Clinical Case
A previously relapse HCV genotype 1 patient

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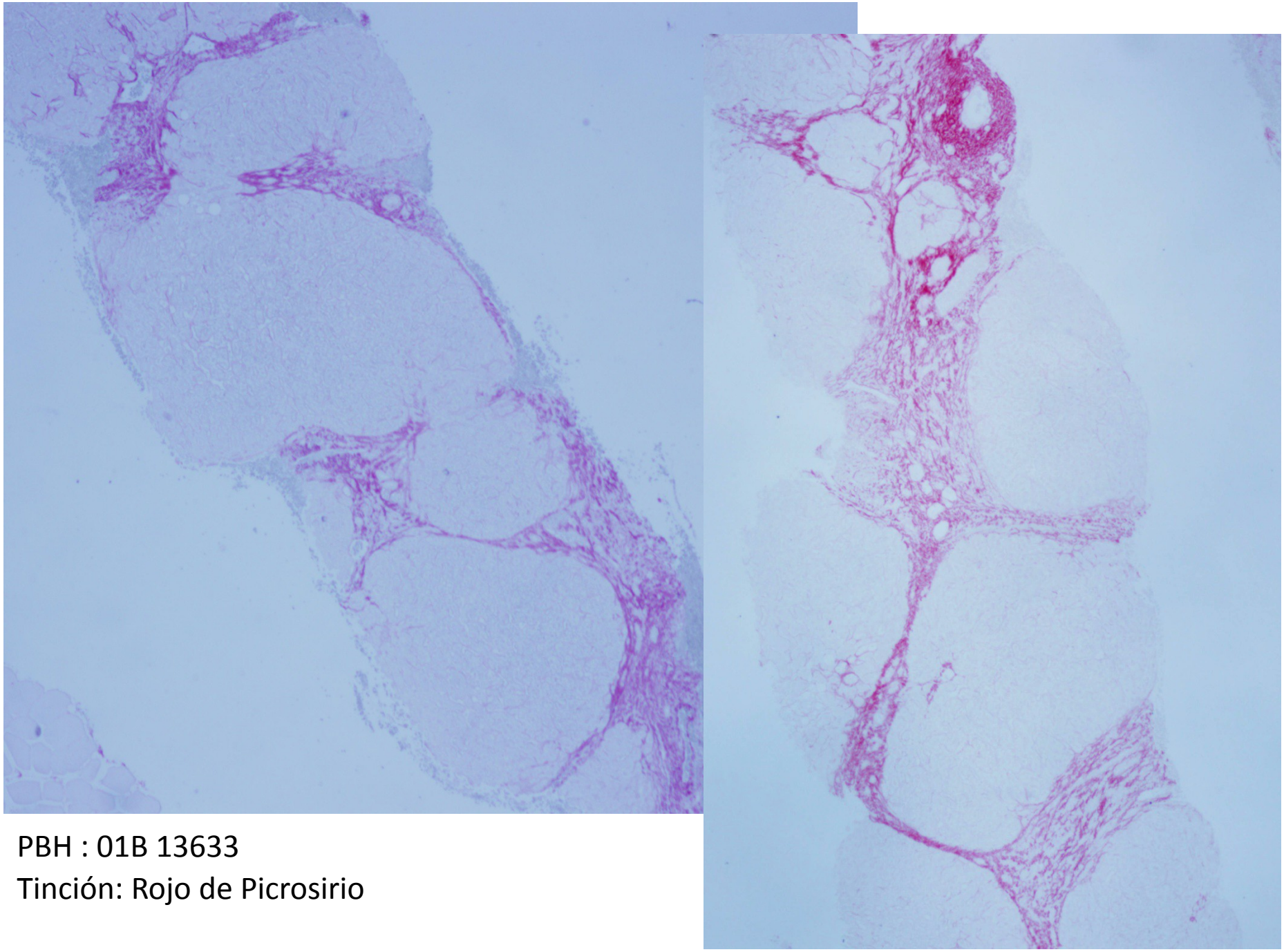
Clinical Case

- A 67-year-old Caucasian man with liver cirrhosis
- HCV genotype 1b
- Treated with PEG-IFN alpha-2b 1.5 µg/kg/wk and RBV 1000 mg/day for 48 weeks in 2001
- No side effects, no anemia
- End of treatment response but he relapsed later on



PBH : 01B 13633

Tinción: Rojo de Picrosirio

January 2013

- He was asymptomatic. BMI 29,4
- Lab tests
  - Hemoglobin 17.3 g/dL
  - platelets 100,000/mm3,
  - creatinine 1.16 mg/dL
  - albumin 4.26 g/dL
  - ALT 453 IU/L
  - Alkaline phosphatase 166 IU/L, GGT 172 IU/L
  - HCV RNA level 2.1x106 IU/mL
  - IL28B polymorphism CC

January 2013

- Liver stiffness 35.8 Kpa and the IQ) was 9.8 Kpa
- Upper endoscopy No varices
- He started triple therapy
  - PEG-IFN alpha-2a 180 µg once a week
  - RBV 600 mg BID
  - TPV 1125 mg BID

At week 4 of triple therapy

- Asymptomatic
- Hemoglobin of 12 g/dL (Drop 5 g/dL)
- ALT 89 IU/L, platelets 72,600/mm
- HCV RNA 93 IU/mL

What is the recommended therapy duration?

- 12 weeks
- 24 weeks
- 48 weeks
- Stop now

EASL Guidelines 2014

- Cirrhotic patients had inferior outcomes in all treatment groups and response-guided therapy is not licensed for cirrhotic patients, irrespective of the prior treatment response to dual therapy

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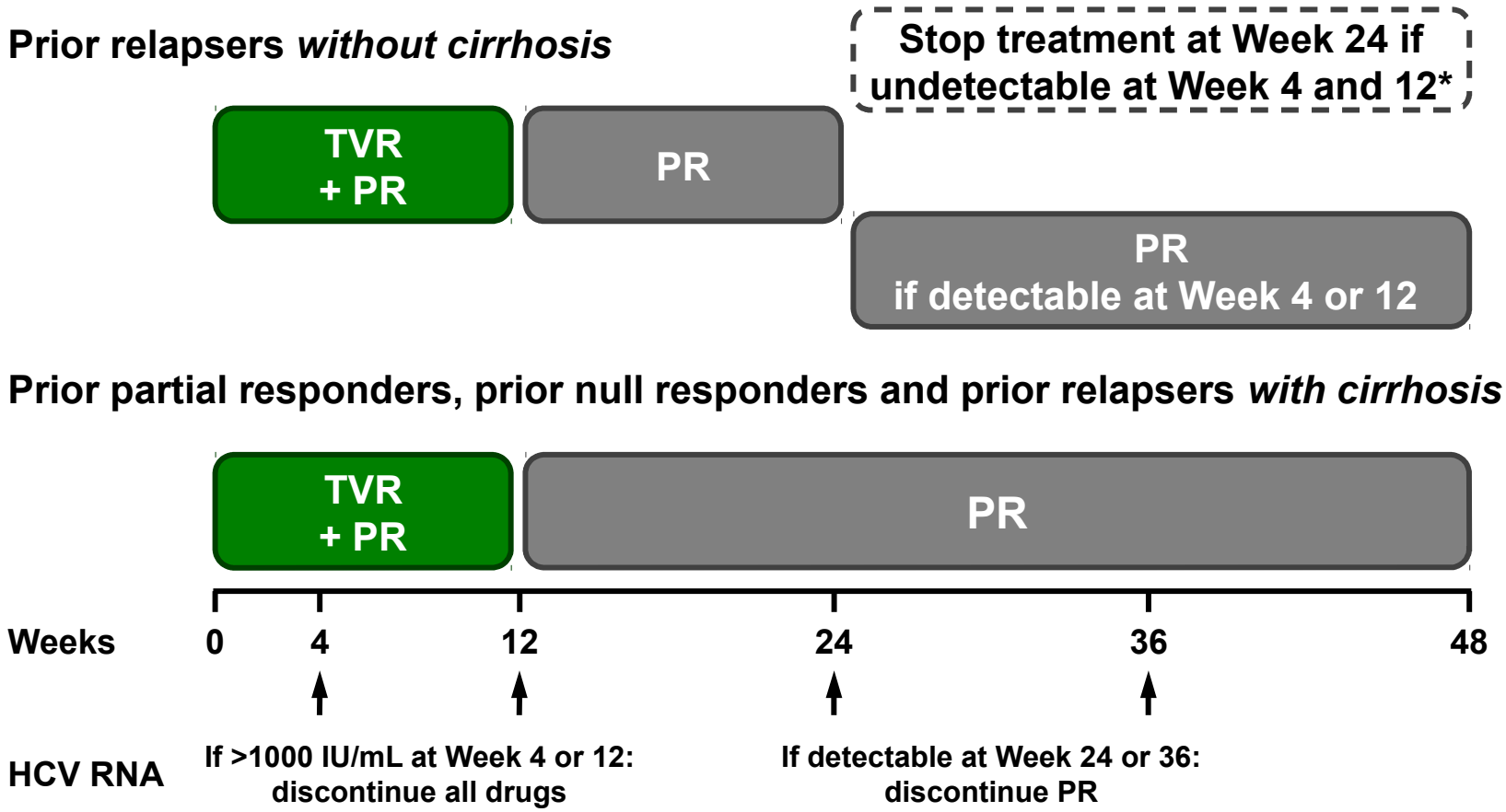
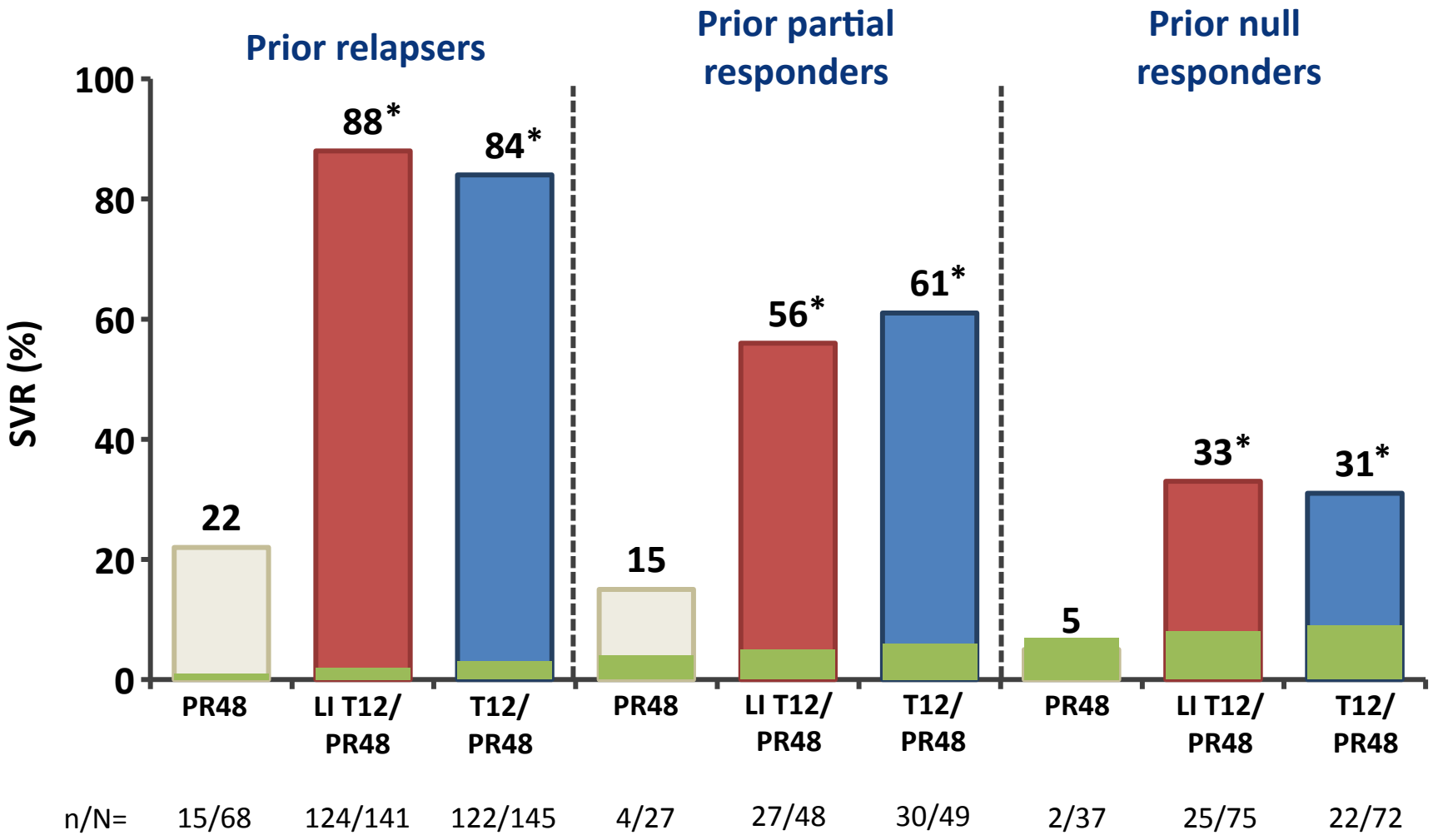
TVR regimen in genotype 1 HCV-infected patients: patients with prior treatment failure



*In Phase III studies, a sensitive real-time PCR assay with a limit of quantification of 25 IU/mL and a limit of detection of 10–15 IU/mL was used to determine whether HCV RNA levels were undetectable. Detectable HCV RNA below the lower limit of assay quantification should not be used as a substitute for 'undetectable' for making decisions on treatment duration, as this may lead to an insufficient duration of therapy and higher relapse rates. In prior null responders, consideration should be given to conducting an HCV RNA test between Weeks 4 and 12 and if HCV RNA >1000 IU/mL all drugs should be stopped

INCIVO (telaprevir) EU SmPC

REALIZE (TVR): SVR in prior relapsers, partial responders and null responders



*P<0.001 vs PR48

SVR, considered virologic cure, was defined as HCV RNA <25 IU/mL at last observation within the Week 72 visit window. In case of missing data, the last HCV RNA data point from Week 12 of follow-up onwards was used

INCIVO (telaprevir) EU SmPC

At 8 weeks of treatment

- The patient complained of asthenia and fatigue
- Hb 8.7 g/dL
- ALT 71 IU/l
- HCV RNA <15 IU/mL
- Creatinine 1,97 mg/dl (<1.17 mg/dl)
- eGF 34 mL/min/
- RBV doses were reduced to 600 mg

At week 11

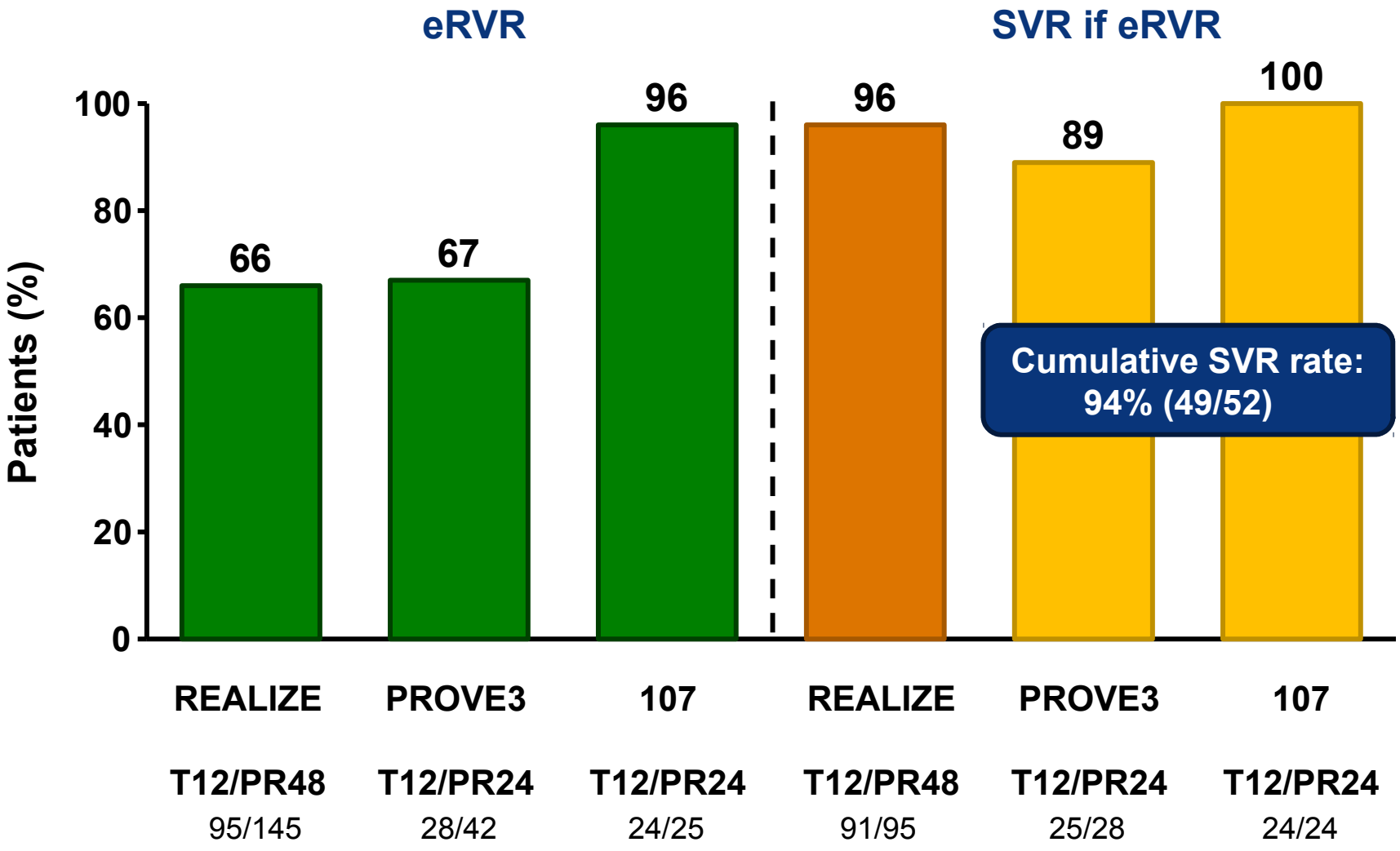
- Fatigue and asthenia had increased
- Dyspnea on mild exertion
- A pruriginous skin rash developed over his body
- The patient did not like to continue therapy
- TPV, RBV, and PEG-IFN were stopped.

At week 11

- Hemoglobin 6.3 g/dL
- Creatinine 2.01 mg/dL
- eGFR 32 mL/min/1.73m2
- HCV RNA was undetectable
- Packed red blood cells were administered

Can the duration of treatment be shortened in treatment-experienced, genotype 1-infected patients receiving DAA-based therapy?

TVR: eRVR and SVR rates among prior relapsers in Phase II and III trials



eRVR: HCV RNA undetectable at Weeks 4 and 12

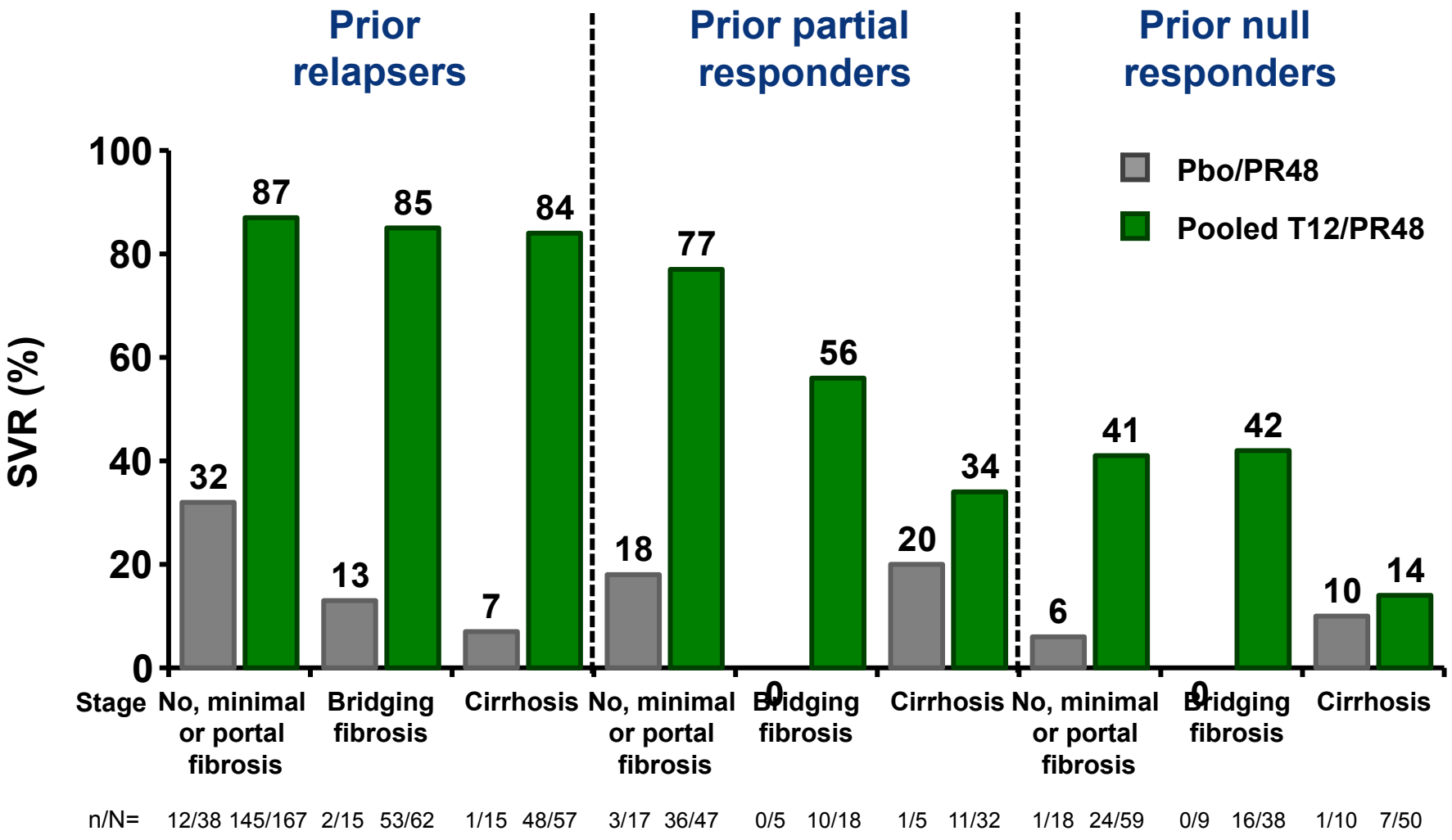
Adda N, et al. CDDW/CASL 2012. A26

Outcome

- After these measures, the symptoms gradually improved and renal function and hg levels returned to normal in 3 weeks.
- 24 weeks after stopping treatment, HCV RNA remains undetectable

What is the rate of SVR with DAAs in patients with fibrosis/cirrhosis?

REALIZE (TVR): SVR by BL fibrosis stage and prior response to PR

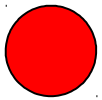


SVR was defined as HCV RNA <25 IU/mL at last observation within the Week 72 visit window. In case of missing data, the last HCV RNA data point from Week 12 of follow-up onwards was used

Pol S, et al. Hepatology 2011;54(Suppl. S1):374A

- SVR was achieved with only 11 weeks of triple therapy with TPV.

What is the frequency of severe anemia (Hb <8,5 g/dl)?



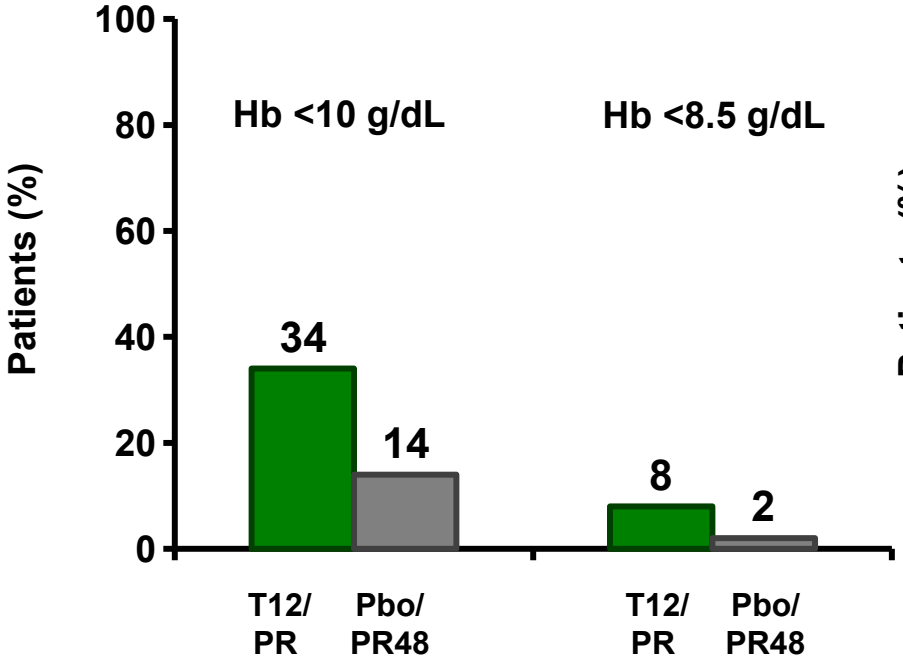
30%

< 10%

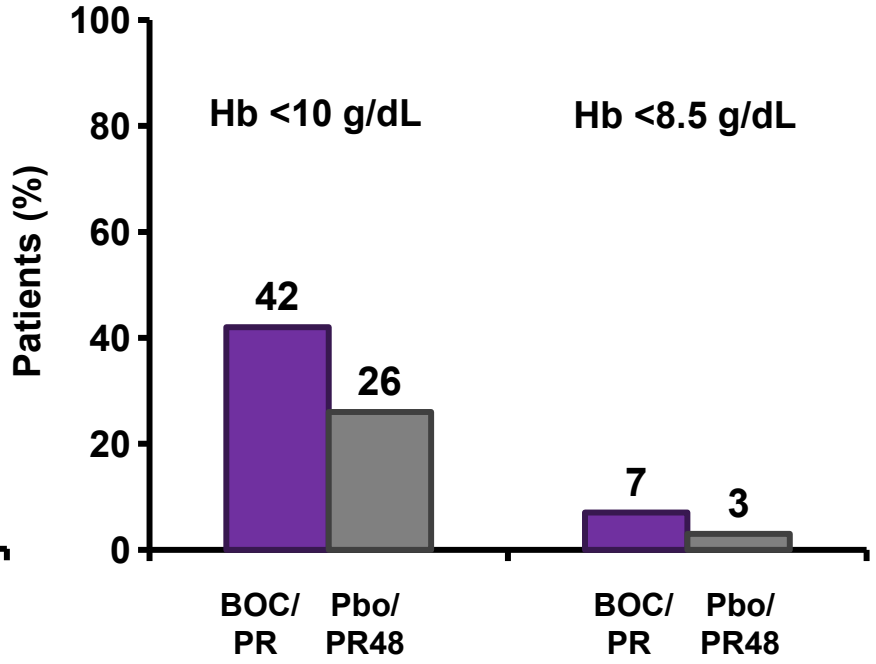
It is related to the presence of cirrhosis

Frequency of anemia with TVR and BOC

TVR
Phase II and III Pbo-controlled studies



BOC
SPRINT-1/2 and RESPOND-2 studies



INCIVO (telaprevir) EU SmPC
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252343.pdf

REALIZE subanalysis in cirrhotics: AEs in ≥25% of TVR-treated patients over course of therapy

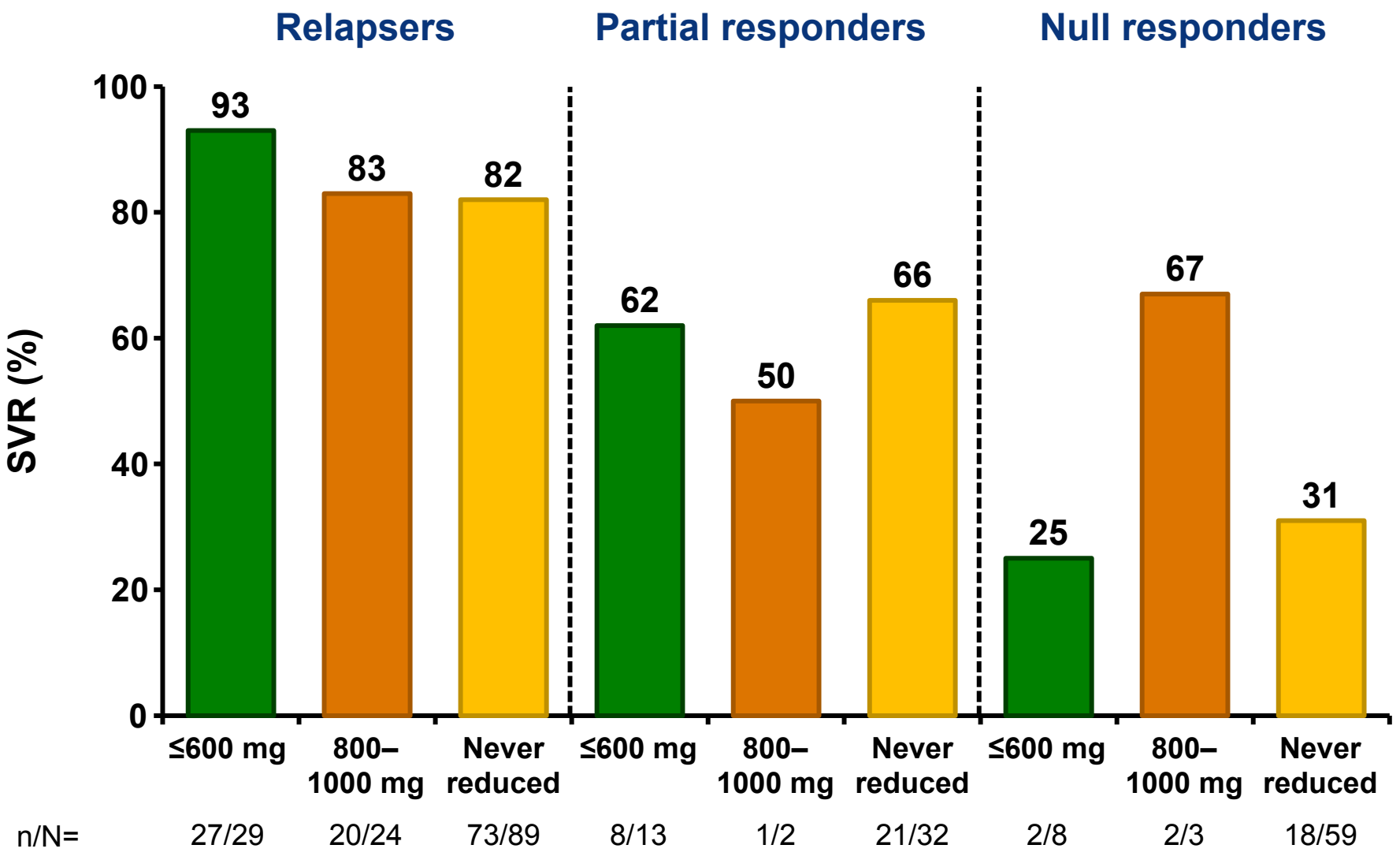
AE, n (%)	Cirrhotics (F4) (N=139)	Non-cirrhotics (F0–3) (N=391)
Rash SSC	93 (67)	206 (53)
Pruritus SSC	82 (59)	205 (52)
Fatigue	62 (45)	214 (55)
Headache	54 (39)	167 (43)
Anemia SSC*	59 (42)	134 (34)
Nausea	52 (37)	129 (33)
Influenza-like illness	55 (40)	124 (32)
Insomnia	39 (28)	113 (29)
Anorectal symptoms‡	33 (24)	101 (26)
Diarrhea	33 (24)	102 (26)
Pyrexia	34 (25)	97 (25)

*Anemia reported by the investigator as an AE (not necessarily defined by Hb levels)

‡Grouped term including several different AEs in the anorectal area

Poordad, et al. Hepatology 2011;54(Suppl. S1):374A

REALIZE (TVR): no impact of RBV DR on SVR (T12/PR48 arm)



Sulkowski MS, et al. J Hepatol 2012;56(Suppl. 2):S459–60

BL factors associated with developing anemia during treatment

Pre treatment factors associated with developing anemia during TVR treatment (multivariate logistic regression):

- Older age: OR: 0.92 (95% CI: 0.88, 0.96) per year
- Lower BMI: OR: 0.91 (95% CI: 0.86, 0.97) per year
- Lower BL Hb: OR: 0.58 (95% CI: 0.44, 0.77) per year

Incidence of treatment-emergent anemia was greater in women (64%) vs men (27%)

Zeuzem S, et al. Hepatology 2012;56(Suppl. 4):564A

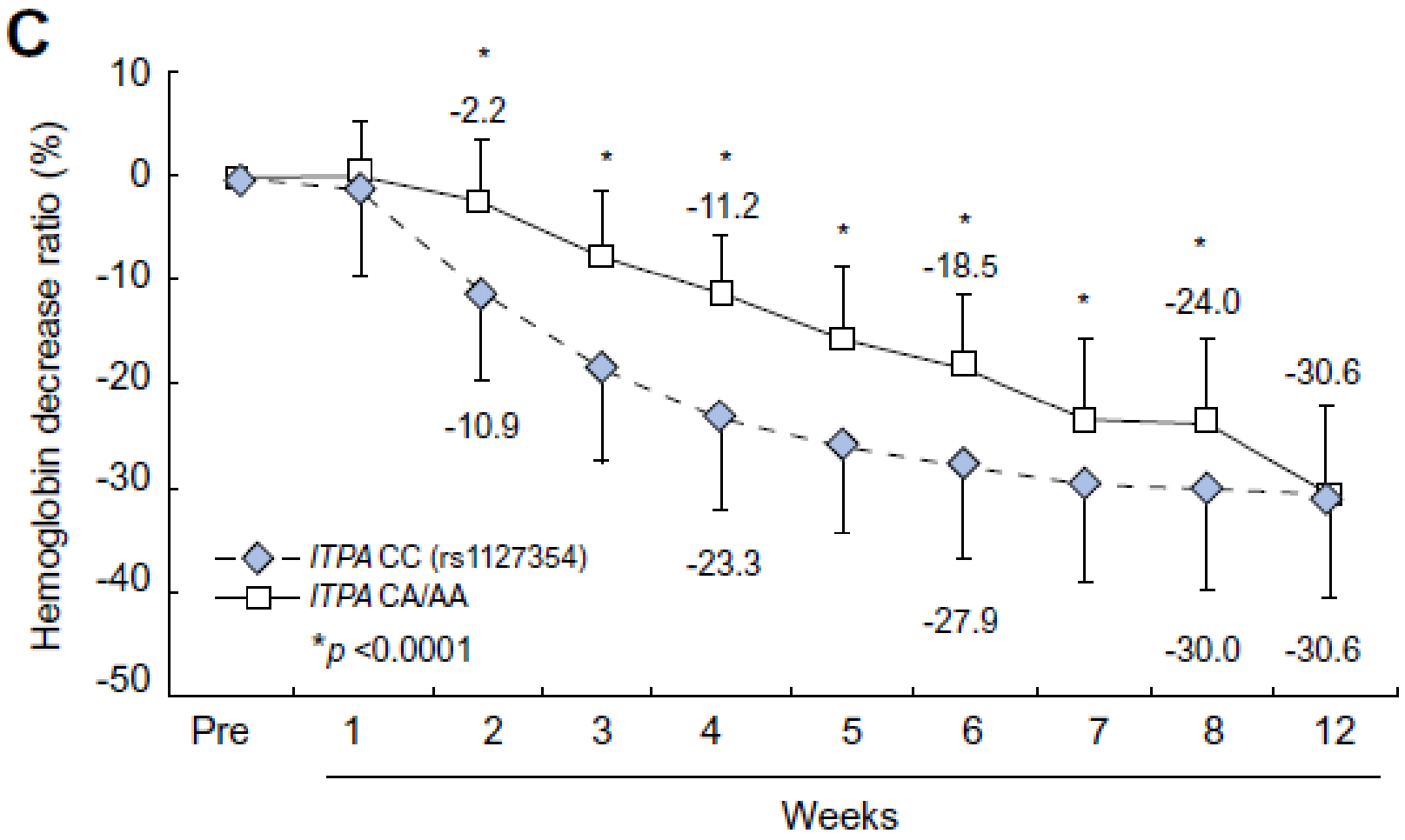
Additional Information

Inosine triphosphate pyrophosphatase (ITPA) polymorphismrs

rs 1127354 C/C rs7270101 A/A

eGFR baseline 68 mL/min

Mean Hb decrease ratio during antiviral treatment stratified by ITPA SNPs



Ogawa E, et al J Hepatol 2013

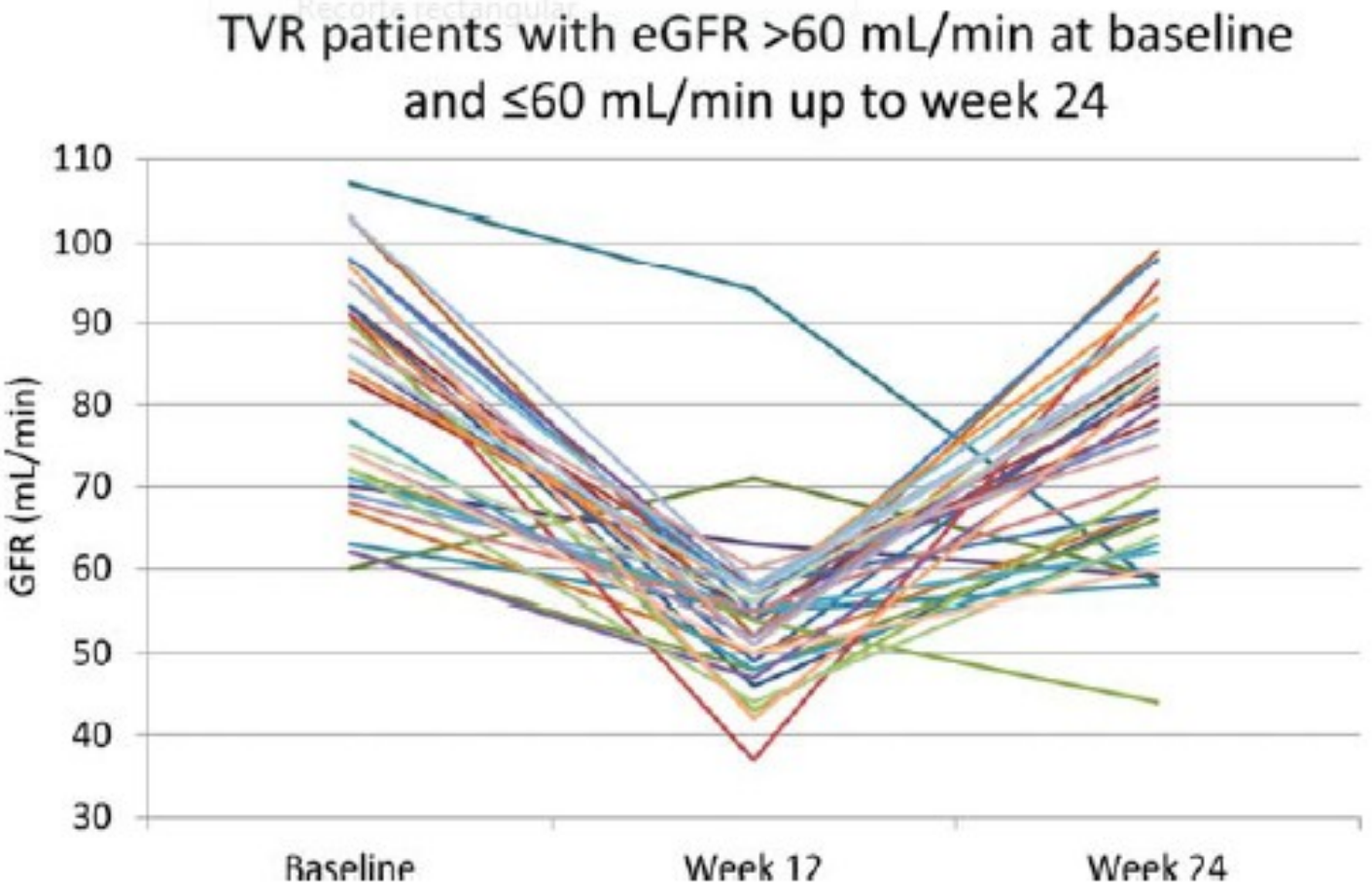
ITPA Genotyping Enables Identification of Patients with a higher risk of early severe anemia on triple therapy

96 genotype 1 CHC patients treated with triple therapy including TVP (N=55) and BOC (N=41) were studied.

rs1127354 Major allele C	rs7270101 Major allele A	ITPA Deficiency	Number of cases	Hb≥3g/dL decline at week 4 PI	Hb<10g/dL at week 4 PI
C/C	A/A	0%	63 (66%)	40 (60%)	21 (33%)
C/C	A/C	40%	19 (20%)	4 (21%)	2 (11%)
C/A	A/A	70%	8 (8%)	1 (13%)	0
C/A	A/C	90%	6 (6%)	0	0

Camos S et al. AASLD 2013

Course of eGFR in individual patients treated with TLV until week 12 with eGFR >60 mL/min at baseline and eGFR 60 mL/min up to week 24



Mauuss S et al. Hepatology 2014

Risk factors for severe anemia according to the ITPA (rs1127354) of CHC patients treated with telaprevir triple therapy.

Characteristic	*ITPA* CC, n = 227		
	Severe anemia, n = 90	Non-severe anemia, n = 137	*p* value
Age (yr)	64 (57-68)	61 (53-65)	0.0004
Men, n (%)	29 (32.2)	74 (54.0)	0.0011
Body mass index (kg/m^2)	22.8 (20.9-25.0)	23.4 (21.8-25.6)	0.0939
Alanine aminotransferase (IU/L)	49 (29-95)	53 (34-94)	0.1157
Serum albumin (g/L)	39 (36-42)	40 (38-43)	0.0083
Estimated glomerular filtration rate (ml/min/1.73 m^2)	76 (69-91)	82 (74-95)	0.0041
α-fetoprotein (ng/ml)	5.4 (3.3-11.0)	5.7 (3.5-12.5)	0.3010
Hemoglobin at baseline (g/L)	132 (125-140)	141 (132-153)	<0.0001
Hemoglobin at week 2 (g/L)	114 (110-123)	125 (117-136)	<0.0001
Platelet count (x10^9/L)	144 (113-197)	153 (117-190)	0.9107
Stage of fibrosis			
F0-2/F3-4, n (%)	37/25 (39.4/50.0)	57/25 (60.6/50.0)	0.2205
Not determined	28	55	
Initial 4 week ribavirin dose (mg/kg/day)	10.0 (7.6-11.0)	9.4 (7.8-10.8)	0.8369
Initial 4 week telaprevir dose (mg/kg/day)	29.9 (25.8-33.2)	28.0 (23.9-31.3)	0.0455

Ogawa E, et al J Hepatol 2013

Multivariable Logistic regression analysis of predictors of severe anemia

Baseline HB levels < 135 g/l (HR 2.53 p=0.0013)

EGFR < 80 ml/min (HR1.82, p=0,0265)

ITPA CC genotype (rs1127354) (HR 2.91;p=0.0024)

Summary

Previous relapse patient achieve a very high SVR rates with Triple therapy, even in patients with cirrhosis

Some patients who discontinue therapy early due to side effects still can achieve high SVR rates