GeSIDA
GRUPO DE ESTUDIO DEL SIDA-SEIMC

Estudios ASTRAL 1, 2, 3 Y 4.

Publicados en la página de web del New England Journal of Medicine en noviembre de 2015

Estudios de fase III con la combinación fija de Sofosbuvir y Velpatasvir (SOF-VEL) para el tratamiento de diferentes grupos de de pacientes con infección crónica por el VHC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection

J. Feld, I.M. Jacobson, C. Hézode, T. Asselah, P.J. Ruane, N. Gruener, A. Abergel, A. Mangia, C.-L. Lai, H.L.Y. Chan, F. Mazzotta, C. Moreno, E. Yoshida, S.D. Shafran, W.J. Towner, T.T. Tran, J. McNally, A. Osinusi, E. Svarovskaia, Y. Zhu, D.M. Brainard, J.G. McHutchison, K. Agarwal, and S. Zeuzem, for the ASTRAL-1 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection

G.R. Foster, N. Afdhal, S.K. Roberts, N. Bräu, E.J. Gane, S. Pianko, E. Lawitz, A. Thompson, M.L. Shiffman, C. Cooper, W.J. Towner, B. Conway, P. Ruane, M. Bourlière, T. Asselah, T. Berg, S. Zeuzem, W. Rosenberg, K. Agarwal, C.A.M. Stedman, H. Mo, H. Dvory-Sobol, L. Han, J. Wang, J. McNally, A. Osinusi, D.M. Brainard, J.G. McHutchison, F. Mazzotta, T.T. Tran, S.C. Gordon, K. Patel, N. Reau, A. Mangia, and M. Sulkowski, for the ASTRAL-2 and ASTRAL-3 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis

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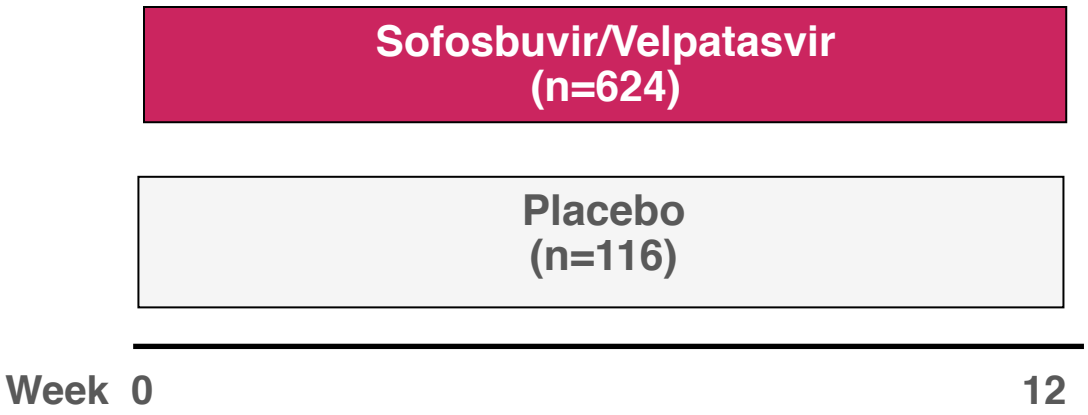
Background

- Velpatasvir (formerly GS-5816, Gilead Sciences) is a new pangenotypic HCV NS5A inhibitor with antiviral activity against HCV replicons in genotypes 1 through 6

- In phase-2 trials, the combination of 400 mg of sofosbuvir (SOF) and 100 mg of velpatasvir (VEL) with or without RBV resulted in high rates of SVR in a broad range of patients with HCV.

ASTRAL-1 Design



- Phase 3, double-blind, placebo-controlled
- HCV genotype 1,2,4,5*, or 6
- HCV RNA $\geq 10^4$ IU/mL
- Treatment-naive or treatment-experienced
- Compensated cirrhosis allowed
- No HBV or HIV

*All genotype 5 patients received SOF-VEL.
Primary endpoint: SVR12 (pre-specified goal of 85%).

Feld JJ, et al. N Engl J Med. 2015;Nov 16. [Epub ahead of print].

ASTRAL-1. Characteristics of the Patients at Baseline

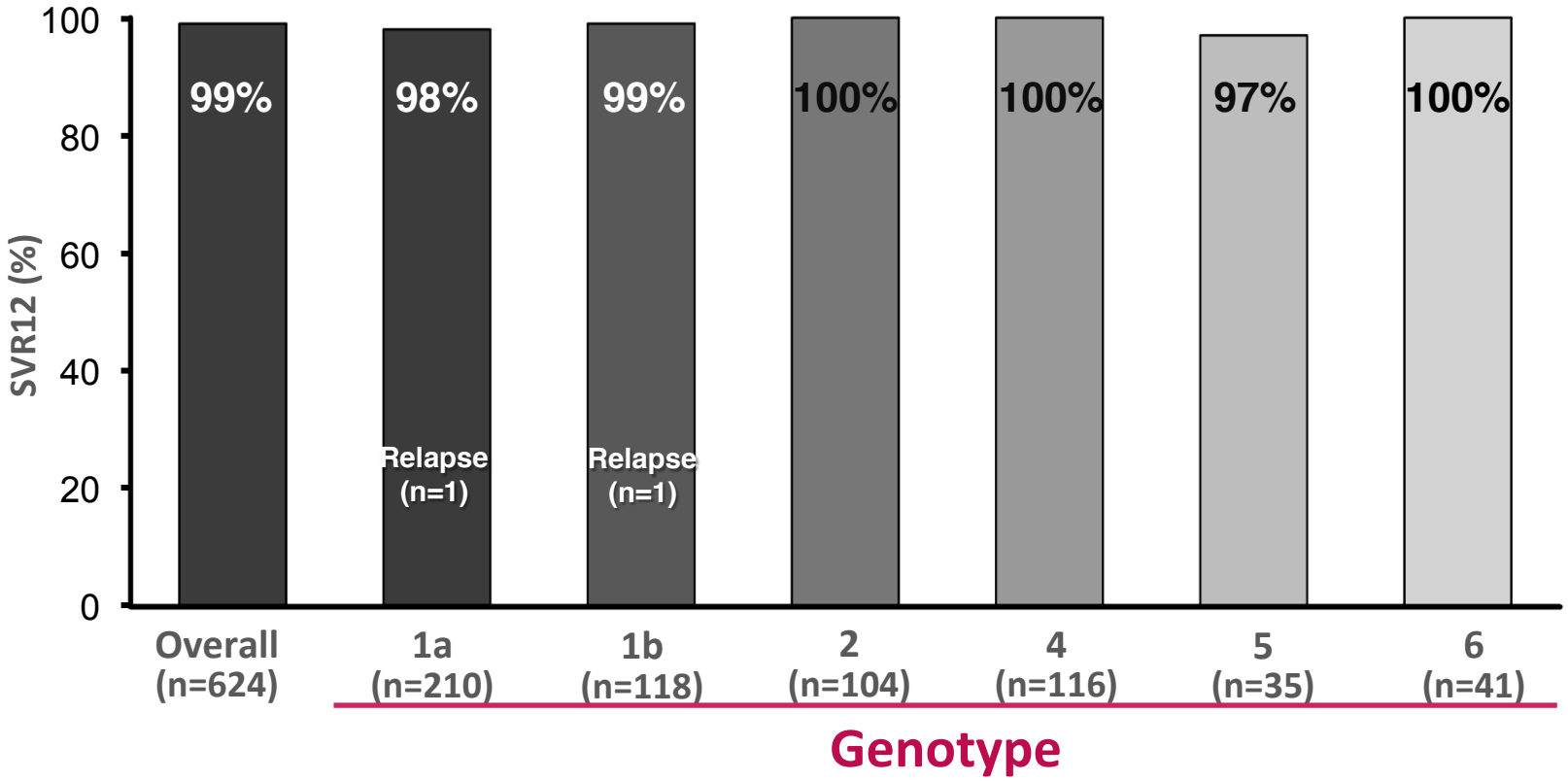
Characteristic	PLBO N=116	SOF-VEL N=624
Mean age (range) — yr.	53 (25–74)	54 (18–82)
Male sex — no. (%)	68 (59)	374 (60)
White Race — no. (%)	90 (78)	493 (79)
HCV genotype		
1a	46 (40)	210 (34)
1b	19 (16)	118 (19)
2	21 (18)	104 (17)
4	22 (19)	116 (19)
5	0	35 (6)
6	8 (7)	41 (7)
Mean HCV RNA — log10 IU/ml	6.3±0.58	6.3±0.66
Compensated cirrhosis — no. (%)	21 (18)	121 (19)
Previous HCV treatment		
No	83/116 (72)	423/624 (68)
Yes	33/116 (28)	201/624 (32)
PI, peg-IFN, and RBV	6/33 (18)	56/201 (28)
Peg-IFN, and RBV	24/33 (73)	122/201 (61)
Non Peg-IFN with or without RBV	3/33 (9)	23/201 (11)

Feld JJ, et al. N Engl J Med. 2015;Nov 16. [Epub ahead of print].

ASTRAL-1:
Efficacy of SOF-VEL HCV Genotypes 1, 2, 4, 5, or 6

Treatment failures 6 (1%)

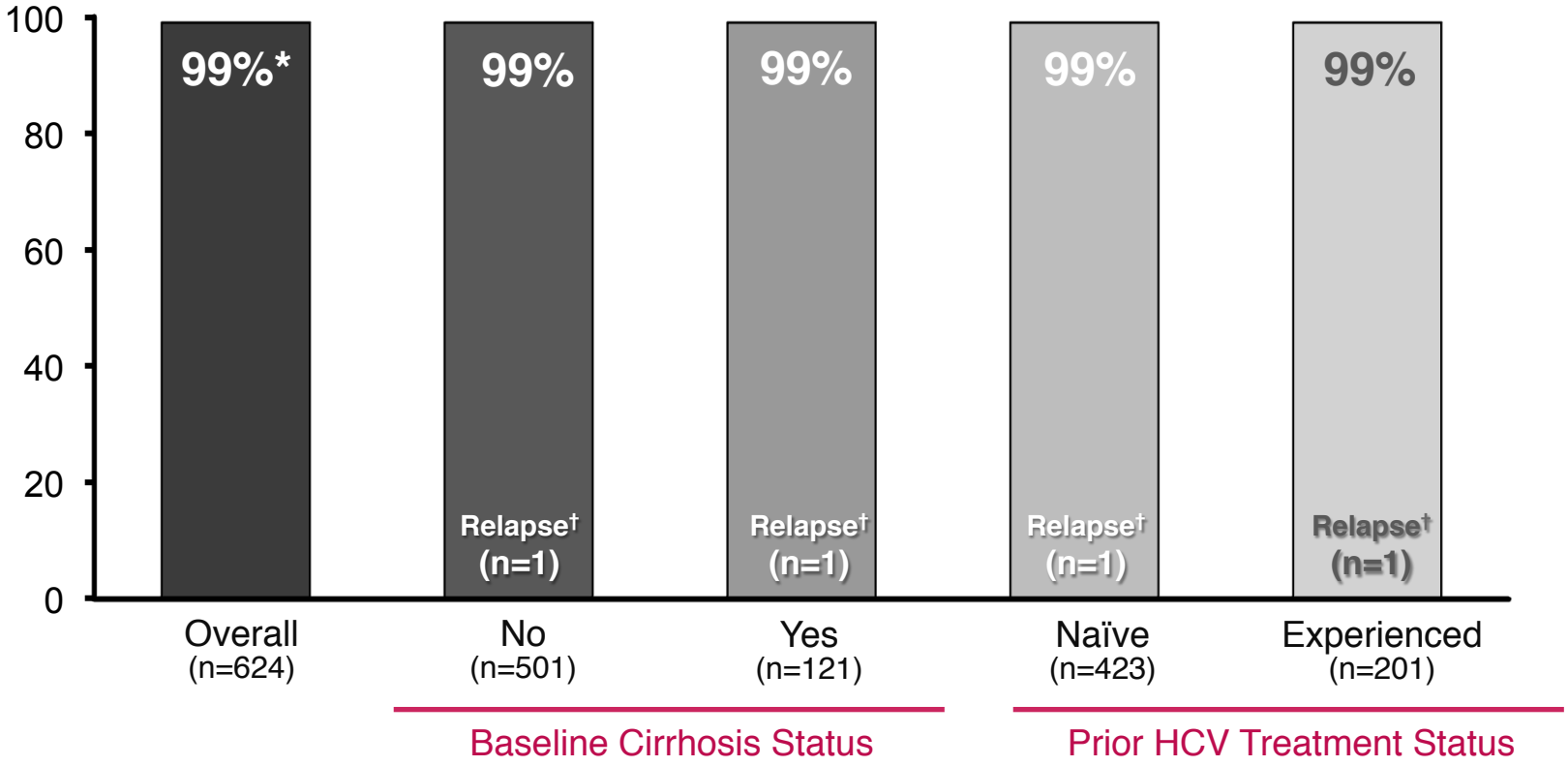
Breakthrough 0, Relapse 2 (<1%), Lost to FU 2 (<1%), withdrawal of consent 1(<1%), Death 1(<1%). **Relapse**: 1) G1a, Rx-naive, non-cirrhotic and 2) G1b, Rx-experienced cirrhotic.



SVR12 for placebo: 0%.

All SOF-VEL groups were superior to the pre-specified SVR12 goal of 85% (P<0.001).

ASTRAL-1: Efficacy of SOF-VEL by Cirrhosis Status and Prior Treatment Experience



*Combined data for genotypes 1, 2, 4, 5, 6: Superior to the pre-specified SVR12 goal of 85% (P<0.001). †Relapse in 2 patients: 1) G1a, Rx-naive, non-cirrhotic and 2) G1b, Rx-experienced cirrhotic.

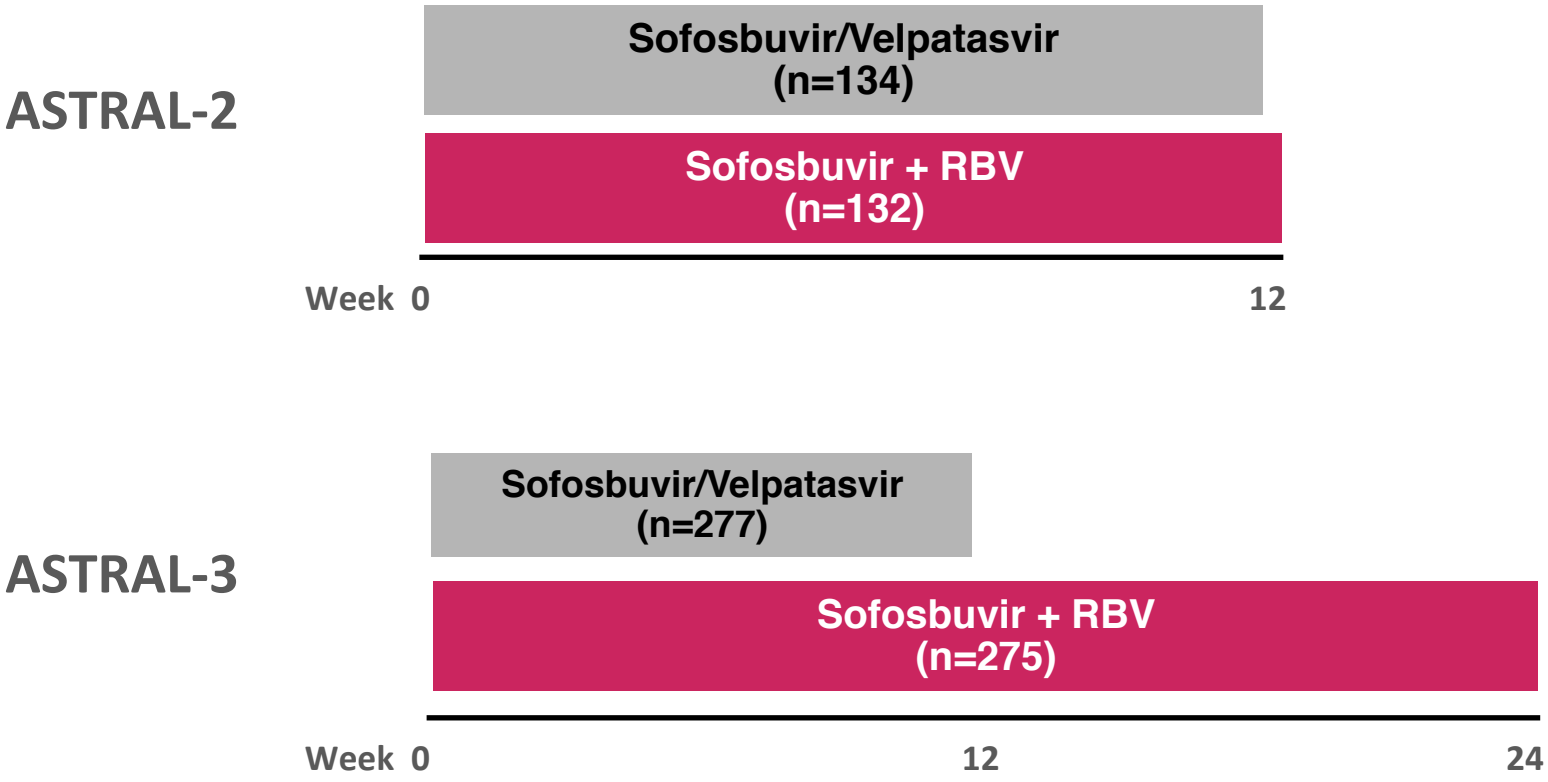
Feld JJ, et al. N Engl J Med. 2015;Nov 16. [Epub ahead of print].

ASTRAL-1: Safety Profile With SOF-VEL in HCV Genotype 1, 2, 4, 5, or 6

- Adverse events (AEs)
  - Similar incidences between SOF-VEL and placebo
  - Discontinuations due to AEs
    - SOF-VEL (n=1)
    - Placebo (n=2)
  - Serious AEs
    - SOF-VEL: 2.4% (15/624 all were not related to study drug)
    - Placebo: none
- Laboratory abnormalities
  - Similar incidence between the SOF-VEL and placebo
  - No grade 3/4 elevations in creatinine or total bilirubin

Feld JJ, et al. N Engl J Med. 2015;Nov 16. [Epub ahead of print].

ASTRAL-2 and ASTRAL-3 Design



- Phase 3, open-label
- HCV genotype 2 and 3
- HCV RNA $\geq 10^4$ IU/mL
- Treatment-naïve or treatment-experienced
- Compensated cirrhosis allowed
- No HBV or HIV

Foster GR, N Engl J Med 2015.

ASTRAL-2 and 3.
Characteristics of the Patients at Baseline

Characteristic	HCV Genotype 2	
	SOF-VEL 12 (N = 134)	SOF-RBV 12 (N = 132)
Mean age (range) — yr	57 (26–81)	57 (23–76)
Male sex — no. (%)	86 (64)	72 (55)
White Race — no. (%)	124 (93)	111 (84)
Mean HCV RNA — log10 IU/ml	6.5 ± 0.78	6.4 ± 0.74
≥800,000 IU/ml — no. (%)	111 (83)	101 (77)
Compensated cirrhosis — no. (%)	19 (14)	19 (14)
Previous HCV treatment — no. (%)		
No	115 (86)	112 (85)
Yes	19 (14)	20 (15)
Response to previous HCV treatment		
No response	3/19 (16)	3/20 (15)
Relapse or breakthrough	16/19 (84)	17/20 (85)

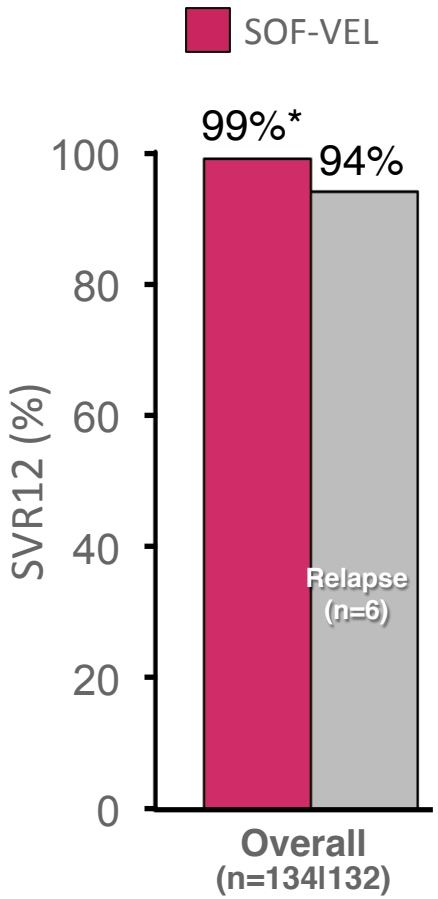
Foster GR, N Engl J Med 2015.

ASTRAL-2 and 3. Characteristics of the Patients at Baseline

Characteristic	HCV Genotype 2		HCV Genotype 3	
	SOF-VEL 12 (N = 134)	SOF-RBV 12 (N = 132)	SOF-VEL 12 (N = 277)	SOF-RBV 24 (N = 275)
Mean age (range) — yr	57 (26–81)	57 (23–76)	49 (21–76)	50 (19–74)
Male sex — no. (%)	86 (64)	72 (55)	170 (61)	174 (63)
White Race — no. (%)	124 (93)	111 (84)	250 (90)	239 (87)
Mean HCV RNA — log10 IU/ml	6.5 ± 0.78	6.4 ± 0.74	6.2 ± 0.72	6.3 ± 0.71
≥800,000 IU/ml — no. (%)	111 (83)	101 (77)	191 (69)	194 (71)
Compensated cirrhosis — no. (%)	19 (14)	19 (14)	80 (29)	83 (30)
Previous HCV treatment — no. (%)				
No	115 (86)	112 (85)	206 (74)	204 (74)
Yes	19 (14)	20 (15)	71 (26)	71 (26)
Response to previous HCV treatment				
No response	3/19 (16)	3/20 (15)	20/71 (28)	24/71 (34)
Relapse or breakthrough	16/19 (84)	17/20 (85)	51/71 (72)	47/71 (66)

Foster GR, N Engl J Med 2015.

ASTRAL-2:
Efficacy of SOF-VEL in HCV Genotype 2

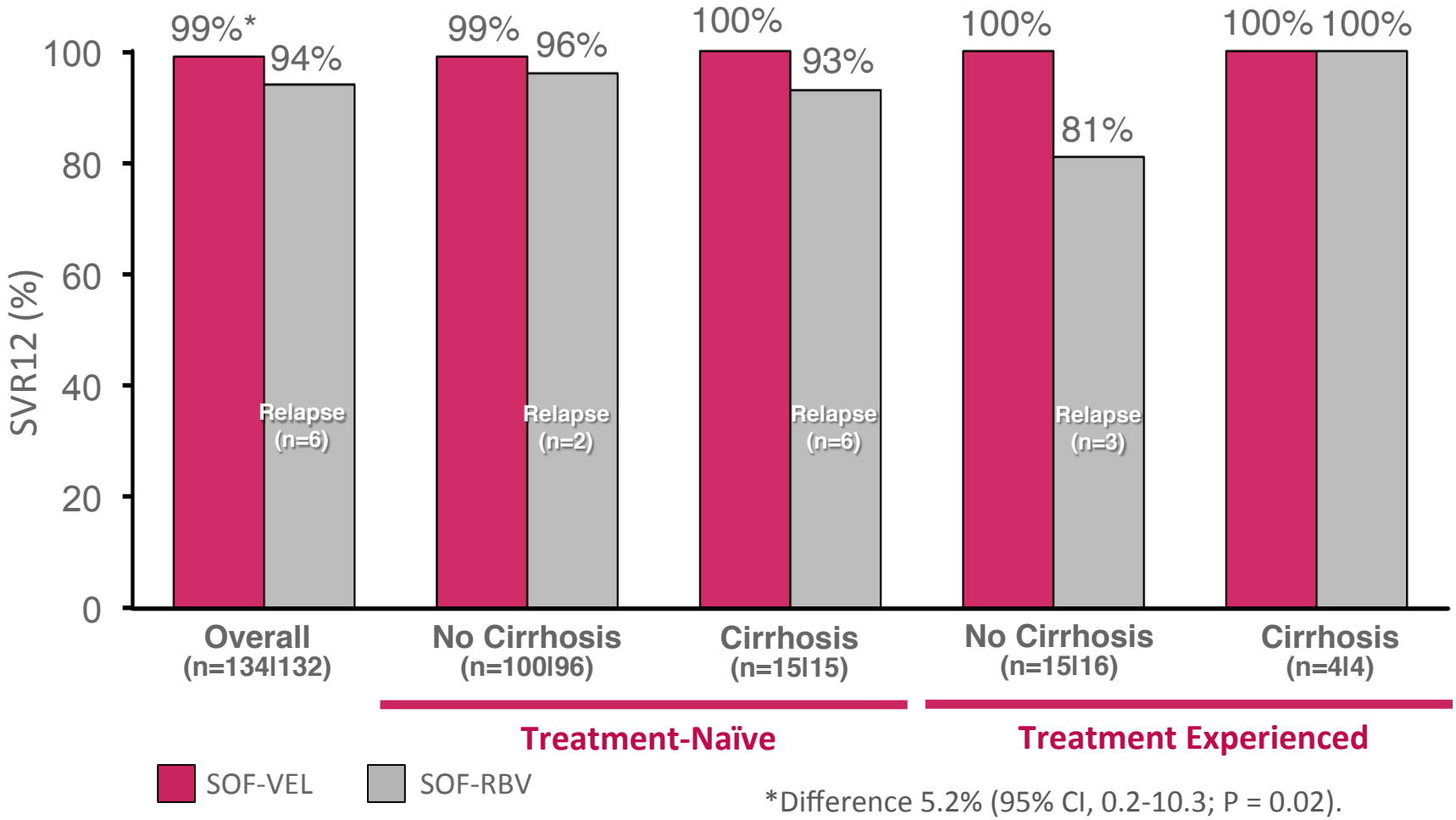


No virologic failures among patients receiving SOF-VEL. One 57-year old black man D/C treatment on day 1 after receiving one dose of the study drug because of AEs

Foster GR, N Engl J Med 2015.

ASTRAL-2: Efficacy of SOF-VEL in HCV Genotype 2

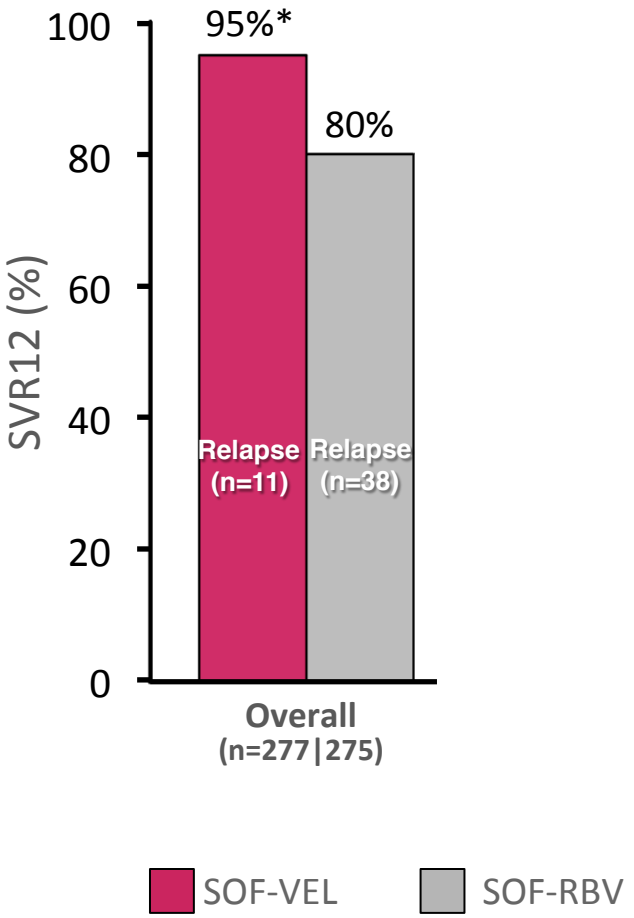
No virologic failures among patients receiving SOF-VEL. One 57-year old black man D/C treatment on day 1 after receiving one dose of the study drug because of AEs



*Difference 5.2% (95% CI, 0.2-10.3; P = 0.02). Met non-inferiority and superiority criteria.

Foster GR, N Engl J Med 2015.

ASTRAL-3: Efficacy of SOF-VEL in HCV Genotype 3

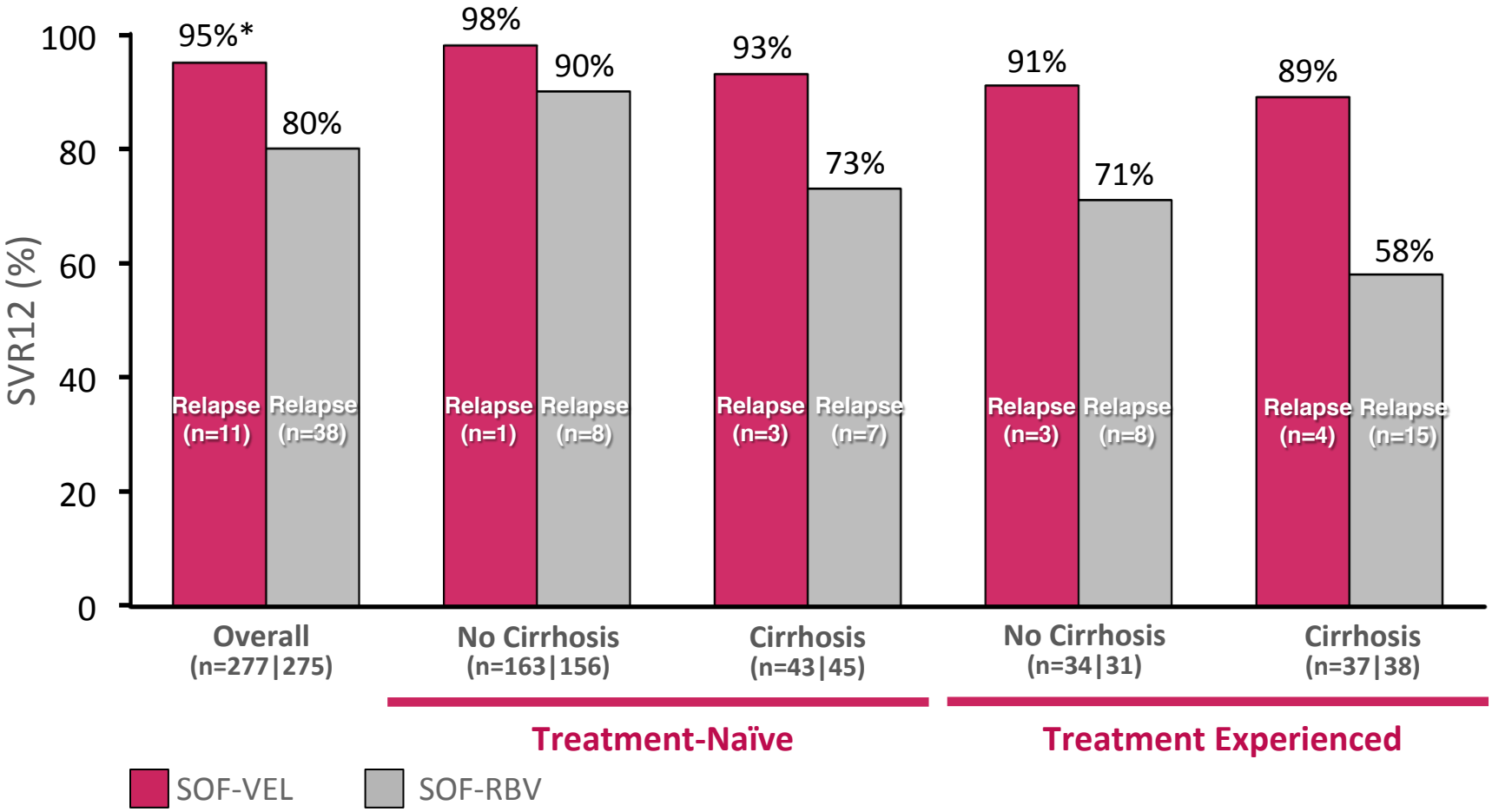


*Difference 14.8% (95% CI, 9.6-20.0; P < 0.001).
Met non-inferiority and superiority criteria.

Foster GR, N Engl J Med 2015.

ASTRAL-3: Efficacy of SOF-VEL in HCV Genotype 3

*Difference 14.8% (95% CI, 9.6-20.0; P < 0.001).
Met non-inferiority and superiority criteria.



Foster GR, N Engl J Med 2015.

ASTRAL-2: Safety Profile With Sofosbuvir/Velpatasvir in HCV Genotype 2

- Common AEs (SOF-VEL versus SOF+RBV)
  - Fatigue: 15% versus 36%
  - Headache: 18% versus 22%
  - Nausea: 10% versus 14%
  - Insomnia: 4% versus 14%
- Discontinuations due to AEs
  - SOF-VEL (n=1)
  - SOF+RBV none
- Deaths (n=2; both in the SOF-VEL arm, not related to study drug)
- Grade 3/4 laboratory abnormalities
  - None in the SOF-VEL arm
  - Hemoglobin <10 g/dL: SOF+RBV (n=6)

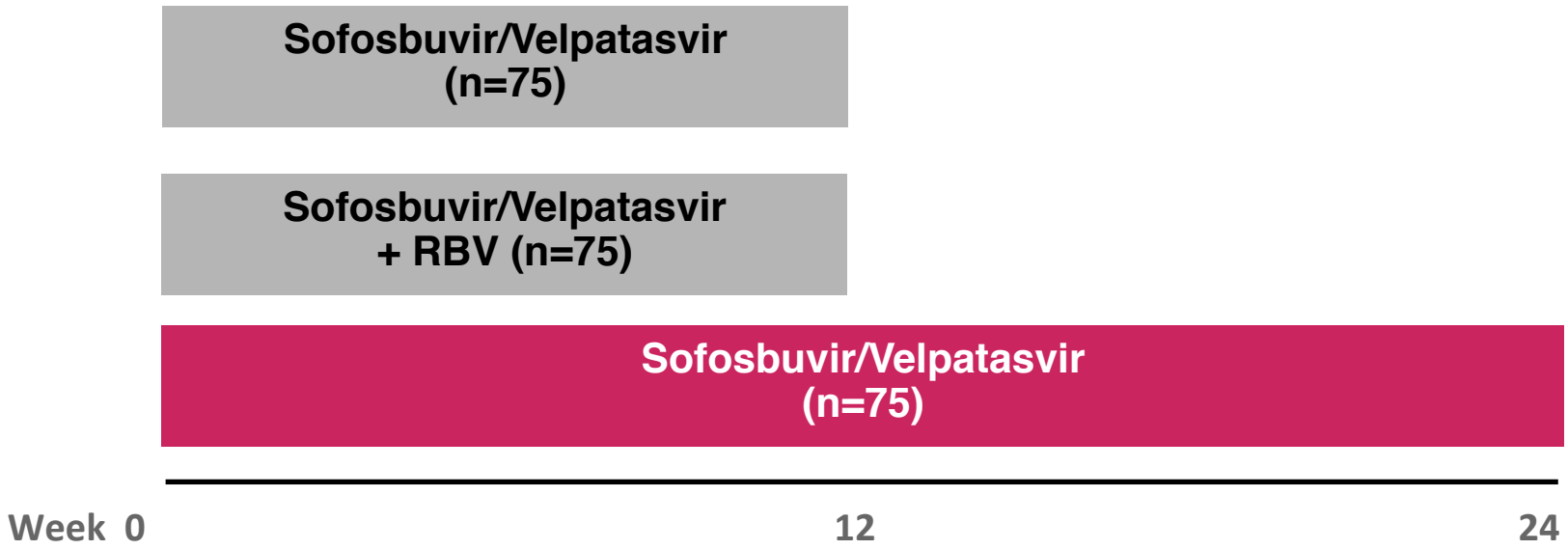
Foster GR, N Engl J Med 2015.

ASTRAL-3: Safety Profile With Sofosbuvir/ Velpatasvir in HCV Genotype 3

- Common AEs (SOF-VEL versus SOF+RBV)
  - Fatigue: 26% versus 38%
  - Insomnia: 11% versus 27%
  - Nausea: 17% versus 21%
- Discontinuations due to AEs
  - SOF-VEL (n=0)
  - SOF+RBV (n=9)
- Deaths (n=3; all in the SOF+RBV arm, not related to study drug)
- Grade 3/4
  - None in the SOF-VEL arm
  - Total bilirubin 2 in the SOF+RBV arm
  - Hemoglobin <10 g/dL: SOF+RBV (n=10)

Foster GR, N Engl J Med 2015.

ASTRAL-4 Design



- Phase 3, open-label
- HCV genotype 1, 2, 3, 4, 6
- Decompensated cirrhosis
- Platelets >30K/mm^3

- HCV treatment-naïve or treatment-experienced
- HCV RNA $\geq 10^4$ IU/mL
- eGFR >50 mL/min

Curry MP, N Engl Med. 2015;Nov 16. [Epub ahead of print].

ASTRAL-4.
Characteristics of the Patients at Baseline I

Characteristic	SOF-VEL 12 N=90	SOF-VEL+RBV 12 N=87	SOF-VEL 24 N=90
Mean age (range) — yr.	58 (42–73)	58 (40–71)	58 (46–72)
Male sex — no. (%)	57 (63)	66 (76)	63 (70)
White Race — no. (%)	79 (88)	79 (91)	81 (90)
HCV genotype			
1a	50 (56)	54 (62)	55 (61)
1b	18 (20)	14 (16)	16 (18)
2	4 (4)	4 (5)	4 (4)
3	14 (16)	13 (15)	12 (13)
4	4 (4)	2 (2)	2 (2)
6	0	0	1 (1)
Mean HCV RNA — log10 IU/ml	6.0±0.5	5.8±0.6	5.9±0.6
Previous HCV treatment — no. (%)	58 (64)	47 (54)	42 (47)
Protease inhibitor regimen	9/58 (16)	12/47 (26)	7/42 (17)
PegIFN – RBV	48/58 (83)	35/47 (74)	35/42 (83)

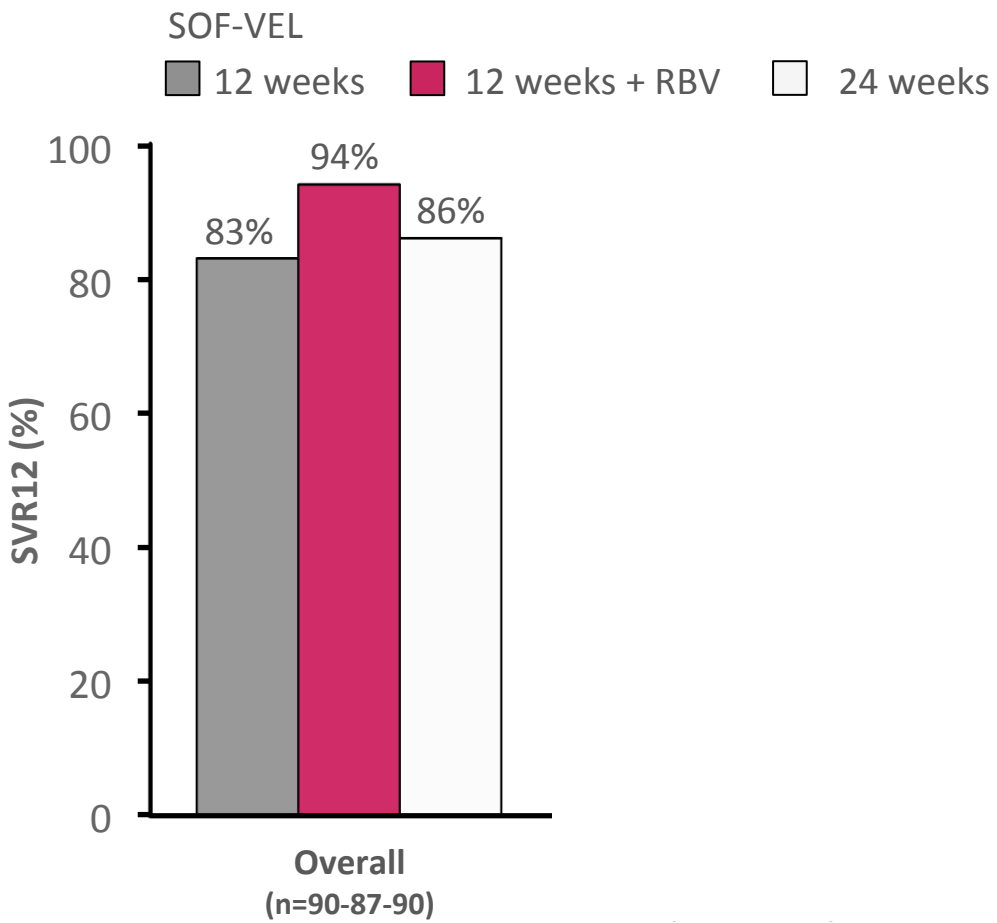
Curry MP, N Engl Med. 2015;Nov 16. [Epub ahead of print].

ASTRAL-4.
Characteristics of the Patients at Baseline II

Characteristic	SOF-VEL 12 N=90	SOF-VEL+RBV 12 N=87	SOF-VEL 24 N=90
CPT score — no. (%)			
≤6	3 (3)	6 (7)	7 (8)
7	36 (40)	23 (26)	21 (23)
8	31 (34)	41 (47)	34 (38)
9	19 (21)	13 (15)	22 (24)
10	1 (1)	4 (5)	6 (7)
MELD score — no. (%)			
<10	36 (40)	29 (33)	26 (29)
10–15	50 (56)	54 (62)	59 (66)
≥16	4 (4)	4 (5)	5 (6)
Ascites — no. (%)			
None	16 (18)	22 (25)	15 (17)
Mild or moderate	72 (80)	61 (70)	74 (82)
Severe	2 (2)	4 (5)	1 (1)
Mean eGFR CG (range) — ml/min	89 (15–169)	90 (50–167)	90 (43–198)

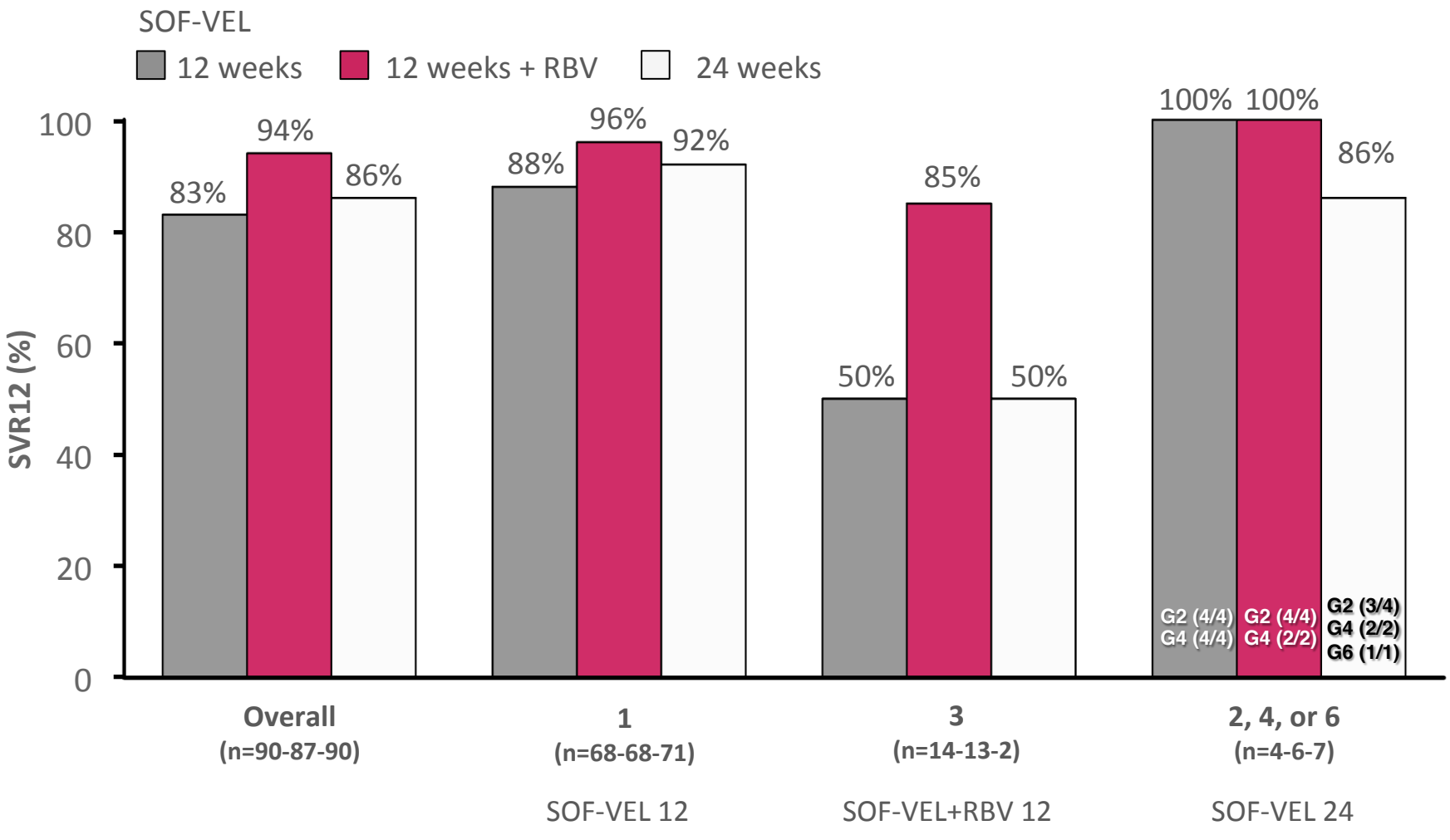
Curry MP, N Engl Med. 2015;Nov 16. [Epub ahead of print].

ASTRAL-4:
Efficacy of SOF-VEL ± RBV in HCV Decompensated Cirrhosis (Genotypes 1,2,4, or 6)



	SOF-VEL 12	SOF-VEL+RBV 12	SOF-VEL 24
Virologic failure	11/90 (12)	3/87 (3)	8/90 (9)
Death	3/90 (3)	2/87 (2)	2/90 (2)
Lost to FU	1/90 (1)	0	3/90 (3)

ASTRAL-4: Efficacy of SOF-VEL ± RBV in HCV Decompensated Cirrhosis (Genotypes 1,2,4, or 6)

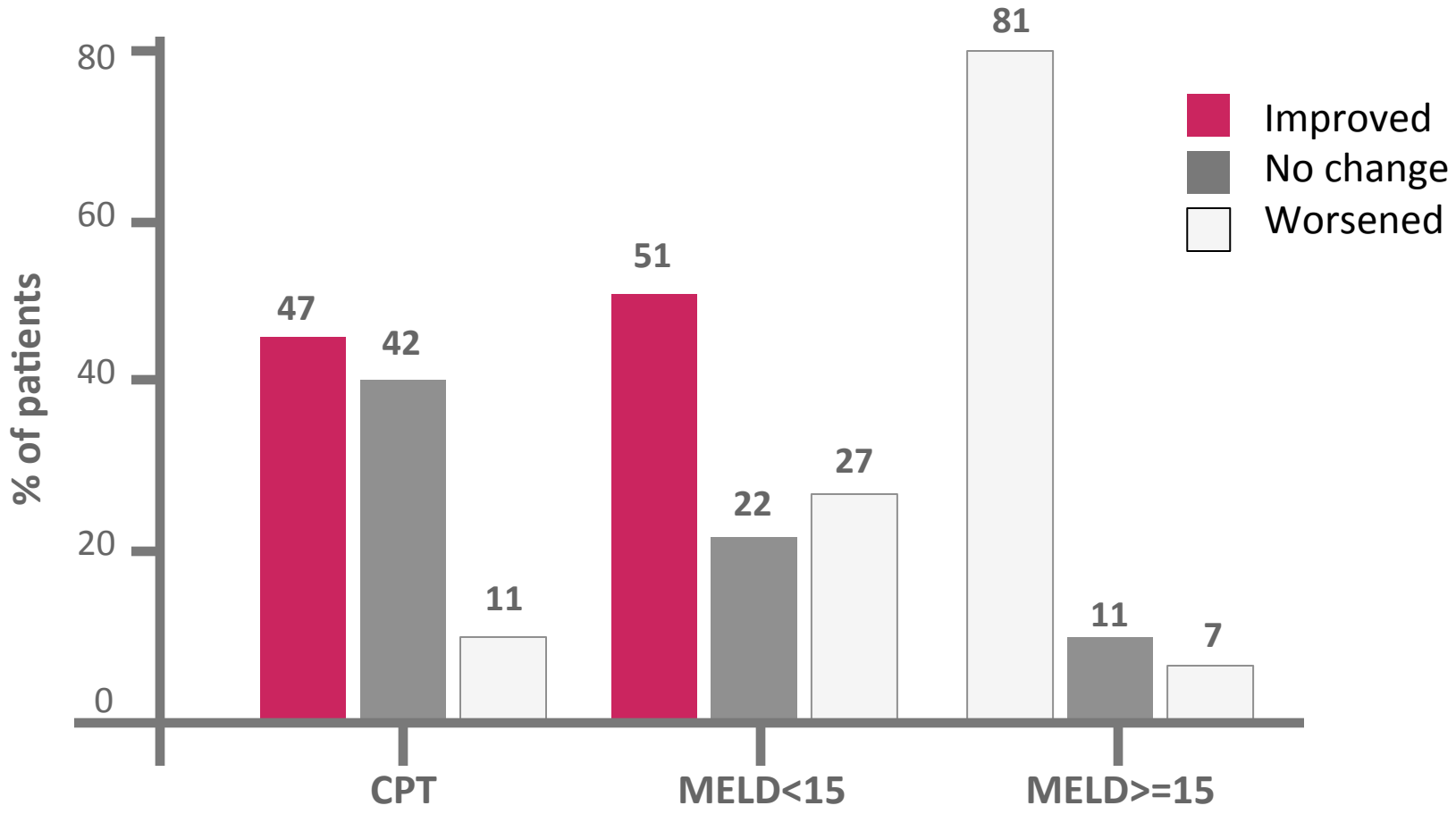


	SOF-VEL 12	SOF-VEL+RBV 12	SOF-VEL 24
Virologic failure	11/90 (12)	3/87 (3)	8/90 (9)
Death	3/90 (3)	2/87 (2)	2/90 (2)
Lost to FU	1/90 (1)	0	3/90 (3)

ASTRAL-4: Change in CPT and MELD Scores With SOF-VEL+ RBV in HCV Decompensated Cirrhosis

CPT score improvements: driven mostly by improvements in albumin and total bilirubin

MELD score improvements: driven mostly by improvements in total bilirubin



Curry MP, N Engl Med. 2015;Nov 16. [Epub ahead of print].

ASTRAL-4: Safety With Sofosbuvir/ Velpatasvir ± RBV in HCV Decompensated Cirrhosis

- Overall safe and well tolerated
  - Discontinuations due to adverse events: 3.4%
- AEs were consistent with clinical sequelae of advanced liver disease
  - Most common AEs
    - Fatigue (33%), nausea (23%), headache (22%)
    - Anemia (with RBV versus no RBV): 31% versus 4%
  - Serious treatment-related AEs
    - RBV: dyspnea
    - SOF-VEL: hepatorenal syndrome peritonitis, sepsis, and hypotension
  - Deaths (n=9), 3 in each arm, none considered treatment related)

Curry MP, N Engl Med. 2015;Nov 16. [Epub ahead of print].

Viral Resistance Testing Deep sequencing

ASTRAL-1	NS5A RAVs were detected at baseline in 257 of 616 patients (42%) for whom sequencing data were available. Of these 257 patients, 255 (99%) had a SVR. NS5B RAVs were detected at baseline in 54 of the 601 patients (9%) for whom sequencing data were available. All 54 patients had a SVR. No S282 variants were detected.
ASTRAL-2	In the SOF-VEL group, NS5A RAVs were detected at baseline in 60% and 10% had NS5B RAVs at baseline. Despite the presence of pretreatment NS5A and NS5B RAVs, no patient receiving SOF-VEL had virologic failure.
ASTRAL-3	Of the 274 patients in the SOF-VEL group who had available data on virologic outcome NS5A RAVs were detected at baseline in 43 (16%), 38 (88%) of which had a SVR. No NS5A RAVs were detected in 231 patients, 225 (97%) of which had a SVR. All 10 patients with baseline NS5B resistance-associated variants had a SVR

Conclusions

1) The results of the ASTRAL-1, ASTRAL-2, and ASTRAL-3 trials show that treatment with SOF-VEL for 12 weeks was highly effective regardless of HCV genotype. The treatment was also effective among patients with compensated cirrhosis.

2) The results of ASTRAL-4 trial showed that SOF-VEL in patients with decompensated cirrhosis caused by chronic HCV infection had high rates of SVR in all three treatment groups. Only 50% of patients with genotype 3 who received SVR alone had a SVR, which suggests that the contribution of RBV may be particularly important in patients with HCV genotype 3 and decompensated cirrhosis.

3) The rate of SVR in patients with HCV genotype 3 was lower in those with NS5A RAVs at baseline than in those without RAVs at baseline. Further research is needed to evaluate potential strategies to increase the rate of SVR in those patients, such as prolongation of therapy or the addition of a third antiviral drug (RBV or an active DAA)