AASLD Update 2015

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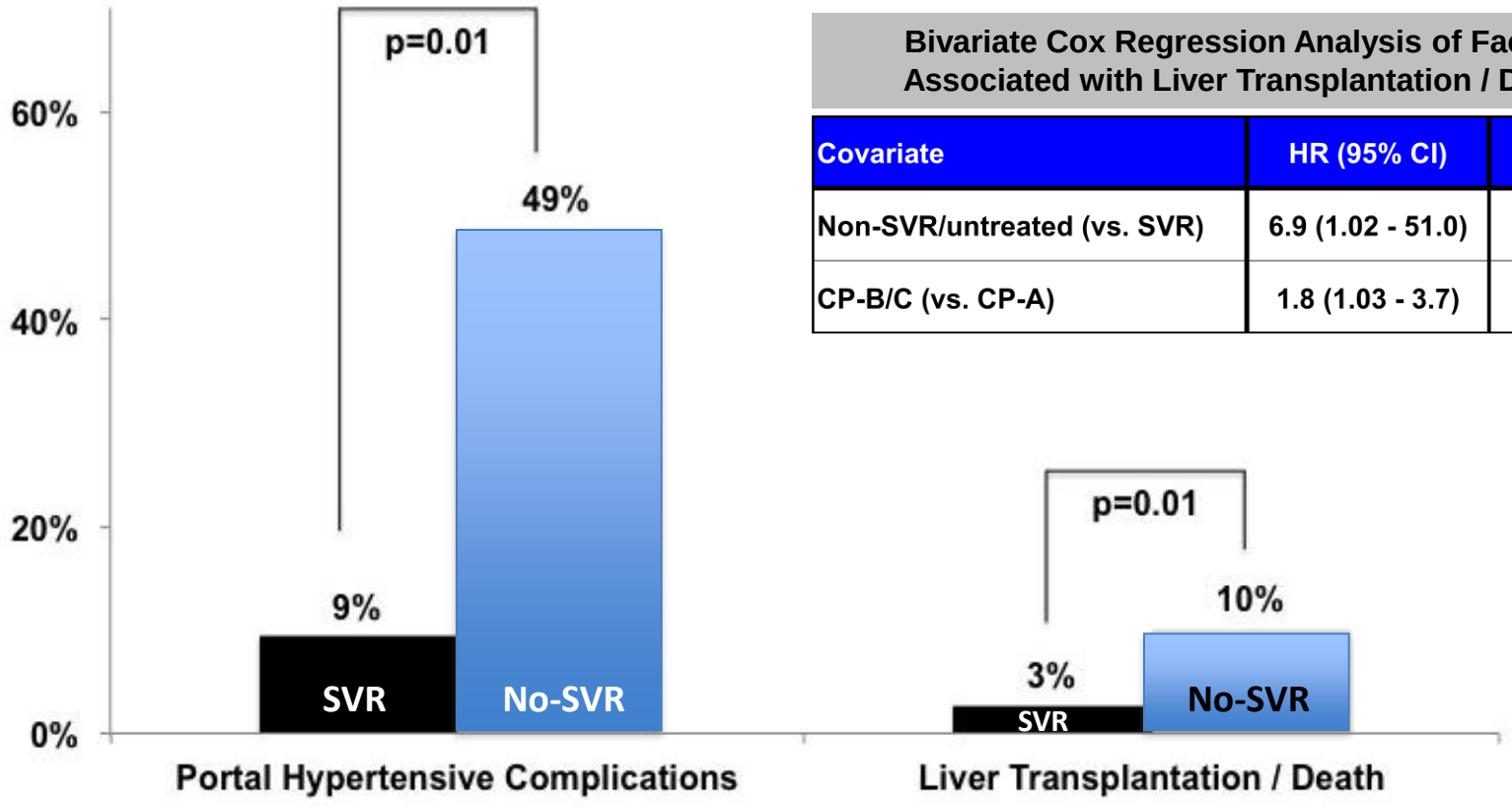
Hepatitis C

SVR Associated with Fewer Cirrhosis-Related Complications

- Multicenter study of patients with compensated/decompensated cirrhosis treated with SMV/SOF ±RBV for 12-24 wks; 84% achieved SVR
- Compared to 269 untreated/non-SVR matched controls
- Median MELD=9 and CP score 6



Bivariate Cox Regression Analysis of Factors Associated with Liver Transplantation / Death

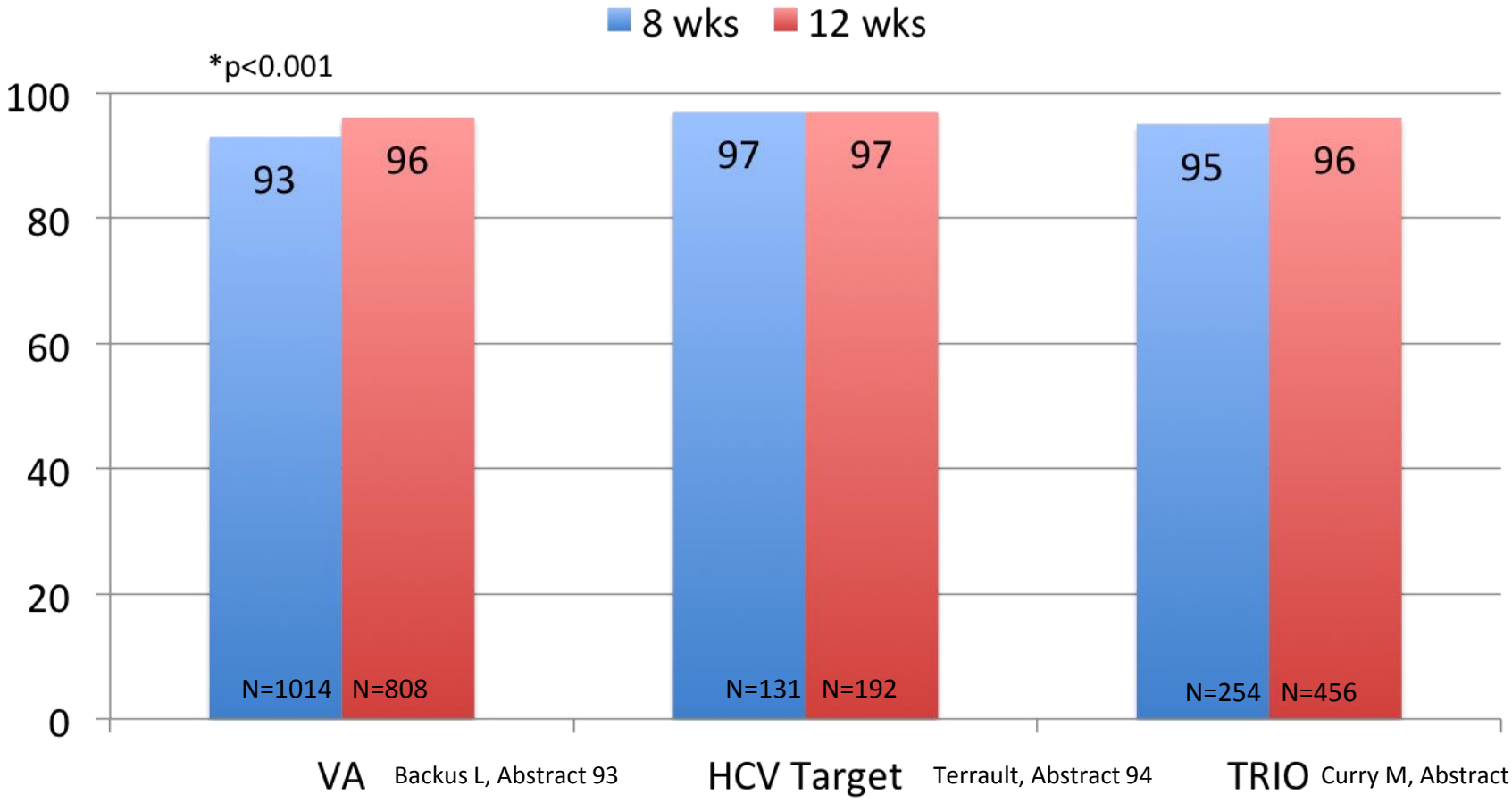
Covariate	HR (95% CI)	p-value
Non-SVR/untreated (vs. SVR)	6.9 (1.02 - 51.0)	0.03
CP-B/C (vs. CP-A)	1.8 (1.03 - 3.7)	0.04

Saxena et al. AASLD 2015, Abstract #1825..

News from the AASLD Meeting

1. Hepatitis C: more advances in therapy
   - Benefits of SVR
   - Real-world experience and factors impacting SVR
   - Unique Populations: acute hepatitis, renal Disease
   - New treatments just around the corner:
     - Grazoprevir/elbasvir and Sofosbuvir/velpatasvir
   - New drugs: new doubles, triples
2. Hepatitis B: new developments in treatment algorithms
   - New drug targets
3. HCC: Refinements in wait-list management of HCC patients
4. NAFLD: Diagnostic tools and new therapies

Real-World Experience with LDV-SOF of Genotype 1 Treatment Naïve, Non-Cirrhotics with HCV VL <6 million IU/mL

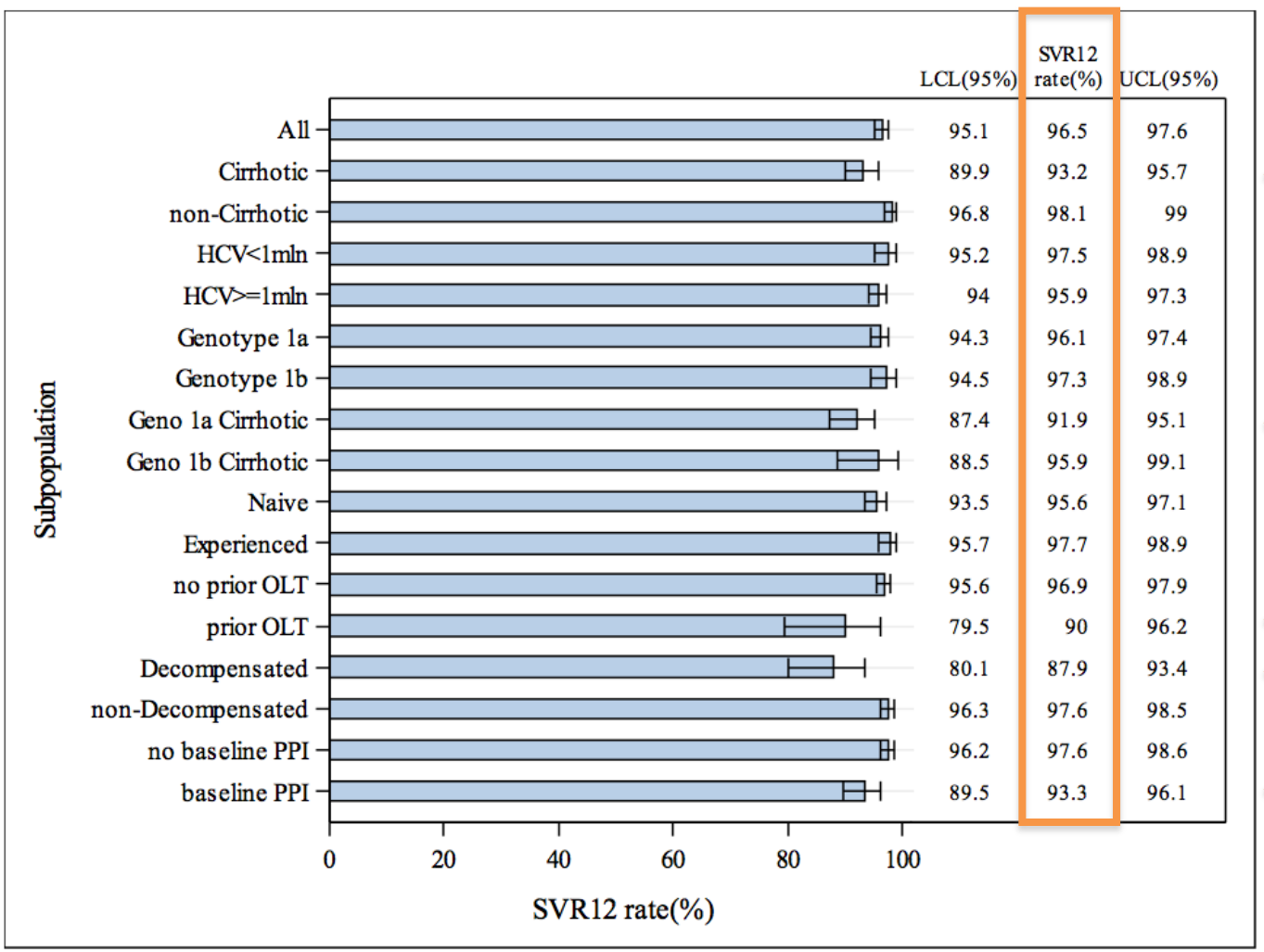


8-wks eligible but received 12 wks	**42%**	**60%**	**50%**

Factors Associated with Lower SVR Rates with LDV-SOF in Genotype 1 Patients

Population (Abstract)	N	Key Characteristics	Predictors of Treatment Failure
VA (Backus, Abstract 93)	3763	Treatment-naïve 29% cirrhosis 37% AA	▪ African-American race ▪ Advanced fibrosis (FIB-4>3.25) ▪ 8 Wks treatment
TRIO (Curry, Abstract 1108;Afdhal, Abstract LB17)	895	Treatment-naïve Non-cirrhotics 18% AA	▪ Academic center ▪ African-American race ▪ Low platelet count ▪ Cirrhosis ▪ Type of DAA therapy
HCV-Target (Terrault, Abstract 94)	969	53% Treatment naïve 38% cirrhosis 20% AA	▪ PPI use at start of treatment ▪ Low albumin ▪ Elevated bilirubin

HCV-TARGET: SVR12 with LDV/SOF Therapy by Subgroups



Completed treatment as of 7/1/2015 and have available virological outcomes.
Patients who discontinued due to AE or were lost to follow-up are excluded.

SVR12: SVR at 12 (±1) weeks post treatment

HCV-TARGET

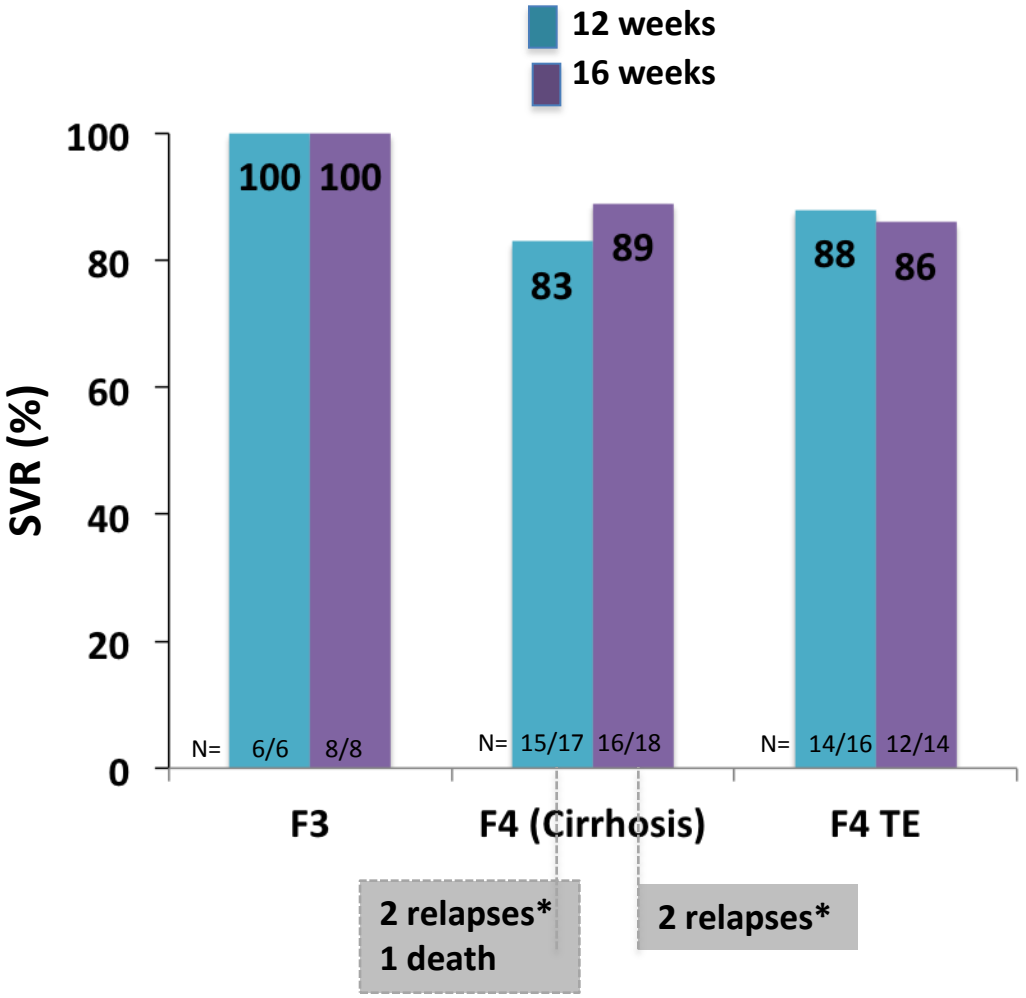
Implications: Treating Genotype 1

- SVR results mirror those in clinical trials --> high rate of success
- 8-wk treatment among treatment-naïve, non-cirrhotic, genotype 1 patients with VL <6 million IU/mL is underutilized
- Cirrhosis/Advanced disease associated with lower SVR rates
- Use of PPI is associated with lower SVR rates
  - Potentially modifiable factor to maximize SVR rates
- African-Americans may have lower response rates
  - Reasons unclear
- Treatment of cirrhotics can reverse/prevent complications of portal hypertension

SOF+DCV+RBV for 12 or 16 Wks for G3 and Advanced Fibrosis/Cirrhosis: ALLY-3+

	DCV+SOF+RBV Overall N = 50
Age, *median (range) yrs*	53.5 (36–73)
Male, *n (%)*	40 (80)
Race, *n (%)*	
White	49 (98)
Asian	1 (2)
***IL28B* non-CC,** *n (%)*	28 (56)
HCV RNA, *median (range) log_{10} IU/mL*	6.87 (4.6–7.8)
HCV RNA category (IU/mL), *n (%)*	
≥ 2 million	38 (76)
≥ 6 million	26 (52)
Fibrosis stage, *n (%)*	
Advanced fibrosis (F3)	14 (28)
Cirrhosis (F4)	36 (72)
Albumin, *median (range) g/L*	43 (33–48)
Platelets, *median (range) × 10^9 cells/L*	161 (63–324)
Prior HCV treatment experience, *n (%)*	
Naive	13 (26)
Experienced[a]	37 (74)
IFN-based regimens	31 (62)
SOF-based regimens[b]	6 (12)

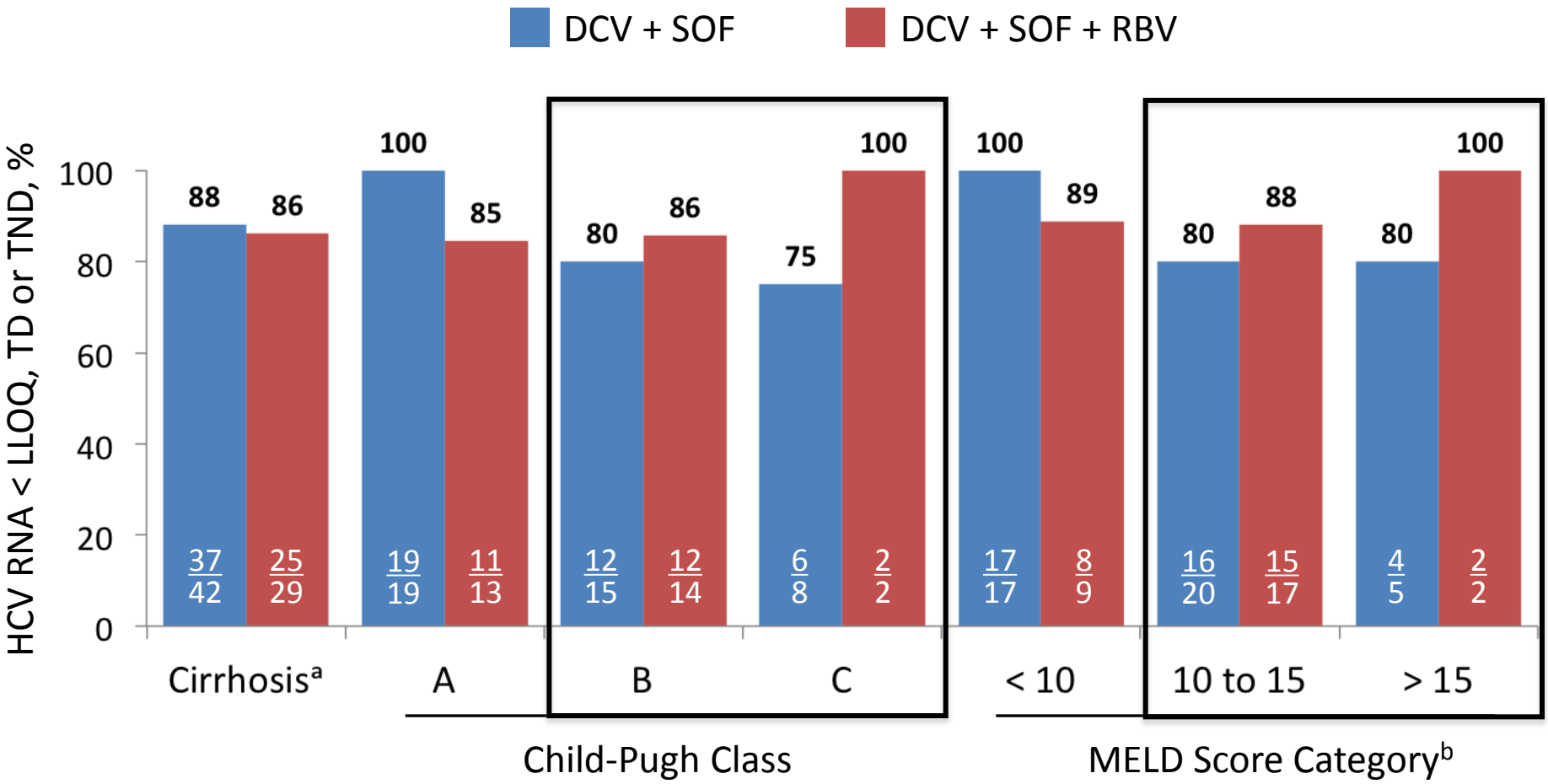
Cirrhosis defined by liver biopsy (Metavir F4), FibroScan (>14.6 kPa), or FibroTest score ≥0.75 and APRI >2



*At failure, all 4 patients had NS5A-Y93H

Leroy V, AASLD 2015:LB-3

European Compassionate Access Program
DCV + SOF ± RBV for 24 Weeks



[a] Excludes 4 patients with indeterminate cirrhosis status and 5 without cirrhosis; all except 1 (DCV+SOF) achieved SVR12;

[b] Excludes 1 cirrhotic patient with missing baseline MELD data; patient discontinued therapy at Week 4 due to AE (non-SVR12).

Welzel T, AASLD 2015, Abstract 37

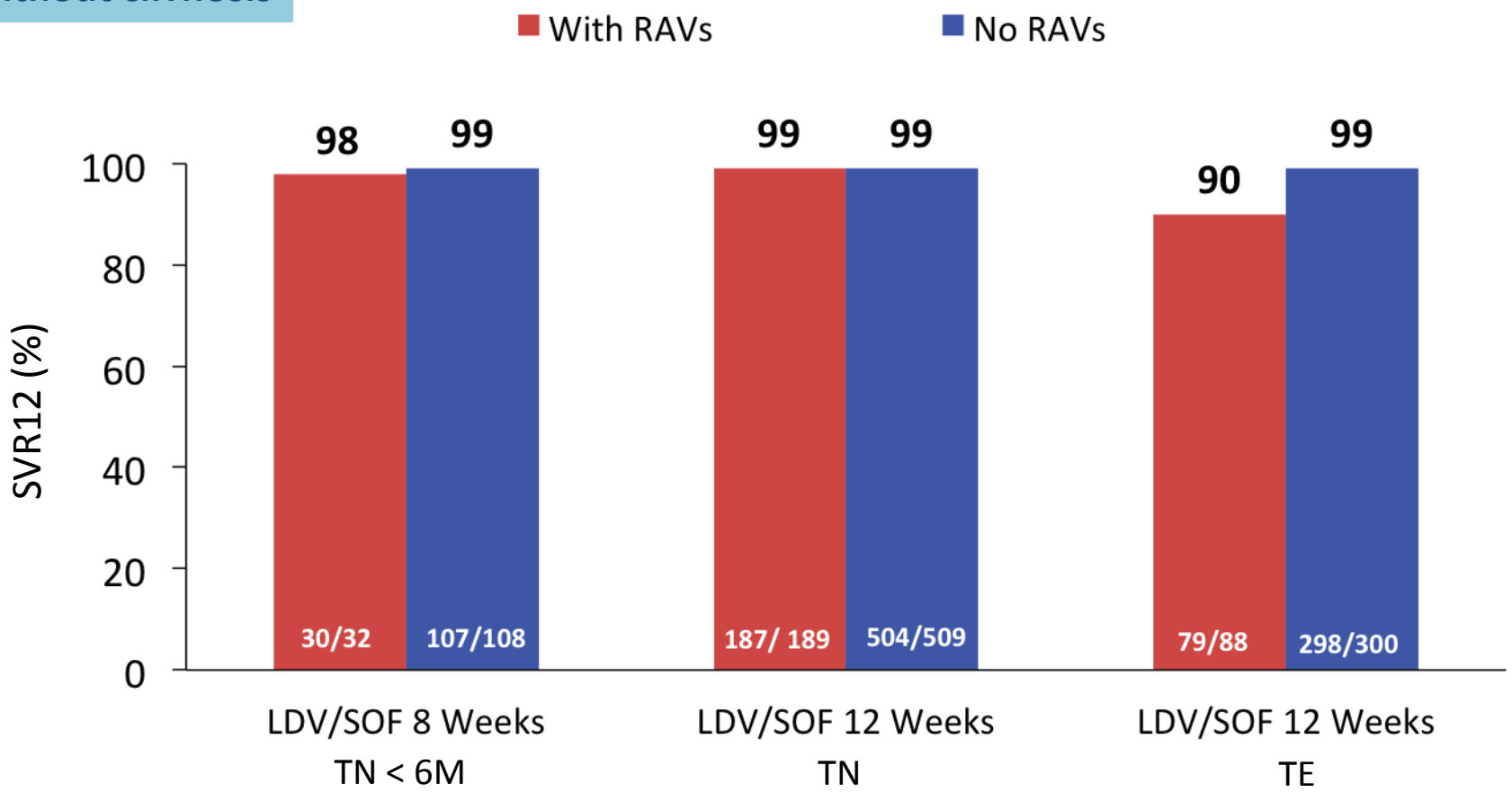
Implications: Genotype 3 and Cirrhosis

- SVR rates DCV+SOF ± RBV can achieve SVR rates of 85-90% in patients with cirrhosis
  - If decompensated cirrhosis, SVR rates ~80%
- If treating cirrhosis, add ribavirin and treat for 12-24 weeks
  - If unable to add ribavirin, treat for 24 weeks with SOF + DCV
- If decompensated cirrhosis, add ribavirin and treat for 24 weeks
- Still room to improve on SVR rates

Efficacy of LDV-SOF in Patients with and without NS5A RAVs at Baseline

Zeuzem S, Abstract 91

Without cirrhosis

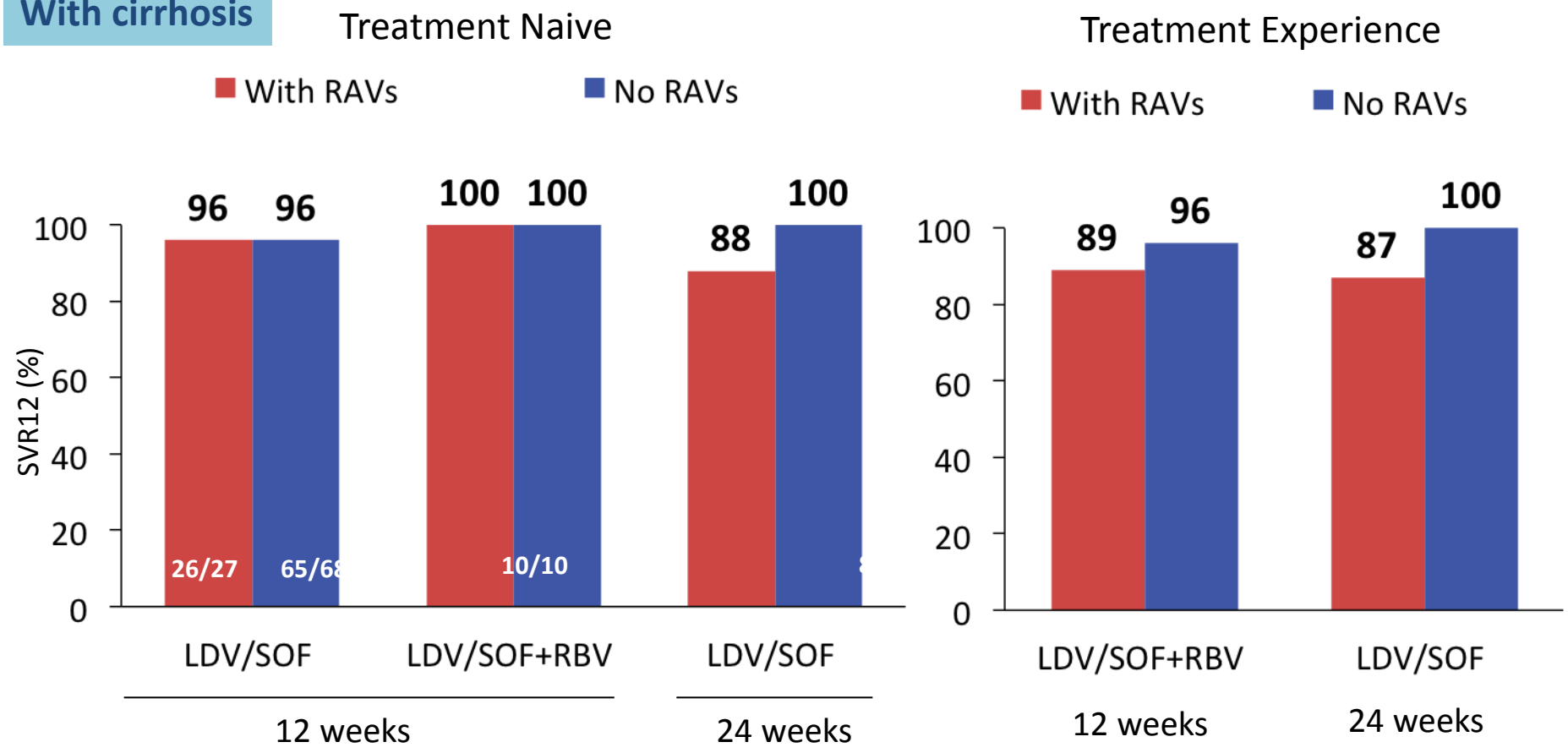


Studies included for analysis:
LDV/SOF 8 weeks: GS-US-337-0118 (LONESTAR 1), GS-US-337-0108 (ION-3); **LDV/SOF 12 Wks TN**: GS-US-GS-US-334-1274 (Bleeding Disorder), GS-US-337-0102 (ION-1), GS-US-337-0108 (ION-3), GS-US-337-0113 (Japan 1), GS-US-337-0115 (ION-4), GS-US-337-0122 (Electron 2), GS-US-337-0131(China), GS-US-337-0118 (LONESTAR 1), GS-US-337-1406, GS-US-337-1468 (LEPTON); **LDV/SOF 12 Wks TE**: GS-US-337-0109 (ION-2), GS-US-337-0113 (Japan 1), GS-US-337-0115 (ION-4), GS-US-337-0124 (SOLAR-2), GS-US-334-1274 (Bleeding Disorder), GS-US-337-0118 (LONESTAR 1) , GS-US-337-0131(China), GS-US-337-1406, GS-US-337-1468 (LEPTON)

Efficacy of LDV-SOF in Patients with and without NS5A RAVs at Baseline

Zeuzem S, Abstract 91

With cirrhosis

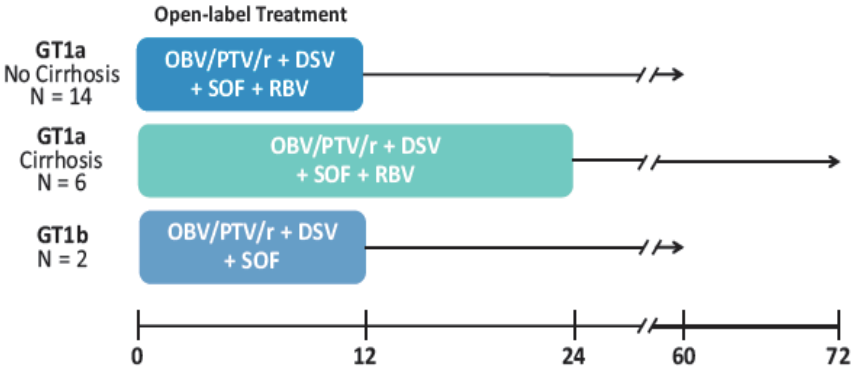


The largest impact of RAVs on treatment outcome was observed in patients with cirrhosis treated for 24 weeks of LDV/SOF (and no ribavirin)

Studies included for analysis:
LDV/SOF 12 Wks: GS-US-334-1274 (Bleeding Disorder), GS-US-337-0102 (ION-1), GS-US-337-0113 (Japan 1), GS-US-337-0115 (ION-4), GS-US-337-0122 (ELECTRON-2), GS-US-337-0131(China), GS-US-337-1406; **LDV/SOF+RBV 12 Wks**: GS-US-337-0102 (ION-1), GS-US-337-0113 (Japan 1), GS-US-337-0122 (ELECTRON-2); **LDV/SOF 24 Wks**: GS-US-337-0102 (ION-1), GS-US-334-1274 (Bleeding Disorder)

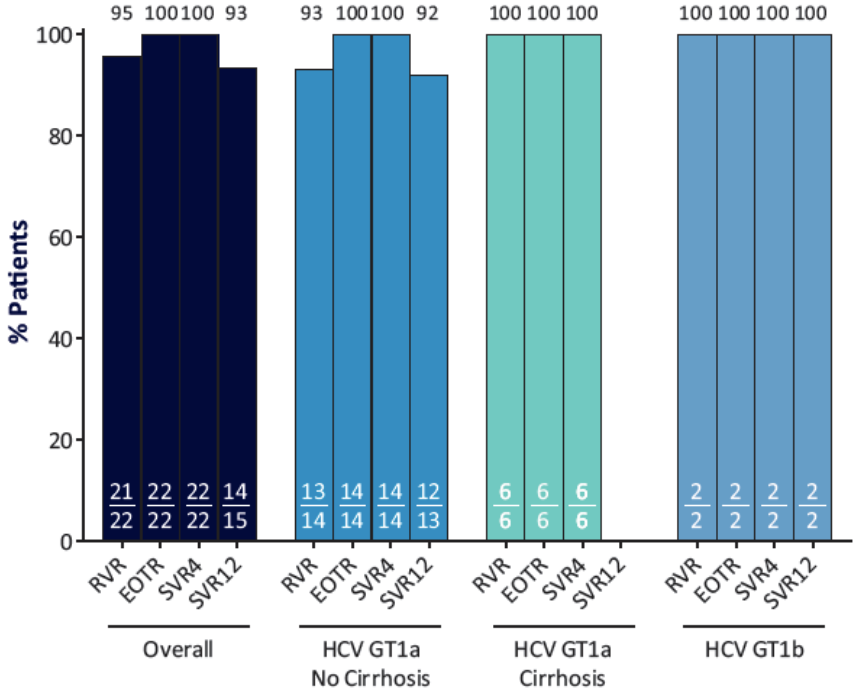
Treatment of DAA Failures with Combination OBV/PTVr/DSB + SOF ± RBV

Figure 1. QUARTZ-I: Open-label, Phase 2, Multicenter Study Design



Prior DAA regimen			
OBV/PTV/r	2 (14)	0	0
OBV/PTV/r + DSV	8 (57)	6 (100)	0
SIM + SOF	0	0	1 (50)
SIM + SAM + RBV	0	0	1 (50)
SOF + RBV	1 (7)	0	0
SOF + PR	1 (7)	0	0
TPV + PR	2 (14)	0	0

Figure 2. Virologic Response During and After Treatment



At baseline:

- **17/22 had ≥1 RAV in 1 or the 3 regions; remaining 5 had Q80K in NS3 only**
- **7 had RAVs in 2 targets; 2 patients had RAVs in all 3 targets**

- Single treatment failure had no RAVs detected

Poordad F, Abstract LB-20

Implications

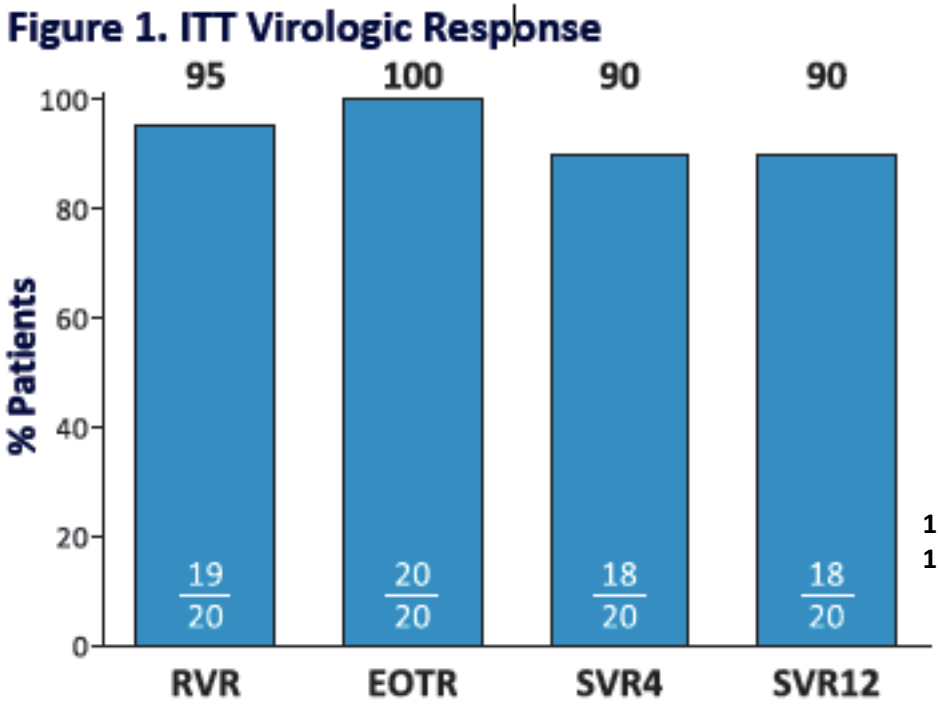
- Baseline testing not recommended by guidelines but there may be role for select testing
- Cirrhotic patients receiving LDV-SOF
  - Consider testing for baseline NS5A RAVs and adding RBV and/or extending treatment if present
- DAA combinations that target multiple targets and includes sofosbuvir may be an strategy to treat patients with DAA resistance (NS3/NS5A)

Endstage Renal Disease/Hemodialysis

RUBY-1

- Ombitasvir/paritaprevir/r + dasabuvir (GT1B) + RBV (GT1A) for 12 wks

Characteristic	N=20 (%)
AA race	14 (70)
IL28B non-CC	14 (70)
Fibrosis Stage F0-2 F3	 16 (80) 4 (20)
CKD 15-30 ≤15 or on dialysis	 6 (30) 14 (70)
GI1A Q80K G1B	10/13 7



Safety Measure	With RBV N=13	Without RBV N=7
Anemia needing dose reduction Anemia →Rx discontinuation	9 (69) 0	N/A
Total bilirubin >1.5 -3 ULN	2 (15)	0
ALT>5 ULN	0	0

Pockros P, AASLD 2015.Abstract 1039

Treatment of Acute Hepatitis C

SLAM-C

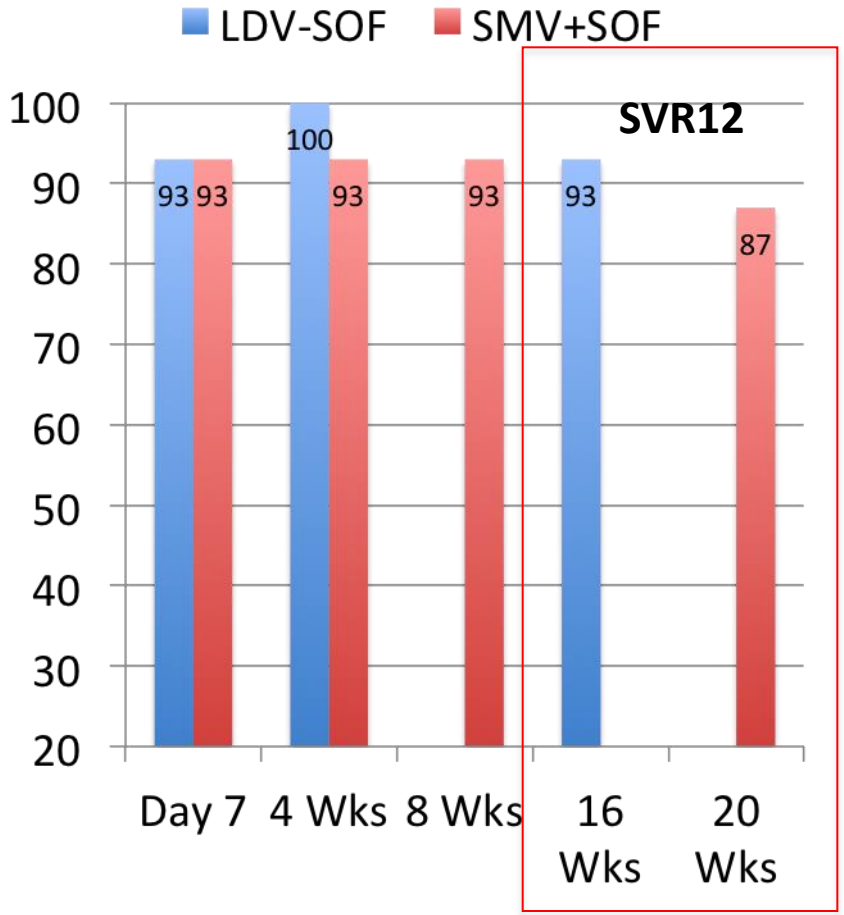
- **Inner city drug rehabilitation centers (N=6) in New York**
- **Two treatments**

  N=14: LDV/SOF for 4 wks or

  N=15: SMV/SOF for 8 wks

Cohort Characteristics

	LDV-SOF N=14	SMV+SOF N=15
M:F	12:2	14:1
Race AA White	9 2	10 2
GT1A/1B Q80K	7/7 3/7	7/8 2/7
IL28 CC	4/14	9/15



None of the treatment failures was due to relapse or VBT

Basu P, AASLD 2015, Abstract 1074

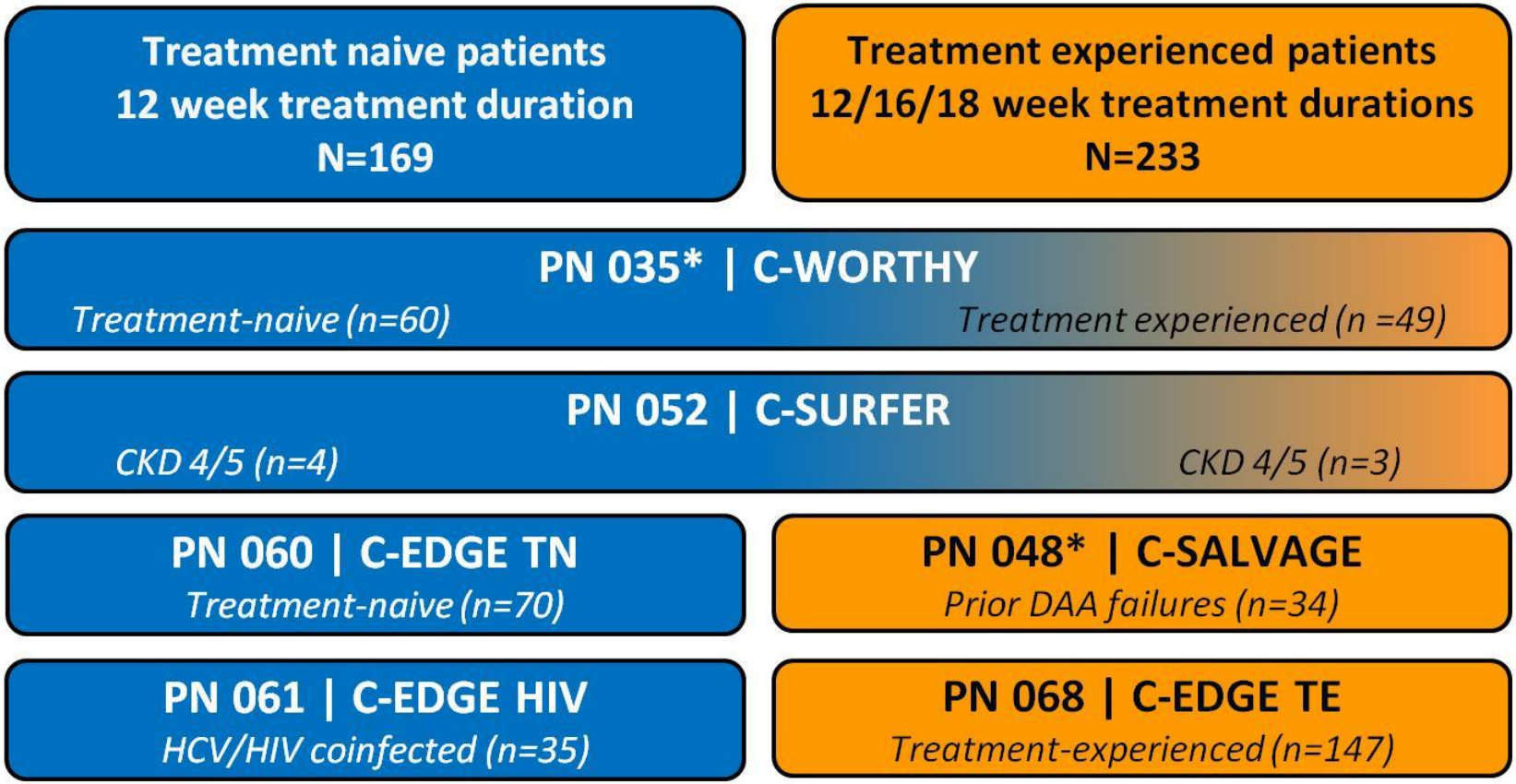
Naggie S, Abstract 1094. SOF + RBV X 12 wks, SVR 59%

New HCV Therapies Just Around the Corner

Elbasvir/Grazoprevir

Sofosbuvir/Velpatisvir

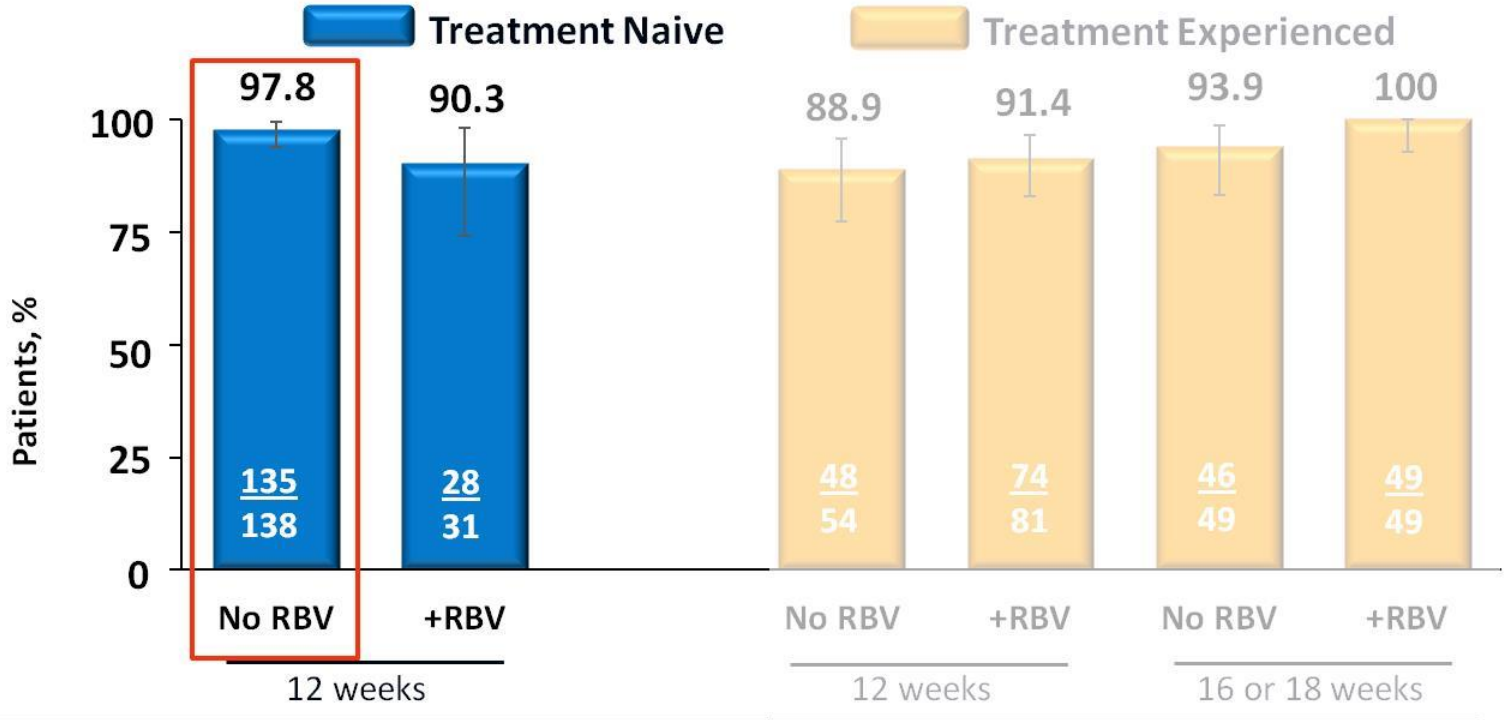
Integrated Analysis of Patients Treated with EBR-GZR with Cirrhosis (N=402)



- HCV genotype 1, 4 and 6, compensated CP-A cirrhosis
- Cirrhosis defined by biopsy, Fibroscan, or APRI + Fibrotest
- Included treatment duration of 12, 16, 18 weeks

Jacobson I, AASLD 2015, Abstract 42

Integrated Analysis of Patients Treated with EBR-GZR with Cirrhosis: Treatment Naive

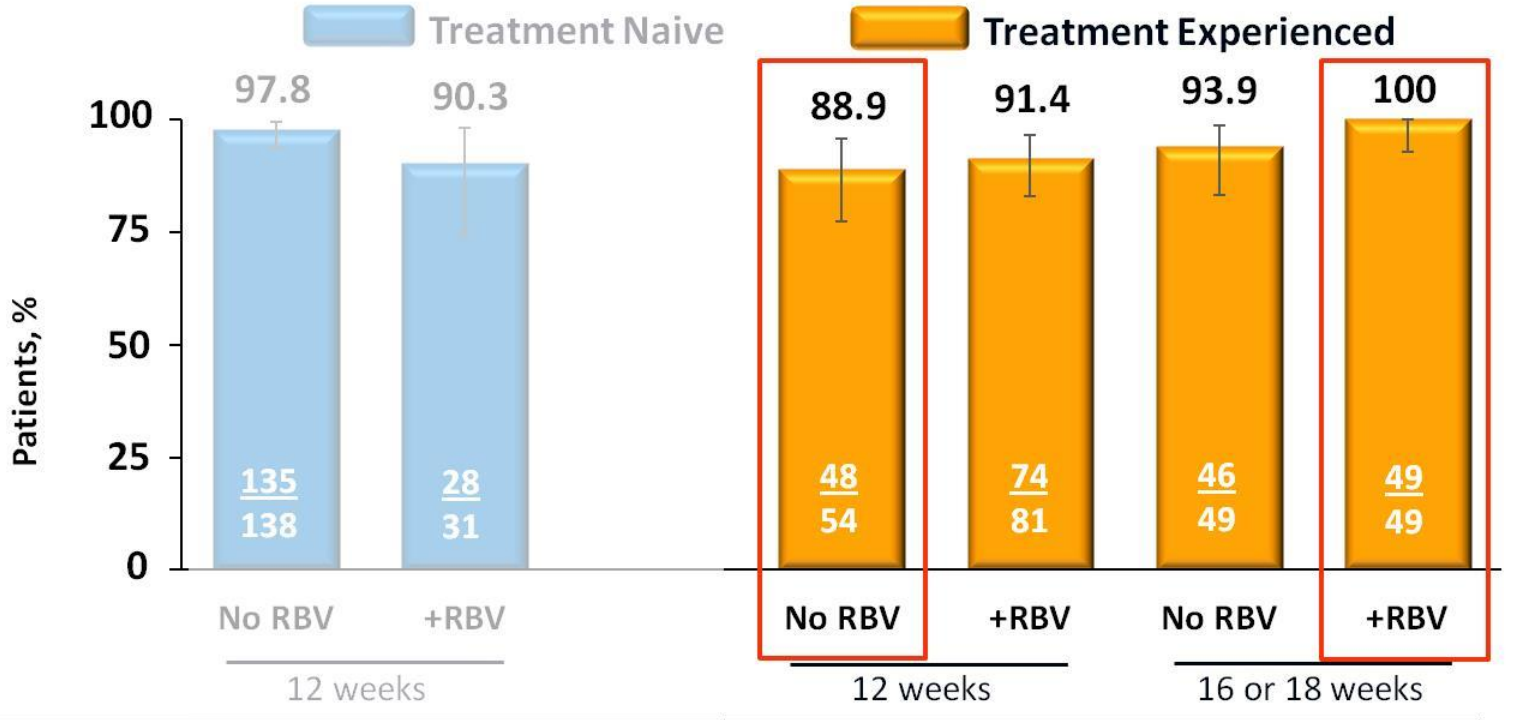


	12 weeks		12 weeks		16 or 18 weeks	
LTFU/Early Discon.	1*	0	2†	1‡	0	0
SVR12 (mFAS§)	98.5% (135/137)	90.3% (28/31)	92.3% (48/52)	92.5% (74/80)	93.9% (46/49)	100.0% (49/49)
Breakthrough	1	1	0	0	0	0
Rebound	0	0	0	0	2	0
Relapse	1	2	4	6	1	0

*Death (coronary artery disease)
†Death (lymphoma) n=1;discontinued due to noncompliance, n=1
‡Death (motor vehicle accident)
§mFAS (modified full analysis set) excludes patients who discontinued treatment for reasons unrelated to study medication

Jacobson I, AASLD 2015, Abstract 42

Integrated Analysis of Patients Treated with EBR-GZR with Cirrhosis: Treatment Experienced



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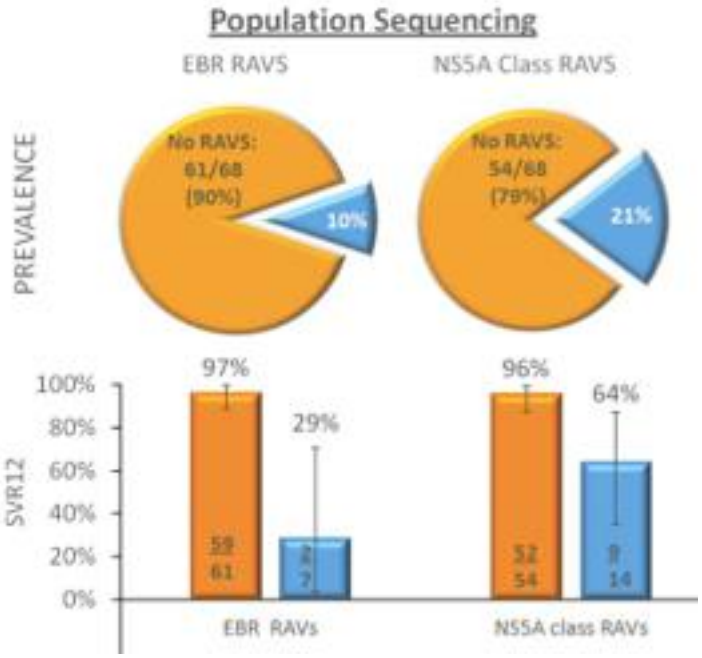
§mFAS (modified full analysis set) excludes patients who discontinued treatment for reasons unrelated to study medication

Jacobson I, AASLD 2015, Abstract 42

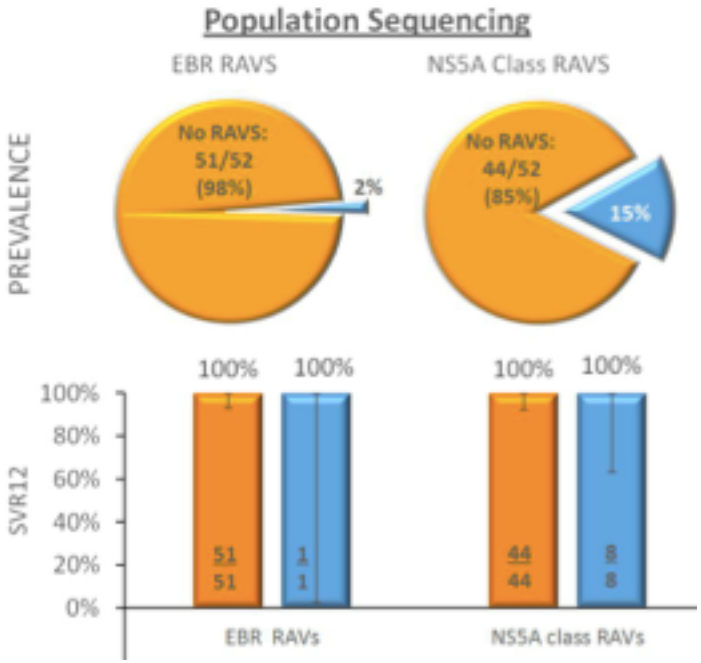
Integrated Analysis of the Prevalence and Impact of Baseline NS5A RAVs in Patients Treated with EBR-GZR

Jacobson I, AASLD 2015, LB-22

- **Prevalence of NS5A RAVs = 20%**
  - **EBR RAVs=~5% TN/relapsers**
  - **EBR RAVs=~10% if TE non-responders**
- **GT1B: minimal impact of baseline EBR RAVs**
- **GT1A:**



12 wks EBR/GZR

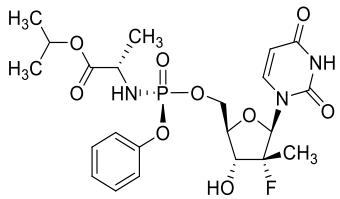


16/18 wks EBR/GZR + RBV

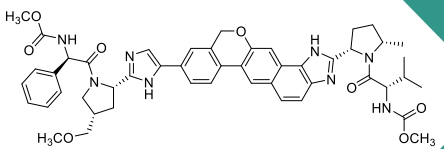
Implications: EBR/GZR ± RBV

- High efficacy across a broad spectrum of patients
- Subgroups in which longer therapy ± RBV may be considered:
  - Treatment experienced (non-responder):
    - 16/18 weeks + RBV if cirrhosis
    - 16/18 weeks + RBV if baseline EBR RAVs
- Safe with rare elevation of ALT (without bilirubin increase)

SOF
Nucleotide
polymerase
inhibitor



- **Sofosbuvir (SOF)[1,2]**
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet



VEL
NS5A
inhibitor

- **Velpatasvir (VEL; GS-5816)[3-5]**
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile

SOF + VEL

- **SOF/VEL FDC**
  - Once daily, oral, FDC (400/100 mg)

1. Jacobson IM, et al. N Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. N Engl J Med 2013;368:1878-87;
3. Cheng G, et al. EASL 2013, poster 1191; 4. German P, et al. EASL 2013, poster 1195; 5. Lawitz E, et al. EASL 2013, poster 1082.

Phase 3 Double-Blind Placebo-Controlled Study of Sofosbuvir/Velpatasvir for 12 Weeks

ASTRAL-1

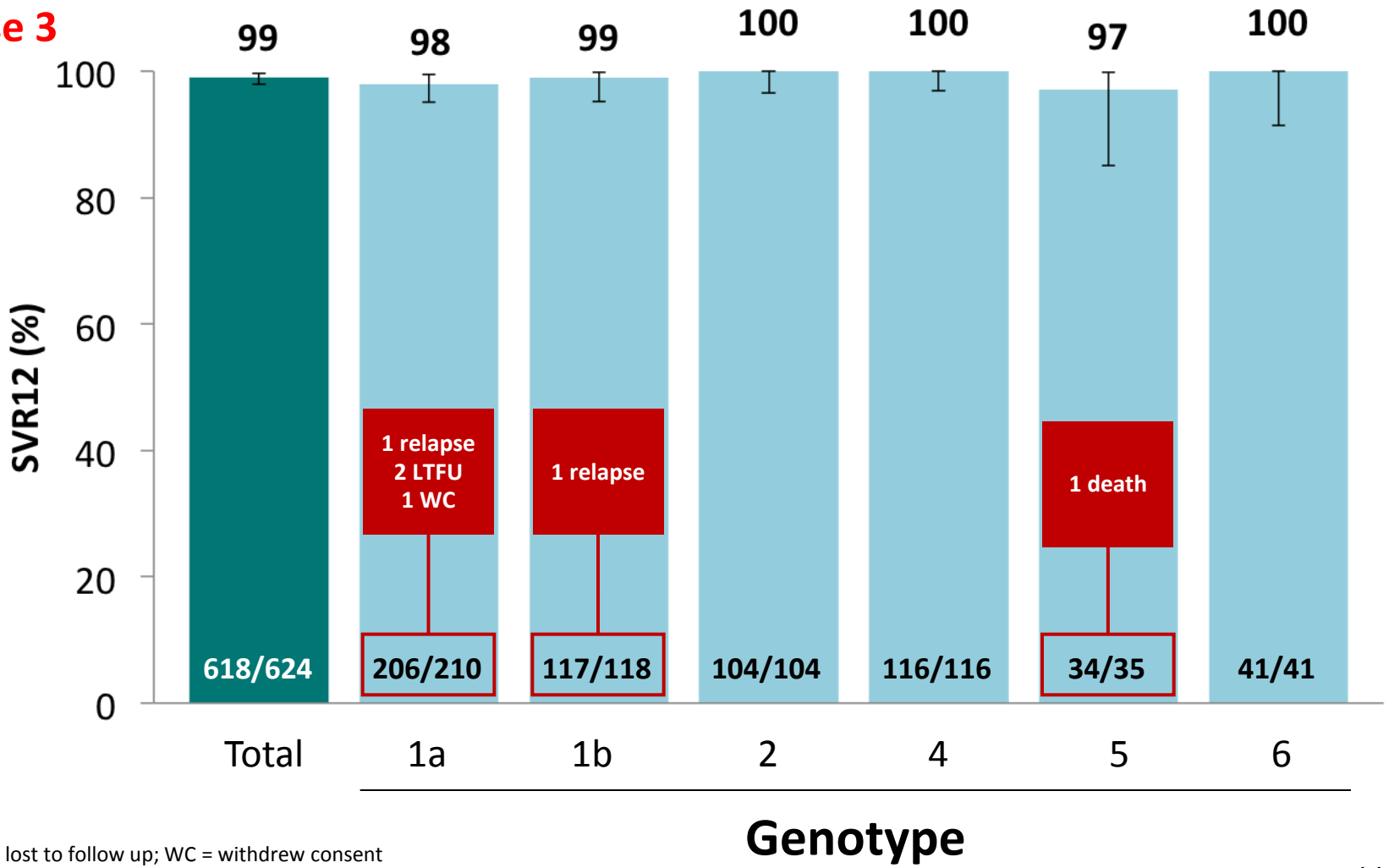
Patient Characteristics, n (%)	Placebo n=116	SOF/VEL n=624
Genotype 1A 1B	 46 (40) 19 (16)	 210 (34) 118 (19)
2	21 (18)	104 (17)
4	22 (19)	116 (19)
5	0	35 (5)
6	8 (7)	41 (7)
Cirrhosis, n (%)	21 (18)	121 (19)
Treatment experienced*, n (%)	33 (28)	201 (32)
IL28B CC, n (%)	36 (31)	186 (30)

SOF/VEL: Pangenotypic activity, fixed dose combination pill

Feld J, LB-2

SOF/VEL for 12 weeks
SVR12 Rates by HCV Genotype

ASTRAL-1:
Phase 3

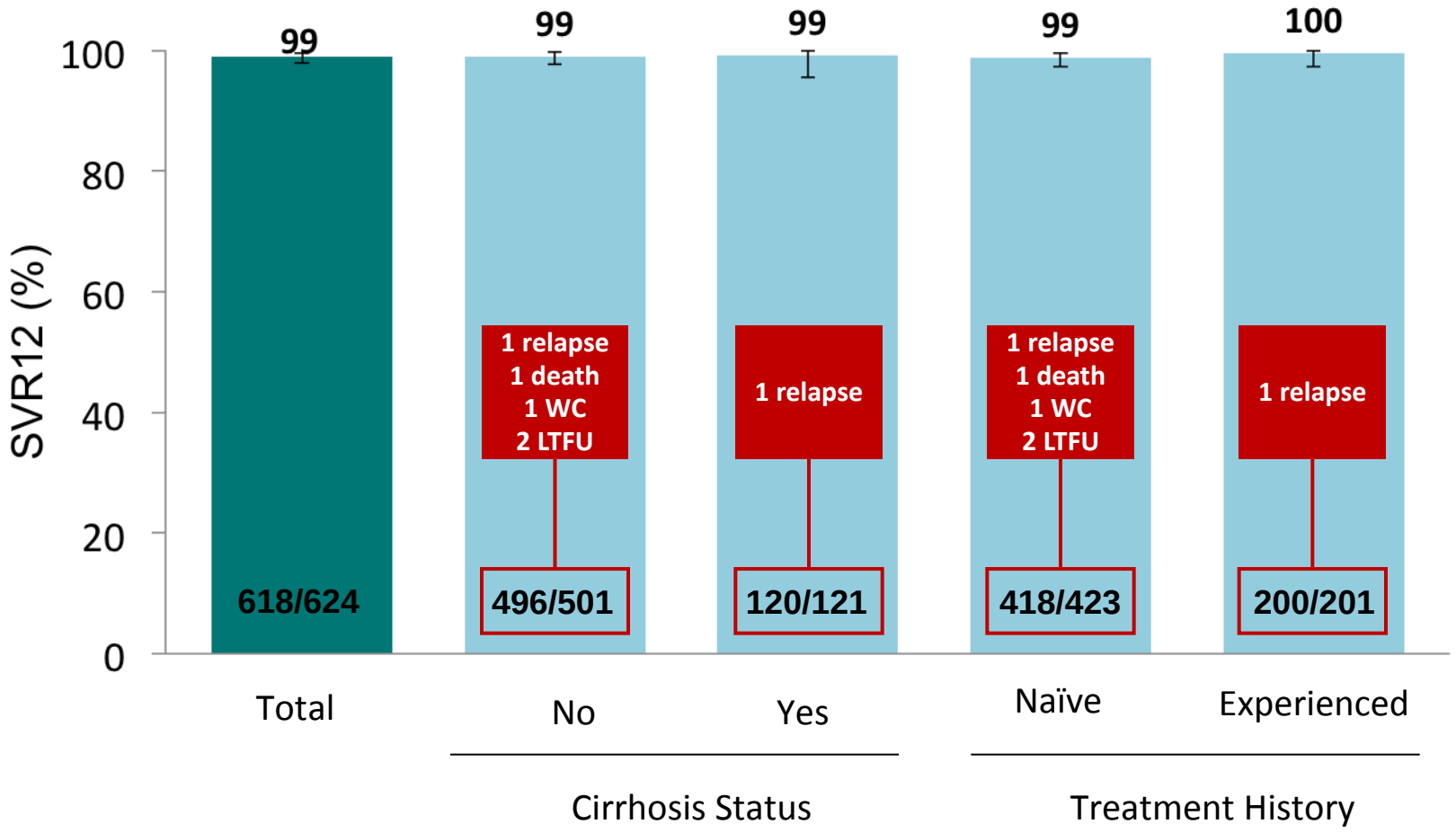


LTFU = lost to follow up; WC = withdrew consent

Feld J, LB-2

SOF/VEL for 12 weeks: SVR12 Rates by Cirrhosis and Prior Treatment

ASTRAL-1

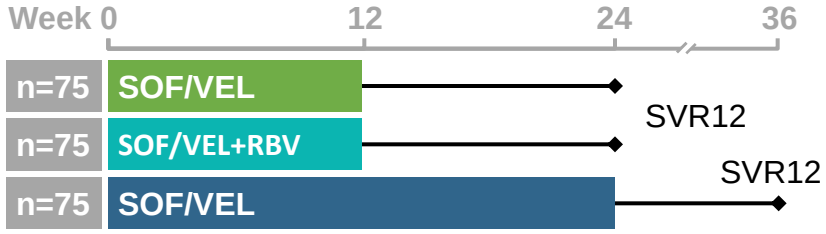


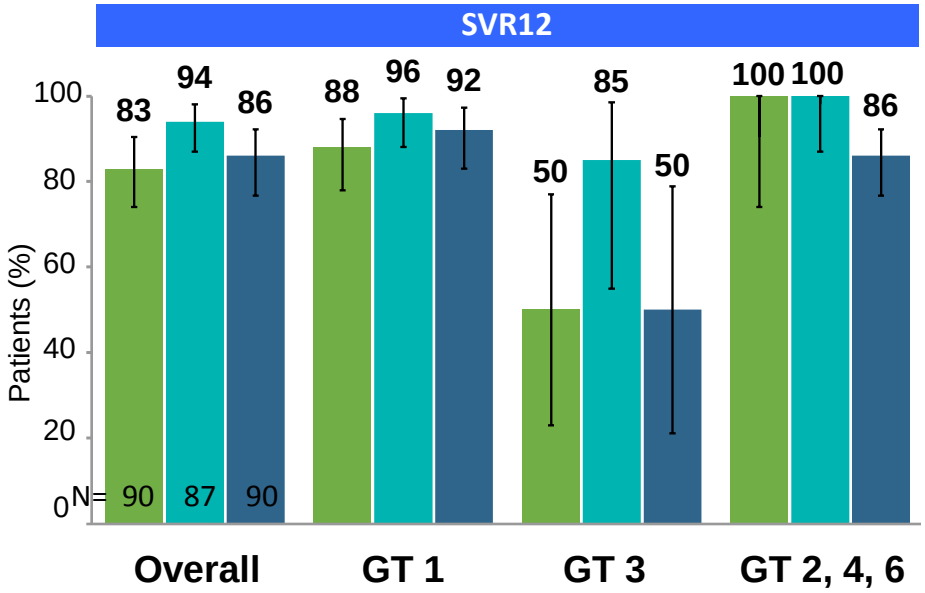
LTFU = lost to follow up; WC = withdrew consent

Feld J, LB-2

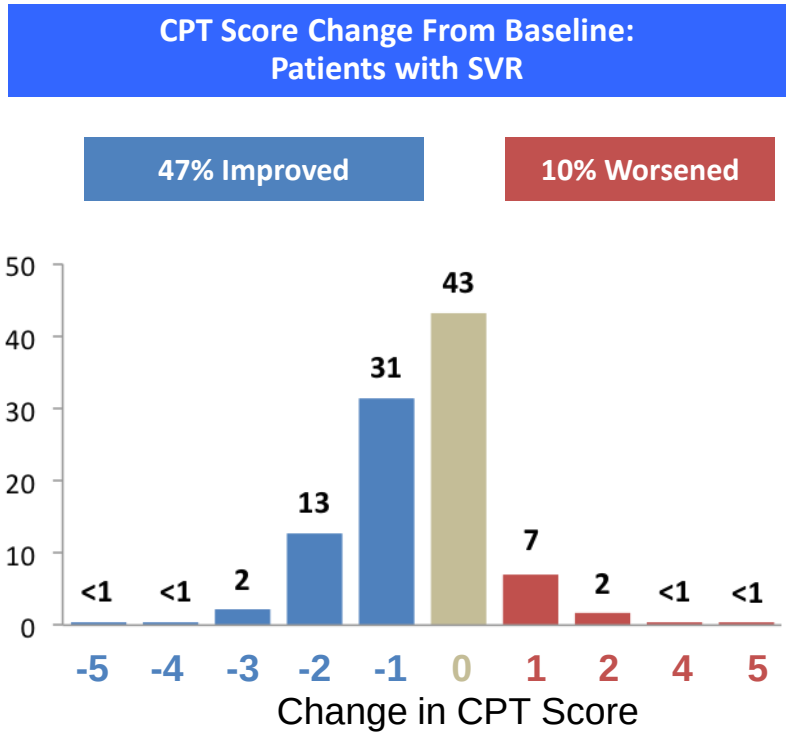
SOF/VEL for Patients With Decompensated Cirrhosis: Phase 3 ASTRAL-4

- HCV GT 1-6 patients with CPT B cirrhosis
- Randomized to once daily, oral, FDC SOF 400 mg/VEL 100 mg ± RBV





	GT1			GT3			GT2,4, 6		
Relapse	5	1	3	6	1	4			
VBT					1	1			
Death/LTFU	3	2	3	1		1			1



- AEs consistent with clinical sequelae of advanced liver disease, RBV toxicity

Charlton M, AASLD 2015: LB #13

Implications: SOF/VEL

- **SOF/VEL for 12 weeks yields high SVR rates in patients with HCV GT 1-6**
- **SOF/VEL is superior to SOF/RBV for 12 wks in GT2**
- **SOF/VEL is superior to SOF/RBV for 24 weeks in GT3**
- **Presence of baseline NS5A RAVs do not appear to impact SVR12**
- **SOF/VEL for 12 weeks was well tolerated, with a safety profile similar to that of placebo treatment**

New Therapies: More Doubles and New Triples

Striving for the penultimate therapy:

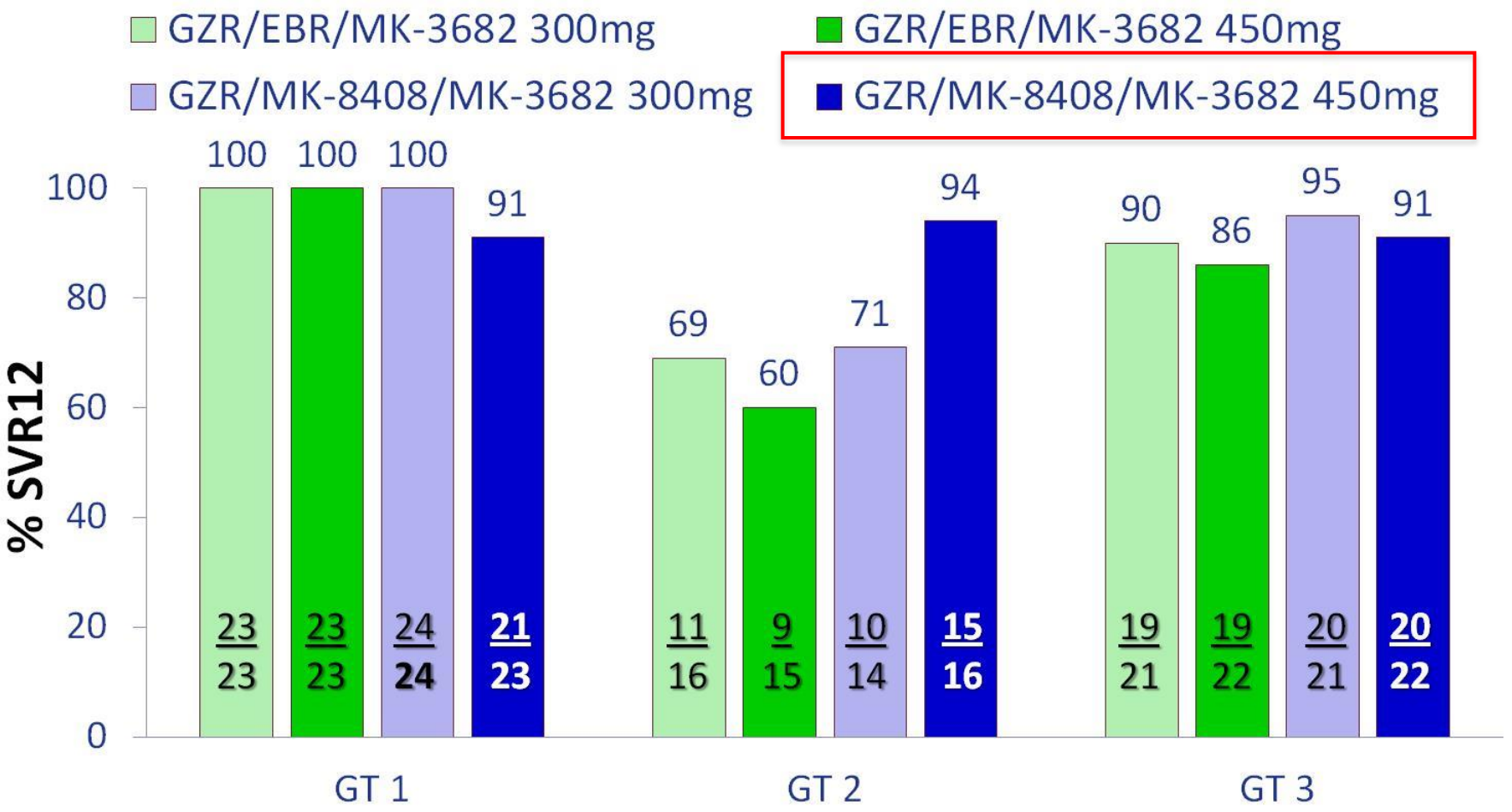
- **Pangenotypic**
- **No need for ribavirin**
- **One pill a day**
- **High barrier to resistance**
- **Short duration (8 wks or less)** ➡

Lower cost
Improved adherence
Reduce emergence of resistance
Simplicity

PI NS5B polymerase inhibitor NS5A inhibitors

GZR/MK-3682 + EBR or MK-8408/for 8 Wks in GT1-3 Patients, Treatment Naïve, No Cirrhosis

C-CREST, Phase 2

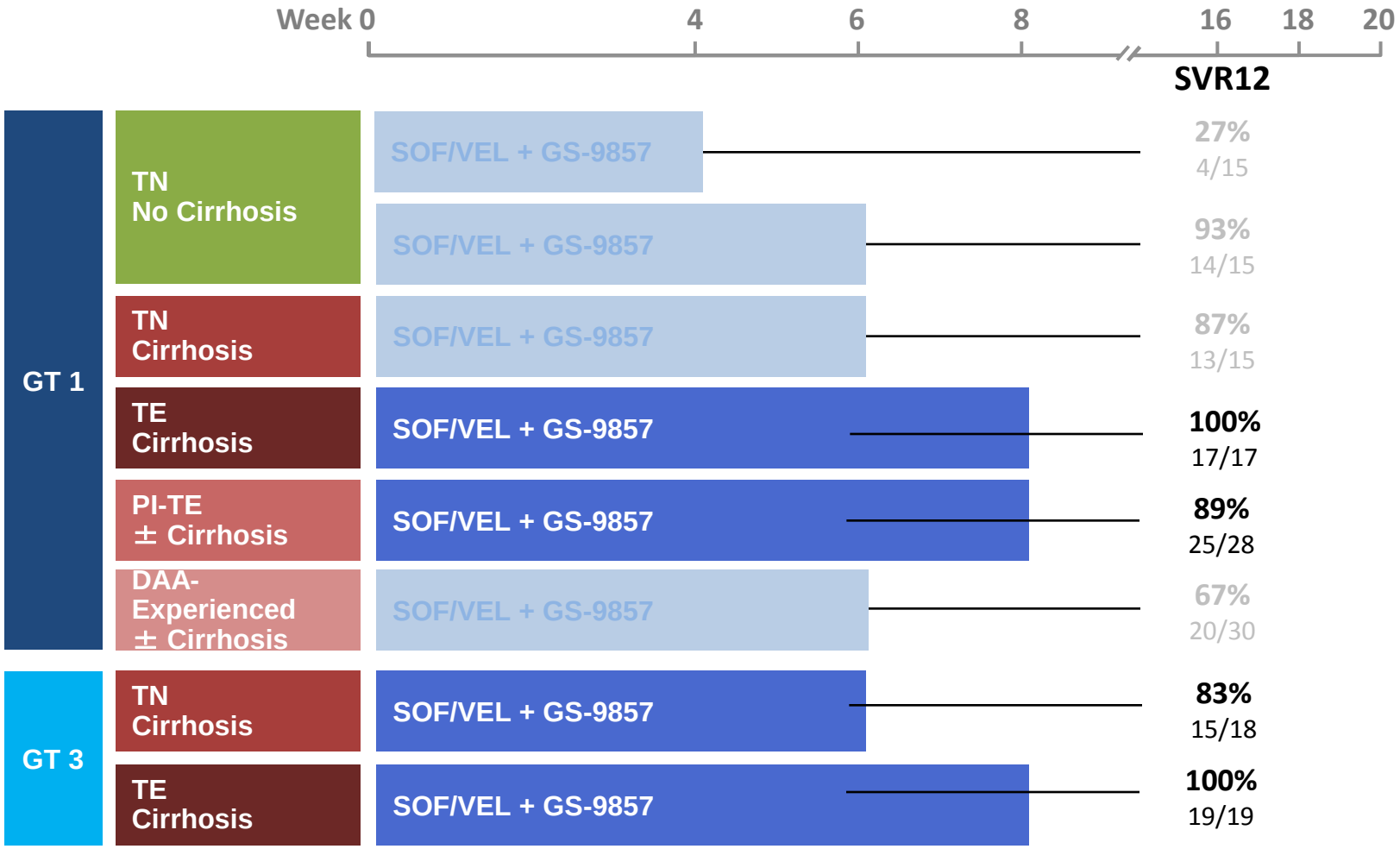


*Primary efficacy: SVR12 of full analysis set (FAS). All 240 enrolled patients completed 8 weeks of treatment and reached follow-up 12 weeks after end of treatment.

Gane E, AASLD 2015, LB15

NS5B polymerase inhibitor /NS5A inhibitor PI

Sofosbuvir/Velpatasvir + GS-9857 for 6 or 8 Weeks in Genotype 1 or 3 HCV-Infected Patients



- **6% (5/82) patients relapsed: 3 GT1a and 2 GT3**
- **Treatment-emergent NS5A RAVs were detected in 1/5 patients**
- **No treatment-emergent NS3 or NS5B RAVs detected**

Gane E, EASL 2015, LP03
Gane E, AASLD 2015,Abstract 38

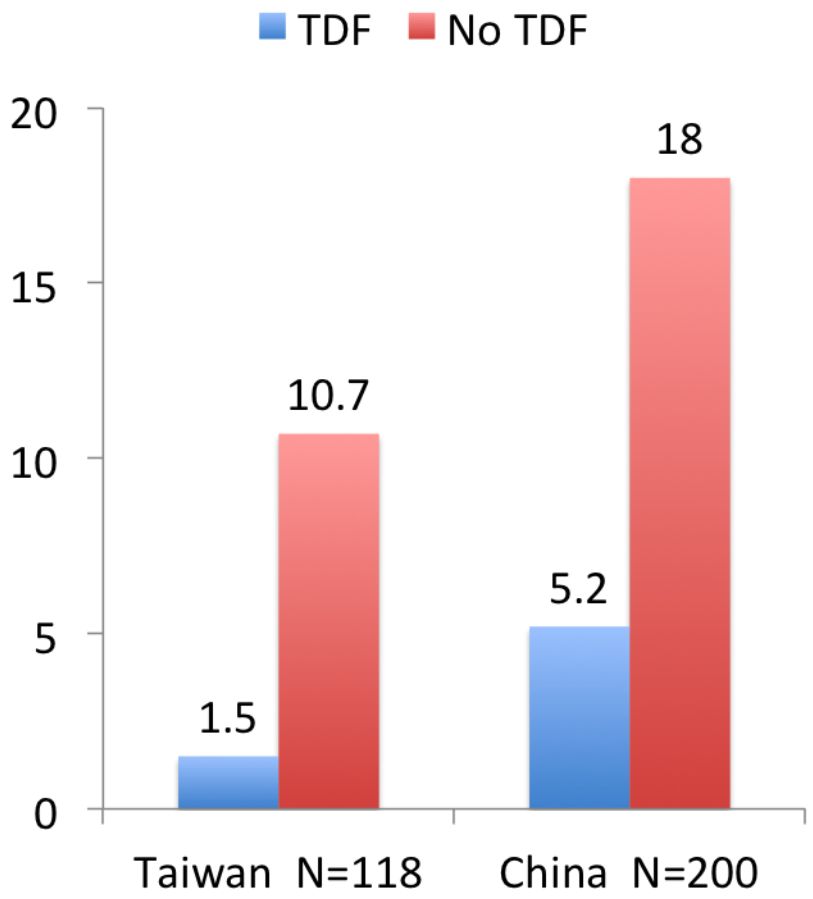
Hepatitis C: Conclusions

- Currently approved drugs achieve SVR rates in clinical practice similar to that of clinical trials
  - Large real life cohorts are identifying the factors associated with treatment failure
- Availability and success of therapies in traditional and new "special populations": ESRD, decompensated cirrhosis, PWID
- More intense scrutiny of the impact of baseline and treatment-emergent RAVs on SVR rates
  - Small but important studies on treatment strategies
- Exciting drug pipeline that is focused on attaining DAA combinations that are pangenotypic, safe, high efficacy AND short duration
- Novel solutions to address enhance awareness, diagnosis and linkage to care – first steps on the cascade of care

Hepatitis B

Prevention of Mother-to-Child Transmission of HBV

- **Pregnant women, HBeAg+, HBV DNA >200,000 IU/mL (mean >8-$\log_{10}$ IU/mL)**
- **Randomized 1:1 to tenofovir (TDF) 300 mg daily starting wk 30-32 gestation through to 4 wks post-partum**
- **All infants received HBIG and vaccination**
- **Maternal Cr and CK levels, rates of congenital anomaly, premature birth, and growth parameters in infants not different between groups**



Chen HL, Hepatology 2015;62(2):375-86.
Pan C, AASLD 2015, San Francisco, Abs #209

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

PRACTICE GUIDELINE

AASLD Guidelines for Treatment of Chronic Hepatitis B

Treatment of CHB in Pregnancy

Recommendations

8A. The AASLD suggests antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL.

Quality/Certainty of Evidence: Low
Strength of Recommendation: Conditional

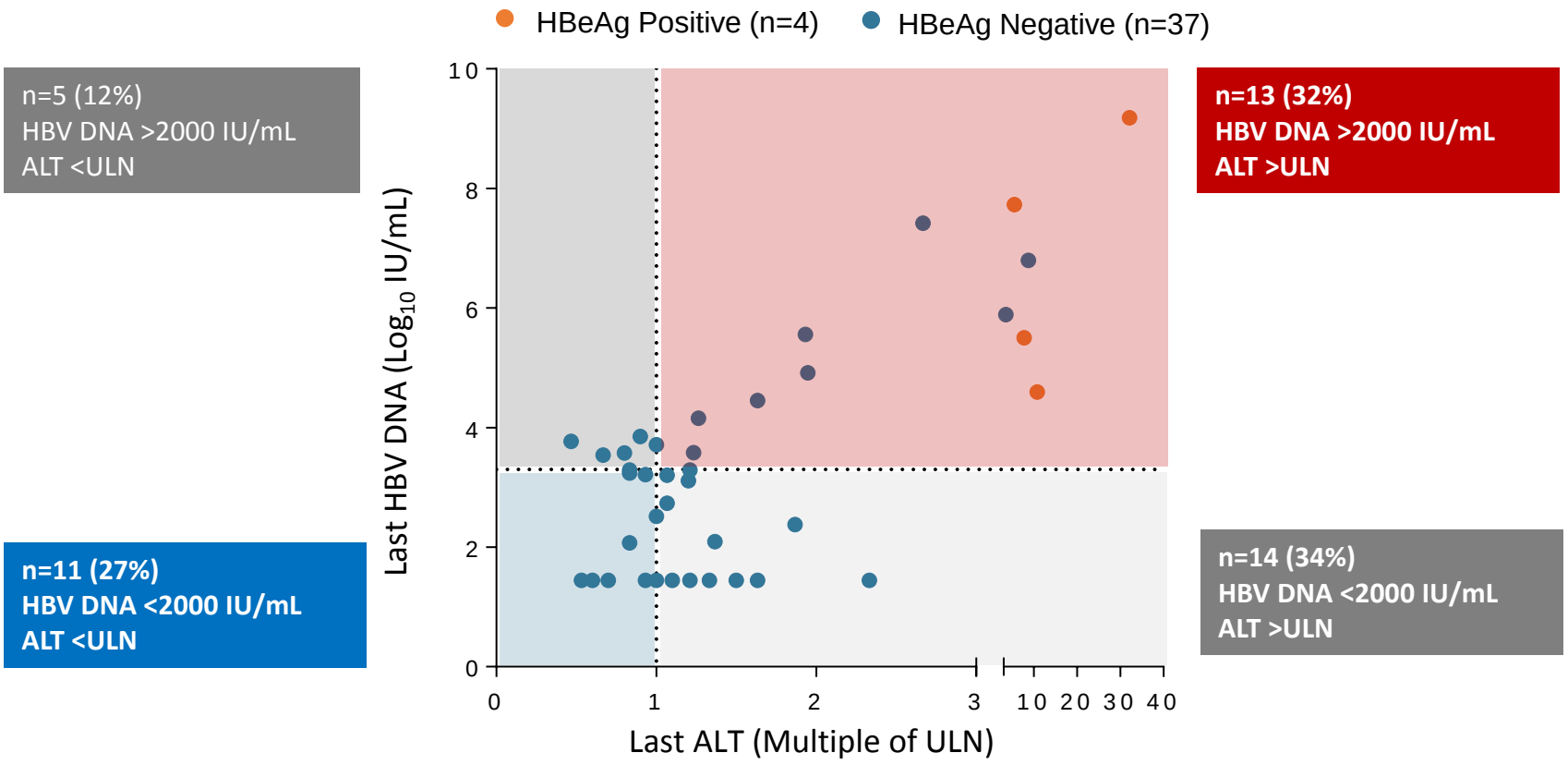
Technical Remarks:

- **Start 28-32 weeks gestation**
- **Tenofovir, telbivudine or lamivudine**
- **Use >200,000 IU/mL HBV DNA to define risk group**
- **Treat to delivery → 3 months post-partum**
- **Monitor for flares**
- **Breastfeeding not contraindicated on treatment**
- **C-section no indicated**

Terrault N et al, Hepatology, 2015

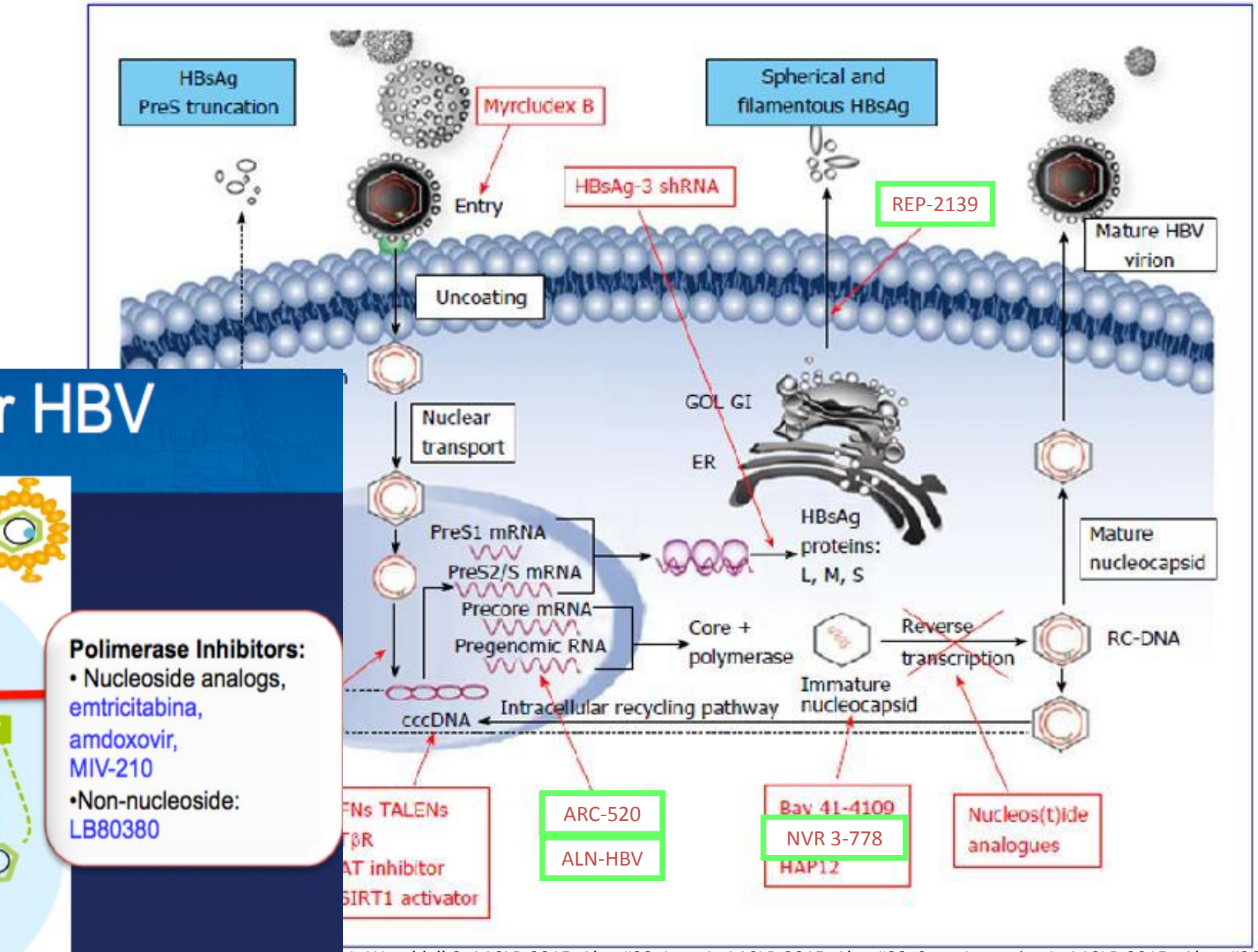
Discontinuation of Tenofovir in Patients with Long-Term Suppression

- N=41 patients from registration trials on ≥8 yrs of continuous tenofovir stopped treatment and followed for 24 wks



- 3 patients (7%) lost HBsAg in first 24 wks post-withdrawal
- None of the HBeAg positive patients had HBV DNA <2000 U/mL or lost HBsAg

Buti M, AASLD 2015, Abstract #243



1; Wooddell C, AASLD 2015, Abst #32, Lam A, AASLD 2015, Abst #33, Sepp-Lorenzino L, AASLD 2015., Abst. #36

HBV: Clinical Implications

- Increasing interest in “finite” therapy for chronic HBV
- Withdrawal of therapy in persons on long-term antiviral suppression
  - A substantial proportion of HBeAg-negative patients may be inactive carriers
  - May enhance rates of HBsAg loss
  - More studies needed
- MTCT requires testing of mothers in 2nd trimester and giving antiviral therapy if HBV DNA >200,000 IU/mL
- New drug targets → early phases of development but lots of enthusiasm

Hepatocellular Carcinoma

Wait-Time and Impact of Post-LT HCC Recurrence

- 3 center study (UCSF, Mayo Rochester, Mayo Jacksonville)
- All adults with HCC within Milan criteria at listing 2002-2012 (n=911)

	Overall	Center 1	Center 2	Center 3	p-value
Dropout (%)	18%	29%	7%	6%	<0.001
Median Time (mo) to Dropout (IQR)	11 (7-17)	12 (7-17)	11 (6-16)	7 (5-9)	0.004

	Overall	Center 1	Center 2	Center 3	p-value
Liver Transplant	81%	71%	93%	94%	<0.001
Median Time (mo) to LT (IQR)	8 (5-14)	13 (9-19)	7 (4-11)	5 (2-7)	<0.001
Wait time to LT					<0.001
<6 months	32%	10%	40%	61%	
6-18 months	54%	62%	58%	37%	
>18 months	14%	28%	2%	2%	

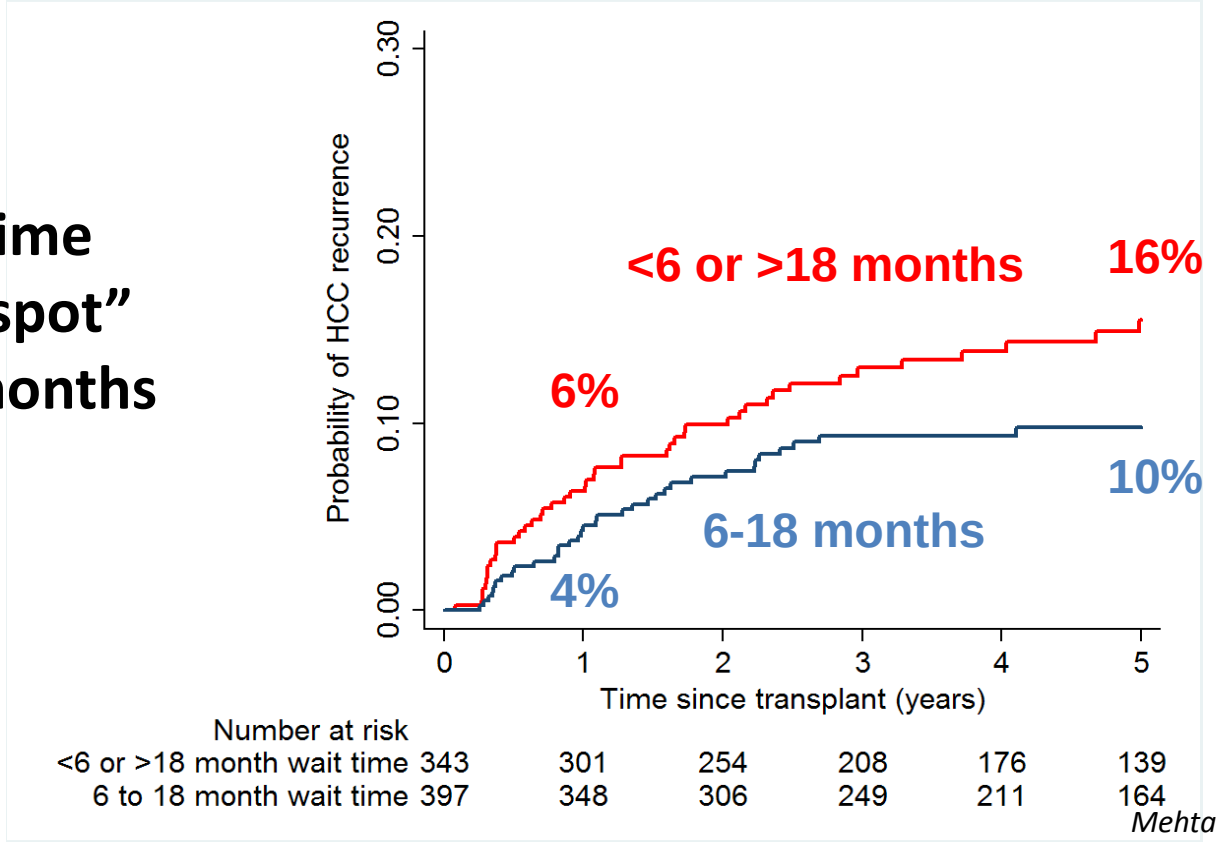
Mehta N, AASLD Abstract #50

Predictors of Recurrence Known Pre-LT

Predictor	Multivariable HR (95% CI)	P-value
Wait Time to LT <6 or >18 mo	1.6 (1.01-2.5)	0.04
AFP at HCC dx >400 vs ≤400	3.0 (1.7-5.5)	<0.001

* Microvascular invasion and beyond Milan criteria additional factors (known only post-LT)

Wait-time "sweet spot" = 6-18 months



p=0.049

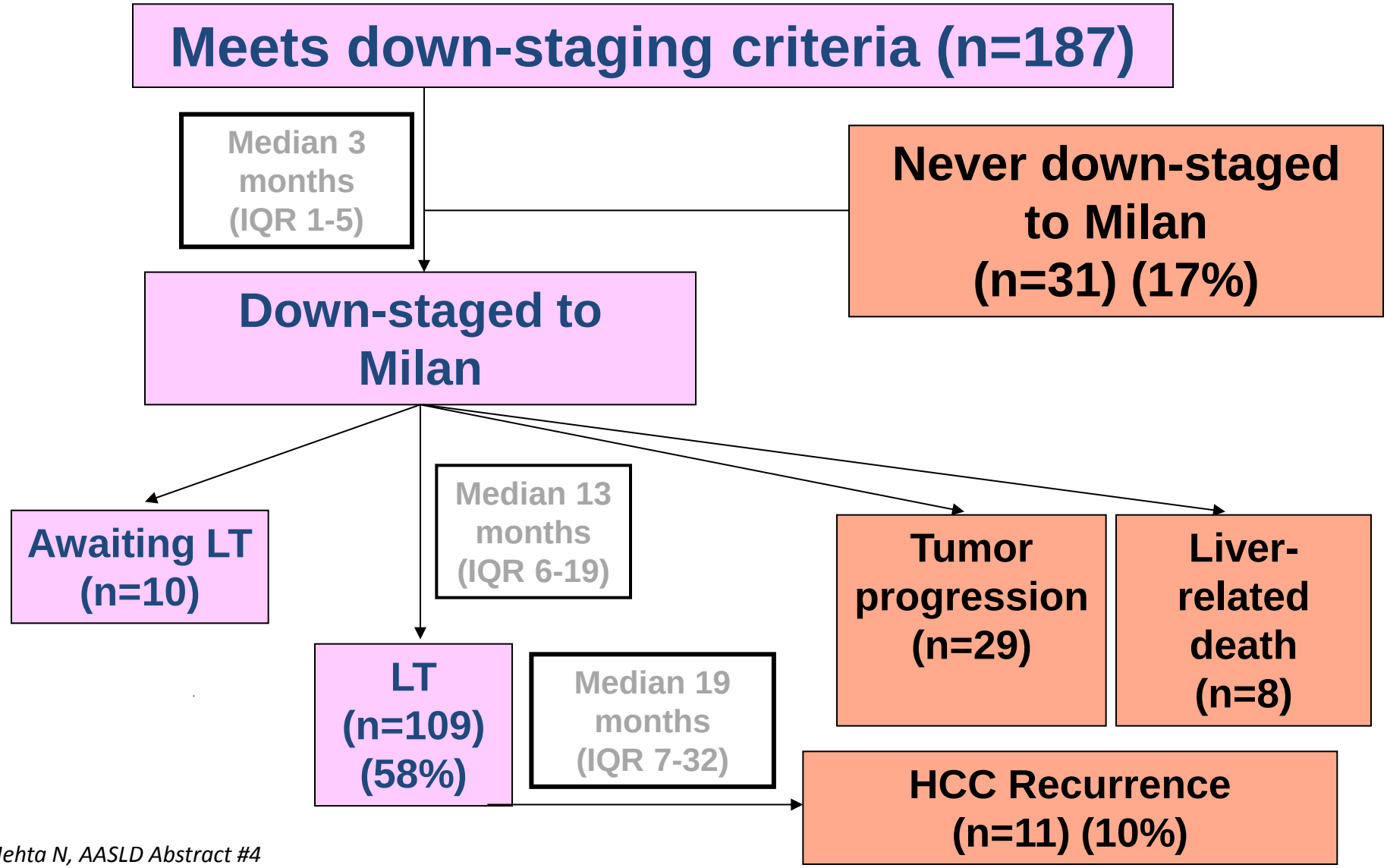
Mehta N, AASLD Abstract #50

REGION 5 Down-Staging Protocol

- **We previously presented preliminary results of a multicenter study from Region 5 on down-staging of HCC to within Milan criteria using a uniform protocol**
  - **UCSF, CPMC and Scripps**
- **58% underwent LT a median of 16 months from 1st down-staging procedure**
    - **5 year post-LT survival 80%**
    - **5 year recurrence-free probability 87%**
- **No center specific differences were found**

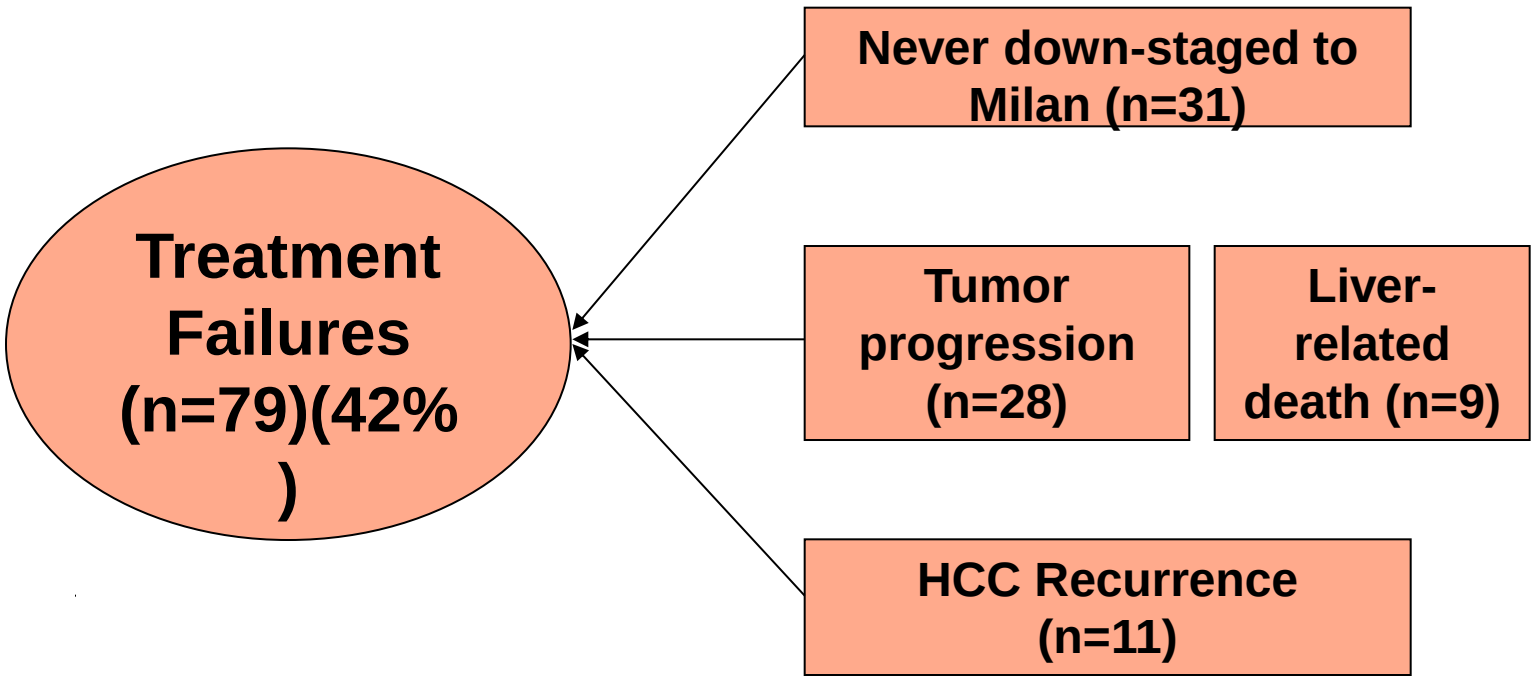
Mehta N et al. Hepatology 2014; 60 (Suppl):253A (AASLD 2014)

Outcomes of Patients Undergoing HCC Down-staging: Intent to Treat



Mehta N, AASLD Abstract #4

Predictors of Failure of Down-Staging of HCC

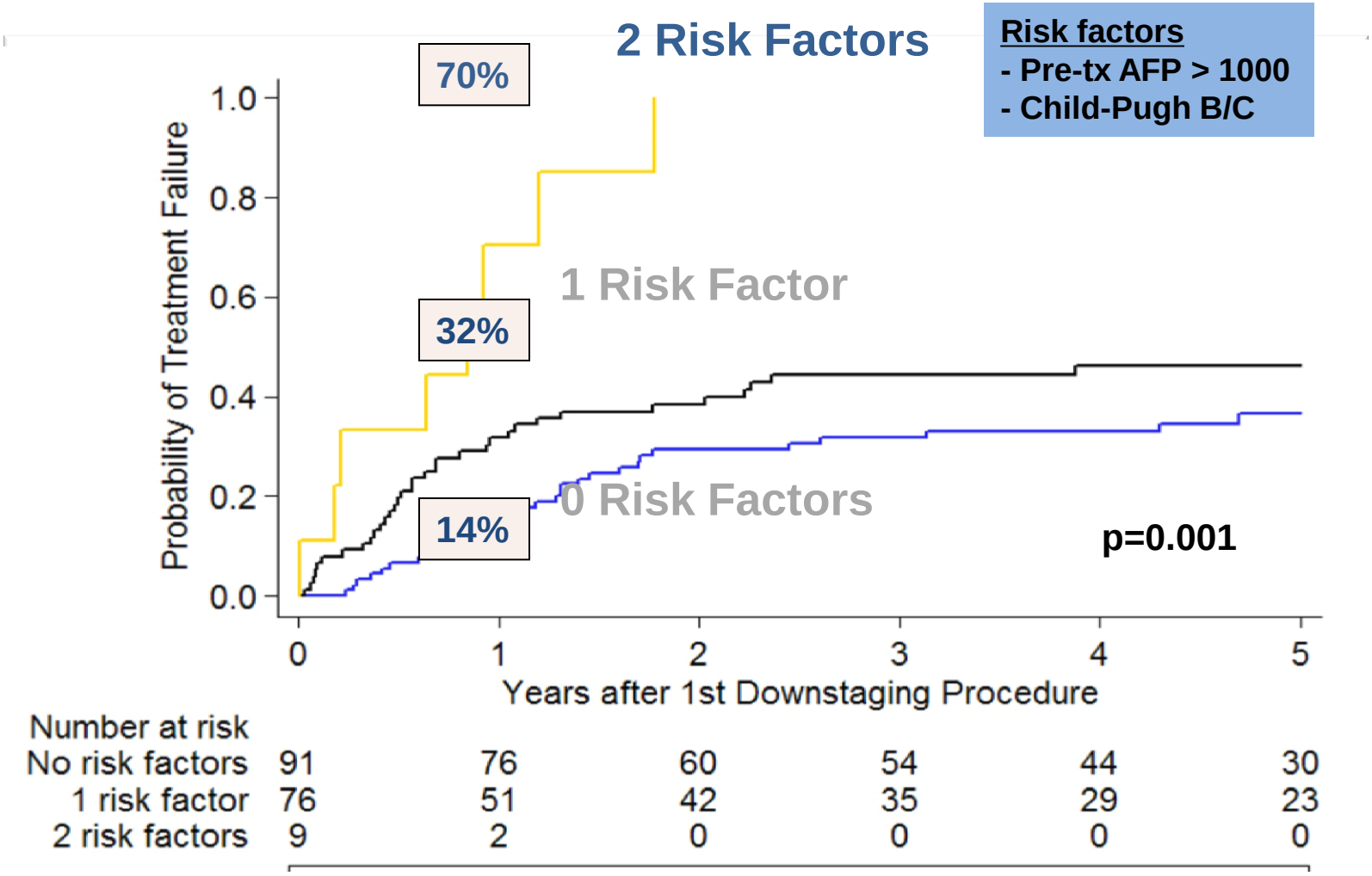


Multivariable Model: Predictors	MV HR (95% CI)	P value
AFP* ≥1000 vs <1000	3.3 (1.8-6.0)	<0.001
Child-Pugh B/C vs A	1.6 (1.02-2.6)	0.04

* Before 1st down-staging procedure

Mehta N, AASLD Abstract #4

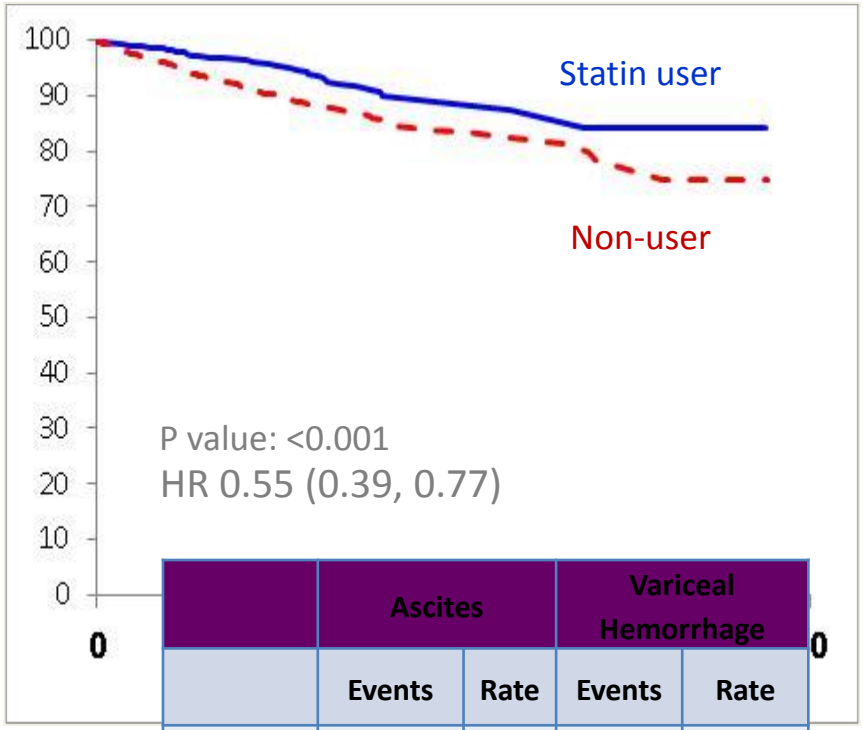
Patients with CP B/C Cirrhosis and AFP >1000 are Poor Candidates for Downstaging



Mehta N, AASLD Abstract #4

Statins Associated with Decreased Risk of Decompensation and Death*

Decompensation



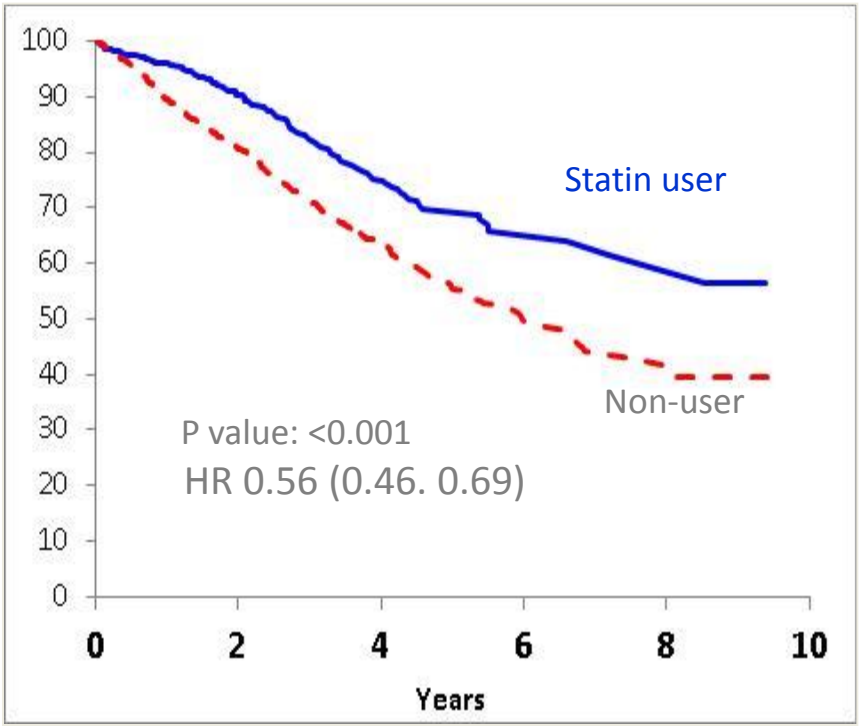
	Ascites		Variceal Hemorrhage	
	Events	Rate	Events	Rate
Non-user	112	2.4	58	1.3
Statin user	26	1.4	9	0.5
	0.59 (0.39,0.91) p=0.02		0.39 (0.19,0.78) p=0.01	

No. at risk

685

2062

Death



No. at risk

685

2062

*HCV Compensated Cirrhosis
Propensity score matched study

Mohanty, Tate and Garcia-Tsao. Gastroenterology 2015 [ePub ahead of print].

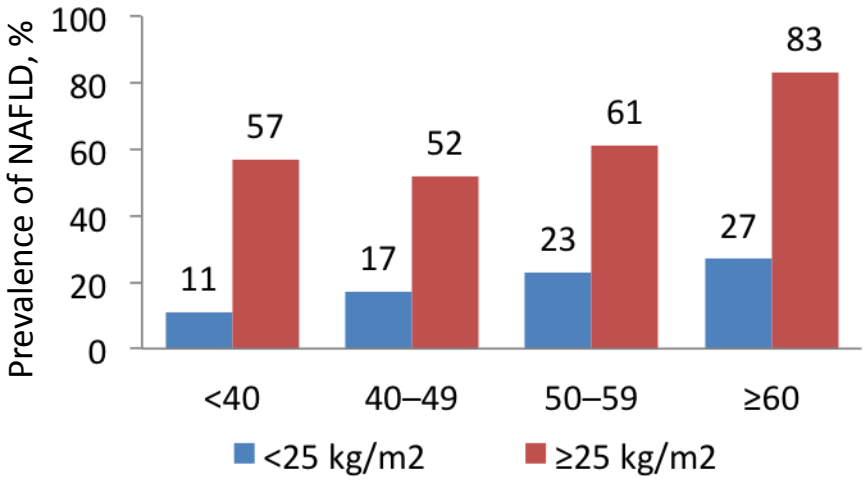
HCC: Clinical Implications

- **HCC patients in Region 5:**
  - **Downstaging is effective in majority → best chance at HCC-free survival**
    - **Those with advanced decompensation and AFP >1000 are poor candidates**
  - **Optimal wait-time is 6-18 months → given new MELD rules, more patients will need to consider "other" donor options**
- **Statins have broader range of benefits and should considered part of our prophylactic measures for compensated cirrhotics**

NASH

"Lean NASH": Prevalence and Severity of NAFLD in Non-Obese Chinese Patients

- **3,000 adults (general population) were invited, 911 participated (non-obese: BMI <25 kg/m^2)**
- **Extensive data**
- **^{1}H-MRS for IHTG quantification and transient elastography**
- **NAFLD prevalence greater in obese patients vs non-obese (60.5% vs 19.3%; p<0.001)**



Factors associated with NAFLD in non-obese

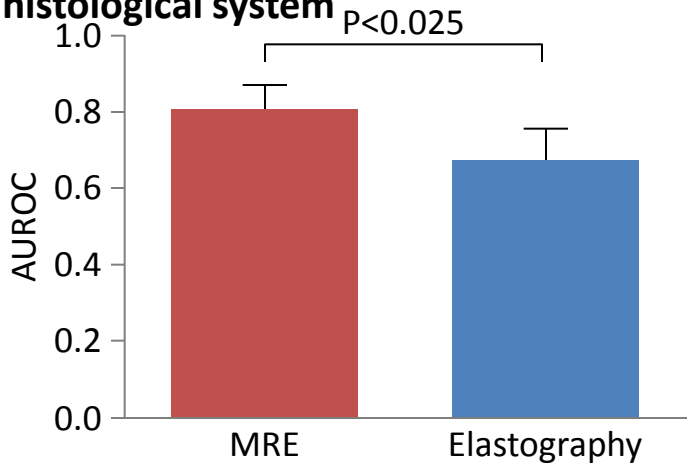
	OR	P
BMI	1.33	0.002
Waist circumference	1.11	<0.001
HbA_{1c}	1.83	0.040
HOMA-IR	1.24	0.001
Ferritin	1.001	0.008
PNPLA3 CG/GG	4.37	<0.001

- 19.3% of non-obese Chinese population has NAFLD
- WC, IR, ferritin, and PNPLA3 gene risk factors of NAFLD in non-obese people

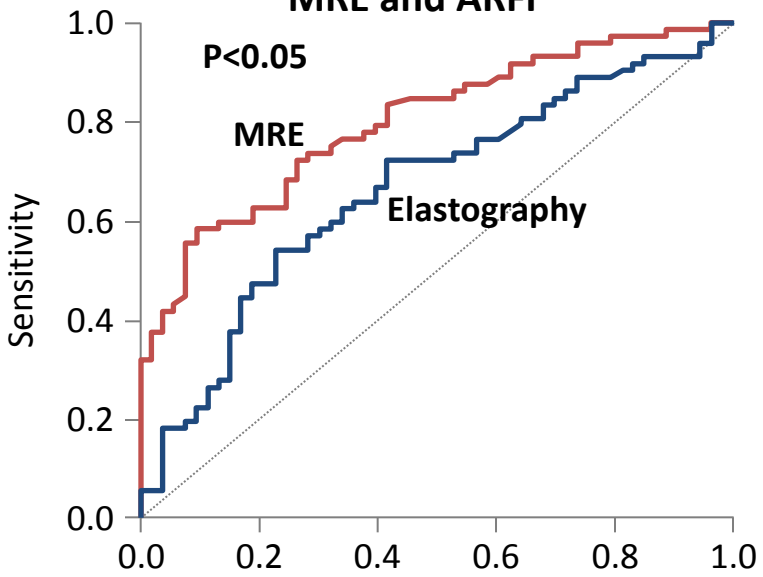
Wong VW, et al. AASLD 2015, San Francisco. #235

MRE Superior to Elastography for the Diagnosis of Fibrosis in Patients with NAFLD

- All patients underwent MRE and elastrography within 1 year of contemporaneous liver biopsy
- Liver biopsies scored using the NASH CRN histological system



ROC curves for 125 consecutive patients with biopsy-proven NAFLD with contemporaneous MRE and ARFI



Diagnostic test parameters of MRE vs ARFI for diagnosing fibrosis

	NAFLD fibrosis	No fibrosis	AUROC (95% CI)	Cut-Off	Sens	Spec	PPV	NPV
MRE	72	53	0.80 (0.72, 0.88)	2.99	58%	91%	89%	62%
Elastography			0.66 (0.57, 0.76)	1.29	54%	77%	77%	55%

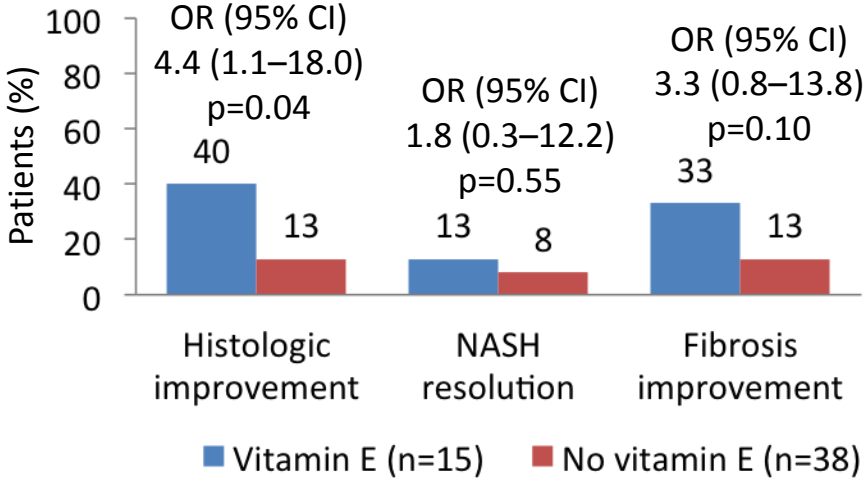
- In patients with BMI <30 kg/m^2, ultrasound may be used; for those ≥30 kg/m^2, MRE should be used

Cui JY, et al. AASLD 2015, San Francisco. #45

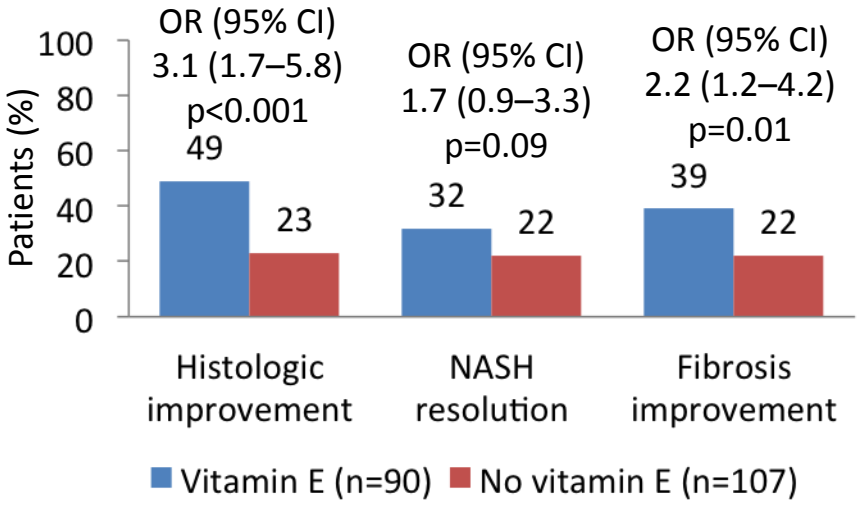
Efficacy and Safety of Vitamin E in NASH Patients with and without DM

- **250 patients from PIVENS and FLINT trials: DM=53, non-DM=197; Vit E=105, no Vit E=145**
- **Two efficacy measures from FLINT: histologic improvement (≥2-point improvement in NAS with no worsening of fibrosis, or NASH resolution**
- **Baseline and end-treatment liver biopsies, and safety assessed**
- **Histologic improvement with Vitamin E in DM and non-DM; NASH resolution and fibrosis improvement in DM only**
- **No association of vitamin E with important adverse safety measures**

Patients <u>with</u> diabetes (N=53)



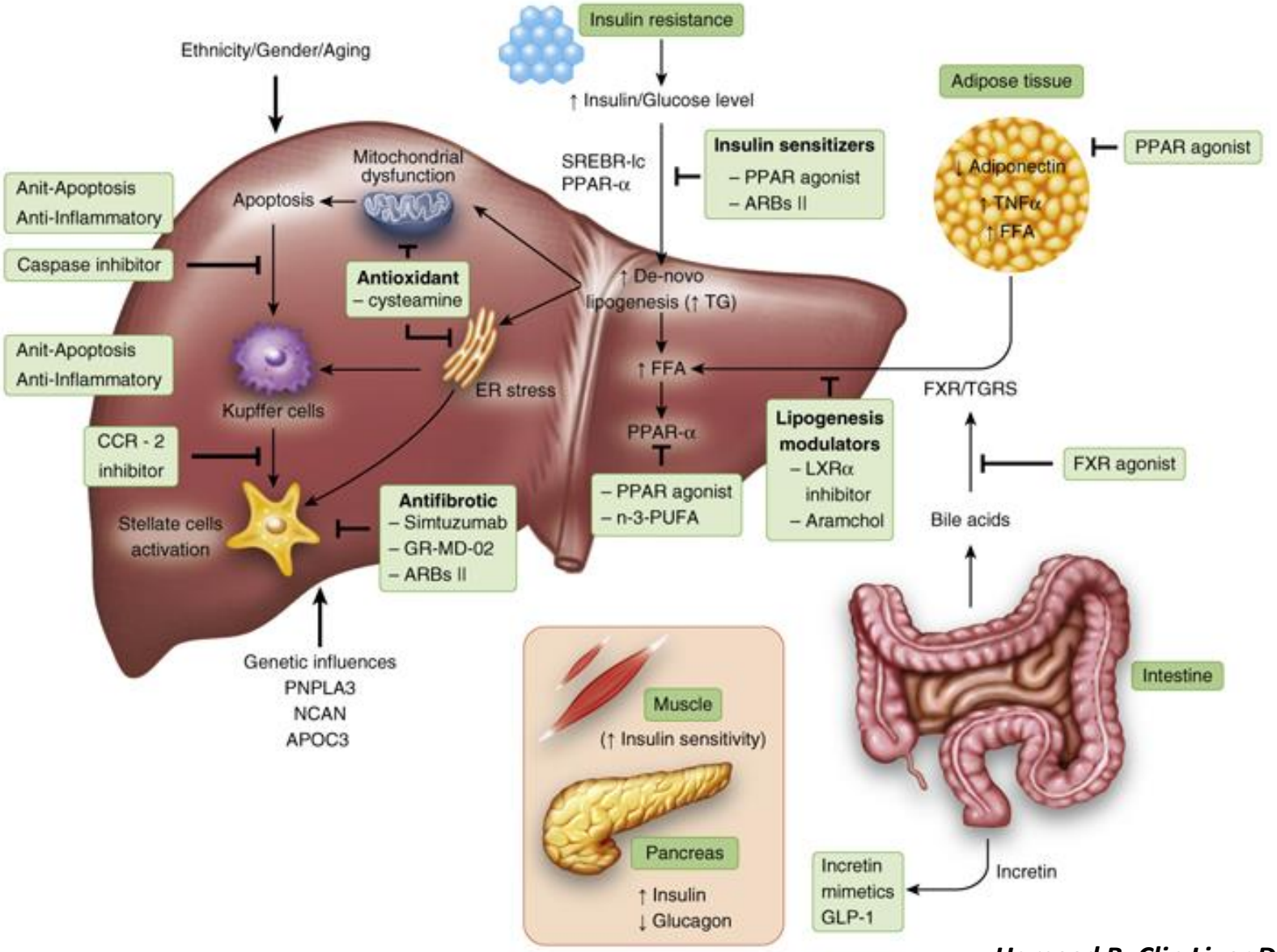
Patients <u>without</u> diabetes (N=197)



Vitamin E was associated with similar significant improvement in NASH histology in both DM and non-DM

Kowdley KV, et al. AASLD 2015, Abstract #107

New Therapies for NASH

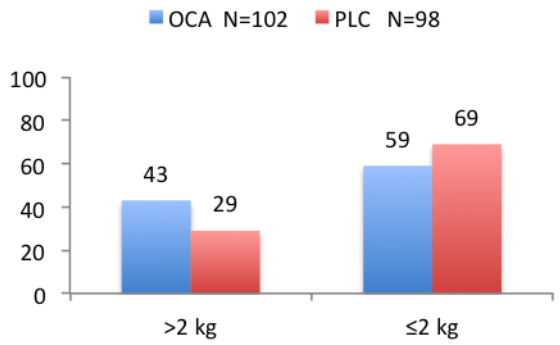


Hameed B, Clin Liver Dis, 2016

Obeticholic Acid Leads to Weight Loss: Additive Effects of Liver Enzymes and Histology NAS Activity

FLINT Trial of adults with biopsy-proven NASH showed OCA (25 mg daily for 72 weeks)

- **Decreased NAS score**
- **Improved fibrosis**



- **Weight loss ≥ 2kg occurred in both arms but more frequent with OCA group.**

Liver Test	OCA			Placebo			OCA vs PLB
	≥ 2 kg loss	< 2kg loss	P value	≥ 2 kg loss	< 2kg loss	P	P
ALT (U/L)	-42	-34	0.15	-30	-10	0.01	<0.001
AST (U/L)	-29	-23	0.14	-15	-5	0.09	0.001

Feature	OCA			Placebo			OCA vs PLB
	≥ 2 kg loss	< 2kg loss	P value	≥ 2 kg loss	< 2kg loss	P value	P value
NAFLD Activity	-2.4	-1.2	<0.001	-1.4	-0.4	0.006	<0.001
Inflammation	-0.7	-0.3	<0.001	-0.3	-0.1	0.14	0.002
Ballooning	-0.6	-0.3	0.04	-0.3	-0.1	0.25	0.05
Steatosis	-1.1	-0.5	<0.001	-0.8	-0.2	<0.001	0.002

Hameed B, AASLD Abstract #236

Obeticholic Acid Leads to Weight Loss: Paradoxical Effects of Lipid Parameters

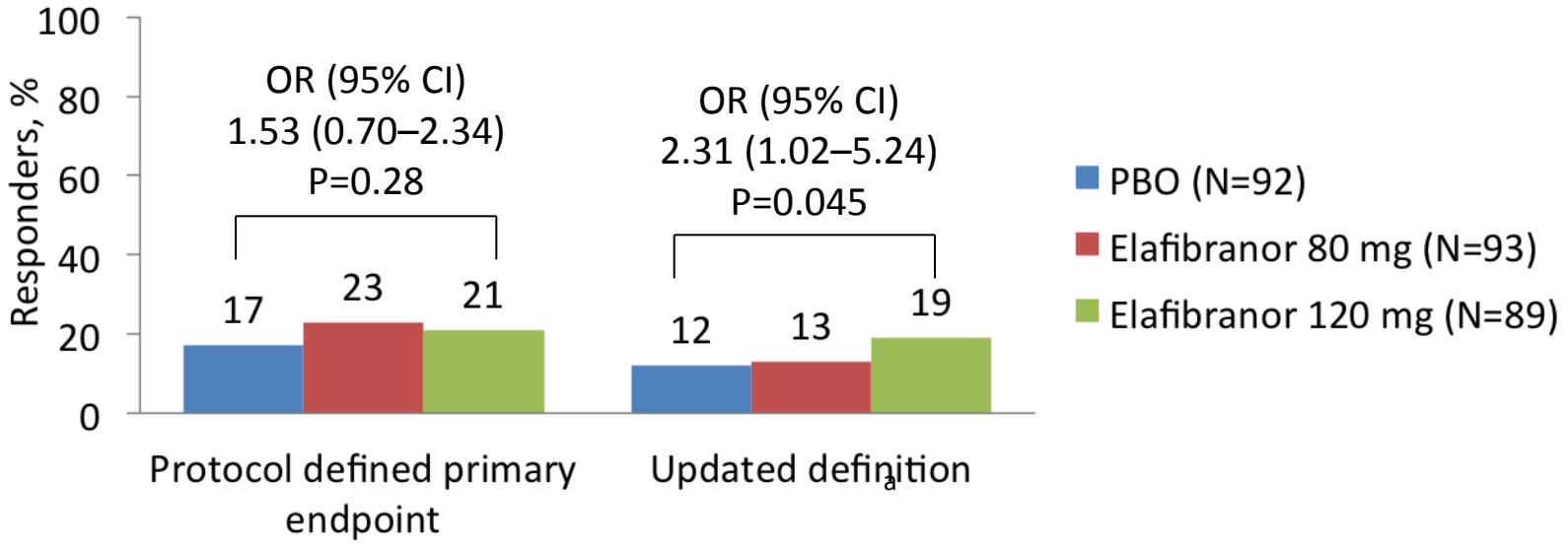
Feature	OCA			Placebo			OCA versus placebo P value
Mean change (mg/dl)	≥ 2 kg loss	< 2kg loss	P value	≥ 2 kg loss	< 2kg loss	P value	
Total cholesterol	+17	0	0.01	-14	0	0.06	0.03
LDL	+22	1	0.002	-13	-3	0.11	0.001
HDL	-1.3	- 0.8	0.69	+3.3	+0.7	0.07	0.001
Triglycerides	-12	-11	0.94	-23	+5	0.40	0.83
Hgb A1c - %	+0.1	+0.1	0.63	-0.5	+0.3	<0.001	0.004
Waist circumference	-3.7	+0.2	0.003	-7.0	+1.6	<0.001	<0.0001

- Total and LDL cholesterol and HbA1C levels improved with weight loss in the placebo group, but worsened with weight loss in the OCA group
- Greater decrease in waist circumference in placebo vs OCA group with weight loss

Hameed B, AASLD Abstract #236

Efficacy of Dual PPAR α-δ agonist, GFT505 in Patients with NASH

- **Phase 2 study: GOLDEN505 trial patients randomized to Elafibranor/GFT505 120 mg QD and PBO (N=274)**
- **No significant effect of Elafibranor on resolution of NASH without worsening of fibrosis as predefined in the protocol**
- **Significant effect of Elafibranor 120 mg observed with newly updated definition of complete resolution of ballooning and either 0 or 1 for lobular inflammation**

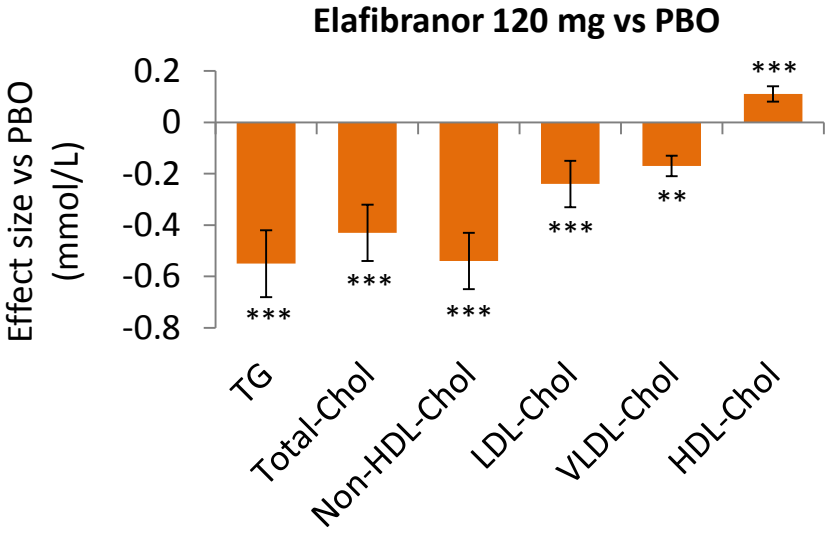


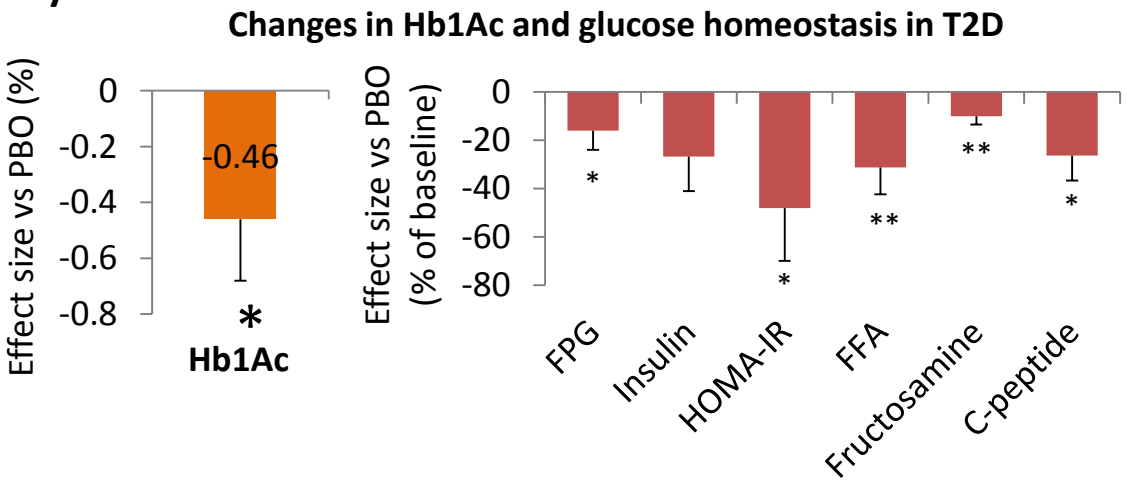
In patients with NAS≥4, Elafibranor 120 mg demonstrates significant activity on resolution of NASH

Ratziu V, et al. AASLD 2015, Abstract #105

Efficacy of Dual PPAR α-δ agonist, GFT505 in Patients with NASH

- GOLDEN505 trial patients randomized to Elafibranor/GFT505 120 mg and PBO
- Highly significant improvement in all components of plasma lipid profile with Elafibranor vs PBO
- Significant decrease in HbA1C and overall improvement of glucose homeostasis and insulin sensitivity obtained on top of concomitant anti-diabetic treatments
- Effects of Elafibranor 120 mg on plasma lipids independent of disease severity (NAS) and BL fibrosis score





The effects of Elafibranor on cardiometabolic parameters are maintained in more severe NASH populations

*p<0·05, **p<0·01, ***p<0.001 vs placebo
Harrison S, et al. AASLD 2015, San Francisco. #162

NASH: Clinical Implications

- Non-invasive tests to diagnosis NAFLD are expanding to include MRE
  - High sensitivity and modest specificity; too expensive to widely applied
  - Elastography will be inaccurate in up to 30% of cases
- NAFLD present in ~20% of non-obese Asians; metabolic risks should prompt consideration of this diagnosis
- Vitamin E is effective in diabetic and non-diabetics with biopsy proven NASH
- OCA causes weight loss and improved liver parameters but paradoxical worsening of metabolic parameters: await phase 3 data
- Encouraging early results with other drug classes


Thank- you