How to optimize treatment in G1 naive patients? (easy to treat patient)

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Disclosure

- VI has received research/grant support from MSD Russia, has served as a board member and or consultant for Abbvie, Vertex, Roche, Novartis, Janssen, and Bristol-Myers Squibb; has served on speakers' bureau for Bristol-Myers Squibb, MSD, Roche and Novartis; and has received travel funding from Bristol-Myers Squibb and MSD Russia.

Clinical case

- Patient F., Russian male, 41 years old, BMI 24,5 kg/m2
- HCV infection diagnosed in 2003 (HCV-ab +, HCV PCR qualitative positive), no history of drug abuse or blood transfusions
- Low alcohol consumption (less 30 ml/week)

In January 2013 he noted fatigue and applied for health service and additional tests were performed:

- Genotype 1b, HCV RNA: 830 000 IU/ml
- Platelets - 240,000/µl, Hb 14,5 g/dl, blood cell counts were normal
- ALT 80 IU/l, AST 56 IU/l, bilirubin 10 mmol/l, GGT 85 IU/l; INR 1.04,
- IL28B - CT

Abdominal US: Portal vein d=10 mm,
Fibroscan 6.9 kPa
Liver biopsy: METAVIR F2

Possible scenarios for the patient

- To treat
  - PEG-IFN+RBV
  - PEG-IFN+RBV+PI (telaprevir/boceprevir)
  - PEG-IFN+RBV+ second wave PI (semiprevir)
  - PEG-IFN+RBV+SOF 12 weeks
- To wait
  - For what? (higher efficacy, better tolerability, easy access for the treatment, lower cost)

Key Factors in Deciding to Treat or Wait

- Patient factors
  - Urgency to treat
  - Likelihood of response
    - HCV genotype
    - Treatment experience
    - IL28B genotype
    - Degree of fibrosis
  - Patient motivation

- Treatment factors
  - Efficacy of current options
  - Safety of current options
  - Duration of therapy
  - Pill burden, dosing frequency
  - Future options and their timelines

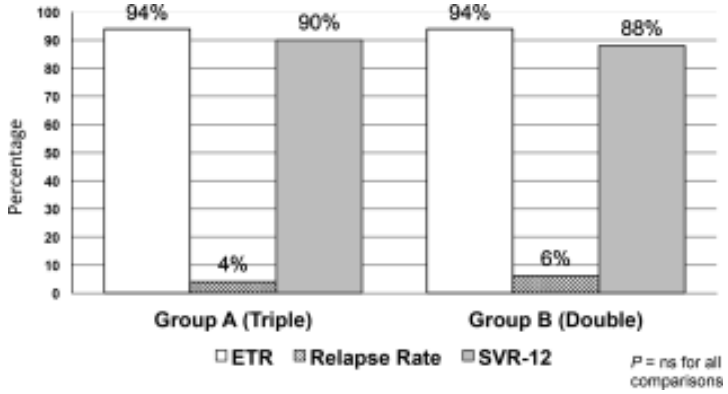
Patient's factors

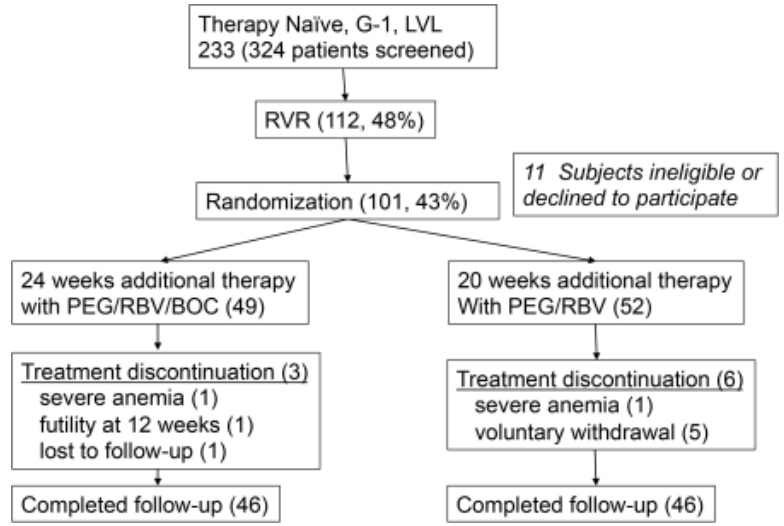
- Favor to SVR
  - Age (<50)
  - Genotype 1b
  - Mild fibrosis
  - Normal BMI
  - No alcohol consumption
- Unfovarable
  - High viral load
  - IL28B non-CC genotype

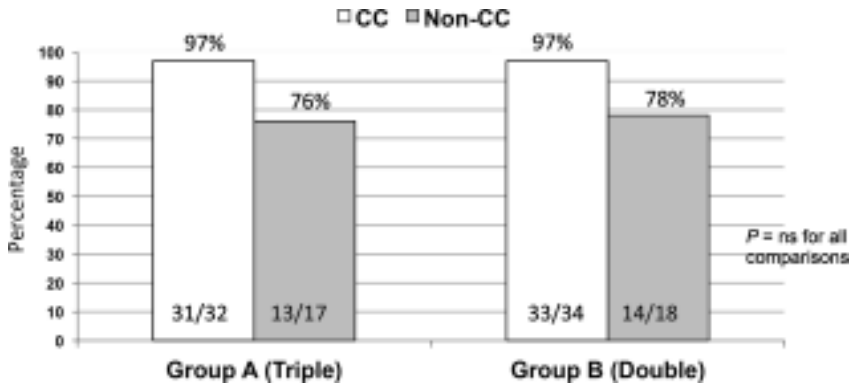
To treat with PEG-IFN based: Dual or Triple?

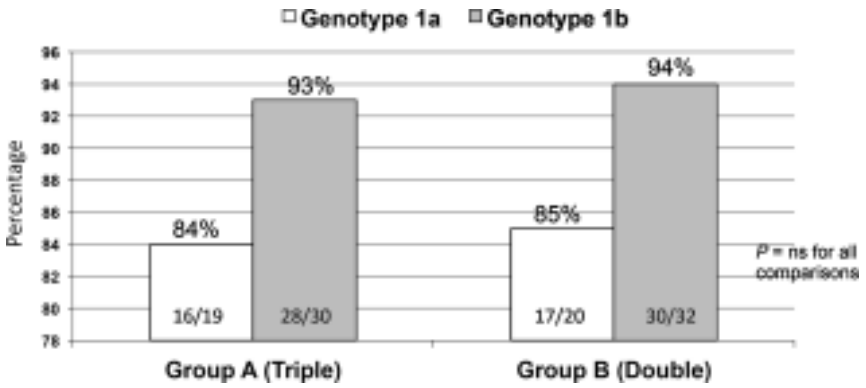
- Key factors for decision in patients with mild fibrosis:
  - Baseline viral load
  - Genotype 1a versus 1b
  - IL28B cc versus non-cc
  - RVR

Hepatitis C genotype 1 virus with low viral load (<600 000 IU/ml) and rapid virologic response to PEG+RBV obviates a protease inhibitor





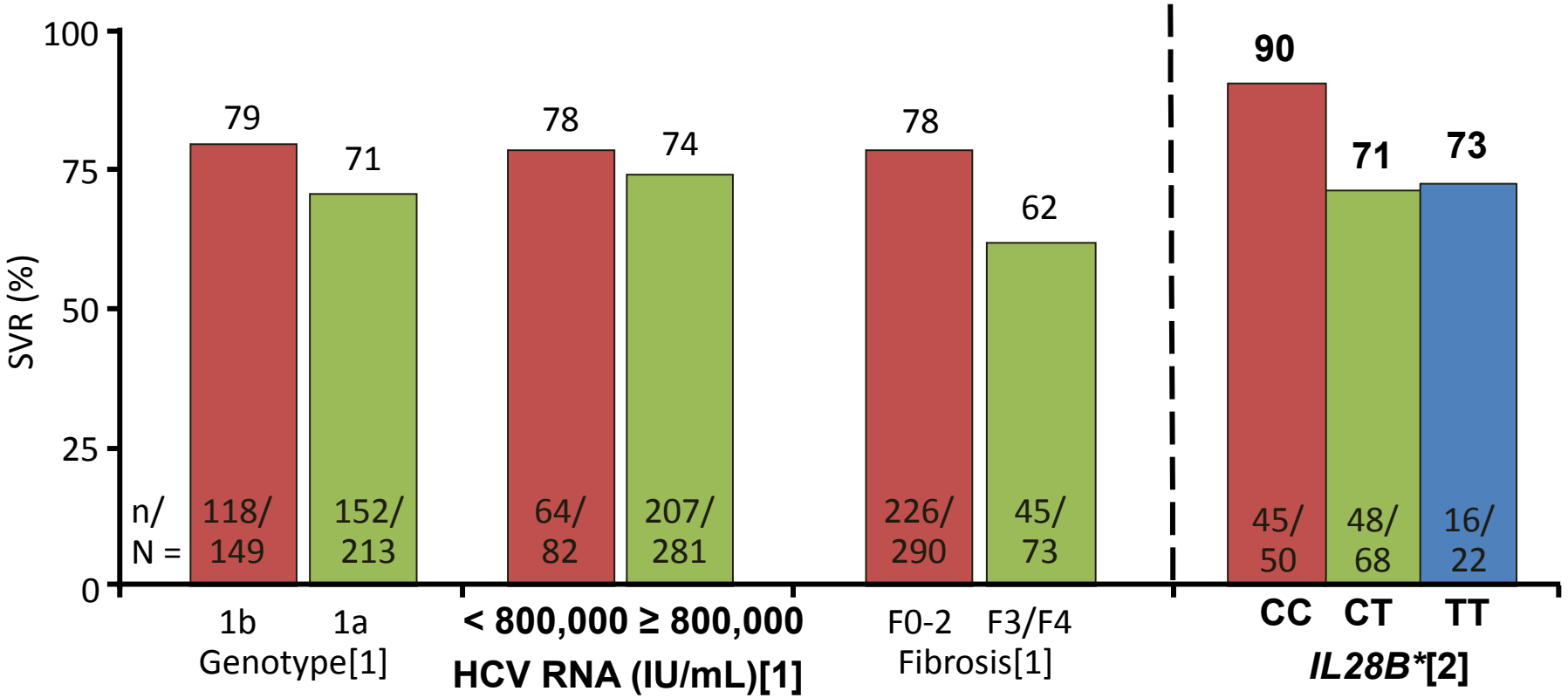




Pearlman BL, Ehleben C. Hepatitis C genotype 1 virus with low viral load and rapid virologic response to peginterferon/ribavirin obviates a protease inhibitor. *Hepatology* 2014; **59**: 71-77.

ADVANCE: Influence of Baseline Patient and Virus Factors on SVR With TVR

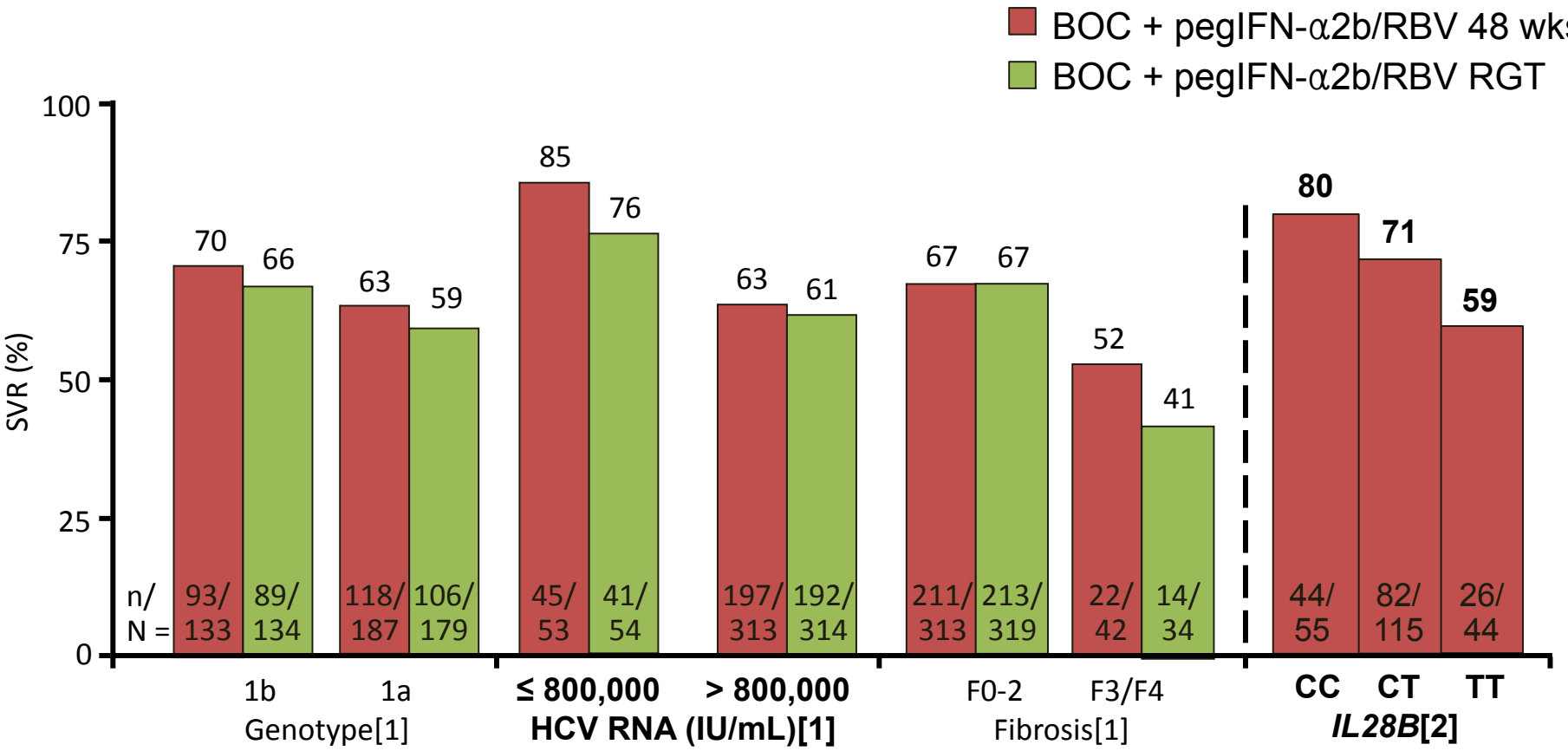
- Data from TVR12 + pegIFN-α2a/RBV arm only



**IL28B* testing was in whites only.

1. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 2. Jacobson IM, et al. EASL 2011. Abstract 1369.

SPRINT-2: Influence of Baseline Patient and Virus Factors on SVR With BOC



1. Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
2. Poordad F, et al. Gastroenterology. 2012;143:608-618.

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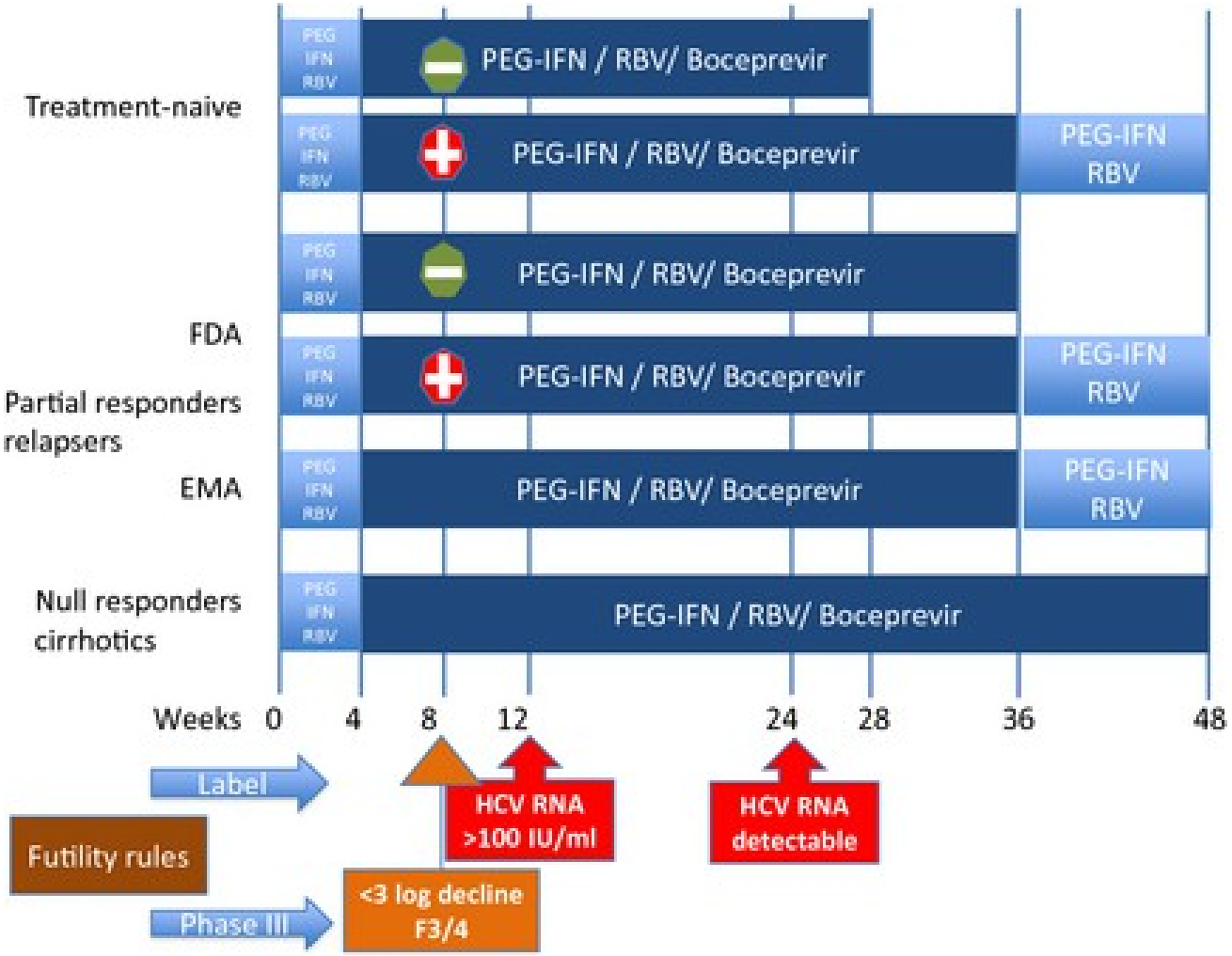
Abdominal US: Portal vein d=10 mm,
Fibroscan 6.9 kPa
Liver biopsy: METAVIR F2

➢ Decision to start treatment: Boc/PEG-IFN/RBV RGT

Treatment and futility rules (BOC)

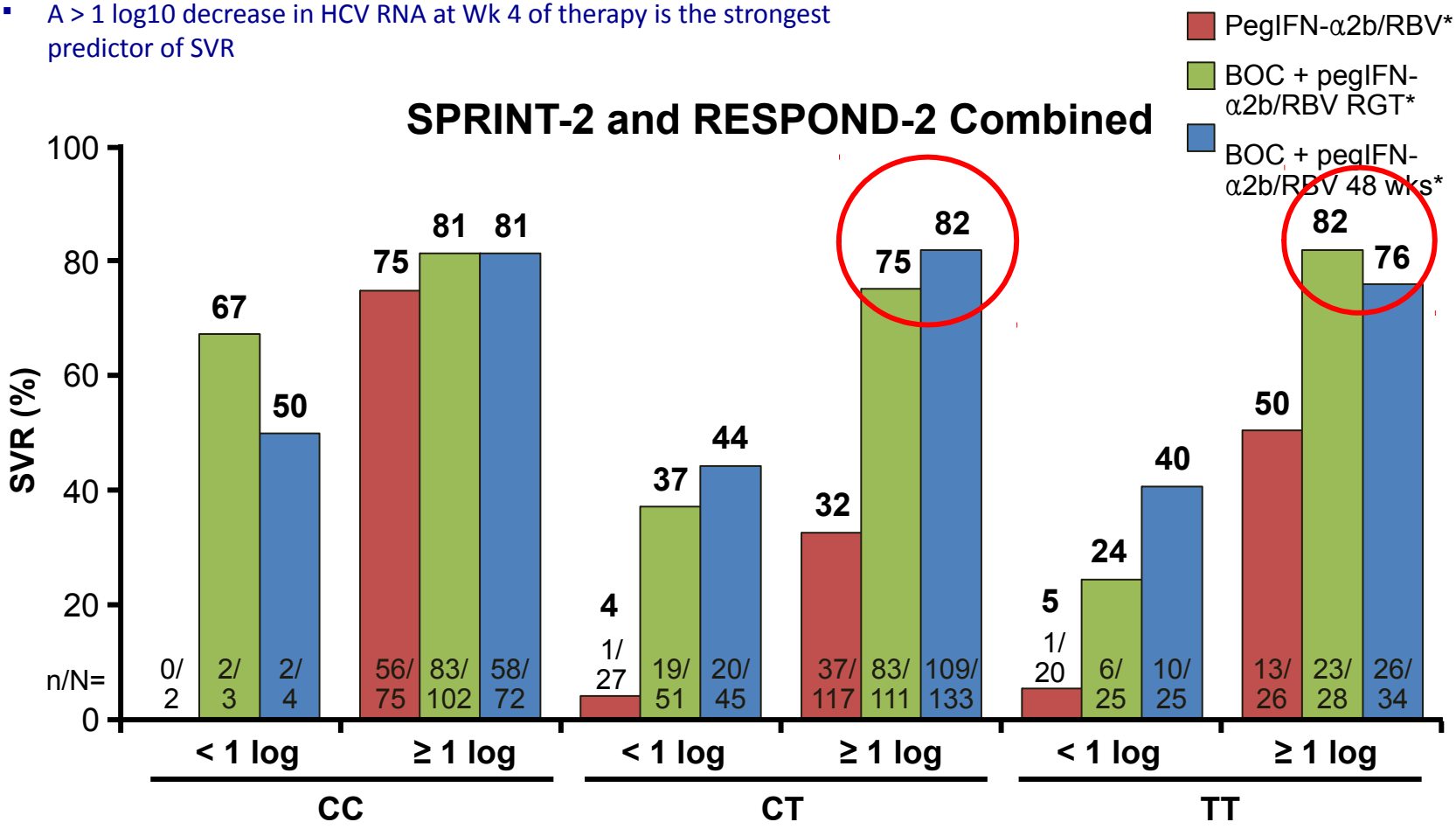


Viral kinetics in patient (week 4 and week 8)

- Baseline viral load: 830 000 IU/ml
- Week 4 viral load (end of lead-in phase): 1650 IU/ml
- Week 8 viral load (week 4 of triple therapy): target not detected in RT-PCR test (<10 IU/ml)
- ALT and AST was normal at week 8
- HB decreased 11,8 g/dl

Early IFN Response (Lead-in) Further Defines Likelihood of SVR for Non-CC Pts

- A > 1 log10 decrease in HCV RNA at Wk 4 of therapy is the strongest predictor of SVR



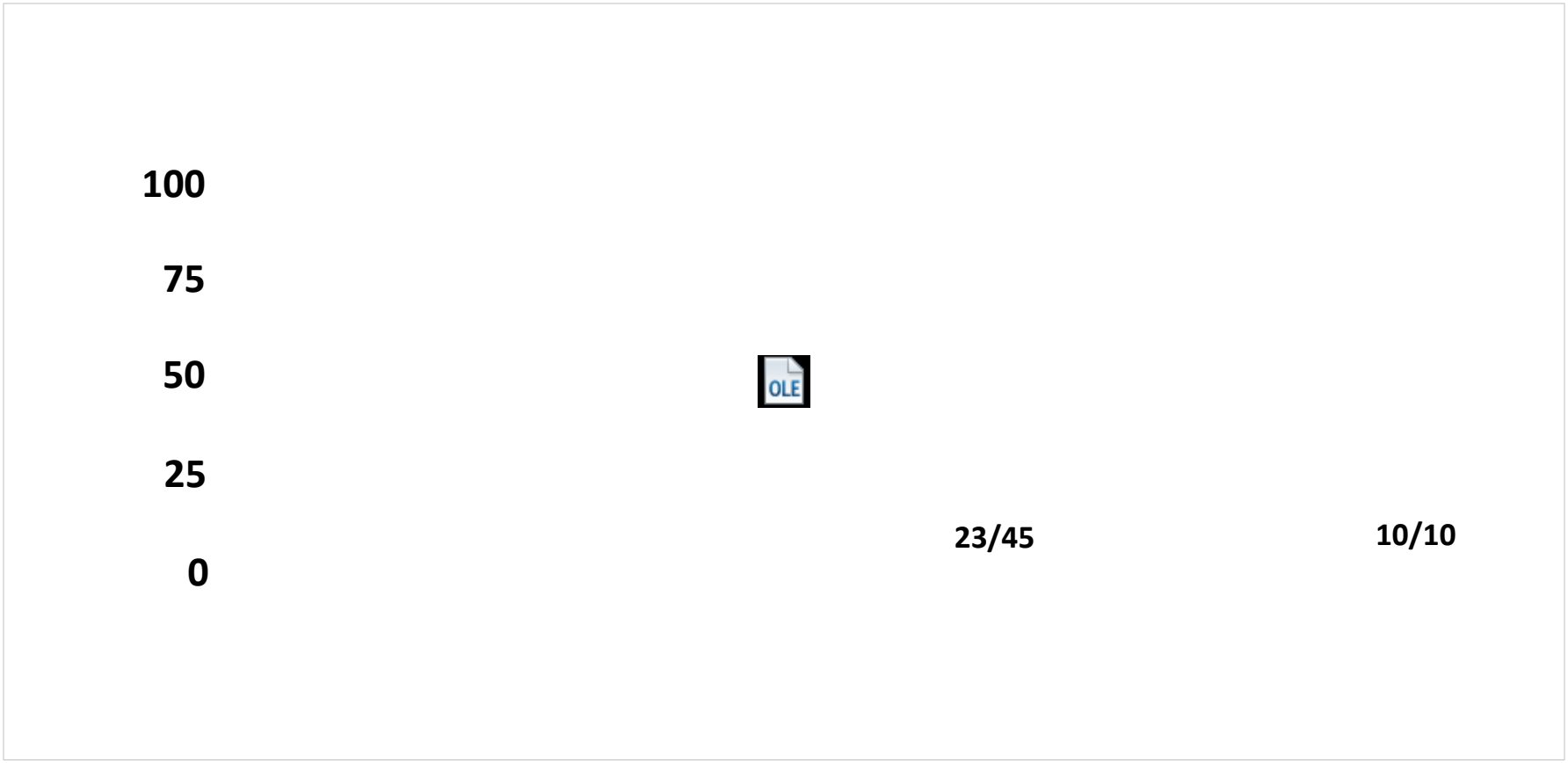
*BOC was administered with pegIFN-α2b in these trials.

Poordad F, et al. Gastroenterology. 2012;143:608-618.

Patient Demographics

	Boceprevir + PR (n = 159)	PR (n = 78)
Sex, n (%)		
Male	95 (59.7)	45 (57.7)
Female	64 (40.3)	33 (42.3)
Age, y, mean (SD)	38.6 (9.8)	38.1 (10.0)
Race		
White	158 (99.4)	77 (98.7)
Asian	1 (0.6)	1 (1.3)
Weight, kg, mean (SD)	78.1 (16.6)	78.5 (16.8)
Body mass index, kg, mean (SD)	25.9 (4.2)	26.0 (4.4)
Previous treatment, n (%)		
Naive	97 (61.0)	48 (61.5)
Experienced	62 (39.0)	30 (38.5)
IL28B genotype, n (%)		
CC allele	22 (13.8)	11 (14.1)
Non-CC allele	137 (86.2)	67 (85.9)
HCV Genotype, n (%)		
G1a	4 (2.5)	0 (0)
G1b	155 (97.5)	78 (100)
Baseline HCV RNA, n (%)		
≤800,000 IU/mL	89 (56.0)	53 (67.9)
>800,000 IU/mL	70 (44.0)	25 (32.1)
Liver histology		
Cirrhosis	7 (4.4)	2 (2.6)
No cirrhosis	152 (95.6)	76 (97.4)

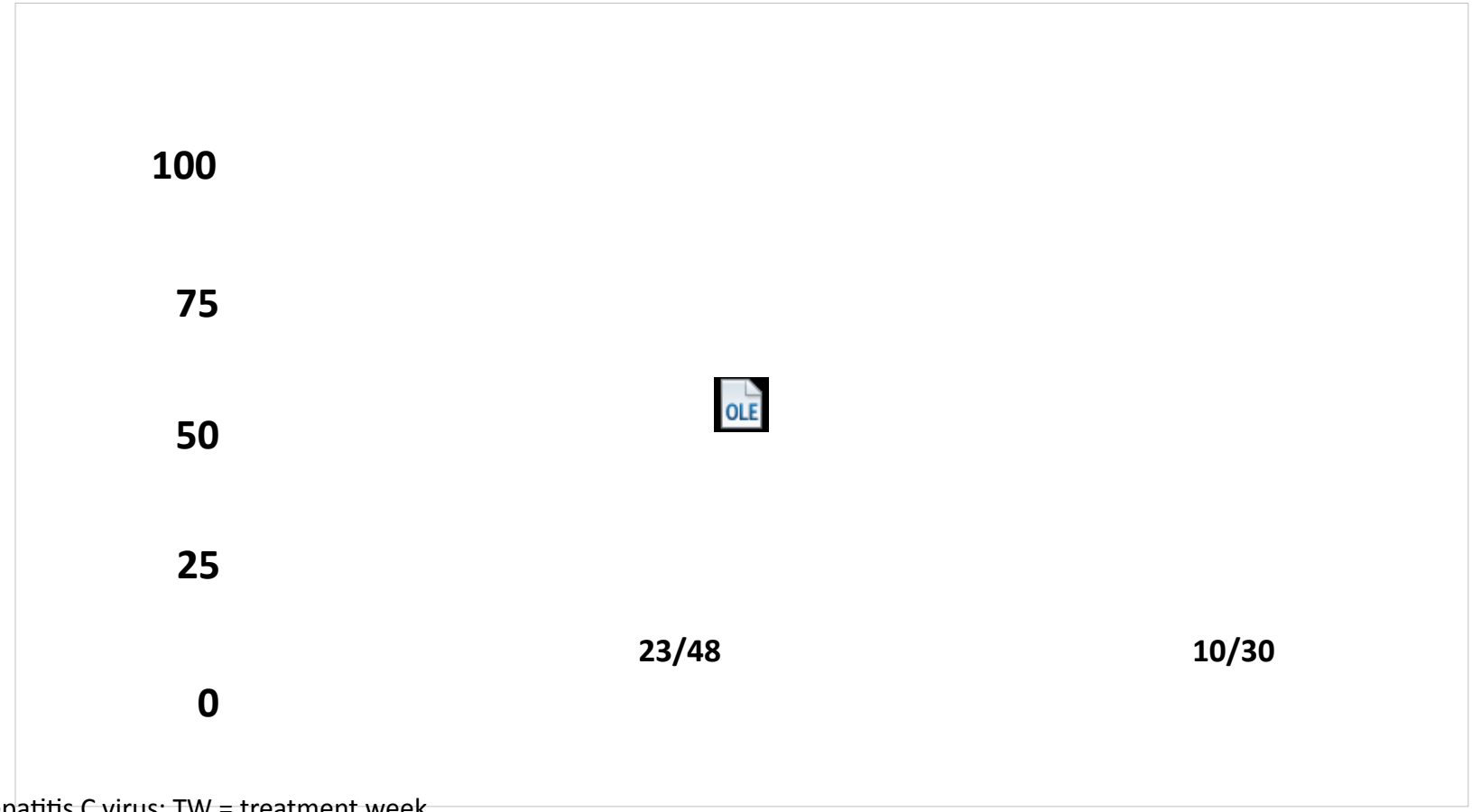
Undetectable HCV RNA at TW8 according to lead-in response



"Null" response: <1 log HCV RNA decline at TW4; Partial response: detectable and ≥1 log HCV RNA decline at TW4; Rapid virologic response: undetectable HCV RNA at TW4.

Isakov et al., Boceprevir Plus Peginterferon Alfa-2B and Ribavirin in Russian Patients With Hepatitis C Virus Genotype 1 Infection: Treatment Week 8 Interim Analysis *Hepatology* 2013; **58**: 1140A.

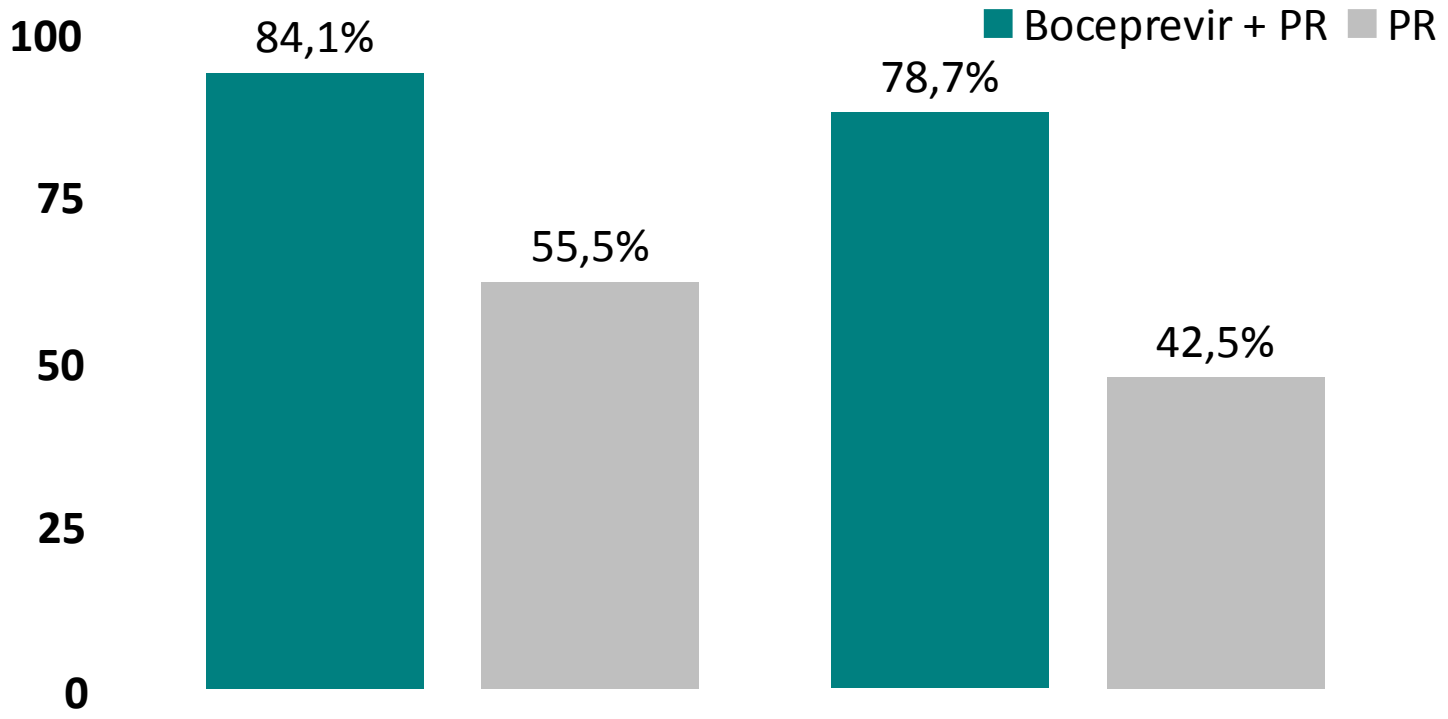
Undetectable HCV RNA at TW8 according to previous therapy



HCV = hepatitis C virus; TW = treatment week.

Isakov et al., Boceprevir Plus Peginterferon Alfa-2B and Ribavirin in Russian Patients With Hepatitis C Virus Genotype 1 Infection: Treatment Week 8 Interim Analysis *Hepatology* 2013; **58**: 1140A.

Projected SVR Based on TW8 Response and Conditional Probabilities*



*Predicted SVR rates are based on TW8 response rates and conditional probabilities from the SPRINT-2 and RESPOND-2 studies. Projected SVR rates include post-TW8 events such as dropouts, virologic failures, and relapsers. The high proportion of patients with undetectable HCV RNA at TW8 in the Russian study predicts high SVR rates.

Isakov et al., Boceprevir Plus Peginterferon Alfa-2B and Ribavirin in Russian Patients With Hepatitis C Virus Genotype 1 Infection: Treatment Week 8 Interim Analysis *Hepatology* 2013; **58**: 1140A.

Patient's data during next weeks of treatment

- Week 12 viral load : target not detected in RT-PCR test (<10 IU/ml)
- Week 24 viral load and week 28 (end of treatment):target not detected in RT-PCR test (<10 IU/ml)
- Week 40 viral load (SVR12): target not detected in RT-PCR test (<10 IU/ml)
- There was not necessary to modify the doses of RBV or PEG-IFN during the treatment.

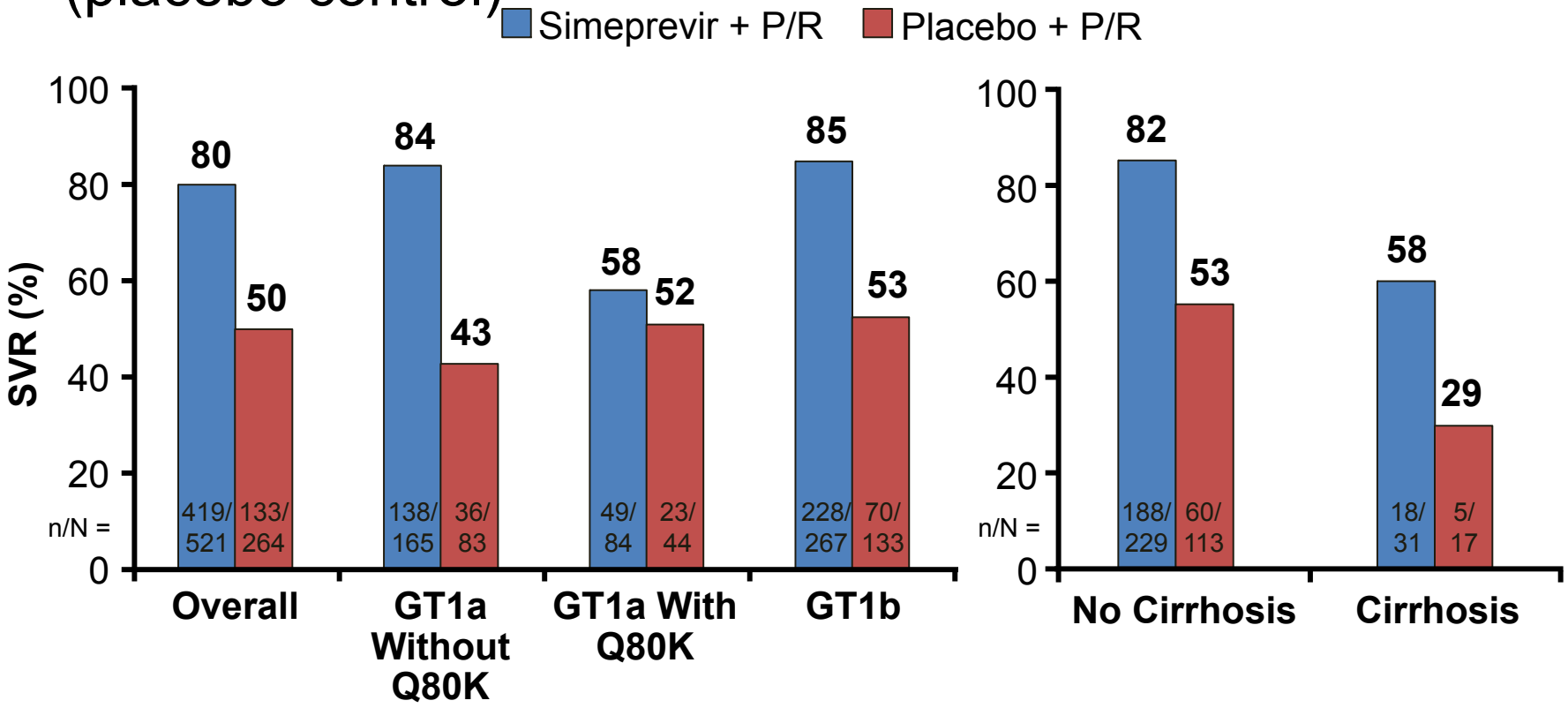
Other PEG-RBV + DAA combinations

- PEG-IFN+RBV+ second wave PI (semiprevir/faldaprevir)
- PEG-IFN+RBV+SOF 12 weeks

which are easier to use and tolerate, but still restricted by adverse events associated with PEG & RBV

Efficacy With Simeprevir + P/R in Tx-Naive GT1 Patients: Phase III Trials

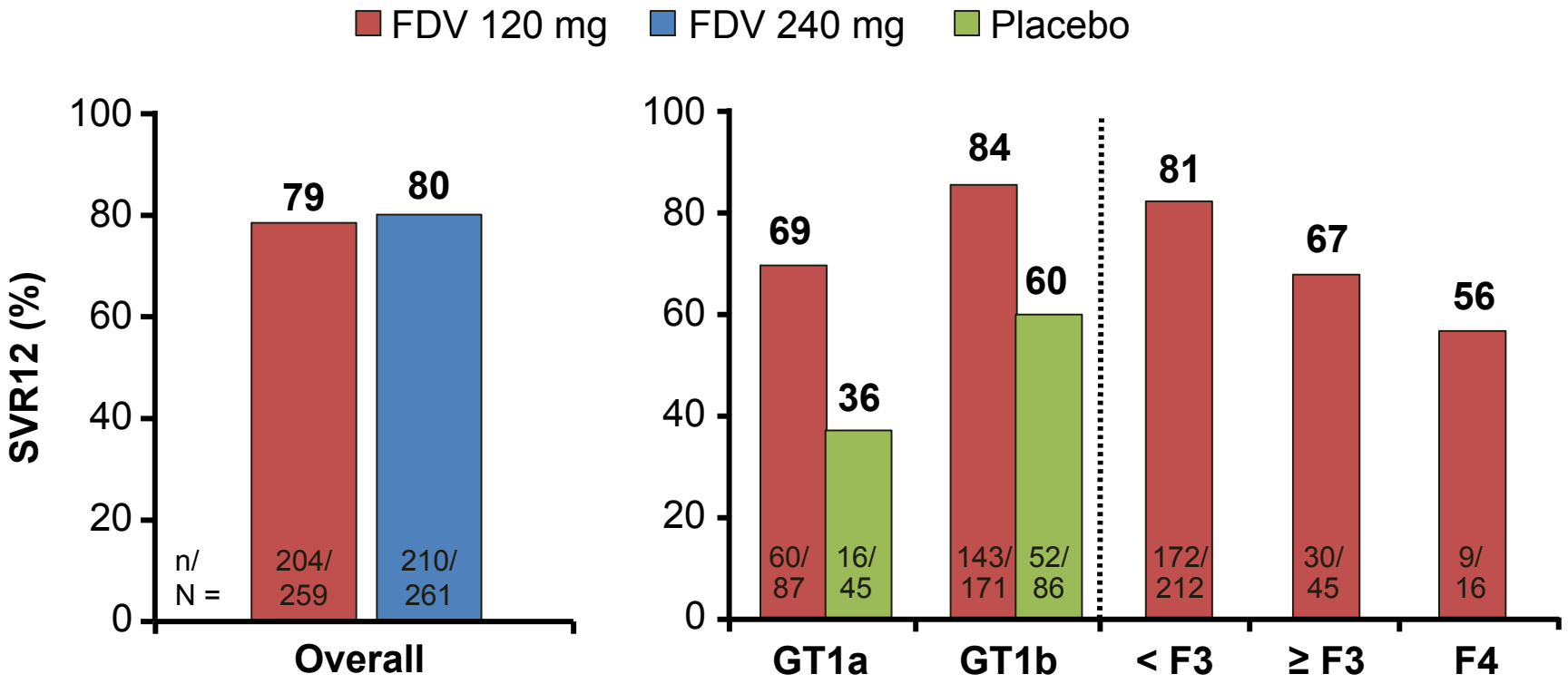
- SMV + P/R for 12 wks followed by 12-36 wks of P/R (placebo control)



Simeprevir prescribing information. Jacobson I, et al. EASL 2013. Abstract 1425.

Efficacy With Faldaprevir + P/R in Tx-Naive GT1 Patients: Phase III Trial

- Faldaprevir + P/R for 12-24 wks followed by 12-36 wks P/R (placebo controlled)

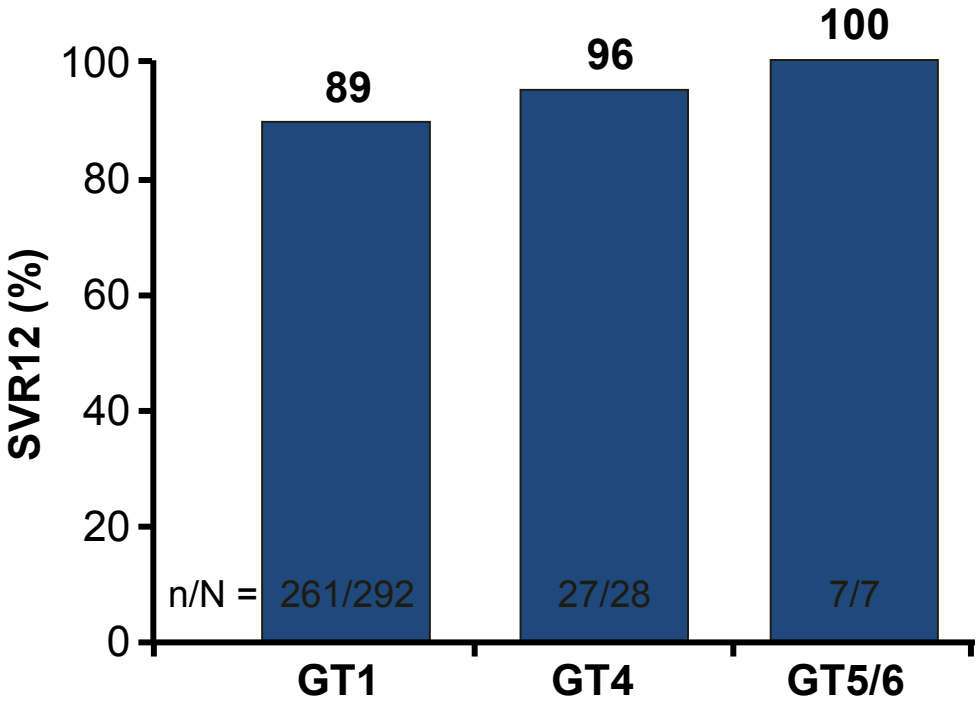


Ferenci P, et al. EASL 2013. Abstract 1416.

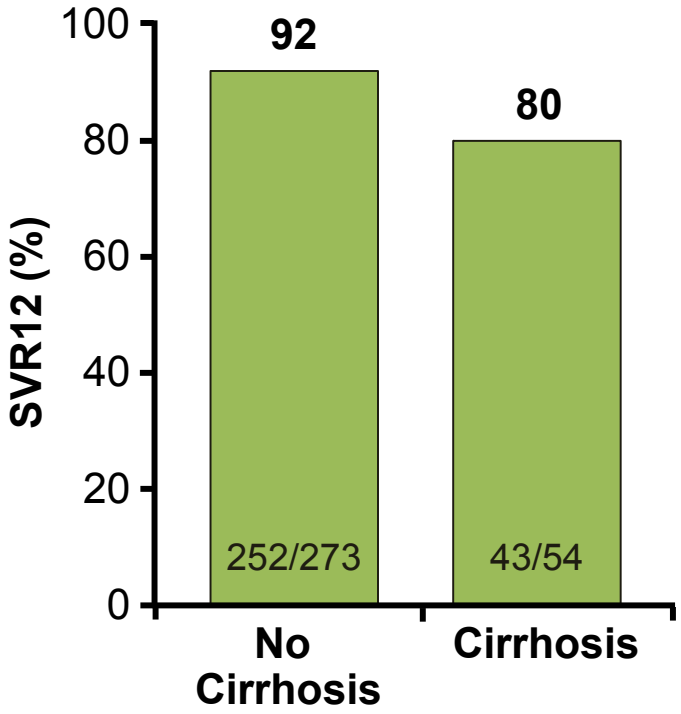
Efficacy With Sofosbuvir + P/R in Tx-Naive GT1/4/5/6 Patients: Phase III Trials

- Single-arm study of sofosbuvir + P/R for 12 wks

SVR12 According to GT



SVR12 According to Fibrosis Level



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

If the SVR is similar….

- Other factors become more important:
  - Safety
  - Cost
  - Access

Lifetime costs with triple therapy at a moderate stage of fibrosis (F2) are lower than at F3-F4 suggesting that this will be more cost-effective

Table: Mean (SD) annual costs attributable to CHC without treatment (in 2010 euros)*

Liver disease stage	Ambulatory	Hospitalization	
		No death	In-hospital death
Fibrosis		1,030 (2,460)	2,260 (7,940)
Mild (F0–F2)			
Never treated	70 (10)		
After treatment failure	53 (12)		
Moderate (F3)			
Never treated	128 (22)		
After treatment failure	86 (15)		
Cirrhosis			
Compensated		3,850 (9,410)	6,400 (11,420)
Never treated	228 (20)		
After treatment failure	71 (18)		
Decompensated	96 (21)		
1st year or stable		12,520 (18,050)	11,060 (11,230)
Accelerated progression		18,890 (27,110)	19,940 (20,640)
Hepatocellular carcinoma	–	13,990 (19,010)	16,640 (14,140)
Liver transplant			
1st year	–	72,590 (85,860)	90,710 (55,460)
Subsequent years	–	3,110 (6,900)	15,910 (23,310)

Discounted lifetime costs increased with the severity of fibrosis at diagnosis: €33,590 (F0 at mean age 47); €36,280 (F1 at mean age 51); €42,150 (F2 at mean age 54); €49,820 (F3 at mean age 56); and €56,370 (cirrhosis at mean age 59). Triple therapy with telaprevir or boceprevir incurred immediate costs of about €37,000, and increased discounted lifetime costs by 20% (F2), 28% (F3), and 79% (F4) as compared to no treatment in HCV mono-infected adult patients.

Schwarzinger M, Deuffic-Burban S, Mallet V, et al. Lifetime costs attributable to chronic hepatitis C from the French healthcare perspective (ANRS no. 12188) (Abstract). J Hepatol 2013; 58(Suppl. 1): S21–2.

Cost-Effectiveness

Table 2. Results of Cost-Effectiveness Analyses: (a) Short-Term Scenario: Sustained Virological Response (SVR); (b) Long-Term Scenario: Life Year Gained (LYG); (C) Long Term Scenario: Quality-Adjusted Life Year (QALY)

(a) Short-Term Scenario

Treatment Strategies	Costs in 2011 Euros	SVR (%)	ICER/SVR Base-Case Analysis (2011 Euros)
Dual therapy	12,673	45.8	–
Boceprevir response-guided therapy	30,805	67.0	85,650
Boceprevir IL28B genotype-guided strategy	28,548	72.0	60,500
Boceprevir RVR-guided strategy	27,622	72.1	56,960
Telaprevir response-guided therapy	46,621	74.5	118,000
Telaprevir IL28B genotype-guided strategy	37,425	79.0	74,600

(b) Long-Term Scenario

Treatment Strategies	Costs in 2011 Euros	LYG	ICER/LYG Base-Case Analysis (2011 Euros)
Dual therapy	18,337	2.57	–
Boceprevir response-guided therapy	34,256	3.75	13,428
Boceprevir IL28B genotype-guided strategy	31,469	4.03	8,936
Boceprevir RVR-guided strategy	30,542	4.04	8,304
Telaprevir response-guided therapy	49,277	4.18	19,204
Telaprevir IL28B genotype-guided strategy	39,620	4.42	11,455

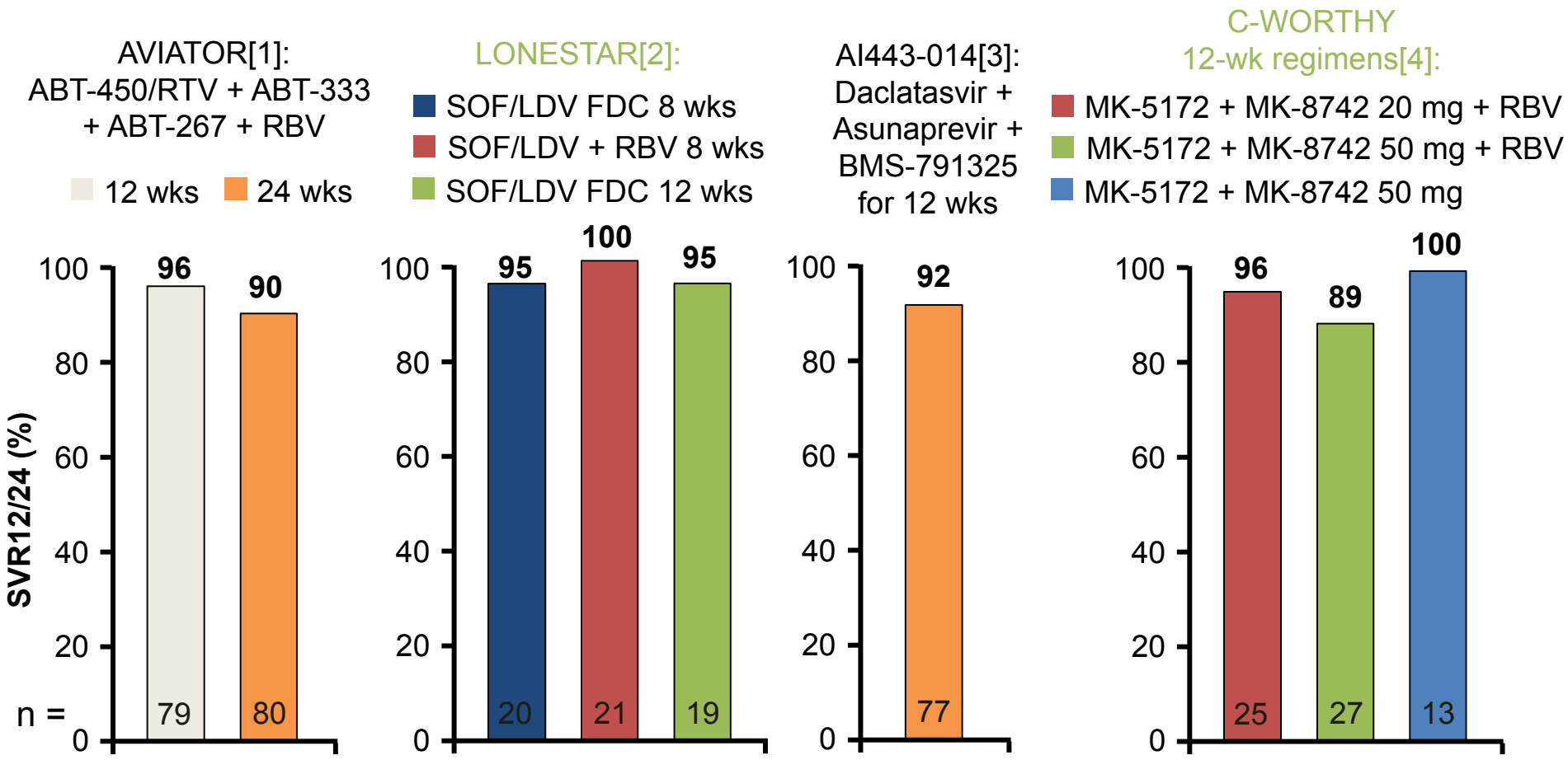
IL28B or RVR guided decision for dual therapy the most cost-effective way to treat chronic HCV GT1 infection

Camma et al., Hepatology 2012

IFN-free regimens: what is the promise for the treatment naïve patients?

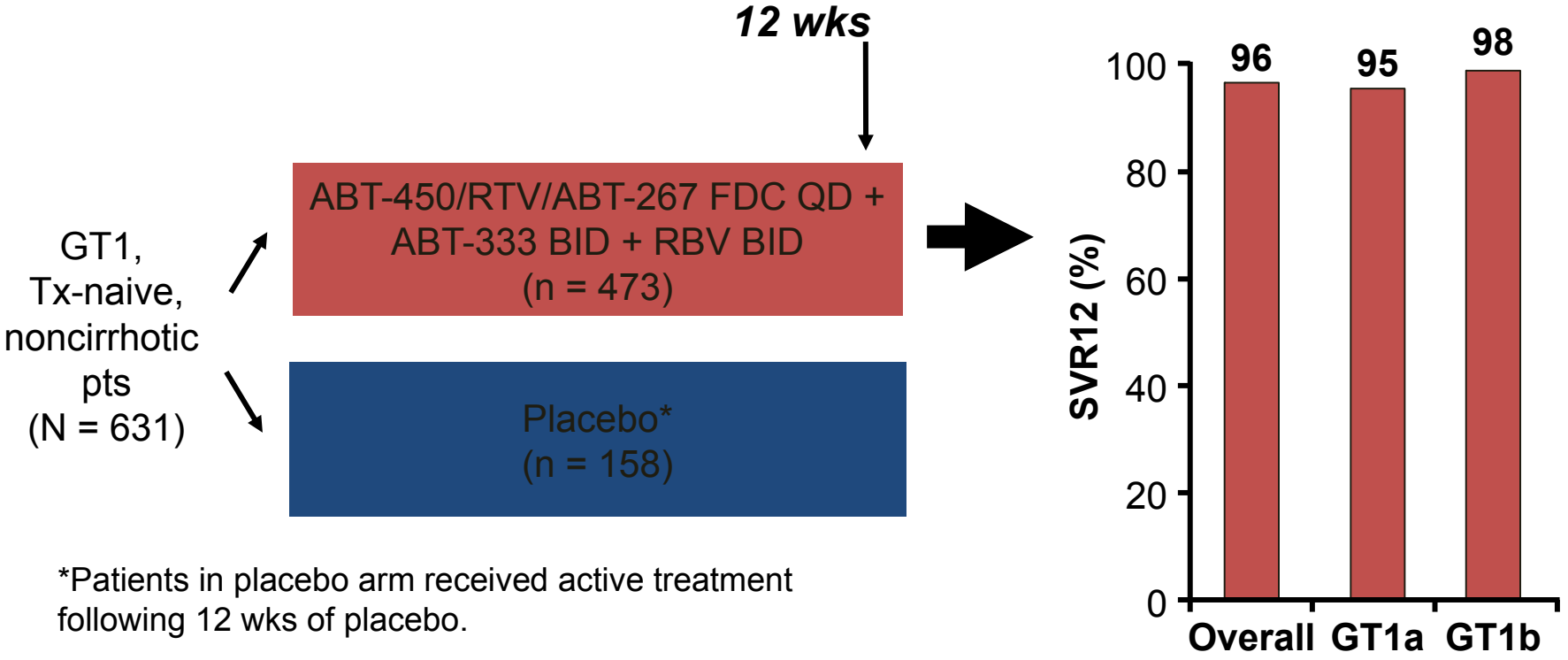
- Higher efficacy
- Better tolerability
- Less indirect expenses

IFN-Free Therapy for Tx-Naive GT1 HCV: Regimens Effective in Both Subtypes



1. Kowdley K, et al. EASL 2013. Abstract 3. 2. Lawitz E, et al. AASLD 2013. Abstract 215.
3. Everson GT, et al. AASLD 2013. Abstract LB-1. 4. Lawitz E, et al. AASLD 2013. Abstract 76.

SAPPHIRE-1: Phase III Study in Treatment-Naive HCV GT1



*Patients in placebo arm received active treatment following 12 wks of placebo.

Press release. November 18, 2013. These data are available in press release format only, have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format before conclusions should be made from these data.

Conclusion

- PEG-RBV+DAA regimens are the first line treatment for genotype 1 naïve patients
  - PEG+RBV dual treatment can be used in patients with IL28B CC-genotype, baseline low viral load and RVR.
- Second wave PI combinations with PEG-RBV demonstrates similar SVR and duration of the treatment, but better safety profile and ease of use.
- SOF + PEG-RBV provides shorter duration and similar SVR
- IFN-free combinations are in the horizon and provide highest efficacy and much better tolerability and ease of use
- When efficacy of the treatment is high and safety is good other factors, like cost and access will be a key in decision making.