Treatment of hepatitis C in 2015

Whom? When? How

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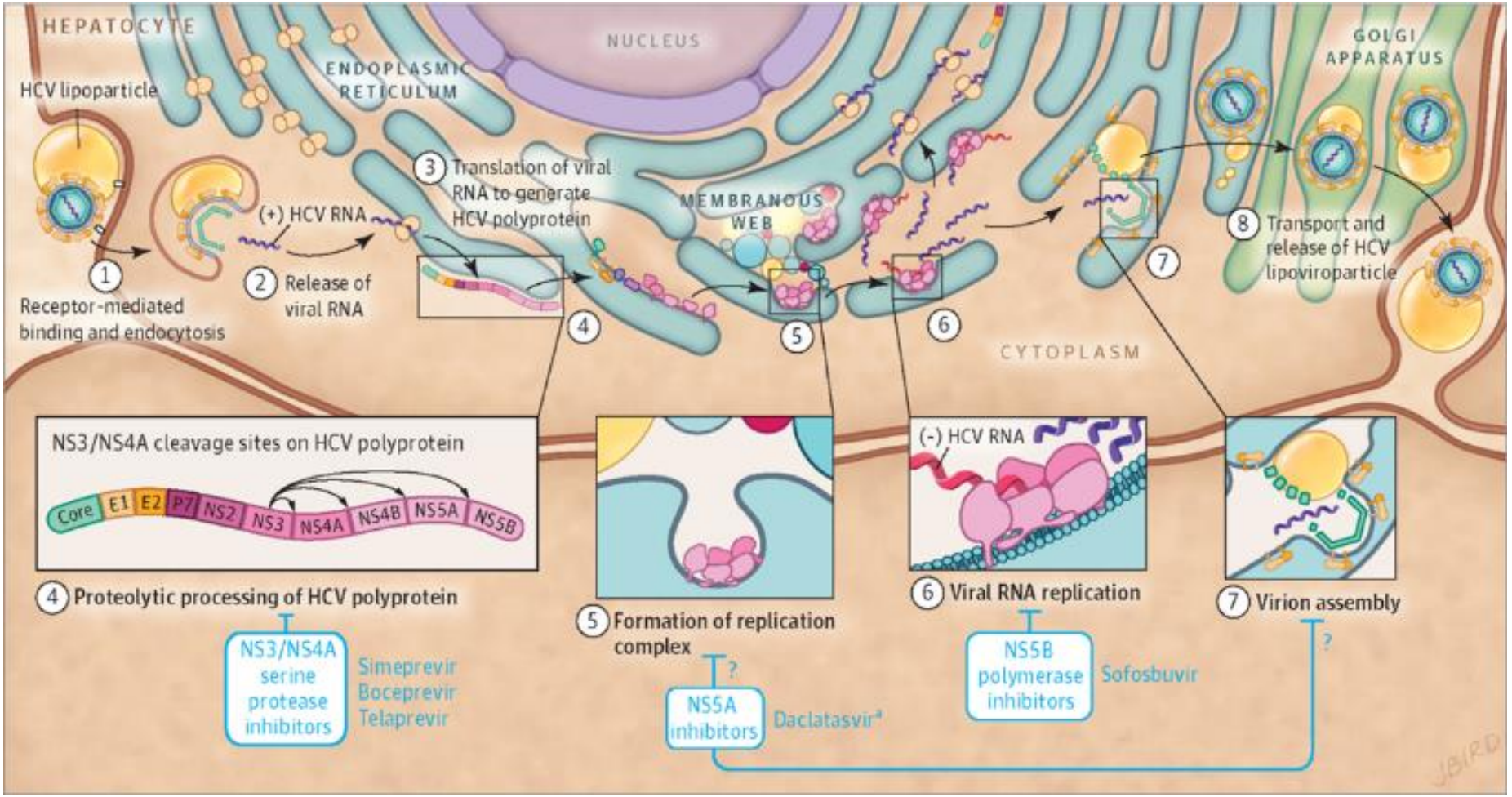
Overview of the hepatitis C virus (HCV) lifecycle and antiviral targets



…previrs
Protease inhibitors

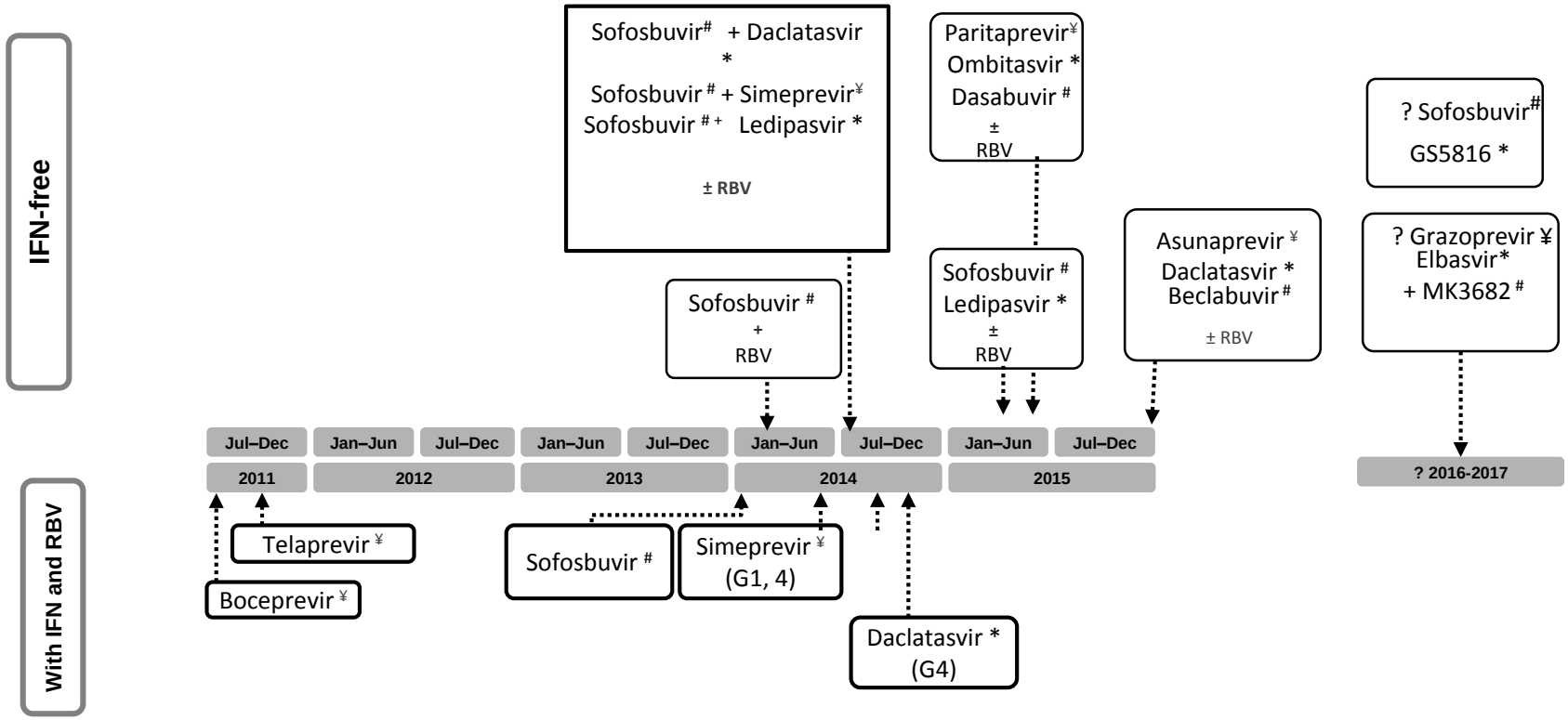
…asvirs
NS5a inhibitors

…buvirs
NS5b nucleotide inhibitors

Kohli A et al *JAMA*. 2014;312:631–40.

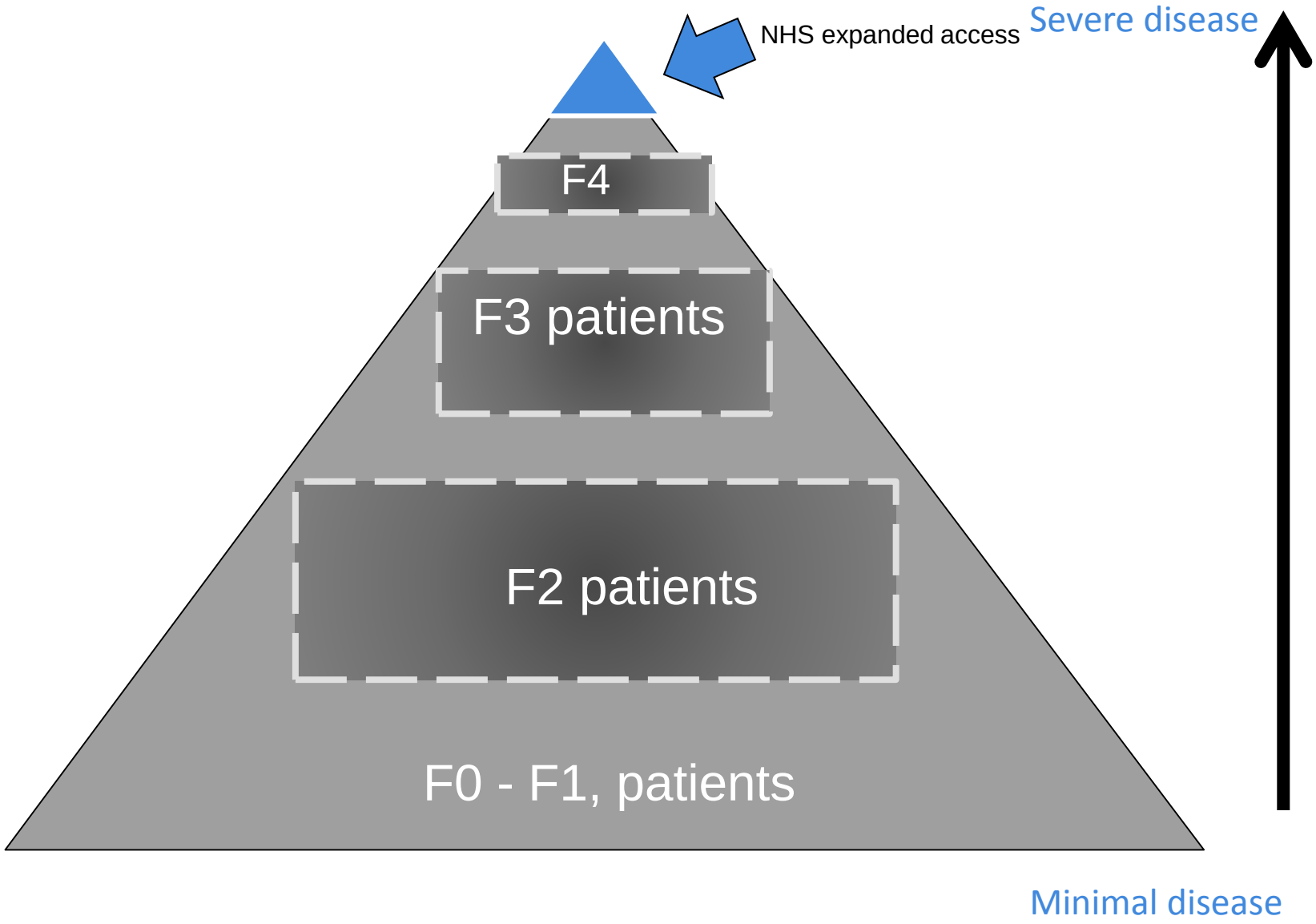
HCV treatments 2015

Approved or imminent approvals: Protease, NS5B and NS5A inhibitors



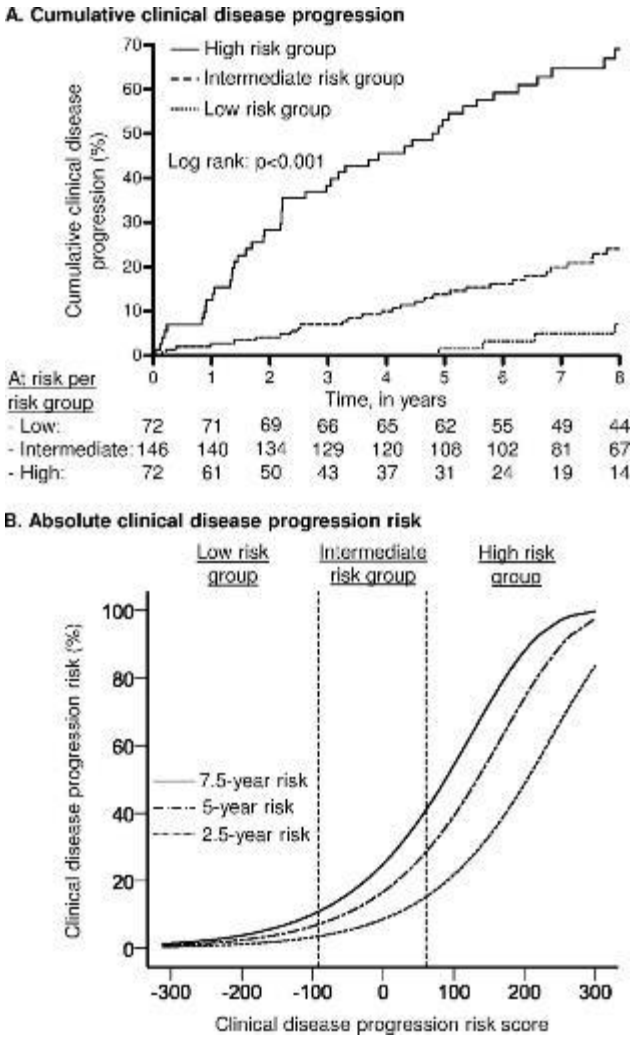
¥ protease inhibitor # NS5B inhibitor * NS5A inhibitor

How will we make treatment choices in the future: Will we have to stratify and select patients because of cost?



Prognosis of patients with chronic HCV infection and compensated advanced liver disease can be accurately assessed with a risk score

van der Meer A J et al. Gut 2014

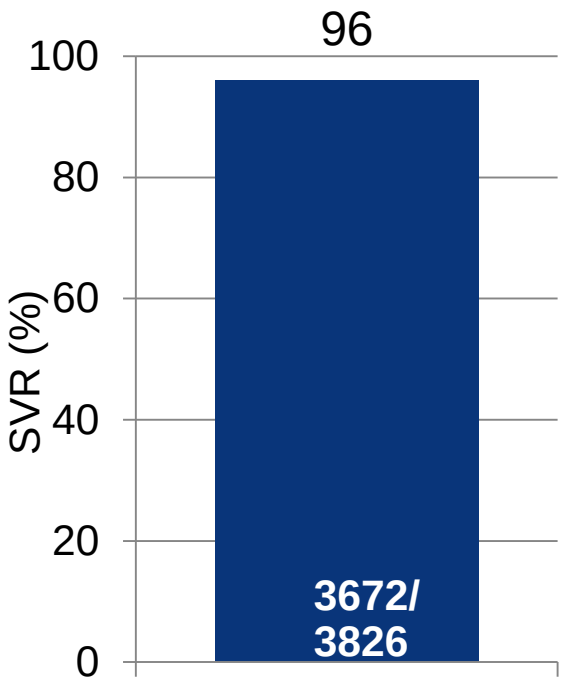


The risk score for clinical disease progression is represented by Rc=(5.2 * age in years) – (2.8 * platelet count per 109/L)+(5.17 – 3 * (platelet count per 109/L)2)+(358.2 * log10(AST/ALT))+(83.7 for male patients)+(60.6 in case of HCV genotype 3).

IFN-free therapy combinations high efficacy Genotype 1

GT 1 IFN free studies published in 2014

Trial	Regimen
ION-1	LDV/SOF ± RBV
ION-2	LDV/SOF ± RBV
ION-3	LDV/SOF ± RBV
SAPPHIRE-I	ABT-450/r/OMB + DAS + RBV
SAPPHIRE-II	ABT-450/r/OMB + DAS + RBV
PEARL-III	ABT-450/r/OMB + DAS ± RBV
PEARL-IV	ABT-450/r/OMB + DAS ± RBV
TURQUOISE-II	ABT-450/r/OMB + DAS + RBV
COSMOS	SOF + SMV ±RBV



(Treatment regimens 8–24 weeks) Included treatment-naïve and -experienced patients

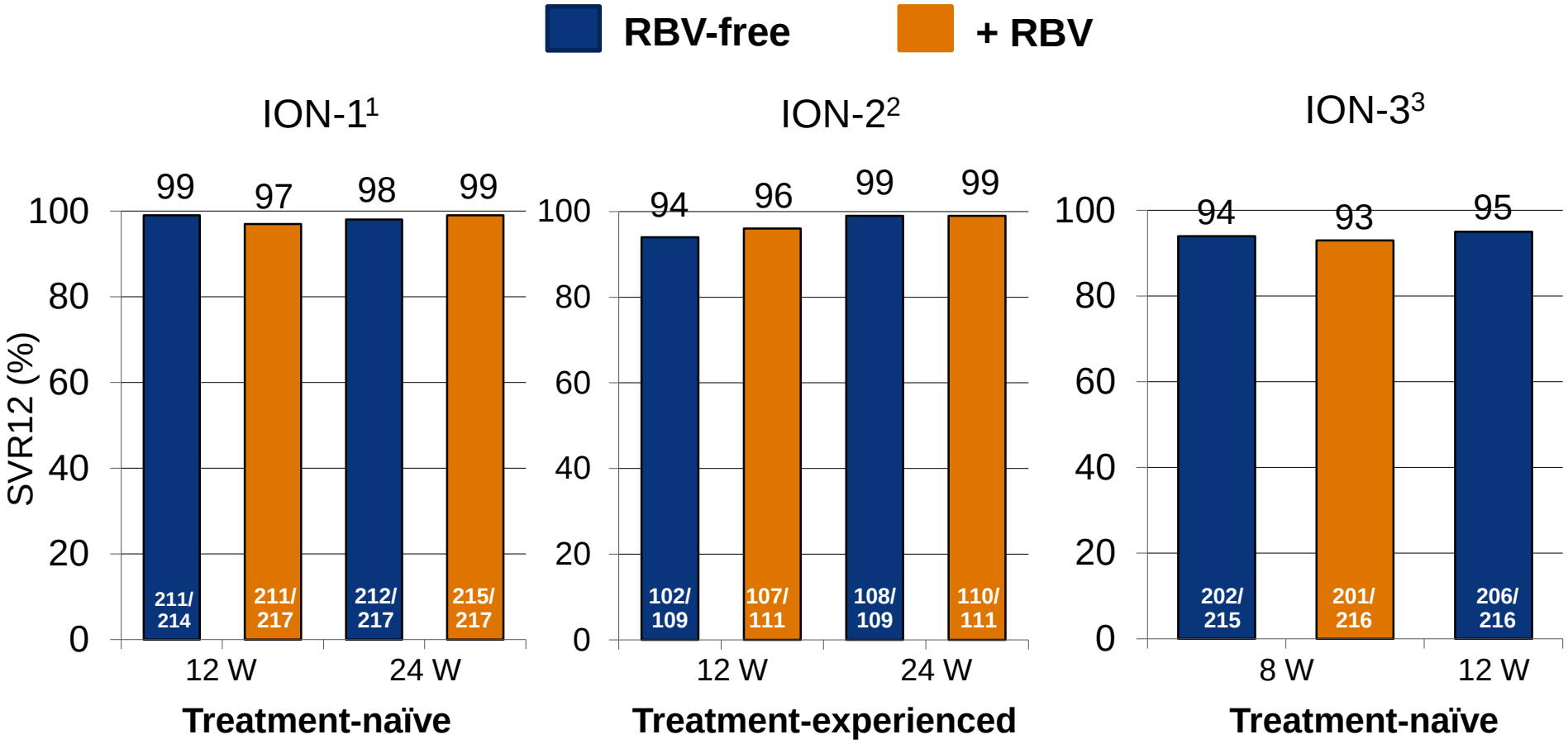
heterogeneous
Phase 3 studies

DAS: dasabuvir; LDV: ledipasvir; OMB: ombitasvir

Liang J, Ghany MG. N Engl J Med 2014;370:2043–7.

Data that provide confidence that RBV is not required for many: but will it be used?

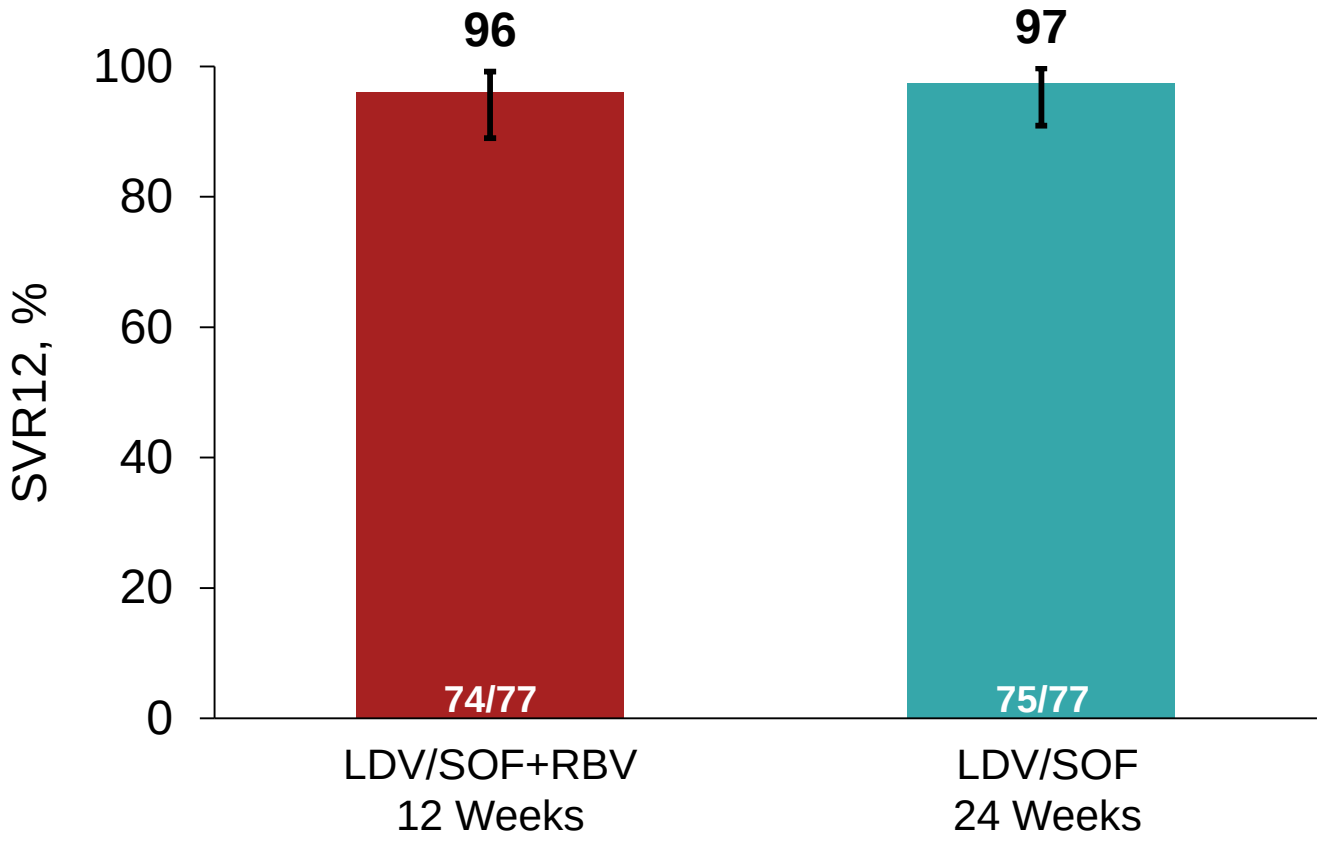
LDV/SOF ± RBV for 8, 12 or 24 weeks in GT 1 patients



1. Afdhal N, et al. N Engl J Med 2014;370:1889–98;
2. Afdhal N, et al. N Engl J Med 2014;370:1483–93;
3. Kowdley KV, et al. N Engl J Med 2014370:1879–88.

SIRIUS: SOF LDV ± RBV

Childs A Cirrhosis treatment experienced



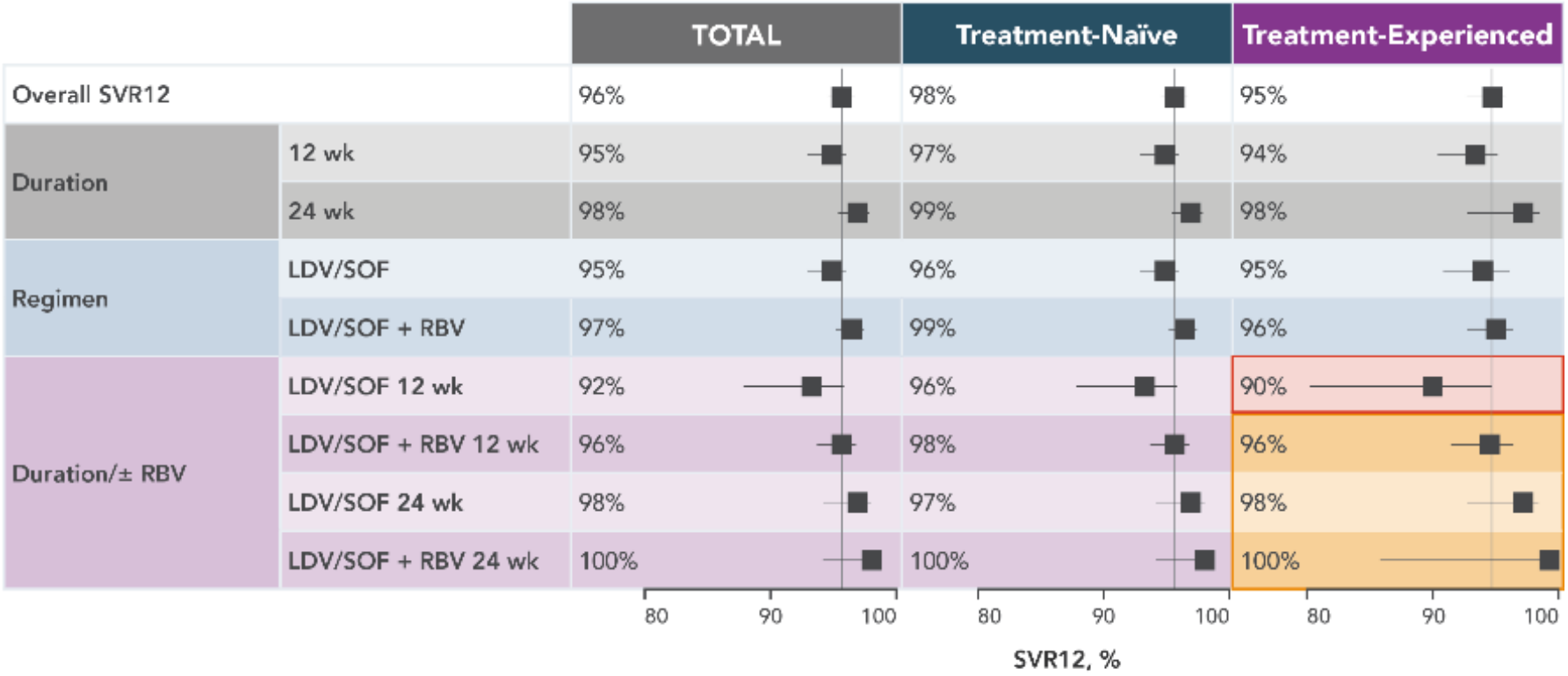
LDV/SOF in treatment experienced cirrhotic patients: 12 vs 24 weeks

Error bars represent 95% confidence intervals.

Bourliere, AASLD, 2014, Oral #LB-6

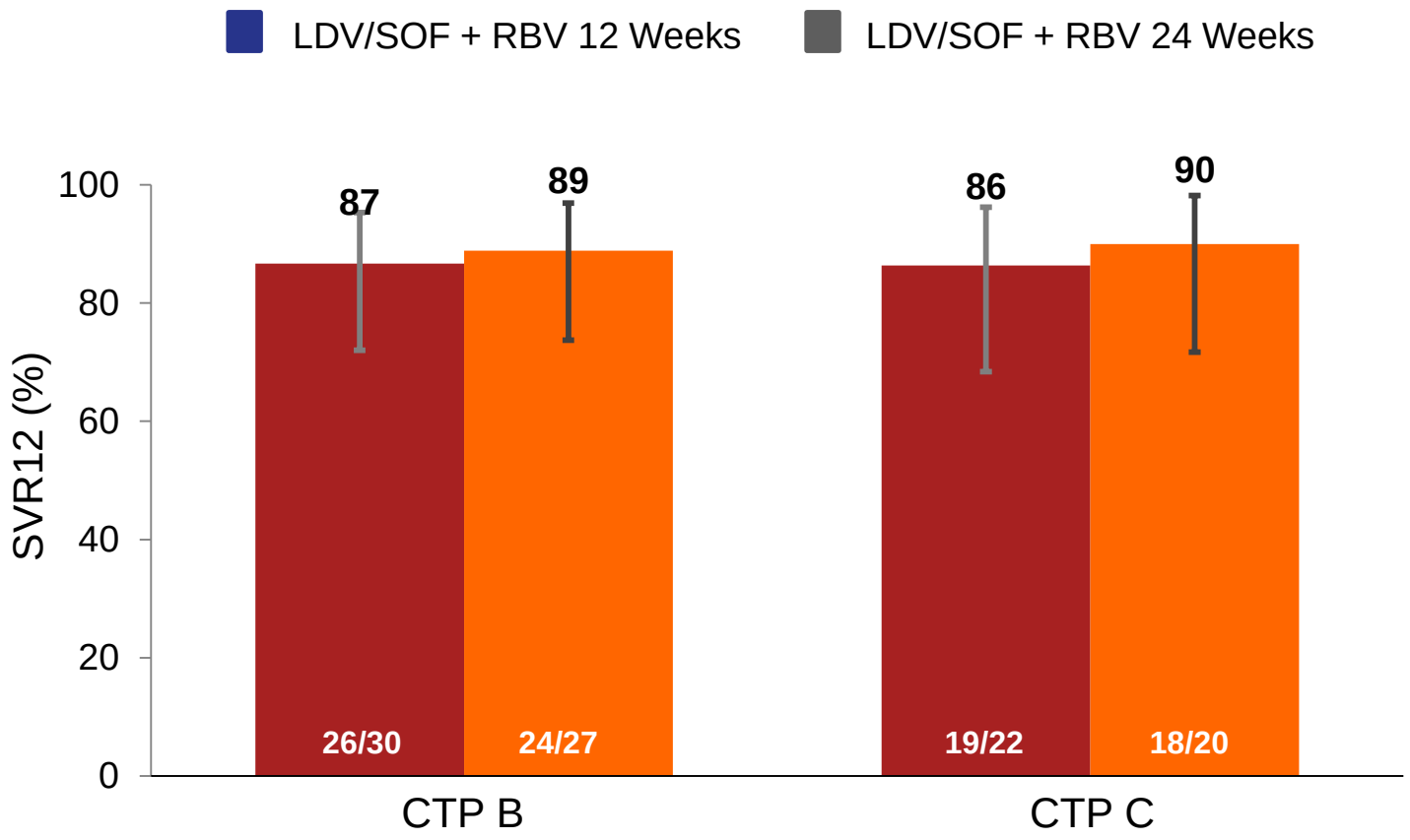
An analysis of > 500 patients compensated cirrhosis treated with ledipasvir + sofosbuvir ± RBV

Results: SVR12 by Treatment Regimen



REFERENCES: 1. Bourliere M *et al*; AASLD, 2014. Oral Presentation

SOLAR-1: LDV/SOF + RBV in decompensated cirrhosis
SOF LDV + RBV for 12 or 24 weeks

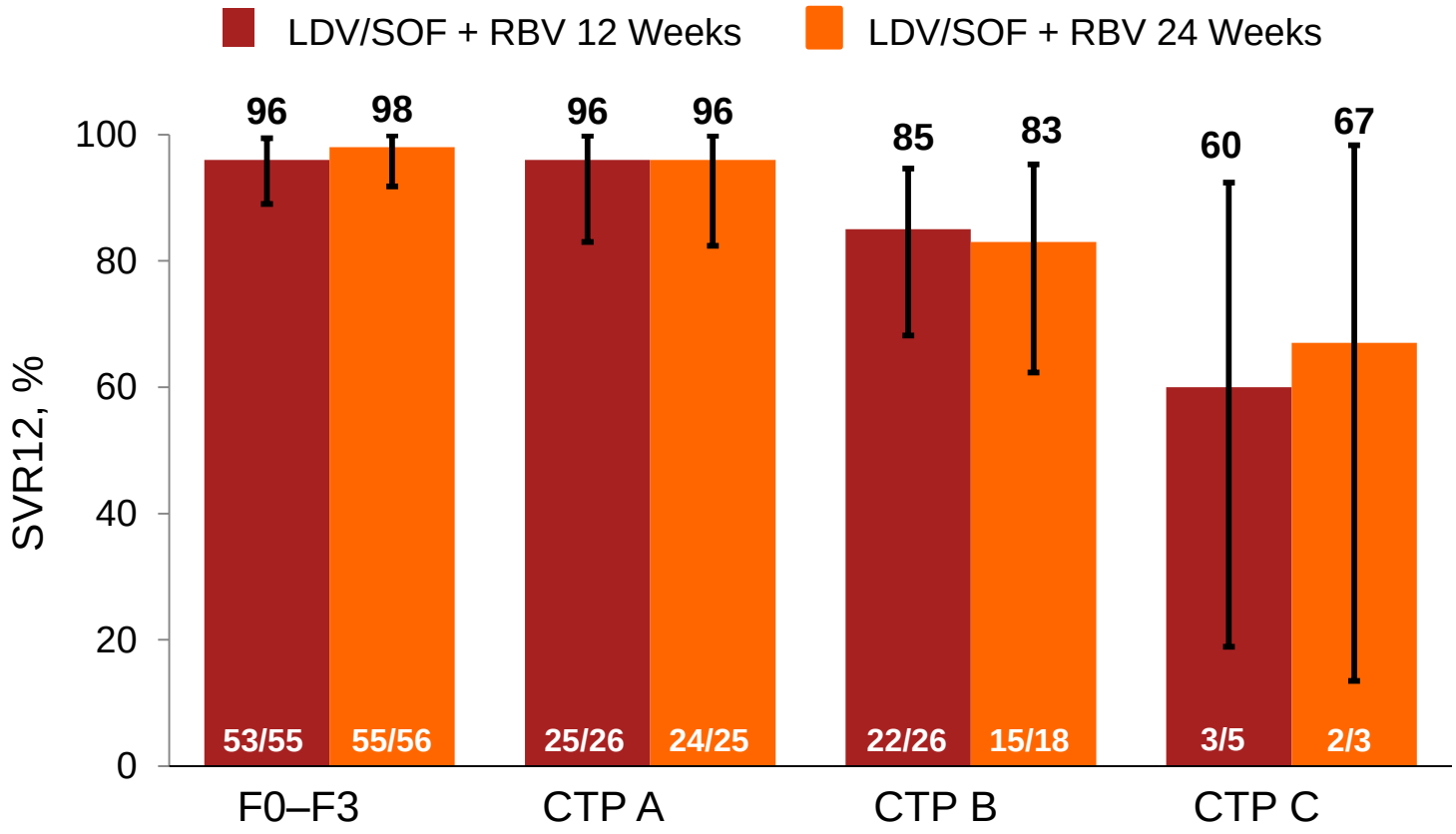


Error bars represent 90% confidence intervals.

Flamm, AASLD, 2014, Oral #239

SOLAR-1: LDV/SOF + RBV in post-transplant

Results: SVR12

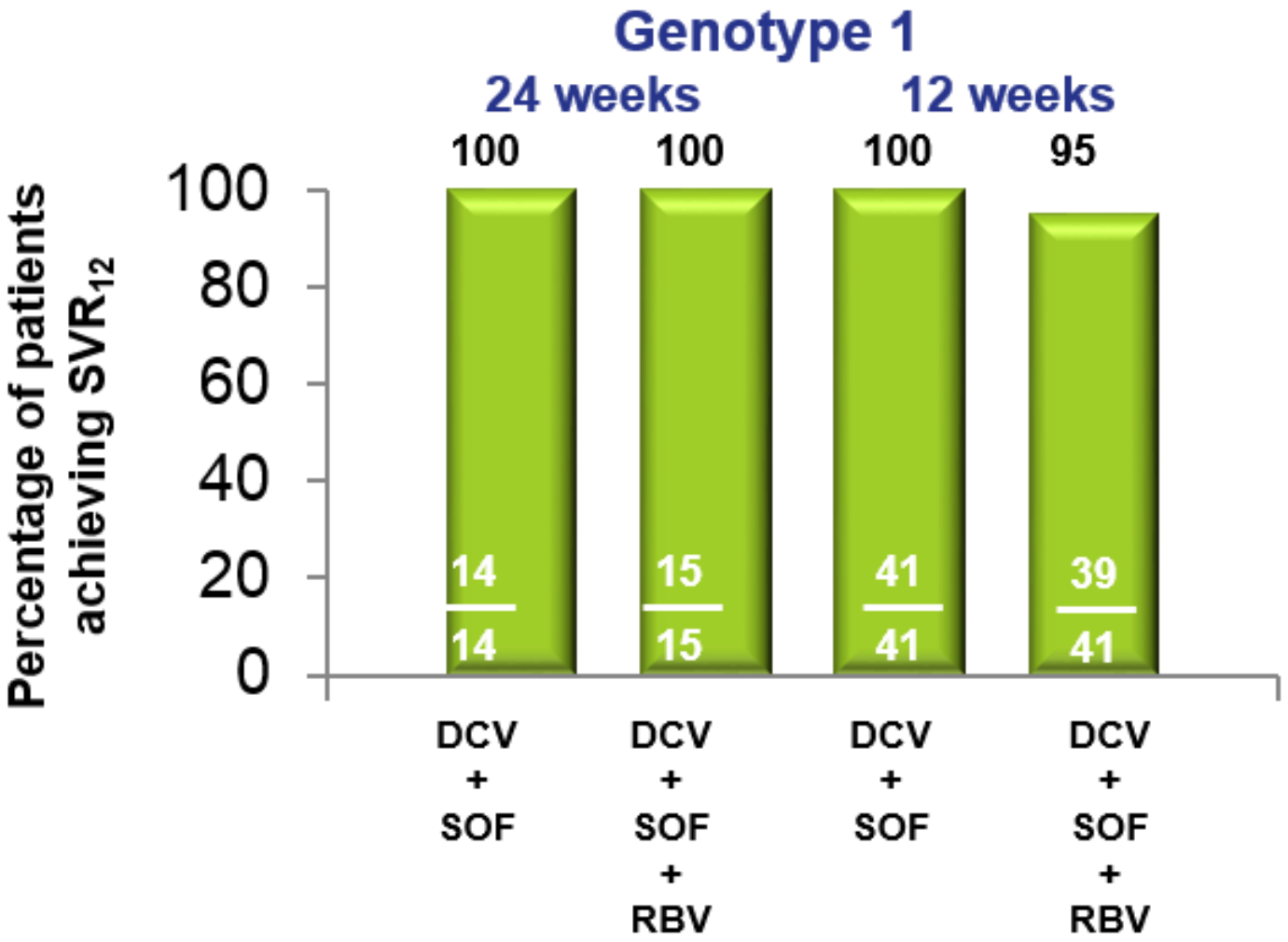


SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Error bars represent 2-sided 90% exact confidence intervals.

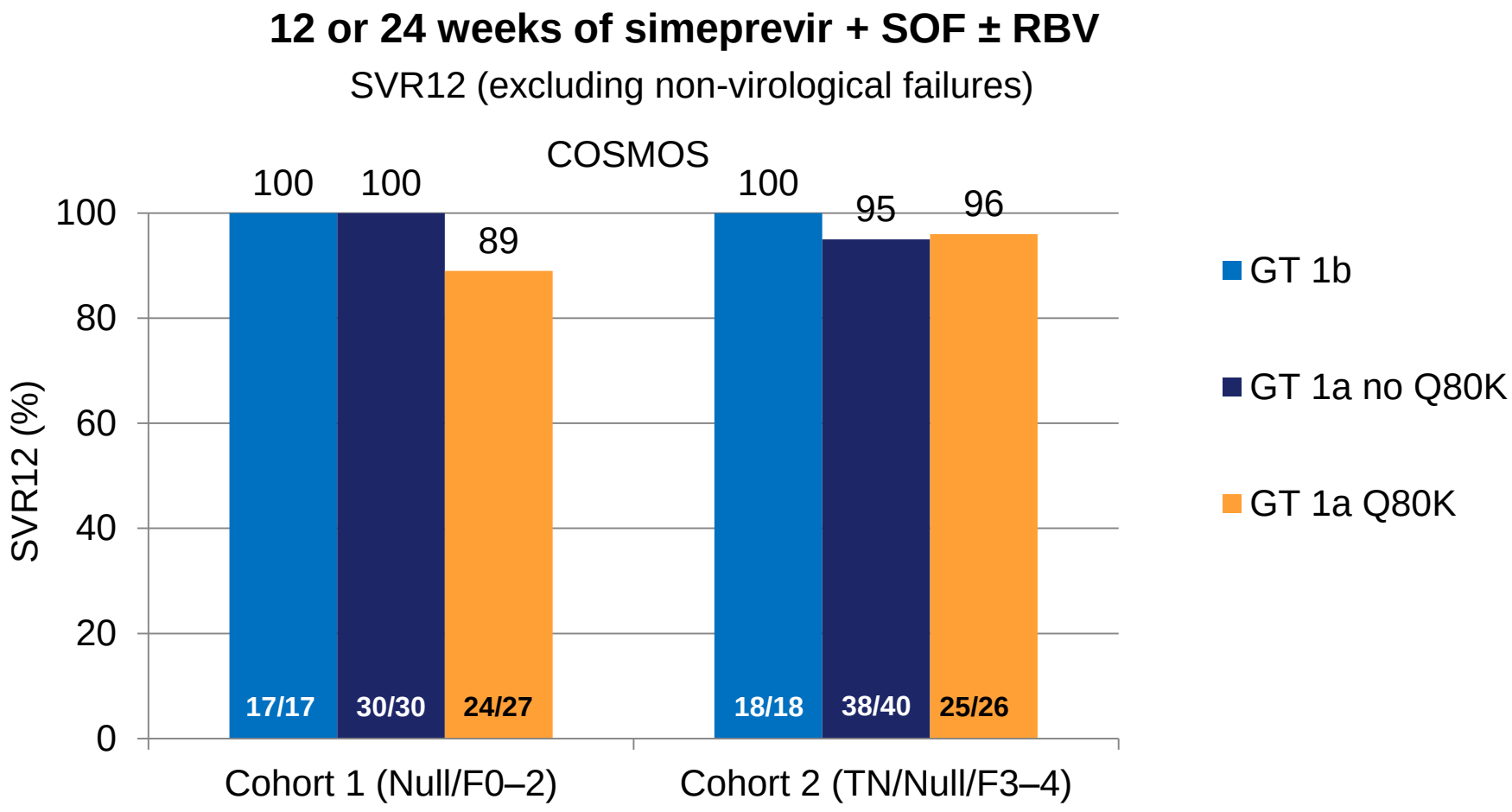
Reddy, AASLD, 2014, Oral #8

DCV + SOF in GT1 treatment naïve patients



1. Sulkowski MS, et al. *N Engl J Med.* 2014;370:211–21 . 3. Daclatasvir summary of product characteristics.

SOF + simeprevir ± RBV in GT 1 patients

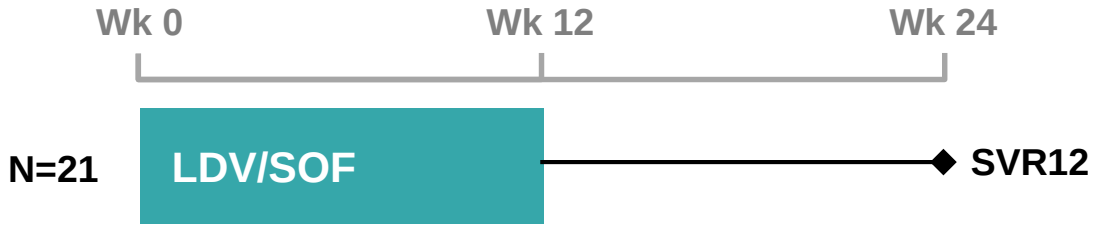


TN: treatment-naïve

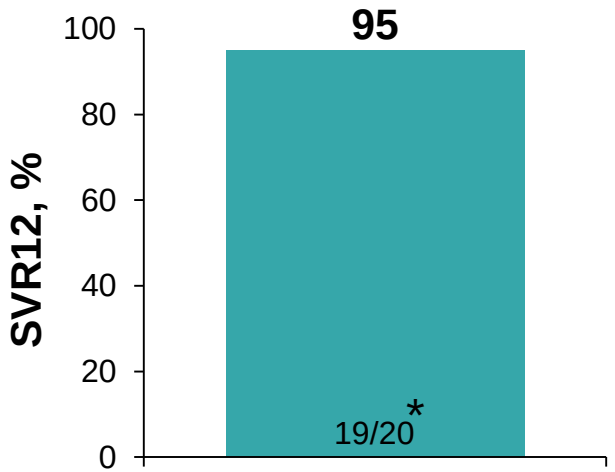
Lawitz E, et al Lancet July 26 2014 epub ahead of print

Treatment for GT 4 with LDV/SOF

Interim results from a single center, open-label, Phase 2a trial of LDV/SOF in HCV GT 4



Demographics	
Age	55 ± 10
Male, n (%)	14 (67)
Black, n (%)	9 (43)
Country of Origin	
Egypt, n (%)	6 (29)
United States, n (%)	5 (24)
Ethiopia, n (%)	4 (19)
Cameroon, n (%)	3 (14)
HCV RNA > 800,000 IU/mL, n (%)	13 (62)
Treatment Experienced, n (%)	8 (38)
Cirrhotic, n (%)	7 (33)



95% SVR12 with LDV/SOF for GT 4 HCV
No patient discontinued due to an AE

*One patient has not reached SVR12 timepoint yet

Kapoor, AASLD, 2014, Oral #240

EU Recommendation treatment (SOF + LDV) Harvoni^{R}, or daclatasvir Genotype 1 or 4

Patient population	Treatment	Duration	Note
Patients without cirrhosis	SOF + LDV	12 weeks	8 weeks in naïve G1 24 weeks in naïve uncertain retreatment option
	SOF + DCV	12 weeks	Consider 24 weeks for TE
Patients with compensated cirrhosis	SOF + LDV	24 weeks	
	SOF + DCV	24 weeks	Shorten 12 weeks TN cirrhosis favourable Consider adding RBV
Patients with decompensated cirrhosis	SOF + LDV + RBV	24 weeks	

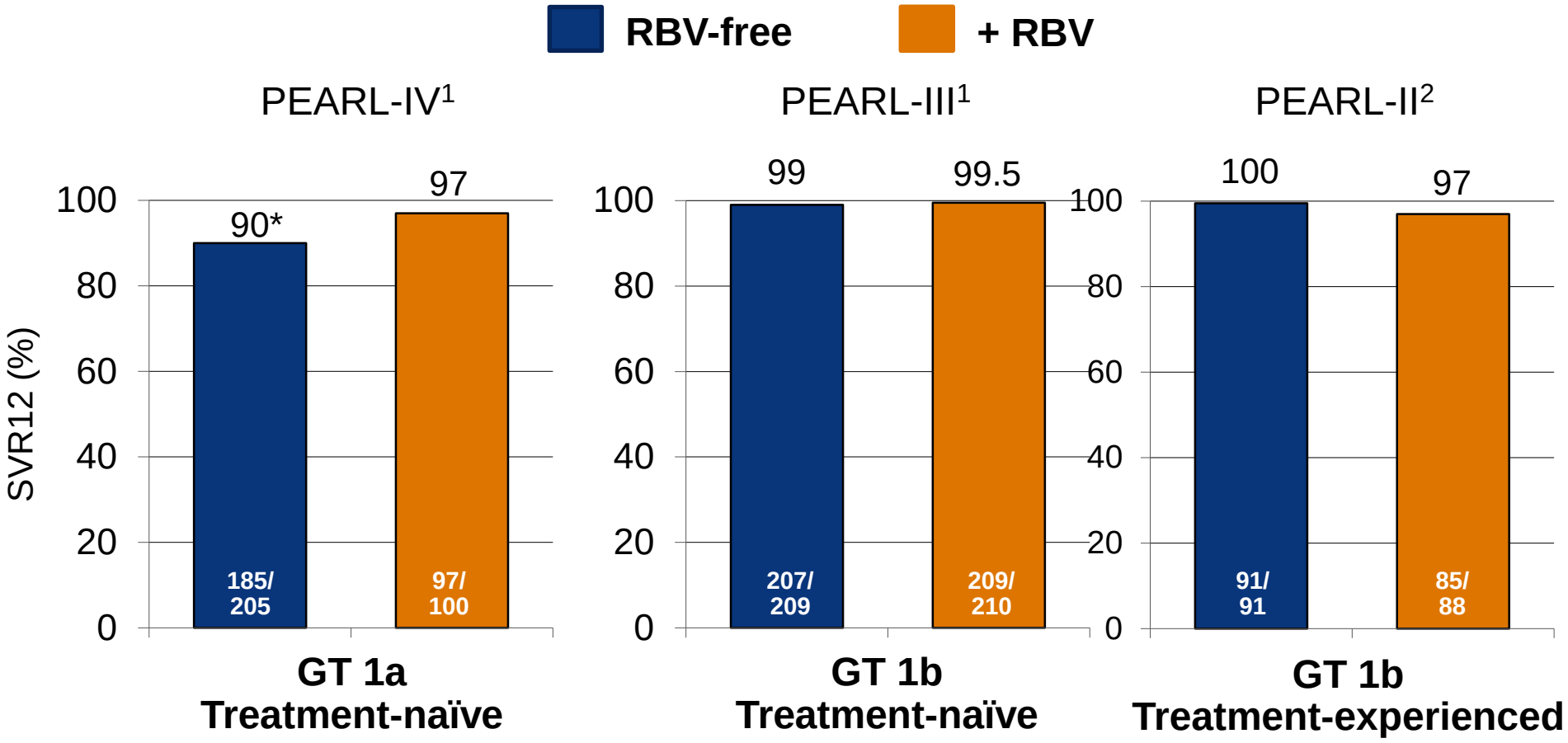
SmPC Gilead Sciences 21 Nov 2014; Daclatasvir SmPC 2014

Sofosbuvir based regiments NS5a inhibitor G1: Usage

- Sofosbuvir + ledipasvir genotype 1
  - treatment naïve without cirrhosis
    - 8-12 weeks without RBV
- Treatment naïve or experienced patients with cirrhosis
    - Compensated cirrhosis: 12 weeks plus ribavirin
- Decompensated cirrhosis (Childs B and C)
    - 12 weeks or 24 weeks with RBV
    - Urgent need to specify duration
    - Pre-treatment and on treatment host and viral factors that presage relapse and to adjust
  - Aim to use regimen that reduces relapses to a minimum (< 10%)
- Sofosbuvir + daclatasvir
  - As above?
- Sofosbuvir + simeprevir: 12 weeks no RBV ? Exposure SMV decompensated

SVR ± RBV with paritaprevir, ombitasvir + dasabuvir in GT 1 patients

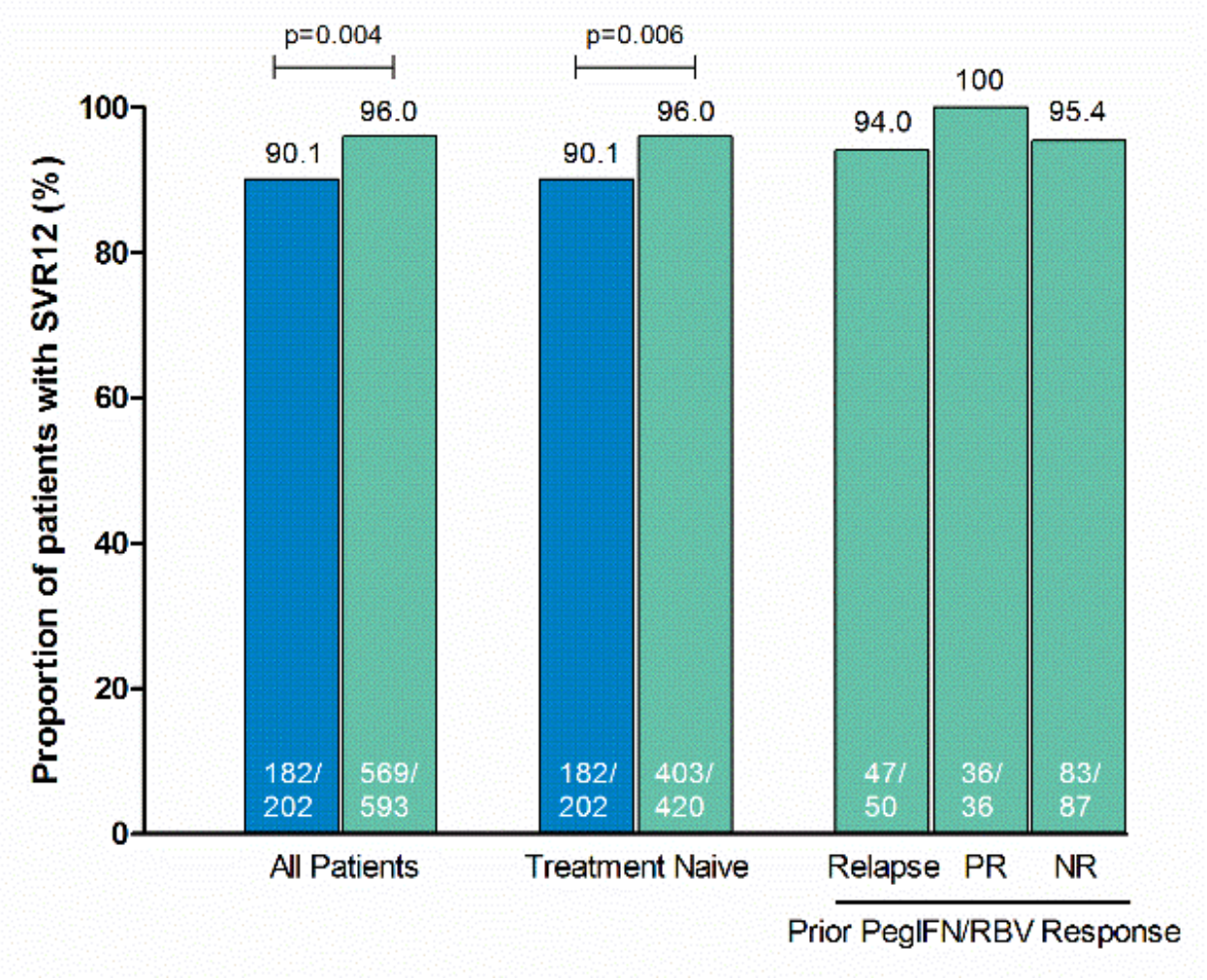
Paritaprevir ombitasvir + dasabuvir for 12 weeks in GT 1 patients



*** RBV-free arm did not meet non-inferiority vs RBV-containing arm**

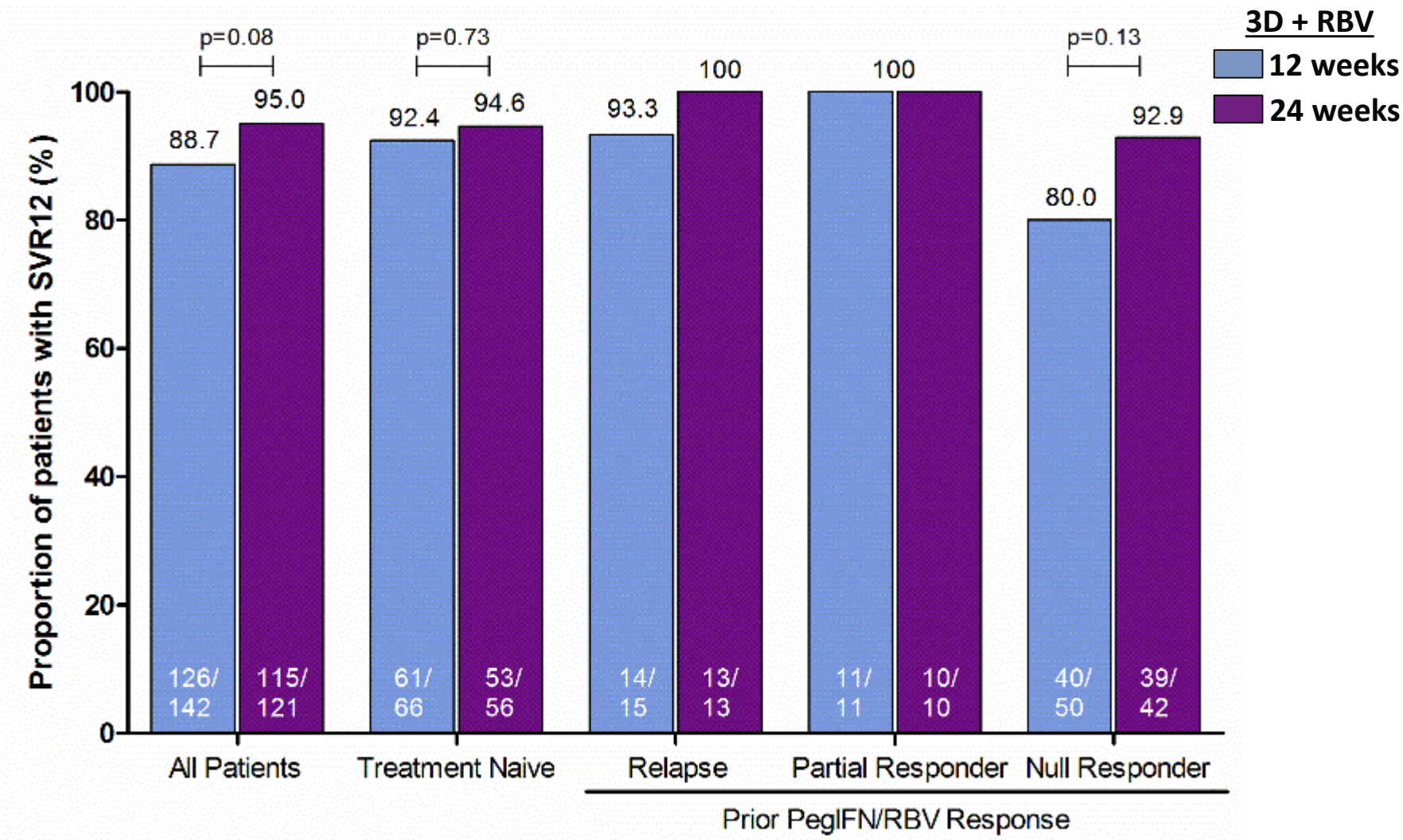
1. Ferenci P, et al. N Engl J Med 2014;370:1983–92;

Paritaprevir ombitasvir + dasabuvir SVR12 in GT 1a



p values from Fisher's exact test
All 3D-treated patients were treatment-naïve at baseline

Paritaprevir ombitasvir + dasabuvir SVR12 in GT 1a cirrhosis TN and TE



p values from Fisher's exact test

Everson et al AASLD 2014

AbbVie Viekirax + Exviera ± RBV G1

Genotype 1b:

Pooled analysis of Phase 3 trials in HCV GT 1b-infected patients without cirrhosis:

- RBV did not increase SVR 12 rates in GT 1b-infected patients and is not required in the treatment of non cirrhotic HCV GT 1b
- RBV recommended for treatment of 1b with cirrhosis

Genotype 1a

Pooled analysis of HCV GT 1a-infected patients with or without cirrhosis from four phase 3 trials:

- GT 1a-infected patients without cirrhosis benefit from inclusion of RBV with SVR 12 rates of 96% with 12 weeks of therapy
- GT1a- infected patients with cirrhosis: longer duration 24 weeks

Viekirax: ombitasvir/paritprevir/ritonavir Exviera: dasabuvir

IFN-free regimens of paritaprevir + ombitasvir ± RBV in G4 patients: PEARL-I study results

- Treatment naive (randomized)

ABT-450/r/OMB (n=44)

ABT-450/r/OMB + RBV (n=42)

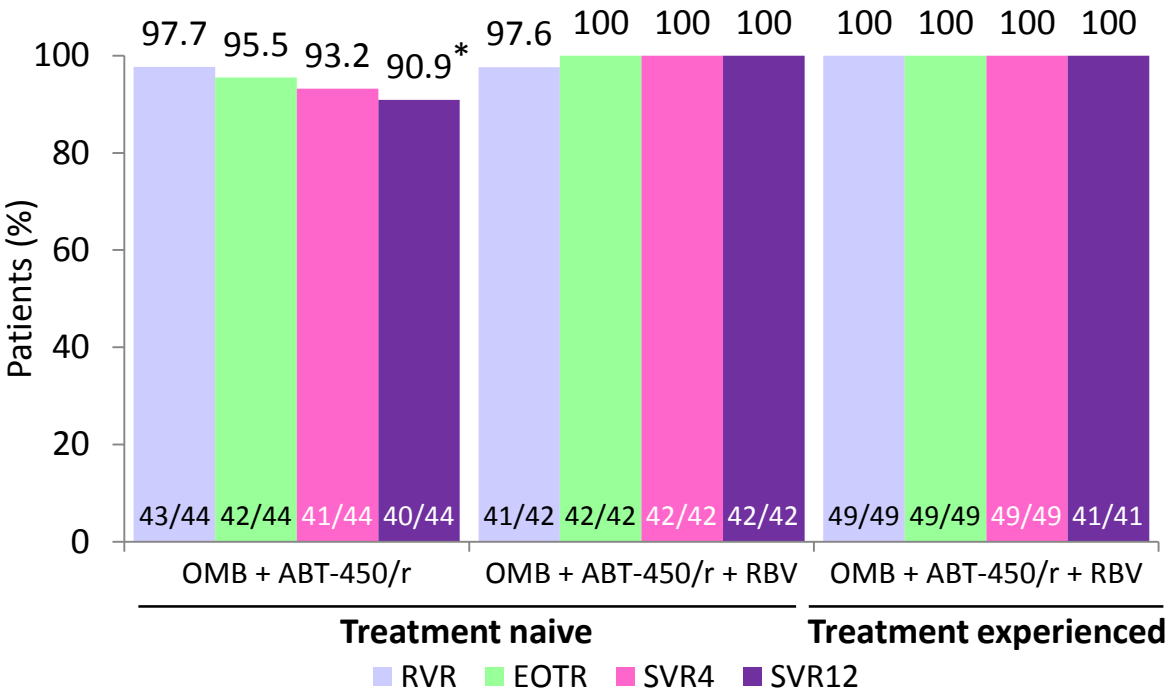
- Treatment-experienced

ABT-450/r/OMB + RBV (n-49)

12 weeks

ABT-450: 150; r: 100 mg; ombitasvir (OMB) 25 mg QD
RBV 1000–1200 mg (BID dosing)

Efficacy in pts receiving OMB + ABT-450/r ± RBV



*3 non-SVR naive patients without RBV had VF: 1 breakthrough, 2 relapses. 2/3 had BL NS5A RAVs

93% F0–2 (no cirrhosis)

Most common AEs: Headache asthenia, fatigue, nausea

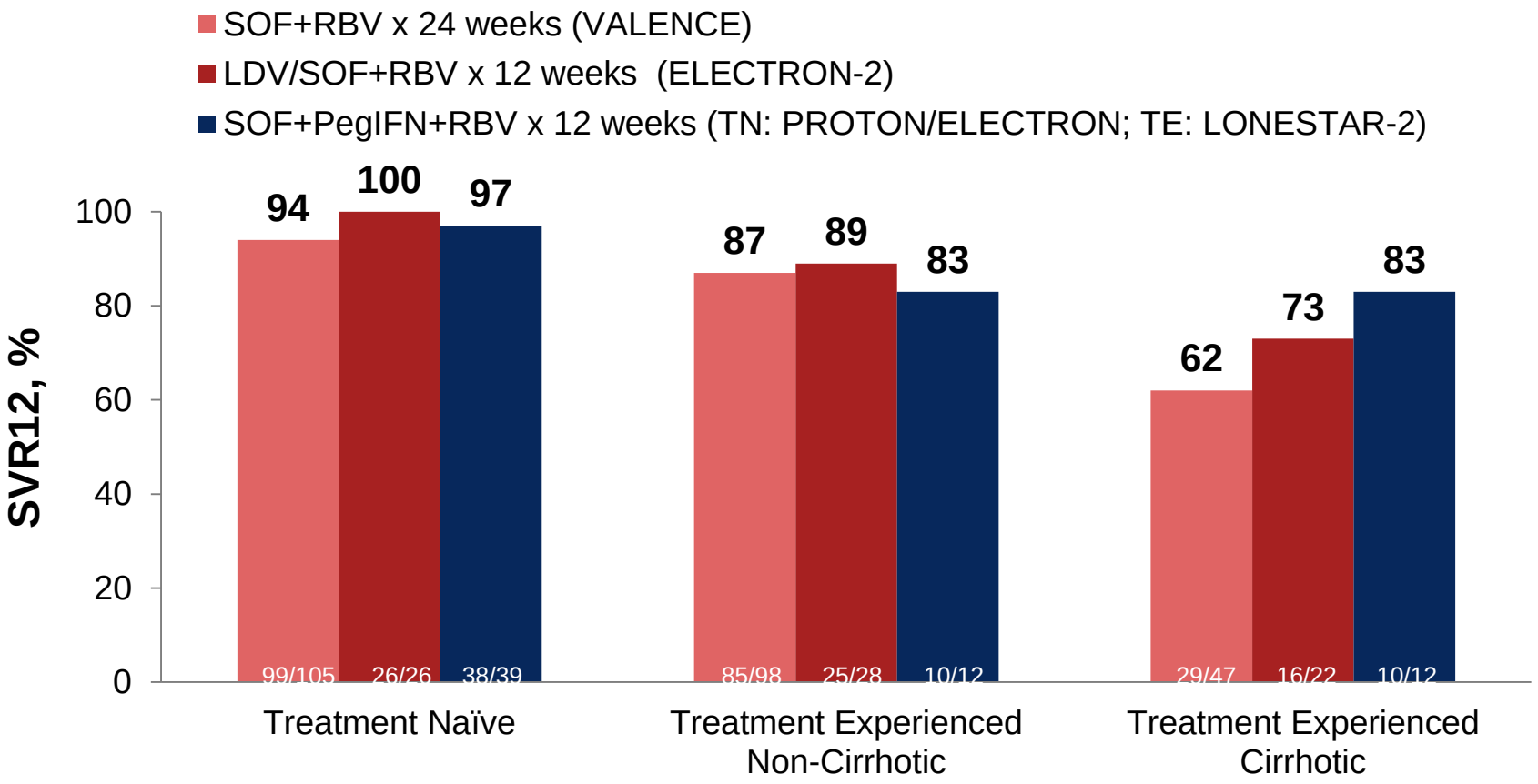
Safety and tolerability of regimen consistent with 3D + RBV regimen in G1

Pol S, et al. AASLD 2014, Boston. #1928

EU prescribing information Viekirax + Exviera

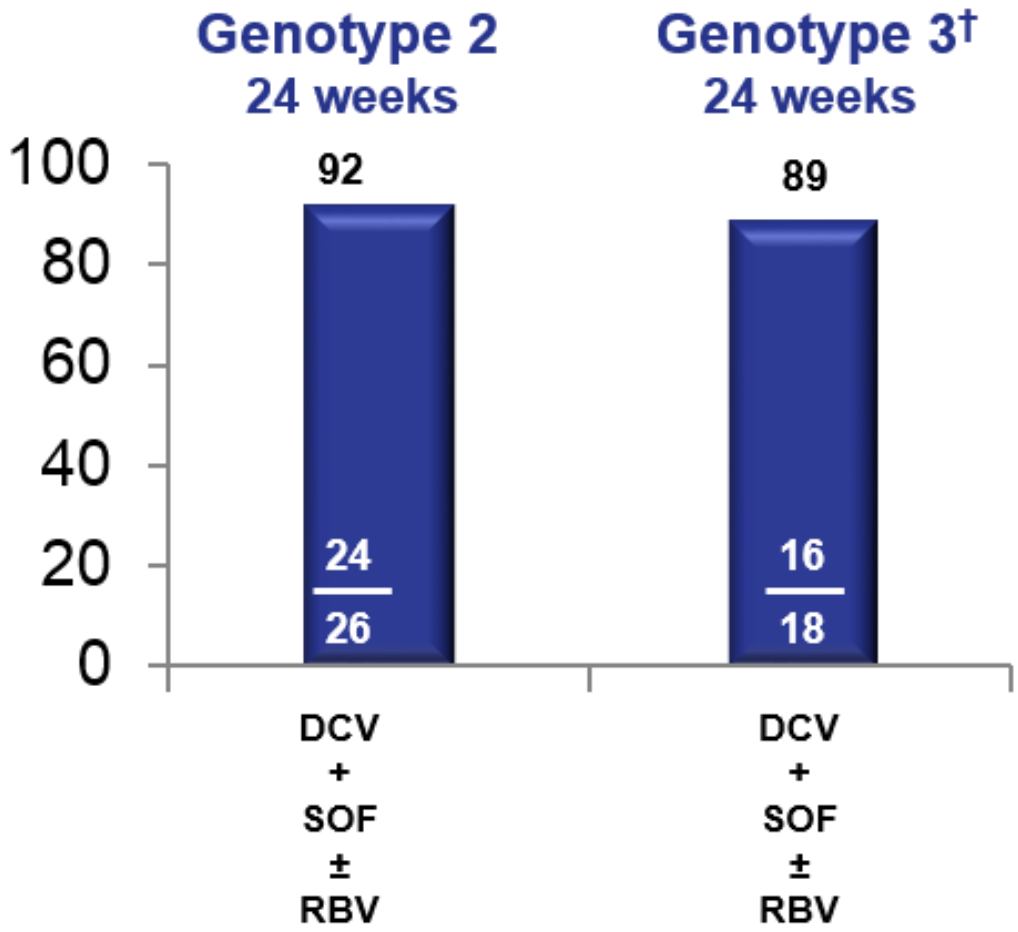
	Cirrhosis	Regimen	RBV	Duration
1b	No	Viekirax + Exviera	No	12 weeks
1b	Yes	Viekirax + Exviera	Yes	12 weeks
1a	No	Viekirax + Exviera	Yes	12 weeks
1a	Yes	Viekirax + Exviera	Yes	24 weeks
4	No	Viekirax	Yes	12 weeks
4	Yes	Viekirax	Yes	24 weeks

SOF-Based Regimens for HCV GT 3
Cross study comparison



Zeuzem S, et al. *NEJM.* 2014.
Gane, EASL, 2014, Oral #6
Gane E et al. NEJM 2013;368:34–44.
Lawitz E et al. Lancet Infect Dis 2013;13:401–408.
Gane, AASLD, 2014, Poster #LB-11

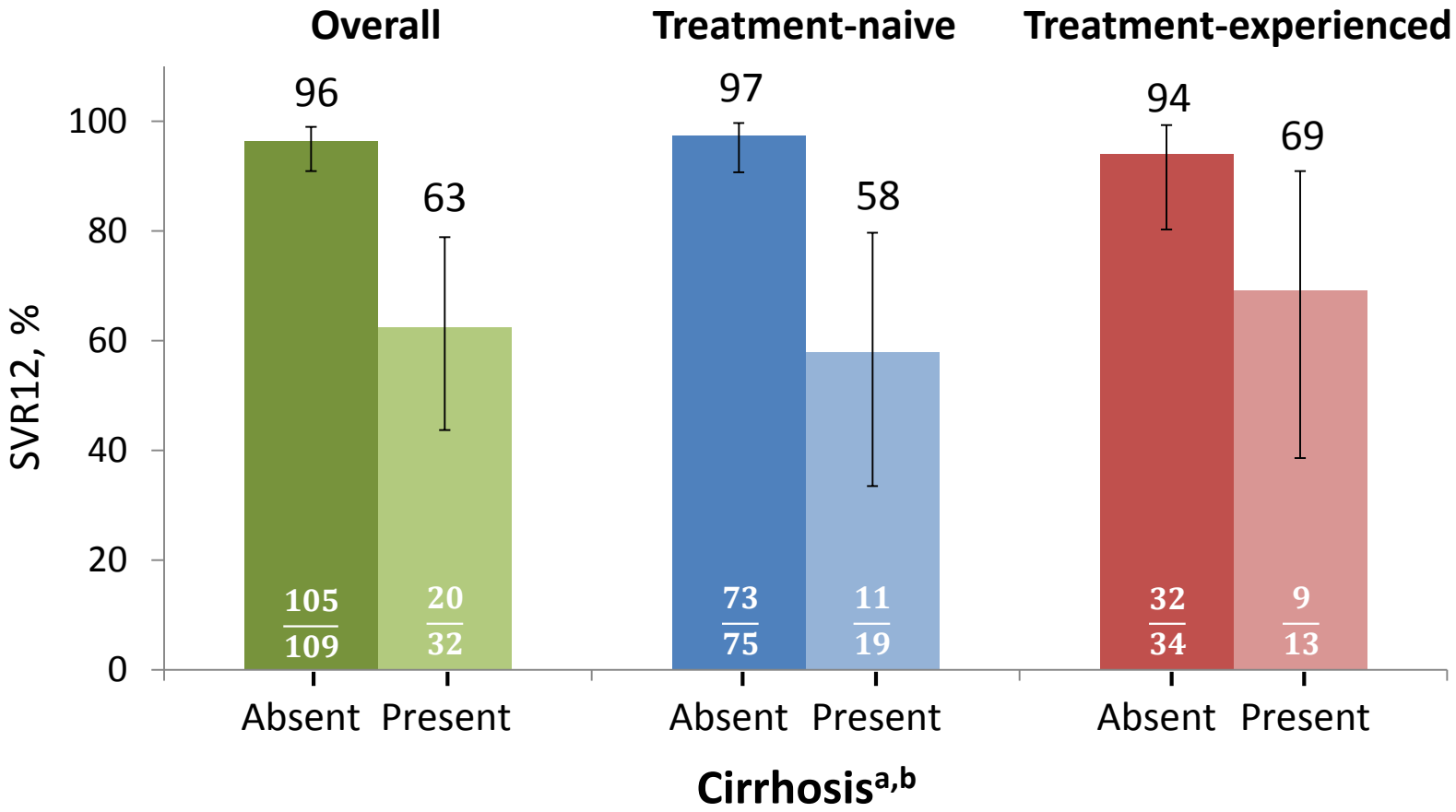
Sofosbuvir + Daclatasvir Genotype 2 or 3 naive



Sulkowski MS, et al. *N Engl J Med.* 2014;370:211–21 . Daclatasvir SmPc Use of RBV

Daclatasvir product summary

All-Oral 12-Week Combination Treatment With Daclatasvir and sofosbuvir in Patients Infected With HCV Genotype 3: ALLY-3 Phase 3



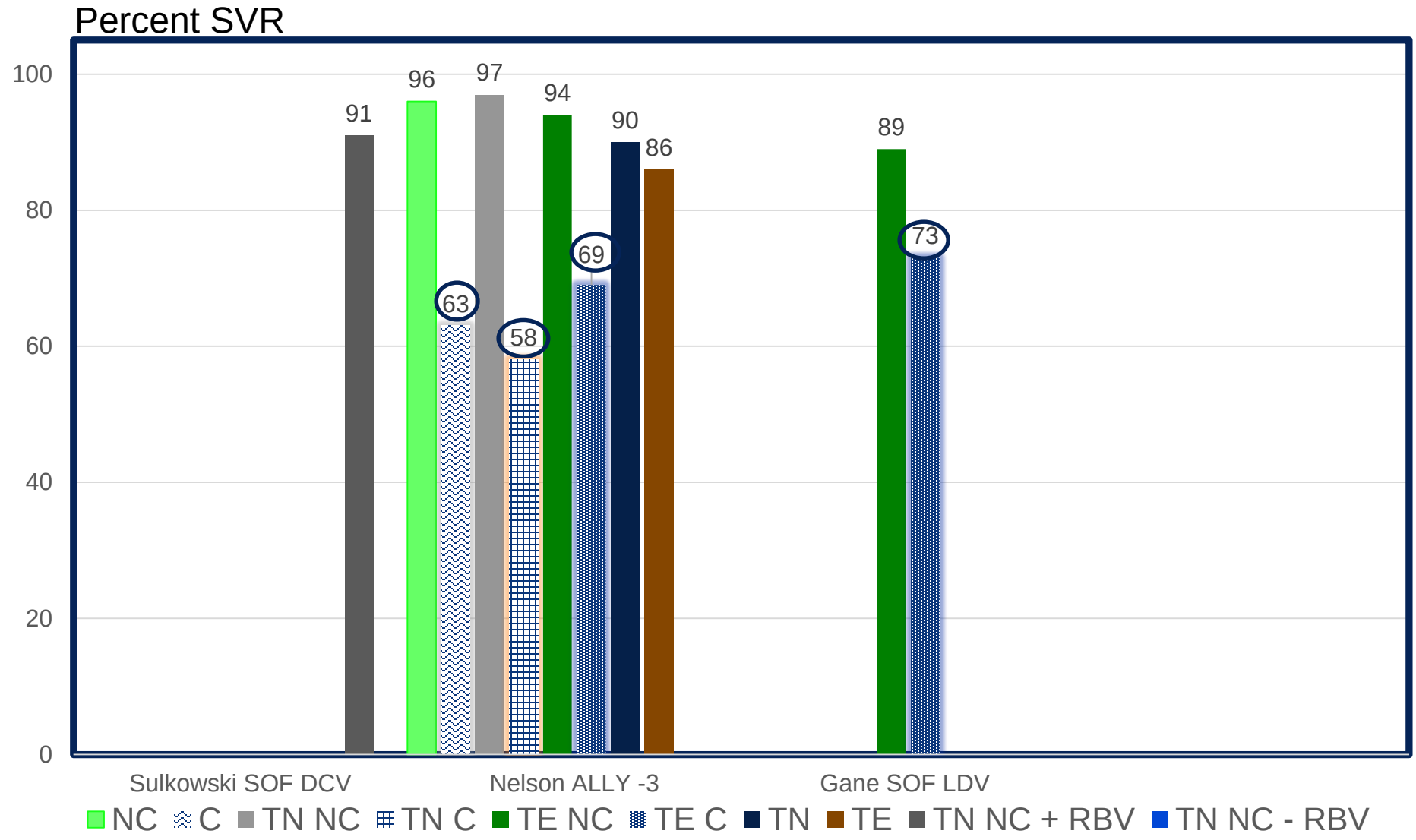
- Among patients with cirrhosis, 34% (11/32) had baseline platelet counts < 100,000/mm^3

[a] Cirrhosis status determined in 141 patients by liver biopsy (METAVIR F4), FibroScan (> 14.6 kPa), or FibroTest score ≥ 0.75 and APRI (aspartate aminotransferase to platelet ratio index) > 2.

[b] Cirrhosis status for 11 patients was inconclusive (FibroTest score > 0.48 to < 0.75 or APRI > 1 to ≤ 2).

Genotype 3 sofosbuvir + NS5A inhibitor: LDV or DCV ± RBV:

Non comparative studies with varying populations and regimens



Sulkowski MS, et al. *N Engl J Med.* 2014;370:211–21 ; Nelson et al AASLD LB3 2014; Gane et al LB11 AASLD 2014

EU Recommendation treatment (SOF + LDV) Harvoni[R] or sofosbuvir + daclatasvir

Genotype 3

Patient population	Treatment	Duration
Cirrhosis and/or prior treatment failure	SOF + LDV + RBV	24 weeks
	SOF + DCV + RBV	24 weeks

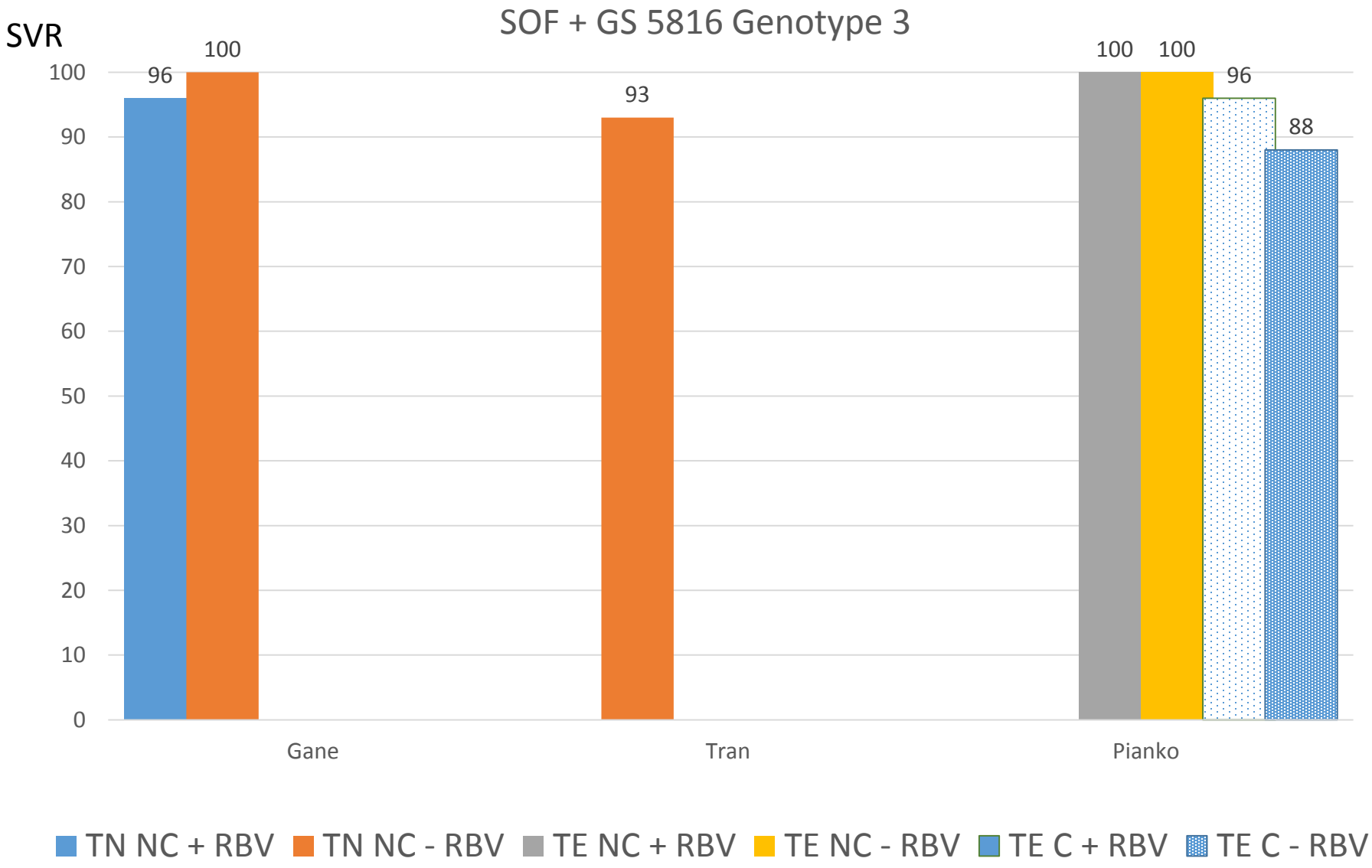
SmPC Gilead Sciences 21 Nov 2014; Daclatasvir SmPC

Conclusion: SOF + NS5a inhibitor for genotype 3

- Satisfactory response (> 90%) can be achieved in treatment naïve non cirrhotic: (94-97%)
  - EU licence is silent?
  - 12 weeks without RBV?
- Higher relapse rates treatment experienced, cirrhosis
- Patients with cirrhosis
  - Lower results without RBV or shorter duration?
  - 58% - 69-73%
  - SmPCs suggests 24 weeks (plus RBV)
- Decompensated cirrhosis
  - Expanded access (UK) will inform

New agents: SOF + GS5816 Genotype 3

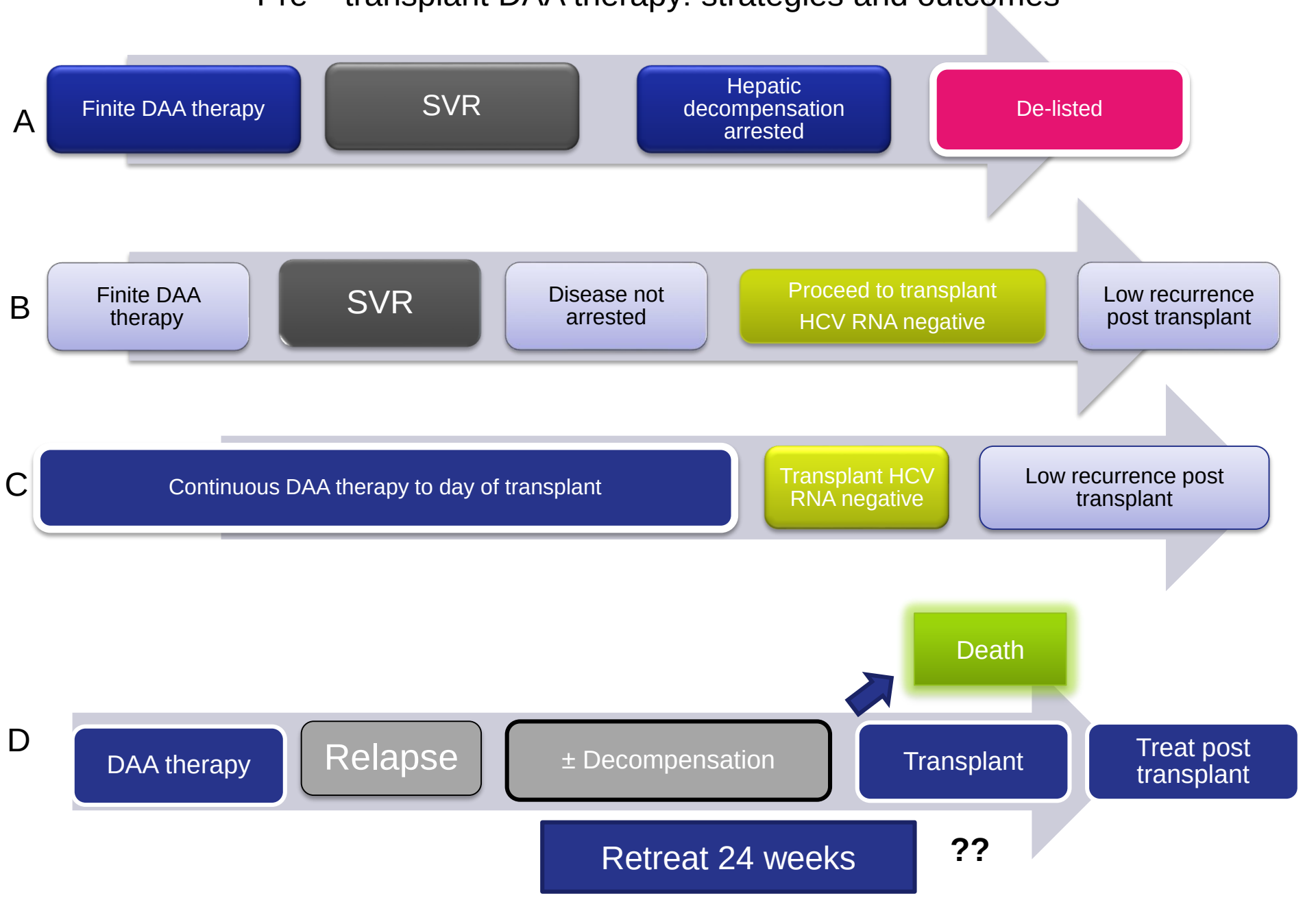
Non comparative studies with varying populations and regimens



Urgent lessons to be learned from DAA IFN free therapy in decompensated cirrhosis

- What degrees of cirrhosis impair response?
  - Higher rates of relapse observed
- What are the consequences of relapse?
- Are pre-existent resistant variants more critical in this group?
- Are there higher rates of adverse events in patients with decompensated cirrhosis?
- What is the optimal duration of therapy for different stages of cirrhosis?
- What is the optimal timing?
- To what degree is disease reversible?

Pre – transplant DAA therapy: strategies and outcomes



Resistance-Associated Variants Present at Time of Virologic Failure in Patients Receiving 3D+RBV

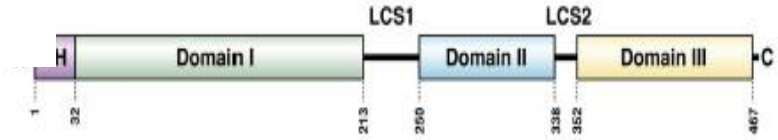
Development of resistance-associated variants occurred in 8/473 (1.7%)

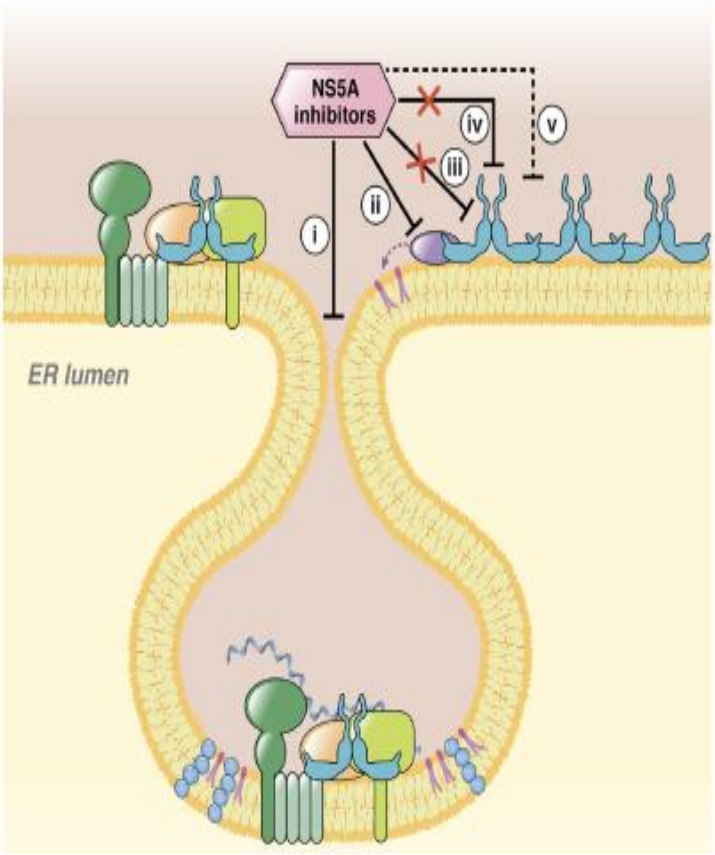
Patient	GT	Type of Virologic Failure	NS3	NS5A	NS5B
1	1a	On-treatment failure at Week 12	R155K, D168V	Q30R	S556G, 559N
2	1a	Relapse at PT Week 2	D168V	M28T	S556G
3	1a	Relapse at PT Week 2	V36A, D168V	M28T	none
4	1a	Relapse at PT Week 8	none	M28V*, H58P*	none
5	1a	Relapse at PT Week 8	D168V	Q30R	Y561H
6	1a	Relapse at PT Week 8	D168V	Q30R	none
7	1a	Relapse at PT Week 12	D168V	Y93N*	S556G
8	1b	Relapse at PT Week 2	Y56H, D168V	L31M*, Y93H*	S556G*

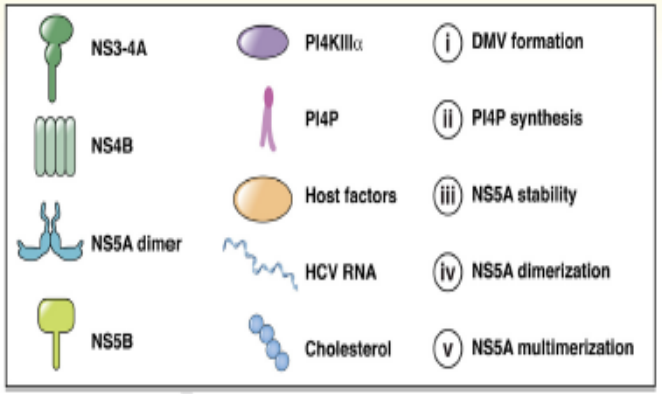
*Variant also present at baseline

Kindly provided by Feld et al NEJM 370: 1594-603 2014

Disruption of virus-induced replication compartment formation by NS5A inhibitors



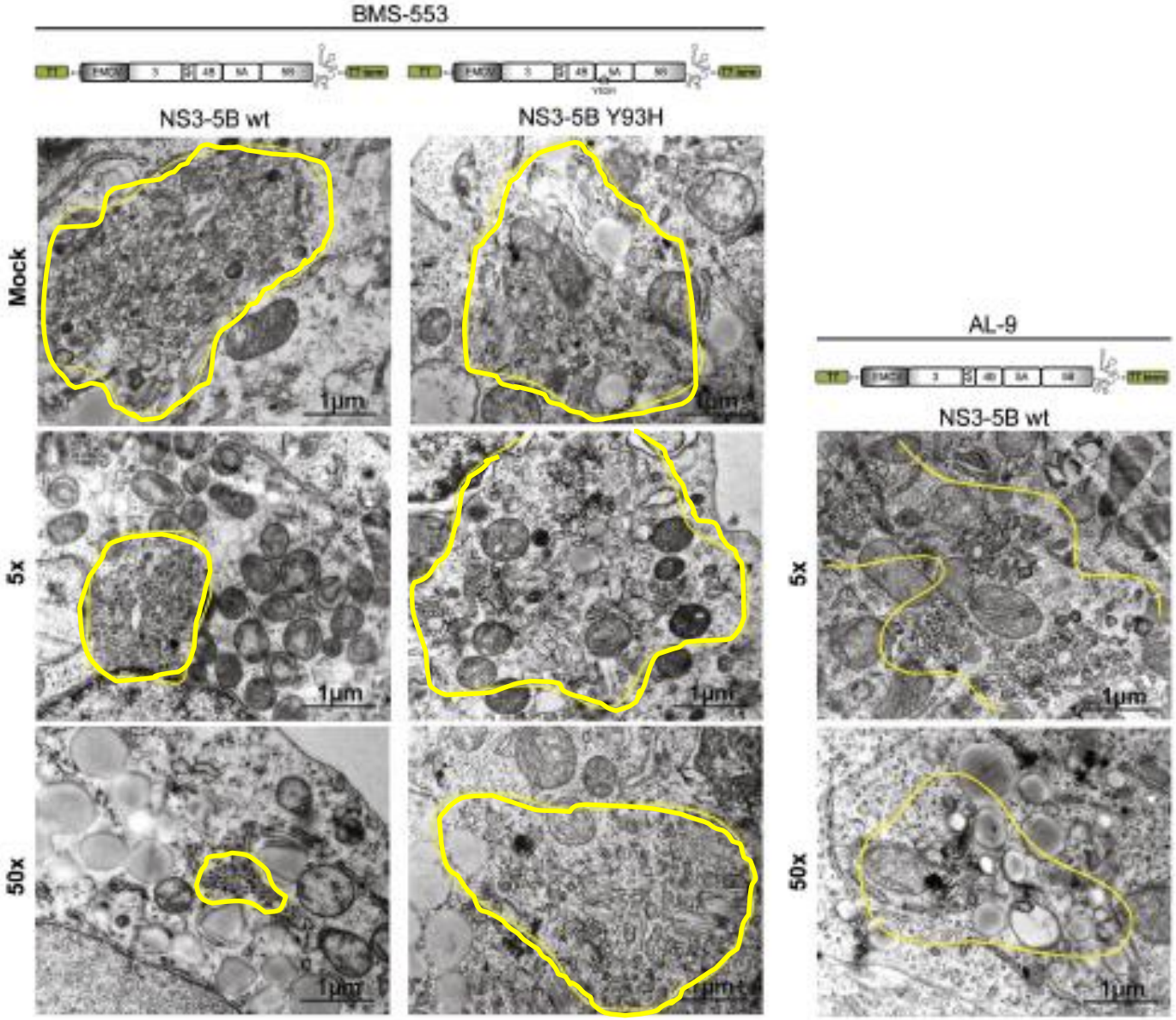




Eyre NS, et al. *Gastroenterology.* 2014 Sep 26. doi: 10.1053/j.gastro.2014.09.024.

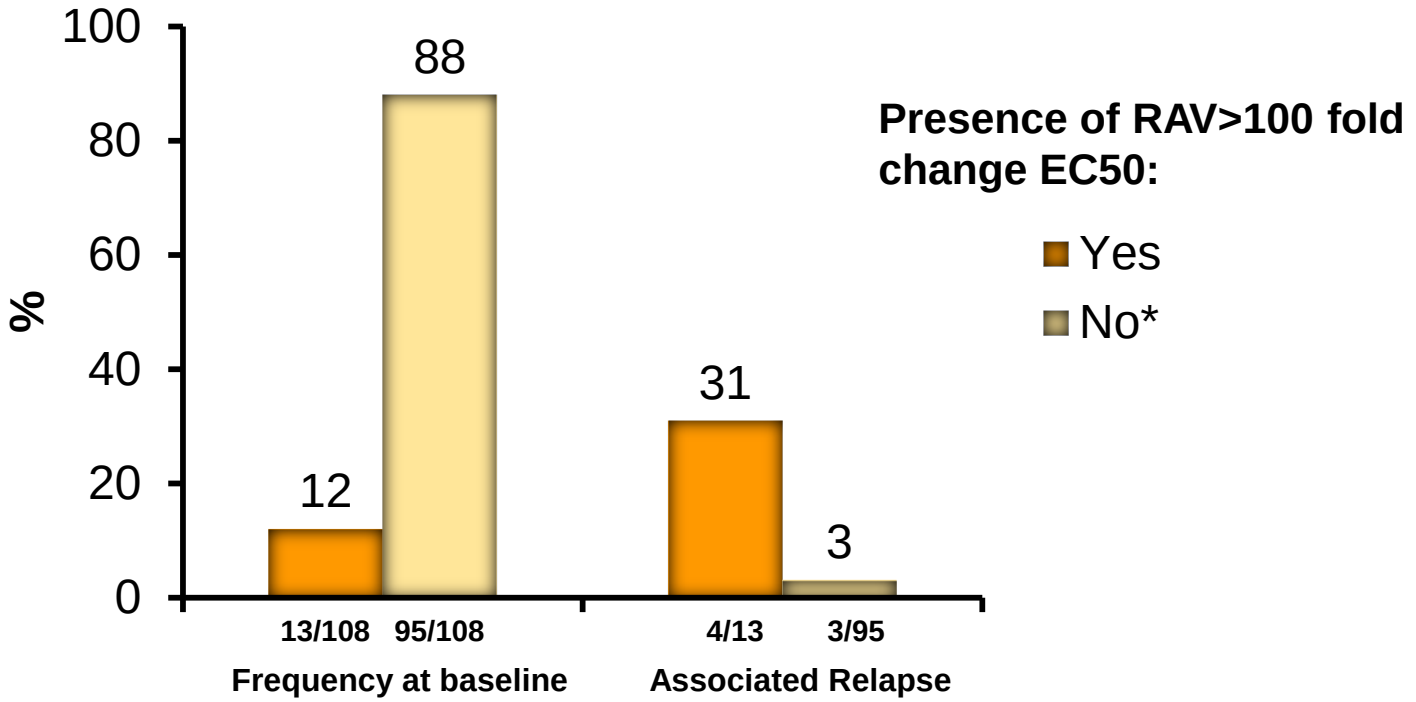
Effect of NS5a inhibitor on membranous web biogenesis

Wild type versus Y93H



Berger et al Gastroenterology epub 2014

ION2: effect of baseline HCV RAVs on treatment outcome with SOF/LDV (12 weeks) in HCV genotype 1 treatment-experienced patients



In the pooled analysis of the **Phase 3 studies**, **16% of patients had baseline NS5A RAVs** identified by population or deep sequencing irrespective of subtype.
Baseline NS5A RAVs were overrepresented in patients who experienced relapse in the Phase 3 studies

NS5A RAVs that conferred > 100-fold shift in EC50 and were observed in patients were the following substitutions in genotype 1a (M28A, Q30H/R/E, L31M/V/I, H58D, Y93H/N/C) or in genotype 1b (Y93H).
*or conferring < 100 FC EC50
RAV: resistance-associated variant

Re-treatment after prior exposure to NS5a inhibitor

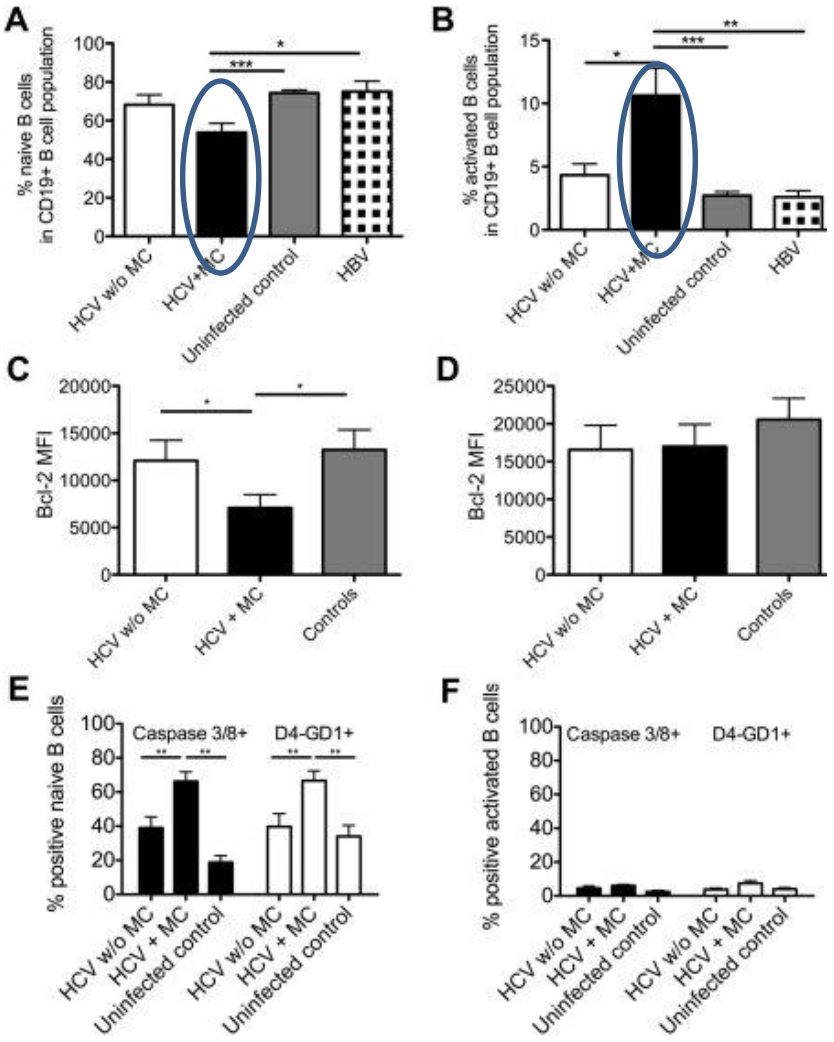
- Majority of patients with pre existing NS5A RAVs respond to NS5A inhibitors
- Selection of NS5A resistance mutations that reduce the susceptibility to LDV or DCV is seen in most failing treatment with SOF LDV or SOF DCV
- Data indicate that such NS5A mutations do not revert on long term follow up
  - Presently no data to prove efficacy of LDV or DCV against high level NS5A resistant mutations
  - Such patients may therefore be dependent on SOF RBV, (longer duration) or other drug classes for clearance of HCV infection
  - Innate immune response?

Wyles et al AASLD 2014; Osinusi Ann Int Med Nov 2014

HCV and cryoglobulinaemia

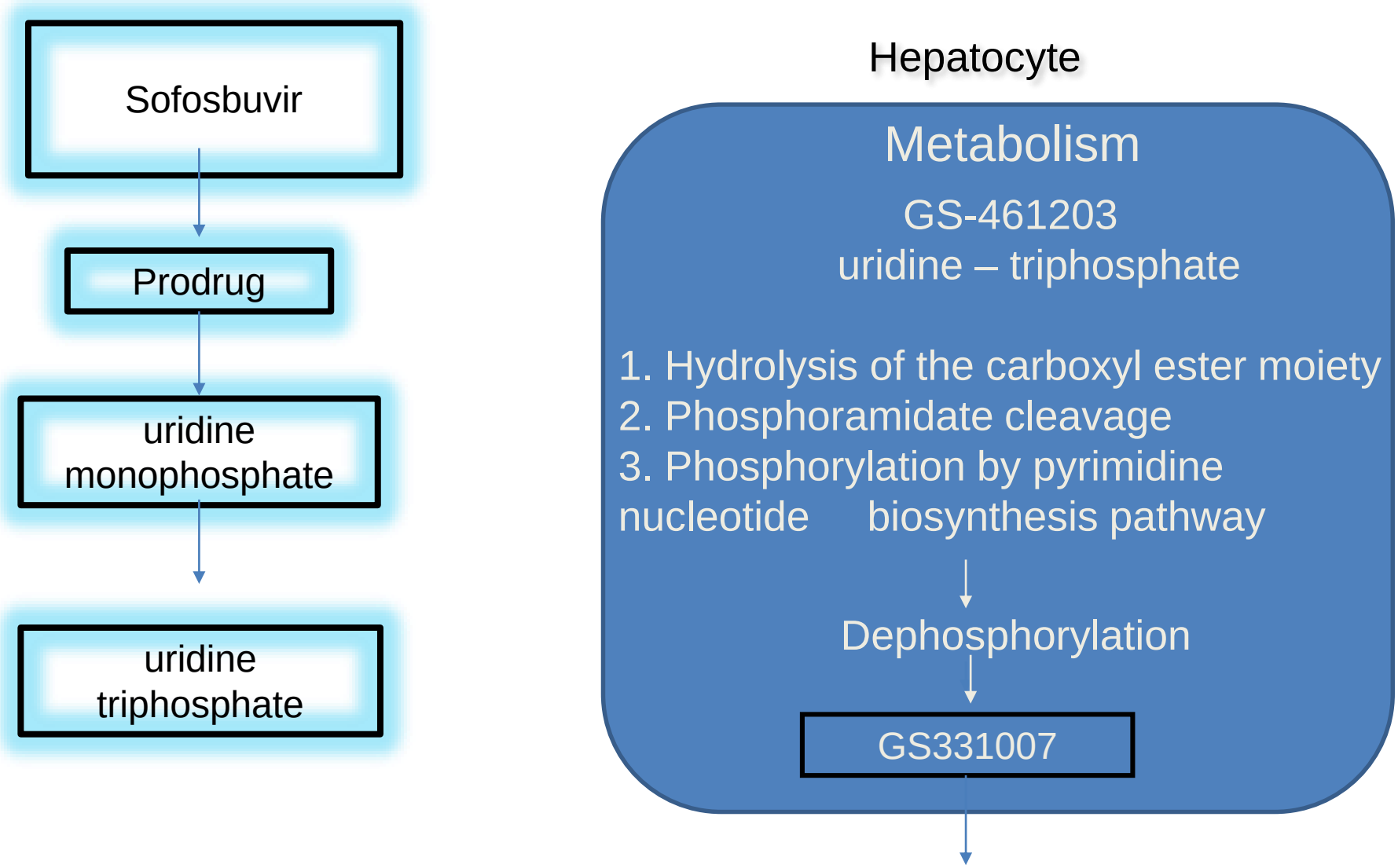
- Cirrhosis, membranous glomerulonephritis, mixed essential cryoglobulinaemia and vasculitis associated chronic hepatitis C.
- HCV continuous stimulus for production of circulating immune complexes which may form cryoprecipiates
- Complement:
  - cold-insoluble immune complex -mediated vasculitis
  - involving small blood vessels different tissues including skin, kidney, peripheral, and central nervous system.
- ***B-cell clonal selection may arise as a result of antigen stimulation***
  - May lead to malignant B-cell proliferation.
- Optimal treatment relies on reducing HCV RNA as the driver of the process?

B cell homeostasis in chronic hepatitis C virus–related mixed cryoglobulinemia is maintained through naïve B cell apoptosis



B cell numbers paradoxically reduced in HCV-infected patients with MC HCV patients
Increased sensitivity of naıve B cells to apoptosis: reduction in size of naıve B cell subset.

Holtz et al, Hepatology Volume 56 pages 1602-1610, 14 OCT 2012



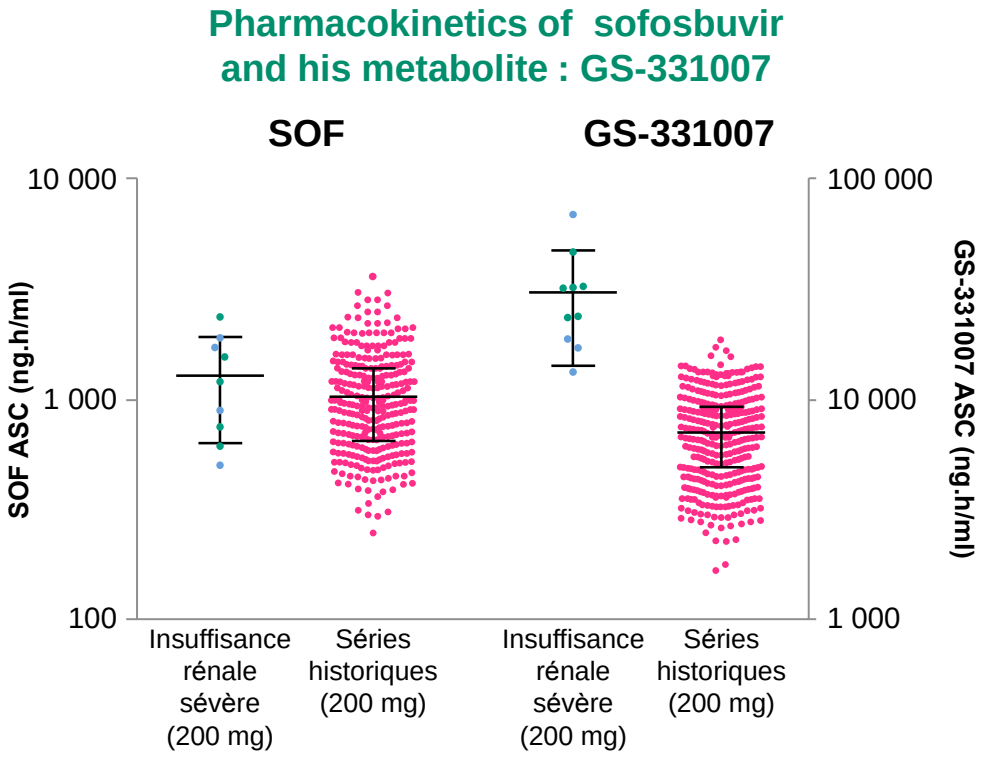
80%, 14%, and 2.5% recovered in urine, faeces, and expired air
Urine: recovered: GS331007 (78%) 3.5% as sofosbuvir.

Sofosbuvir pharmacokinetics in renal impairment

	Sofosbuvir	GS331007	Mild eGFR ≥ 50 and < 80	Moderate eGFR ≥ 30 and < 50	Severe (eGFR < 30	ESRD
Plasma half life	0.48-0.75 hrs	7.2 - 11.8 hrs				
Cmax ng/ml	603	1378				
AUC ng/ml	539	9369				
Sofosbuvir AUC			61%	107%	171%	28% pre 60% post
GS331007			55%	88%	451%	

Safety, efficacy and phramokinetics of Sofosbuvir in ESKD

- 10 patients with ESKD (eGFR < 30 ml/mn) and HCV (GT-1, 7GT-1a, 2 GT-1b and7 GT-3) without cirrhosis. 7/10 were naive ,were treated with SOF 200 mg/j and RBV 200 mg/j.
- Efficacy :
  - HCV RNA undetectable at w2, W4.
  - SVR 12 = SVR 24 = 40 %
  - No relation between AUC and SVR 12
- Safety :
  - 20 % AE (anemia)
  - 4 dose reduction and 1 RBV stopped
  - No SOF discontinuation



→ **Despite favorable pharmacokinetics and good tolerance, efficacy is poor due to partly difficulty of managing ribavirin ?**

AUC appears to be equivalent for sofosbuvir and X4 for GS-331007 compared to patients with normal eGFR but without clinical impact so far.

Gane EJ et al. AASLD 2014: abstr. 966

ABT-450/, ombitasvir with or without dasabuvir in subject with renal impairment

- Phase I multicenter, single dose non fasting open label, 2 period study of 3D and 2D in patients with renal impairement compzred to subject with normal renal function.
- 24 subjects without HCV were compared according to renal function in 4 groups according to creatinine clearance: ≥ 90 ml/mn, between 60 – 89ml /mm, between 30-59 ml/mm and between 15-29 ml/mm.

Compared with subjects with normal Renal function	Mild renal Impairment	Moderate renal impairment	Severe renal impairment
AUC ombitasvir	comparable	comparable	comparable
AUC ABT-450 et dasabuvir	↗ 20 %	↗ 37 %	↗ 50 %
AUC ritonavir	↗ 42 %	↗ 80 %	↗ 114 %

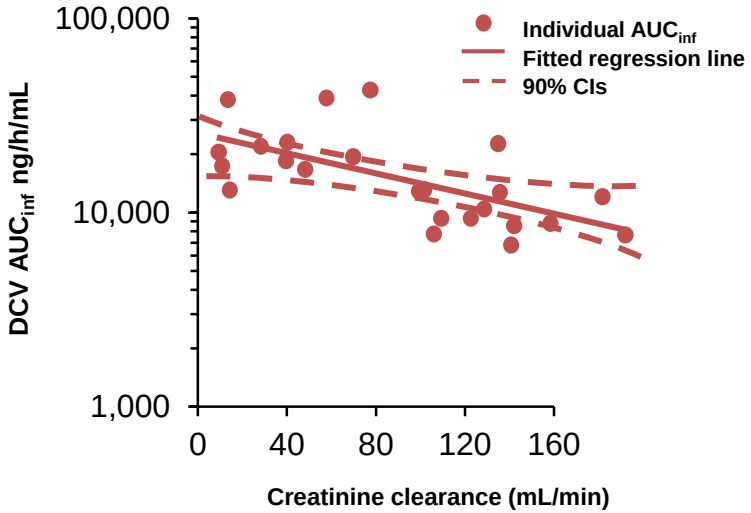
- None of the changes in drug exposures were clinically relevant
- Change in DAA exposure are not clinically relevant for safety

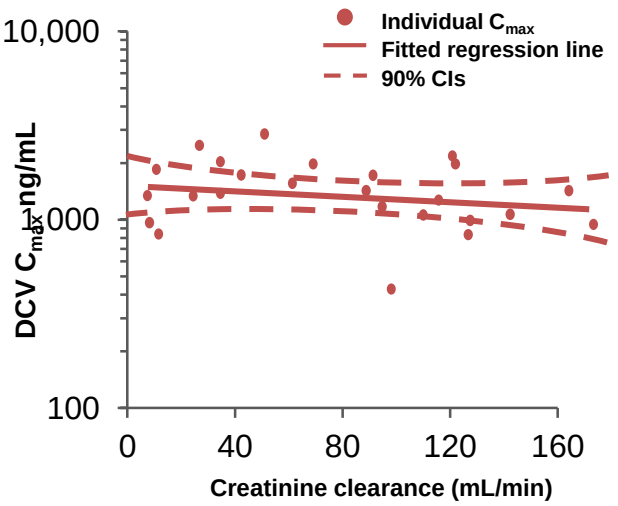
→ **None of the changes in drug exposures were clinically relevant and they do not require dose adjustment.**

→ **Clinical studies in HCV infected patients with renal insufficiency are planned in light of these pharmacokinetic results**

Khatri A et al.AASLD 2014: abstr. 238,

Daclatasvir: dose adjustment not required in subjects with renal impairment





- Compared with a normal creatinine clearance (CrCL; 90 mL/min), AUCinf estimated to increase 1.3-, 1.6- and 1.8-fold for subjects with CrCL values of 60, 30 and 15 mL/min, respectively
  - Similar estimated increases in the AUCinf of unbound free DCV were also observed
  - Increased DCV exposure was within the exposures observed in the population PK and exposure-safety assessment, which has not shown a correlation between higher exposures and adverse events (AEs)
- DCV was generally well-tolerated in subjects with normal renal function or renal impairment of varying degree
- DCV can be administered in subjects with renal impairment without dose modification

CI = confidence interval; CrCL = creatinine clearance; AE = adverse events.

Garimella T, et al. HCV/HIV Clinical Pharmacology Workshop. Poster 2014 P_43

Simeprevir: dose adjustment not required in subjects with renal impairment

Parameter	LS means[a]		LS means ratio	90% CI
	Renal impaired (test)	Healthy controls (reference)		
C_{min}, ng/mL	985.5	577.5	1.71	0.65, 4.50
C_{max}, ng/mL	3459	2588	1.34	0.66, 2.72
AUC_{24h}, ng.h/mL	51710	32010	1.62	0.73, 3.59
	Median[a]		Treatment difference median	90% CI
t_{max}, h	6.0	6.0	0.0	0.0, 2.0

- For subjects with severe renal impairment, SMV C_{min}, C_{max} and AUC_{24h} were about 71%, 34% and 62% higher, respectively, compared with matched healthy controls
  - For t_{max}, no relevant differences were observed between the groups

AUC_{24h}, area under the plasma-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; t_{max}, time to reach C_{max}

[a]N: 8 for reference (healthy controls) and N: 8 for test (renal impaired)

What are the expectations of treatment?

- Likelihood of clinical improvement post SVR
- Other determinants will affect outcome
  - Alcohol, diabetes mellitus, HIV, steatosis?
- Treat before or after transplant?
  - Another instance of informed deferral?

- Longer term outcome: HCC risk
  - Genetic alterations?
  - HCC surveillance

Eradication of HCV disease requires:

- Preventing transmission of incident infection
- Preventing progression to clinical disease

- Watershed moment in the epidemic

Treating: prioritisation strategy

- Population impact:
  - *Key outcomes:*
  - Incident cases of chronic infection
  - Severe liver disease and morbidity
    - In the next 20 years
- Prioritize treatment to either
  - People who inject drugs?
  - Persons with moderate or advanced fibrosis?
- Which approach?

Innes et al 2014

Managing hepatitis C: a few remaining questions for today

- Has an irrevocable switch to interferon free regimens arrived?
- Likelihood of clinical improvement post SVR?
  - Liver function, HCC surveillance
- Other determinants affect outcome
  - Alcohol, diabetes mellitus, HIV, steatosis?
- Treat before or after transplant?
  - Another instance of informed deferral?
- How can the near 100% SVR rates in clinical trials be translated and back engineered in clinical practice?
- How can the same rates be achieved in patients with
  - Decompensated cirrhosis?
  - Patients with relapse following a NS5A containing regimen?
  - Genotype 3 infection?
- How can reinfection be prevented
- How do we align policy strategies?