CONTROVERSIAS EN VHC

Dra. Soledad López Calvo (C.H.U. A Coruña)

VIII Curso Avances en Infección VIH y Hepatitis Virales
Vigo, 1 de Febrero 2014

Lead-in

Pregunta 1

Enfermos monoinfectados con respuesta nula a un tratamiento previo con peg-interferón + ribavirina o en los que se ignora la respuesta a tratamientos previos

Enfermos con fibrosis significativa (≥ F2 ó >7.6 kilopascals)

Antes de iniciar tratamiento se recomienda la valoración de la repuesta tras cuatro semanas de biterapia con interferón pegilado y ribavirina a dosis estándar. Debe considerarse el riesgo de una "monoterapia funcional" en pacientes que no presenten al menos una disminución de 1 log10 en RNA VHC en la semana 4 de biterapia con interferón pegilado y ribavirina.

Si ha habido respuesta añadir un inhibidor de la proteasa (tratamiento triple) y mantener el tratamiento durante 48 semanas.

Si no ha habido respuesta, es decir no ha bajado el RNA del VHC por lo menos 1 log10 a las 4 semanas, se recomienda suspender el tratamiento interferón pegilado y ribavirina, y no iniciar tratamiento con triple terapia.

Sensibilidad al Interferón

En pacientes pretratados y no respondedores puede existir una respuesta alterada al Interferón.

Al menos algún grado de sensibilidad al IFN es necesaria para conseguir una Respuesta Viral Sostenida.

Aquellos pacientes que son insensibles al IFN tienen riesgo de desarrollar cepas resistentes a los Inhibidores de Proteasa durante el tratamiento

Asselah T, et al. Gut 2008; 57: 516–24, Susser S, et al. Hepatology 2009; 50: 1709–18, Susser S, et al. J Clin Virol 2011; 52: 321–7

.

Main Findings

- SVR rates significantly higher with boceprevir-containing regimens vs pegIFN/RBV control ($P < .001$) regardless of previous response
  - SVR rates with boceprevir-containing regimens higher among previous relapsers vs nonresponders

SVR, %	BPR RGT (n = 162)	B44PR48 (n = 161)	PR48 (n = 80)
Overall	59*	66*	21
Response to pegIFN/RBV lead-in			
▪ HCV RNA decrease < 1 $\log_{10}$ IU/mL	33	34	0
▪ HCV RNA decrease ≥ 1 $\log_{10}$ IU/mL	73	79	25

*$P < .001$ vs PR48 control arm.

Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

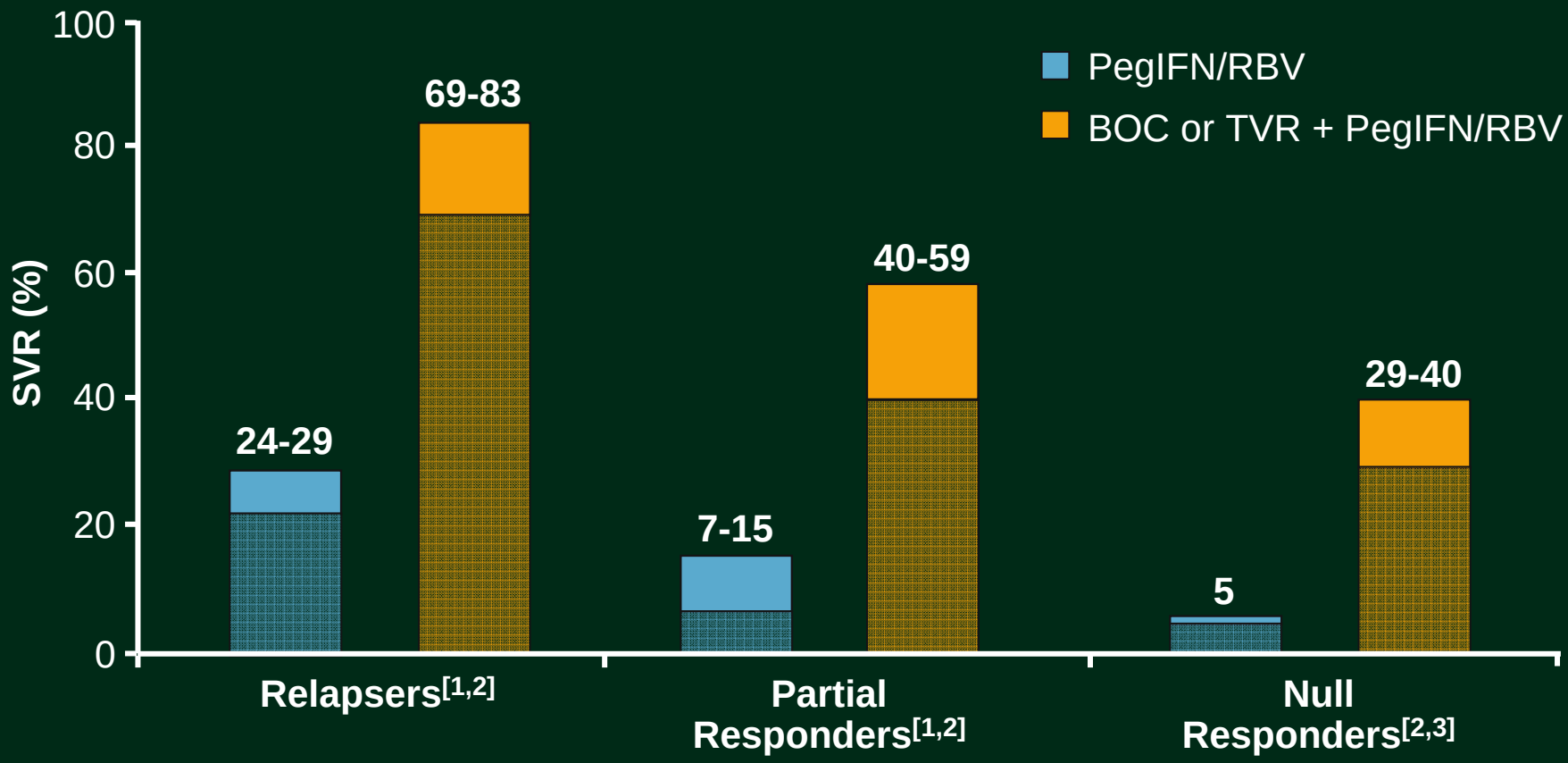
Razones para hacer Lead in

- Paciente “null responder”o sin documentar respuesta previa→Documento consenso AEMPS
- Valorar probabilidades de RVS.
- Valorar posibles efectos secundarios.
- Información valiosa para médico y paciente
- Si uso Boceprevir.→Estudios de registro.

Boceprevir

Pregunta 2

A Major Advance: GT1 Treatment Failures



1. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 2. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 3. Bronowicki JP, et al. EASL 2012. Abstract 11.

Main Findings

- SVR rates significantly higher with boceprevir-containing regimens vs pegIFN/RBV control ($P < .001$) regardless of previous response
  - SVR rates with boceprevir-containing regimens higher among previous relapsers vs nonresponders

SVR, %	BPR RGT (n = 162)	B44PR48 (n = 161)	PR48 (n = 80)
Overall	59*	66*	21
Previous response			
▪ Previous nonresponder	40	52	7
▪ Previous relapse	69	75	29
Response to pegIFN/RBV lead-in			
▪ HCV RNA decrease < 1 $\log_{10}$ IU/mL	33	34	0
▪ HCV RNA decrease ≥ 1 $\log_{10}$ IU/mL	73	79	25

*$P < .001$ vs PR48 control arm.

Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

Main Findings

- SVR rates numerically higher with boceprevir-containing regimens vs pegIFN/RBV control across all subgroups analyzed
  - Higher SVR rates attained with boceprevir in many difficult-to-treat populations

SVR, %	BPR RGT	B44PR48	PR48
Race			
▪ Nonblack	58 (84/144)	68 (97/142)	24 (16/68)
▪ Black	61 (11/18)	53 (10/19)	8 (1/12)
HCV subtype			
▪ 1a	50 (37/74)	61 (47/77)	24 (9/38)
▪ 1b	65 (49/75)	73 (49/67)	22 (8/36)
HCV RNA			
▪ ≤ 800,000 IU/mL	80 (12/15)	80 (16/20)	40 (6/15)
▪ > 800,000 IU/mL	56 (83/147)	65 (91/141)	17 (11/65)
Liver histology, %			
▪ No/minimal/portal fibrosis	66 (77/117)	68 (81/119)	23 (14/61)
▪ Bridging fibrosis/cirrhosis	44 (14/32)	68 (21/31)	13 (2/15)
▪ Cirrhosis	35 (6/17)	77 (17/22)	0 (0/10)

Bacon BR, et al. N Engl J Med. 2011;364:1207-1217.

Estudio PROVID: Boceprevir en pretratados incluyendo null responders

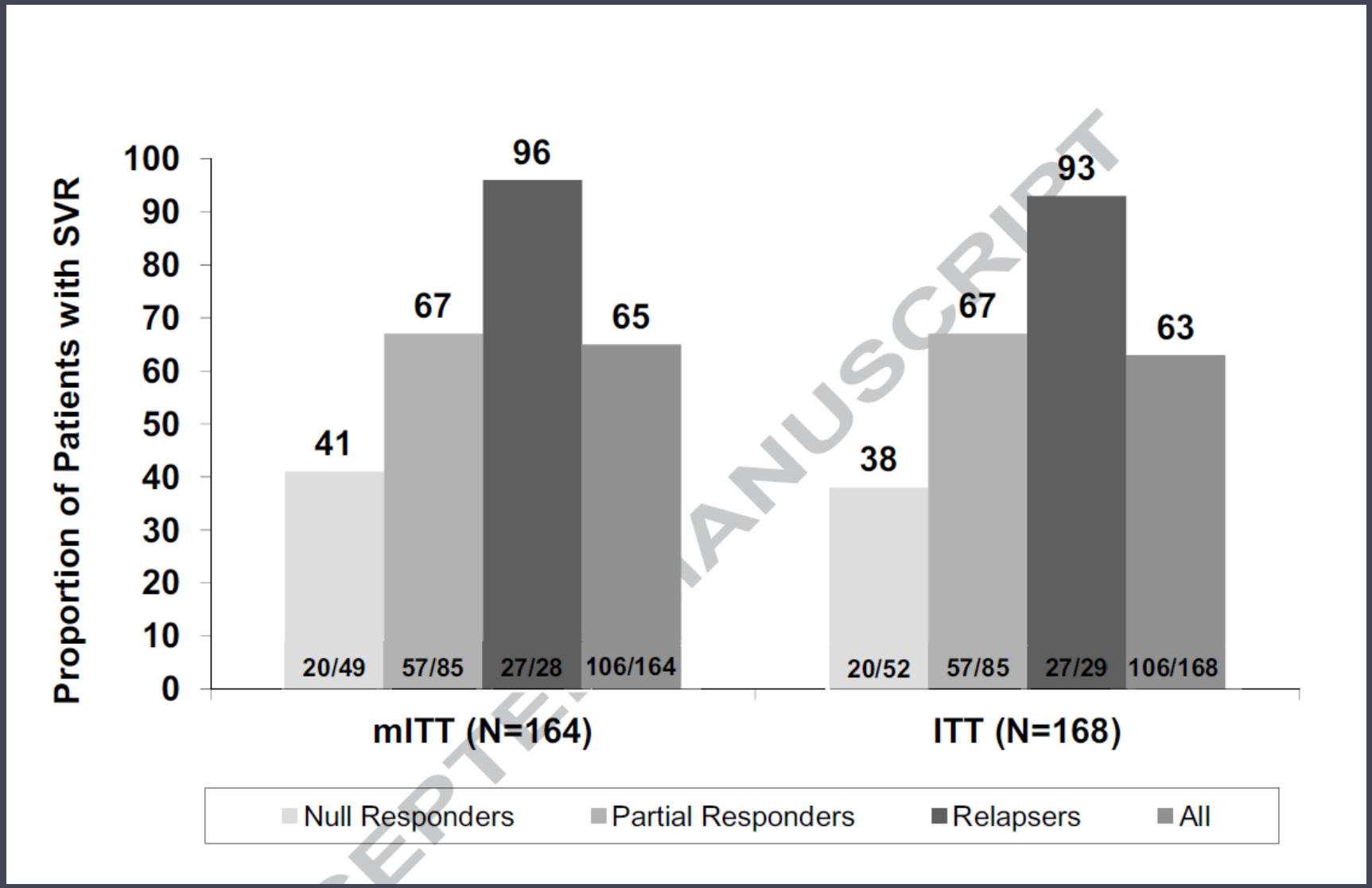
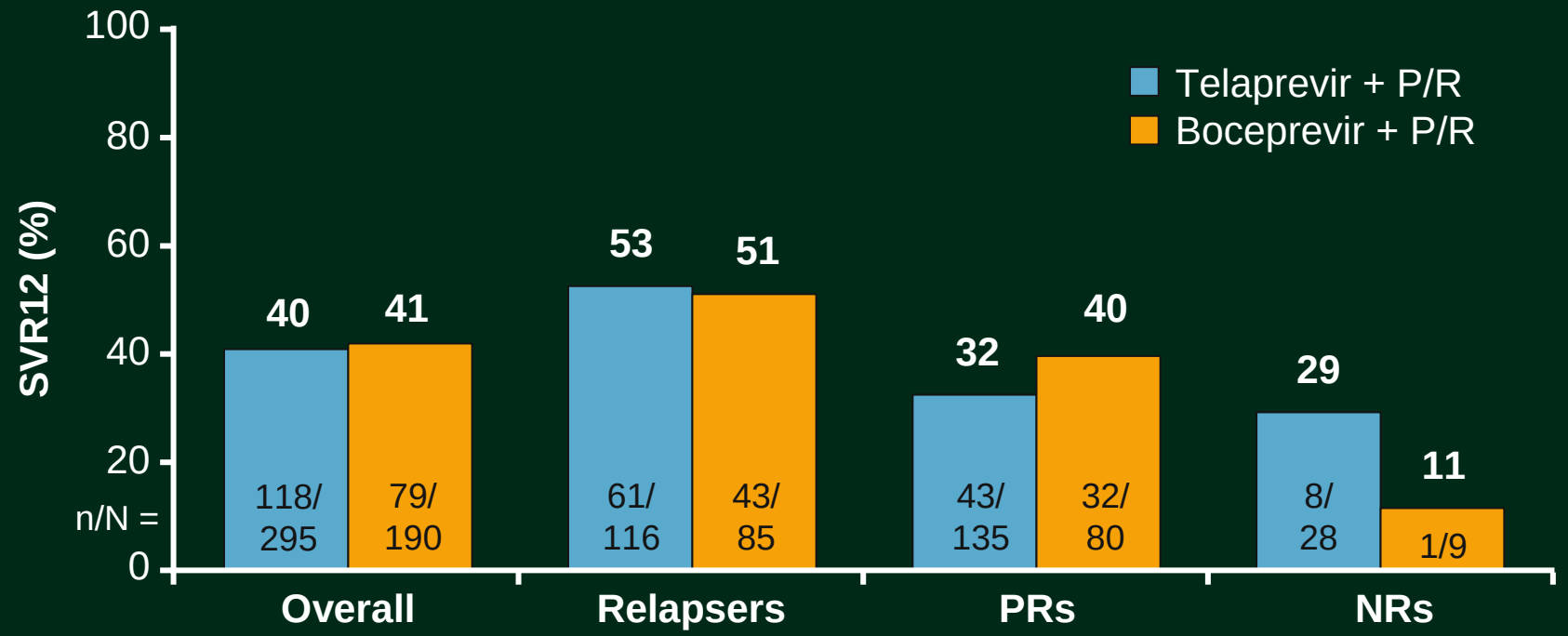


Table 2. Response rates observed with boceprevir and telaprevir

	Boceprevir* (%)	Telaprevir† (%)
Treatment naïve		
Overall SVR	70–71	75
Treatment naïve – SVR with RVR‡		
Treated for 24 weeks	96	89–92
Treated for 48 weeks	96	90
Treatment naïve – SVR with delayed virologic response	66–75	64
Treatment naïve patients achieving RVR	56	58–60
Retreat of previous non-responders (SVR)		
Prior relapse	69–75	84–88
Prior partial response	40–52	56–61
Prior null response	NA	31–33
Interferon sensitive by lead-in	73–79	NA
Interferon insensitive by lead-in	33–34	NA
SVR by IL28B genotype		
CC	90–79	80–82
CT	60–71	65–71
TT	61–73	55–59

CUPIC: Telaprevir or Boceprevir + P/R in GT1 Treatment-Experienced Cirrhotics



Risk of Death or Severe Complications, % (n/N)	Platelet Count > 100,000 cells/mm³	Platelet Count ≤ 100,000 cells/mm³
Albumin ≥ 35 g/L	3.4 (10/298)	4.3 (3/69)
Albumin < 35 g/L	7.1 (2/28)	44.1 (15/34)

Fontaine H, et al. EASL 2013. Abstract 60. Hezode C, et al. J Hepatol. 2013;59:434-441.

Efectos adversos de Telaprevir y Boceprevir

Table 2. Safety profile of triple therapy.

Events	TVR (n = 292)	BOC (n = 205)
Serious adverse event, n (%)	132 (45.2)*	67 (32.7)*
Premature discontinuation/due to SAEs, n (%)	66 (22.6)/43 (14.7)	54 (26.3)/15 (7.3)
Death, n (%)	5 (1.7)	1 (0.5)
Grade 3/4 infection, n (%)	19 (6.5)	5 (2.4)
Grade 3/4 hepatic decompensation, n (%)	6 (2.0)	6 (2.9)
Grade 3/4 asthenia, n (%)	16 (5.5)	12 (5.8)
Grade 3 rash/SCAR, n (%)	14 (4.8)/0	0/0
Renal failure (creatinine clearance <50 ml/min), n (%)	5 (1.7)	0
Anaemia, n (%)		
Grade 2: 8.0 to ≤9.0 g/dl	55 (18.8)	48 (23.4)
Grade 3/4: <8.0 g/dl	34 (11.6)	9 (4.4)
Erythropoietin use	157 (53.8)	95 (46.3)
Blood transfusion	47 (16.1)	13 (6.3)
RBV dose reduction or discontinuation	50 (17.1)	30 (14.6)
Neutropenia, n (%)		
Grade 3: 500 to <750/mm^3	6 (2.0)	2 (1.0)
Grade 4: <500/mm^3	2 (0.7)	7 (3.4)
Granulocyte-stimulating agent use	7 (2.4)	9 (4.4)
Thrombocytopenia, n (%)		
Grade 3: 20,000 to <50,000/mm^3	28 (9.6)	10 (4.9)
Grade 4: <20,000/mm^3	9 (3.1)	3 (1.5)
Thrombopoietin use	4 (1.4)	2 (1.0)
PegIFN dose reduction or discontinuation	89 (30.5)	71 (34.6)
COSTES (Tratamiento completo Euros)	31.400	29.037

IFN Peg+Sofosbuvir+RBV

Pregunta 3

Sofosbuvir + P/R for GT1 HCV: Approved Indications

- Sofosbuvir 400 mg/day with or without food, administered with P/R
- All GT1 patients receive same regimen, regardless of previous treatment history or fibrosis level

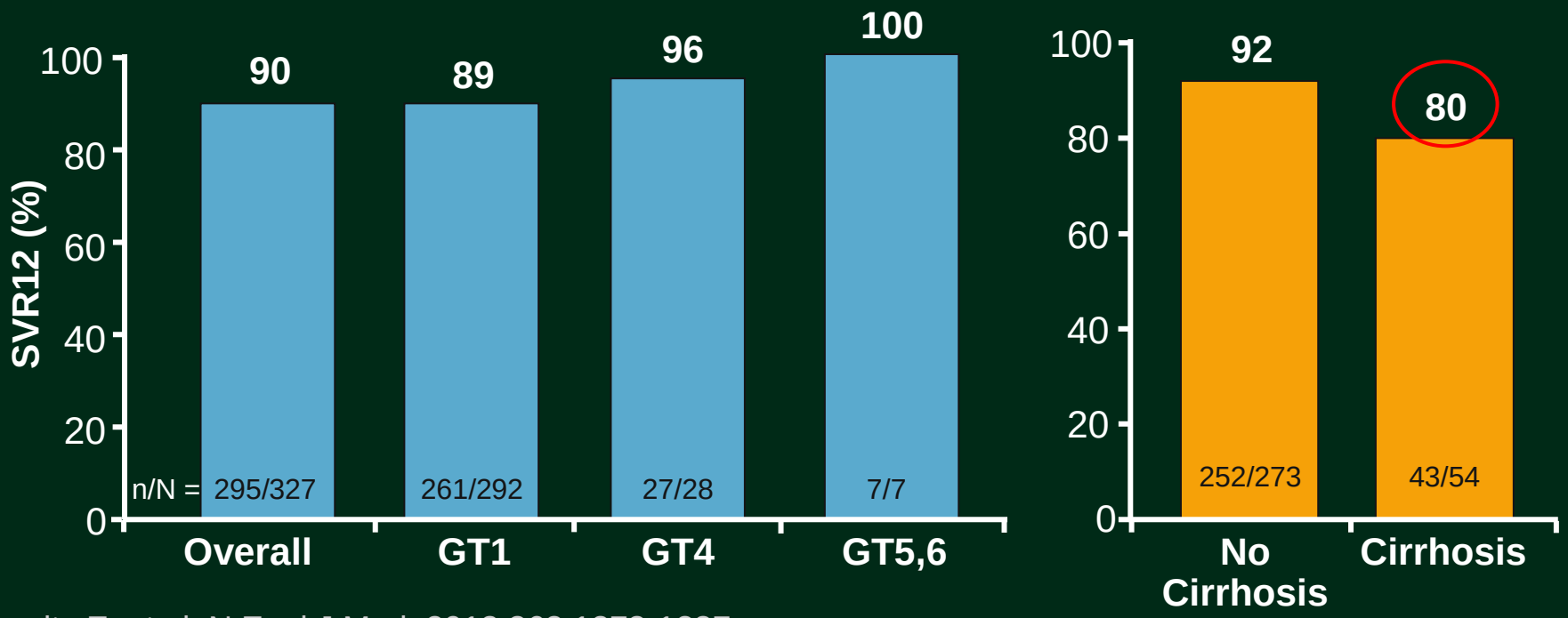
12 weeks

Sofosbuvir + P/R

Sofosbuvir [package insert]. December 2013.

NEUTRINO: Sofosbuvir + P/R for 12 Weeks in Treatment-Naive GT 1/4/5/6 HCV

- Open-label, single-arm study of sofosbuvir 400 mg QD + P/R for 12 weeks in treatment-naive patients with GT1/4/5/6 HCV
  - 17% cirrhosis; 89% GT1; 9% GT4; < 1% GT5; 2% GT6



Lawitz E, et al. N Engl J Med. 2013;368:1878-1887.

NEUTRINO: Resistencias

- All cases of virologic failure due to relapse
- Sequencing performed in all 28 patients with relapse and 1 additional patient who discontinued therapy with HCV RNA > 1000 IU/mL
  - No S282T mutations identified by population sequencing or deep sequencing
  - Other NS5B genetic variants not associated with any change in phenotypic susceptibility to sofosbuvir or ribavirin

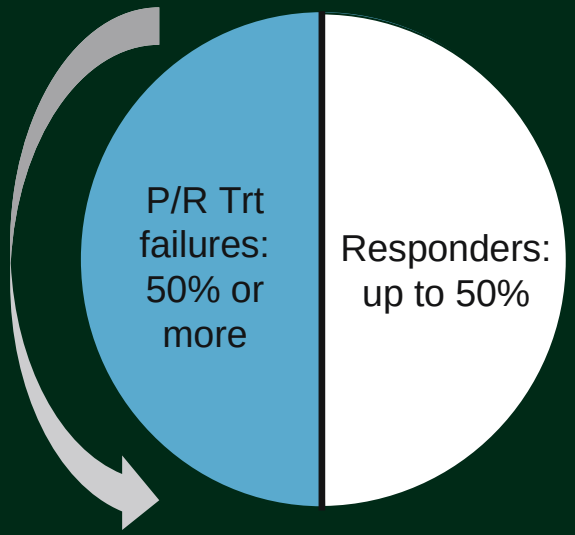
NEUTRINO: Efectos secundarios

- Regimen generally well tolerated
  - Low overall rates of grade 3/4 AEs, serious AEs, and treatment discontinuation due to AEs
  - Laboratory abnormalities consistent with toxicity profile of peginterferon/ribavirin

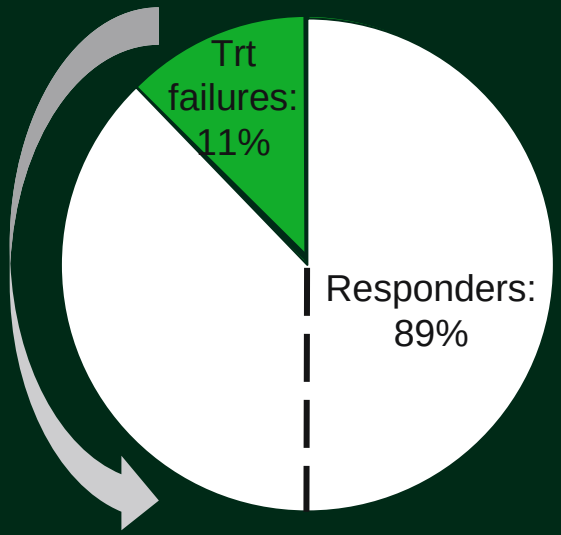
Lawitz E, et al. N Engl J Med. 2013;368:1878-1887

FDA Exploratory Analysis: Predicted Efficacy of SOF + P/R in Trt-Expd GT1 HCV

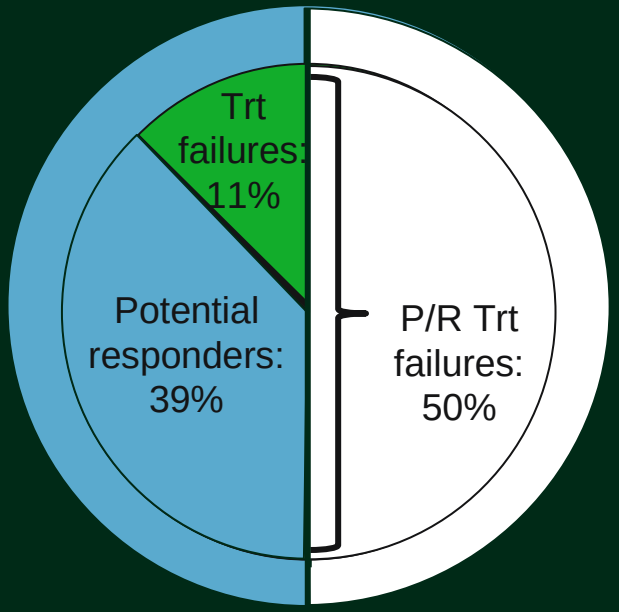
Historical PegIFN/RBV Response



NEUTRINO Response Rates



Predicting SVR in P/R Trt-Experienced

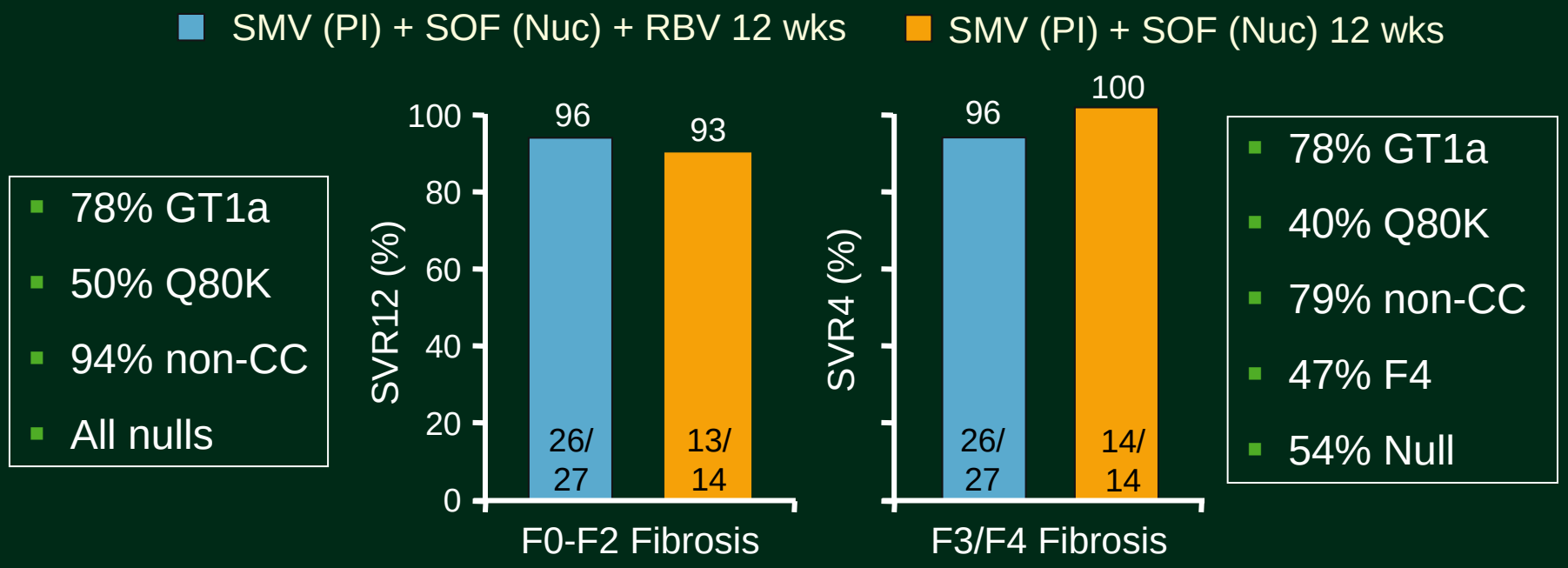


Patients who would have failed P/R therapy likely contributed to increased SVR rates with SOF therapy

Predicted SVR in GT1 P/R Trt-Expd population: 78% (39/50)

Sofosbuvir FDA hearing. October 25, 2013.

Simeprevir + Sofosbuvir in Trt-Naive Pts and Nulls (COSMOS)



- Major caveats: small n, no plan for phase III trial

Jacobson I, et al. AASLD 2013. Abstract LB-3.

American Association for the Study of Liver Diseases

AASLD

IDSA

Infectious Diseases Society of America

The most current version of the HCV Guidance exists on *Recommendations for Testing, Managing, and Treating Hepatitis C.* (http://www.hcvguidelines.org)

RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED

Recommended regimen for HCV genotype 1 PEG/RBV (without an HCV protease inhibitor) nonresponder patients:

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility

Rating: Class IIa, Level B

Alternative regimen for PEG/RBV (with or without an HCV protease inhibitor) nonresponder patients with HCV genotype 1 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 to 24 weeks is an alternative for retreatment of IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class IIb, Level C

29 Enero 2014