IFN-free therapy in naïve HCV GT1 patients

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Disclosures

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Consultant/Speaker : AbbVie, Achillion, BMS, Gilead, Janssen, Merck, Roche.

IFN-free therapy in naïve HCV GT1 patients

1 Introduction : Direct-acting antivirals (DAAs)

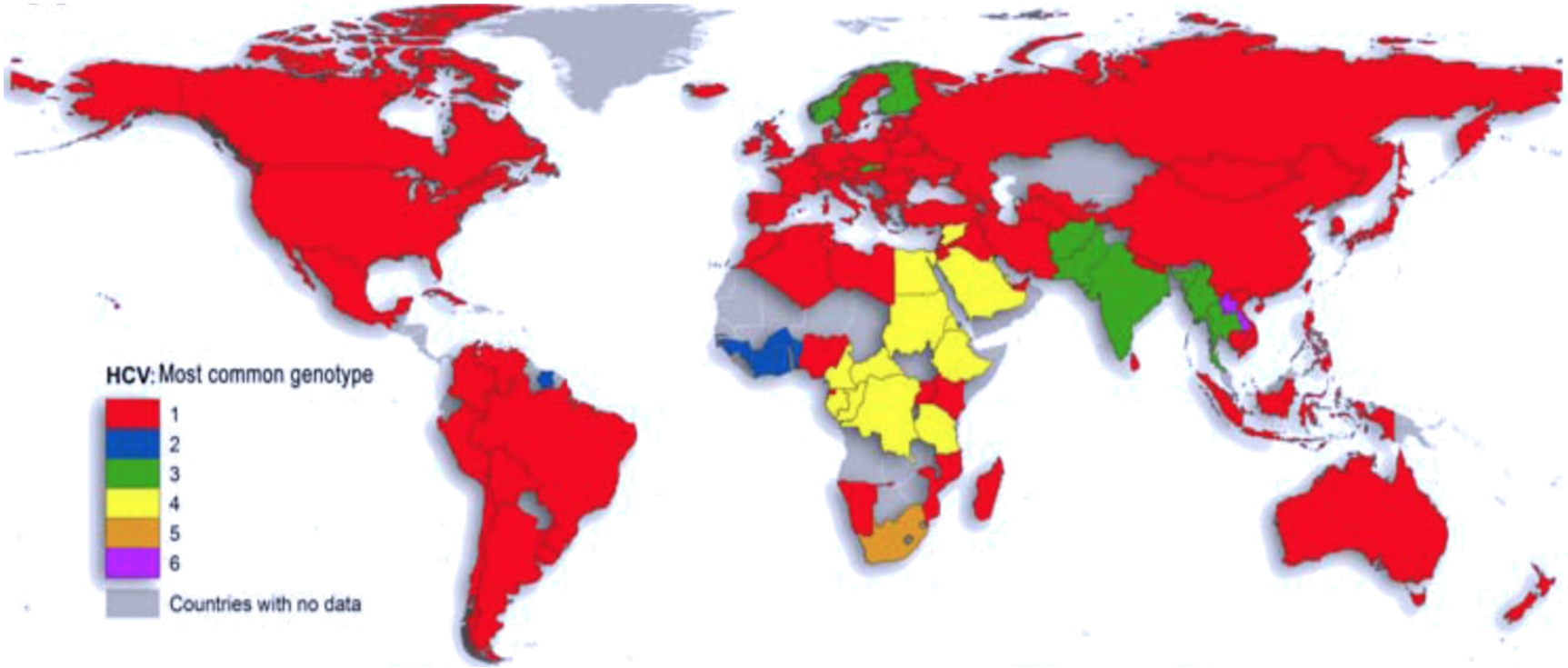
2 Real-life data

3 IFN-free treatment (available/phase III)

4 Take home messages

HCV Genotype Distribution Worldwide

- HCV a global health challenge with ~150-180 Million chronic HCV infections
- Genotype 1 is the most prevalent in most countries



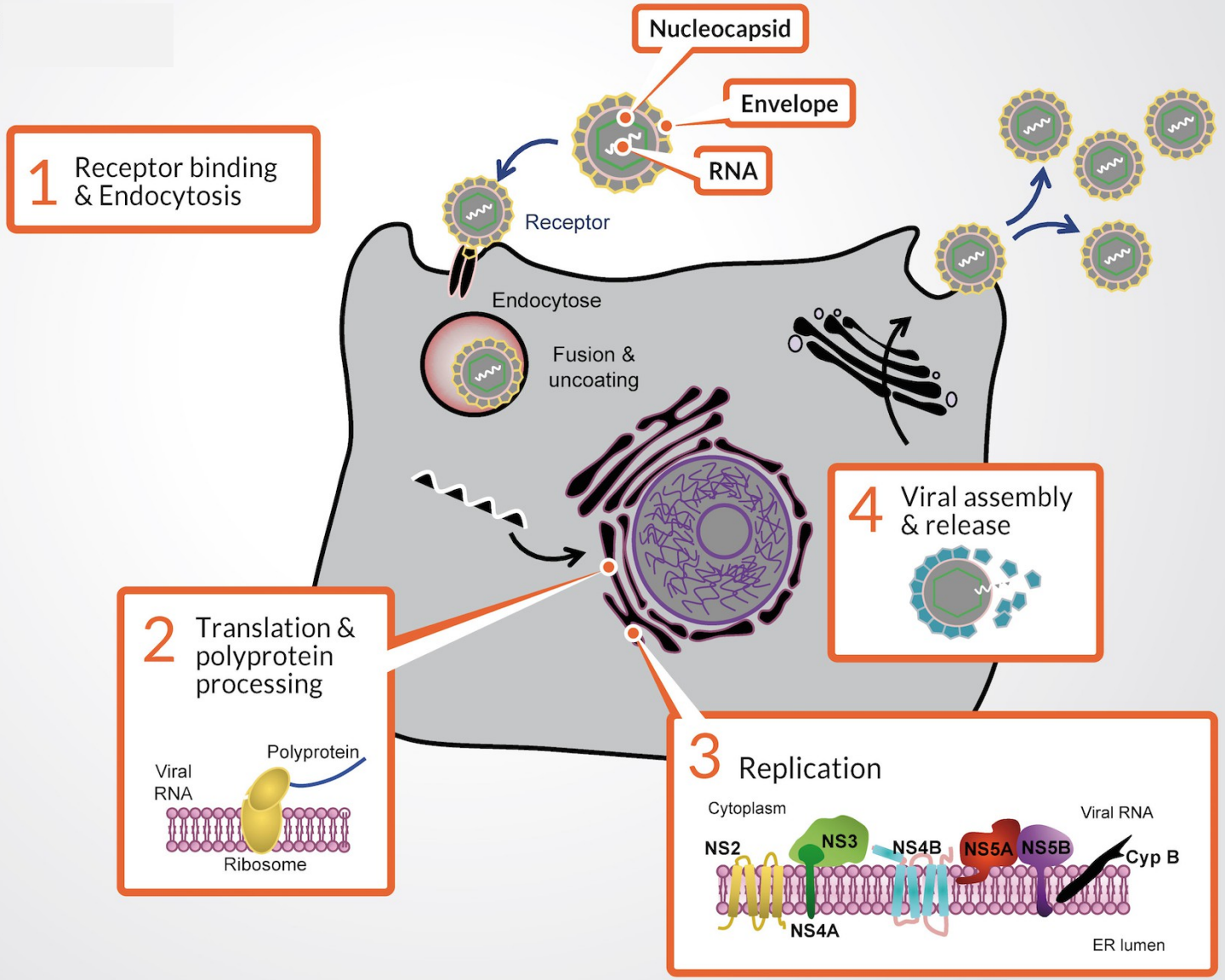
1. Gower, E., et al., J Hepatol 2014; 61:S45–S57; 2. Messina J. et al. Hepatology, 2015;61:77-87

Goals obtained with Sustained Virological Response (SVR)

- Eradicate the virus (HCV clearance) = cure
- Reduce Necroinflammation
- Stop the progression of fibrosis
- Prevent Cirrhosis & its complications
- Prevent Hepatocellular-carcinoma
- Increase Survival

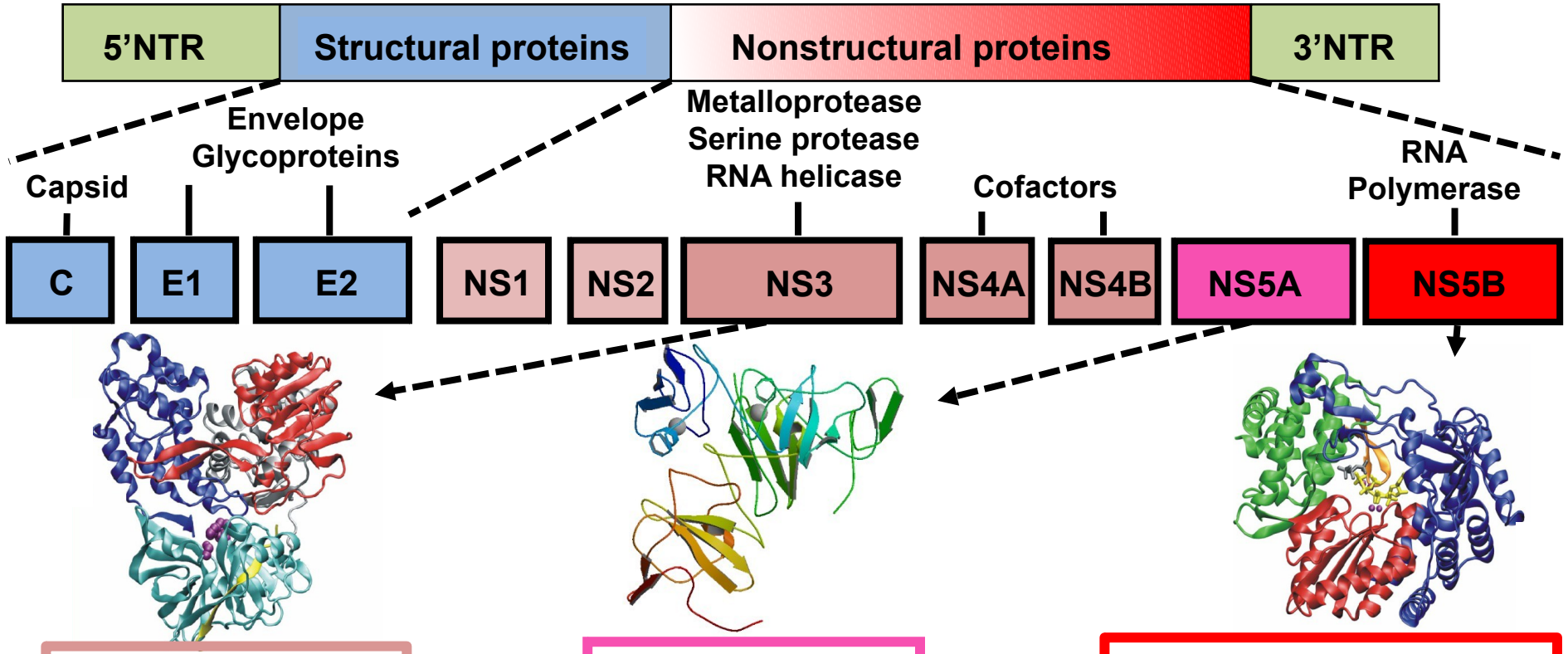
Maylin et al. Gastroenterology 2008; **3**: 821–9.
Asselah et al. Liver Int. 2015;35 S1:56-64.

Knowledge of the viral cycle



Asselah et al. Liver Int. 2015;35 S1:56-64.

Direct-acting antivirals (DAAs)



Protease Inhibitors
« …PREVIR»
- Telaprevir
- Boceprevir
- Simeprevir
- Asunaprevir
- ABT-450
- MK-5172
- Sovaprevir
- ACH-2684

NS5A Inhibitors
« …ASVIR»
- Daclatasvir
- Ledipasvir
- ABT-267
- GS-5816
- ACH-3102
- PPI-668
- GSK-2336805
- Samatasvir
- MK-8742

Polymerase Inhibitors
« ….UVIR »

Nucs	Non-Nucs
Sofosbuvir	ABT-333
VX-135	
IDX-20963	BMS-791325
ACH-3422	PPI-383
	GS-9669
	TMC-647055

Schinazi R, Halfon P, Marcellin P, Asselah T. Liver Int 2014; 34 S1:69-78.

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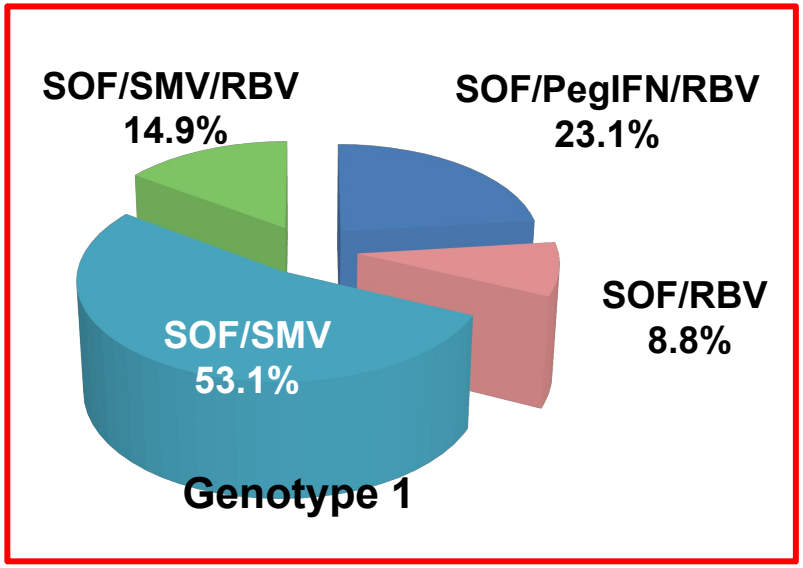
HCV-TARGET

Safety and Efficacy : Real Life Data

Real-world observational study of 2,063 patients treated with DAAs at academic (n=38) and community medical centers (n=15) in North America and Europe

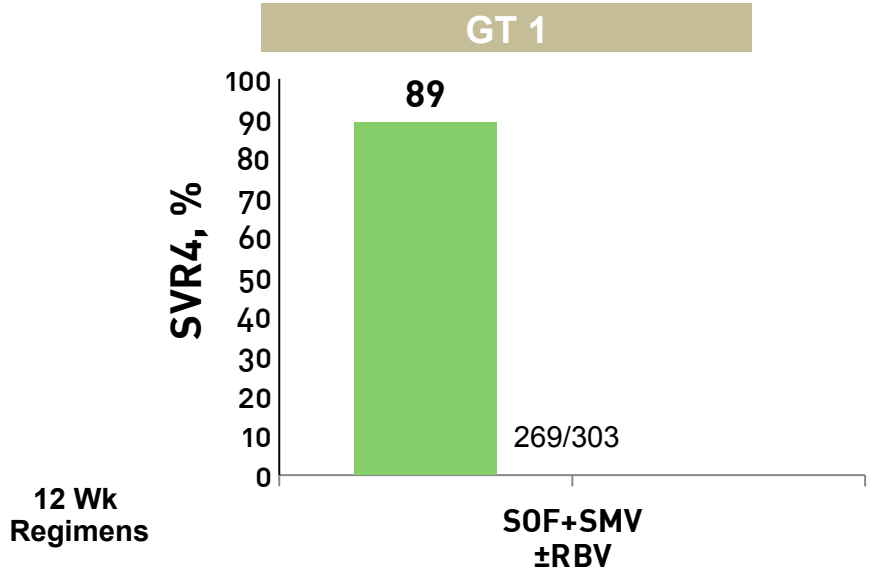
Started Therapy HCV-TARGET 2.0
N=2063

- **SOF/P/R** N=384
- **SOF/RBV** N=667
- **SOF/SMV** N=784
- **SOF/SMV/RBV** N=228



Jensen, AASLD, 2014, Oral #45

Efficacy and Safety of DAAs Regimens in Real Life



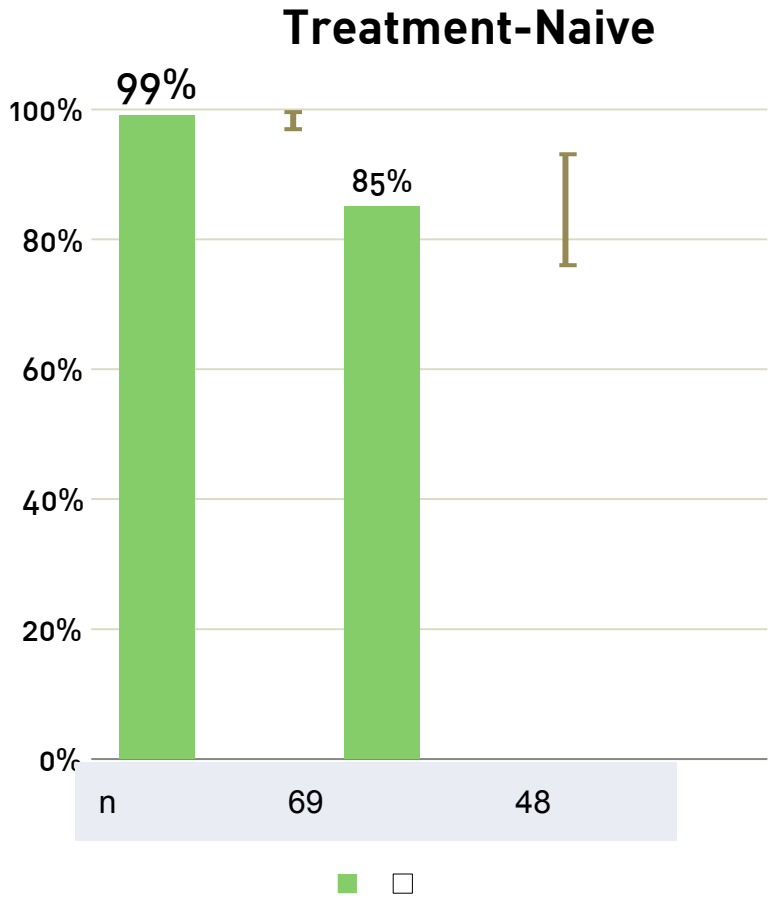
n (%)	SOF+SMV ±RBV n=228	SOF+SMV n=784	Total n=2063
Completed treatment	189 (82.9)	663 (84.6)	1613 (78.2)
Ongoing treatment	32 (14.0)	101 (12.9)	379 (18.4)
D/C Prematurely*	7 (3.1)	20 (2.6)	71 (3.4)
AE	5 (2.2)	16 (2.0)	44 (2.1)
Death	2 (0.9)	6 (0.8)	12 (0.6)

*Not all premature D/C are summarized. Full list available in final slides.

Jensen, AASLD, 2014, Oral #45

SVR12 for Genotype 1 Patients (Per Protocol)

- Data collected from academic (n=31) and community practices (n=119)
- ~52% of patients were treated with SOF/SMV



Discontinuation Rates by Reason	GT1 SMV + SOF ± RBV
Adverse Events	1.4% (4)
Non-Adherence	1.8% (5)

Dieterich, AASLD, 2014, Oral #46

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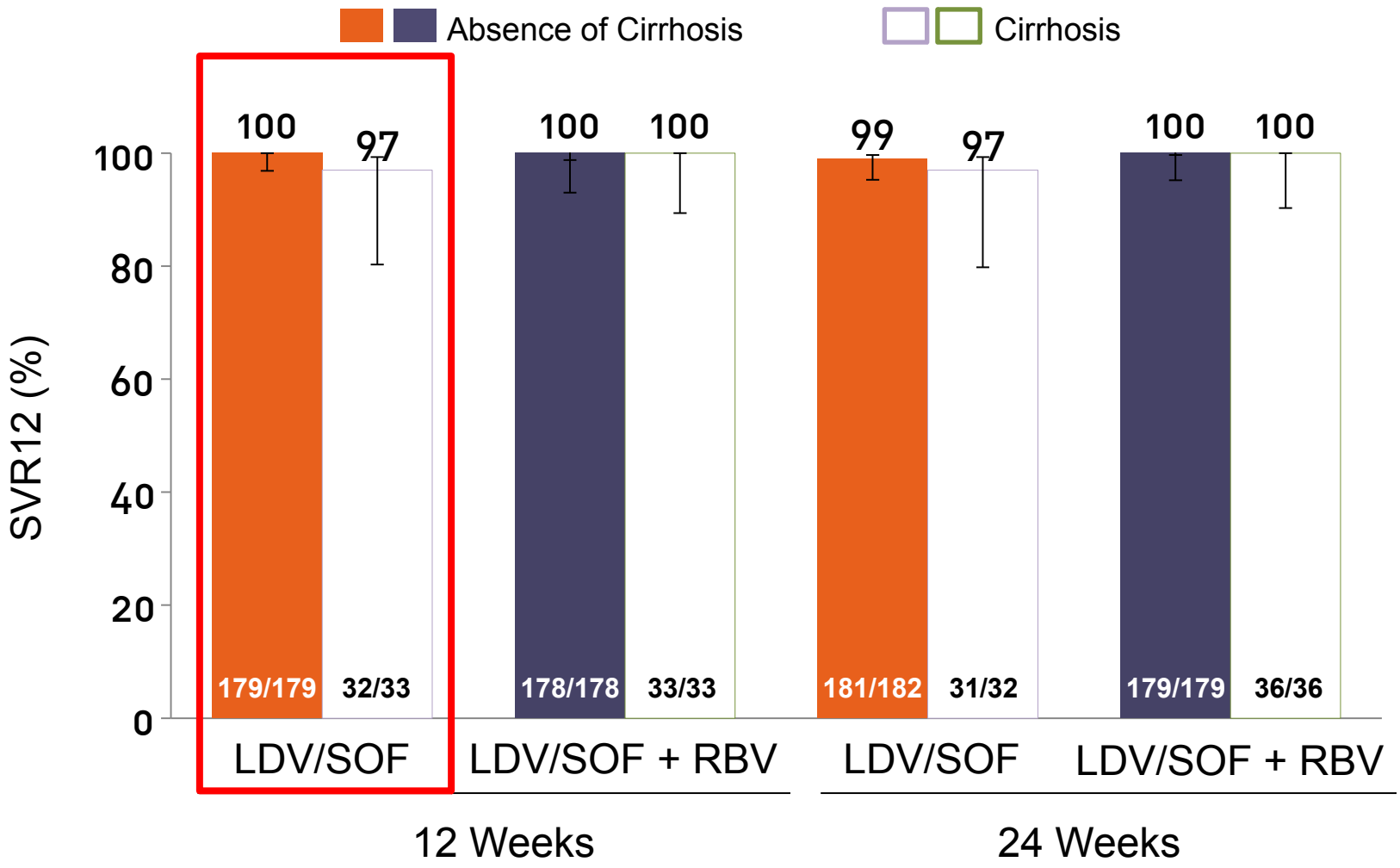
Direct-Acting Antivirals

	Nucleotide NS5B inhibitors	Non-nucleoside NS5B inhibitors	NS5A Replication complex inhibitors	Protease inhibitors
Gilead	Sofosbuvir	GS-9669	Ledipasvir GS 5816	GS-9451 GS-9857
Abbvie		Dasabuvir	Ombitasvir ABT-530	Paritaprevir/r ABT-493
Merck (MSD)	MK-3682 IDX-459	MK-8876	Elbasvir MK-8408 Samatasvir	Boceprevir Grazoprevir
BMS		BMS-325	Daclatasvir	Asunaprevir
Janssen (J&J)		TMC-055/r	GSK-2336805	Simeprevir Telaprevir
Achillion	ACH-3422		ACH-3102	Sovaprevir

Asselah et al. Liver Int. 2015;35 S1:56-64.

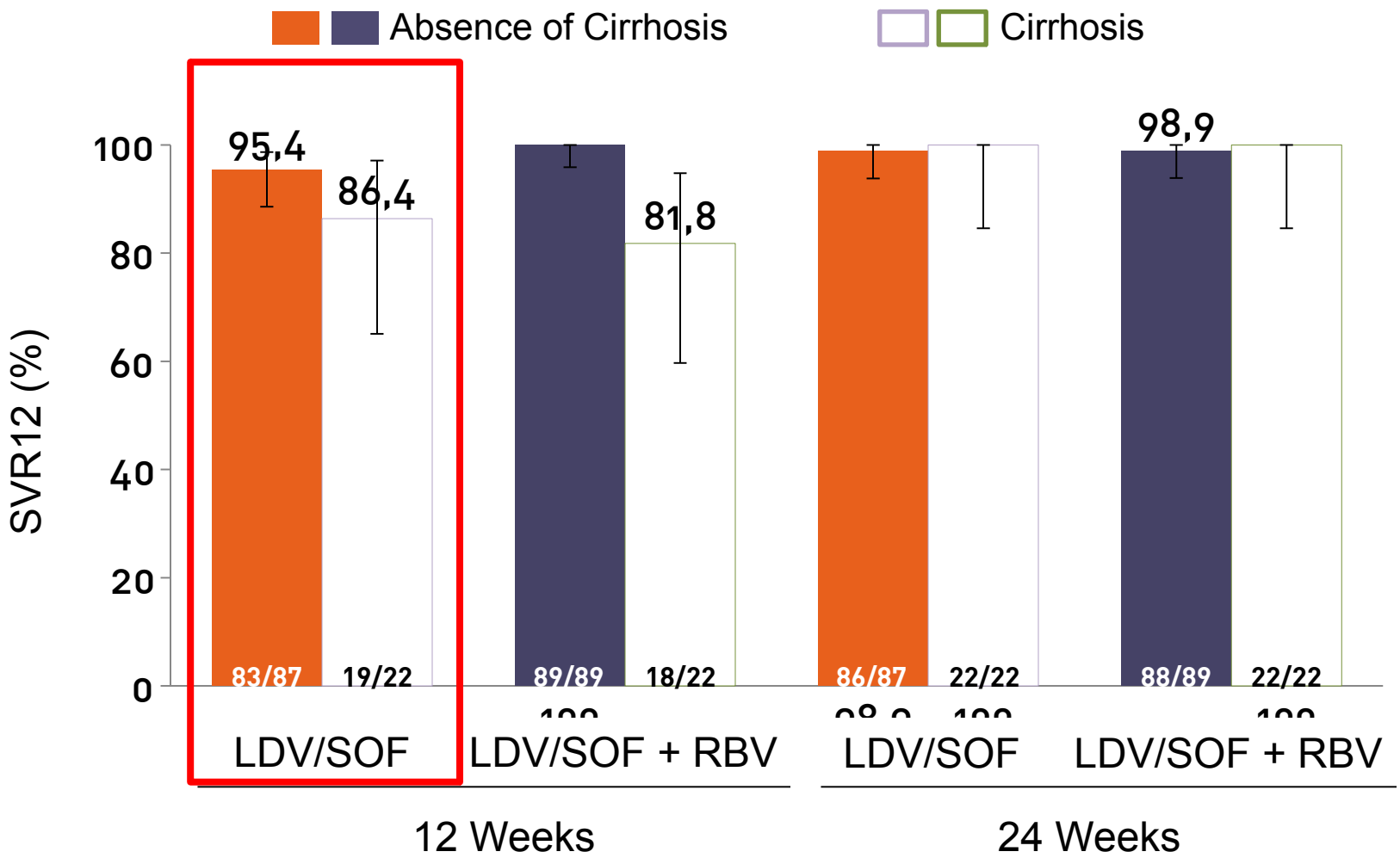
GT 1 Naïve (ION-1)
SVR12 by Presence of Cirrhosis



Error bars represent 95% confidence intervals

Afdhal N, et al. NEJM 2014; 370(20): 1889-98.

SVR12: Absence of Cirrhosis vs. Cirrhosis (ION-2)

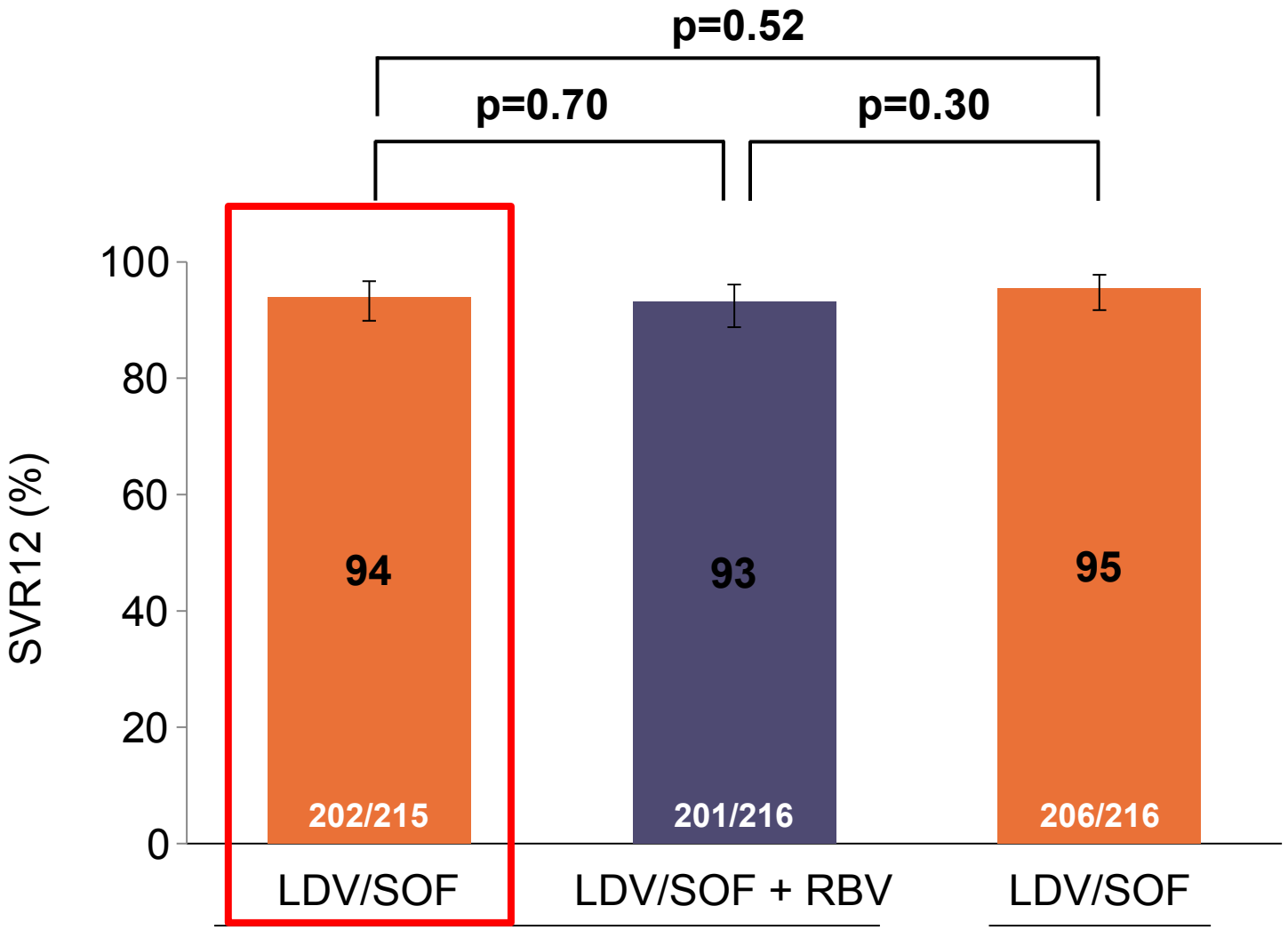


Error bars represent 95% confidence intervals

Asselah-PHC2015-9/18

Afdhal N, et al. NEJM 2014; 370(20): 1889-98.

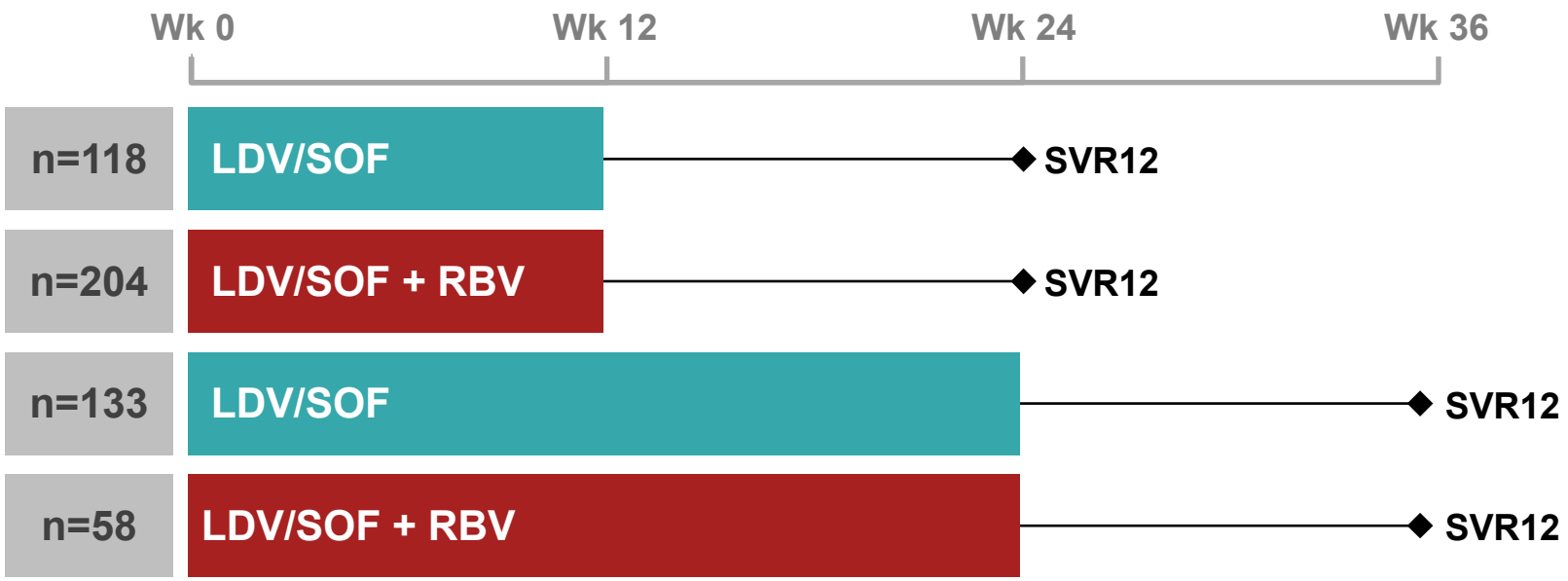
ION-3: Naïve Non-Cirrhotic GT 1 HCV Results: Non-Inferiority Comparison



Error bars represent 95% confidence intervals.

Kowdley K, et al. NEJM 2014;370(20):1879-88.

An Integrated Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with LDV/SOF±RBV

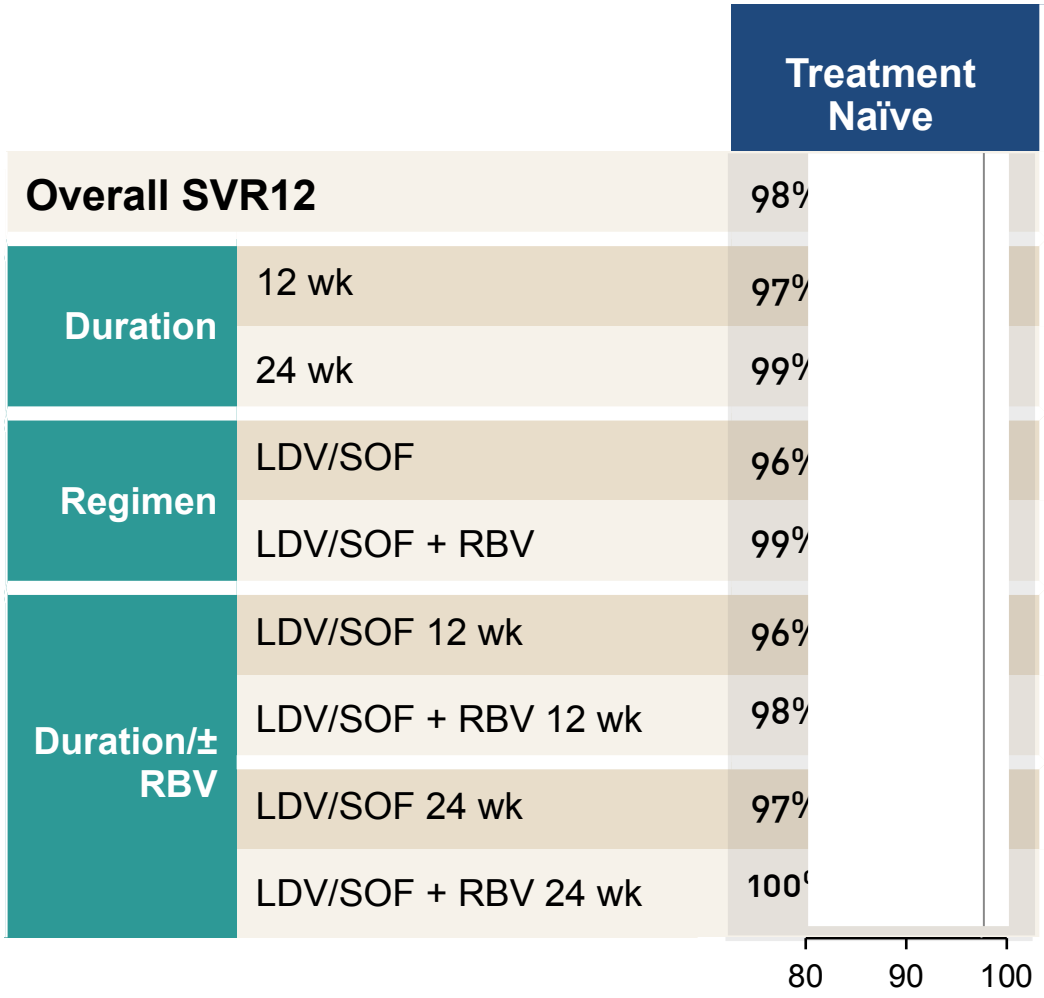


513 patients with HCV GT 1, compensated cirrhosis
Pooled data from Phase 2 and 3 LDV/SOF ± RBV studies

LONESTAR, ELECTRON, ELECTRON-2, Japan phase 3 study, ION-1, ION-2, SIRIUS
Primary efficacy endpoint: SVR12

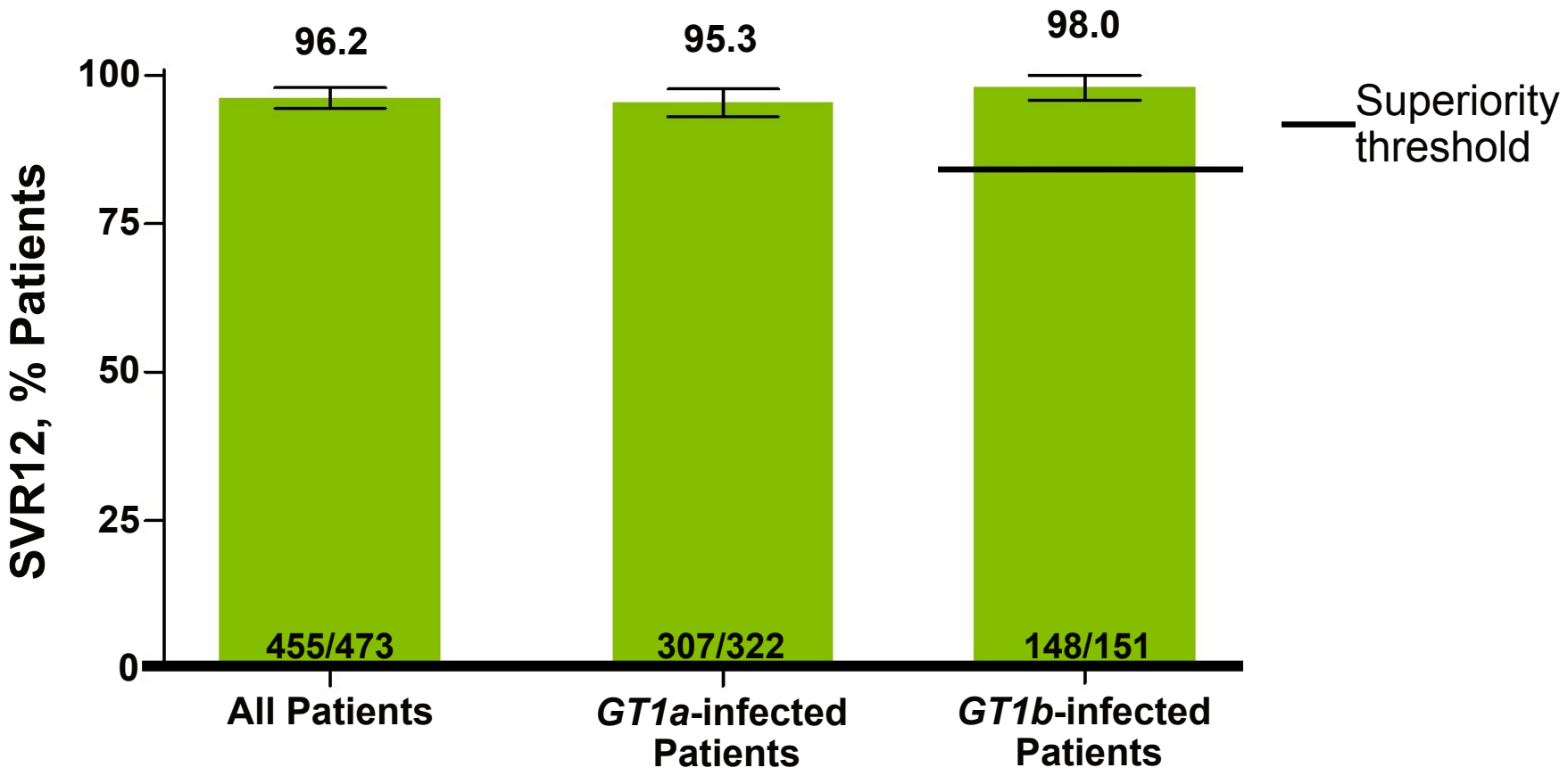
Bourliere, AASLD, 2014, Oral #82

Results: SVR12 by Treatment Regimen



Bourliere, AASLD, 2014, Oral #82

SAPPHIRE-I : Naïve GT1 HCV



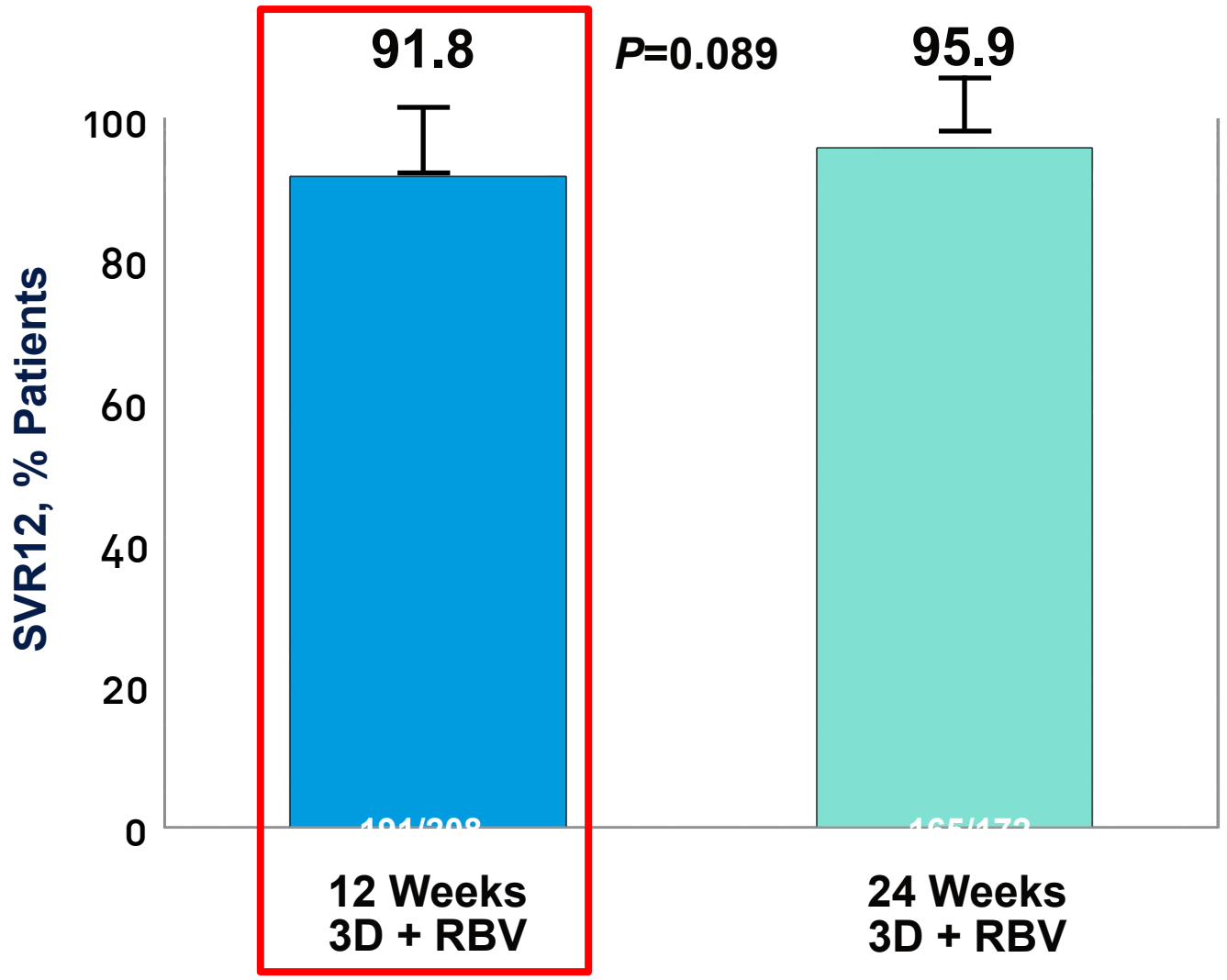
3D: Co-formulated Paritaprevir (ABT-450)/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID

RBV: 1000-1200 mg daily according to body weight (<75 kg and ≥75kg, respectively)

The ITT SVR12 rate of 98.0% (95% CI, 95.8-100) in GT1b-infected patients is superior to a calculated historical SVR12 control rate of 80% (95% CI, 75.0-84.0)

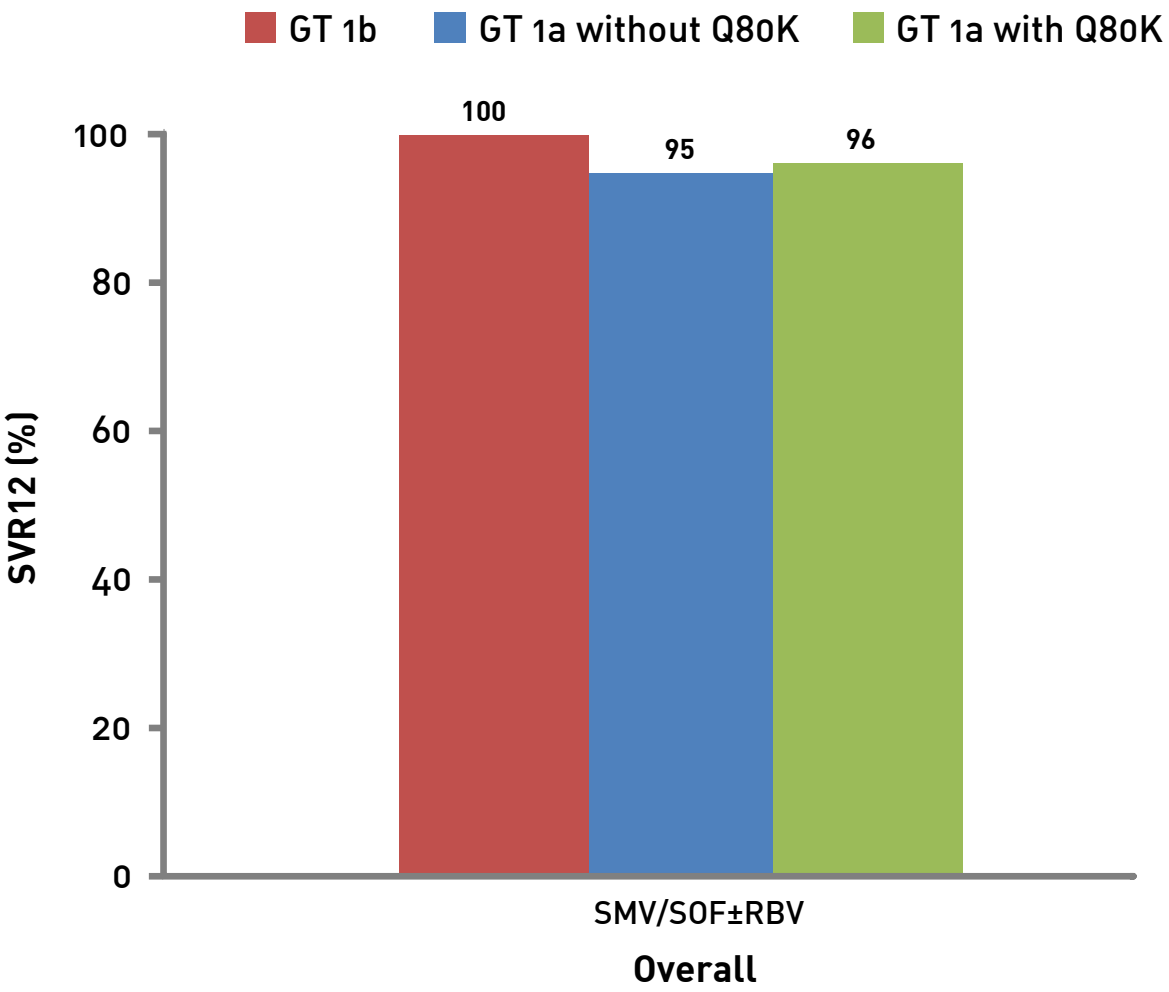
Feld et al. NEJM 2014;370(17):1594-603.

TURQUOISE-II: GT1- Cirrhotic Patients (N=380)



Poordad et al. *NEJM* 2014;370(21):1973-82.

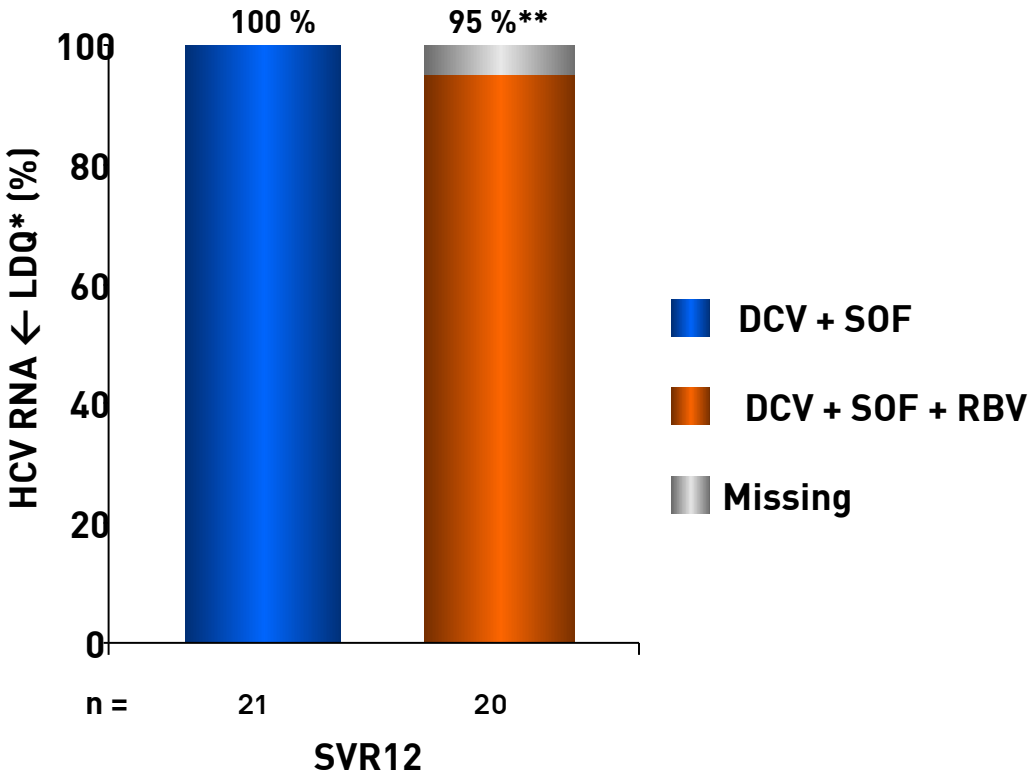
SIM/SOF: COSMOS Cohort 2: METAVIR F3-F4, prior null responders or treatment-naïve (SVR12)



*Excluding patients who discontinued for non-virologic reasons
GT, genotype; non-VF, non-virologic failure; RBV, ribavirin
SMV, simeprevir; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after planned treatment end

Lawitz et al. Lancet 2014; 384(9956):1756-65.

Daclatasvir (NS5AI) + Sofosbuvir (NI)

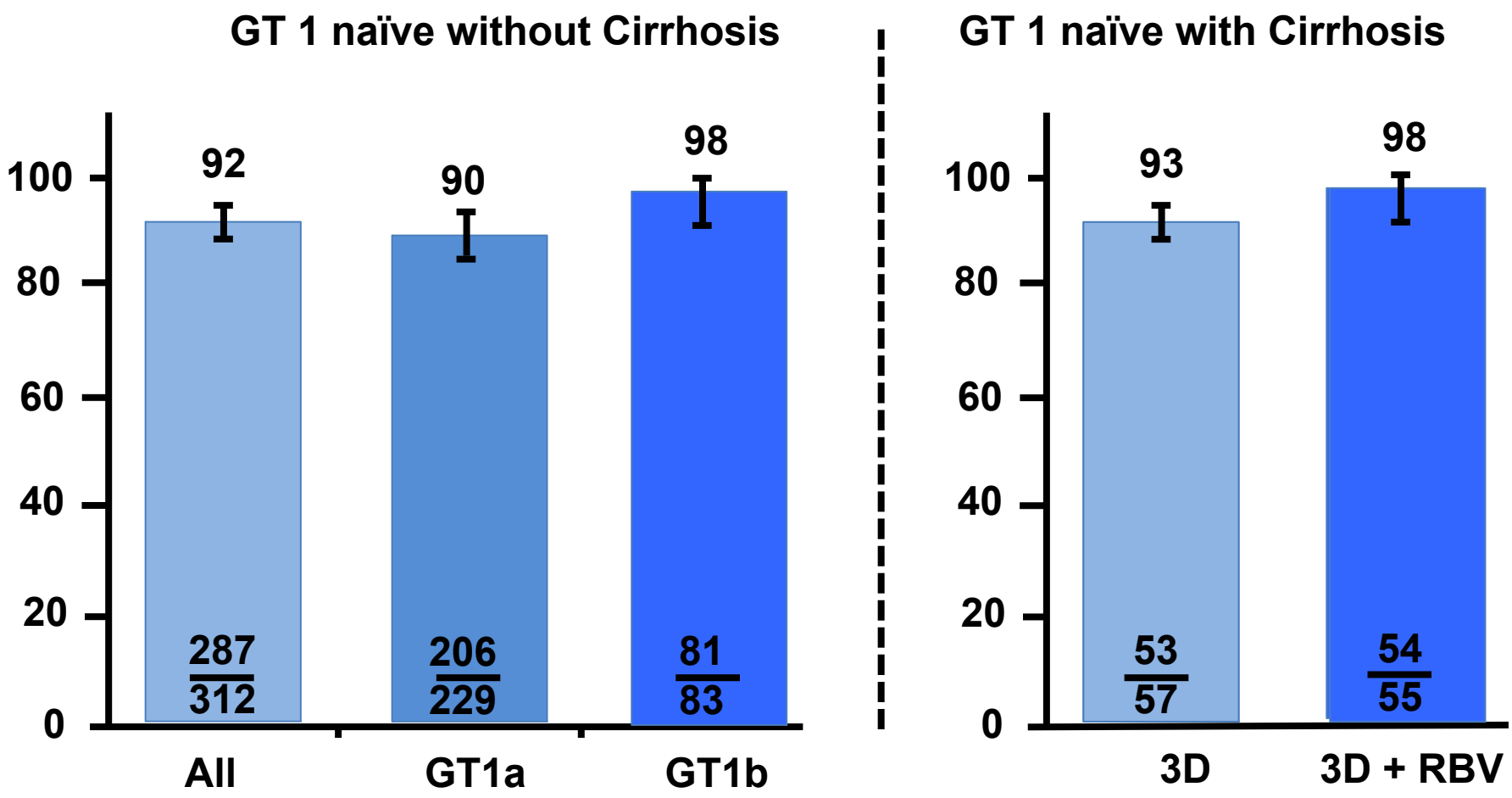


** missing data

*LDQ : ARN VHC < 25 UI/ml

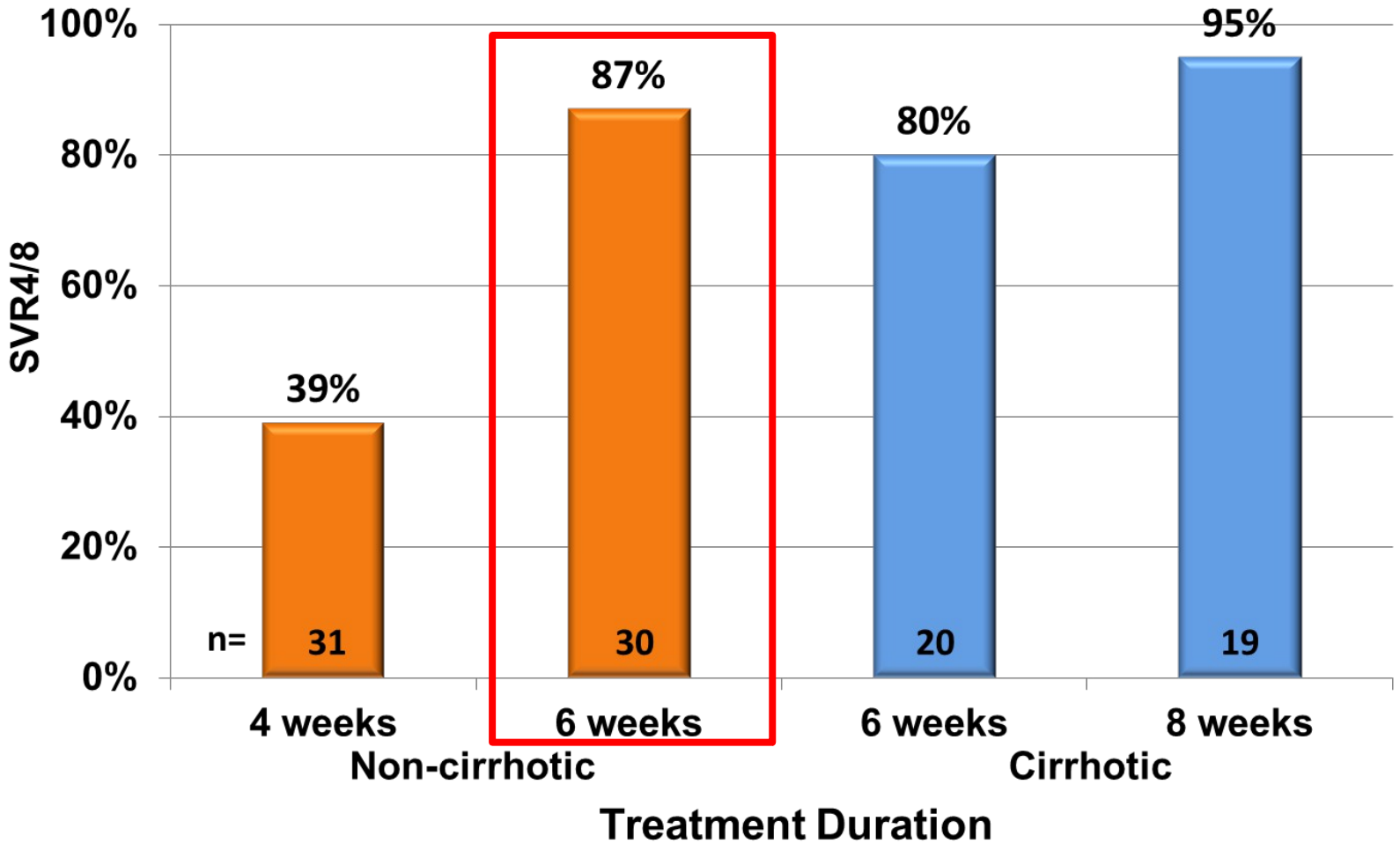
Sulkowski et al. NEJM 2014, 16; 370:211-21.

Daclatasvir + Asunaprevir + BMS-791325



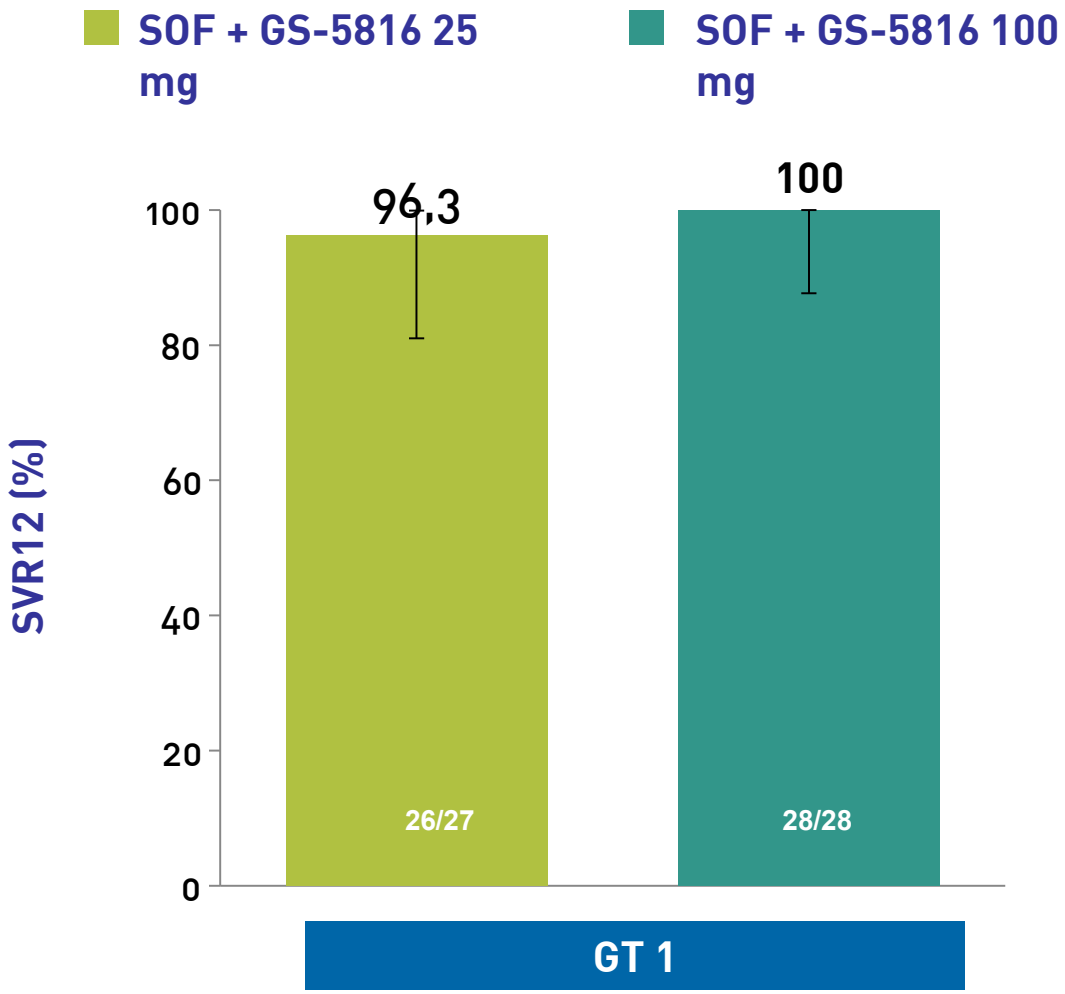
Poordad et al. AASLD 2014, LB 7

C-SWIFT: Grazoprevir (MK-5172) + Elbasvir (MK-8742) +Sofosbuvir



Lawitz et al. AASLD 2014, LB33.

Sofosbuvir + GS 5816 (8-12 weeks)
GT1 Naïves Non-Cirrhotic



Tran et al. AASLD 2014, A80

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4 Take home messages

Naïve HCV GT1 : Treatment options available in 2015

- Sofosbuvir/Ledipasvir *(Harvoni)*

  No cirrhosis 8 w; Cirrhosis 12 w

  - Paritoprevir/r/Ombitasvir *(Viekira)* + Dasabuvir *(Exviera)* + RBV 12 w

  Genotype 1b : without RBV

- Sofosbuvir *(Sovaldi)* + Simeprevir *(Olysio) 12w*

- Sofosbuvir *(Sovaldi)* + Daclatasvir *(Daklinza) 12w*

Take Home Messages
IFN-free therapy in naïve HCV GT1 patients

1. Numerous DAAs with different mode of action are under development.
2. Combining DAAs result in high efficacy (SVR > 90%), and short treatment duration (8 or 12 weeks).
3. How far we can go by shortening treatment duration (4, 6 or 8 weeks) is under evaluation.
4. Will treatment fit all patients (genotypes, cirrhotics, etc.) or shall we need « a la carte » treatment ?
5. Real-life data are mandatory : we expect decrease in SVR of 5-10% because of compliance or other factors (disease severity, DDI, etc…).
6. Improvement in screening and access to treatment is a future challenge.

References

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1. Maylin et al. *Gastroenterology* 2008; 3: 821–9.
2. Schinazi et al. Liver Int 2014; 34 Suppl 1:69-78.
3. Asselah et al. Liver Int. 2015;35 S1:56-64.
4. Afdhal et al. NEJM 2014; 370(20): 1889-98.
5. Kowdley et al. NEJM 2014; 370(20):1879-88.
6. Lawitz et al. Lancet 2014; 384(9956):1756-65.
7. Sulkowski et al. NEJM 2014; 370(3): 211-21.
8. Feld et al. NEJM 2014; 370(17):1594-603.
9. Poordad et al. NEJM 2014; 370(21):1973-82.
10. Estrabaud et al. J Hepatol 2012; 57: 1110–25.