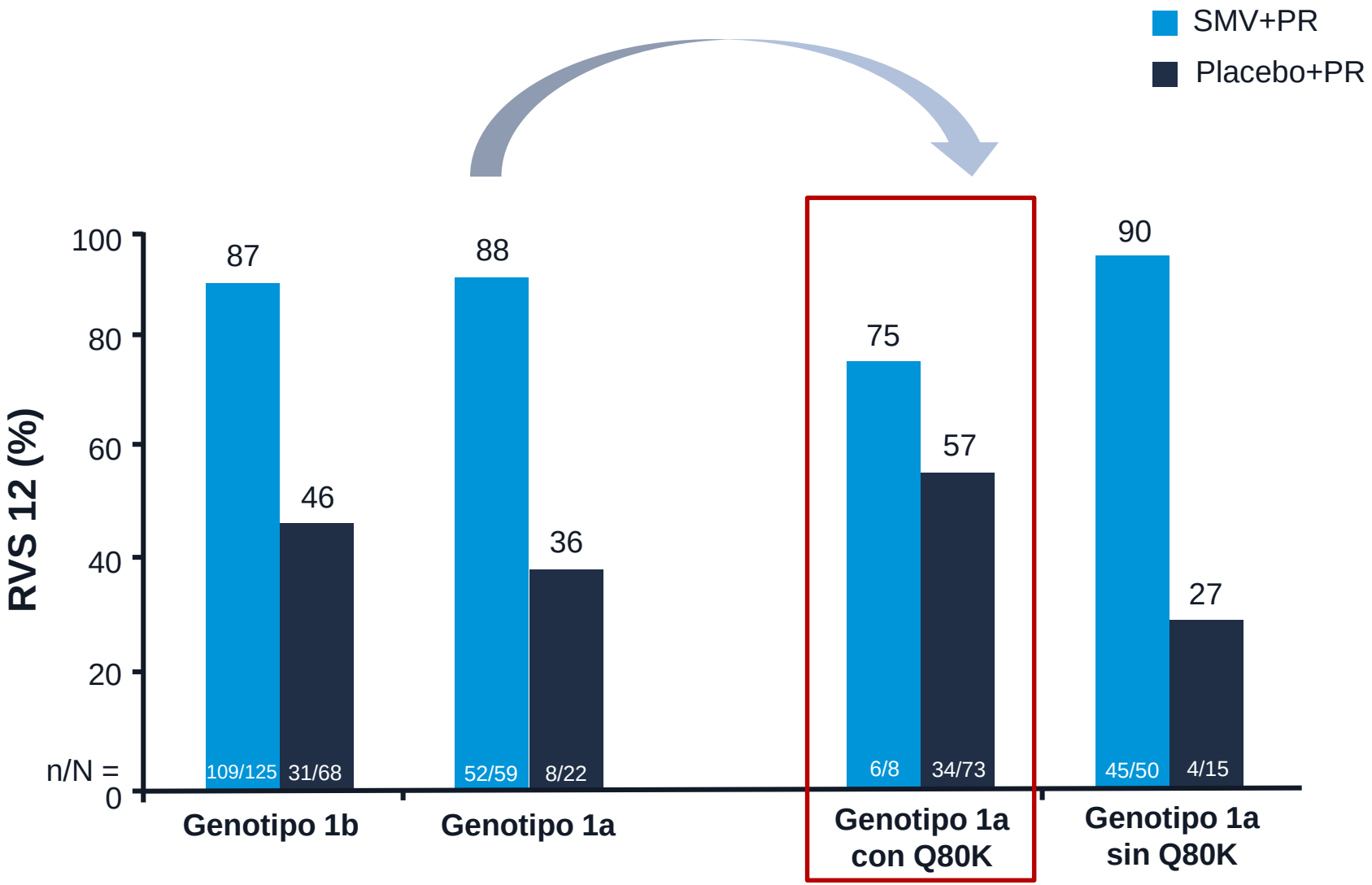
- Naives: 16%
- No respondedores: 31%
- Intolerantes a IFN: 47%

***Daclatasvir (DCV)**: inhibidor de NS5A*

***Asunaprevir (ASV)**: inhibidor de NS3*

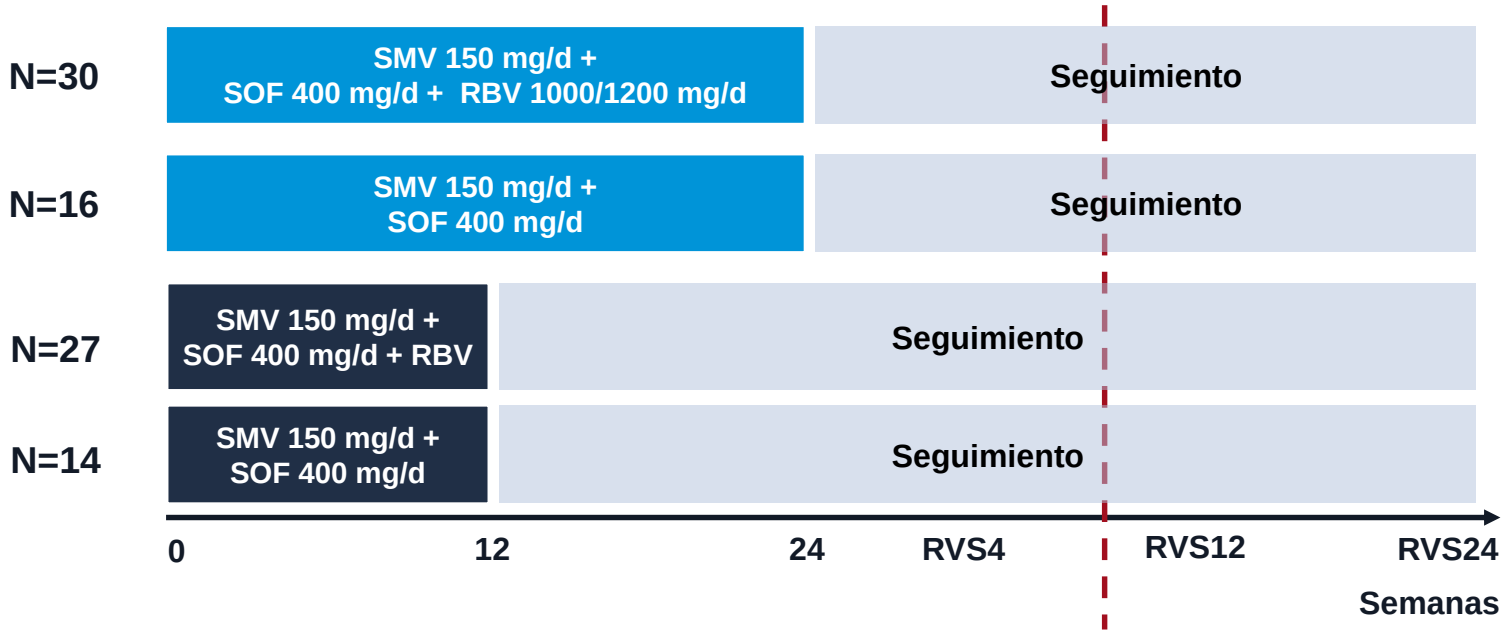
4.-Otros estudios (telegráfico) priorizando SOF, SMP y DCV...

PROMISE: Simeprevir + PegIFN + RBV en genotipo 1. Pacientes europeos recaedores a PegIFN+RBV



COSMOS: eficacia de la combinación de Simeprevir + Sofosbuvir en pacientes con fibrosis avanzada (fase II)

- Cohorte 2:
  - naive y null responders: 46/54%
  - F3-F4: 53/47%
- Aleatorización: 2:1:2:1

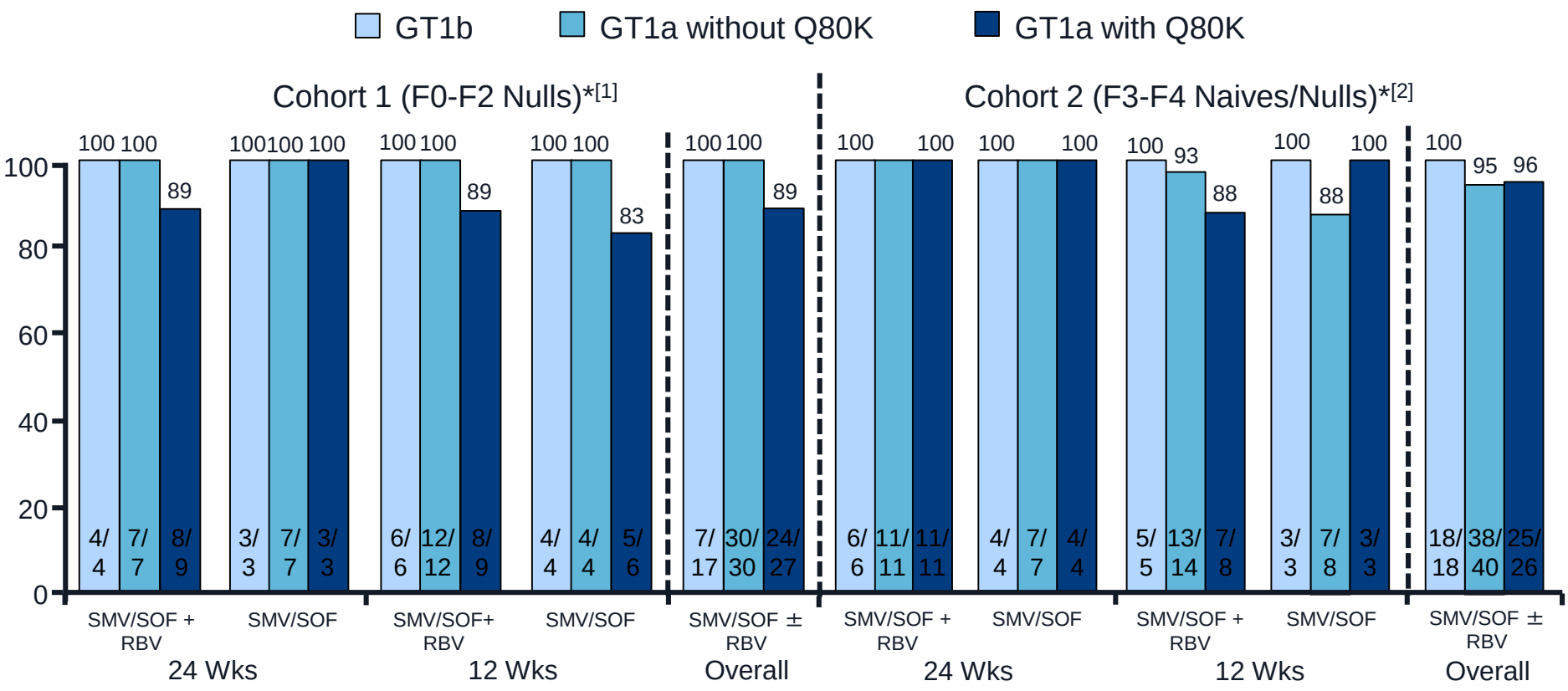


***Simeprevir (SMV)**: inhibidor de NS3/4A*

***Sofosbuvir (SOF)**: inhibidor de NS5B*

1. Sulkowski M, et al. EASL 2014. Abstract O7. 2. Lawitz E, et al. EASL 2014. Abstract O165.

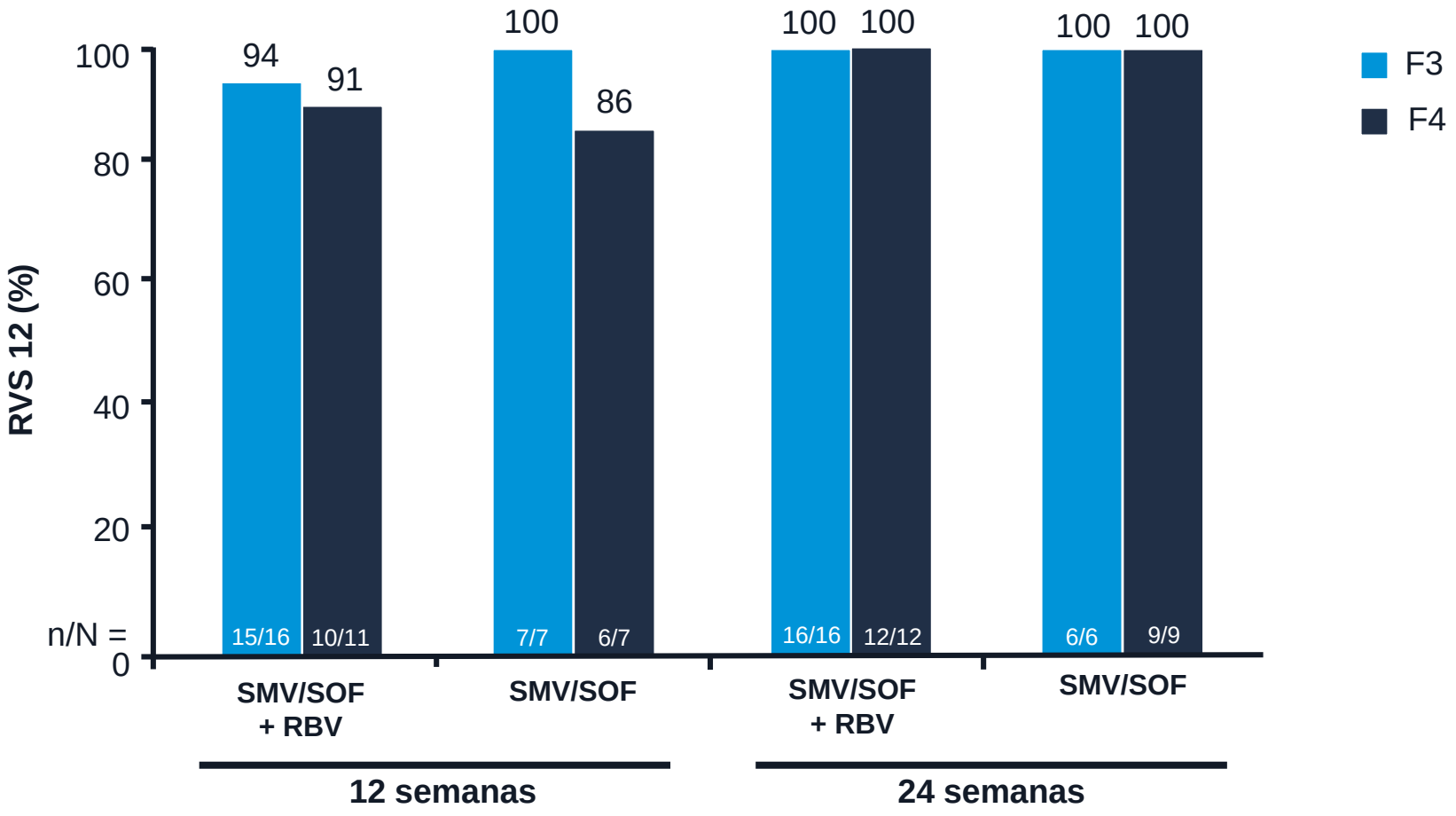
COSMOS: SVR12 in Cohorts 1 and 2 by HCV Subgenotype and Baseline Q80K



*Excluding patients who discontinued for nonvirologic reasons.

1. Sulkowski M, et al. EASL 2014. Abstract O7. 2. Lawitz E, et al. EASL 2014. Abstract O165.

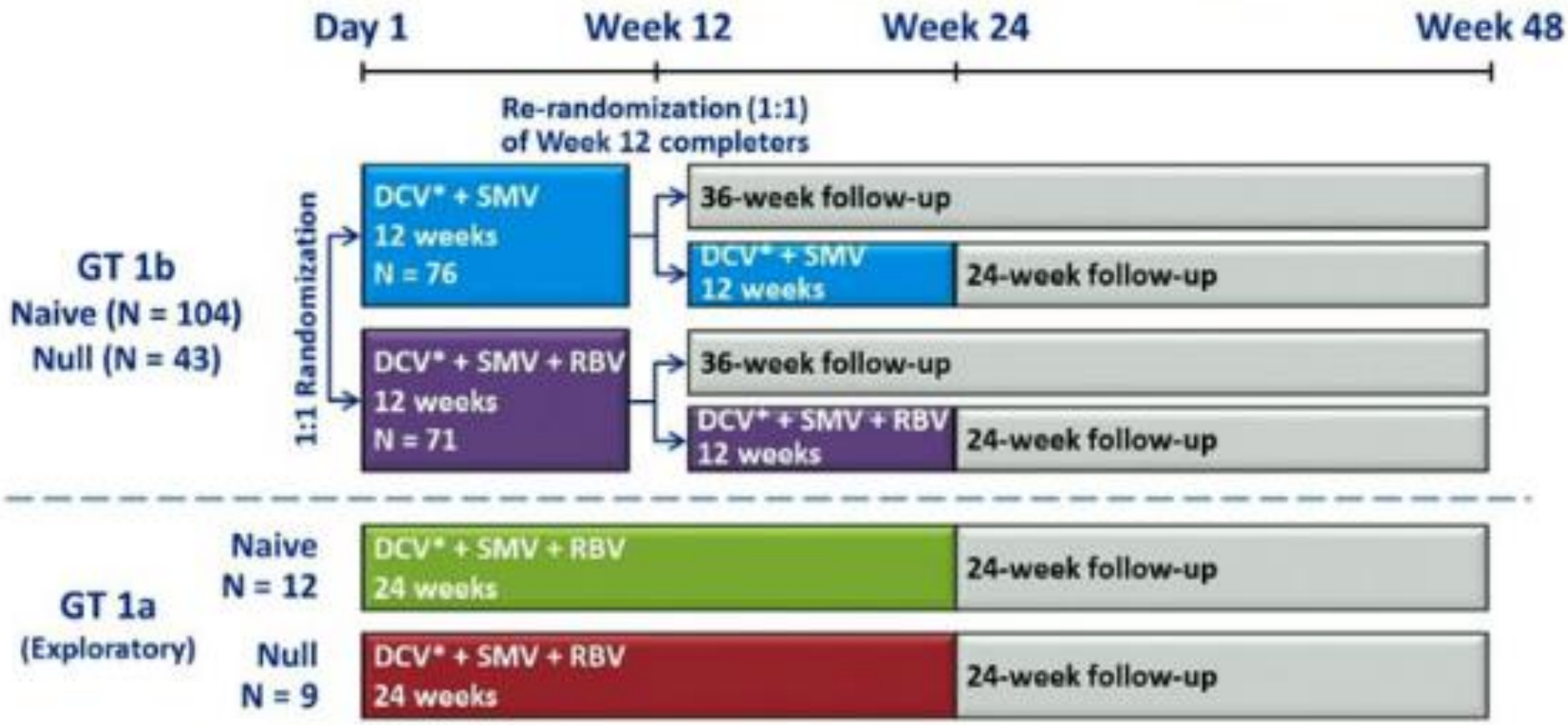
COSMOS: es necesario establecer la duración óptima del tratamiento en pacientes con cirrosis hepática



- **3 recaídas en pacientes tratados 12 semanas**

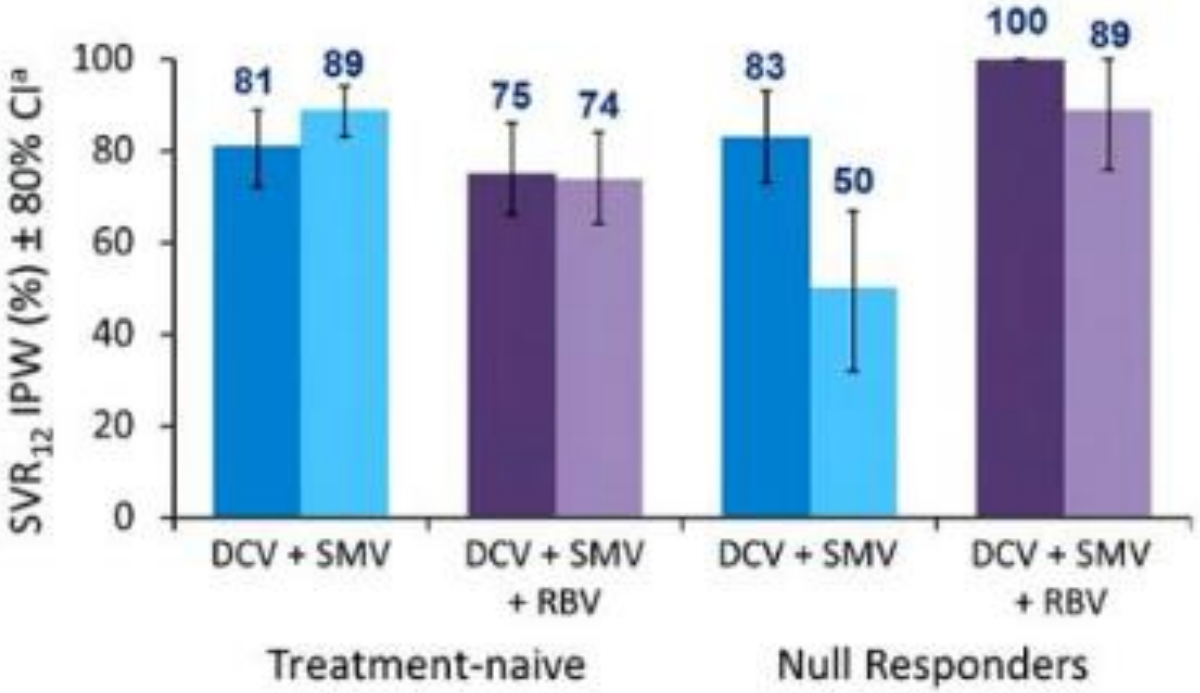
1. Sulkowski M, et al. EASL 2014. Abstract O7. 2. Lawitz E, et al. EASL 2014. Abstract O165.

LEAGUE-1 (AI444-062)
Randomized, Open-label, Phase 2 Study



- *DCV 30 mg QD (low dose) + SMV 150 mg QD ± weight-based RBV
  - DCV dose selection - PK data in healthy volunteers showing 2-fold increase in DCV (60 mg) exposure when dosed in combination with SMV (150 mg)
  - In this study, DCV exposure due to co-administration with SMV was less than anticipated

SVR_{12} by Treatment Duration: GT 1b



[a]SVR_{12} IPW (inverse probability weighting) estimates SVR_{12} to account for patients who discontinued prior to Week 12 and were not re-randomized

SVR_{12} – Week 12 Completers

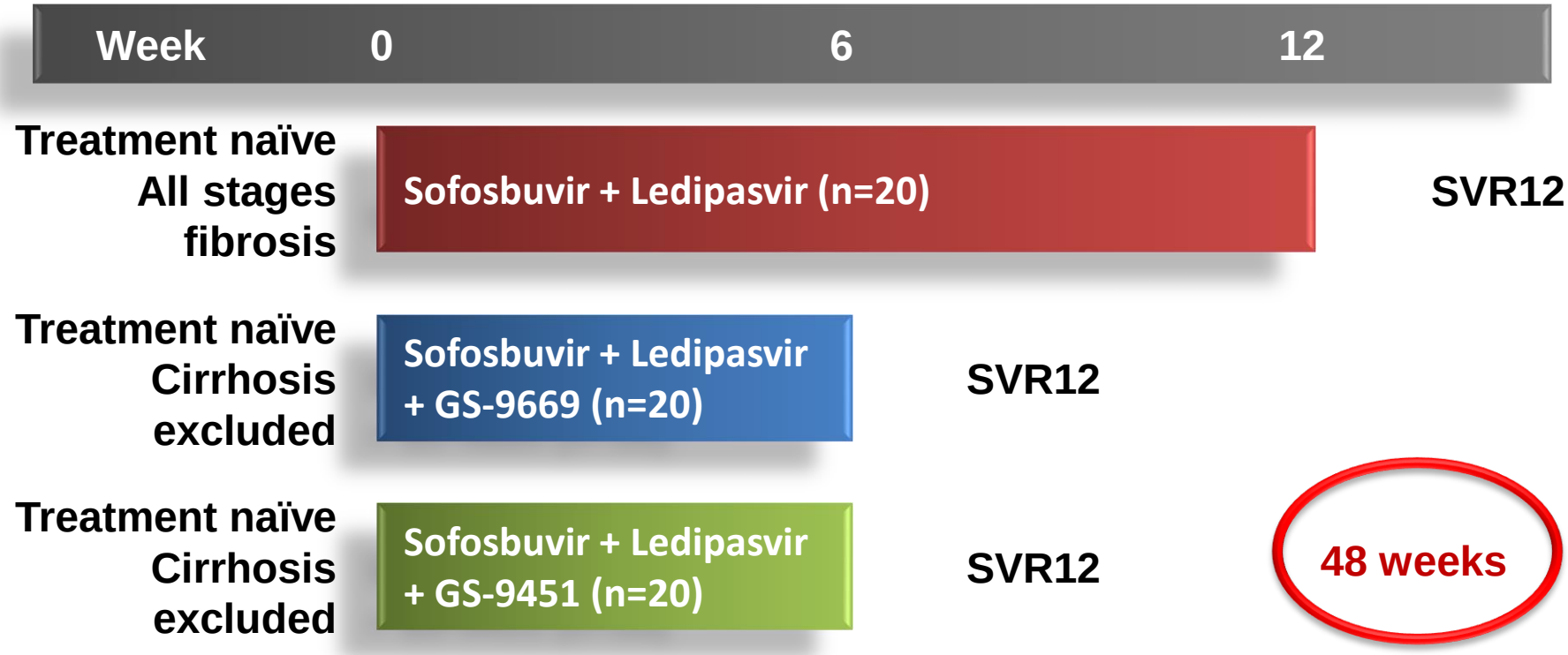
Includes patients who completed Week 12 and were re-randomized

n/N (%)	DCV + SMV		DCV + SMV + RBV	
	12 weeks	24 weeks	12 weeks	24 weeks
Treatment-naive	20/22 (91)	24/24 (100)	20/23 (87)	18/21 (86)
Null responder	9/9 (100)	6/10 (60)	11/11 (100)	8/9 (89)

Zeuzem et al. CROI 2014.

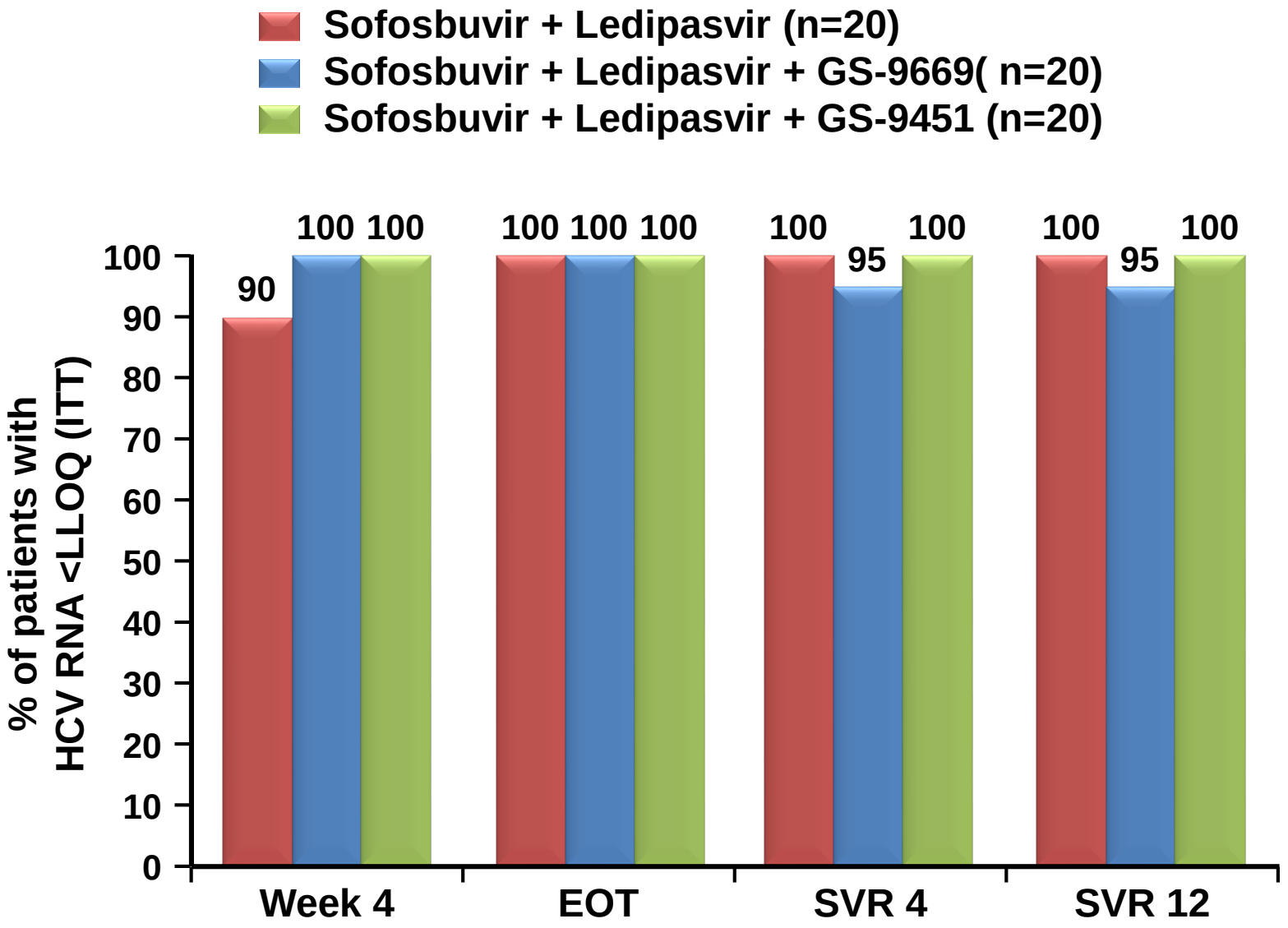
Synergy Trial. Study Design

- 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



Kohli A, et al. CROI 2014. Abstract 27LB

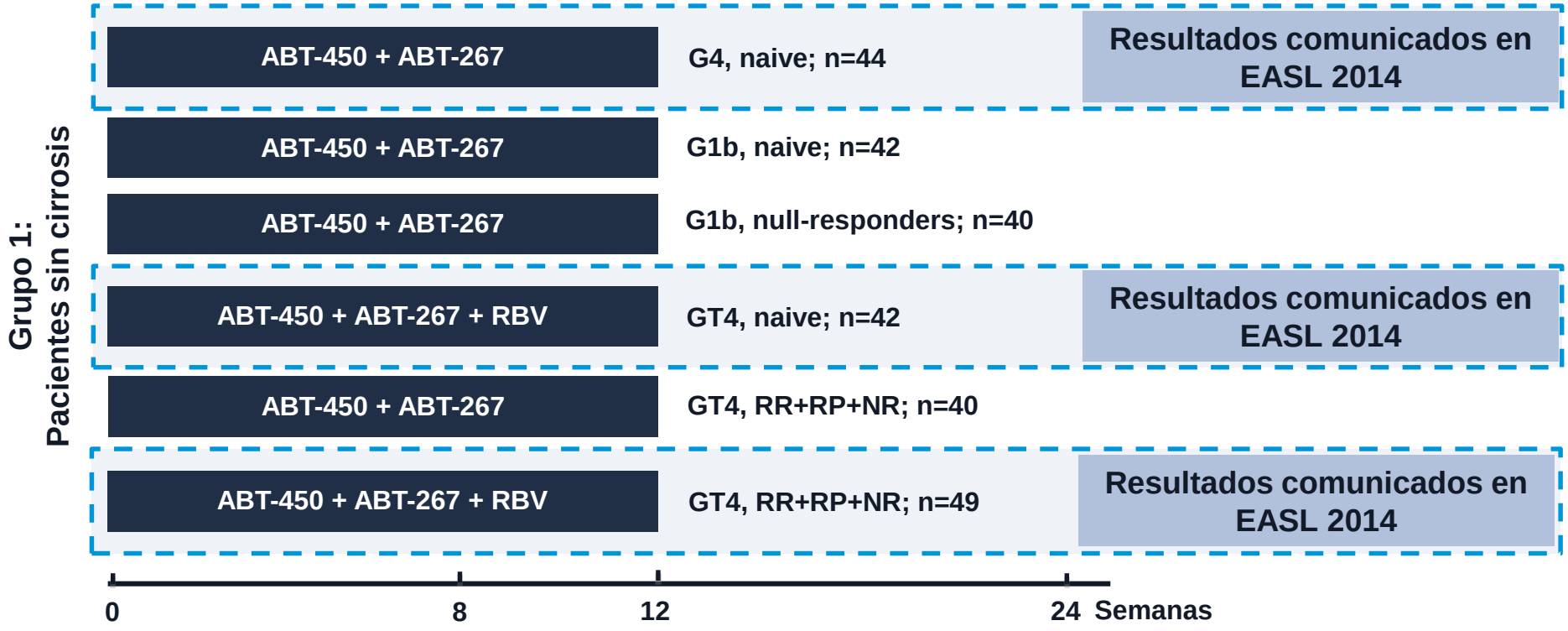
Synergy Trial. Treatment Response (ITT)



Kohli A, et al. CROI 2014. Abstract 27LB.

PEARL 1: eficacia de la combinación de ABT-450/r + ombitasvir con/sin ribavirina en genotipo 4 (fase IIb)

- No incluye pacientes con cirrosis
- Resultados preliminares: RVS12 en genotipo 4 naive y RVS4 en no respondedores

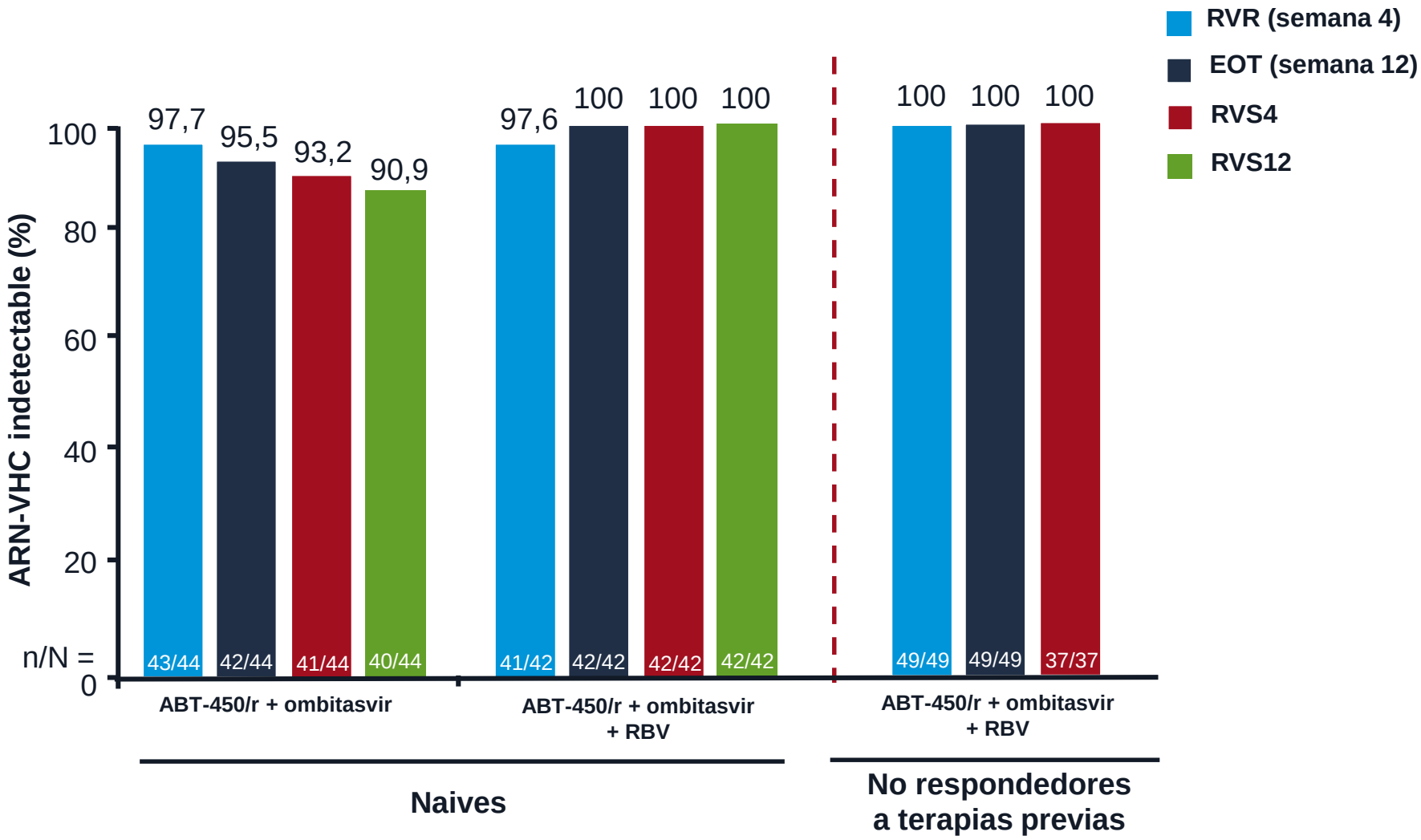


***ABT-450**: inhibidor NS3/4A*

***Ombitasvir (ABT-267)**: inhibidor NS5A*

PEARL 1: Eficacia de la combinación de ABT-450/r + ombitasvir con/sin ribavirina en genotipo 4 (fase IIb)

- Mejores resultados con ribavirina:

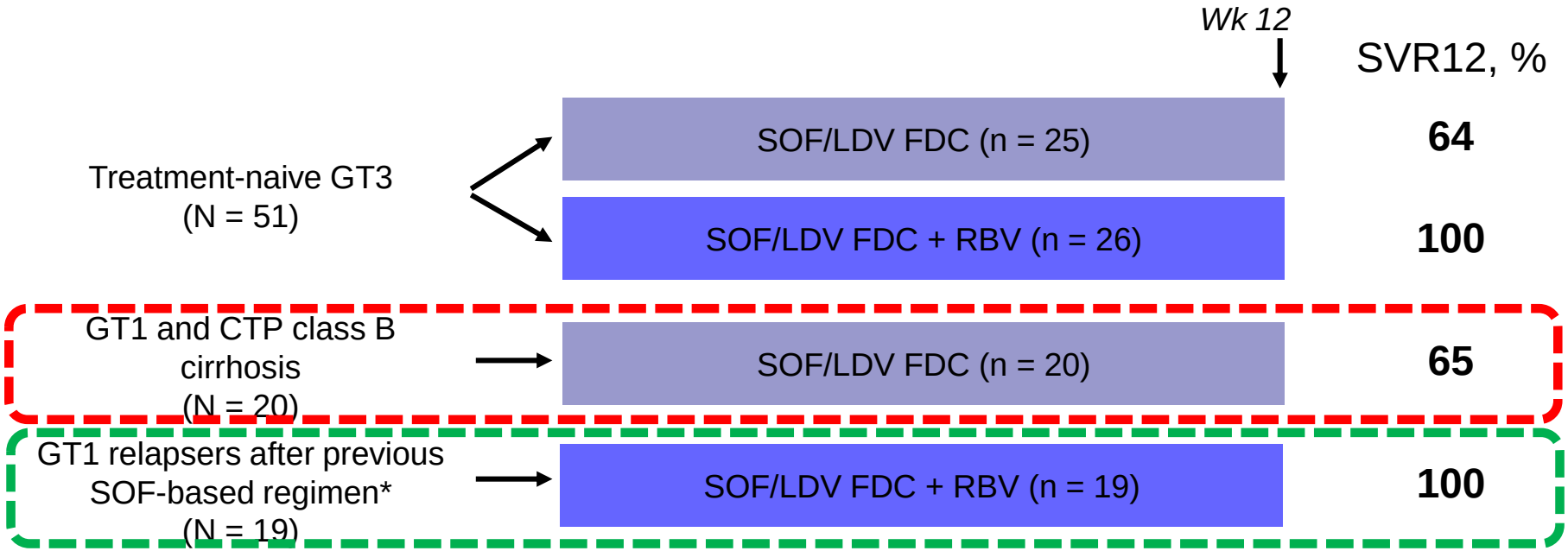


Hezode C. et al. EASL 2014, Londres 10-12 Abril #58A

5.-Ttos en Cirrosis Avanzada, Trasplante y Retratamientos...

ELECTRON 2: SOF/LDV FDC ± RBV in Diverse Hard-to-Treat Patients

- Partially randomized, open-label phase II trial



Sofosbuvir/ledipasvir 400/90 mg FDC tablet once daily; weight-based RBV 1000-1200 mg/day.

*Includes 10 patients who received SOF + RBV for 12 wks, 8 patients who received SOF/LDV + RBV for 6 wks, and 1 patient who received SOF + GS-9669 (NN NS5B) + RBV for 12 wks.

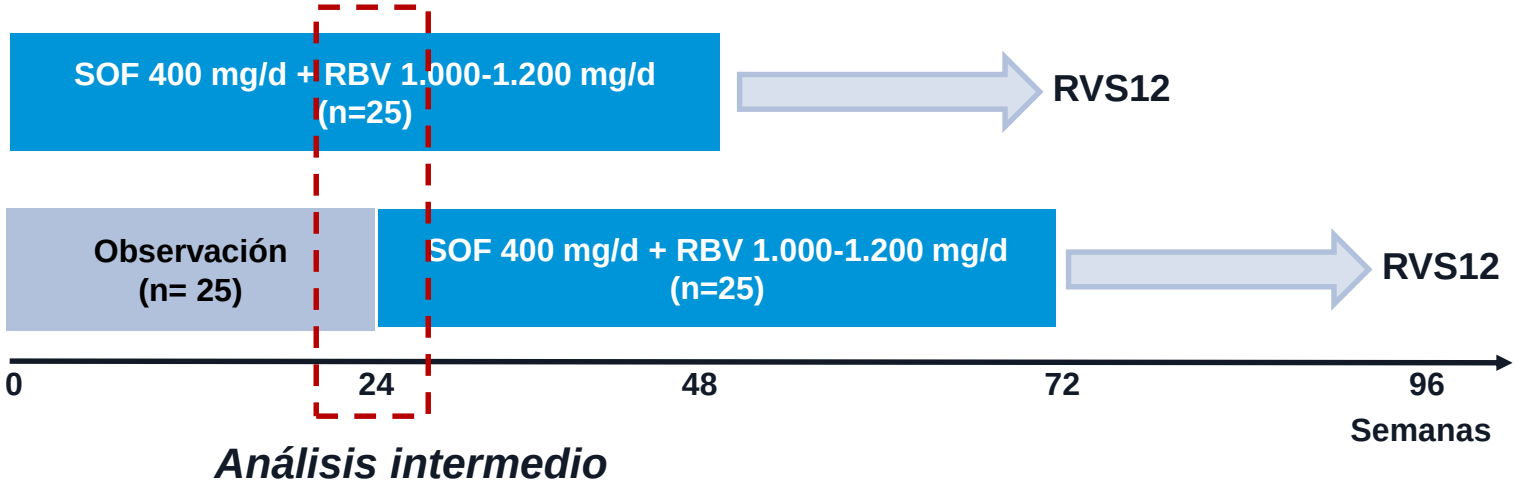
Gane EJ, et al. EASL 2014. Abstract O6.

ELECTRON-2: Sofosbuvir + Ledipasvir en pacientes con genotipo 1 y cirrosis descompensada Child-Pugh B

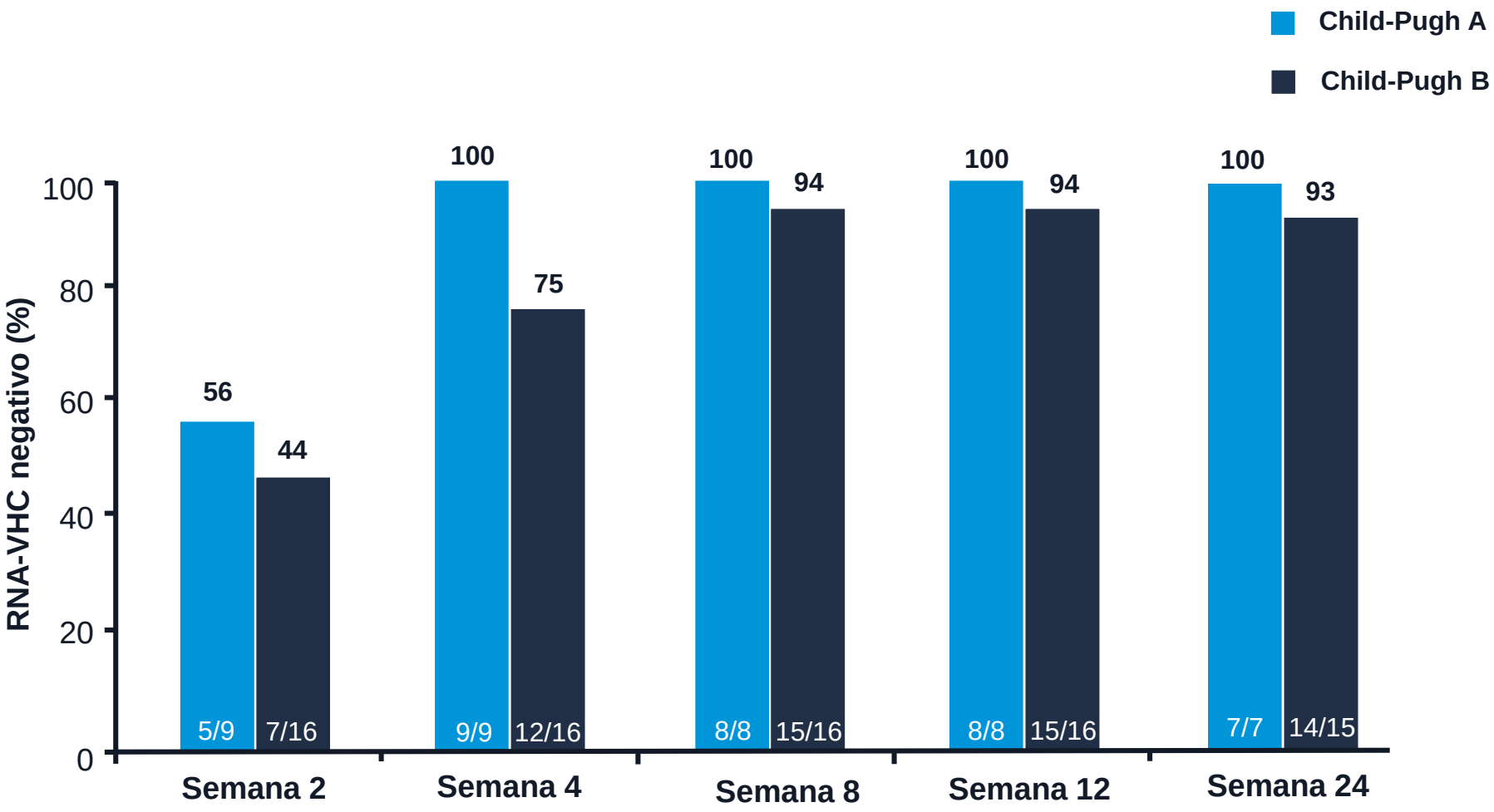
- **Objetivo**: evaluar la eficacia y seguridad de SOF/LDV x 12 semanas en 20 pacientes con cirrosis descompensada (Child-Pugh B).
- **Características basales**:
  - Ascitis: 20%
  - Encefalopatía hepática: 30%
  - Bilirrubina total (md, rango): 1,5 (0,7-3,7)
  - Albúmina (md, rango): 3,1 (2,3-3,8)
  - INR (md, rango): 1,2 (1,0-3,0)
- **Eficacia**:
  - **RVS12: 13 de 20 pacientes (65%)**
  - Tipo de no respuesta: 7 recaídas (35%)
- **Seguridad**:
  - Efectos adversos graves: 2/20 (10%)
  - Interrupción del tratamiento por efectos adversos: 0/20
  - Hemoglobina < 10 g/dL: 1/20 (5%)

Mejoría de la función hepática tras 24 semanas de Sofosbuvir + RBV en pacientes con cirrosis avanzada

- **Objetivo:** explorar la eficacia y seguridad de SOF + RBV en pacientes cirróticos con hipertensión portal: Child-Pugh 5-9 y varices esofágicas.
- Evaluación del gradiente de presión venosa hepática (GPVH) a las semanas: 0, 24 y 72.
- **Características basales:**
  - GPVH > 12 mmHg en el 78%
  - Child-Pugh 7-10: 60%
  - MELD: < 10 en 32%, 10-15 en 58%, > 15 en 10%
  - Ascitis: 30%



Sofosbuvir + RBV en pacientes con cirrosis avanzada: respuesta virológica intra-tratamiento

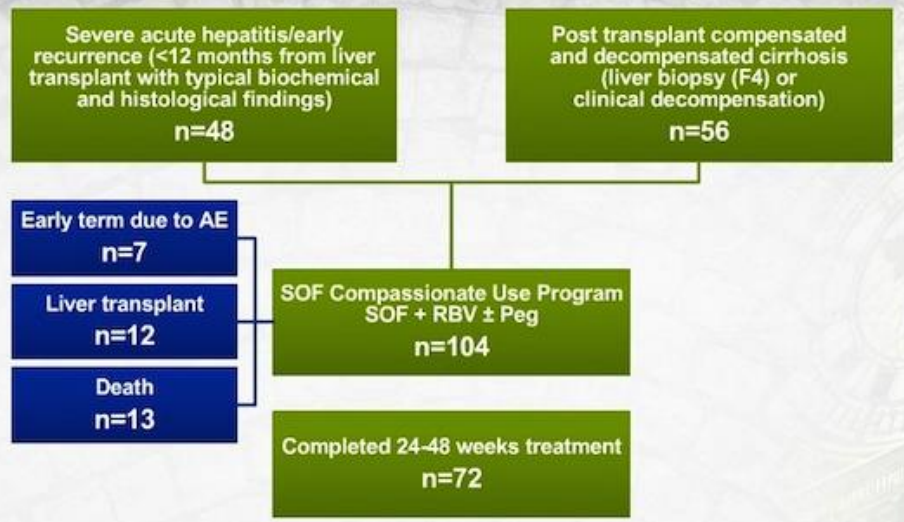


Sofosbuvir + RBV en pacientes con cirrosis avanzada: reducción de eventos clínicos y seguridad

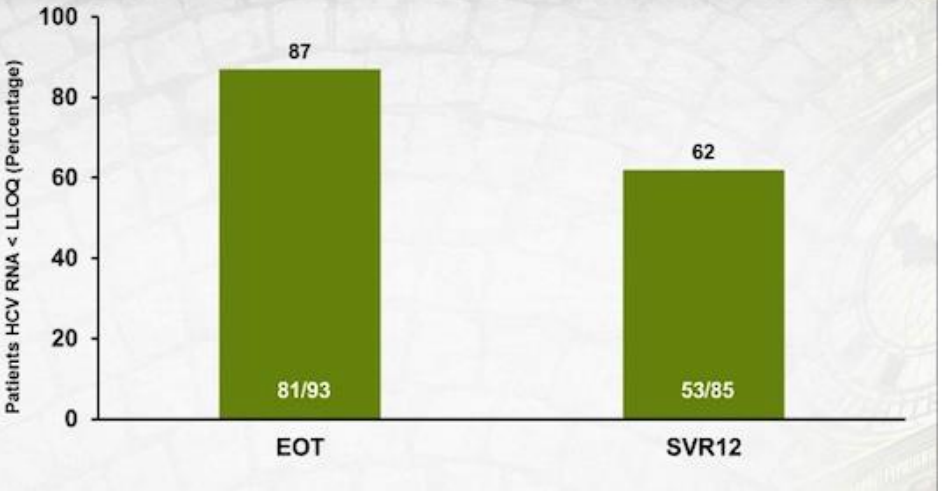
	Ascitis		Encefalopatía	
Pacientes (n)	SOF+RBV (n= 25)	Observación (n= 25)	SOF + RBV (n= 25)	Observación (n= 25)
Basal	6	9	5	2
Semana 12	5	8	3	3
Semana 24	0	7	0	4

- **Perfil de seguridad:**
  - Mayor incidencia de náuseas (32%), astenia (24%), prurito (24%), rash (16%), insomnio (16%).
  - Efectos adversos graves: 16% en ambos grupos (SOF+RBV vs. observación).
  - Interrupción del tratamiento por efectos adversos: 4% vs. 0% (1 paciente con SOF + RBV).

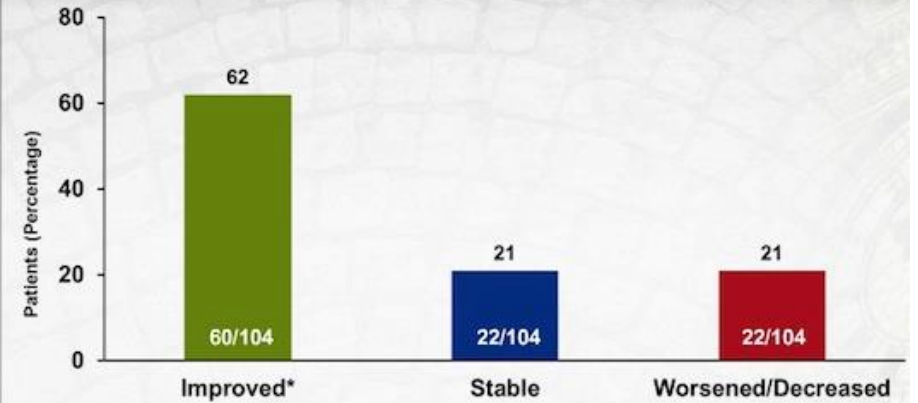
SOF Compassionate Use Program Results: Patient Disposition



Results: Overall Virologic Response

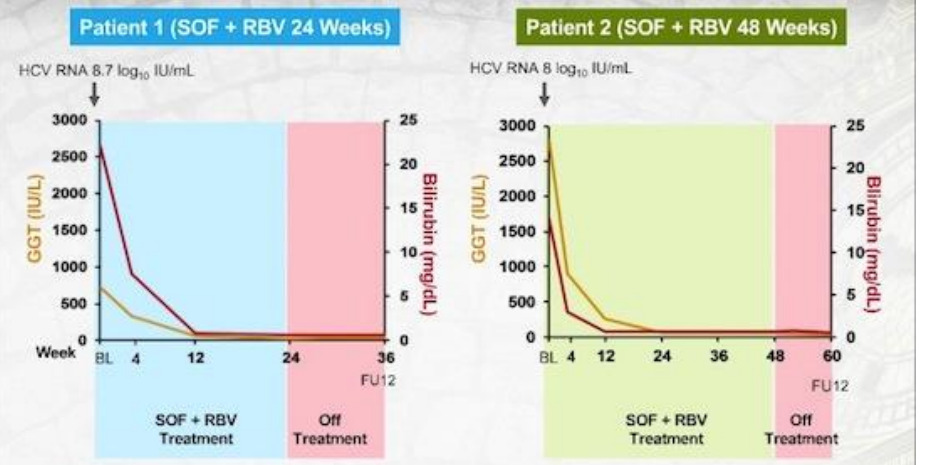


Results: Clinical Outcomes



- All patients who received ≥1 dose of SOF are included

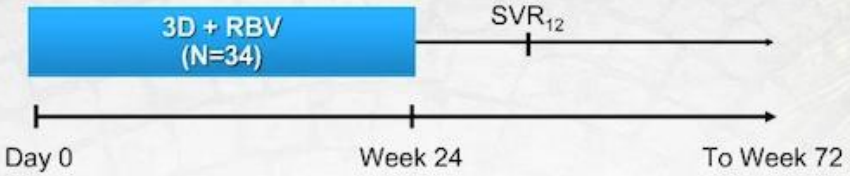
Clinical Cases: Fibrosing Cholestatic Hepatitis (2 Patients with FCH)



- Viral load undetectable by Week 4 (Patient 1) and Week 12 (Patient 2) resulting in SVR_{12}

Forns X, et al. 49 th EASL 2014 Abstract O62.

Study M12-999: Design

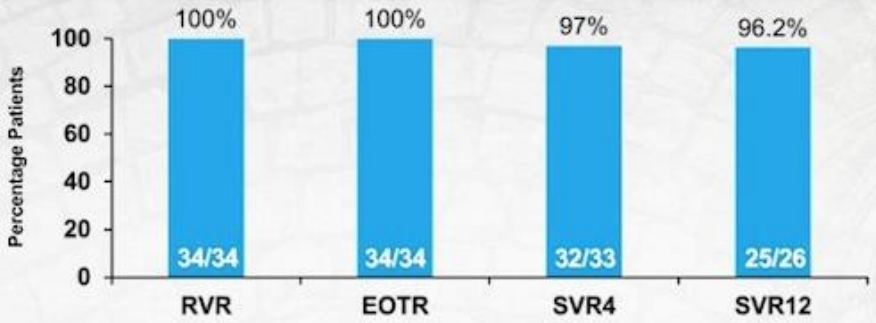


- 3D: co-formulated ABT-450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID
- RBV: dosing was managed at the discretion of the investigator and closely monitored per protocol

Study M12-999: Calcineurin Inhibitor (CNI) Dosing with 3D Regimen

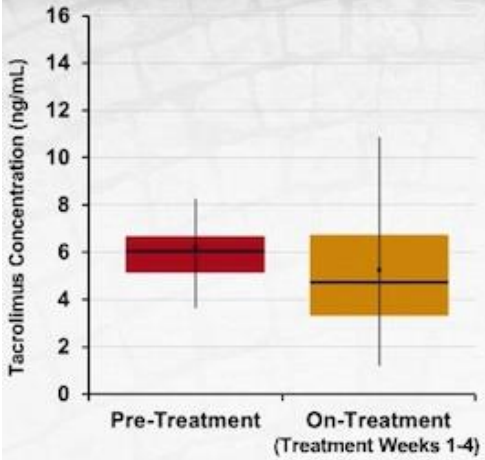
- A phase 1 drug-drug interaction study demonstrated that dosing tacrolimus (TAC) or cyclosporine (CYA) with the 3D regimen compared to either alone resulted in a:
  - 7-fold increase in TAC half-life
  - 3-fold increase in CYA half-life
- Based on these findings, recommended dosing during 3D treatment was:
  - TAC
    - 0.5 mg once weekly or
    - 0.2 mg every 3 days
  - CYA
    - 1/5 of the daily pre-3D treatment dose given once daily

Study M12-999: Preliminary Efficacy Results



- No patient had breakthrough
- One patient had a relapse (post-treatment day 3)
  - At the time of relapse, this patient had R155K in NS3 protease, M28T+Q30R in NS5A, and G554S+G557R in NS5B, none of which were present at baseline

Study M12-999: Pre-Treatment and On-Treatment Tacrolimus C_{trough} Concentrations



- C_{trough} levels were comparable pre-treatment and on-treatment
- TAC dose was 0.5 to 1.0 mg at 1-2 week intervals for most patients
- 4 patients experienced a TAC level >15 ng/mL (15.7-34.0 ng/mL)
  - All 4 patients had TAC dosing errors
  - 2 patients had associated creatinine increases (1.8 and 1.4 mg/dL), which normalized when dosing was corrected

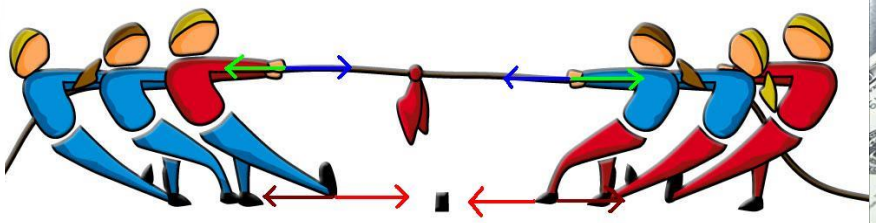
Kwo P, et al. 49 th EASL 2014 Abstract O114.

Conclusiones....

Conclusiones Monoinfección VHC

- **Nuevos fármacos**: **Impresionante eficacia** y **tolerancia**.
  - Datos incontestables de múltiples ensayos clínicos fase III (publicados en NEJM).
  - Posible ttos triples ultracortos de 6-8 S con similar eficacia que dobles a 12 S**.**
  - En cirróticos en general parece que mejor 24 S y también mejor + RBV.
  - En Null responders (+++ tto triple previo) quizás también mejor + RBV y 12-24 S depende de DAA utilizados.
  - Posibilidad de tto en cirrosis descompensadas (child B) con buena tolerancia, aceptables datos preliminares de RVS y disminución clara de complicaciones.
  - Datos acumulativos muy buenos también en trasplantados y pocas interacciones con los inmunosupresores.

Hoy se impone la variable coste-eficacia…



Pero cuando hablamos de curación es difícil que algo no sea coste-eficaz…