Update EASL 2013: New HCV Therapies

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Overview of the State of Antiviral Therapy for HCV

- Refinements of current DAAs
- Triple therapy: PEG/RBV + DAA
- Quad therapy: PEG/RBV+ 2 DAAs
- Interferon sparing DAA regimens
- Difficult to treat populations

Telaprevir or Boceprevir + PegIFN/RBV Superior SVR in Treatment Naïve HCV G1

	TVR (ADVANCE)		BOC (SPRINT-2)	
	TVR12/PR RGT 750 mg q8h	**PEG/R**	**BOC/PR RGT (non-AA/AA) 800 mg tid**	**PEG/R (non-AA/AA)**
SVR	75%	44%	67/42%	40/23%

Jacobson I et al, NEJM 2011; 364:2405-2416
Poordad F et al, NEJM 2011; 364:1195-1206

Issues with 1st Generation PIs: Toxicities

	ADVANCE (TVR)		SPRINT-2 (BOC)	
	TVR12/PR	PR	BOC-RGT	PR
D/C for AEs	10%	7%	12%	16%
D/C for rash	7%	1%	--	--
Anemia (<10/<8.5 g/dL)	36%/9%	14%/2%	45%/5%	26%/4%

Jacobson I et al, Poordad F et al, NEJM 2011

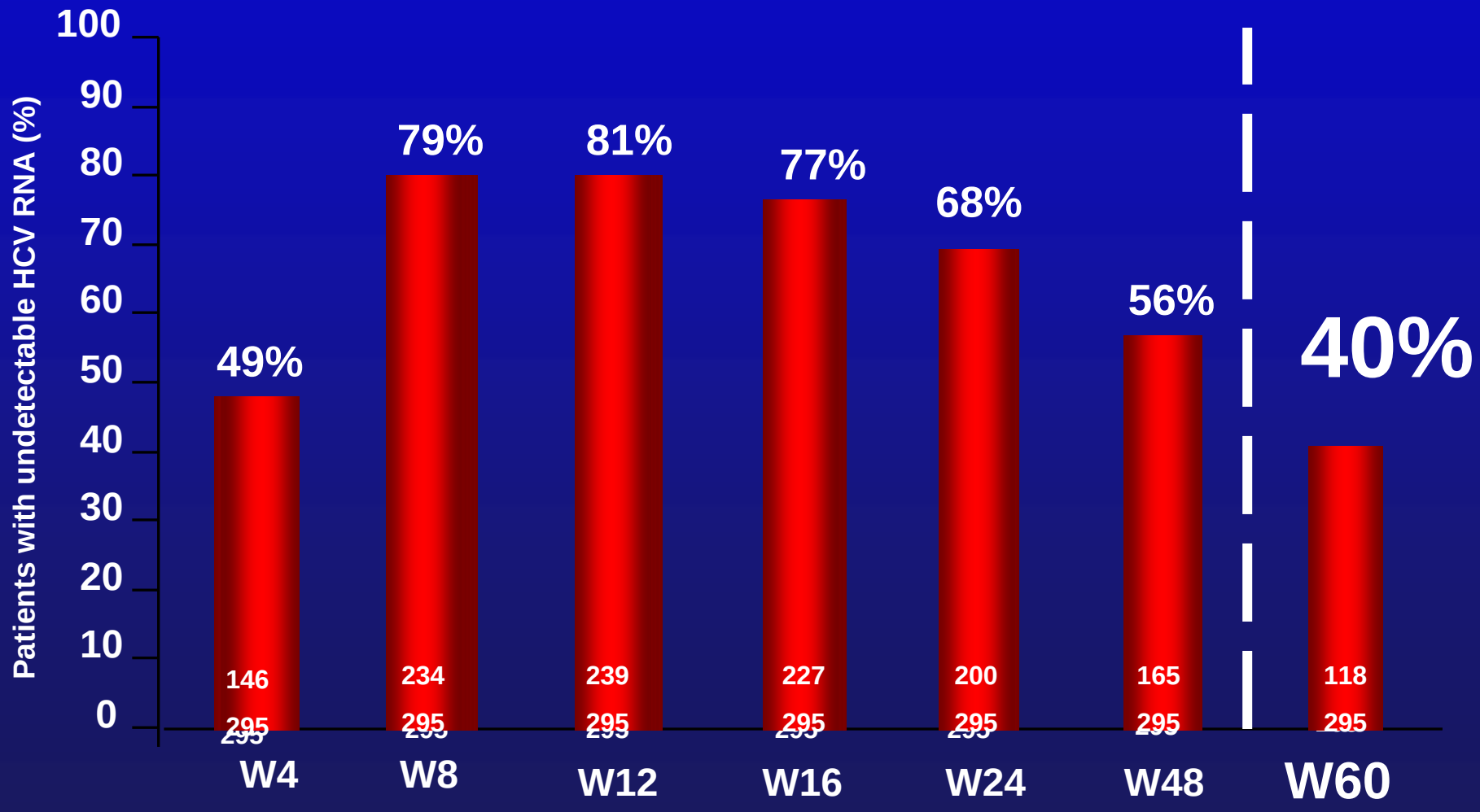
SVR12 Rates and Safety of Triple Therapy Including Telaprevir or Boceprevir in 485 Cirrhotic Non-Responders Treated in the French Early Access Program

(ANRS CO20-CUPIC)

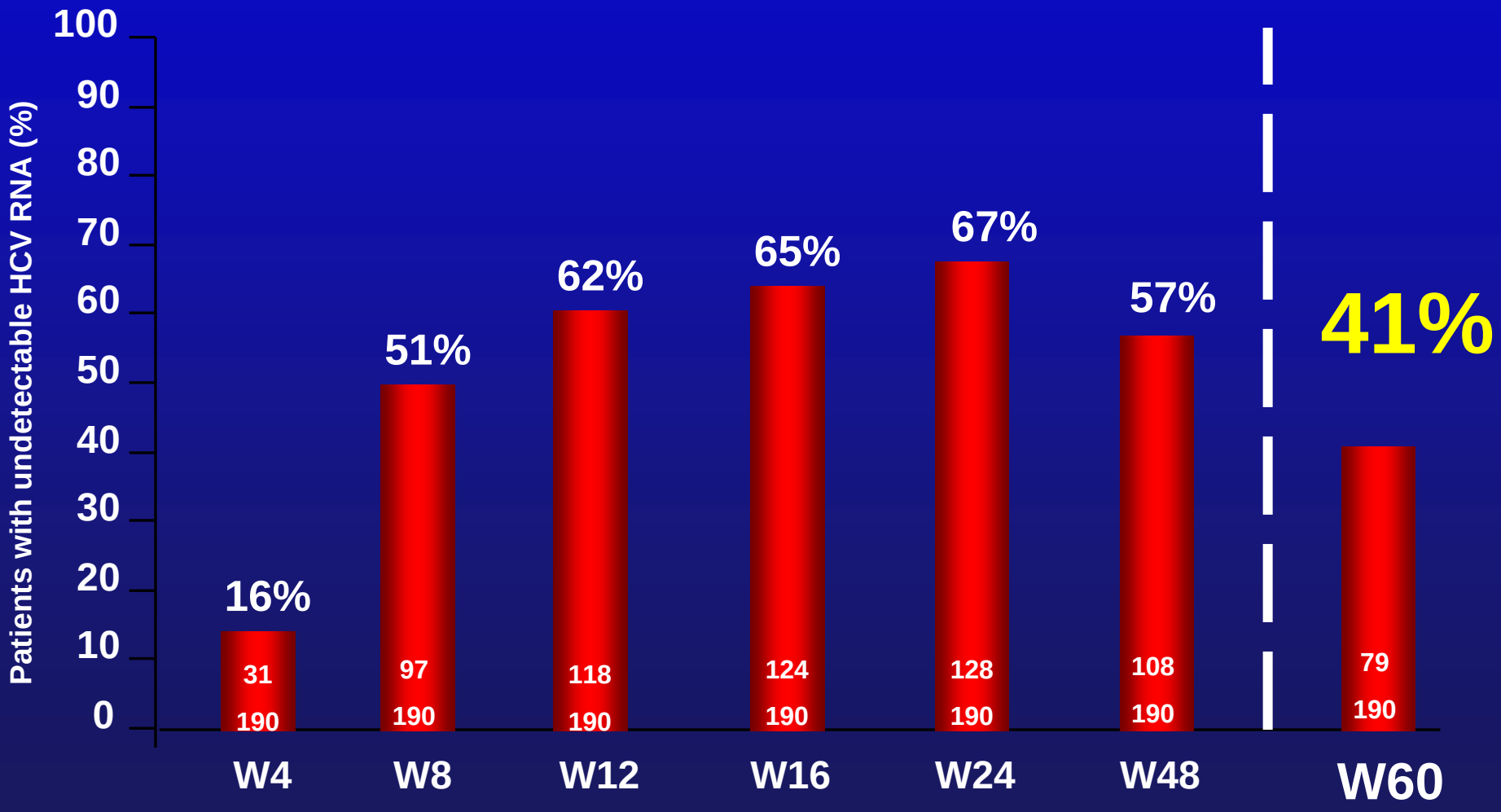
H Fontaine[1], C Hézode[2], C Dorival[3], D Larrey[4], F Zoulim[5],V de Ledinghen[6], V Canva[7], L Alric[8], M Bourlière[9], S Pol[1], T Poynard[10], G Riachi[11], PH Bernard[12], JJ Raabe[13], J Gournay[14], S Métivier[15], JM Pawlotsky[16], D Samuel[17], Y Barthe[3], F Carrat[3], JP Bronowicki[18], for the ANRS CO 20 CUPIC study group.

1.Hôpital Cochin, Paris, 2. Hôpital Henri Mondor, Créteil, 3. UMR-S 707, Paris, 4. Hôpital Saint-Eloi, Montpellier, 5. INSERM U871, Lyon, France, 6.Hôpital Haut Lêvèque, Bordeaux, France 7. Hôpital Clude Hurriez, Lille, France, 8. Médecine Interne, Hôpital Purpan, Toulouse, 9. Fondation Saint-Joseph, Marseille, France, 10. Hépatologie, Hôpital de la Pitié-Salpétrière, Paris, France 11. Hôpital Charles Nicolle, Rouen, France, 12. Hôptal Saint-André, Bordeaux, France, 13. Hôpital Bon Secours, Metz, France, 14. Hôpital Universitaire de Nantes, Nantes, France 15. Hépatogastroentérologie, Hôpital Purpan, Toulouse, France, 16. Hôpital Henri Mondor, Créteil, France 17. Hôpital Paul Brousse, Villejuif, France 17. Hôpital de Brabois, Nancy, France

Telaprevir: Virological Response (ITT)



Boceprevir: Virological Response (ITT)



Telaprevir : SVR_{12} Safety Findings

Patients, n (% patients with at least one event)	Telaprevir n = 295
Serious adverse events (SAEs)*	535 in 160 patients (54.2%)
Premature discontinuation / due to SAEs	139 (47.1%) / 63 (21.3%)
Death	7 (2.4 %)
Infection (Grade 3/4) (3 septicemia, 1 variceal hemmoragia, 1 enkephalopthy, 1 pulmonary neoplasia, 1 pulmonary infection)	27 (9.1 %)
Hepatic decompensation (Grade 3/4)	15 (5.1 %)
Rash (grade 3/SCAR)	16 (5.4 %) / 2 (0.6 %)
Anemia (Grade 3/4 : Hb < 8 g/dL)	38 (12.9 %)
EPO use / blood transfusion	168 (57 %) / 53 (18 %)
GCSF use	8 (2.7 %)
TPO use	6 (2 %)

* SAEs in patients; SCAR: severe cutaneous adverse reaction

Boceprevir : SVR_{12} Safety Findings

Patients, n (% patients with at least one event)	Boceprevir n = 190
Serious adverse events (SAEs)*	321 in 97 patients (51.0%)
Premature discontinuation / due to SAEs	80 (42.1%) / 27 (14.2%)
Death (1 pulmonary infection, 1 anevrysmal beeding, 1 septicemia)	3 (1.6 %)
Infection (Grade 3/4)	8 (4.2 %)
Hepatic decompensation (Grade 3/4)	9 (4.7 %)
Rash (grade 3/SCAR)	2 (1.0 %)
Anemia (Grade 3/4: Hb < 8 g/dL)	19 (10.0 %)
EPO use / blood transfusion	119 (62.6 %) / 26 (13.7 %)
GCSF use	13 (6.8 %)
TPO use	3 (1.6 %)

* SAEs in patients; SCAR: severe cutaneous adverse reaction

H1

Multivariate Analysis: Baseline Predictors of SVR

Predictors	OR	95% CI	p-value
Relapser vs Partial or null responders	2.03	1.38-3.00	0.0003
Genotype 1b vs Genotype non 1b	1.92	1.3-2.84	0.0011

H1 Si tu as, pas obligatoire si le nombre de malades n'est pas important

Hezode, 4/4/2013

Multivariate Analysis: Baseline Predictors of Severe Complications*

Predictors	OR	95%CI	p-value
Platelet count $\leq$100,000/mm^3	3.11	1.32-7.73	0.0098
Serum albumin level <35 g/L	6.33	2.66-15.07	<0.0001

* Death, severe infection and hepatic decompensation, n=32 (6.4%)

High SVR Rates (SVR4) for 12-Week Total Telaprevir Combination Therapy in *IL28B* CC Treatment-Naïves and Prior Relapsers With G1 Chronic Hepatitis C: CONCISE Interim Analysis

DR Nelson,[1] F Poordad,[2] JJ Feld,[3] MW Fried,[4] IM Jacobson,[5] PJ Pockros,[6] MS Sulkowski,[7] S Zeuzem,[8] L Bengtsson,[9] S George,[9] MI Friedman,[9] on behalf of the CONCISE Study Team

Figure 1. Treatment Regimen for Randomized Patients With RVR Who Complete 12 Weeks of T/PR Therapy

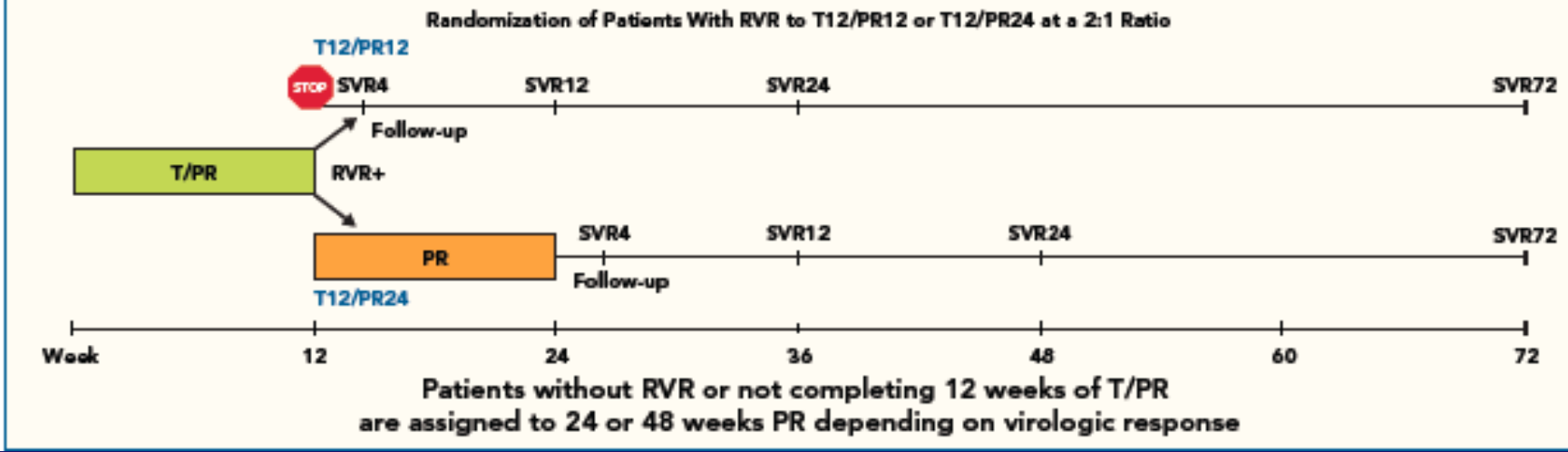


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Figure 2. Patient Disposition

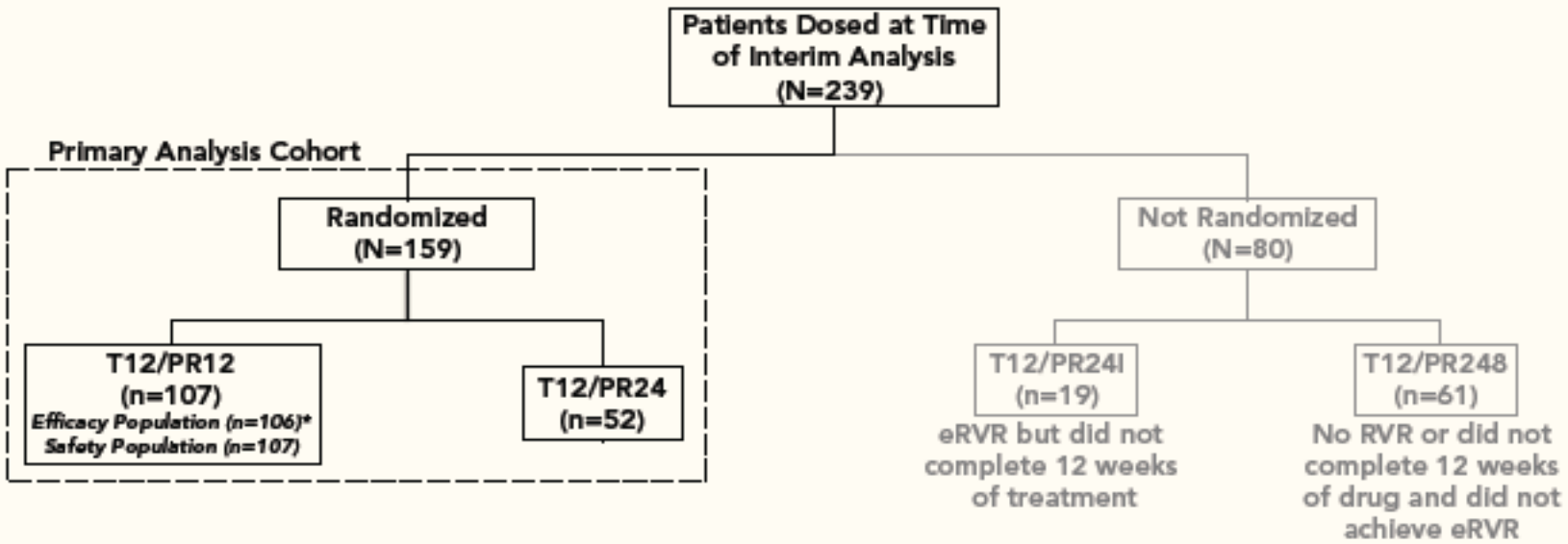
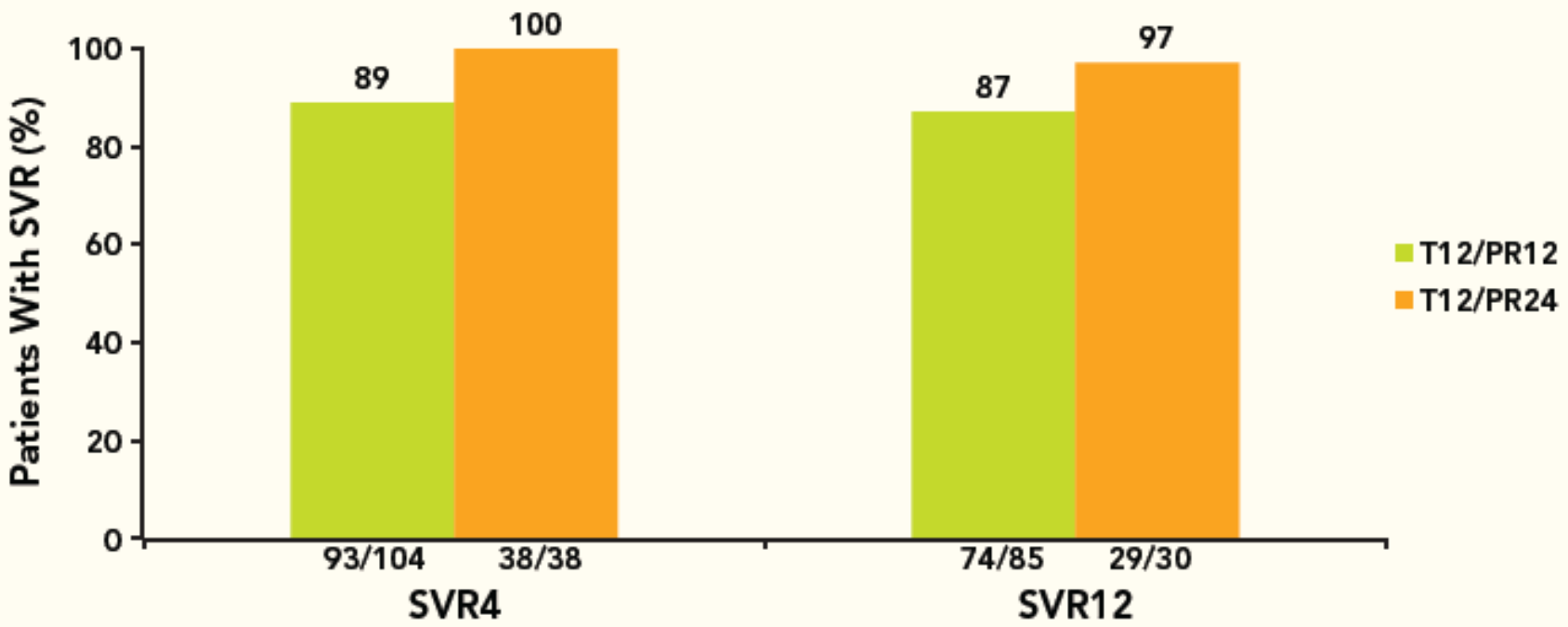
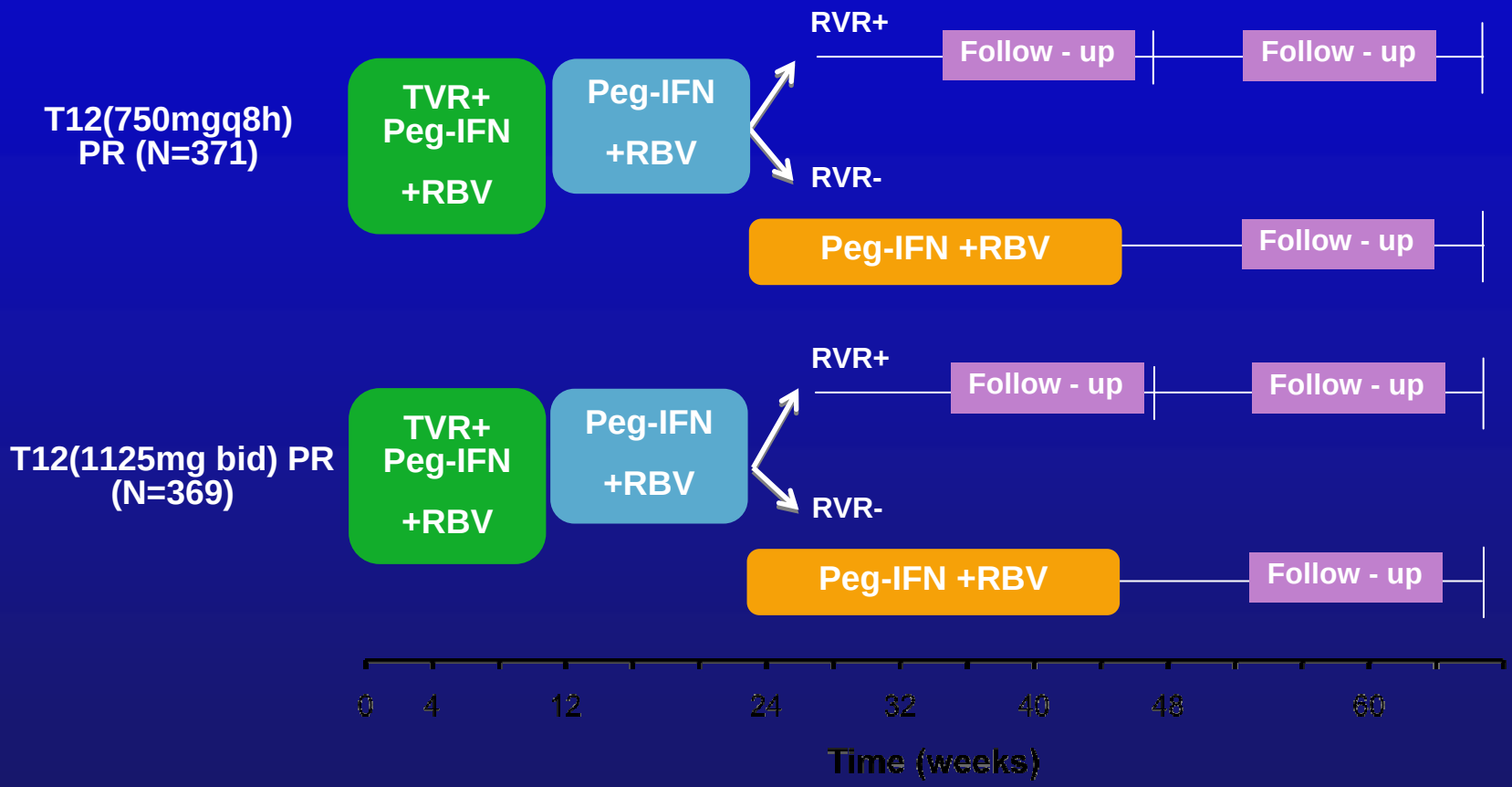


Figure 3. Sustained Virologic Response at Weeks 4 and 12 for Randomized Patients Treated With T12/PR12 and T12/PR24



HCV RNA was measured using the Roche COBAS TaqMan HCV RNA Assay (v2.0), LLOQ – 25 IU/mL, HCV RNA values <LLOQ were reported as either HCV RNA not detected or <25 IU/mL detected.
SVR4 and SVR12, sustained viral response at 4 and 12 weeks, respectively.

OPTIMIZE Study: Study Design



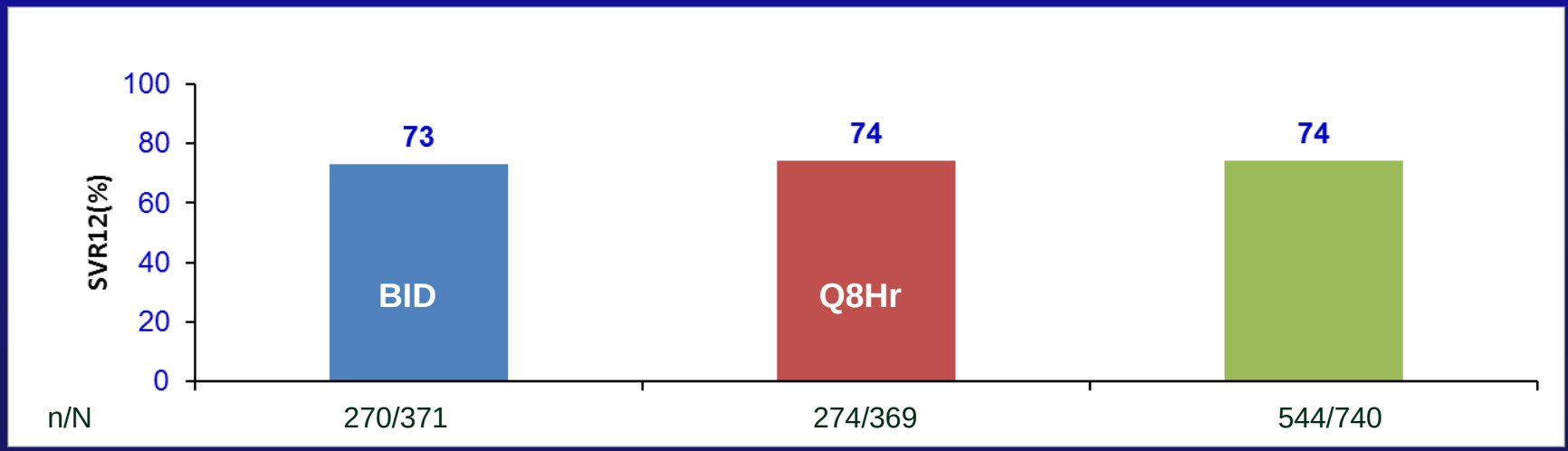
RVR+ = patient achieved HCV RNA <25 IU/mL, target not detected at Week 4 of treatment. All study drugs were stopped if HCV RNA levels were >1000 IU/mL at Week 4 or 25 IU/mL at Weeks 12, 24, 32 or 40.Randomization was stratified by liver fibrosis status (F0–F2; F3–F4) and IL28B subtype (CC, CT, TT).Peg-IFN alfa-2a 180 µg/week; RBV 1000–1200 mg/day; RVR = rapid virologic response.

Buti M, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. LB-8.

OPTIMIZE Study: Efficacy

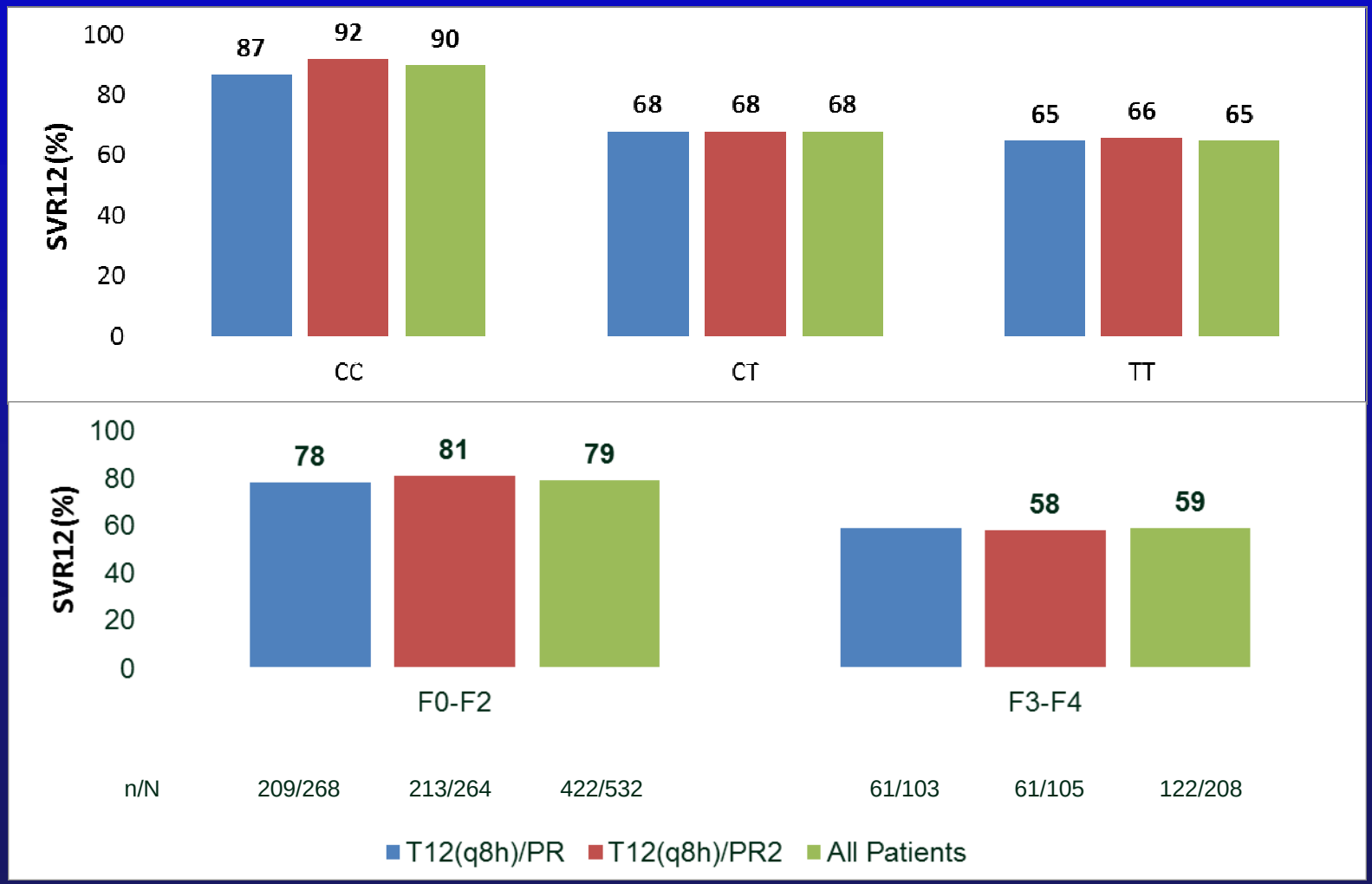
SVR12 was 74% in the T12 (bid)/PR group versus 73% in the T12 (q8h)/PR group

- The difference between T12(bid)/PR and T12(q8h)/PR was 1.5% with a 95% CI: –4.9 to 12.0
- The lower limit of the 95% CI (–4.9%) was well above the predetermined noninferiority margin of –11%



Buti M, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. LB-8.

OPTIMIZE Study: SVR12 in the T12(bid)/PR Group, T12(q8h)/PR Group and All Patients by a) IL28B Status and b) Fibrosis Stage



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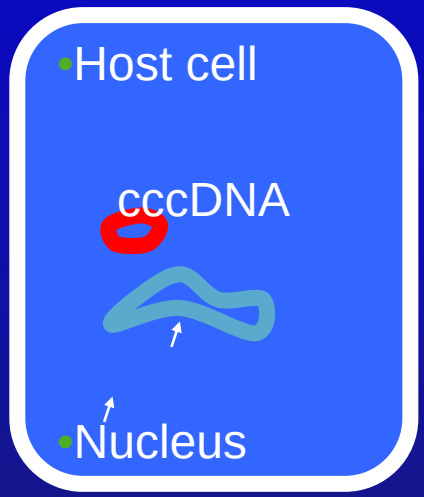
Hepatitis C Differs from HIV and HBV No long-term or Latent Reservoir

HBV

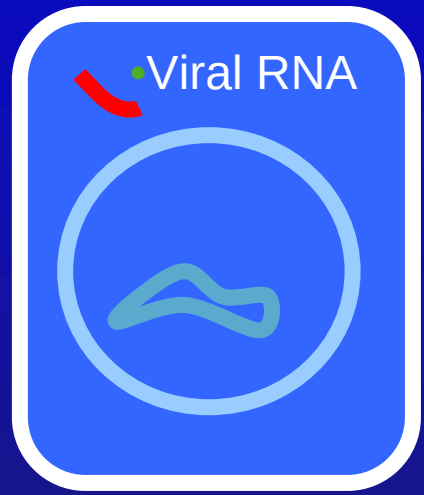


- TREATMENT
  - Long-term suppression of viral replication

HIV

- TREATMENT
  - Long-term
  - suppression of viral replication[2,3]

HCV

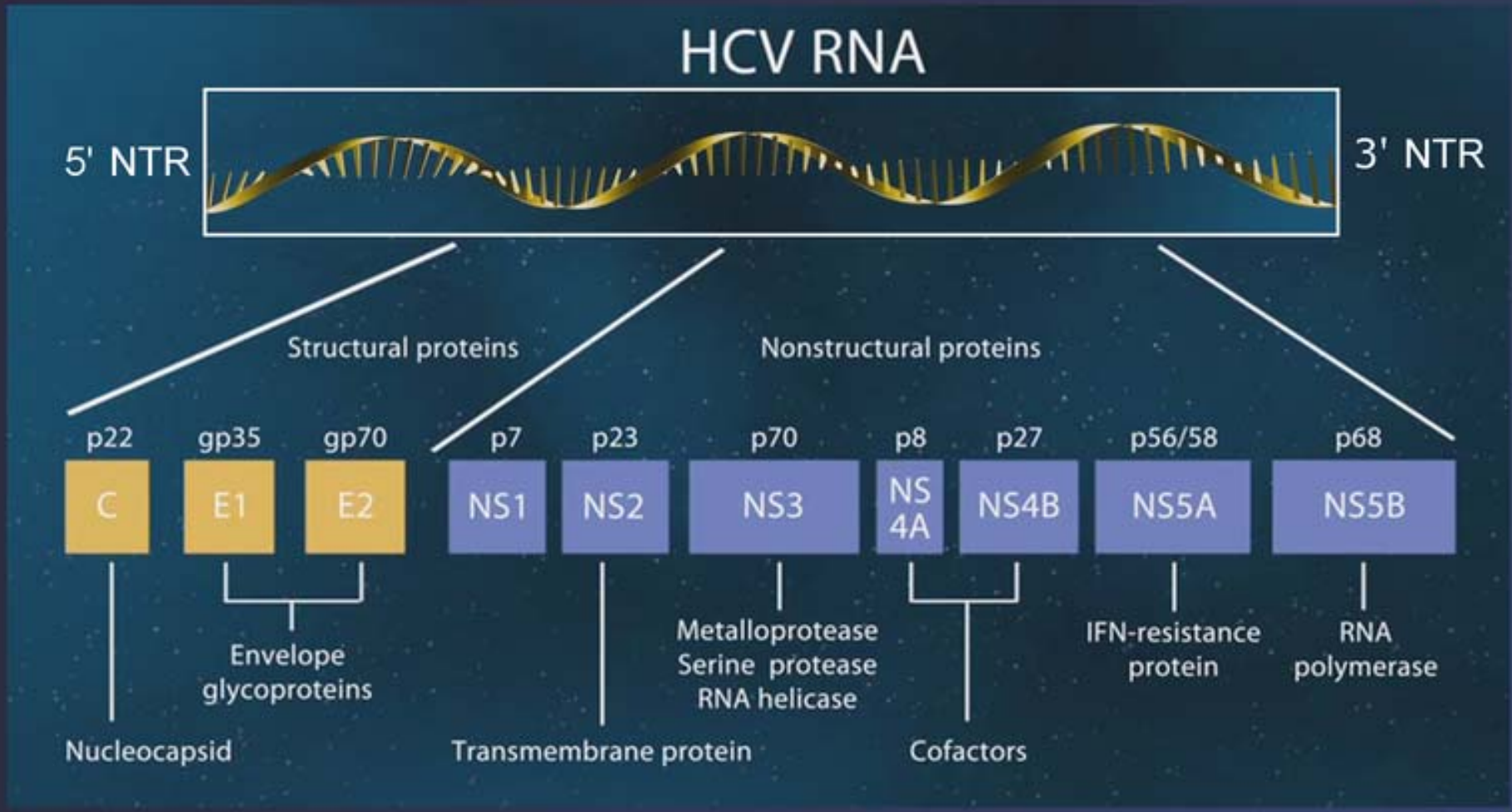


- TREATMENT
  - Viral Eradication = Cure

- cccDNA = covalently closed circular DNA

1. Pawlotsky JM. *J Hepatol* 2006;44:S10-S13; 2. Siliciano JD, Siliciano RF. *J Antimicrob Chemother* 2004;54:6-9;
3. Lucas GM. *J Antimicrob Chemother* 2005;55:413-416

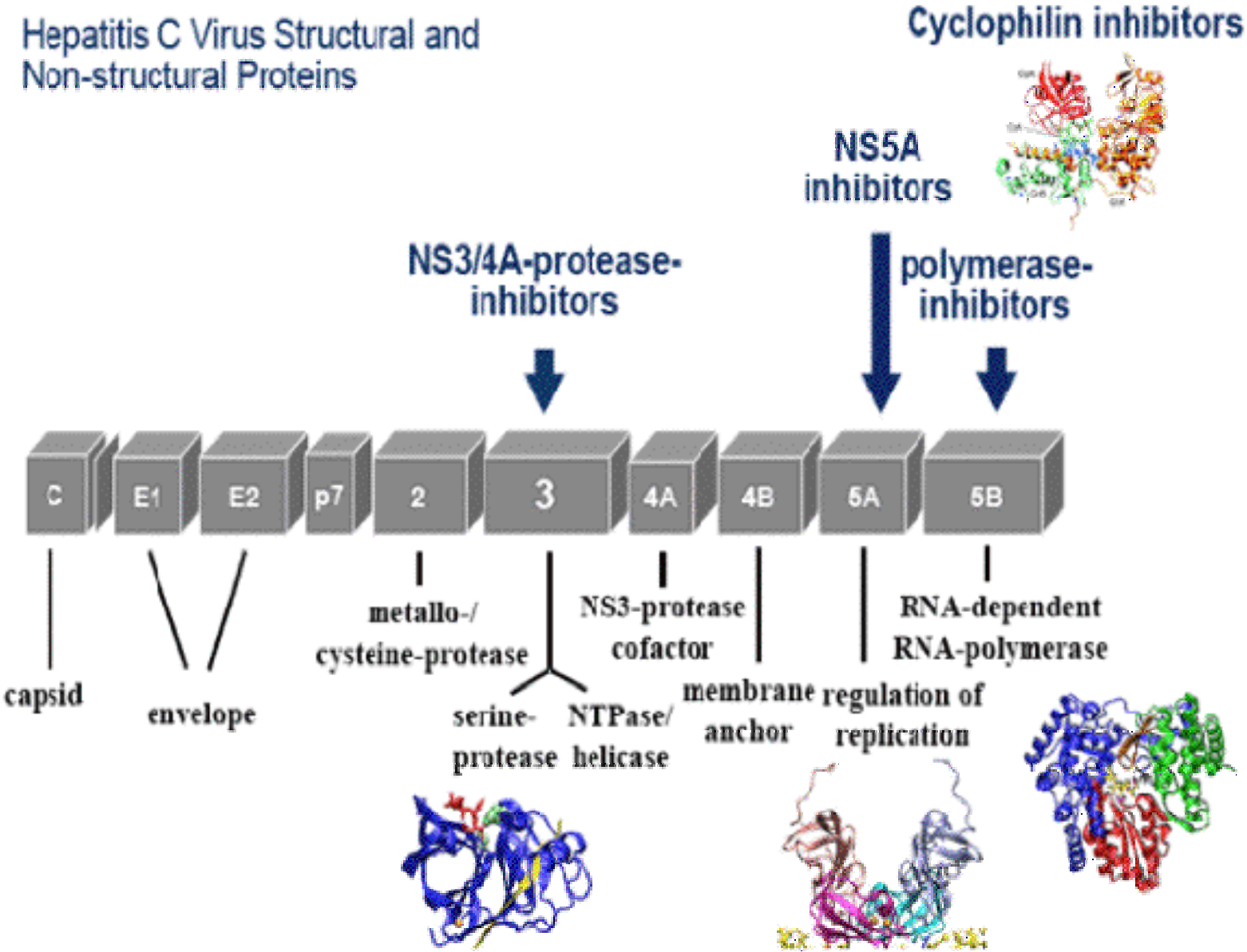
HCV Viral Genome and Associated Proteins



Bartenschlager R, Lohmann V. *J Gen Virol.* 2000;81(pt 7):1631–1648.

Main targets of direct antiviral agents (DAA)

Hepatitis C Virus Structural and Non-structural Proteins



Characteristics of HCV DAA Classes

Characteristic	Protease inhibitors	Nucleos(t)ide Polymerase inhibitors	Nonnucleoside Polymerase inhibitors	NS5A inhibitors
Potency	High; Variable among HCV genotypes	Moderate-high; Consistent across genotype, subtype	Variable; Variable among HCV genotypes	High; multiple HCV genotypes
Barrier to Resistance	Low 1a < 1b	High; 1a = 1b	Very Low 1a < 1b	Low 1a < 1b
Drug Interaction Potential	High	Low	Variable	Low to moderate
Toxicity	Rash Anemia ↑Bilirubin	Mitochondrial Nuc interactions (ART, RBV)	Variable	Variable
Pharmacokinetics	Variable; QD to TID	QD	Variable; QD to TID	QD
Comments	2nd gen PIs: better barrier, pangenotypic	Single target Active site	Allosteric; Many targets	Multiple antiviral MOA

Lack Of Cross-Resistance Between Peg-IFN/RBV &/Or A Combination Of Antiviral Agents May Provide An Opportunity For Elimination Of Resistant Variants

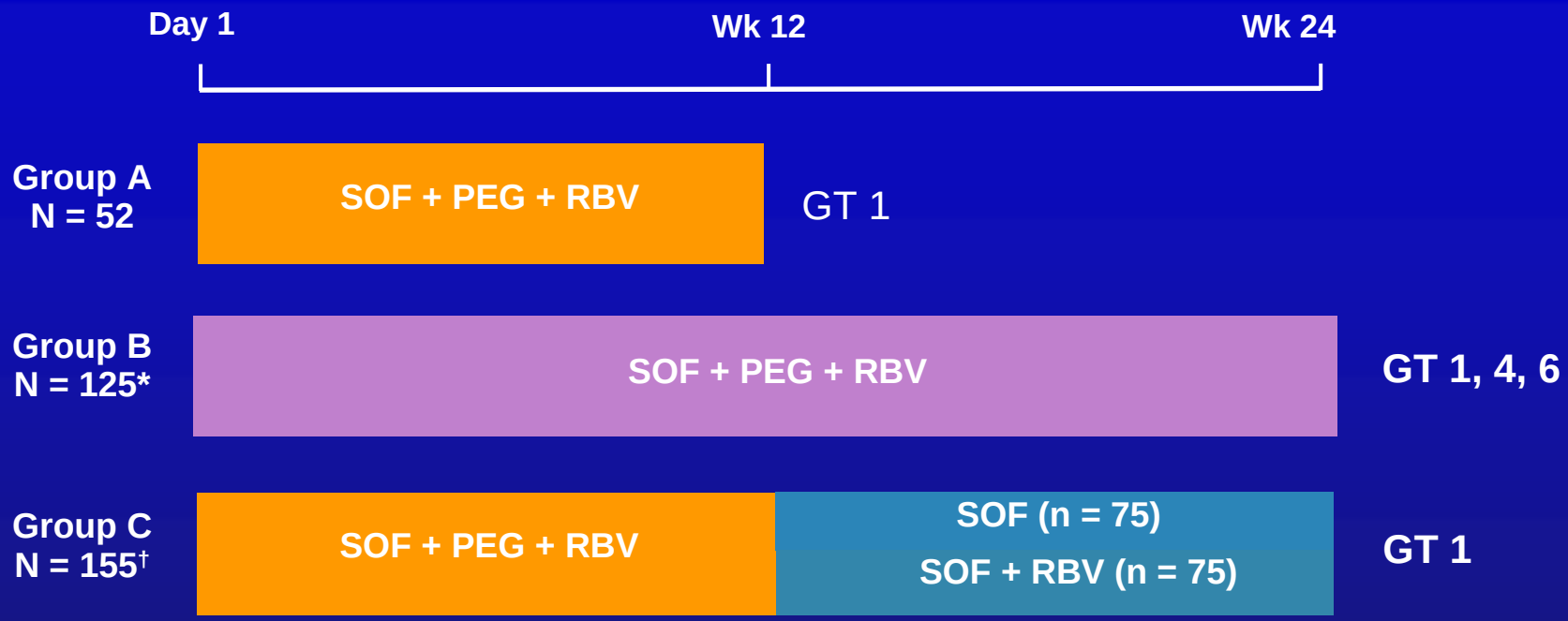
Target	Variant	NS3 Linear	NS3 Macrocyclic	NS5A inhibitor	NS5B nucleoside	NS5B Palm	NS5B Thumb	NS5B Finger	IFN	RBV
NS3 Protease	V36M	R	S	S	S	S	S	S	S	S
	T54A	R	S	S	S	S	S	S	S	S
	R155K	R	R	S	S	S	S	S	S	S
	A156T	R	R	S	S	S	S	S	S	S
	D168V	S	R	S	S	S	S	S	S	S
NS5A	L28V	S	S	R	S	S	S	S	S	S
	Y93H	S	S	R	S	S	S	S	S	S
NS5B	S282T	S	S	S	R	S	S	S	S	S
	C316Y	S	S	S	S	R	S	S	S	S
	M414T	S	S	S	S	R	S	S	S	S
	R422K	S	S	S	S	S	R	S	S	S
	M423T	S	S	S	S	S	R	S	S	S
	P495S	S	S	S	S	S	S	R	S	S

S = Susceptible
(< 4 fold shift in HCV replicon EC50)

R = Resistant
(>4 fold increase in EC50)

Triple Therapy:
PEG + RBV + DAA

ATOMIC Study Design
Sofosbuvir + PegIFN/RBV



Non-cirrhotic, treatment-naïve patients with HCV genotype 1 were randomized 1:2:3 into open-label arms

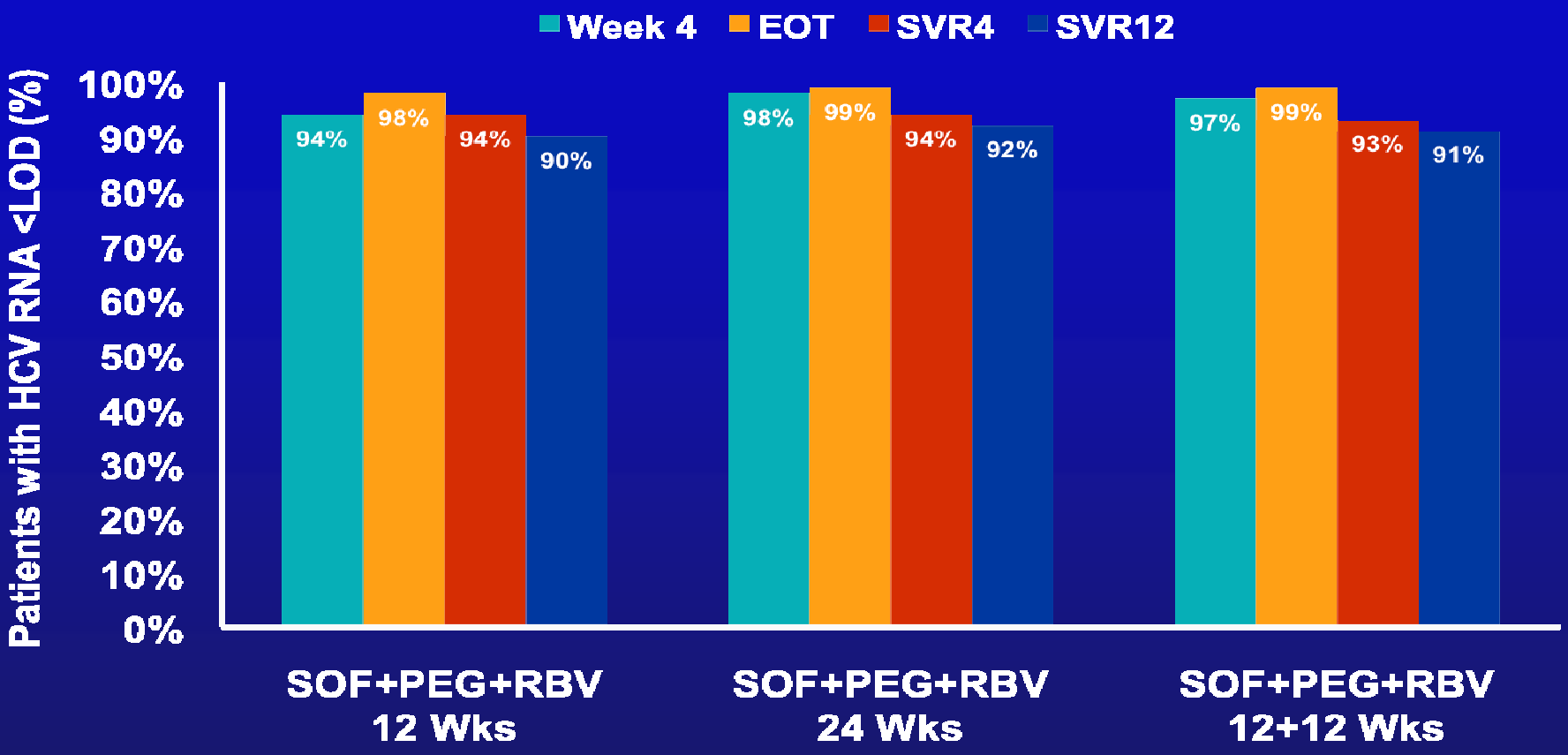
HCV RNA analyzed by TaqMan® HCV Test 2.0 (LOD: 15 IU/mL)

*Of the 125 patients enrolled in Arm B, 11 were genotype 4 and five were genotype 6

†Five of the 155 patients were not re-randomized at Week 12

Hassanein T, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. 230.

ATOMIC Study: 90% SVR_{12}: Sofosbuvir + PegIFN/RBV 12-Week Regimen

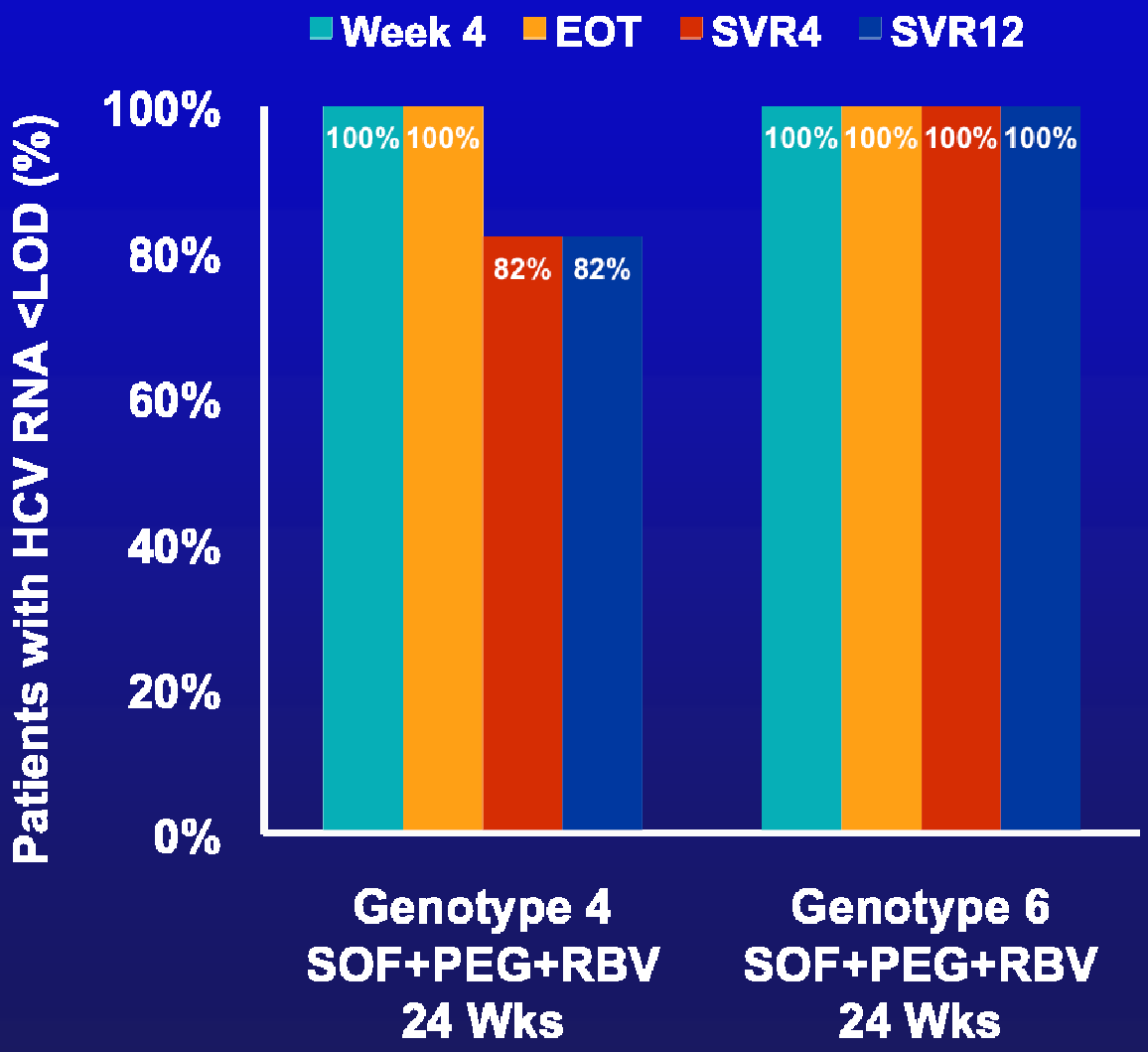


11 patients (1 in the 12 Wk group) who achieved SVR12 were subsequently lost to follow-up resulting in SVR24 rate of 88% with 12 weeks of Rx

No relapse after SVR12 was seen in any group

Hassanein T, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. 230.

ATOMIC Study: High Efficacy in HCV G-4 and G-6



- 11 patients with HCV GT-4 achieved RVR
- None had virologic failure
- Two were LTFU without post-treatment data
- All 5 patients with HCV GT-6 achieved SVR24

Hassanein T, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. 230.

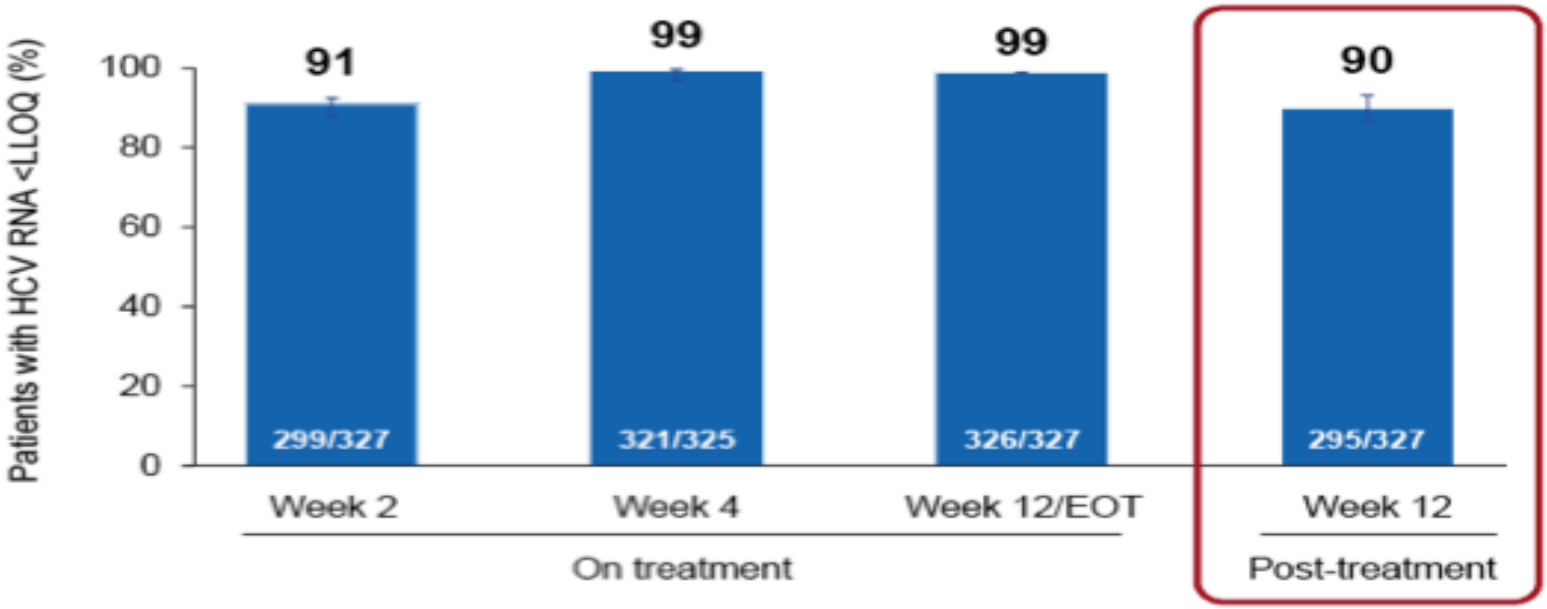
NEUTRINO Study: Sofosbuvir + PegIFN/RBV for 12 Weeks: 90% SVR_{12} in Treatment-Naïve HCV Genotypes 1, 4, 5, and 6

	SOF + Peg-IFN + RBV N=327
Mean age, y (range)	52 (19–70)
Male, n (%)	209 (64)
Black, n (%)	54 (17)
Hispanic, n (%)	46 (14)
Mean BMI, kg/m^2 (range)	29 (18–56)
IL28B CC, n (%)	95 (29)
GT 1, n (%)	292 (89)
GT 4/5/6, n (%)	35 (11)
Mean baseline HCV RNA, log_{10} IU/mL (range)	6.4 (2.1–7.6)
Cirrhosis, n (%)	54 (17)

Gane E, et al. EASL 48th Annual MeetingApril 24th - 28th 2013The Netherlands, Amsterdam

NEUTRINO Study: Sofosbuvir + PegIFN/RBV for 12 Weeks: 90% SVR_{12} in Treatment-Naïve HCV Genotypes 1, 4, 5, and 6

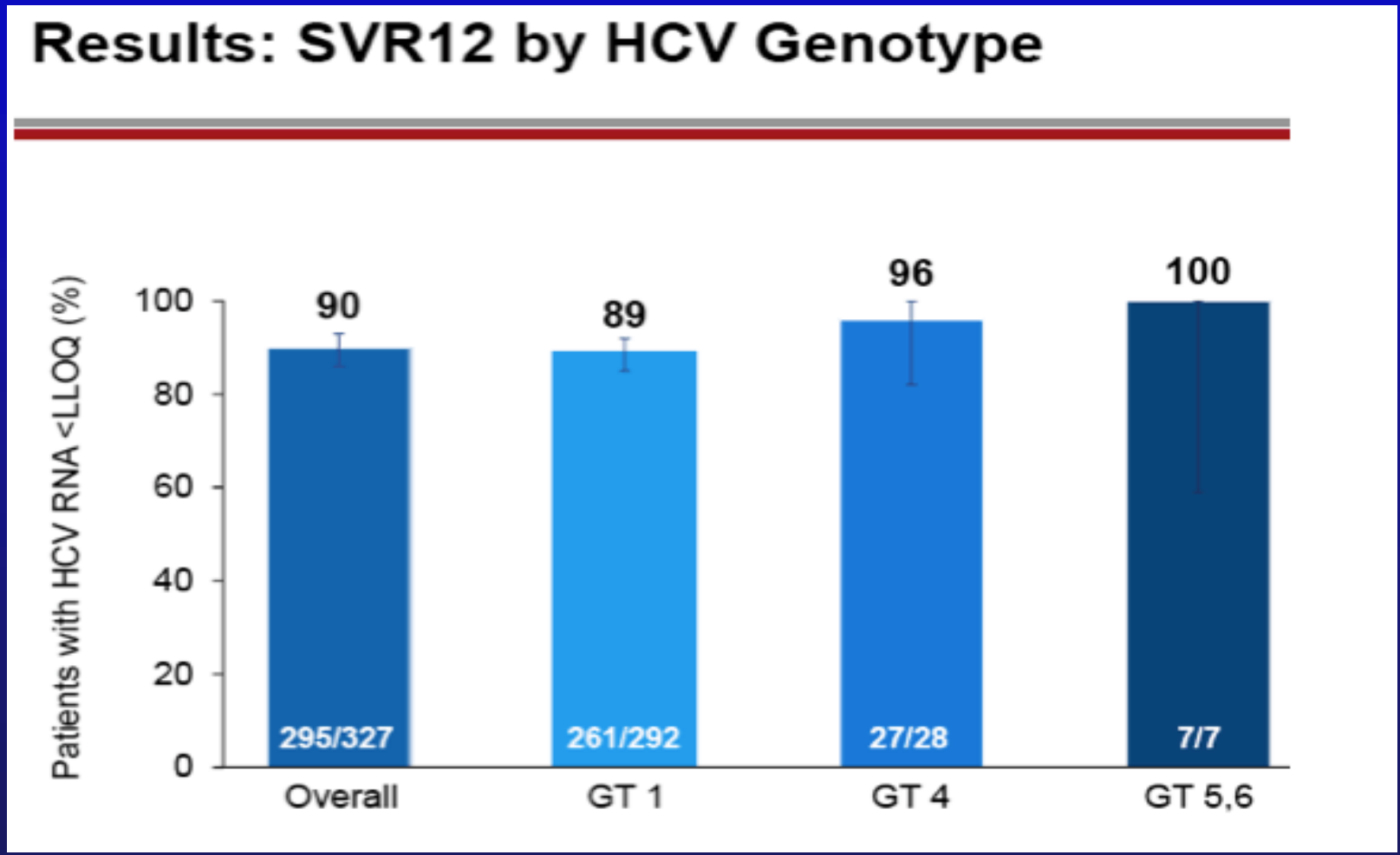
Results: Virologic Response



- Study met primary endpoint of superiority over historic control rate of 60% ($p < 0.001$)
- Relapse accounted for all virologic failures

Error bars represent 95% confidence intervals

NEUTRINO Study: Sofosbuvir + PegIFN/RBV for 12 Weeks: 90% SVR_{12} in Treatment-Naïve HCV Genotypes 1, 4, 5, and 6



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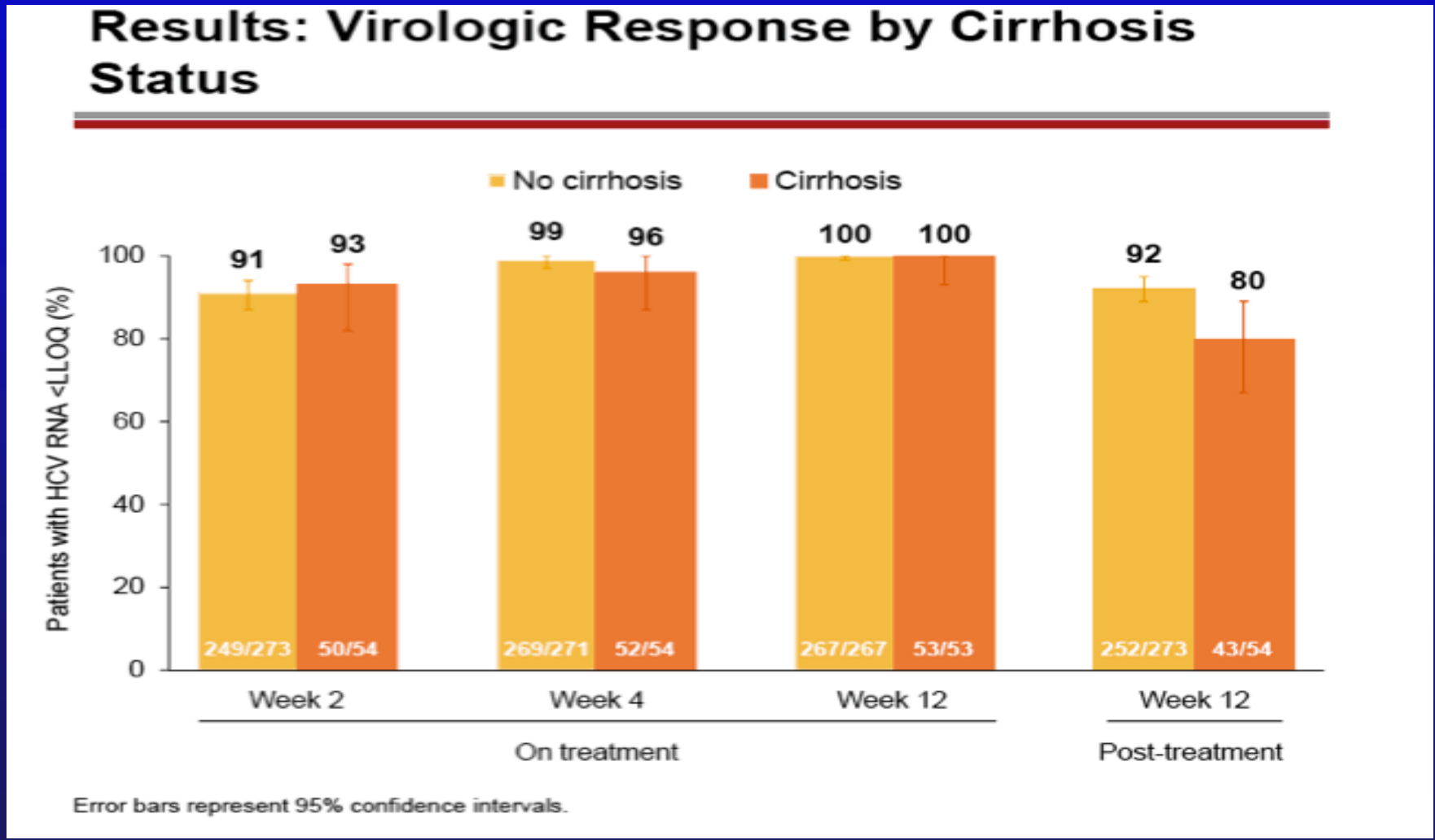

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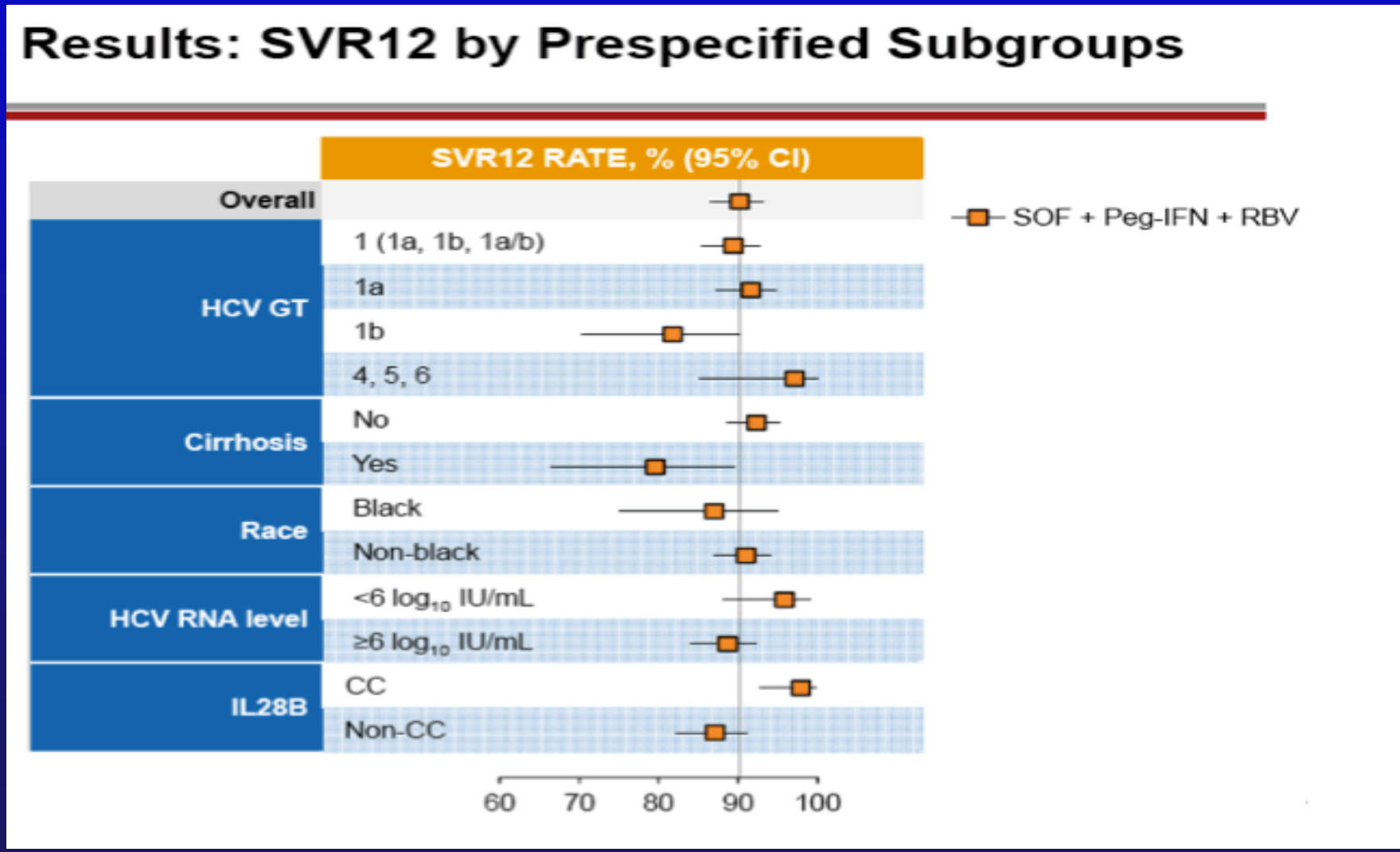
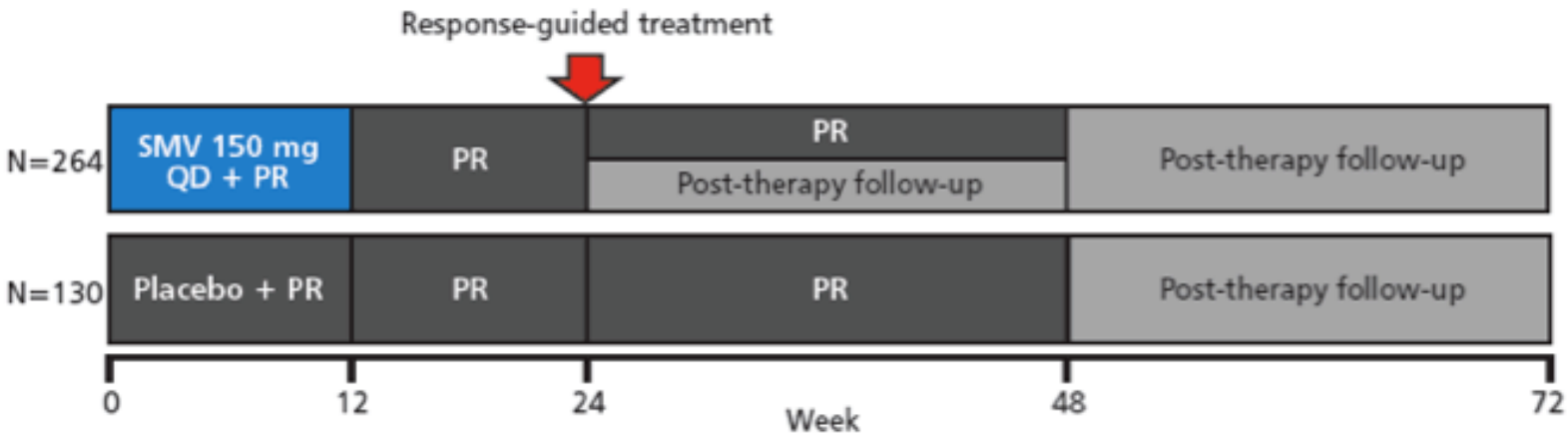


QUEST-1 (Phase III) Study: Simeprevir (TMC435) + PegIFN/RBV HCV G1 Treatment-Naïve Patients

FIGURE 1: QUEST-1 (TMC435-C208) trial design.



RGT in simeprevir arm: if HCV RNA <25 IU/mL at Week 4 and undetectable at Week 12, complete treatment at Week 24. Stopping rules : if HCV RNA >1000 IU/mL Week 4, stop SMV/placebo; if HCV RNA <2log$_{10}$ IU/mL reduction at Week 12, or confirmed ≥25 IU/mL at Week 24 or 36, stop all treatment.

PR, peginterferon α-2a 180 μg/wk + ribavirin 1000-1200mg/day; QD, once-daily.

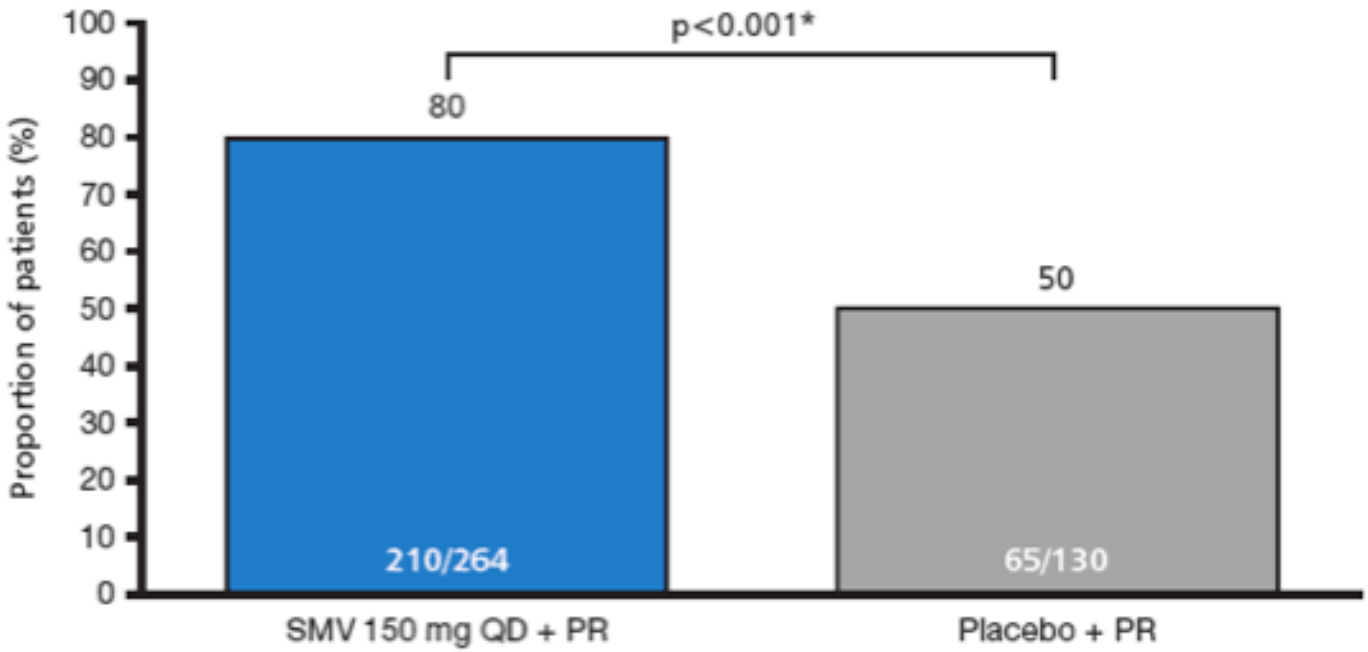
QUEST-1 (Phase III) Study: Simeprevir (TMC435) + PegIFN/RBV HCV G1 Treatment-Naïve Patients

		SMV 150 mg QD + PegIFN/RBV (N=264)	Pbo + PegIFN/RBV (N=130)
Patient demographics			
Female, %		44	43
Race, %	White	87	94
	Black/African American	10	3
	Asian	2	2
Median age, years		48	48
Median Body Mass Index, kg/m²		27	27
IL28B genotype, %	CC	29	29
	Non-CC	71	72
Disease characteristics			
Median HCV RNA, $\log_{10}$ IU/mL		6.5	6.4
HCV RNA >800,000 IU/mL, %		83	74
Genotype 1a, %		56	57
Genotype 1b, %		44	43
METAVIR score, %	F0-F1	45	39
	F2	25	31
	F3	18	18
	F4	12	13

Jacobson I, et al. EASL 24 April - 28 April 2013 · Amsterdam, The Netherlands

QUEST-1 (Phase III) Study: Simeprevir (TMC435) + PegIFN/RBV HCV G1 Treatment-Naïve Patients

FIGURE 2: Sustained virological response (SVR12).



*controlling for stratification factors.

PR, peginterferon α-2a + ribavirin; SVR12, sustained virological response (HCV RNA undetectable) 12 weeks after planned treatment end.

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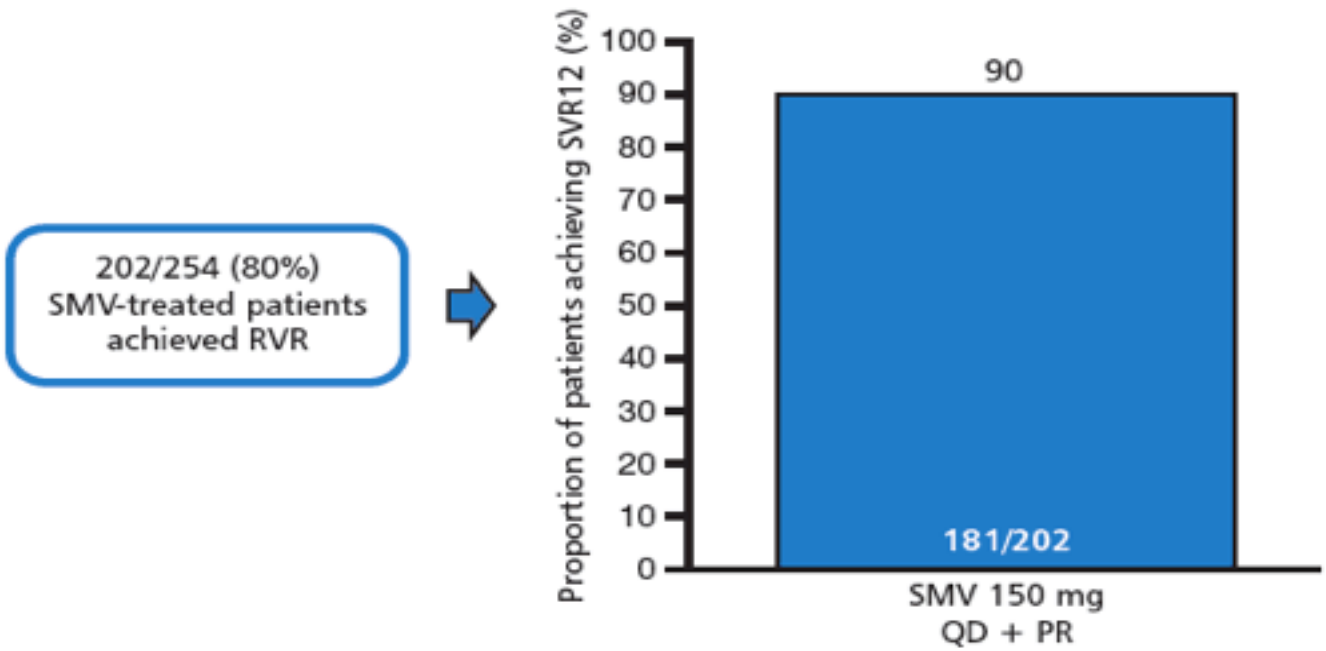
QUEST-1 (Phase III) Study: Simeprevir (TMC435) + PegIFN/RBV HCV G1 Treatment-Naïve Patients

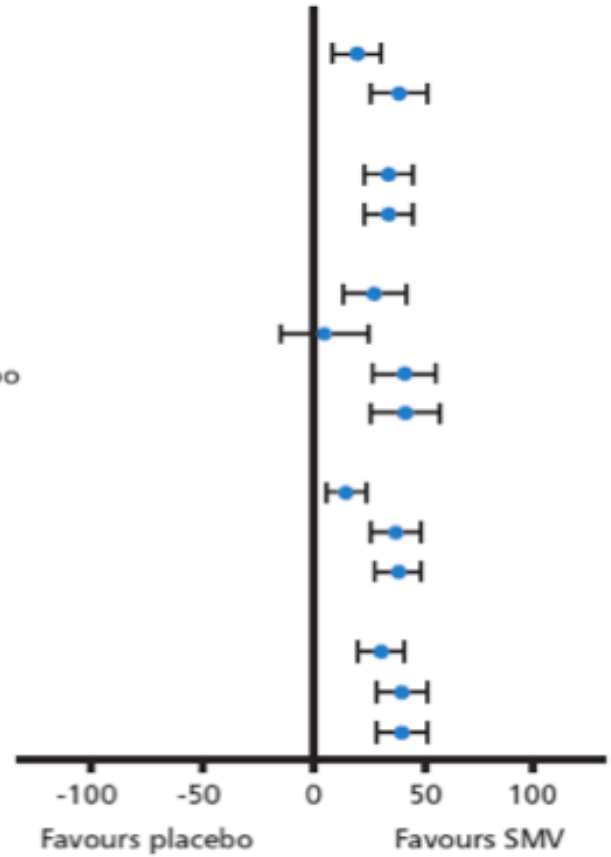
FIGURE 3: Rapid virological response (RVR) and subsequent sustained virological response (SVR12).



PR, peginterferon α-2a + ribavirin; RVR, rapid virologic response (HCV RNA undetectable) at Week 4; SVR12, sustained virological response (HCV RNA undetectable) 12 weeks after planned treatment end.

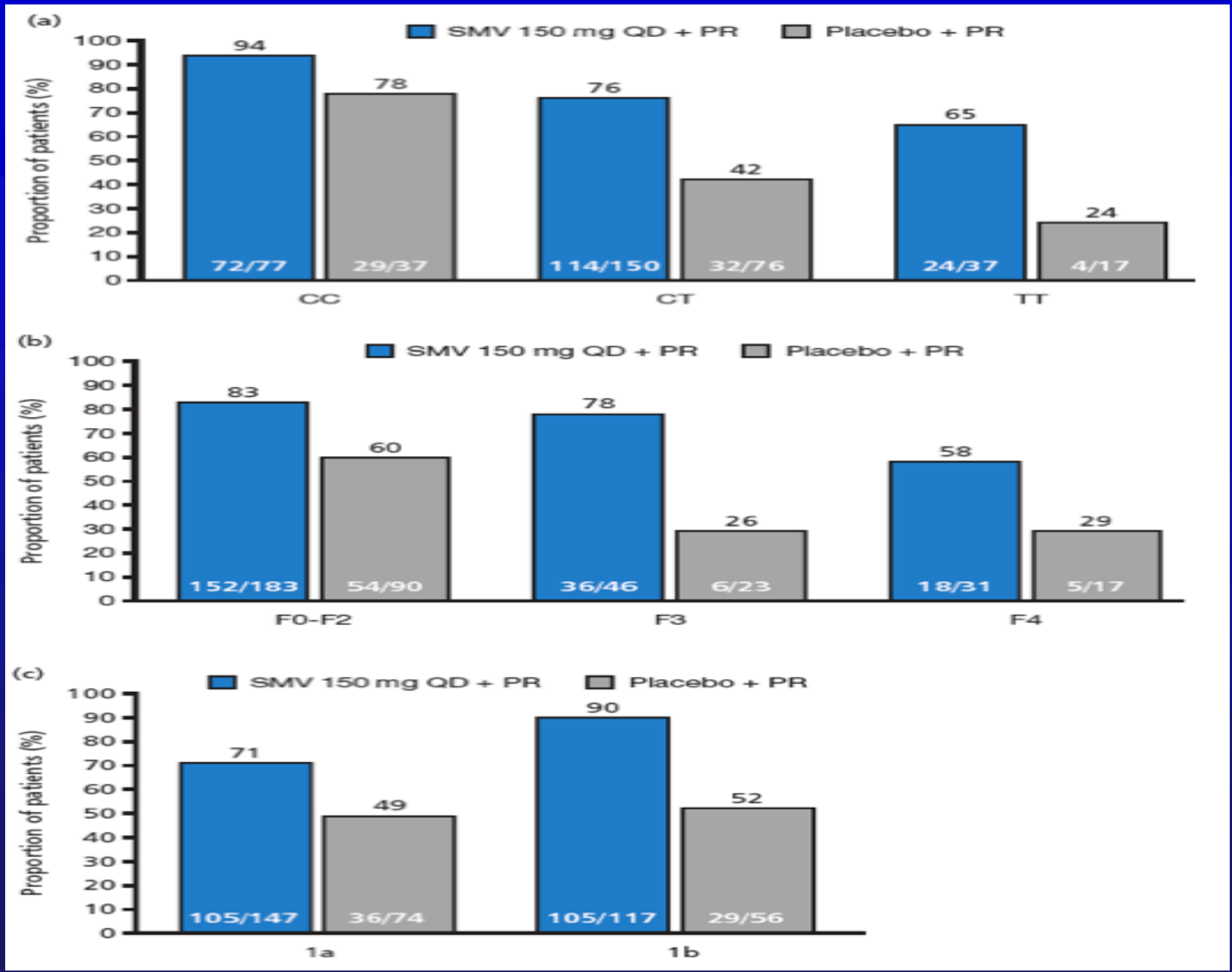
QUEST-1 (Phase III) Study: Simeprevir (TMC435) + PegIFN/RBV HCV G1 Treatment-Naïve Patients

FIGURE 5: Differences in SVR12 by subgroup (95% CIs).



Subgroup	Difference in proportions and 95% CI	n= SMV	Pbo
Baseline HCV RNA			
≤800,000 IU/mL	19.6 (9.2; 30.1)	46	34
>800,000 IU/mL	38.2 (26.7; 49.7)	218	96
Gender			
Male	34.7 (23.6; 45.9)	148	74
Female	34.5 (22.9; 46.0)	116	56
HCV genotype			
1a/other	28.2 (13.4; 42.9)	147	74
with baseline Q80K vs Pbo	4.7 (-14.6; 24.1)	60	74
without baseline Q80K vs Pbo	40.3 (25.8; 54.8)	86	74
1b	42.1 (26.5; 57.6)	117	56
IL28B			
CC	14.8 (6.4; 23.2)	77	37
CT	38.0 (26.7; 49.2)	150	76
TT	38.8 (28.1; 49.5)	37	17
METAVIR score			
F0-F2	31.1 (20.3; 41.9)	183	90
F3	40.6 (28.9; 52.3)	46	23
F4	40.7 (29.5; 51.8)	31	17

PR, peginterferon α-2a + ribavirin; SVR12, sustained virological response (HCV RNA undetectable) 12 weeks after planned treatment end.



Jacobson I, et al. EASL 24 April - 28 April 2013 · Amsterdam, The Netherlands

	SMV 150 mg QD + PR (N=264)	Pbo + PR (N=130)
Grade 1 or 2 AE	72	65
Grade 3 or 4 AE	23	29
Serious AE	3	4
AE leading to discontinuation of SMV/placebo	3	3
Most common AEs (≥25% in SMV arm)[1]		
Fatigue	40	38
Headache	31	37
Pruritus	21	11
Other AEs of interest[1]		
Increased bilirubin	9	4
Rash (any type)	27	25
Photosensitivity conditions	3	1
Neutropenia	19	11
Anaemia	16	11

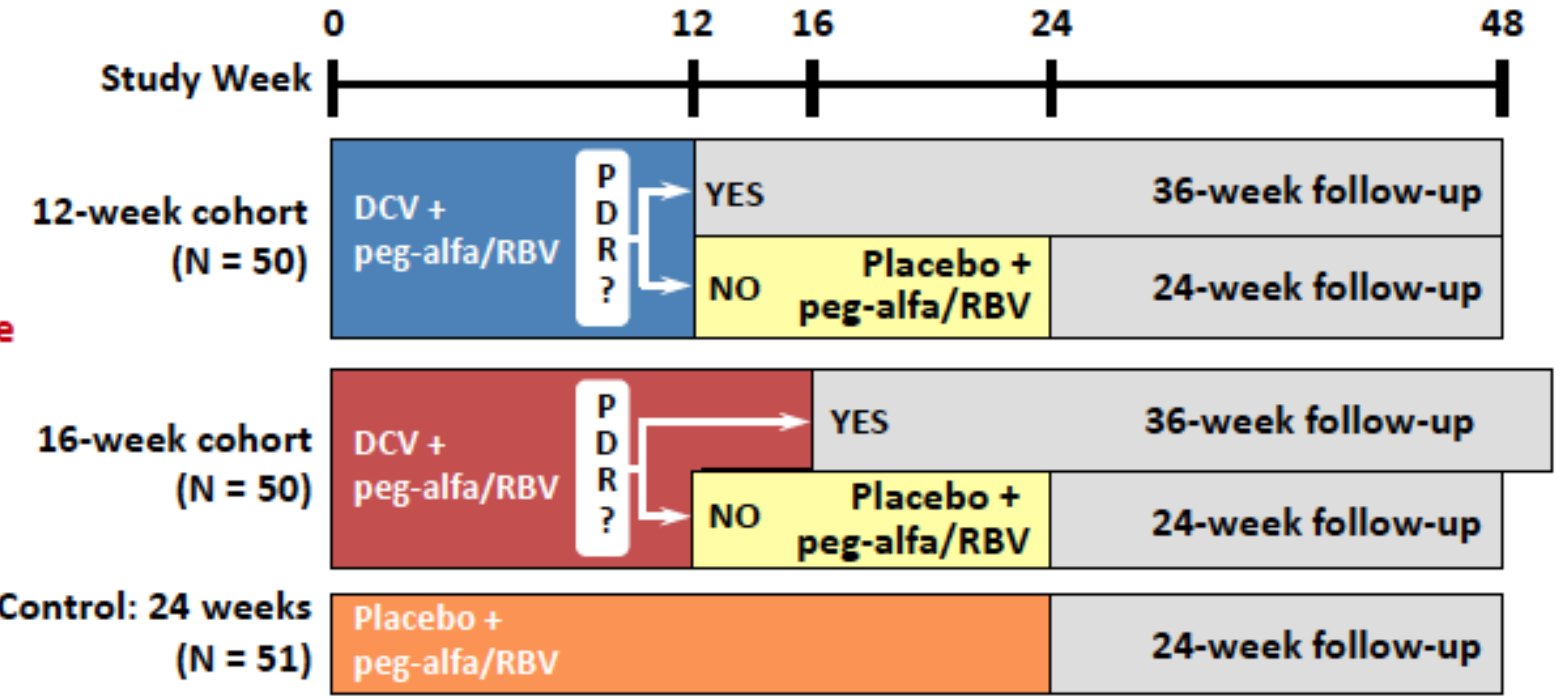
[1]Preferred terms, as assessed by the investigator.

DACLATASVIR COMBINED WITH PEGINTERFERON ALFA-2A AND RIBAVIRIN FOR 12 OR 16 WEEKS IN PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 2 OR 3 INFECTION: COMMAND GT 2/3 STUDY

Dore GJ, Lawitz E, Hézode C, Shafran S, Ramji A, Tatum H, Taliani G, Tran A, Brunetto M, Zaltron S, Strasser S, Weis N, Ghesquiere W, Lee S, Larrey D, Pol S, Harley H, George J, Fung S, de Lédinghen V, Hagens P, Cohen D, Cooney E, Noviello S, Hughes EA

The International Liver Congress™ 2013:
The 48th Annual Meeting of the European Association for the Study of the Liver
Amsterdam, The Netherlands, April 24–28, 2013
Oral 1418

Study Design

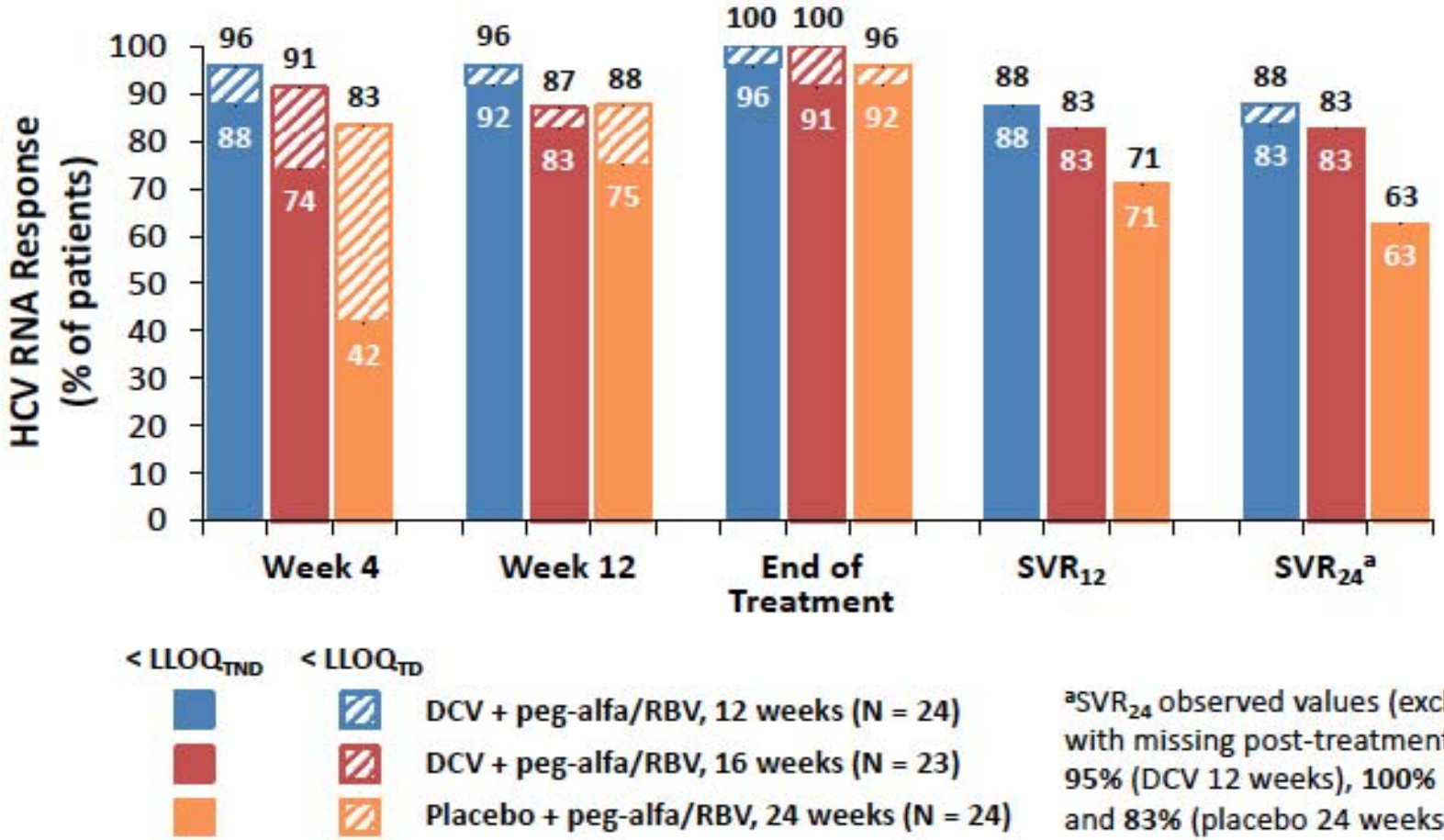


Randomization stratified by HCV genotype; modified intent-to-treat analysis

- Protocol-defined response (PDR): HCV RNA < $LLOQ_{TND\ or\ TD}$ at Week 4 and < $LLOQ_{TND}$ at Week 10
  - DCV recipients without PDR discontinued DCV at Week 12 and received an additional 12 weeks of placebo + peg-alfa/RBV
- Primary efficacy endpoint: HCV RNA < $LLOQ_{TND}$ 24 weeks post treatment (SVR_{24})

LLOQ, lower limit of quantitation; TD, target detected (detectable but < LLOQ); TND, target not detected (undetectable). HCV RNA determined by COBAS TaqMan HCV v2.0 assay (Roche), LLOQ = 25 IU/mL.

Virologic Endpoints: GT 2



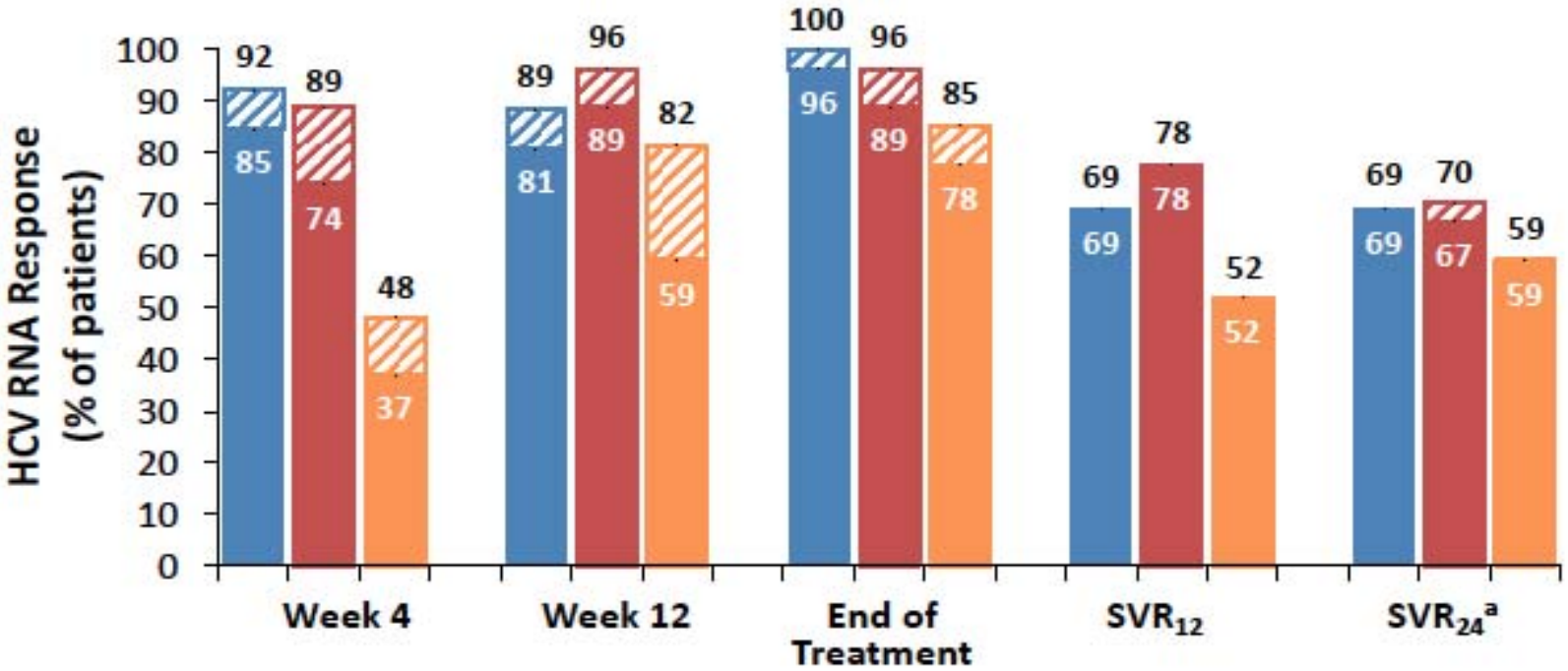
mITT analysis

[a]SVR_{24} observed values (excluding patients with missing post-treatment data): **95%** (DCV 12 weeks), **100%** (DCV 16 weeks), and **83%** (placebo 24 weeks).

LLOQ, lower limit of quantitation; mITT, modified intent to treat;
TD, target detected (detectable but < LLOQ); TND, target not detected (undetectable).

Dore GJ, *et al.* EASL2013, Oral 1418. COMMAND GT 2/3

Virologic Endpoints: GT 3

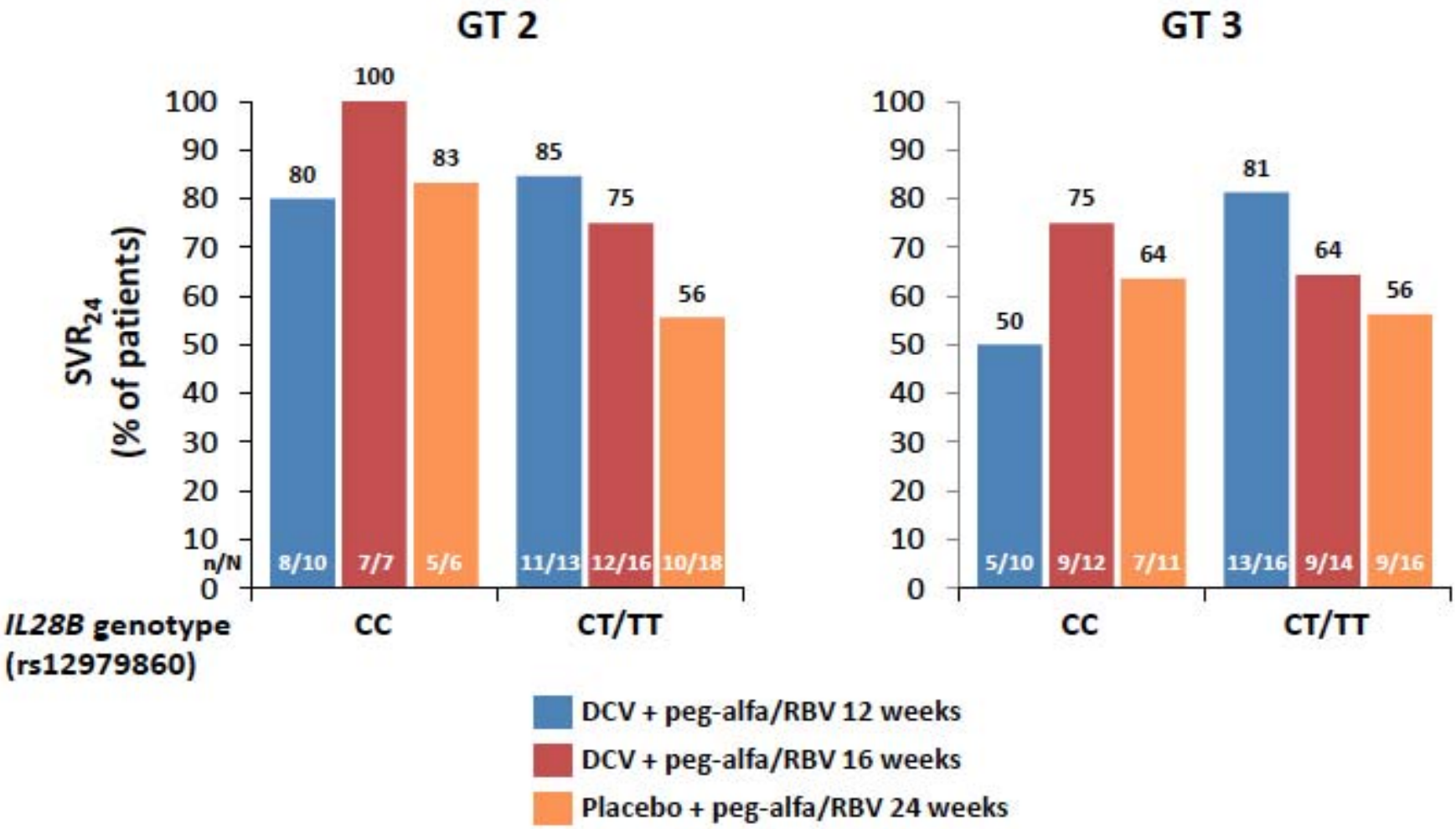


[a]SVR_{24} observed values (excluding patients with missing post-treatment data): 72% (DCV 12 weeks), 69% (DCV 16 weeks), and 70% (placebo 24 weeks).

LLOQ, lower limit of quantitation; mITT, modified intent to treat;
TD, target detected (detectable but < LLOQ); TND, target not detected (undetectable).

Dore GJ, *et al.* EASL2013, Oral 1418. COMMAND GT 2/3

SVR_{24} by *IL28B* Genotype

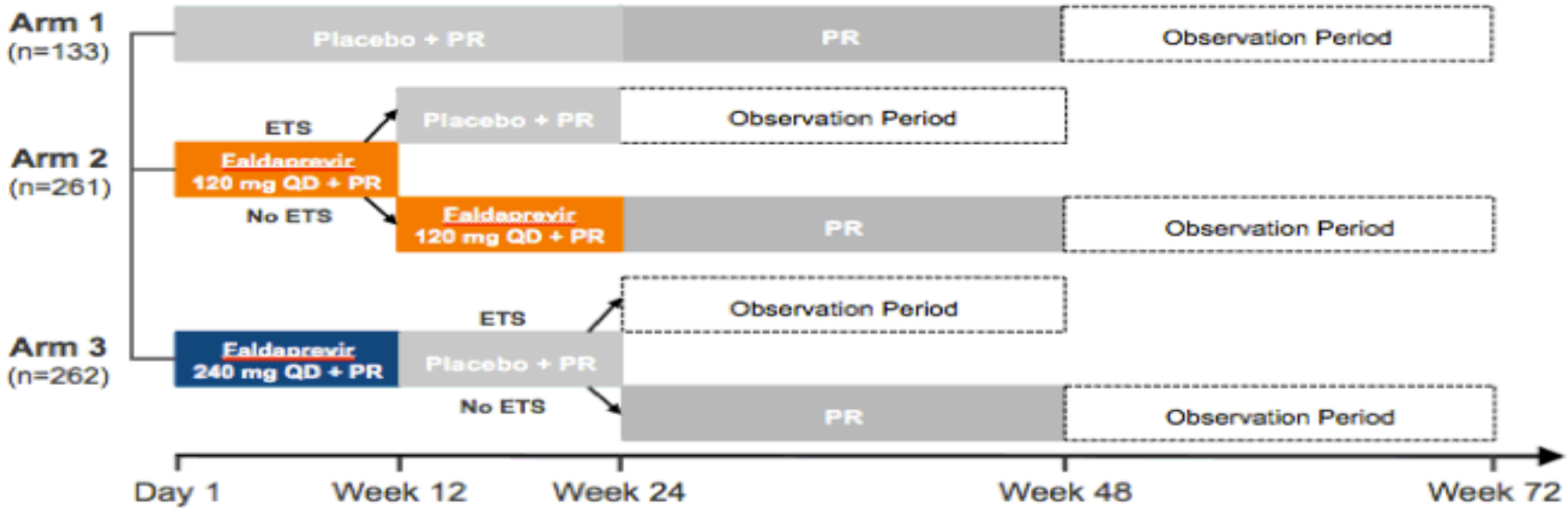


Dore GJ, *et al.* EASL2013, Oral 1418. COMMAND GT 2/3

FALDAPREVIR + PEGIFN ALFA-2A AND RBV IN CHRONIC HCV G1 TREATMENT-NAIVE PATIENTS

Study design

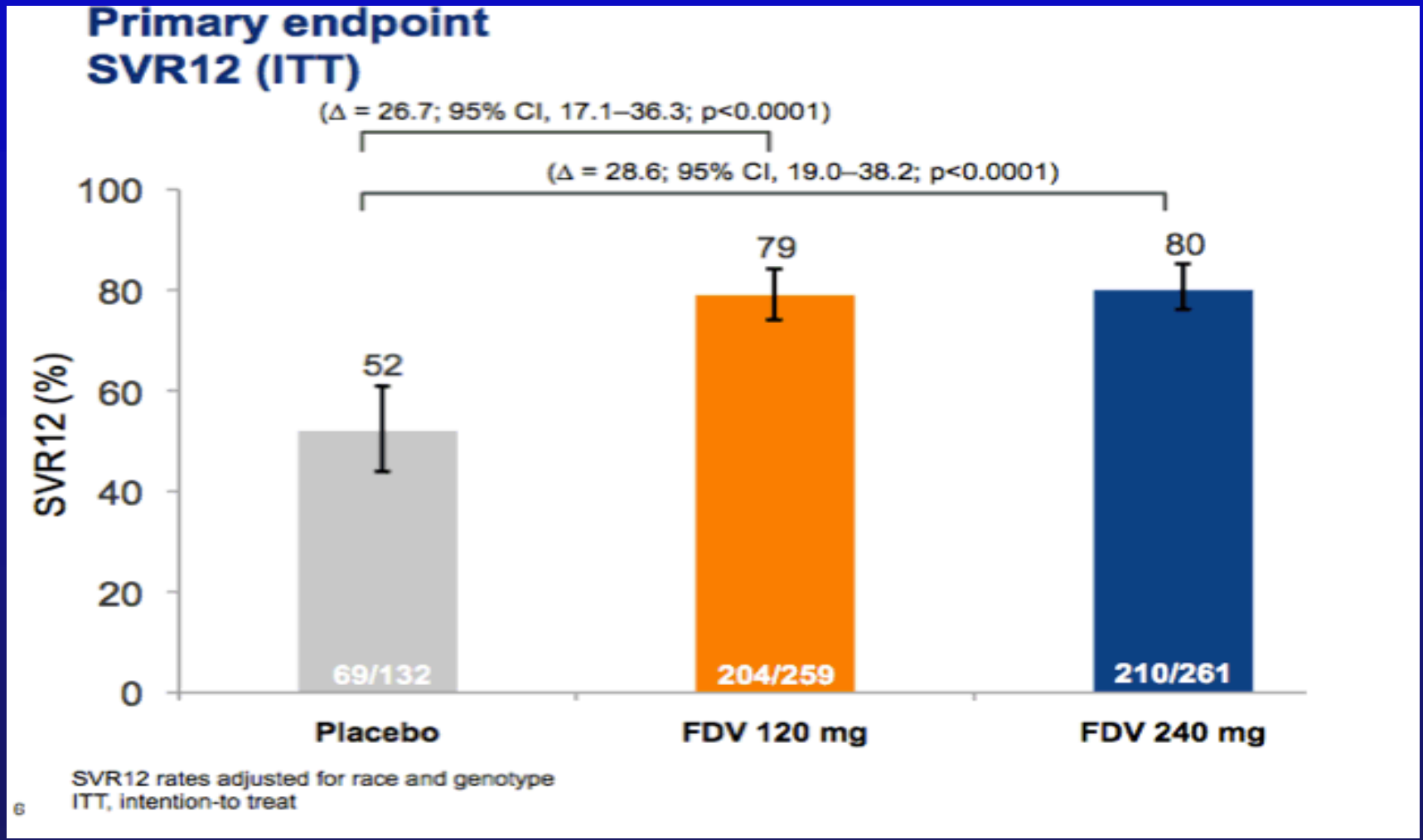
PR, pegylated interferon α2a 180 µg/week and weight-based ribavirin



- **Patients enrolled from Europe and Japan**
- **Eligibility: Treatment naive, GT1 infection, no HBV or HIV coinfection, adult, platelets >90,000 cells/mm^3**
- **Primary endpoint: SVR 12 weeks after completion of all treatment**

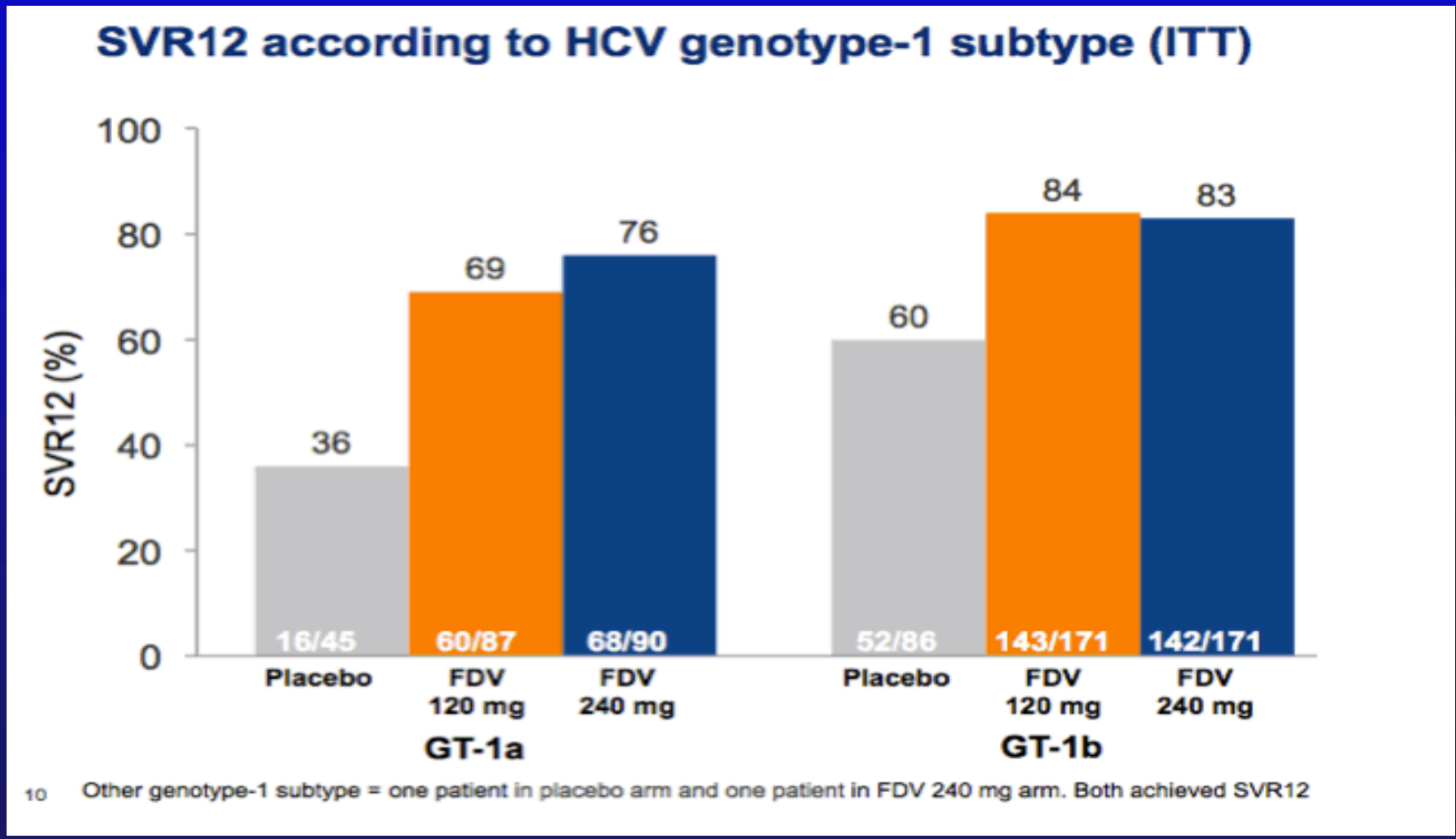
Ferenci P, et al. EASL April 24th - 28th 2013The Netherlands, Amsterdam

FALDAPREVIR + PEGIFN ALFA-2A AND RBV IN CHRONIC HCV G1 TREATMENT-NAIVE PATIENTS



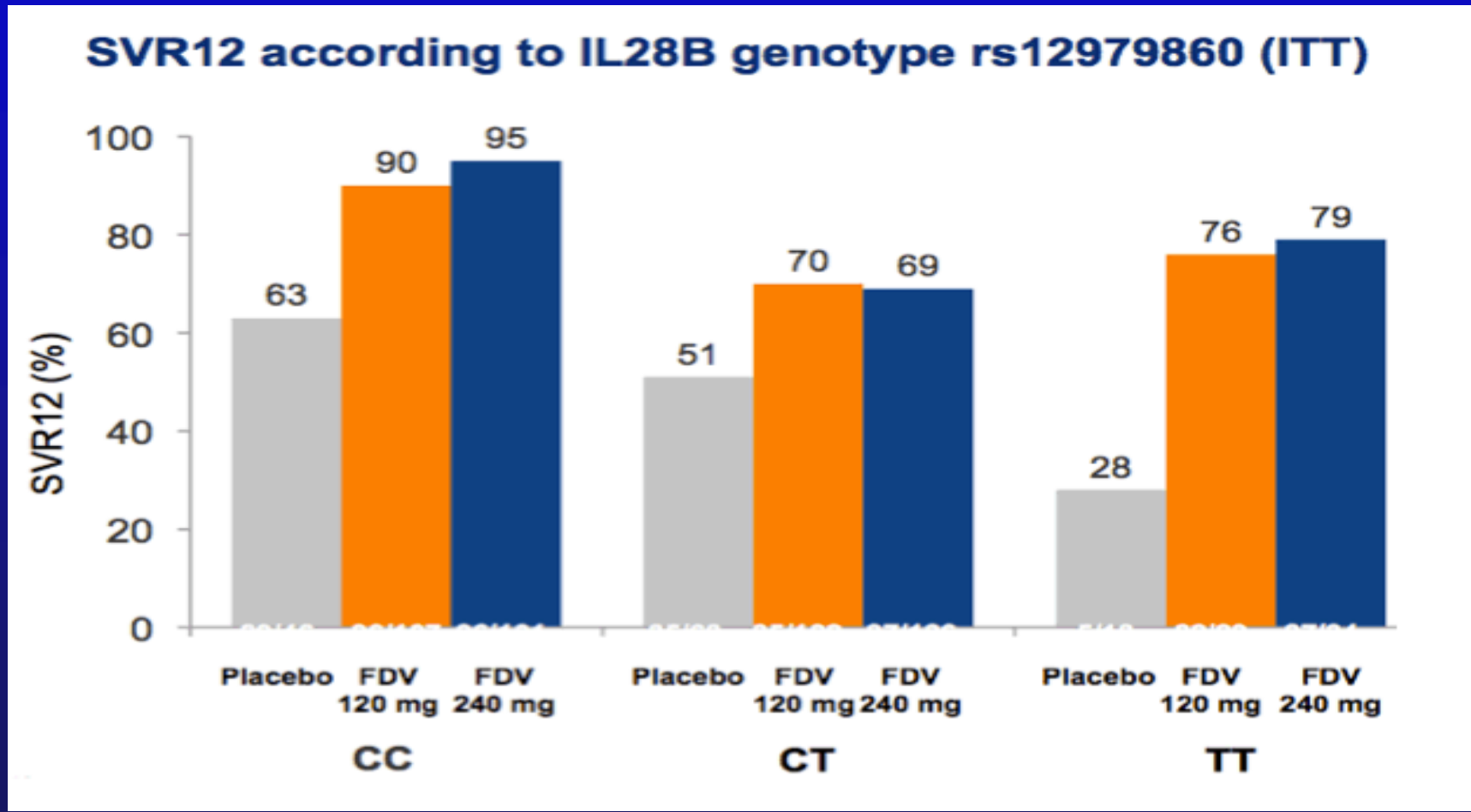
Ferenci P, et al. EASL April 24th - 28th 2013The Netherlands, Amsterdam

FALDAPREVIR + PEGIFN ALFA-2A AND RBV IN CHRONIC HCV G1 TREATMENT-NAIVE PATIENTS



Ferenci P, et al. EASL April 24th - 28th 2013The Netherlands, Amsterdam

FALDAPREVIR + PEGIFN ALFA-2A AND RBV IN CHRONIC HCV G1 TREATMENT-NAIVE PATIENTS

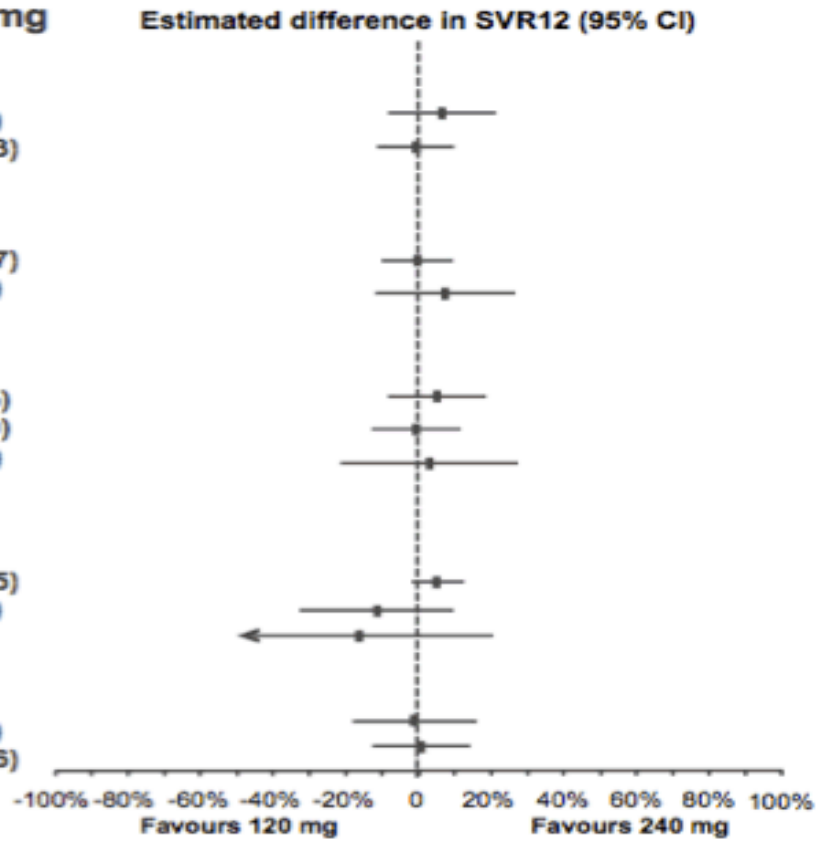


Ferenci P, et al. EASL April 24th - 28th 2013The Netherlands, Amsterdam

FALDAPREVIR + PEGIFN ALFA-2A AND RBV IN CHRONIC HCV G1 TREATMENT-NAIVE PATIENTS

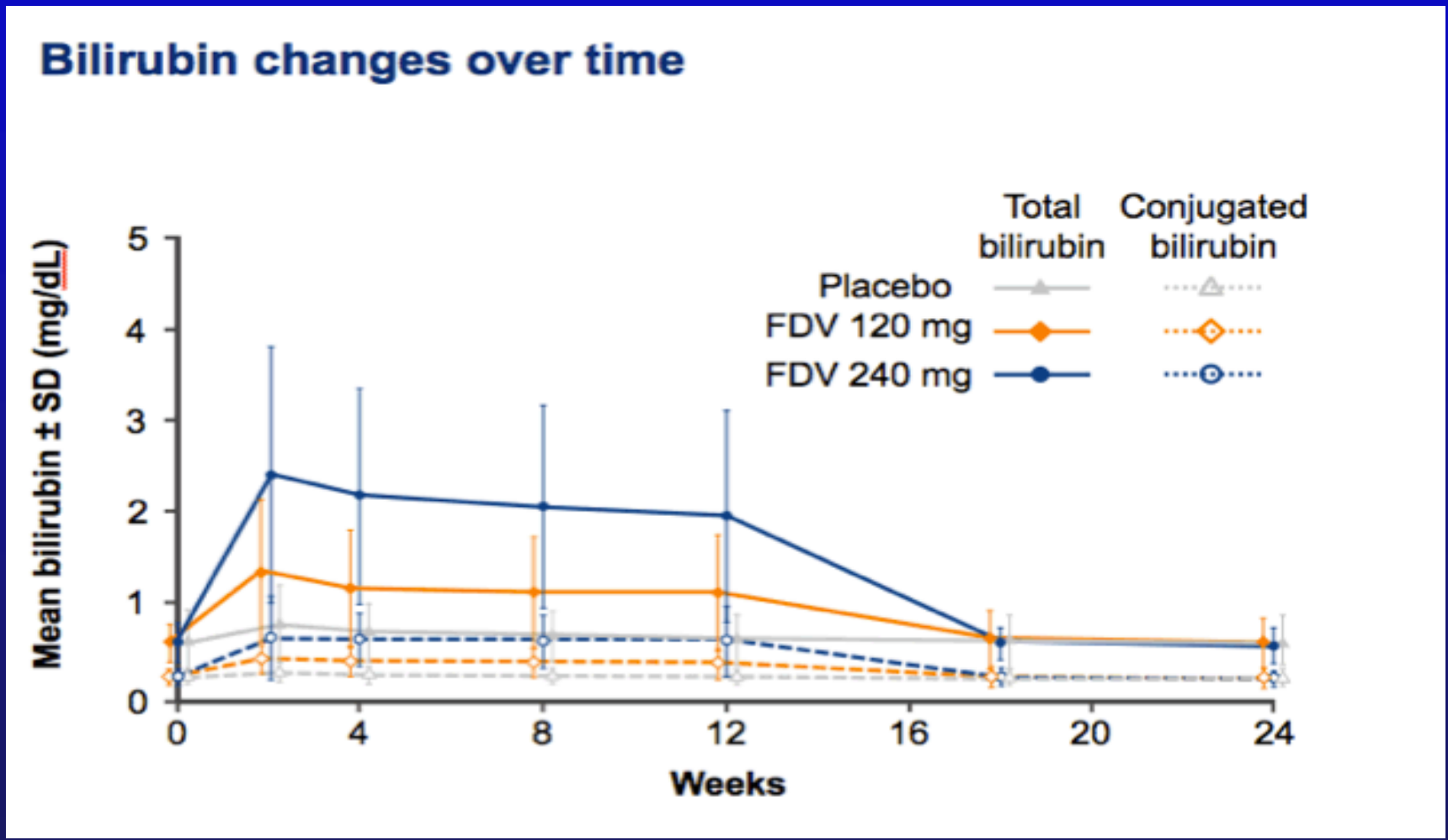
SVR12 for FDV 120 mg vs 240 mg

n/N (%)	FDV 120 mg	FDV 240 mg
Genotype		
1a	60/87 (69)	68/90 (76)
1b	143/171 (84)	142/171 (83)
Race		
Caucasian	157/203 (77)	158/205 (77)
Asian	44/52 (85)	47/51 (92)
IL28B		
CC	96/107 (90)	96/101 (95)
CT	85/122 (70)	87/126 (69)
TT	22/29 (76)	27/34 (79)
Fibrosis stage		
<F3	172/212 (81)	187/219 (85)
≥F3	30/45 (67)	23/42 (55)
Cirrhosis	9/16 (56)	6/15 (40)
Baseline HCV RNA		
<800 000 IU/mL	54/58 (93)	70/76 (92)
≥800 000 IU/mL	150/201 (75)	140/185 (76)



Ferenci P, et al. EASL April 24th - 28th 2013The Netherlands, Amsterdam

FALDAPREVIR + PEGIFN ALFA-2A AND RBV IN CHRONIC HCV G1 TREATMENT-NAIVE PATIENTS



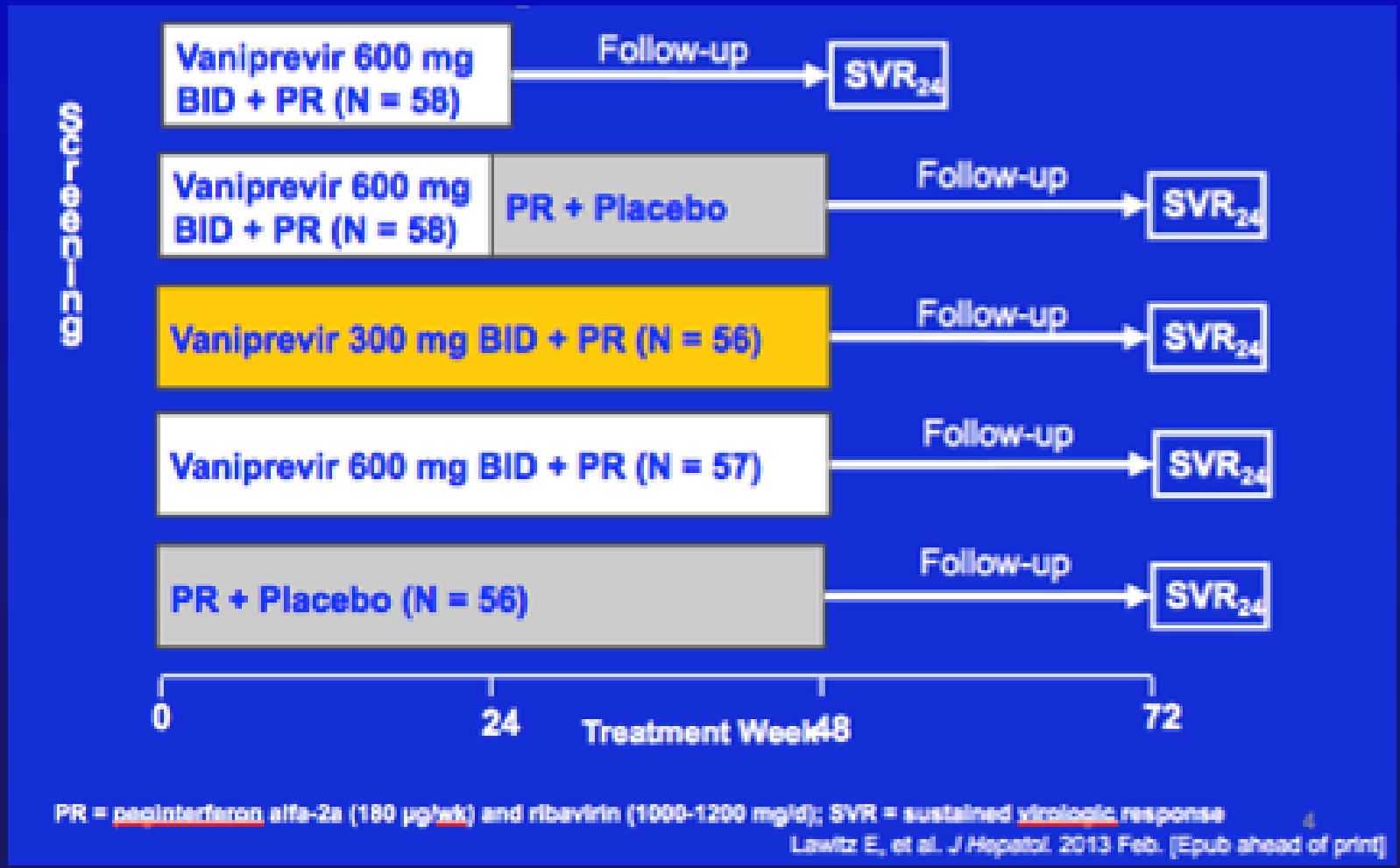
Ferenci P, et al. EASL April 24th - 28th 2013The Netherlands, Amsterdam

Sustained Viral Response and Safety of Vaniprevir (MK-7009) in Cirrhotic, Treatment-Experienced Patients with Genotype 1 HCV Infection Who Have Failed Previous Pegylated Interferon and Ribavirin

48th Annual Meeting of the European Association for Study of The LiverAmsterdam, The Netherlands, April 24-28, 2013

Maribel Rodriguez-Torres, Albrecht Stoehr, Edward Gane, Lawrence Serfaty, Eric Lawitz, Michael Bourque, Sanhita Bhanja, Richard Barnard, Peggy Hwang, Niloufar Mobashery

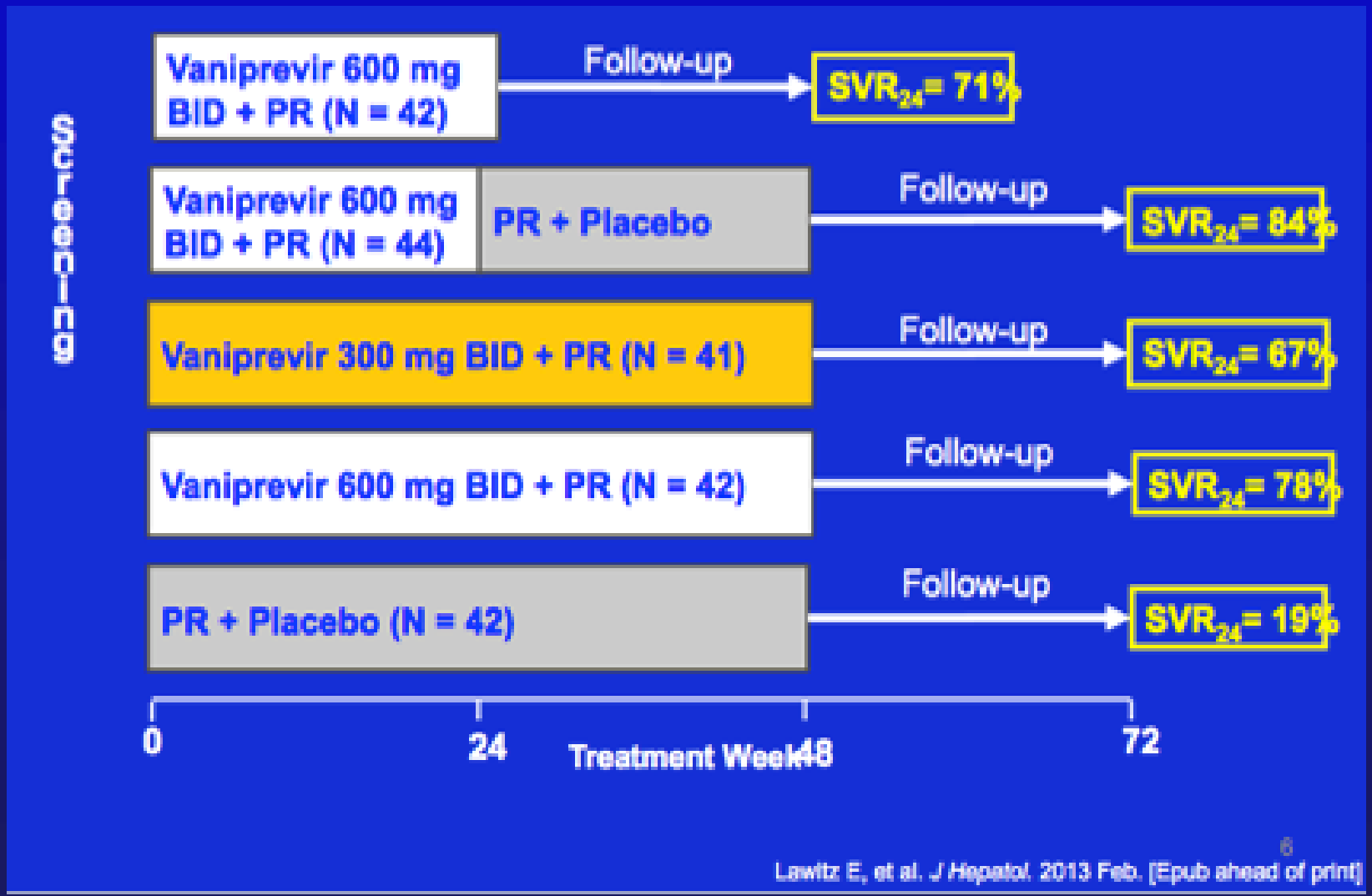
Phase 2b Study in Non-cirrhotic and Cirrhotic Patients with HCV G1 Non-Responders to Prior PegIFN/ RBV



PR = peginterferon alfa-2a (180 µg/wk) and ribavirin (1000-1200 mg/d); SVR = sustained virologic response

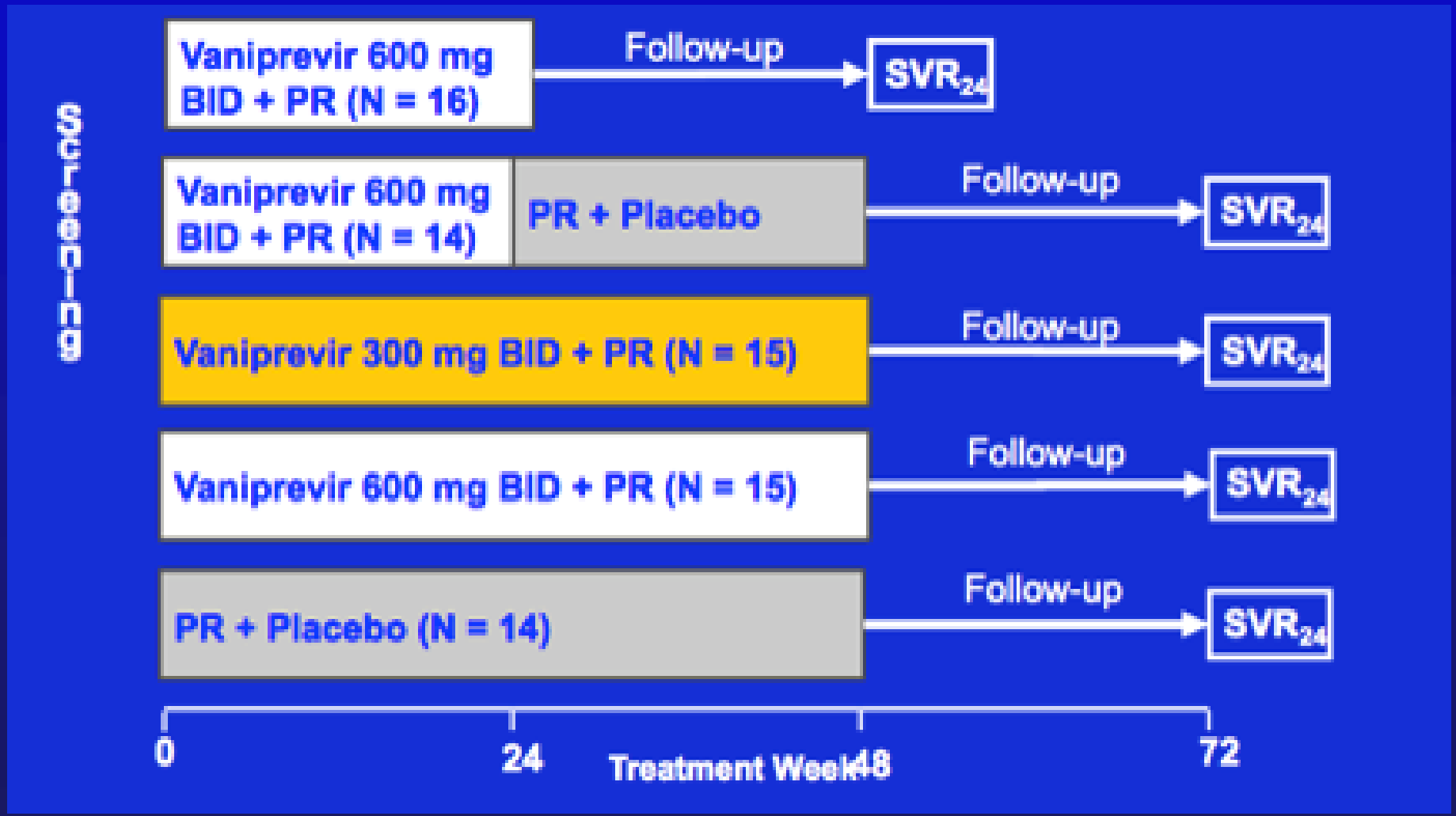
Lawitz E, et al. *J Hepatol*. 2013 Feb. [Epub ahead of print]

Phase 2b Study in Non-cirrhotic Patients with HCV G1 Non-Responders to Prior PegIFN/ RBV

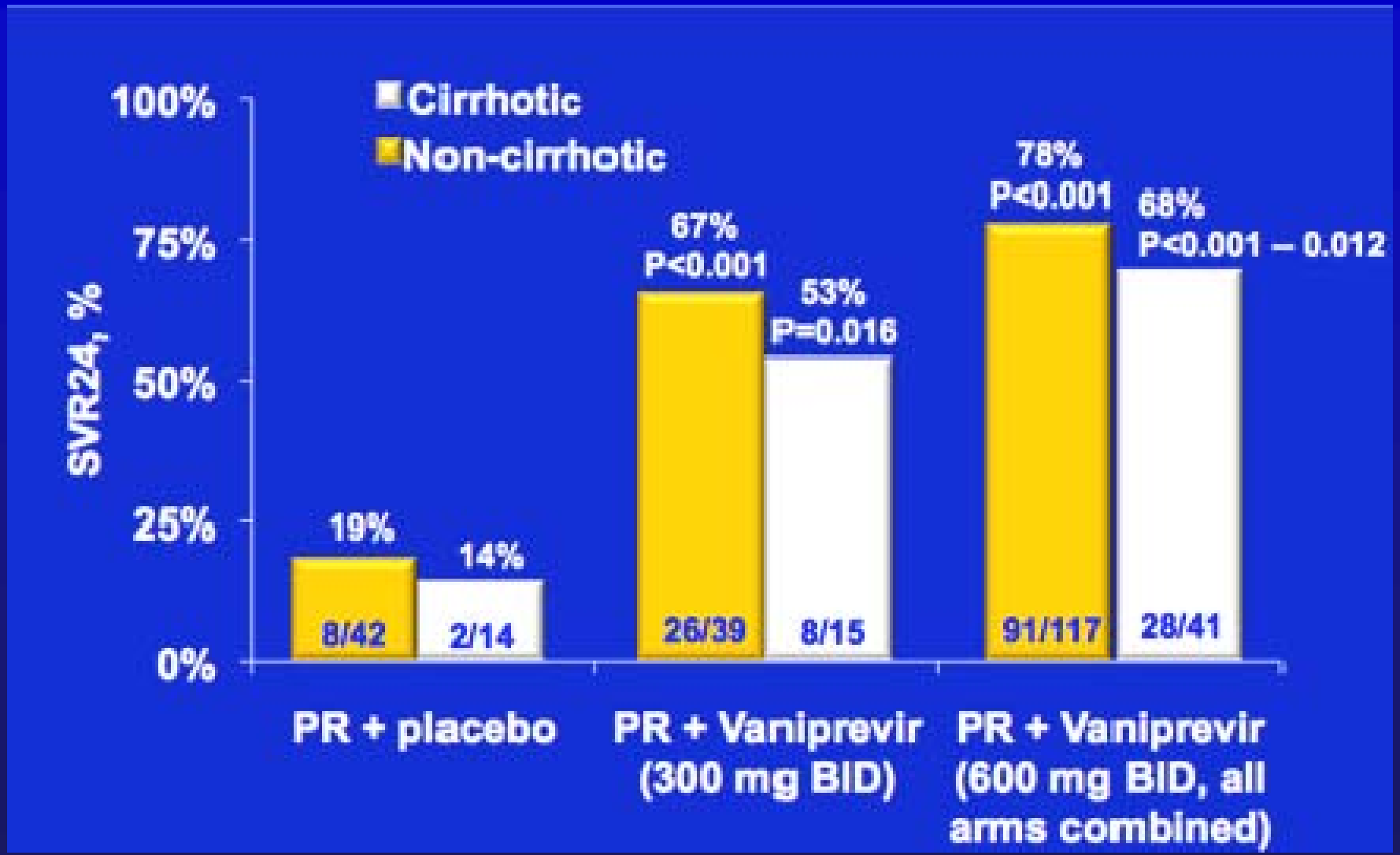


Lawitz E, et al. *J Hepatol.* 2013 Feb. [Epub ahead of print]

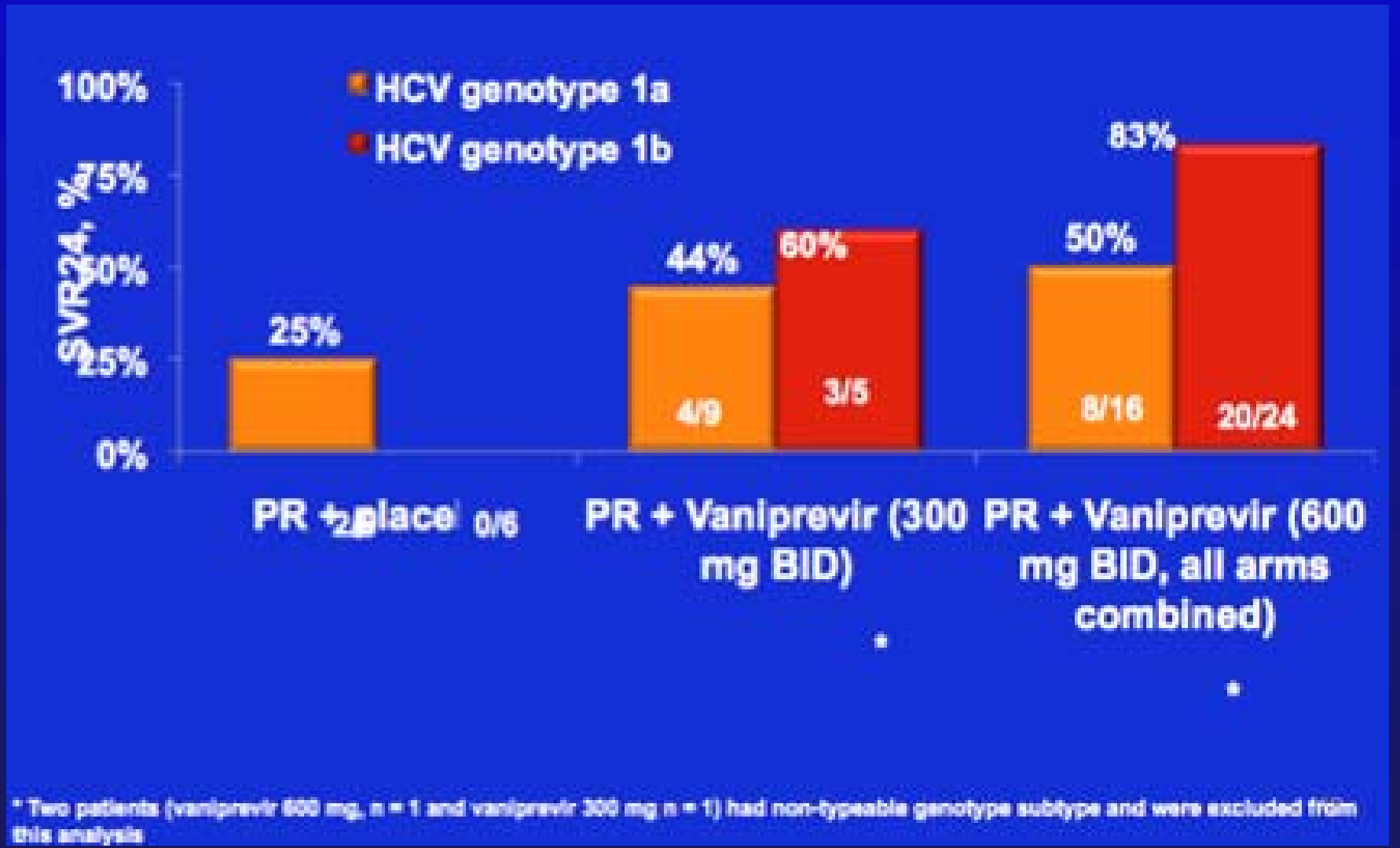
Phase 2b Study in Cirrhotic Patients with HCV G1 Non-Responders to Prior PegIFN/ RBV



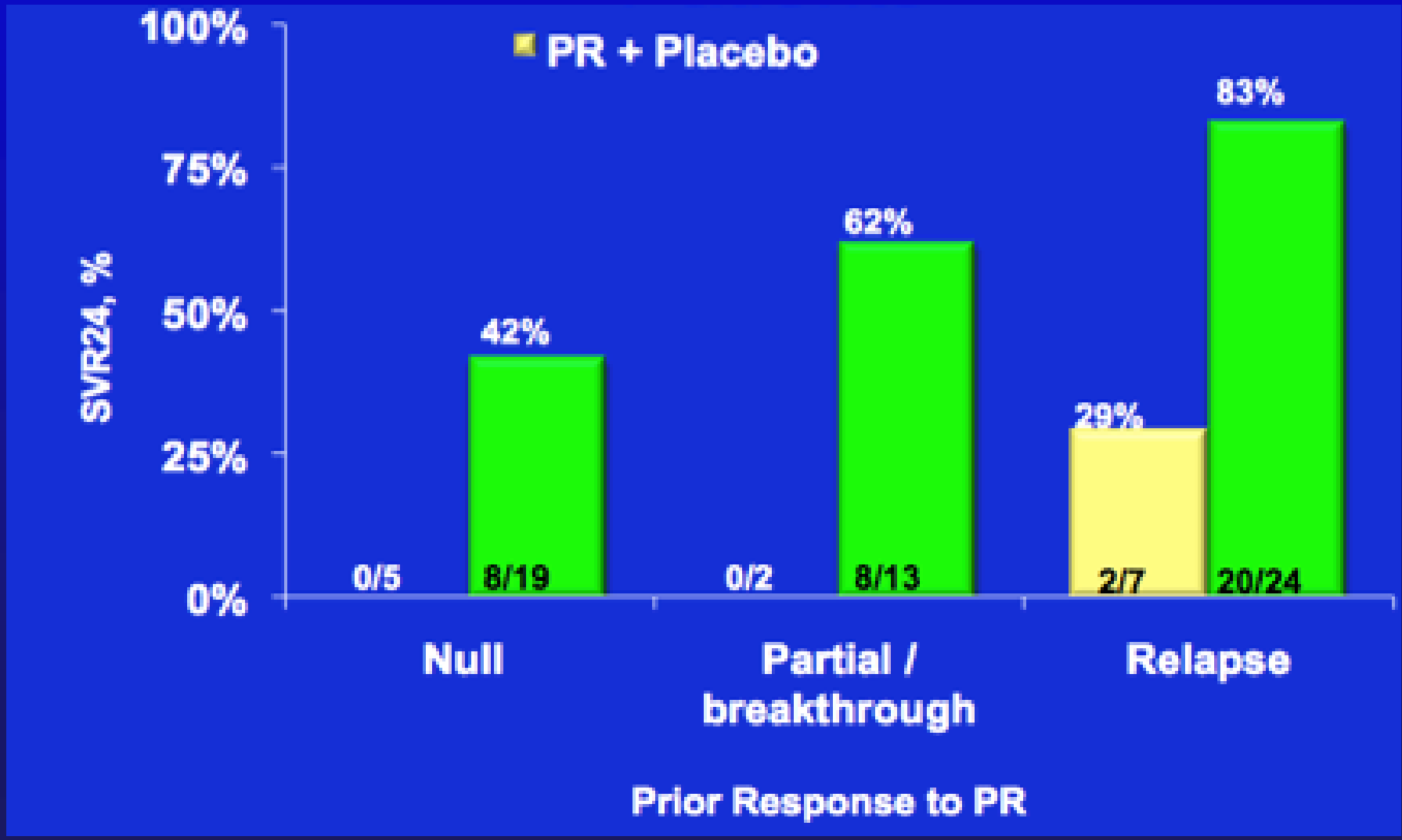
Sustained Virologic Response



Sustained Virologic Response: G1a vs. G1b Cirrhotic Patients



Sustained Virologic Response by Prior Response to PegIFN/RBVR in Cirrhotic Patients



Conclusions

- In G1 cirrhotic prior non-responders to PR, Vaniprevir +PR Demonstrates significant improvement in SVR compared to PR
- Virological failure was principally due to the emergence of virus encoding RAVs at D168 or R155K
- Vaniprevir was generally well tolerated in cirrhotic patients
  - No hepatic decompensation or increase in cytopenias during therapy
  - High rates of gastrointestinal AEs compared to control (all mild to moderate, and low rates of discontinuations)
- Phase 3 evaluation of vaniprevir 300 mg BID + PR in Japan is nearly completed

Quad Therapy:
PEG + RBV + 2 DAAs

Interferon Plus Multiple DAAs

Expectations:

- RVR >80%
- SVR 70-80%
- Improved tolerability and side effects
- RGT strategy
- 8-12 week therapy for easy-to-treat patients
- Increased efficacy in null responders

SVR in G1 Null Responders with Combination of DCV (NS5A) and ASV (NS3) ± PR

N=101 null responders

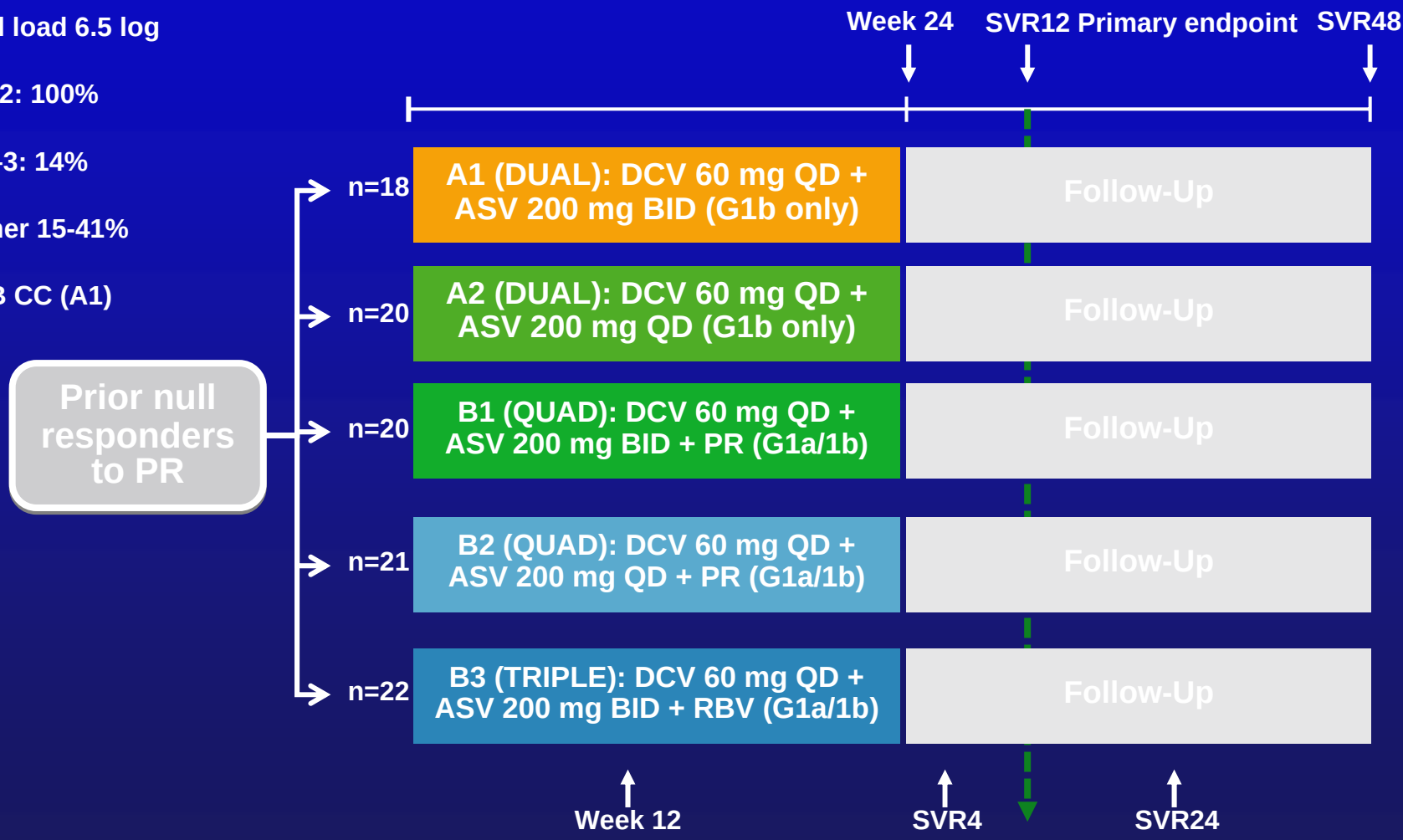
Mean viral load 6.5 log

G1b: A1–2: 100%

B1–3: 14%

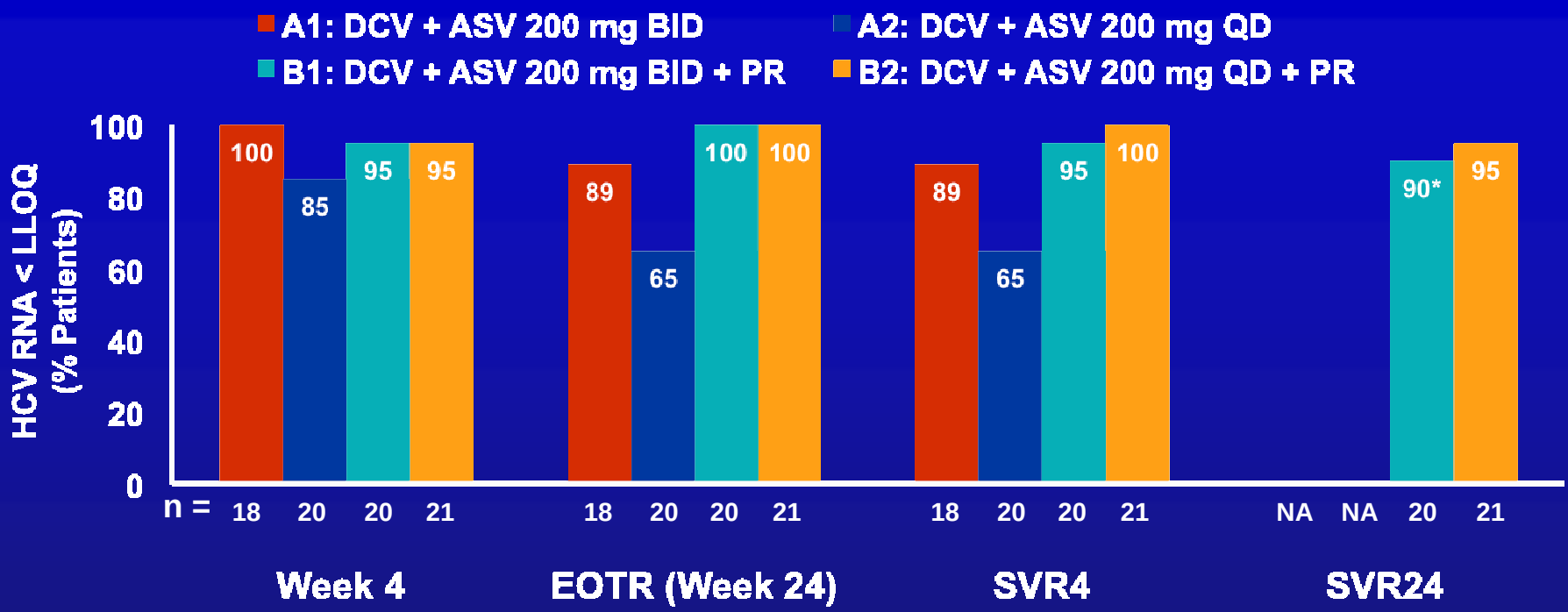
F3 or higher 15-41%

One IL28B CC (A1)



Lok AS, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. 79.

DUAL and QUAD Therapy



2 patients relapsed — 1 at PT Week 4 (B1); 1 at PT Week 12 (B2)

Safety DUAL: Headache and diarrhea most common AEs

QUAD: Addition of IFN AEs

Resistance: Failure results in dual class (NS5A and NS3) resistance

*1 pt missed 24 wk follow up – failure on ITT analysis

Lok AS, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. 79.

PegIFN Lambda + RBV in Combination with Daclatasvir or Asunaprevir in HCV G1 Japanese Patients: SVR4 Results from the D-LITE Japanese sub-study

21 treatment-naive patients

All HCV G1b

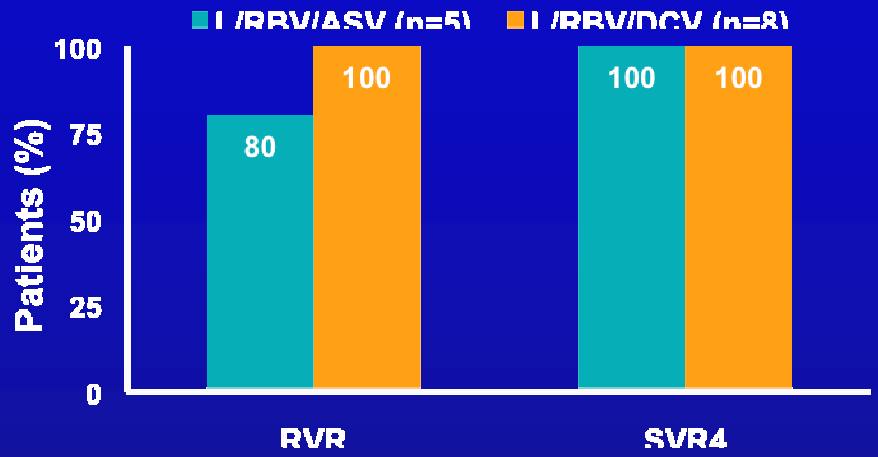
Assigned to

- PEG-IFN lambda (L) / RBV / DCV
- L / RBV / ASV
- PEG-IFN alfa-2a / R / placebo

Lambda and alfa dosed at 180 µg QW; DCV 60 mg QD; ASV 200 mg BID; RBV weight-based BID

Only DAA recipients with PDR had post-treatment data through Week 4

L/RBV/DCV better tolerated than L/RBV/ASV



PDR+ Subjects, n (%)	L/RBV/ASV (n=5)	L/RBV/DCV (n=8)
SAEs	1 (20)	0
AE-related discontinuations	2 (40)	0
Grade 3-4 AEs	4 (80)	1 (14)†
Grade 3-4 hemaglobin	1 (20)	0
Grade 3-4 ALT	3 (60)	0
Grade 3-4 AST	4 (80)	0
Grade 3-4 total bilirubin	1 (20)	0

† Transient leukopenia

Izumi N, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. 234.

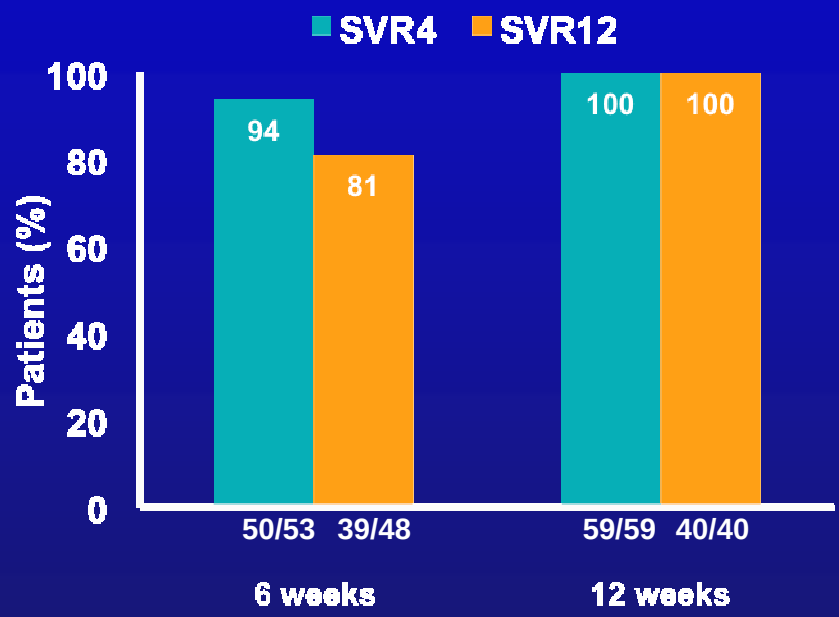
Six Weeks of a NS5A Inhibitor (GS-5885), Protease Inhibitor (GS-9451) plus PegIFN/RBV (PR) Achieves High SVR4 Rates in genotype 1 IL28B CC Treatment Naïve HCV Patients: Interim Results of a Prospective, Randomized Trial

PR+GS-5885+GS-9451 (Arm 1)
vs PR (Arm 2)

Arm 1: If HCV RNA <LLQ (vRVR)
at Week 2 with Week 4 RVR,
re-randomized to receive 6 or 12 weeks

Arm 2: If HCV RNA<LLQ at
Week 4, received 24 weeks of PR

Quad therapy for 24 weeks for vRVR
failures in Arm 1, RVR failures in Arm 2



Thompson AJ, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. 759.

Interferon-Free Regimens

Phase 3 Randomized Controlled Trial of All-Oral Treatment With Sofosbuvir + Ribavirin for 12 Weeks Compared to 24 Weeks of PEG + Ribavirin in Treatment-Naïve GT 2/3 HCV-Infected Patients (FISSION)

Edward Gane[1], Eric Lawitz[2], Maribel Rodriguez-Torres[3], Stuart Gordon[4], Hadas Dvory-Sobol[5], Sarah Arterburn[5], John McNally[5], Diana M. Brainard[5], William T. Symonds[5], John G. McHutchison[5], Aasim Sheikh[6], Alessandra Mangia[7]

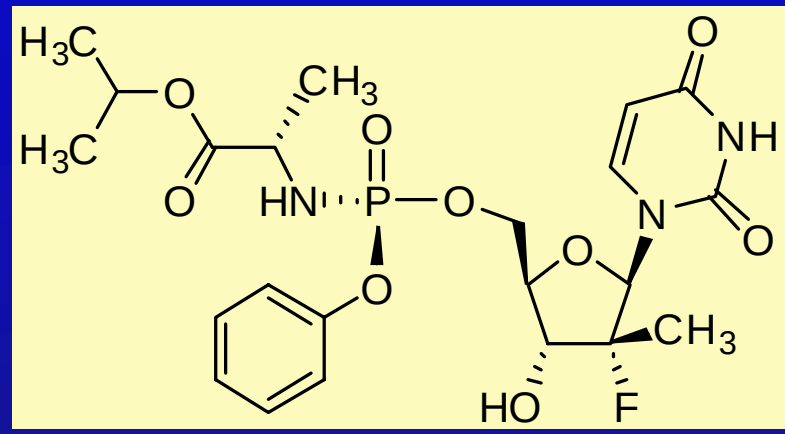
[1]Auckland City Hospital, Auckland, New Zealand; [2]Texas Liver Institute, San Antonio, TX, USA; [3]Fundacion de Investigacion, San Juan, Puerto Rico; [4]Henry Ford Health Systems, Detroit, MI, USA; [5]Gilead Sciences, Inc., Foster City, CA, USA; [6]GI Specialists of Georgia, Marietta, GA, USA;

[7]"Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Italy

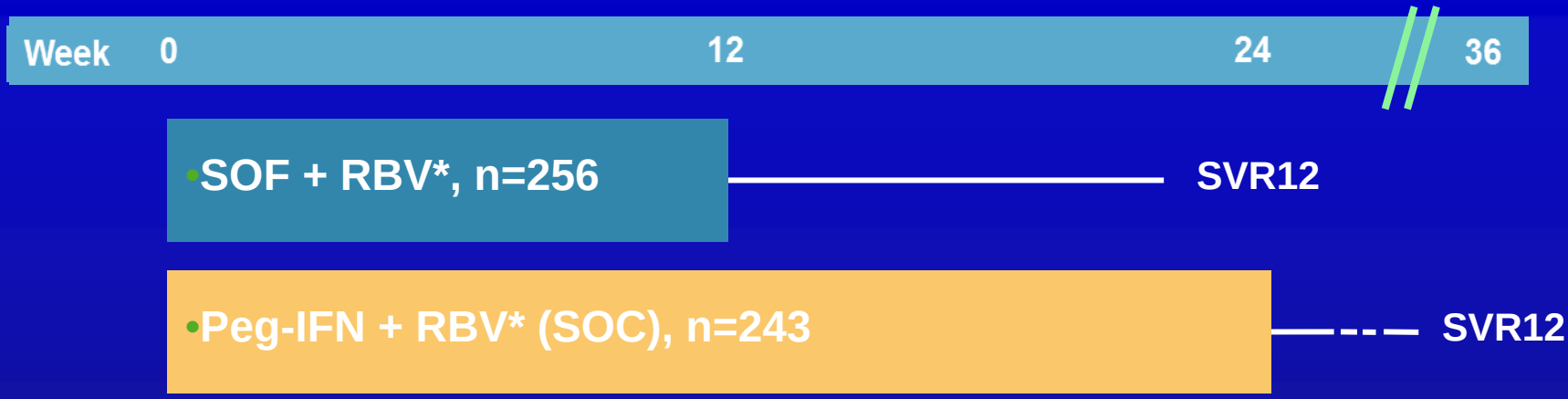
•**International Liver Congress 2013, Amsterdam**

Sofosbuvir (SOF, GS-7977)

- HCV-specific nucleotide polymerase inhibitor (chain terminator)
- Potent antiviral activity against HCV genotypes 1–6
- High barrier to resistance
- Once-daily, oral, 400-mg tablet
- Favorable clinical pharmacology profile
  - No food effect
  - No significant drug interactions
- Generally safe and well tolerated in clinical studies to date (>2000 patients)
  - No safety signal in preclinical/clinical studies



Study Design



***RBV dose 1000-1200 mg/day for SOF + RBV and 800 mg/day for Peg-IFN + RBV.**

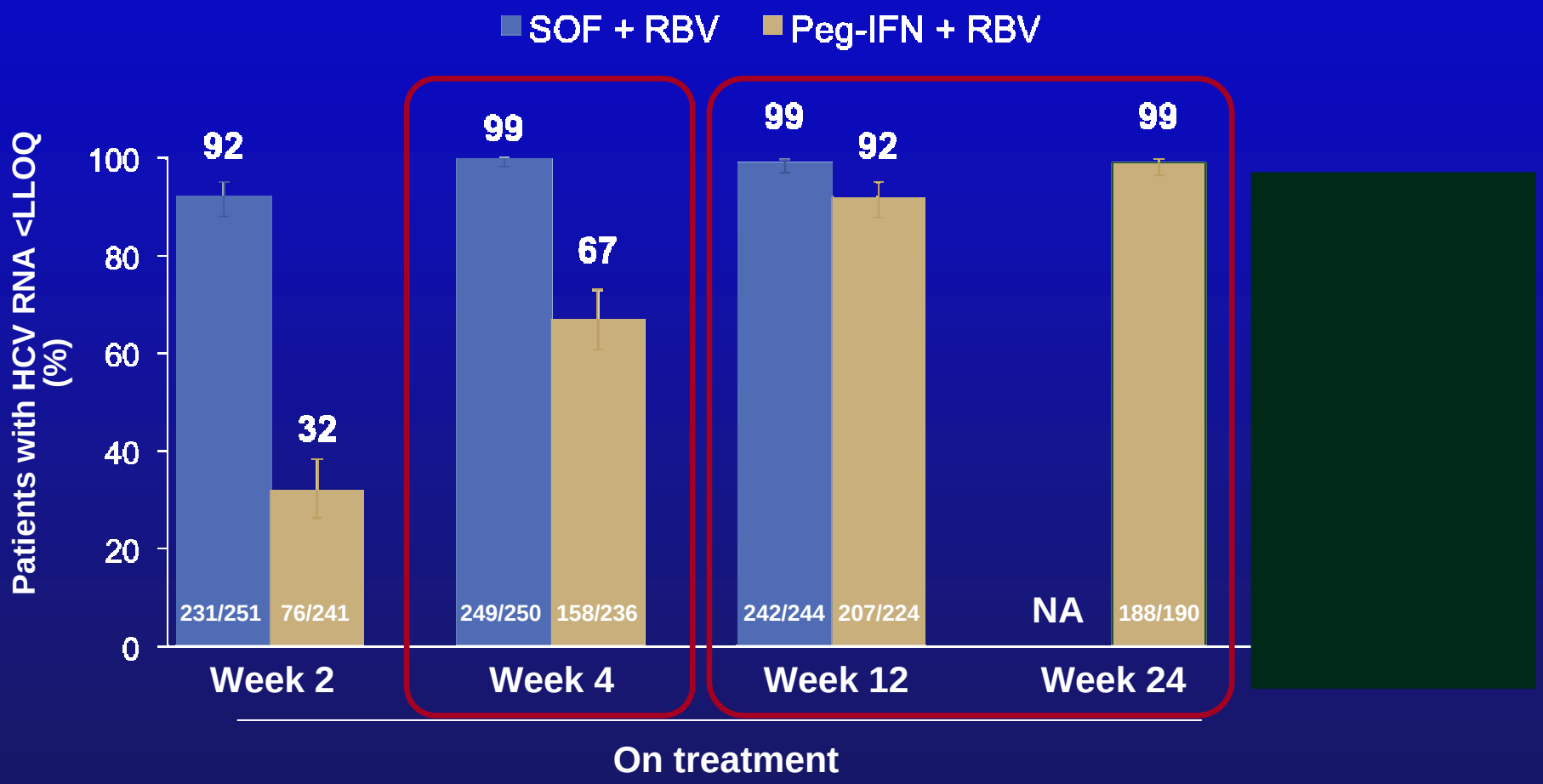
Treatment-naïve, genotype 2 or 3 HCV-infected patients

- Targeted 3:1 enrollment of genotype 3:genotype 2 patients
- Targeted 20% enrollment of patients with cirrhosis

Expanded inclusion criteria

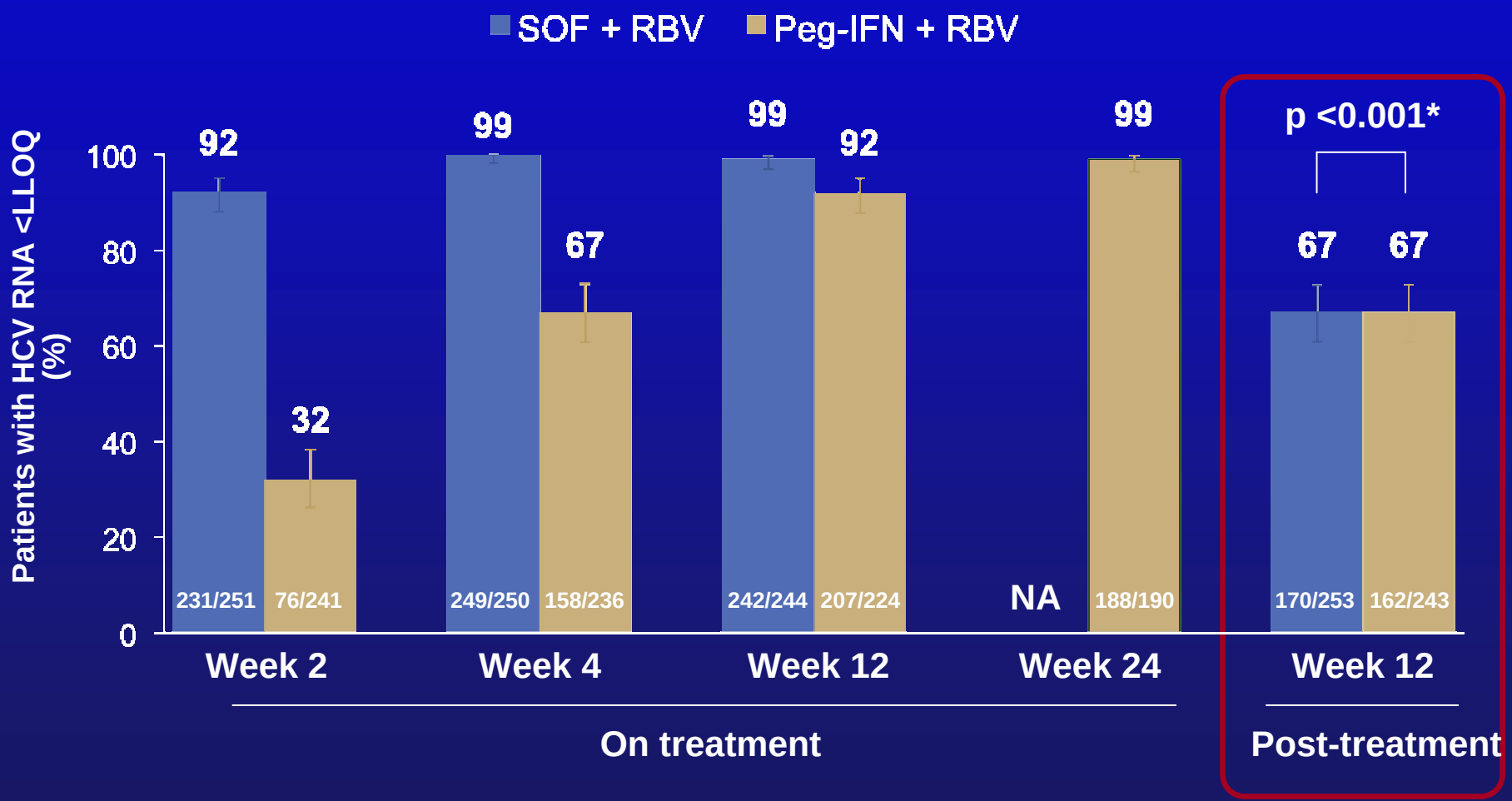
- No upper limit to age or BMI
- Opioid substitution permitted
- Platelet count >75,000/mm^3 (cirrhotic)

Results: Virologic Response



Error bars represent 95% confidence intervals.

Results: Virologic Response



*Study met primary endpoint of noninferiority of SOF + RBV to Peg-IFN + RBV.

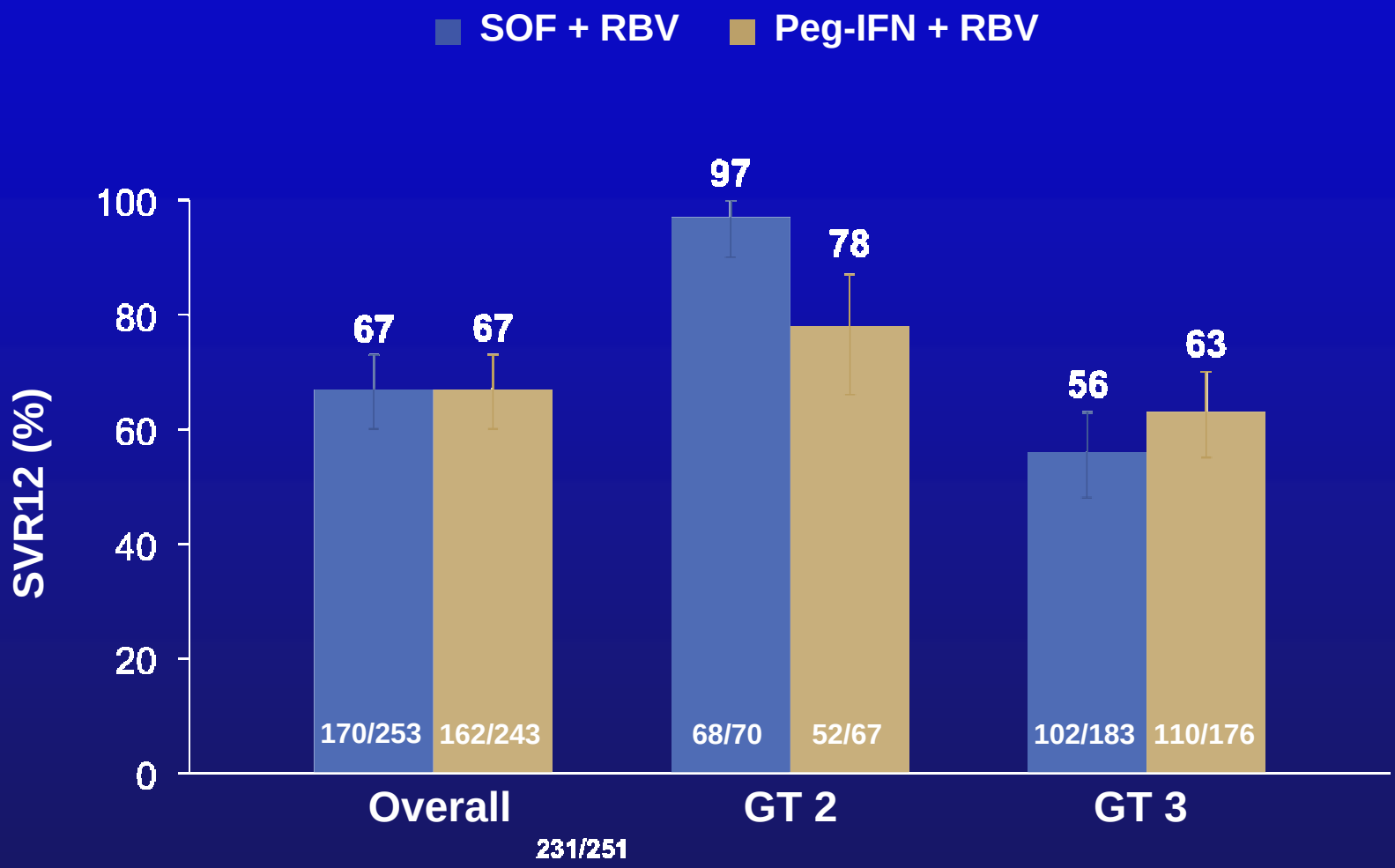
Error bars represent 95% confidence intervals.

Results: Virologic Outcomes

Outcome, n (%)	SOF + RBV n=253	Peg-IFN + RBV n=243
SVR12	170 (67)	162 (67)
Patients without SVR12	83 (33)	81 (33)
On-treatment failure*	1 (<1)†	18 (7)
Relapse	74 (30)	46 (21)
Other	8 (3)	17 (7)

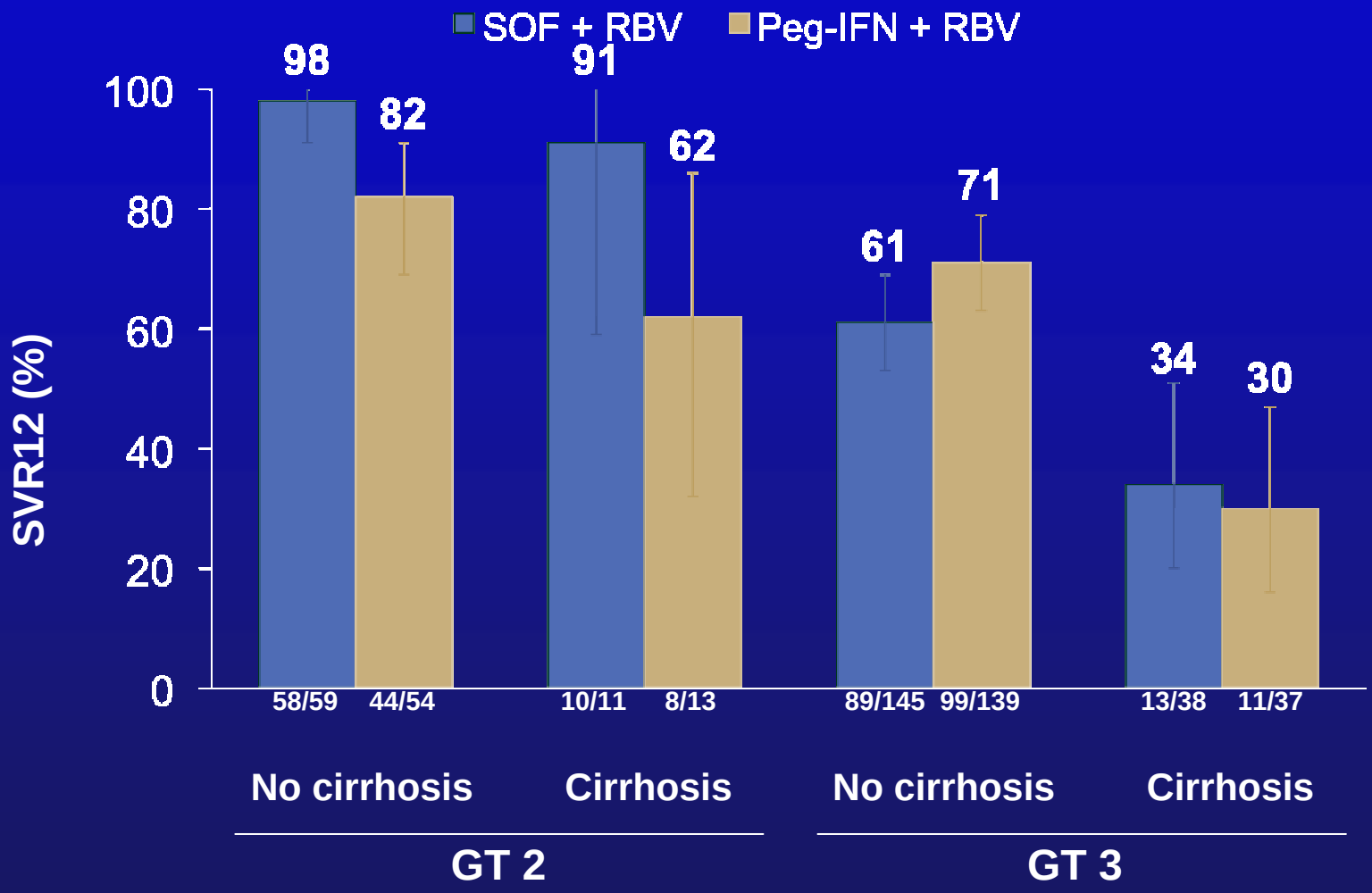
- *Breakthrough, rebound, nonresponse (HCV RNA >LLOQ through Week 12);
†Patient with breakthrough had undetectable plasma drug levels after Week 4.

Results: SVR12 Rates by HCV Genotype



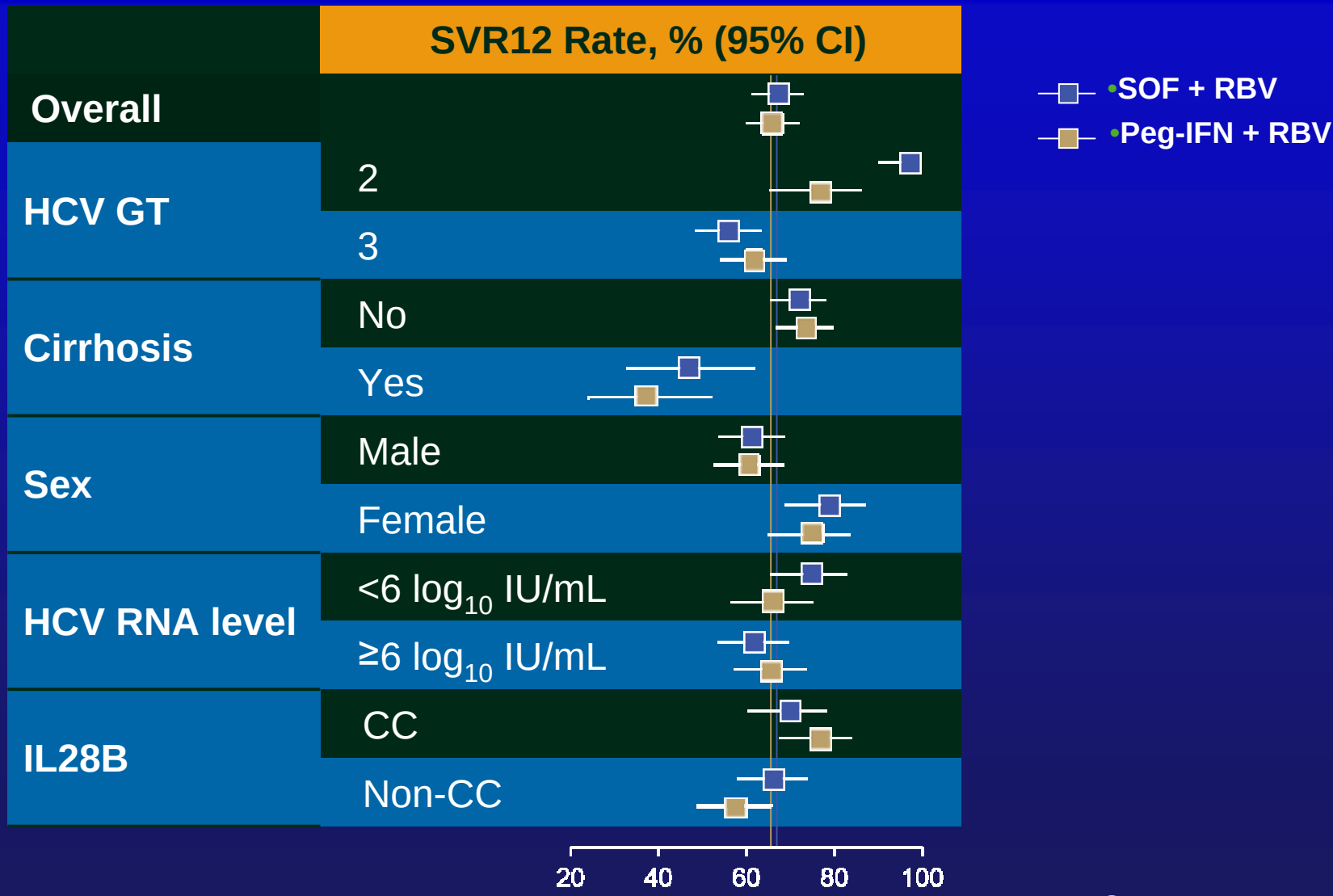
Error bars represent 95% confidence intervals.

Results: SVR_{12} by Genotype and Cirrhosis



Error bars represent 95% confidence intervals.

Results: SVR_{12} by Prespecified Subgroups



Results: Resistance Analysis

- Sequencing performed in 79 SOF + RBV patients who did not achieve SVR12
- No S282T mutations observed by population or deep sequencing (1% cutoff)
- No change in susceptibility to SOF or RBV observed by phenotypic analyses of other NS5B substitutions

Results: Safety Summary

	Patients, n (%)	SOF + RBV*	Peg-IFN + RBV*
Overall safety	AEs	220 (86)	233 (96)
	Grade ≥3 AEs	18 (7)	45 (19)
	Serious AEs	7 (3)	3 (1)
	Treatment discontinuation due to AEs	3 (1)	26 (11)
Hematologic abnormalities	Hemoglobin <10.0 g/dL	23 (9)	35 (15)
	Hemoglobin <8.5 g/dL	1 (<1)	4 (2)
	Absolute neutrophil count <750/mm^3	0	36 (15)
	Platelets <50,000/mm^3	0	18/242 (7)

*RBV dose 1000-1200 mg/day for SOF + RBV and 800 mg/day for Peg-IFN + RBV.

All Oral Therapy With Sofosbuvir + Ribavirin for 12 or 16 Weeks in Treatment-Experienced Genotype 2/3 HCV-Infected Patients: Results of the Phase 3 FUSION Trial

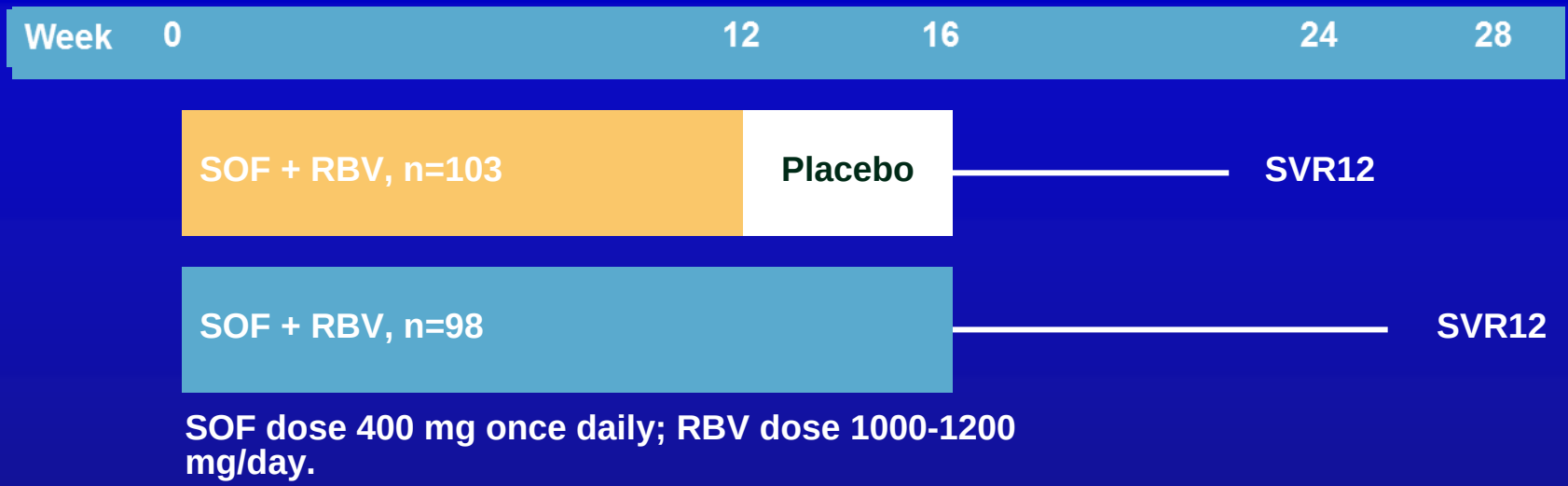
David Nelson[1], Jordan Feld[2], Kris V. Kowdley[3], M. Tarek Al-Assi[4], Ming Lin[5], Hongmei Mo[5], John McNally[5], Diana M. Brainard[5], William T. Symonds[5], John G. McHutchison[5], Keyur Patel[6], Stuart Gordon[7]

[1]University of Florida, Gainesville, FL, USA; [2]University of Toronto, Ontario, Canada; [3]Digestive Disease Institute, Virginia Mason Medical Center, Seattle, WA, USA;

[4]Texas Digestive Disease Consultants, Arlington, TX, USA; [5]Gilead Sciences, Inc., Foster City, CA, USA; [6]Duke University, Durham, NC, USA; [7]Henry Ford Health Systems, Detroit, MI, USA

•**International Liver Congress 2013, Amsterdam**

Study Design



SOF dose 400 mg once daily; RBV dose 1000-1200 mg/day.

Genotype 2 or 3 HCV-infected patients who had failed prior interferon-based treatment

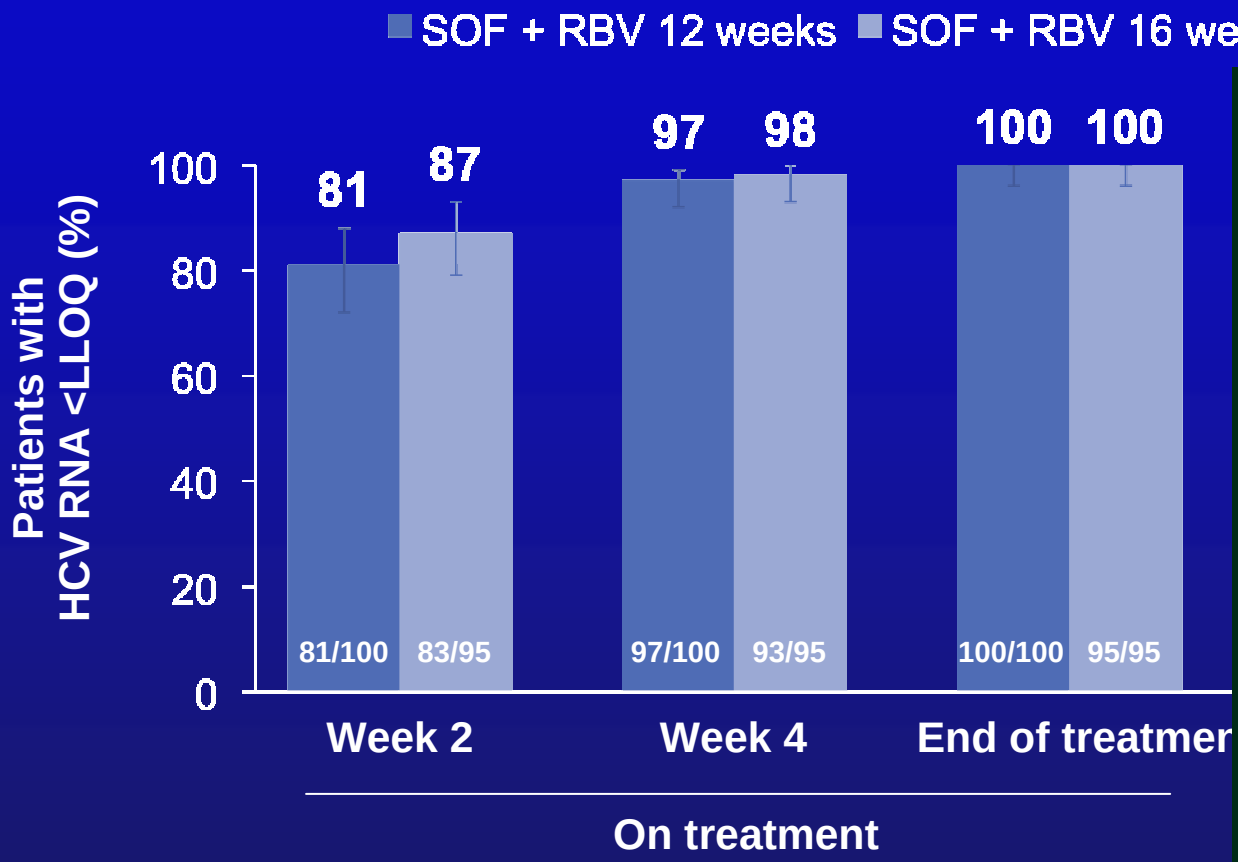
Expanded inclusion criteria

- Targeted 30% enrollment of patients with cirrhosis
- No upper limit to age or BMI
- Platelet count ≥50,000/mm^3, no neutrophil minimum

Randomized (1:1), double blind, placebo controlled

Stratified by cirrhosis and genotype

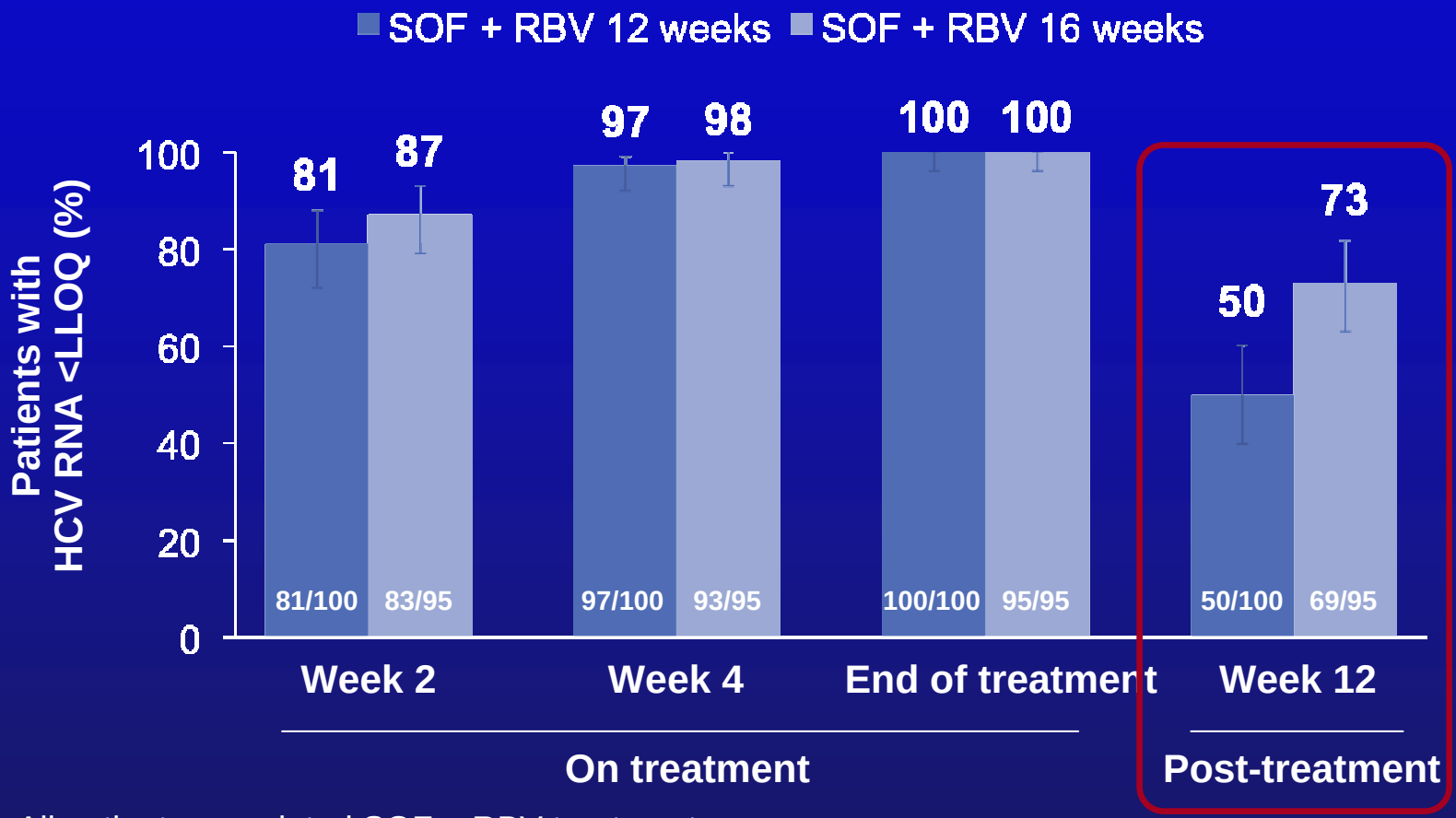
Results: Virologic Response



All patients completed SOF + RBV treatment

Error bars represent 95% confidence intervals.

Results: Virologic Response



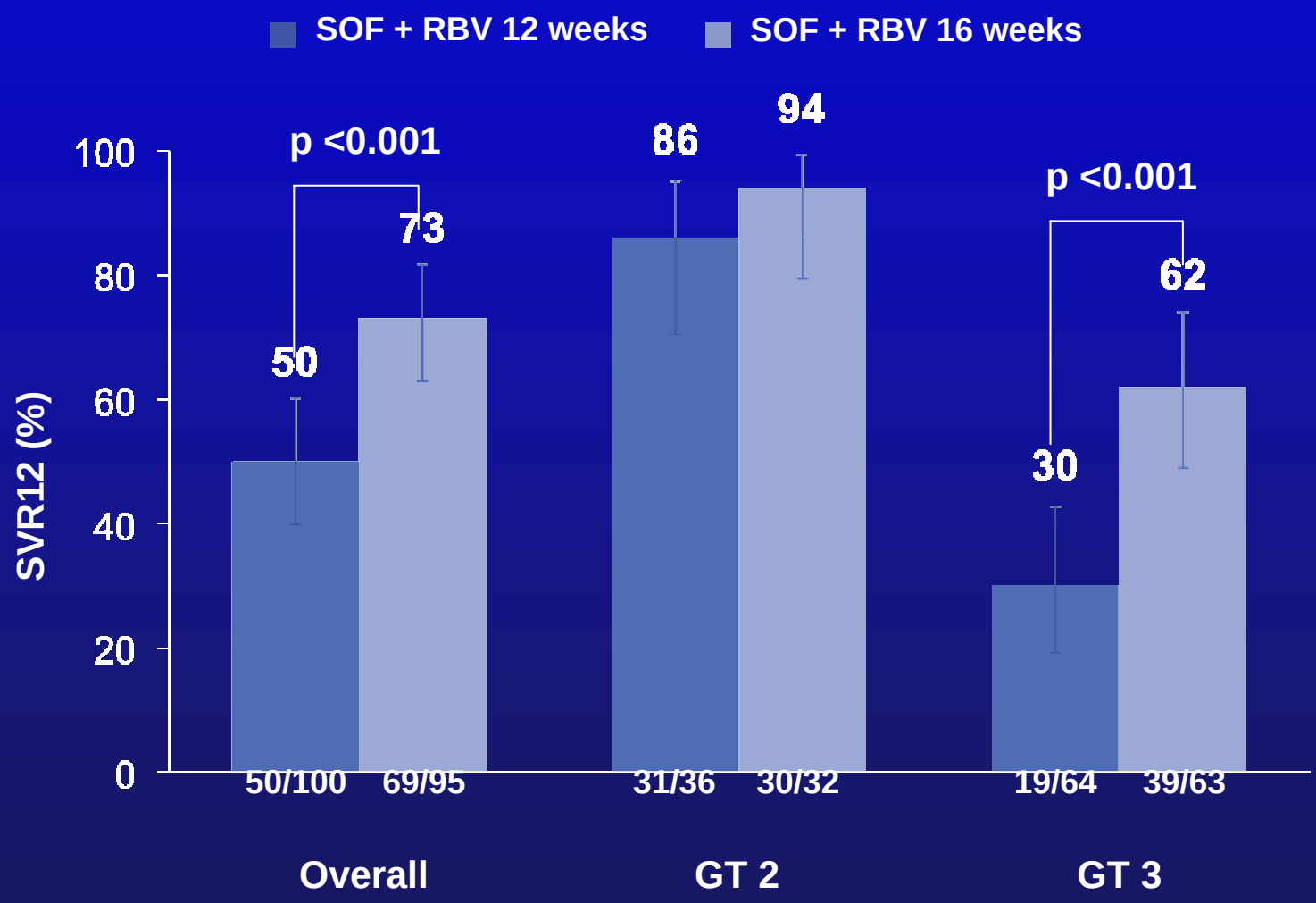
All patients completed SOF + RBV treatment

Study met primary endpoint of superiority in each arm over historical control rate of 25% ($p < 0.001$ for both)

Relapse accounted for all virologic failures

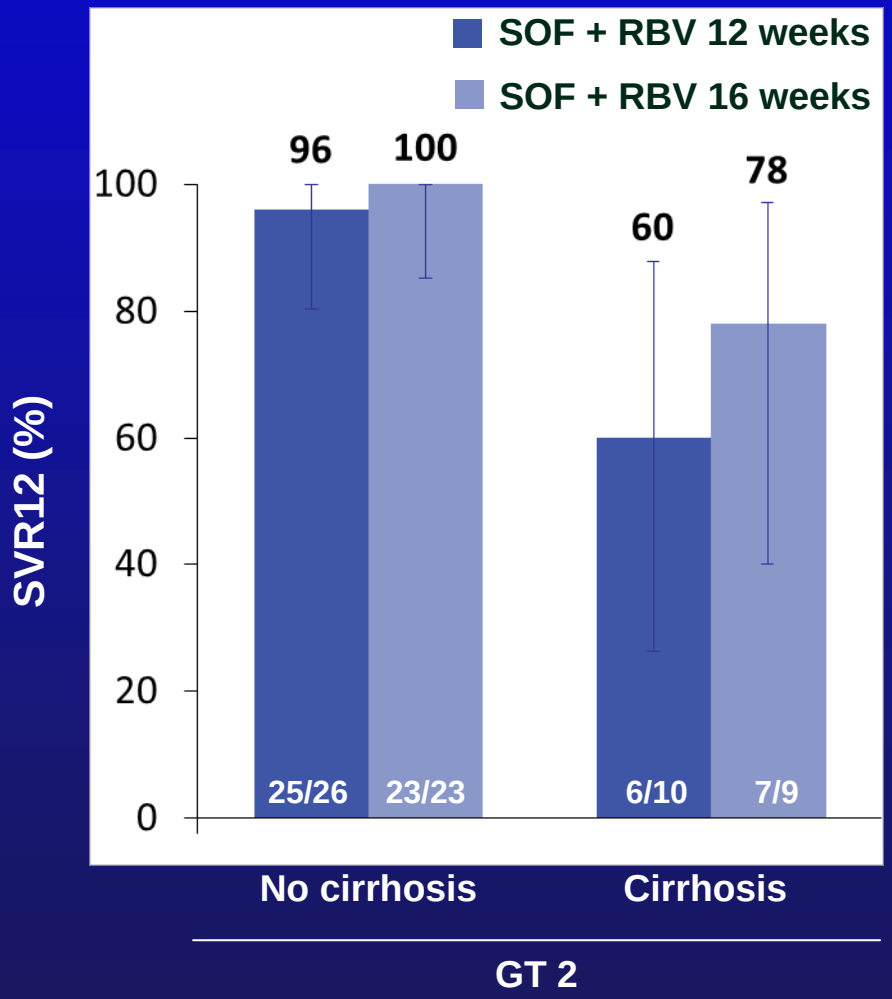
Error bars represent 95% confidence intervals.

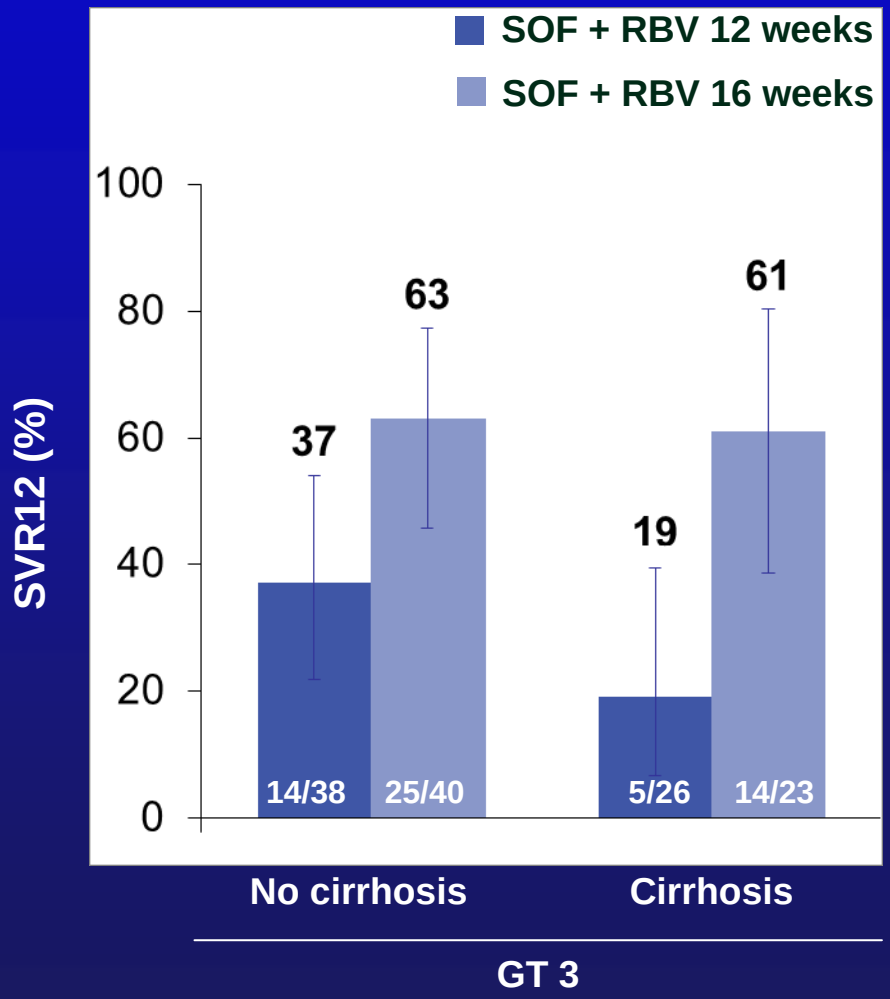
Results: SVR12 by HCV Genotype



Error bars represent 95% confidence intervals.

Results: SVR_{12} in HCV G2/G3 Patients with and without Cirrhosis





Error bars represent 95% confidence intervals.

Results: Safety Summary

	Patients, n (%)	SOF + RBV 12 weeks n=103	SOF + RBV 16 weeks n=98
Overall safety	AEs	92 (89)	86 (88)
	Grade 3–4 AEs	8 (8)	4 (4)
	Serious AEs	5 (5)	3 (3)
	Treatment discontinuation due to AEs	1 (1)*	0
Hematologic abnormalities	Hemoglobin <10 g/dL	10 (10)	5 (5)
	Hemoglobin <8.5 g/dL	2 (2)	0
	Absolute neutrophil count <750/mm^3	1 (1)	0
	Platelets <50,000/mm^3	2 (2)	0

*A single patient discontinued treatment during placebo treatment period (advanced HCC diagnosed).

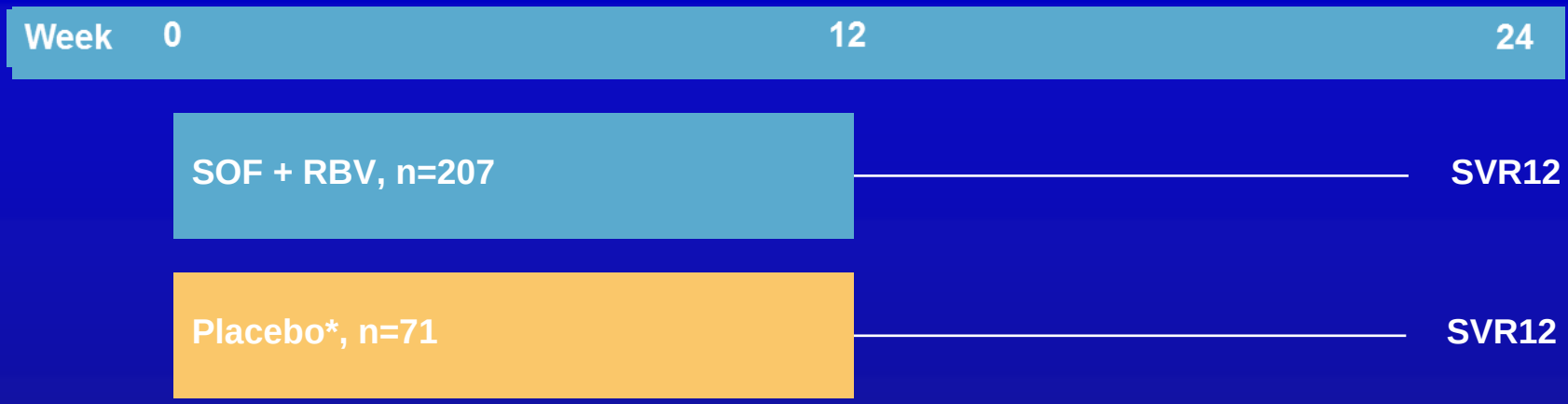
Treatment With Sofosbuvir + Ribavirin for 12 Weeks Achieves SVR12 of 78% in GT 2/3 Interferon-Ineligible, -Intolerant, or -Unwilling Patients: Results of the Phase 3 POSITRON Trial

Ira M. Jacobson[1], Eric M. Yoshida[2], Mark Sulkowski[3], David R. Nelson[4], Evguenia Svarovskaia[5], Di An[5], John McNally[5], Diana M. Brainard[5], William T. Symonds[5], John G. McHutchison[5], Stephen Pianko[6], Kris V. Kowdley[7]

[1]Weill Cornell Medical College, New York, NY, USA; [2]University of British Columbia, Vancouver, Canada; [3]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]University of Florida, Gainesville, FL, USA; [5]Gilead Sciences, Inc., Foster City, CA, USA; [6]Monash Medical Centre and Monash University, Melbourne, Victoria, Australia; [7]Digestive Disease Institute, Virginia Mason Medical Center, Seattle, WA, USA

•**International Liver Congress 2013, Amsterdam**

Study Design



SOF dose 400 mg once daily; RBV dose 1000-1200 mg/day.

Genotype 2 or 3 IFN-ineligible, -intolerant, or -unwilling patients

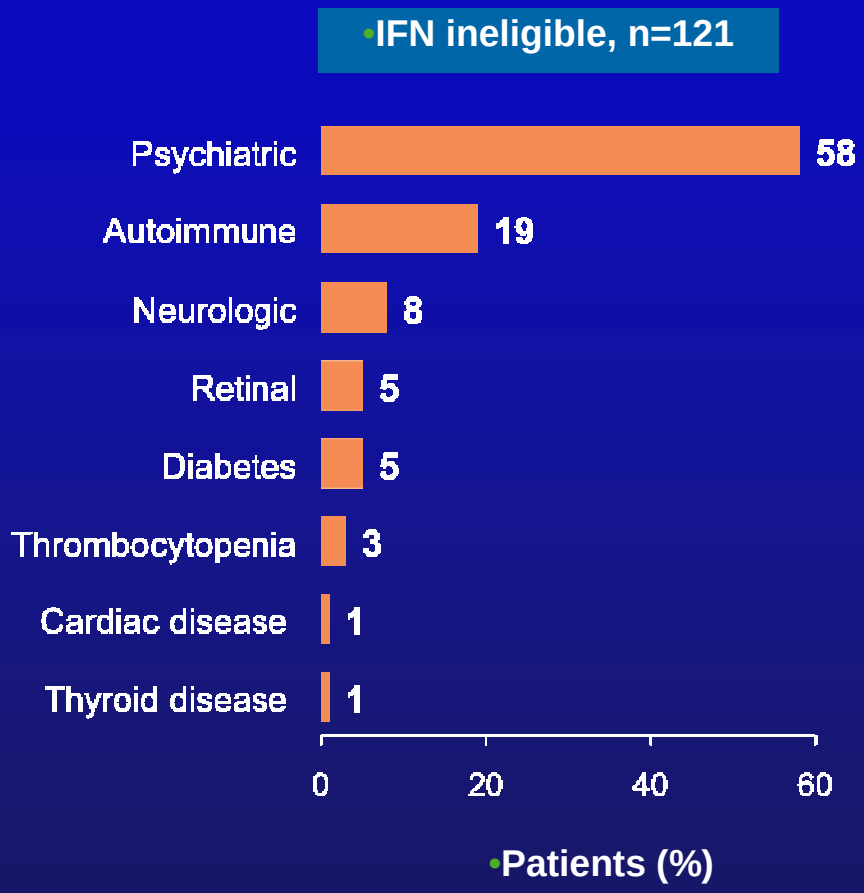
Expanded inclusion criteria

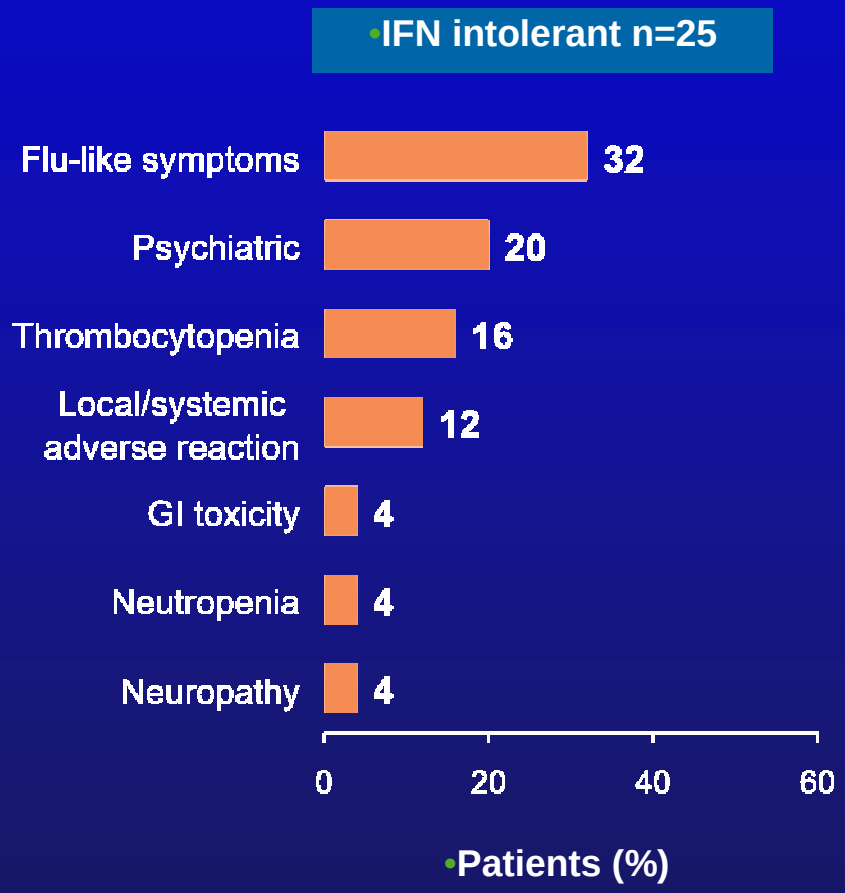
- Targeted 20% enrollment of patients with cirrhosis
- No upper limit to age or BMI
- No lower limit to platelets or neutrophils

Randomized (3:1), double blind, placebo controlled

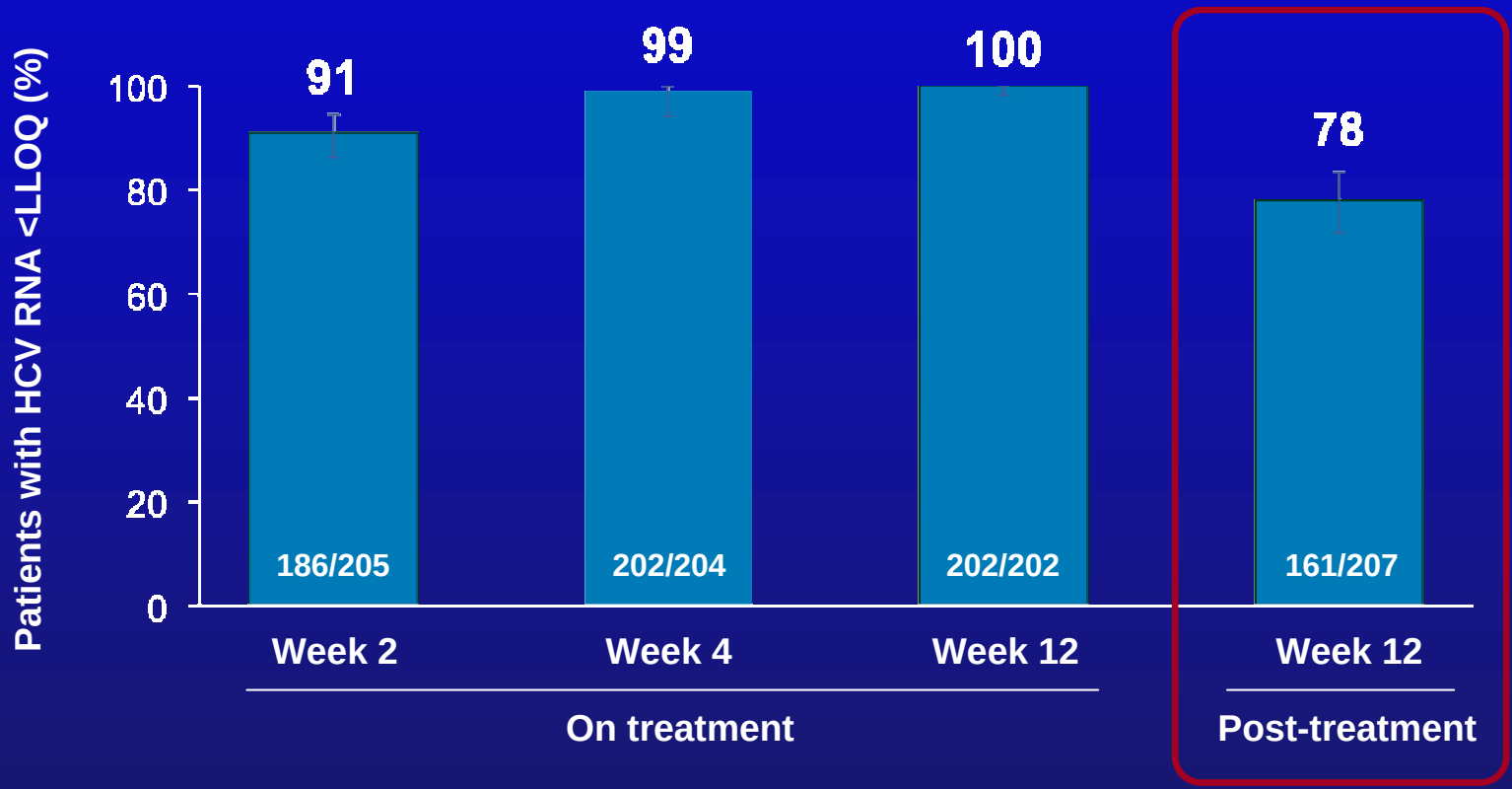
Stratified by presence or absence of cirrhosis

Reasons for Interferon Ineligibility or Intolerance





Results: Virologic Response



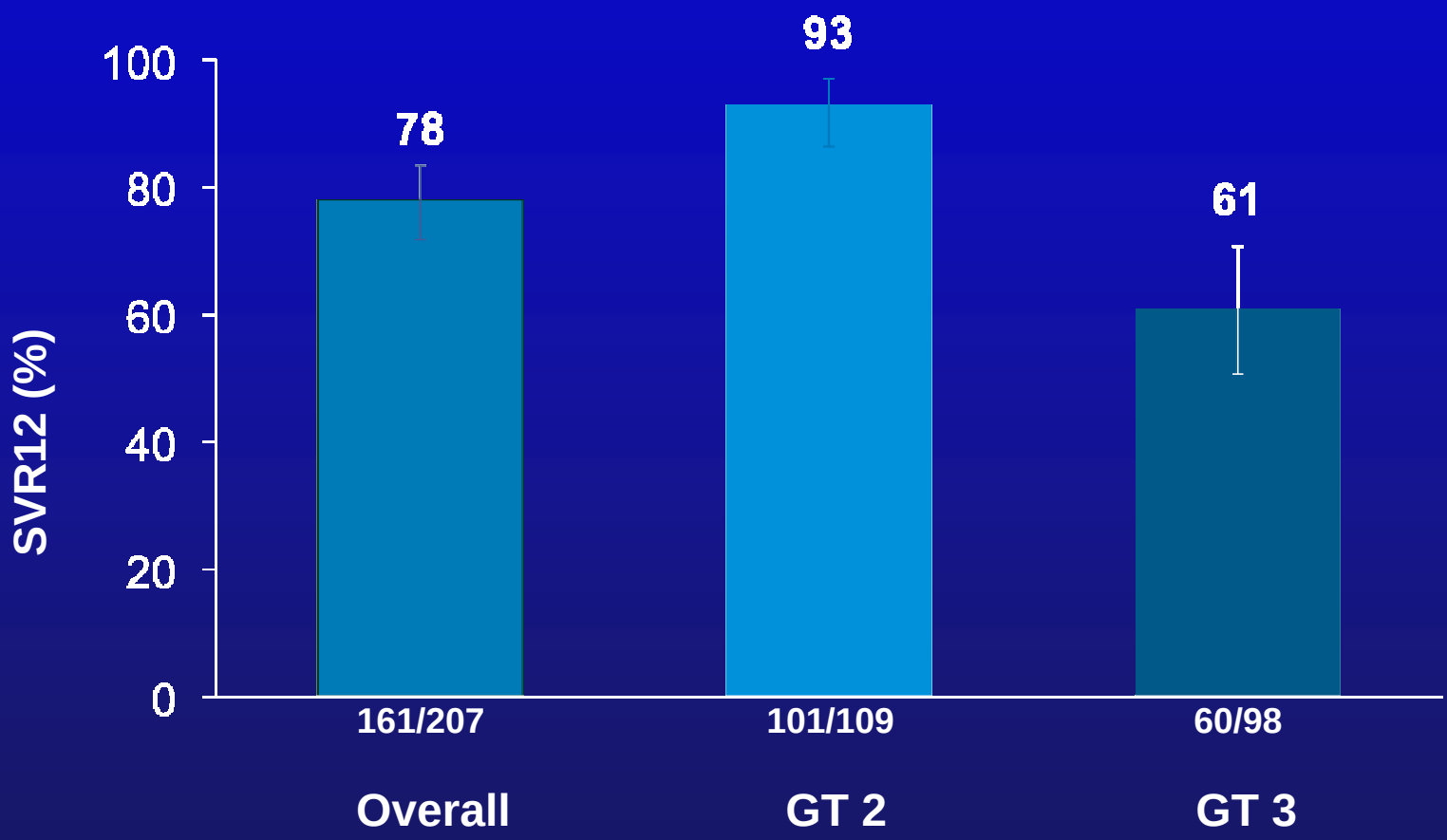
SVR12 rate was 0% in placebo recipients

Study met primary endpoint of superiority over placebo (p <0.001)

Relapse accounted for all virologic failures

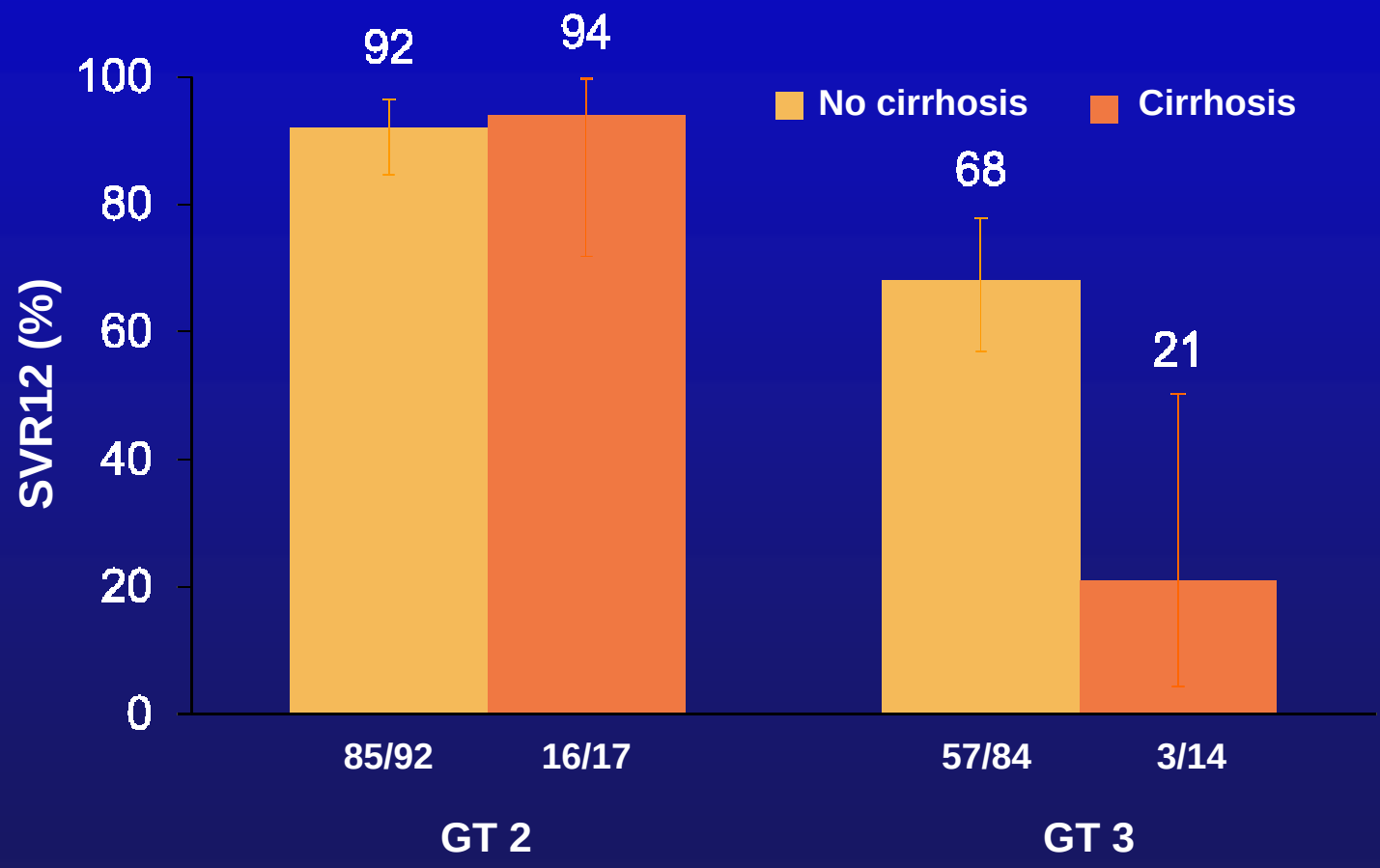
Error bars represent 95% confidence intervals.

Results: SVR_{12} by HCV Genotype



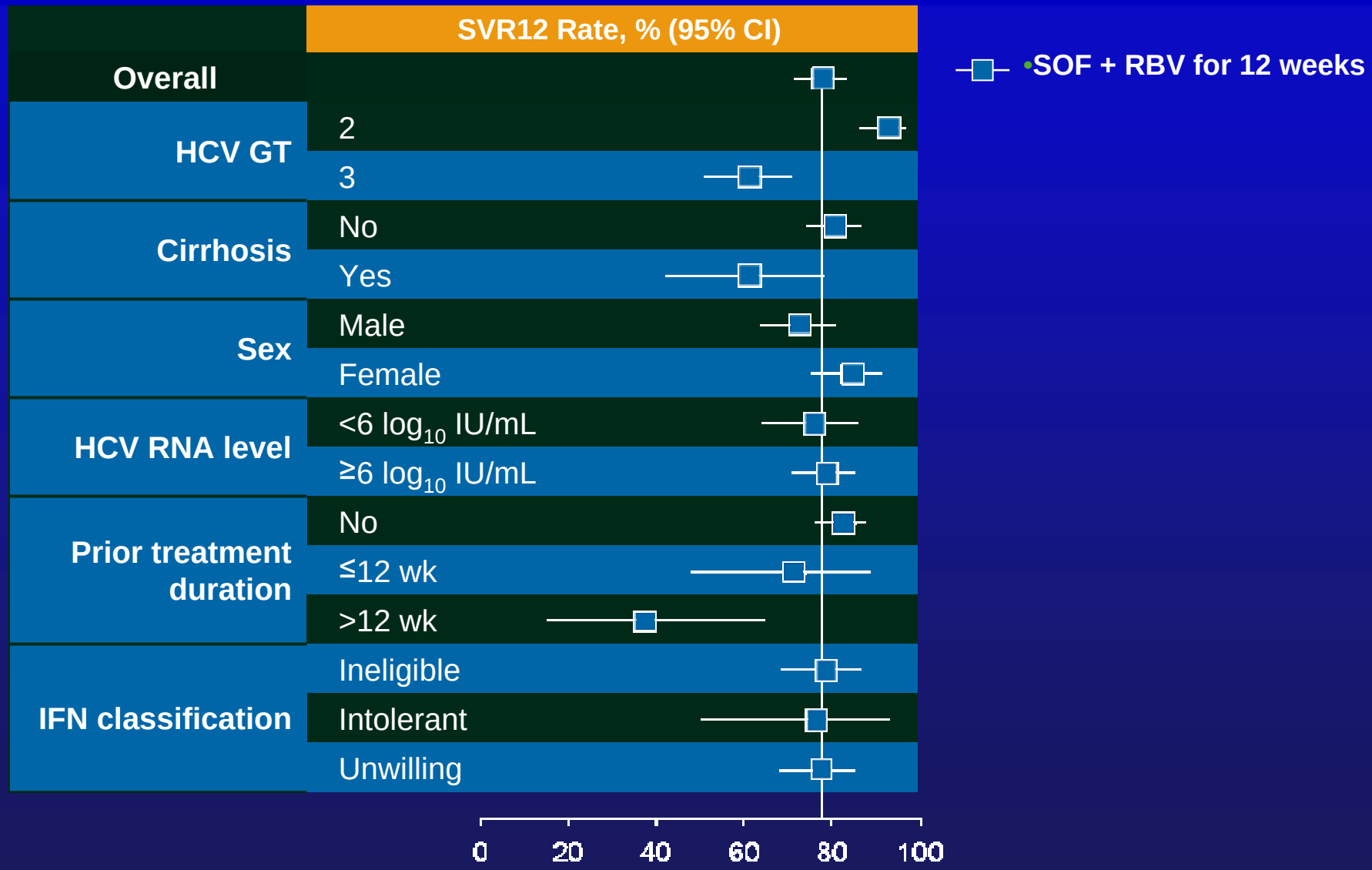
Error bars represent 95% confidence intervals.

Results: SVR_{12} by Cirrhosis Status



Error bars represent 95% confidence intervals.

Results: SVR_{12} by Prespecified Subgroups



SAFETY AND EFFICACY OF INTERFERON-FREE REGIMENS OF ABT-450/r, ABT-267, ABT-333 +/- RIBAVIRIN IN PATIENTS WITH CHRONIC HCV GT1 INFECTION: RESULTS FROM THE AVIATOR STUDY

Kris V. Kowdley[1], Eric Lawitz[2], Fred Poordad[2], Daniel E. Cohen[3], David Nelson[4], Stefan Zeuzem[5], Gregory T. Everson[6], Paul Kwo[7], Graham R Foster[8], Mark Sulkowski[9], Wangang Xie[3], Lois Larsen[3], Amit Khatri[3], Thomas Podsadecki[3], Barry Bernstein[3]

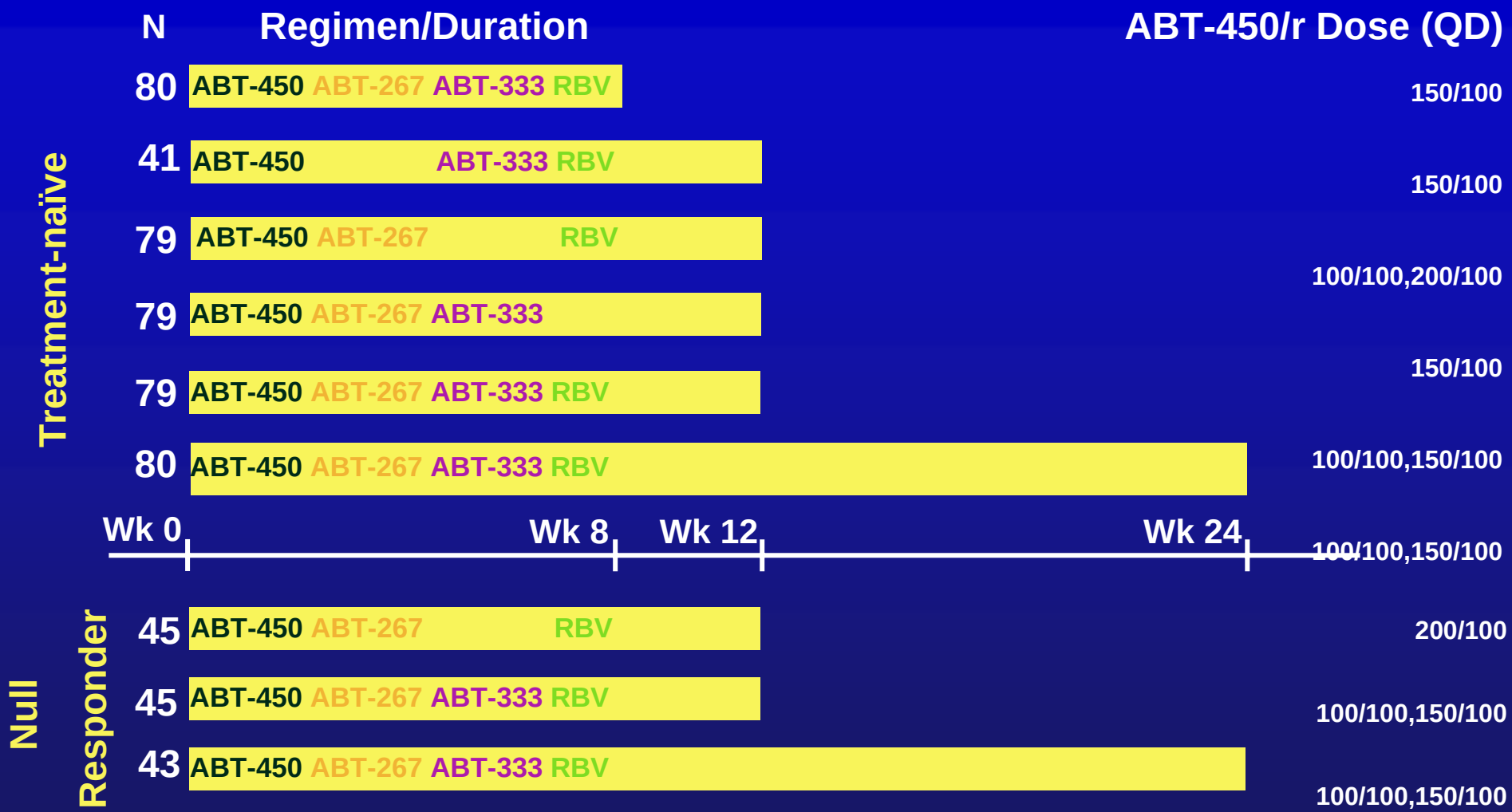
1: Digestive Disease Institute, Virginia Mason Medical Center, Seattle, WA; 2: The Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX; 3: AbbVie Inc., North Chicago IL; 4: University of Florida College of Medicine, Gainesville, FL; 5: J.W. Goethe University, Frankfurt, Germany; 6: University of Colorado Denver, Aurora, CO; 7: Indiana University, Indianapolis, IN; 8: Queen Marys University of London, Barts Health, London, United Kingdom; 9: Johns Hopkins University, Baltimore, MD

48th Annual Meeting of the European Association for the Study of the Liver

• Amsterdam, The Netherlands •

25 April 2013

M11-652 Study, N=571



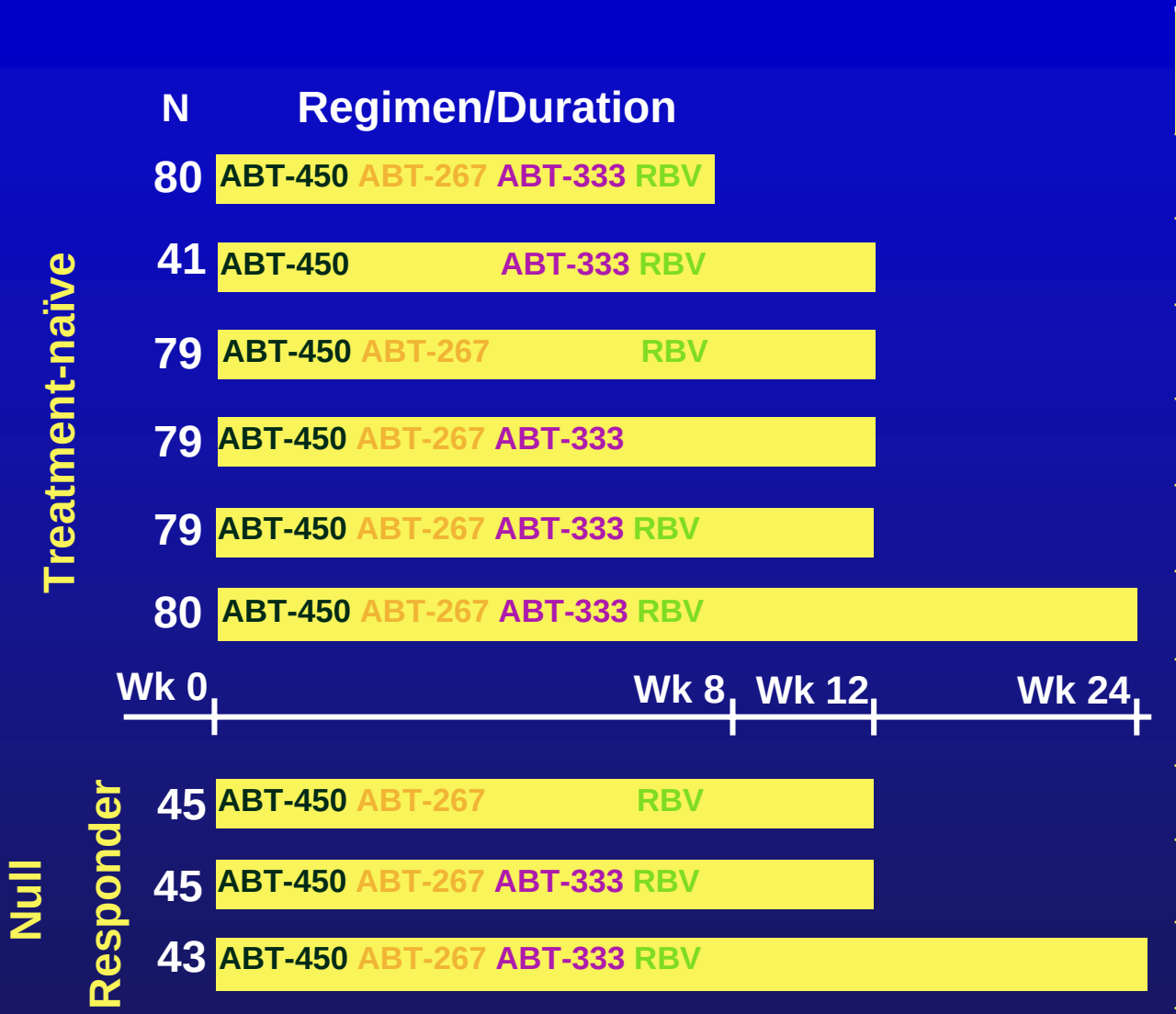
ABT-267 25mg QD; ABT-333 400mg BID; RBV weight-based 1000-1200 mg daily dose divided BID

All patients to be followed through 48 weeks post-treatment

Baseline Characteristics
All Groups n=571

Duration	Treatment-naïve						Null Responders		
	8 wks	12 wks				24 wks	12 wks		24 wks
Regimen	450/r 267 333 RBV	450/r 333 RBV	450/r 267 RBV	450/r 267 333	450/r 267 333 RBV	450/r 267 333 RBV	450/r 267 RBV	450/r 267 333 RBV	450/r 267 333 RBV
N=	**80**	**41**	**79**	**79**	**79**	**80**	**45**	**45**	**43**
Male, %	58	44	57	57	56	43	60	62	63
White race, %	85	85	77	81	80	94	78	84	88
Age, Mean	50	51	50	48	50	52	51	50	53
IL28B CC, %	28	34	27	29	28	28	2	4	2
Baseline log_{10} HCV RNA, Mean	6.6	6.6	6.5	6.5	6.5	6.6	6.6	6.6	6.8
GT1a, %	70	71	66	68	68	68	59	62	63

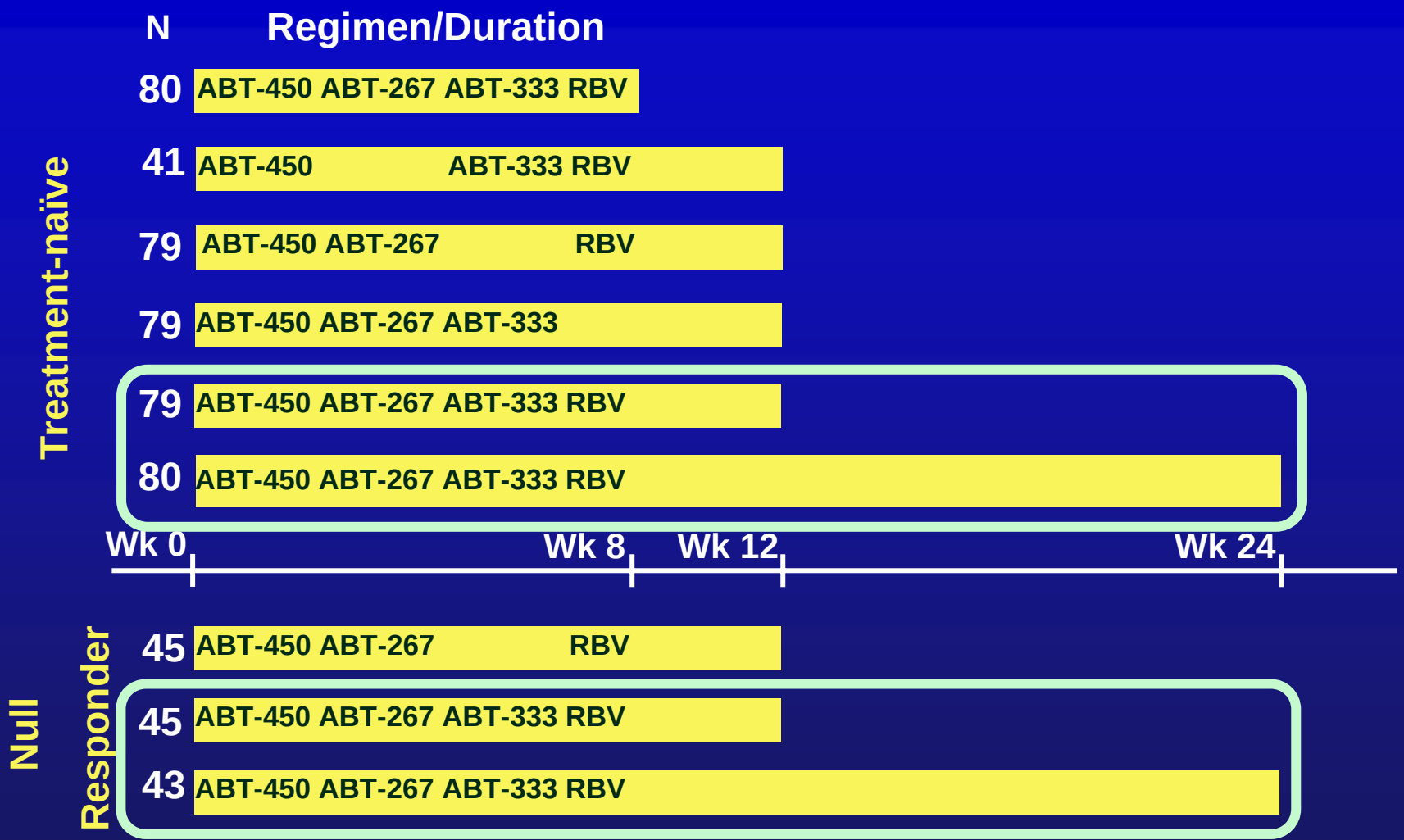
Response Rates, All Groups, N=571



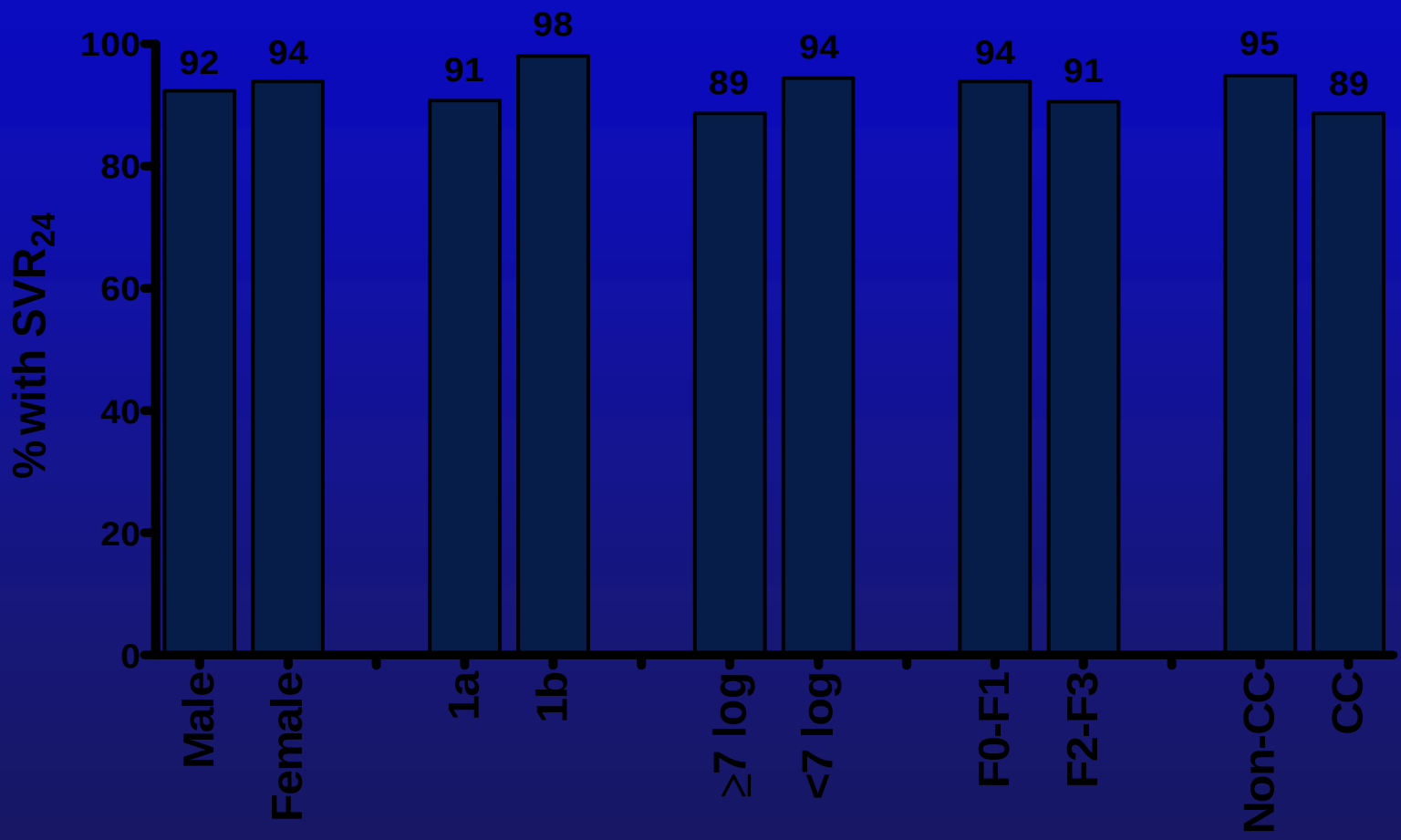
SVR_{12} %	SVR_{24}* %	Breakthrough /Relapse
89	88	0 / 10
85	83	1 / 4
91	89	1 / 8
90	87	1 / 5
99	96	0 / 1
93	90	0 / 2
89	89	0 / 5
93	93	3 / 0
98	95	1 / 0

* 8 patients with SVR_{12} have not returned for >24 weeks and are counted as virologic failures for SVR_{24}; 3 patients relapsed between SVR_{12} and SVR_{24}.

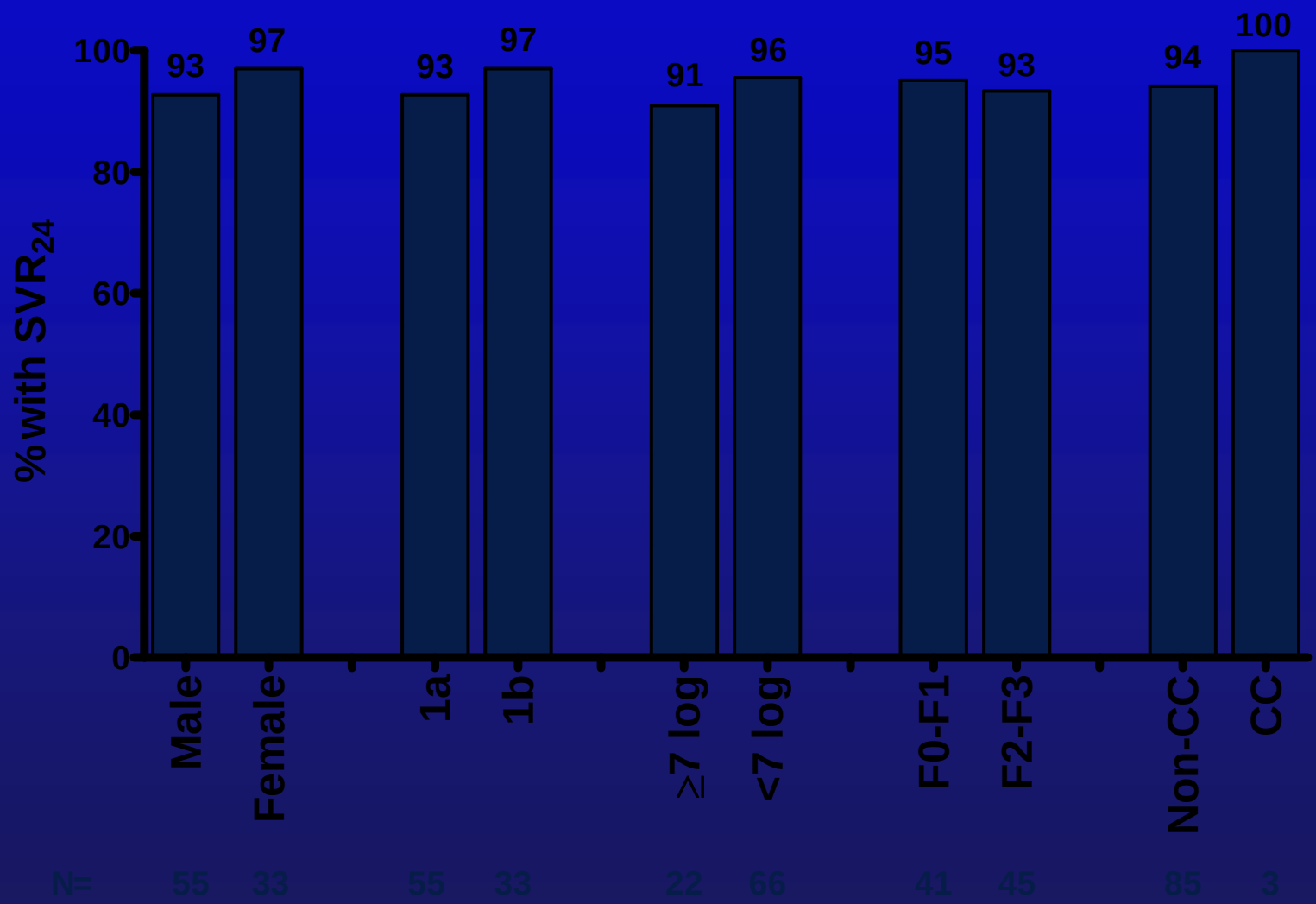
Subgroup Analysis of SVR_{24} :12- and 24-Week Treatment Arms of 3 DAA + RBV, N=247



SVR_{24} by Baseline Subgroups – Treatment-Naïve Patients



SVR_{24} by Baseline Subgroups – Null Responders



Most Common Adverse Events (12- and 24-week arms of 3 DAA + RBV) by Prior Peg/RBV Experience

The majority of adverse events were mild

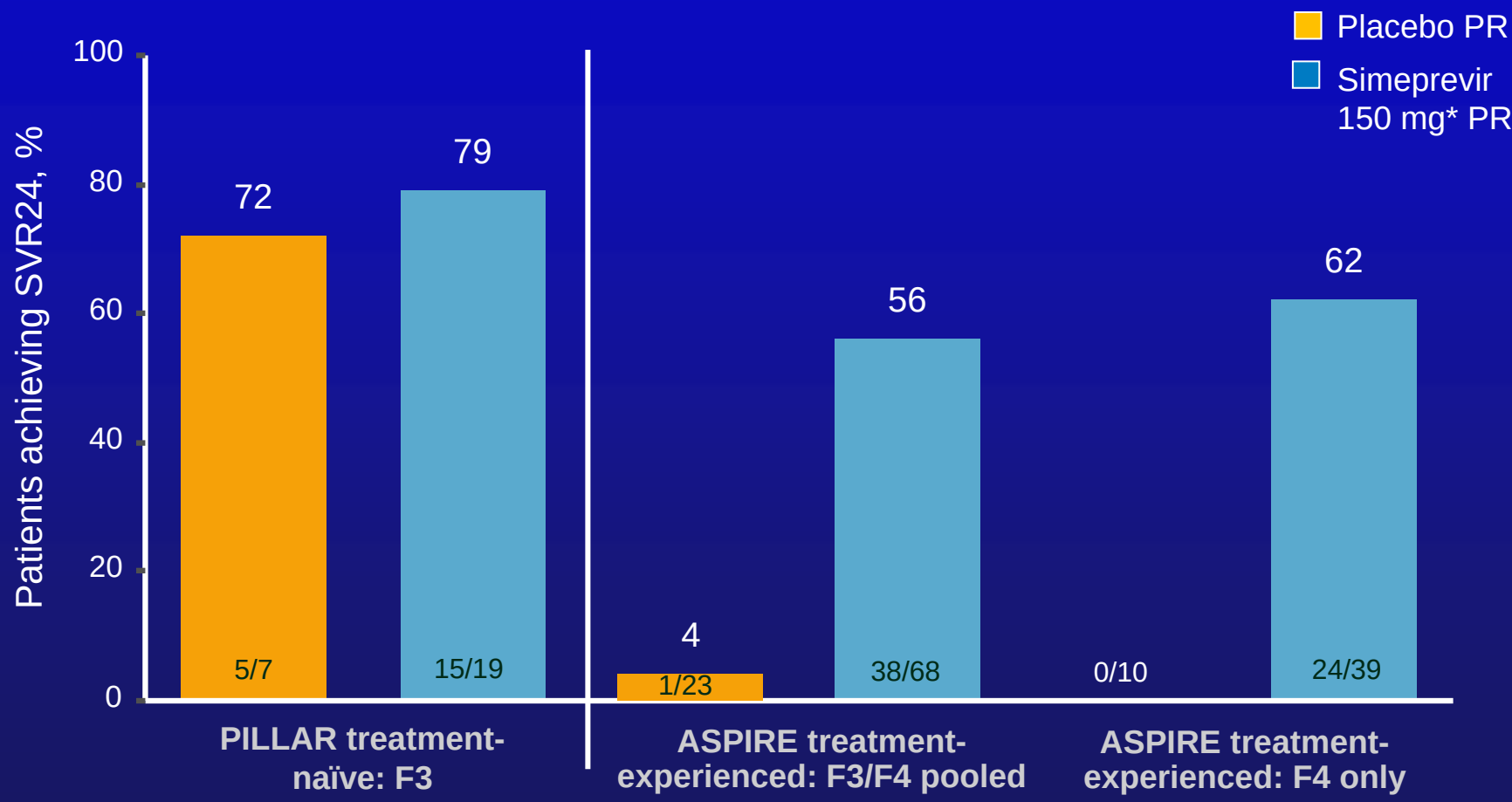
Event, %	3 DAAs + RBV		
	Total (N =247)	Treatment-Naïve (N =159)	Null Responders (N = 88)
Headache	31.2	31.4	30.7
Fatigue	29.6	32.7	23.9
Nausea	22.7	24.5	19.3
Insomnia	19.8	22.6	14.8
Diarrhea	15.0	13.2	18.2

Grade 3 or Grade 4 Laboratory Abnormalities (12- and 24-week arms of 3 DAA + RBV)

Grade 3 event, n	3 DAAs + RBV		
	Pooled (N =247)	Treatment-Naïve (N =159)	Null Responders (N = 88)
ALT >5x – 20x ULN	1	1	0
AST >5x – 20x ULN	0	0	0
Alkaline Phosphatase >3x – 20x ULN	0	0	0
Total bilirubin > 3x – 10xULN	6	4	2
Hemoglobin < 8.0 – 6.5 g/dL	0	0	0
Grade 4 event, n			
ALT > 20x ULN	0	0	0
AST > 20x ULN	0	0	0
Alkaline Phosphatase > 20x ULN	0	0	0
Total bilirubin > 10x ULN	0	0	0
Hemoglobin < 6.5 g/dL	0	0	0

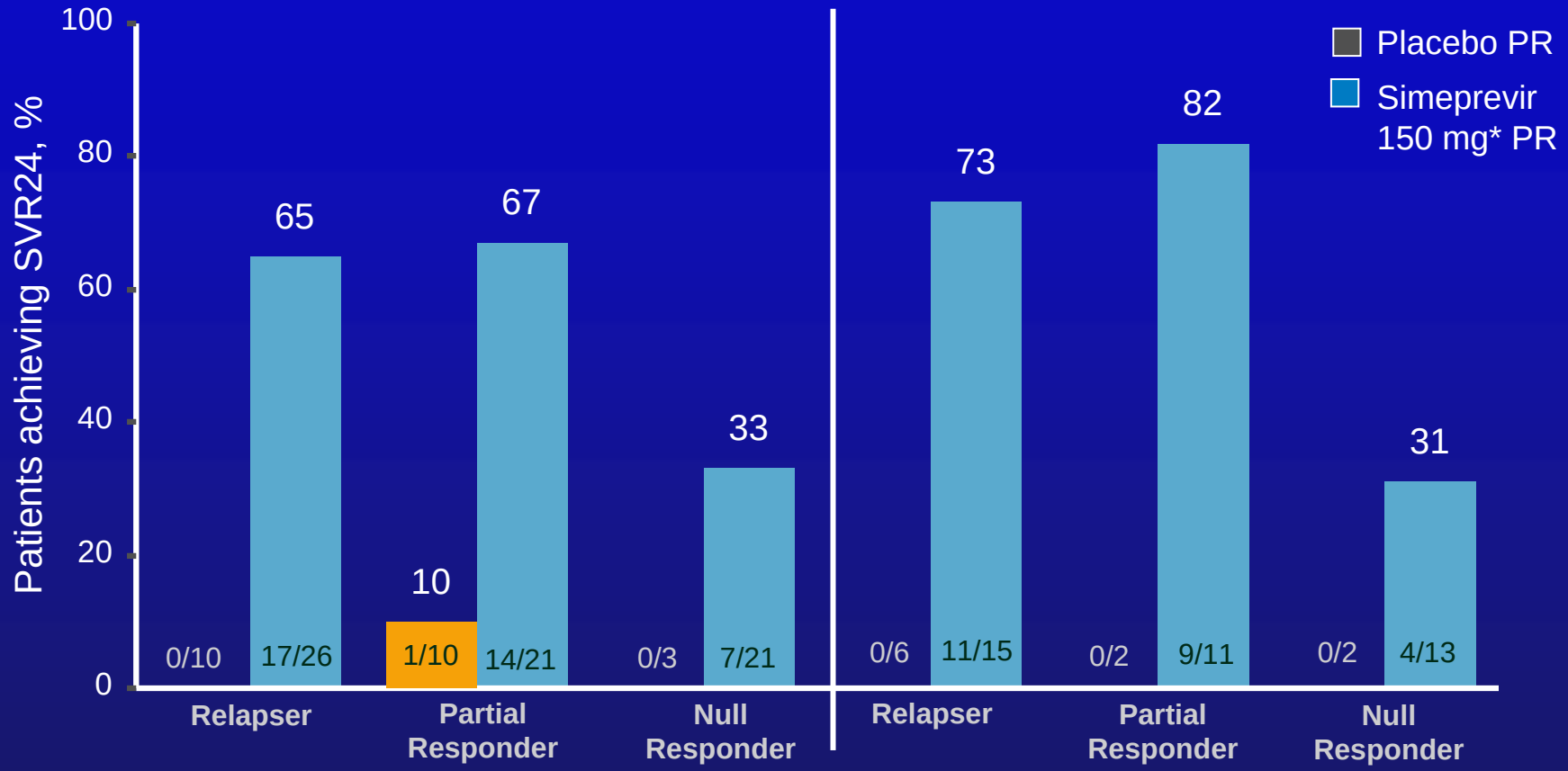
Difficult to Treat Populations
3 Abstracts

P/R/Simeprevir (TMC435)/PegIFN/RBV in HCV G1 Naïve and Experienced: Proportion of F3 and F4 patients achieving SVR24



Poordad F, et al. AASLD 2012. Abstract 83

Treatment-experienced: SVR24 by Prior PegIFN/RBV Response in F3/F4 patients



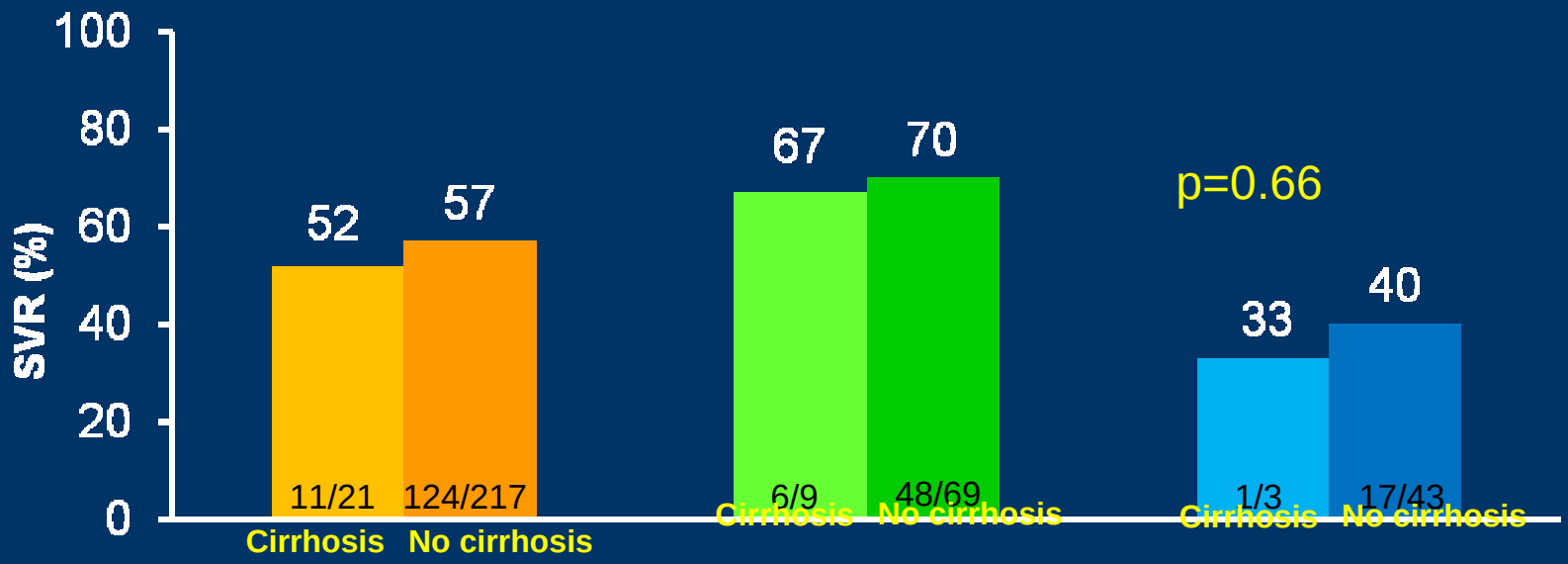
ASPIRE treatment-experienced: F3/F4 pooled

ASPIRE treatment-experienced: F4 only

Poordad F, et al. AASLD 2012. Abstract 83

SOUND-C2: Cirrhotics

- **Faldaprevir (PI) + BI 207127 (NNI) +/- RBV for 16 to 40 weeks**
- **Sub-study in cirrhosis (n=33; 9%)**
- **SVR_{12} in cirrhotics: G1a: 43 to 50% vs G1b: 57 to 80%**



BI 7127 dosing	TID	BID	TID
Duration (weeks)	16, 28 & 40	28	28
RBV +/-	+	+	-

Soriano V et al. AASLD 2012. Abstract 84

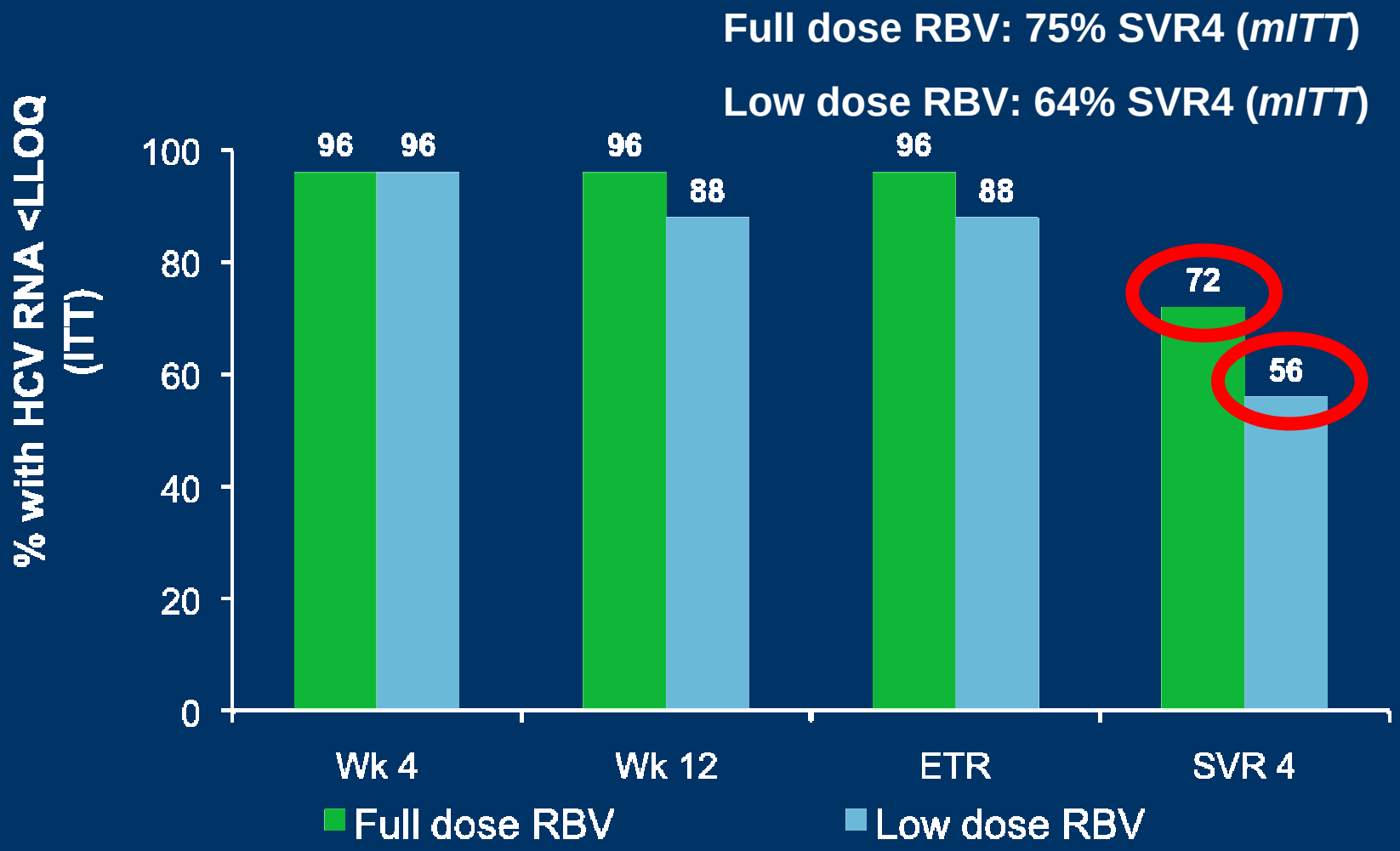
NIAID Study: Sofosbuvir + RBV in Washington DC

Baseline Demographics

	GS-7977+Full dose RBV N=10	GS-7977+Full dose RBV N=25	GS-7977+Low dose RBV N=25
Median age (range)	54 (30-65)	54 (30-65)	55 (26-78)
Male sex(%)	4 (40%)	20 (80%)	14 (56%)
Genotype 1a(%)	6 (60%)	20 (80%)	16 (64%)
African American (%)	9 (90%)	18 (72%)	23 (92%)
Median BMI (range)	26 (22-43)	18 (72%)	23 (92%)
IL28B CT/TT (%)	6 (67%)	21 (84%)	21 (84%)
Median HCV RNA log (IQR)	6.85 (5.80-7.21)	6.16 (5.37-6.41)	6.05 (5.49-6.36)
Advanced fibrosis (%)	0	6 (24%)	7 (28%)

Osinusi A, et al. AASLD 2012. Abstract LB-4.

Treatment Response: Part 2



1 drop out at week 3

3 drop outs by week 8

Osinusi A, et al. AASLD 2012. Abstract LB-4.

Sustained Virologic Response With Daclatasvir Plus Sofosbuvir ± Ribavirin (RBV) in Chronic HCV Genotype (GT) 1-Infected Patients Who Previously Failed Telaprevir (TVR) or Boceprevir (BOC)

Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T,

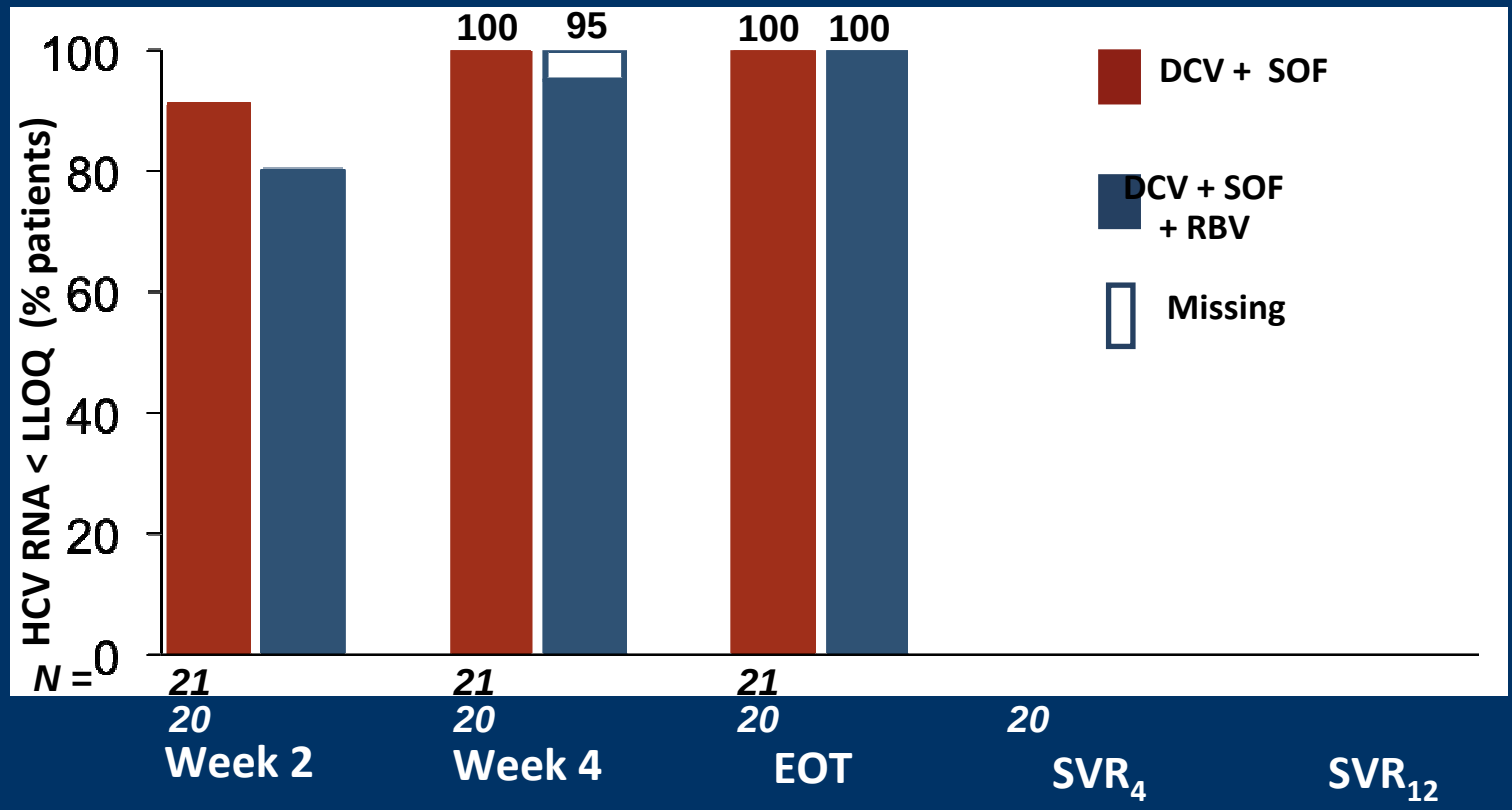
Wind-Rotolo M, Huang S-P, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, and Grasela DM for the AI444-040 Study Group

The International Liver Congress™ 2013:
The 48th Annual Meeting of the European Association for the Study of the Liver
Amsterdam, The Netherlands, April 24–28, 2013
Oral LB-1417

Baseline Demographics and Disease Characteristics

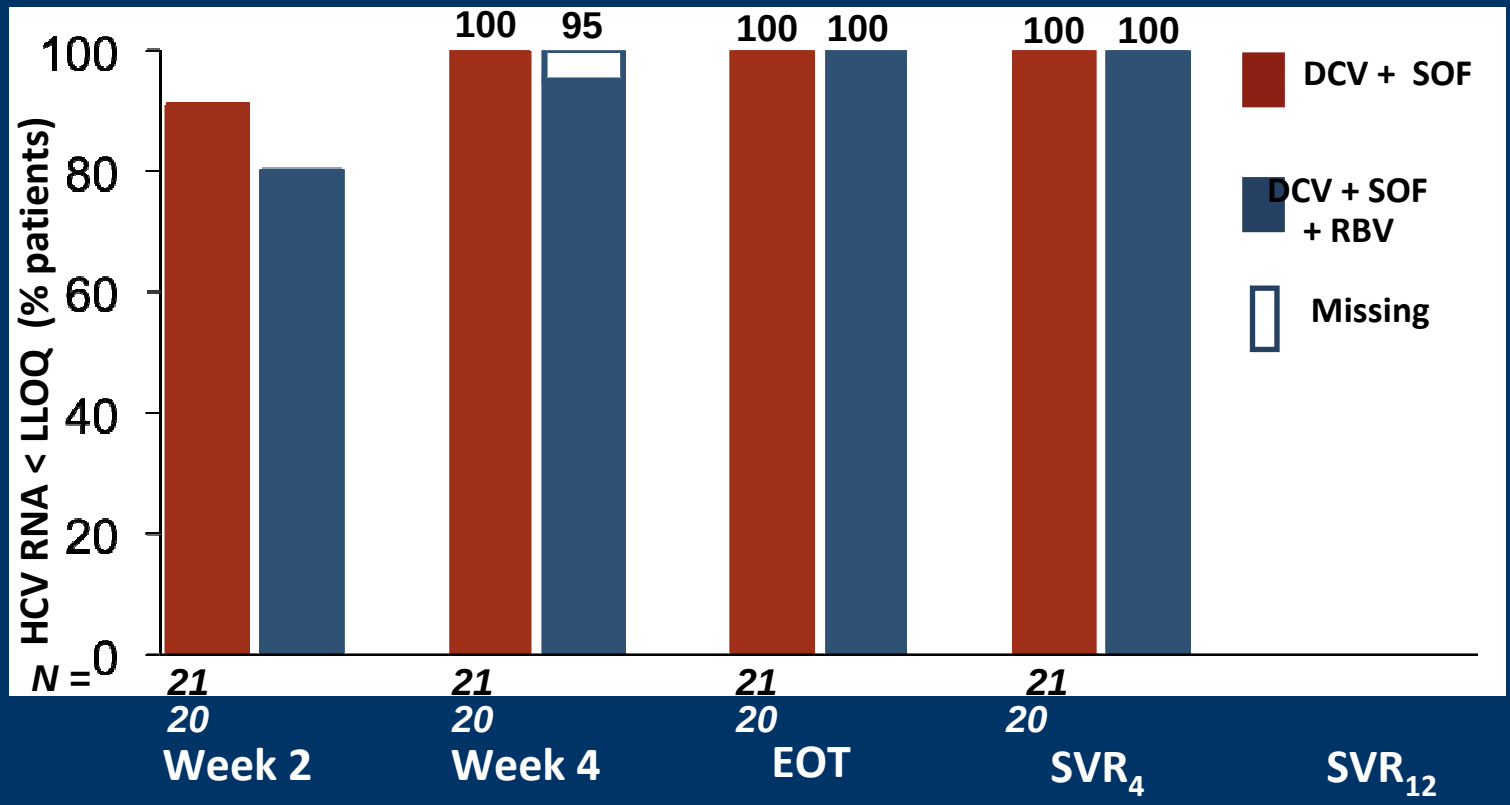
Parameter	DCV + SOF (n = 21)	DCV + SOF + RBV (n = 20)
Age, median years	59	57
Male, n (%)	13 (62)	12 (60)
Race, n (%) White Black/AA Asian	 19 (90) 2 (10)	 18 (90) 1 (5) 1 (5)
Hispanic/Latino ethnicity, n (%)	3 (14)	4 (20)
HCV RNA, mean $\log_{10}$ IU/mL (SD)	6.3 (0.4)	6.3 (0.4)
HCV genotype 1a, n (%)	16 (76)	17 (85)
IL28B genotype CT or TT, n (%)	20 (95)	20 (100)
METAVIR score[a,b] n (%) F0 – F1 ≥ F2	 2 (10) 17 (81)	 3 (15) 17 (85)
Prior TVR[c], n (%) Prior BOC[c], n (%)	15 (71) 7 (33)	18 (90) 2 (10)
Prior breakthrough or nonresponse, n (%)	12 (57)	17 (85)
NS3 polymorphisms conferring TVR or BOC resistance, n (%)	10 (48)	9 (45)
NS5A polymorphisms conferring DCV resistance, n (%)	2 (10)	1 (5)

Virologic Response During and After Treatment (mITT)



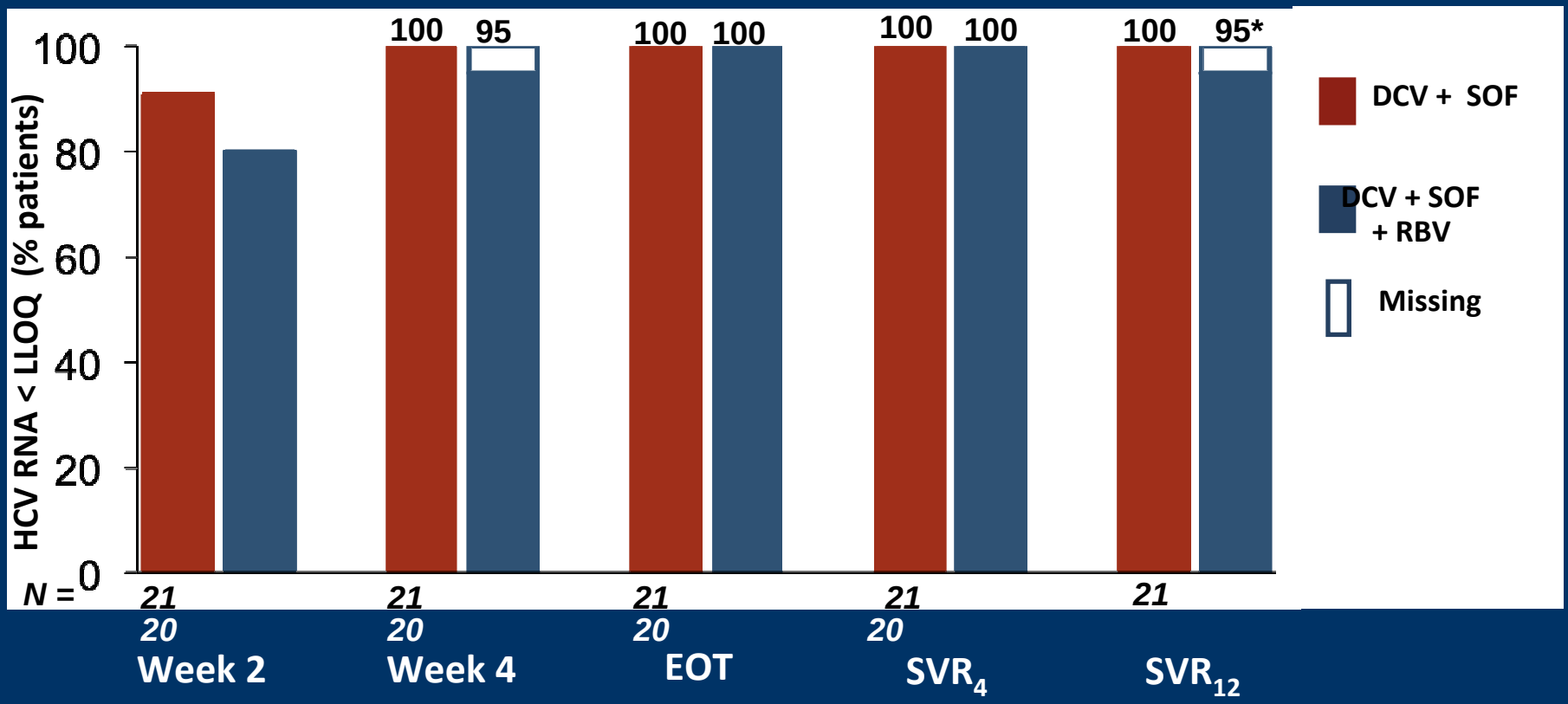
No virologic breakthrough or treatment discontinuations through EOT

Virologic Response During and After Treatment (mITT)



No virologic breakthrough or treatment discontinuations through EOT

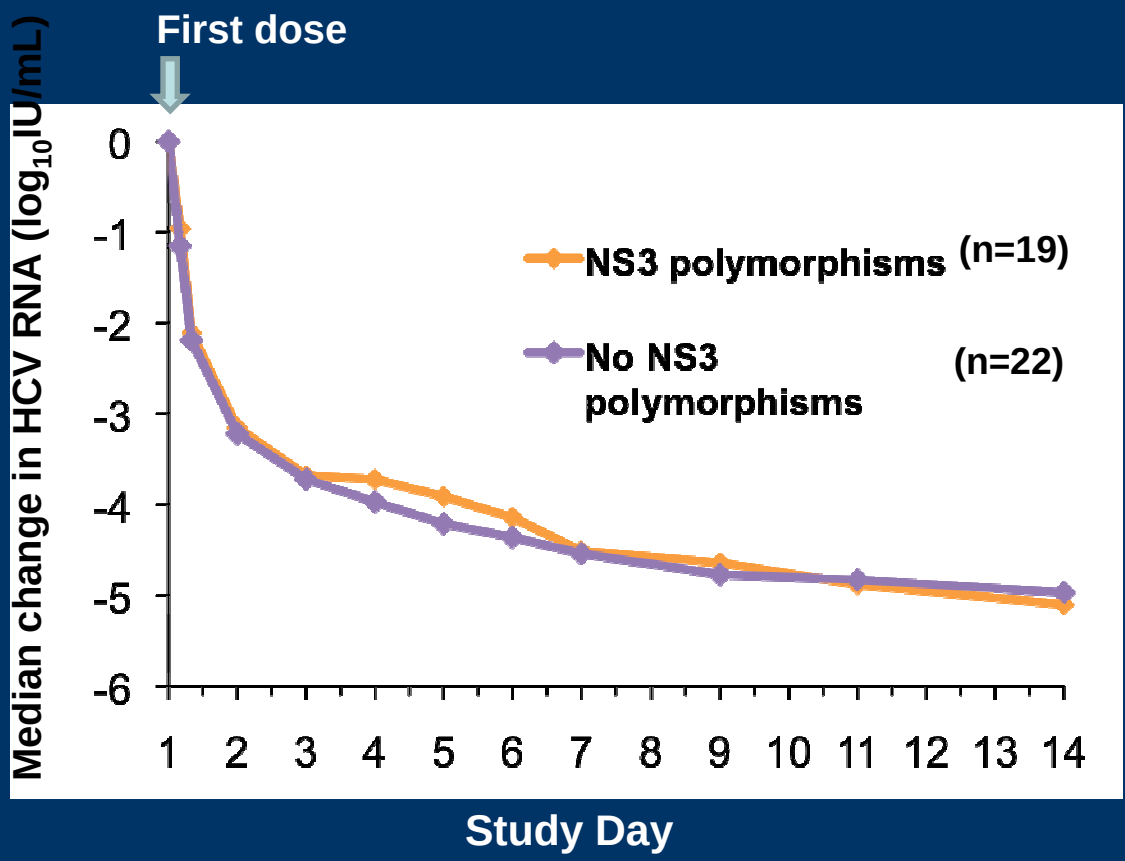
Virologic Response During and After Treatment (mITT)



- 1 patient missing at post-treatment (PT) Week 12: HCV RNA was undetectable at PT Week 4 and at PT Week 24 (preliminary)
- 21/41 patients have reached PT Week 24; all have achieved SVR_{24}

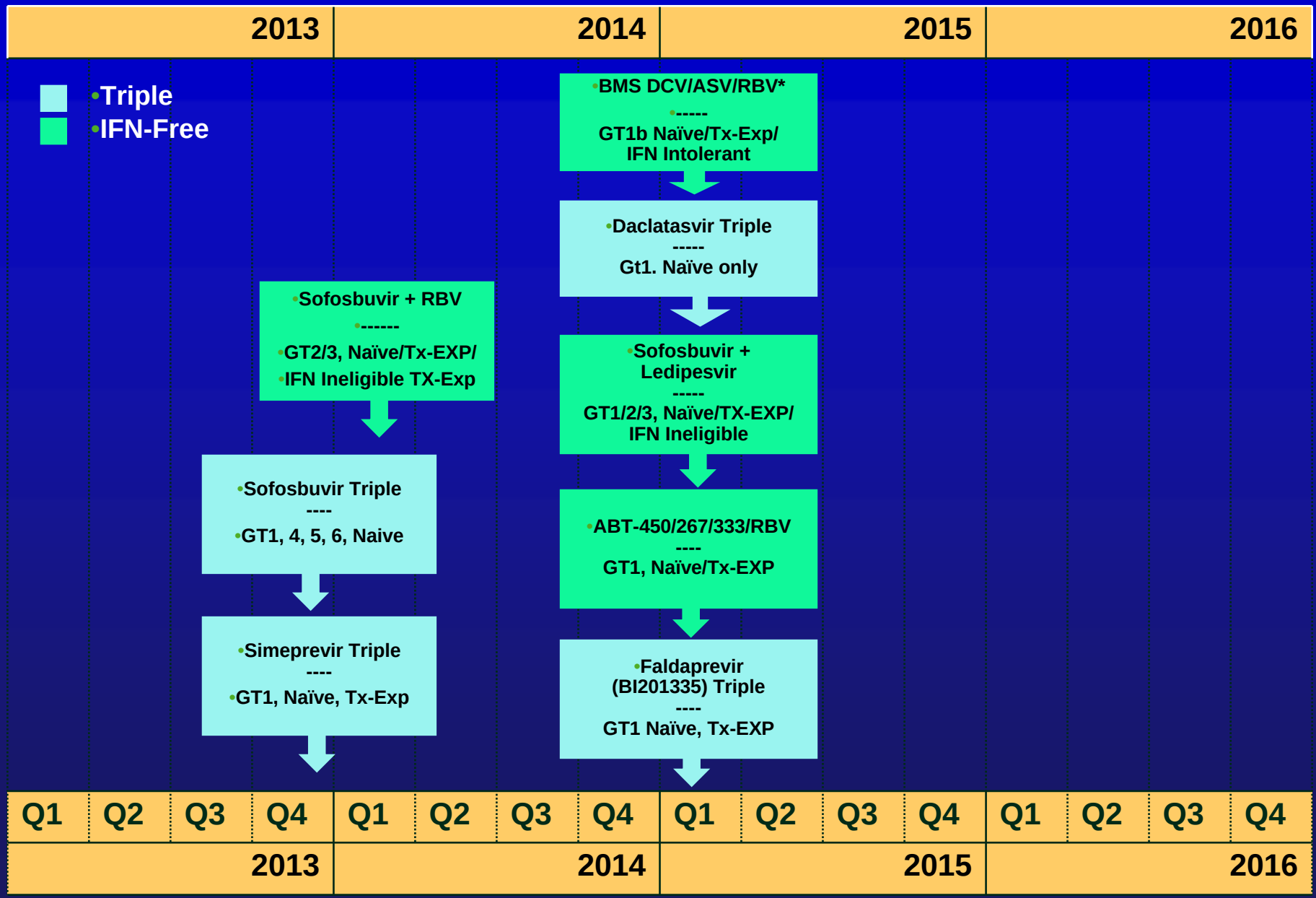
Virologic Response by Presence or Absence of Baseline NS3 Polymorphisms

Patients with NS3 polymorphisms, n	
V36M-R155K	6
R155K	3
V36L-R155K	1
T54S-R155K	1
T54S-V55I-R155K	1
V36M	1
V36M-V55I	1
V36M-V55A-R155K	1
V36M-R155K-I170T	1
V36A	1
V55A	1
V170T	1

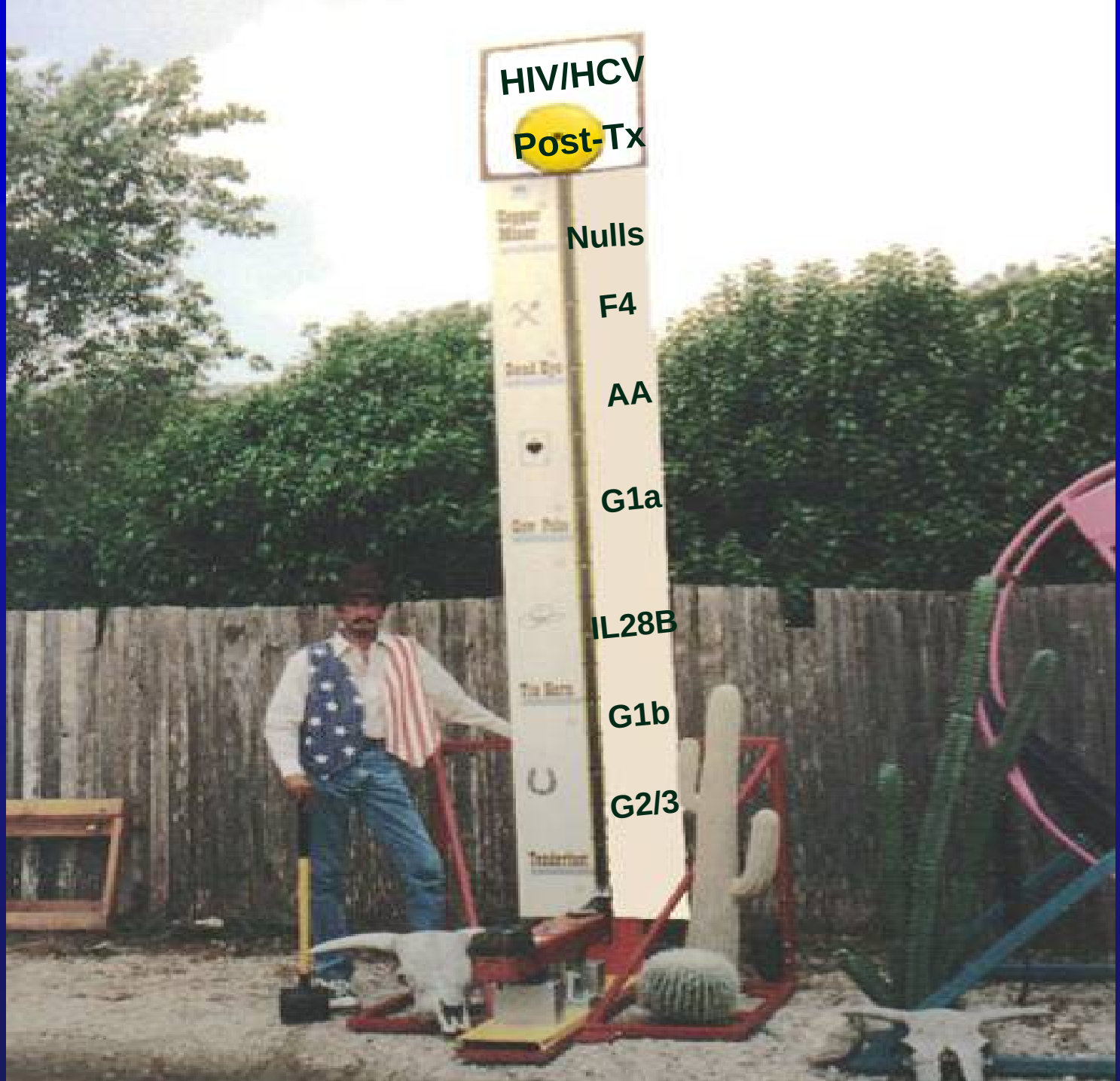


	↑ SVR	↓ SEs	↓ Pills	Freq	No IFN?
Triple Regimens with PR					
TMC-435	+	√	√	qd	-
BI-201335	+	√	√	qd	-
Daclatasvir	+	√	√	qd	-
Sofosbuvir (G1)	++	√	√	qd	-
Danoprevir/r	++	√	√	bid	-
QUAD Regimens					
BMS (PR+NS5A+PI) nulls	+++	±	√	bid	-
VX (PR+PI+NNI)	+++	±	-	bid	-
Roche (PR+DNV/r + MCB)	++	±	-	bid	-
GS (PR+PI+NS5A) short course	+++	±	-	bid	-
All Oral Regimens					
BMS (NS5A+PI) G1b null	+	√	√	qd	√
BMS (NS5A+PI+NNI) G1a/b	+++	√	√	qd	√
BI (PI+NNI+/- RBV)	++	√	√	bid	√
GS (NI+RBV) G2/3, 1	+++, ++	√	√	qd	√
GS (NI+NS5A+RBV)	+++	√	√	qd	√
Alisporivir ± RBV G2/3	+	√	±	qd	√
VX (PI+NNI) + RBV	+-++	√	±	bid	√
ABT (PI/r+NS5A+NNI)+/-R	+++	√	±	bid	√

Projected Timing for New Regimen Launches



•* Precise timing TBD


HIV/HCV
Post-Tx
Nulls
F4
AA
G1a
IL28B
G1b
G2/3