



Addressing Unmet
Medical Needs in **HCV**
Genotype 3

A C A S E - B A S E D A P P R O A C H

Moderator

Duncan Webster, BSc, BA, MA, MD, FRCPC

Internist,

Infectious Disease Physician, Department of Medicine

Medical Microbiologist,

Department of Laboratory Medicine, Saint John Regional
Hospital

Associate Professor,

Dalhousie University, Faculty of Medicine

Memorial University, Faculty of Medicine

Objectives

- Identify treatment options available to various patient populations with HCV genotype (GT) 3
- Review efficacy, safety, and tolerability data of different therapeutic options
- Recognize the expanding treatment armamentarium of HCV

Agenda

7:15 – 7:45 am	Registration and Breakfast	
7:45 – 7:50 am	Opening Remarks	Dr. Duncan Webster
7:50 – 8:35 am	Presentation <i>Addressing Unmet Medical Needs in Genotype 3 HCV: A Case-based Approach</i>	Dr. Karen Doucette
8:35 – 8:45 am	Question & Answer, Discussion, and Closing Remarks	Dr. Duncan Webster

Speaker

Karen Doucette, MD, MSc (Epi), FRCPC

Associate Professor,

Division of Infectious Diseases,

Department of Medicine

University of Alberta

Conflicts of Interest

Dr. Karen Doucette

Dr. Duncan Webster

Advisory Board /
Consultant

AbbVie

Speaker's Bureau

Grants /
Honorarium

Gilead, Hoffmann-LaRoche

Clinical Trial
Involvement (Within
Past Two Years)

AbbVie, BMS, Gilead, Janssen, Merck

Housekeeping

- Please save your questions for the Q&A Period.
During this period:
 - You may ask your question by raising your hand.
 - Cue cards have also been provided. These can be completed and handed in at any time to one of the coordinators circulating the room.
- Please complete the attendance sheet.
- Your feedback is important. Please complete the evaluation form.

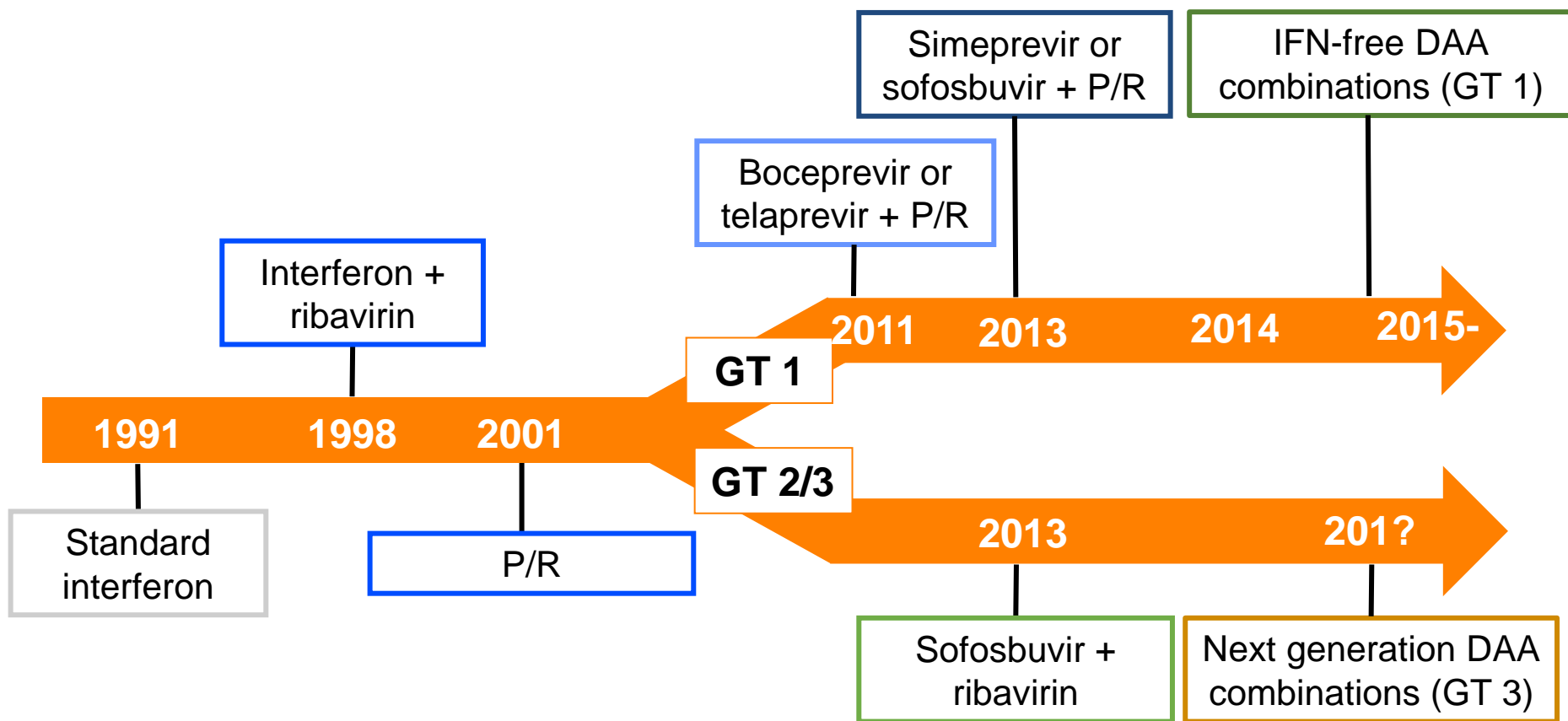
Addressing Unmet Medical Needs in HCV Genotype 3



Karen Doucette, MD, MSc (Epi), FRCPC

Associate Professor,
Division of Infectious Diseases,
Department of Medicine
University of Alberta

HCV Therapy Past, Present, and Future



HCV GT 3

Pathogenesis

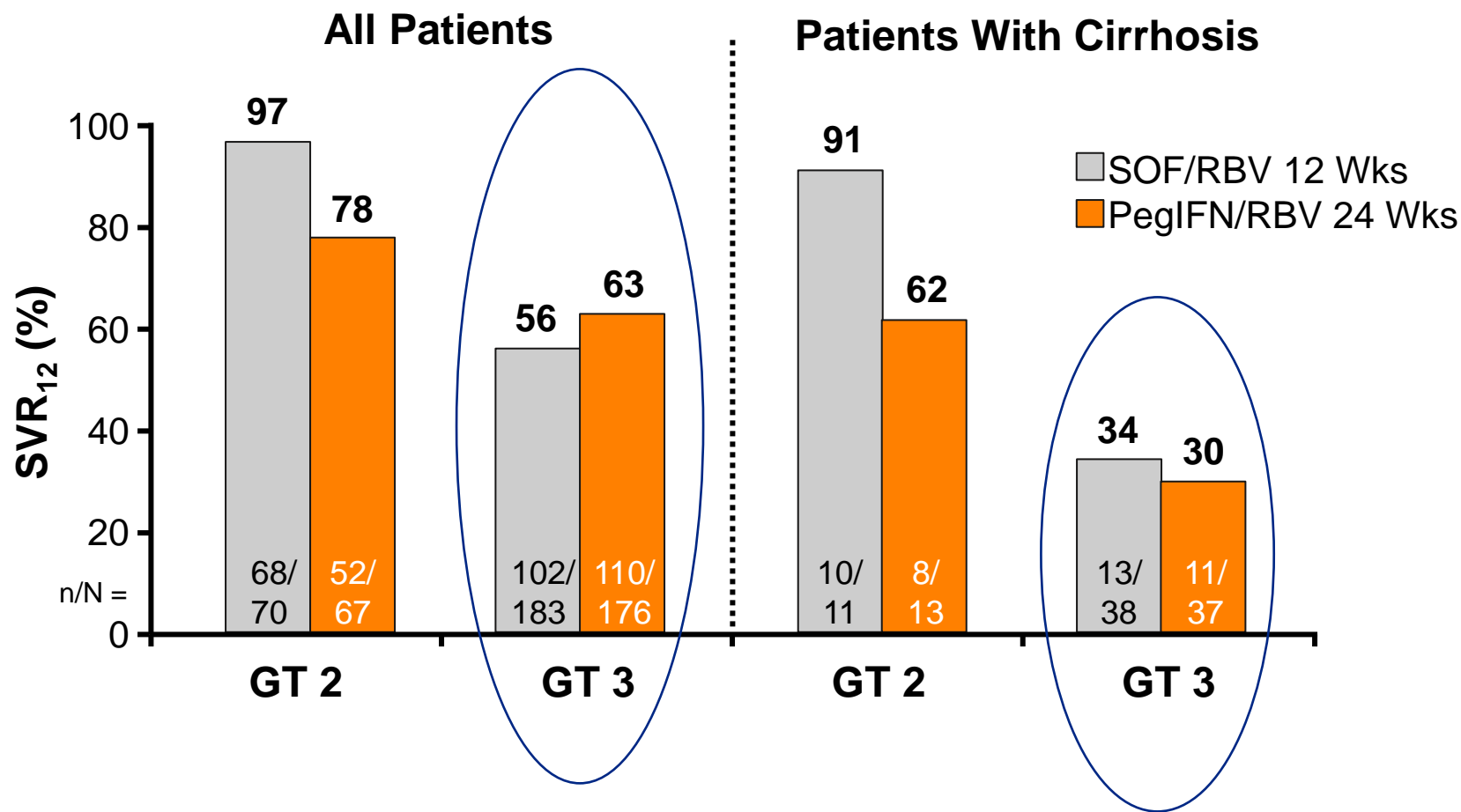
- GT 3 HCV is most pathogenic
 - Increased risk of cirrhosis and hepatocellular carcinoma
- HCV infection associated with steatosis and requires lipids for replication and assembly; the host serum lipid profile is modified by HCV
- Direct involvement of HCV
 - Steatosis is more frequent and severe in patients with GT 3 HCV
 - The severity of steatosis correlates with HCV RNA levels in patients with GT 3 infection
 - Steatosis decreases with successful antiviral therapy
 - In HCV-infected patients, steatosis due to metabolic syndrome is associated with increased liver disease progression and reduced response to therapy
- With this, and recent changes in HCV treatment, GT 3 is now the most difficult HCV infection to treat

Case 1: Naïve

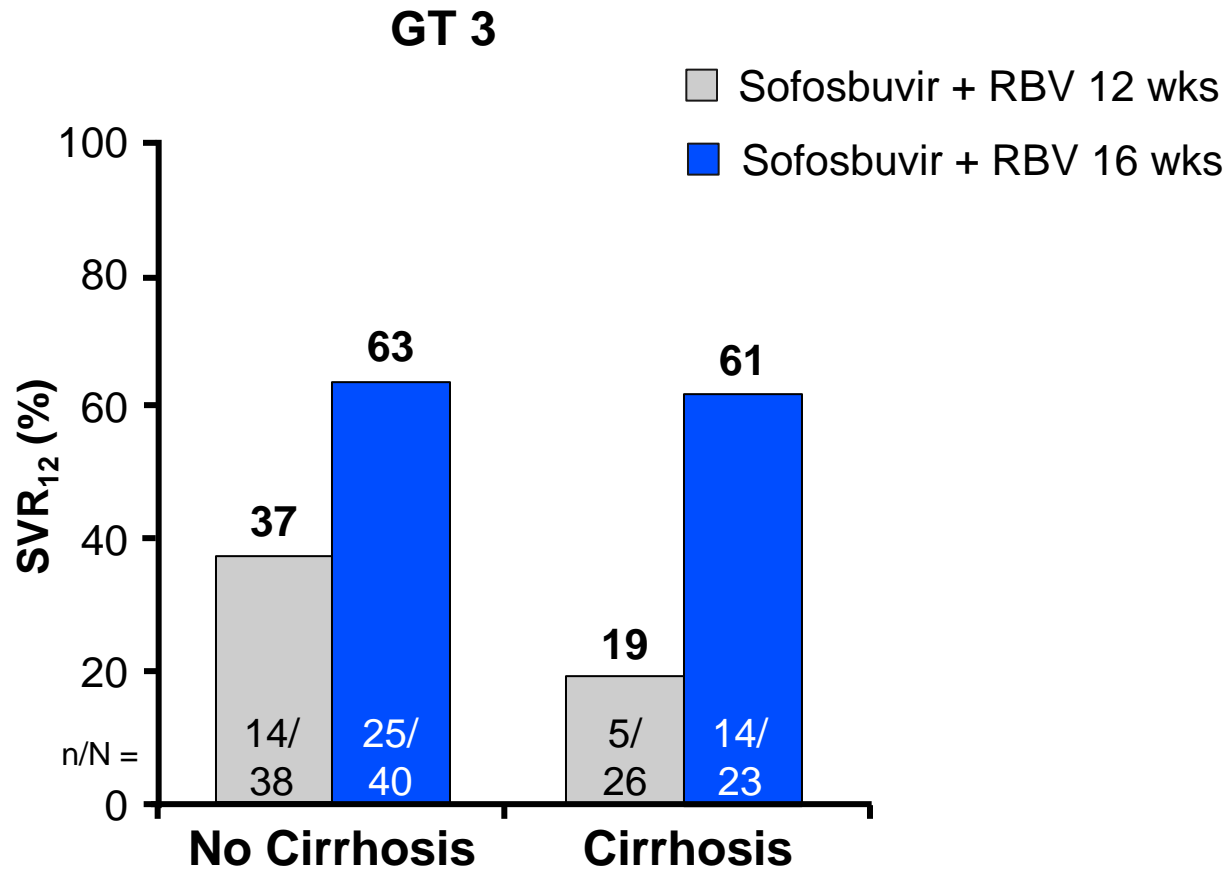
- 41M with GT 3 HCV
- Treatment naïve
- Comorbidities: obesity (BMI 35), schizophrenia
- Meds: risperidone, clonazepam, methadone
- FibroScan[®] 8.4 kPa (F2 fibrosis)

FISSION

Poorer Response to SOF/RBV in GT 3 vs. GT 2 Naïves, Especially Cirrhotics



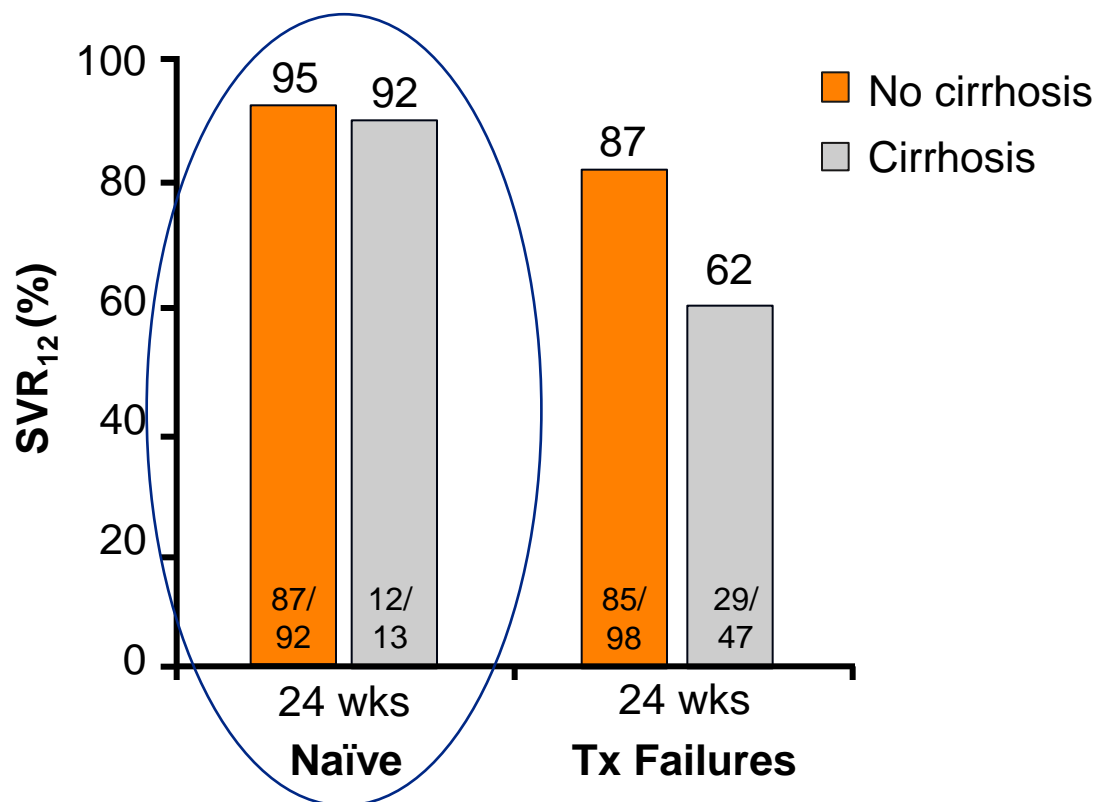
Impact of Cirrhosis and Duration on SVR Rates



VALENCE

SOF + RBV in IFN-naïve and IFN-experienced Patients With GT 3 HCV

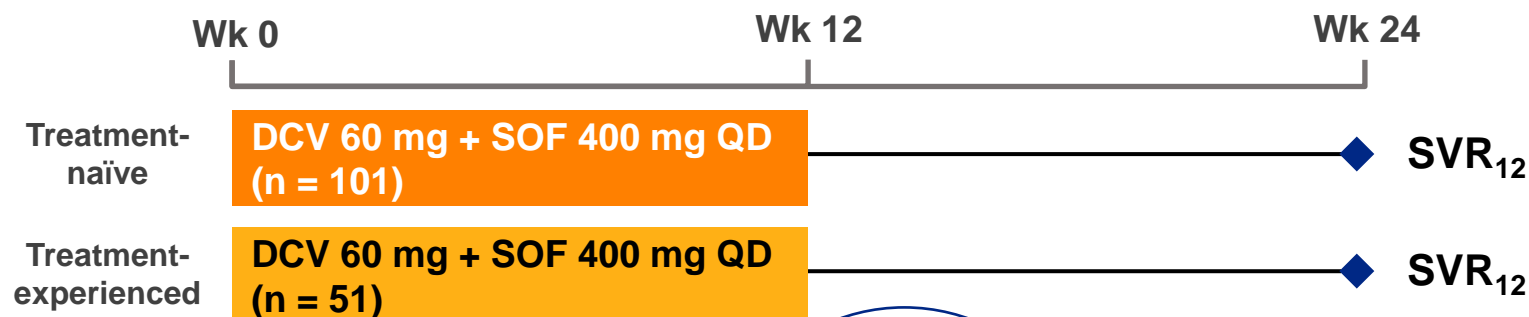
- Phase III study



ALLY-3

All-oral 12-week Combination Treatment with DCV + SOF in HCV GT 3

Efficacy and safety of daclatasvir (DCV) + SOF for 12 weeks in GT 3 TN or TE



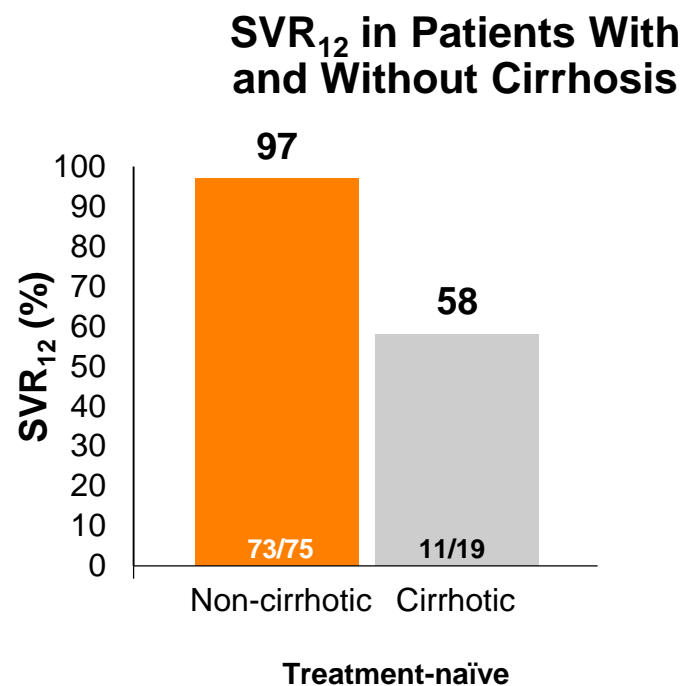
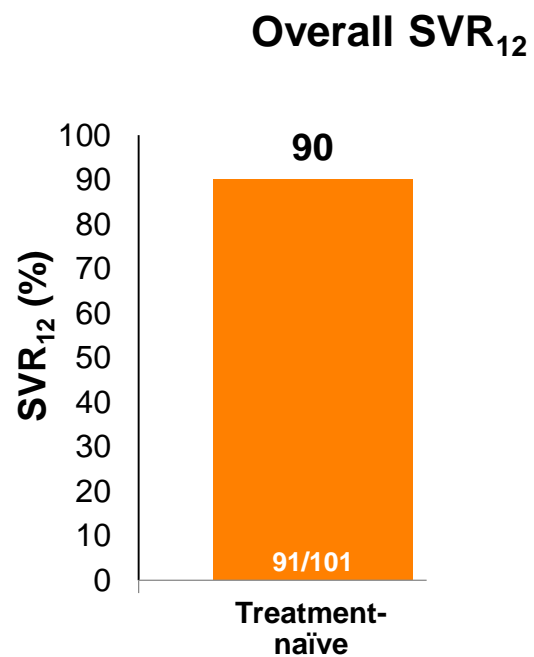
	Treatment-naïve n = 101	Treatment-experienced ^a n = 51
Age, median years (range)	53 (24-67)	58 (40-73)
Male, n (%)	58 (57)	32 (63)
Race, n (%)		
White	92 (91)	45 (88)
Black	4 (4)	2 (4)
HCV RNA ≥ 800 IU/mL, n (%)	70 (69)	38 (75)
Cirrhosis, n (%)	19 (19)	13 (25)
<i>IL28B</i> non-CC genotype, n (%)	61 (60)	31 (61)
Prior treatment failure, n (%)		
Relapse	-	31 (61)
Null response	-	7 (14)
Partial response	-	2 (4)

a. Patients who previously failed treatment with SOF (n = 7) or alisporivir (n = 2) were included

ALLY-3

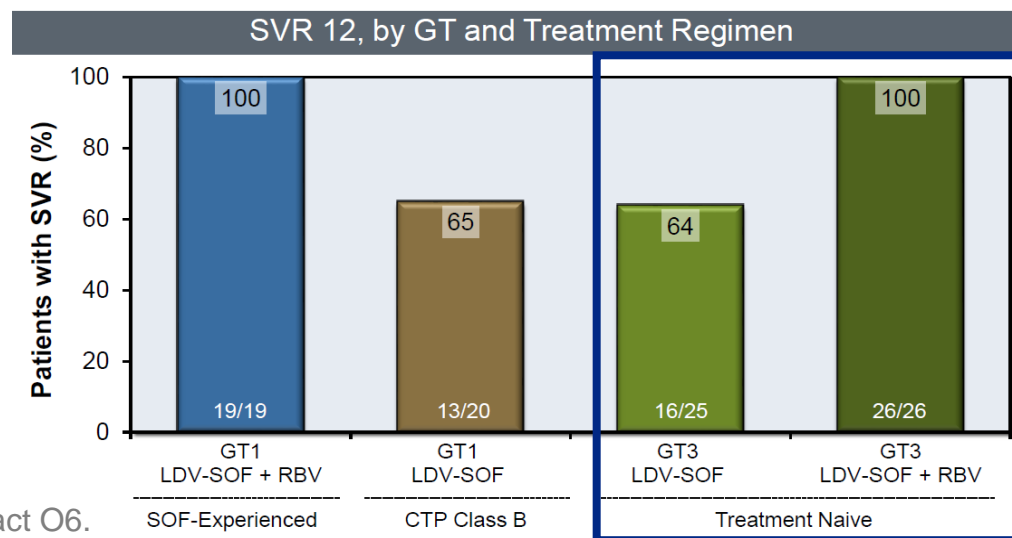
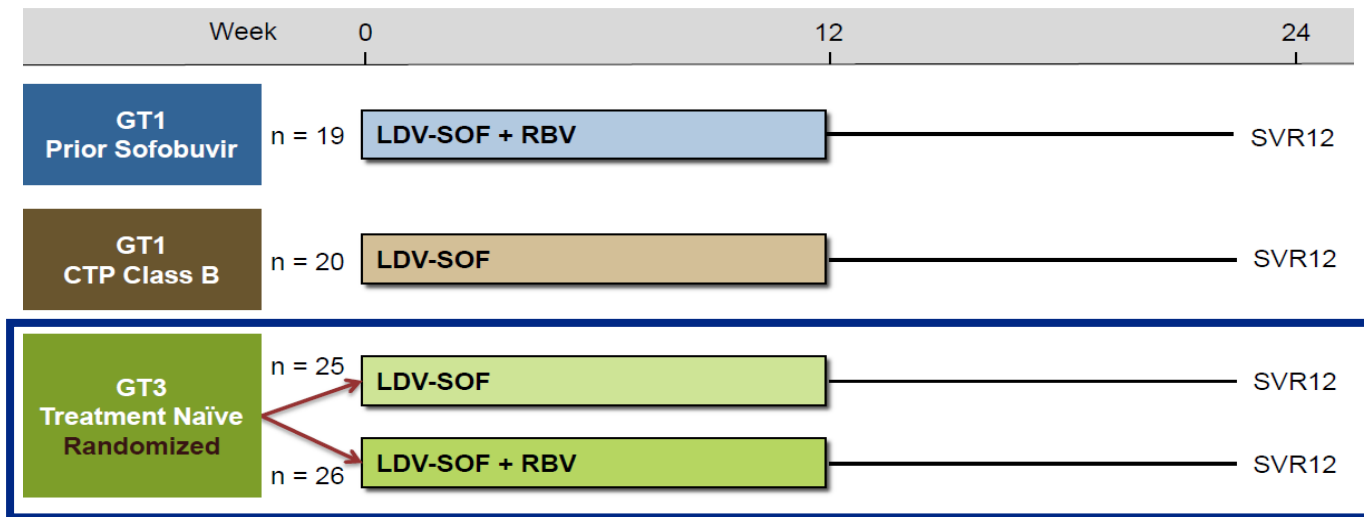
DCV + SOF x 12 weeks in HCV GT 3

SVR₁₂ Results



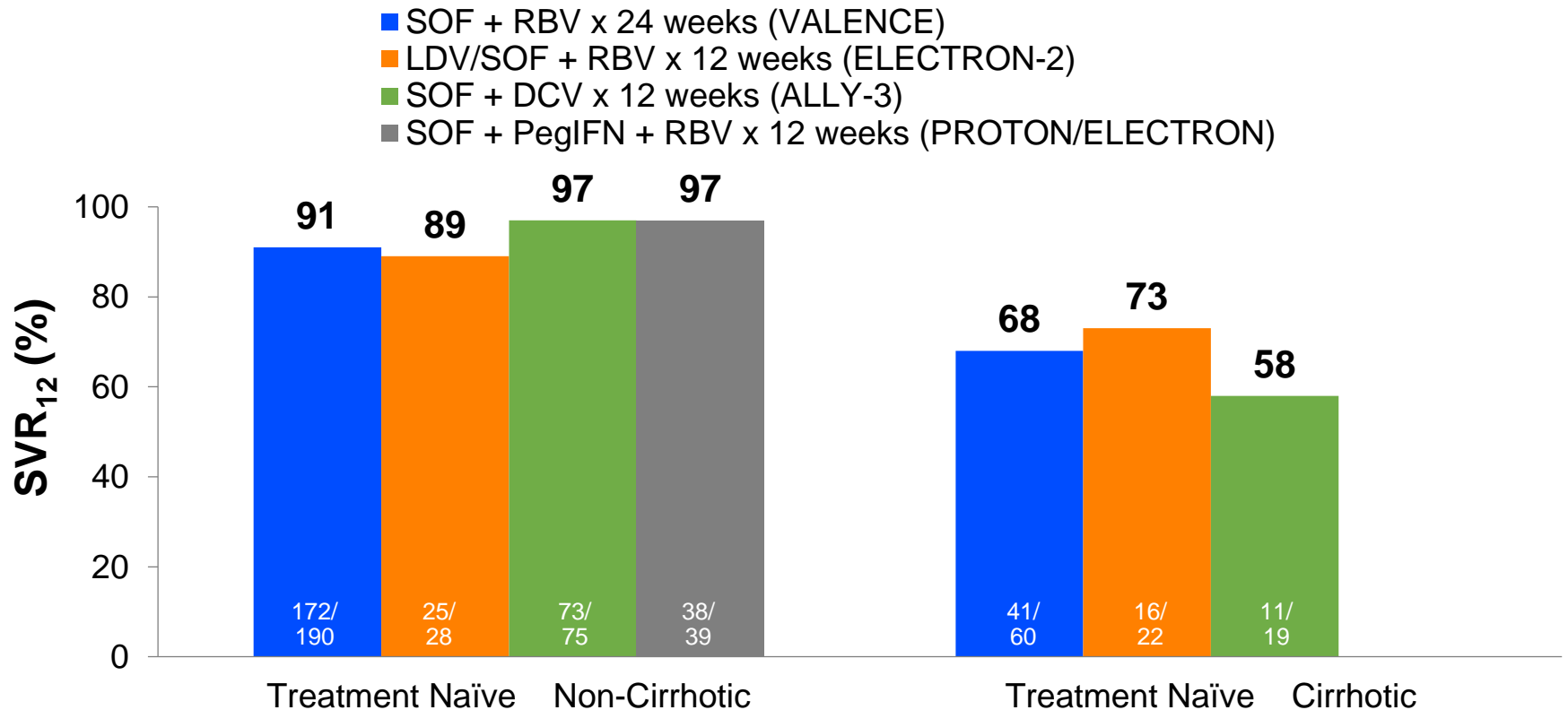
ELECTRON-2

Sofosbuvir-Ledipasvir ± Ribavirin in GT 1 & 3



Cross-Study Comparison: VALENCE, ELECTRON-2, ALLY-3, and PROTON/ELECTRON

Regimens for HCV GT 3: Treatment-naïve



Similar SVR₁₂ rates in TN HCV GT 3; response in cirrhotics still not optimal.

Sofosbuvir Common Drug Review

Recommendations: August 18, 2014

- **Patients with GT 3 CHC infection, in combination with RBV:**
 - A fibrosis stage of F2, F3, or F4
 - Previous treatment experience with PegIFN/RBV or a medical contraindication to PegIFN/RBV
 - 24 weeks
- **Other therapies in Canada:**
 - SOF/LDV: no Health Canada indication
 - Daclatasvir...
 - Approved in Europe and Japan
 - EASL Guidelines: option for GT 3: 12 weeks SOF + DCV in naïve patients

Case 2:

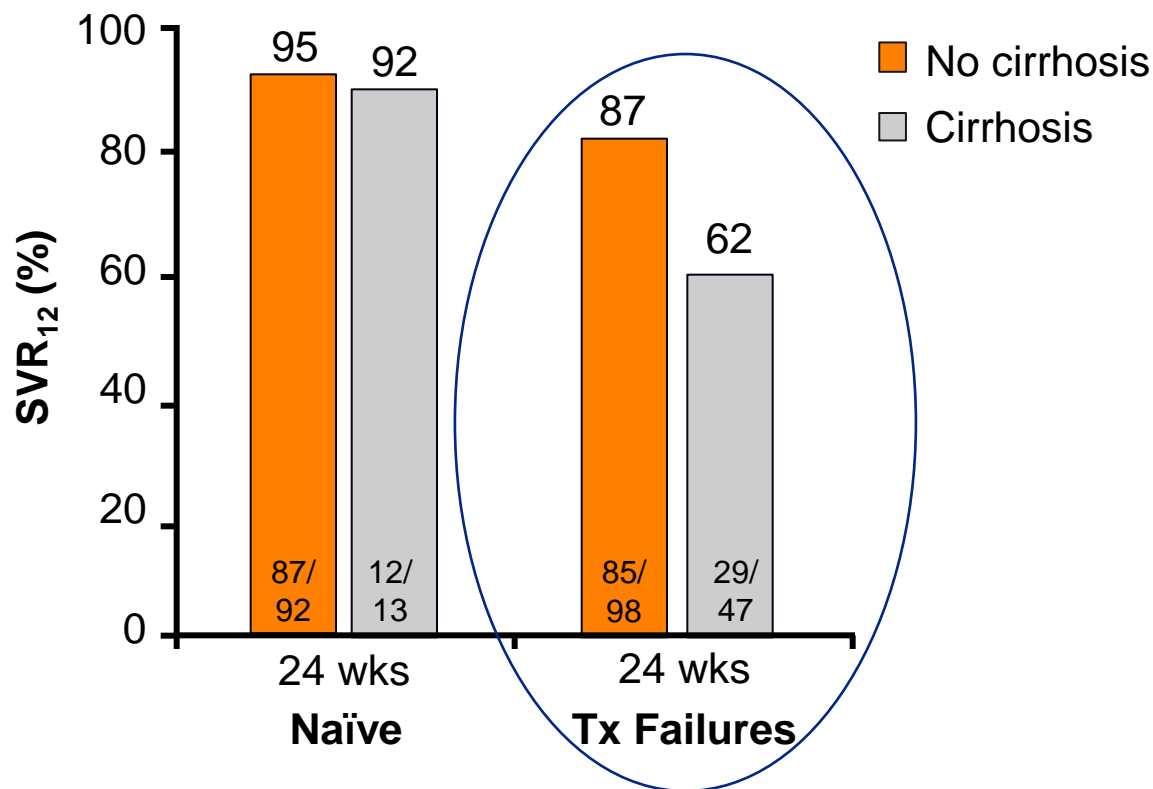
Cirrhotic Treatment-experienced

- 54M with GT 3 HCV
- 2007: Biopsy proven cirrhosis
 - PegIFN and ribavirin 800 mg for 24 weeks
 - No on-treatment assessment of virologic response; EOT negative
 - Relapsed
- 2011: Retreated PegIFN and weight-based ribavirin 1,400 mg;
 - Week 4 RNA neg, completed 24 weeks
 - Relapsed
- Stable, normal synthetic function
 - What now?

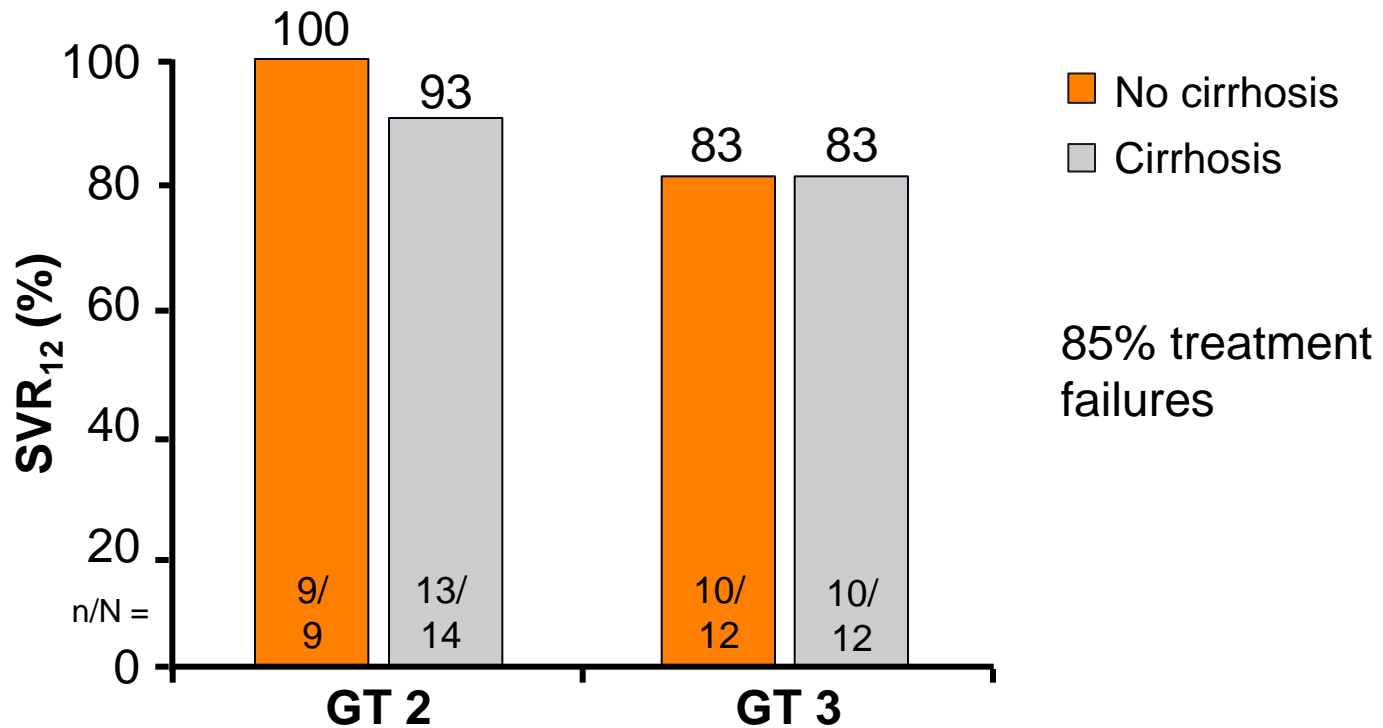
VALENCE

SOF + RBV in IFN-naïve and IFN-experienced Patients With GT 3 HCV

- Phase III study



PegIFN/RBV + SOF x 12 Wks in GT 2 or GT 3 Patients (Phase II)



BOSON

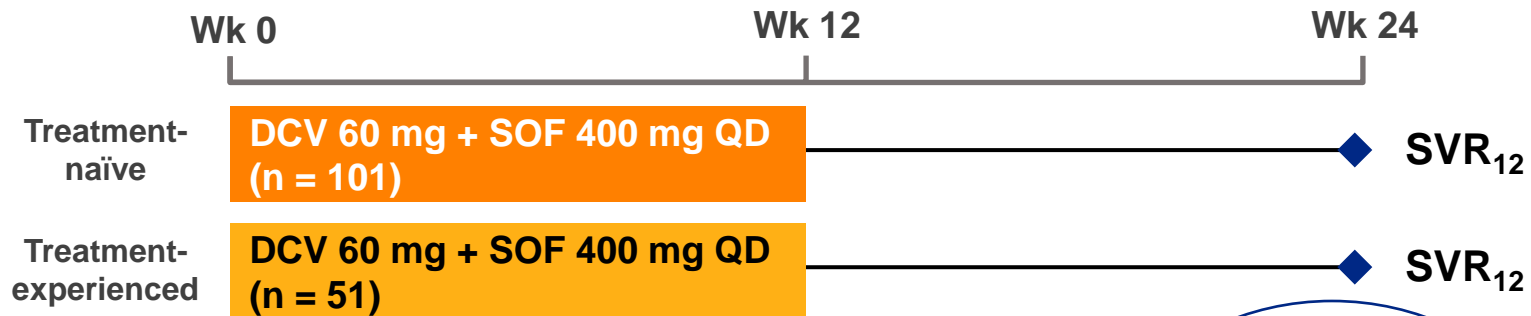
Open-label Study of Sofosbuvir + RBV With or Without PegIFN Alfa-2a in GT 2 or 3 CHC

- GT 3 mono-infected subjects, including cirrhosis
 - Treatment-naïve
 - Treatment failures
- GT 2 cirrhotic treatment failure
- Subjects randomized to 1:1:1 to 3 arms:
 - SOF + RBV x 16 weeks
 - SOF + RBV x 24 weeks
 - P + R + SOF x 12 weeks

ALLY-3

All-Oral 12-week Combination Treatment with DCV+SOF in HCV GT 3

Efficacy and safety of daclatasvir (DCV) + SOF for 12 weeks in GT 3 TN or TE

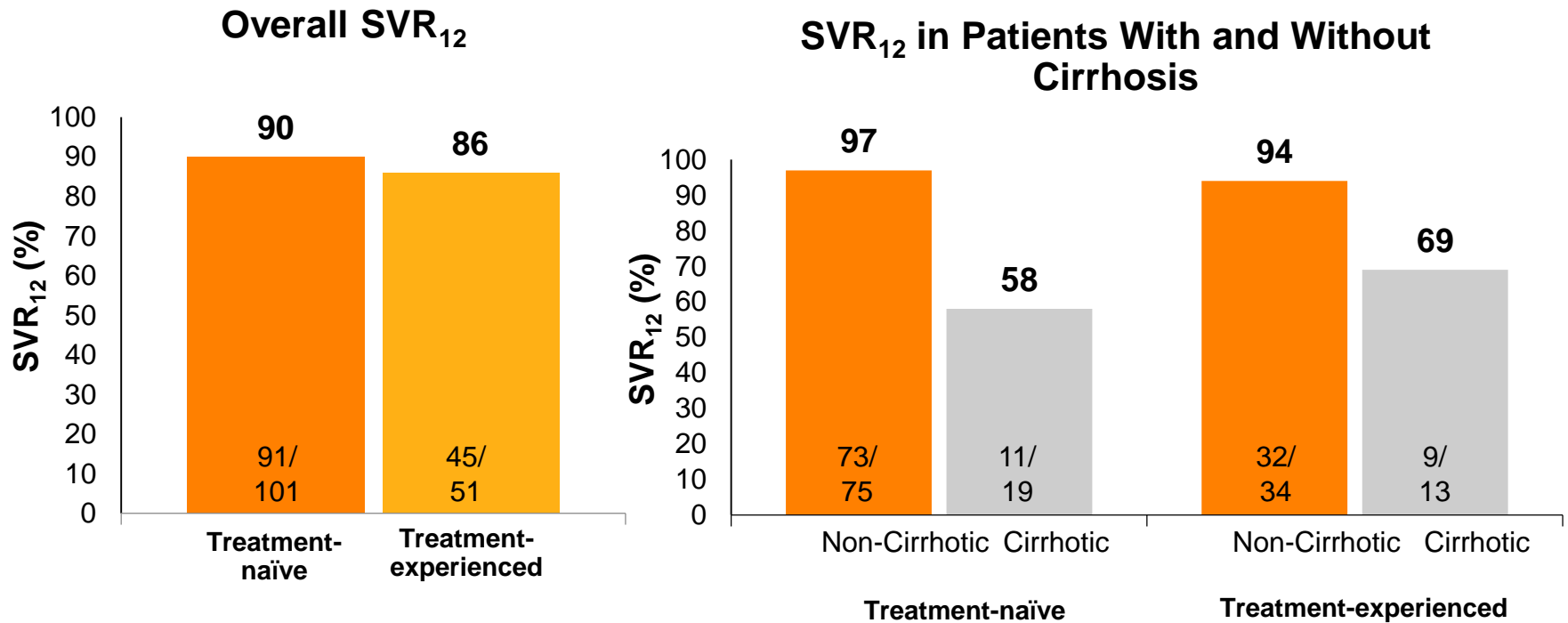


	Treatment-naïve n = 101	Treatment-experienced ^a n = 51
Age, median years (range)	53 (24-67)	58 (40-73)
Male, n (%)	58 (57)	32 (63)
Race, n (%)		
White	92 (91)	45 (88)
Black	4 (4)	2 (4)
HCV RNA ≥ 800 IU/mL, n (%)	70 (69)	38 (75)
Cirrhosis, n (%)	19 (19)	13 (25)
<i>IL28B</i> non-CC genotype, n (%)	61 (60)	31 (61)
Prior treatment failure, n (%)		
Relapse	-	31 (61)
Null response	-	7 (14)
Partial response	-	2 (4)

a. Patients who previously failed treatment with SOF (n = 7) or alisporivir (n = 2) were included

ALLY-3

DCV + SOF x 12 weeks in HCV GT 3 SVR₁₂ Results



ALLY-3

Safety and Tolerability of SOF + DCV x 12 Wks in GT 3 HCV Patients

Parameter, n (%)*	All Patients (N = 152)
Death	0
Serious AEs	1 (1) [†]
AEs leading to discontinuation	0
Grade 3/4 AEs	3 (2) [‡] /0
AEs in ≥ 10% of patients (all grades)	
▪ Headache	30 (20)
▪ Fatigue	29 (19)
▪ Nausea	18 (12)
Grade 3/4 laboratory abnormalities	
▪ Hemoglobin < 9.0 g/dL	0
▪ Absolute lymphocytes < 0.5 x 10 ⁹ /L	1 (1)
▪ Platelets < 50 x 10 ⁹ /L	2 (1)
▪ International normalized ratio > 2 x ULN	2 (1)
▪ Lipase > 3 x ULN	3 (2)

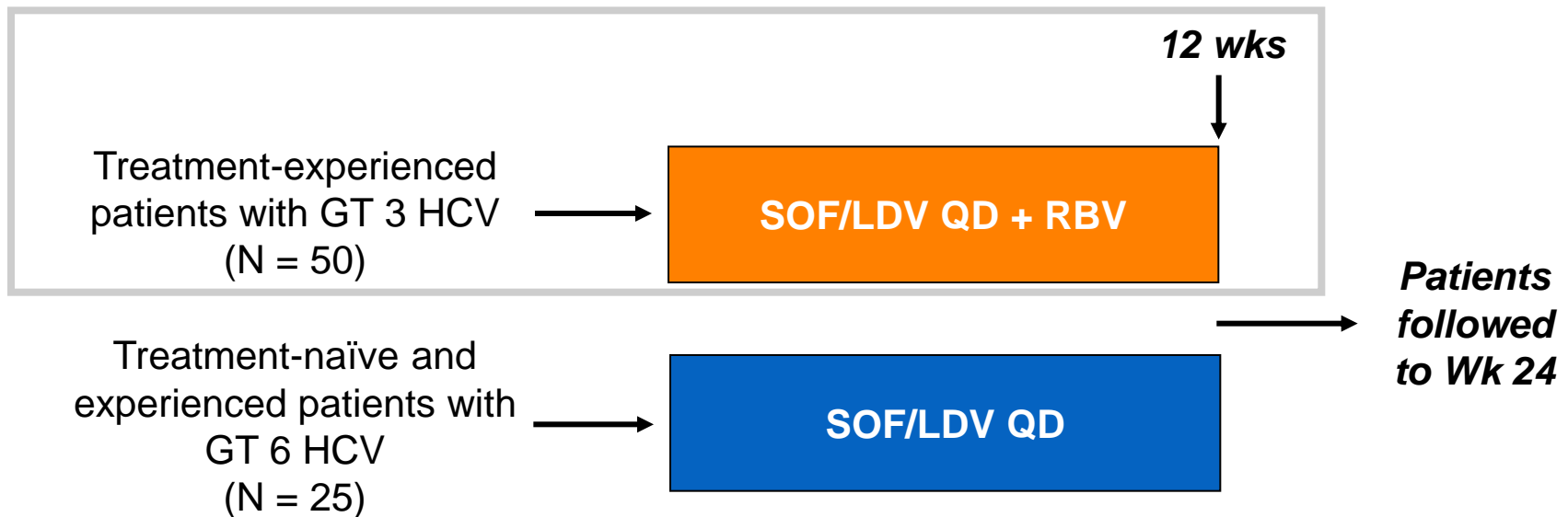
*On-treatment events for death and AEs; treatment-emergent events for grade 3/4 laboratory abnormalities.

[†]1 event of gastrointestinal hemorrhage at Wk 2, considered not related to study treatment.

[‡]Arthralgia in 1 patient; food poisoning, nausea, and vomiting in 1 patient; and serious AE of gastrointestinal hemorrhage in 1 patient.

SOF/LDV ± RBV x 12 Wks in Treatment-naïve and Experienced Patients With GT 3 or 6 HCV

- Non-randomized, open-label Phase III trial
- Primary endpoint: SVR₁₂
- Cirrhosis present in 44% of GT 3 patients and 8% of GT 6 patients

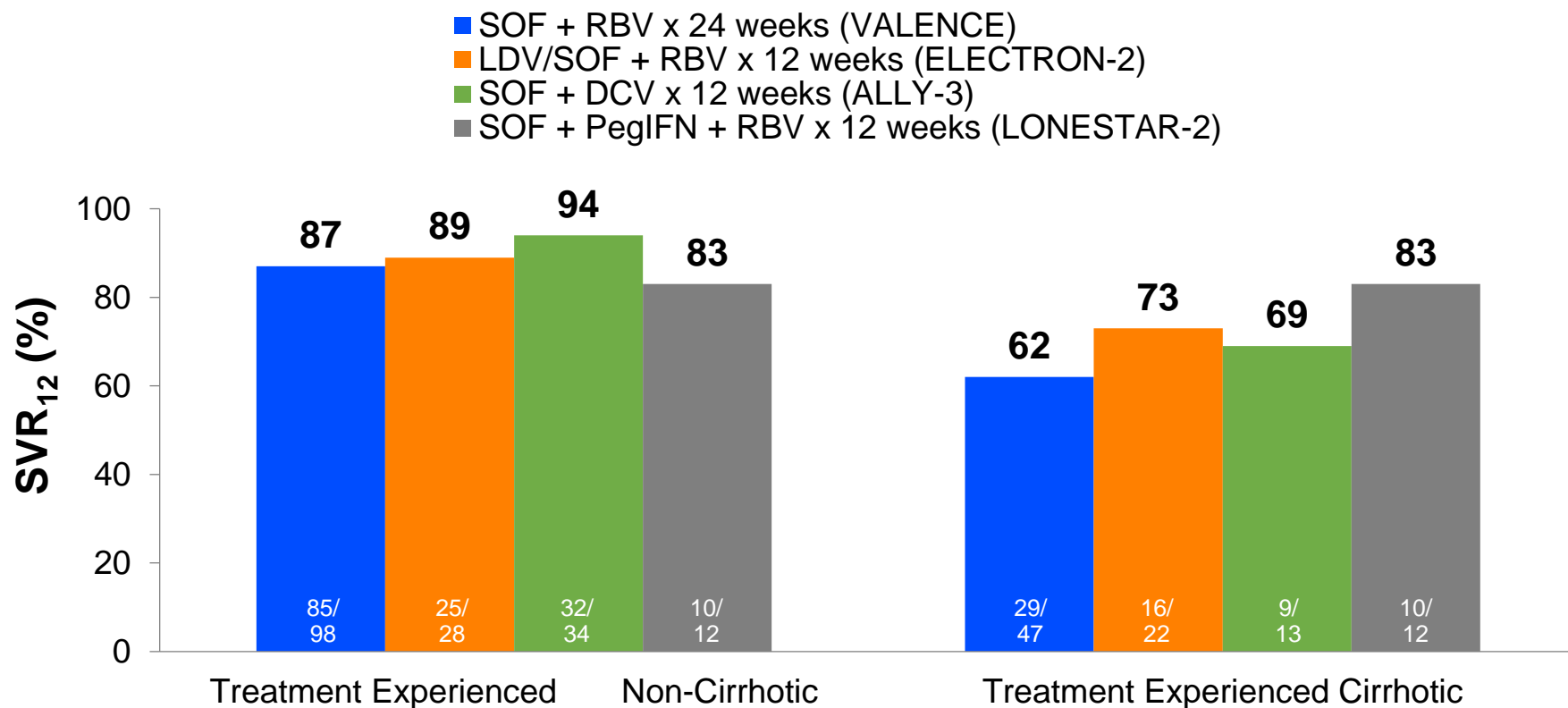


Efficacy of SOF/LDV ± RBV x 12 Wks in Patients With GT 3 or 6 HCV

SVR ₁₂ , % (n/N)	GT 3	GT 6
	Tx-experienced Patients	
Overall	82 (41/50)	96 (24/25)
By cirrhosis status		
▪ No cirrhosis	89 (25/28)	NR
▪ Cirrhosis	73 (16/22)	NR

- GT 3 HCV remains difficult to treat, particularly in treatment-experienced cirrhotic patients

Cross-Study Comparison: VALENCE, ELECTRON-2, ALLY-3, and LONESTAR-2 Regimens for HCV GT 3: Treatment-experienced



Similar SVR₁₂ rates in TE HCV GT 3 non-cirrhotic; Peg/RBV/SOF may be better in TE cirrhotics (await BOSON)

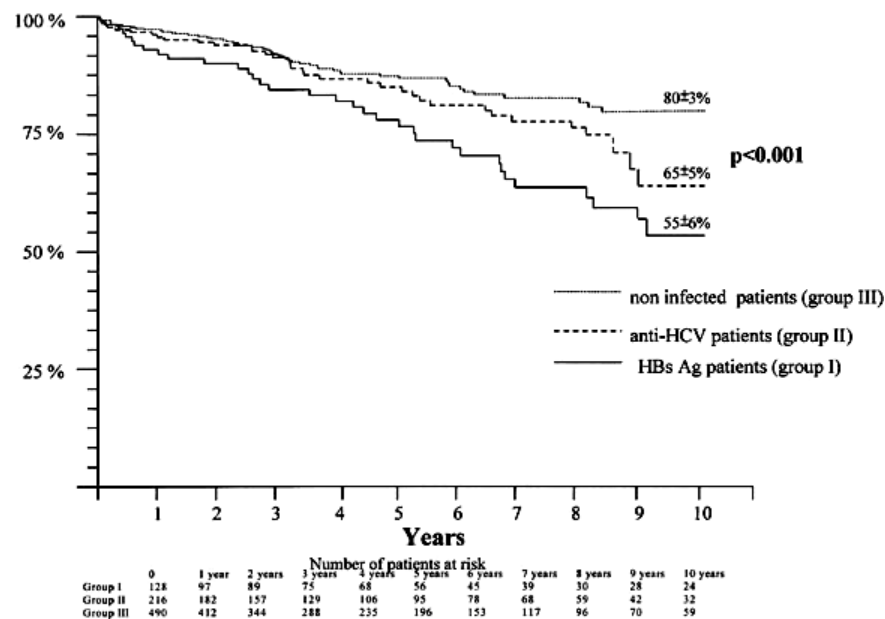
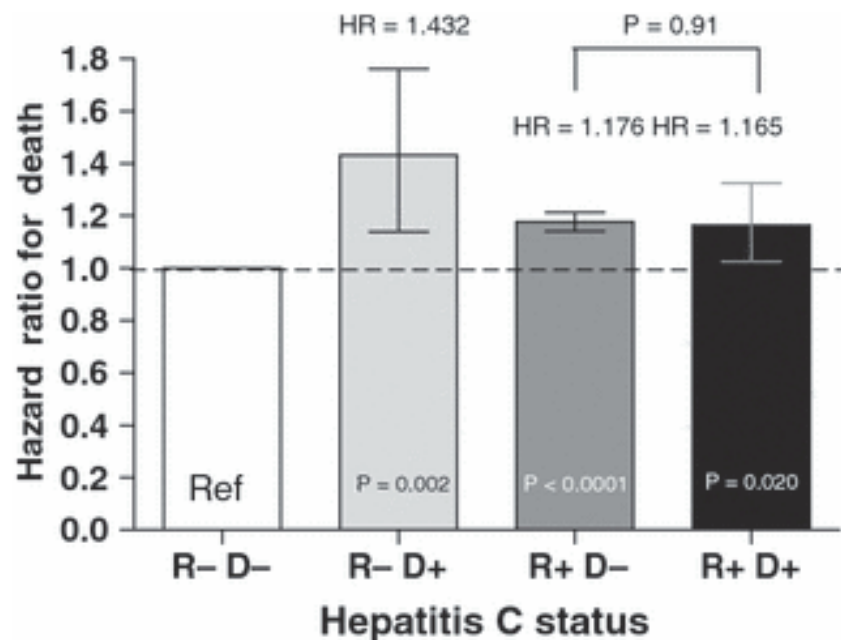
Case 3:

Post-transplant

- 58M HCV GT 3 and ESRD due to polycystic kidney disease
- 2009
 - Liver biopsy F2 fibrosis
 - Treated pegIFN and reduced dose ribavirin; relapsed
- 2010
 - Deceased donor renal transplant; uncomplicated, CR ~ 85 mmol/L
 - Tacrolimus, mycophenolate sodium and prednisone 2.5 mg every other day
- Progressive rise in liver stiffness to 15.5 kPa April 2014 and 21.5 March 2015 with mild splenomegaly, platelets 120, albumin 35

HCV Post-SOT

- HCV progression accelerated post transplant
 - Liver: 20%-25% cirrhosis by 5 years
 - Renal: Increased risk of death from liver disease at 10 years (survival 66% vs. 80%)
- Increased risk of extrahepatic complications
 - Post-transplant diabetes
 - Recurrent or *de novo* glomerulonephritis
 - Coronary vasculopathy (heart transplant)
 - May increase risk of PTLD



Interferon-free Therapy: A “Game-changer” Pre- and Post-transplant

- Pre-transplant
 - Liver: IFN-based therapy contraindicated in decompensated; poor response and tolerability even in compensated
 - Non-hepatic: Ribavirin relatively contraindicated in ESRD; IFN-based therapy poorly tolerated in ESRD, advanced lung disease, and contraindicated in severe cardiac disease
- Post-transplant
 - Liver: Low SVR, poor tolerability of IFN-based therapy; HCV recurrence the most significant factor impacting outcomes
 - Non-hepatic: IFN contraindicated due to risk of IFN-induced rejection

Safety and Efficacy Of New DAA-based Therapy for Hepatitis C Post-transplant: Interval Results from HCV-TARGET

- Prospective observational (US, Germany, Canada)
- N = 237
 - Peg/RBV/SOF: 30 SIM/SOF: 117
 - SOF/RBV: 58 SIM/SOF/RBV: 32
- GT 1 SIM/SOF ± RBV: 68 evaluable, 90% SVR₄
 - 86% cirrhotics vs. 94% non-cirrhotics
 - 83% 1a vs. 95% 1b
 - 77% MELD > 10 vs. 92% ≤ 10
- Peg/RBV/SOF SVR 83% (GT 1); 100% (GT 3)
- SOF/RBV SVR 90% (GT 2); 60% (GT 3)

SOLAR-1

LDV/SOF + RBV for Treatment of HCV in Patients with Post-transplant Recurrence

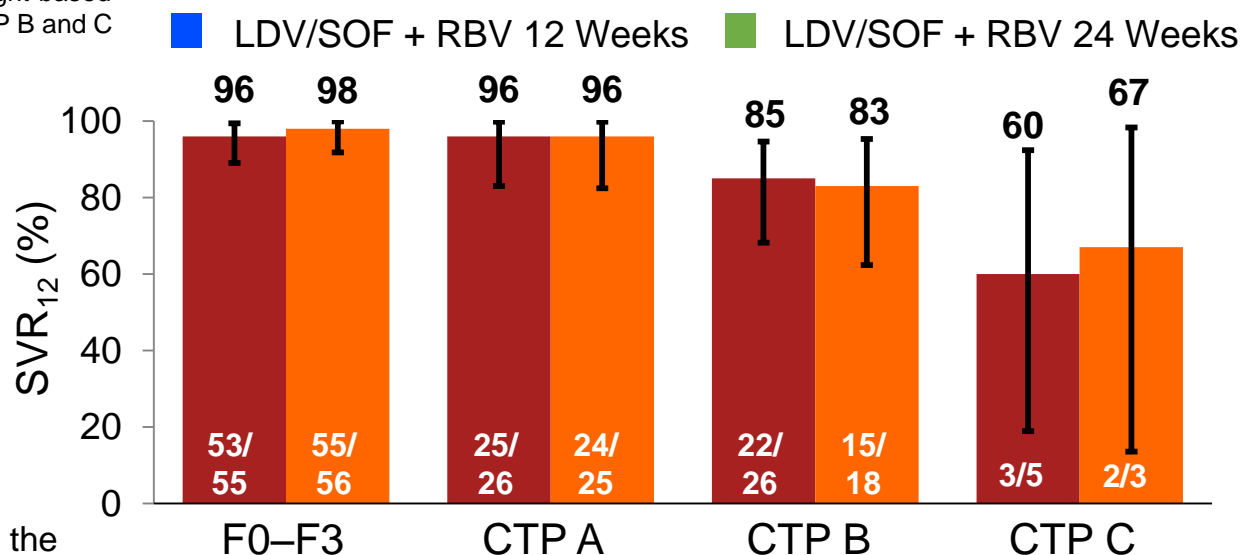
Prospective, multicenter study in TN and TE HCV GT 1 and 4 patients, who were post-liver transplantation received 12 or 24 weeks of LDV/SOF + RBV*



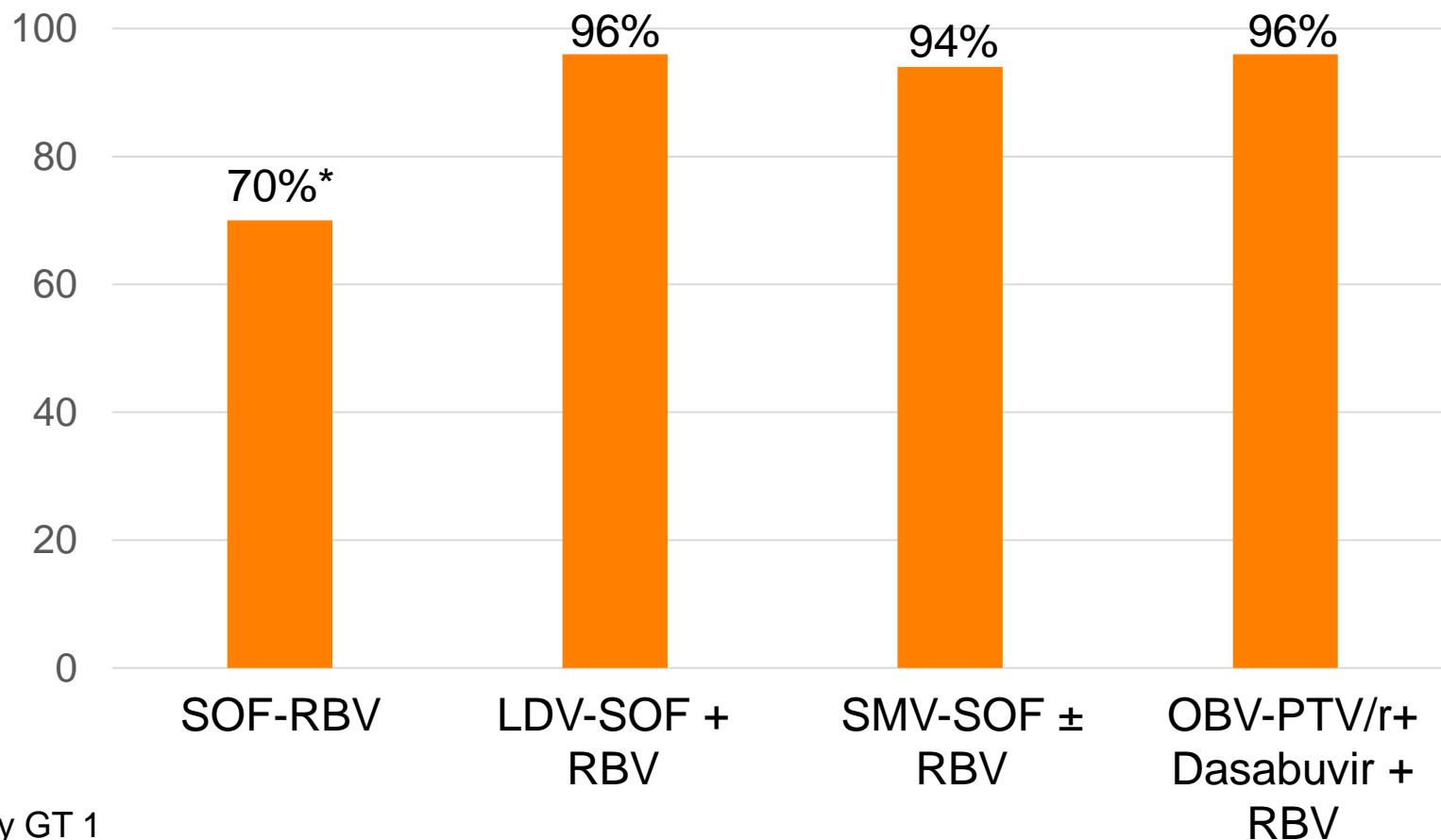
*RBV dosing: F0–F3 and CTP A cirrhosis: weight-based (< 75 kg = 1,000 mg; ≥ 75 kg = 1,200 mg); CTP B and C cirrhosis: dose escalation, 600 mg-1,200 mg/d

High rate of SVR₁₂ irrespective of disease severity or duration of therapy

Error bars represent 2-sided 90% exact confidence intervals.
8 CTP B 24-week and 1 CTP C 24-week subjects have not reached the Week 12 post treatment visit.



Efficacy of DAA Combos in GT 1 Liver Transplant Recipients without Cirrhosis



*Mostly GT 1

High Efficacy and Favorable Safety Profile of Daclatasvir-based All-oral Antiviral Therapy in Liver Transplant Recipients with Severe Recurrent HCV

HCV RNA Level, n (%)	Baseline	EOT	≥ 12 Weeks After
	(N = 30)	(n = 24) ^a	EOT (n = 12) ^b
Undetectable	1 (3)	19 (79)	9 (75)
Detectable, but < 43 IU/mL	0	5 (21)	2 (17)
43 to < 999 IU/mL	2 (7)	0	0
999 to < 1,000,000 IU/mL	12 (40)	0	1 (8)
≥ 1,000,000 IU/mL	15 (50)	0	0

EOT, end of treatment

^a 6 patients died during treatment

^b 12 patients did not have sufficient follow-up at the time of data collection

Studies on PK/PD in Patients With Renal and Hepatic Impairment

DAA	Primary Metabolic Pathway	<u>Suitable in Patients With Cirrhosis</u>			Suitable if Renal Impairment
		CTP-A	CTP-B	CTP-C	
Sofosbuvir	Renal	Yes	Yes	Yes	Not if CrCl < 30 mL/min
Ledipasvir	Hepatic	Yes	Yes	Yes	Unknown
Daclatasvir	Hepatic	Yes	Yes	Yes	Yes

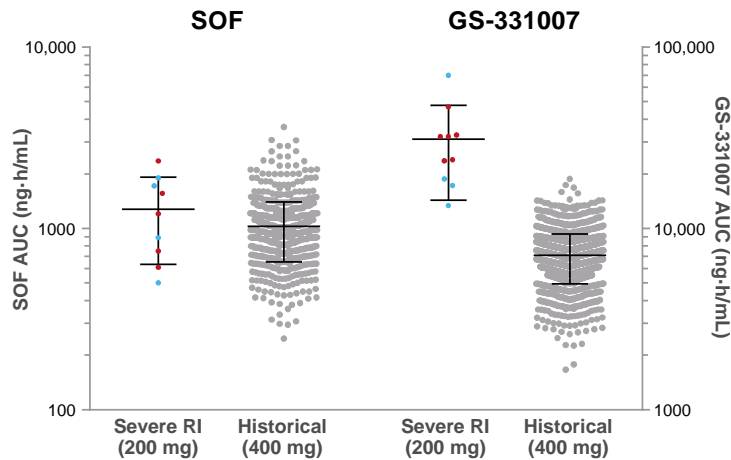
Bifano M, et al. AASLD 2011. Abstract 1362. Garimella K, et al. Clinical Pharm 2014. Abstract P43. Sofosbuvir [package insert]. Simeprevir [package insert]. Khatri A, et al. AASLD 2012. Abstract 758. German, et al. AASLD 2013. Abstract 467. Kirby R, et al. Clinical Pharm 2013. Abstract PO20.

SOF Renal Insufficiency Study

SOF + RBV in Patients with Severe Renal Impairment

- Similar rapid virologic decline observed to those with normal renal function
- SVR₄ and SVR₁₂: 40%

SOF and GS-331007 Pharmacokinetics



Dots indicate patients with SVR₄ (blue dots) or viral relapse (red dots).

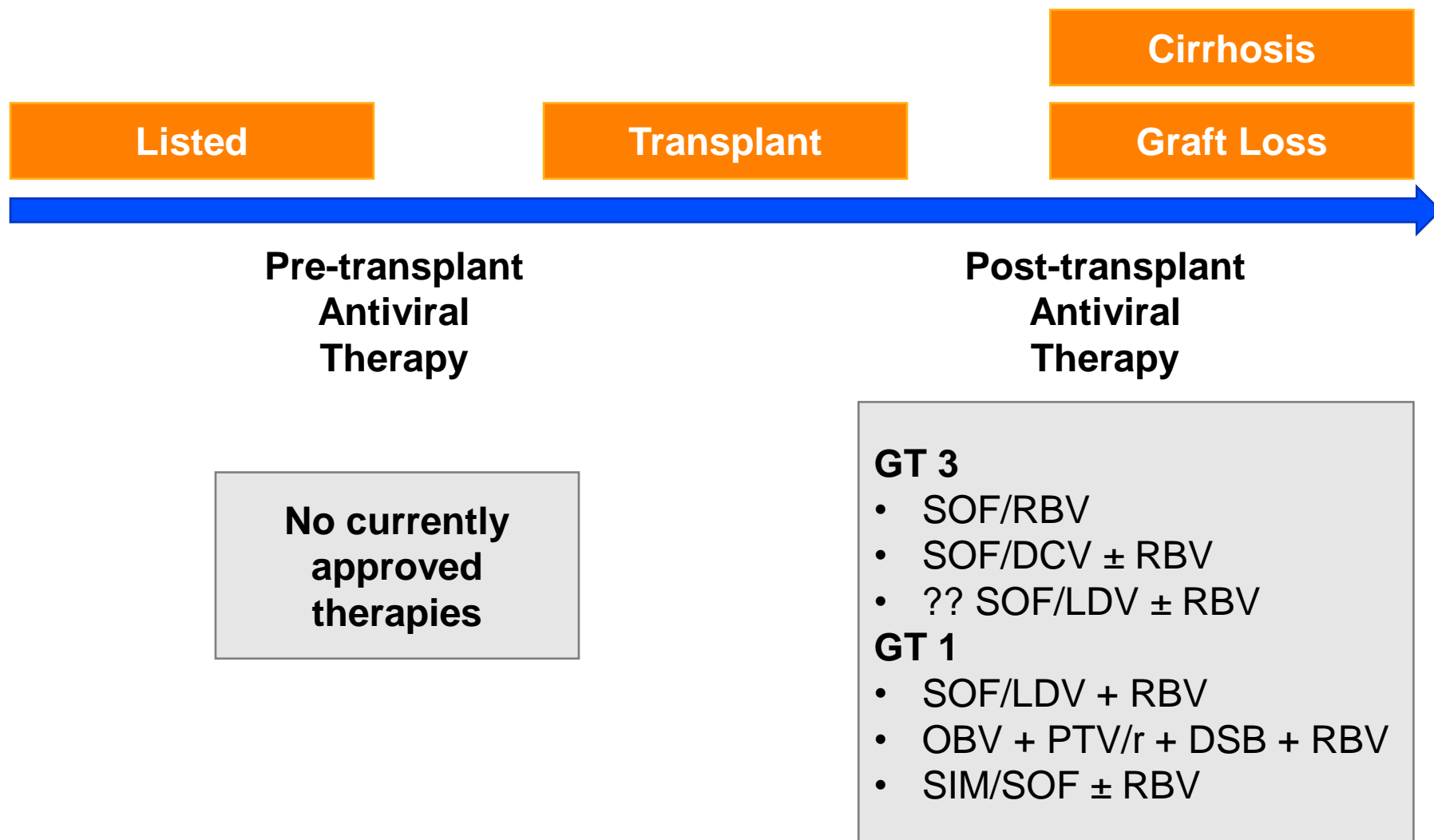
- Comparable SOF and ~ 4-fold higher GS-331007 exposures compared with historical HCV-infected population

Adverse Events	SOF 200 mg + RBV N = 10
Anemia	5
Headache	4
Pruritus	3
Rash	3
Muscle spasms	2
Hypoesthesia	2
Insomnia	2
Irritability	2

- Mean eGFR change from baseline to EOT (Week 24): -3.12 mL/min
- No treatment-emergent clinically significant ECG results

SOF 200 mg + RBV was safe and relatively well-tolerated in patients with severe renal impairment with exacerbation of anemia via RBV-induced hemolysis as primary AE

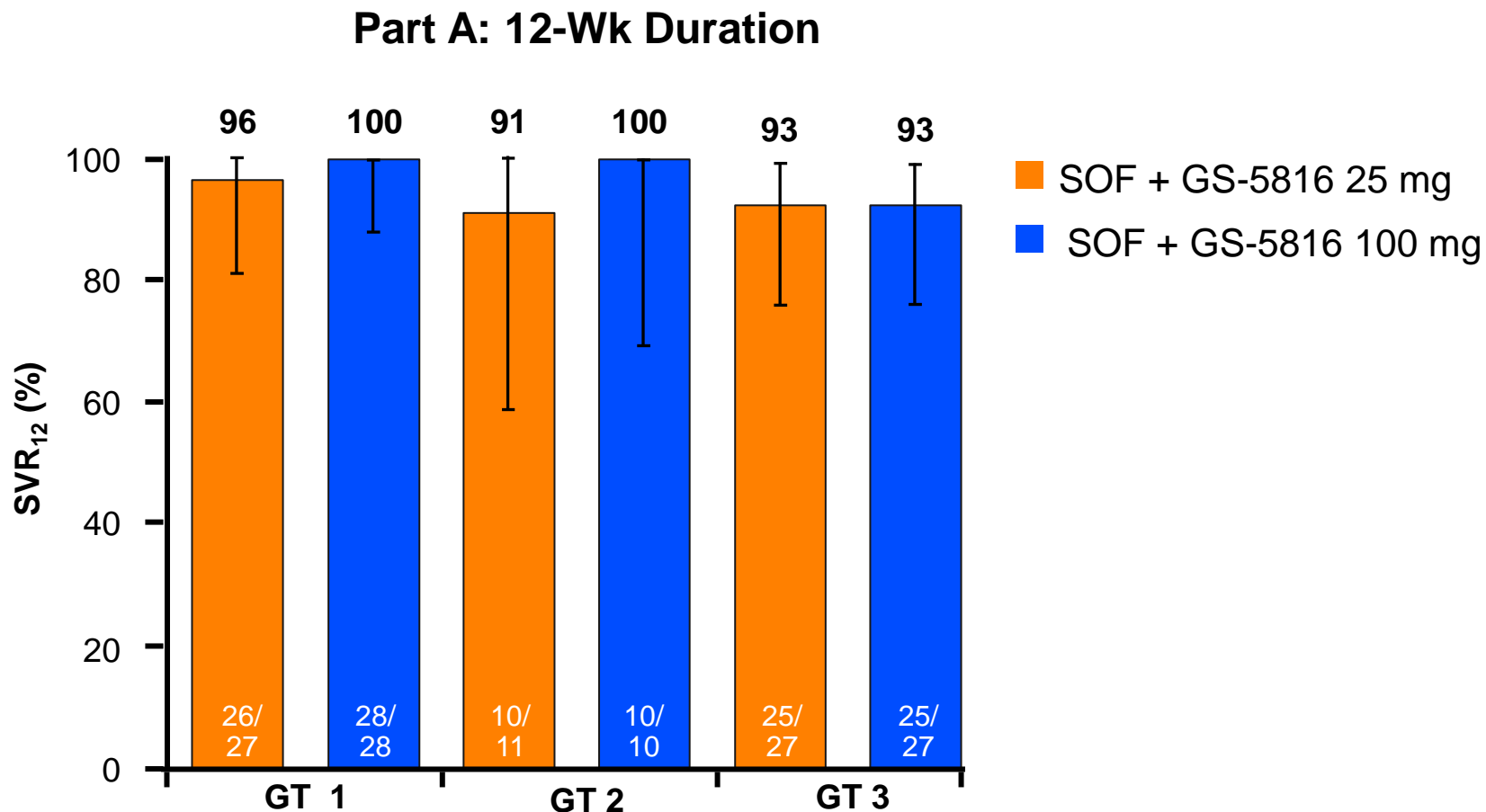
Opportunities to Treat HCV in Non-Hepatic SOT Patients





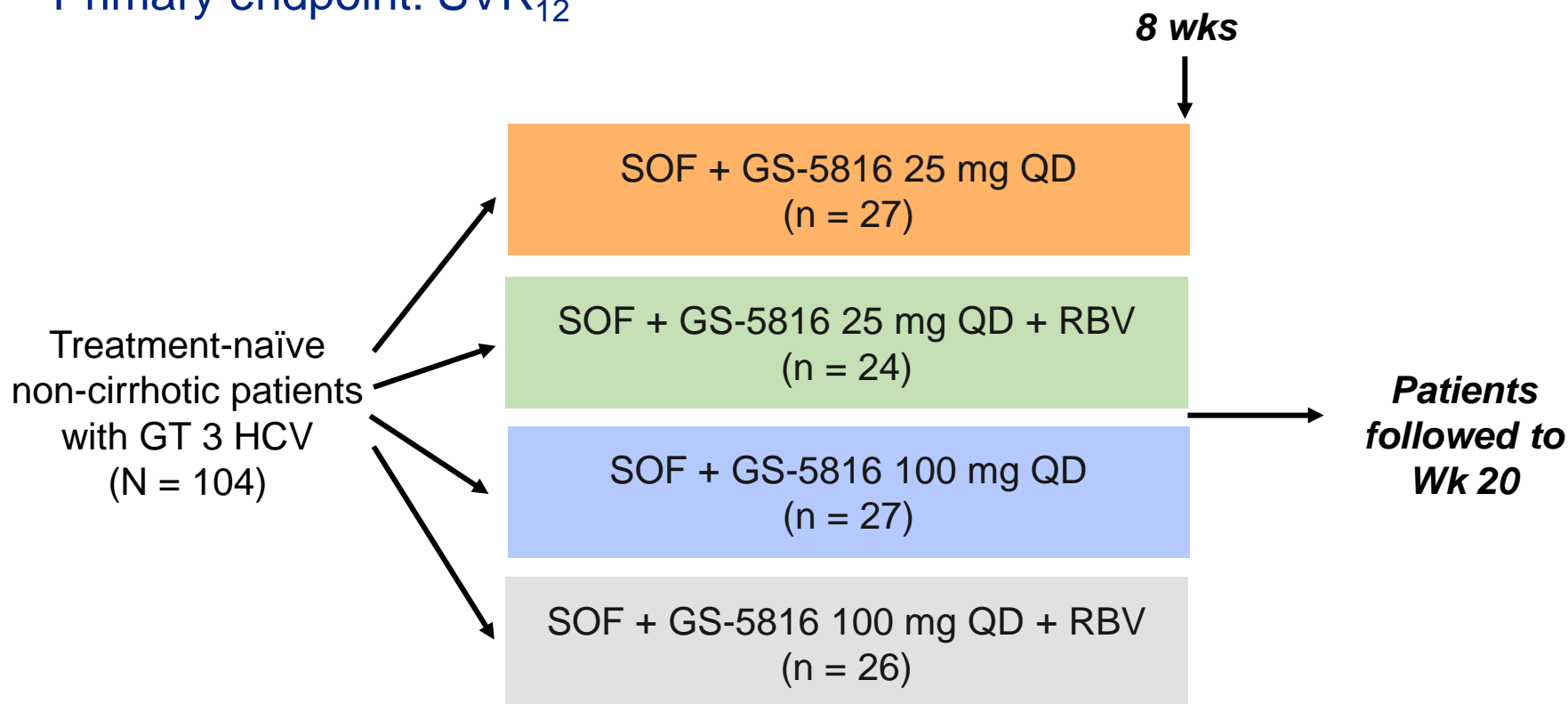
What Is Next in GT 3 HCV?

SVR₁₂ With SOF + GS-5816: 12 Wks Effective in GT 1, 2, and 3



SOF + GS-5816 ± RBV x 8 Wks in Non-cirrhotic Patients With GT 3 HCV

- Randomized, open-label Phase II trial
- Primary endpoint: SVR₁₂



SVR₁₂ With SOF + GS-5816 ± RBV x 8 Wks in Non-cirrhotic GT 3 Patients

SVR ₁₂ , % (n/N)	GT 3 Non-cirrhotic Patients			
	SOF + GS-5816 25 mg (n = 27)	SOF + GS-5816 25 mg + RBV (n = 24)	SOF + GS-5816 100 mg (n = 27)	SOF + GS-5816 100 mg + RBV (n = 26)
Overall	100	88	96	100

- Baseline NS5A RAVs had no effect on efficacy

clinicaltrials.gov

- **Safety and Efficacy Study of Daclatasvir 60 mg, Sofosbuvir 400 mg, and Ribavirin (Dosed Based Upon Weight) in Subjects With Chronic Genotype 3 Hepatitis C Infection With or Without Prior Treatment Experience and Compensated Advanced Cirrhosis for 12 or 16 Weeks** (recruiting NCT02319031)
- **Study to Evaluate the Safety and Efficacy of Daclatasvir/Sofosbuvir/Ribavirin for 16 Versus 24 Weeks for HCV Genotype 3 Cirrhotics** (recruiting NCT02304159)
 - This is a randomized, open label, single center safety and efficacy study. At least 40 cirrhotic subjects with HCV GT 3 will receive standard of care treatment of sofosbuvir and ribavirin (SOF/RBV) as well as 60 mg daily of **daclatasvir** (investigational product). Subjects will be randomized in a 1:1 to receive either:
 - Group A: 16 weeks of DCV/SOF/RBV
 - Group B: 24 weeks of DCV/SOF/RBV

Conclusions

- GT 3 HCV is the most difficult to cure in 2015
 - Particularly those with cirrhosis and prior treatment failure
- PegIFN-based therapy remains the backbone of therapy for many
 - Public funding
 - In treatment-experienced cirrhotics, this may be the best therapy
- On the horizon:
 - SOF/GS-5816/RBV
 - SOF/DCV/RBV
- Paradigm shift of HCV therapy in organ transplantation
 - Renal failure remains a contraindication to SOF-based therapy
 - ?Use of HCV-infected donors

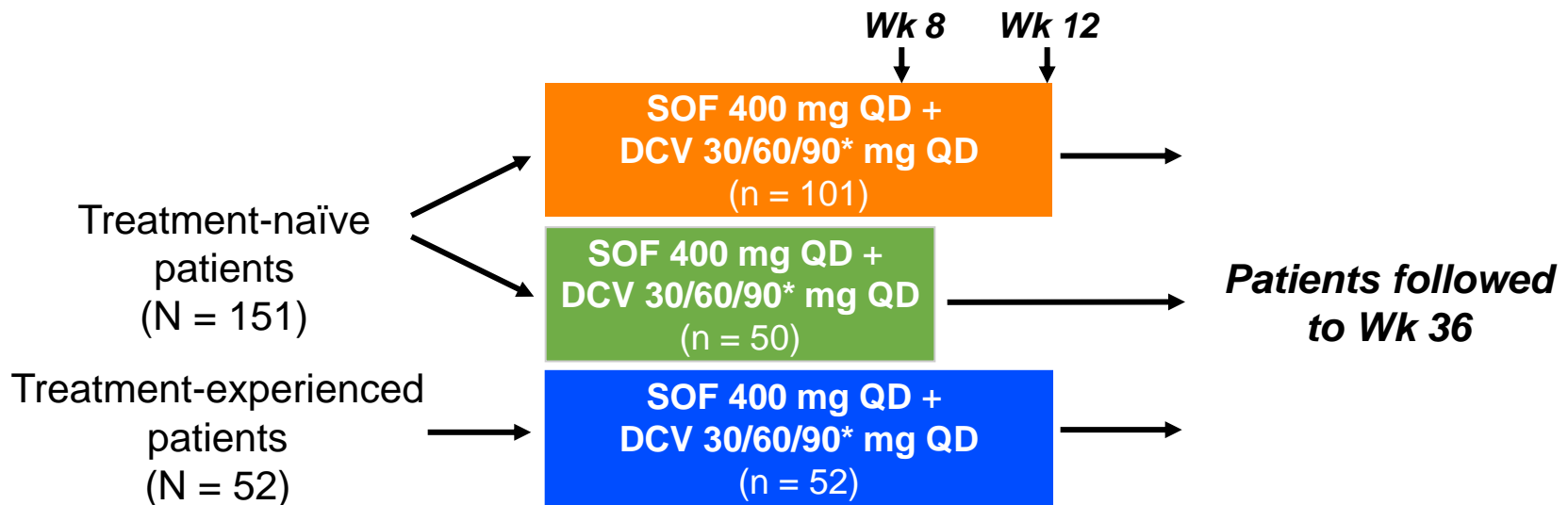
A hand holding a stethoscope, symbolizing healthcare or medicine. The image is a close-up of a hand holding a stethoscope, with the chest piece resting on the palm and the tubing extending downwards. The background is a solid blue color.

Questions?

ALLY-2

SOF + DCV in GT 1-6 HCV/HIV- Coinfected Patients

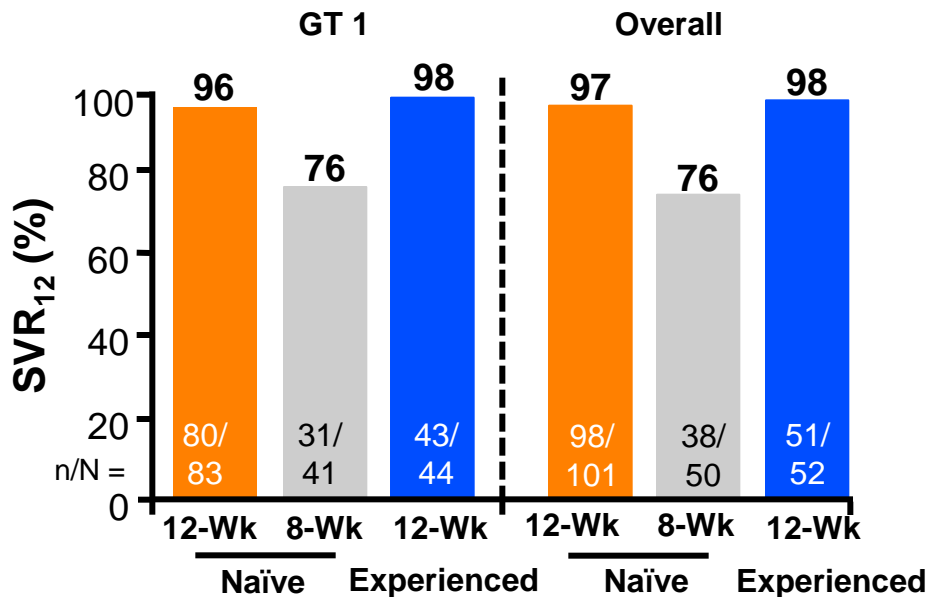
- Phase III open-label study
- Non GT 1 < 20% in each cohort; compensated cirrhosis < 50% overall; HIV-1 RNA < 50 c/mL and CD4+ ≥ 100 in patients on ART; CD4 ≥ 350 in patients not on ART
- ART allowed: PI/RTV, NRTIs, NNRTIs, INSTIs, MVC, ENF
- Primary endpoint: SVR₁₂ in GT 1 naïve patients treated for 12 wks



*Standard dose of 60 mg adjusted for ART: 30 mg with RTV; 90 mg with NNRTIs except RPV.

Virologic Outcomes With SOF + DCV in HIV/HCV-Coinfected Patients

- High SVR₁₂ rates with 12 wks SOF + DCV
- Large decline in SVR rate with shortening to 8 wks

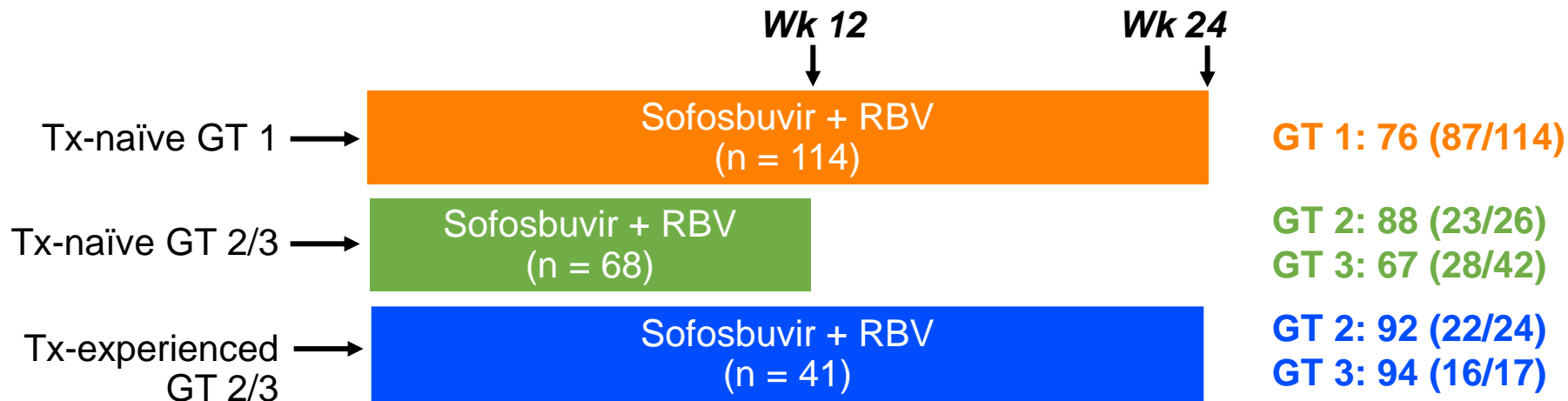


- In 12-wk groups analyzed by GT, 100% with SVR₁₂ except GT 1a
 - GT 1a-naïve: 96%; experienced: 97%
- Similar SVR₁₂ rates in patients with or without baseline NS5A RAVs
- 12 patients with relapse, 10 in 8-wk arm
 - 1 in 8-wk arm had emergent NS5A RAVs
- No NS5B RAVs at BL or time of failure
- No discontinuation of therapy due to AEs
- 10 patients with HIV-1 RNA > 50 at EOT
 - 8 with repeat testing; 7 with suppression without change in ART; 1 with HIV-1 RNA of 59; 2 LTFU
- 2 with HIV VF = HIV-1 RNA ≥ 400 c/mL

PHOTON-1

Sofosbuvir + RBV in GT 1-3 HCV Patients Coinfected With HIV

- Non-randomized, open-label Phase III study; primary endpoint: SVR₁₂
- Stable ART (HIV-1 RNA < 50 copies/mL for > 8 wks before enrollment)
- 95% on ART: TDF/FTC, 100%; EFV, 35%; ATV/RTV, 17%; DRV/RTV, 15%; RAL, 16%; RPV, 6%
- Cirrhosis at baseline: GT 1, 4%; GT 2/3 Tx-naïve, 10%; GT 2/3 Tx-experienced: 24%

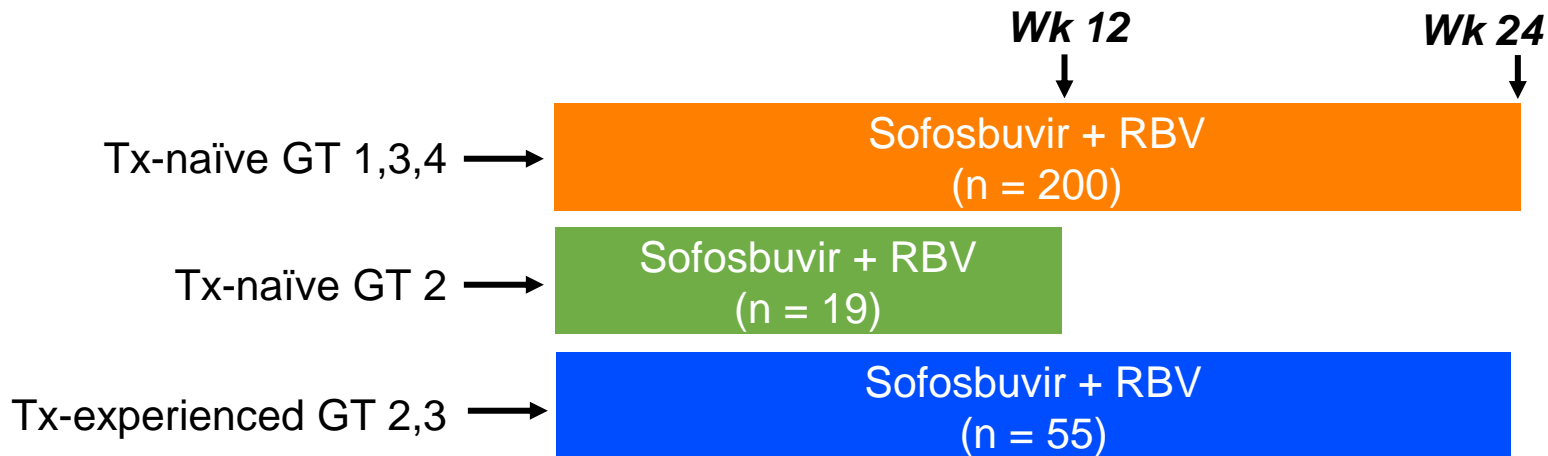


Sofosbuvir 400 mg QD; weight-based RBV 1,000 or 1,200 mg/day

PHOTON-2

Sofosbuvir + RBV in GT 1-4 HCV Patients Coinfected With HIV

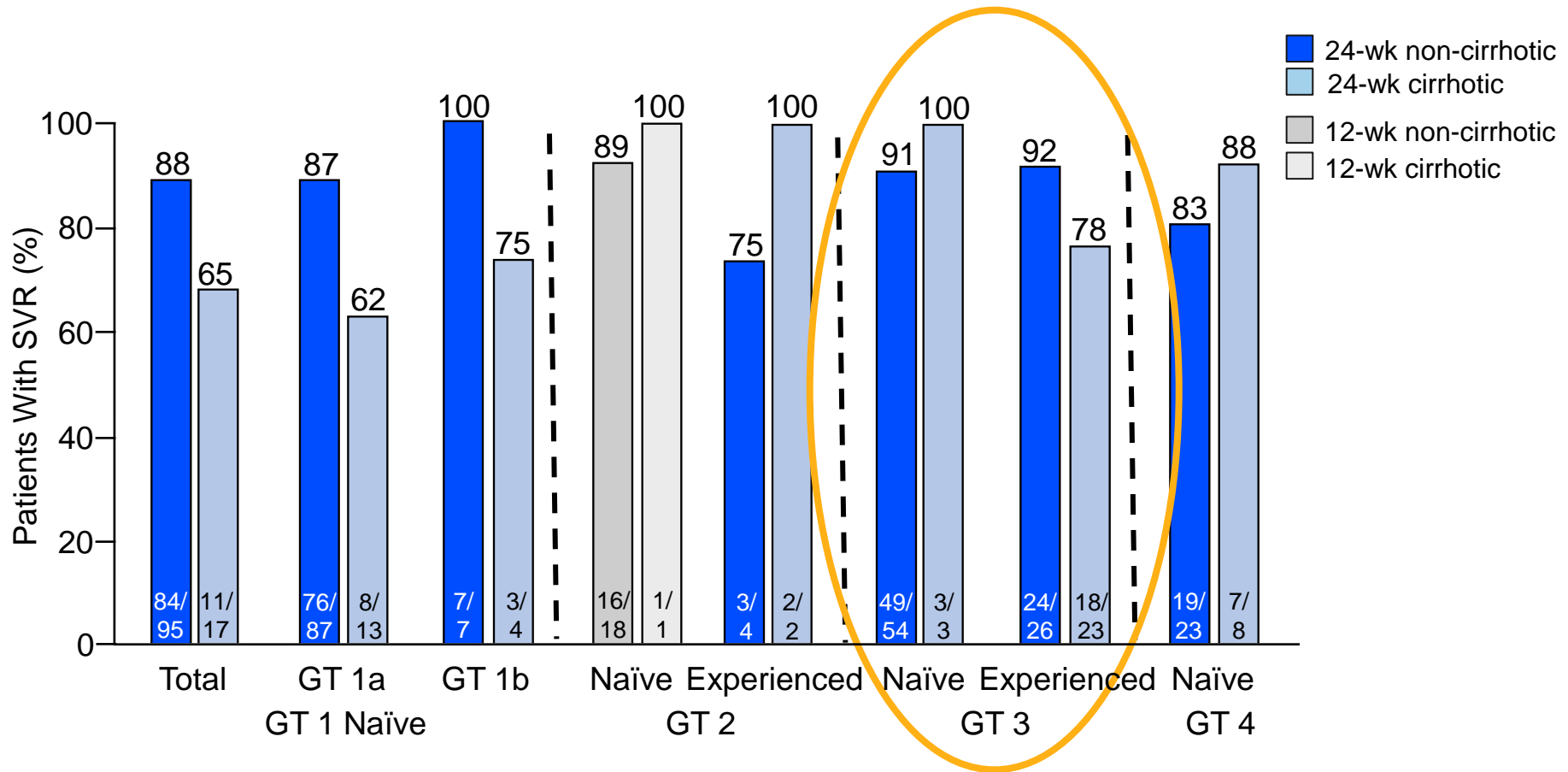
- Non-randomized, open-label Phase III study; primary endpoint: SVR₁₂
- Stable ART (HIV-1 RNA < 50 copies/mL for ≥ 8 wks before enrollment)
- 97% on ART: TDF/FTC, 100%; EFV, 25%; ATV/RTV, 17%; DRV/RTV, 21%; RAL; 23%; RPV, 5%
- Cirrhosis at baseline: All patients, 20%; Tx-naïve patients, 13%; Tx-experienced patients, 45%



Sofosbuvir 400 mg QD; weight-based RBV 1,000 or 1,200 mg/day

PHOTON-2

SVR₁₂ by GT and Cirrhosis



- Absolute CD4+ count—but not CD4%—decreased, consistent with effect of RBV on lymphocytes