Therapeutic Strategies for HCV Non-Genotype 1

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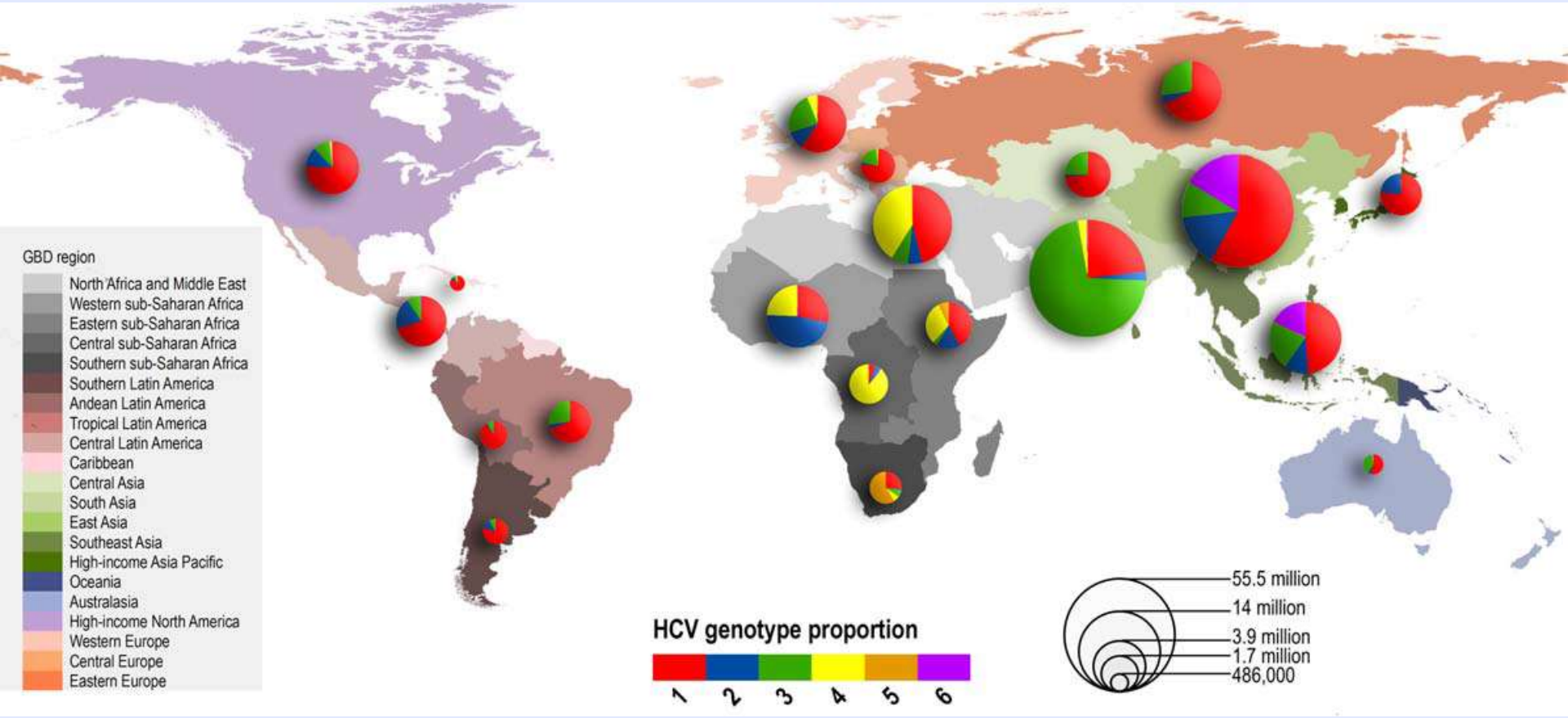
Overview

- Genotype non 1 HCV
- Scope of the problem
- Who is the ‘hard-to-cure’ population?
- Is there truly one regimen and duration for everyone?

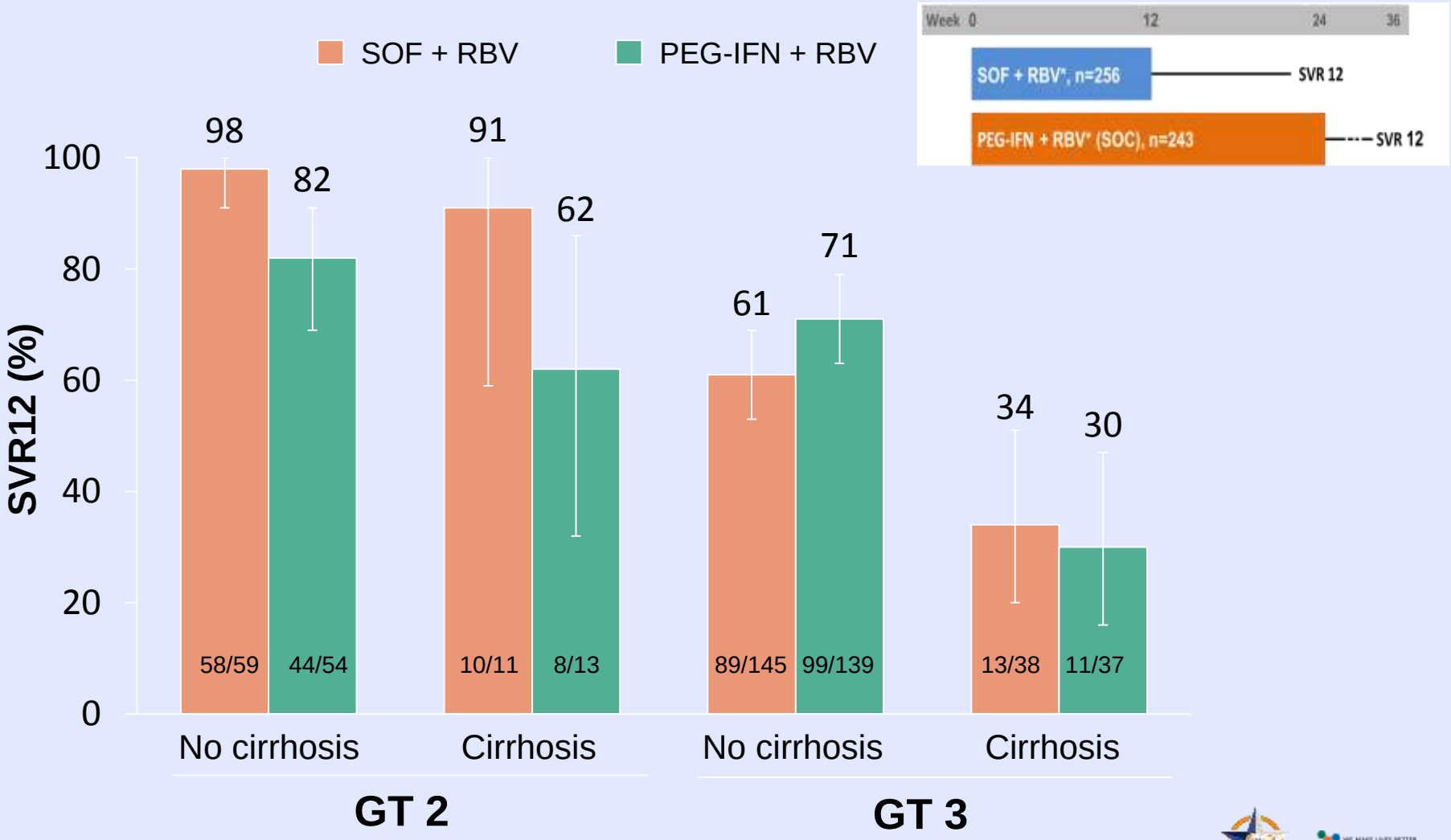
Distribution and Prevalence of HCV Genotypes:
Genotype 1b is most common worldwide, followed by G3



Messina JP et al, *Hepatology*, 2015; 61: 77-87.

Geno 2/3 Therapy Today

SOF + RBV vs PEG + RBV in G2 and G3: FISSION
SVR12 by HCV Genotype and Cirrhosis Status



Lawitz et al. 2014

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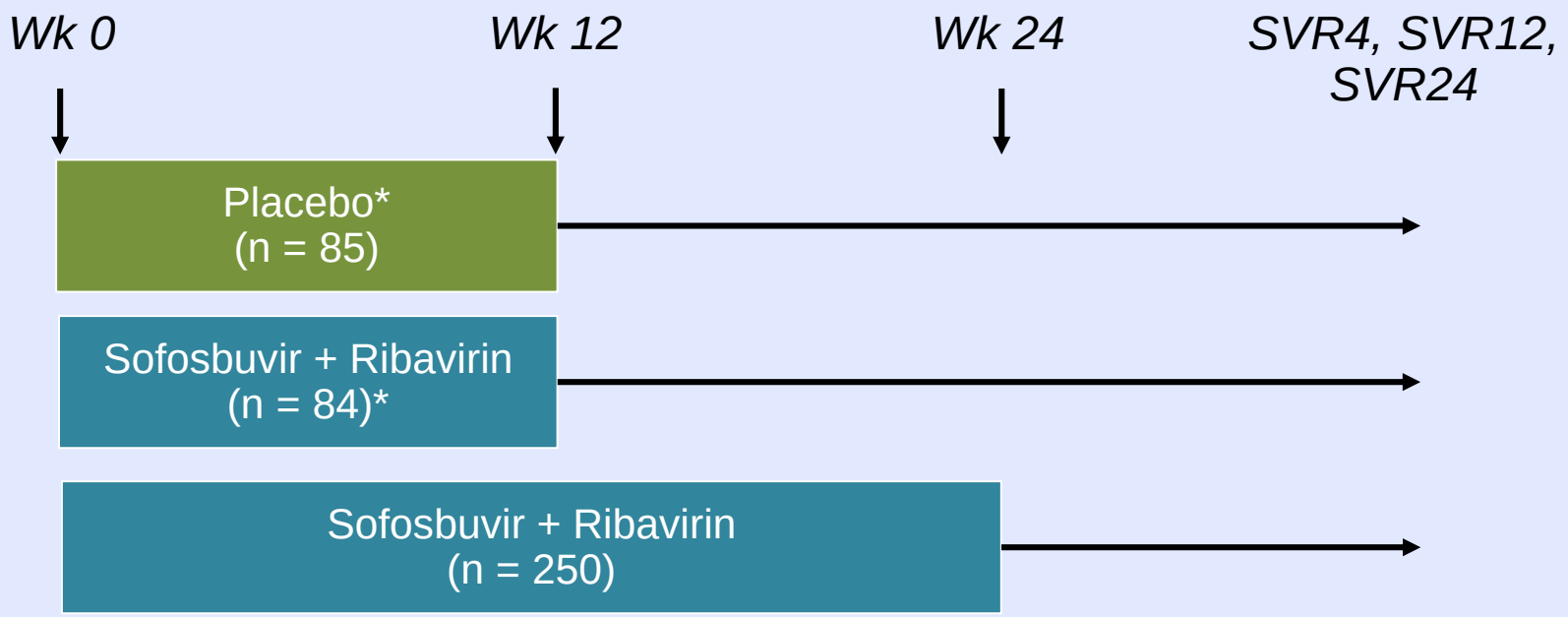
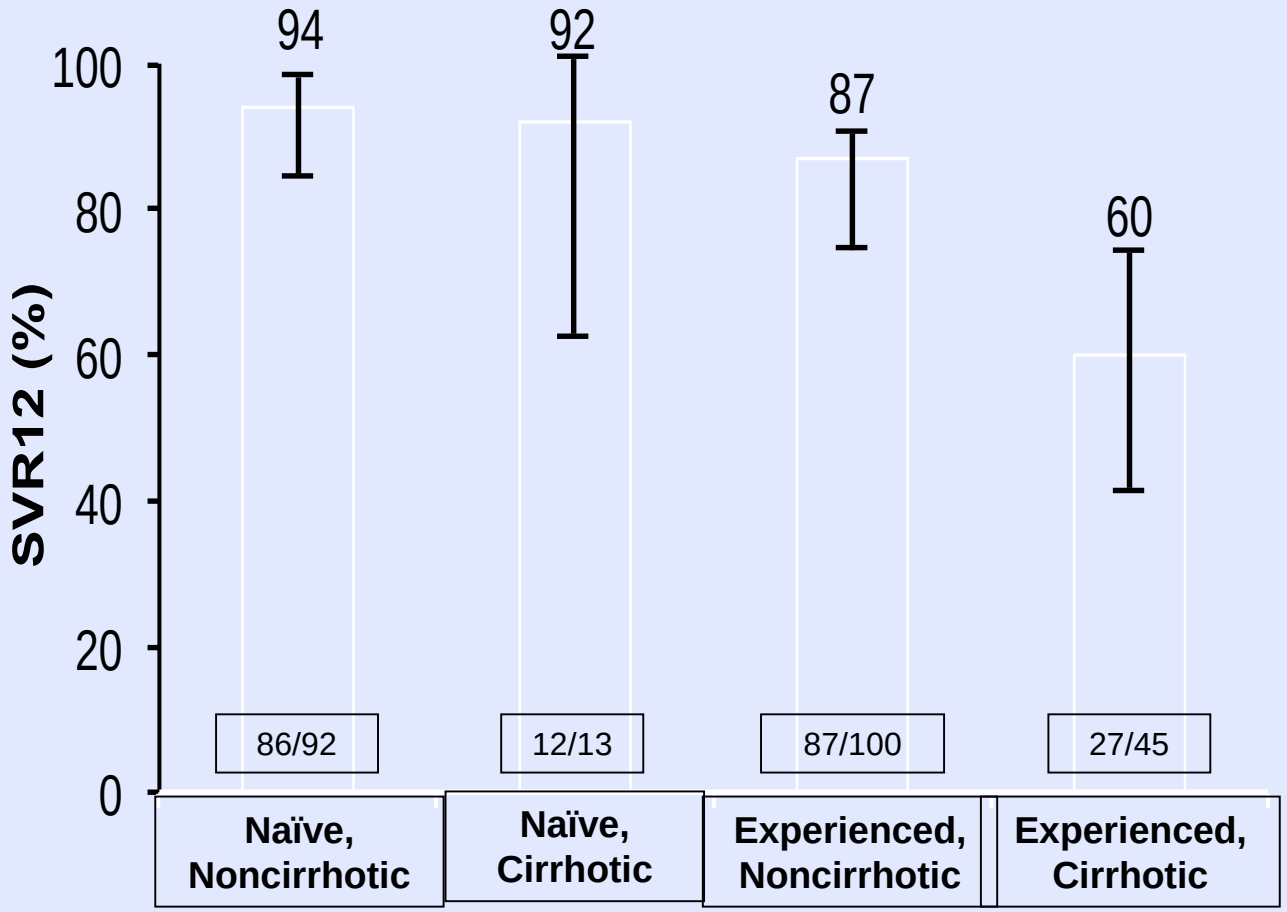
VALENCE: Study Design



*Protocol amended to eliminate placebo arm and to extend treatment duration to 24 weeks for patients with genotype 3 HCV irrespective of prior treatment history.

Zeuzem S, et al. *N Engl J Med*. 2014;370:1993-2001

SVR12 in GT 3 Patients Treated for 24 Weeks



Zeuzem S, et al. *N Engl J Med*. 2014;370:1993-2001

AASLD/IDSA Recommendations for Genotype 2 HCV Treatment-Naive Pts

Population	Recommended Regimen	Duration
Treatment naive and previous relapsers, genotype 2	Sofosbuvir 400 mg + RBV 1000-1200 mg/day	12 wks

- Alternative regimens: none
- Regimens specifically not recommended:
  - PegIFN/RBV x 24 wks
  - Monotherapy with pegIFN, RBV, or DAA
  - TVR-, BOC-, SMV-based regimens

AASLD/IDSA treatment recommendations.

AASLD/IDSA Recommendations for Genotype 2 HCV Treatment-Experienced Pts

Population	Recommended Regimen	Duration
Nonresponse to previous treatment with pegIFN/RBV	Sofosbuvir 400 mg + RBV 1000-1200 mg/day	12 wks*

Population	Recommended Regimen	Duration
Nonresponse to previous treatment with pegIFN/RBV with IFN eligibility	Sofosbuvir 400 mg + pegIFN + RBV 1000-1200 mg/day	12 wks

- Regimens specifically not recommended:
  - PegIFN/RBV ± TVR or BOC
  - Monotherapy with pegIFN, RBV, or DAA

AASLD/IDSA treatment recommendations.

AASLD/IDSA Recommendations for Genotype 3 HCV Treatment-Naive Pts

Population	Recommended Regimen	Duration
Regardless of IFN eligibility	Sofosbuvir 400 mg + RBV 1000-1200 mg/day	24 wks
Population	**Recommended Regimen**	**Duration**
Only consider if eligible for IFN	Sofosbuvir 400 mg + pegIFN + RBV 1000-1200 mg/day	12 wks

- Not recommended:
  - PegIFN/RBV for 24-48 wks
  - Monotherapy with pegIFN, RBV, or a DAA
  - Telaprevir, boceprevir, simeprevir

AASLD/IDSA treatment recommendations.

AASLD/IDSA Recommendations for Genotype 3 HCV Treatment-Experienced

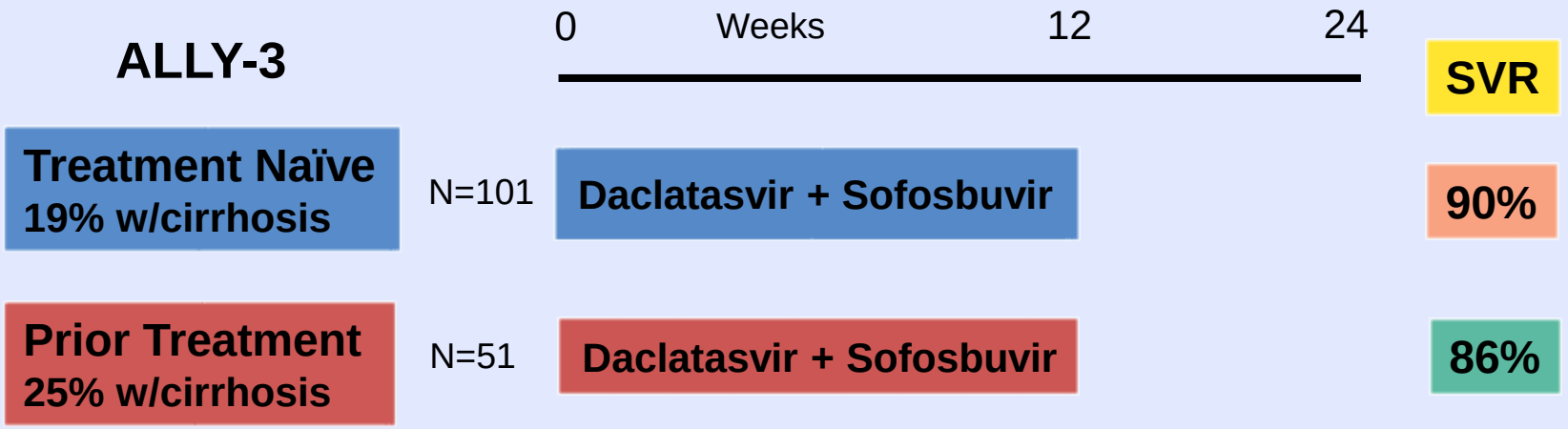
Population	Recommended Regimen	Duration
Regardless of IFN eligibility	Sofosbuvir 400 mg + RBV 1000-1200 mg/day	Regardless of IFN eligibility

Population	Recommended Regimen	Duration
Consider only if eligible for IFN	Sofosbuvir 400 mg + pegIFN + RBV 1000-1200 mg/day	12 wks

- Not recommended:
  - PegIFN/RBV ± telaprevir, boceprevir, simeprevir
  - Monotherapy with pegIFN, RBV, or a DAA

AASLD/IDSA treatment recommendations.

All-Oral 12-week Combination of Daclatasvir (NS5A) and Sofosbuvir (NUC) in Patients with Genotype 3: ALLY-3



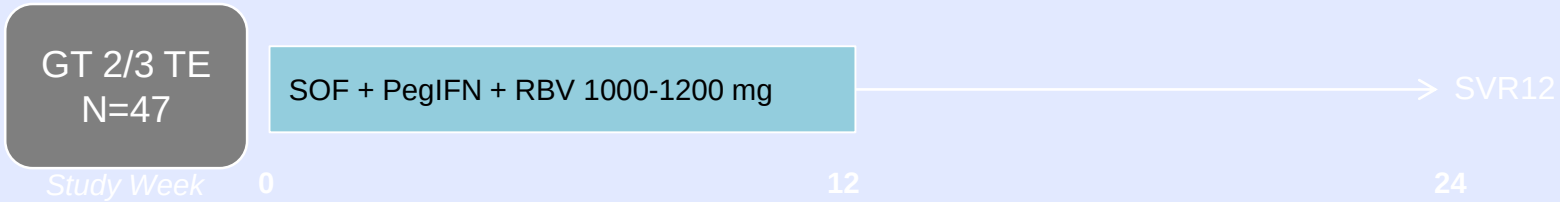
SVR F0-F3 = 96% (105/19)
SVR F4 = 63% (20/32)

- **Key demographics: Cirrhosis= 21%, Prior SOF failures = 7**
- **Most AE mild fatigue, headache, nausea, diarrhea**
- **Relapse occurred in 16/152 (11%), most relapsers were cirrhotic**

Nelson, AASLD 2014, LB-3

LONESTAR-2 Study Design and Demographics

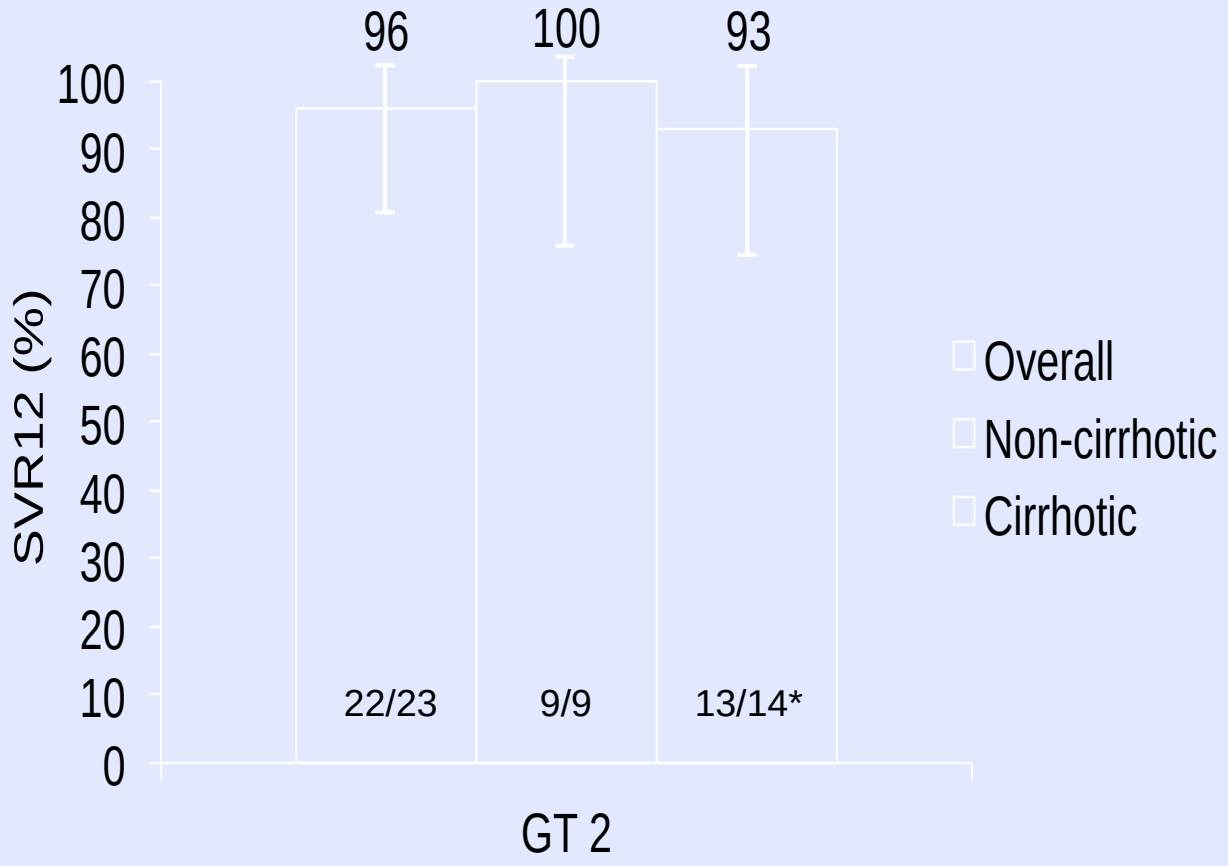
Open-label, Phase 2 study of the efficacy of SOF + PegIFN + RBV for 12 weeks in treatment-experienced patients with GT 2 or 3



Mean age (range), y	56 (39–72)
Male, n (%)	32 (68)
White, n (%)	45 (96)
Hispanic, n (%)	21 (45)
Mean BMI (range), kg/m^2	31 (21–53)
IL28B CC, n (%)	17 (36)
HCV GT 3, n (%)	24 (51)
Mean BL HCV RNA (range), $\log_{10}$ IU/mL	6 (4–7)
Cirrhosis, n (%)	26 (55)
Prior relapse/breakthrough, n (%)	40 (85)

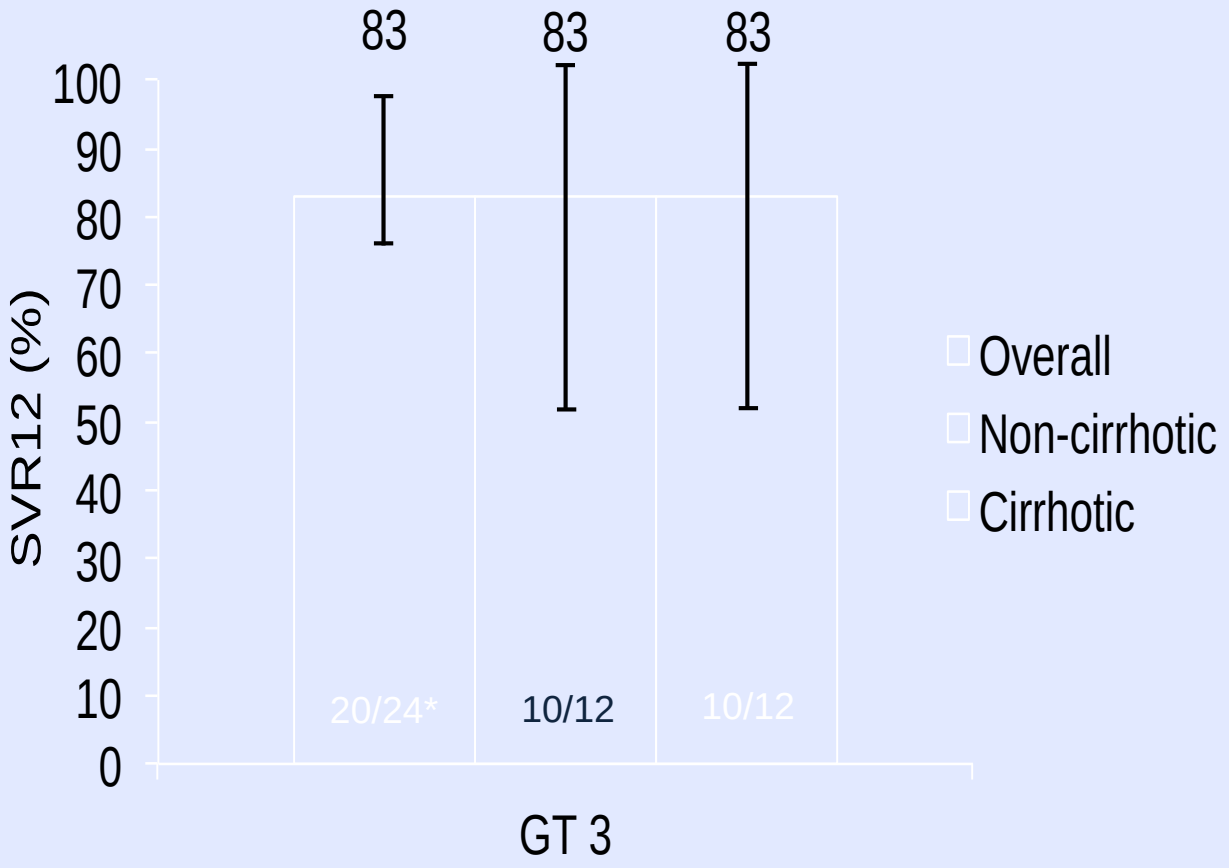
Lawitz E, et al. AASLD 2013. Washington, DC. Oral #LB-4

SOF + PegIFN + RBV in HCV GT 2 Treatment-Experienced Patients LONESTAR-2 Virologic Response



*The 1 cirrhotic patient who did not achieve SVR prematurely discontinued therapy without <LLOQ
LLOQ, lower limit of quantification
Lawitz E, et al. AASLD 2013. Washington, DC. Oral #LB-4

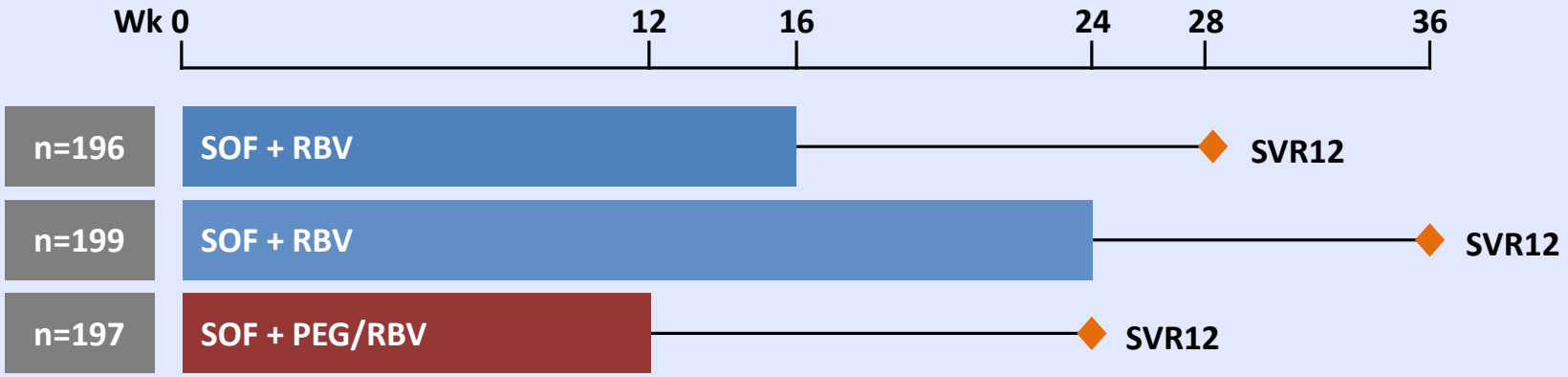
SOF + PegIFN + RBV in HCV GT 3 Treatment-Experienced Patients LONESTAR-2 Virologic Response



*2 relapses; 2 lost to follow-up

Lawitz E, et al. AASLD 2013. Washington, DC. Oral #LB-4

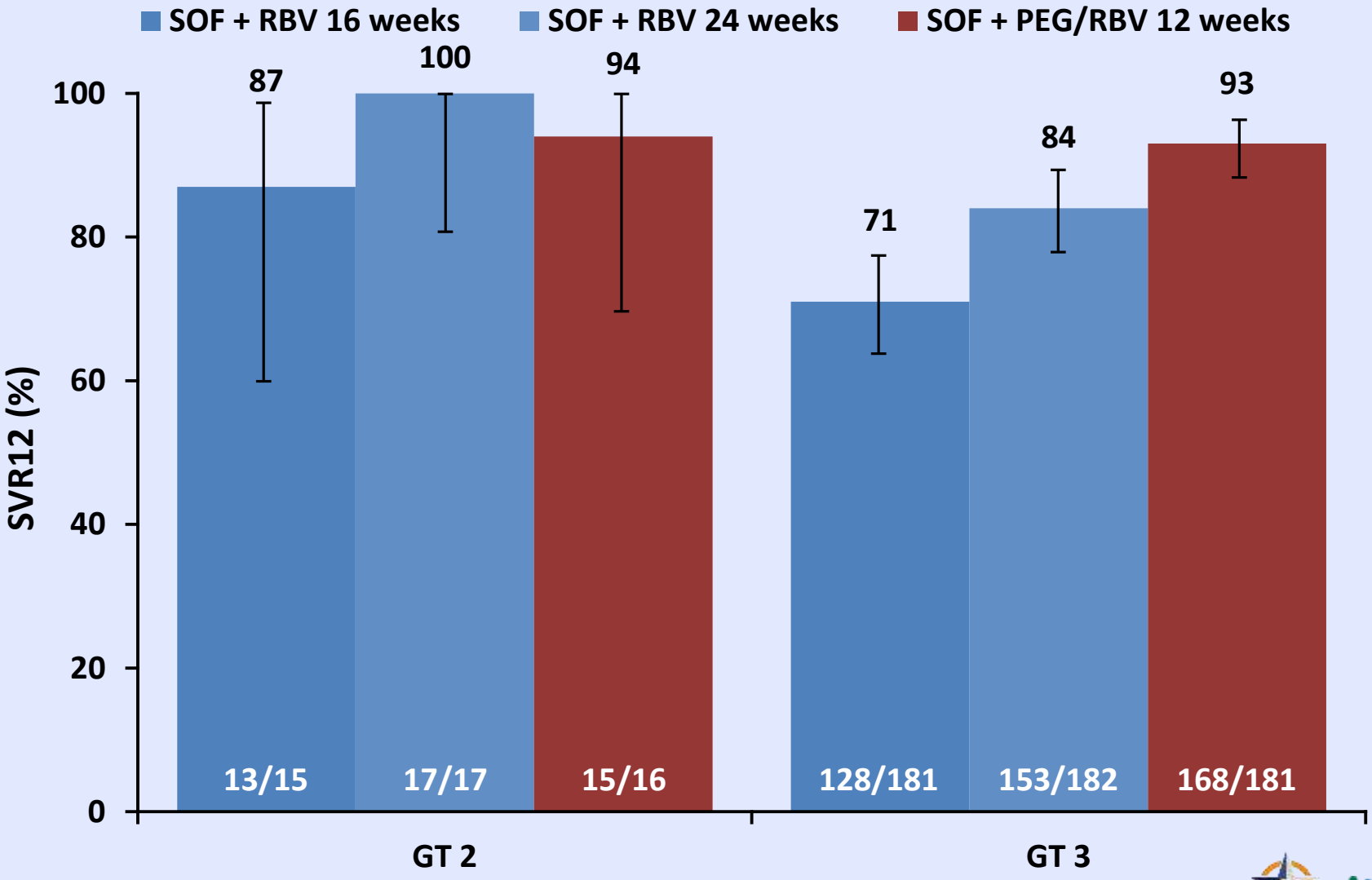
SOF/RBV/PegIFN for 12 Weeks vs. SOF/RBV for 16 or 24 Weeks in GT 2 or 3



	SOF + RBV 16 weeks n=196	SOF + RBV 24 weeks n=199	SOF + PEG/RBV 12 weeks n=197	Total n=592
Mean age, y (range)	51 (20-69)	49 (23-71)	50 (19-73)	50 (19-73)
Male, n (%)	134 (68)	129 (65)	132 (67)	395 (67)
Asian, n (%)	28 (14)	26 (13)	25 (13)	79 (13)
Mean BMI, kg/m^2 (range)	28 (18-50)	28 (18-55)	28 (19-45)	28 (18-55)
IL28B CC, n (%)	75 (38)	73 (37)	78 (40)	226 (38)
HCV genotype 3, n (%)	181 (92)	182 (92)	181 (92)	544 (92)
Mean baseline HCV RNA, $\log_{10}$ IU/mL (range)	6.3 (4.0-7.6)	6.2 (3.3-7.6)	6.3 (3.7-7.5)	6.3 (3.3-7.6)
Treatment experienced, n (%)	105 (54)	105 (53)	103 (52)	313 (53)
Cirrhosis, n (%)	72 (37)	73 (37)	74 (38)	219 (37)

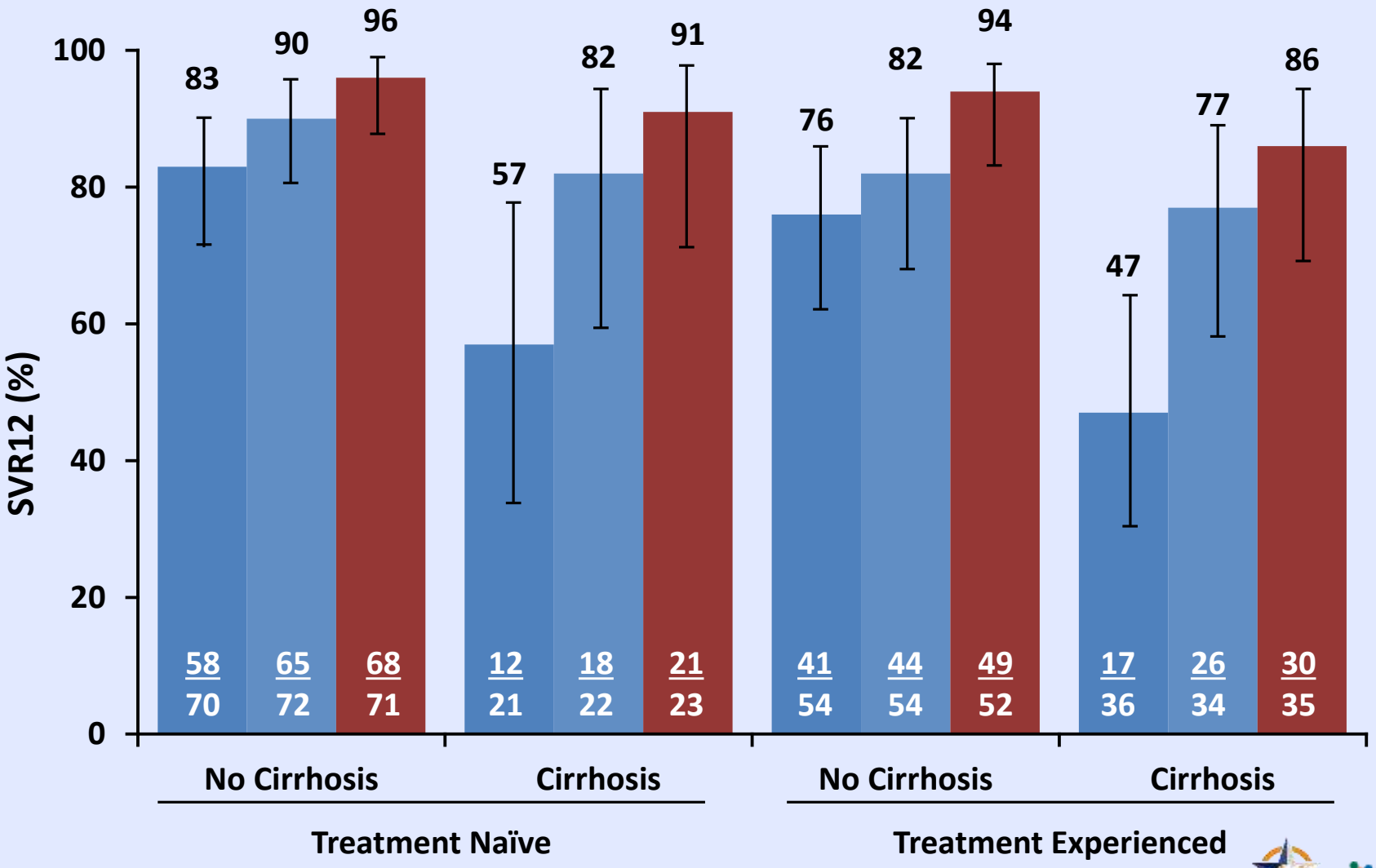
Foster G, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. LO5.

SVR12



Foster G, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. LO5.

SVR12 By Prior Treatment and Cirrhosis



Foster G, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. LO5.

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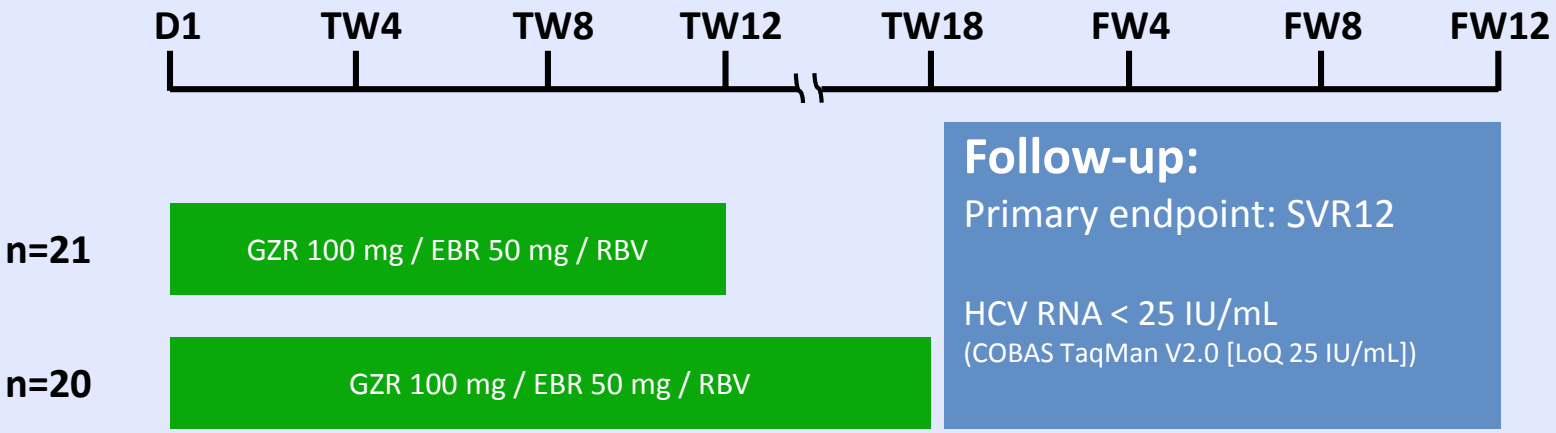
Safety

	Patients, n (%)	SOF + RBV 16 weeks n=196	SOF + RBV 24 weeks n=199	SOF + PEG/RBV 12 weeks n=197
Overall Safety	AEs	185 (94)	188 (95)	195 (99)
	Grade 3-4 AE	11 (6)	7 (4)	15 (8)
	Serious AE	8 (4)	10 (5)	12 (6)
	Treatment D/C due to AE	3 (2)	2 (1)	1 (<1)
	Death	0	0	0
Laboratory Abnormalities	Grade 3-4	30 (15)	29 (15)	74 (38)
	Hb <10g/dL	7 (4)	12 (6)	24 (12)
	Hb <8.5 g/dL	0	0	2 (1)
	Platelets <50,000/mm^3	1 (<1)	0	9 (5)

Foster G, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. LO5.

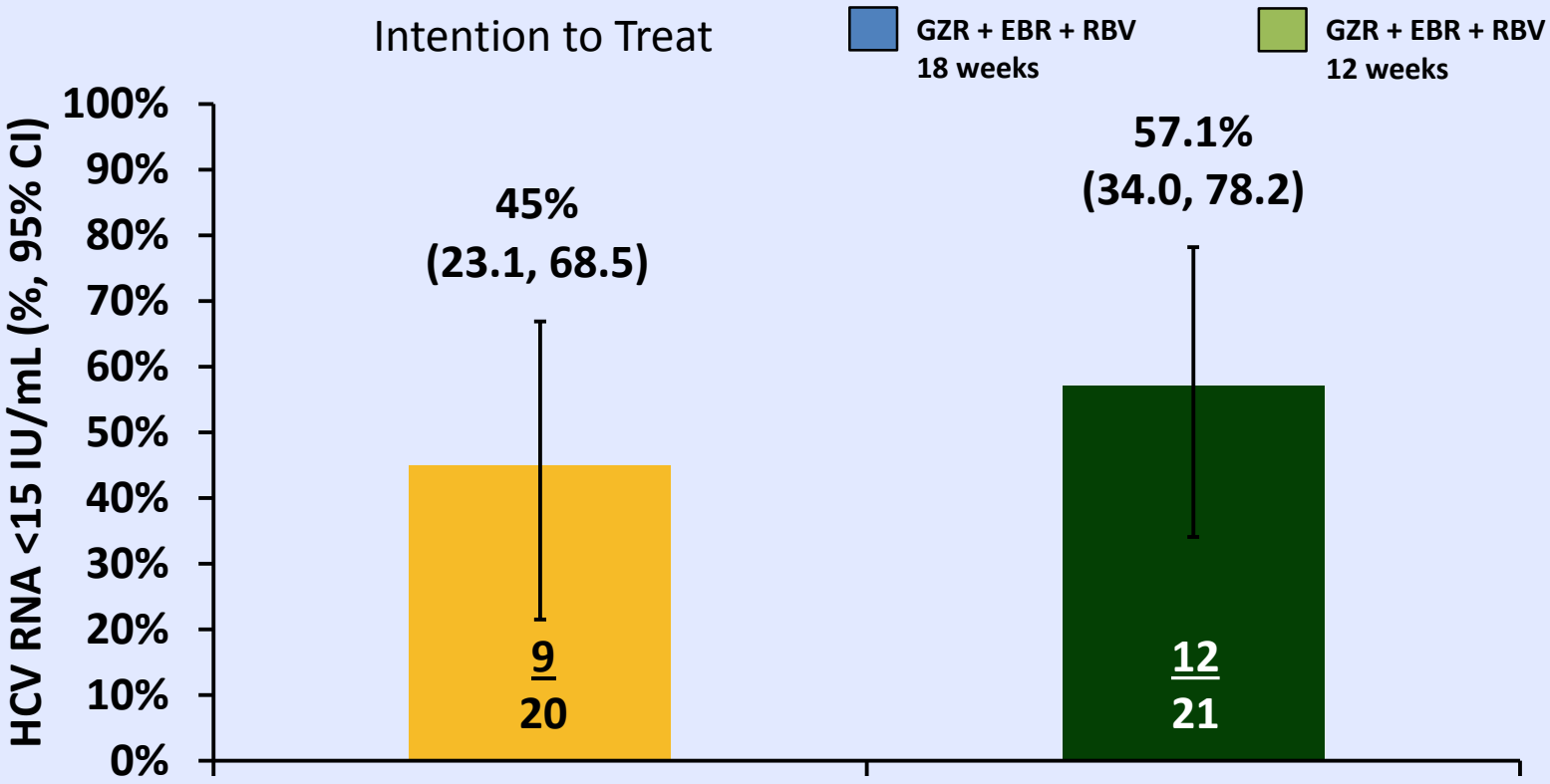
C-WORTHY: Study Design



- Treatment-naive patients with HCV GT3 infection
- Cirrhotic and HIV coinfected patients excluded
- Randomized 1:1
- Treatment durations of 12 or 18 weeks
- All patients received weight-based ribavirin

Gane E, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. P0776.

C-WORTHY: SVR12 Results

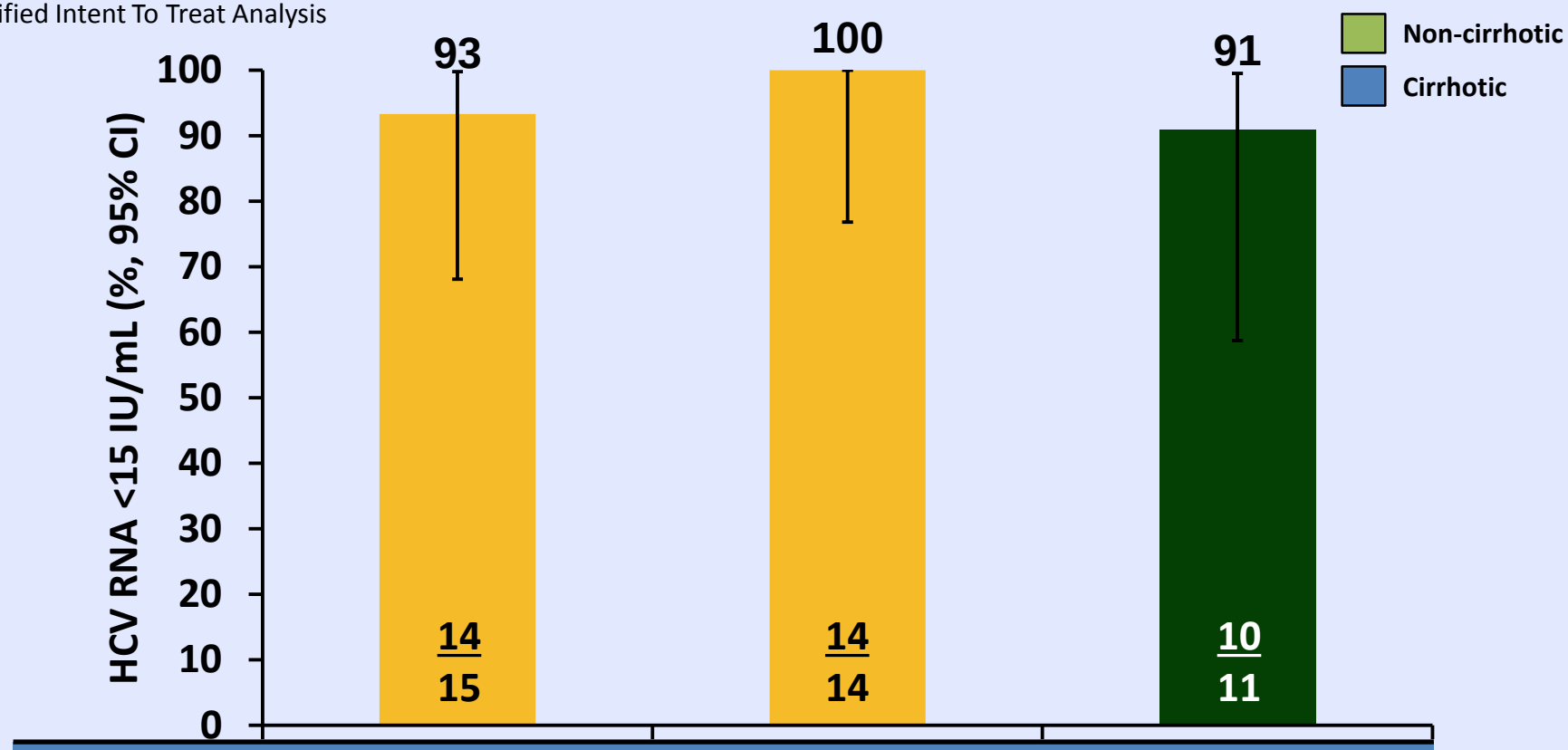


Non-virologic failure, n	1	2
Rebound, n	3	2
Breakthrough, n	6	5
Futility, n	1	0
Relapse, n	0	0

Gane E, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. P0776.

C-SWIFT: SVR Results - HCV 3

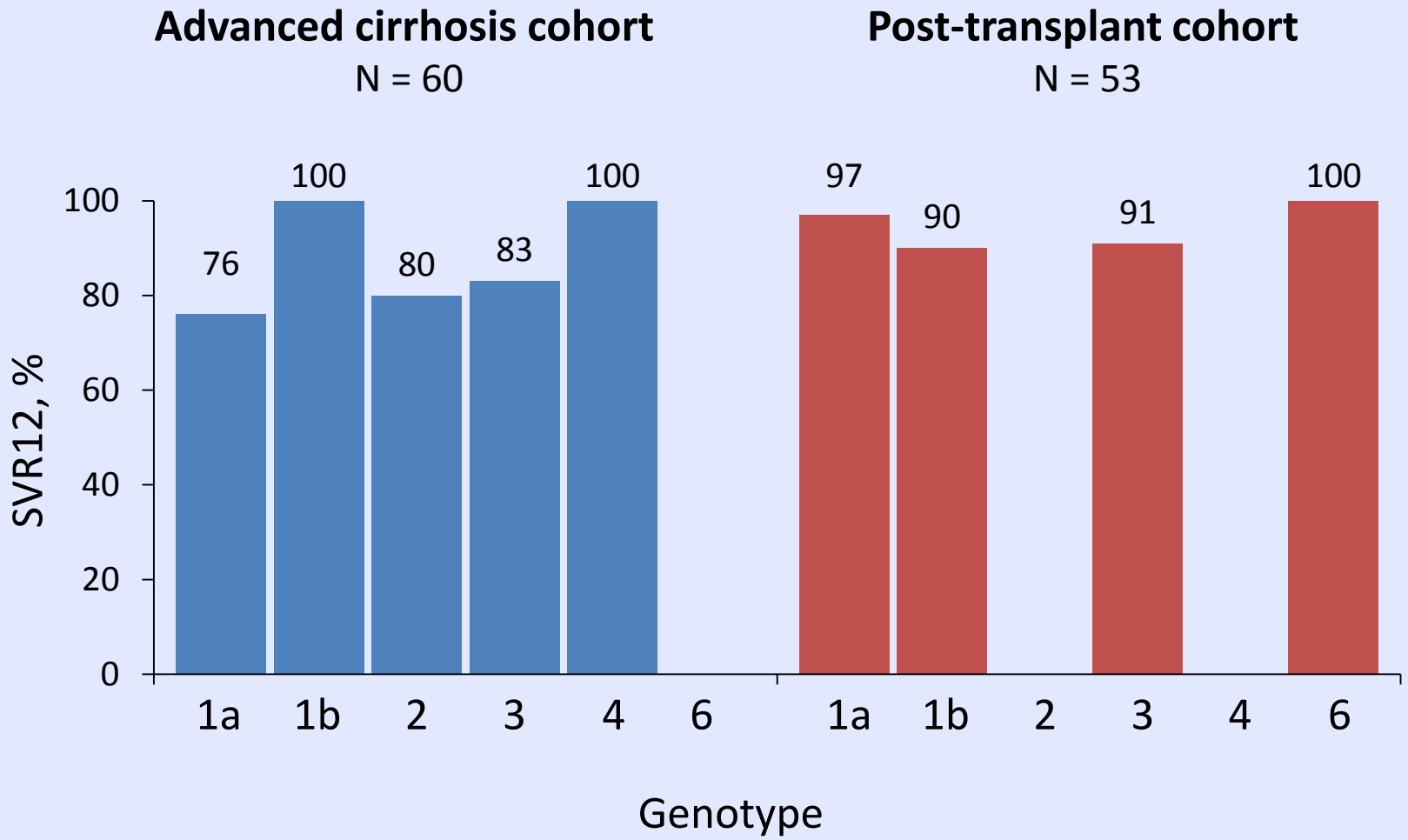
Modified Intent To Treat Analysis



Treatment Duration	8 Weeks	12 Weeks	12 Weeks
Breakthrough	0	0	0
Relapse	1	0	1
Early discon.	0	0	1*

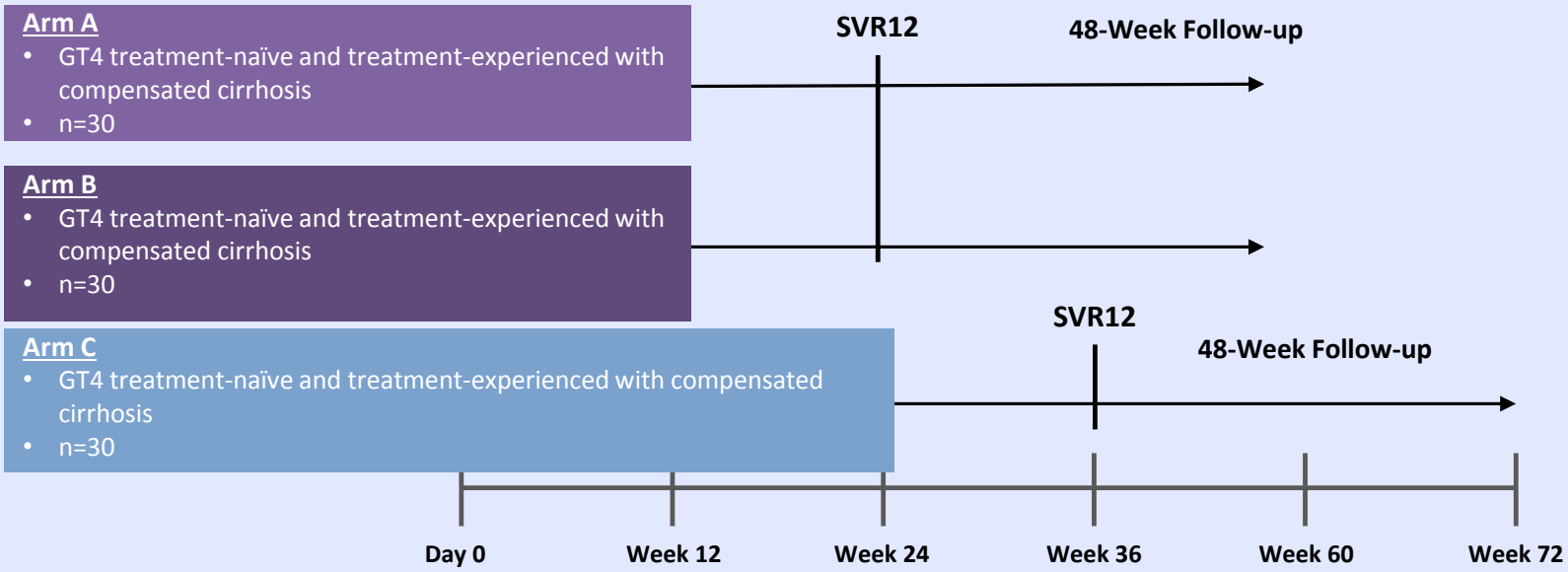
Poordad F, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O006.

SVR12 by HCV Genotype in Ally-1

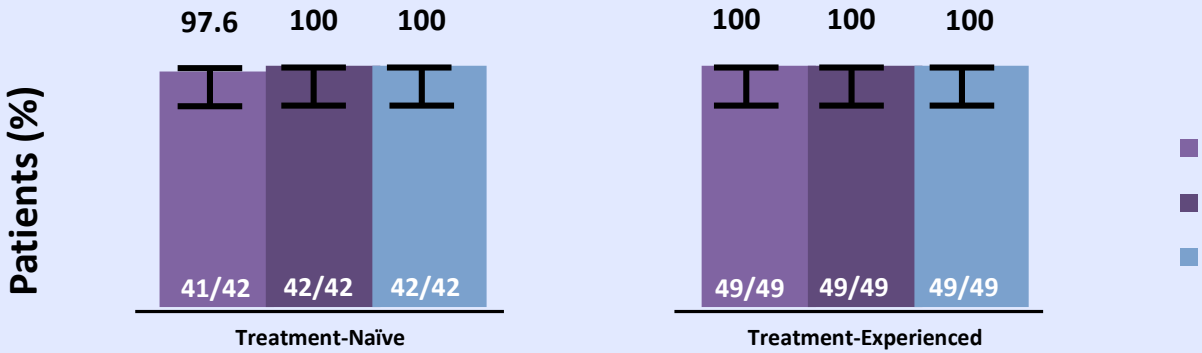


Poordad, et al. EASL 2015

OBV/PTV/r with RBV in HCV GT4 +/- Cirrhosis



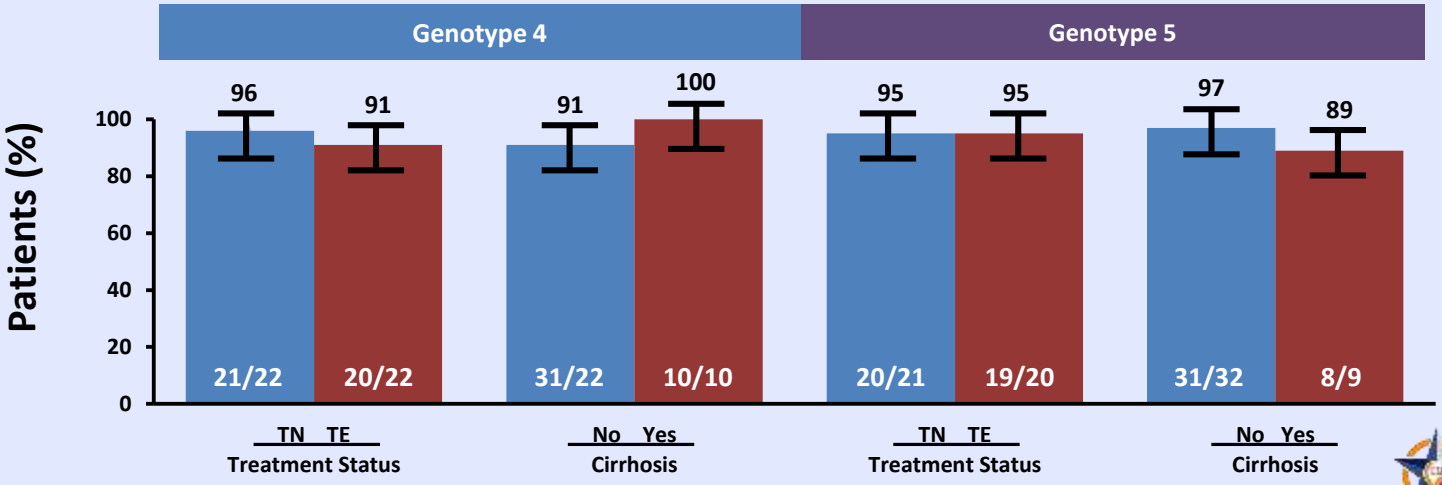
PEARL-I: Efficacy of OBV/PTV/r + RBV in Treatment-Naïve and Treatment-Experienced Noncirrhotic Subjects With GT4 Infection



Doss W, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. P1351.

LDV/SOF for GT4 or GT5 HCV Infection

	Genotype 4		Genotype 5	
	Naïve n=22	Experienced n=22	Naïve n=21	Experienced n=20
Mean age, years (range)	52 (21-69)	50 (30-62)	61 (40-78)	64 (50-79)
Male, n (%)	11 (50)	17 (77)	11 (52)	10 (50)
White, n (%)	19 (86)	17 (77)	21 (100)	20 (100)
Mean BMI, kg/m^2 (range)	25 (19-35)	25 (20-36)	24 (18-30)	27 (19-39)
Cirrhosis, n (%)	1 (5)	9-(41)	3 (14)	6 (30)
IL28B non-CC, n(%)	15 (68)	21 (95)	8 (38)	14 (70)
Mean HCV RNA, $\log_{10}$ IU/ml (range)	6.0 (5.1-6.8)	6.3 (5.6-7.5)	6.2 (5.3-6.9)	6.6 (5.7-7.1)



Aberel A, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O056.

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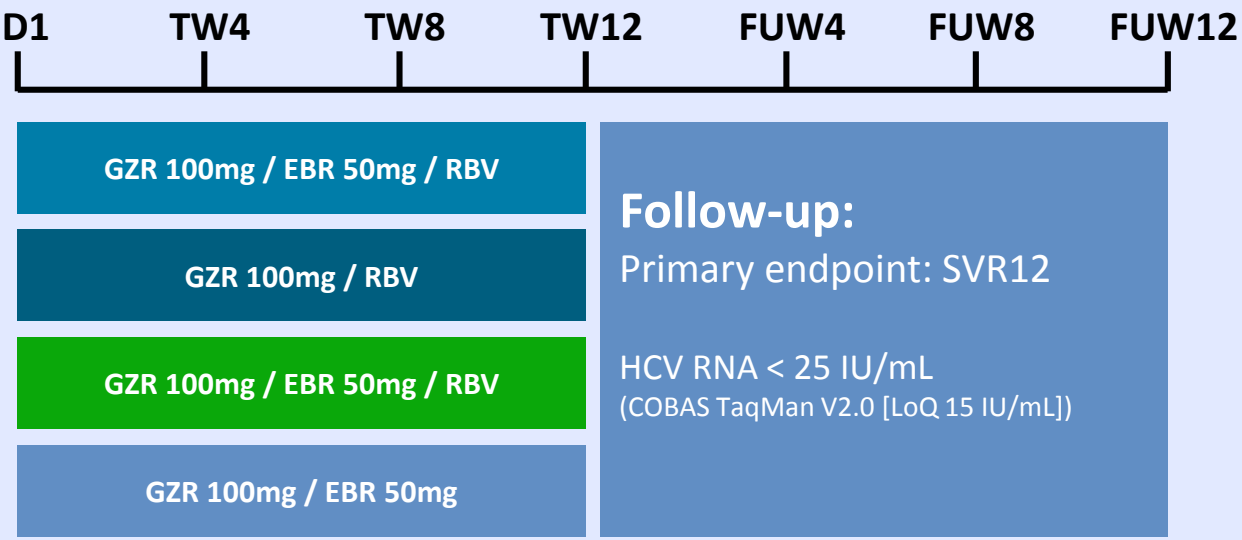
C-SCAPE: Study Design

Patients per arm (n)				
G2	G4	G5	G6	ALL
30	-	-	-	30
30	-	-	-	30
-	10	4	5	19
-	10	4	5	19

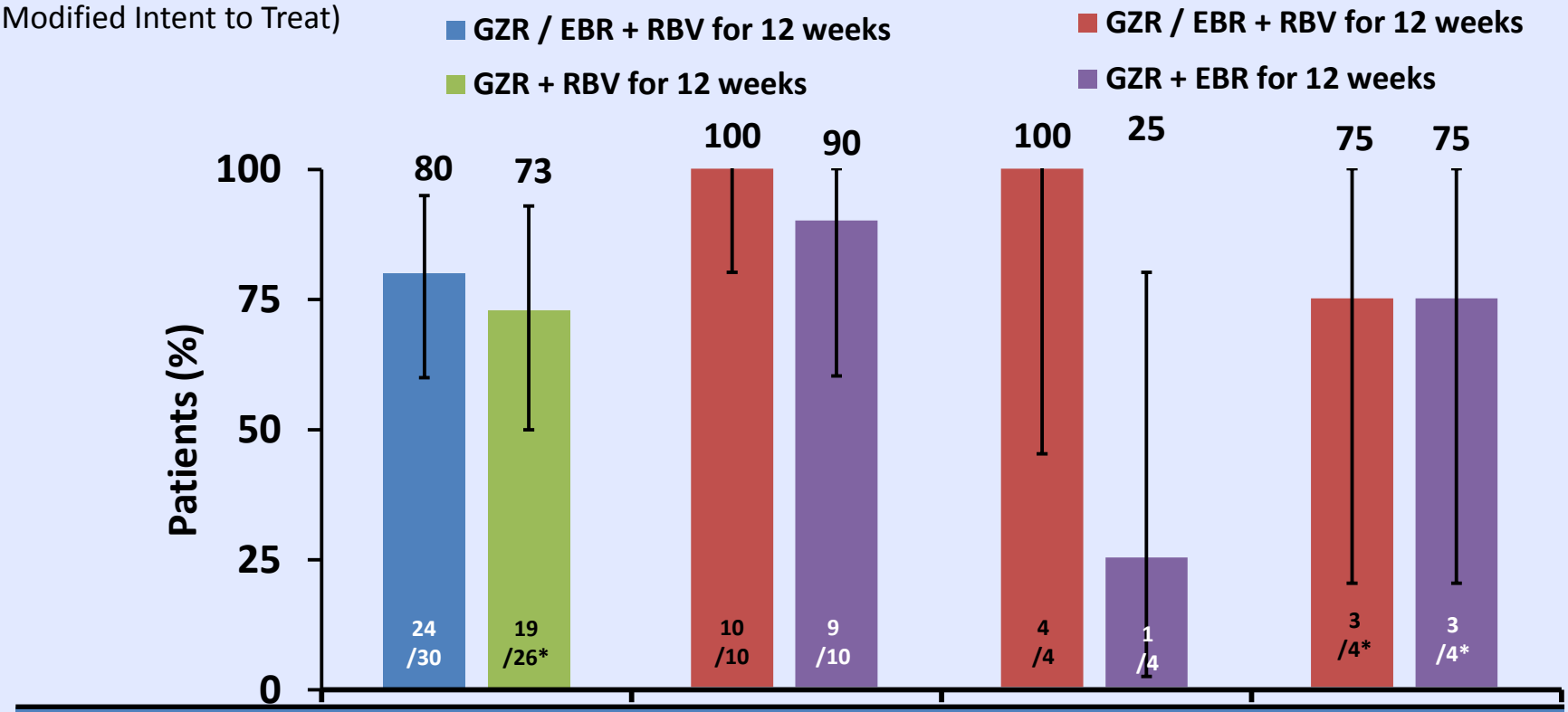


- Treatment-naive, GT2, 4, 5, 6
- Non-cirrhotic, HCV monoinfected
- G2 patients assessed for a polymorphism at amino position 31 within NS5A
  - Preclinical data demonstrate a lower potency for EBR in methionine (M) compared to leucine (L) at position 31

Brown A, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. P0771.

C-SCAPE: SVR12 Results

(Modified Intent to Treat)



	Genotype 2		Genotype 4		Genotype 5		Genotype 6	
Relapse (n)	3	3	0	0	0	2	1	0
Breakthrough (n)	1	3	0	0	0	1	0	1
Futility (n)	0	1†	0	0	0	0	0	0
LTFU/Admin discon (n)	2	0	0	1	0	0	0	0

Brown A, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. P0771.

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Summary

- We currently have good therapy for geno 2, but it uses RBV
  - Geno 2 cirrhotics can be challenging
- Geno 3 is the biggest challenge, esp cirrhotics
- Geno 4 responds well to most regimens
- Geno 5 has very little data
- Geno 6 appears to respond much like geno 1

Conclusion

- We may never have one therapy for all genotypes
- Small SVR differences between regimens will dictate how we treat them
- Cirrhotics clearly are different and need either longer duration, or different regimens in some cases