What's new in Hepatology

AASLD 2016

CWN Spearman

C Kassianides

What's new in Hepatology? AASLD 2016

CWN SPEARMAN

Hepatitis C

Alcoholic liver disease

Cholestatic Liver Disease

- Primary biliary Cholangitis
- Primary Sclerosing cholangitis

Cirrhosis

C KASSIANIDES

Hepatitis B

NASH

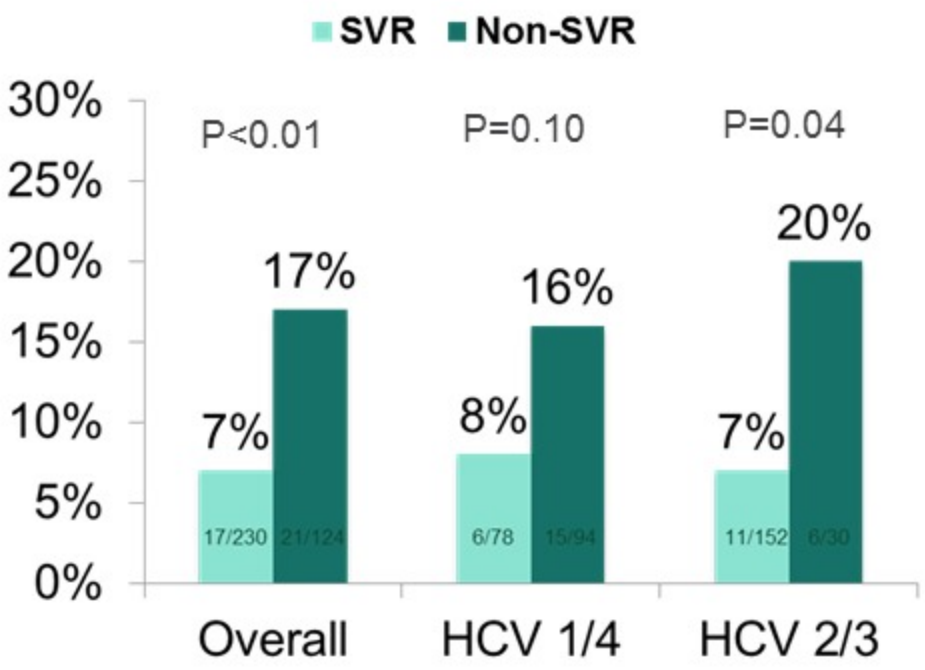
HEPATITIS C

Hepatitis C : ERA of DAAs

- **CURE is now possible for : SVR >90%**
  - Treatment naïve, experienced and cirrhotic patients
  - HIV/HCV co-infection
  - Liver transplant patients
- **SVR improves prognosis of non-cirrhotic and cirrhotic HCV pts**
  - Concerns re HCC and Hepatitis B reactivation on DAA therapy
  - Re-infection risks must be addressed: harm reduction programmes
- **SVR improves both all-cause and liver-related mortality**
- **All patients with chronic hepatitis C are candidates for Rx**
- **Prioritise patients with :**
  - Advanced fibrosis or cirrhosis
  - HIV/HBV co-infection
  - Extrahepatic manifestations
  - Transplant patients

SVR and Prevention of Diabetes/Insulin Resistance

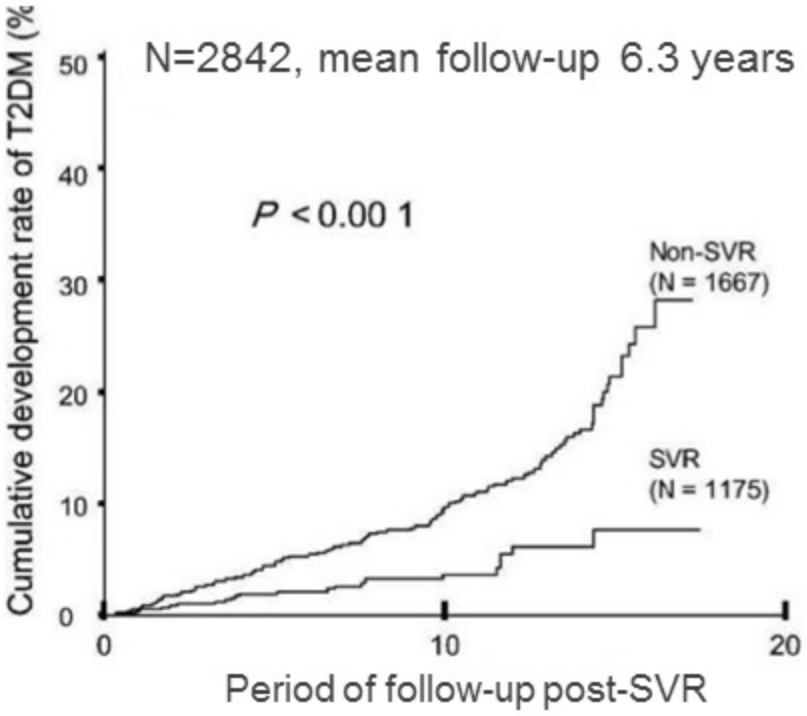
SVR reduced the rate of de novo insulin resistance evaluated 2 years later



N=384, 71% non-advanced fibrosis
HOMA-IR done pre and 24 mos post-treatment

Aghemo A. Hepatology.2012;56:1681-7

SVR reduces the incidence of type 2 diabetes* by ~60%

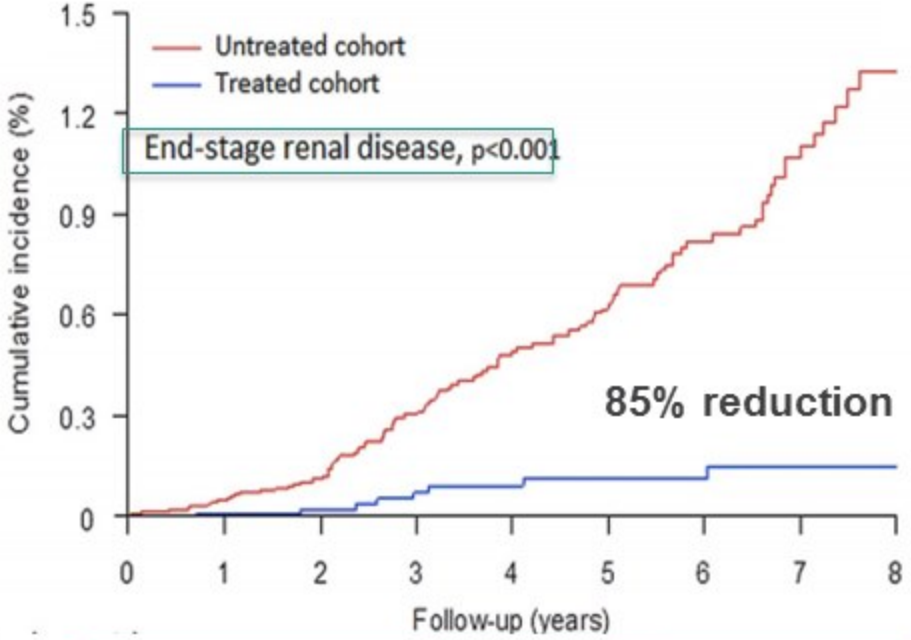


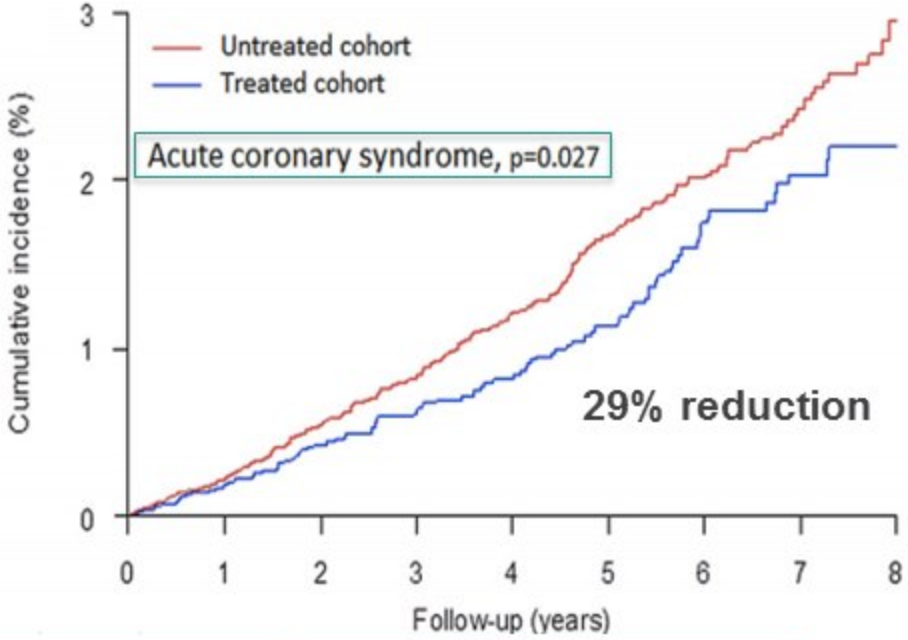
*Independent of age, cirrhosis and prediabetes at baseline

Arase Y, et al. Hepatology 2009; 49:739-44

Treatment Associated with Reduced Rates of Renal and Cardiovascular Outcomes

- Population-based cohort from Taiwan, HCV treated (n=12,384)with SVR compared to propensity matched untreated HCV controls (N=24,768)



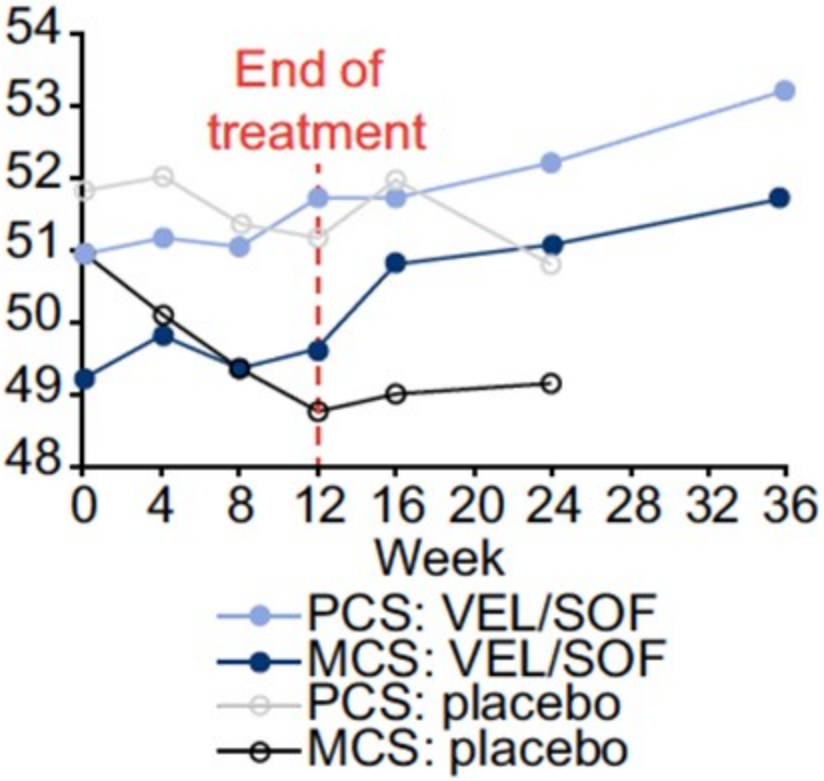


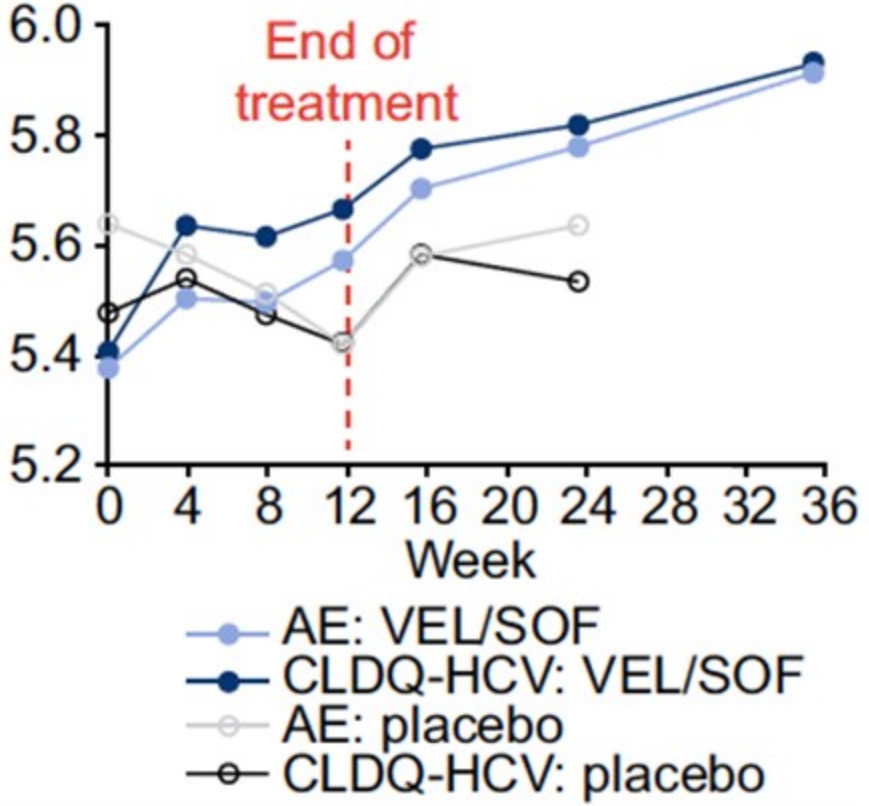
ESRD	95% CI	aHR	ACS	aHR	95% CI
Overall	0.15	0.07-0.31	Overall	0.77	0.62-0.97
No cirrhosis	**0.12**	**0.05-0.30**	**No cirrhosis**	**0.77**	**0.60-0.99**
Cirrhosis	0.26	0.08-0.87	Cirrhosis	0.80	0.62-0.97

Hsu YC, Gut 2015;64:495-503

Improvements in Physical & Mental Function

- N=624 [618 with SVR] and116 placebo; 81% without cirrhosis



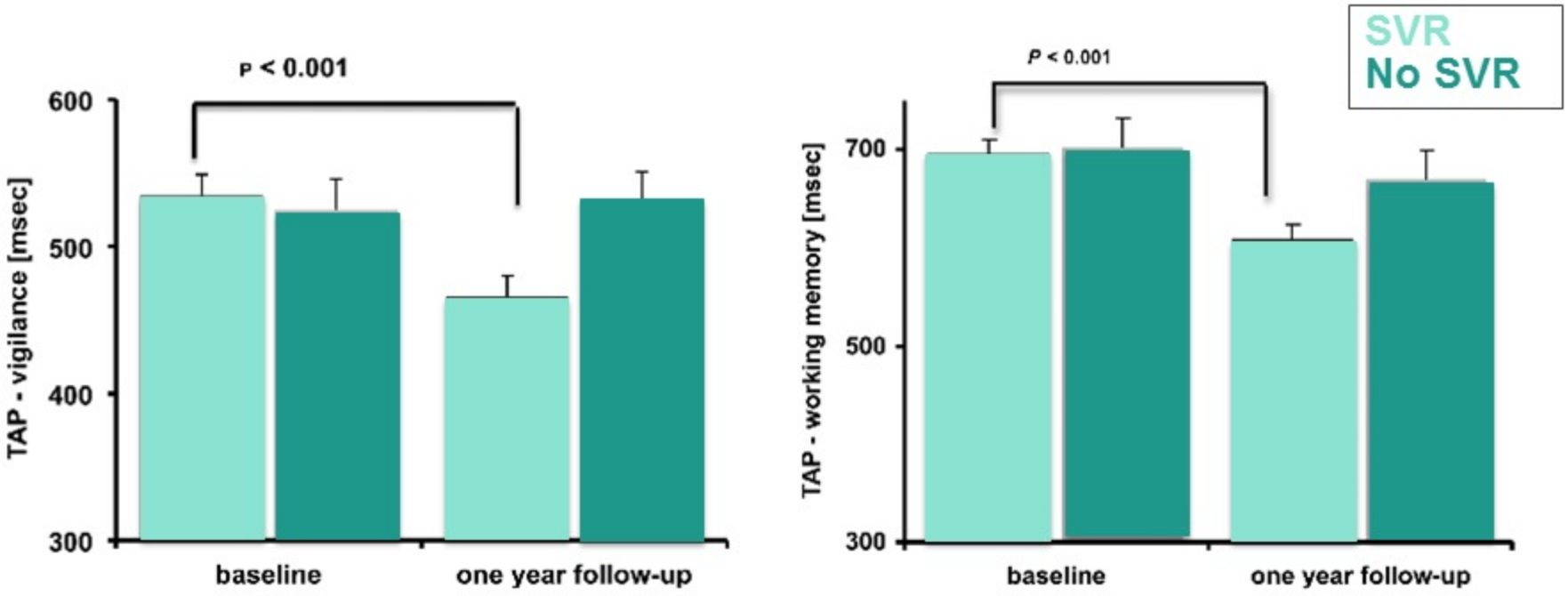


Improvement in patients on DAA therapy versus placebo as early as 4 weeks of treatment and continues after treatment ends

Younossi Z, J Hepatol. 2016 Jul;65(1):33-9

Improvement of Neurocognitive Function with SVR

- N=168 treated with peg-IFN based therapy; median age 43 yrs, 85% without cirrhosis; N=116 with SVR
- Computer-assisted neuropsychological tests; tested at baseline and 1 yr post-EOT



TAP=Test Battery of Attentional Performance

Vigilance: measures reaction times to assess sustained attention

Working memory: measures reaction times to assess ability to manage a continuous flow of information with short-term memory

Kraus MR, et al Hepatology 2013; 58:497-504

HCV Treatment : The Future ?

- Pan-genotypic DAA
- Shorter duration with minimal monitoring: 8, 12 & 16 wks
- Aim for Test and treat: Are we ready ?
- Better DAA Options in 2016 for:
    - Genotype 3
    - Stage 4 kidney disease/dialysis
    - Decompensated cirrhosis

In 2016: What our new therapeutic options?

GILEAD'S PROGRAMME

- **EPCLUSA**

  Sofosbuvir (NS5B)/Velpastasvir (NS5A)

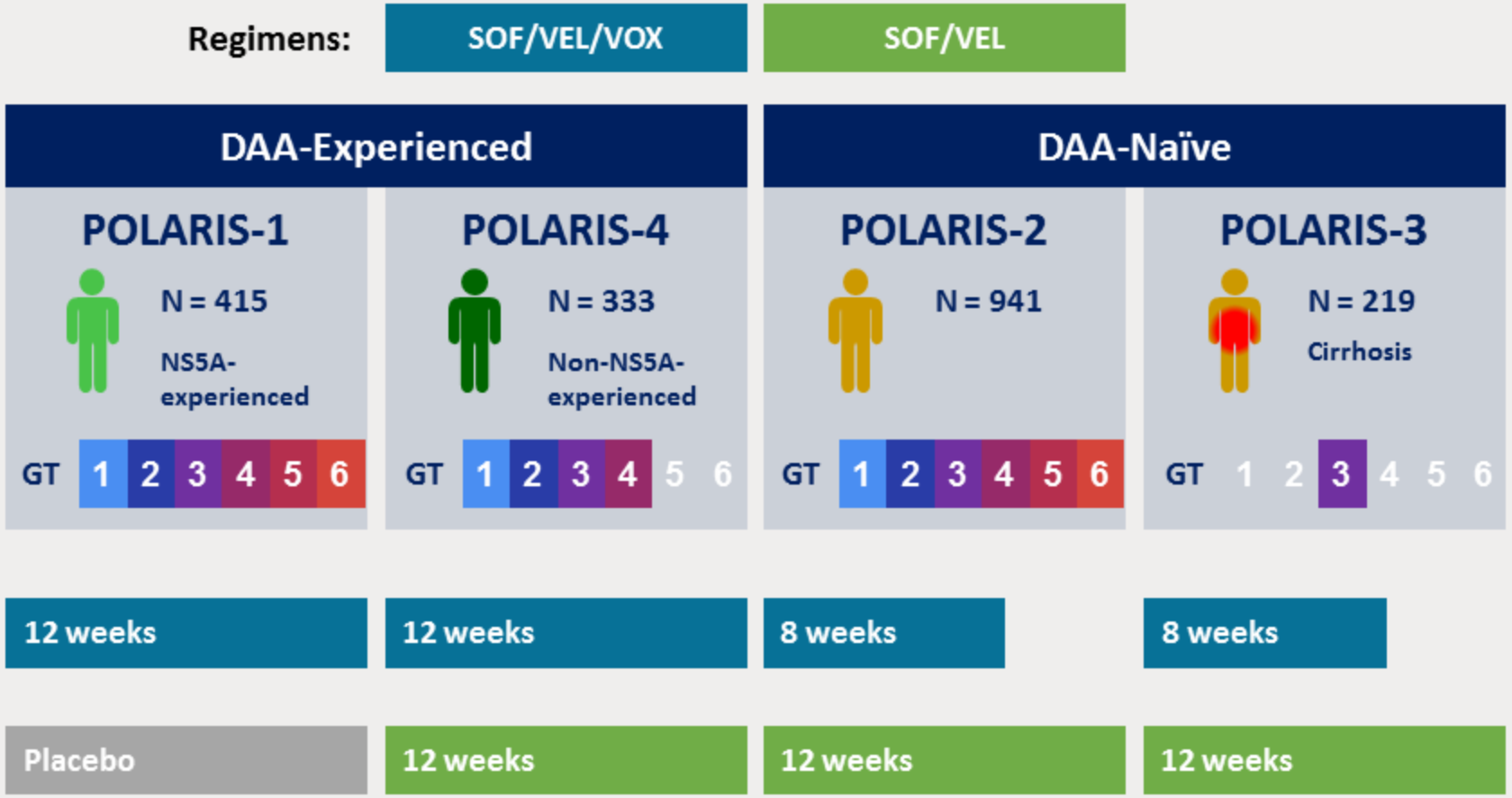
  - Pangenotypic FDC
  - ASTRAL1-4 Studies: >90% SVR
    - GT 1-6; Rx naïve and experienced; cirrhosis & decompensated dis
  - FDA approved in June 2016

- **Sofosbuvir/Velpatasvir/Voxilaprevir (NS3/4A)**

  - Pangenotypic FDC
  - POLARIS 1-4 Studies

POLARIS Program

- **Sofosbuvir (NS5B) / Velpatasvir (NS5A) / Voxilaprevir (NS3/4A)**

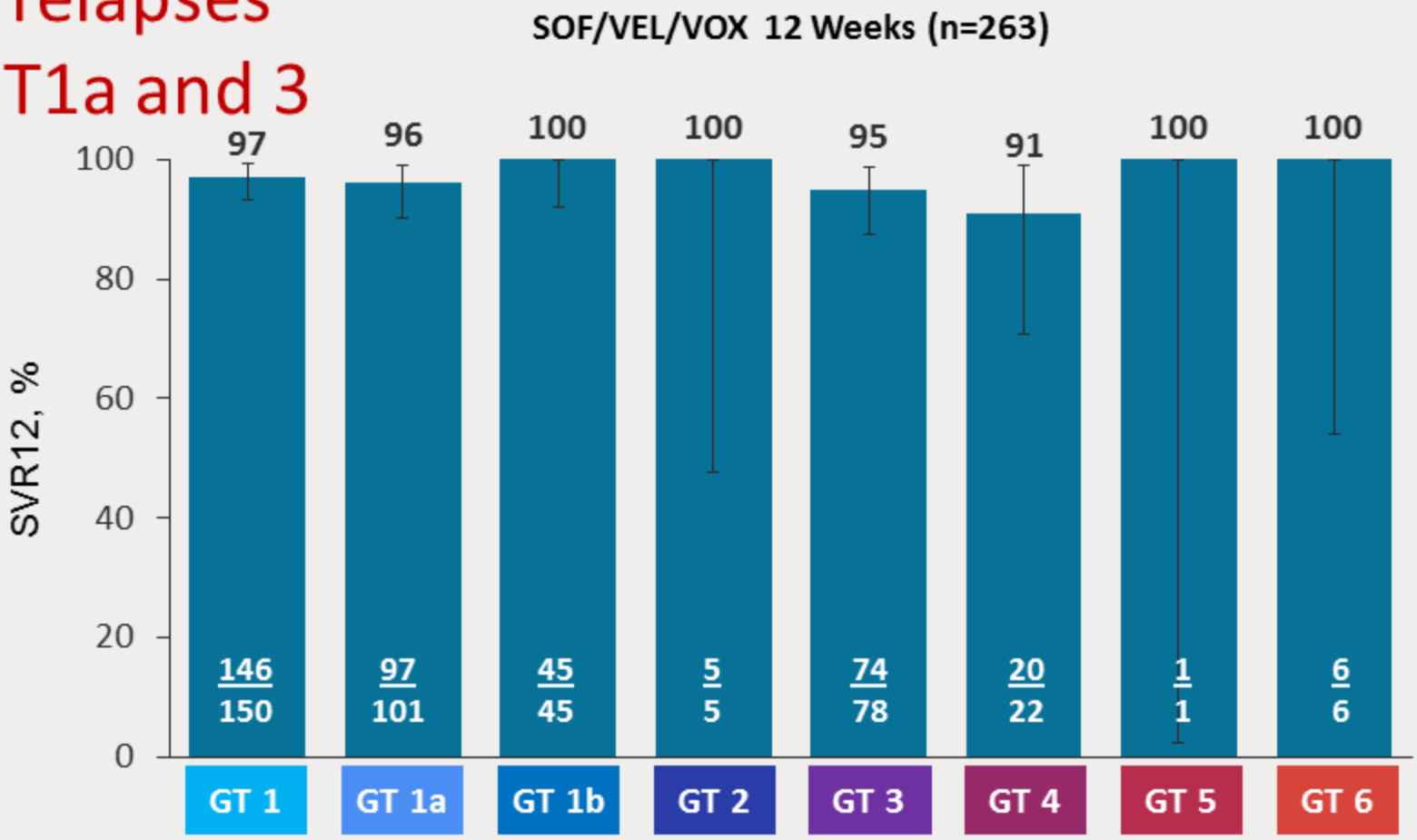


Polaris-1: SVR12 by Genotype

NS5A experienced

6 relapses

GT1a and 3

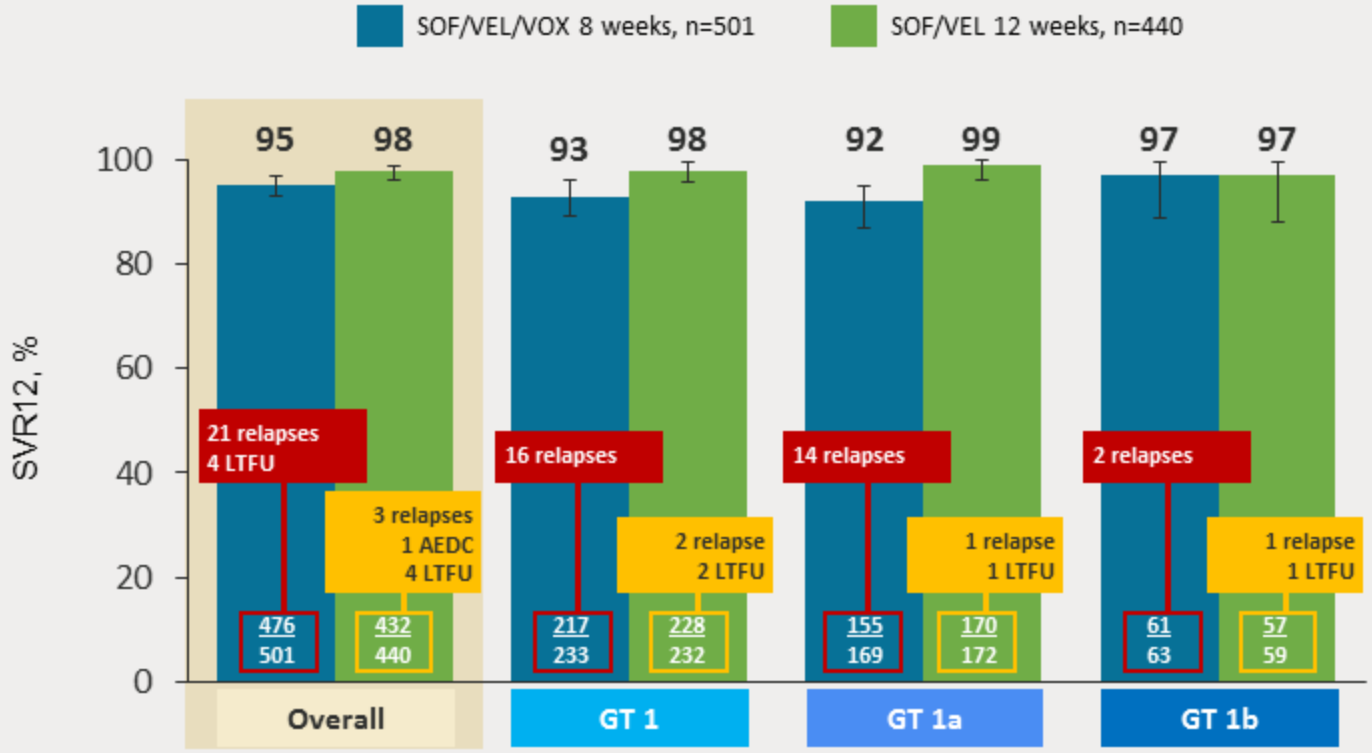


Error bars represent 95% confidence intervals.

Bourlière et al, AASLD 2016

Polaris-2: SVR12 by Genotype (GT 1)

DAA Naive



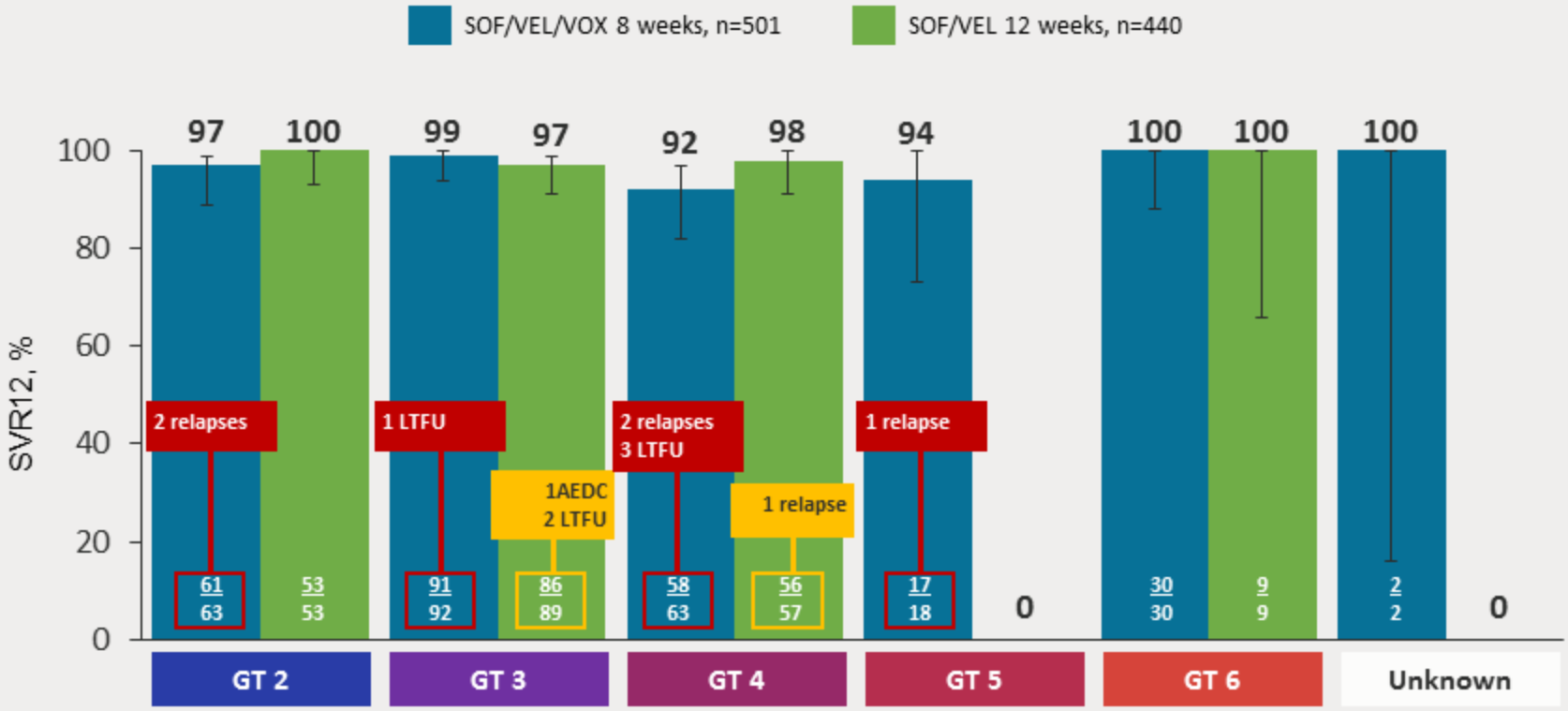
Jacobson et al AASLD 2016

AEDC, Discontinuation due to AE. Error bars represent 95% confidence intervals.

2 of 2 patients (100%) with GT 1 Other achieved SVR12 (1 each in the SOF/VEL/VOX and SOF/VEL groups).

Polaris-2: SVR12 by Genotype (GT 2–6)

DAA naive

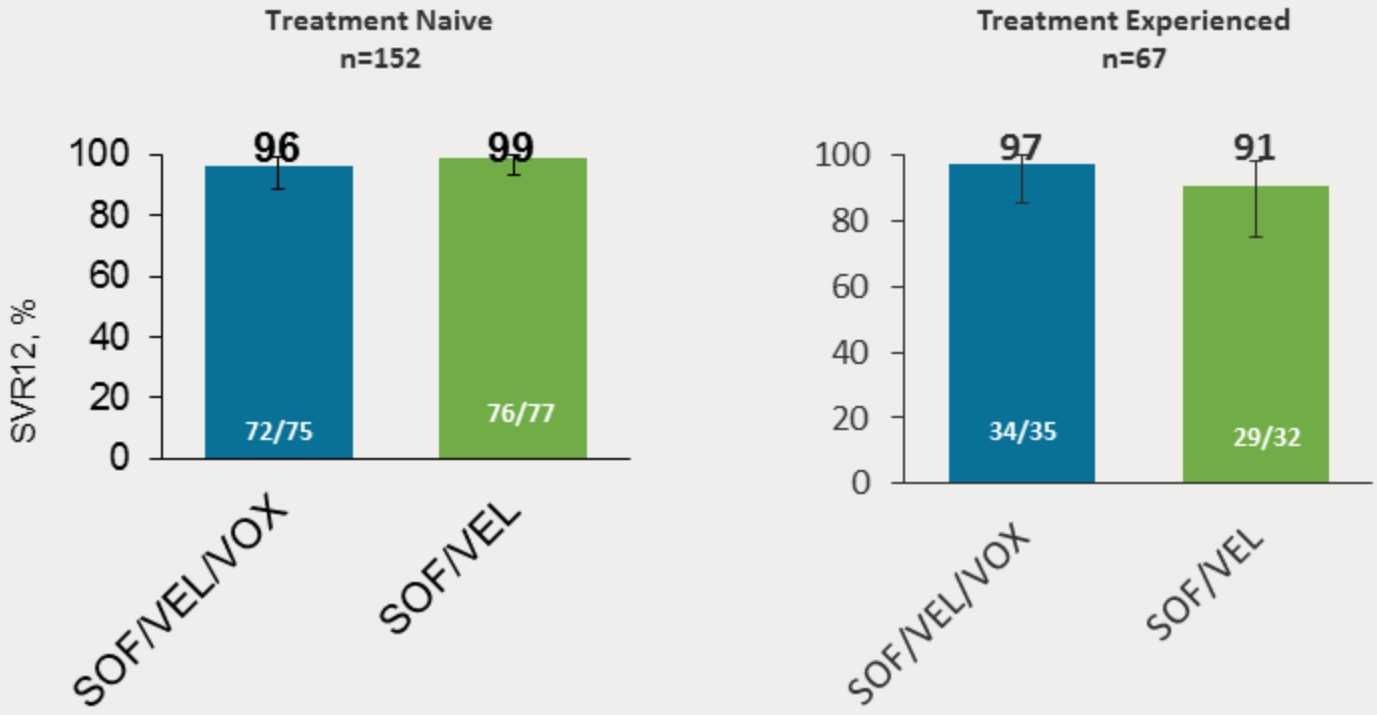


Jacobson et al AASLD 2016

AEDC, Discontinuation due to AE. Error bars represent 95% confidence intervals.

Polaris-3: SVR12 by Prior Treatment

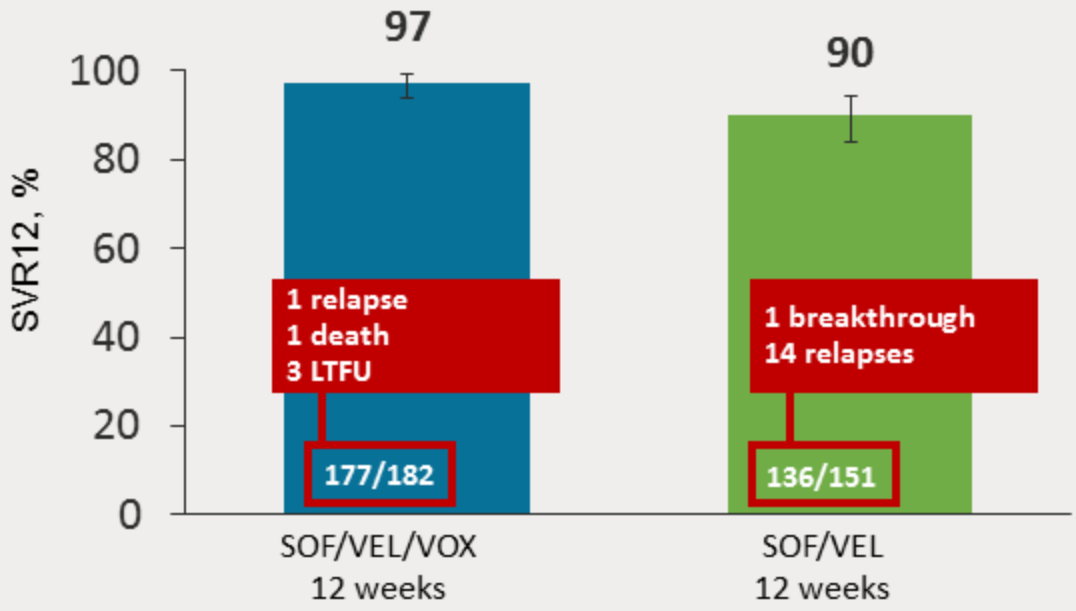
GT 3 Cirrhosis



Foster et al. AASLD 2016

Polaris-4: SVR12

non-NS5A DAA experienced



Difference driven by GT1a and 3

Zeuzem et al. AASLD 2016

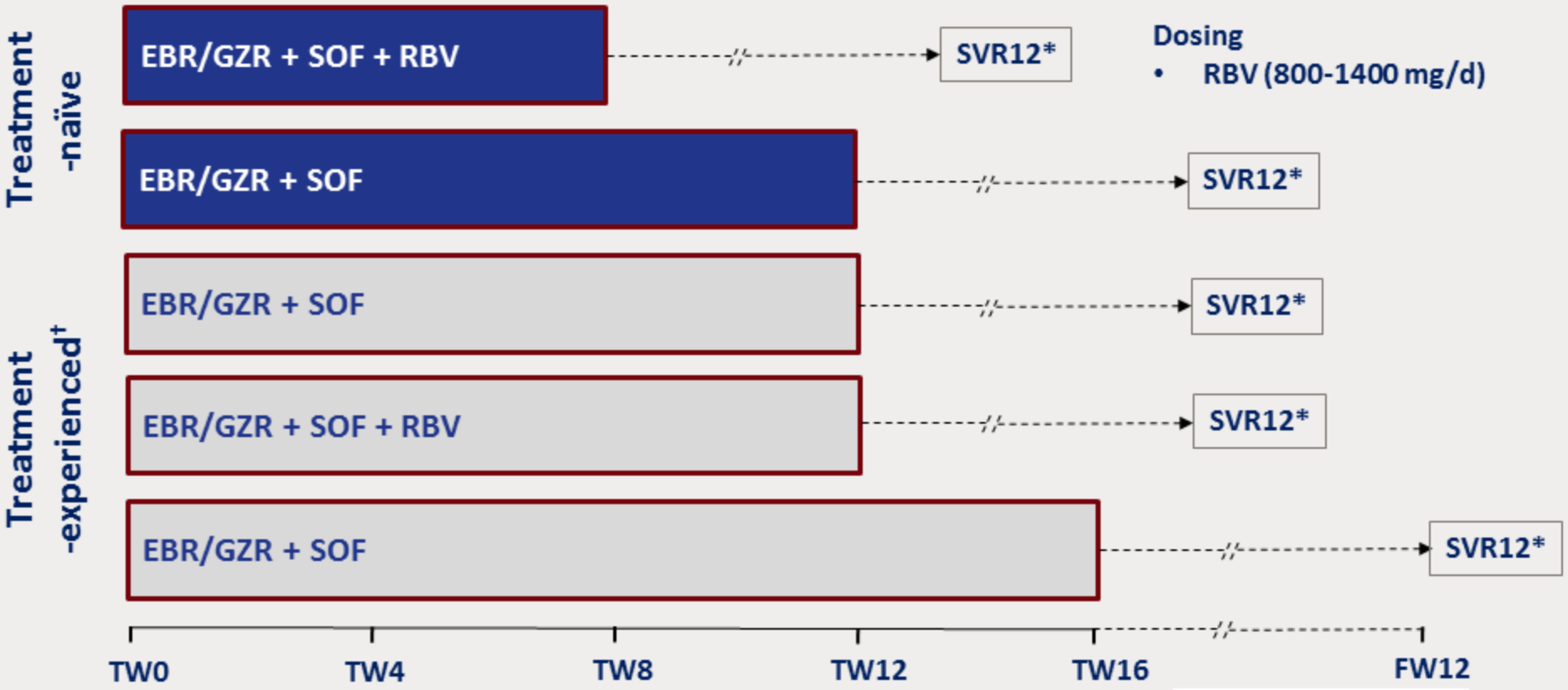
Error bars represent 95% confidence intervals.

MERCK 2016 PROGRAMME

- **Grazoprevir (NS3A/4A) + Elbasvir (NS5A) + SOF**
- **MK-3682/Grazoprevir (NS3A/4A)/Ruzasvir (NS5A)**

C-ISLE: EBR/GZR/SOF in GT3 cirrhotics

Grazoprevir (NS3A/4A) + Elbasvir (NS5A) + SOF ± RIBA

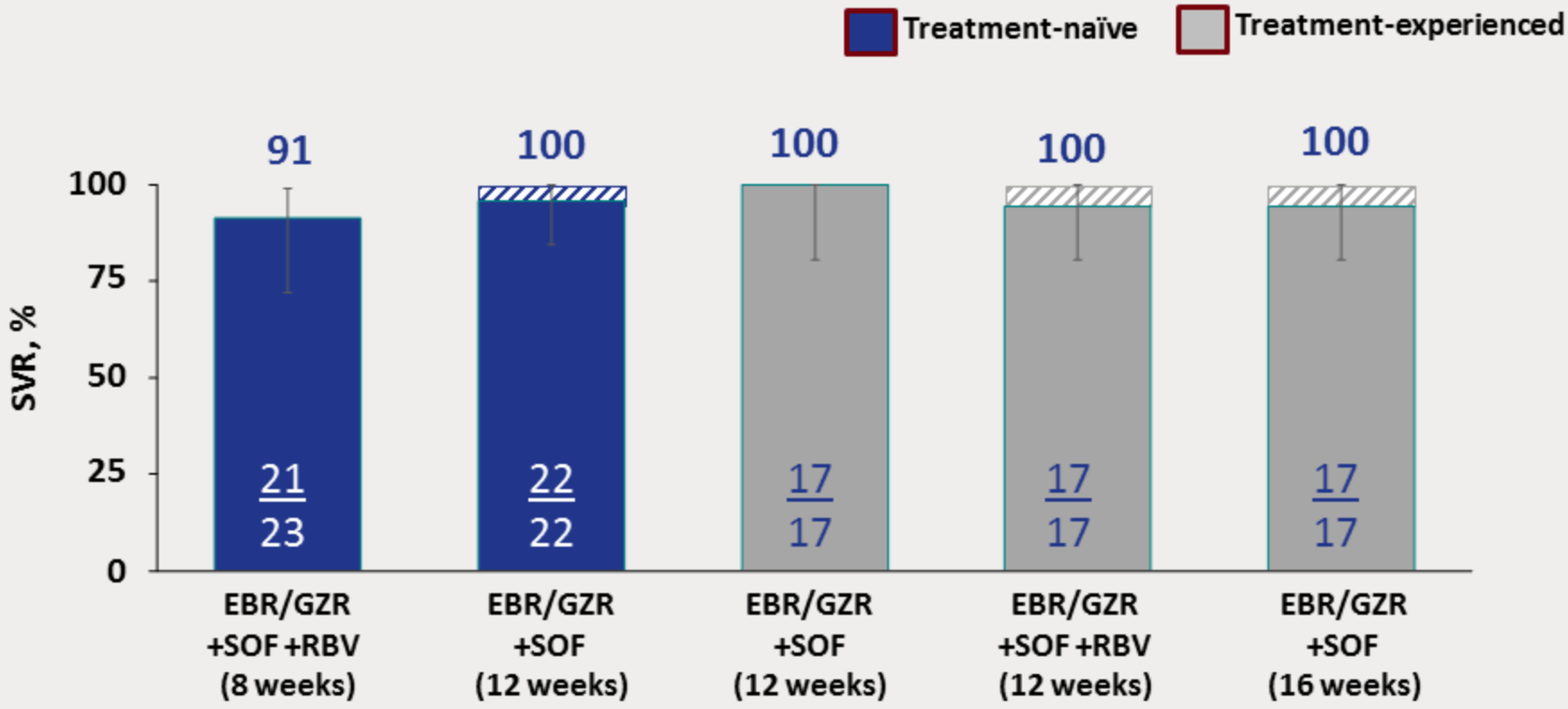


Foster et al AASLD 2016

*Primary endpoint: HCV RNA <15 IU/mL

C-Isle: SVR12 (modified Full analysis set)

Genotype 3 Cirrhotics: Grazoprevir (NS3A/4A) + Elbasvir (NS5A) + SOF ± RIBA



Relapse	2	0	0	0	0

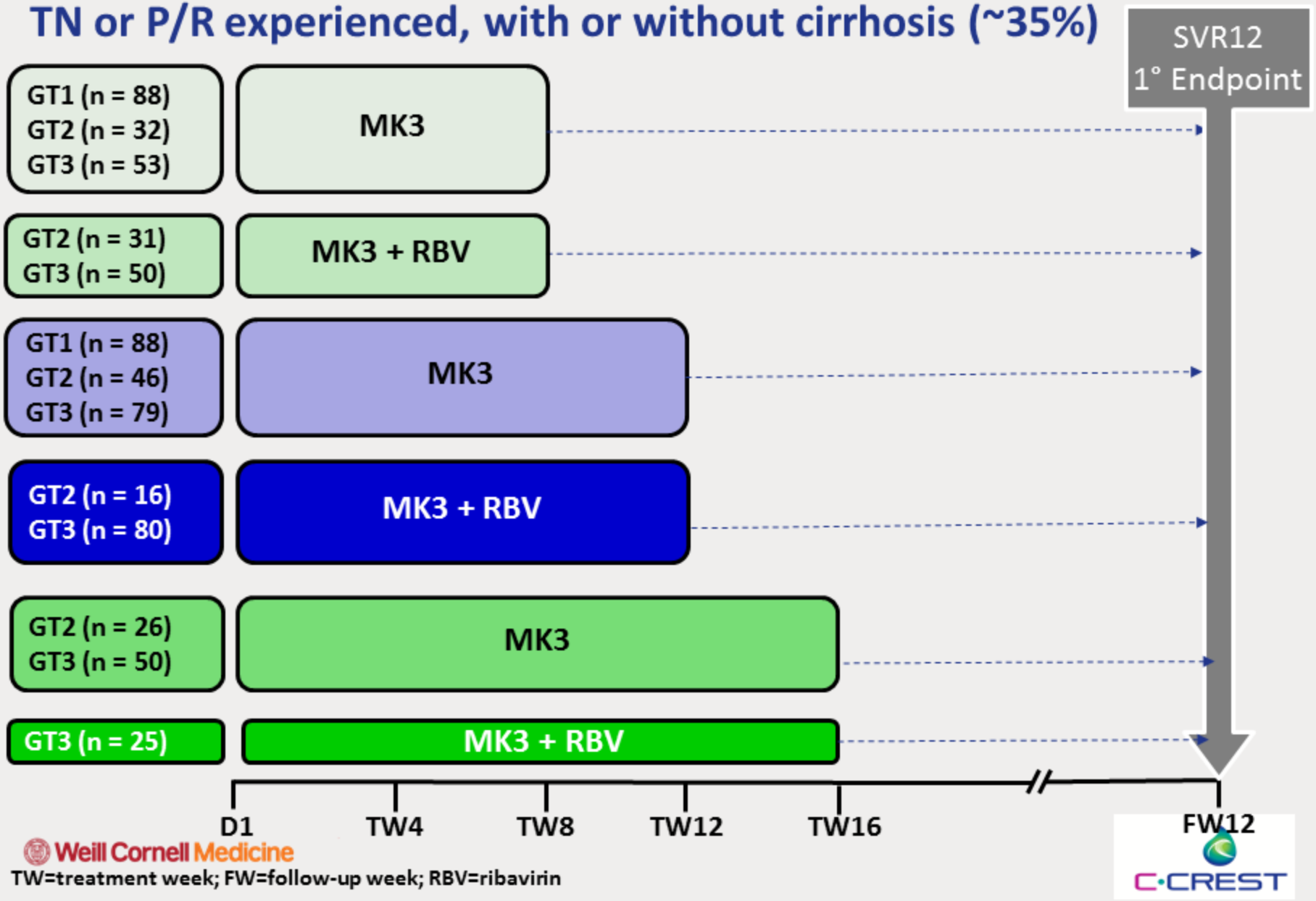
Modified full analysis set includes excludes patients who discontinued treatment for reasons unrelated to study medication

Foster et al AASLD 2016

MK-3682 GZR RZR

C-CREST (MK3: MK-3682/Grazoprevir/Ruzasvir; N=664)

TN or P/R experienced, with or without cirrhosis (~35%)



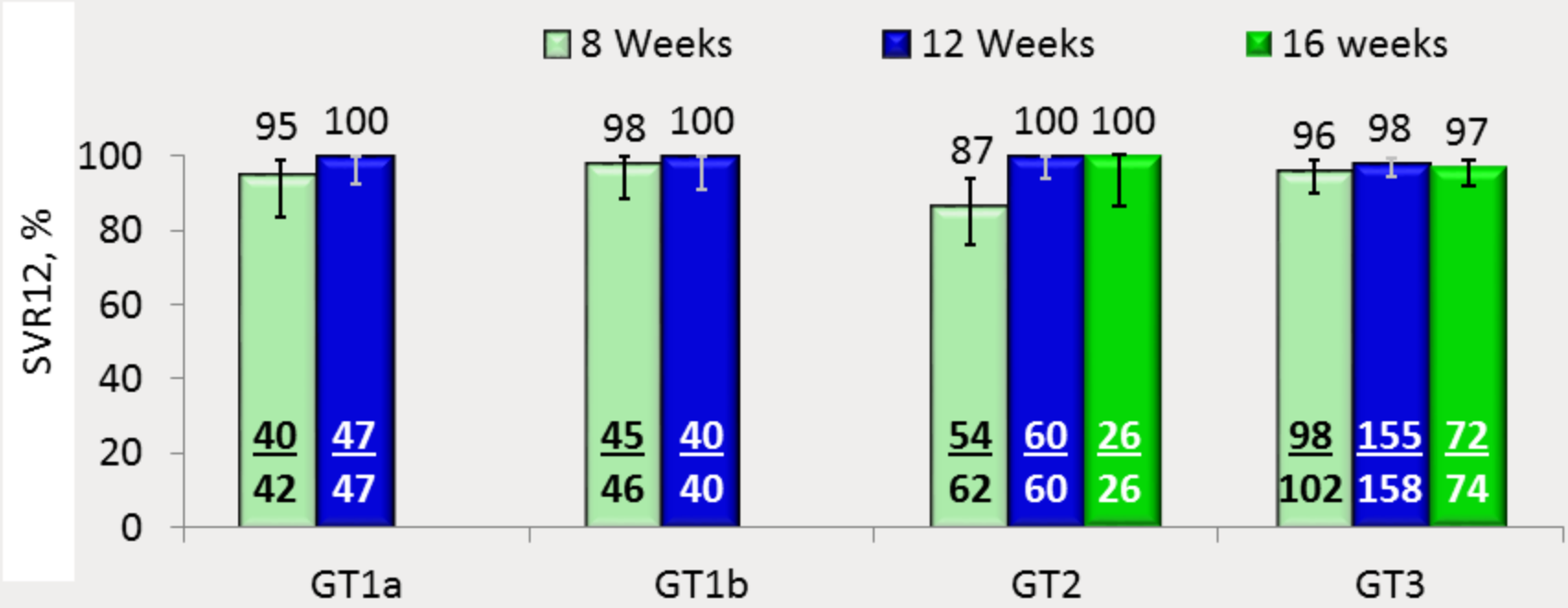
Weill Cornell Medicine

TW=treatment week; FW=follow-up week; RBV=ribavirin

C-CREST

SVR12 (Per Protocol): 8, 12 or 16 Weeks

MK-3682/Grazoprevir/Ruzasvir



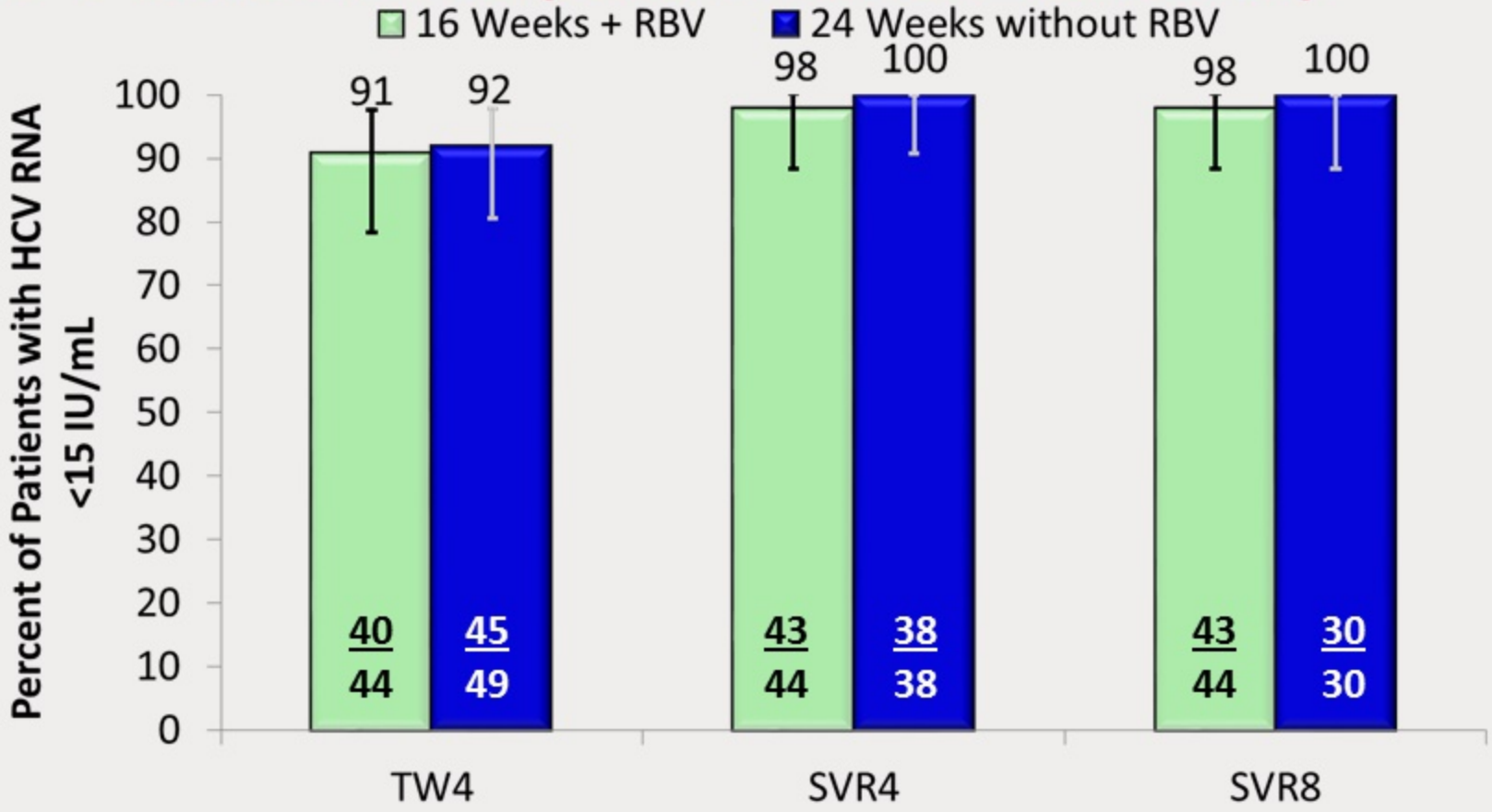
Relapses	2	0		1	0		7	0	0		4	3	2
Discontinuation (DR-AE)	0	0		0	0		1*	0	0		0	0	0

No difference with ribavirin or based on cirrhosis or prior P/R Rx

Lawitz et al
AASLD 2016

* One GT2 patient treated with 8 weeks + RBV discontinued at Day 5 due to drug-related AEs of fatigue, malaise

C-Surge: MK3: MK-3682/Grazoprevir/Ruzasvir GT 1 Failed DAA (SOF/LDV or EBR/GZR)



No virologic failure or impact of RAS (Y93 >40%)

Wyles et al AASLD 2016

Abbvie's DAA 2016 Programme

- **Glecaprevir (NS3A/4A) / Pibrentasvir (NS5A)**

Glecaprevir (formerly ABT-493) + Pibrentasvir (formerly ABT-530)

ENDURANCE Trials

GT1 non-cirrhotic including
HIV co-infection: 8 vs 12 weeks

GT2 placebo-controlled: 12 weeks
GT3 active comparator: 12 weeks
GT4-6: 12 weeks

MAGELLAN Trials

GT1,4-6 prior DAA failures:
12 vs 16 weeks

EXPEDITION Trials

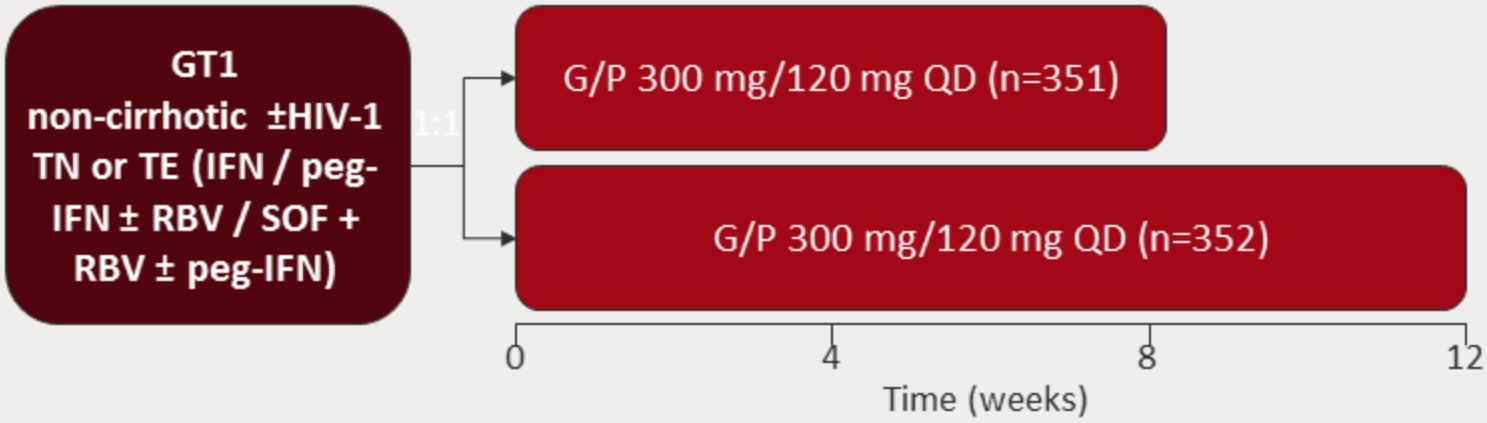
GT1, 2, 4-6 cirrhotic
GT1-6 severe renal impairment

SURVEYOR Trials

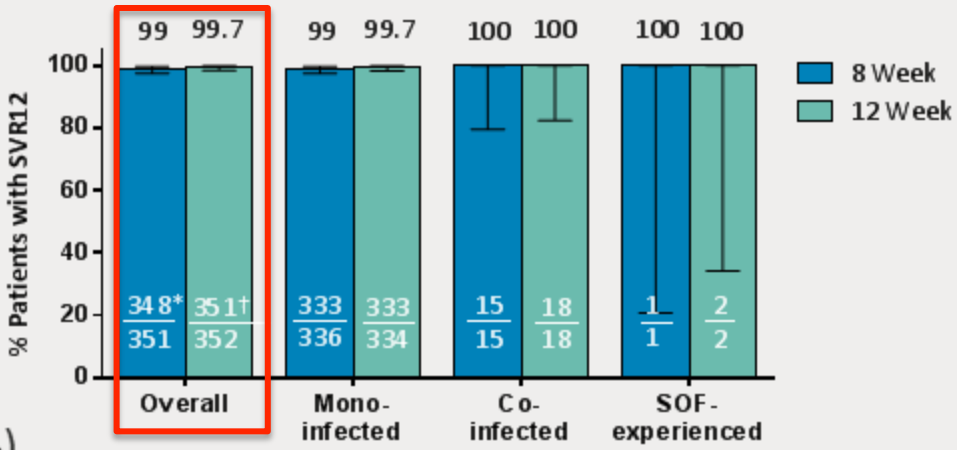
GT2, 4-6 non-cirrhotic: 8 weeks
GT3 cirrhotic and/or TE: 12 vs 16 weeks

ENDURANCE-1: G/P for 8 or 12 weeks
GT1 Non-cirrhotics, no NS5-A

Glecapravir/Pribrentasvir



Demographics	Patients N=703
GT1a	43%
F2–F3	15%

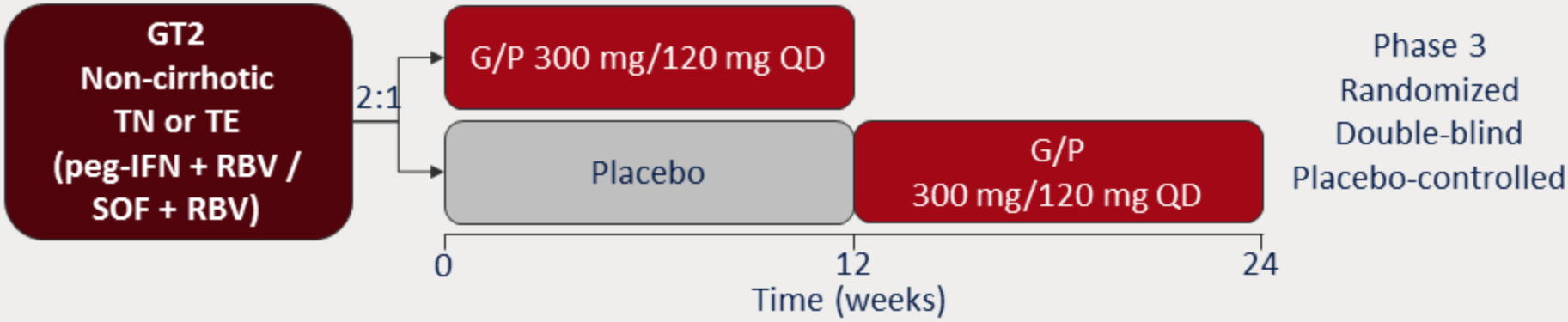


One virologic failure (8 weeks),
No impact of pre-existing RAS (NS5A ~25%)

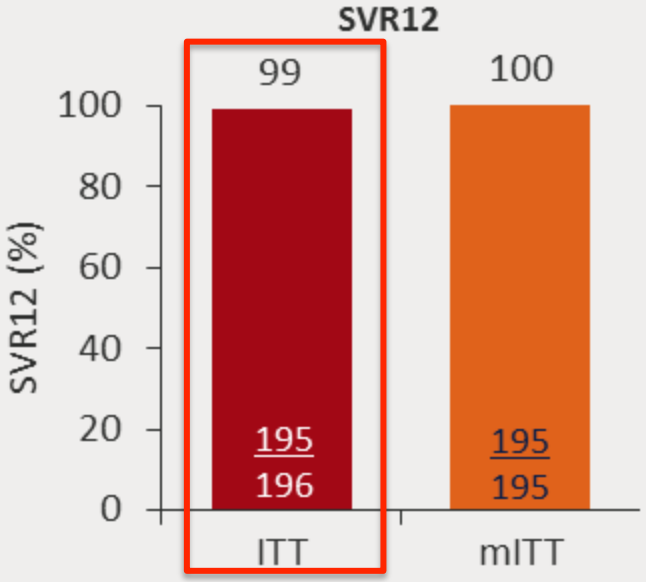
Zeuzem et al AASLD 2016

ENDURANCE-2: G/P x 12 12 weeks
GT2 without Cirrhosis, No NS5A

Glecapravir/Pribrentasvir



Characteristic	G/P N=202	Placebo N=100
Fibrosis Stage, n (%)		
F0-F1	154 (76)	85 (85)
F2	18 (9)	9 (9)
F3	30 (15)	6 (6)
Treatment experienced, n (%)	61 (30)	29 (29)
PPI use, n (%)	22 (11)	11 (11)

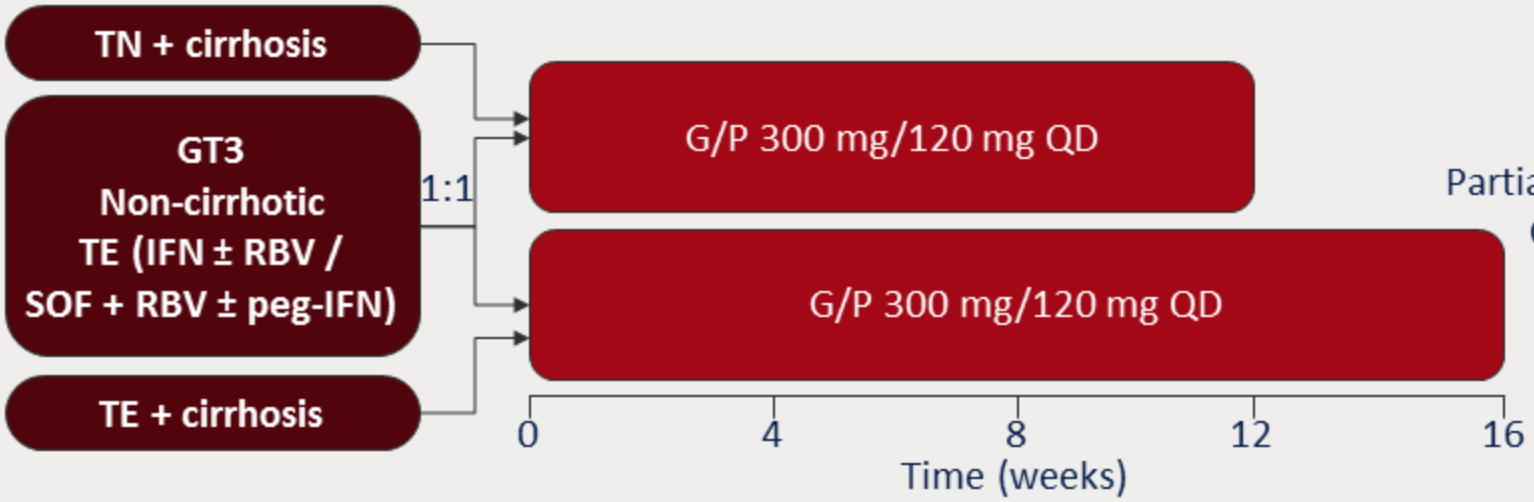


ITT population: excludes 6 SOF-experienced patients, all of whom achieved SVR12

mITT population: ITT population excluding 1 non-virologic failure who achieved SVR4

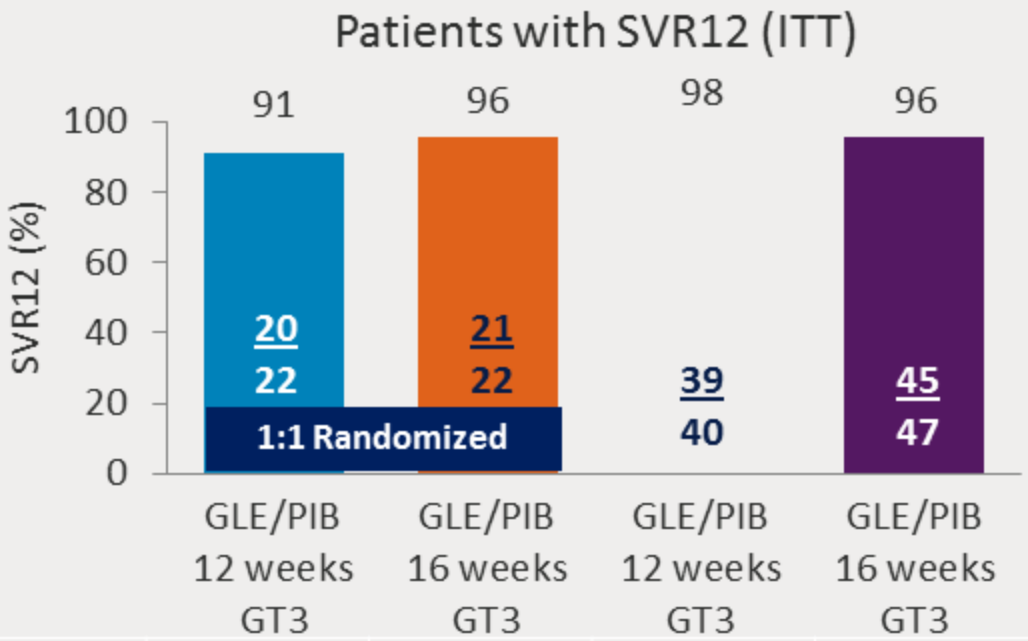
#73, Kowdley AASLD 2016

SURVEYOR-II, PART 3: G/P for 12-16 weeks
GT3 Infection with Prior Treatment Experience (no NS5A) and/or Cirrhosis



TE w/o Cirrhosis 12 Weeks N = 22	TE w/o Cirrhosis 16 Weeks N = 22	TN w/ Cirrhosis 12 Weeks N = 40	TE w/ Cirrhosis 16 Weeks N = 47

SURVEYOR-II, PART 3: G/P for 12-16 weeks
GT3 Infection with Prior Treatment Experience (no NS5A) and/or Cirrhosis



Cirrhosis	–	–	+	+
Treatment-experienced	+	+	–	+

#113, Wyles et at AASLD 2016

SURVEYOR-II, Part 4: G/P for 8 weeks
GT2, 4, 5, or 6 without Cirrhosis No NS5A experience

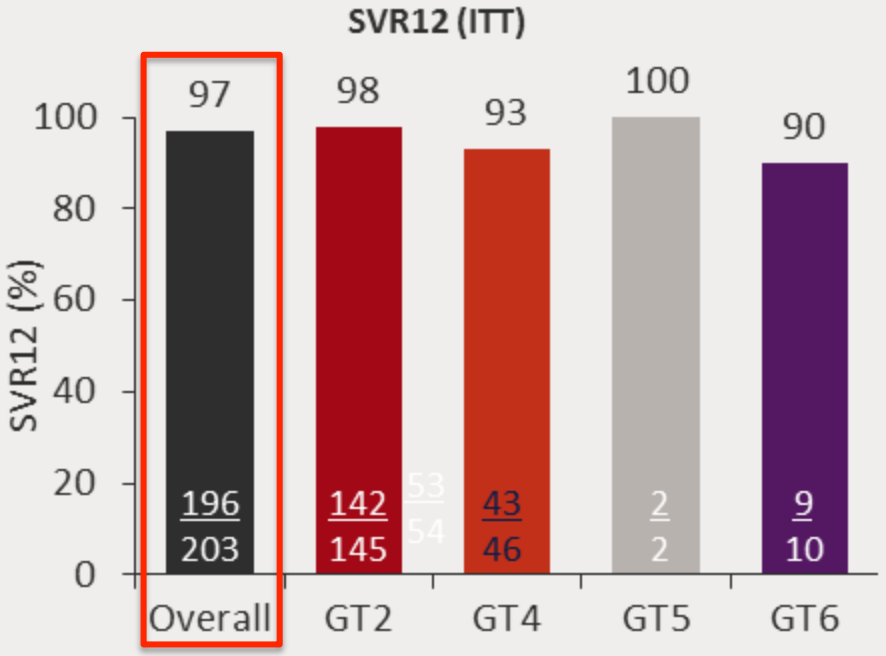
Phase 2, open-label, randomized, multicentre study

GT2, 4, 5, 6 Non-cirrhotic TN or TE (IFN- or SOF-based regimens)

→ G/P 300 mg/120 mg QD (N=203)

0 — 4 — 8 Time (weeks)

ENDURANCE-4: The safety and efficacy of 12-week G/P treatment were similar to SURVEYOR-II, Part 4



#LB-15, Hassanein at al AASLD 2016

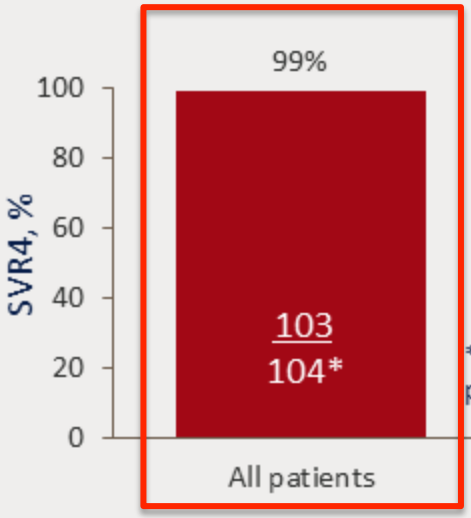
EXPEDITION-IV: G/P for 12 weeks in Renal Impairment GT1–6 with or without cirrhosis, P/R +/- SOF (No NS5A)

GT1–6 ± compensated cirrhosis TN or TE (IFN- or SOF-based regimens) **eGFR <30 mL/min/1.73 m²**

→ G/P 300 mg/120 mg QD (N=104)

0 — 4 — 8 — 12 Time (weeks)

Demographics	Patients N=104
Treatment-experienced	42%
Compensated cirrhosis	19%
GT1/2/3/4/5/6	52%/16%/11%/19%/1%/1%
CKD stage 4	13%
CKD stage 5	87%
Dialysis	82%



*The patient not achieving SVR4 prematurely discontinued treatment

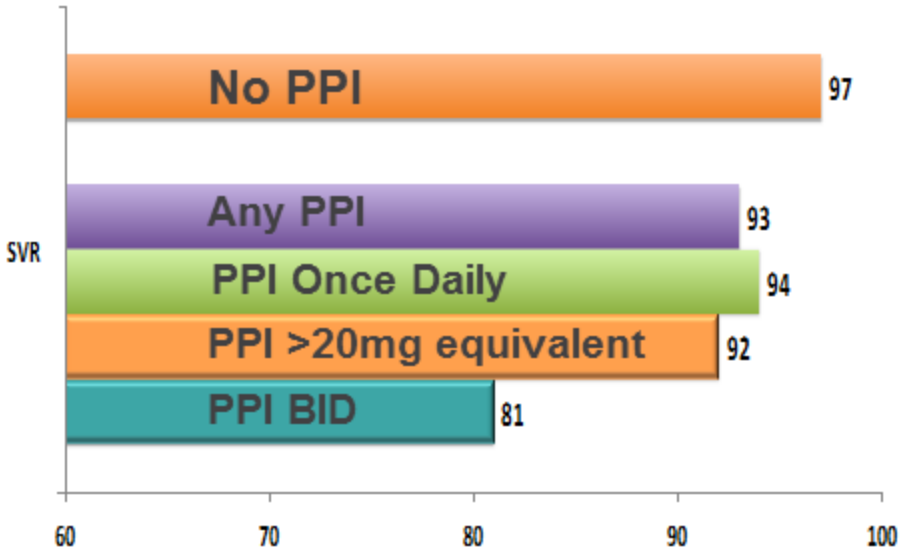
- Four AEs (4%) led to study drug discontinuation
- One patient died after achieving SVR4 due to a serious AE not related to study drug (intracerebral hemorrhage)

#LB-11, Gane et al AASLD 2016

Impact of PPI on Efficacy of LDV-SOF Therapy

HCV-Target

- PPI use at baseline was independent predictor of SVR
- OR=0.41 (95% CI: 0.25-0.67)



Terrault N, Gastroenterology 2016

TRIO

Propensity-Matched Cohorts

Group	All N=887	Cirrhosis N=337
No PPI	97%	96%
High dose PPI	98%	96%
BID PPI	91%	77%*
Any PPI	98%	96%

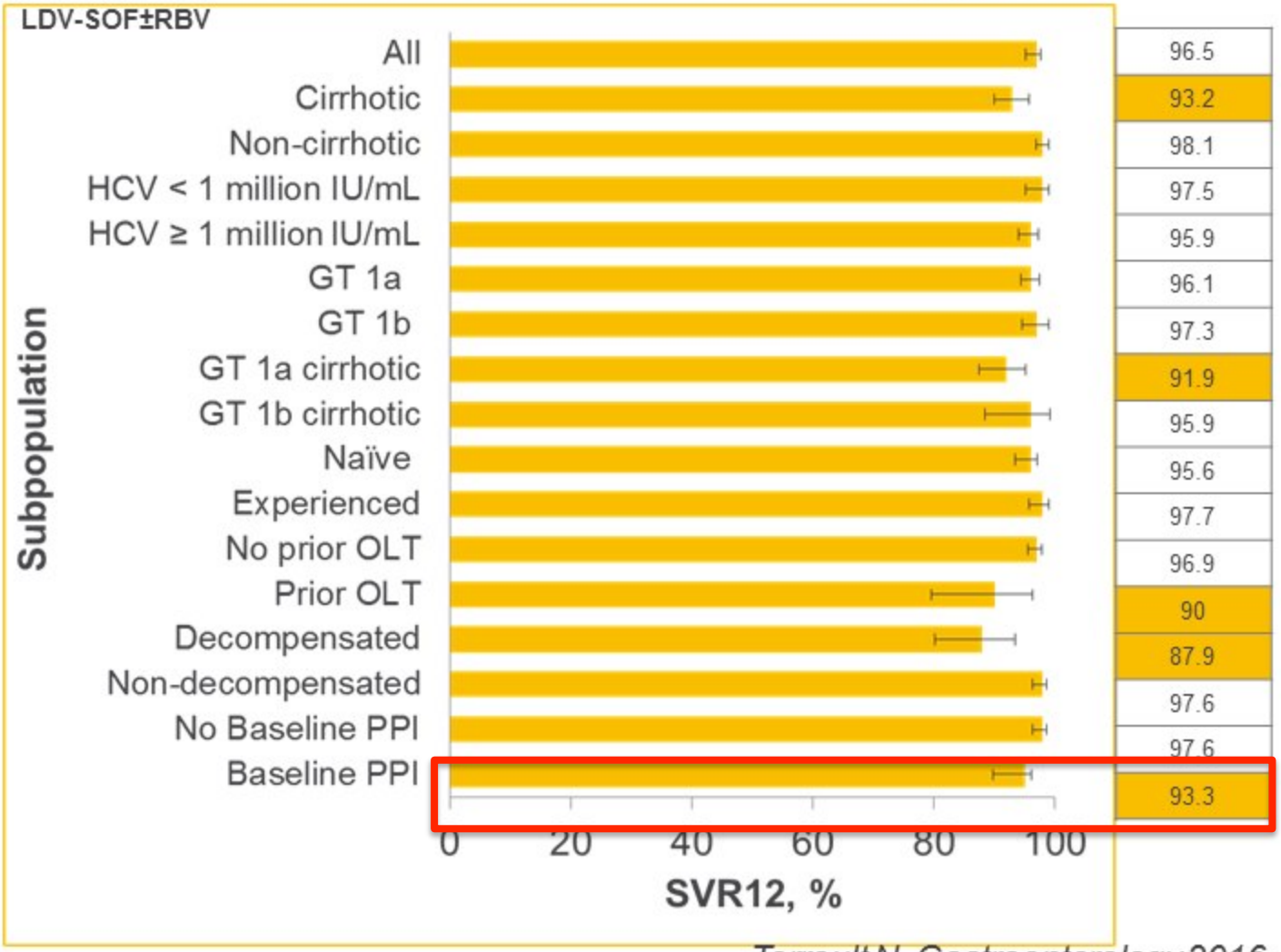
*P=0.05

- Only twice daily PPI at baseline associated with lower SVR
- Effect most marked in cirrhotics

Tapper E, Hepatology 2016

Multiplicity of Negative Predictors Impacts SVR Rates in Patients with Genotype 1

- Cirrhosis
- Child-Pugh Score
- Prior Treatment
- Baseline RASs
- Subgeno-type 1A
- BMI, PPI, Adherence



Terrault N, Gastroenterology 2016

Chronic HCV, DAA's and HCC

Italian Study: 3075 pts with chronic hepatitis C infection: Follow-up for mean of 300.8 days after the start of DAA therapy

- **Cumulative incidence rates of HCC not significantly different:**
  - F3 advanced fibrosis (0.23% per person per year)
  - Child-Pugh A cirrhotics (1.64% per person per year)
  - Child-Pugh B cirrhotics (2.92% per person per year)
- **Incidence rates no different from historic control cohorts** with similar patients from the same geographic region (Northern Italy) who did not receive antiviral therapy
- **Fibrosis and cirrhosis stage is the driving factor**, not oral direct-acting antiviral agents
- **Severity of HCC did appear to correlate with antiviral therapy over a 540-day follow-up period**
  - 5 (12.2%) pts had portal vein thromboses & 4 (9.7%) had extra-hepatic metastases

Disease Severity in the 41 Patients Who Developed HCC

Disease Severity	n	%
1 nodule, with typical vascular patterns	20	48.8
2 or 3 nodules	5	12.2
>3 nodules or infiltrative hepatocellular carcinoma	16	39.0

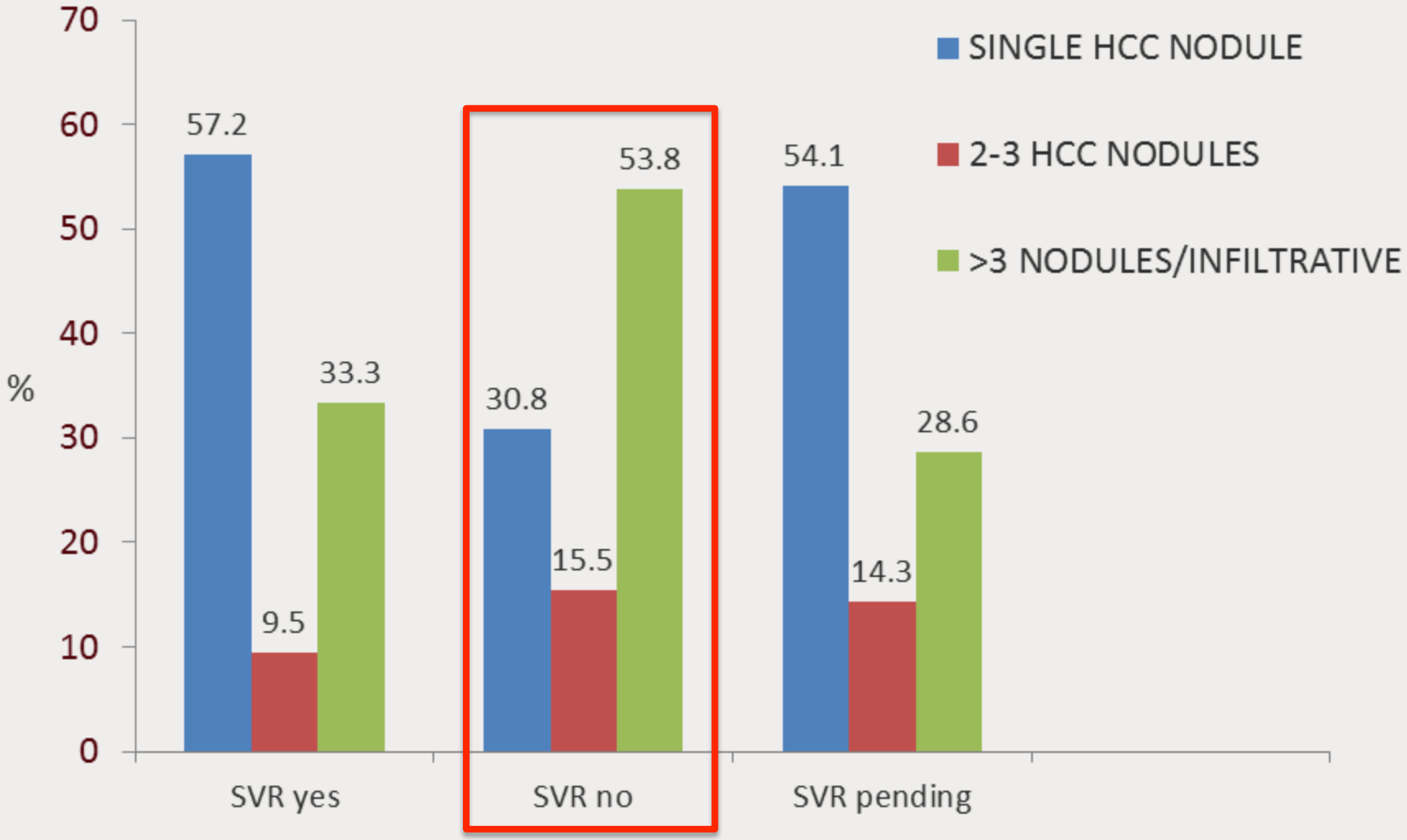
- **At 12 weeks, HCC more aggressive in pts who did not achieve SVR12** vs pts with SVR vs undetermined response (53.8% vs 33.3% vs 28.6%)
- HCC diagnosed at wk 4 in 3 patients, at wk 8 in 3 patients, at wk 12 in 6 patients, from wk 12 - 23 in 13 patients, and after EOT in 16 pts

Multivariate Analysis: SVR12 significant predictor of HCC: HR 0.20; *P* = .001

- Changes in immunologic and molecular microenvironment in liver and in tumor suppression mechanisms, which could allow or even promote the growth of previously undiagnosed microscopic hepatocellular carcinoma foci

Romano et al; Abstract 19; November 13, 2016

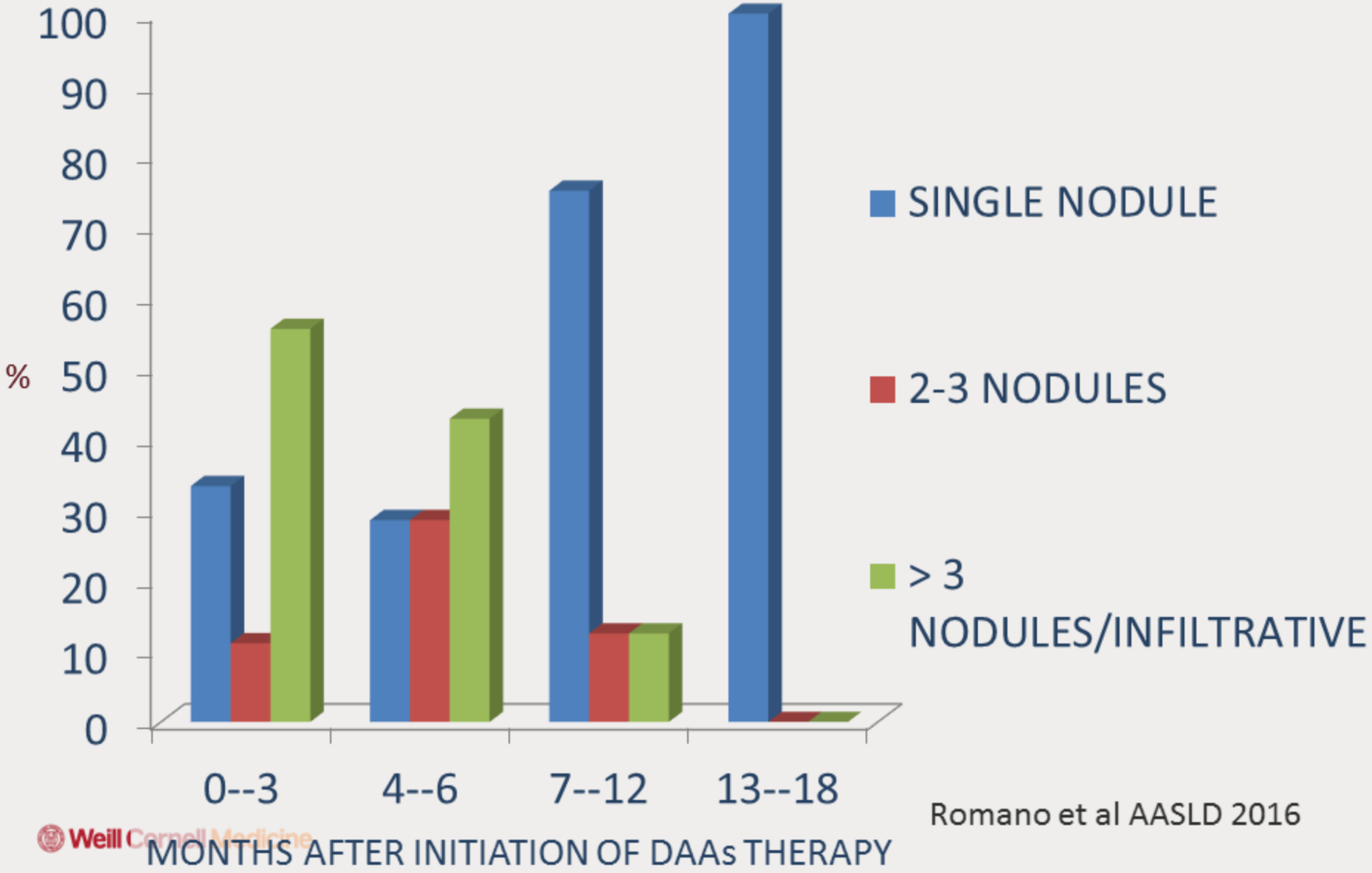
HCC PATTERNS IN RELATION TO SVR



Weill Cornell Medicine

Romano et al AASLD 2016

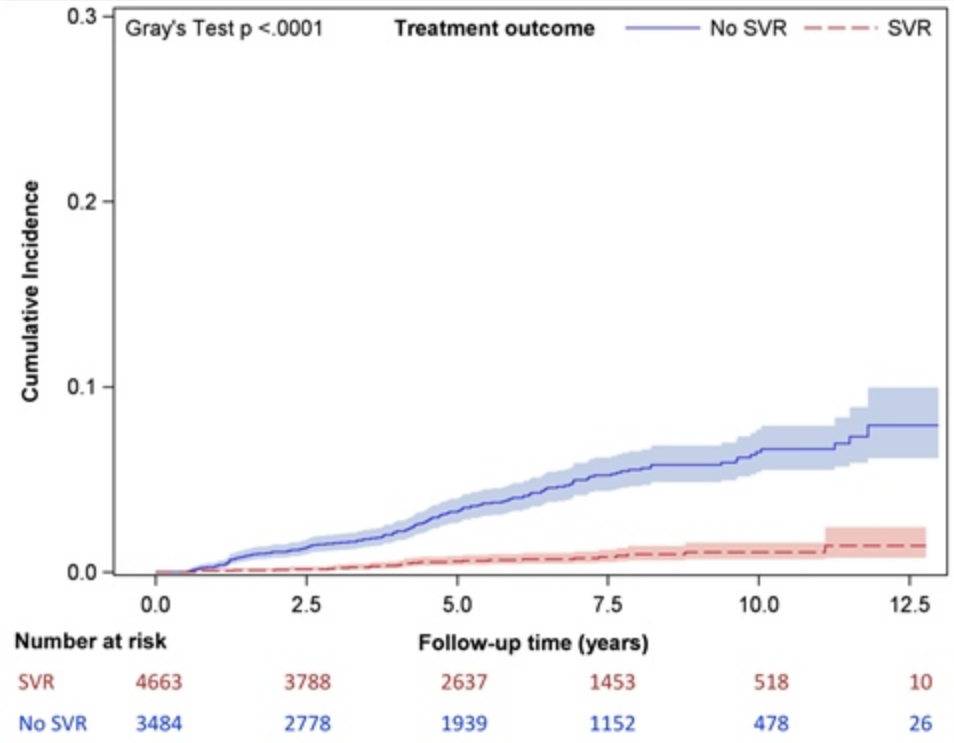
PATTERNS OF HCC DEVELOPMENT IN RELATION TO TIMING OF DAA TREATMENT



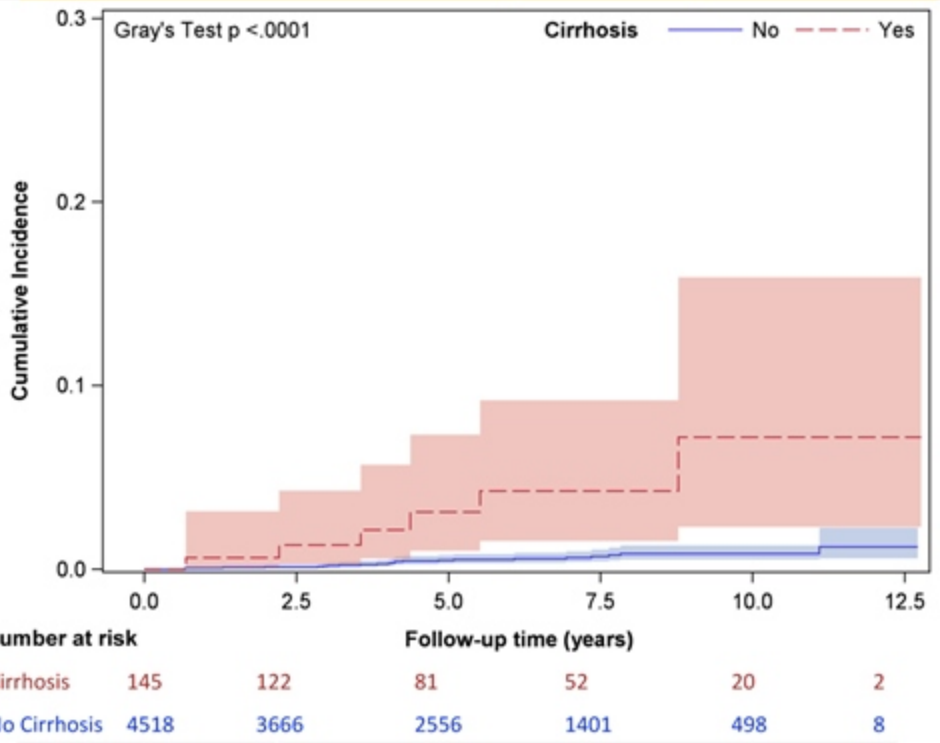
Romano et al AASLD 2016

Cumulative incidence of HCC by SVR & cirrhosis

Cumulative incidence of HCC by SVR



Cumulative incidence post SVR by cirrhosis



	N	HCC	Incidence rate
SVR	4663	29	1.1/1000 PY
No SVR	3484	145	7.2/1000 PY

	Incidence rate (95%CI)/ 1000 PY	
	SVR	No SVR
Cirrhosis	7.0 (3.2, 15.6)	20.1 (13.7, 29.5)
No Cirrhosis	0.9 (0.6, 1.3)	6.3 (5.3, 7.5)

BC Centre for Disease Control

Median follow-up: 5.6 years

Janjua et al AASLD 2016

HTC British Columbia Hepatitis Testers Cohort

HCV : Late Relapse or Reinfection

Systematic review & meta-analysis: 59 studies (>9000 pts)

- Mono-HCV infected "low-risk" patients;
- Mono-HCV infected "high-risk" patients : PWUD or prisoners
- HIV/HCV co-infected patient

Overall 5 year recurrence rates

- Low-risk patients : 0.95%
- High-risk patients : 10.67%
- HCV/HIV co-infected patients : 15.02%

Increase in reinfection rather than late relapse

- Prevention campaigns for individuals at high-risk of HCV re-exposure

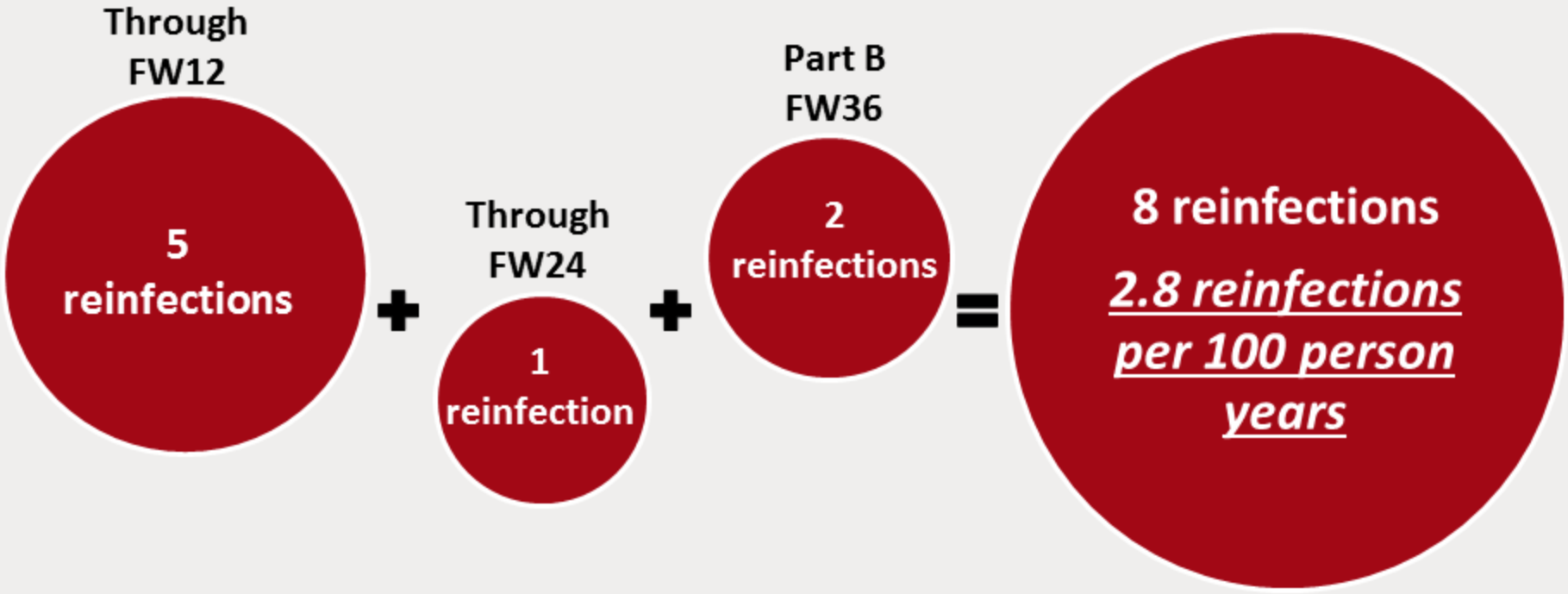
Simmons et al; Clin Infect Dis 2016, Jan 19

C-EDGE Co-Star

Incidence of reinfection post SVR in 199 patients on OST

~50% illicit drug use

Grazoprevir/Elbasvir



8 Total Reinfections From End of Treatment Through All Available Follow-up

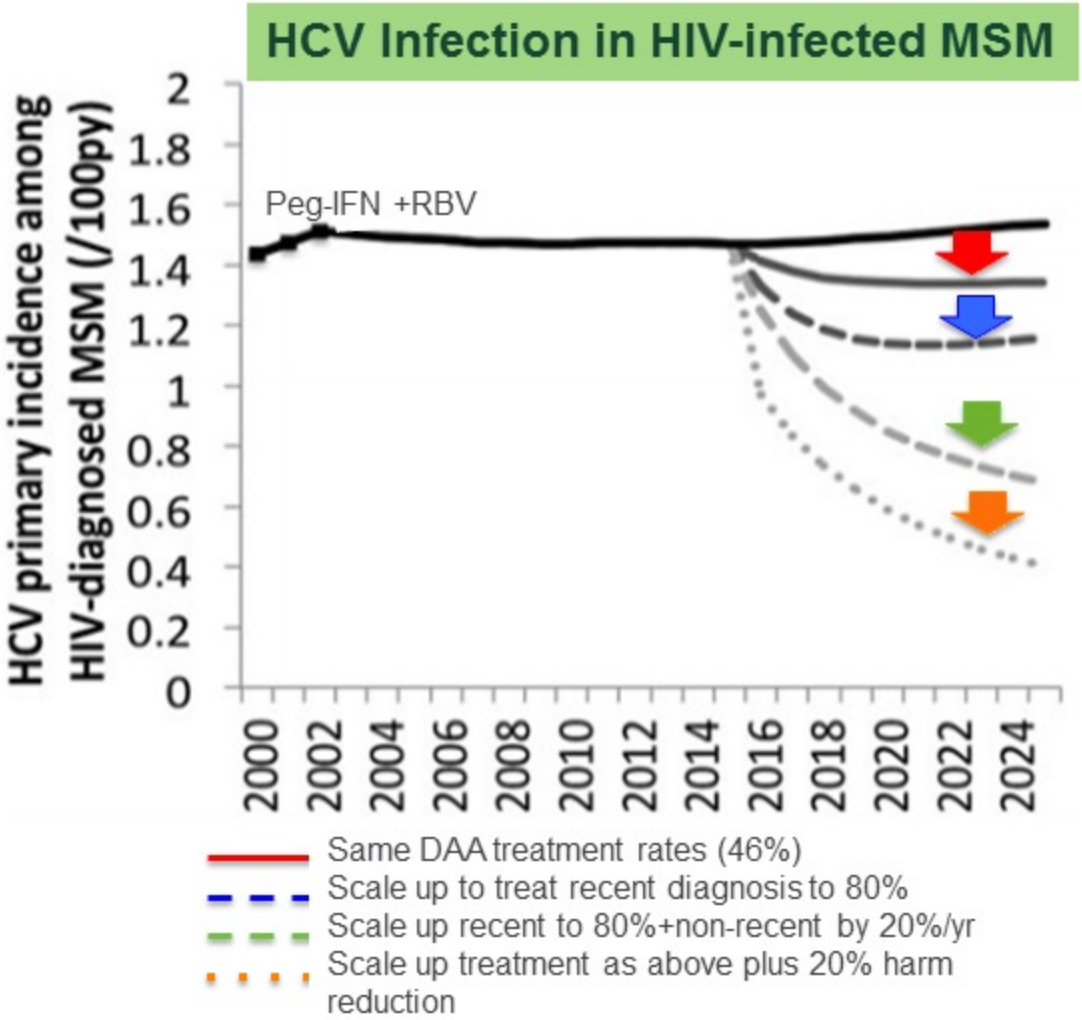
- **286.8 person-years of follow-up**
- **2.8 reinfections per 100 person years (95% CI: 1.2, 5.5)**

Dore et al AASLD 2016

Treatment to Prevent Transmission to Others

- Women of child-bearing age
- PWIDs
- MSM with HIV

- Treatment of persons in these subgroups reduces prevalent and incident infections
- In PWIDs and MSM with HIV, need to treat early disease to achieve elimination



Martin NK, Clin Infect Dis 2016;62:1072-80

Hepatitis B Reactivation : DAA therapy

US FDA received 24 unique reports of HBV-R associated with DAA Rx

- **Boxed warning**
- **2 fatal outcomes and 1 liver transplantation**
- **HBV-R: Pts were heterogeneous:** HCV genotype, DAA received, and baseline HBV viral parameters
- **At baseline:** 7 patients had detectable HBV VL, 4 patients had a positive HBsAg and undetectable HBV VL, & 3 patients had negative HBsAg and undetectable HBV VL
- The remaining cases either did not report these data points, or data were interpretable
- Despite provider knowledge of baseline HBV status, **delay in diagnosis and treatment of HBV-R was noted in 5 cases**, with possible delay in 3 others
- **Limitations: Spontaneous reporting system** subject to variable data quality and underreporting
- Unable to estimate incidence of DAA associated HBV-R, and ability to make causal inference is limited
- **Patients with history of HBV require clinical monitoring while on DAA's**
  - Need full HBV serology

Bersoff-Matcha et al, LB Abstract 17, AASLD 2016

Hepatitis B Reactivation : DAA therapy

Meta-analysis 35 studies involving 1121 CHC patients

- 30 studies were using interferon
- All studies reported SVR rates, 26 studies reported HBV reactivation, 22 studies reported occurrence of hepatitis due to HBV reactivation

Overall SVR rate was 47% in HBV/HCV co-infected patients

- SVR rate: Interferon (43%) and DAAs (100%); $p<0.001$

Overall HBV reactivation rate 12.3%: IFN (12.4%) & DAAs (12.2%, p=0.90)

Overall incidence of hepatitis due to HBV reactivation

- 0.3% (0-1.1% in IFN treated) vs. 0.2 -33.2% with DAAs, p=0.02
- Most cases HBV reactivation occurred during follow-up of IFN treatment (3 wks to 72 months post-treatment)
- **All cases were observed during DAAs treatment** (4 to 11 wks during Rx)

Wang et al; Abstract 918, AASLD 2016

Liver Tx: DAA Therapy and Purgatory MELD: Fact or Fiction?

UNOS database: 20,411 HCV waitlist LT candidates:

- 10,606 candidates 18 months pre-DAA: May 2012 to October 2013
- 9,805 candidates in post-DAA period: January 2014 to June 2015

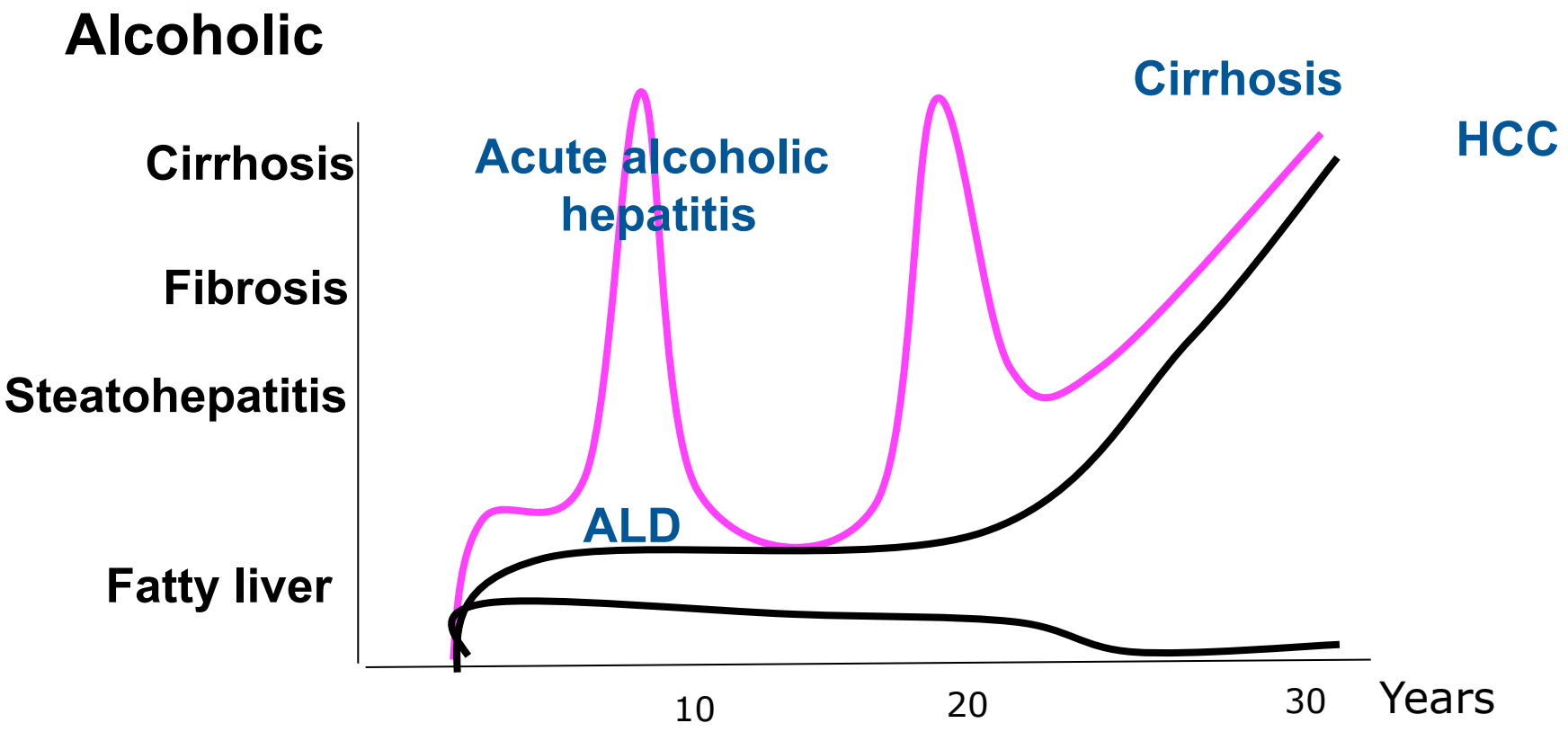
Compared to pre-DAA period

- HCV waitlist LT candidates during post-DAA : significantly lower rate
  - Removal due to death (7.4 % to 11.5%, $p < 0.01$)
  - Too sick to transplant (7.9% to 11.3%, $p < 0.01$)
- Post-DAA HCV waitlist LT candidates had a significantly lower rate of liver transplantation (29.9% to 38.7%, $p < 0.01$)

This should be taken into account in setting of poor donor access

Cholankeril et al, Abstract 859, AASLD 2016

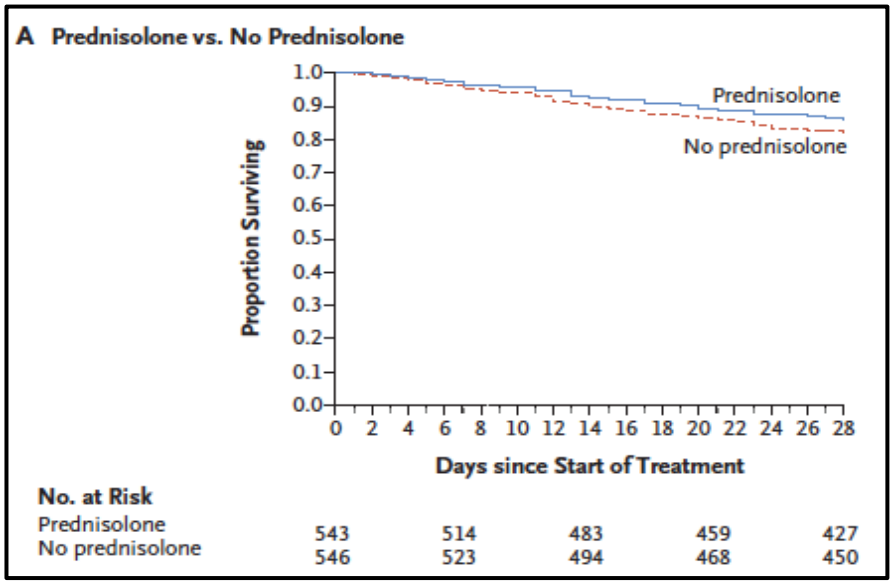
Alcoholic Liver Disease

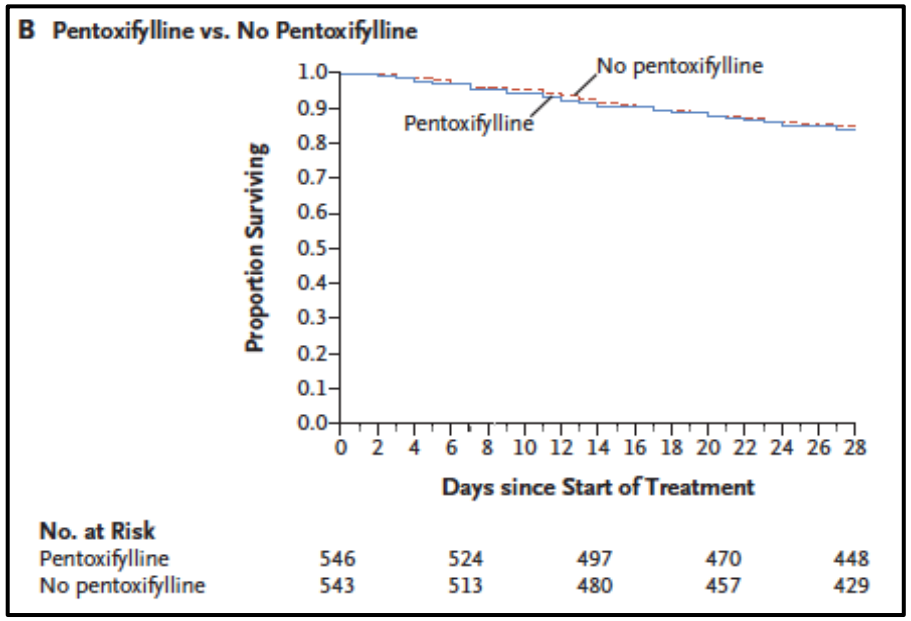


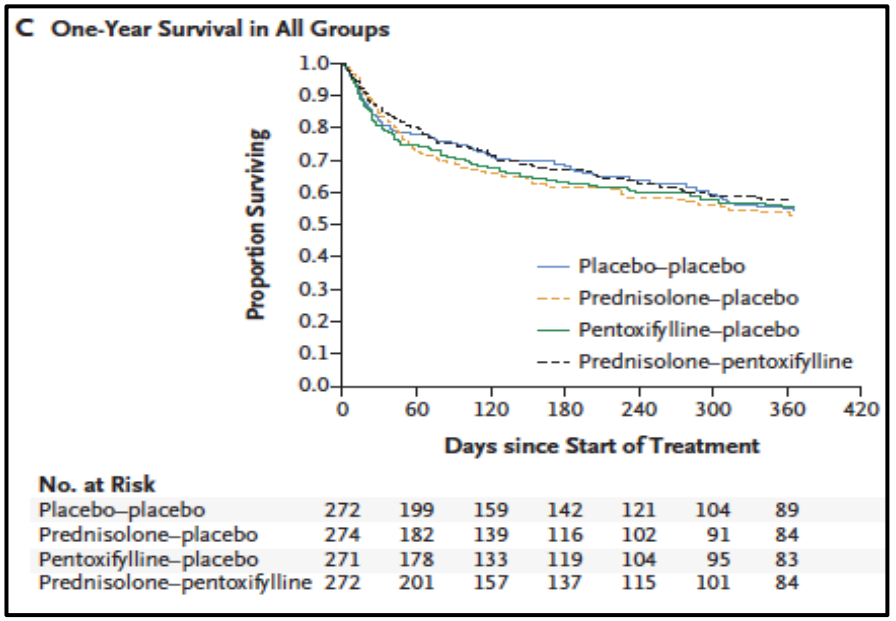
STOPAH Trial : Prednisolone or Pentoxifylline for AH

Multicenter, double-blind, randomized trial: 1103 pts

- Prednisolone reduction : 28-day mortality
  14% (Pred) vs 19% (PTX) vs 17% (placebo)
- No outcome improvement : 90 days or 1 yr
- Prednisone: serious infections 13% vs 7%
- 37% completely abstinent at 1yr





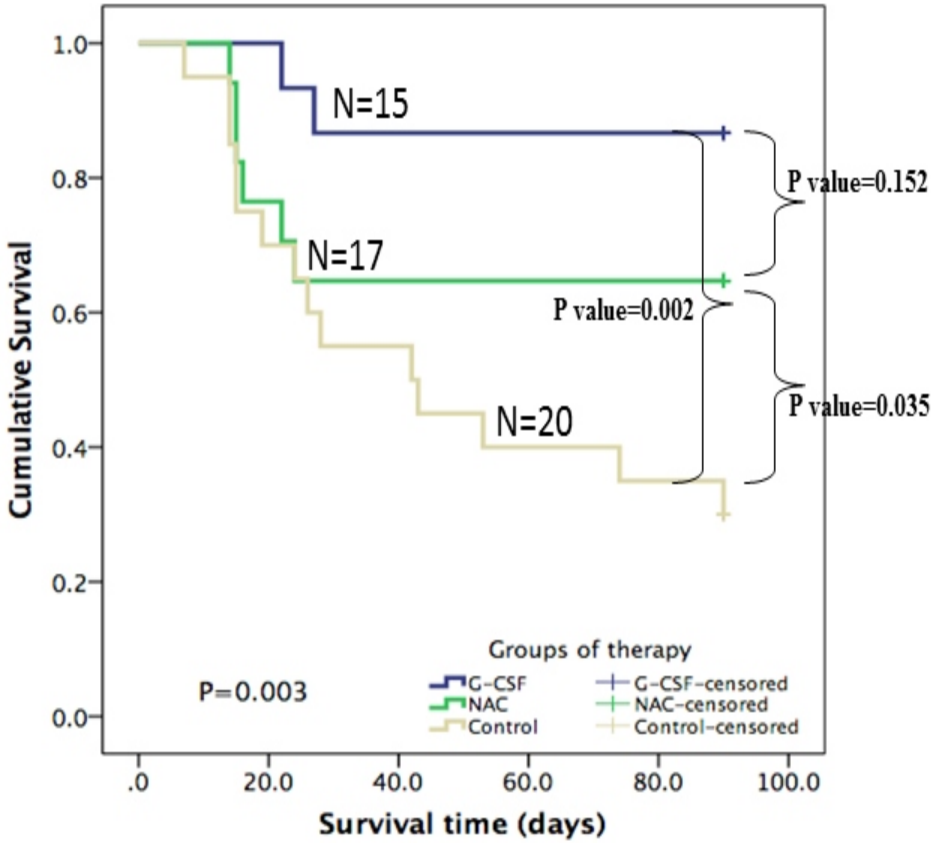


NEJM 2015;372 (17):1619

Abstinence and 1-Year Mortality

Alcohol consumption at Day 90	Odds Ratio for 1-year mortality			
	n	**Odds ratio**	95% Confidence Interval	p-value
Abstinent	321	**1.0**	Reference	
Not reduced	50	**2.99**	1.47 - 6.05	<0.001
Reduced but above safety limits	48	**2.28**	1.07 - 4.86	0.032
Reduced to below safety limits	59	**2.17**	1.07 - 4.39	0.031

Granulocyte-Colony Stimulating Factor (G-CSF) plus N-Acetyl Cysteine (NAC) in Severe Alcoholic Hepatitis

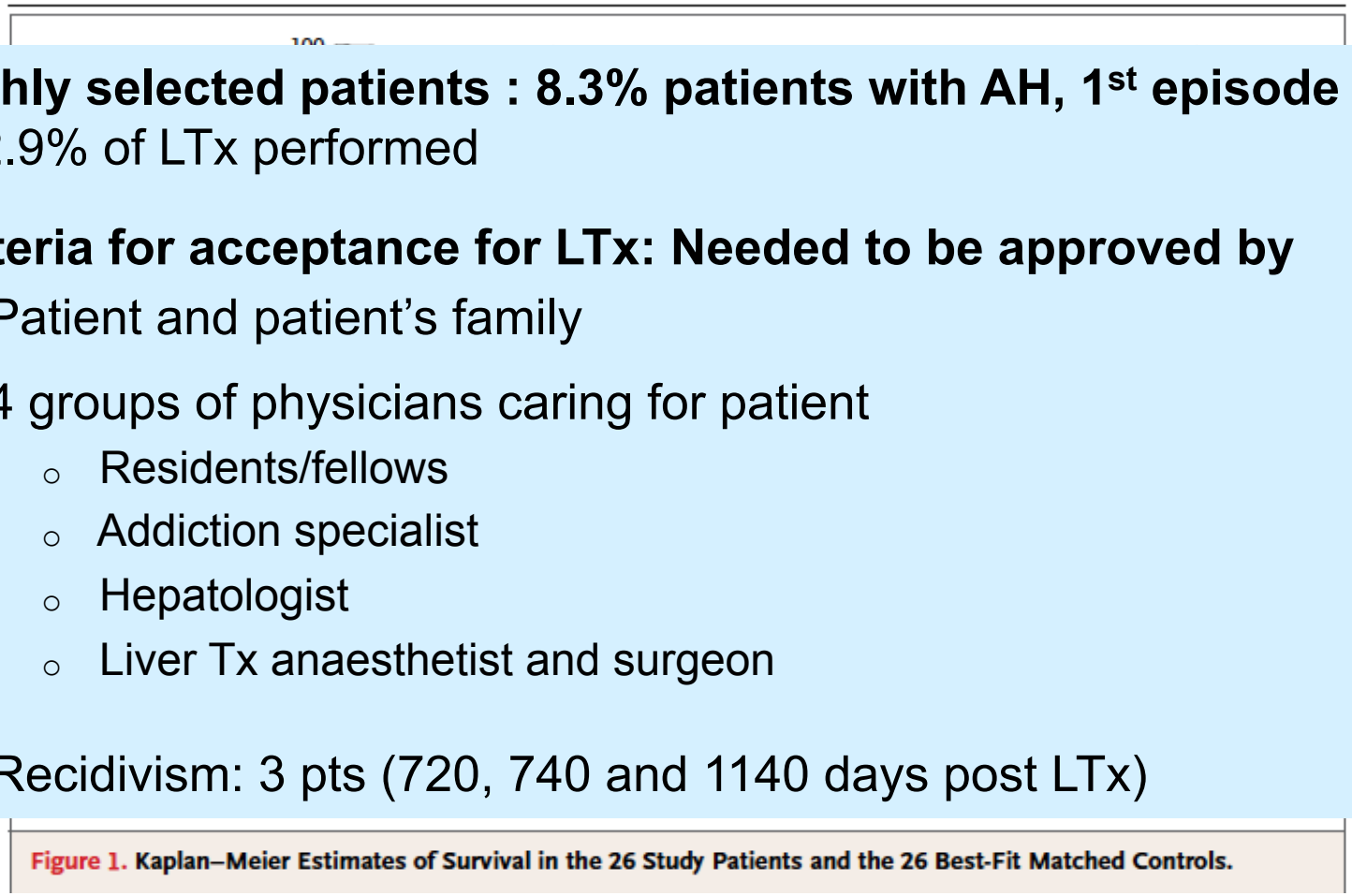


- Rationale: GCSF +/- NAC is superior to placebo
- Underpowered (NEED DEFINITIVE TRIAL)

Abstract # LB4, Sharma et al, PGI Chandigarh

Liver Transplantation in Acute Alcoholic Hepatitis

Multicentre Franco-Belgian Study: 26 pts failed to respond to prednisone (Lille score >0.45. Received LTx, mean of 13 days after stopping steroids



Highly selected patients : 8.3% patients with AH, 1st episode

- 2.9% of LTx performed

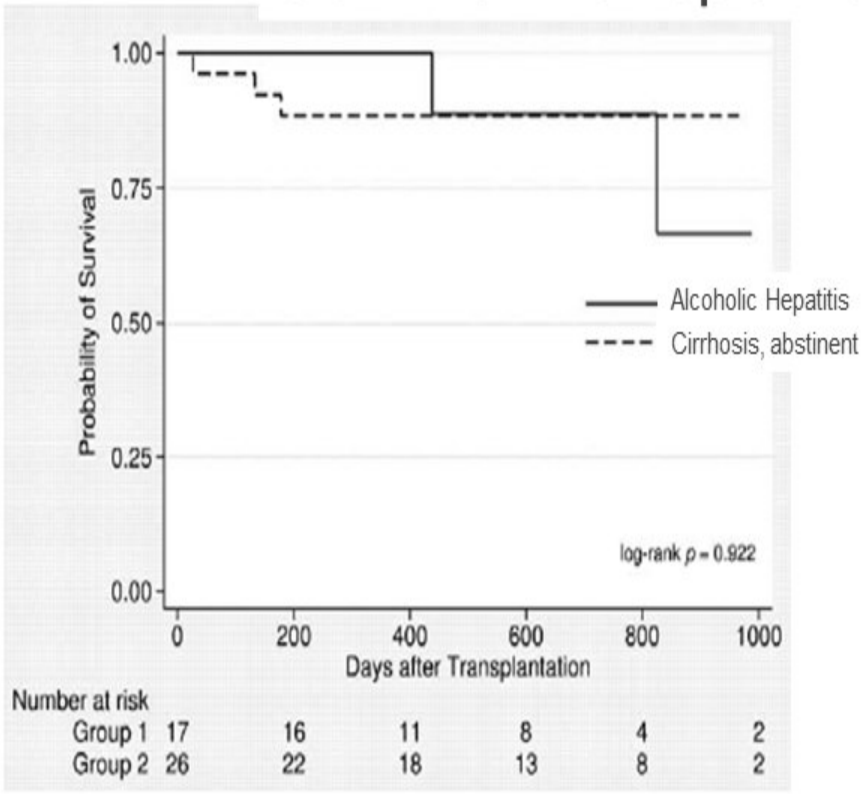
Criteria for acceptance for LTx: Needed to be approved by

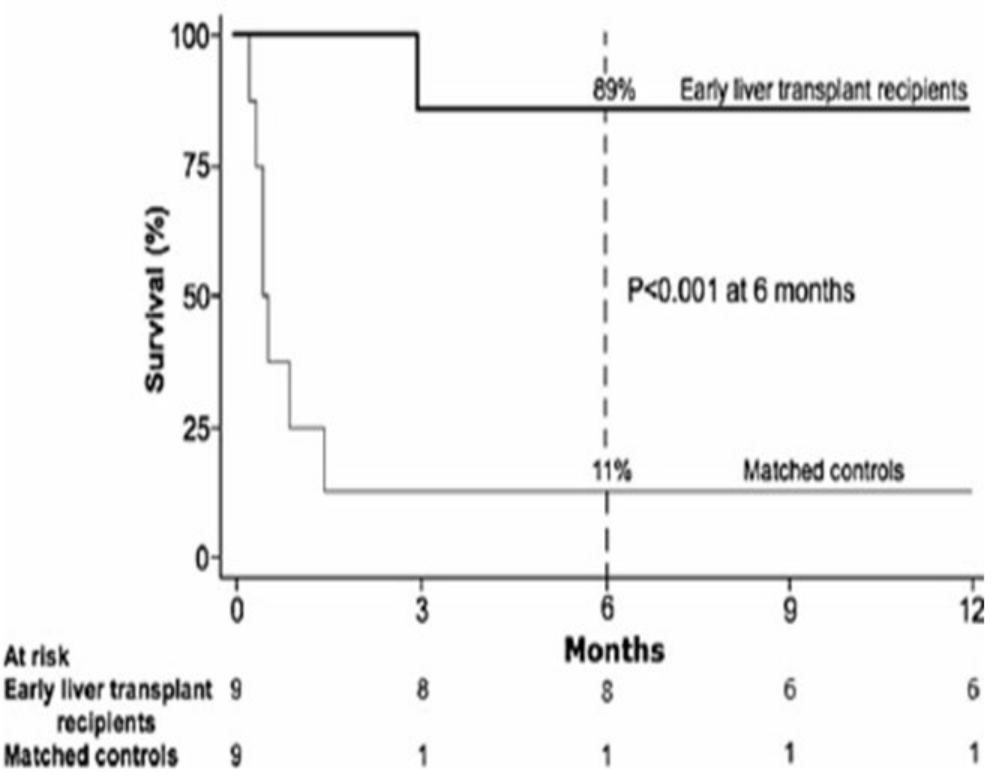
- Patient and patient's family
- 4 groups of physicians caring for patient
  - Residents/fellows
  - Addiction specialist
  - Hepatologist
  - Liver Tx anaesthetist and surgeon
- Recidivism: 3 pts (720, 740 and 1140 days post LTx)

Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

NEJM 2011;365(19): 1790

US Liver Transplantation for Alcoholic Hepatitis





17 patients with AH vs. 26 abstinent cirrhosis
100% survival at 1-year in AH
Recidivism: AH: 23.5% vs. Cirrhosis: 29.2%
Harmful drinking: AH: 23.5% vs. Cirrhosis: 11.5%

Lee Ann Surgery 2016

9 patients with AH vs. matched AH (no OLTX)
89% 6-month survival (and 1-year survival)
Recidivism: 2 slips (minor alcohol use)
1 harmful drinking (12.

Im Am J Transplant 2016

Alcoholic Cirrhosis and Statins

Propensity score matched cohort: 2275 pts compensated cirrhosis and 1435 pts with decompensated cirrhosis

- 25% patients on statins in each group
- **Primary end point:** Incidence of death at 15 years
- **Mortality Rates Halved**

Cirrhosis Group	Statin Users	Nonusers	*P* Value
Compensated			
Incidence of death at 15 years	31%	50%	<.0001
Median survival	7.8 years	3.5 years	<.0001
Decompensated			
Incidence of death at 15 years	38%	54%	<.0001
Median survival	3.9 years	2.2 years	<.0001

- Improved survival in patients with Child-Pugh class A or B cirrhosis, but not in patients with class C

Gastroenterology. 2016;150:1160-1170.e3)

Alcoholic Cirrhosis and Statins

Mortality rates lower in statin users

- Compensated cirrhosis (86 vs 199 per 1000 person-years)
  - Adjusted HR 0.45; *P* < .0001
- Decompensated cirrhosis (132 vs 290 per 1000 person-years);
  - Adjusted HR, 0.55; *P* <.0001

Risk for decompensation: Secondary end point

- Lower in statin users (10% vs 25%; adjusted HR 0.31; *P* < .0001)
- Statins are thought to have an anti-inflammatory effect on the liver
- Reduces portal hypertension, a prognostic marker for death

Propensity score matching was used to rule out as many confounders

Gastroenterology. 2016;150:1160-1170.e3

CHOLESTATIC LIVER DISEASE

PBC

- **Chronic immune-mediated lymphocytic cholangitis**
- Early diagnosis and initiation of UDCA (13-15 mg/kg/day)
  - 66% patients have expected survival equivalent to general population
  - Only a minority will develop cirrhosis

Proposed Name change: Primary Biliary Cholangitis

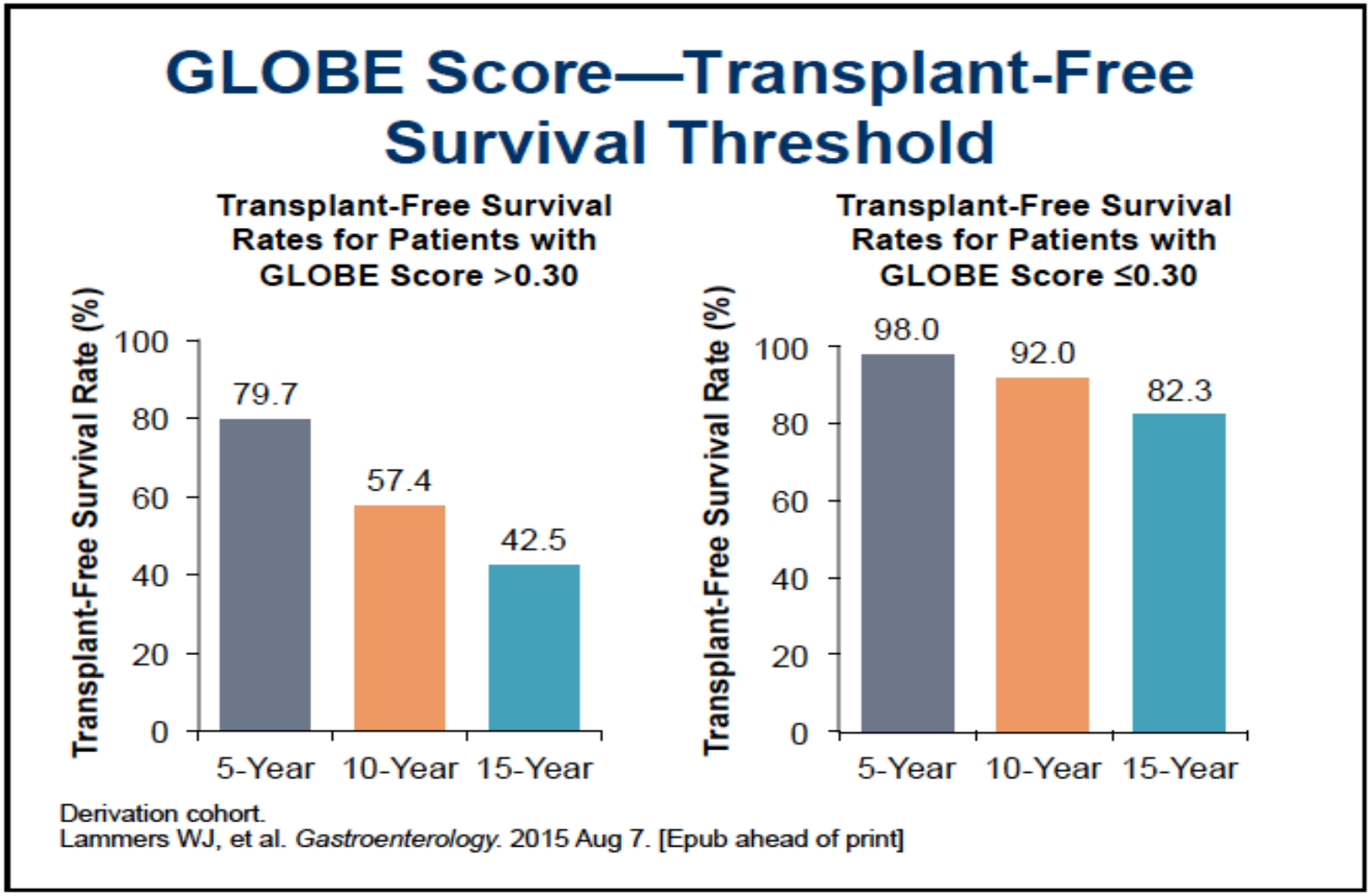
- Proposed by Dame Sheila Sherlock in 1959 !
- Accepted in 2015 by AASLD, EASL and AGA

Can we stratify risk of progression to cirrhosis ?

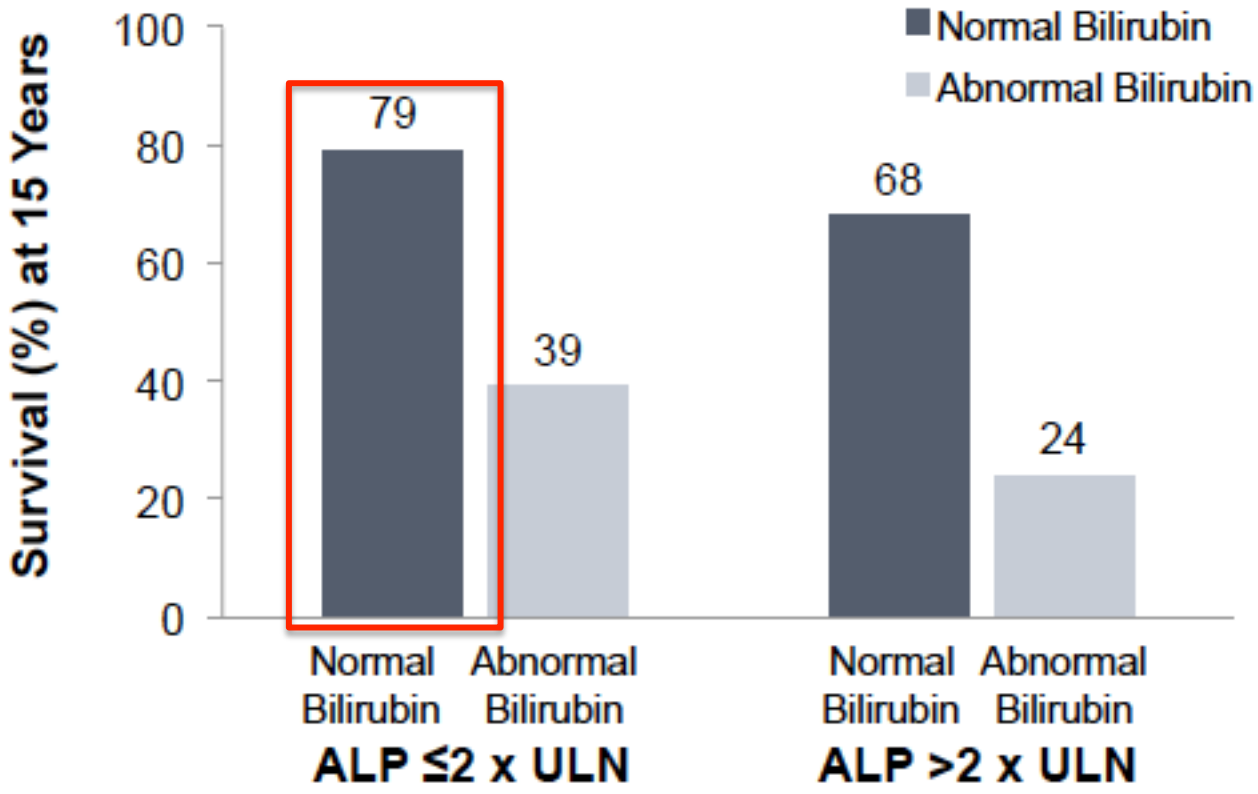
On treatment (UDCA) biochemical response at 1 year– most robust endpoint to stratify risk of progression and potential need for 2nd line Rx

- **GLOBE score:** http://globalpbc.com/globe
- **UK-PBC risk score:** http://www.uk-pbc.com/resources/tools/riskcalculator/

GLOBE score : (0.044378 * age at start of UDCA therapy + 0.93982 * NL(Bili x ULN) at 1 year)) + (0.335648 * NL(ALP x ULN at 1year)) – 2.266708 * Alb x LLN at 1 year – 0.002581 * PLT at 1 year) + 1.216865



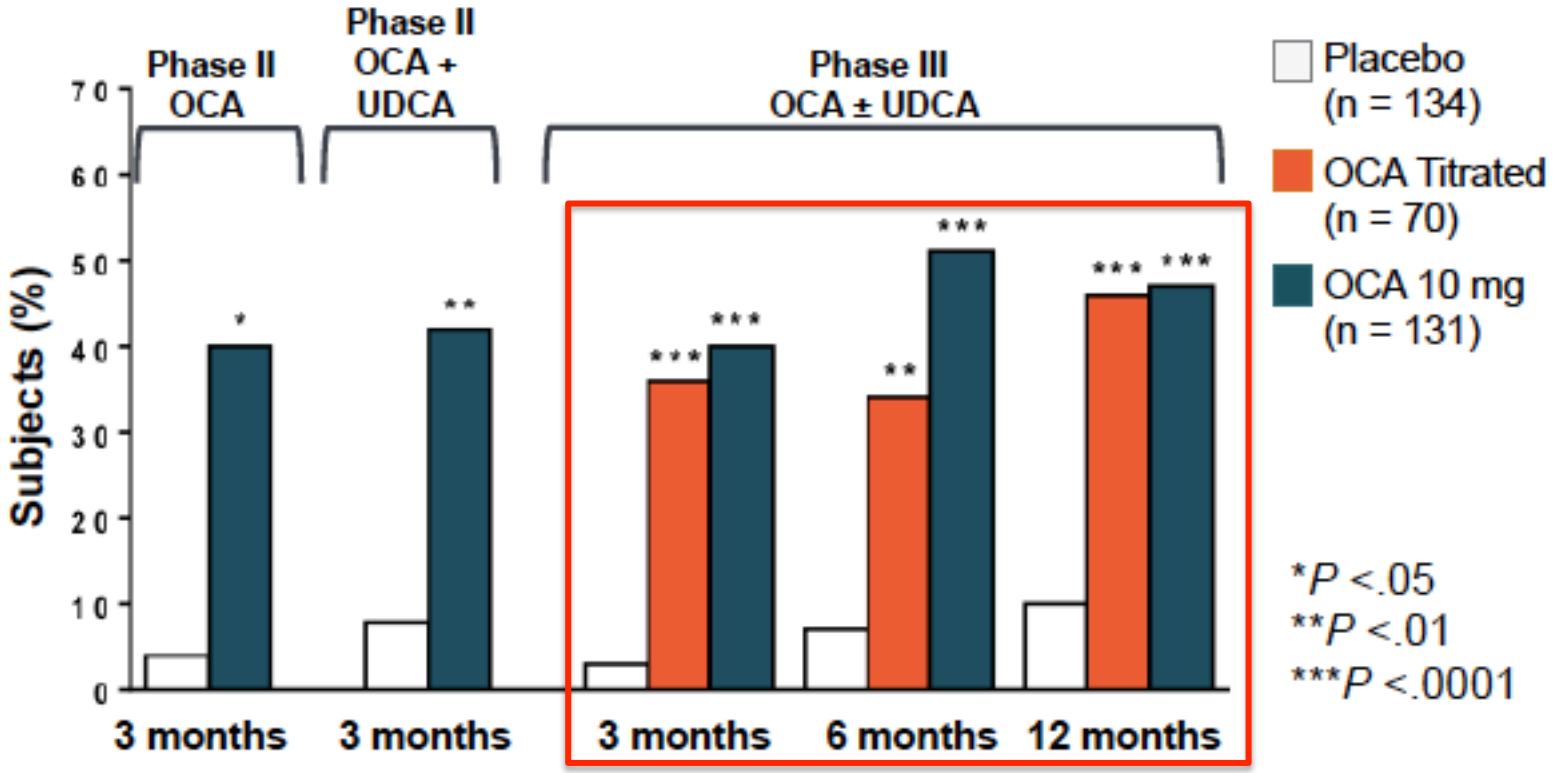
Predictive Significance of ALP and Bilirubin Values



Abbreviations: ALP, alkaline phosphatase; ULN, upper limit of normal.
Lammers WJ, et al. *Gastroenterology*. 2014;147:1338-1349.

OCA International Trials—Subjects Achieving Composite Endpoint

Primary Endpoint: Composite endpoint of ALP <1.67 x ULN, ≥15% ALP reduction, normal bilirubin

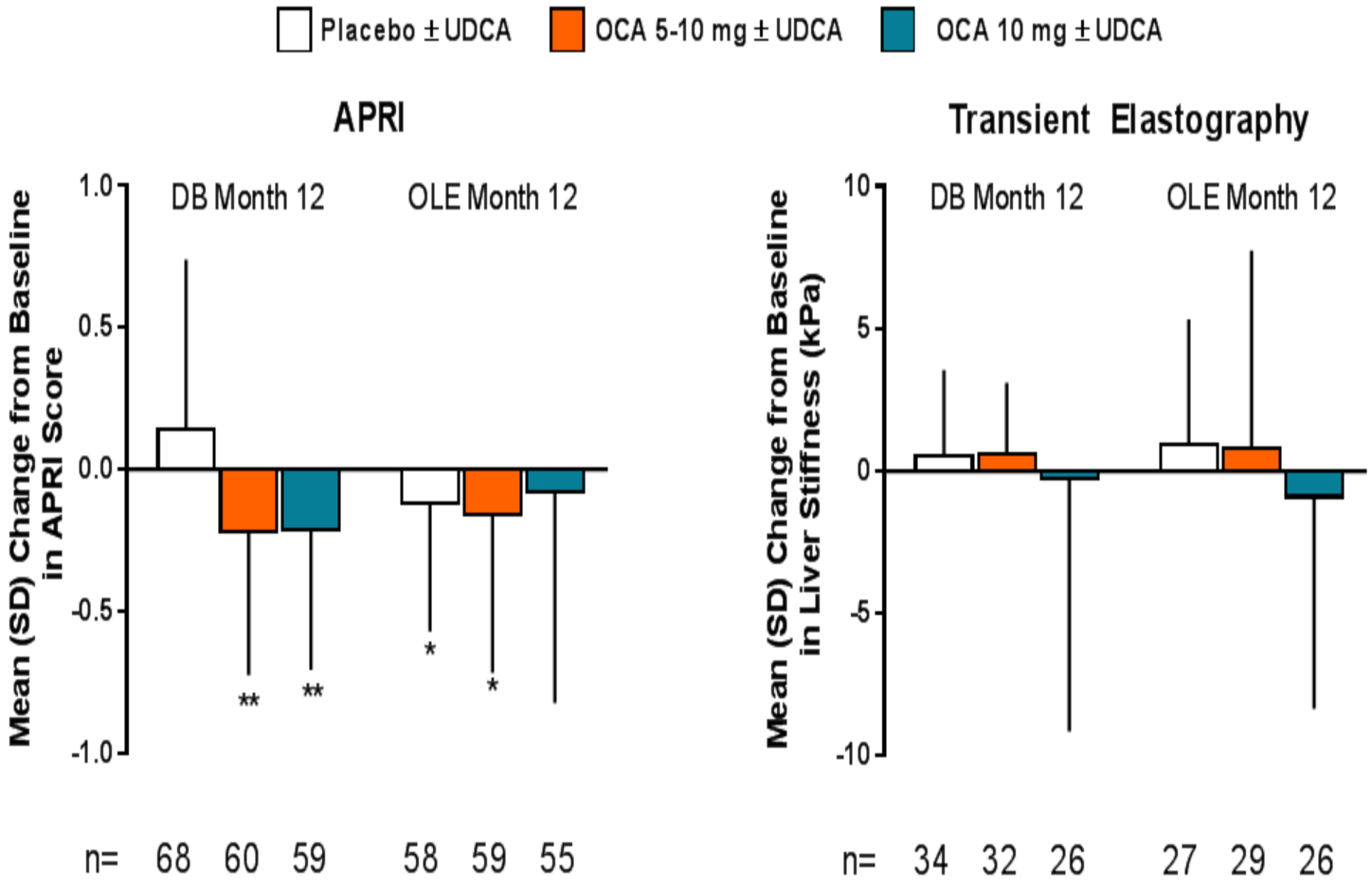


Abbreviations: ALP, alkaline phosphatase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Kowdley K, et al. Paper presented at: DDW 2015; May 16-19, 2015; Washington, DC. Abstract 657.

Graphic courtesy of Kris V. Kowdley, MD.

Long-Term Effect of Obeticholic Acid on Transient Elastography and AST to Platelet Ratio Index in Patients with PBC

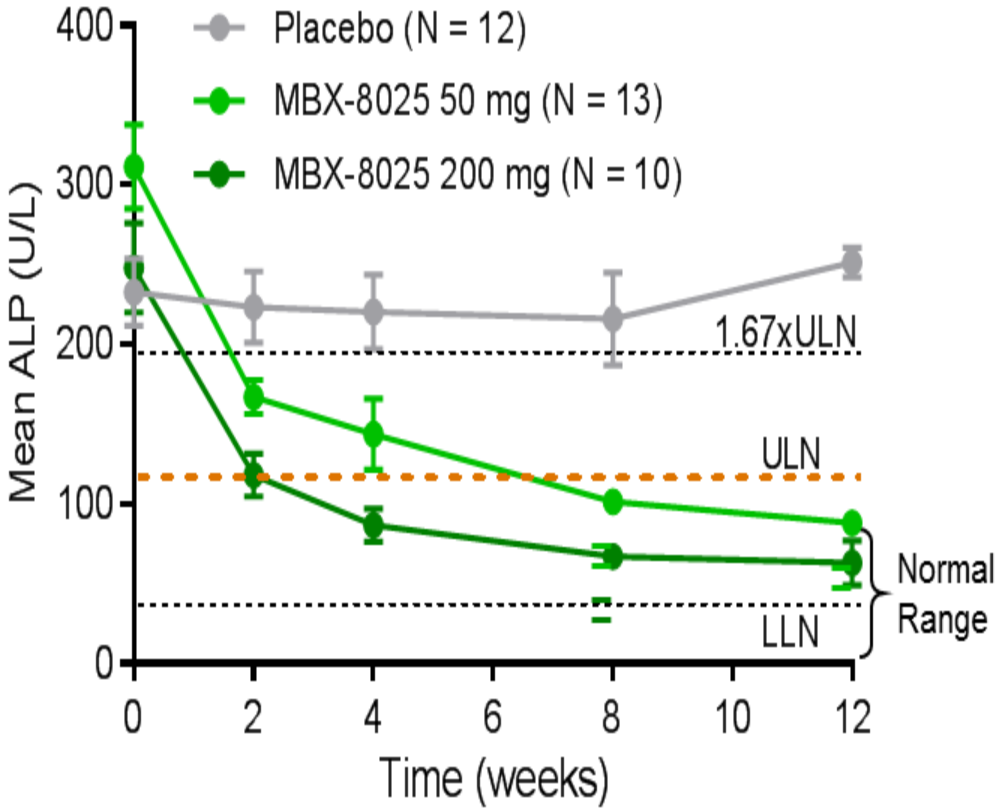


Abstract # 209: Hirschfield et al

A phase 2 proof of concept study of MBX-8025 in patients with Primary Biliary Cholangitis (PBC) who are inadequate responders to ursodeoxycholic acid (UDCA)

AASLD

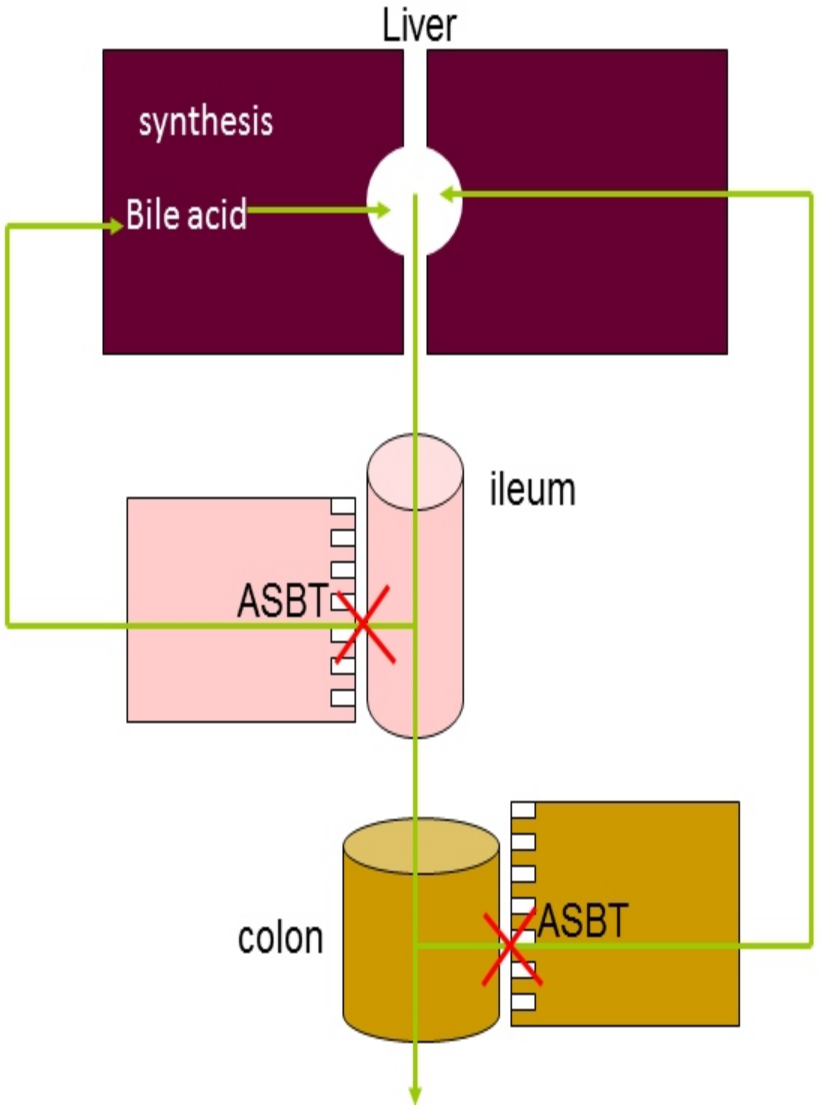
- Phase 2A, PPAR-delta for PBC with non-response to UDCA
- Dose-dependent transaminase elevation

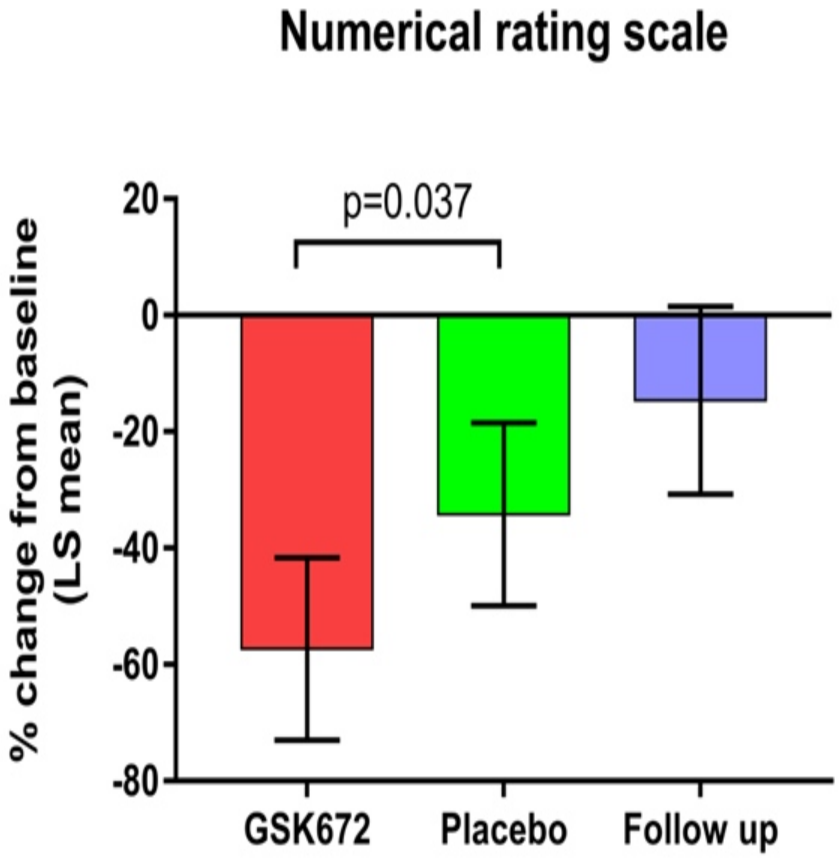


ABSTRACT # LB9 Jones et al

AASLD

NRS Itch Intensity: % change from baseline





Abstract # 205, Hegade et al

PSC

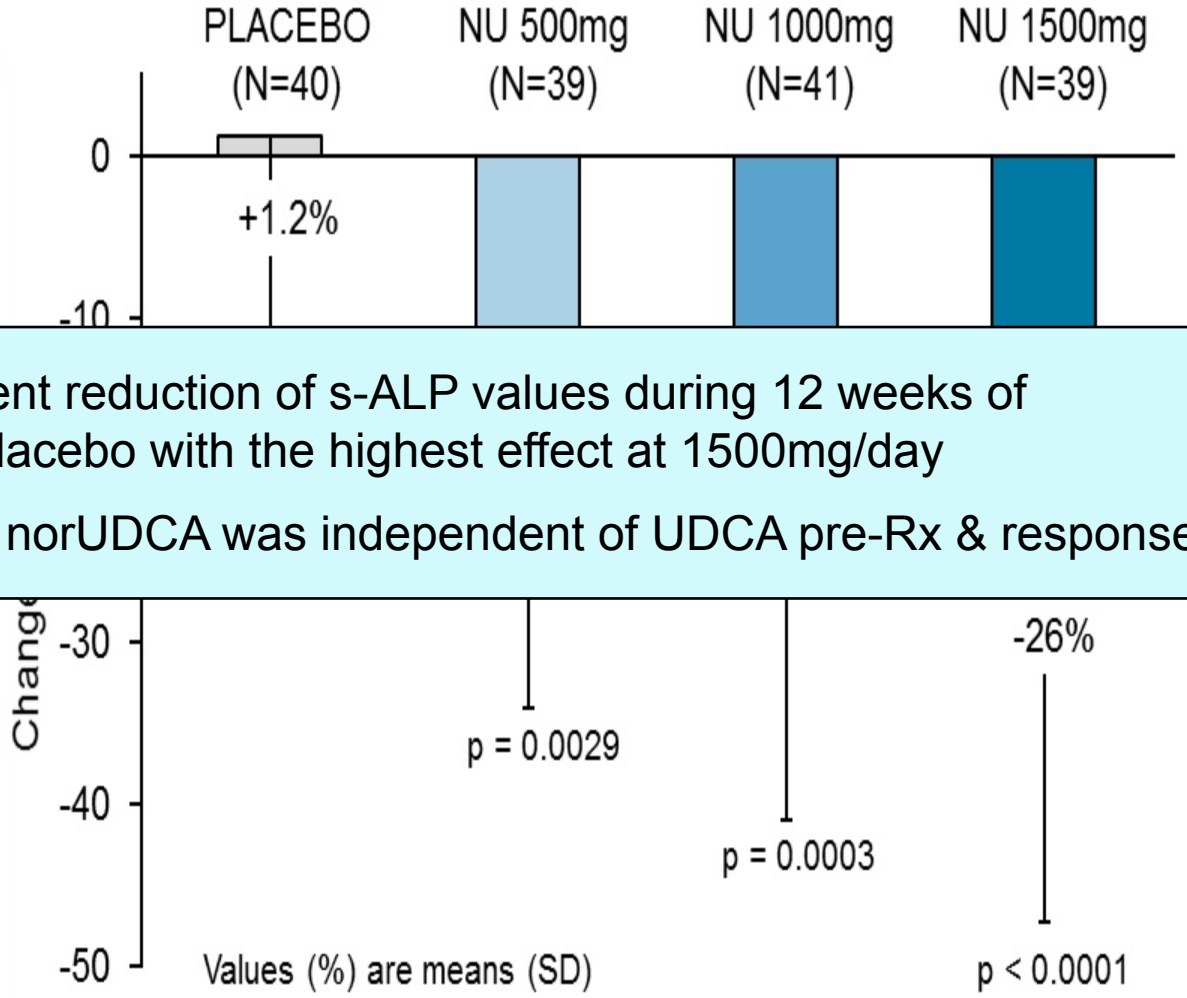
- ***MRCP*** preferred diagnostic imaging
- ***Liver biopsy:*** Small duct PSC or AIH overlap
- Test IgG4 at least once
- **UDCA doses ≥28 mg/kg/day should not be used**
- **Better Px:** Normalisation of liver biochemistry spontaneously or UDCA
  - ***20 mg/kg/day frequently used in clinical practice***
- Routine stenting after dilatation of dominant stricture not recommended
- Dominant strictures should be evaluated: Biopsies, brushings & FISH
- **Refer for Liver Transplant when MELD>14**
  - Increased risk of ischaemic cholangiopathy with DCD organs
- Annual colonoscopy, preferably chromoendoscopy: PSC + colitis
- PSC without IBD: colonoscopy every 3-5 years
- Screening for CCA with cross-sectional imaging and serial CA19-9 every 6-12 months

Am J Gastro 2015;110:646

NOR-URSODEOXYCHOLIC ACID FOR PRIMARY SCLEROSING CHOLANGITIS

AASLD

- 24-norUDCA is side chain shortened UDCA
- European study
- 12 week study
- Alk Phos Endpoint



Significant dose-dependent reduction of s-ALP values during 12 weeks of norUDCA compared to placebo with the highest effect at 1500mg/day

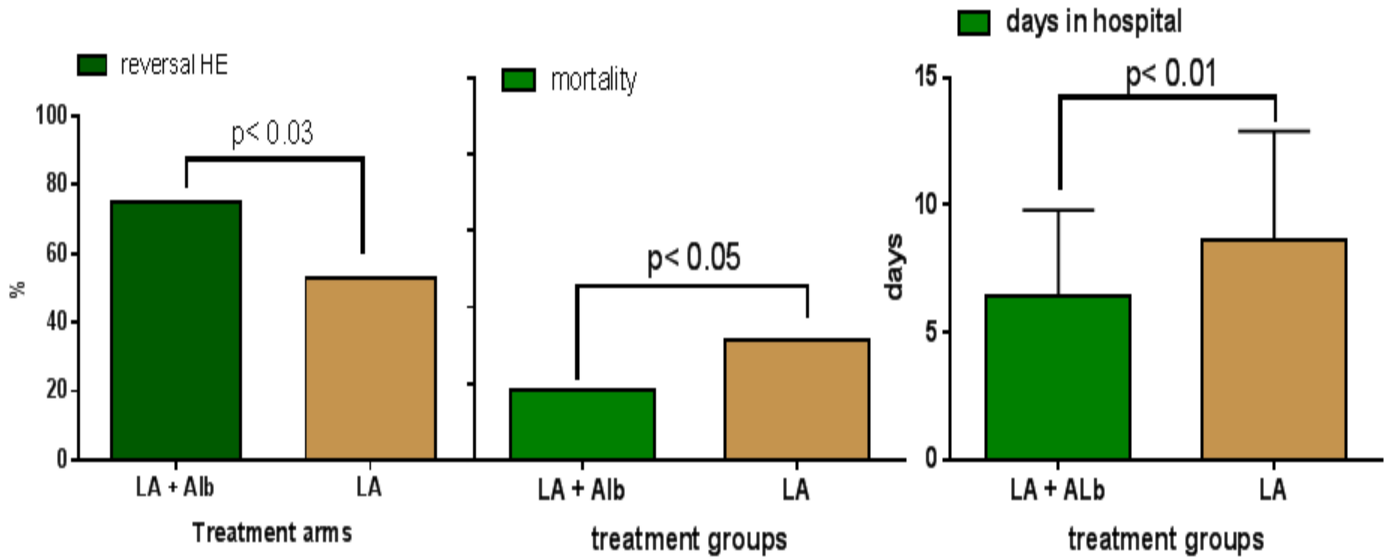
Biochemical response to norUDCA was independent of UDCA pre-Rx & response

Trauner et al, Abstract # 210

➢ *nor*UDCA (NU) reduces ALP in a dose-dependent fashion

CIRRHOSIS

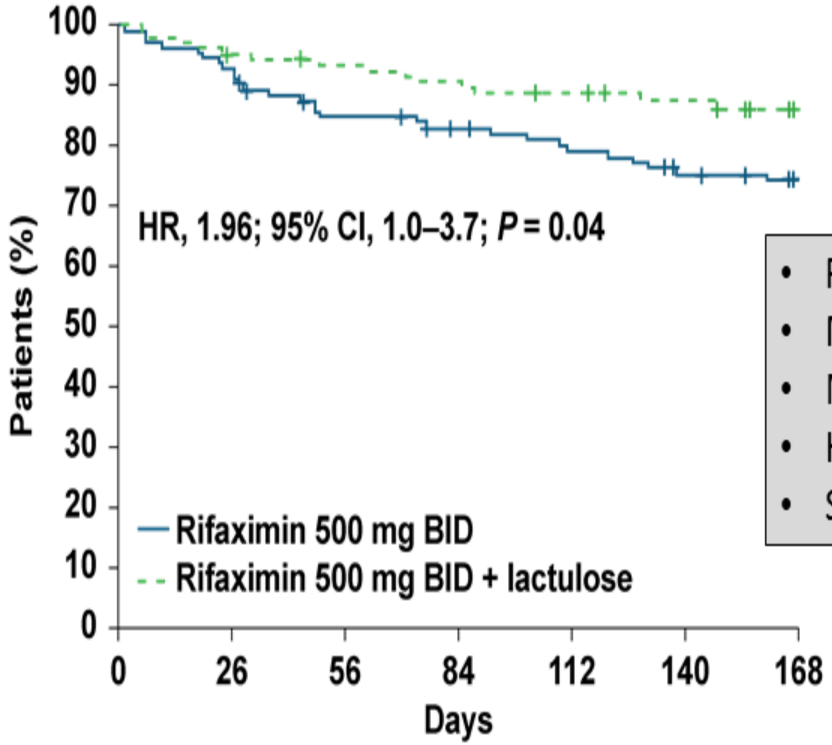
A randomized controlled trial comparing lactulose + albumin vs lactulose alone for hepatic encephalopathy



- Prospective, randomized controlled trial
- N= 120 (60 in each arm)
- Main difference was related to sepsis-related death

Abstract # 247. Sharma et al, ILBS and GB Pant Hospital, New Delhi

Efficacy and Safety of Rifaximin Monotherapy Versus Lactulose Combination Therapy for the Prevention of Overt Hepatic Encephalopathy (HE) Recurrence

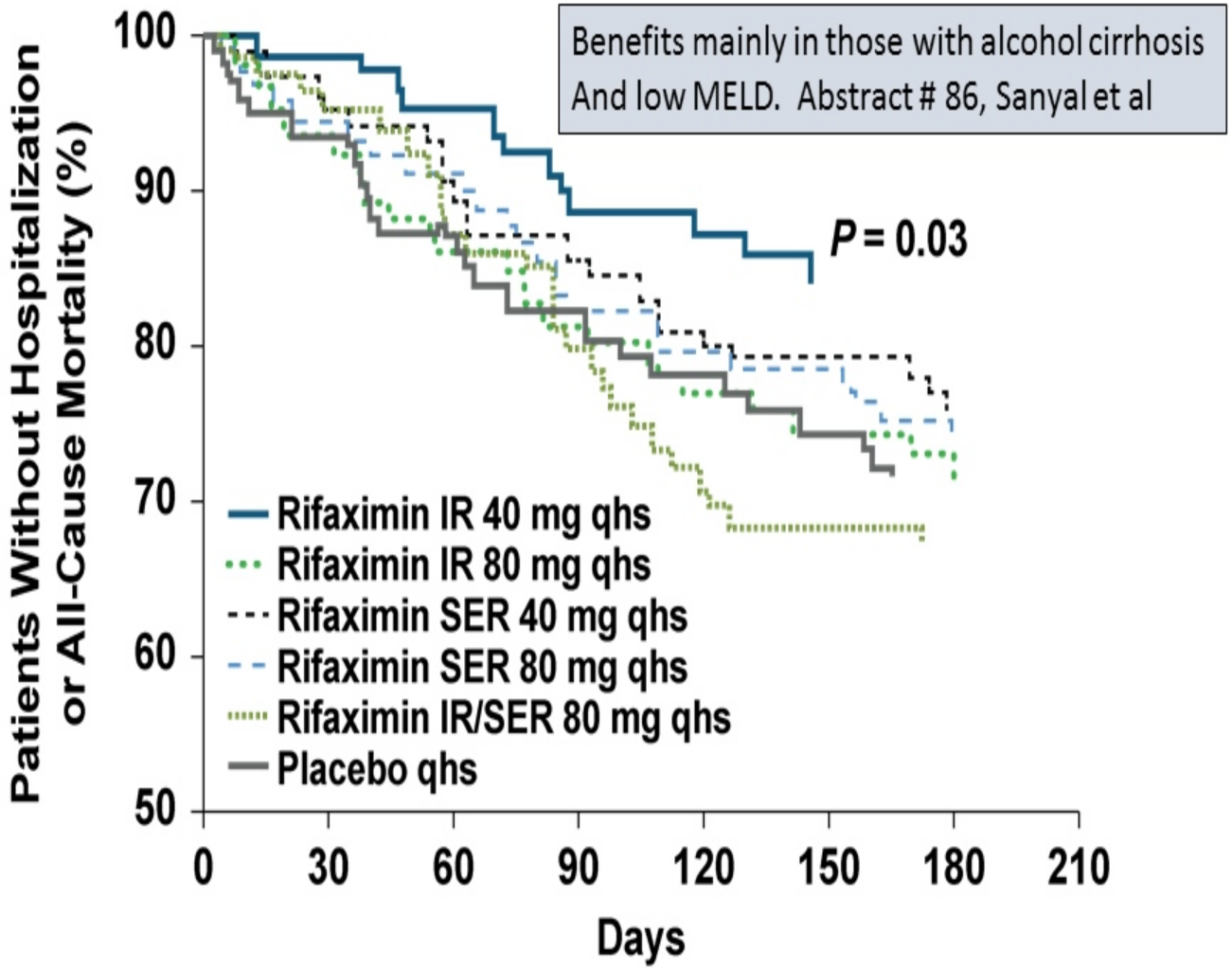


- Phase 4 open label 24 wk study
- Multi-center
- N= 222
- Hospitalization less in combo (ns)
- Safety profile similar

During 6 months breakthrough HE was reported in fewer patients treated with rifaximin + lactulose (13.9%) vs rifaximin alone (24.8%)

Abstract # 248: Sanyal et al, Salix Pharmaceuticals

Rifaximin IR 40 mg improved all cause mortality + hospitalization composite clinically meaningful benefit endpoint



Abstracts 2064: Bajaj et al, Salix Pharmaceuticals

*Patients with more frequent surveillance were diagnosed with earlier staged HCC

Characteristics	Surveillance < q 12 months (N = 287)	Surveillance > q 12 months (N= 148)	P-value
Portal vein thrombosis	6.7%	21.3%	**<0.0001**
Tumor size >5 cm	23.3%	22.9%	0.952
BCLC Stage 0 or A	56.8%	63.6%	0.504
Received OLT or surgical resection	27.5%	16.7%	0.270
Milan criteria for liver transplants	66.0%	50.0%	**<0.037**
UCSF criteria for liver transplants	81.9%	67.9%	**<0.031**

***On multivariate analysis:**

- Age and sex were not significant predictors for adherence, while
- **Significant independent predictors for adherence:** Asian ethnicity (HR 2.4,1.8-3.3), presence of hepatic decompensation (HR 2.3, 1.8-3.1), and **more frequent clinical visits (HR 1.4 [per visit], 1.1-1.8)**

Tran, Nguyen et al AASLD 2016. Oral #57