HCV: Current Management and Controversies

Steven L. Flamm MD
Chief, Liver Transplantation Program
Professor of Medicine and Surgery
Northwestern Feinberg School of Medicine

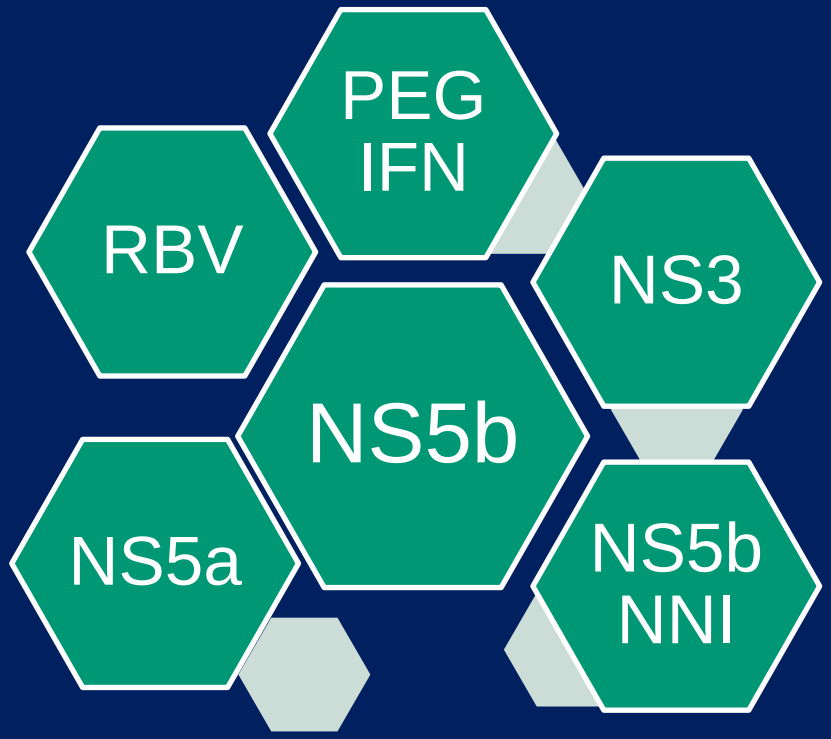
Who Should Be Treated?

Recommendations:

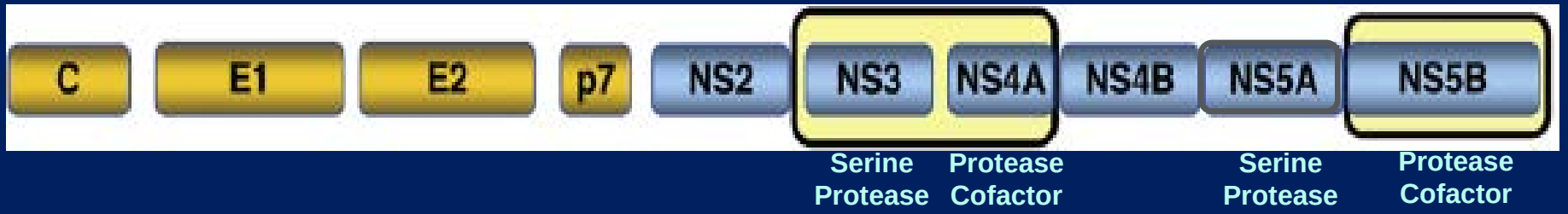
1. Antiviral treatment is recommended for all patients with chronic HCV infection, except those with limited life expectancy due to nonhepatic causes. (1-A)

2. If resources limit the ability to treat all infected patients immediately as recommended, then it is most appropriate to treat those at greatest risk of disease complications before treating those with less advanced disease (see Tables3 and 4 for ratings).

The components of treatment in HCV infection



DAAs: Key Characteristics



	Protease Inhibitors	Nucleos(t)ide Polymerase Inhibitors	Non-Nucleoside Polymerase Inhibitors	NS5A Inhibitors
Potency	High (varies by HCV genotype)	Moderate-to-high (consistent across HCV genotypes, subtype)	Variable (HCV genotypes)	High (multiple HCV genotypes)
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, ↑ Bilirubin	Mitochondrial, NRTI interactions (ART, RBV)	Variable	Variable
Dosing	qd to tid	qd to bid	qd to tid	qd
Comments	2nd generation PIs (higher barrier to resistance, pan-genotype)	Single target Active site	Allosteric Many targets	Multiple antiviral MOA

NRTIs = nucleoside reverse transcriptase inhibitors; PIs = protease inhibitors

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

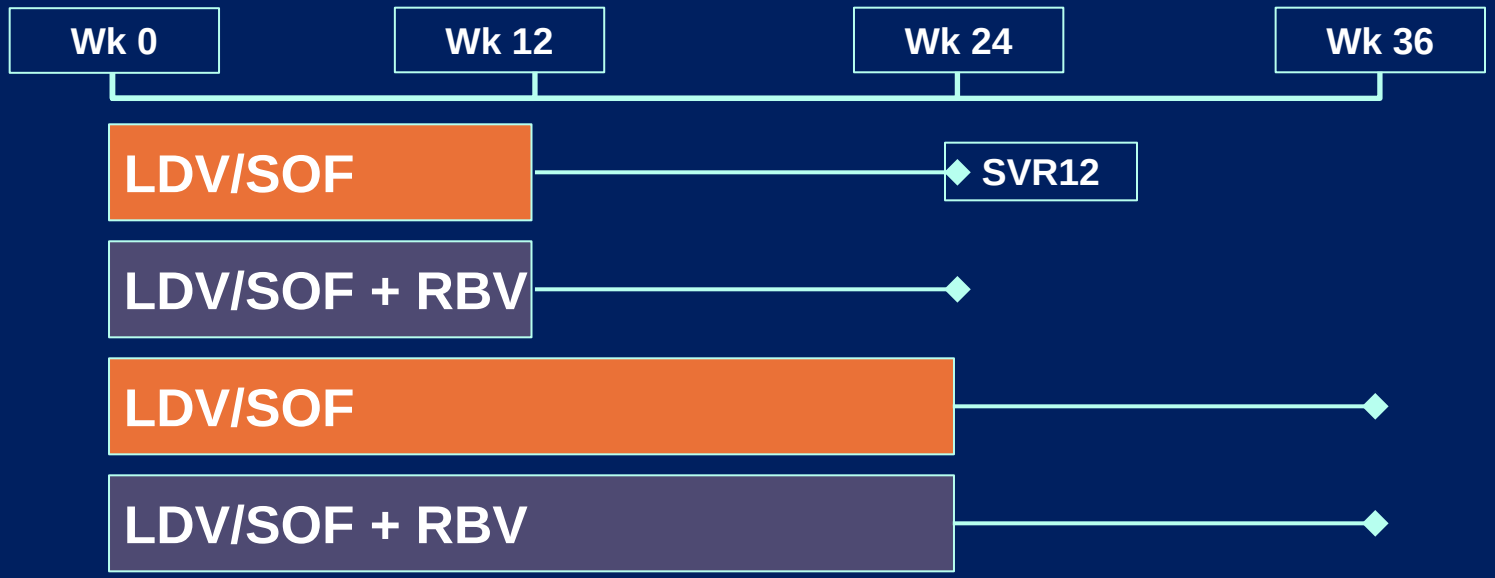
2016 Treatment Options for HCV

FDA Approval	NS3/4A Protease Inhibitor	Nucleotide NS5B Polymerase Inhibitor	Non-Nucleoside NS5B Polymerase Inhibitor	NS5A Replication Complex Inhibitor	Other
2013	Simeprevir				PegIFN + RBV
2013		Sofosbuvir			PegIFN + RBV
2013		Sofosbuvir			RBV
2014		Sofosbuvir		Ledipasvir	± RBV
2014	Simeprevir	Sofosbuvir			
2014	Paritaprevir		Dasabuvir	Ombitasvir	± RBV
2015		Sofosbuvir		Daclatasvir	± RBV
2016	Grazoprevir			Elbasvir	
2016		Sofosbuvir		Velpatasvir	

Newly Diagnosed HCV Patient: Which Treatment Option?

- Monitor patient?
- Would you order any of the following test?
  - HIV and hepatitis B testing
  - Drug and alcohol screen
  - Liver biopsy
  - Fibrosure®
  - Shear wave elastography
  - MR elastography
- Initiate antiviral therapy?

Study Design GT 1 Treatment-Naïve (ION-1)

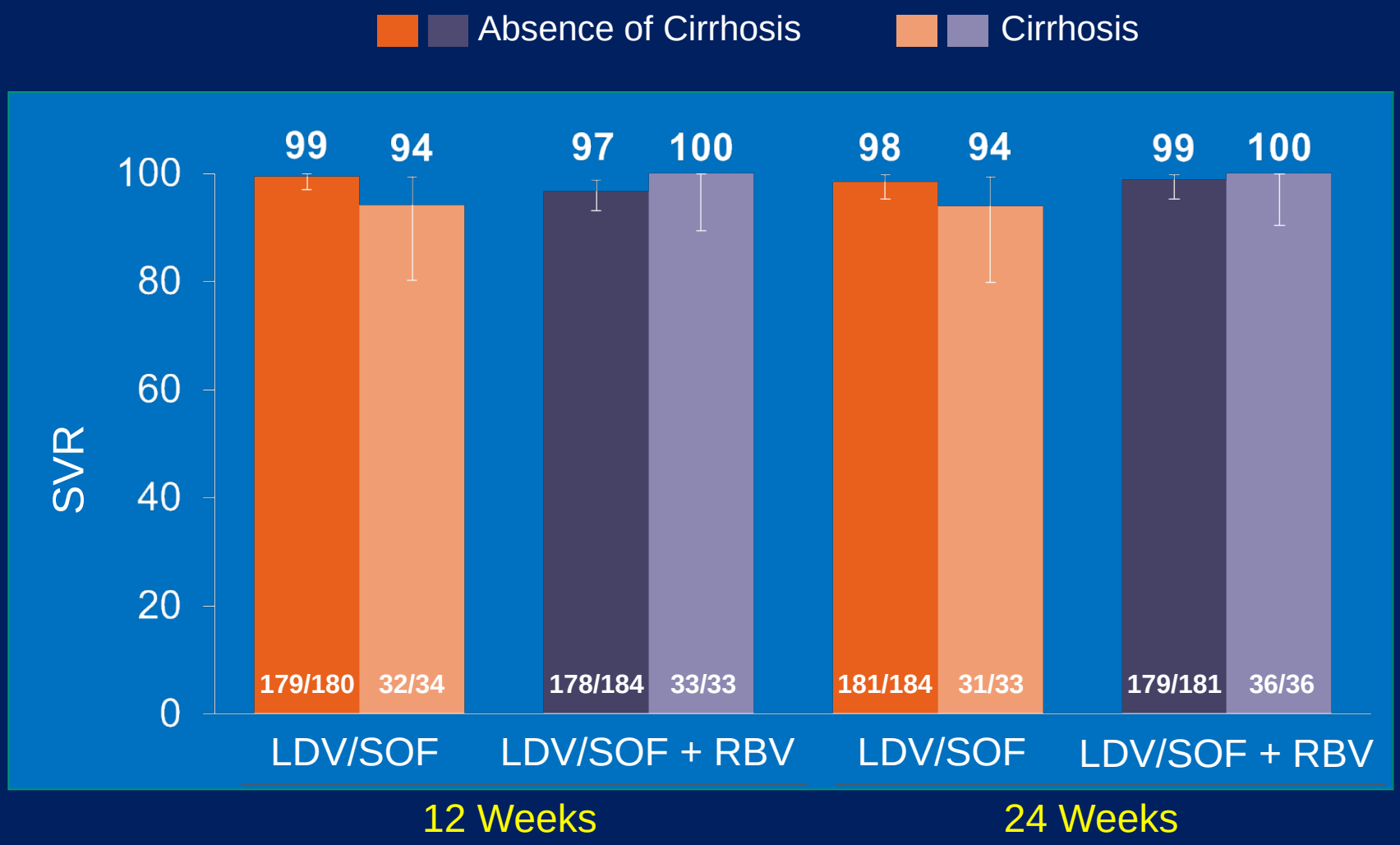


- GT 1 HCV treatment-naïve patients in Europe and USA
- Broad inclusion criteria
  - Targeted 20% enrollment of patients with cirrhosis
  - No upper age or BMI limit
  - Platelet count ≥50,000/mm^3, no neutrophil minimum
- 865 patients randomized 1:1:1:1 across four arms
- Stratified by HCV subtype (1a or 1b) and cirrhosis

Afdhal et al. NEJM 2014;370:1889-98

SVR12: Absence of Cirrhosis vs Cirrhosis

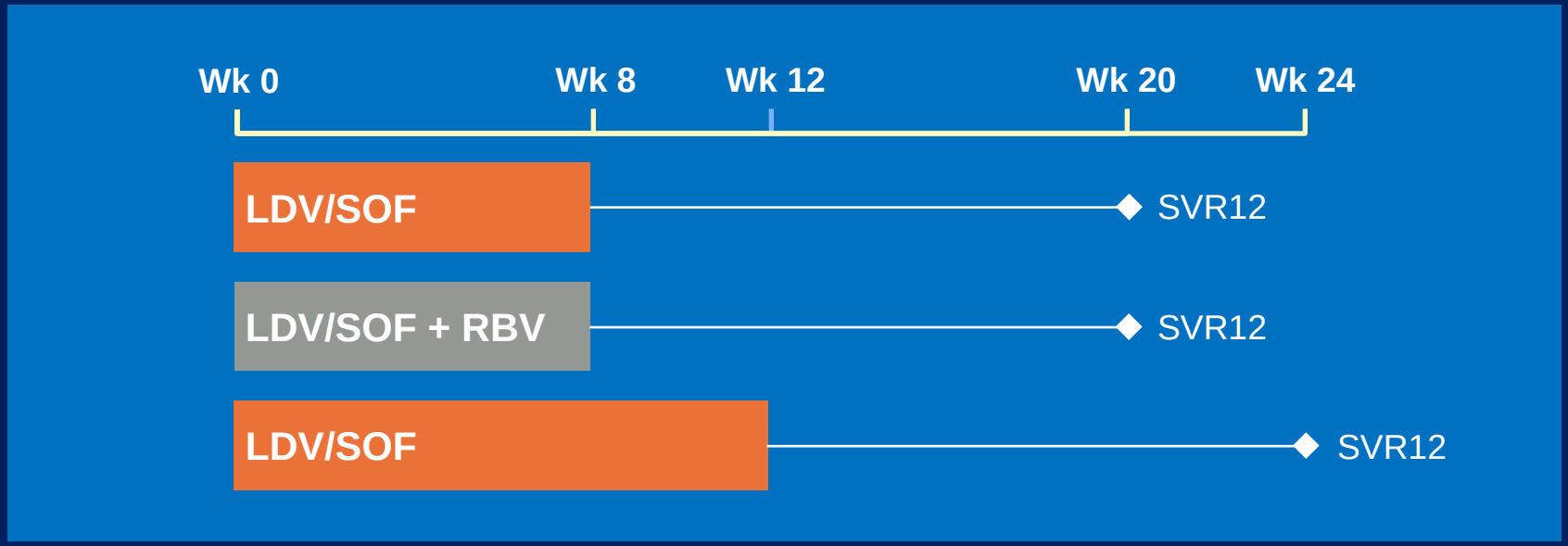
GT 1 Treatment-Naïve (ION-1)



Error bars represent 95% confidence intervals.

GT 1 Treatment-Naïve (ION-3) :

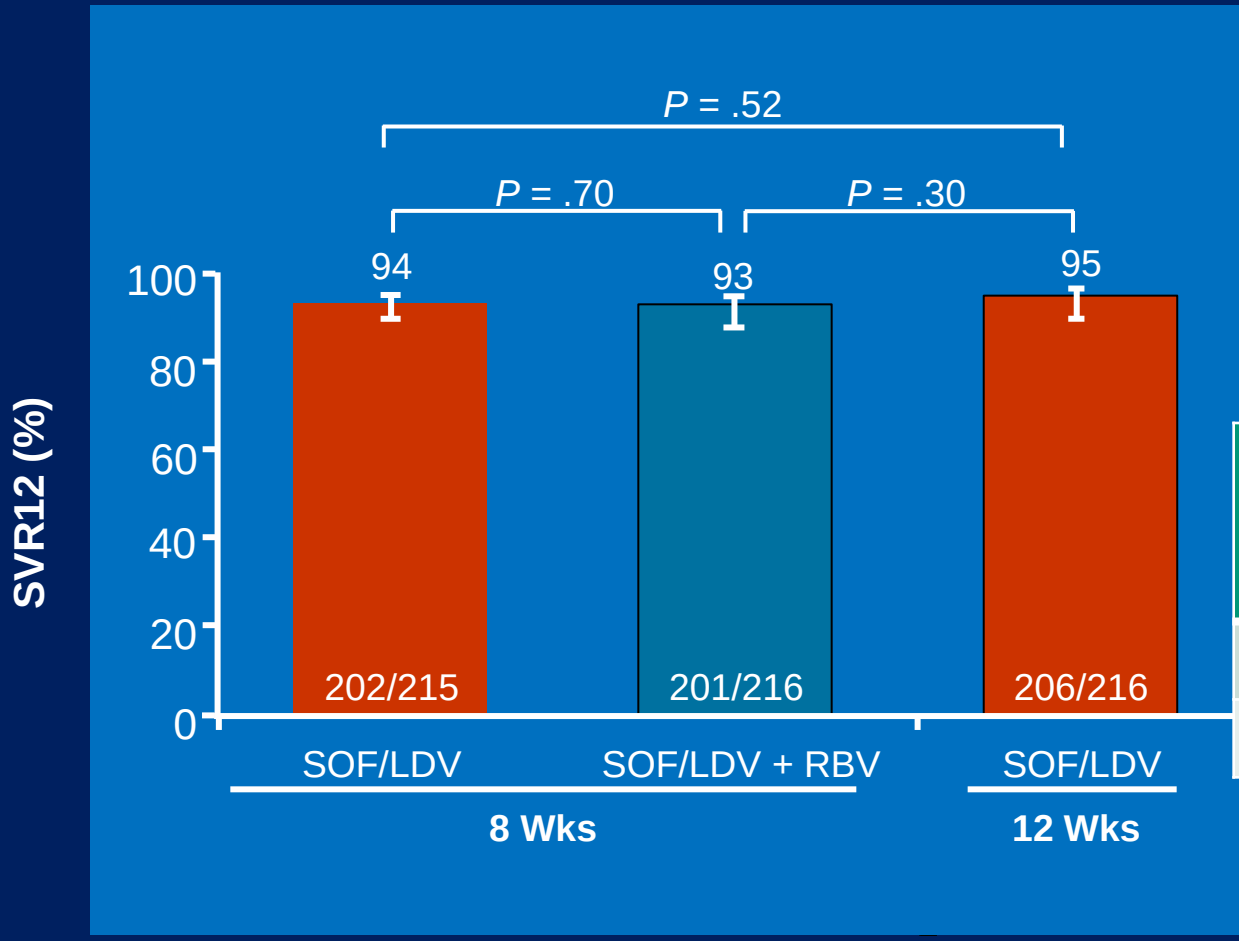
8 weeks of therapy with SOF/LDV leads to high SVR rates in non-cirrhotic naïve patients



- GT 1 treatment-naïve patients without cirrhosis
- Broad inclusion criteria
  - No upper age or BMI limit
  - Opiate substitution therapy allowed
- 647 patients randomized 1:1:1 across three arms
- Stratified by HCV subtype (1a or 1b)

Kowdley KV et al. NEJM 2014; 370:1879-88

ION 3: SVR12 With 8 or 12 Wks SOF/LDV ± RBV in Tx-Naive Non-cirrhotic Patients



Post hoc analysis notes high SVR rates in those with HCV RNA < 6 X 10^6 IU/ml

Treatment Duration SOF/LDV	SVR (%) with Baseline HCV RNA <6 million IU/mL
8 wks	97 (119/123)
12 wks	96 (126/131)

SVR12 rates did not differ by GT1a vs GT1b in any treatment arm

Virologic failure: 23 relapses (11 in 8-wk SOF/LDV, 9 in 8-wk SOF/LDV/RBV, 3 in 12-wk SOF/LDV)

LDV/SOF: Points To Consider

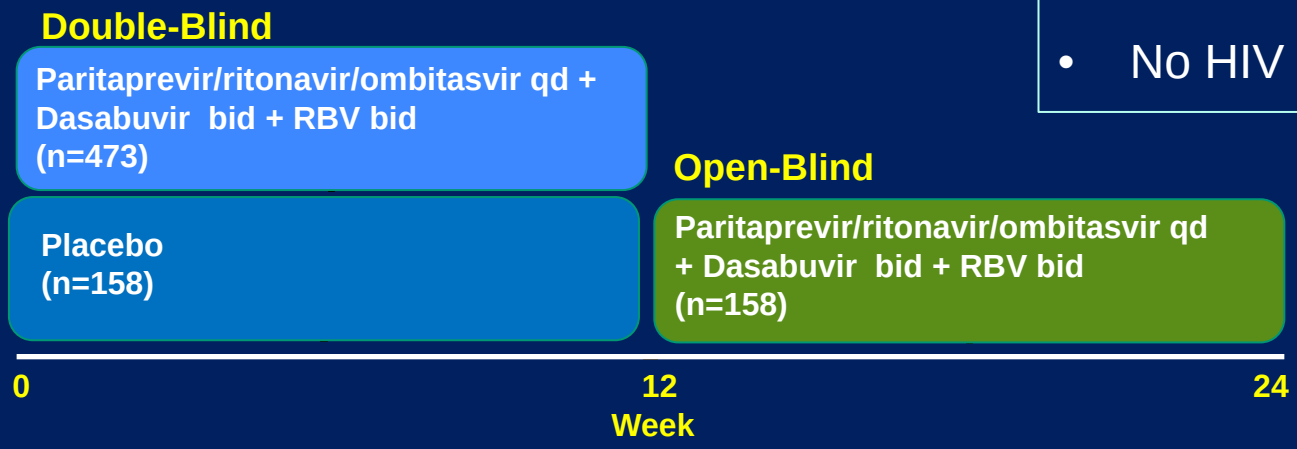
- For GT 1, treatment-experienced, compensated cirrhotics, should 12 weeks of LDV/SOF/RBV be considered instead of the approved 24 weeks of LDV/SOF?
- Renal disease
  - No dosage adjustment required in patients with mild or moderate renal disease (GFR $\geq$30)
  - No safety/efficacy data available in patients with severe or ESRD requiring dialysis
- P-gp inducers (e.g., rifampin, St. John's wort) may significantly decrease LDV/SOF plasma concentrations and concomitant use not recommended
- Co-administration with amiodarone is not recommended due to post marketing cases of symptomatic bradycardia, including fatal cardiac arrest and cases requiring pacemaker intervention[1]

1Ledipasvir/sofosbuvir (HARVONI™) Prescribing Information. Gilead Sciences, Foster City, CA. March, 2015.

SAPPHIRE-I: PTV/OMB/DSB + RBV in HCV GT1

Inclusion Criteria

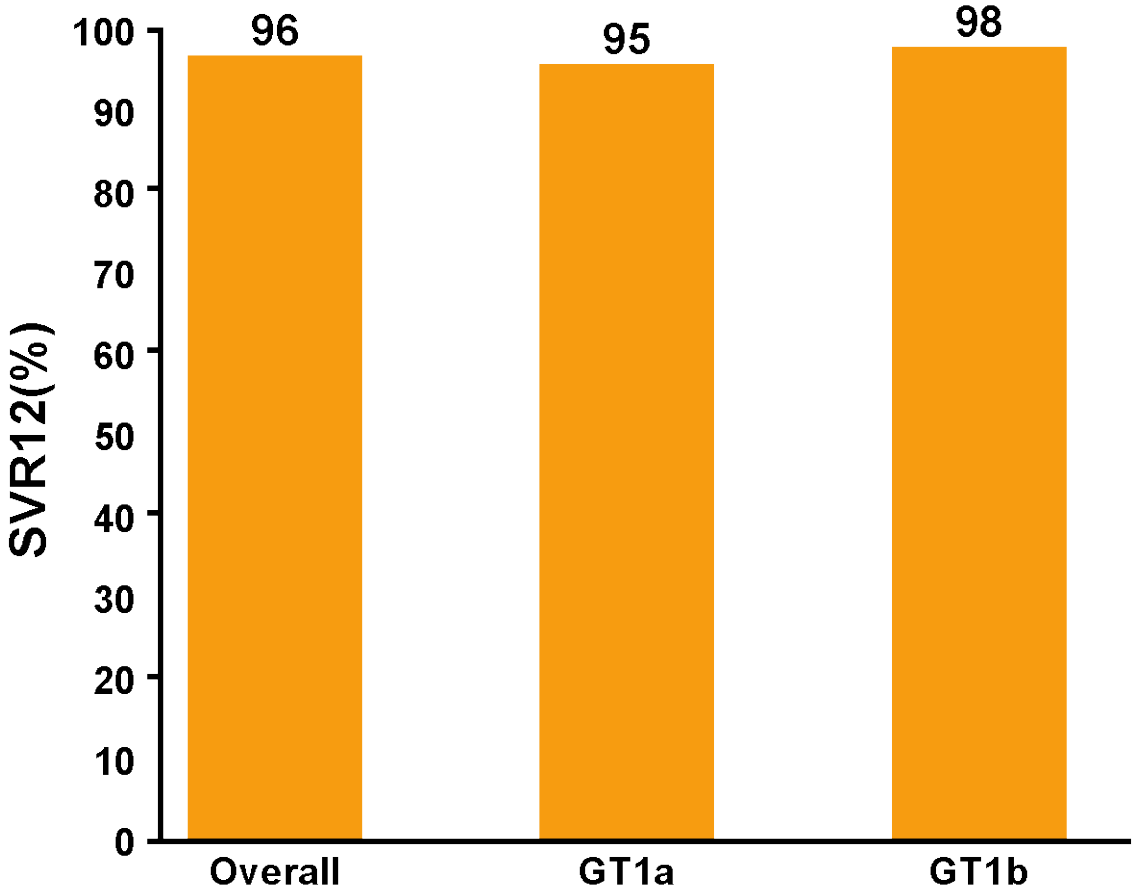
- HCV GT1
- Treatment-naïve
- No cirrhosis
- No HIV or HBV



- Paritaprevir/r (150/100 mg) co-formulated with ombitasvir (25 mg) and administered once daily. Dasabuvir (250 mg) + RBV (weight-based dosing) administered twice daily.
- *After week 12, placebo patients received open-label paritaprevir/r/ombitasvir + dasabuvir + RBV for 12 weeks.
- Primary outcome: SVR12.

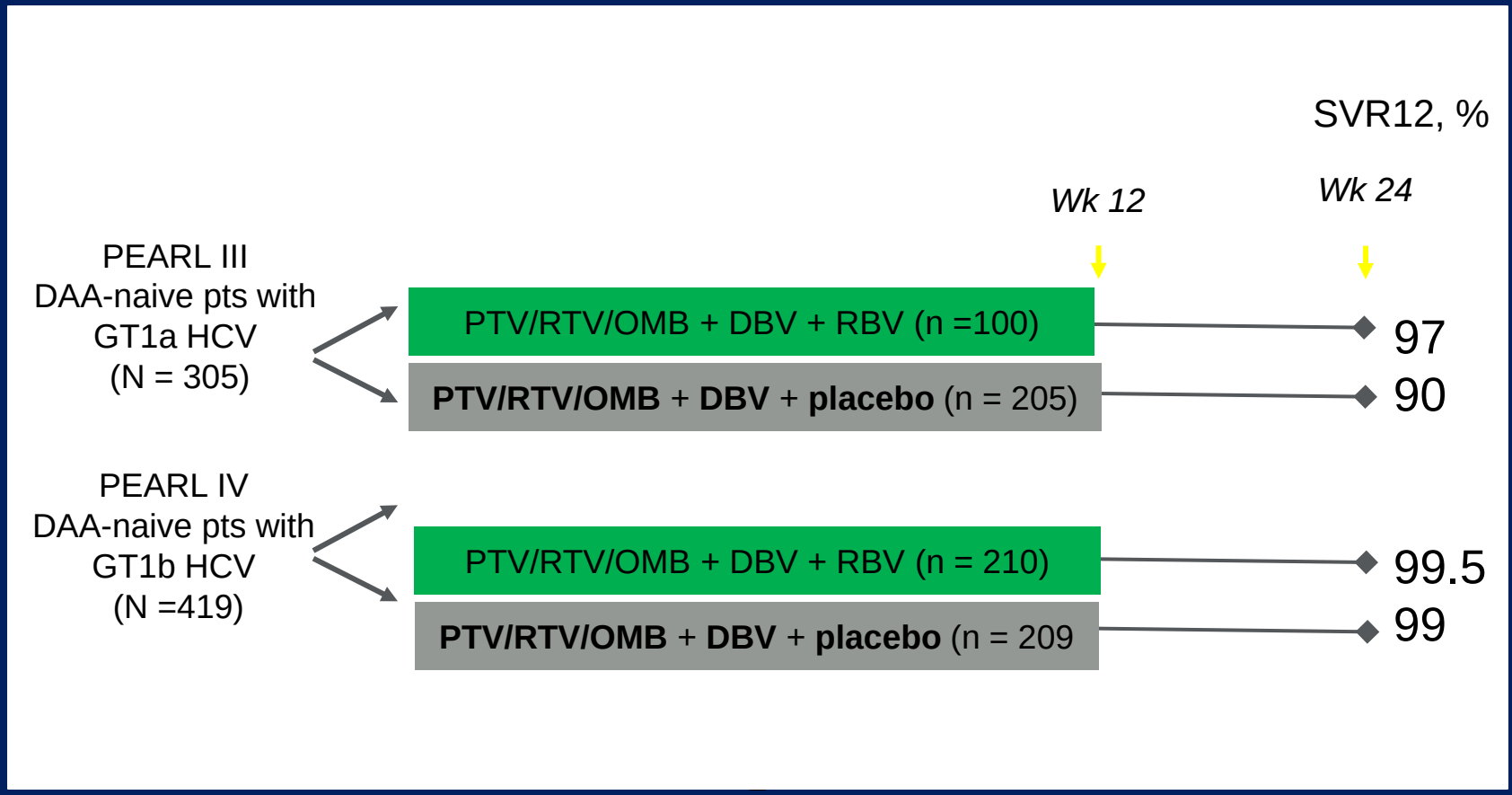
Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.

SAPPHIRE-I Results: ITT SVR12 Rates



Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.

Paritaprevir/ RTV Ombitasvir + Dasabuvir ± RBV in GT1 Patients Without Cirrhosis: Is RBV Necessary? (PEARL III and PEARL IV)



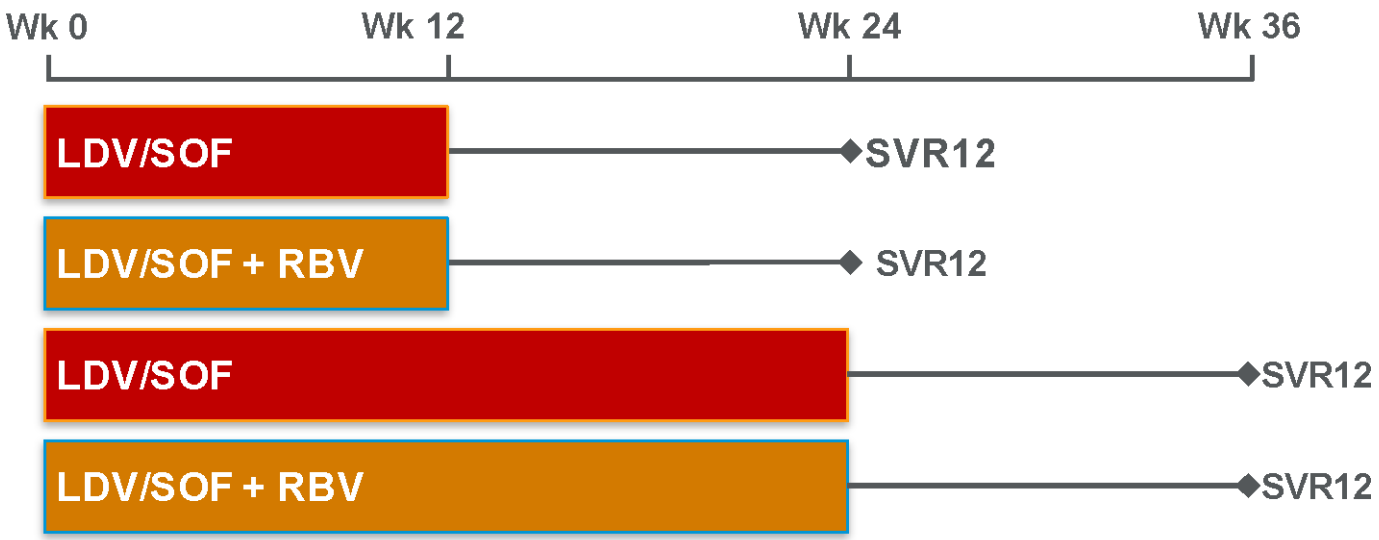
Ferenci P et al. N Engl J Med 2014;370:1983-1992.

PTV/RTV/OMV + DSV: Points to Consider

- No dosage adjustment required in patients with mild, moderate or severe renal impairment[1,2]
- Regimen is not recommended in patients with decompensated liver disease[2]
- Drug:drug interaction: Contraindications
  - Drugs highly dependent on CYP3A for clearance, strong inducers of CYP3A or CYP2C8 and strong inhibitors of CYP2C8
  - Some examples: gemfibrozil, rifampin, St. John's wort, lovastatin, simvastatin, efavirenz
  - Ethinyl estradiol-containing medications must be discontinued prior to starting therapy because of risk for elevated ALT[2]
- Rosuvastatin and pravastatin: Okay to use; however, dose of rosuvastatin should not exceed 10 mg/day and pravastatin should not exceed 40 mg/day[2]
- Omeprazole: Monitor patients for decreased efficacy of omeprazole and consider increasing dose (no more than 40 mg/day) in patients whose symptoms are not well controlled[2]

[1]Khatri A et al., AASLD 2014. Abstract 238
[2]Viekira Package Insert. AbbVie Inc., North Chicago, IL. February 2015.

GT 1 Treatment-Experienced (ION-2): Study Design

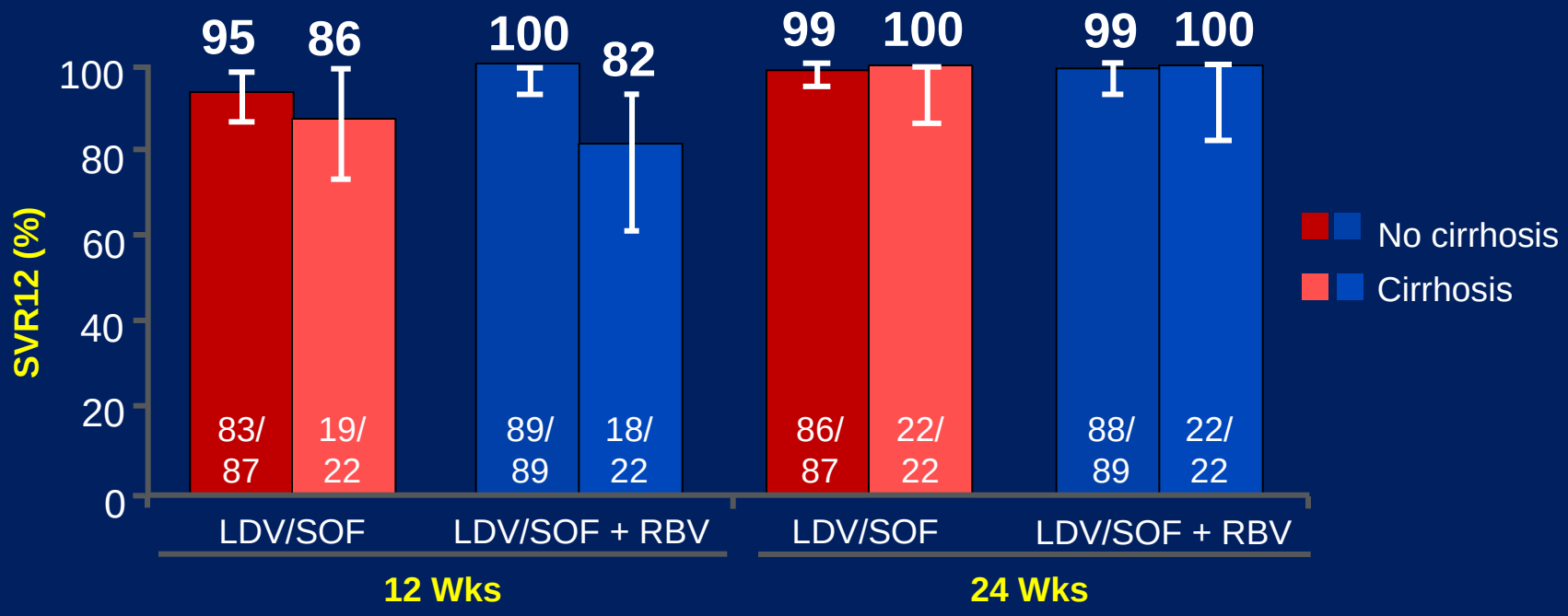


- GT 1 HCV patients who had failed prior IFN-based therapy, including regimens containing a NS3/4A protease inhibitor
- Broad inclusion criteria
  - Targeted 20% enrollment of patients with cirrhosis
  - No upper age or BMI limit
  - Platelet count ≥50,000/mm3, no neutrophil minimum
- 440 patients randomized 1:1:1:1 across four arms
- Stratified by HCV subtype (1a or 1b), cirrhosis, prior treatment response

Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

ION 2: SVR12 With 12 or 24 Wks of SOF/LDV ± RBV by Cirrhosis Status

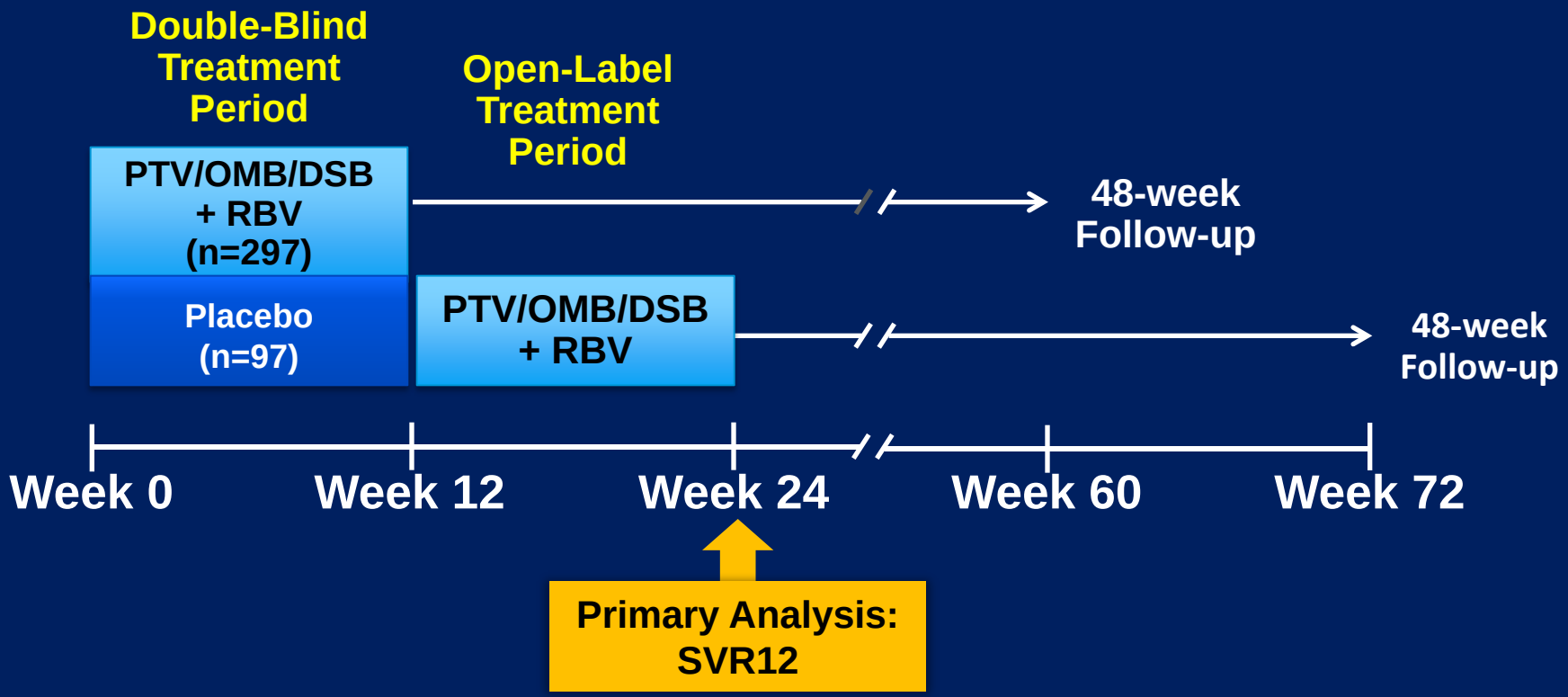
24 Week Duration for Cirrhosis Patients



- SVR12 rates were significantly lower in cirrhotic vs non-cirrhotic patients in the pooled 12-wk arms
- Previous treatment with protease inhibitor or did not matter

Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

SAPPHIRE-II: GT1 Treatment-experienced Patients

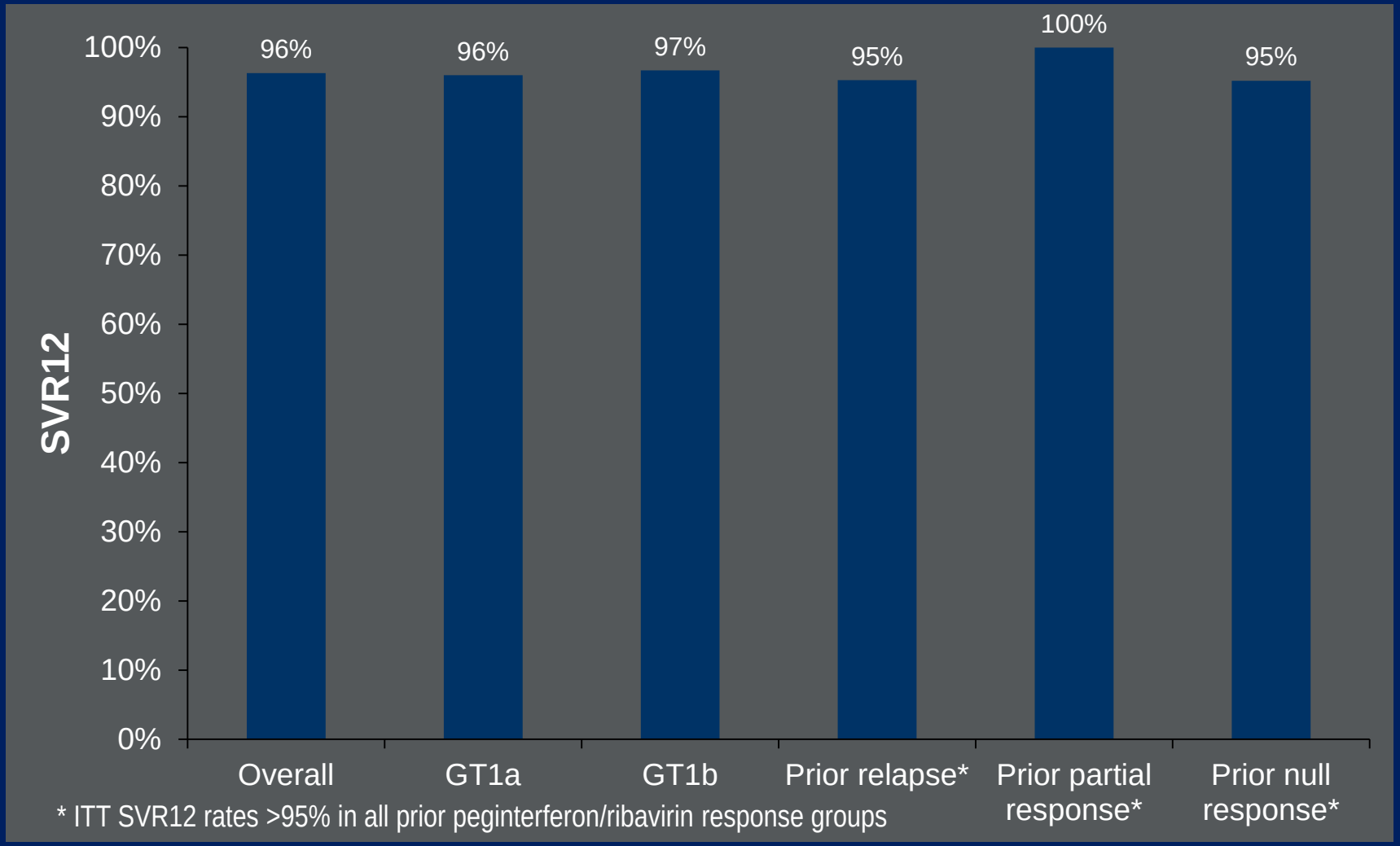


PTV/OMB/DSB: co-formulated Paritaprevir/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID

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

Zeuzem S, et al. N Engl J Med. 2014;370:1604-1614.

SAPPHIRE-II Results: ITT SVR12 Rates in Treatment-experienced Patients

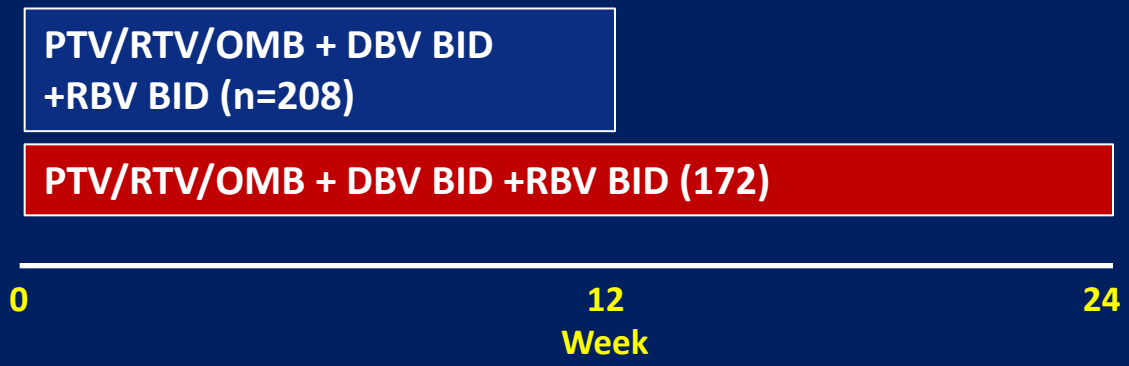


Zeuzem S, et al. N Engl J Med. 2014;370:1604-1614.

Paritaprevir/ RTV Ombitasvir + Dasabuvir + RBV in HCV Genotype 1 Cirrhosis (TURQUOISE-II):

Phase 3 Study

- **Key eligibility criteria**
  - HCV genotype 1
  - Treatment-naïve and treatment-experienced
  - Compensated cirrhosis (Child-Pugh score <6)
  - HCV RNA >10K IU/mL
  - No HIV or HBV

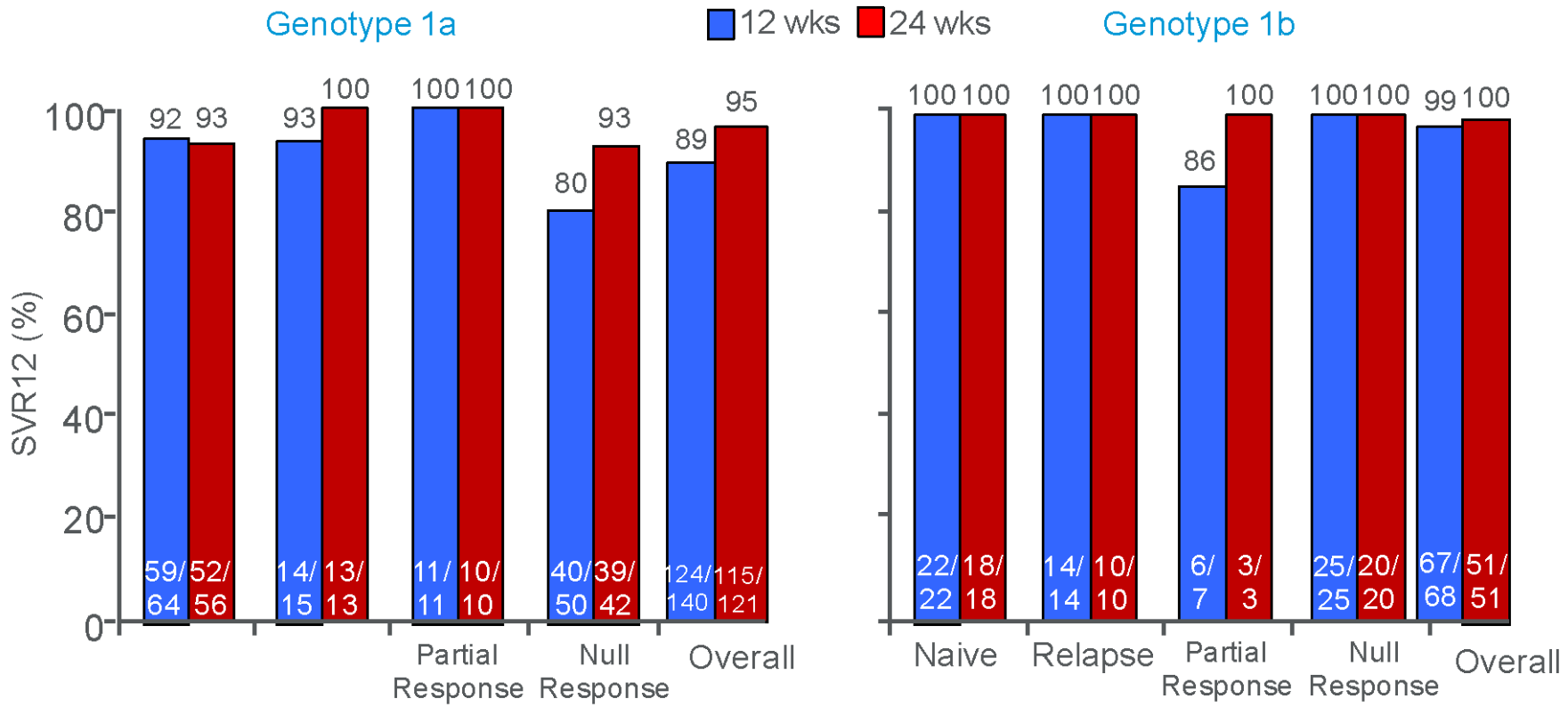


- Paritaprevir/ RTV (150/100 mg) co-formulated with Ombitasvir (25 mg) and administered once-daily. Dasabuvir (250 mg) + RBV (weight-based dosing) administered twice-daily.

- Primary outcome: SVR12.

Zeuzem S, et al. N Engl J Med. 2014;370:1604-1614.

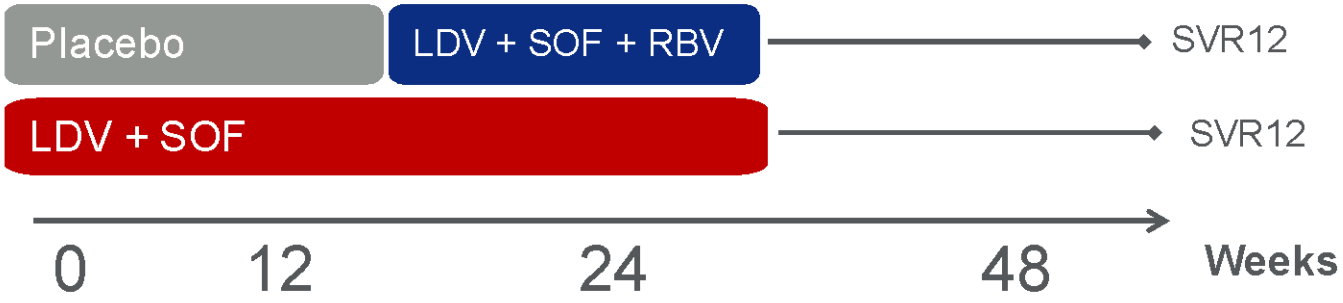
TURQUOISE II: 12 vs 24 Wks OMV/PTV/RTV + DSV + RBV in Cirrhotics



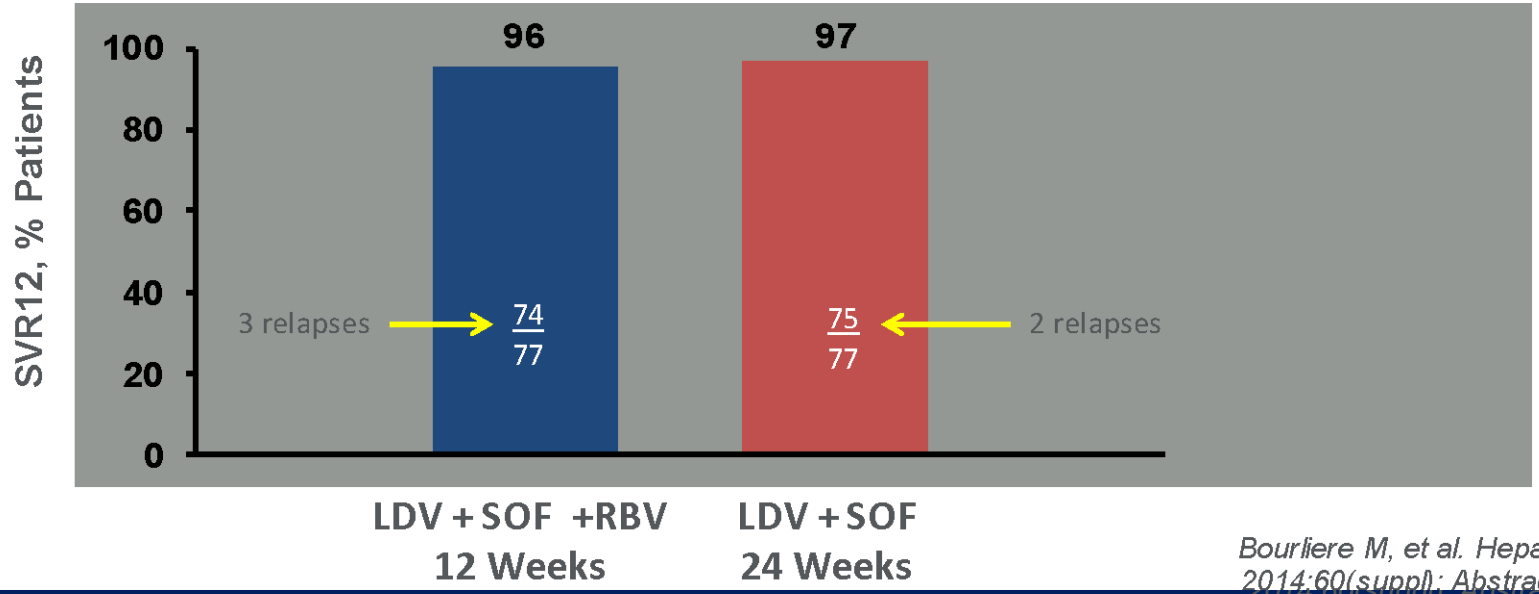
Poordad F, et al. EASL 2014. Abstract O163. Poordad F, et al al. N Engl J Med. 2014;370:1973-1982.

SIRIUS: Ledipasvir + Sofosbuvir in Compensated Cirrhosis After Failure of Triple Therapy

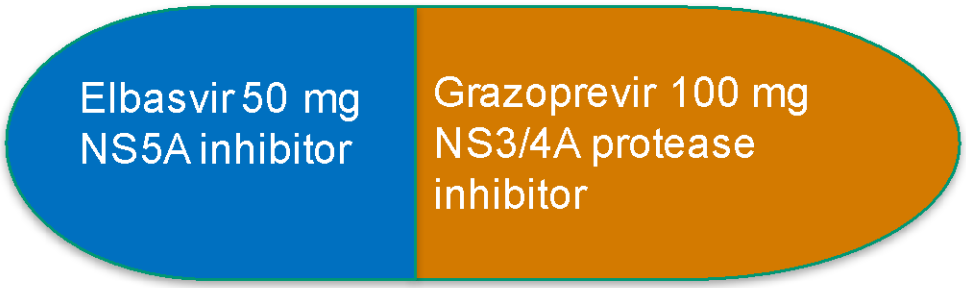
12 Weeks Alone Versus 24 Weeks With RBV



Genotype 1
Treatment-experienced: Did not achieve SVR after sequential PR and PR + protease inhibitor therapy



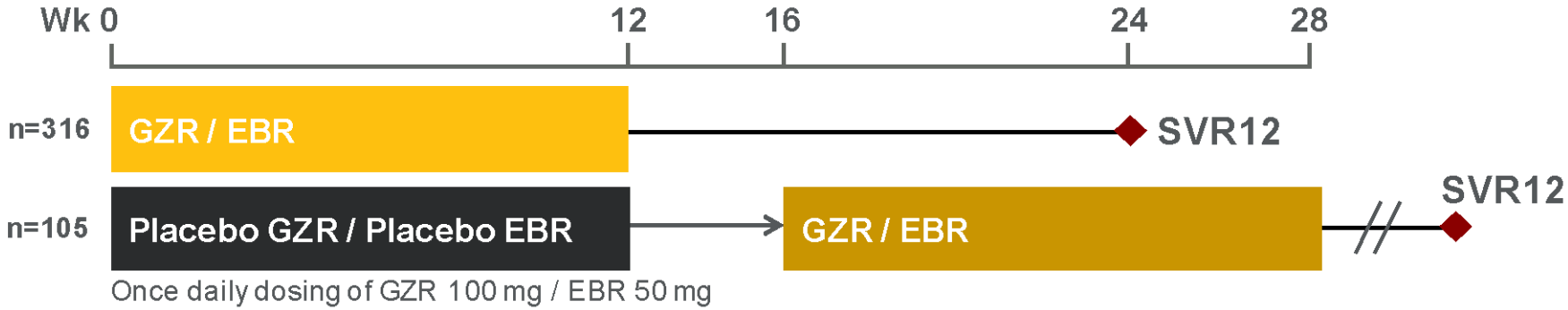
Bourliere M, et al. Hepatology. 2014;60(suppl); Abstract LB-6



- Elbasvir- grazoprevir fixed dose combination
  - Indication: genotypes 1 or 4 infection
  - Dosing: once daily with or without food
  - Metabolism: primarily CYP3A
  - Excretion: > 90% feces, < 1% urine
  - Contraindications
    - Child Pugh B & C
    - Concomitant use of OATP 1B1/3 inhibitors, strong inducers of CYP3A, and efavirenz

Zepatier FDA package insert 2016.

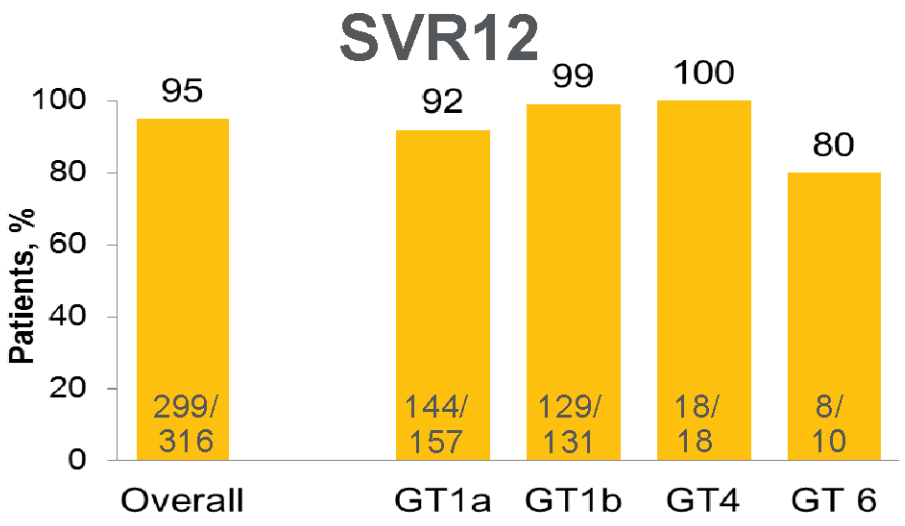
C-EDGE TN (Phase 3): GZR/EBR for 12 Weeks in TN GT 1, 4, or 6 Patients



Patients	GZR + EBR n=316	Placebo n=105	Total n=421
Age, years, mean (SD)	52.2 (11.1)	53.8 (11.2)	52.6 (11.2)
Male, n (%)	171 (54)	56 (53)	227 (54)
HCV genotype, n (%)			
1a	157 (50)	54 (51)	211 (50)
1b	131 (42)	40 (38)	171 (41)
4	18 (6)	8 (8)	26 (6)
6	10 (3)	3 (3)	13 (3)
Baseline HCV RNA > 800,000 IU/mL, n (%)	222 (70)	66 (63)	288 (68)
Cirrhosis, n (%)	70 (22)	22 (21)	92 (22)

Zeuzem, et al. Ann Intern Med 2015.

C-EDGE TN: GZR/EBR for 12 Weeks in TN GT 1, 4, or 6 Patients



Non-VF, n	4	3	1	0	0
Breakthrough, n	1	1	0	0	0
Relapse, n	12	9	1	0	2

Safety Overview

	GZR/EBR n=316	Placebo N=105
SAE, n (%)	9 (3)	3 (3)
D/C due to AE, n (%)	3 (1)	1 (1)
Death	2 (<1)*	0

*1 autopsy documented coronary disease (presumed arrhythmia); 1 strangulated hiatal hernia

Relapse primarily occurred in GT 1a and GT 6 patients

Zeuzem, et al. Ann Intern Med 2015.

HCV GT1a and Impact of Baseline NS5A Polymorphisms on SVR12

NS5A Polymorphism Status	EBR-GZR x 12 weeks SVR12% (n/N)	EBR-GZR + RBV x 16 weeks SVR12% (n/N)
Without baseline NS5A polymorphism (M28, Q30, L31, or Y93)	98% (441/450)	100% (49/49)
With baseline NS5A polymorphism (M28*, Q30*, L31*, or Y93*)	70% (39/56)	100% (6/6)

Abbreviations: GT = genotype; EBR = elbasvir; GZR = grazoprevir
*Any change from GT1a reference

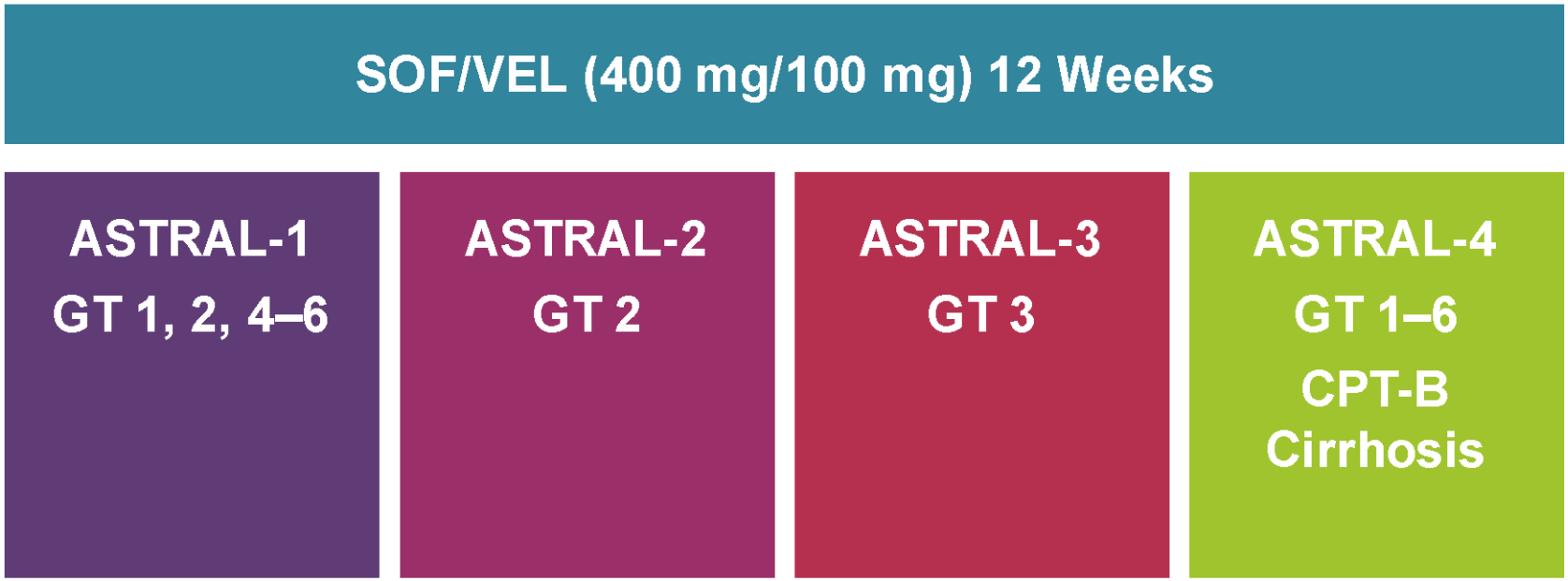
Zapatier Prescribing Information. Merck & Co., Inc.

FDA Indications

Patient populations			Elbasvir-grazoprevir regimen	
Genotype	Treatment status	NS5A baseline polymorphisms	Ribavirin	Duration
1a	Treatment-naïve or PegIFN/RBV experienced	Absent	No	12 weeks
1a	Treatment-naïve or PegIFN/RBV experienced	Present	Yes	16 weeks
1b	Treatment-naïve or PegIFN/RBV experienced	N/A	No	12 weeks
1a or 1b	PegIFN/RBV/protease inhibitor experienced	N/A	Yes	12 weeks
4	Treatment-naïve	N/A	No	12 weeks
4	PegIFN/RBV experienced	N/A	Yes	16 weeks

Zepatier FDA package insert 2016.

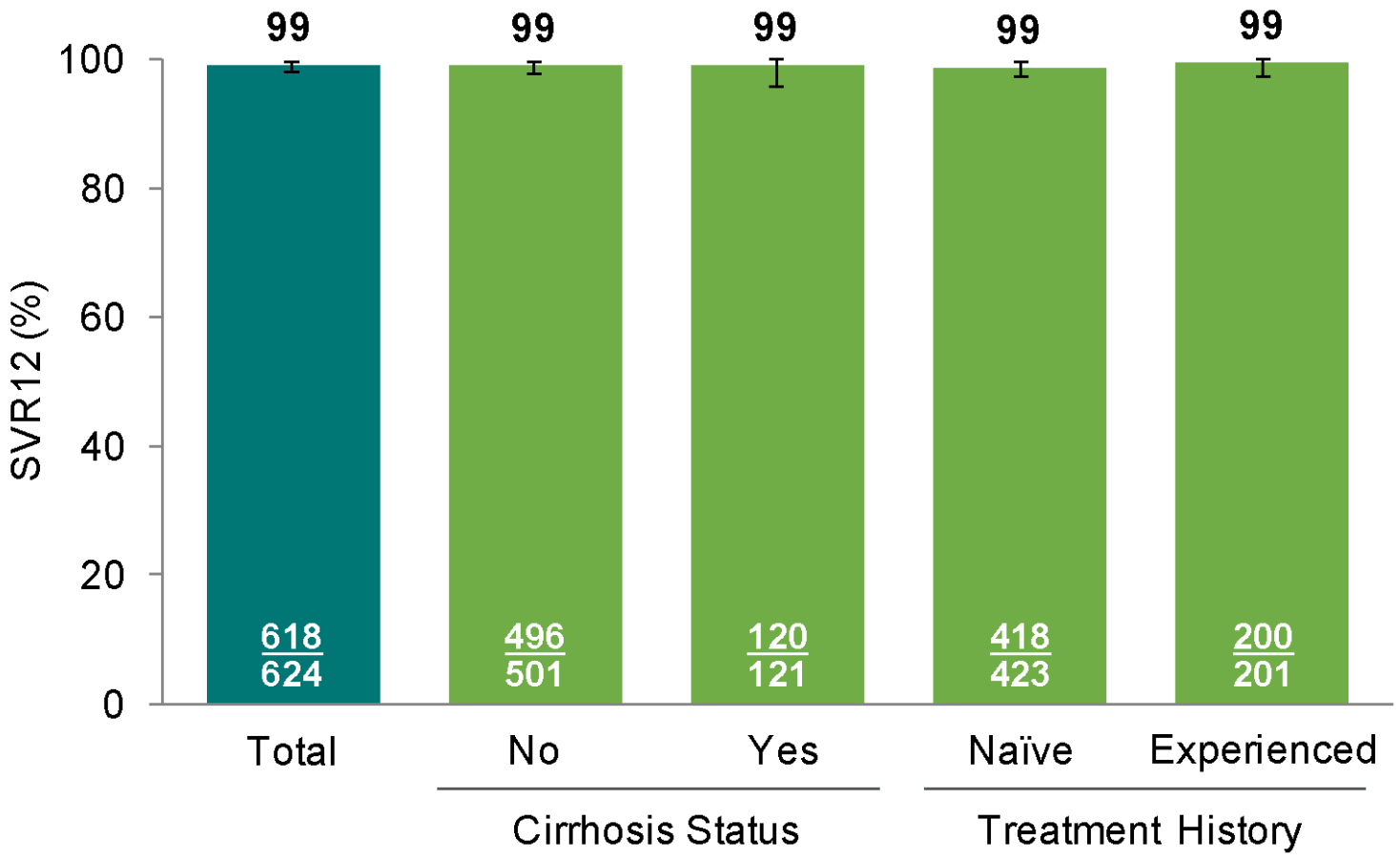
The ASTRAL Program



Foster GR, et al. N Engl J Med. 2015 Dec 31;373(27):2608-17.
Feld JJ et al. N Engl J Med. 2015 Dec 31;373(27):2599-607.
Curry MP et al. N Engl J Med. 2015 Dec 31;373(27):2618-28.

Results: SVR12 by Cirrhosis or Prior Treatment

ASTRAL-1, SOF/VEL



Feld JJ et al. N Engl J Med. 2015 Dec 31;373(27):2599-607.

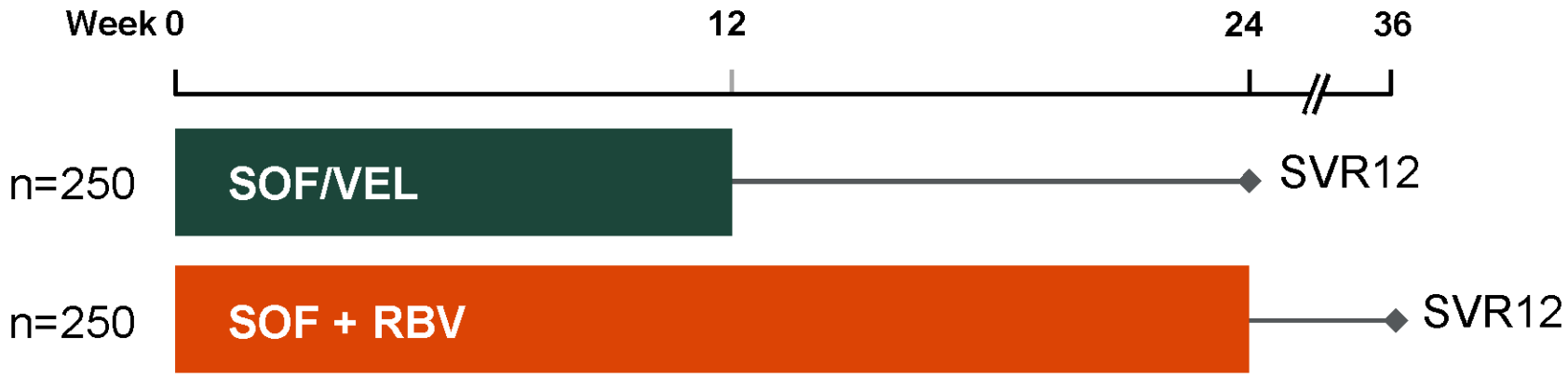
FDA Approval for 100 mg velpatasvir and 400 mg sofosbuvir (Epclusa) - June 2016

- **All genotypes(1-6)**
- Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A) EPCLUSA for 12 weeks
- Patients with decompensated cirrhosis (Child-Pugh B and C) EPCLUSA + ribavirin for 12 weeks
- FDC administered once daily with or without food.
- No dose adjustment is warranted in the setting of moderate (Child
- Pugh Class B) or severe (Child Pugh class C) hepatic impairment.

Prescribing Information for EPCLUSA® (sofosbuvir and velpatasvir) Gilead Sciences 06/2016.

Study Design

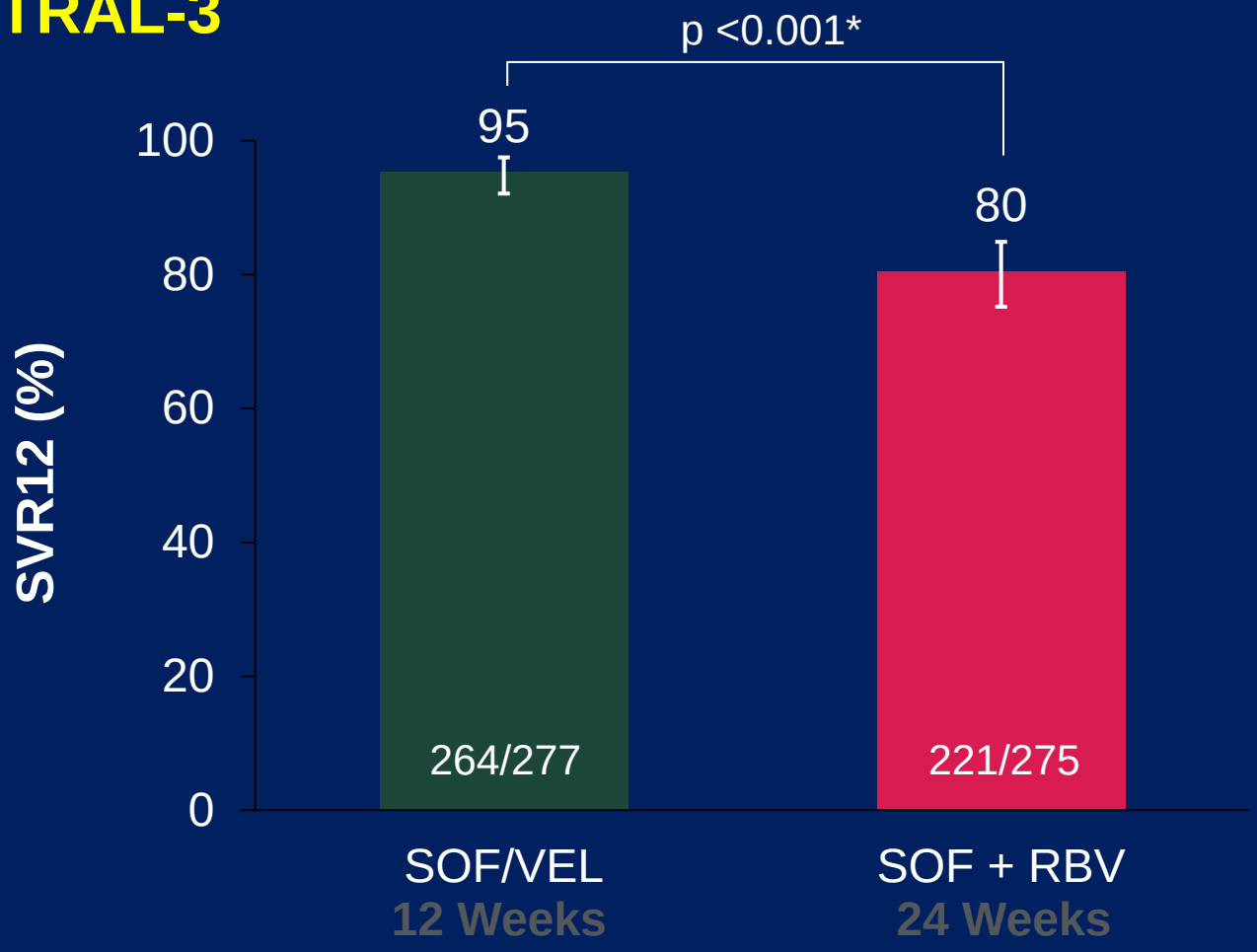
ASTRAL-3



- Open-label, active-comparator trial
- Broad inclusion criteria
- 1:1 randomization to SOF/VEL or SOF + RBV
  - Stratified by prior treatment (TN/TE) and cirrhosi (presence/absence)
- Conducted at 76 sites in US, Canada, UK, Germany, France, Italy, Australia, and New Zealand

Results: SVR12

ASTRAL-3



* P-value for superiority of SOF/VEL compared with SOF+RBV. Error bars represent 95% confidence intervals.

Controversy: HBV reactivation DAA therapy?

- Mechanism is well described – cure HCV and HBV can replicate
- IFN more protective since maintains HBV activity
- What is reactivation – viral or clinical with real hepatitis (ALT elevation)
- Who is at risk
- How to screen
- Who to treat

Hepatitis B reactivation associated with DAA therapy for hepatitis C: A review of spontaneous post-marketing cases

FAERS database search 11/22/13 – 10/15/16

- 29 cases identified (5 in USA, 19 in Japan, 5 other)
  - 3 decompensated: 2/3 death; 1/3 OLT
  - Mean time to reactivation 53 days (most 4–8 wks)
  - No specific DAA regimen the culprit

Days to event (n=28)	Mean 53
	Median 46
	Range 14–196

BL HBV viral parameters	HBsAg (+) n=13
	HBsAg (-) n=4
	HBsAg not reported n=12
	HBcAb (+) n=6
	HBcAb not reported n=23
	HBsAg (-) n=3
	HBsAb not reported n=26
	HBV DNA undetectable n=16
	HBV DNA detectable n=9
	HBV DNA BL either not reported or detectability unclear n=4
Outcome	Death n=2
	Transplant n=1
	Hospitalization n=6
	Other n=20

DAA therapy	
Discontinued	n=10
Completed	n=13
Not reported	n=6
Treatment for HBV	
Entecavir	n=9
Tenofovir	n=6
Tenofovir/embtricitabine	n=1
Not reported	n=6
No treatment	n=7

- 16/29 initiated HBV therapy
- 7/16 delayed (7–60 days) with 1 death

Treatment delay	Yes n=7
	Possible n=7
	No delay n=2
	No tx given or tx not stated n=13

FAERS: FDA Adverse Event Reporting System

Bersoff-Matcha SJ, et al. AASLD 2016, Boston. #LB-17

Hepatitis B reactivation associated with DAA therapy for hepatitis C

Case #	HBs Ag	HBs Ab	HBc Ab	Hbe Ag	Hbe Ag	HBV DNA in IU	DAA
1				Neg	Pos	2700 (elevated)	Viekira Pak/RBV
2	Pos		Pos	Neg	Pos	2.5 log (elevated)	DCV/ASV
3				Neg	Pos	Undetectable	DCV/ASV
4	Pos			Neg	Pos	3.9 log (elevated)	DCV/ASV
5				Neg	Pos	2300 (elevated)	SMV/SOF
6	Neg	Neg	Pos			Undetectable	SMV/SOF
7	Neg	Neg	Pos			Undetectable	SMV/SOF/RBV
8	Pos					244 (elevated)	SOF/RBV
9	Neg	Neg	Pos	Neg	Pos	Undetectable	LDV/SOF
10	Pos					Undetectable	LDV/SOF
11			Pos			Undetectable	LDV/SOF
12	Pos			Neg	Pos	Undetectable	SMV/SOF/RBV
13	Pos			Neg	Pos	Undetectable	SOF/RBV
14	Pos					1.3 log (elevated)	LDV/SOF
15	Pos			Neg	Pos	2.7 log (elevated)	DCV/ASV
16						Undetectable	LDV/SOF
17	Pos		Pos	Neg	Neg	Undetectable	DCV/SOF/RBV
18				Neg	Pos	3.6 log (elevated)	LDV/SOF
19	Pos			Neg	Pos	<2.1 log	DCV/ASV
20	Pos			Neg	Pos	Undetectable	DCV/ASV
21				Neg	Neg	Undetectable	DCV/ASV
22						<2.1 log	DCV/ASV
23						Undetectable	LDV/SOF
24				Neg		3.3 log (elevated)	DCV/ASV
25						Undetectable	DCV/ASV
26	Pos					<2.1 log	LDV/SOF
27						Undetectable	DCV/ASV
28	Neg					NR	LDV/SOF/RBV
29	Pos				Pos	Undetectable	LDV/SOF

Incomplete database limits interpretation (concurrent meds, control group, incomplete lab eval.)

Who should be prophylaxed?

- S Ag positive + viremia vs all S Ag positive?

Isolated core positive, unlikely to reactivate but should be monitored on HCV therapy

Blank cell = test result not reported

Bersoff-Matcha SJ, et al. AASLD 2016, Boston. #LB-17

Controversy: HCC and DAA therapy?

- HCC recurrence may be increased after DAA treatment
- Recurrent and de novo HCC may be more aggressive
- No real rationale
- No control
- Significant lead time bias

HCC Risk Persists After DAA Therapy in Pts With HCV-Related Cirrhosis

Retrospective analysis of 344 HCV-infected pts with CP A or B cirrhosis treated with DAAs (SVR: 89%)

- Pts followed for 12-24 wks after treatment completion
- No HCC at baseline, but previous HCC permitted

Overall HCC incidence after DAA therapy: 7.6%

- In pts without previous HCC: 3.2%
- In pts with previous HCC: 29.0%

More advanced liver disease and previous HCC significant risk factors for HCC after DAAs

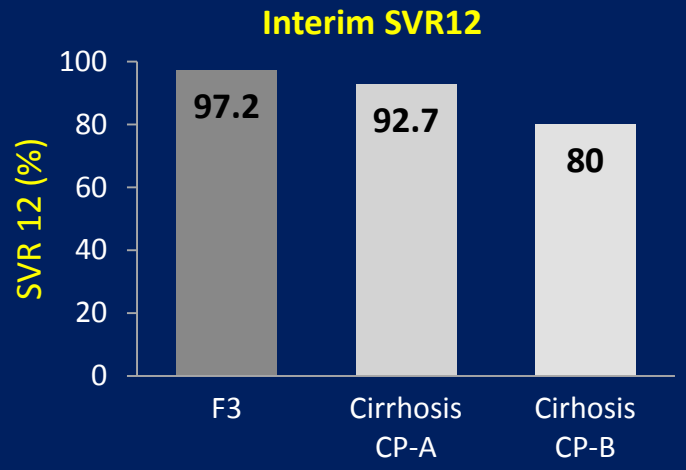
Factor	No HCC (n = 318)	HCC (n = 26)	*P* Value
CP class B, %	10.1	26.9	.02
Mean liver stiffness, kPa	23.2	28.1	.01
Liver stiffness, n			.005
▪ kPa < 21.3	134	5	
▪ kPa > 21.3	101	16	
Mean platelets, x 1000/mm^3	124.4	102.3	.02
Previous HCC, n			.0001
▪ Yes	42	17	
▪ No	276	9	

Buonfiglioli F, et al. EASL 2016. Abstract LBP506.

Romano: Incidence and Pattern of "De Novo" Hepatocellular Carcinoma in HCV Patients Treated with Oral DAAs

Incidence of "de novo" HCC in 3075 patients with HCV and advanced liver disease treated with DAAs and monitored by the NAVIGATORE web-based platform in Italy (Jan 2015 – June 2016)

Mean follow-up from initiation of DAA therapy was 300.8 days



41 patients developed HCC - Incidence:

- Overall: **1.64%/pt-yr** (95% CI: 1.18–2.21)
- F3: **0.23%/pt-yr** (95%CI: 0.01–1.27)
- CP-A: **1.64%/pt-yr** (95% CI: 1.14–2.28)
- CP-B: **2.92%/pt-yr** (95% CI: 1.07–6.36)

Multivariate Cox's regression			
	HR	**95% CI**	**P**
APRI score ≥2.5	1.83	0.89–3.75	**0.099**
SVR-12	0.20	0.09–0.41	**0.001**

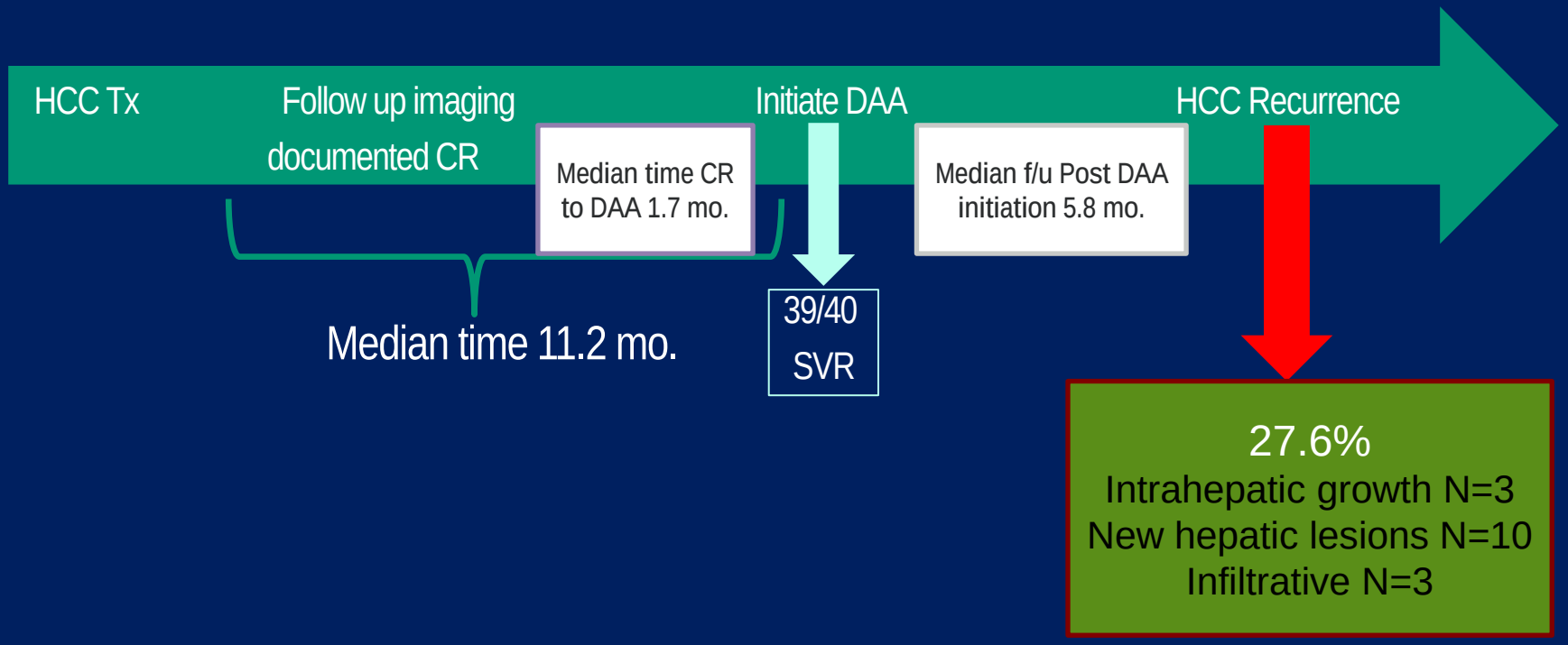
Subgroup	**HCC incidence in cirrhotics, % pt-yr**
Males / Females	1.93 / 1.94
GT1 / 2 / 3 / 4	1.7 / 2.05 / 2.44 / 2.28
CPA / CPB	1.64 / 2.92
SOF/RBV	3.32
SOF/LDV ± RBV	1.45
SOF/SIM ± RBV	1.35
SOF/DCV ± RBV	1.12
OBV/PTV/r + DSV ± RBV	1.88
APRI	
<2.5	1.52
≥2.5	3.27
SVR-12	
Yes	8.38
No	1.55

Cirrhotic patients with HCV treated with DAAs are not at increased of developing HCC compared with untreated patients

HCC Recurrence Post DAA Therapy

Retrospective study: 58 pts. with HCC with HCV tx with DAA

- 35% resection, 55% ablation, 10% TACE
- BCLC 0 =16, BCLC A = 42



Unexpected high rate of tumor recurrence that coincided with SVR!

Reig M. et al J Hep 2016

Risk of incident HCC following HCV treatment with sof-containing regimens

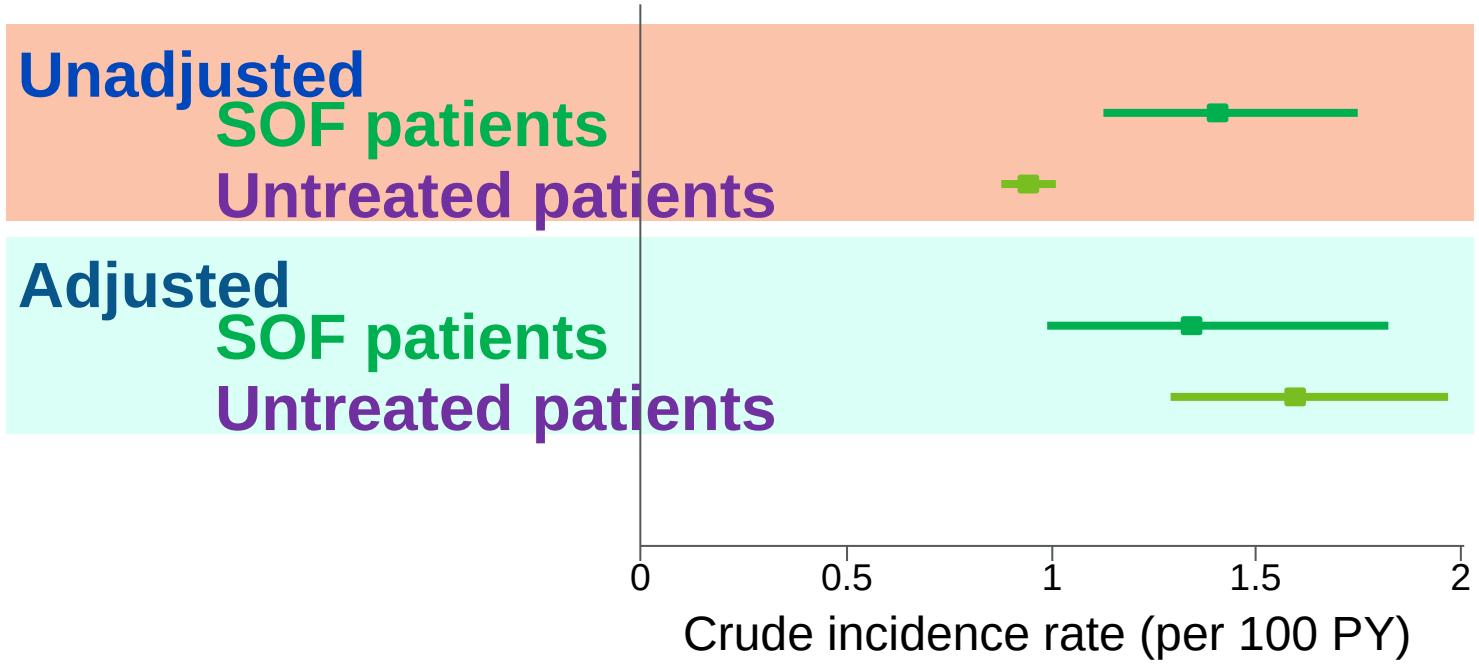
Quintiles/IMS PharMetrics Plus™ Claims dataset, including U.S. administrative claims for ~110 M patient lives from 01 Jan 2006 to 30 Sep, 2015

Characteristics of SOF-treated HCV and untreated HCV cohorts		SOF-treated HCV n	SOF-treated HCV (%)	Untreated HCV n	Untreated HCV (%)
Total		9,616	100.0	95,274	100.0
Age	18–34 y	468	4.9	10,946	11.5
	35–44 y	607	6.3	9,843	10.3
	45–54 y	2,313	24.1	26,017	27.3
	55+ y	6,228	64.8	48,468	50.9
Sex	Female	3,275	34.1	40,284	42.3
	Male	6,341	65.9	54,990	57.7
Prior portal hypertension		1,101	11.4	2,944	3.1
Prior cirrhosis		3,517	36.6	10,940	11.5
Prior use of statins		1,090	11.3	17,231	18.1
Prior substance abuse		4,172	43.4	42,416	44.5
Prior use of anti-diabetic meds		1,460	15.2	12,295	12.9
Prior unspecified non-alcoholic liver disease		370	3.8	1,712	1.8
Prior transaminase elevation		3,050	31.7	17,683	18.6
Prior cancer (any)		5,017	52.2	42,550	44.7
Prior hepatic encephalopathy		379	3.9	1,526	1.6
Prior end stage liver disease		342	3.6	1,569	1.6
Follow-up time (days)	Mean (SD)	222	(141)	383	(184)
	Median (min/max)	184	(31–582)	442	(31–574)

Chokkalingam AP, et al. AASLD 2016, Boston. #739

Risk of incident liver cancer following HCV treatment with sofosbuvir-containing regimens

Cumulative incidence rates of liver cancer in each cohort, before and after adjustment for covariantes



Before adjustment for significant covariates, liver cancer incidence appears higher in SOF-treated patients vs. untreated patients

- After adjustment for significant covariates, rates in SOF-treated patients are not higher; indeed, they are nominally lower than rates among untreated patients
- Age, gender, baseline cirrhosis status, and baseline portal hypertension are important covariates that must be considered

After adjustment for covariates, no increased risk of incident HCC associated with SOF treatment vs. no HCV treatment

Limitations

- Determination of cohort entry, outcomes, and covariates is based diagnostic or drug codes recorded in database
- No data on SVR

Chokkalingam AP, et al. AASLD 2016, Boston. #739

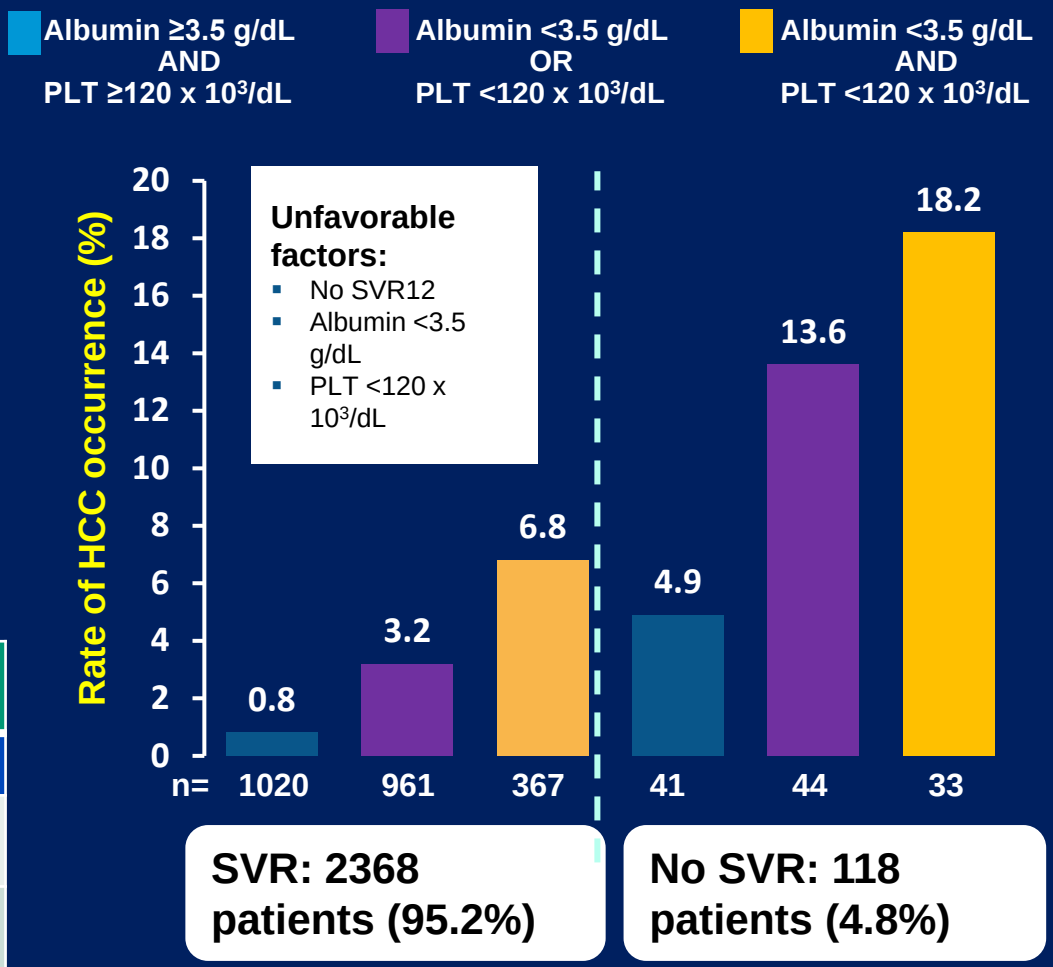
Occurrence of HCC in patients with HCV related liver disease treated with DAAs

RESIST-HCV: Prospective Sicilian cohort

- Evaluated 2466 patients with cirrhosis + DAAs
- Liver US every 6 months before, during and after antiviral treatment 78 de novo HCCs (3.1%) over a median follow-up of 14 months
- SVR, incidence 2.4%; no SVR, incidence, 7.5%
- Within Milan criteria: SVR, 84.4%; no SVR 42.8%

Multivariable Cox proportional hazards model for HCC

		HR	HR (95% CI)	p
Albumin (g/dL):	≥3.5 <3.5	1.82	1.15–2.90	0.011
Platelets (x10^3/dL):	≥120 <20	3.83	2.08–7.04	<0.001
SVR12 No SVR12		3.29	1.83–5.29	<0.001



- SVR was **not associated** with increased risk of HCC nor with more 'aggressive' patterns
- Predictors of HCC include no SVR, low albumin (<3.5 g/dL) and platelets (<120,000/dL)

Calvaruso V, et al. EASL 2017, Amsterdam. #PS-038

Summary

- **Other important issues:**
  - How do we find all of these hepatitis C patients?
  - Linkage to care
  - How do we pay for all of this treatment?
  - How short can we go? 6 weeks? 8 weeks?