HCV Therapies: State of the Art

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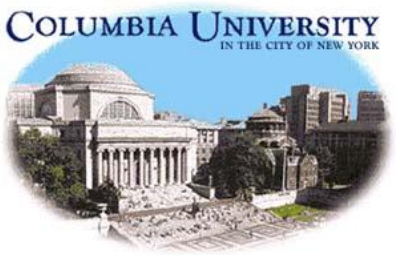
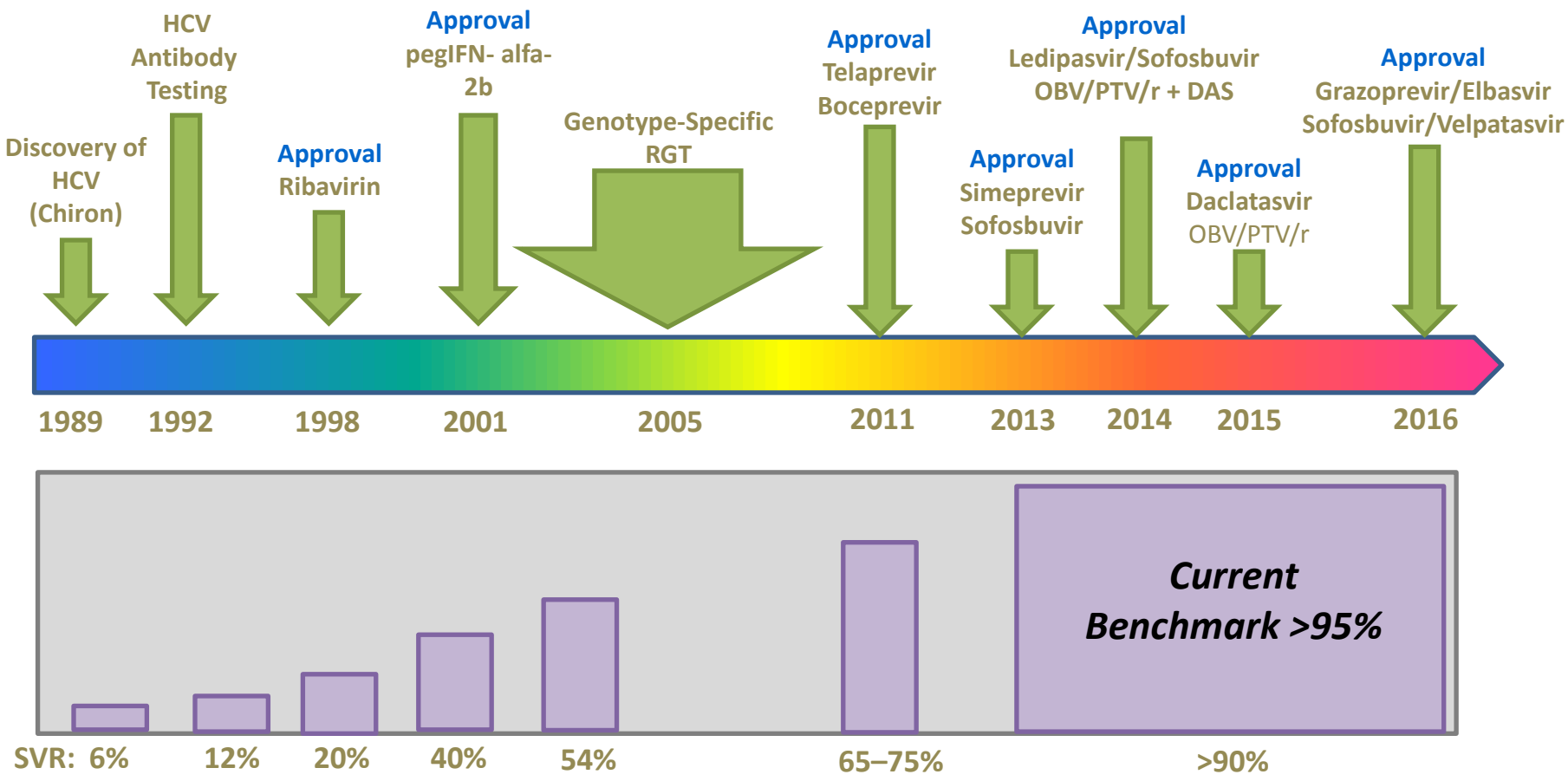


Learning Objectives

- Evaluate the current treatment options for the management of treatment-naive patients with HCV genotype 1 infection
- Assess the current treatment options for the management of treatment-experienced patients with HCV genotype 1 infection
- Outline the major issues in the current treatment of HCV infection

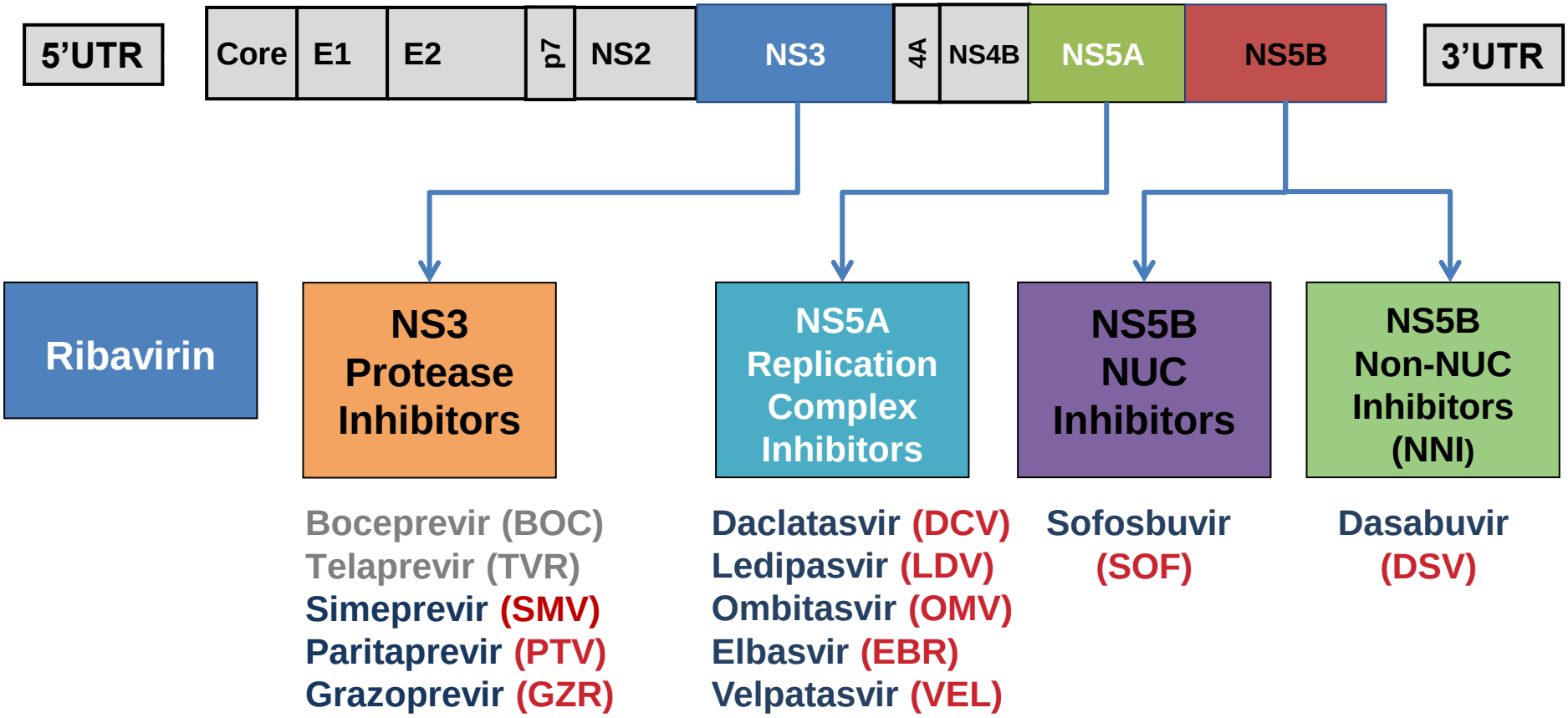
Evolving Landscape of HCV Therapy



pegIFN-alfa 2b = peg-interferon alfa-2b; RGT = response-guided therapy; OBV/PTV/r + DAS = ombitasvir/paritaprevir and ritonavir + dasabuvir (or 3D).

Houghton M. *Liver Int*. 2009;29(Suppl 1):82-88; Carithers RL, et al. *Hepatology*. 1997;26(3 Suppl 1):S83-S88; Zeuzem S, et al. *N Engl J Med*. 2000;343(23):1666-1672; Poynard T, et al. *Lancet*. 1998;352(9138):1426-1432; McHutchison JG, et al. *N Engl J Med*. 1998;339(21):1485-1492; Lindsay KL, et al. *Hepatology*. 2001;34(2):395-403; Fried MW, et al. *N Engl J Med*. 2002;347(13):975-982; Manns MP, et al. *Lancet*. 2001;58(9286):958-965; Poordad F, et al. *N Engl J Med*. 2011;364(13):1195-1206; Jacobson IM, et al. *N Engl J Med*. 2011;364(25):2405-2416; Lawitz E, et al. *N Engl J Med*. 2013;368(20):1878-1887; Jacobson IM, et al. *Lancet*. 2014;384(9941):403-413; Afdhal N, et al. *N Engl J Med*. 2014;370(20):1889-1898; Nelson DR, et al. *Hepatology*. 2015;61(4):1127-1135; Zeusem S, et al. *Ann Intern Med*. 2015;163(1):1-13.

FDA-Approved Direct-Acting Antiviral Agents (DAAs) from Multiple Classes



	Protease Inhibitors	Nucleos(t)ide Polymerase Inhibitors	Non-nucleoside Polymerase Inhibitors	NS5A Inhibitors
Specific Agents	Telaprevir Boceprevir Simeprevir Paritaprevir Grazoprevir	Sofosbuvir	Dasabuvir	Ledipasvir Daclatasvir, Ombitasvir Elbasvir Velpatasvir
Potency	High (varies by genotype)	Moderate-to-high (pangenotypic)	Variable (varies by genotype)	High (some pan-genotypic)
Barrier to resistance	Low (1a<1b)	High (1a =1b)	Very low (1a<1b)	Low (1a<1b)
Potential for drug interactions	High	Low	Variable	Low-to-moderate
Toxicity	Rash, anemia, jaundice, liver injury	Mitochondrial	Variable	Variable
Dosing	qd to tid	qd to bid	qd to tid	qd
Comments	2nd generation PIs (higher barrier to resistance, pan-genotypic)	Single target active site	Allosteric Many targets	Multiple antiviral MOA
Predominant Metabolism	Hepatic	Renal	Hepatic	Hepatic

Modified from Schaefer EA, et al. *Gastroenterology.* 2012;142:1340-1350.

Protease inhibitor

Polymerase inhibitor

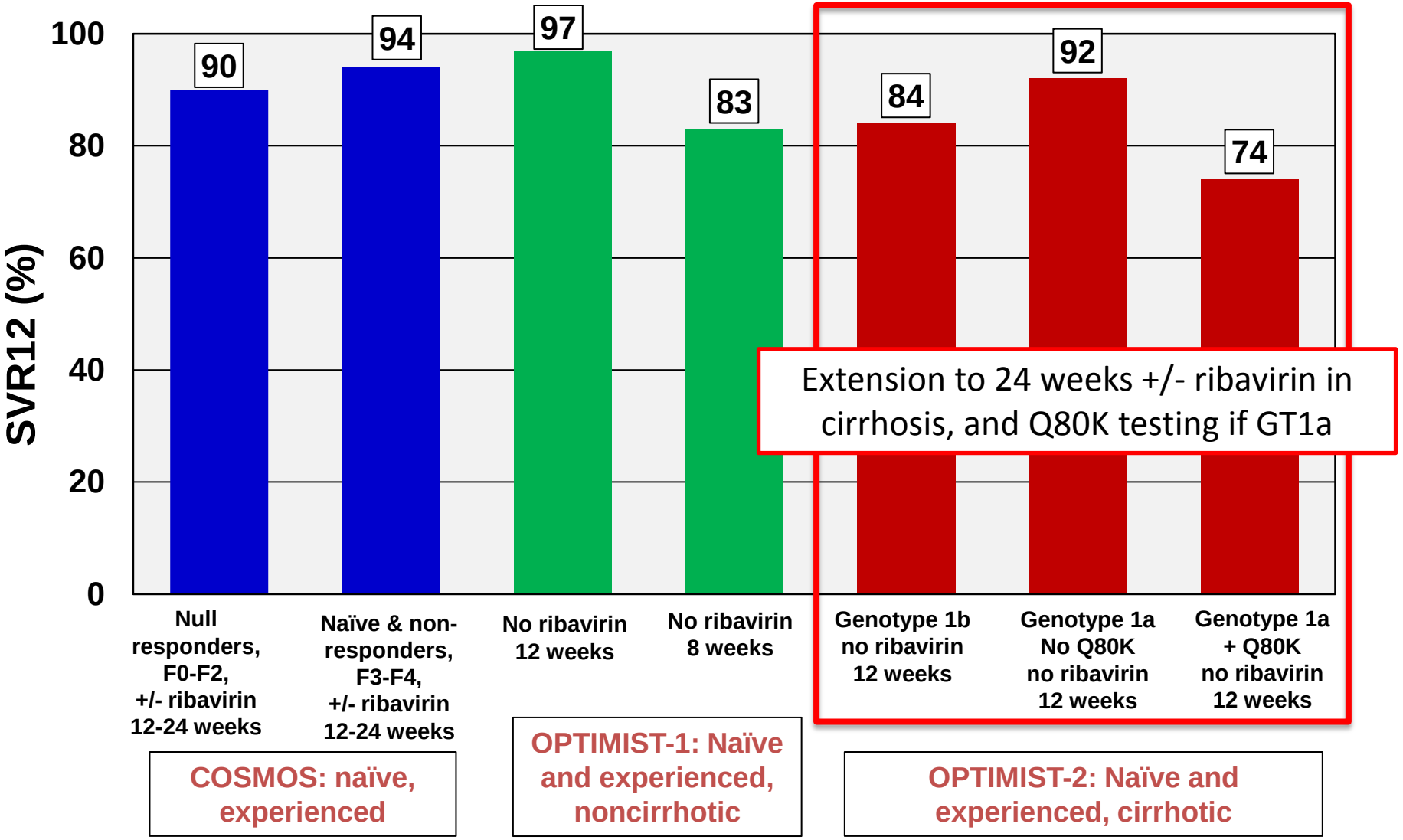
Sofosbuvir + simeprevir

- Indications
  - FDA
    - Genotype 1
  - AASLD/IDSA
    - Genotype 1

- Benefits
  - First IFN-free regimen available

- Limitations
  - May need baseline RAS testing and ribavirin
  - Not recommended for decompensated cirrhosis

Simeprevir + Sofosbuvir



Kwo P, et al, Hepatology 2016; Lawitz E, et al. Hepatology 2015.

Polymerase inhibitor
NS5A inhibitor

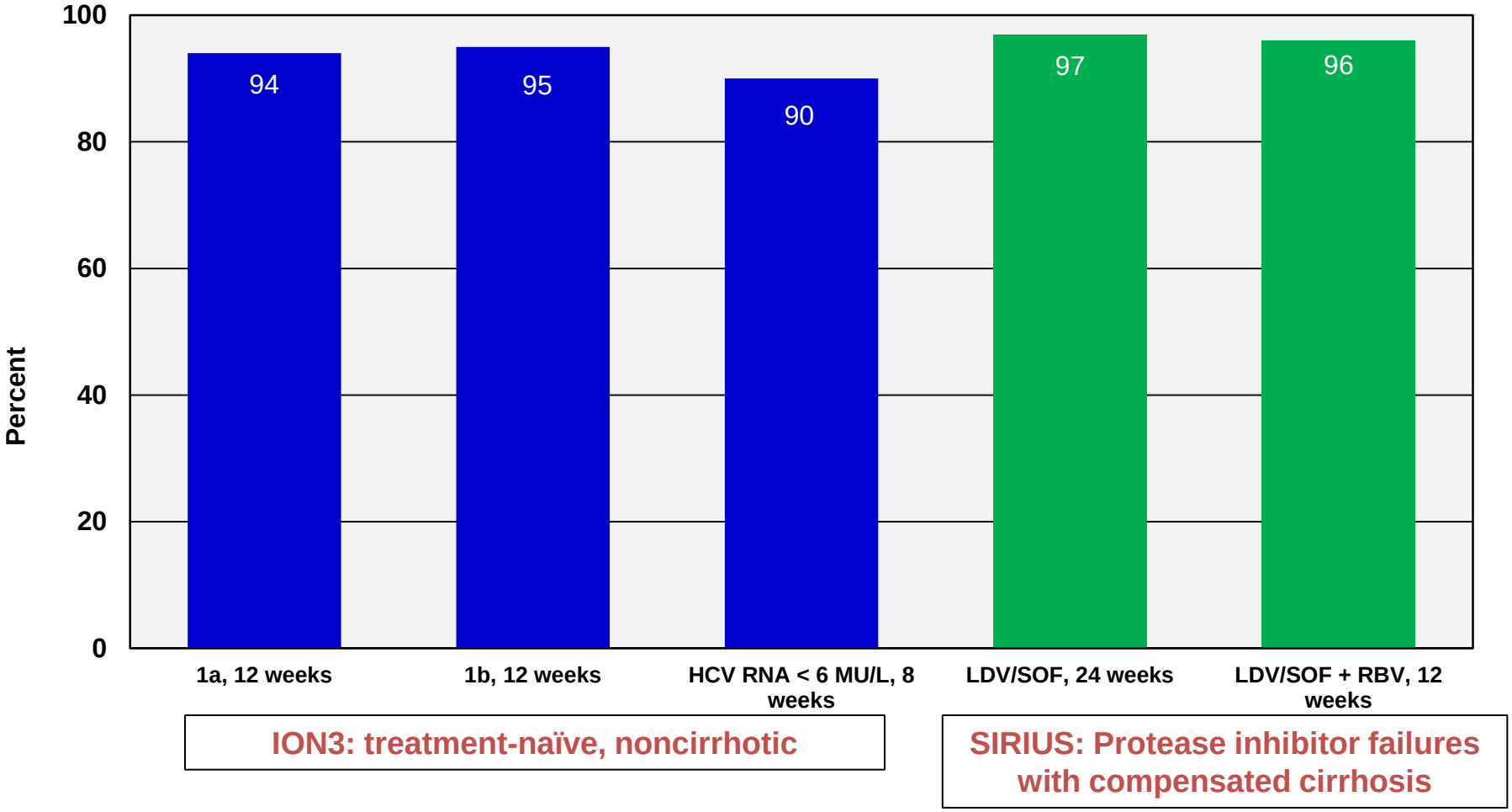
Sofosbuvir + Ledipasvir

- Indications
  - FDA
    - Genotype 1
  - AASLD/IDSA
    - Genotypes 1, 4, 5, 6

- Benefits
  - Regimen for many treatment failure patients
  - Ribavirin-free for many
  - Decompensated cirrhosis
  - Low pill burden

- Limitations
  - Not recommended in advanced renal insufficiency

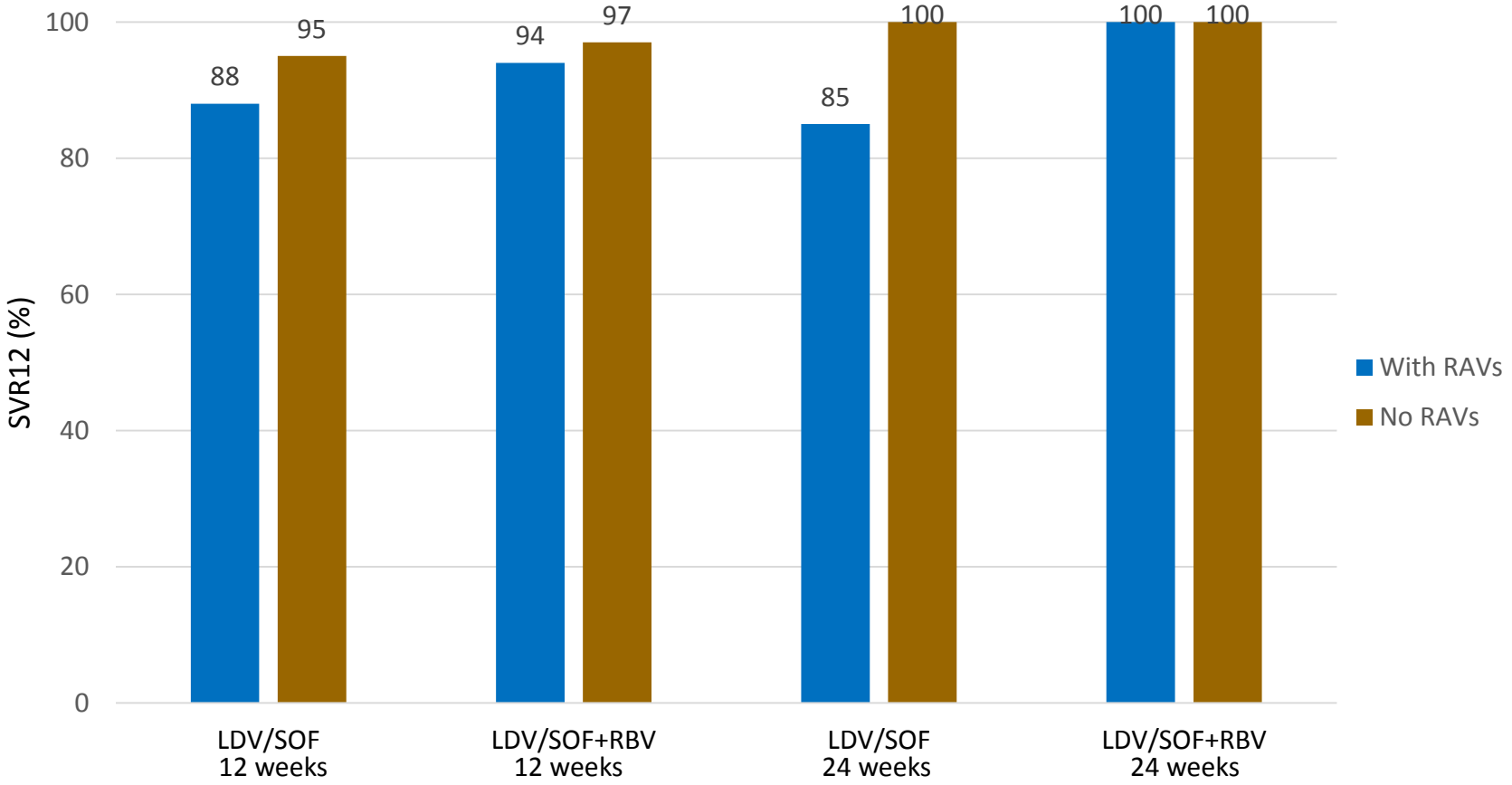
Sofosbuvir + Ledipasvir



Kowdley KV, et al. NEJM 2014; Bourliere M, et al. Lancet Infect Dis 2015.

Sofosbuvir/ledipasvir and NS5A RAVs

- Pooled analysis of 2,144 participants of phase 2/3 studies
- 16% with detectable NS5A RAS at baseline

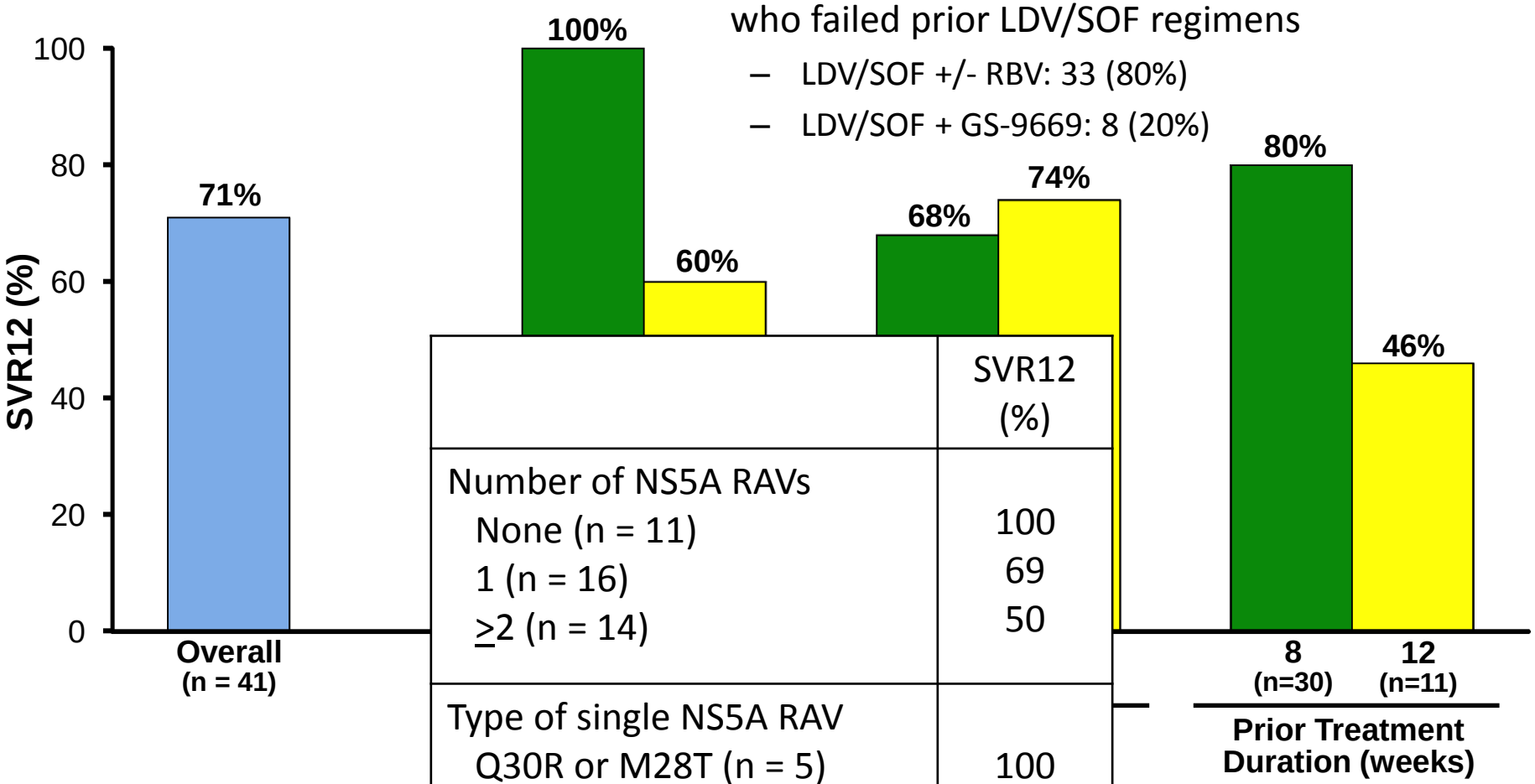


Baseline NS5A RASs have minimal effects on SVR to LDV/SOF, and these effects may be overcome by extending treatment duration or through treatment intensification.

Sarrazin C, et al. Gastroenterolog 2016

Ledipasvir/Sofosbuvir for 24 weeks for Previous Ledipasvir/Sofosbuvir Failures

- G1 treatment-experienced patients who failed prior LDV/SOF regimens
  - LDV/SOF +/- RBV: 33 (80%)
  - LDV/SOF + GS-9669: 8 (20%)



	SVR12 (%)
Number of NS5A RAVs	
None (n = 11)	100
1 (n = 16)	69
≥2 (n = 14)	50
Type of single NS5A RAV	
Q30R or M28T (n = 5)	100
L41M (n = 5)	80
Y93H/N (n = 6)	33

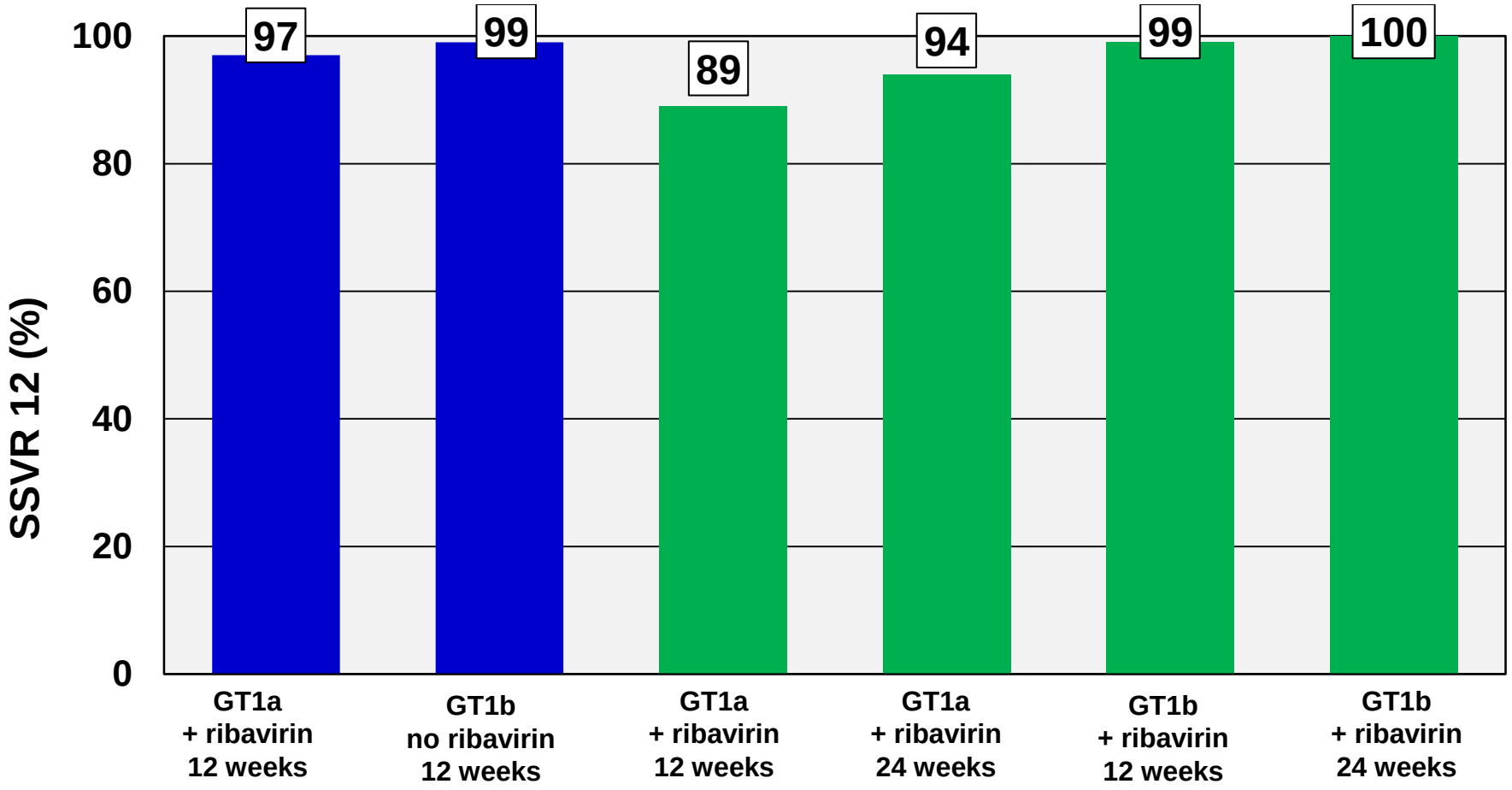
Lawitz E, et al. EASL 2016.

Polymerase inhibitor
NS5A inhibitor
Protease inhibitor

Paritaprevir/ritonavir + Ombitasvir + Dasabuvir

- Indications
  - FDA:
    - Genotypes 1, 4 (no dasabuvir)
  - AASLD/IDSA
    - Genotypes 1, 4 (no dasabuvir)
- Benefits
  - 3 agents against different targets
  - Large development program, including cirrhosis
  - Not renally metabolized
- Limitations
  - Ribavirin for genotype 1a
  - Not recommended for decompensated cirrhosis

Paritaprevir/ritonavir + Ombitasvir + Dasabuvir ± Ribavirin for Genotype 1 HCV

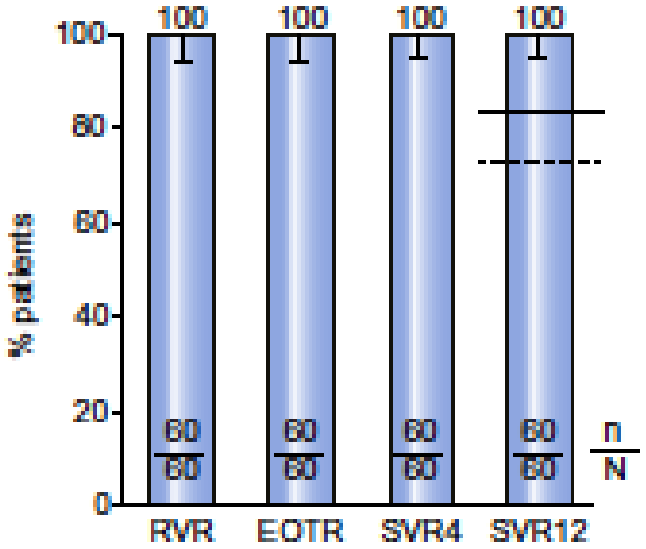


PEARL III & IV: treatment-naïve, noncirrhotic

TURQUOISE II: compensated cirrhosis, naïve and experienced

100% SVR12 with PAR/r + OMB + DAS *without* RBV for GT1b with Cirrhosis

- TURQUOISE III: phase IIIB, open-label, single-arm trial
- 60 patients with compensated cirrhosis
- 55% treatment-experienced
- Most common AEs fatigue (20%), diarrhea (20%), headache (18%)
- One SAE: possible drug interaction with nisoldipine
- 20% with Grade 2 bilirubin elevation

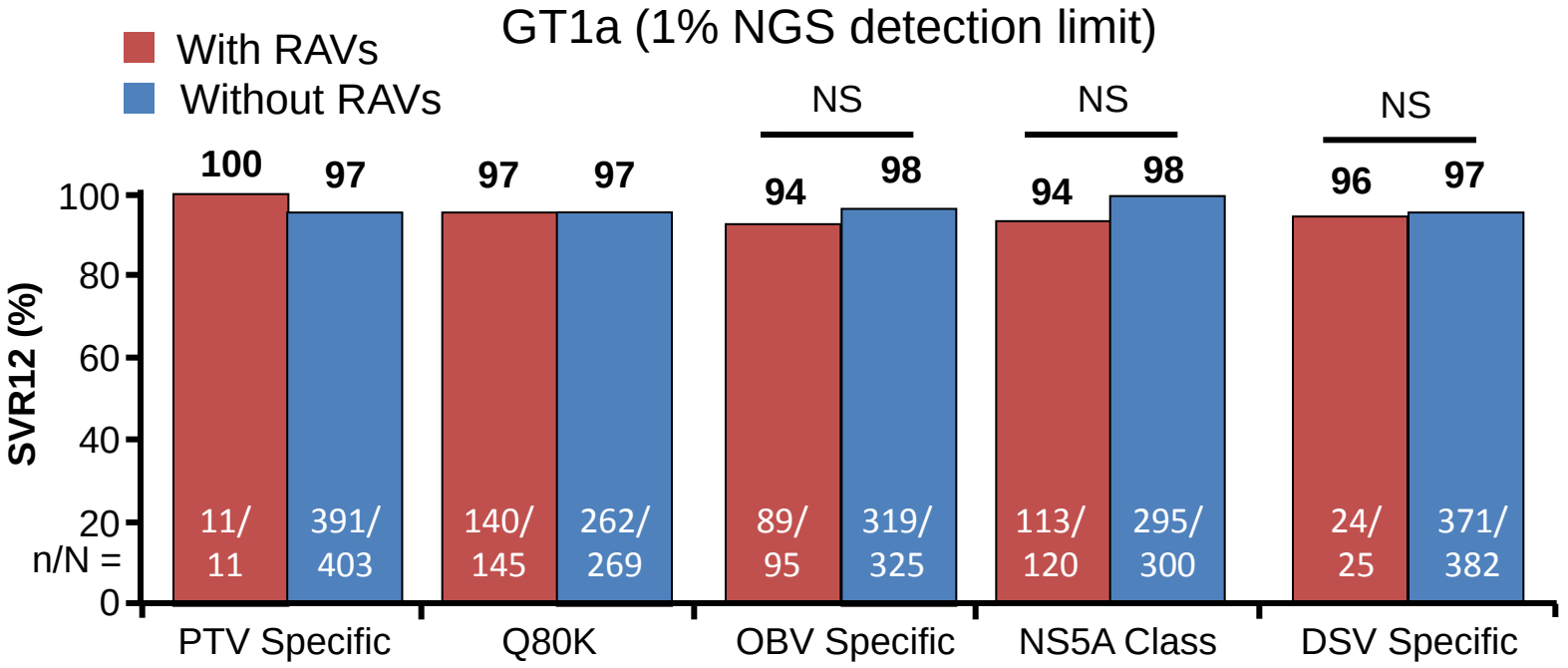


PrOD *without* ribavirin for GT 1b, regardless of prior treatment or the presence of cirrhosis

Feld JJ, et al. J Hepatol, 2015.

Impact of Baseline RASs on Efficacy of OBV/PTV/RTV + DSV ± RBV

- Analysis of data from 5 phase III trials using NGS; all pts treated with OBV/PTV/RTV + DSV ± RBV **on label** (based on subgenotype, previous treatment, and cirrhosis)
  - SVR12 rate 100% in pts with GT1b HCV, regardless of BL RAVs



Sarrazin C, et al. EASL 2016.

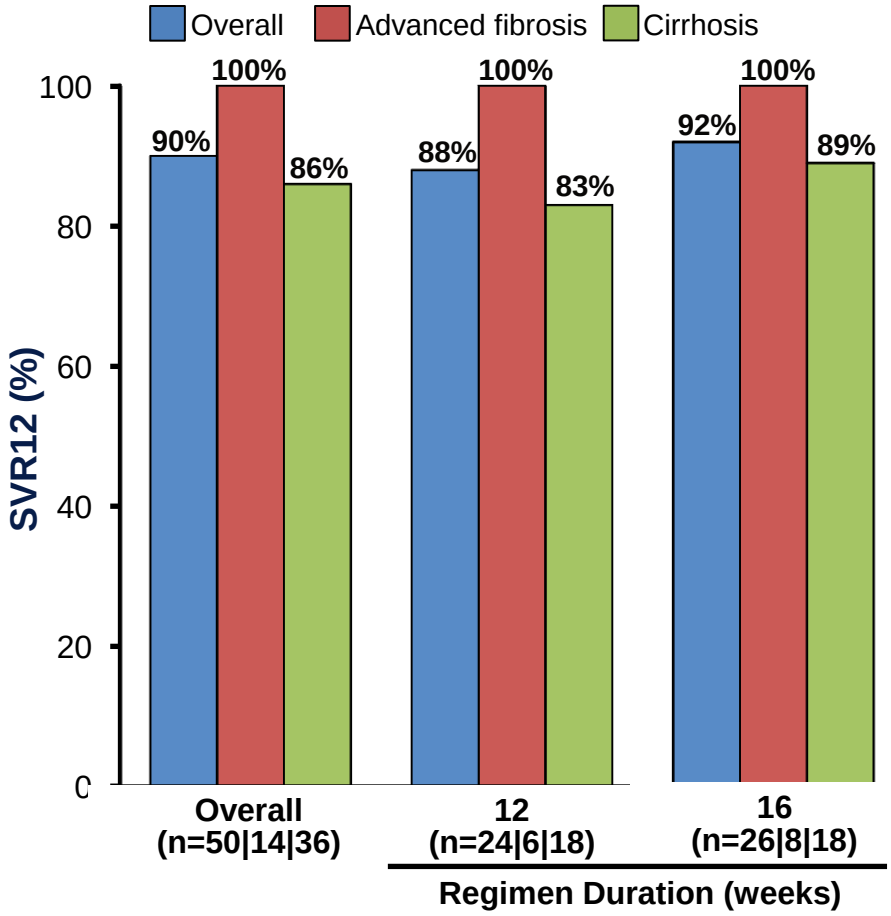
Polymerase inhibitor
NS5A inhibitor

Sofosbuvir + Daclatasvir

- Indications
  - FDA:
    - Genotype 3
  - AASLD/IDSA:
    - Genotypes 1, 2, 3
- Benefits
  - Pangenotypic
  - Flexibility with DDIs
  - Decompensated cirrhosis
- Limitations
  - Access outside genotype 3
  - Not recommended in advanced renal insufficiency

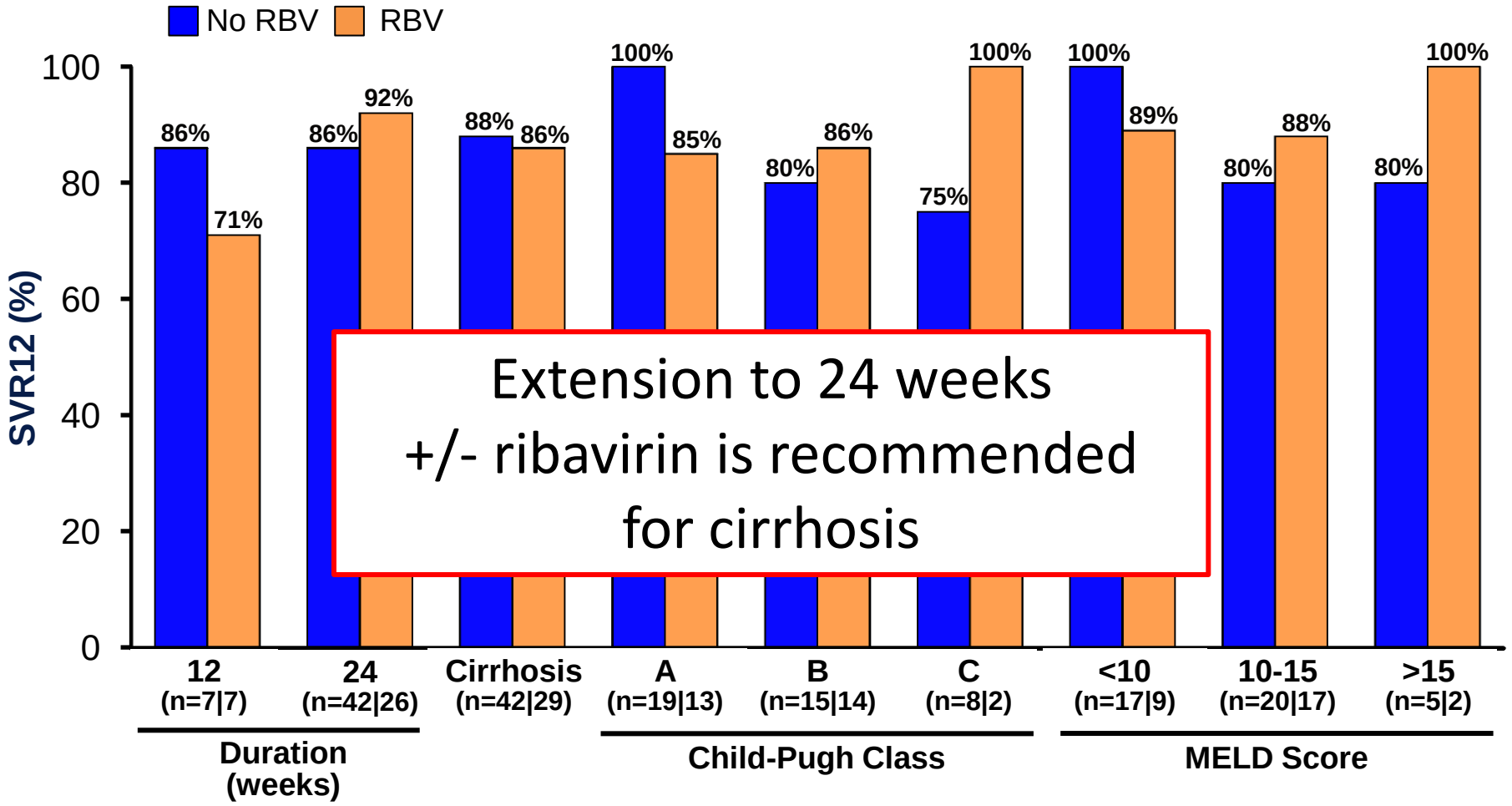
ALLY 3+: Daclatasvir + Sofosbuvir + Ribavirin for GT3

- No virologic breakthroughs
- Relapse (n = 4)
  - All cirrhotics (2 in each arm)
  - All had Y93H RAV at relapse
- Overall well tolerated
  - No discontinuations
  - RBV dose reduction in 12%
  - Treatment-emergent grade 3/4 laboratory abnormalities
    - Hemoglobin <9.0 g/dL 2%
    - Total bilirubin >2.5x ULN 4%



Leroy V, et al. Hepatology, 2016.

European Compassionate Use Program: Daclatasvir + Sofosbuvir ± RBV in HCV Genotype 3 Cirrhosis



Welzel TM, et al. Hepatology. 2015:62(suppl S1)

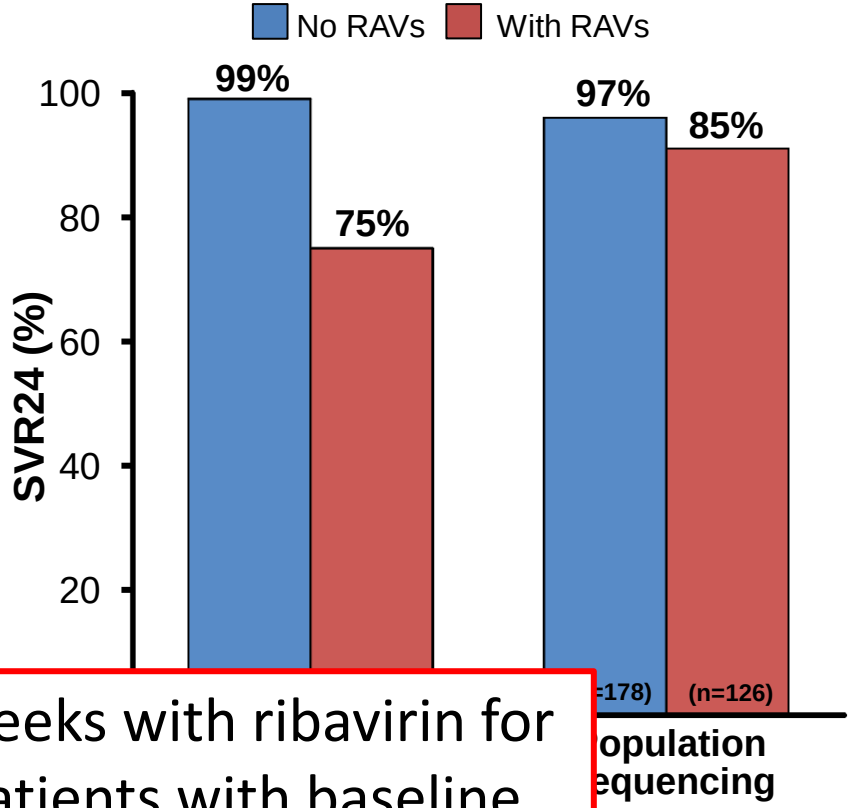
Protease inhibitor
NS5A inhibitor

Elbasvir + Grazoprevir

- Indications
  - FDA:
    - Genotype 1, 4
  - AASLD/IDSA:
    - Genotypes 1, 4
- Benefits
  - Approved for use with advanced renal insufficiency
  - Low pill burden
- Limitations
  - May need baseline RAS testing and ribavirin
  - Not recommended for decompensated cirrhosis

C-EDGE: Final SVR24 Data with Elbasvir/Grazoprevir in TN, HCV GTs 1, 4, or 6

- Phase 3, double-blind, randomized to ELB/GRZ for 12 weeks (n = 316) or placebo and delayed treatment (n = 105)
- Overall SVR24 rate: 94%
  - Genotype 1a/1b: 93%/99%
  - Genotype 4/6: 100%/62%
- Overall relapse rate: 4%
  - 1 confirmed relapse between SVR12 and SVR24
- Lower SVR24 rates in *genotype 1a* with RAVs at positions 28, 30, 31



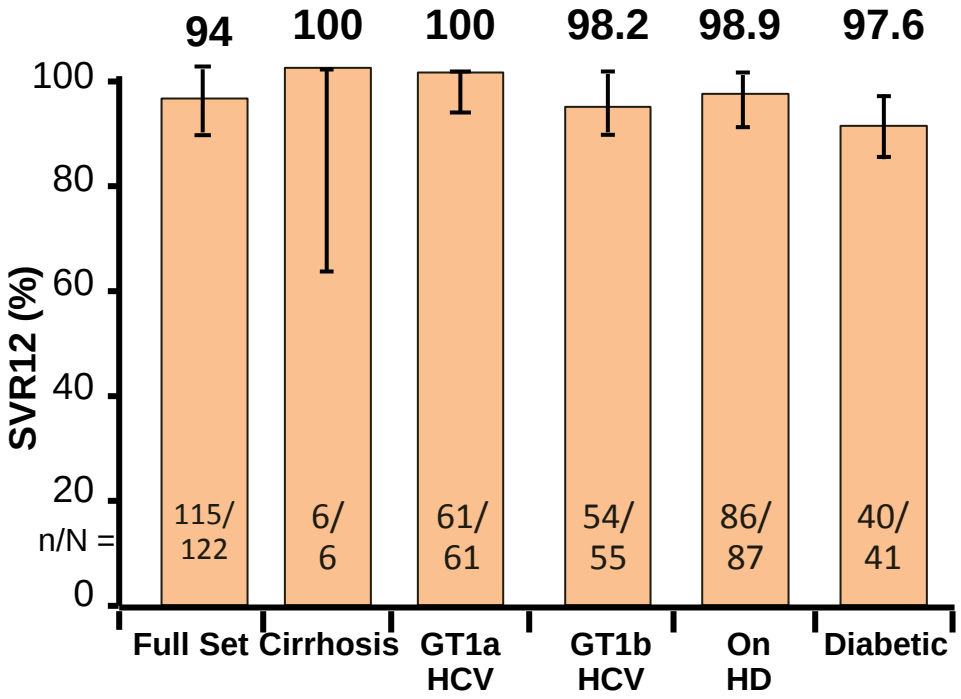
Prolong treatment to 16 weeks with ribavirin for TN and TE genotype 1a patients with baseline NS5A RAVs

2015;163:1-13.

Zeuzem S, et al. *J Hepatol.* 2016;64(suppl 2):S821. Abstract SAT-266.

C-SURFER: Grazoprevir + Elbasvir in Stage 4 and 5 Chronic Kidney Disease

- 224 patients
- GT 1 HCV
- 12 weeks (randomized to immediate or delayed)
- 6% cirrhotic, 20% TE
- 75% on HD
- Well tolerated, no evidence of worsening of renal function



Roth D, et al. Lancet, 2015.

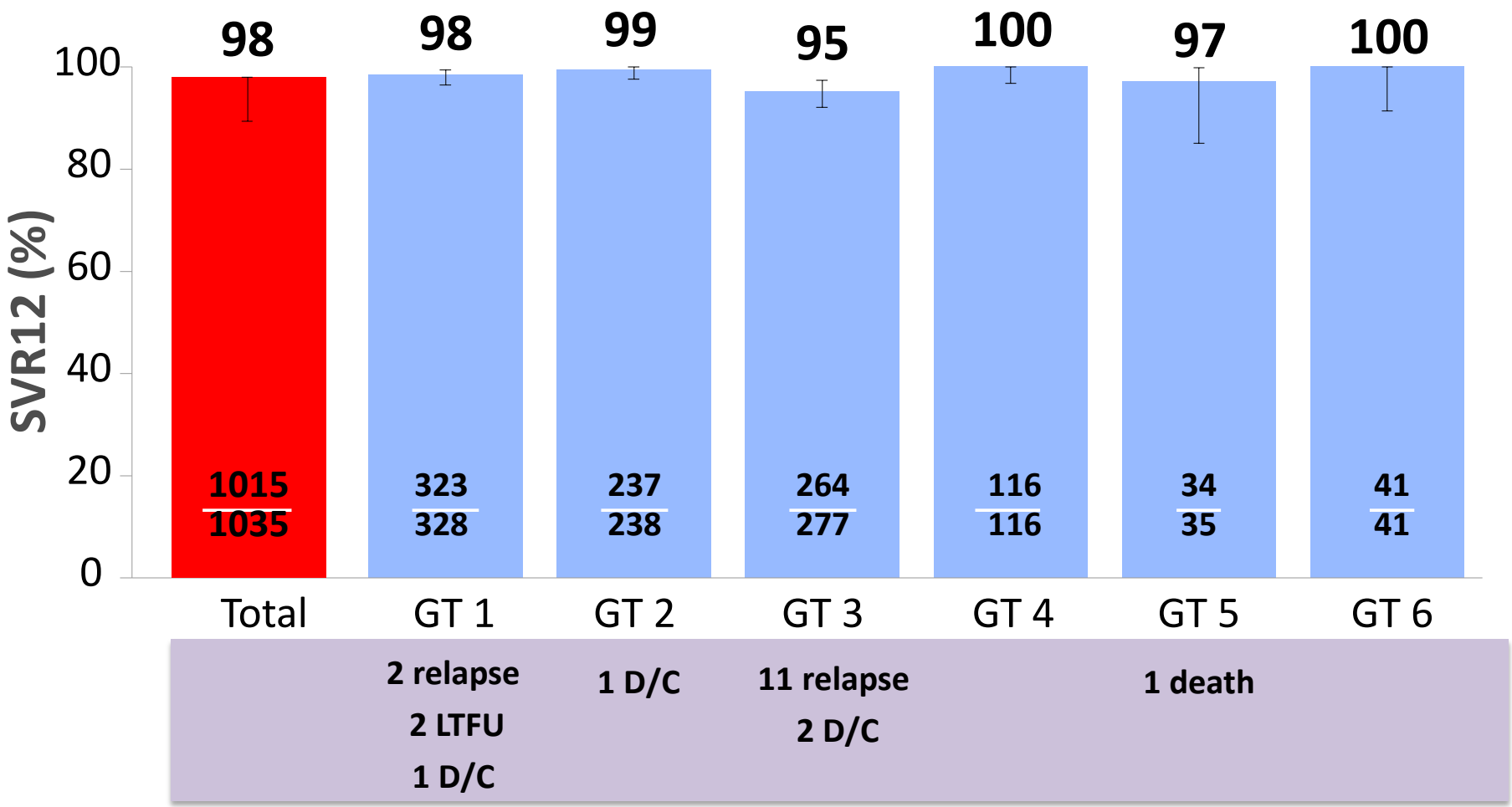
Polymerase inhibitor

NS5A inhibitor

Sofosbuvir + Velpatasvir

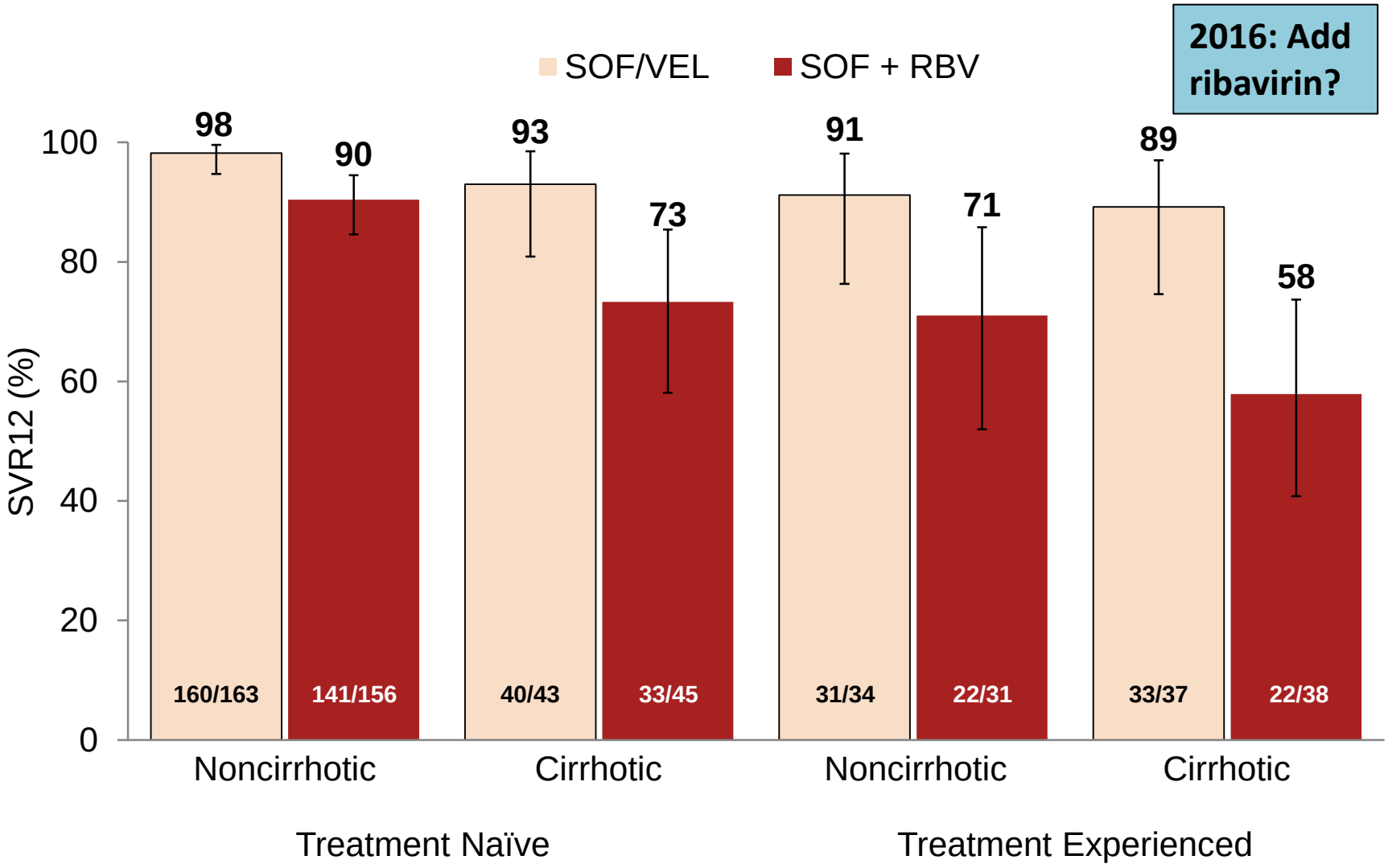
- Indications
  - FDA:
    - Genotypes 1, 2, 3, 4, 5, 6
  - AASLD/IDSA:
    - Genotypes 1, 2, 3, 4, 5, 6
- Benefits
  - Pangenotypic
  - Regimen for many treatment failure patients
  - Ribavirin-free for many
  - Decompensated cirrhosis
  - Low pill burden
- Limitations
  - Access outside genotype 3
  - Not recommended in advanced renal insufficiency

Sofosbuvir + Velpatasvir for 12 Weeks



Agarwal, EASL 2016.

SOF/VEL 12 wks vs SOF/RBV 24 wks G3



Mangia, AASLD, 2015;Foster GR, et al. New Engl J Med. 2015.

AASLD/IDSA Guidance

	SOF + PEG + RBV	SOF + RBV	SIM + SOF	LDV + SOF	PAR/r + OMB+ DAS	DAC + SOF	ELB + GRZ	VEL + SOF
GT	**NS5B**	**NS5B**	**PI + NS5B**	**NS5A + NS5B**	**PI + NS5A + NS5B**	**NS5A + NS5B**	**PI + NS5A**	**NS5A + NS5B**
1			**Naïve PEG/R Exp**	**Naïve PEG/R Exp PI Exp**	**Naïve PEG/R Exp**	**Naïve PEG/R Exp PI Exp**	**Naïve PEG/R Exp PI Exp**	**Naïve PEG/R Exp PI Exp**
2						**Naïve PEG/R Exp SOF/R Exp**		**Naïve PEG/R Exp SOF/R Exp**
3						**Naïve PEG/R Exp SOF/R Exp**		**Naïve PEG/R Exp SOF/R Exp**
4				**Naïve PEG/R Exp**	**Naïve PEG/R Exp (no DAS)**		**Naïve PEG/R Exp**	**Naïve PEG/R Exp**
5				**Naïve PEG/R Exp**				**Naïve PEG/R Exp**
6				**Naïve PEG/R Exp**				**Naïve PEG/R Exp**

Recommended Alternative

www.hcvguidelines.org, accessed March 2017

NS5A resistance
DAA Failures (prior NS5A Inhibitor)

Prior Regimen	Retreatment Regimen	Duration
SOF + RBV +/- PEG	SOF/LDV + RBV	12-24 weeks
PI + PEG + RBV	SOF/LDV +/- RBV SOF/VEL SOF + DAC +/- RBV ELB/GRZ + RBV	12-24 weeks 12 weeks 12-24 weeks 12-16 weeks
SOF + SIM NS5A	• Defer treatment unless urgent, pending additional data and availability of newer regimens • Test for NS3 protease and NS5A inhibitor resistance-associated substitutions • Use of SOF-based therapy for extended duration (24 weeks), add RBV if can tolerate; consider triple or quadruple DAA regimen if possible	

http://www.hcvguidelines.org. Accessed March, 2017.

Paritaprevir/ritonavir + Ombitasvir + Dasabuvir in cirrhosis

- FDA Drug Safety Communication
- 26 worldwide cases
  - 10 hepatic failure resulting in transplantation or death
  - 16 patients with liver dysfunction
- In most, liver injury within 1 to 4 weeks of starting
- “Transaminase elevations did not appear to be a predominant presentation in the cases with advanced liver disease”

Contraindicated in moderate to severe hepatic impairment (CTP B and C) and monitored closely in compensated cirrhosis (labs at least every 4 weeks)

www.fda.gov

HBV Reactivation Associated with HCV DAA Therapy

Query of the FDA Adverse Event Reporting System (FAERS) for cases of HBV-R associated with HCV DAAs from 11/22/2013–10/15/2016

Descriptive Characteristics	Data
# of cases/geography	• 29 cases (5 in US, 19 Japan, 5 in other)
Timing	• Temporally related to HCV therapy and occurred within 4-8 weeks (mean time to HBV-R was 53 days)
Baseline HBV viral parameters	• HBsAg+ (n = 13) (n = 12 not reported); HBcAb+ (n = 6) (n = 23 not reported); HBV DNA undetectable/detectable (n = 16/9)
Outcome	• Death (n = 2) (due to decompensated liver failure); transplant (n = 1); hospitalization (n = 6); other (n = 20)
Specific DAAs used	• SOF-based (n = 16); DCV+ASV (n = 11); PI-based (n = 2)
HBV treatment	• In 16 patients who received HBV treatment, treatment was delayed in ≥7 cases (44%); 1 of these 7 patients died; possible delay in ≥7 other cases (1 had a liver transplant)

Health care professionals *should screen all patients for evidence of current or prior HBV infection before starting treatment with DAAs, and monitor patients using blood tests for HBV flare-ups or reactivation during treatment and post-treatment follow-up.*

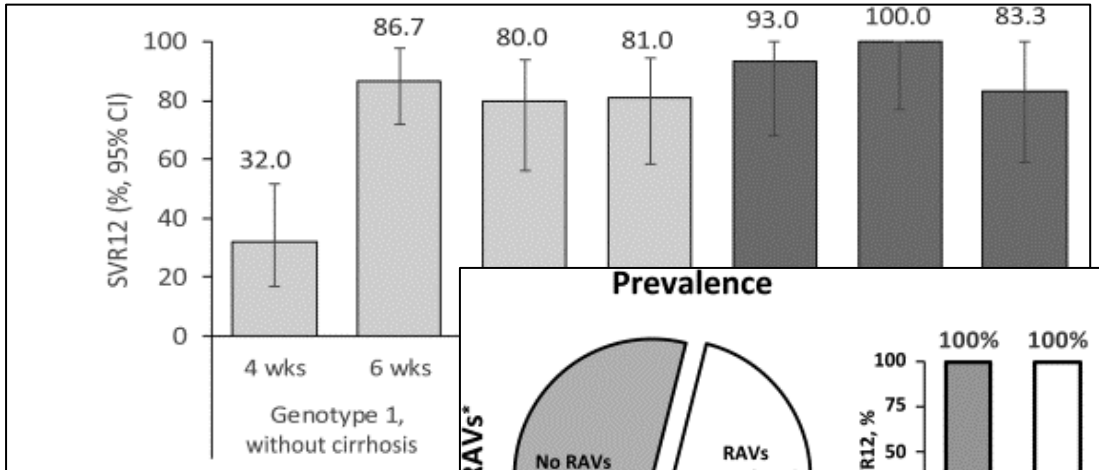
*HBV-R is defined as the abrupt increase in HBV replication in a patient with inactive or resolved HBV (HBsAg positive or negative, respectively), and hepatitis B core antibody (HBcAb) positive

Bersoff-Matcha , AASLD 2016, Poster LB-17

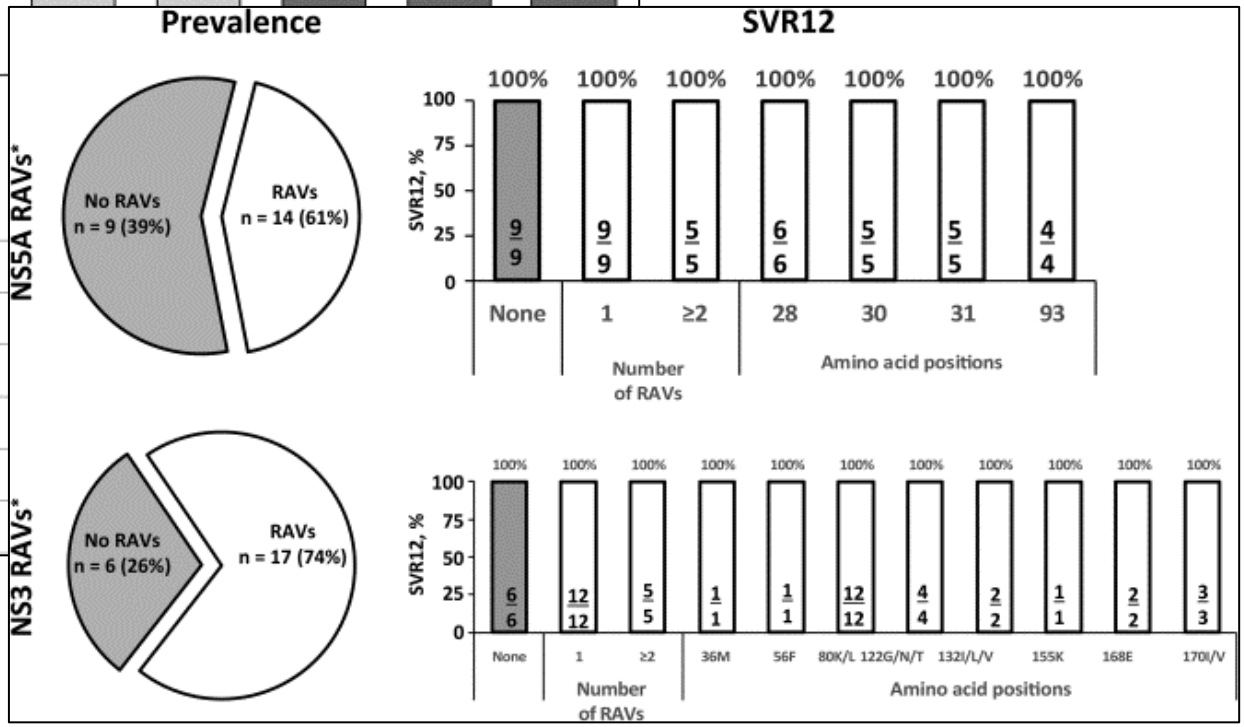
Remaining Challenges

- Patients who require ongoing optimization:
  - Genotypes non-1
  - High-level resistance
  - Advanced renal insufficiency
  - Decompensated cirrhosis
- Regimen questions:
  - Shorter duration
  - One pill daily, ribavirin-free for all

Grazoprevir/Elbasvir + Sofosbuvir



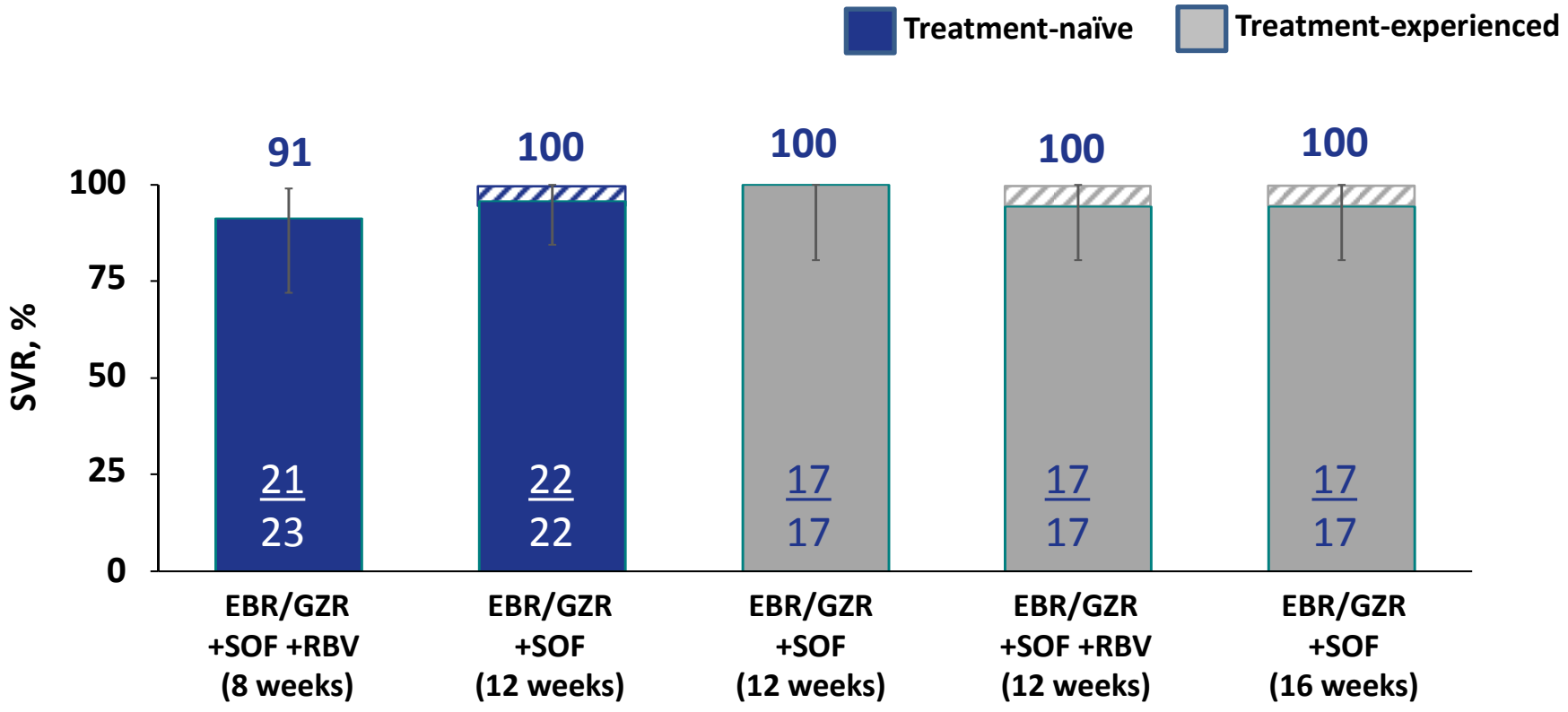
Total Patients	31	30
SVR	10	26
Nonvirologic failure	1	0
Breakthrough	0	0
Relapse	20	4
Reinfection	0	0



Treatment-naïve, GT 1 and 3

Lawitz E, et al. Hepatology 2017.

C-ISLE: EBR/GZR + SOF in GT 3 and Cirrhosis



Relapse	**2**	**0**	**0**	**0**	**0**

- Modified full analysis set includes excludes patients who discontinued treatment for reasons unrelated to study medication
- Baseline NS5A RAS did not impact SVR

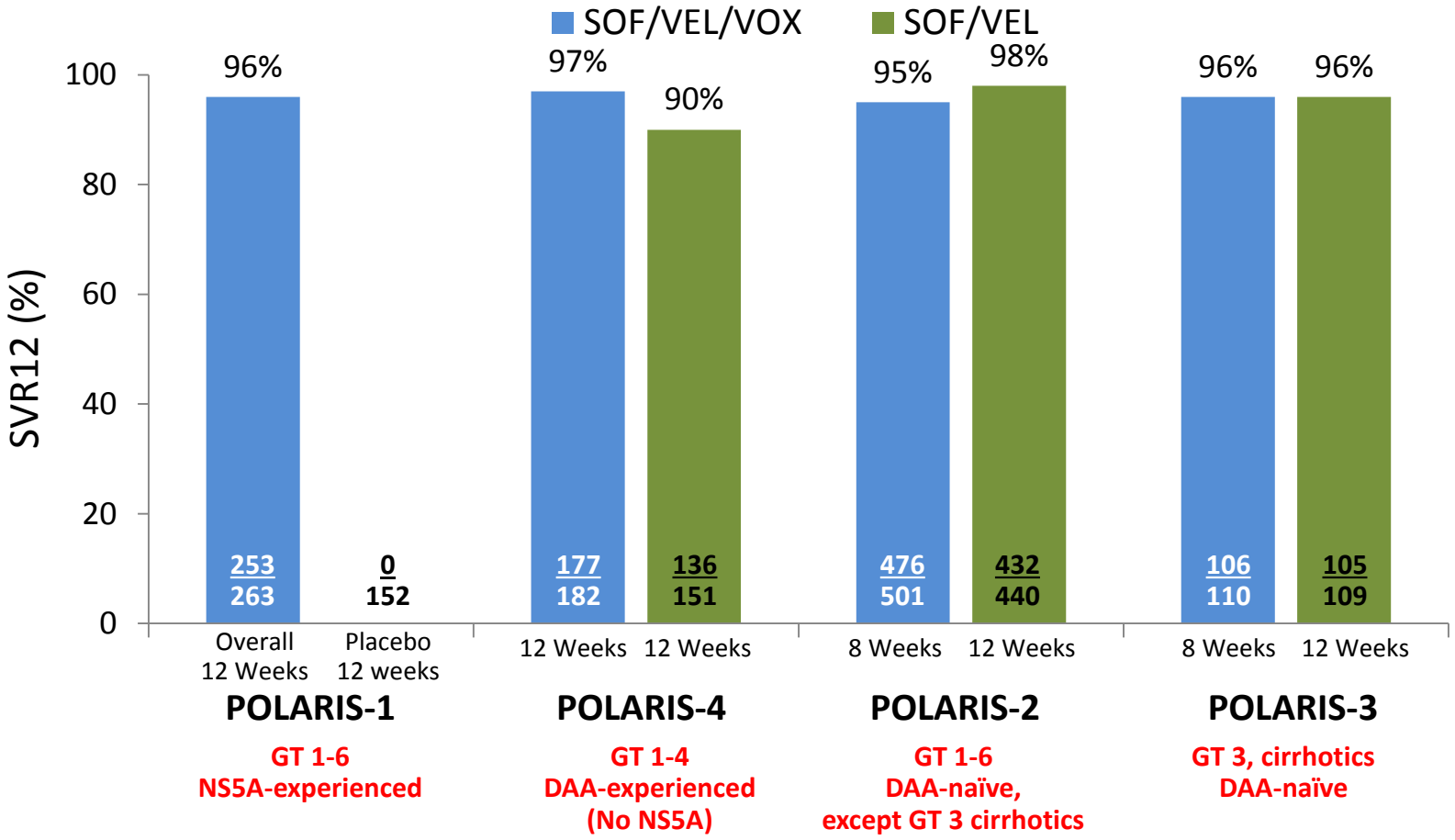
Foster et al AASLD 2016

DAAs in Late-Stage Clinical Development

	NS3/4A Protease Inhibitors	Nucleotide NS5B Polymerase Inhibitors	Non-nucleoside NS5B Polymerase Inhibitors	NS5A Replication Complex Inhibitors	Cyclophilin Inhibitors
Approved	Simeprevir Boceprevir Telaprevir Paritaprevir/r **Grazoprevir**	**Sofosbuvir**	Dasabuvir	Ledipasvir Ombitasvir Daclatasvir Elbasvir **Velpatasvir**	
Phase 3	**Voxilaprevir** Asunaprevir **Glecaprevir**	**MK-3682**	Beclabuvir	**Pibrentasvir** **Ruzasvir**	
Phase 2	GS-9256 Sovaprevir	ACH-3422	ABT-072 GS-9669 TMC-647055	Odalasvir GSK2336805 PPI-668	SCY-635

*Not all-inclusive.

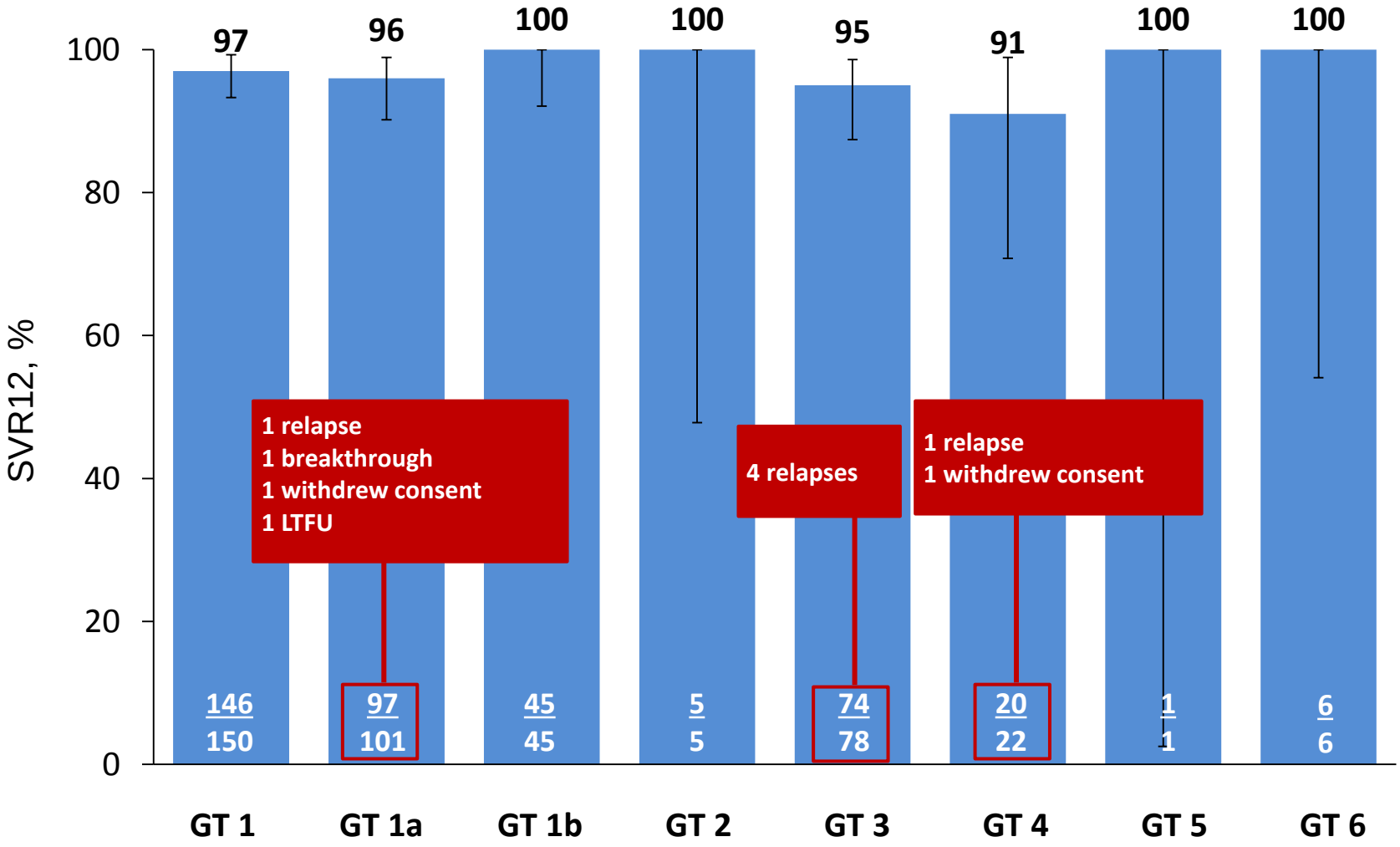
Sofosbuvir/Velpatasvir/Voxilaprevir



SOF/VEL/VOX for 12 weeks provides a STR for all DAA-experienced patients and SOF/VEL for 12 weeks provides a STR for DAA-naive patients regardless of cirrhosis status

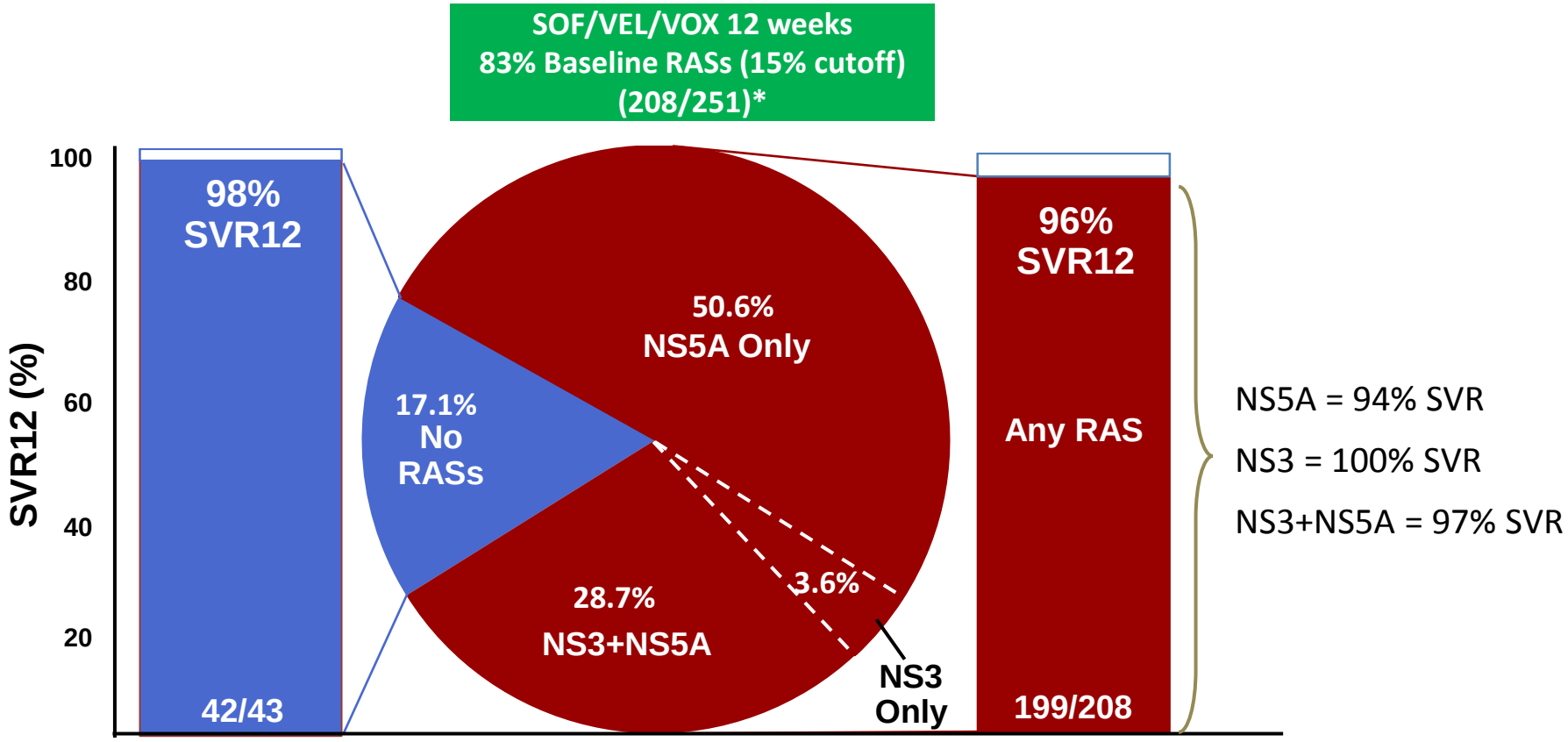
Bourliere M, AASLD 2016; Zeuzem S, AASLD 2016; Jacobson IM, AASLD 2016; Foster GR, AASLD 2016.

POLARIS-1: SOF/VEL/VOX for 12 Wks in NS5A Inhibitor-Experienced HCV GT 1–6



Bourliere M, AASLD 2016.

POLARIS 1: Baseline Resistance Associated Substitutions (RAS)

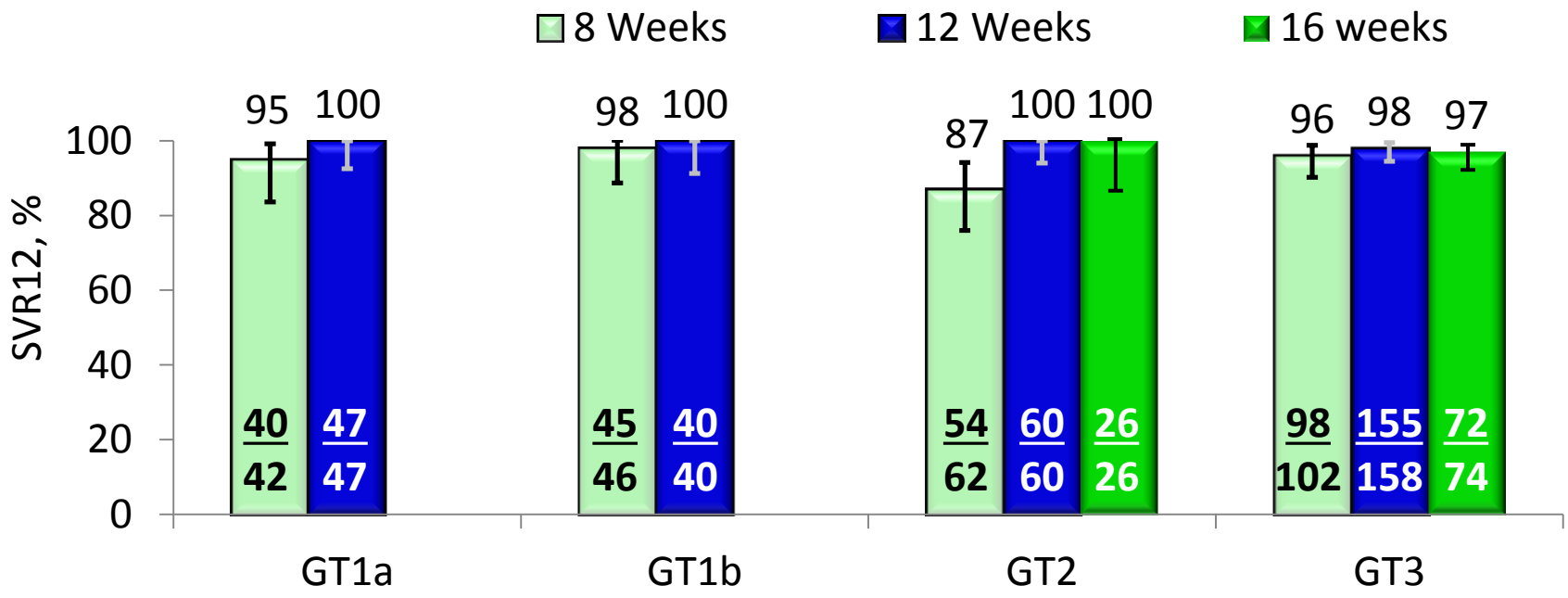


- 2 patients had S282T at baseline; both achieved SVR12

Bourliere M, AASLD 2016, Oral 194

Bourliere M, AASLD 2016.

C-CREST: MK-3682/Grazoprevir/Ruzasvir (MK3)

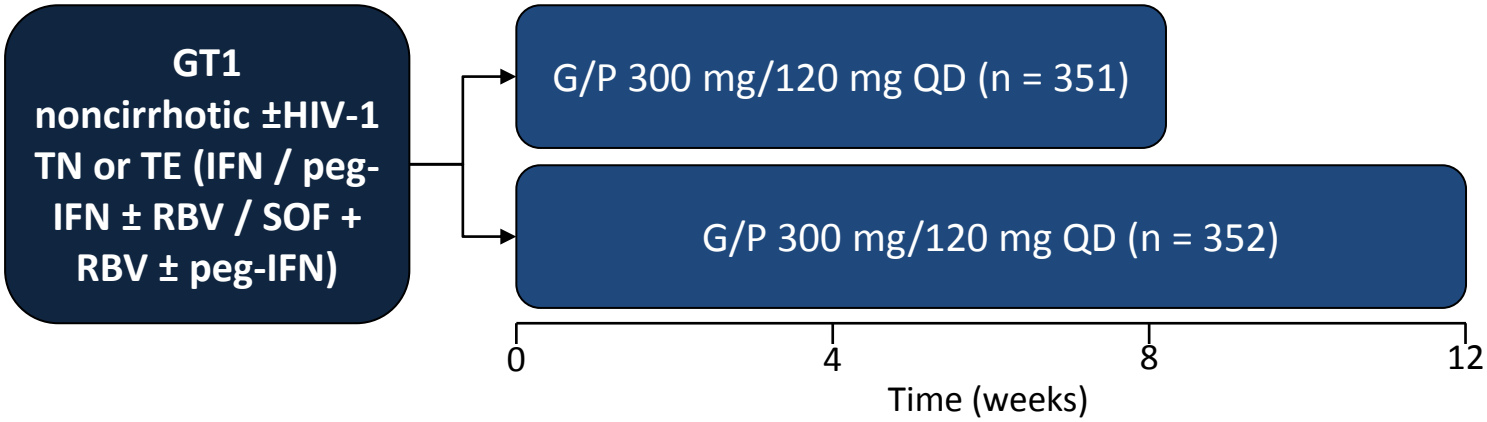


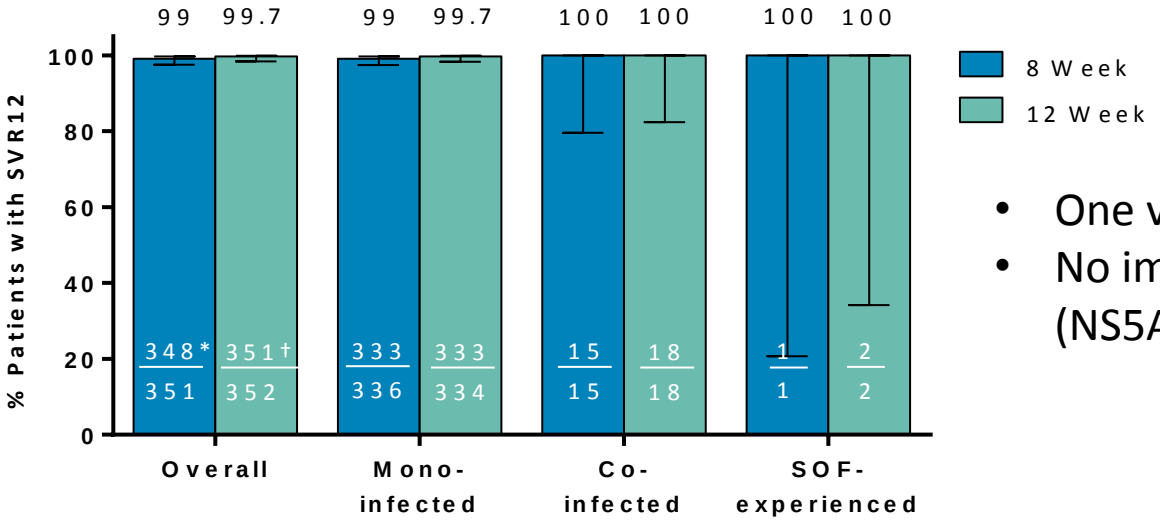
Relapses	**2**	**0**		**1**	**0**		**7**	**0**	**0**	**4**	**3**	**2**
Discontinuation (DR-AE)	**0**	**0**		**0**	**0**		**1***	**0**	**0**	**0**	**0**	**0**

- No difference with ribavirin or based on cirrhosis or prior P/R Rx
- One GT2 patient treated with 8 weeks + RBV discontinued at Day 5 due to drug-related AEs (fatigue, malaise)

Lawitz et al, AASLD 2016.

ENDURANCE-1: G/P for 8 or 12 Weeks GT1 Noncirrhotics, no NS5A



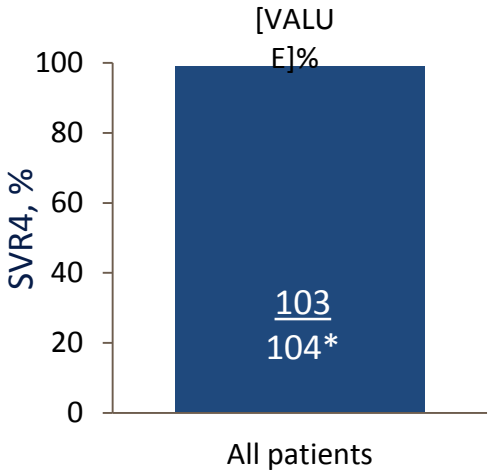


- One virologic failure (Wk 8)
- No impact of preexisting RAS (NS5A ~25%)

Zeuzem et al, AASLD 2016.

EXPEDITION-IV: G/P for 12 Weeks in Renal Impairment (GFR <30 mL/min)

- 104 patients with GT1–6 ± compensated cirrhosis TN or TE (IFN- or SOF-based regimens)
- eGFR <30 mL/min/1.73 m



Demographics	Patients N = 104
Treatment-experienced	42%
Compensated cirrhosis	19%
GT1/2/3/4/5/6	52%/16%/11%/19%/1%/1%
CKD stage 4 CKD stage 5 Dialysis	13% 87% 82%

- The patient not achieving SVR4 prematurely discontinued treatment
- 4 AEs (4%) led to study drug discontinuation
- 1 patient died after achieving SVR4 due to a serious AE not related to study drug (intracerebral hemorrhage)

Gane et al, AASLD 2016.

Conclusions

- HCV treatment continues to rapidly evolve
- Pangenotypic regimens are now available, with additional options on the horizon
- Progressively smaller groups of patients remain underserved by the regimens available
- Controversies remain: impact on liver function, HCC risk, treatment in renal failure, drug-drug interactions
- Expanding access will be the key to realizing the full potential of these DAA regimens to impact HCV-related morbidity and mortality

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