Infectivology Today

“Progressi nella terapia con DAA: dalla triplice ai regimi IFN-*free*”

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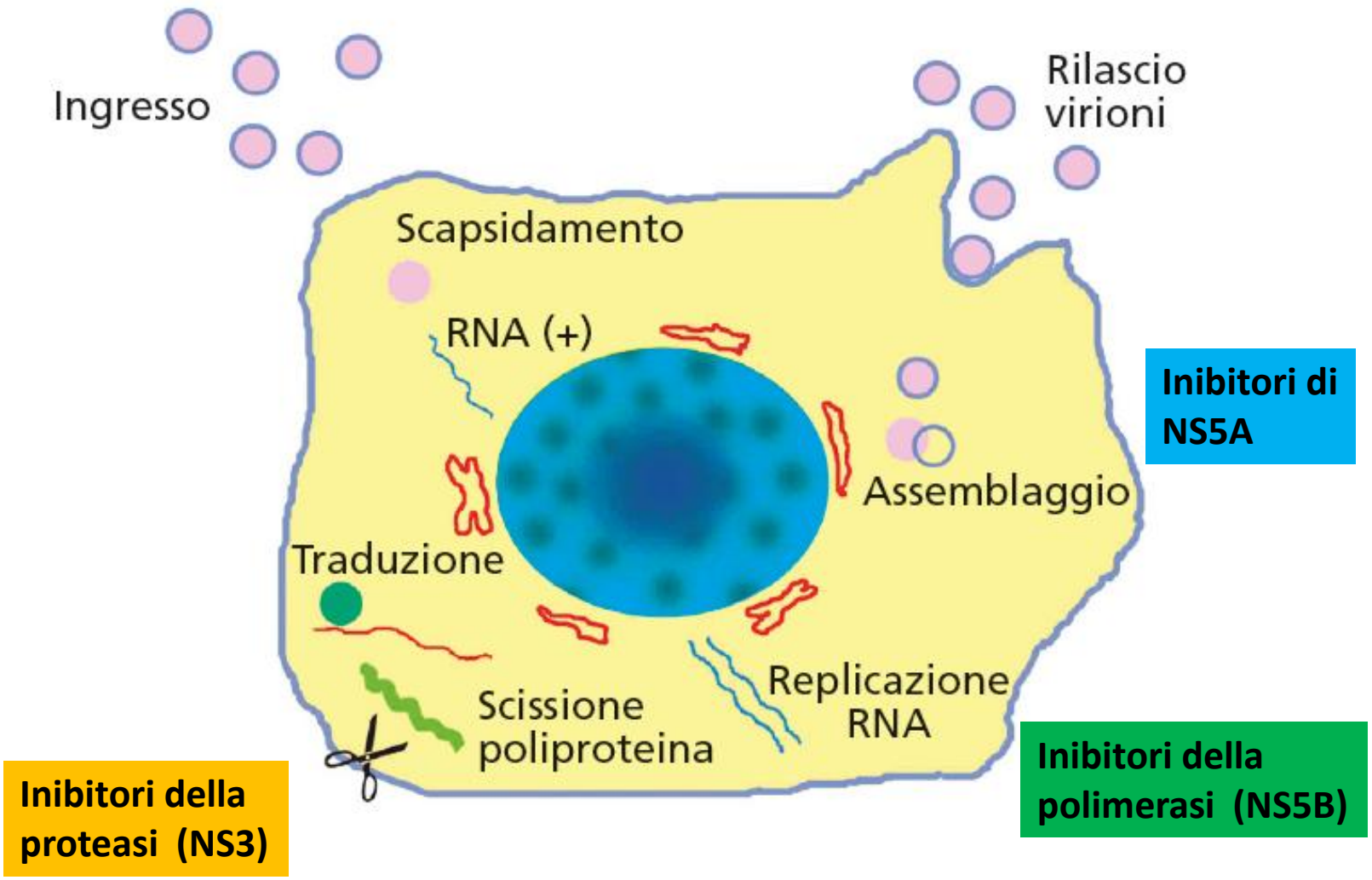
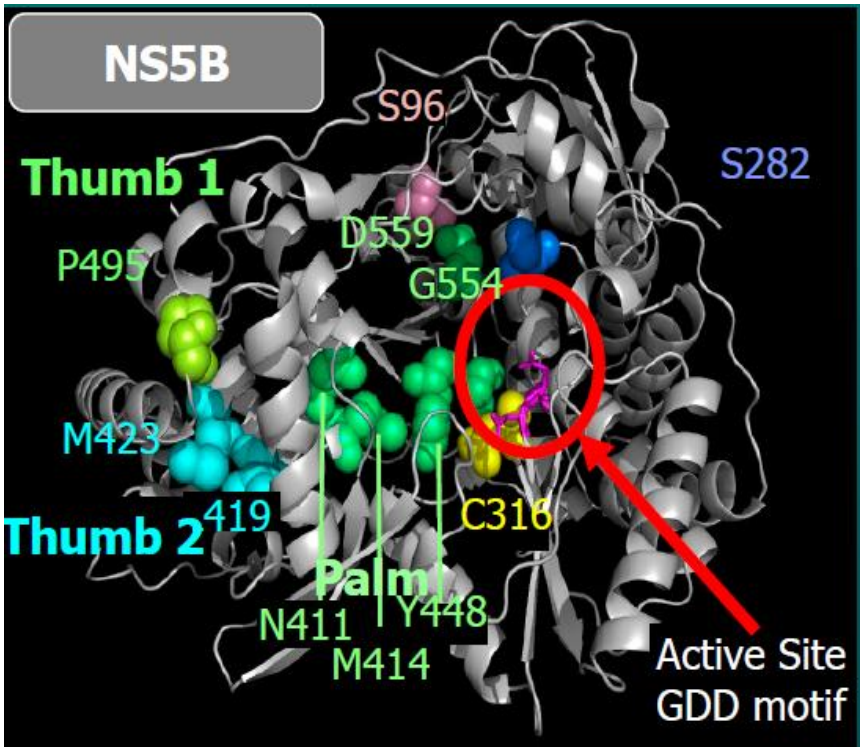
Ciclo di HCV e bersagli degli antivirali



Da:Gaeta et al. In: Moroni- Malattie Infettive,Ed. 2014

NS5B POL inhibitors



Active

Active Site

- GS-6620
- sofosbuvir
- TMC-649128
- IDX-184
- GS-938
- mericitabine

Allosteric

Thumb 1

- BI207127
- BMS-791325

Thumb 2

- VX-222
- filibuvir
- GS-9669

Palm

- ABT-333
- ABT-072
- GS-9190
- setrobuvir

NS5A inhibitors

- NS5A has no known enzymatic activity

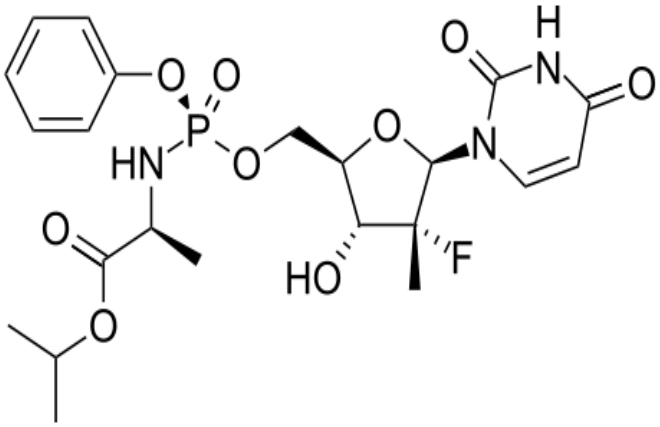
- It plays essential roles in both viral genome replication and virus particle assembly

- NS5A inhibitors:
  - Interact with the NS5A N-terminus of Domain I
  - Block both *cis*- and *trans*-acting functions of NS5A
  - Alter the subcellular localization of NS5A into functional replication complexes therefore suppressing HCV RNA replication
  - Current drugs under development:
    - **Ombitasvir** (ABT-267) , **Daclatasvir**, **Ledipasvir**, PPI-461

Gao, M. Nature, 2010; **465:** 96-100; Lemm, J.A. J Virol, 2010; 84 (**1):** 482-491; Fridell, R.A. J Virol 2011; 85(14): 7312-20; Lee, C. Virol 2011; 414(1):10-8

SOFOSBUVIR

- Nucleotide analog Pol inhibitor
- High genetic barrier
- Pan-genotypic
- One daily dose (400 mg)
- No food effect
- No drug interaction
- Generally safe and well-tolerated in clinical studies to date (>3,000 patients)



NEUTRINO - Sofo + PR in geno 1-4-5-6, for 12 weeks
FISSION – SOFO + RBV in geno 2/3
FUSION – SOFO + RBV in geno 2/3 experienced

Combination with other DAA:

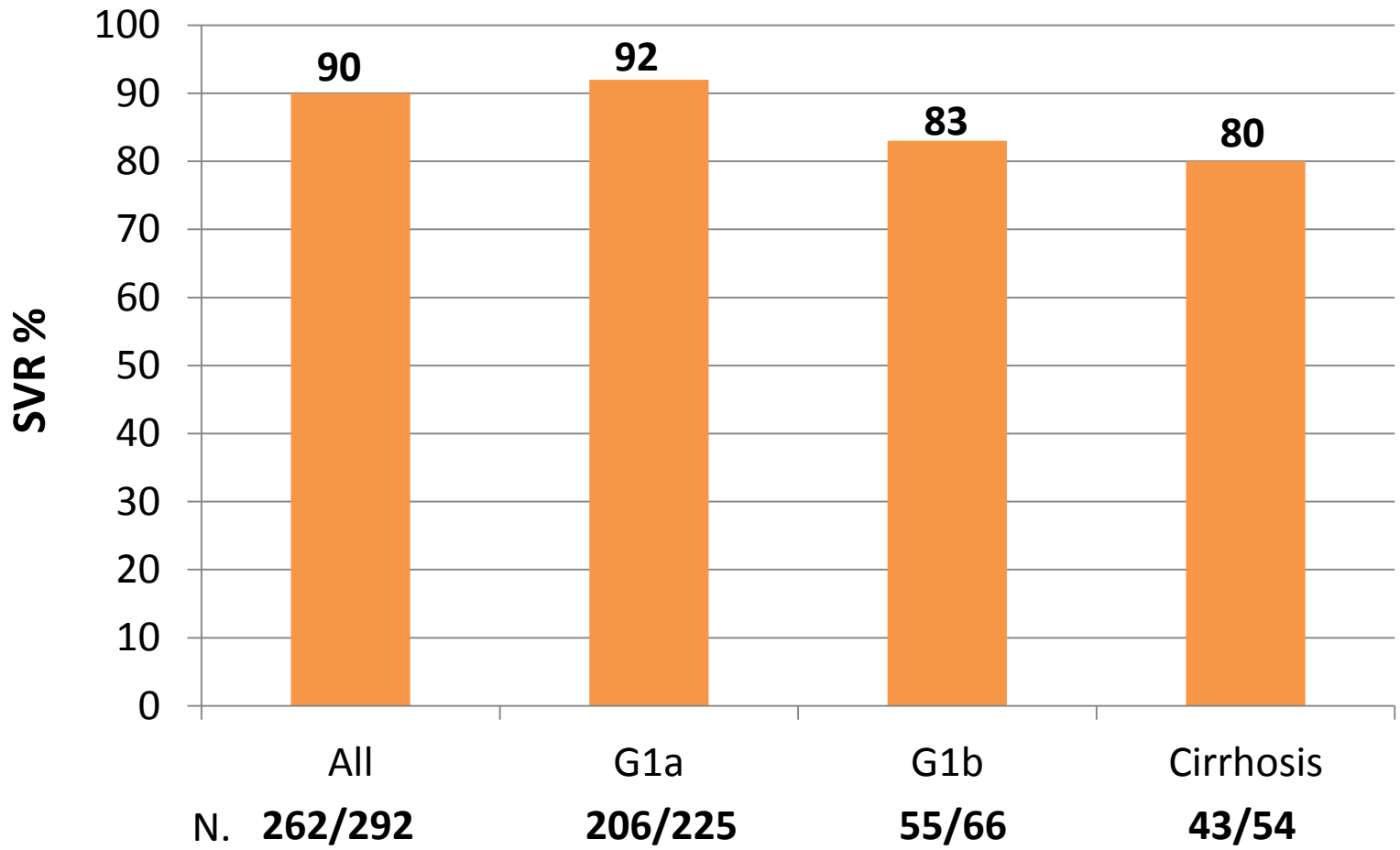
SOFO + LEDIPASVIR ± RBV
SOFO + SIMEPREVIR ± RBV
SOFO + Daclatasvir± RBV

Combinazioni con Sofosbuvir nel genotipo 1

Patient population (Study number/name)	Regimen/duration	Subgroup	SVR12 rate % (n/N)
Treatment-naïve[a] (NEUTRINO)	SOF + PEG-IFN + RBV 12 weeks	Overall	90% (262/292)
		GT 1a	92% (206/225)
		GT 1b	83% (55/66)
		No cirrhosis	93% (253/273)
		Cirrhosis	80% (43/54)
Treatment-naïve and co-infected with HIV (PHOTON-1)	SOF + RBV 24 weeks	Overall	76% (87/114)
		GT 1a	82% (74/90)
		GT 1b	54% (13/24)
		No cirrhosis	77% (84/109)
		Cirrhosis	60% (3/5)
Treatment-naïve (QUANTUM[b] and 11-1-0258[b])	SOF + RBV 24 weeks	Overall[c]	65% (104/159)
		GT 1a[c]	69% (84/121)
		GT 1b[c]	53% (20/38)
		No cirrhosis[c]	68% (100/148)
		Cirrhosis[c]	36% (4/11)

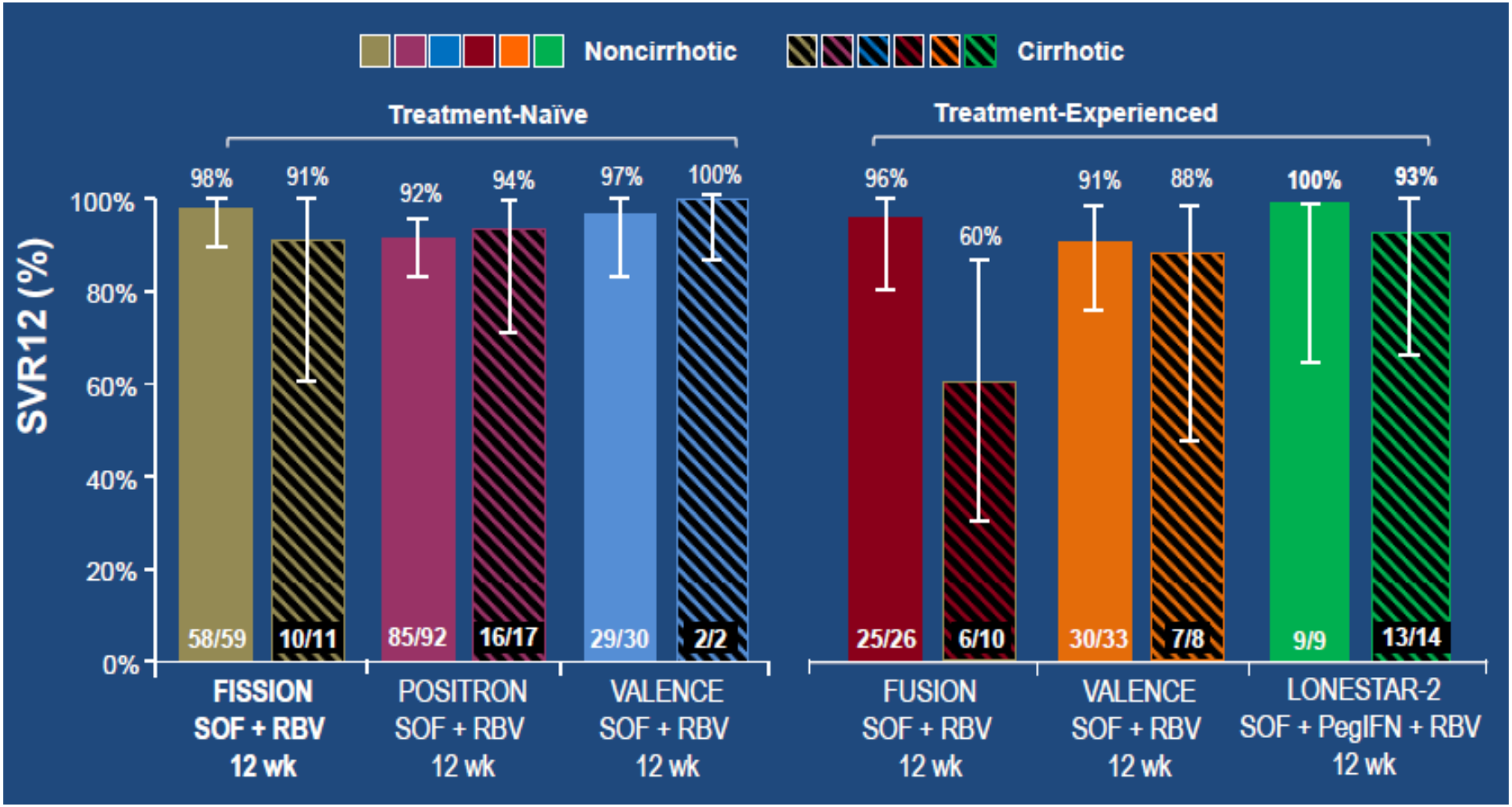
SVR rates in HCV-1 with SOF +PR

Single arm study; enrolled 327 patients with HCV genotype 1, 4, 5, or 6



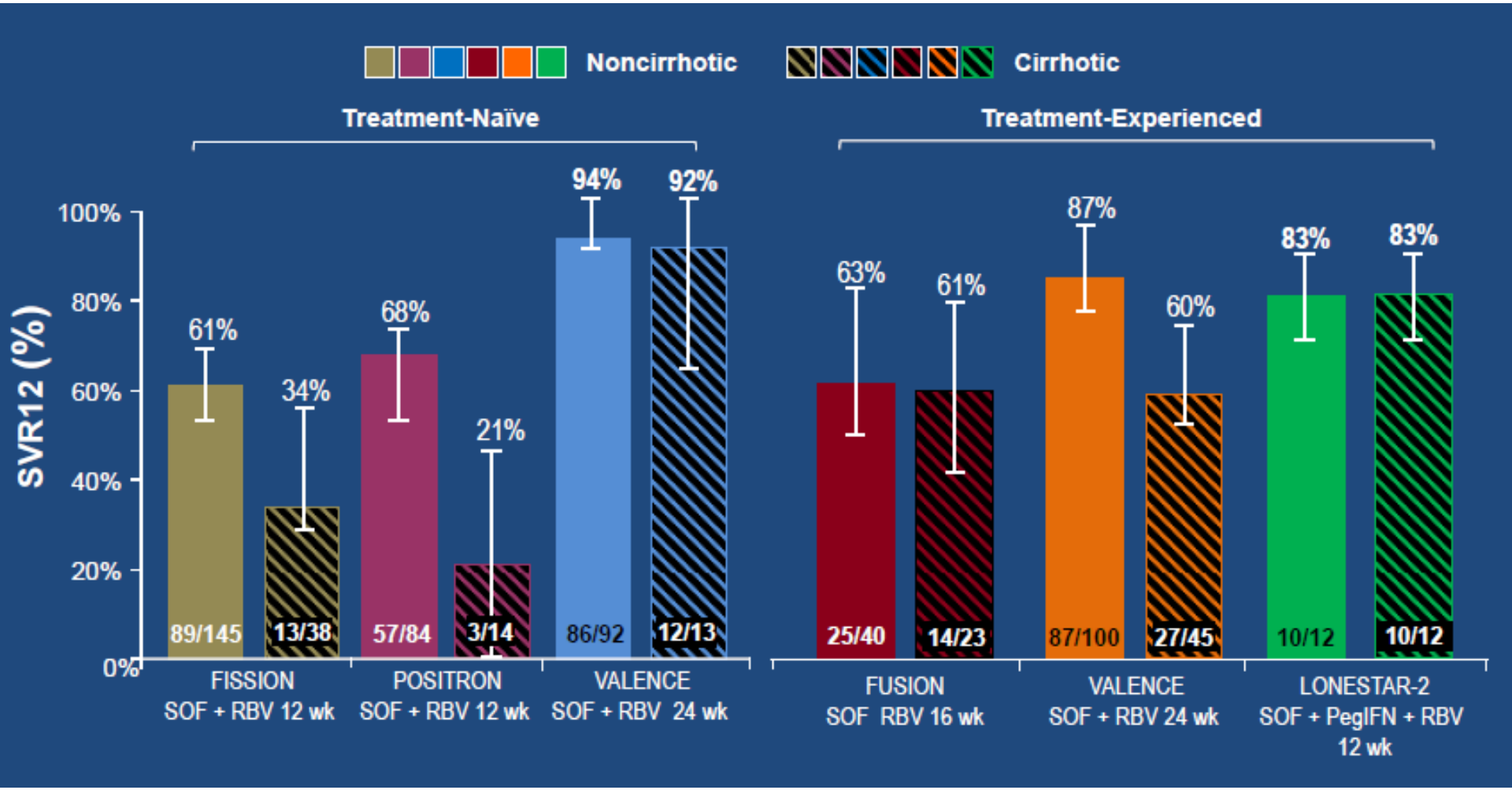
Lawitz, N Engl J Med 2013; 368:1878-1887

SVR nel genotipo 2



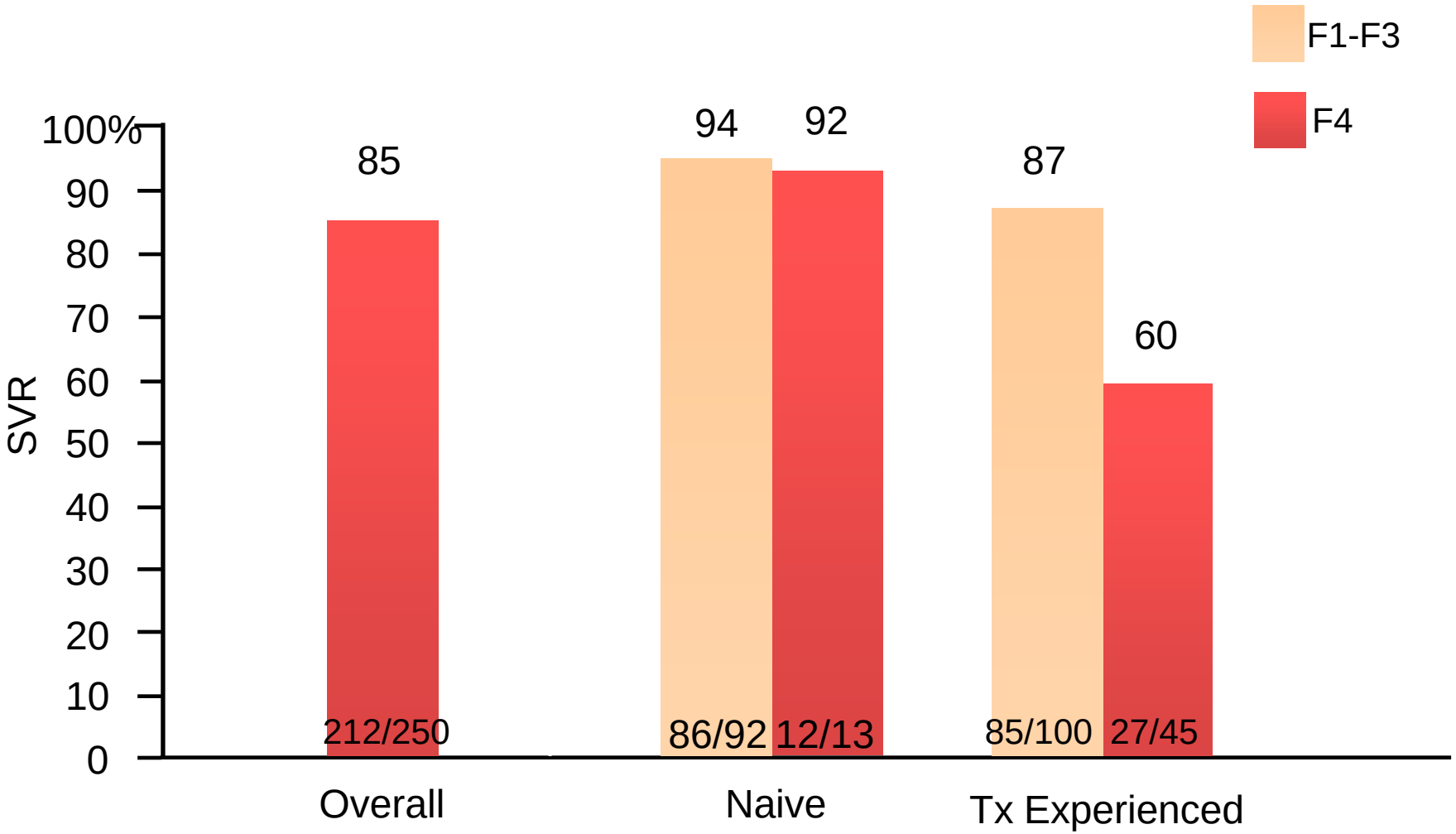
Jacobson IM, et al. *N Engl J Med.2013;368(20):1867-77*
Lawitz, N Engl J Med 2013; 368:1878-1887

SVR nel genotipo 3



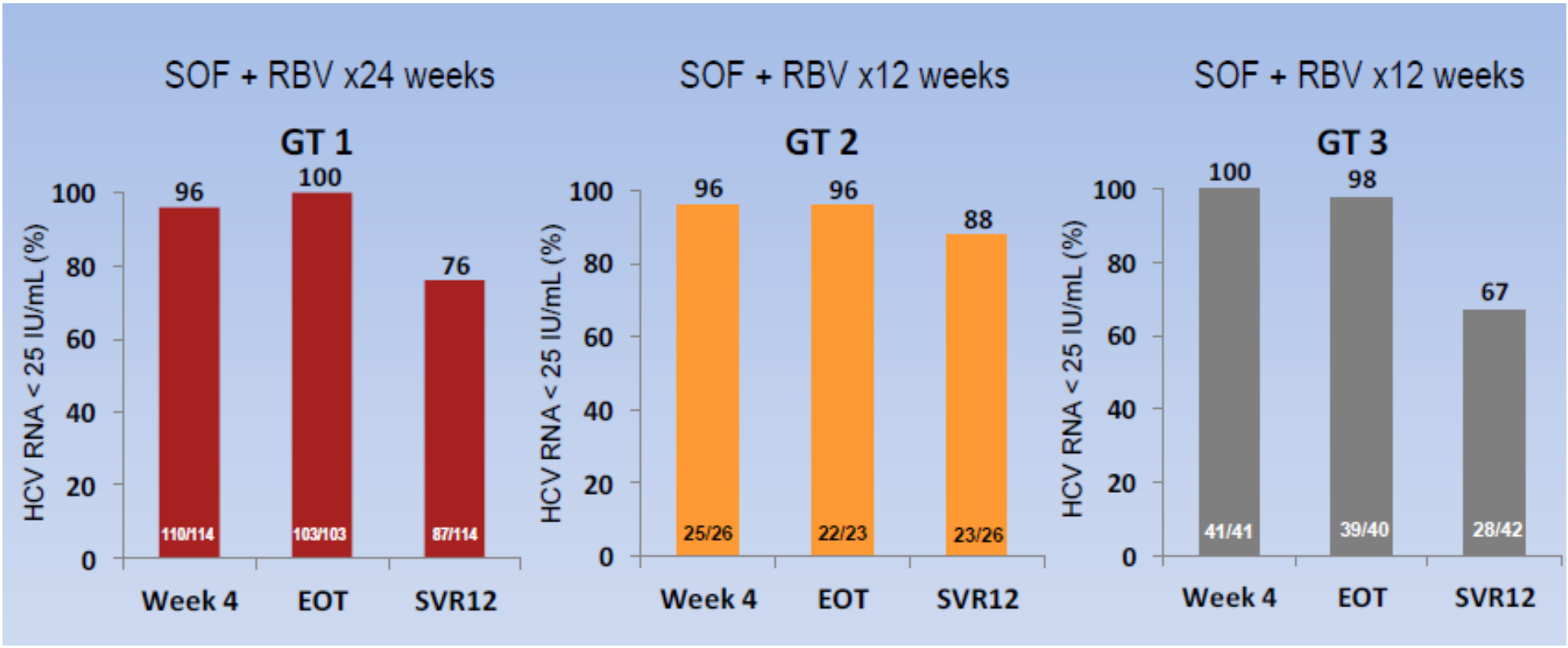
Jacobson IM, et al. *N Engl J Med.2013;368(20):1867-77*
Lawitz, N Engl J Med 2013; 368:1878-1887

VALENCE: SVR to SOF + Rbv for 24 Weeks in HCV-3 Patients



Zeuzem S., AASLD 2013

SOF + RBV in Treatment-Naive HIV/HCV Coinfection PHOTON-1 Virologic Response



SVR Gen 1a = 82%
Gen 1b = 54%

Sulkowski MS, et al. AASLD 2013. Washington, DC. Oral #212

Indicazioni attuali di Sofosbuvir

Popolazione di pazienti*	Trattamento	Durata
Pazienti con CHC di genotipo 1, 4, 5 o 6	Sovaldi + ribavirina + peginterferone alfa	12 settimane[a, b]
	Sovaldi + ribavirina Da utilizzare solo per i pazienti non eleggibili o intolleranti a peginterferone alfa (vedere paragrafo 4.4)	24 settimane
Pazienti con CHC di genotipo 2	Sovaldi + ribavirina	12 settimane[b]
Pazienti con CHC di genotipo 3	Sovaldi + ribavirina + peginterferone alfa	12 settimane[b]
	Sovaldi + ribavirina	24 settimane
Pazienti con CHC in attesa di trapianto di fegato	Sovaldi + ribavirina	Fino al trapianto di fegato[c]

*Include i pazienti con co-infezione da virus dell'immunodeficienza umana (HIV).

Problemi aperti con Sofosbuvir

- Non vi sono dati di fase 3 in pazienti experienced
- Non sperimentato in null responder alla triplice attuale
- Pochi pazienti G1b con cirrosi
- Assenza di dati nel cirrotico scompensato
- Il genotipo 3 è il più difficile

SIMEPREVIR

- HCV NS3/4A protease inhibitor
  - Competitive reversible macrocyclic non-convalent inhibitor of NS3/4A protease
  - Broad genotype coverage with antiviral activity against HCV genotype 1, 2, 4, 5 and 6 isolates

- One 150 mg capsule, once-daily dosing with food
  - Exposure increased by ~60% with any type of food
  - Targeted to the liver, substrate of transporter OATP
  - Excretion primarily via feces, minimal in urine (<1%)
  - Metabolism primarily via CYP3A

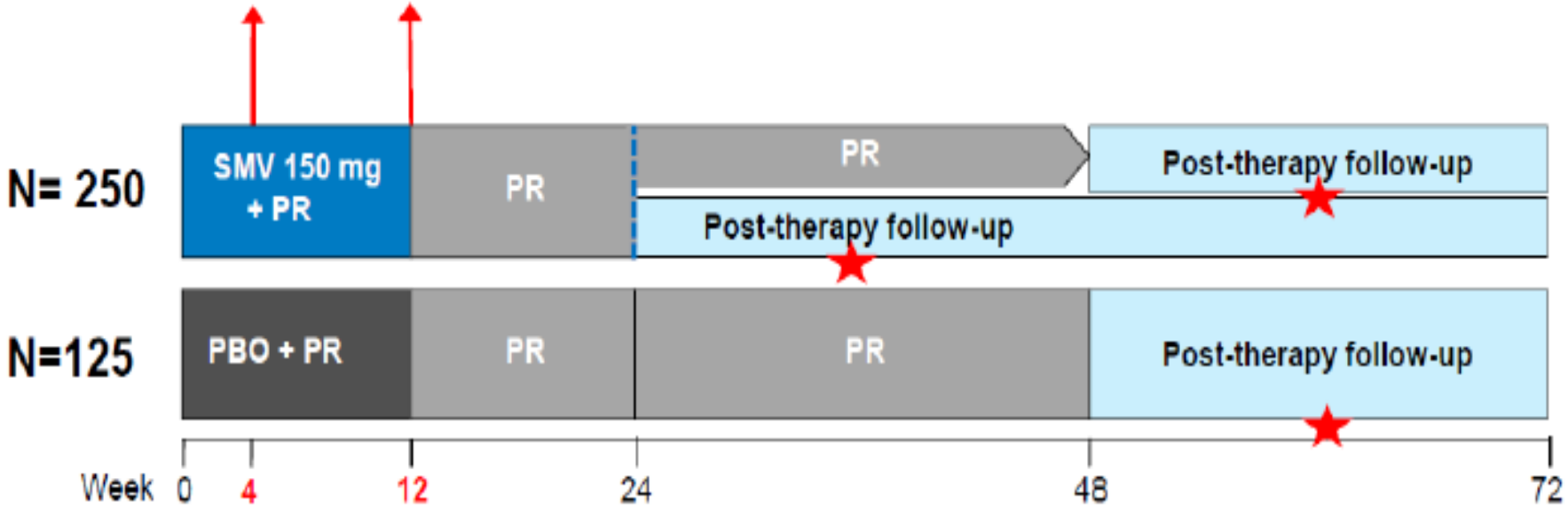
OATP = organic anion transporter protein; CYP3A = cytochrome P450 3A

SIMEPREVIR: disegno dei trial

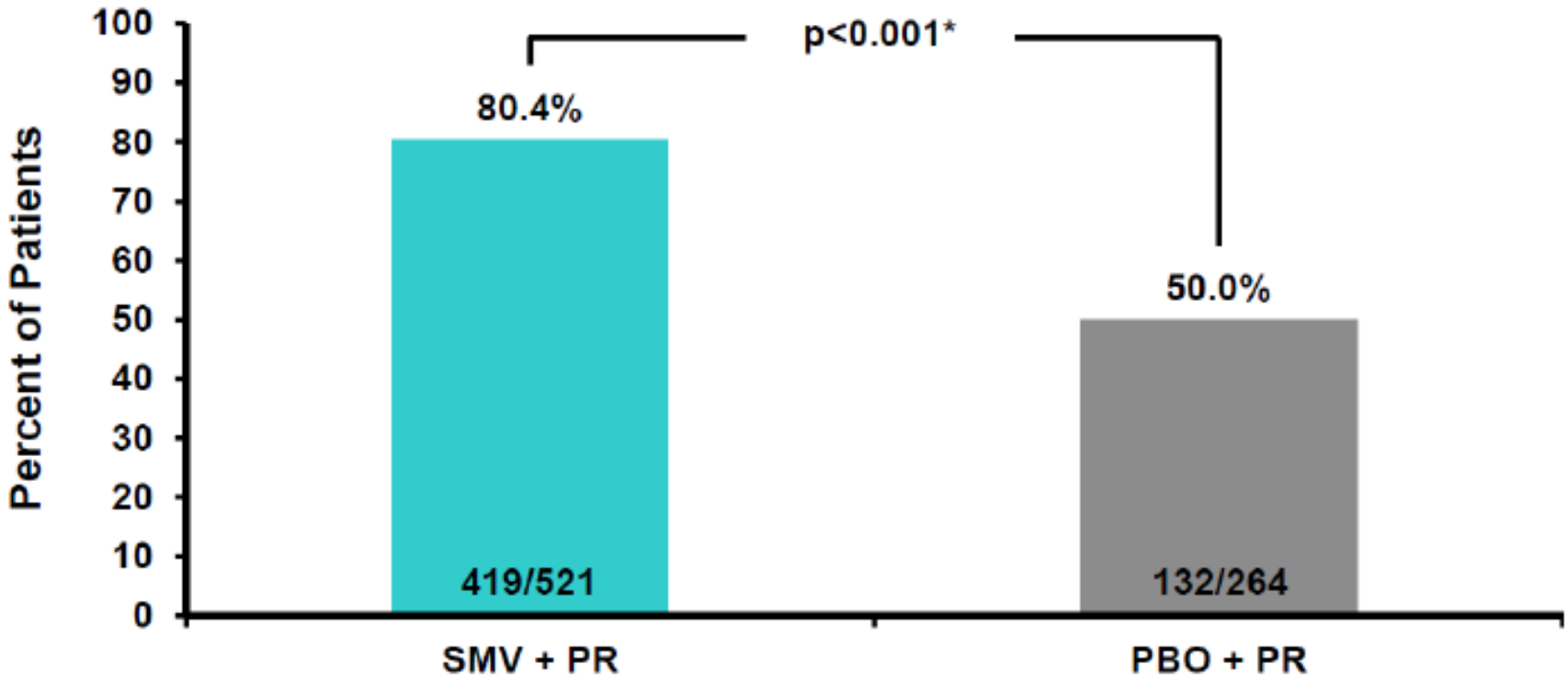
(QUEST-1; QUEST-2; PROMISE)

Response-Guided Therapy (RGT) criteria to guide PR treatment duration:

- HCV RNA <25 IU/mL at Week 4 and HCV RNA undetectable at Week 12 → 24 weeks
- HCV RNA ≥25 IU/mL at Week 4 or HCV RNA detectable at Week 12 → 48 weeks

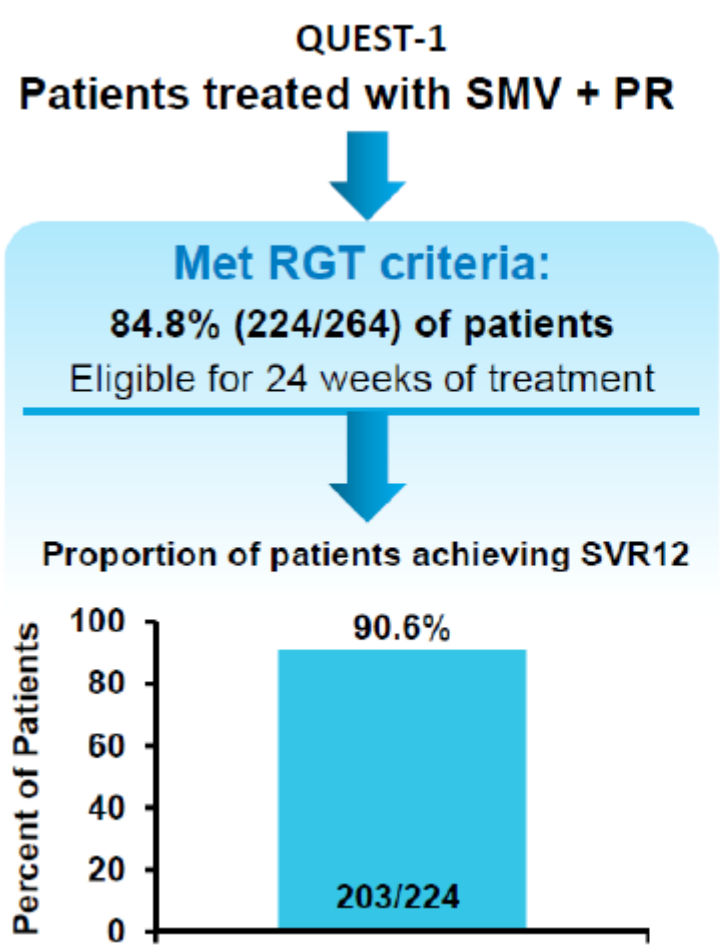


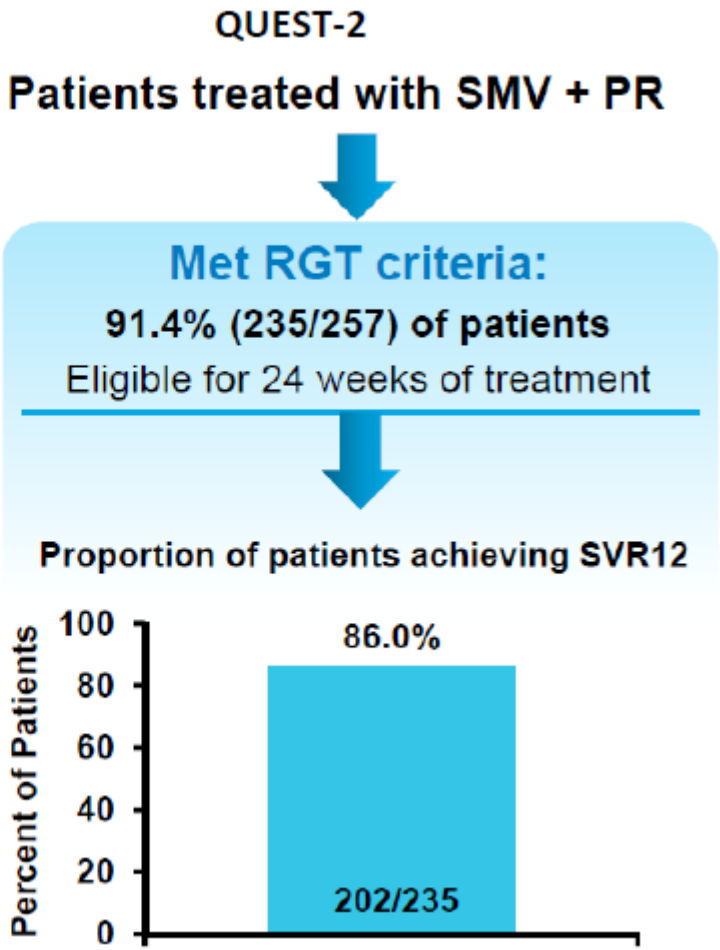
QUEST-1 (C208) and QUEST-2 (C216) – Treatment-Naïve: Primary Analysis Efficacy Pooling



FDA Antiviral Drugs Advisory Committee Meeting, 24 October 2013

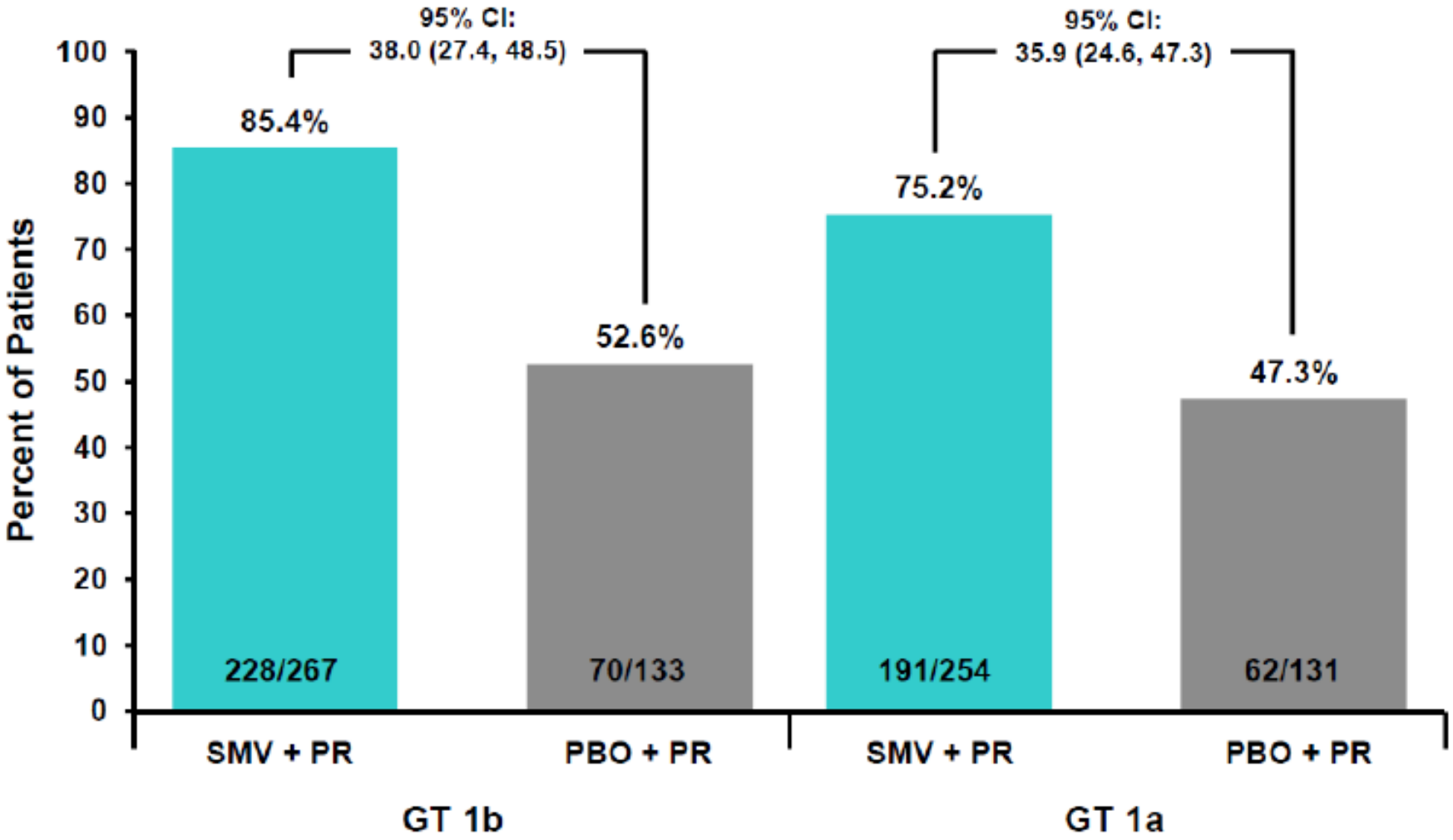
Treatment-Naïve: RGT Duration and SVR12





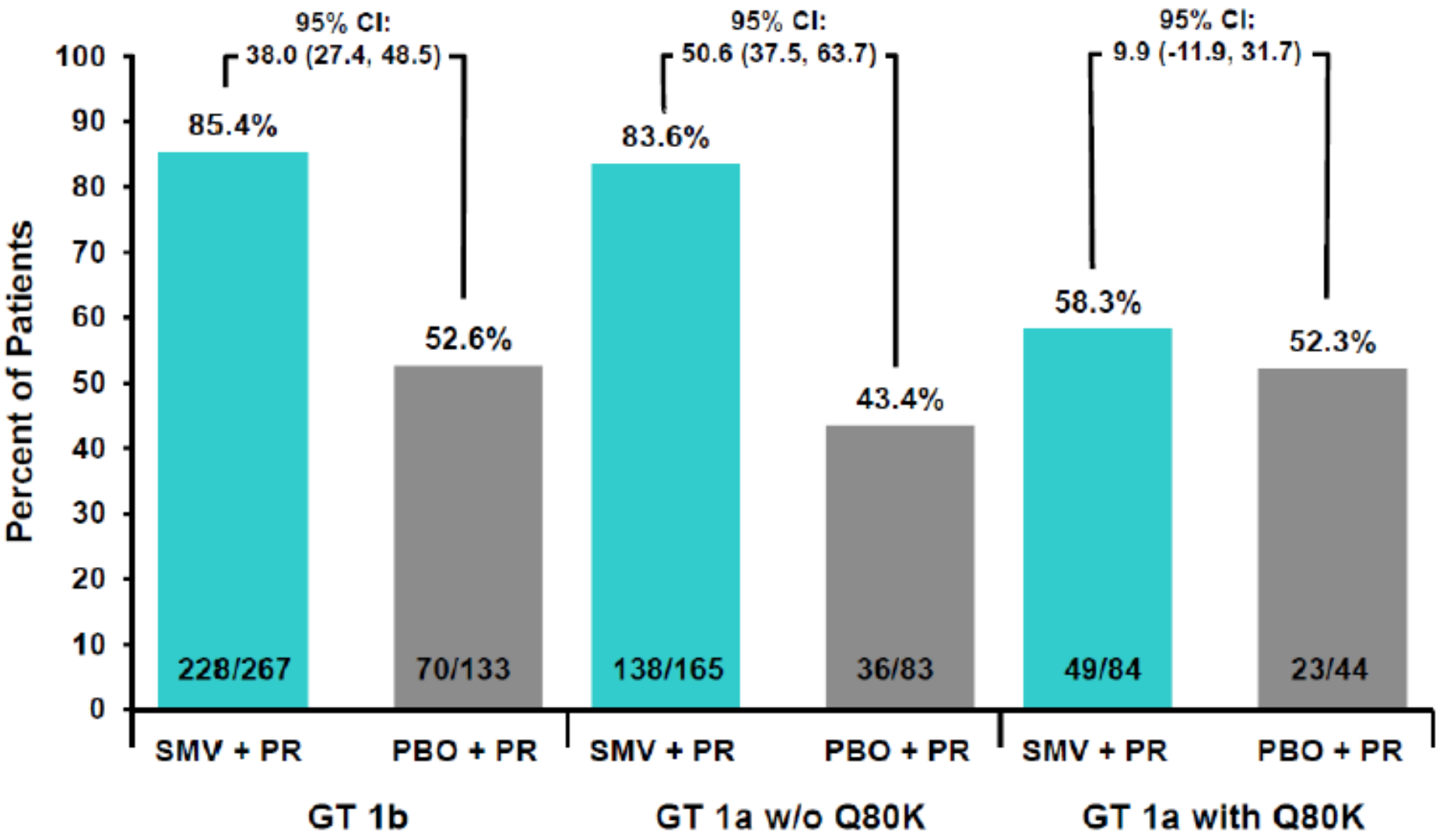
FDA Antiviral Drugs Advisory Committee Meeting, 24 October 2013

Proportion of Patients with SVR according to G1a/G1b



FDA Antiviral Drugs Advisory Committee Meeting , 24 October 2013

Genotype 1a and 1b With and Without Q80
Proportion of Patients with SVR



FDA Antiviral Drugs Advisory Committee Meeting , 24 October 2013

OLYSIO prescribing information

Table 1: Duration of Treatment with OLYSIO, Peginterferon Alfa and Ribavirin

	Treatment with OLYSIO, Peginterferon alfa and Ribavirin*	Treatment with Peginterferon alfa and Ribavirin*	Total Treatment Duration*
Treatment-naïve and prior relapser patients† including those with cirrhosis	First 12 weeks	Additional 12 weeks	24 weeks
Prior non-responder patients‡ (including partial and null responders) including those with cirrhosis	First 12 weeks	Additional 36 weeks	48 weeks

THERAPY SHOULD BE STOPPED IF HCV-RNA > 25 IU/mL AT WEEK 4

SIDE EFFECTS AND WARNING with Simeprevir

- Photosensitivity
- Rash
- Hyperbilirubinaemia (transporter)
- DDI
- Systemic exposure variable in HCV infected

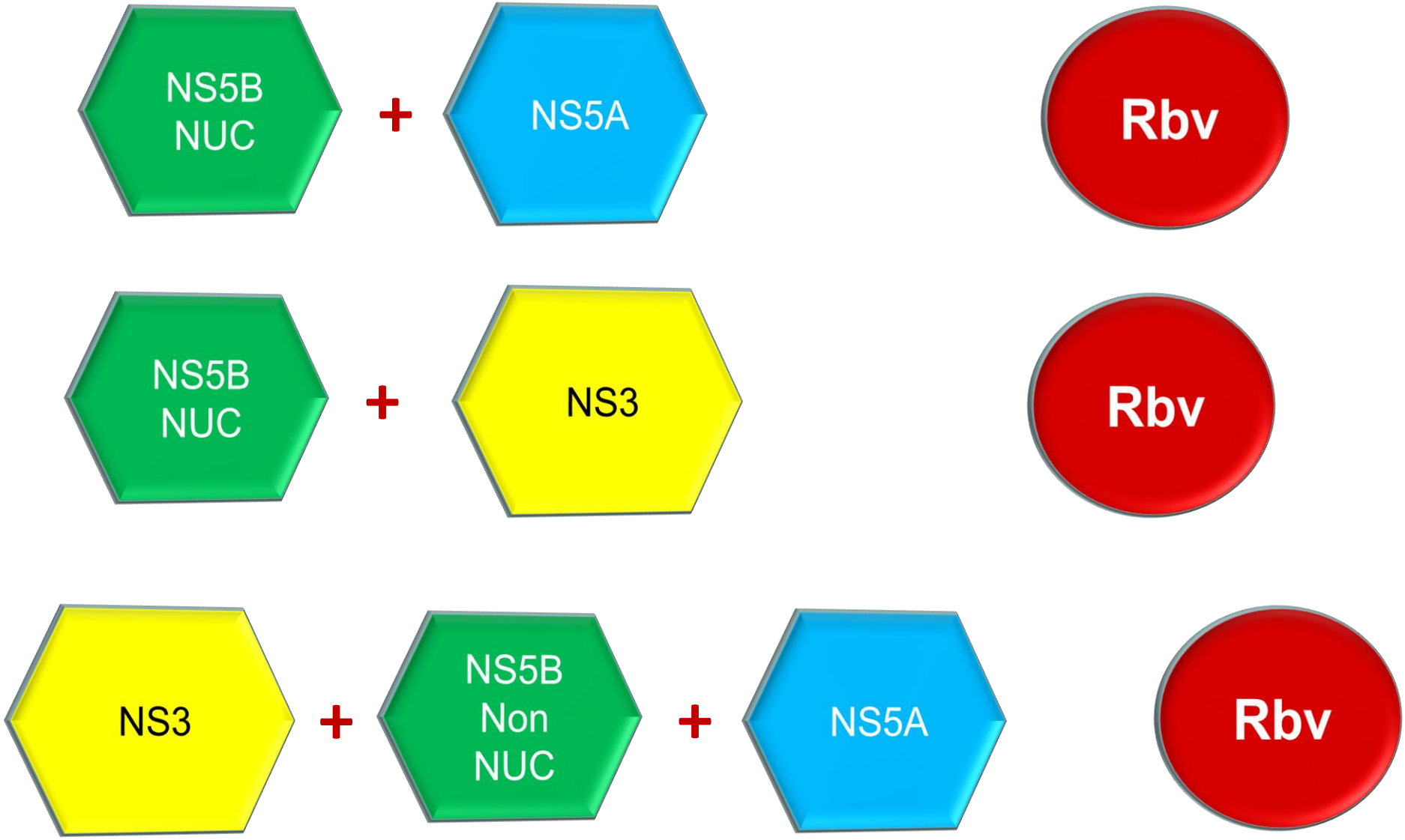
The next step

All oral combinations :

SOFOSBUVIR + SIMEPREVIR
SOFOSBUVIR + LEDIPASVIR
SOFOSBUVIR + DACLATASVIR
SIMEPREVIR + DACLATASVIR
ABBVIE COCKTAIL

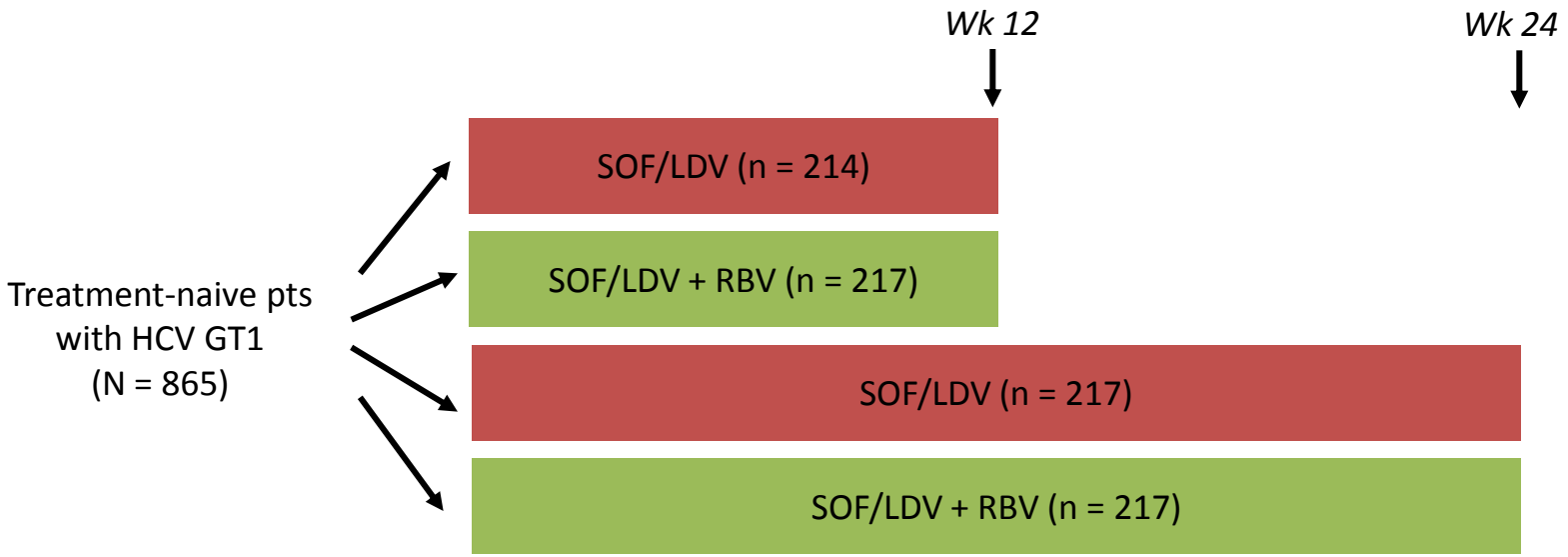
SVR > 90 %

Drug combination development



ION 1: SOF/LDV FDC ± RBV for 12 or 24 Wks in Treatment-Naive GT1 Patients

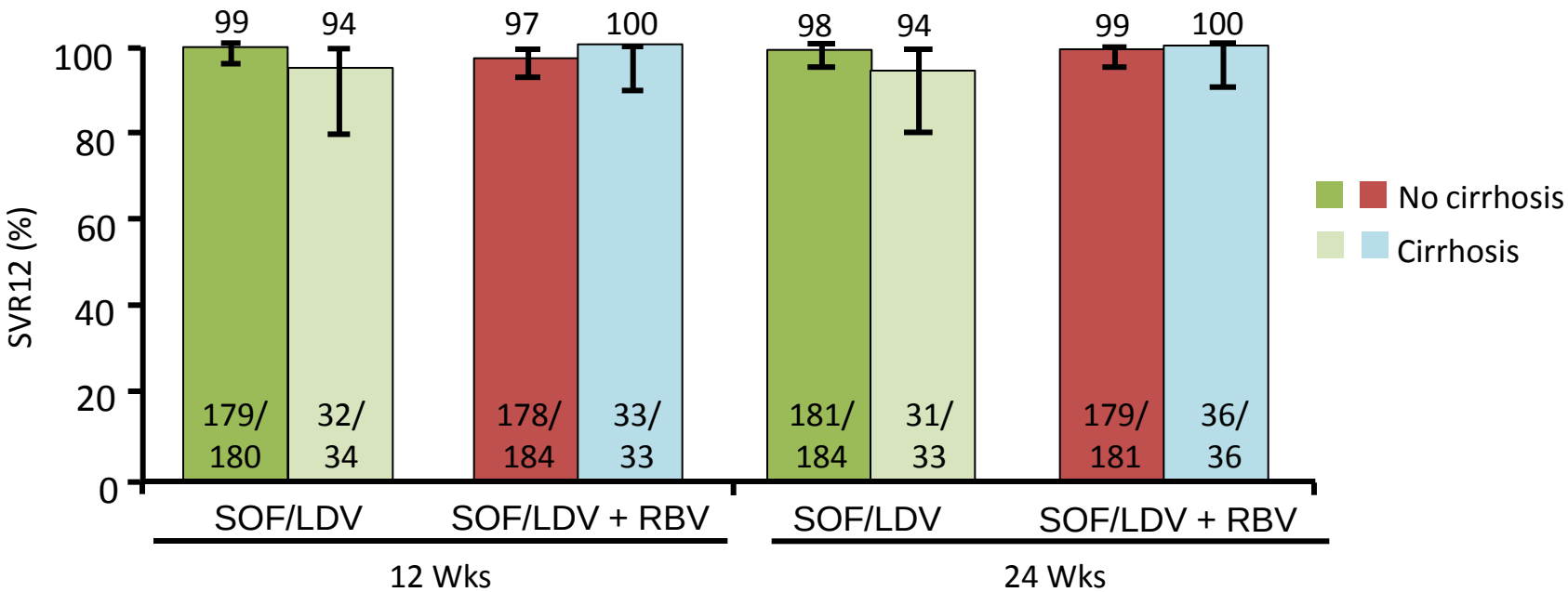
- Open-label phase III trial[1,2]
- 15% to 17% of participants had cirrhosis



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

Mangia A, et al. EASL 2014. Abstract O164. Afdhal N, et al. N Engl J Med. 2014;[Epub ahead of print].

ION 1: SVR12 With 12 or 24 Wks SOF/LDV ± RBV in Tx-Naive Pts by Cirrhosis Status

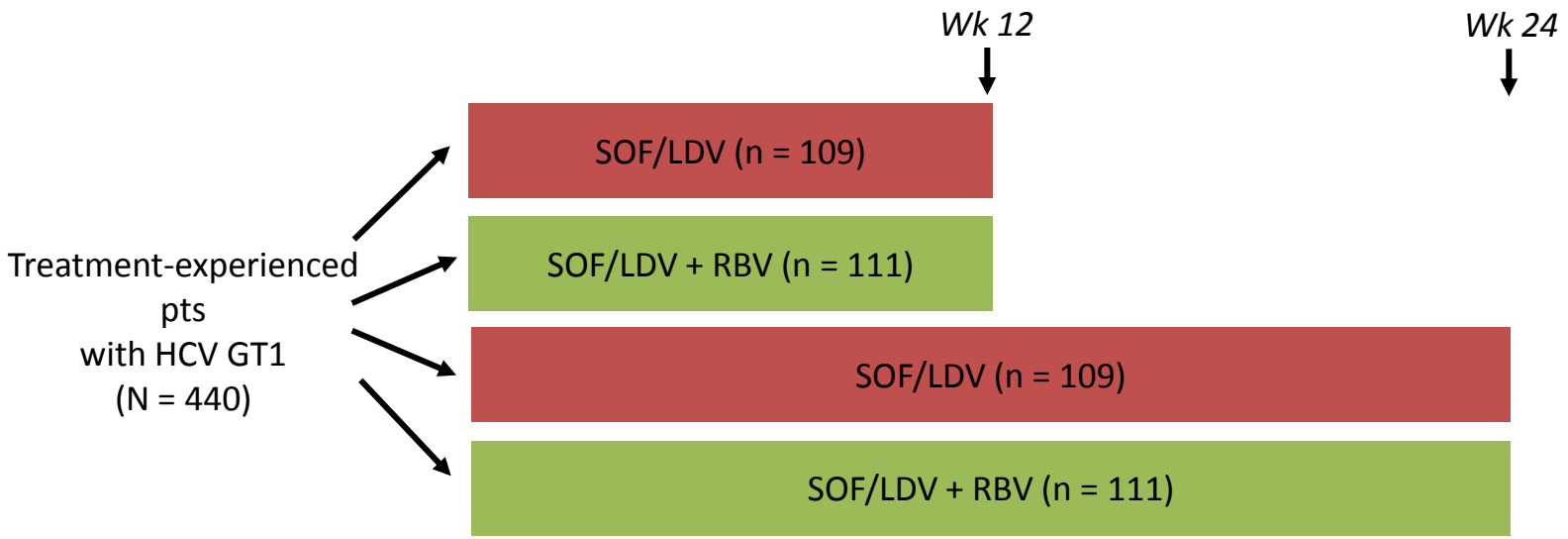


- SVR12 rates did not differ by GT1a vs GT1b in any treatment arm
- Virologic failure: 1 breakthrough in 24-wk SOF/LDV; 2 relapses (1 in 12-wk SOF/LDV, 1 in 24-wk SOF/LDV)
- 16% of patients had NS5A resistance-associated variants at baseline; 96% of these achieved SVR12

Mangia A, et al. EASL 2014. Abstract O164. Afdhal N, et al. N Engl J Med. 2014;[Epub ahead of print].

ION 2: SOF/LDV FDC ± RBV for 12 or 24 Wks in Treatment-Experienced GT1 Pts

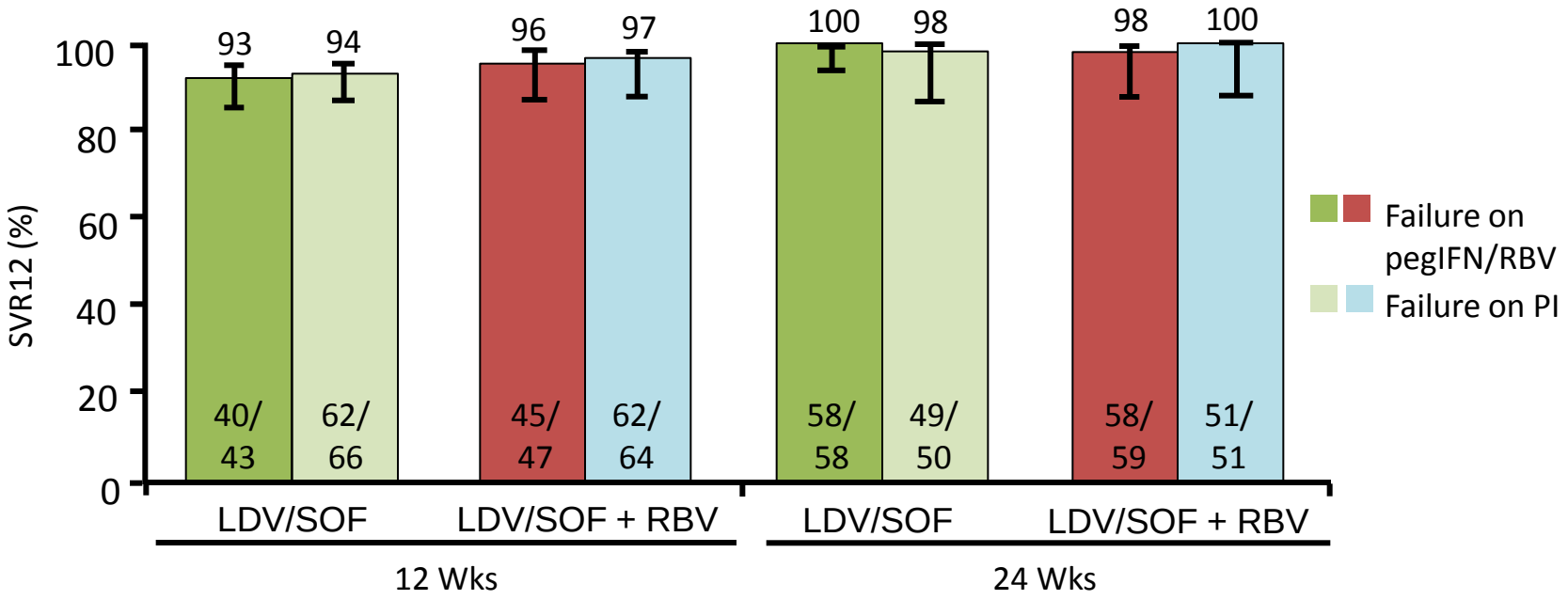
- Open-label phase III trial[1,2]
- 20% of participants had cirrhosis, 41% to 46% were previous nonresponders, and 46% to 61% had failed a PI



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

1. Afdhal N, et al. EASL 2014. Abstract O109. 2. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

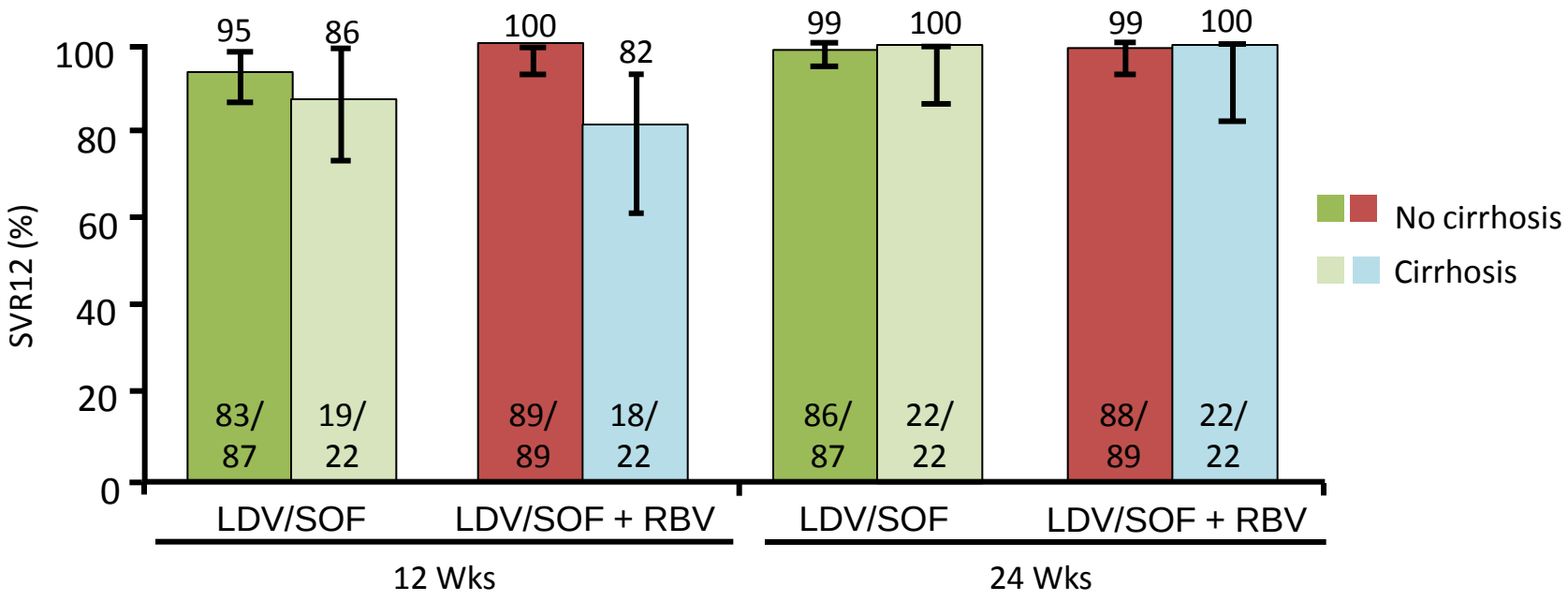
ION 2: SVR12 With 12 or 24 Wks SOF/LDV ± RBV by Treatment History



- Virologic failure: 1 breakthrough in 24-wk SOF/LDV/RBV due to nonadherence; 11 relapses (7 in 12-wk SOF/LDV, 4 in 12-wk SOF/LDV/RBV)
- 14% of patients had NS5A resistance-associated variants at baseline; 89% of these achieved SVR12

Afdhal N, et al. EASL 2014. Abstract O109. *Afdhal N, et al. N Engl. J Med. 2014;370:1483-1493.*

ION 2: SVR12 With 12 or 24 Wks of SOF/LDV ± RBV by Cirrhosis Status



- SVR12 rates were significantly lower in cirrhotic vs noncirrhotic patients in the pooled 12-wk arms

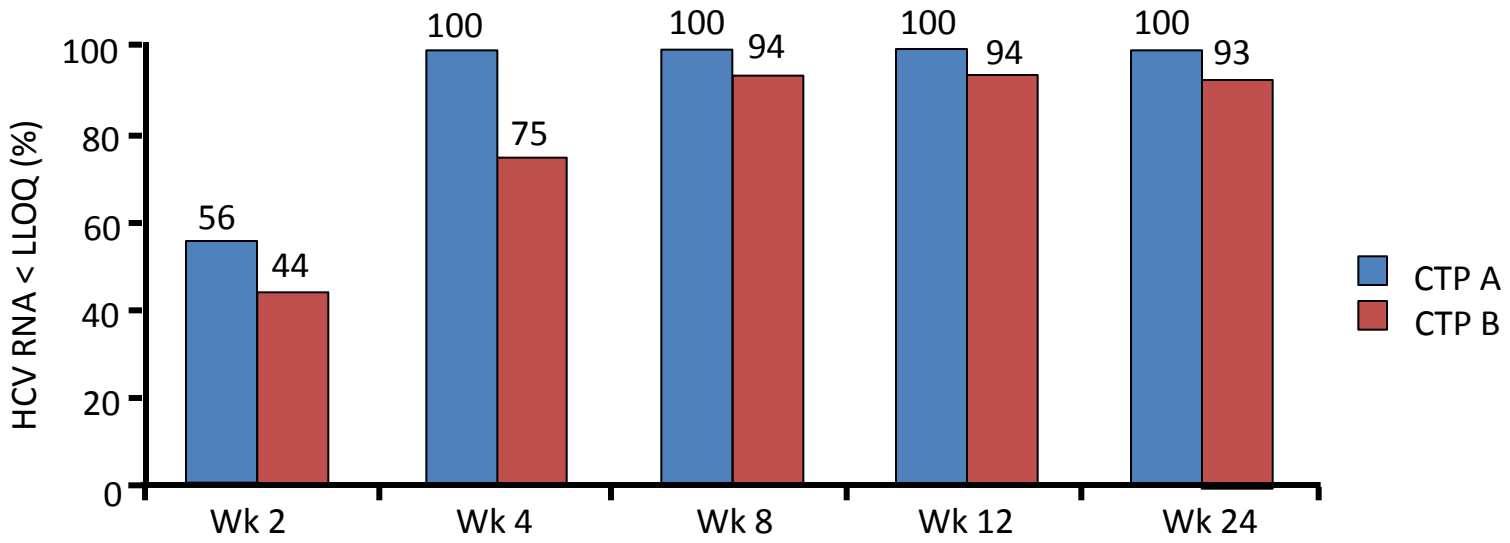
Afdhal N, et al. EASL 2014. Abstract O109. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

ION 2: Adverse Events

AEs, n (%)	12 Wks		24 Wks	
	SOF/LDV (n = 109)	SOF/LDV + RBV (n = 111)	SOF/LDV (n = 109)	SOF/LDV + RBV (n = 111)
Any AE	73 (67)	96 (86)	88 (81)	100 (90)
Grade 3/4 AEs	2 (2)	3 (3)	10 (9)	8 (7)
Any serious AE	0	0	6 (6)	3 (3)
AE leading to discontinuation	0	0	0	0
Grade 3/4 laboratory abnormalities	5 (5)	15 (14)	9 (8)	27 (24)
▪ Hemoglobin < 10 g/dL	0	2 (2)	0	9 (8)
▪ Hemoglobin < 8.5 g/dL	0	0	0	2 (2)

Afdhal N, et al. EASL 2014. Abstract O109. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

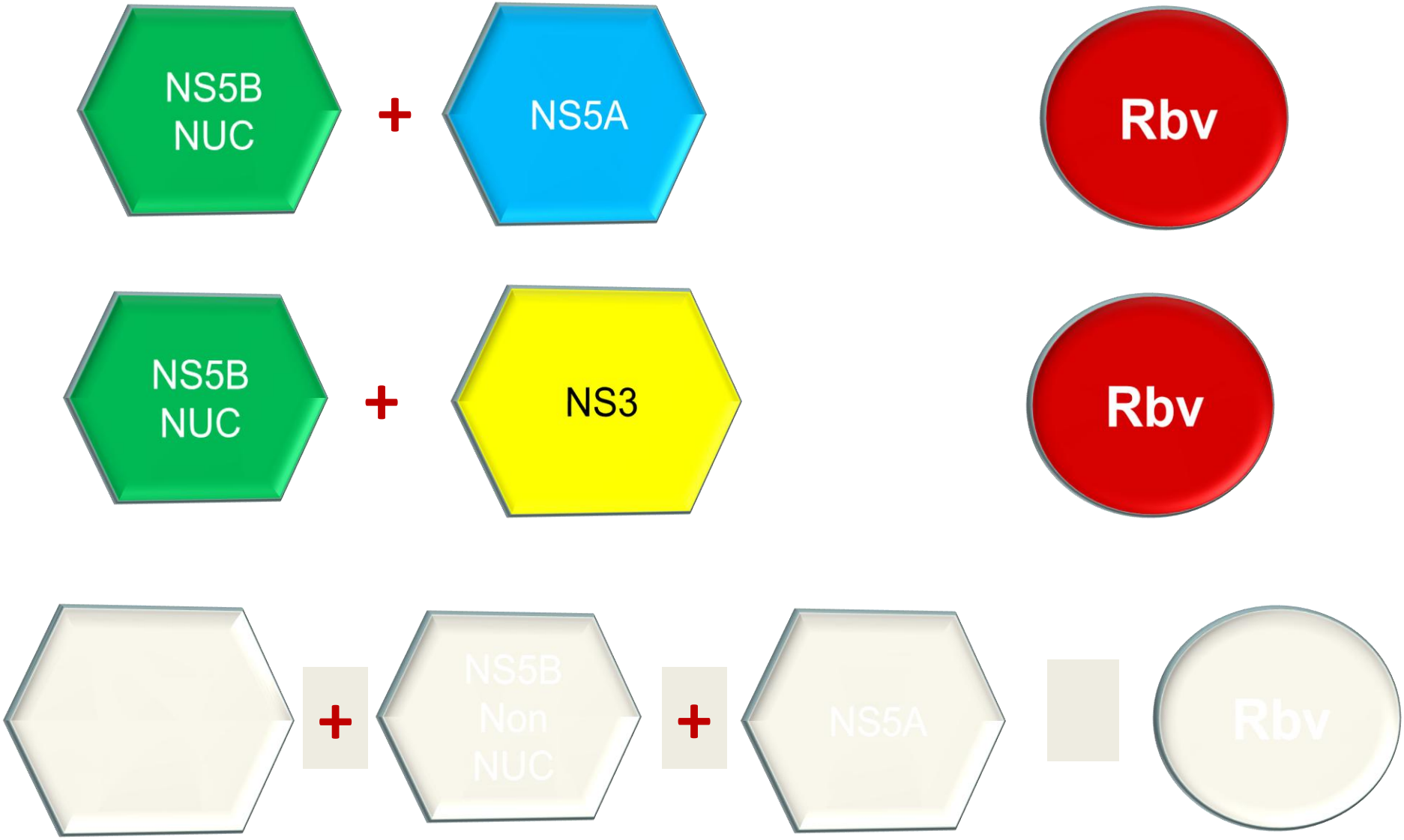
Virologic Response to SOF + RBV in Patients With Portal Hypertension



Clinical Events, n	Ascites		Hepatic Encephalopathy	
	SOF + RBV (n = 25)	Observation (n = 25)	SOF + RBV (n = 25)	Observation (n = 25)
Baseline	6	9	5	2
Wk 12	5	8	3	3
Wk 24	0	7	0	4

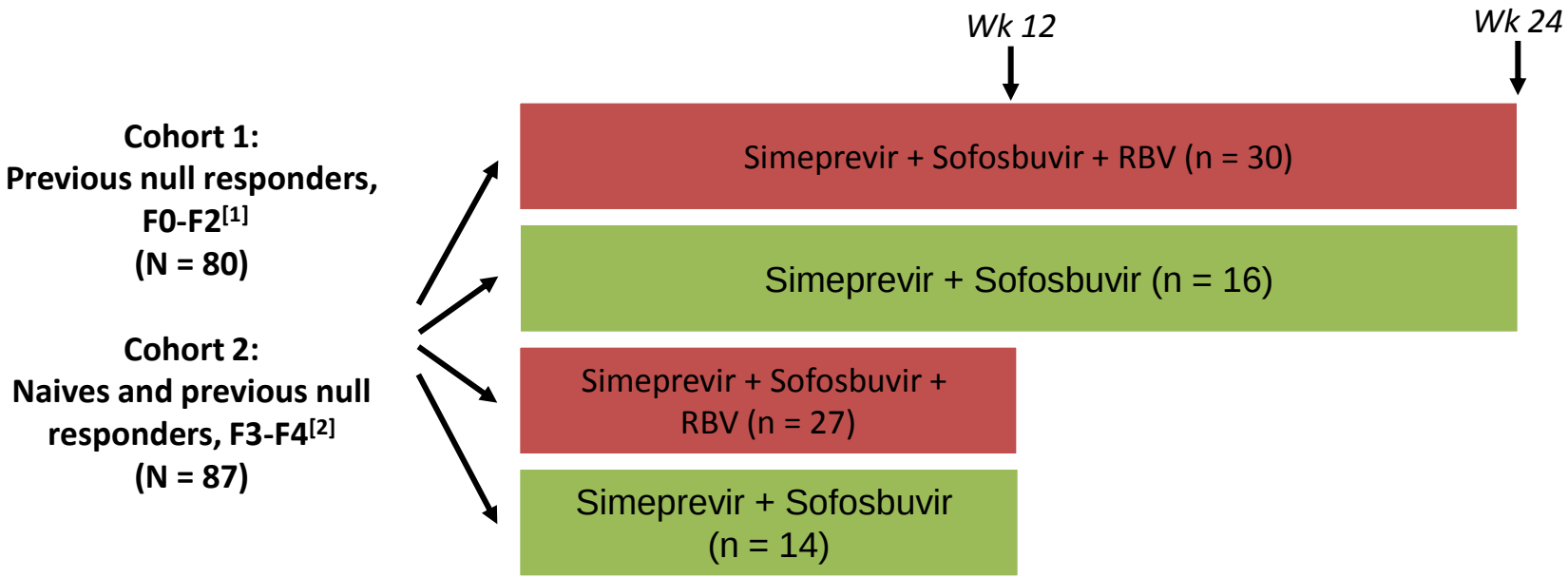
Afdhal N, et al. EASL 2014. Abstract O68.

Drug combination development



COSMOS: Simeprevir + Sofosbuvir ± RBV in Genotype 1 HCV Patients

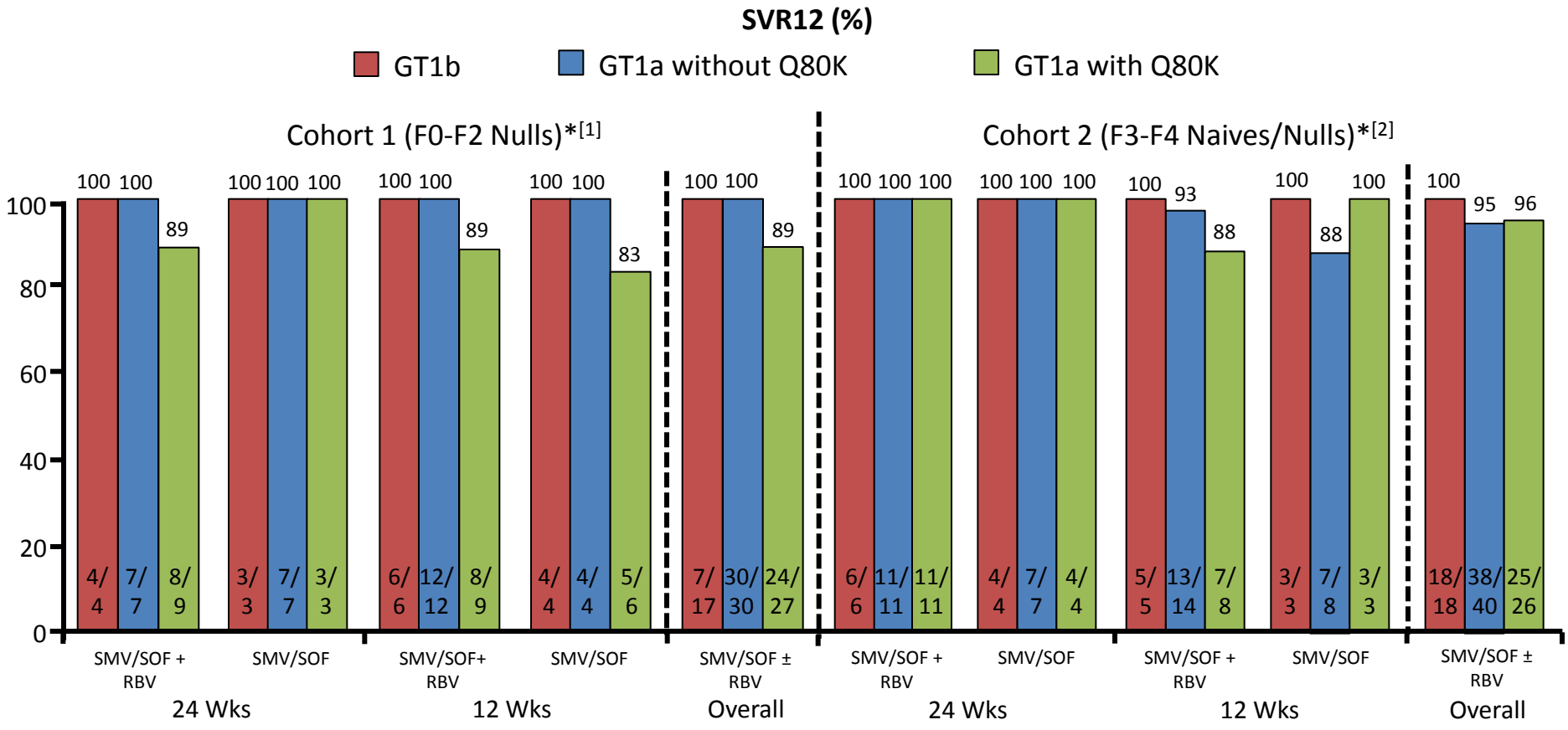
- Randomized phase IIa study



Simeprevir 150 mg QD; sofosbuvir 400 mg QD; weight-based RBV 1000-1200 mg/day.

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

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

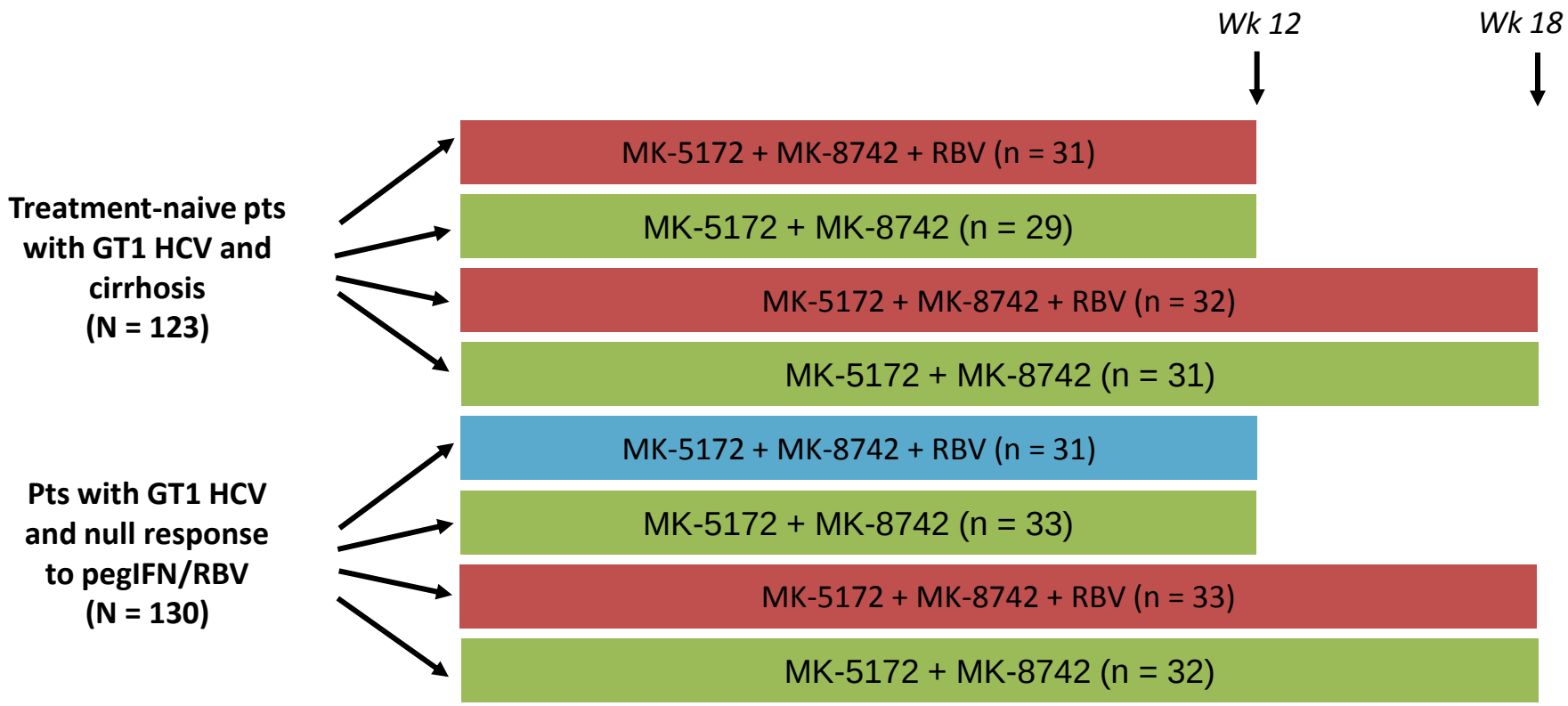


*Excluding patients who discontinued for nonvirologic reasons.

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

C-WORTHY: MK-5172 + MK-8742 ± RBV in GT1 Cirrhotics and Null Responders

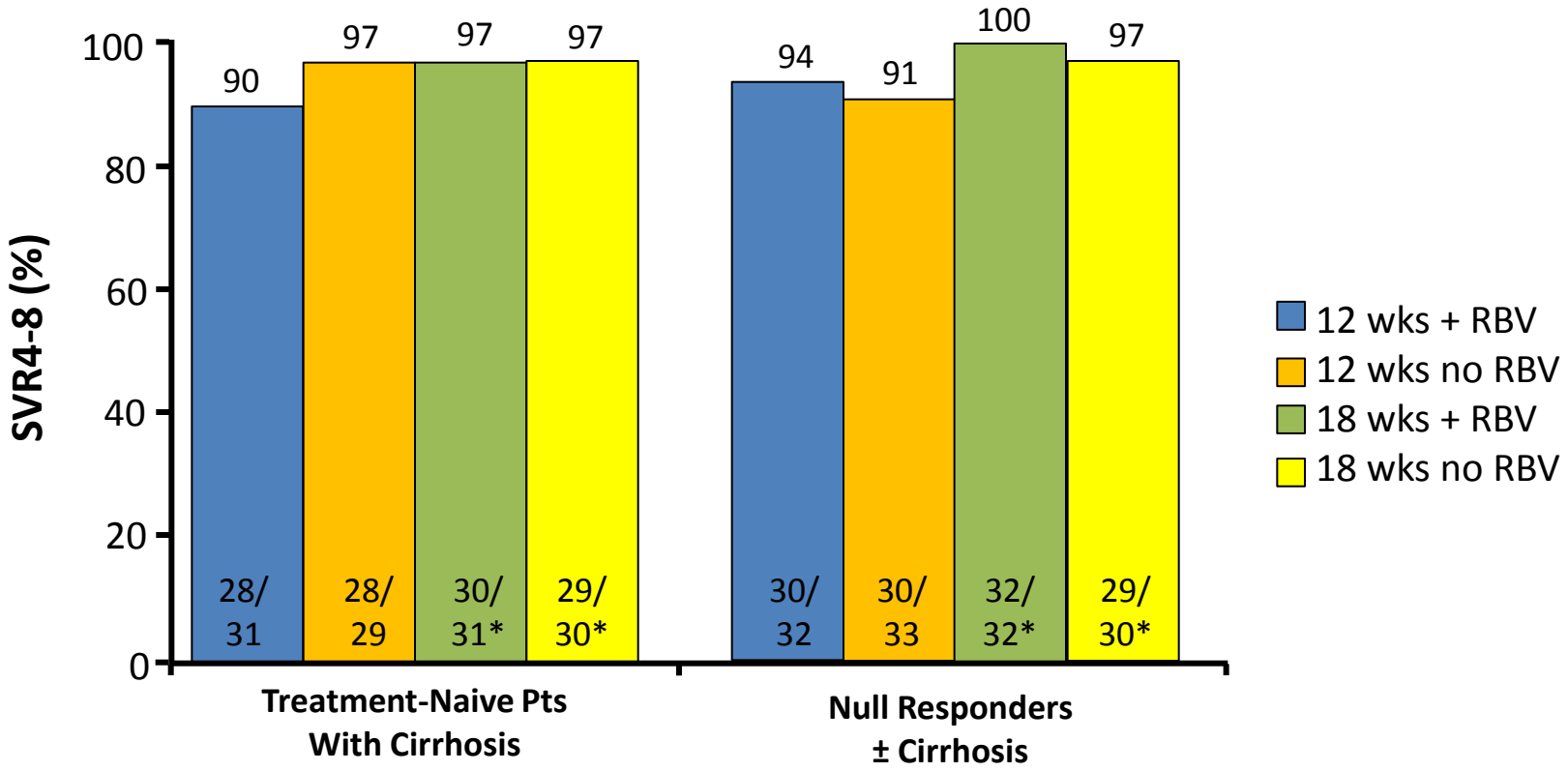
- Interim results from a randomized phase IIb trial
- Primary endpoint: SVR12



MK-5172 100 mg once daily; MK-8742 50 mg once daily, RBV 1000-1200 mg divided twice daily.

Lawitz E, et al. EASL 2014. Abstract O61.

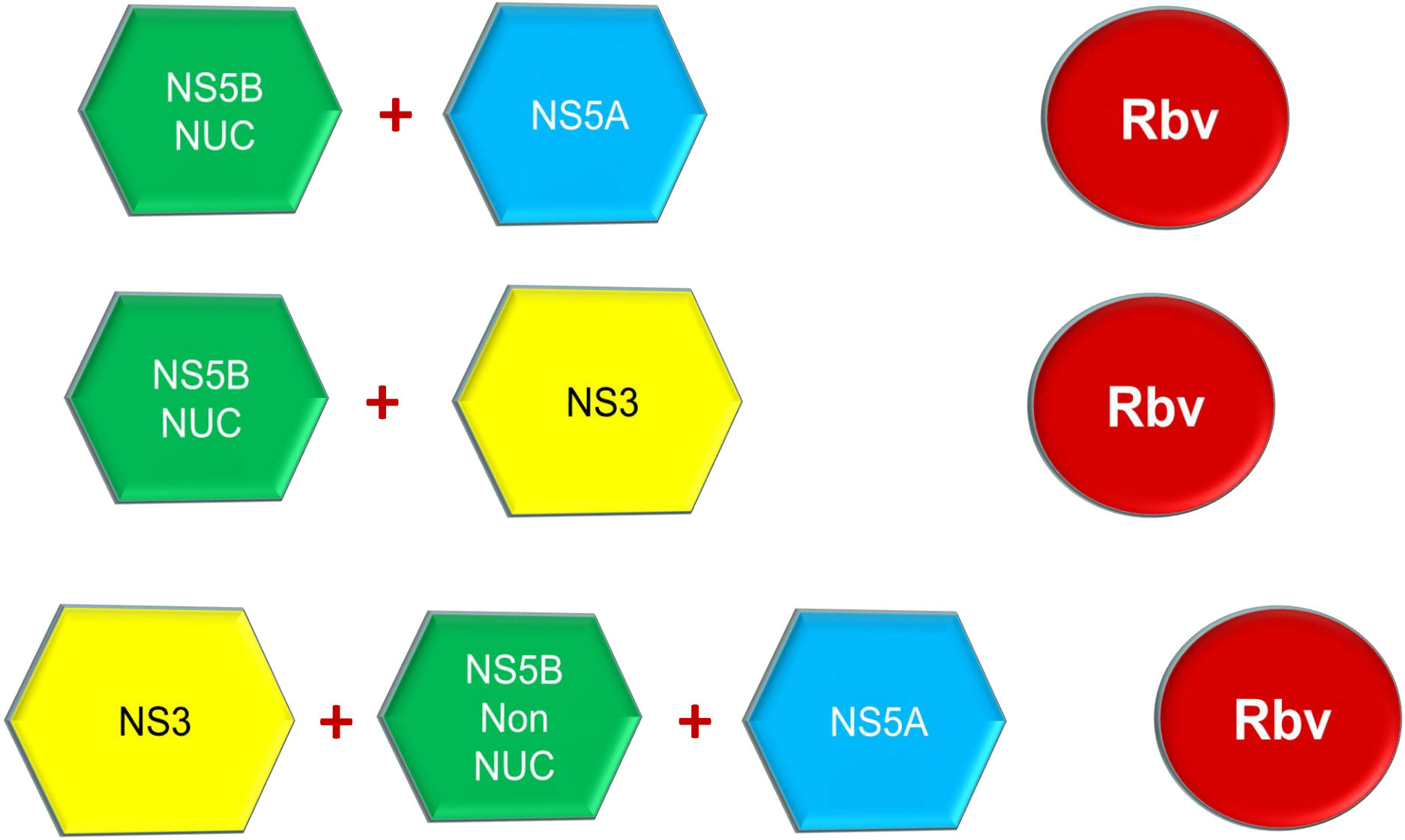
C-WORTHY: Interim Results in Treatment-Naive Cirrhotic Pts and Null Responders



*Excludes patients who have not yet reached SVR4 time point.

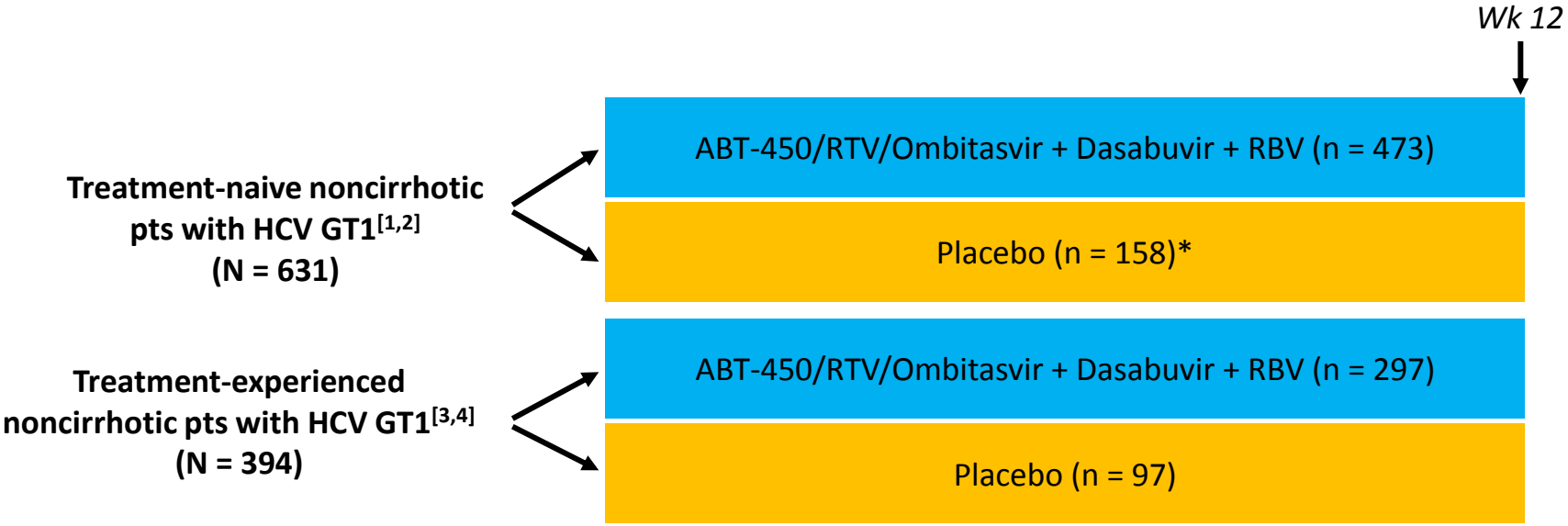
Lawitz E, et al. EASL 2014. Abstract O61.

Drug combination development



SAPPHIRE I & II: ABT-450/RTV/Ombitasvir + Dasabuvir + RBV in Noncirrhotic GT1 Pts

- Double-blind, placebo-controlled phase III trials in treatment-naive (SAPPHIRE I) and treatment-experienced (SAPPHIRE II) GT1 HCV pts

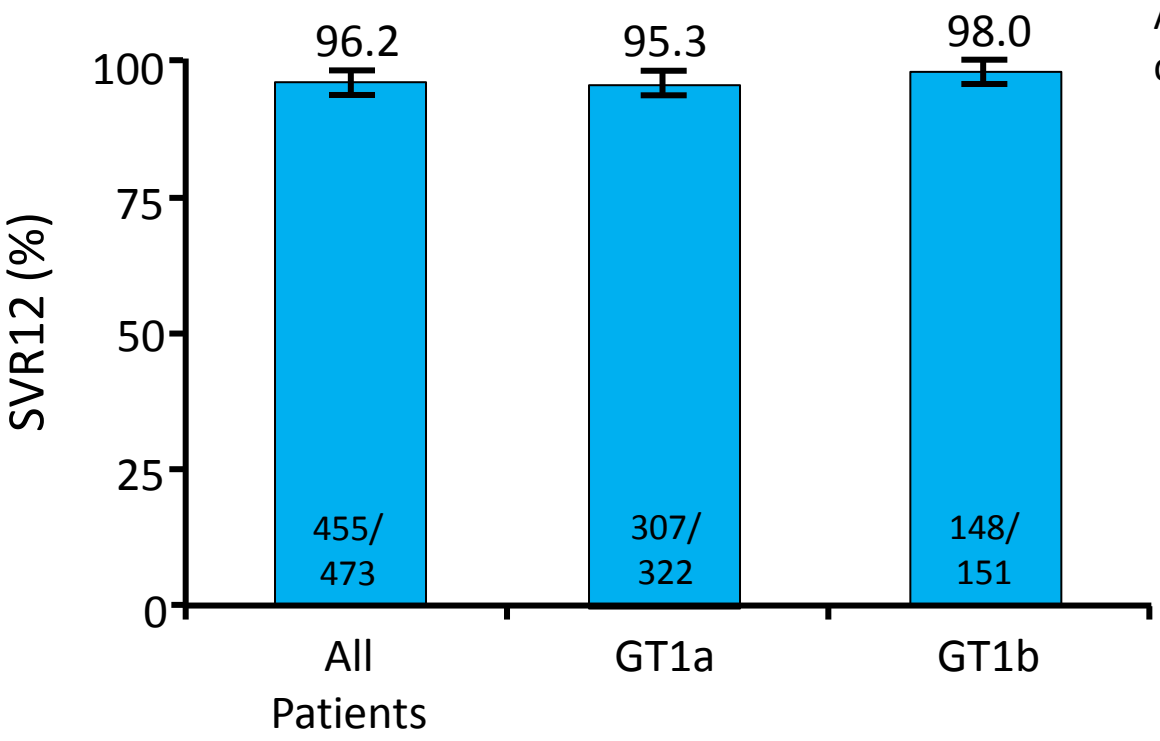


ABT-450/RTV/ombitasvir 150/100/25 mg once daily; dasabuvir 250 mg twice daily; RBV 1000-1200 mg/day.

*Placebo recipients crossed over to active treatment regimen at Wk 12.

1. Feld JJ, et al. EASL 2014. Abstract O60. Reproduced with permission. 2. Feld JJ, et al. N Engl J Med. 2014;370:1594-1603. 3. Zeuzem S, et al. EASL 2014. Abstract O1. 4. Zeuzem S, et al. N Engl J Med. 2014;370:1604-1614.

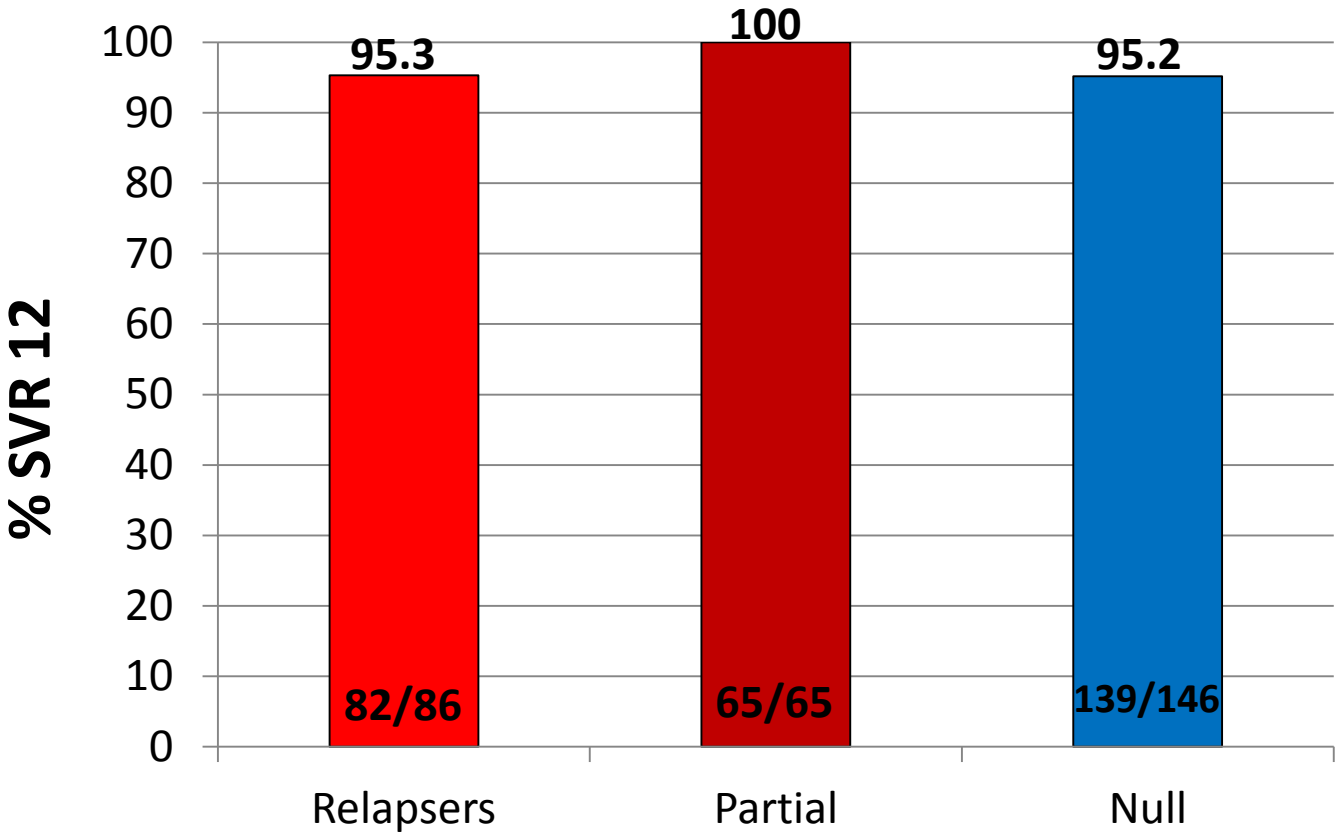
SAPPHIRE I: SVR12 With 3 DAAs + RBV in Treatment-Naive Pts by HCV subtype



ABT-450/ombitasvir + dasabuvir + RBV

1. Feld JJ, et al. EASL 2014. Abstract O60. Reproduced with permission. 2. Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.

SAPPHIRE-II Study: 12 weeks of treatment with ABT-450/r + ABT-267 (Ombitasvir) + ABT-333 (Dasabuvir) and RBV in non-cirrhotic, GT1 treatment-experienced patients



Zeuzem, NEJM 2014

SAPPHIRE I and II: Adverse Events

AEs	SAPPHIRE I		SAPPHIRE II	
	3 DAA + RBV (n = 473)	Placebo (n = 158)	3 DAA + RBV (n = 297)	Placebo (n = 97)
Any AE, n (%)	414 (87.5)	116 (73.4)	271 (91.2)	80 (82.5)
AE leading to D/C, n (%)	3 (0.6)	1 (0.6)	3 (1.0)	0
Any serious AE, n (%)	10 (2.1)	0	6 (2.0)	1 (1.0)
Grade 3/4 lab events, n/N (%)				
▪ ALT	4/469 (0.9)	7/158 (4.4)	5/296 (1.7)	3/96 (3.1)
▪ AST	3/469 (0.6)	3/158 (1.9)	3/296 (1.0)	1/96 (1.0)
▪ Alkaline phosphatase	0	0	0	0
▪ Creatinine	–	–	2/297 (0.7)	0
▪ Total bilirubin	13/469 (2.8)	0	7/296 (2.4)	0
▪ Hemoglobin < 8 g/dL	0	0	1/296 (0.3)	0
Hemoglobin < 10 to 8 g/dL, %	5.8	0	4.7	0

Feld JJ, et al. N Engl J Med. 2014;370:1594-1603. Zeuzem S, et al. N Engl J Med. 2014;370:1604-1614.

A new standard of response for G1 patients

An SVR > 90%

Peg-IFN + RBV	G1 patients with favorable predictors (IL-28 CC; no cirrhosis; RVR)
Triple with PI	G1 patients with favorable predictors
IFN-free combination	All treated (no predictors)

Personalization of therapy based on HCV genotype – presence of cirrhosis

Chi trattare oggi

La triplice terapia con telaprevir o boceprevir è ad oggi la sola terapia registrata e rimborsabile

Possibilità:

Fruire delle nuove terapie attraverso l'inserimento in un trial clinico

Programmi di uso compassionevole (limitati)

Trattare con la triplice attuale

Rinviare il trattamento