TREATMENT OF PATIENT WITH GENOTYPE 3 HCV

Andy Ustianowski
Manchester, UK

Outline

- What is special about G3?
- Treatment:
  - What are the options?
  - What is the data?
  - What do guidelines say?

HCV GT-3 compared with other genotypes

HCC, hepatocellular carcinoma; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response.

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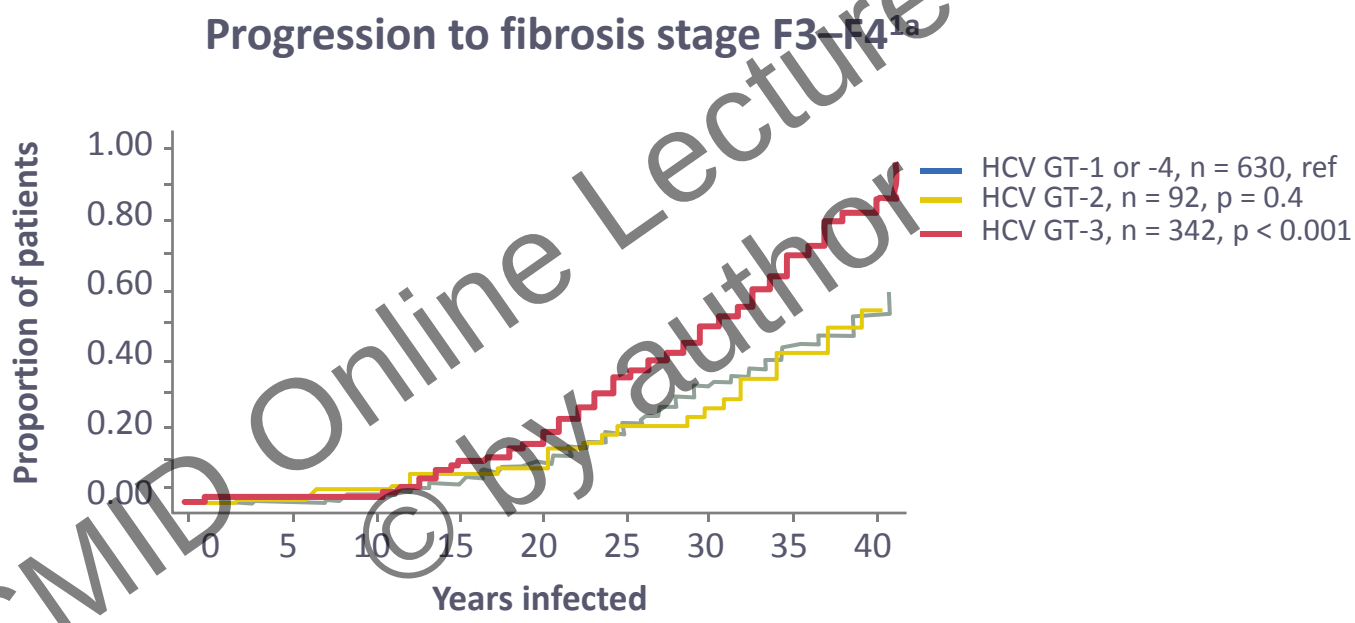
HCV GT-3 is associated with rapid fibrosis progression



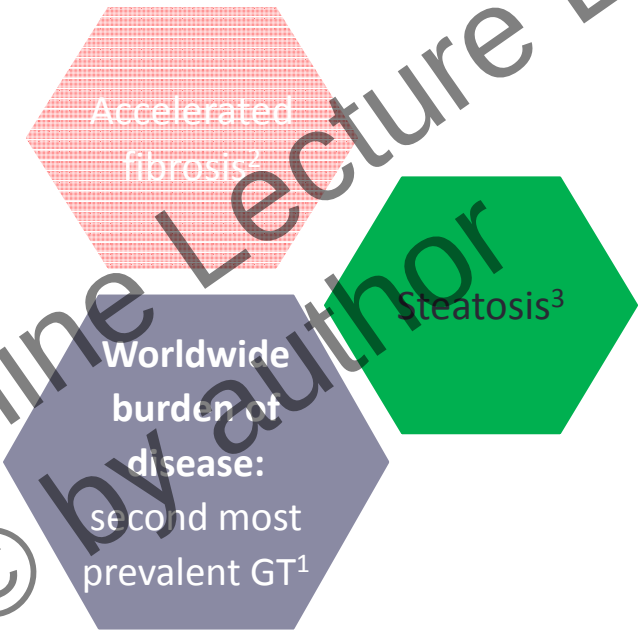
- Maximum likelihood estimation showed GT-3 to be robustly associated with accelerated fibrosis progression compared with other genotypes[1]
- The cytopathic effect of steatosis induced by HCV GT-3 infection is thought to be a major contributor to the accelerated fibrogenesis observed in these patients[2,3]

[a]Markov modelling of biopsies and genotypes in 1189 Swiss patients with HCV.

Figure adapted from: 1. Bochud PY, et al. J Hepatol 2009;51:655–66.

2. Tapper EB, Afdhal NH. J Viral Hepat 2013;20:669–77. 3. Leandro G, et al. Gastroenterology 2006;130:1636–42.

HCV GT-3 compared with other genotypes



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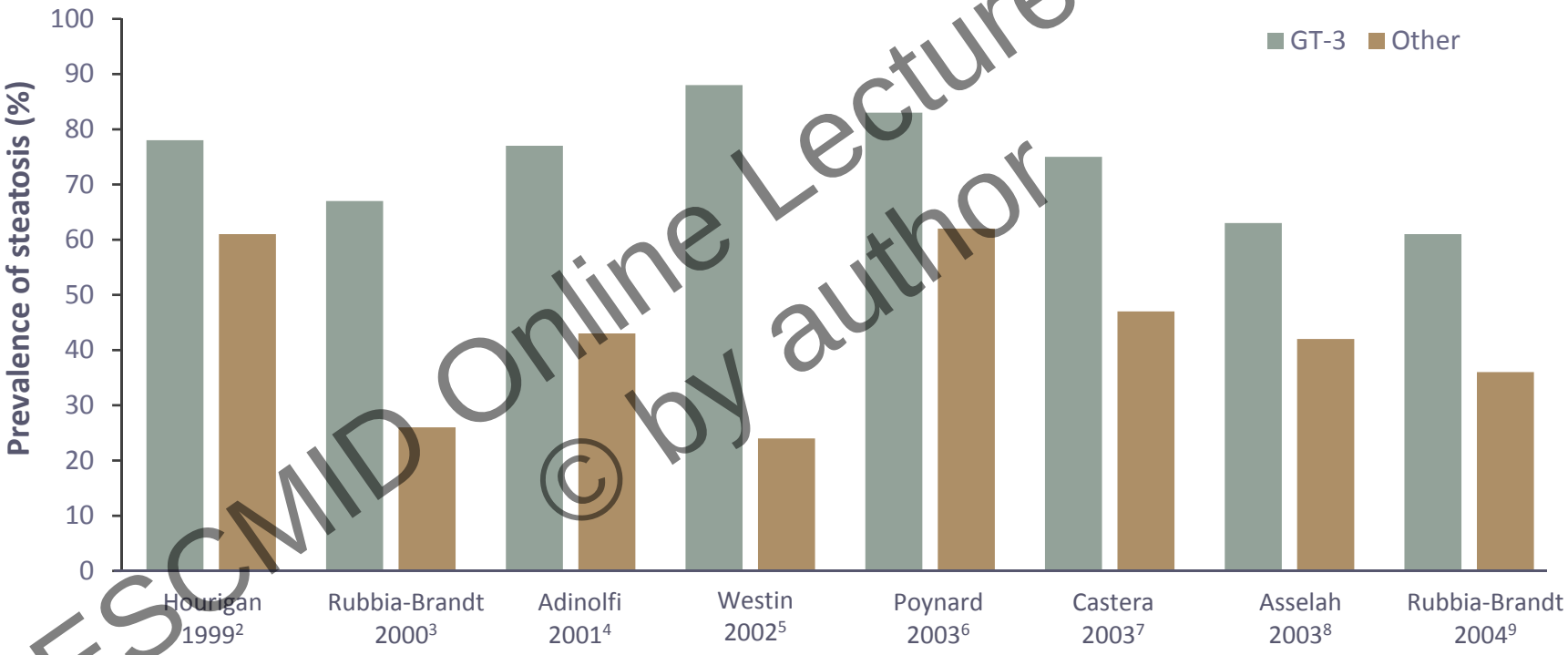
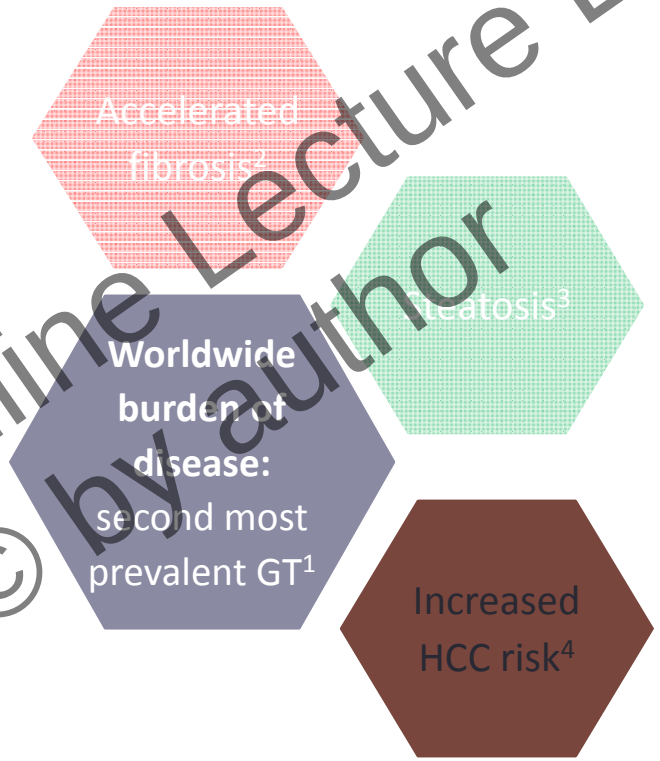
HCV GT-3 is more commonly associated with steatosis than other genotypes[1]



- Steatosis may be responsible for accelerated fibrosis progression and lower SVR[1]
- An analysis of 14 studies from 1997 to 2004, steatosis was reported in 73% (501/685) of patients with GT-3 HCV and in 50% (1468/2932) of patients with non-GT-3 HCV infection[1]

Figure adapted from 1. Asselah T, et al. Gut 2006;55:123. 2. Hourigan LF, et al. Hepatology 1999;29:1215–9. 3. Rubbia-Brandt L, et al. J Hepatol 2000;33:106–15. 4. Adinolfi LE, et al. Hepatology 2001;33:1358–64. 5. Westin J, et al. J Hepatol 2002;37:837–42. 6. Poynard T, et al. Hepatology 2003;38:75–85. 7. Castéra L, et al. Gut 2003;52:288–92. 8. Asselah T, et al. Gut 2003;52:1638–43. 9. Rubbia-Brandt L, et al. Gut 2004;53:406–12.

HCV GT-3 compared with other genotypes



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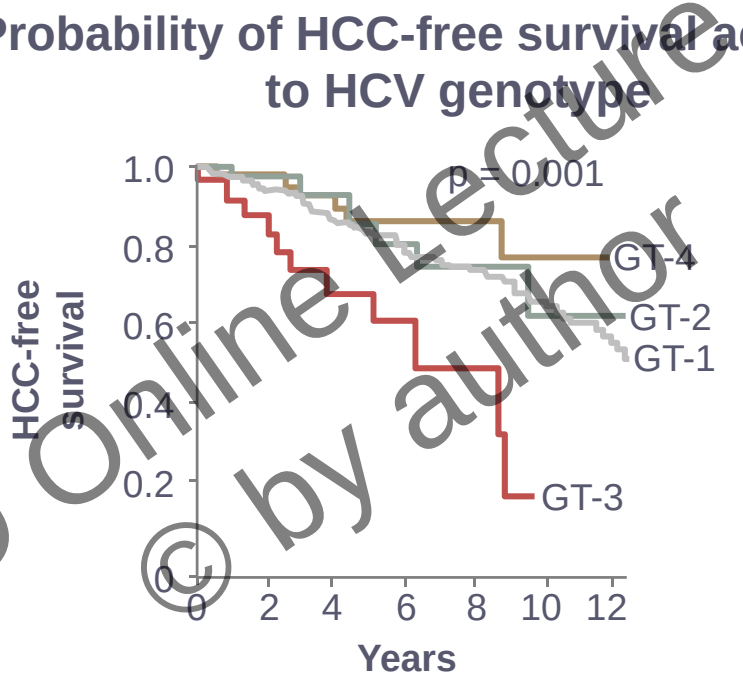
HCV GT-3 is associated with increased risk of HCC in patients with cirrhosis



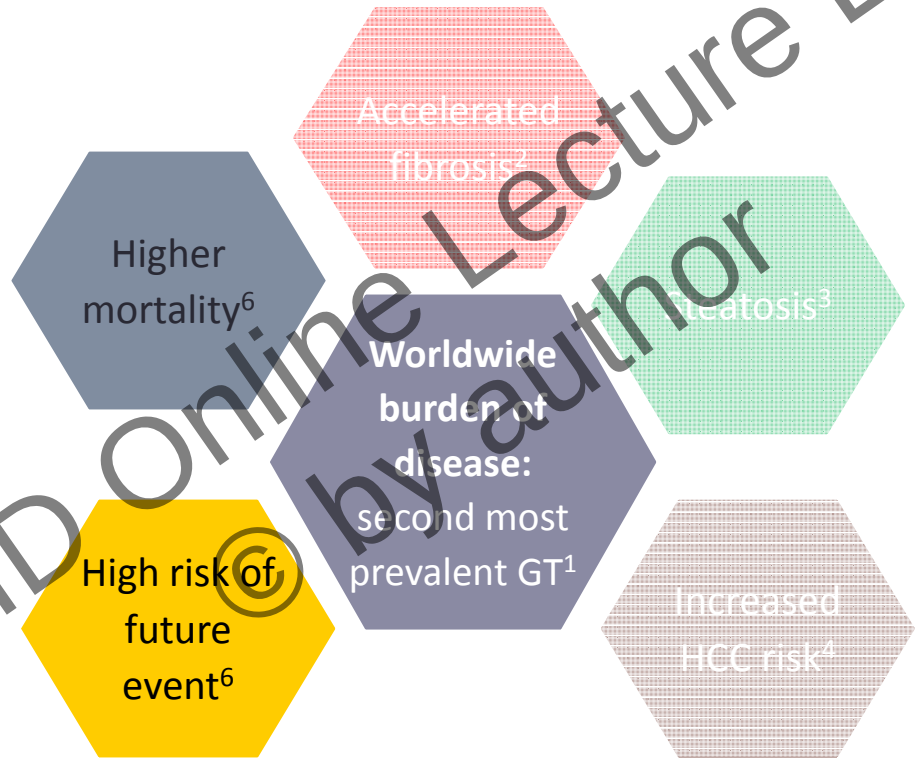
Higher incidence of HCC seems to be independent of well-known risk factors, including grade of steatosis

- Steatosis was more frequent in GT-3 patients, but its grade was not associated with HCC development

Retrospective study of 353 patients with cirrhotic HCV in France, prospectively followed and screened for HCC between 1994 and 2007. Log-rank test and Cox model were used to compare the actuarial incidence of HCC between genotype subgroups.

Adapted from Nkontchou G, et al. J Viral Hepat 2011;18:e516–22.

HCV GT-3 compared with other genotypes



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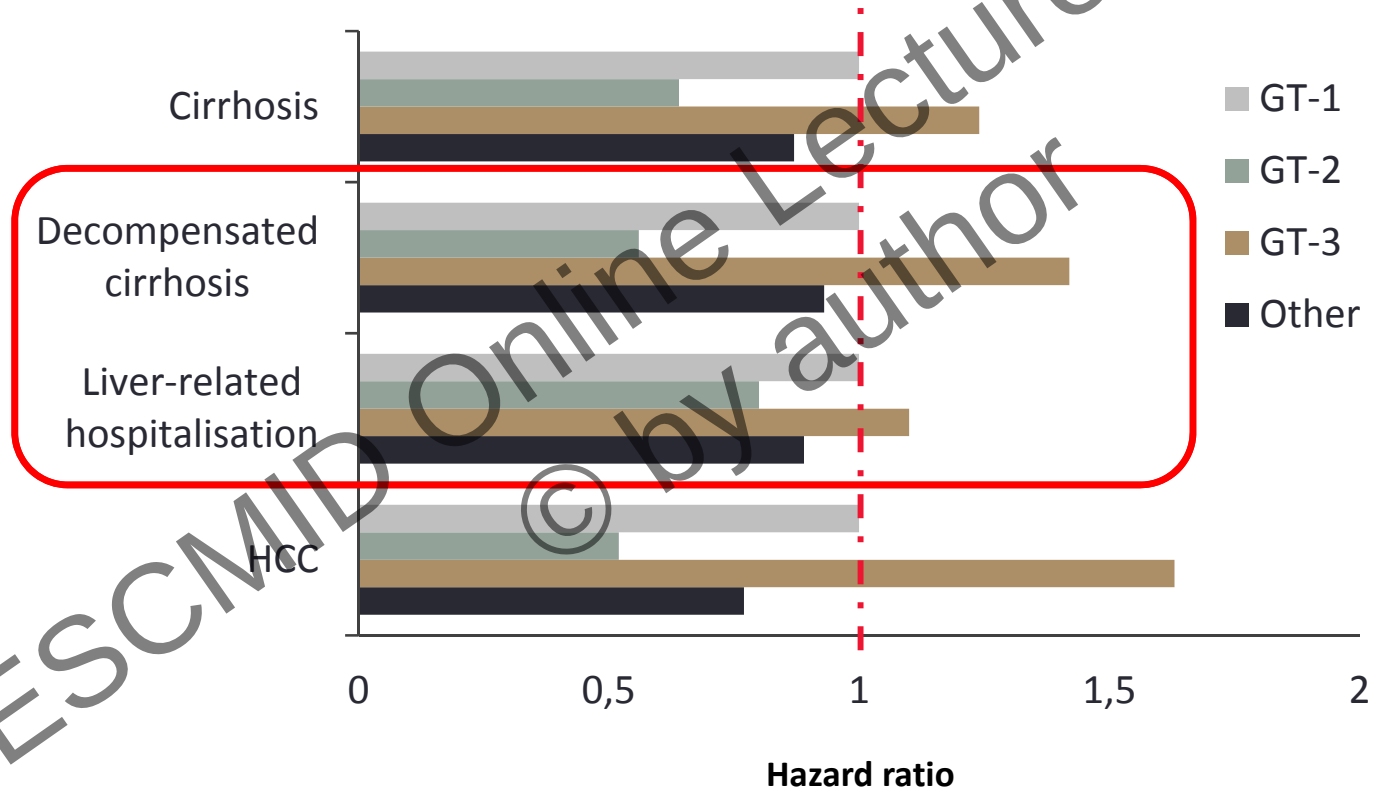
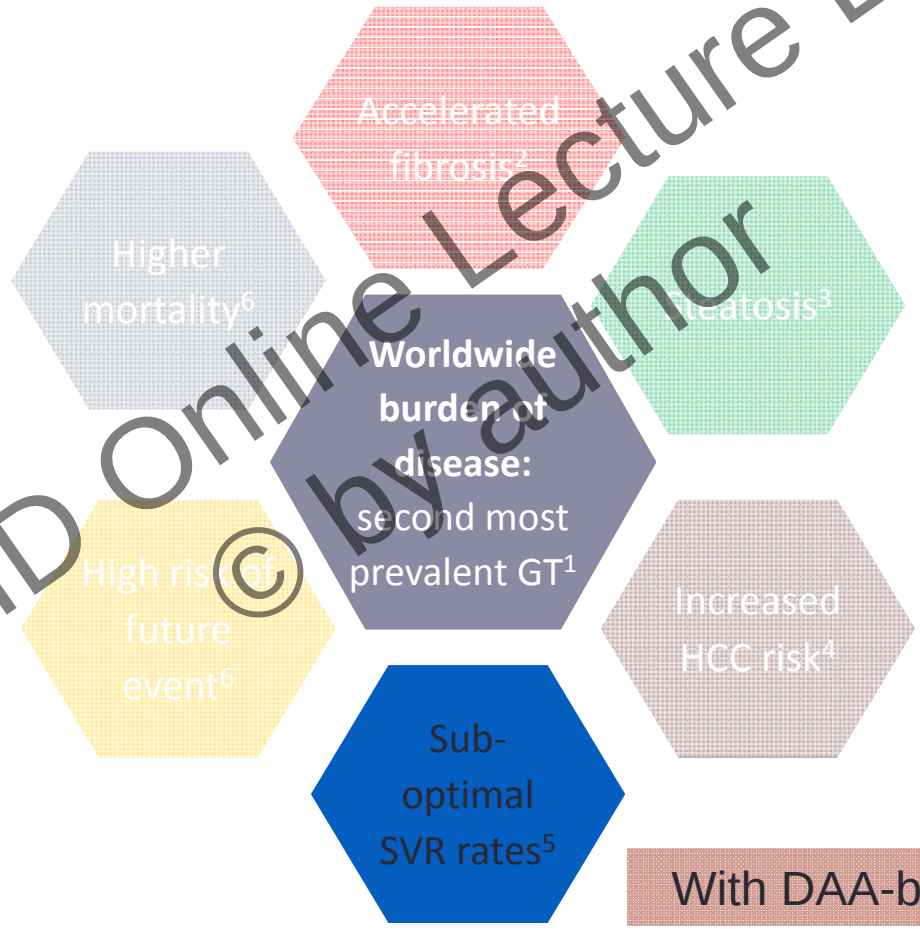
HCV GT-3 patients are at a higher risk for late-stage liver disease events and death



Observational cohort study of 28,769 patients with HCV from the VA CCR, which compiled electronic medical records data from 1999 to the present.
CCR, HCV clinical registry; VA, Veterans Affairs.
Adapted from McCombs J, et al. JAMA Intern Med 2014;174:204–12.

HCV GT-3 compared with other genotypes



With DAA-based therapies

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The ‘hard to treat’ genotype with the highest ‘unmet medical need’ has became G3

JOURNAL OF VIRAL HEPATITIS

Journal of Viral Hepatitis, 2013, **20**, 669–677 doi:10.1111/jvh.12168

REVIEW

Is 3 the new 1? perspectives on virology, natural history and treatment for hepatitis C genotype 3

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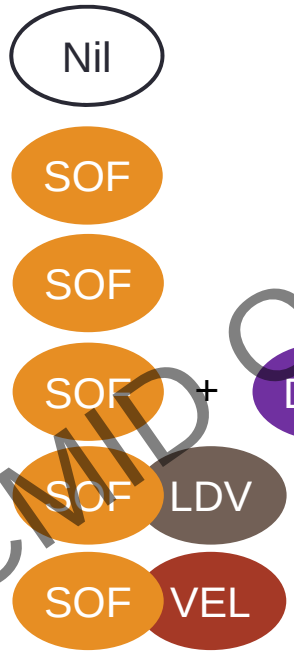
Received July 2013; accepted for publication July 2013

Theoretically: Regimens for G3……



PEG-IFN + RBV

+ PEG-IFN + RBV

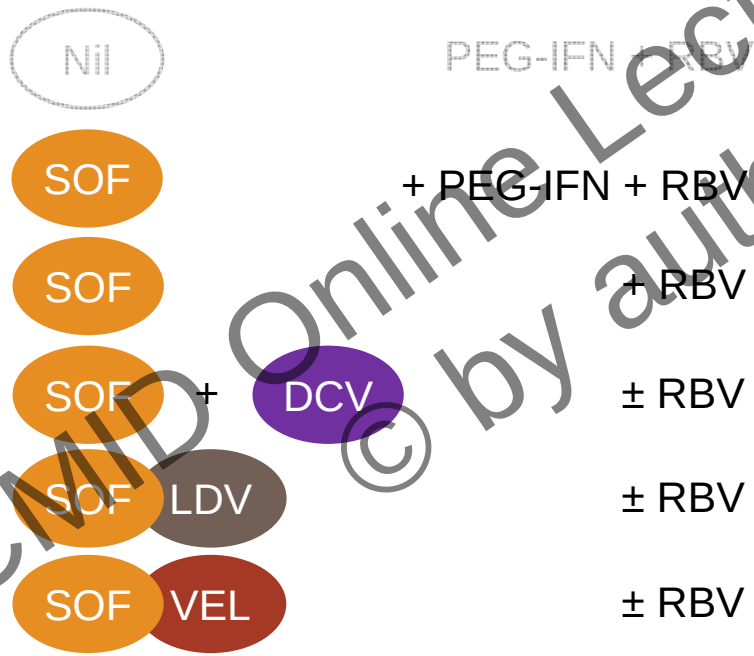
+ RBV

± RBV

± RBV

± RBV

Theoretically: Regimens for G3…



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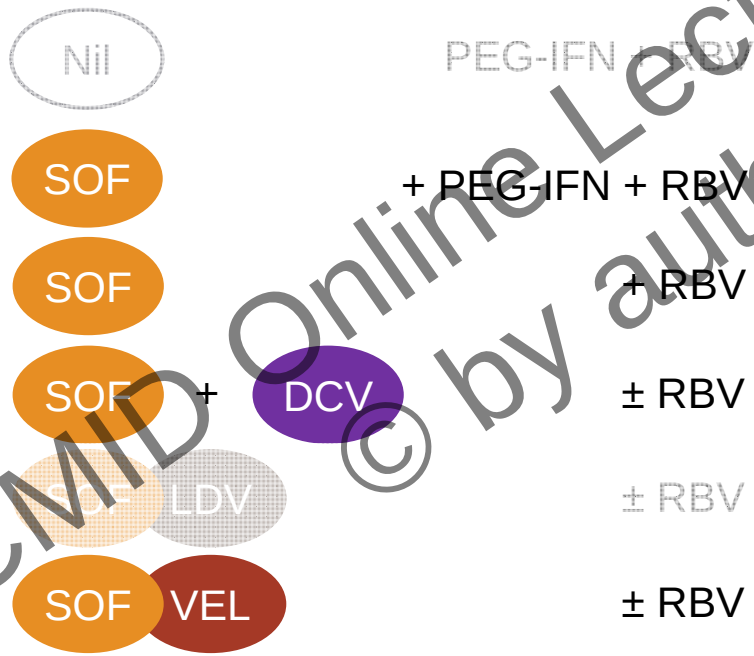
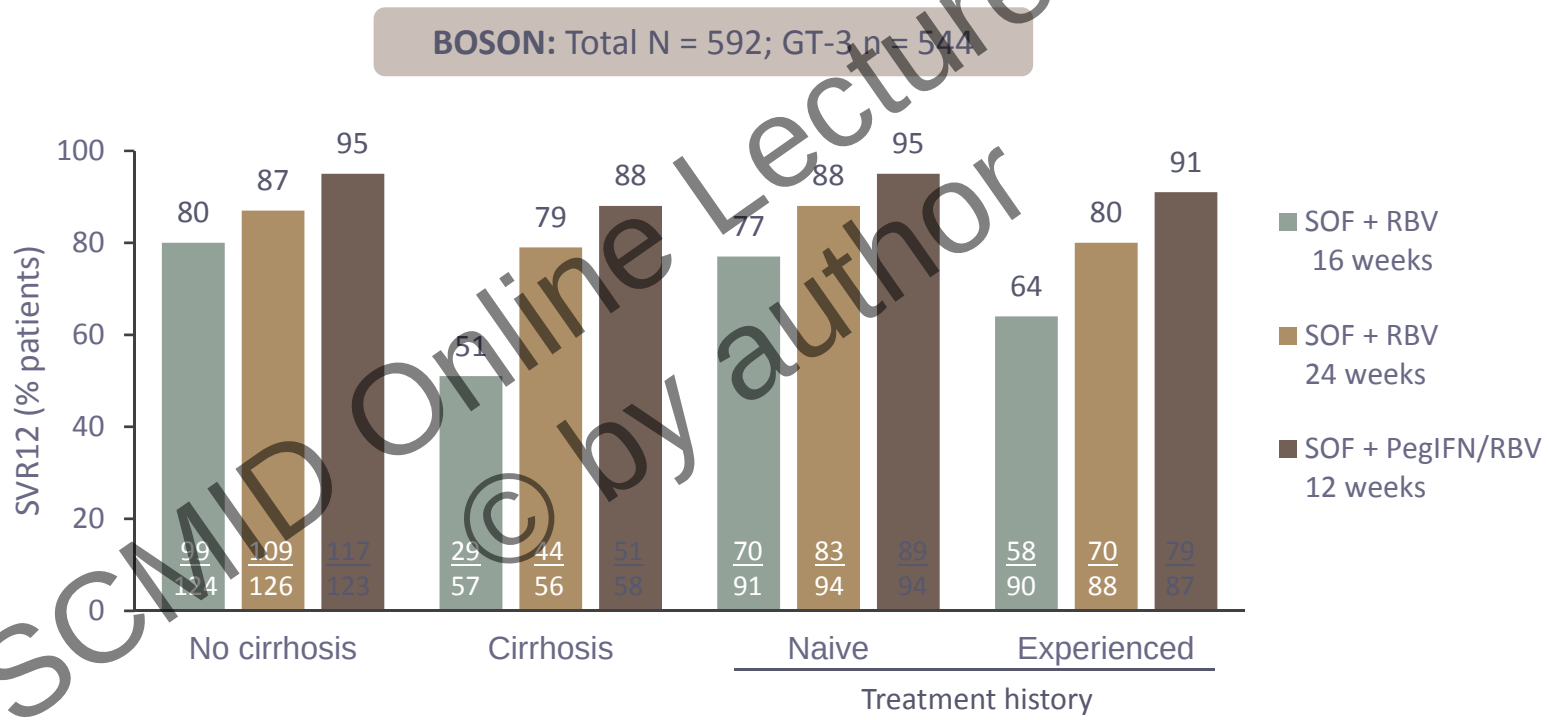


SVR12 with SOF+RBV or SOF+PegIFN/RBV in GT-3 (BOSON)



Tx discontinuations and AE: DC due to AEs (overall population) SOF + RBV 16 weeks 2 (2%); SOF + RBV 24 weeks 2 (1%) and

12%)
7%) and rash (14%)
ausea (25%), rash (20%), influenza-like illness (19%),

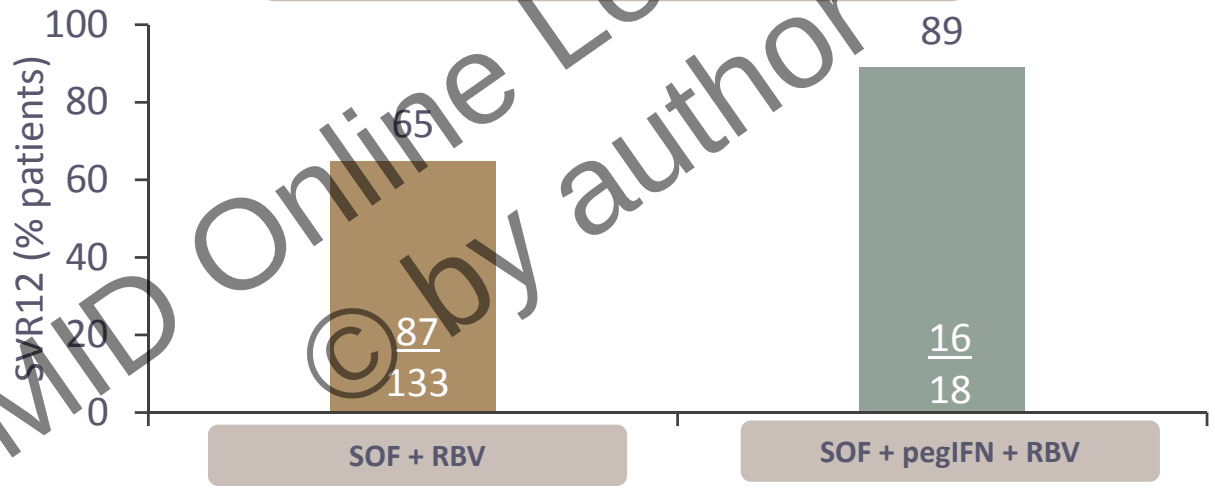
So: it looks like…

- 16 weeks of SOF/R not as good as 24 weeks
- 24 weeks SOF/R not as good as 12 weeks SOF & P/R

Adatpted from Foster G, et al. Presented at EASL 2015; Abstract L05.

SOF+RBV also not as good in US and EU real-life data in GT-3

HCV TARGET registry:
n = 322 GT-3 and -4 patients
GT-3 cohort: n = 247[a]



Tx discontinuations and AE:

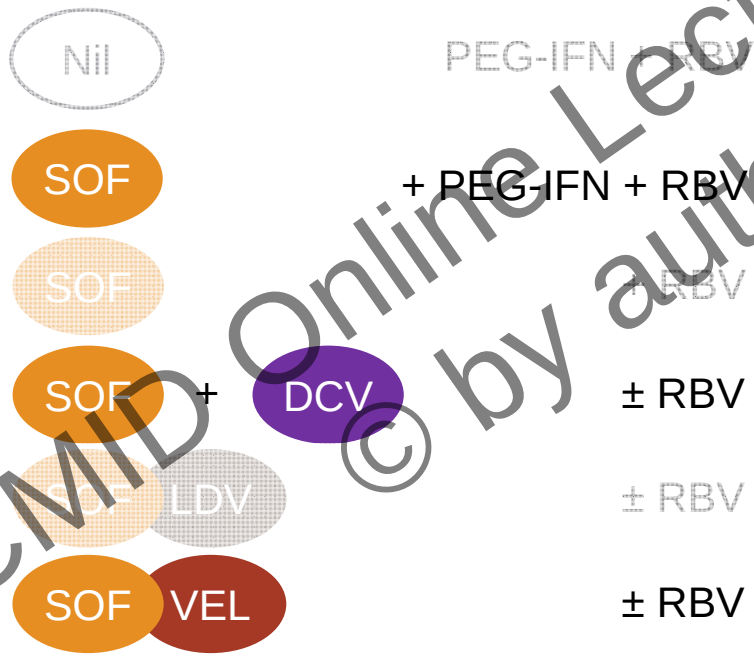
DC due to AE: SOF + RBV (3%); SOF + pegIFN + RBV (0%)

AEs in > 10% of patients: SOF + RBV – fatigue (43%), influenza-like illness (29%), rash (24%), headache (19%) and anaemia (19%)

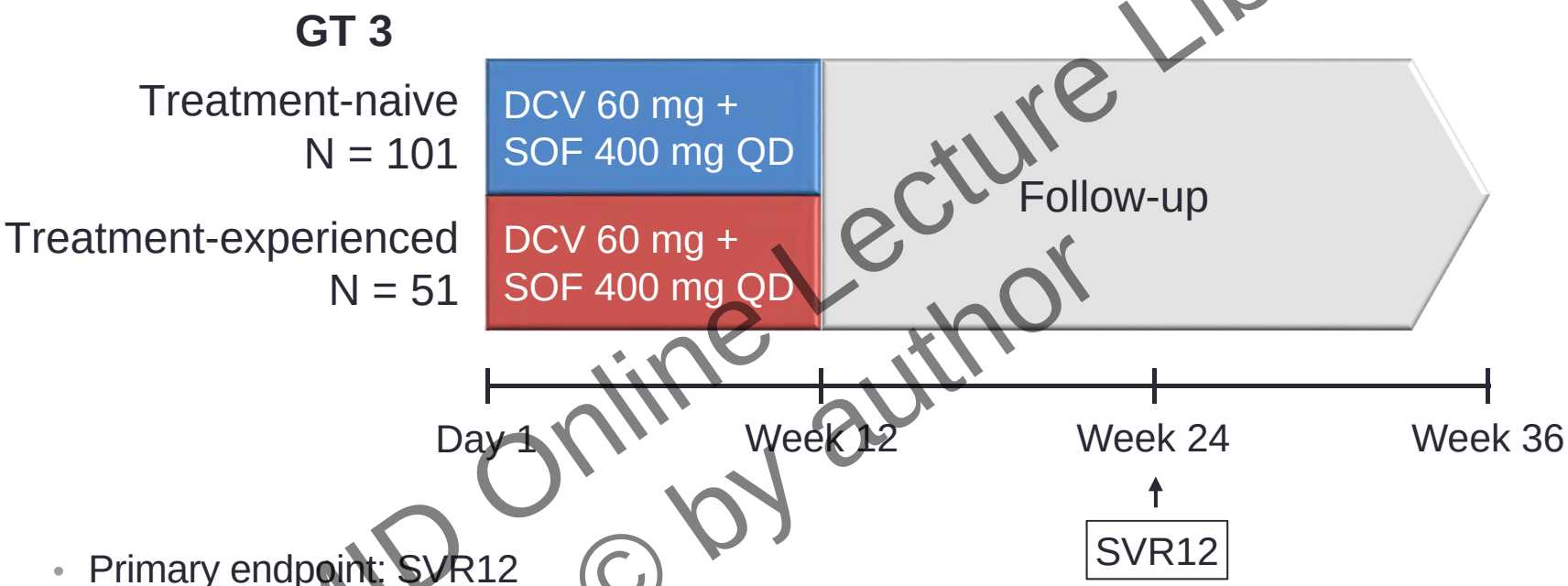
SOF + pegIFN + RBV – fatigue (37%), anaemia (22%), headache (20%), nausea (16%), insomnia (15%), depression (12%) and influenza-like illness, rash and dyspnoea (11% each)

[a]92% SOF + RBV; 47% treatment-experienced; 52% cirrhotic (24% advanced cirrhosis), MELD score (median) = 8–10.
HCV-TARGET, a consortium of more than 50 academic and community medical centres in the US, Canada and Germany.
Adapted from Alqahtani S, et al. Presented at EASL 2015; Abstract P0840.

Regimens for G3….



ALLY-3



- Primary endpoint: SVR12
  - HCV RNA < lower limit of assay quantitation (LLOQ) at posttreatment Week 12[a]
- Eligible patients
  - Age ≥ 18 years with chronic GT 3 infection and HCV RNA ≥ 10,000 IU/mL
  - Treatment-naive or -experienced (prior treatment failures), including patients with cirrhosis
  - Those who received prior treatment with NS5A inhibitors were excluded

[a] Assessed using the Roche HCV COBAS TaqMan Test v2.0 (LLOQ 25 IU/mL).

Adapted from: Nelson D, et al. Hepatology 2015;61:1127–35.

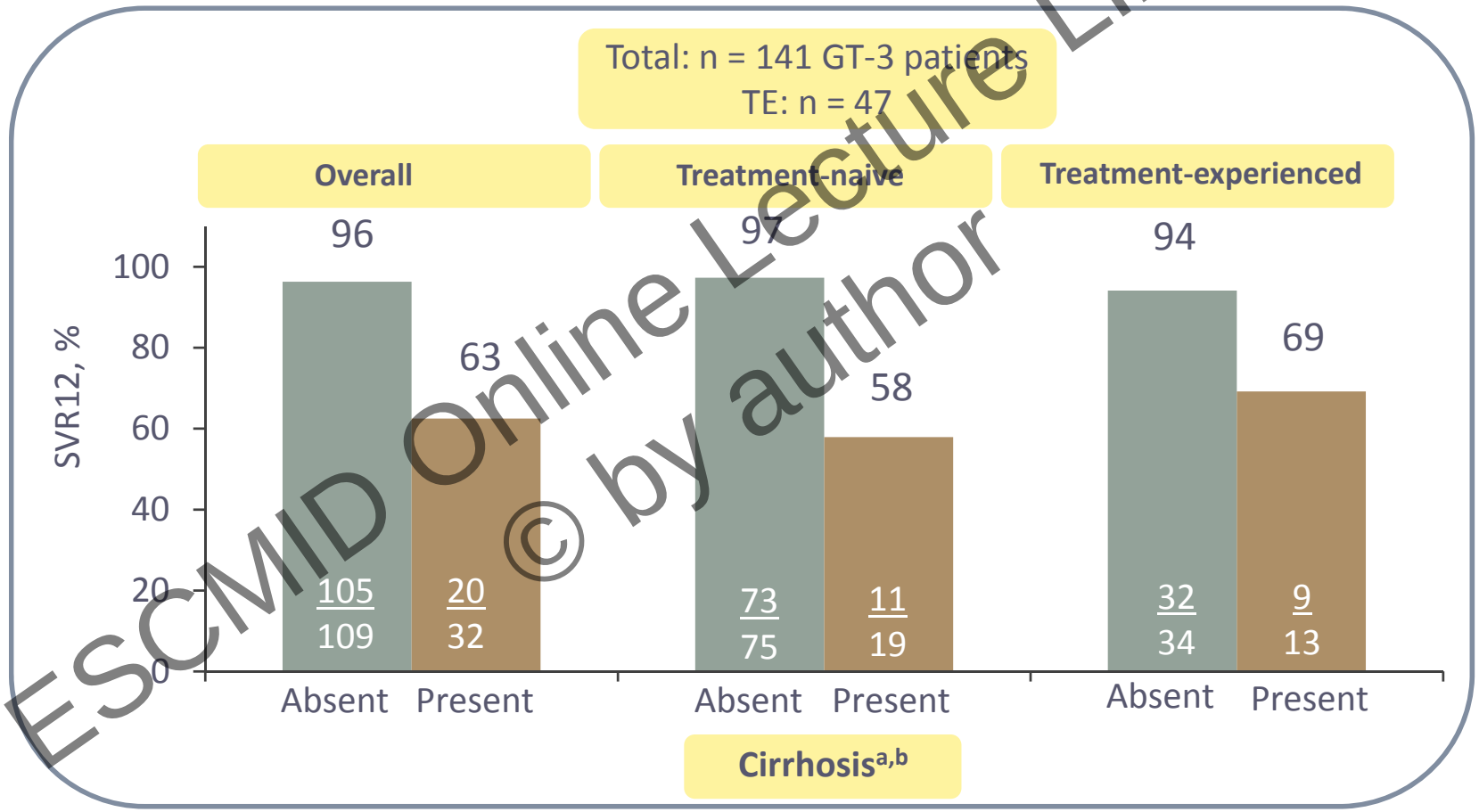
ALLY-3: Baseline demographics

Parameter	Treatment-Naive (N = 101)	Treatment-Experienced[a] (N = 51)
Age, median years (range)	53 (24-67)	58 (40-73)
Male, n (%)	58 (57)	32 (63)
Race, n (%)		
White	92 (91)	45 (88)
Black	4 (4)	2 (4)
Asian	5 (5)	2 (4)
Other	0	2 (4)[b]
HCV RNA, n (%)		
< 800,000 IU/mL	31 (31)	13 (25)
≥ 800,000 IU/mL	70 (69)	38 (75)
Cirrhosis, n (%)[c]	19 (19)	13 (25)
IL28B genotype, n (%)		
CC	40 (40)	20 (39)
Non-CC	61 (60)	31 (61)
Prior treatment failure, n (%)		
Relapse	–	31 (61)
Null response	–	7 (14)
Partial response	–	2 (4)
Other (intolerant, VBT)	–	11 (22)

[a] Patients who previously failed treatment with sofosbuvir (n = 7) or alisporivir (n = 2) were included.
[b] American Indian/Alaska native.
[c] Cirrhosis determined by liver biopsy (METAVIR F4; n = 14), FibroScan (> 14.6 kPa, n = 11), or FibroTest score ≥ 0.75 and APRI (aspartate aminotransferase to platelet ratio index) > 2 (n = 7).
VBT, virologic breakthrough.

Adapted from: Nelson D, et al. Hepatology 2015;61:1127–35.

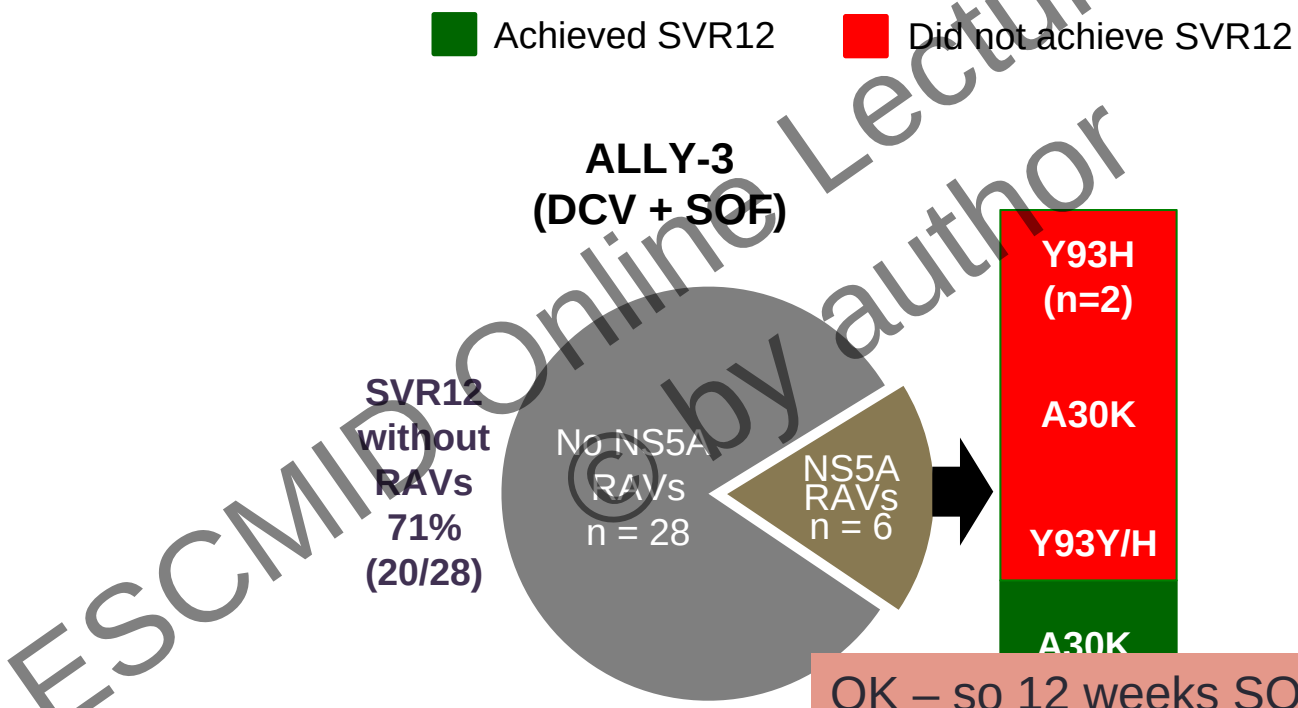
DCV + SOF, 12 weeks without RBV (ALLY-3)



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 > 2.
[b] Cirrhosis status for 11 patients was missing or inconclusive (FibroTest score > 0.48 to < 0.75 or APRI > 1 to ≤ 2).
APRI, aspartate aminotransferase to platelet ratio index.
Adapted from: Nelson D, et al. Hepatology 2015;61:1127–35.

ALLY-3 post hoc analysis: NS5A RAVs at baseline and failure in patients with cirrhosis



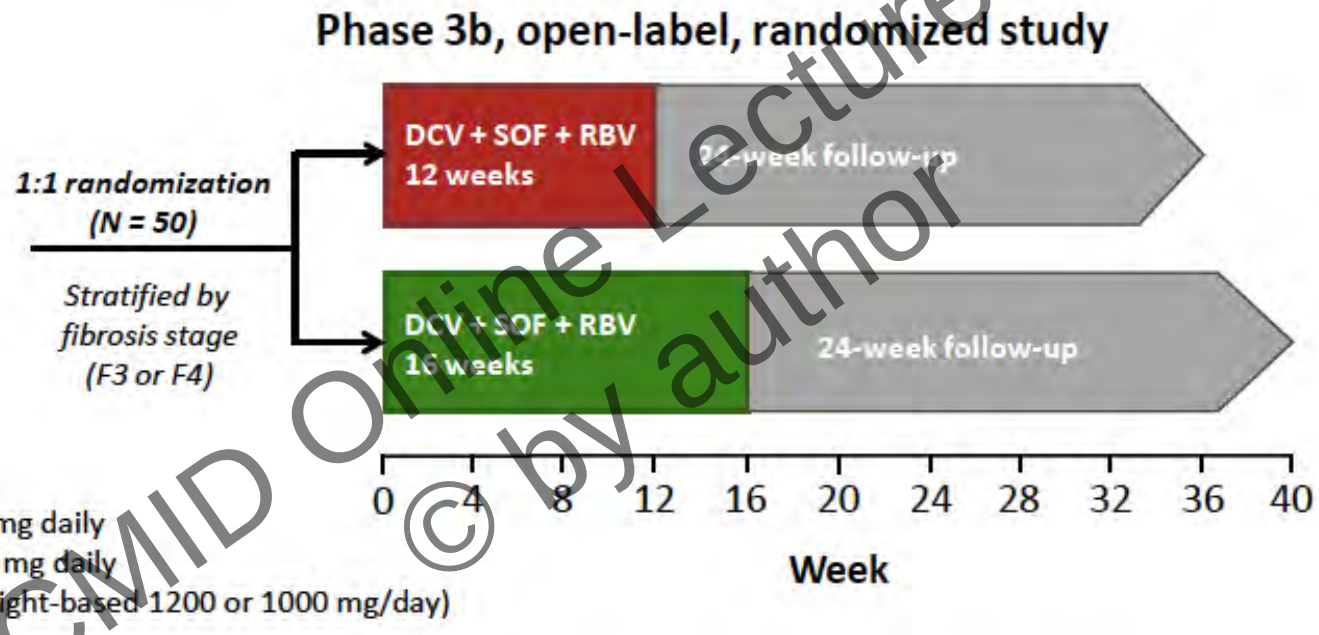
OK – so 12 weeks SOF/DCV good for non-cirrhotics

But poor for cirrhotics….

Could we add RBV or give for longer or both?

Adapted from: Kowdley et al. EASL 2016, poster SAT-199.

ALLY-3+



DCV 60 mg daily
SOF 400 mg daily
RBV (weight-based 1200 or 1000 mg/day)

Primary efficacy endpoint: SVR12

- HCV RNA <$LLOQ_{TD/TND}$ (next observation carried backward) by Roche COBAS TaqMan v2.0 assay (LLOQ 25 IU/mL)

Safety endpoints

- Frequencies of serious AEs, discontinuations due to AEs, grade 3/4 AEs, and laboratory abnormalities

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LLOQ = Lower limit of Quantification, TD = Target detected, TND = Target not detected, IU = International Units, AEs = Adverse Events

ALLY-3+: Demographics

	DCV+SOF+RBV Overall N = 50	DCV+SOF+RBV 12 Weeks N = 24	DCV+SOF+RBV 16 Weeks N = 26
Age, *median (range) years*	53.5 (36–73)	53.0 (36–73)	56.0 (42–62)
Male, *n (%)*	40 (80)	18 (75)	22 (85)
Race, *n (%)*			
White	49 (98)	23 (96)	26 (100)
Asian	1 (2)	1 (4)	0
***IL28B* non-CC,** *n (%)*	28 (56)	13 (54)	15 (58)
HCV RNA, *median (range) $\log_{10}$ IU/mL*	6.87 (4.6–7.8)	6.70 (4.6–7.6)	6.91 (4.7–7.8)
HCV RNA category (IU/mL), *n (%)*			
≥ 2 million	38 (76)	18 (75)	20 (77)
≥ 6 million	26 (52)	11 (46)	15 (58)
Fibrosis stage, *n (%)*			
Advanced fibrosis (F3)	14 (28)	6 (25)	8 (31)
Cirrhosis (F4)	36 (72)	18 (75)	18 (69)
Albumin, *median (range) g/L*	43 (33–48)	43.0 (33–47)	42.5 (34–48)
Platelets, *median (range) × 10^9 cells/L*	161 (63–324)	161 (63–299)	155 (84–324)
Prior HCV treatment experience, *n (%)*			
Naive	13 (26)	6 (25)	7 (27)
Experienced[a]	37 (74)	18 (75)	19 (73)
IFN-based regimens	31 (62)	15 (63)	16 (62)
SOF-based regimens[b]	6 (12)	3 (13)	3 (12)

[a]Includes 30 patients with cirrhosis (F4); 7 patients with advanced fibrosis (F3); [b] Includes 5 patients (12-week, n = 2; 16-week, n = 3) who relapsed after a previous SOF + RBV regimen, and 1 patient (12-week) who relapsed after SOF + IFN/RBV.

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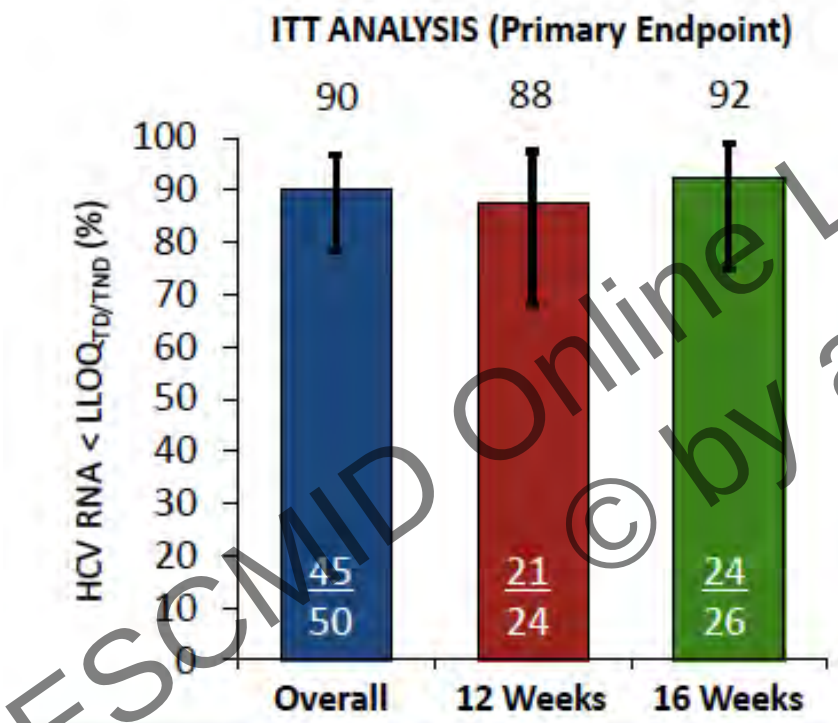
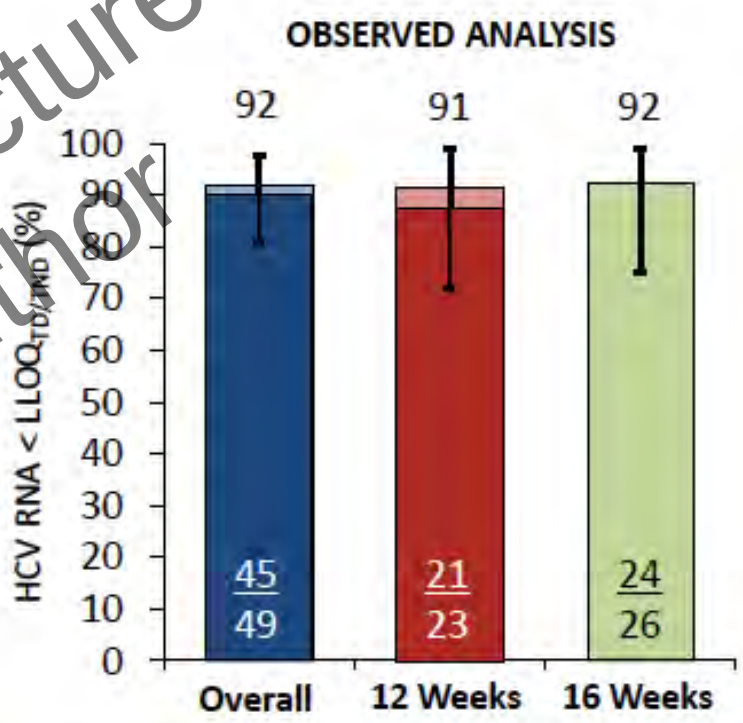
ALLY-3+: Overall results F3&F4



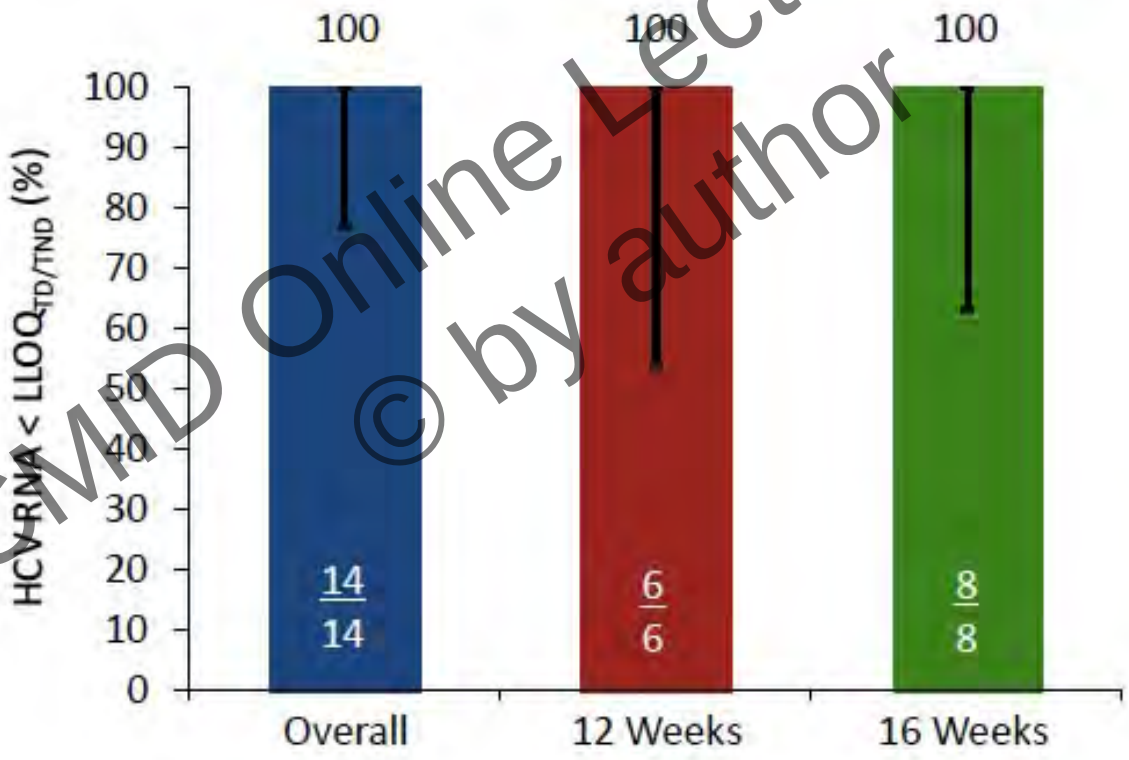
	Overall	12 Weeks	16 Weeks
VBT[a]	0	0	0
Relapse[b]	4	2	2
Death[c]	1	1	0



	Overall	12 Weeks	16 Weeks
VBT[a]	0	0	0
Relapse[b]	4	2	2

[a] VBT (virologic breakthrough): confirmed HCV RNA ≥ 1 $\log_{10}$ IU/mL above nadir, or ≥ LLOQ if previously < LLOQ TD or TND;
[b] Relapse: confirmed HCV RNA ≥ LLOQ at any posttreatment visit following < $LLOQ_{TND}$ at end of treatment;
[c] Dilated cardiomyopathy on Day 72, not related to treatment.

ALLY-3+: F3 patients



[a] Diagnosed by FibroScan ≥ 9.6 to < 12.5 kPa (n = 9), FibroScan ≥ 12.5 – 14.6 kPa (n = 4), liver biopsy, (n = 1).

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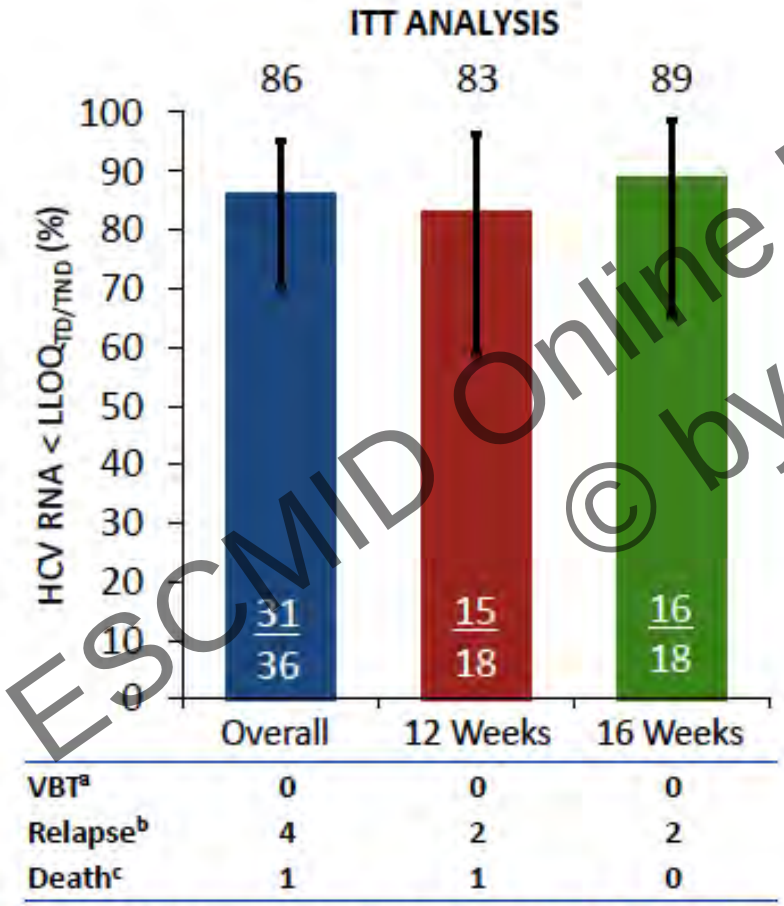
ALLY-3+: F4 patients



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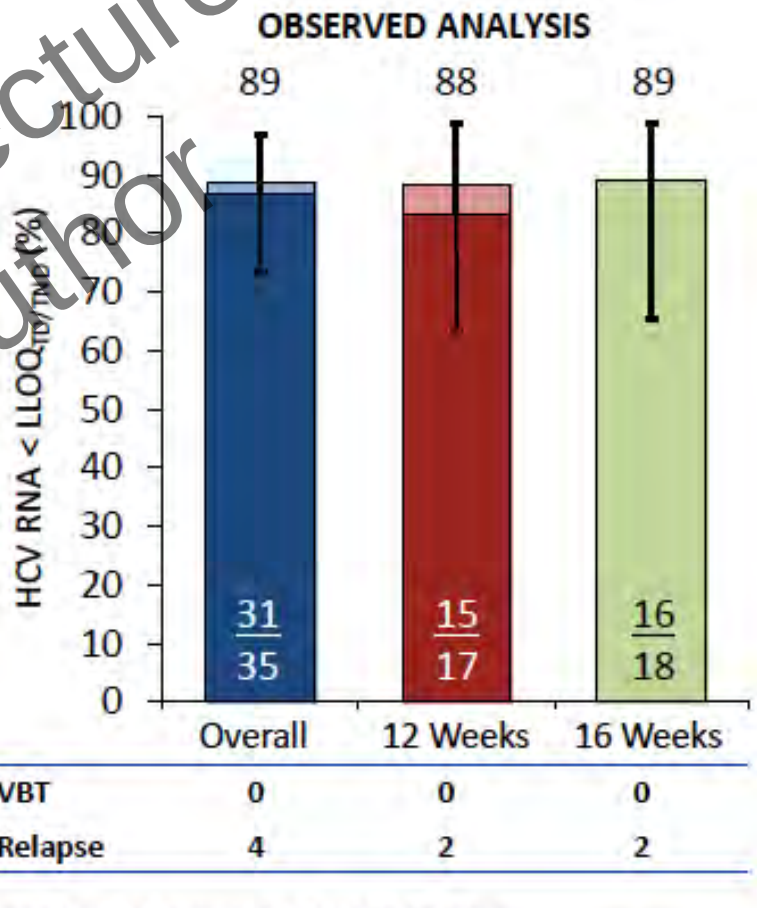

	Overall	12 Weeks	16 Weeks
VBT	0	0	0
Relapse	4	2	2

[a] VBT (virologic breakthrough): confirmed HCV RNA ≥ 1 $\log_{10}$ IU/mL above nadir, or ≥ LLOQ if previously < LLOQ TD or TND;
[b] Relapse: confirmed HCV RNA ≥ LLOQ at any posttreatment visit following < LLOQ$_{TND}$ at end of treatment;
[c] Dilated cardiomyopathy on Day 72, not related to treatment; cirrhosis status diagnosed by liver biopsy (F4) n = 9; FibroScan ≥ 14.6, n = 27.

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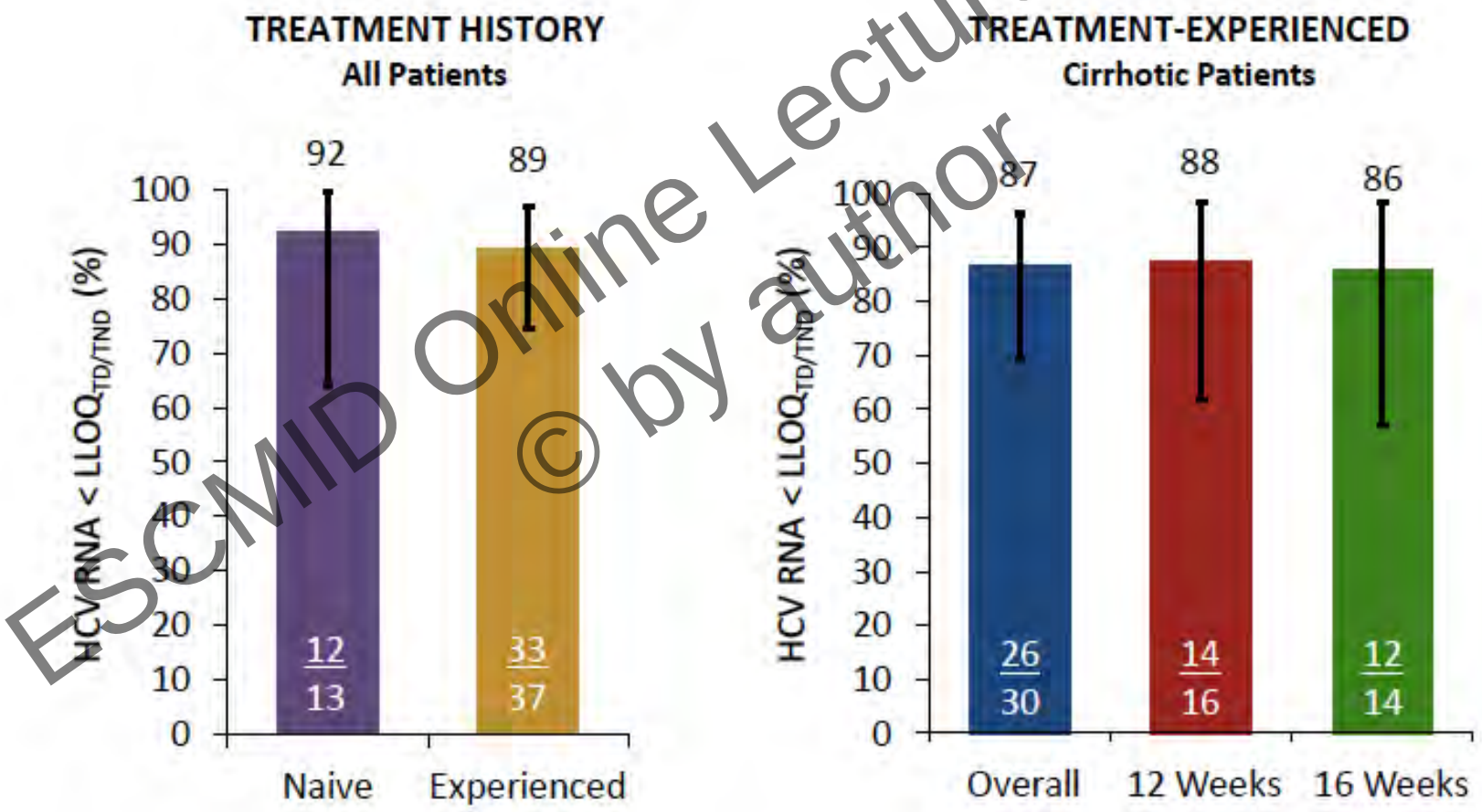
ALLY-3+: Treatment-experienced patients



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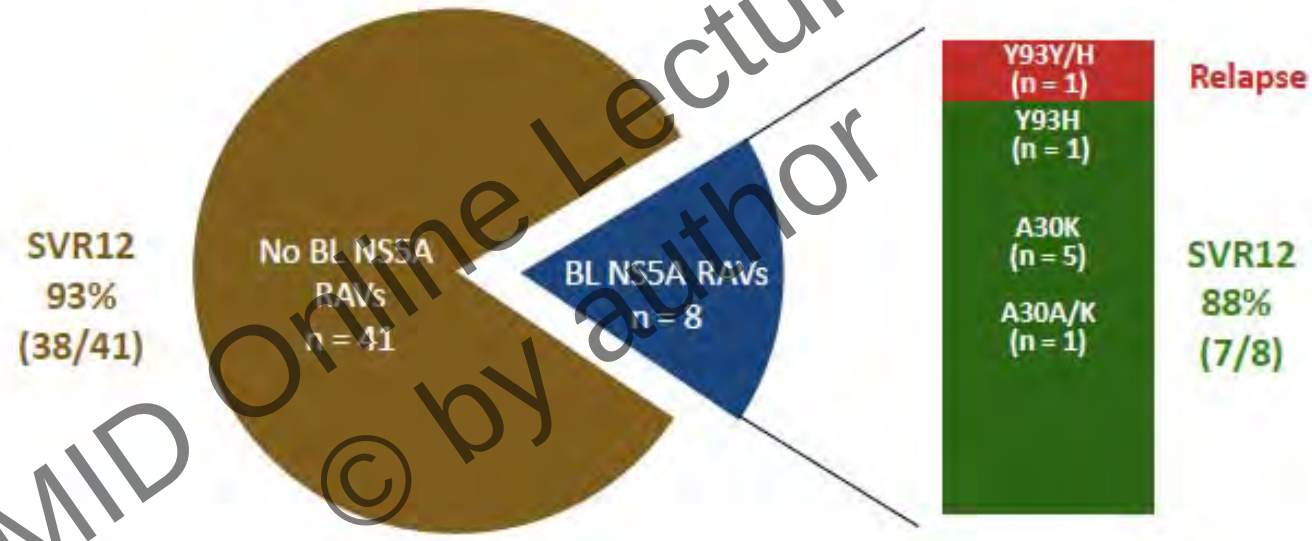
ALLY-3+: Baseline RAVs



- At failure, all 4 patients who relapsed had NS5A-Y93H
- No SOF-associated RAVs in NS5B were observed at baseline or relapse (sensitivity ≥ 1%)
  - S282T or any substitution at L159, L320, or V321

Resistance assessed by population sequencing (sensitivity≥ 10%)

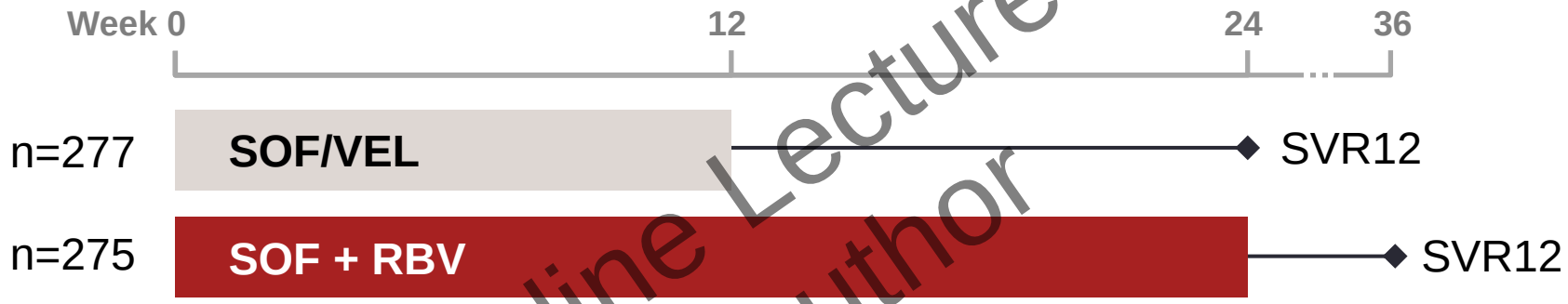
Assessment of baseline RAVs on SVR12 excludes 1 patient without RAVs who died of dilated cardiomyopathy on Day 72, unrelated to treatment. One relapse without A30K or Y93H had baseline M28I polymorphism not present at failure. M28I does not affect DCV susceptibility *in vitro*.

Leroy et al, Oral LB-3- AASLD Oral LB-3The Liver Meeting 2015® San Francisco, CA, 13–17 November 2015

BL = Baseline, RAV = Resistance associated Mutations

SOF/VEL for 12 Weeks Compared to SOF+RBV for 24 Weeks in GT 3 HCV-Infected Patients

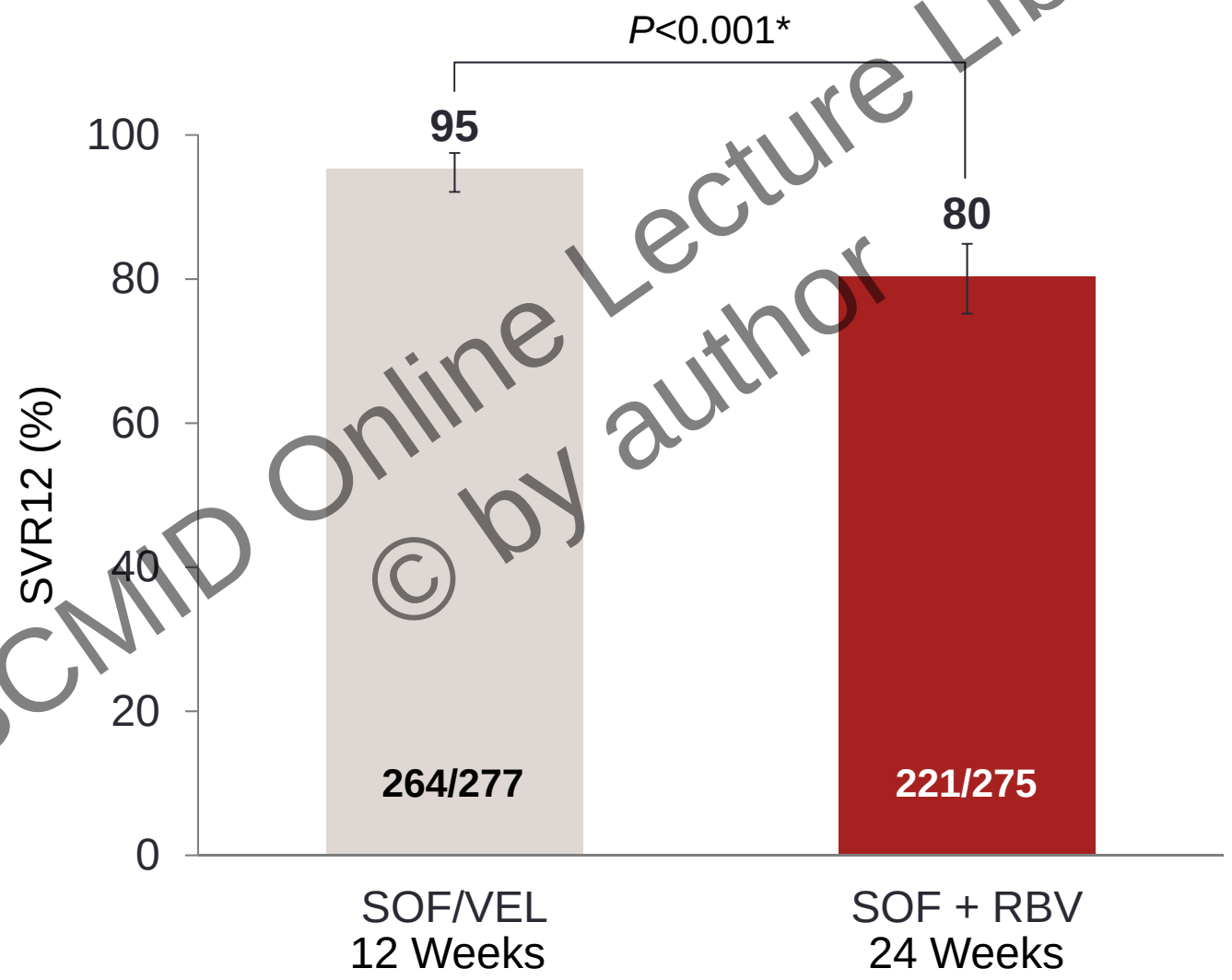
Phase 3, open-label, randomised study of SOF/VEL for 12 weeks in GT 3



	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)	26.4 (16.6–48.2)	26.6 (16.9–56.2)
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 (SD)	6.2 (0.7)	6.3 (0.7)

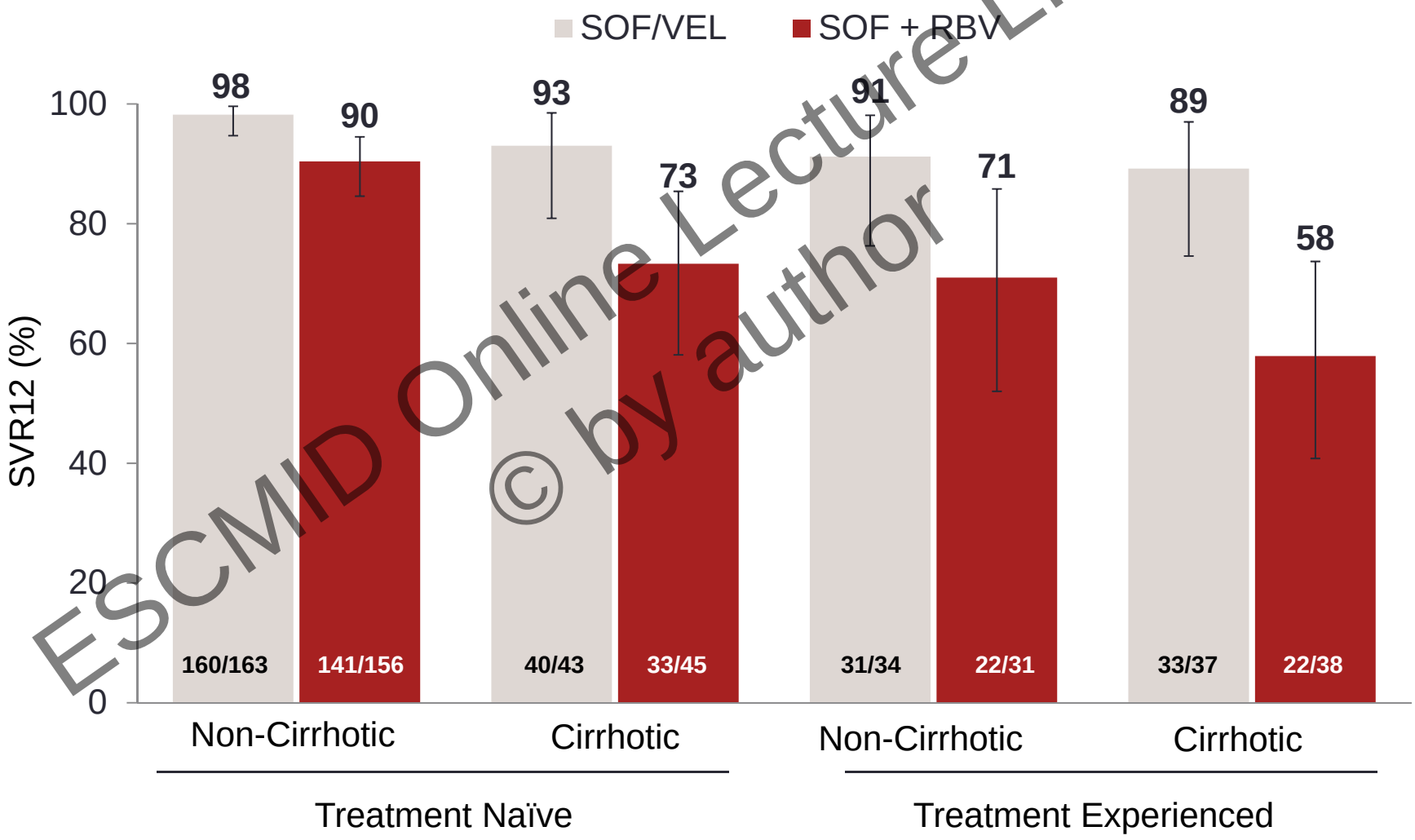
Mangia, AASLD, 2015, 249. Foster GR, et al. *New Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512612

ASTRAL-3: SVR12



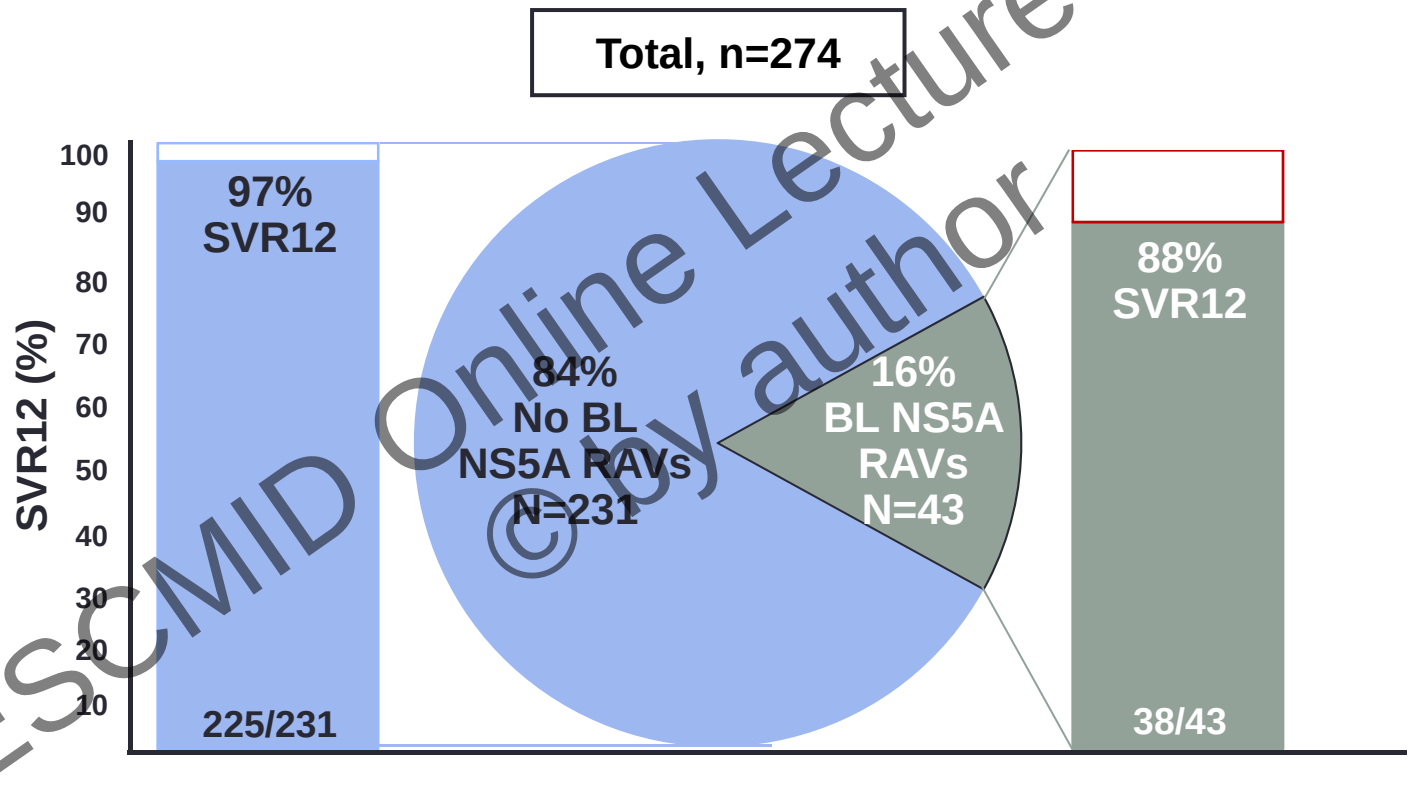
**P*-value for superiority of SOF/VEL compared with SOF+RBV.
Error bars represent 95% confidence intervals.
Mangia, AASLD, 2015, 249. Foster GR, et al. *New Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512612

ASTRAL-3: SVR12 by Cirrhosis Status and Treatment History



Mangia, AASLD, 2015, 249. Foster GR, et al. *New Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512612

ASTRAL-3: Resistance Analysis (1% cut-off)



- SVR12 was 84% (21/25) in patients with Y93H

Mangia, AASLD, 2015, 249. Foster GR, et al. *New Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512612

SVR12 per negative predictor

Patients, n(%)		SVR% (n/n)						
		GT1 n=328	GT2 n=238	GT3 n=277	GT4 n=116	GT5 n=35	GT6 n=41	Total n=1035
Cirrhosis	Yes	99 (72/73)	100 (29/29)	91 (73/80)	100 (27/27)	100 (5/5)	100 (6/6)	96 (212/220)
	No	98 (251/255)	99 (207/208)	97 (191/197)	100 (89/89)	97 (28/29)	100 (35/35)	99 (801/813)
Platelets	<100 x 10^3/µL	95 (20/21)	100 (4/4)	88 (22/25)	100 (8/8)	100 (1/1)	100 (3/3)	94 (58/62)
	≥100 x 10^3/µL	99 (303/307)	99 (233/234)	96 (242/252)	100 (108/108)	97 (33/34)	100 (38/38)	98 (957/973)
Albumin	<3.5 mg/dL	100 (6/6)	100 (1/1)	88 (7/8)	100 (6/6)	0	0	95 (20/21)
	≥3.5 mg/dL	98 (317/322)	99 (236/237)	96 (257/269)	100 (110/110)	97 (34/35)	100 (41/41)	98 (995/1014)
FibroScan	≥15 kPa	100 (30/30)	100 (9/9)	90 (36/40)	100 (17/17)	100 (4/4)	100 (5/5)	96 (101/105)
	<15 kPa	98 (154/158)	99 (118/119)	97 (152/156)	100 (74/74)	95 (19/20)	100 (22/22)	98 (539/549)
Treatment experienced	Experienced	99 (109/110)	100 (44/44)	90 (64/71)	100 (52/52)	100 (11/11)	100 (3/3)	97 (283/291)
	Naïve	98 (214/218)	99 (193/194)	97 (200/206)	100 (64/64)	96 (23/24)	100 (38/38)	98 (732/744)
NS5A RAVs (15% cut off)	With RAVs	96 (48/50)	100 (146/146)	87 (27/31)	100 (69/69)	100 (3/3)	100 (19/19)	98 (312/318)
	Without RAVs	99 (275/278)	99 (89/90)	96 (236/245)	100 (46/46)	97 (31/32)	100 (21/21)	98 (698/712)

Integrated Efficacy: SVR12 by Number of Negative Predictive Factors

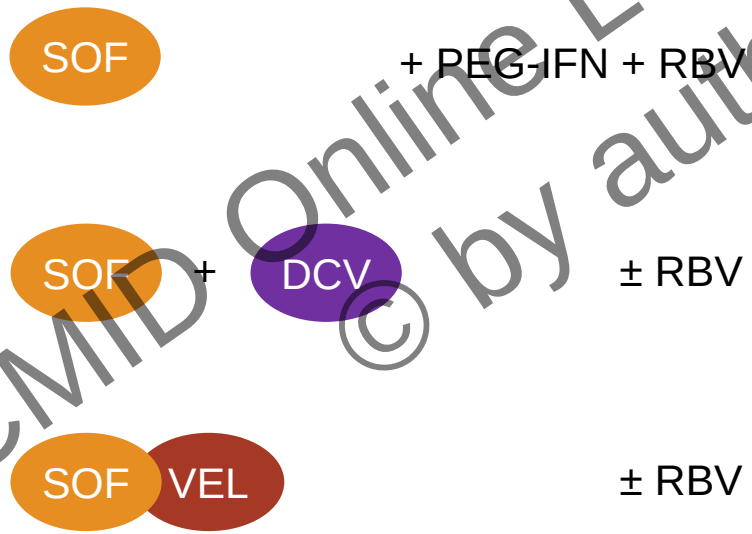
Patients, n/N (%)	GT1 n=328	GT2 n=238	GT3 n=277	GT4 n=116	GT5 n=35	GT6 n=41	Total N=1035
Overall	323/328 (98)	237/238 (99)	264/277 (95)	116/116 (100)	34/35 (97)	41/41 (100)	1015/1035 (98)
0 factor	33/33 (100)	13/13 (100)	53/53 (100)	11/11 (100)	3/4 (75)	5/5 (100)	118/119 (99)
1 factor	148/151 (98)	80/81 (99)	108/111 (97)	31/31 (100)	21/21 (100)	17/17 (100)	405/412 (98)
2 factors	96/97 (99)	111/111 (100)	74/78 (95)	40/40 (100)	6/6 (100)	15/15 (100)	342/347 (99)
3 factors	44/45 (98)	30/30 (100)	29/34 (85)	25/25 (100)	4/4 (100)	4/4 (100)	136/142 (96)
4 factors	2/2 (100)	3/3 (100)	0/1 (0)	9/9 (100)	0	0	14/15 (93)

Baseline factors analysed included presence of NS5A RAVs, presence of cirrhosis, baseline HCV RNA ≥800 IU/mL, and prior HCV treatment.

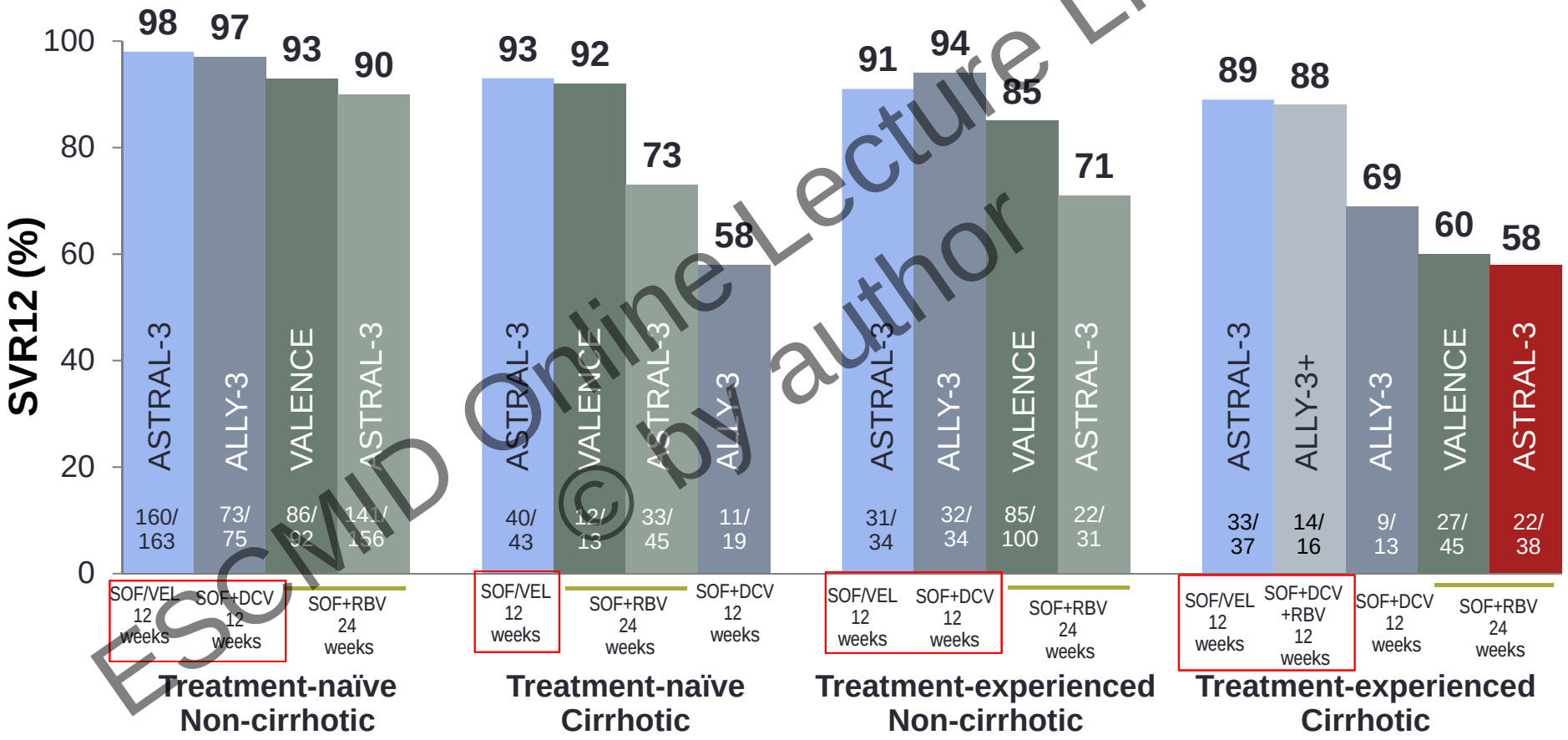
High SVR12 rates with SOF/VEL for 12 weeks were achieved by patients with multiple factors historically associated with virologic failure

Agarwal, EASL 2016, Poster SAT-195

So: Regimens for G3….



SVR of SOF-Based Regimens for HCV GT 3 by Prior Treatment Experience and Cirrhosis Status



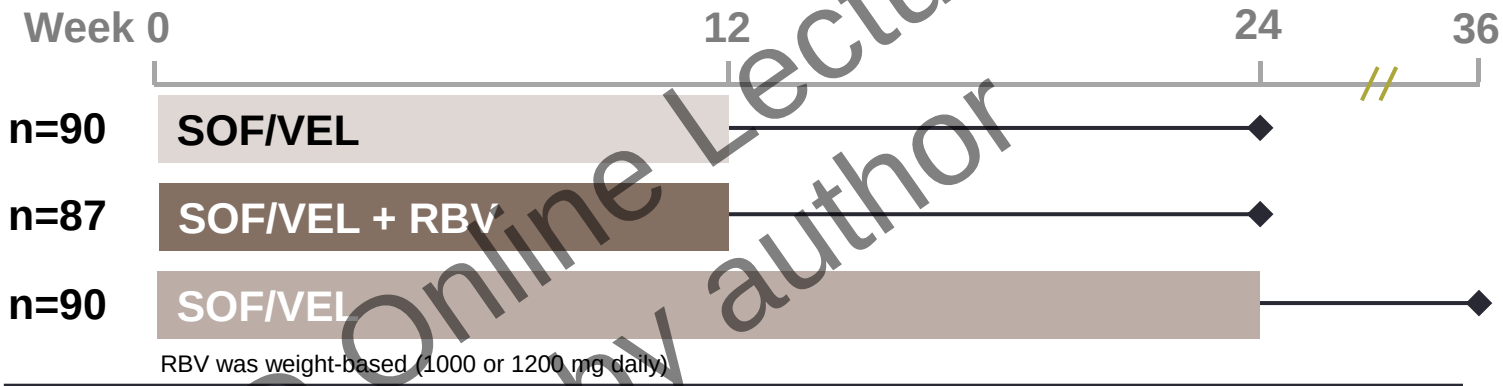
DISCLAIMER: These graphics serve to illustrate SVRs obtained between different regimens from different studies and therefore not directly comparable

*SOF+DCV+RBV for 16 weeks resulted in SVR of 86% (12/14) in treatment-experienced, cirrhotic patients

Foster GR, et al. *N Engl J Med* 2015;373(27):2608-2617; SOVALDI®▼ SmPC Gilead Sciences, January 2016; Daklinza®▼ SmPC, Bristol-Myers Squibb, January 2016; Nelson, *Hepatology* 2015;61(4):1127-1135; Leroy V. et al. *Hepatology* 2016;63(5):1430-1441

SOF/VEL ± RBV in HCV Patients with Decompensated Liver Disease

Phase 3, open-label, randomised study of SOF/VEL±RBV for 12 or 24 weeks in patients with HCV GT 1, 2, 3, 4, 6 and decompensated liver disease



RBV was weight-based (1000 or 1200 mg daily)

Patients	SOF/VEL 12 weeks n=90	SOF/VEL+RBV 12 weeks n=87	SOF/VEL 24 weeks n=90
Median MELD (range)	10 (6–24)	10 (6–18)	11 (6–19)
MELD < 15, n (%)	86 (96)	83 (95)	85 (84)
CTP B, n (%)	86 (96)	77 (89)	77 (86)
Ascites, n (%)	74 (82)	65 (75)	75 (83)
Encephalopathy, n (%)	52 (58)	54 (62)	59 (66)

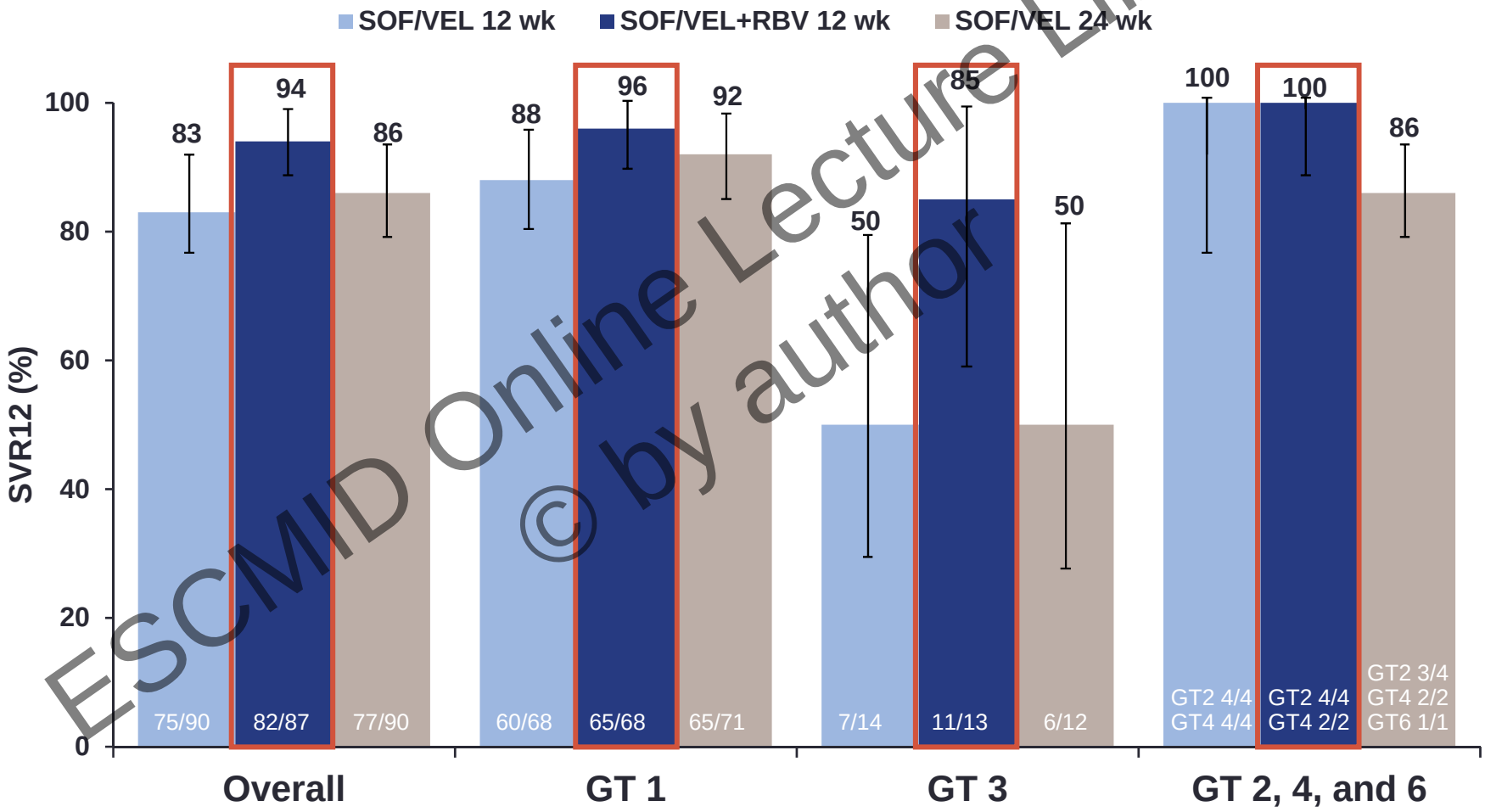
Charlton, AASLD, 2015, LB-13. Curry MP, et al. *New Engl J Med.*2015. DOI: 10.1056/NEJMoa1512614

Baseline Host and Viral Characteristics

Patients	SOF/VEL 12 weeks n=90	SOF/VEL+RBV 12 weeks n=87	SOF/VEL 24 weeks n=90
Mean age, years (range)	58 (42-73)	58 (40-71)	58 (46-72)
Male, n (%)	57 (63)	66 (76)	63 (70)
White, n (%)	79 (88)	79 (91)	81 (90)
Prior HCV treatment, n (%)	58 (64)	47 (54)	42 (47)
IL28B non-CC, n (%)	70 (78)	65 (75)	68 (76)
HCV RNA, $\log_{10}$ IU/mL (SD)	6.0 (0.5)	5.9 (0.6)	5.9 (0.6)
HCT GT 1, n (%)	68 (76)	68 (78)	71 (79)
HCV GT 3, n (%)	14 (16)	13 (15)	12 (13)
HCV GT 2/4/6, n (%)	8 (9)	6 (7)	7 (8)

Charlton, AASLD, 2015, LB-13. Curry MP, et al. *New Engl J Med.*2015. DOI: 10.1056/NEJMoa1512614

SVR12



SOF/VEL + RBV resulted in highest SVR12 in patients with decompensated liver disease

*Patient with nondetectable drug levels at time of virologic failure.

Charlton M, et al., AASLD, 2015, #LB-13

EASL Guidelines 2016

I would be tempted to say only need RBV if decompensated or very severe… and only 12 weeks needed

Patients	Treatment-naïve or -experienced	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	…vir/ …previr/ …vir and …abuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir
Genotype 3	Treatment-naïve	No	12 wk, no ribavirin		No	No	12 wk, no ribavirin	No
	Treatment-experienced		12 wk with ribavirin[c] or 24 wk, no ribavirin				12 wk with ribavirin[c] or 24 wk, no ribavirin	

And SOF/P/R could still be an option in some patients if issues with availability

Thank you….