Treatment of HCV G1 infection after initial treatment failure: 2016

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Disclosure Information

- Dr. Vargas receives research grant support paid directly to his institution from:
  - Gilead
  - Bristol Myers
  - Merck
  - AbbVie
- He also serves in the ABIM test writing committee. No discussion of ABIM test materials will take place

Outline

- Viral Genotype 1a treatment after PEGIFN/RBV failure
  - Non-Cirrhotic
    - Recommended
    - Alternatives
  - Compensated Cirrhotic
    - Recommended
    - Alternatives
- Viral Genotype 1b treatment after PEGIFN/RBV failure
  - Non-Cirrhotic
    - Recommended
    - Alternatives
  - Compensated Cirrhotic
    - Recommended
    - Alternatives

Outline

- Viral Genotype 1 treatment after SOF/RBV failure
  - Non-Cirrhotic
    - Recommended
    - Alternatives
  - Compensated Cirrhotic
    - Recommended
    - Alternatives

Outline

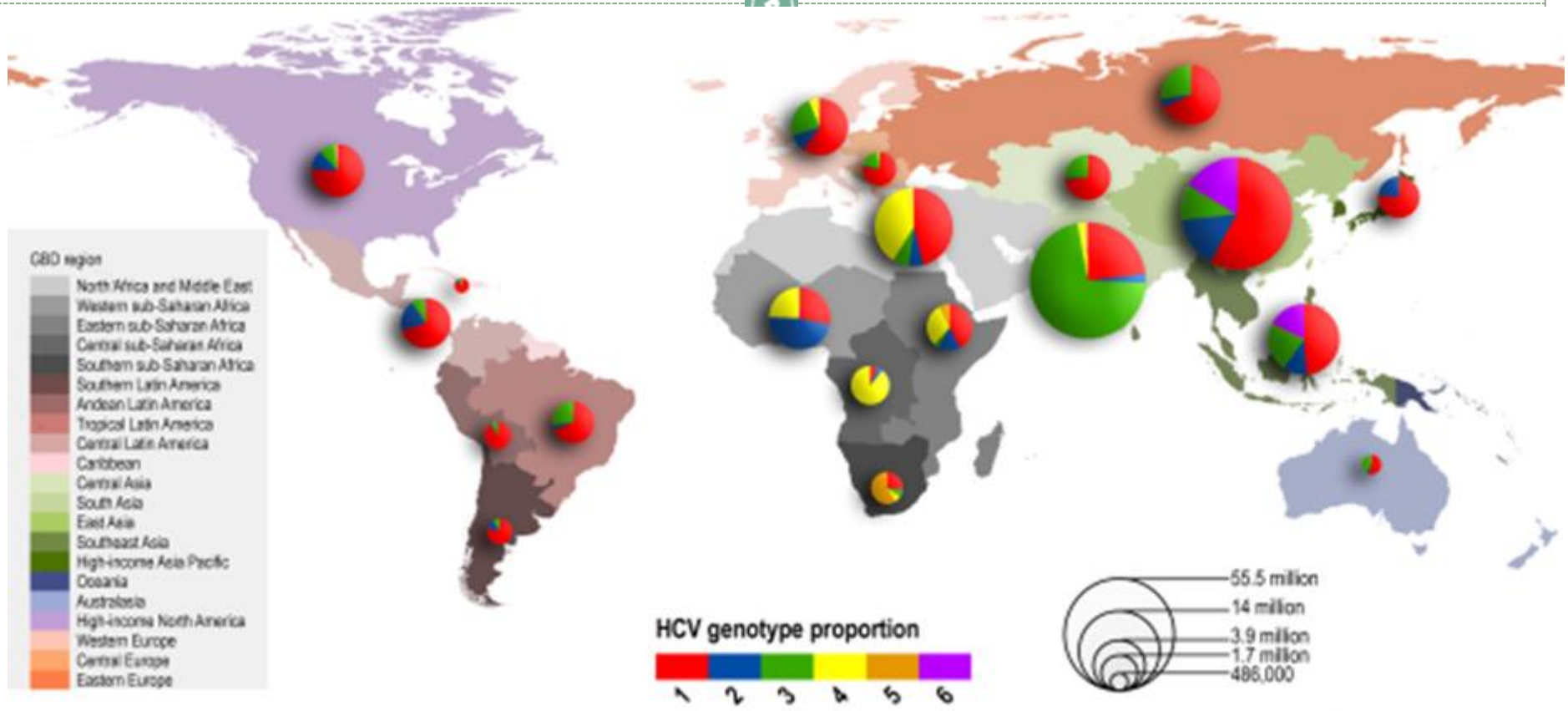
- Viral Genotype 1 treatment after NS3 inhibitor +(PEGIFN/RBV) failure
  - Telaprevir, Boceprevir or Simeprevir
  - Non-Cirrhotic
    - Recommended
    - Alternatives
  - Compensated Cirrhotic
    - Recommended
    - Alternatives

Treatment Candidates

Worldwide Burden of Disease due to HCV is Increasing

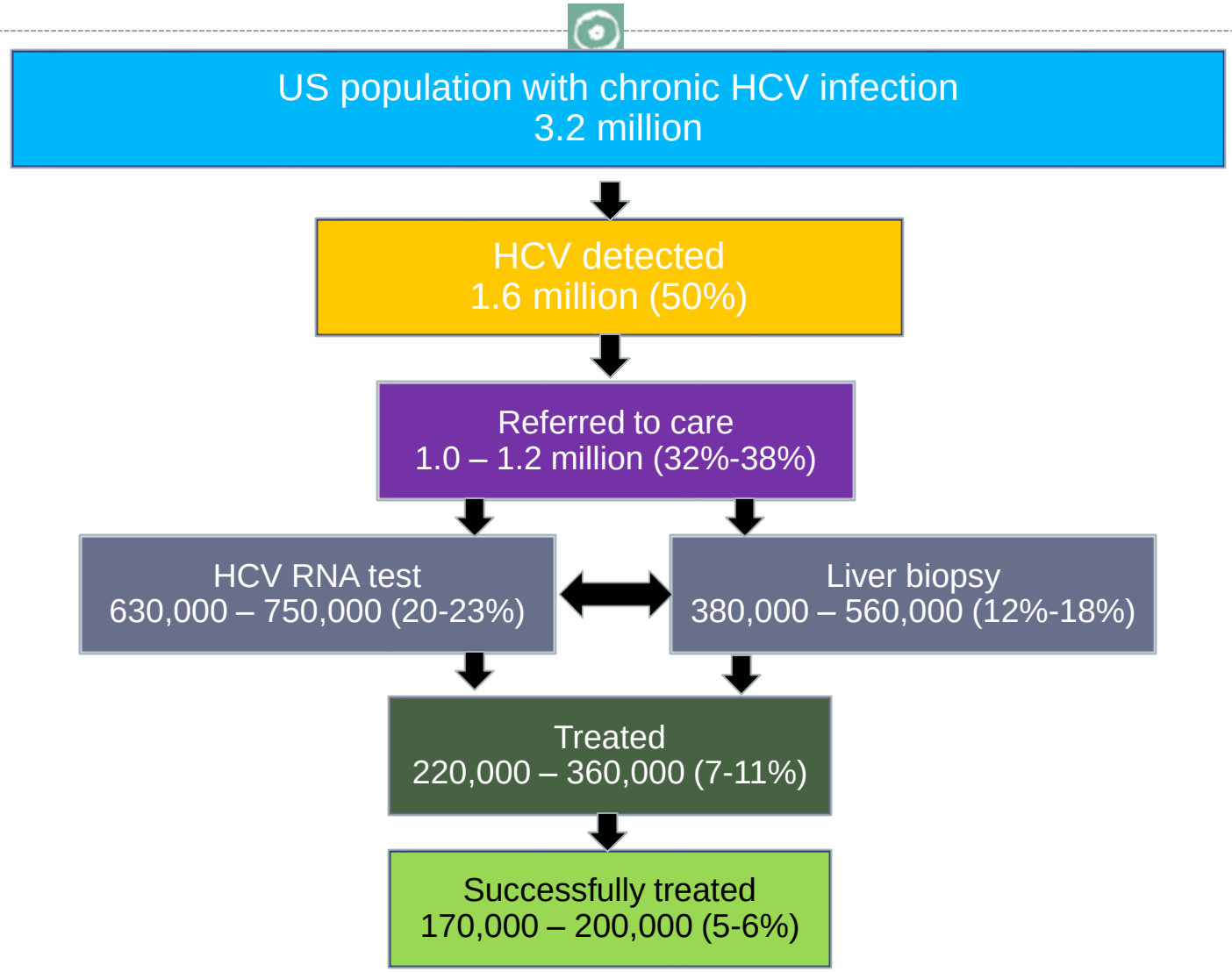
- WHO estimates 130-170 million people, (3% of world's population) HCV infected and at risk of cirrhosis/HCC
- There are 3 to 4 million new infections/yr
- HCV is responsible for 50–76% of all HCC and 50-60% of all liver transplants in the developed world
- HCV-associated cirrhosis leads to liver failure and death in about 20%-25% of cirrhotic patients

HCV Global Genotype Distribution



Messina, Hepatology 2014

Current Status of HCV in the US: Screening and Linkage to Care Rates Remain Low



Holmberg, NEJM 2013

Who should be treated?

Overriding principles in recommendations are that:

1-HCV infection is a **curable** disease
2-**All** HCV infected patients should receive treatment
3-There are several groups of patients who should receive treatment **immediately** as they derive highest benefit:

a) Patients with cirrhosis
b) Recipients of Liver Transplantation who remain HCV+
c) HIV/HCV co-infected patients
d) Patients with extra-hepatic manifestations of HCV
-Cryoglobulinemia
-B-cell lymphoma
-Porphyria cutanea tarda

Who should be treated?

Consideration should also be given to the possibility HCV treatment potentially decreasing transmission of HCV in the community, thus the following populations should be treated:

1-Prision inmates
2-HIV/HCV+ men who have sex with men
3-Clinicians at high risk of transmission to patients
4-IVD users

There are patients who should not receive treatment, specifically those with life threatening illness whose treatment would not change their immediate survival (12mo)

Regimen Basics

IAS–USA
International AntiViral Society–USA

Ledipasvir and Sofosbuvir

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Ledipasvir/Sofosbuvir (LDV/SOF)

- Ledipasvir (LDV) is an NS5A complex inhibitor
- Sofosbuvir (SOF) is an NS5B nucleoside inhibitor
- Approved in US 2014 for treatment of HCV G1 disease
- Fixed dose combination (FDC) as a single pill,

  90mg LDV/400mg SOF
- Pivotal registration trials for this discussion were ION 1,2,3

Ledipasvir/Sofosbuvir

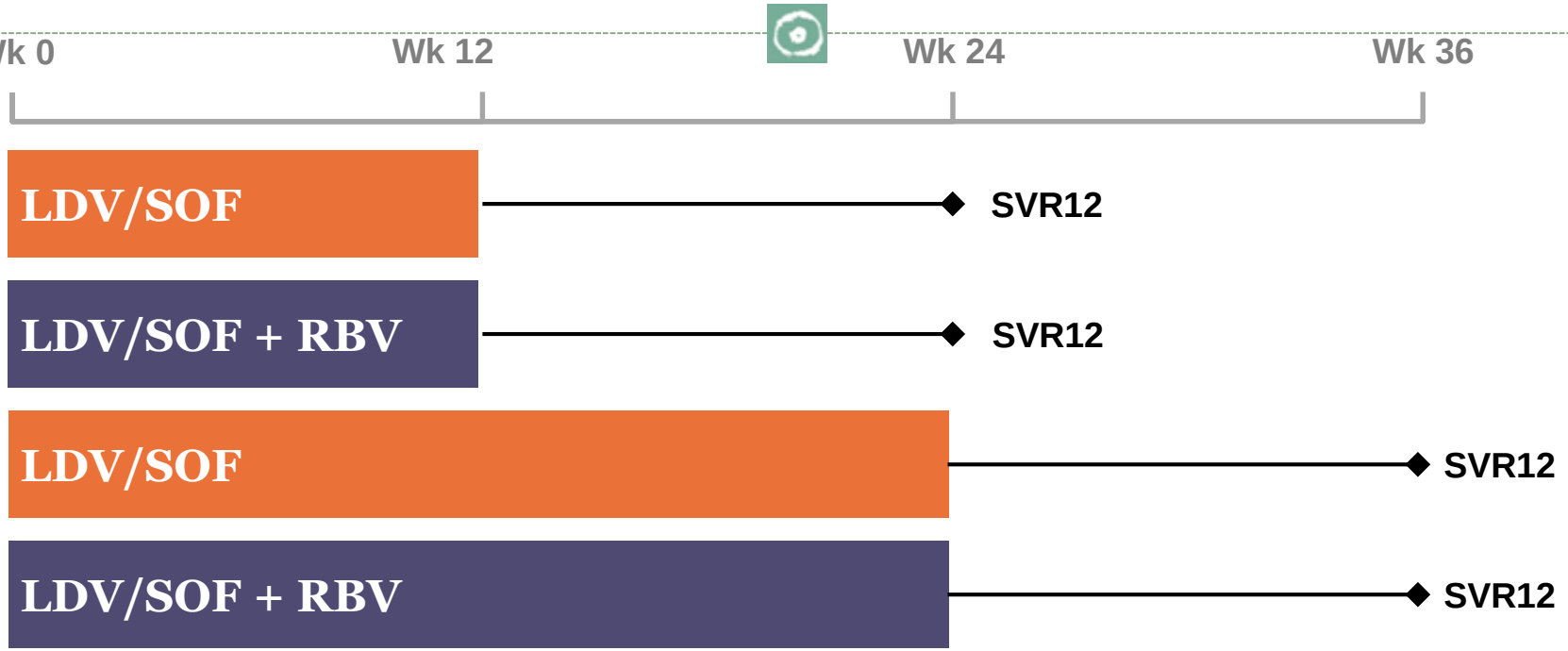
- Special considerations:
  - To be avoided in patients with GFR<30mg/dL
  - Co-administration with amiodarone can cause life-threatening bradycardias
  - Has excellent profile in patients with compensated cirrhosis
  - Avoid the use of PPI as LDV absorption is decreased

ION Studies: Pivotal LDV/SOF studies

- ION-1: FDC for 12 or 24 weeks ± RBV in treatment naïve patients Afdhal *et al.*, NEJM 2014, 370:1889
- ION-3 FDC for 8 weeks± RBV vs 12 weeks in treatment naïve patients Kowdley *et al.*, NEJM 2014, 370: 1879
- ION-2 FDC for 12 or 24 weeks ± RBV in treatment experienced patients (cirrhotics included) Afdhal *et al.*, NEJM 2014, 370:1483

Study Design

GT 1 Treatment-Experienced (ION-2)

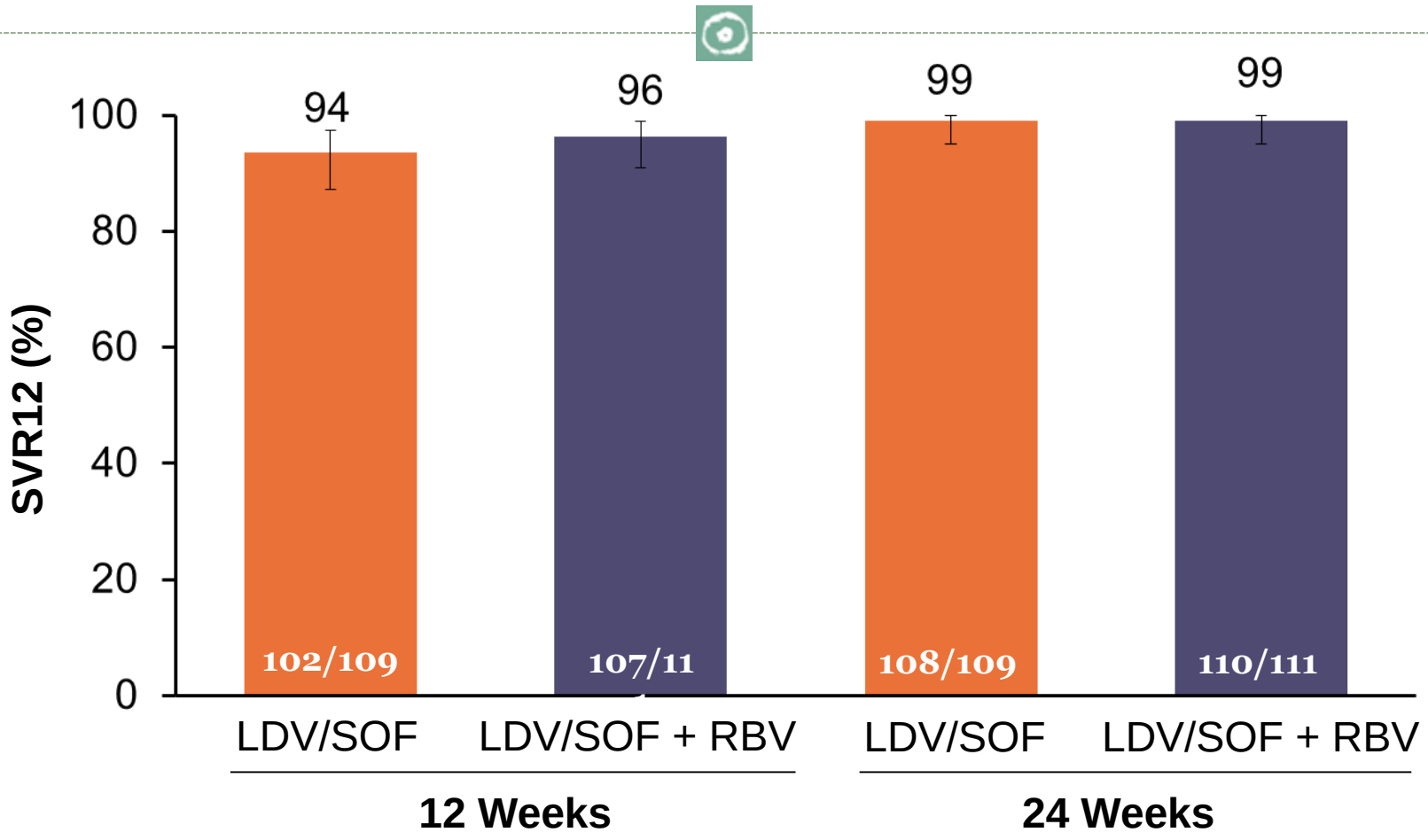


- GT 1 HCV patients who had failed prior IFN-based therapy, including regimens containing a NS3/4A protease inhibitor
- Broad inclusion criteria
- 440 patients randomized 1:1:1:1 across four arms
- Stratified by HCV subtype (1a or 1b), cirrhosis, prior treatment response

Afdhal *et al.*, NEJM 2014, 370:1483

Results: SVR12

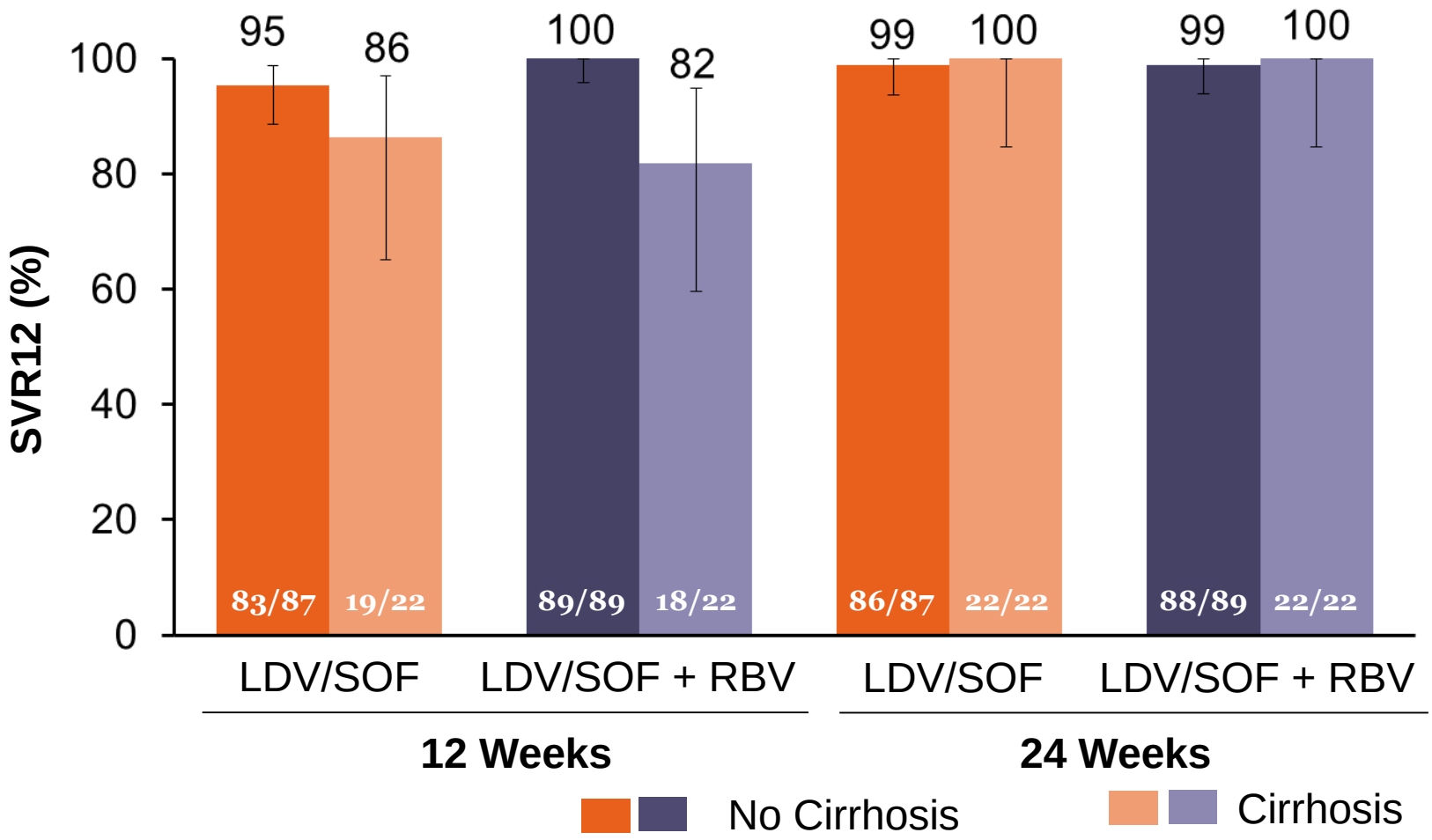
GT 1 Treatment-Experienced (ION-2)



Error bars represent 95% confidence intervals

SVR12: Absence of Cirrhosis vs Cirrhosis

GT 1 Treatment-Experienced (ION-2)

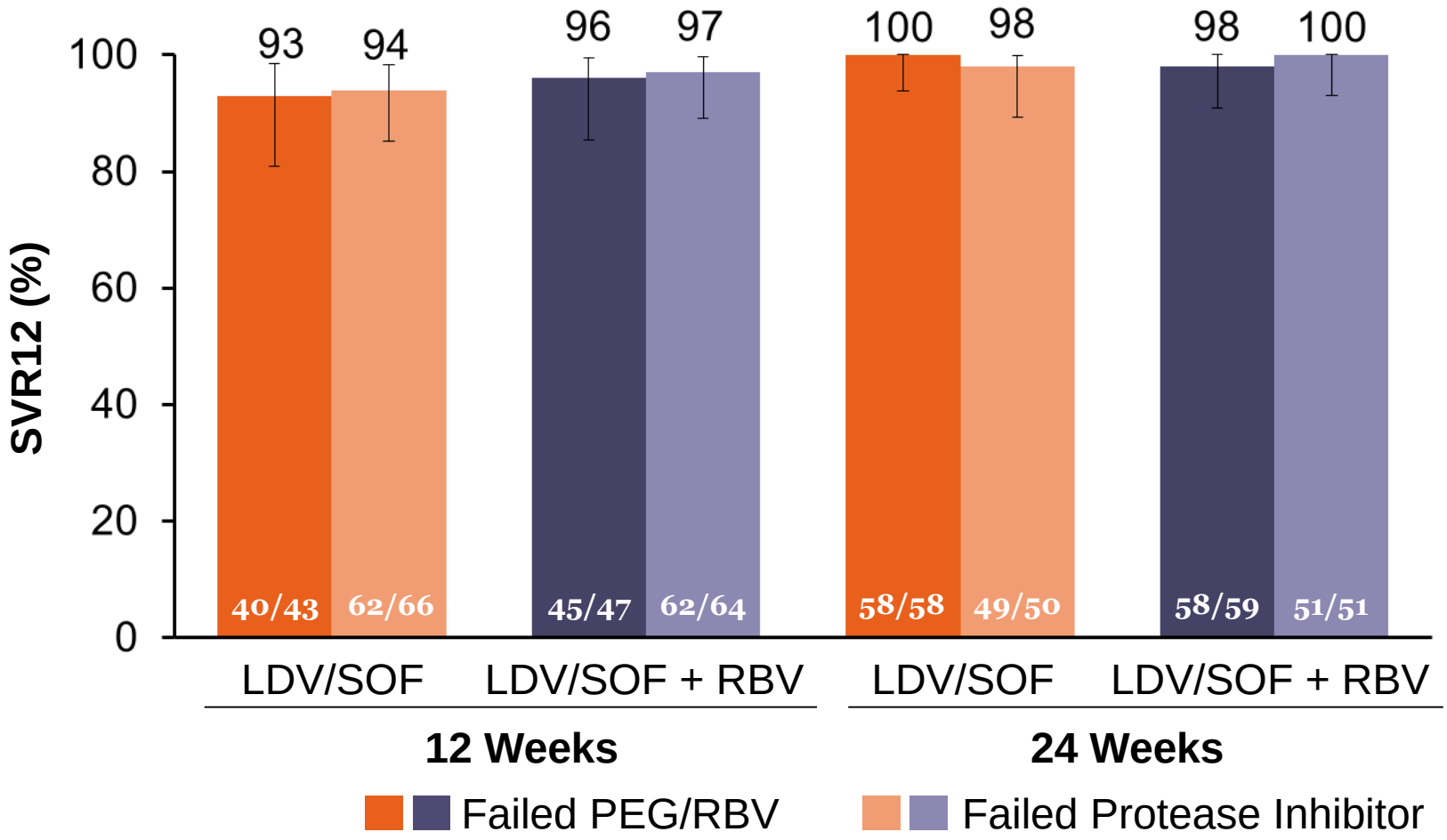


Error bars represent 95% confidence intervals.

Afdhal *et al.*, NEJM 2014, 370:1483

SVR12: PEG/RBV vs PI + PEG/RBV Failures

GT 1 Treatment-Experienced (ION-2)



Error bars represent 95% confidence intervals.

Afdhal *et al.*, NEJM 2014, 370:1483

Conclusions Across Phase 3 SOF/LDV Studies

SOF/LDV effective across G1 patients

- Treatment experienced
  - Very effective
  - 12 weeks adequate for non-cirrhotic
  - 24 weeks preferable for cirrhotic
  - RBV of no benefit

Simeprevir and Sofosbuvir

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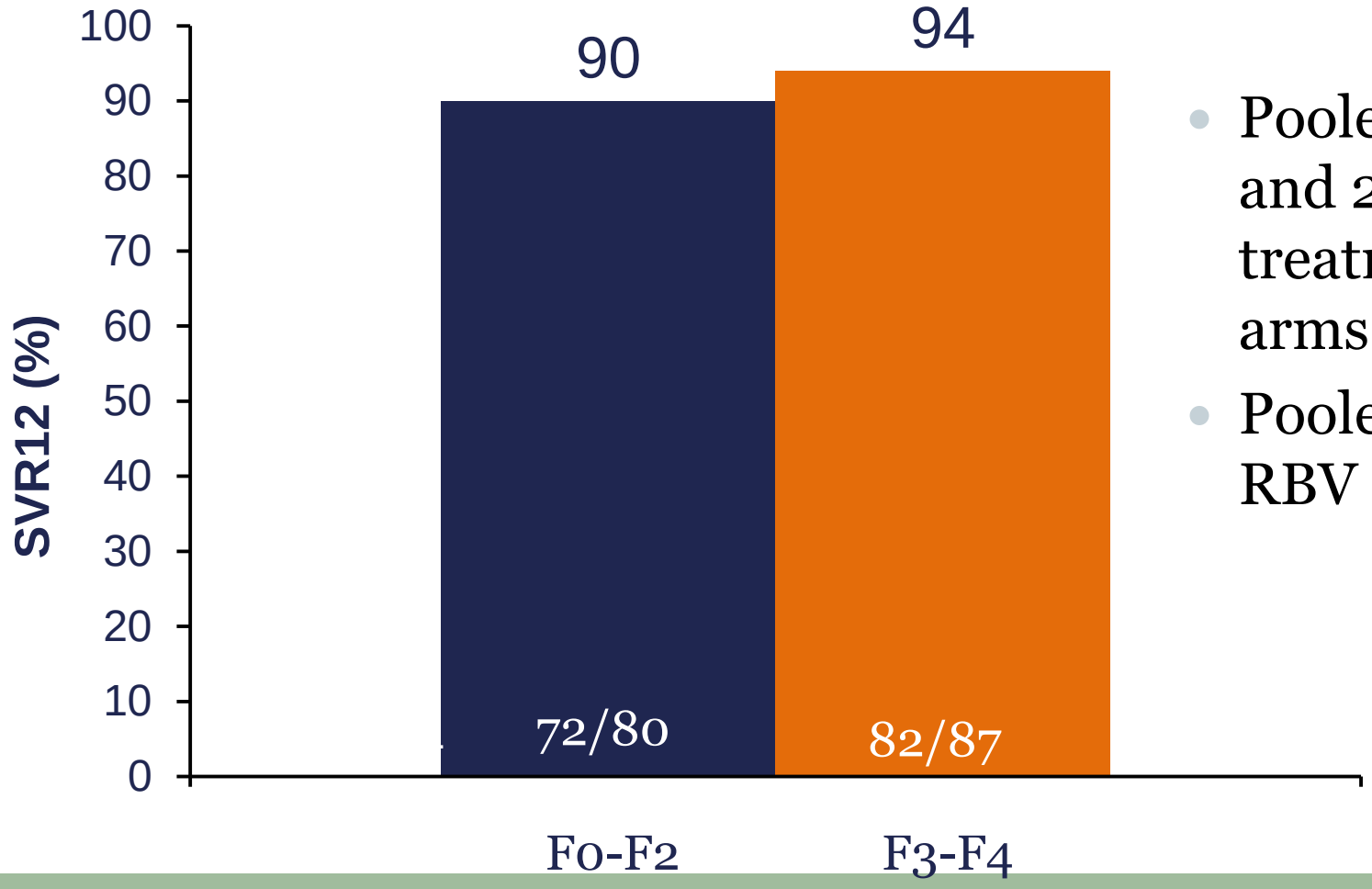
Simeprevir and Sofosbuvir

- Approved separately for different indications
- Simeprevir is a second wave, first generation NS3/4a Protease Inhibitor
- Sofosbuvir is a nucleotide polymerase inhibitor
- The combination was tested as proof of concept IFN free regimen for G1 in the Phase II COSMOS study
- Treatment outside clinical trials very successful

SMV/SOF +/- RBV: SVR12 in TN and NR (COSMOS)



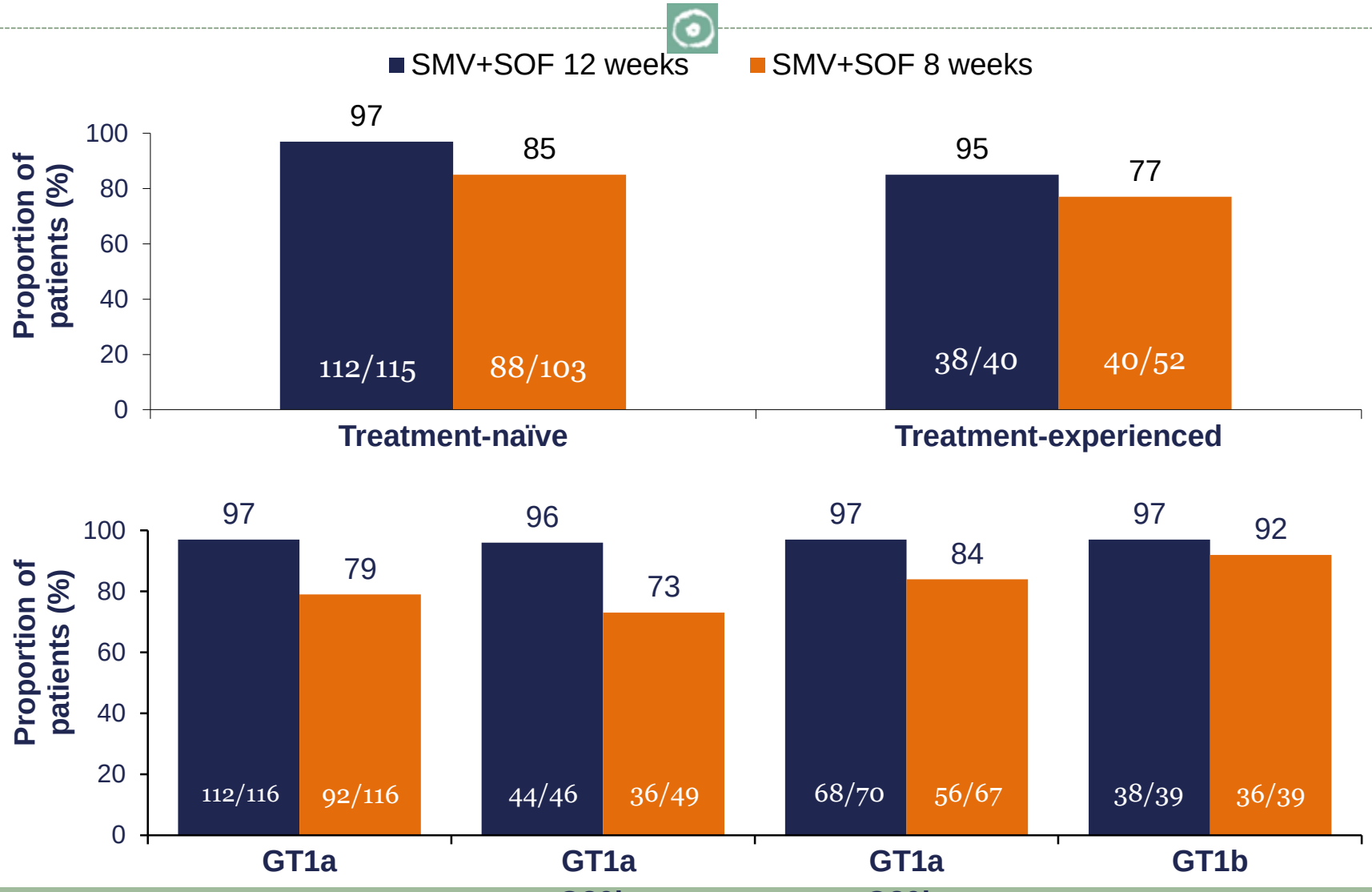
- Pooled 12 and 24 week treatment arms
- Pooled +/- RBV arms

Lawitz *et al.*, *Lancet*, 2014

SMV/SOF COSMOS: Summary

- FDA approved the combination in November 2014 based on this study
- RBV did not improve SVR12
  - RBV may not be necessary (small numbers: 2/3 patients received RBV)
- Non-cirrhotics: 12 week treatment
- Cirrhotics: 24 week treatment (naïve or experienced)
- Phase 3 results recently published

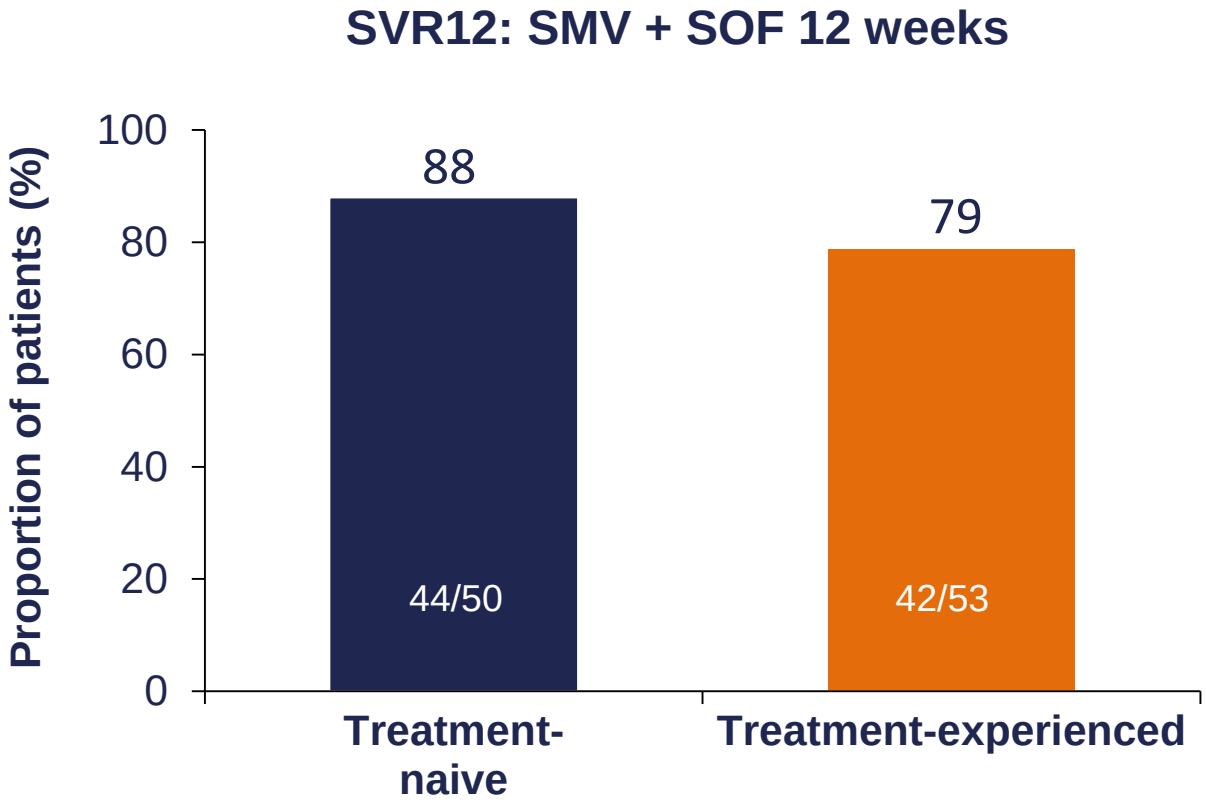
SMV/SOF in GT 1 Non-cirrhotics (OPTIMIST-1)



Kwo et al., Hepatology 2016

OPTIMIST-2: SVR12

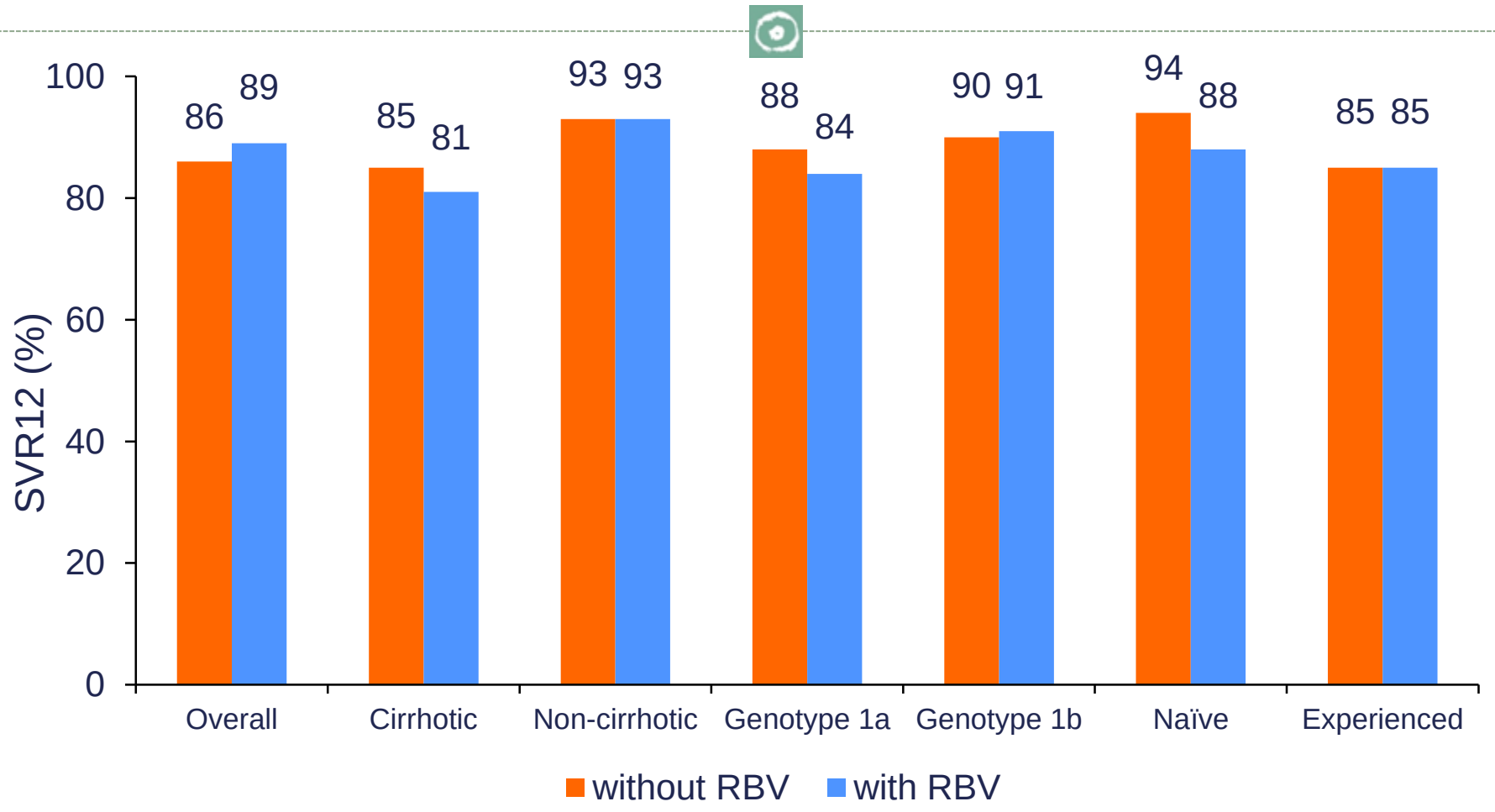
SMV+SOF for 12 Weeks in Cirrhotics



Implication: SMV+SOF insufficient for GT1 cirrhotics

Lawitz E, et al. Hepatology 2016 epublish

Adjusted SVR4 for SOF/SMV±RBV (HCV TARGET)



Sulkowski, et al. Gastroenterology 2016, 150:419

Simeprevir/Sofosbuvir

Special Considerations

- Screening GT 1a patients for the presence of Q80K polymorphism important if cirrhotic or considering re-treatment
- No dosage adjustment of SMV required in patients with mild, moderate or severe renal impairment
- Drug:drug interactions
  - Co-administration of SMV with drugs that are moderate/strong inducers or inhibitors of CYP3A may significantly affect the plasma concentrations of SMV.
  - Co-administration of amiodarone with sofosbuvir in combination with SMV may result in serious symptomatic bradycardia and is not recommended

Elbasvir and Grazoprevir

IAS–USA
International AIDS Society–USA

Elbasvir/Grazoprevir

- Grazoprevir Second generation NS3/4a protease inhibitor
- Elbasvir Second generation NS5A complex inhibitor
- As with all PI inhibitors, drug-drug interactions should be closely scrutinized and package insert should be closely followed
- The use of this regimen should be considered in G1a patients after reviewing for the presence of NS5A specific RAV's

Elbasvir/Grazoprevir

- RAV testing at population level (detecting mutations in >10-25% of the quasispecies) is felt to be adequate at this time
- RAV testing to genotypes other than 1 not widely available
- NS5A mutations that are impactful to EBV are:
  - M28A/G/T
  - Q30D/E/H/G/K/L/R
  - L31F/M/V
  - Y93C/H/N/S

GZR/EBR/RBV x 12 Weeks: SVR12 in GT 1 Prior PI Failures By Subgroup (C-SALVAGE)

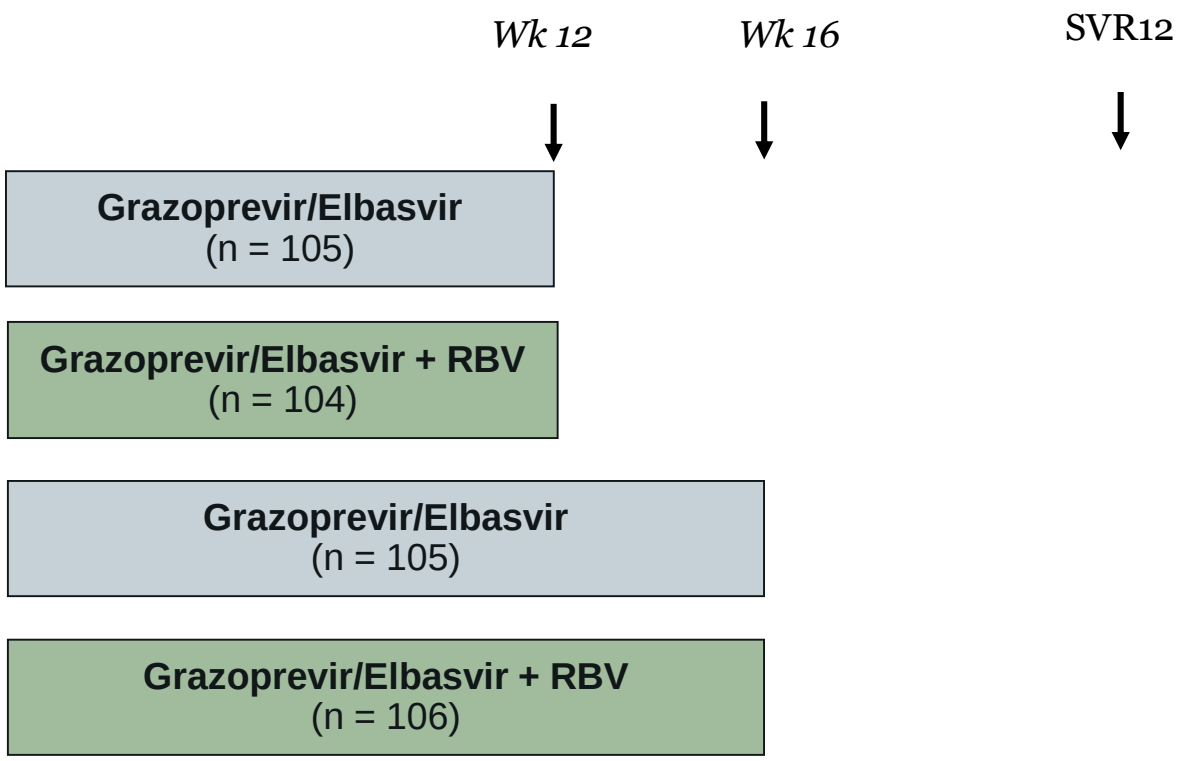
	All Subjects N = 79	
SVR12	**76**	**(96.2%)**
Relapse	3	(3.8%)
By Prior PI Therapy		
Boceprevir	27/28	(96%)
Telaprevir	41/43	(95%)
Simeprevir	8/8	(100%)
By Prior Failure Category		
On treatment failure	38/40	(95%)
Relapse	25/26	(96%)
Intolerance	13/13	(100%)
By Time Since Therapy		
<1.1 year	22/24	(92%)
≥1.1 year	46/46	(100%)
By Presence of NS3 RAVs		
Absent	43/43	(100%)
Present	31/34	(91%)

	All Subjects N = 79	
SVR12	**76**	**(96.2%)**
By Genotype		
G1a	28/30	(93%)
G1b	48/49	(98%)
By Cirrhosis		
Yes	32/34	(94%)
No	44/45	(98%)
By Viral Load		
≤800,000 IU/mL	27/29	(93%)
>800,000 IU/mL	49/50	(98%)

Highly efficacious in patients who failed first generation protease inhibitor/PEG/RBV treatment

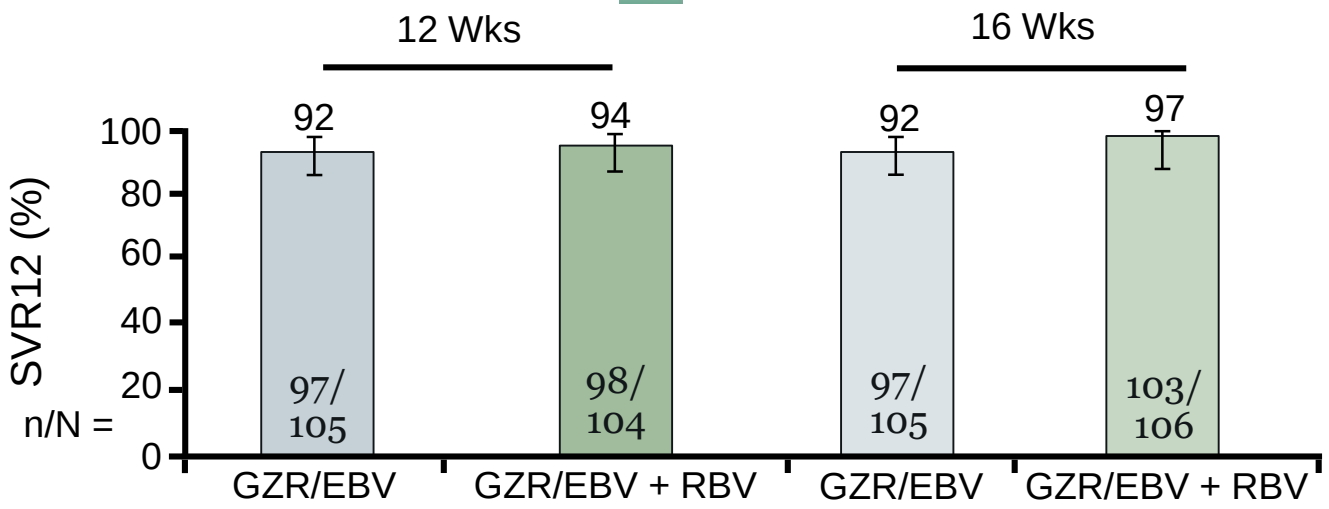
Forns *et al.*, J Hepat 2015

Grazoprevir/Elbasvir ± RBV for TE Patients
C-EDGE TE:



DFC grazoprevir/elbasvir dosed orally 100 mg/50 mg once daily; weight-based RBV

C-EDGE TE: Efficacy Results

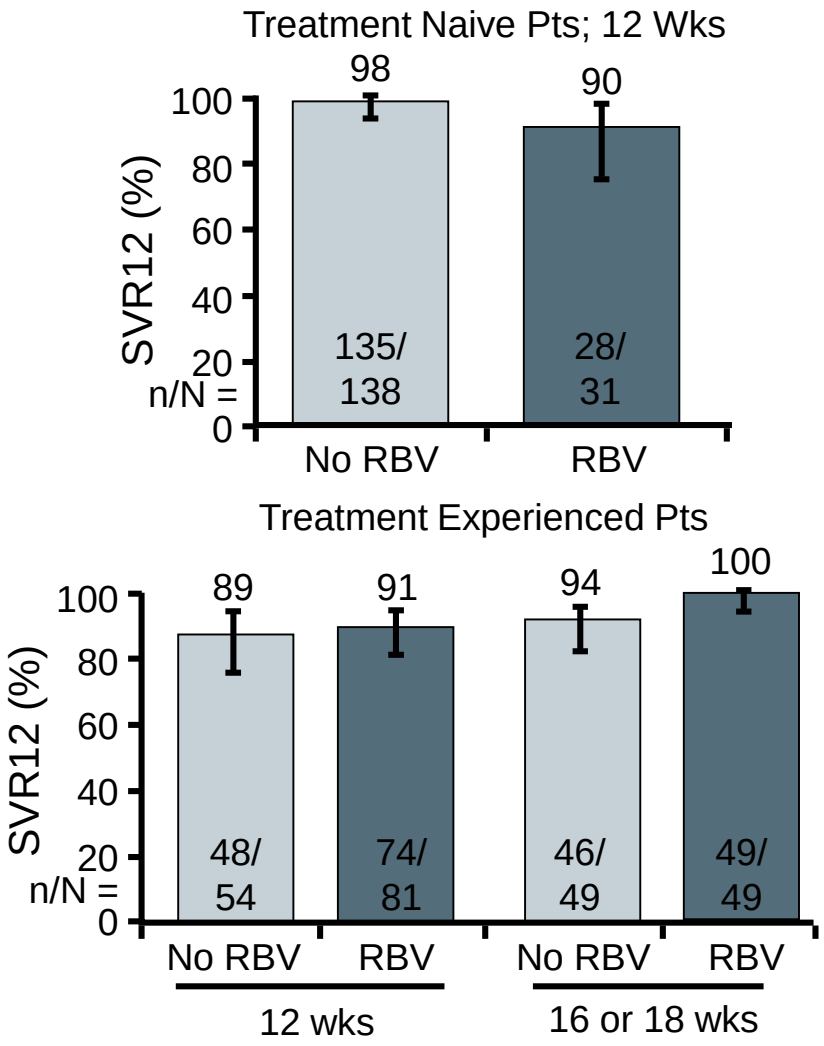


Breakthrough	0	0	1	0
Rebound	0	0	2	0
Relapse	6	6	4	0
LTFU/Early DC	2	0	1	3

- Cirrhosis patients did very well (in G1a, slightly less efficacy)
- Pre-existing NS5A high fold RAVs (>5fold shift) to EBV reduced efficacy significantly (SVR 52%)

Kwo P, et al. EASL 2015. Abstract

Elbasvir/Grazoprevir in Compensated Cirrhosis: SVR12



- **Treatment-naive pts**: SVR12 rates similar regardless of RBV use and platelets level.
  - SVR12 rate range across subgroups treated without RBV: 96% to 100%
- **Previous relapsers**: SVR12 rates not affected by duration or RBV use
- **Previous nonresponders**: SVR12 rates lower with 12-wk
  - GT1: 92% vs 100%
  - GT4: 67% vs 100%

Paritaprevir/r, Ombitasvir, Dasbuvir ± Ribavirin (3D)

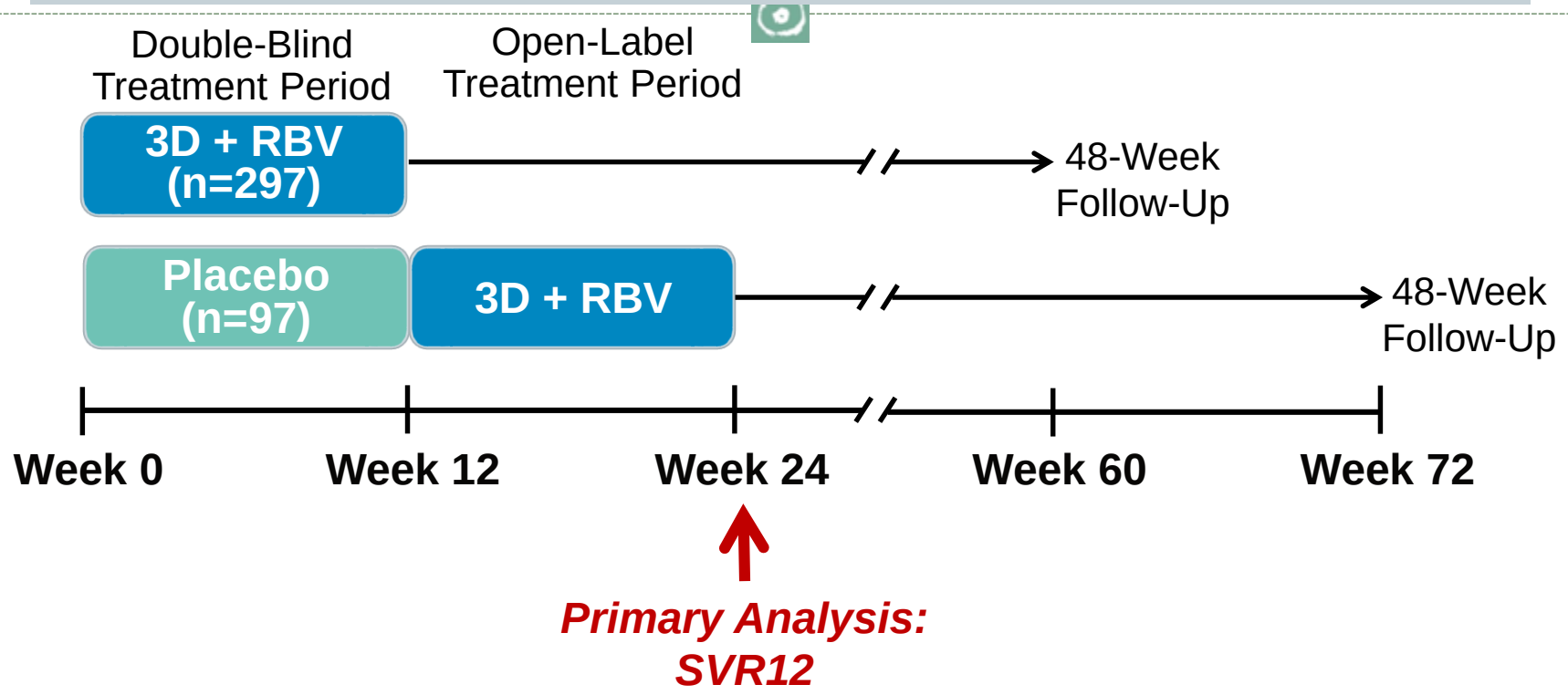
3D

- Paritaprevir is a *ritonavir* boosted NS3/4a protease inhibitor
- Ombitasvir is an NS5A complex blocker
  - FDC preparation
- Dasabuvir is a non-nucleoside inhibitor (administered twice daily)
- Ribavirin administration is required in G1a, not in most cases with G1b

Pivotal 3D regimen studies

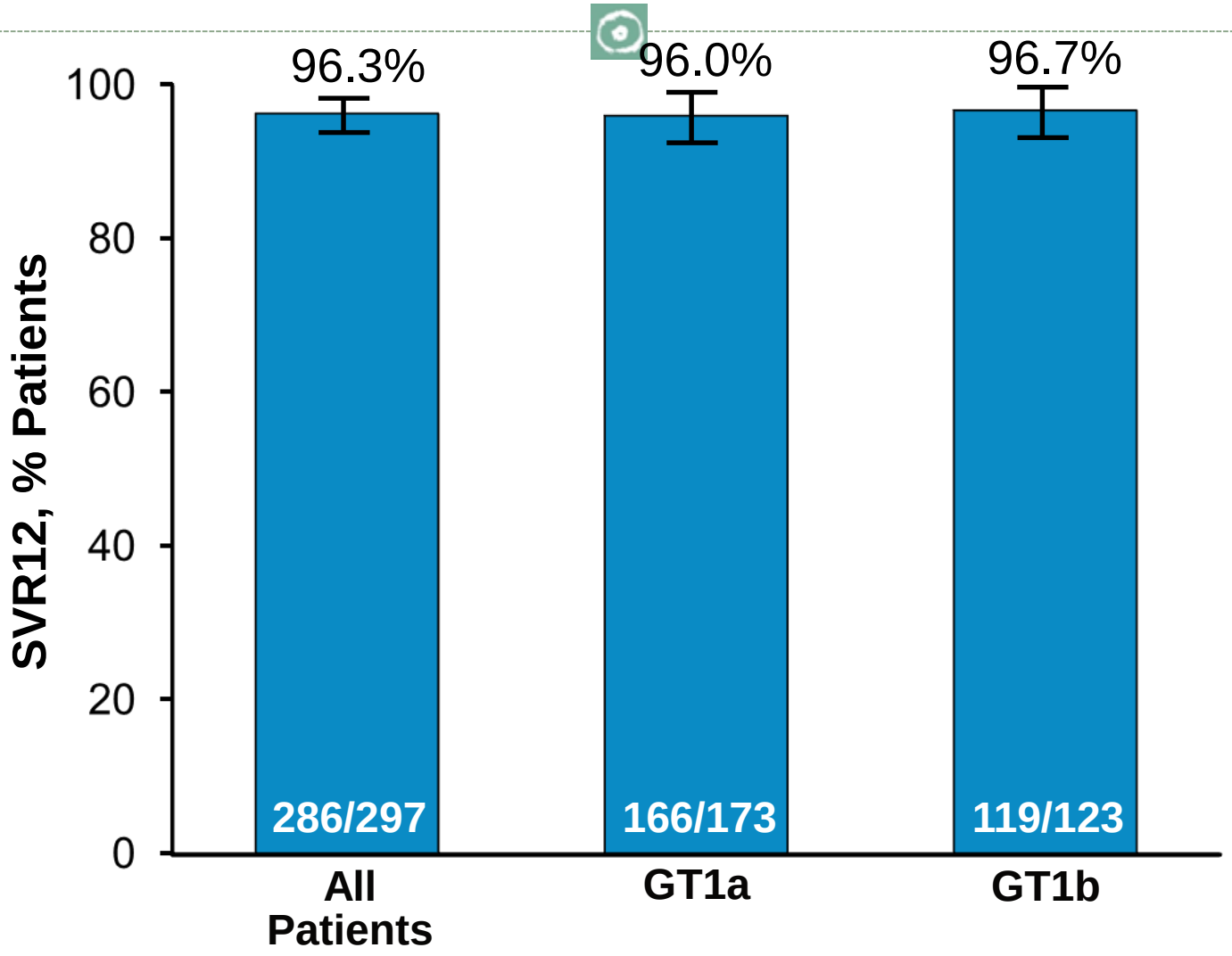
- SAPPHIRE I: Placebo-Controlled, 12-Week Regimen Of Paritaprevir/r/Ombitasvir, Dasabuvir, and Ribavirin in **Treatment-Naïve** Adults With HCV Genotype 1 Feld, NEJM 2014
- SAPPHIRE II: Placebo-Controlled, 12-Week Regimen Of Paritaprevir/r/Ombitasvir, Dasabuvir, and Ribavirin in **Treatment-Experienced** Adults With HCV Genotype 1 Zeuzem, NEJM 2014
- TURQUOISE-II: Open label, 12 vs 24-week Regimen Of Paritaprevir/r/Ombitasvir, Dasabuvir, and Ribavirin in HCV G1-infected patients with **Compensated Cirrhosis** Poordad, NEJM 2014

SAPPHIRE-II: Placebo-Controlled Design (N=394)



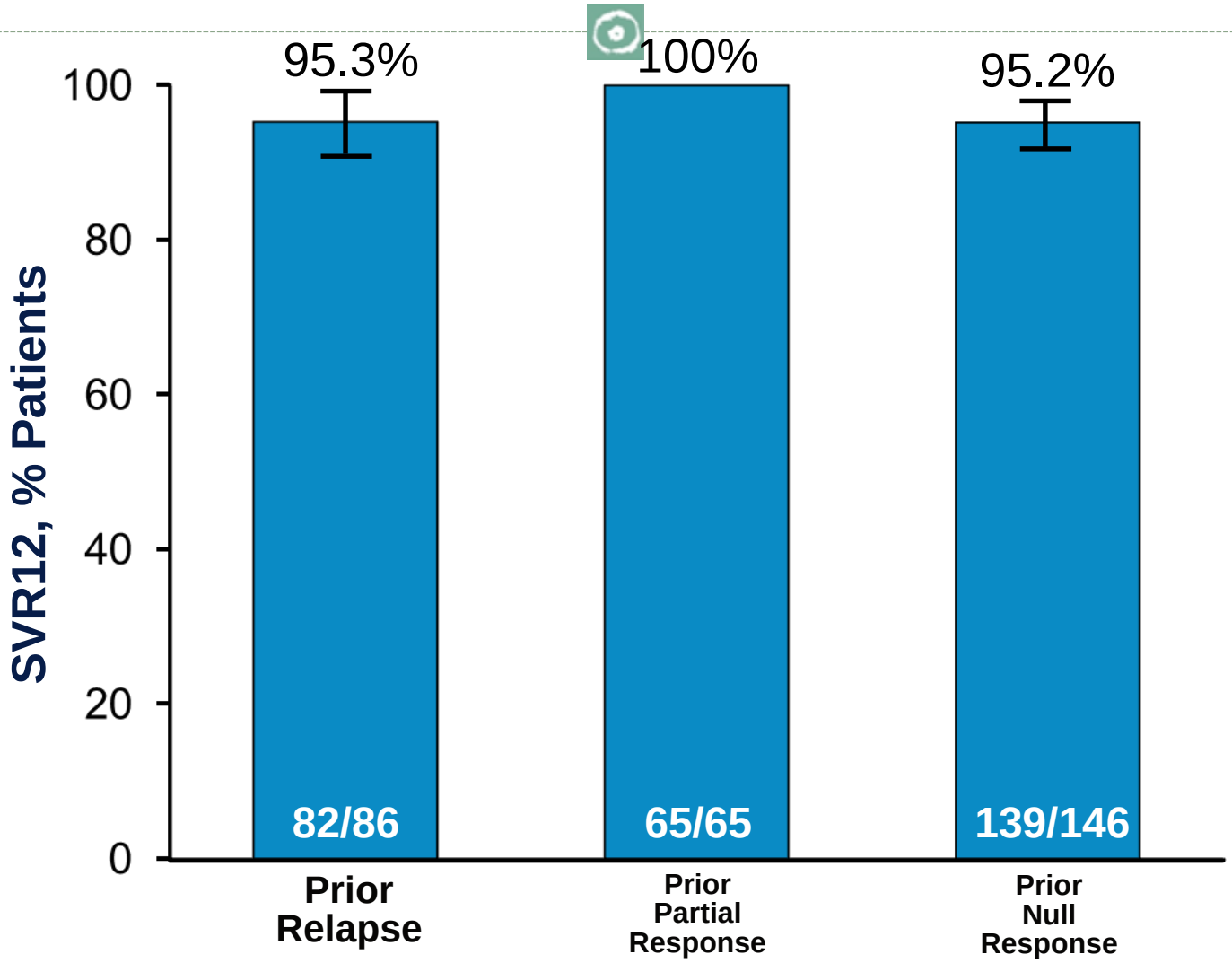
- 3D: co-formulated ABT-450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID
- RBV: 1000-1200 mg daily according to body weight (<75 kg and >75kg, respectively)

SAPPHIRE-II:SVR12 Rates (Superior to SOC)



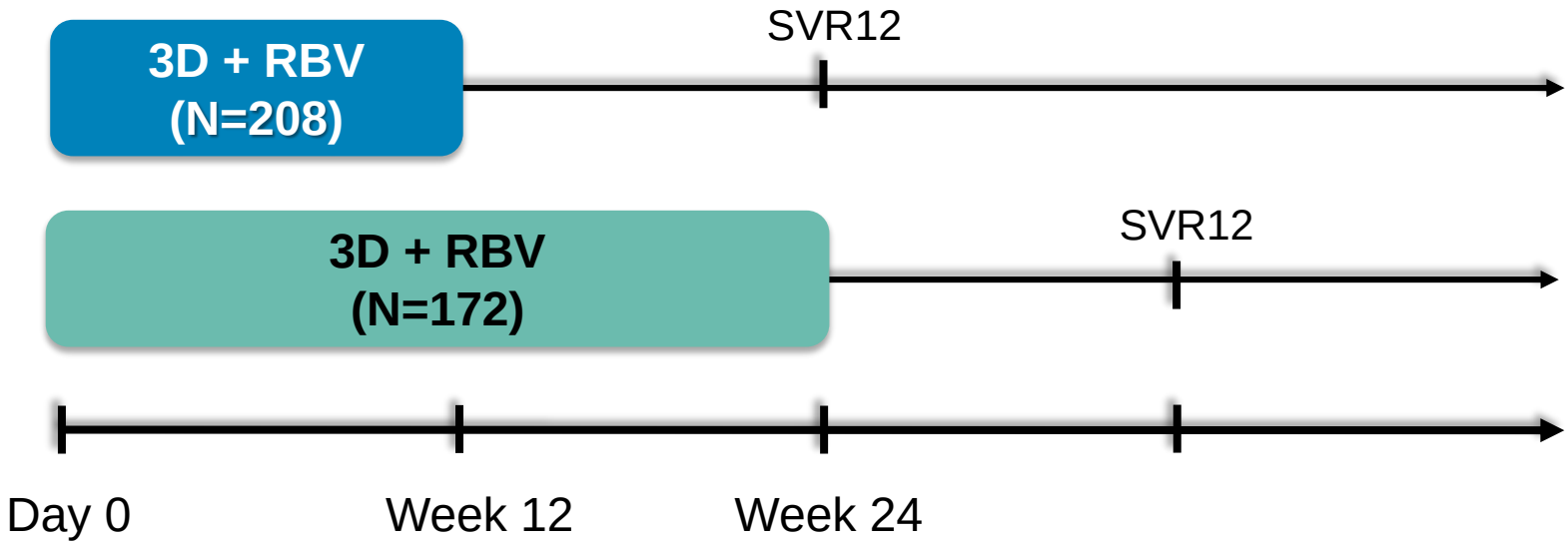
Zeuzem, NEJM 2014

SAPPHIRE-II Results: ITT SVR12 Rates >95% in All Prior PEG/RBV Non Response Groups



Zeuzem, NEJM 2014

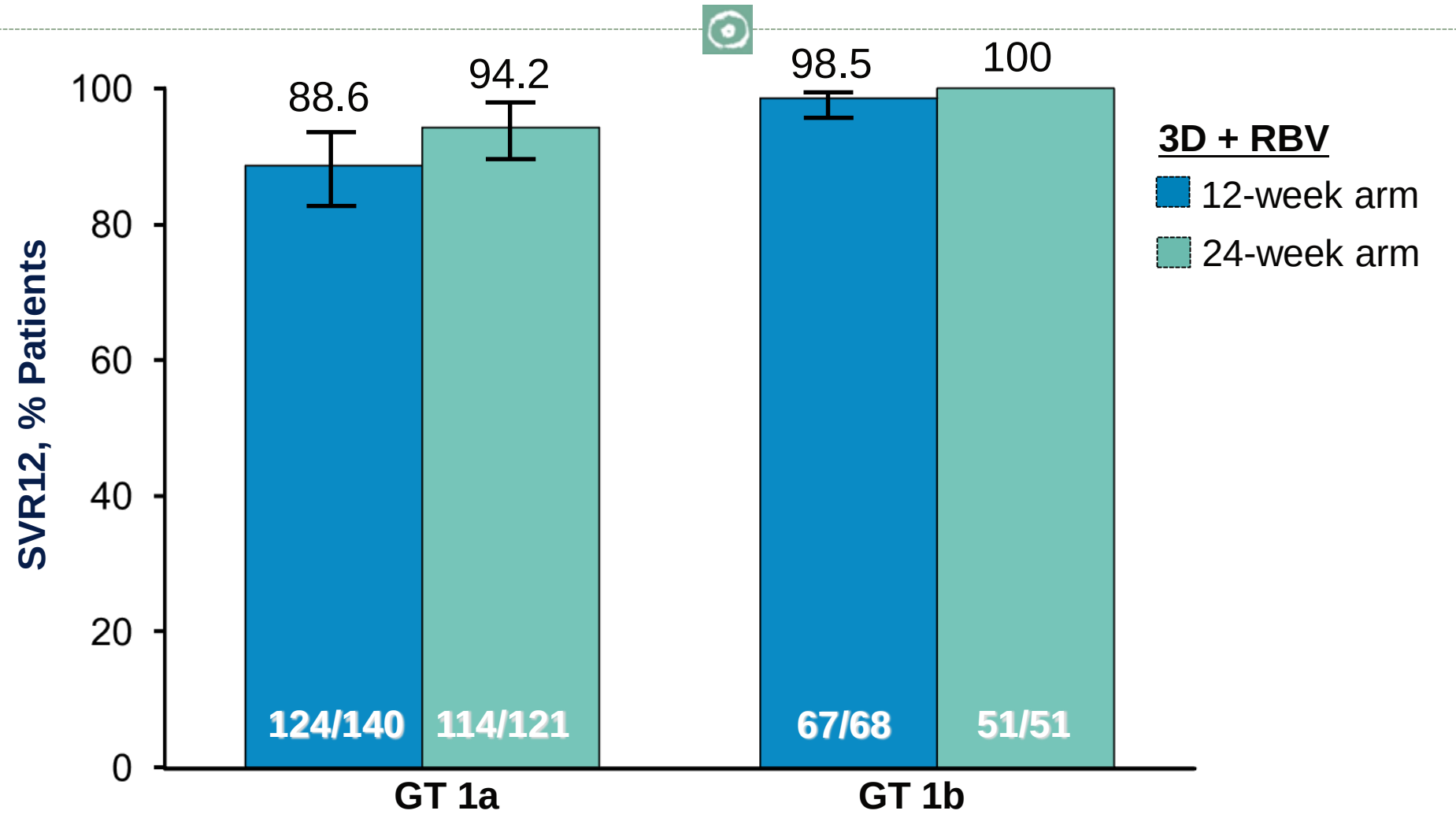
TURQUOISE-II Study Design: Phase 3 380 GT1-Infected Cirrhotics



- 3D: co-formulated 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)

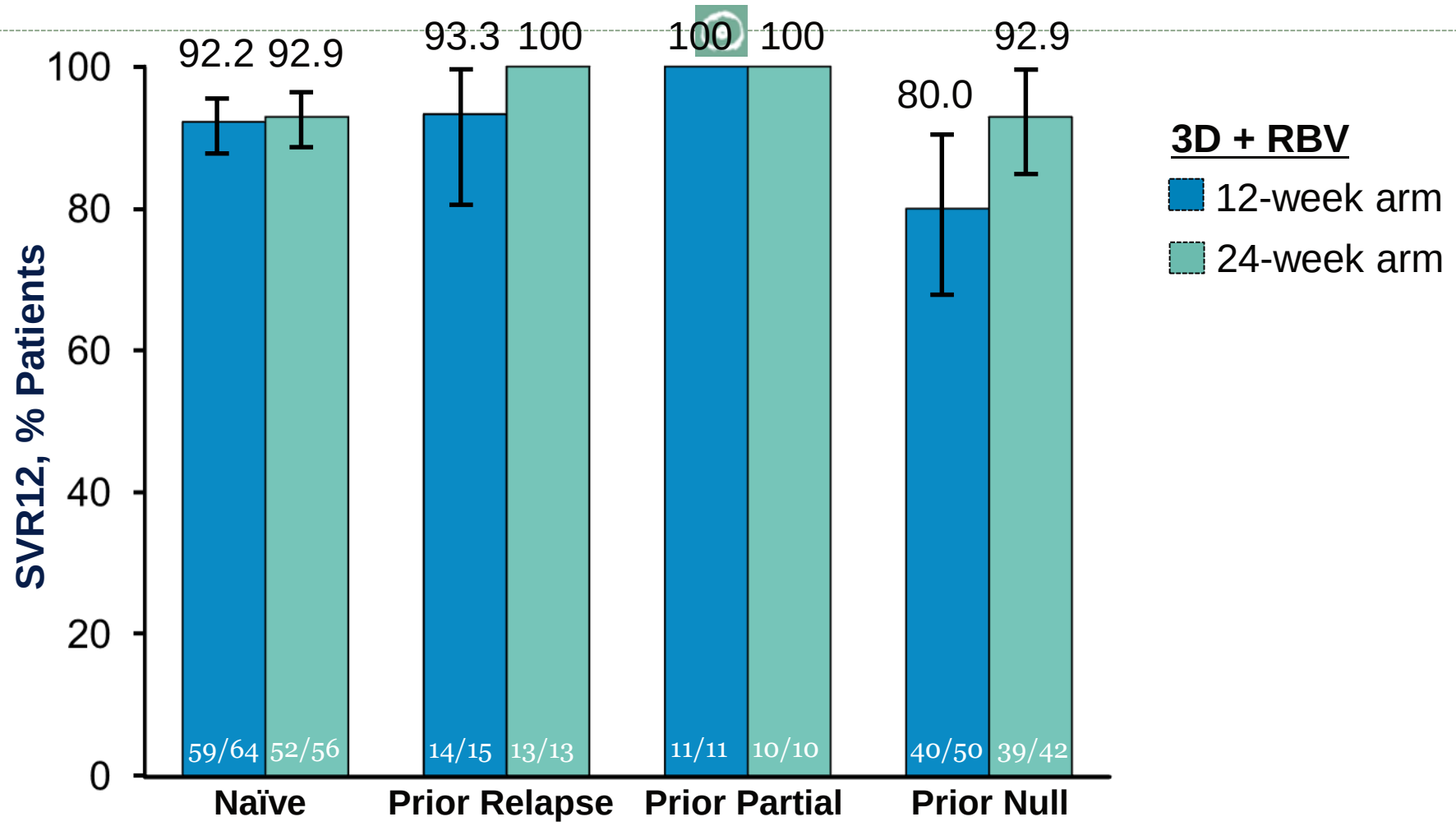
Poordad, NEJM 2014 370: 1973

TURQUOISE-II Results: ITT SVR12 Rates by HCV Subtype



Poordad, NEJM 2014 370: 1973

TURQUOISE-II: SVR12 Rates by TE in G1a



Poordad, NEJM 2014 370: 1973

Conclusions G1 Phase 3 Program 3D regimen

- Treatment with PI + NS5A + NNI + RBV
- Treatment-naïve and treatment experienced non-cirrhotic
  - Very effective 12 week regimen – 96% SVR
  - Very well tolerated – compared to placebo
  - Similar G1a and G1b
  - 1 breakthrough, infrequent relapse
- Cirrhosis
  - Largest cirrhotic trial
  - Highly effective
  - 24 weeks necessary for G1a null responders, 12 adequate for everyone else
  - *Safety has been raised as an issue post-marketing*

Daclatasvir (containing regimens)

IAS–USA
International AIDS Society–USA

Daclatasvir (DCV)

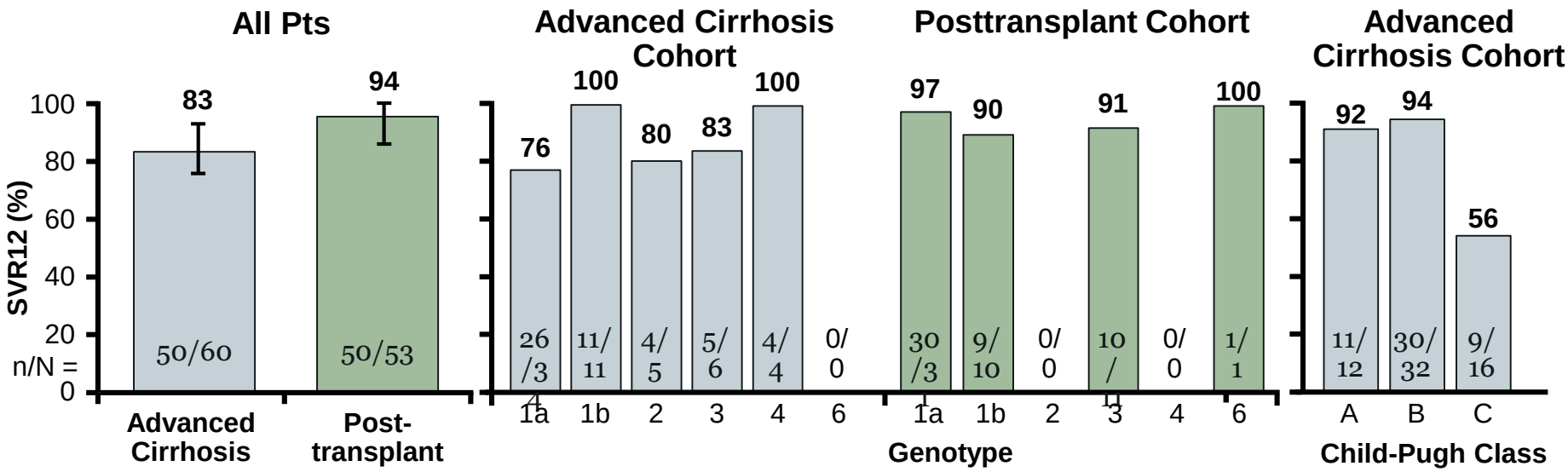
- Daclatasvir is a potent, pan-genotypic activity NS5A agent
- It has been shown to work well with a SOF-based regimen
- Licensed outside of US with PI based regimens for G1b disease

ALLY-1: SOF + DCV + RBV in Cirrhotic or Posttransplant HCV-Infected Pts

- Multicenter, open-label phase III trial
- Enrolled advanced cirrhosis (n = 60) or post–liver transplant (n = 53) pts
  - 95% and 96% of pts were white, 40% and 42% were treatment naive, 75% and 77% were infected with GT1 HCV
- Treatment
  - 12 wks of daclatasvir 60 mg QD + sofosbuvir 400 mg QD + RBV
    - Initial RBV dose 600 mg/day, adjusted to 1000 mg/day
  - Pts transplantated could receive 12 additional wks of therapy immediately after transplantation
  - Individuals relapsing following 12 wks were offered re-treatment with the same regimen for 24 wks

Poordad F, *et al.* Hepatology 2016 epublish

ALLY-1: Key Results

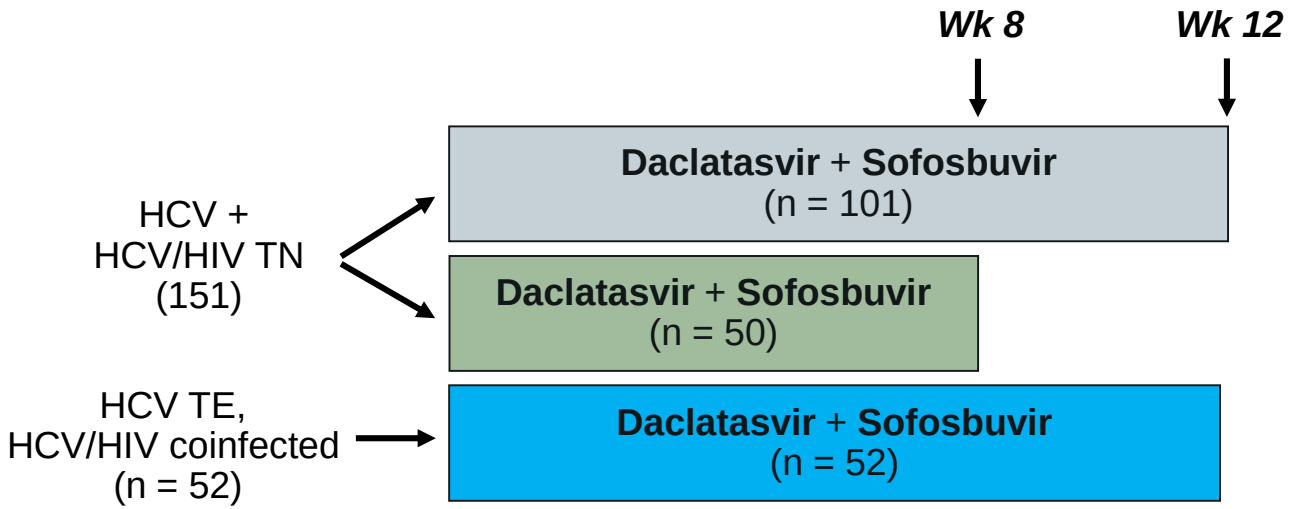


- In subgroup analysis of pts in the advanced cirrhosis group, those who were Child-Pugh class C (n = 16) or had albumin < 2.8 g/dL (n = 18) had SVR12 rates of 56%
- 10/10 pts who relapsed in the advanced cirrhosis group had NS5A RAVs at virologic failure; 4 of 10 pts had NS5A RAVs at baseline
- 3/3 pts who relapsed in the posttransplantation group had NS5A RAVs at virologic failure; none had NS5A RAVs at baseline

Poordad F, et al. Hepatology 2016 (epublish)

ALLY-2: Daclatasvir + Sofosbuvir for HIV/HCV Coinfection

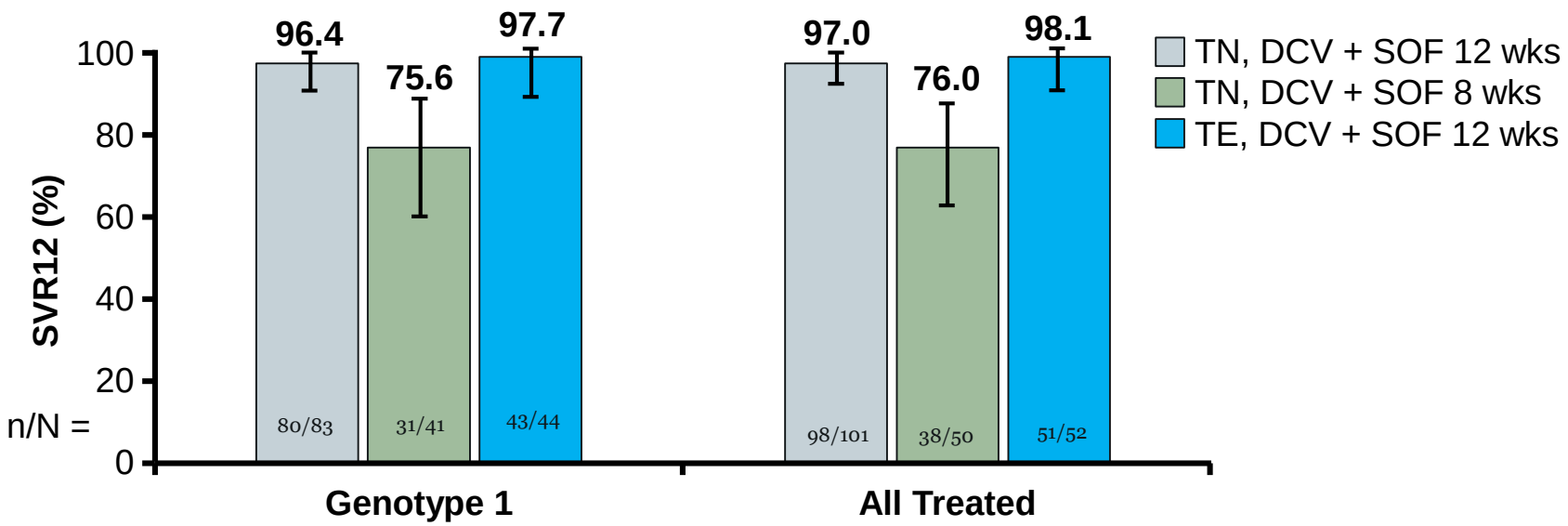
- Multicenter, randomized phase 3 study



Daclatasvir 60 mg QD, (adjusted for ART). Sofosbuvir 400 mg QD.

- Treatment arms well matched at baseline
- GT1 HCV infection most prevalent (> 80% per arm)
- Cirrhosis more common on TE arm (29% vs 9% to 10% in TN)
- Most HIV patients on ART

ALLY-2



- No significant differences in SVR12 rates by HCV genotype, HCV disease characteristics, CD4+ cell count, or ART use in either 8-wk or 12-wk arms
- Ongoing control of HIV disease maintained without need for ART modification
- 28 of 32 pts with NS5A RAVs achieved SVR12
  - Among 4 pts with NS5A RAVS who did not achieve SVR12, 3 were in 8-wk arm
  - Emergent NS5A Q30 RAVs detected in 3 of 13 pts with virologic failure

Wyles DL, *et al.* NEJM 2015

Recommended Regimens

- Regimens with a * represent alternatives. These may still be the best options in some patient populations

G1a IFN/RBV failure (non cirrhotic)

Regimen	Considerations
EBV/GZP daily for 12 wks	Obtain NS5A RAV testing 16 weeks if high risk *
LDV/SOF daily for 12 wks	
PTV/OBV/DBV+RBV 12 wks	
SMV/SOF daily for 12 wks	Obtain NS3/4A RAV testing
DCV/SOF daily for 12 wks	Less data driving this regimen

G1a IFN/RBV failure (comp. cirrhotic)

Regimen	Considerations
EBV/GZP daily for 12 wks	Obtain NS5A RAV testing 16 weeks if high risk*
LDV/SOF daily for 24 wks	May add RBV and treat 12wks
PTV/OBV/DBV+RBV for 24wks	*Monitor pts closely, only compensated*!*
SMV/SOF (± RBV) daily for 24 wks	Obtain NS3/4A RAV testing*
DCV/SOF (±RBV) daily for 24 wks	Less data driving this regimen*

AASLD/IDSA Treatment Guidelines (www.hcvguidelines.org)

G1b IFN/RBV failure (non cirrhotic)

Regimen	Considerations
EBV/GZP daily for 12 wks	
LDV/SOF daily for 12 wks	
PTV/OBV/DBV+RBV 12 wks	
SMV/SOF daily for 12 wks	
DCV/SOF daily for 12 wks	Less data driving this regimen

G1b IFN/RBV failure (comp. cirrhotic)

Regimen	Considerations
EBV/GZP daily for 12 wks	
LDV/SOF daily for 24 wks	May add RBV and treat 12wks
PTV/OBV/DBV for 12 wks	*Monitor pts closely, only compensated*!
SMV/SOF (±RBV) daily for 24 wks	Obtain NS3/4A RAV testing*
DCV/SOF (±RBV) daily for 24 wks	Less data driving this regimen*

G1 SOF/RBV failure

Regimen	Considerations
LDV/SOF +RBV daily for 12 wks	In non-cirrhotic
LDV/SOF +RBV for 24wks	In comp. cirrhotic
DCV/SOF +RBV daily for 24 wks	Less data driving this regimen*

G1 NS3 PI/P/R failure (non-cirrhotic)

Regimen	Considerations
LDV/SOF daily for 12 wks	
EBV/GZP daily for 12 wks	High risk extend to 16 wks
DCV/SOF daily for 12 wks	

G1 NS3 PI/P/R failure (comp. cirrhosis)

Regimen	Considerations
LDV/SOF +RBV daily for 12 wks	
LDV/SOF for 24wks	
EBV/GZP(±RBV) 12 wks	In G1a with high fold NS5A variants (extend to 16 wks)
DCV/SOF (±RBV) daily for 24 wks	Less data driving this regimen

G1 LDV/SOF failure (non-cirrhotic)

Regimen	Considerations
LDV/SOF (±RBV) daily for 24 wks	NS5A variant analysis recommended
SMV/SOF (±RBV) for 12 wks	

G1 LDV/SOF failure (cirrhosis)

Regimen	Considerations
LDV/SOF + RBV daily for 24 wks	NS5A variant analysis recommended
SMV/SOF (±RBV) for 24wks*	If treatment is urgent, RAV analysis prior to avoid futility

G1 SMV/SOF failure

- If urgent therapy may want to look at NS3/NS5A variants and consider value of tailoring regimens that have likelihood of success
- May want to await introduction of new regimens

http://www.hcvguidelines.org/

Recommendations for Testing, Managing, and Treating Hepatitis C

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America

Summary

- HCV G1 is the most common viral type in USA
- HCV is a curable disease
- Careful documentation of prior failure will facilitate rescue therapies
- Access to treatment remains a significant challenge
- Knowledge of the regimens and expected results facilitates high rates of response to treatment