Treatment of HCV in 2016

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Conflicts of Interest

- Speaker and consultancy fees received from
- AbbVie, BI, BMS, Gilead, Janssen, Roche, Merck, Novartis, Springbank, Achillion, Idenix

HCV in 2016
A whistle stop tour

- Genotype 1
- Genotype 3
- Who to treat first

HCV in 2016
A whistle stop tour

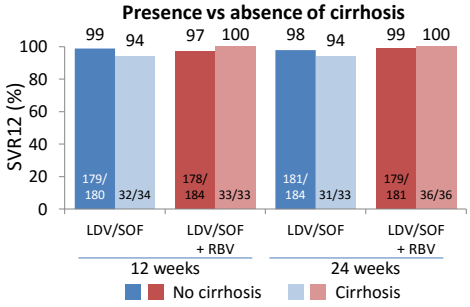
- Genotype 1
- Genotype 3
- Who to treat first

Genotype 1 without Interferon

- Two strategies emerging:-
- Sofosbuvir + anything
- Potent protease + 1 or 2 other drugs

All oral FDC LDV/SOF ± RBV for 12 or 24 weeks in treatment-naive G1 HCV patients: Phase 3 ION-1 study

- AIM: Evaluate LDV/SOF for 12 and 24 weeks in HCV treatment-naive G1 patients
- 865 patients randomized to LDV/SOF or LDV/SOF + RBV for 12 or 24 weeks

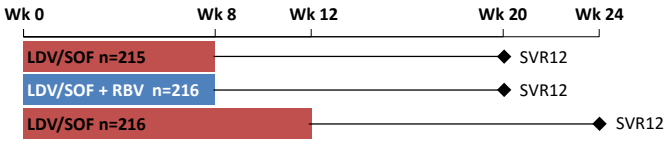


- 99% SVR rate following LDV/SOF for 12 wks
- RBV and extended treatment did not improve efficacy

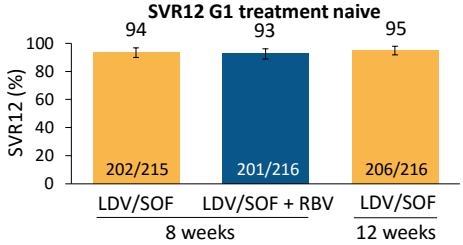
- RBV associated with higher rates of AEs

Afdahl NEJM 2014;370:1889

Sofosbuvir/ledipasvir ± RBV for 8 weeks vs 12 weeks in treatment-naive non-cirrhotic G1 HCV-infected patients



- Stratified by HCV subtype (1a or 1b)
- G1 treatment-naive patients without cirrhosis

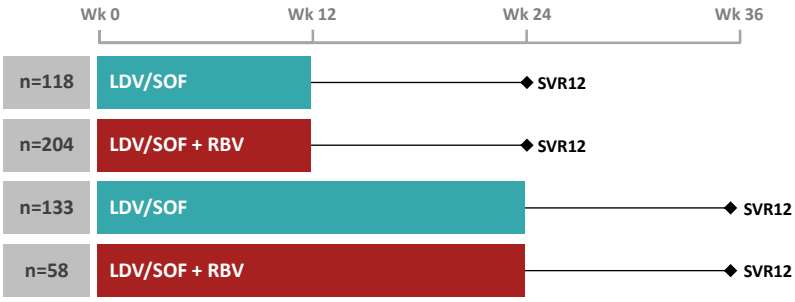


- 8 weeks without RBV not statistically inferior
- Without cirrhosis 8 weeks is the right duration

Kowdley K.V, et al. NEJM 2014;370:1879

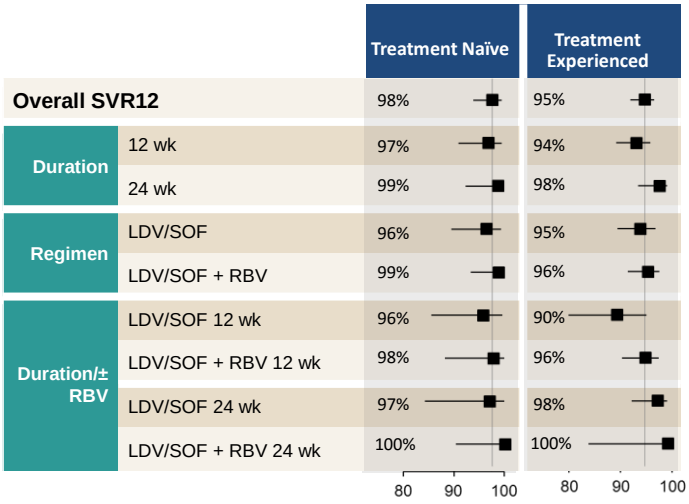
An Integrated Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with LDV/SOF±RBV

- 513 patients with HCV GT 1, compensated cirrhosis
- Pooled data from Phase 2 and 3 LDV/SOF ± RBV studies
  - LONESTAR, ELECTRON, ELECTRON-2, Japan phase 3 study, ION-1, ION-2, SIRIUS
- Primary efficacy endpoint: SVR12



Bourliere, AASLD, 2014, Oral #82

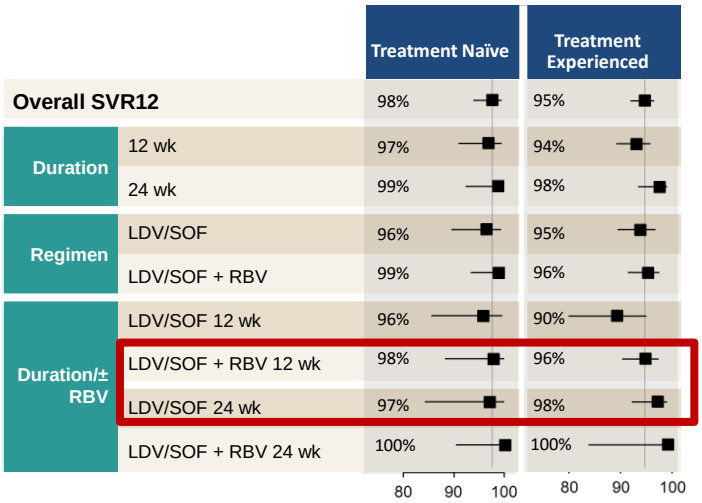
Results: SVR12 by Treatment Regimen



Among TE cirrhotic patients, 12 weeks of LDV/SOF + RBV resulted in similar SVR rates to 24 weeks of LDV/SOF alone

Bourliere, AASLD, 2014, Oral #82

Results: SVR12 by Treatment Regimen



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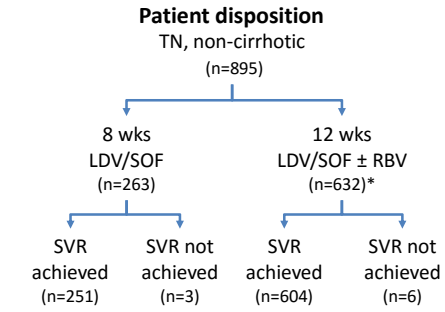
Bourliere, AASLD, 2014, Oral #82

Sofosbuvir + Ledipasvir

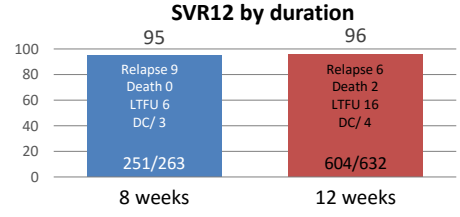
- A single tablet
- Cures most G1 in 8 weeks – side effect free
- Cures cirrhosis in 12 weeks
  (needs ribavirin, some side effects)

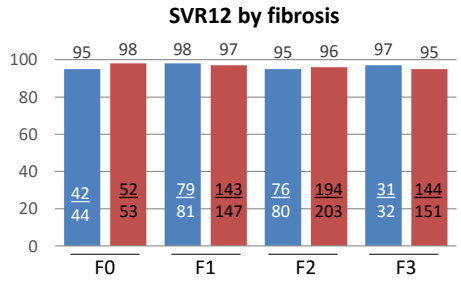
Real-world experience from the TRIO Network:

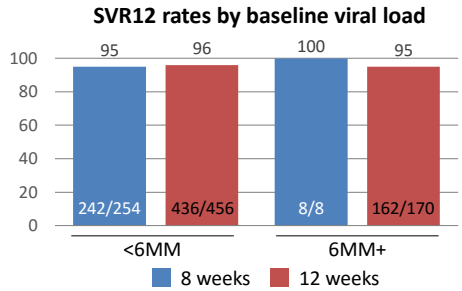
Effectiveness of 8 or 12 week LDV/SOF in treatment-naive patients with non-cirrhotic, G1 HCV



*21 Patients were on 12 weeks of LDV/SOF+RBV







Curry M, et al. AASLD 2015, San Francisco. #1046

Real-world experience from the TRIO Network:
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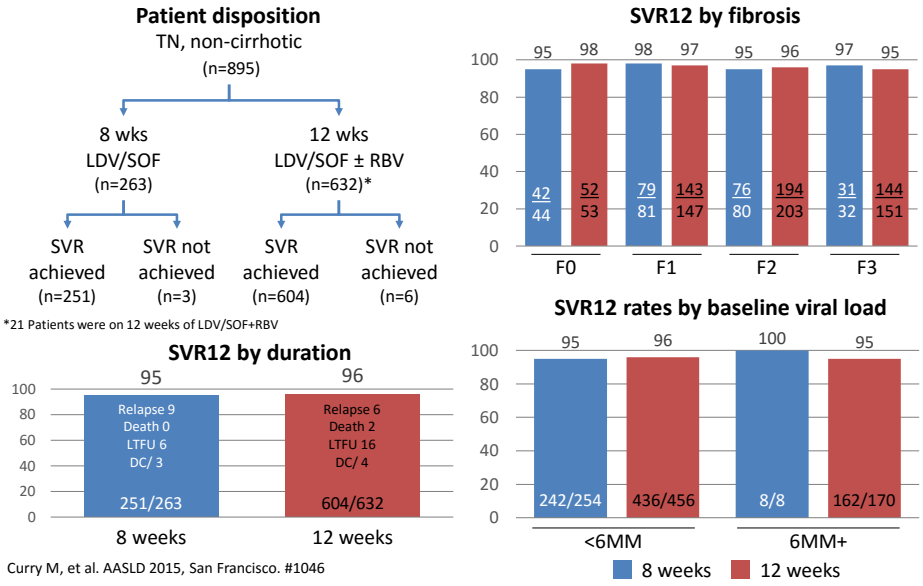


Curry M, et al. AASLD 2015, San Francisco. #1046

Protease based regimens

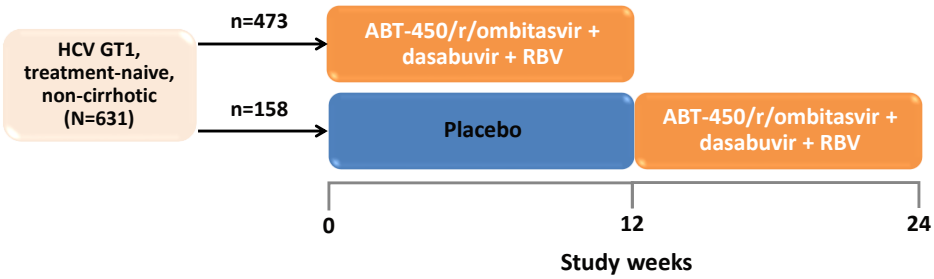
- Potent protease plus 1 or 2 drugs

Two options:-

- Paritaprevir/Ombitasvir + Dasabuvir
- OR
- Grazoprevir/elbasvir

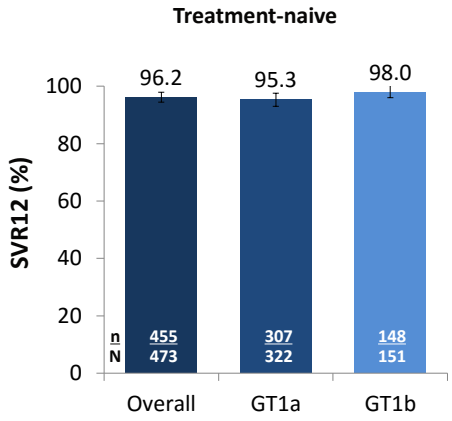
SAPPHIRE-I: GT1 treatment-naive patients

- ABT-450/r/ABT-267 (ombitasvir) + ABT-333 (dasabuvir) + RBV



- ABT-450/r/ombitasvir = 150/100/25 mg QD co-formulated; dasabuvir = 250 mg BID; RBV = 1000–1200 mg weight-based BID.
- Feld JJ, *et al NEJM 2014:370:1594*].

SAPPHIRE-I: GT1 treatment-naive patients — SVR12 rates by HCV GT1 subtype

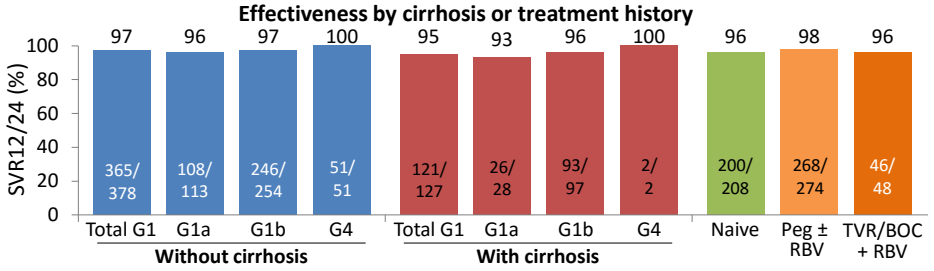


Error bars: 95% CI.

AbbVie Regimes

- For naïve 1a patients (+/- cirrhosis):-
  12 weeks '3D' with ribavirin
- For naïve 1b patients (- cirrhosis)
  12 weeks '3D' without ribavirin
  (add ribavirin for cirrhosis)
- For experienced patients with cirrhosis extend for 24 weeks in 1a non-responders

Real-world safety and effectiveness of OBV/PTV/r with DSV and/or RBV in the **German hepatitis C Registry**

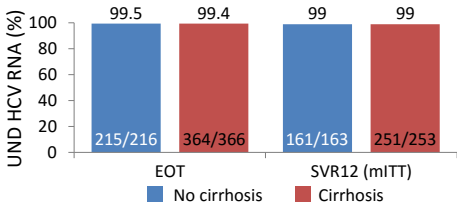


Safety, n (%)		2D/3D -RBV (n=436)	2D/3D + RBV (n=353)	2D/3D -RBV (n=44)	2D/3D + RBV (n=184)
Any AE		185 (42)	201 (57)	20 (45)	119 (65)
Any SAE		5 (1)	8 (2)	0	8 (4)
RBV dose mod.		-	26 (7)	-	18 (10)
Death		2 (0.5)	0	0	0
D/C due to AE		2 (0.5)	4 (1)	0	9 (5)
AEs in ≥5%of patients	Fatigue	80 (18)	97 (27)	8 (18)	58 (32)
	Pruritus	33 (8)	40 (11)	2 (5)	26 (14)
	Headache	35 (8)	35 (10)	5 (11)	16 (9)
	Insomnia	17 (4)	29 (8)	0	18 (10)
	Nausea	16 (4)	20 (6)	3 (7)	12 (7)
	Anemia	1 (0.2)	15 (4)	0	20 (11)

Real-world safety and effectiveness of OBV/PTV/r with DSV and/or RBV in the **German hepatitis C Registry**

Israeli experience: 3D ± RBV in G1 patients with advanced fibrosis

Virologic response: G1 cirrhosis vs no cirrhosis



Premature discontinuation of treatment

n (%)	3D ± RBV (n=23)
Patient discretion	3 (0.4)
Serious adverse event*	12 (1.8)
Liver decompensation†	8 (1.2)

*3 pts achieved SVR12; †4 pts achieved SVR12

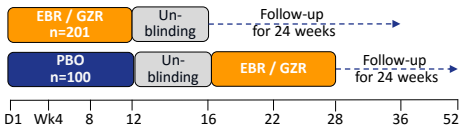
- **Predictors of decompensation**
  - **Age >75 years**, p=0.005
  - **MELD score >10**, p=0.01
  - **Previous decompensation**, p<0.001

- 3D ± RBV in real world: 95–100% SVR G1/4, including cirrhosis
- Safety and tolerance good but impact of RBV
- Not recommended for CPB & C: Risk of decompensation

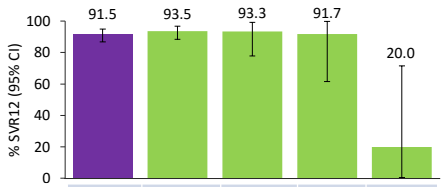
Hinrichsen H, et al. EASL 2016, Barcelona. #GS07; Zuckerman E, et al. EASL 2016, Barcelona. #PS004

C-EDGE CO-STAR: Efficacy of GZR + EBR in PWID receiving opioid agonist therapy (OAT)

- Phase 3, double-blind RCT in pts on OAT for >3 months
  - Adherence >80% of appointments
  - G 1, 4, 6, or mixed ± HIV coinfection
  - TN, 20% with cirrhosis
  - 7% HIV coinfected
  - 58% had positive DOA at Day 1 (excl. OAT)

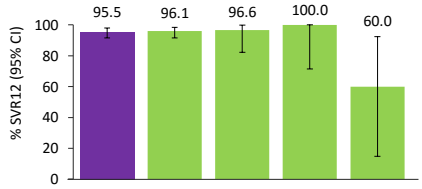


- **Efficacy: SVR12 (Full Analysis Set, FAS)**



	All	G1a	G1b	G4	G6
	184/201	144/154	28/30	11/12	1/5
Relapse	7	4	1	0	2
Reinfection	5	3	0	0	2
LTFU or non-VF d/c	5	3	1	1	0

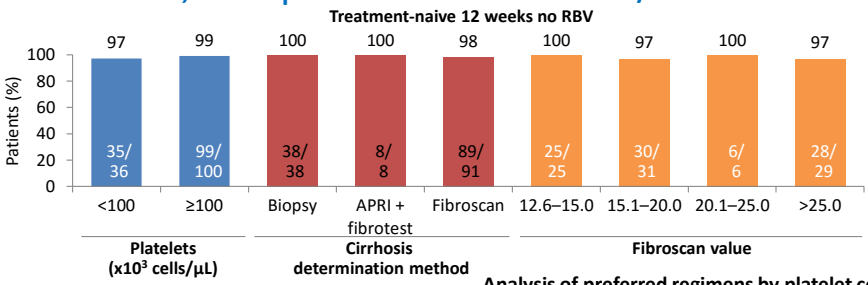
- **Efficacy: SVR12 (Modified FAS)**



	All	G1a	G1b	G4	G6
	189/198	147/153	28/29	11/11	3/5
Failures					
Relapse	7	4	1	0	2
d/c	2	2	0	0	0
Reinfection – counted as success					
	5	3	0	0	2
LTFU or non-VF discontinuation – excluded from mFAS analysis					
	3	1	1	1	0

Dore G, et al. AASLD 2015, San Francisco. #40

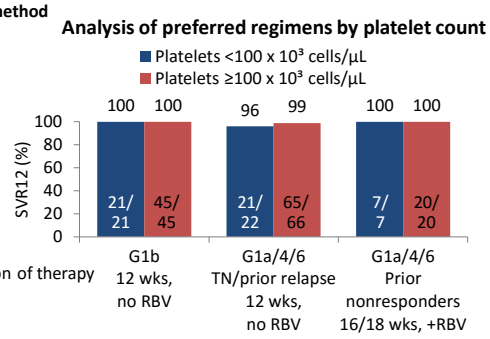
Integrated analysis of compensated cirrhotic G1, 4, or 6 pts treated with GZR/EBR



Treatment-experienced, preferred regimens

G1 TE pts SVR12, % (n/N)	12 wks no RBV (n=47)	16/18 wks + RBV (n=44)
Prior relapse	100 (10/10)	100 (11/11)
Prior nonresponder	91.9 (34/37)	100 (33/33)

- Relapsers may require only 12 wks of therapy
- Prior nonresponders appear to benefit from prolongation of therapy



Jacobson IM, et al. AASLD 2015, San Francisco. #42

Genotype 1 CURED!

- All patients with Genotype 1 can be cured with current therapies

Genotype 1
CURED!

- All patients with Genotype 1 can be cured with current therapies

- BUT
- It is not quite as simple as it seems
- Avoid PPIs with ledipasvir
- Extend therapy to 24 weeks with experienced G1a with Paritaprevir based regimens
- Consider looking for RAVs with G1a receiving Gras/Elb

HCV in 2016
A whistle stop tour

- Genotype 1

- Genotype 3

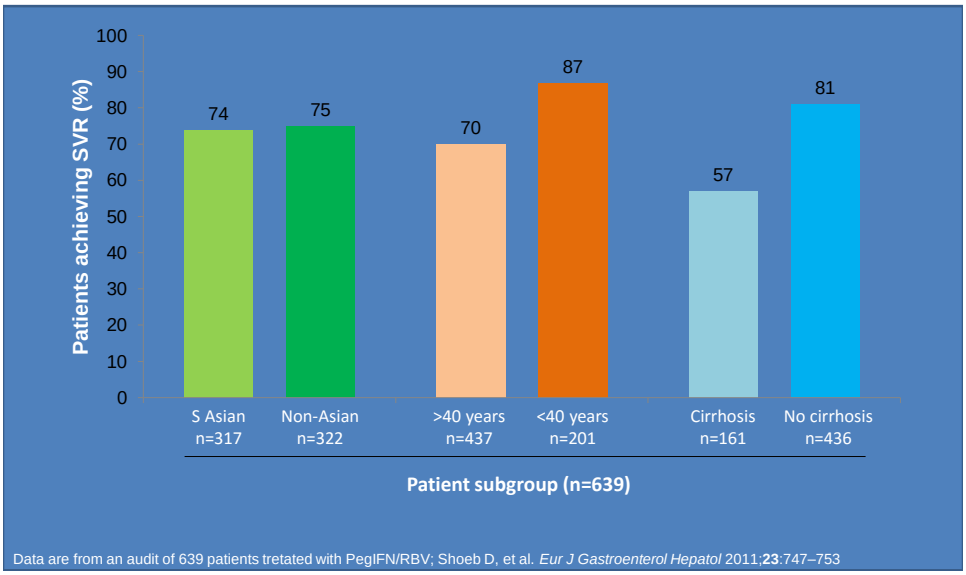
- Who to treat first

Genotype 3
A tricky customer

Non-cirrhotic is easy to cure
(even cheap IFN/Riba works)

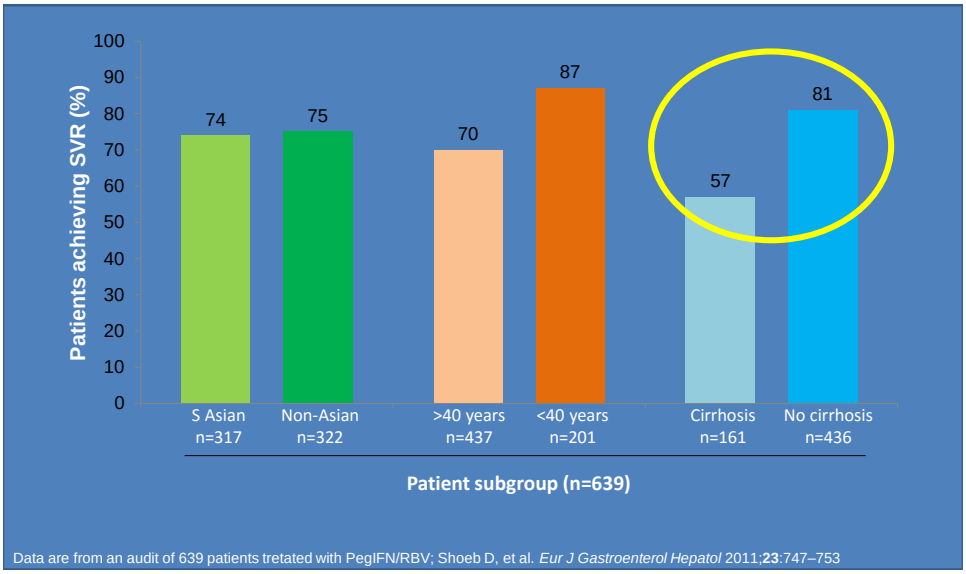
Cirrhotic is hard to cure

Genotype 3
PegIFN + Ribavirin



Data are from an audit of 639 patients tretated with PegIFN/RBV; Shoeb D, et al. *Eur J Gastroenterol Hepatol* 2011;**23**:747–753

Genotype 3
PegIFN + Ribavirin

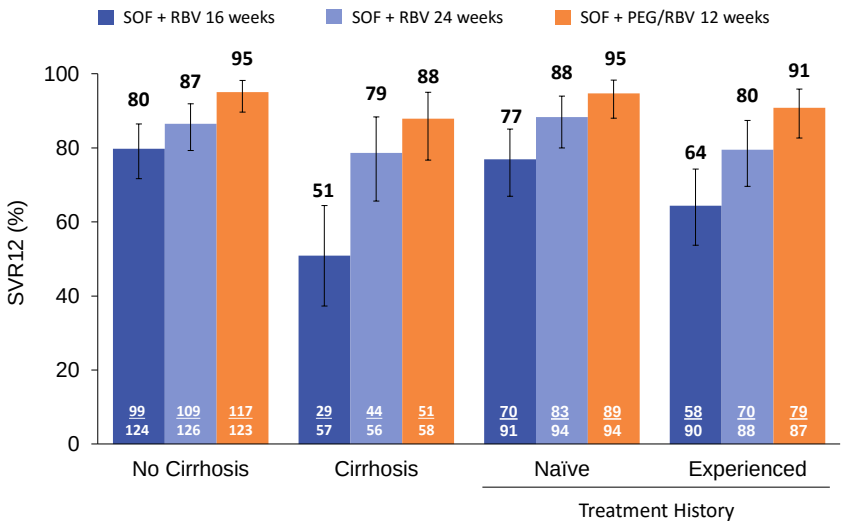


Data are from an audit of 639 patients tretated with PegIFN/RBV; Shoeb D, et al. *Eur J Gastroenterol Hepatol* 2011;**23**:747–753

Sofosbuvir in G3

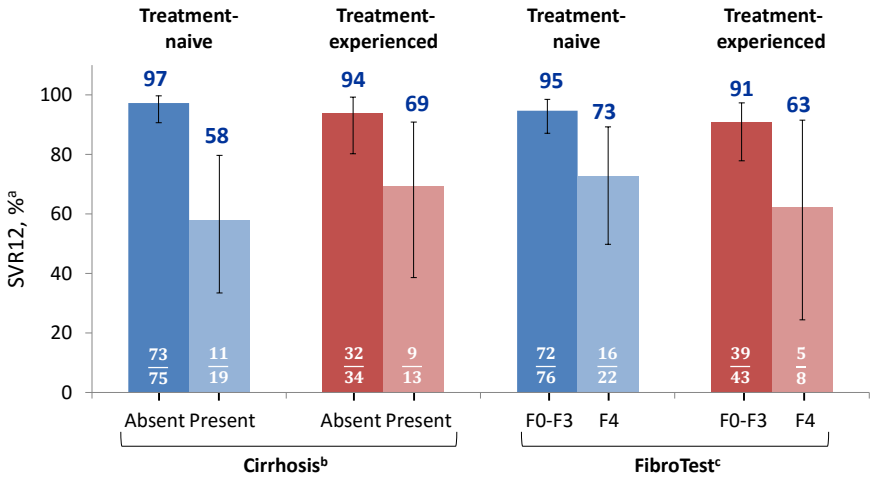
- Not quite so potent
- Needs a good friend

Results: SVR12 in GT 3



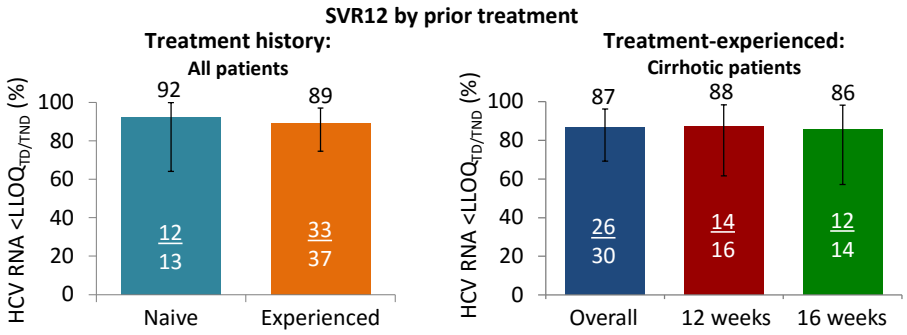
- intervals.

G3 Without Interferon



[a] HCV RNA < LLOQ (25 IU/mL); error bars reflect 95% confidence intervals.
[b] Cirrhosis determined by liver biopsy (METAVIR > F3), FibroScan (> 14.6 kPa), or FibroTest score ≥ 0.75 and aspartate aminotransferase to platelet ratio index > 2.
[c] FibroTest assessments could have been performed up to Day 1 (baseline).

ALLY-3+ Phase 3 Study: All-oral treatment with DCV + SOF + RBV for 12 or 16 weeks in HCV G3-infected patients with advanced fibrosis or cirrhosis



- Efficacious (90% SVR12) for G3 patients with advanced fibrosis or compensated cirrhosis, a population in urgent need of treatment
  - Comparable SVR12 for 12- (88%) and 16-weeks (92%)
  - No on-treatment VFs; two relapses in each treatment arm
- 100% SVR12 among patients with advanced fibrosis, 86% among patients with cirrhosis

Leroy V, et al. AASLD 2015, San Francisco. #LB-3

Genotype 3
Not quite there yet

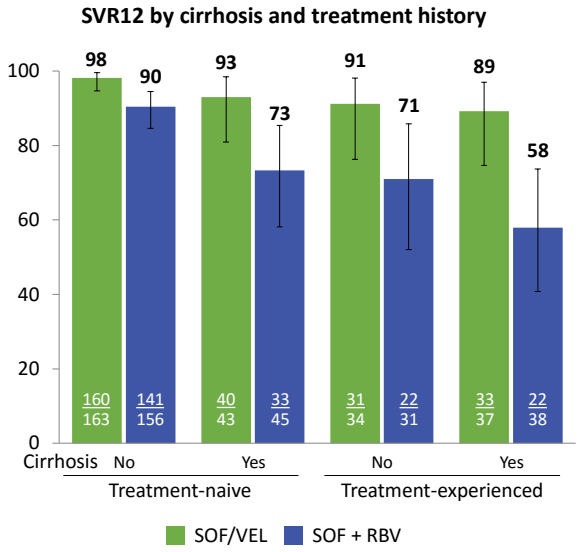
- Current regimens not quite good enough
- What about future regimens?

ASTRAL-3 Phase 3 Study: SOF/VEL FDC for 12 weeks compared to SOF + RBV for 24 weeks in G3 HCV infected patients

	SOF/VEL 12 weeks n=277	SOF + RBV 24 weeks n=275
Mean age, y (range)	49 (21–76)	50 (19–74)
Male, n (%)	170 (61)	174 (63)
White, n (%)	250 (90)	239 (87)
Mean BMI, kg/m^2 (range)	26 (17–48)	27 (17–56)
Cirrhosis, n (%)	80 (29)	83 (30)
Treatment experienced, n (%)	71 (26)	71 (26)
IL28B CC, n (%)	105 (38)	111 (40)
HCV RNA, $\log_{10}$ IU/mL (range)	6.2 (3.7–7.5)	6.3 (3.6–7.5)

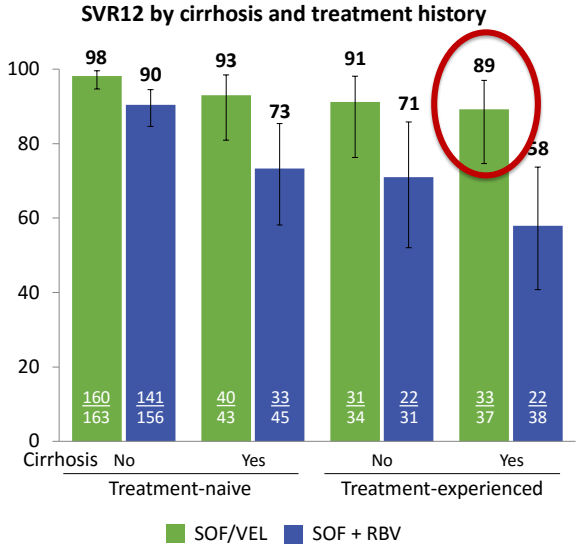
Foster GR, et al. NEJM 2015

ASTRAL-3 Phase 3 Study: SOF/VEL FDC for 12 weeks compared to SOF + RBV for 24 weeks in G3 HCV infected patients



Foster GR, et al. NEJM 2015

ASTRAL-3 Phase 3 Study: SOF/VEL FDC for 12 weeks compared to SOF + RBV for 24 weeks in G3 HCV infected patients



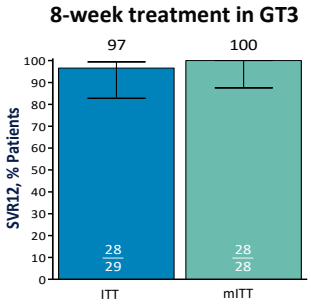
Foster GR, et al. NEJM 2015

ABT-493 + ABT-530 for 8 Weeks in Treatment-Naive HCV GT3-Infected Patients Without Cirrhosis: SURVEYOR-II

Study to explore shorter treatment duration of 8 weeks with ABT-493 + ABT-530 in treatment-naive GT3-infected patients without cirrhosis (part of SURVEYOR-II Part 2 study)

Patient demographics	N = 29
Male, n (%)	15 (52)
White race, n (%)	26 (90)
Age, mean years (range)	42 (27–66)
BMI, mean kg/m^2, ± SD	26 ± 3.8
HCV RNA, mean $\log_{10}$ IU/mL (range)	6.5 (5.0–7.5)
HCV GT3a*, n (%)	25 (86)
Baseline fibrosis stage, n (%)	
F0–F1	20 (69)
F2	2 (7)
F3	7 (24)

Targets with Baseline Variants	N = 28[†]
Any variants n (%)	13 (46)
Both NS3 and NS5A variants, n	1
NS3 only, n	2
NS5A only, n	10

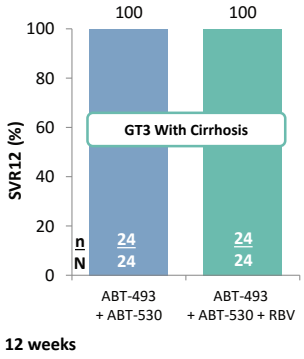


*Subgenotype was not determined for 3 patients; †Sequencing results pending for 1 patient;
‡1 patient withdrew consent after treatment week 6 due to intolerance of blood draws and had undetectable HCV RNA at the time of d/c.

Muir AJ, *et al. J Hepatol* 2016; **64**(Suppl 2):S186 (oral presentation).

ABT-493 + ABT-530 ± RBV for 12 Weeks in Treatment-Naive HCV GT3-Infected Patients With Cirrhosis: SURVEYOR-II

Part of SURVEYOR-II, an open-label, multicenter phase 2 trial evaluating the safety and efficacy of co-administered ABT-493 and ABT-530 ± RBV for GT3 infection in treatment-naive patients with compensated cirrhosis (12 weeks)



Event	ABT-493 + ABT-530 (N = 24)	ABT-493 + ABT-530 + RBV (N = 24)
Serious AE, n (%)	1 (4)*	2 (8)†
AE leading to study d/c, n	0	0
ALT, grade ≥2 (> 3 x ULN), n	0	0
AST, grade ≥2 (> 3 x ULN), n	0	0
Total bilirubin, n		
Grade 2	1	7
Grade 3	1‡	0
Hemoglobin, n		
Grade 2	0	1

No ALT elevations

* Tibia fracture on PT Day 15 (assessed as unrelated to study drug);
† Anemia on Day 30 (assessed as possibly related to RBV);
delusional disorder on PT Day 3 (assessed as possibly related to ABT-493, ABT-530 and RBV following admitted amphetamine and alcohol use the same day);
‡ Patient with elevated baseline bilirubin had grade 3 total bilirubin elevation on Day 44 that resolved post treatment.

Kwo P, *et al. J Hepatol* 2016; **64**(Suppl 2):S208 (oral presentation).

G3 Cirrhosis – Still a problem with nucleotides

- Sofosbuvir + NS5A inhibitors are not perfect in G3 cirrhosis
- New protease based regimens may be required

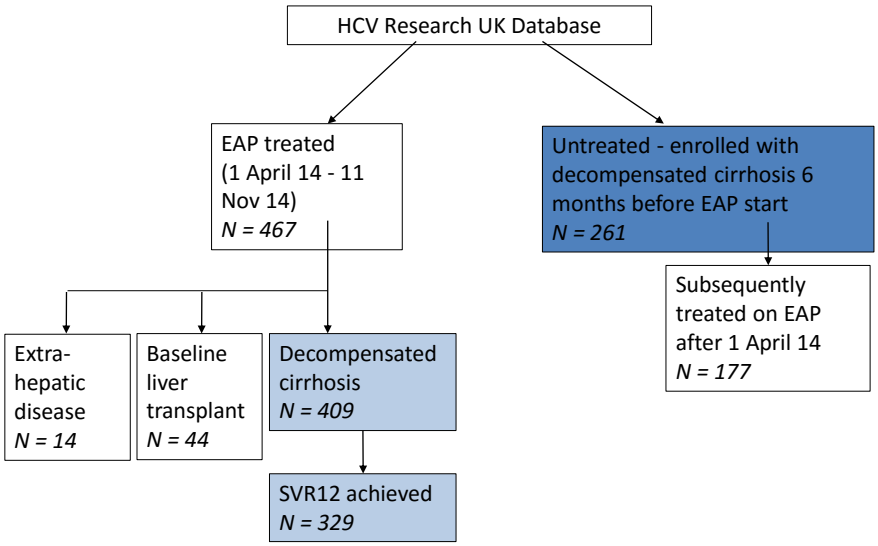
HCV in 2016
A whistle stop tour

- Genotype 1
- Genotype 3
- Who to treat first

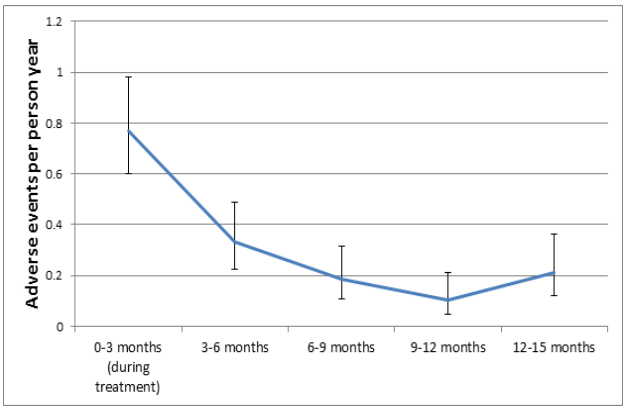
We can't treat everyone now!

- There needs to be some prioritisation
- For now it is easy – prioritise the sick
- Once we have treated the sick…….

English Early Access Programme Long term follow up

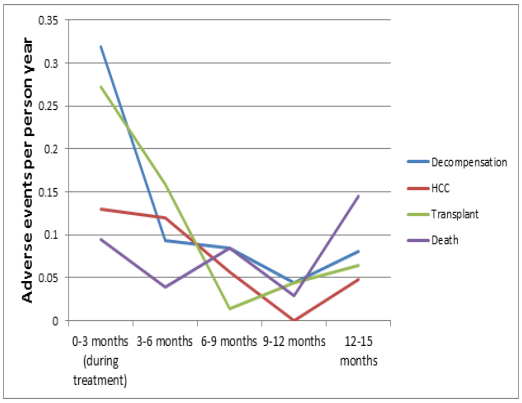


Adverse Events Over Time for Virological Responders- 15 months



Adverse events were most frequent during treatment and decreased with time

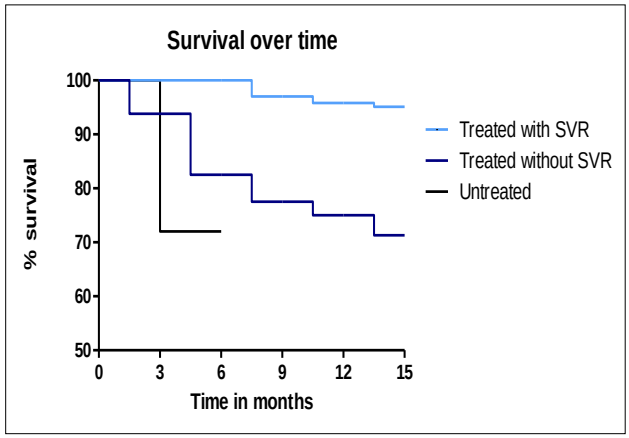
Adverse Events Over Time for Virological Responders- 15 months



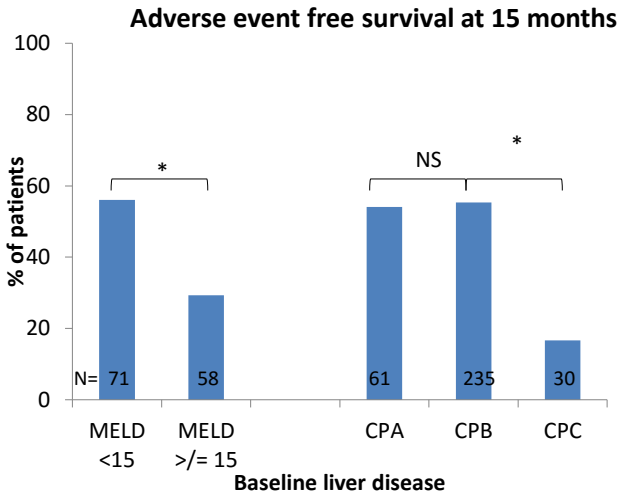
Overall in 329 patients over 15 months:

- Decompensation 21.3% (n=70)
- HCC 6.4% (21)
- Liver transplant 12.2% (40)
- Deaths 4.9% (16)

Survival - Improved in SVR patients over non-SVR



Which Patients Benefit from Viral Clearance?



* p< 0.05

Impact of focussed HCV programme

Who to treat next……

- Once the cirrhotics have been treated who is next in line……..

HCV Therapy in 2016

- Most patients can be cured
- Therapy is not quite as easy as it appears
- The challenge now is to deliver