

CCO Official Conference Coverage: Clinical Impact of New Data From AASLD 2015

CCO Official Conference Coverage

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Summary of Direct-Acting Antivirals Discussed in This Slideset

Drug	Abbreviation	Class
ABT-493	-	NS3/4A protease inhibitor
ABT-530	-	NS5A inhibitor
Daclatasvir	DCV	NS5A inhibitor
Dasabuvir	DSV	NS5B nonnucleoside polymerase inhibitor
Elbasvir	EBR	NS5A inhibitor
Grazoprevir	GZR	NS3/4A protease inhibitor
GS-9451	-	NS3/4A protease inhibitor
GS-9669	-	NS5B nonnucleoside polymerase inhibitor
GS-9857	-	NS3/4A protease inhibitor
Ledipasvir	LDV	NS5A inhibitor
Ombitasvir	OBV	NS5A inhibitor
Paritaprevir	PTV	NS3/4A protease inhibitor
Simeprevir	SMV	NS3/4A protease inhibitor
Sofosbuvir	SOF	NS5B nucleotide polymerase inhibitor
Velpatasvir (formerly GS-5816)	VEL	NS5A inhibitor



Currently Available HCV Therapies



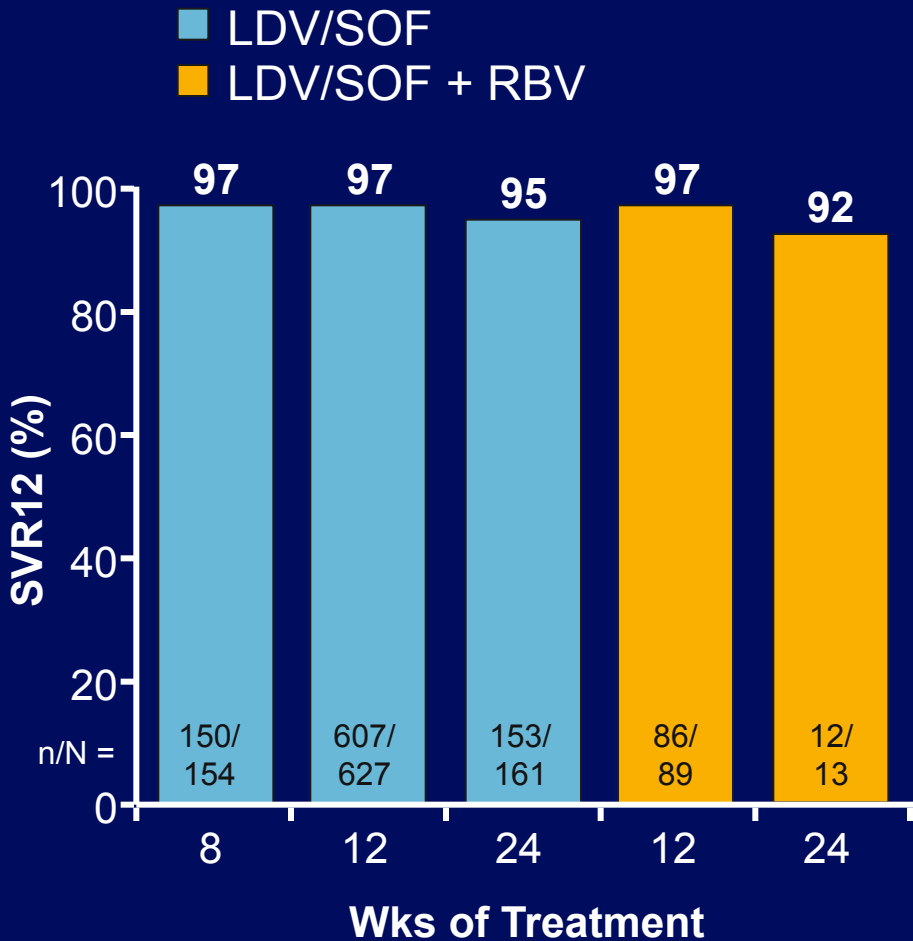
HCV-TARGET: Multicenter, Prospective, Observational Cohort Study

- 44 academic/17 community medical centers in North America/Europe
- Current analysis includes medical record data from sequential pts with GT1 HCV treated with LDV/SOF regimens

Baseline Characteristic, %	LDV/SOF 8 Wks (n = 154)	LDV/SOF 12 Wks (n = 627)	LDV/SOF 24 Wks (n = 161)	LDV/SOF Other (n = 27)	LDV/SOF + RBV 12 Wks (n = 89)	LDV/SOF + RBV 24 Wks (n = 13)	LDV/SOF + RBV Other (n = 3)
Treatment status							
▪Exp'd	4	40	97	48	67	92	67
▪DAA exp'd	1	10	32	19	16	39	33
Subgenotype							
▪1a	66	65	68	78	57	62	67
▪1b	29	28	21	15	34	23	33
Cirrhosis							
▪ Decompensated	2	9	27	19	19	31	33
PPI use	20	26	34	30	35	46	33



HCV-TARGET: SVR12 With 8-, 12-, or 24-Wk Ledipasvir/Sofosbuvir ± Ribavirin



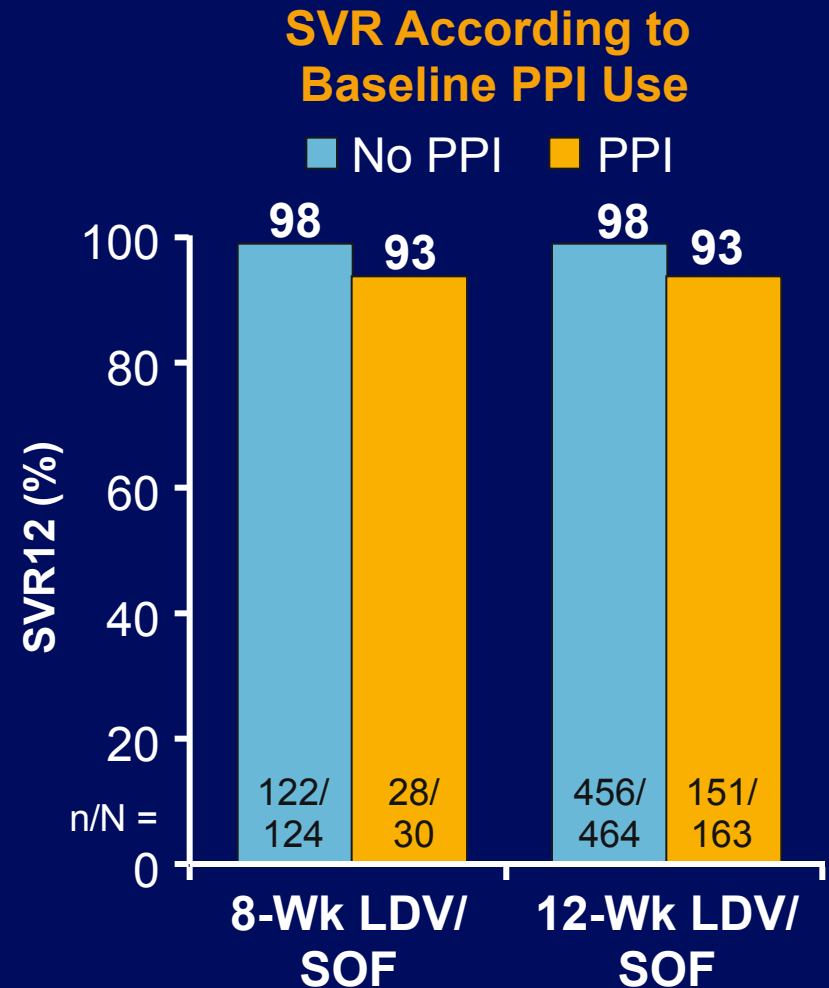
- Only 131 out of 323 pts who qualified for 8-wk treatment (treatment naive, no cirrhosis, and baseline HCV RNA \leq 6 million IU/mL) received 8-wk regimen

Tx Outcome in Pts Qualifying for 8-Wk Regimen	LDV/SOF 8 Wks (n = 131)	LDV/SOF 12 Wks (n = 192)
SVR12, %	97	97
Failure, %	3	3
SVR12 according to Wk 4 HCV RNA, % (n/N)	(n = 99)	(n = 133)
<ul style="list-style-type: none"> Below limit of quantification 	97 (89/92)	97 (114/117)
<ul style="list-style-type: none"> Quantifiable 	100 (7/7)	94 (15/16)



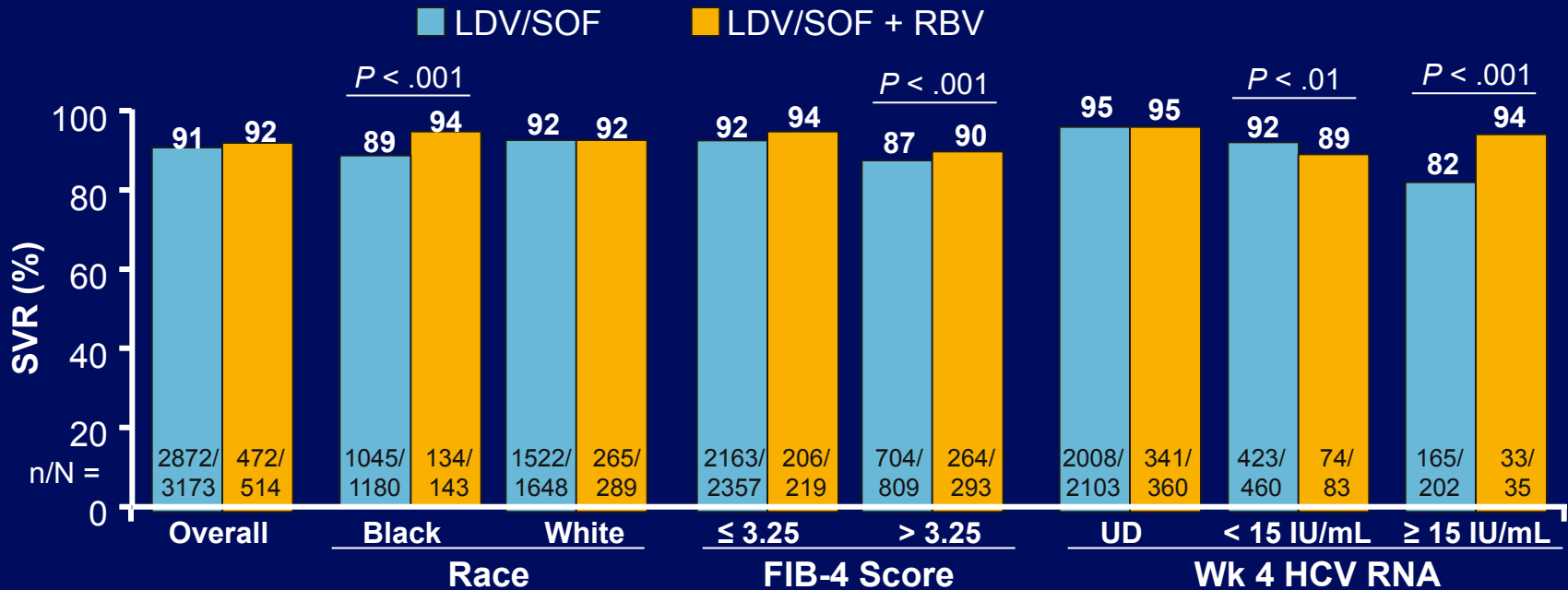
HCV-TARGET: Baseline Predictors of SVR in Pts Receiving Ledipasvir/Sofosbuvir

Baseline Predictor	OR (95% CI)	P Value
Albumin \geq 3.5 g/dL	4.59 (2.06-9.85)	< .001
Platelet count, 1000/mm ³	1.01 (1.00-1.02)	< .001
Total bilirubin \leq 1.2 mg/dL	3.65 (1.71-7.51)	.001
Hemoglobin, g/dL	1.22 (1.01-1.46)	.030
No cirrhosis	3.87 (1.91-8.23)	< .001
Compensated liver disease	5.49 (2.62-11.16)	< .001
No baseline PPI	3.02 (1.51-6.05)	.001



VA: Ledipasvir/Sofosbuvir ± Ribavirin for 8 or 12 Wks in Tx-Naive Pts With GT1 HCV

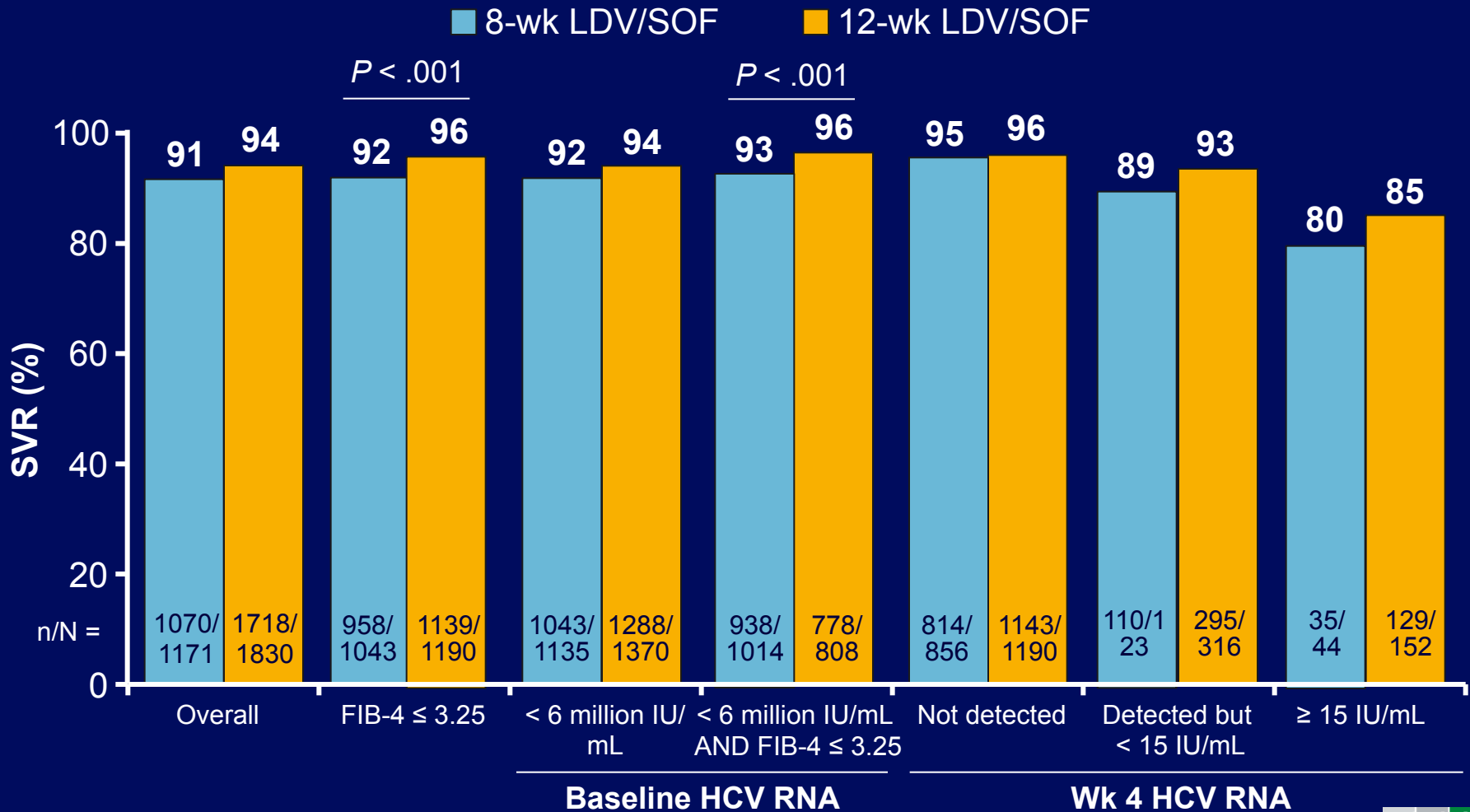
- Observational, ITT analysis of pts in 124 VA facilities (N = 4365)



Predictor of SVR With 8 or 12 Wks of Tx	OR (95% CI)	P Value
Black race	0.60 (0.44-0.83)	< .01
FIB-4 score > 3.25	0.47 (0.33-0.65)	< .001
8-wk treatment duration	0.54 (0.40-0.74)	< .001

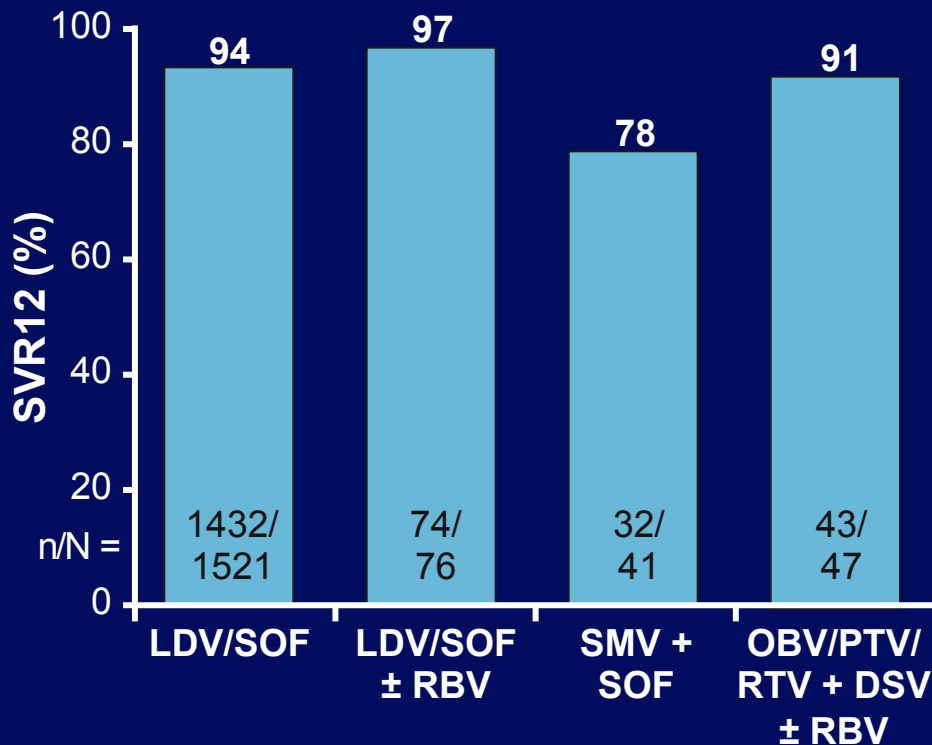


VA: SVR With 8-Wk vs 12-Wk Ledipasvir/Sofosbuvir



TRIO: Real-World Analysis of Predictors of DAA-Based Tx Failure in GT1 HCV

- Data obtained on GT1 HCV from Trio Health program
 - Includes pts with GT1 HCV who received 12-wk LDV/SOF, OBV/PTV/RTV + DSV, or SMV + SOF-based Tx 10/2014-3/2015 (N = 1685)

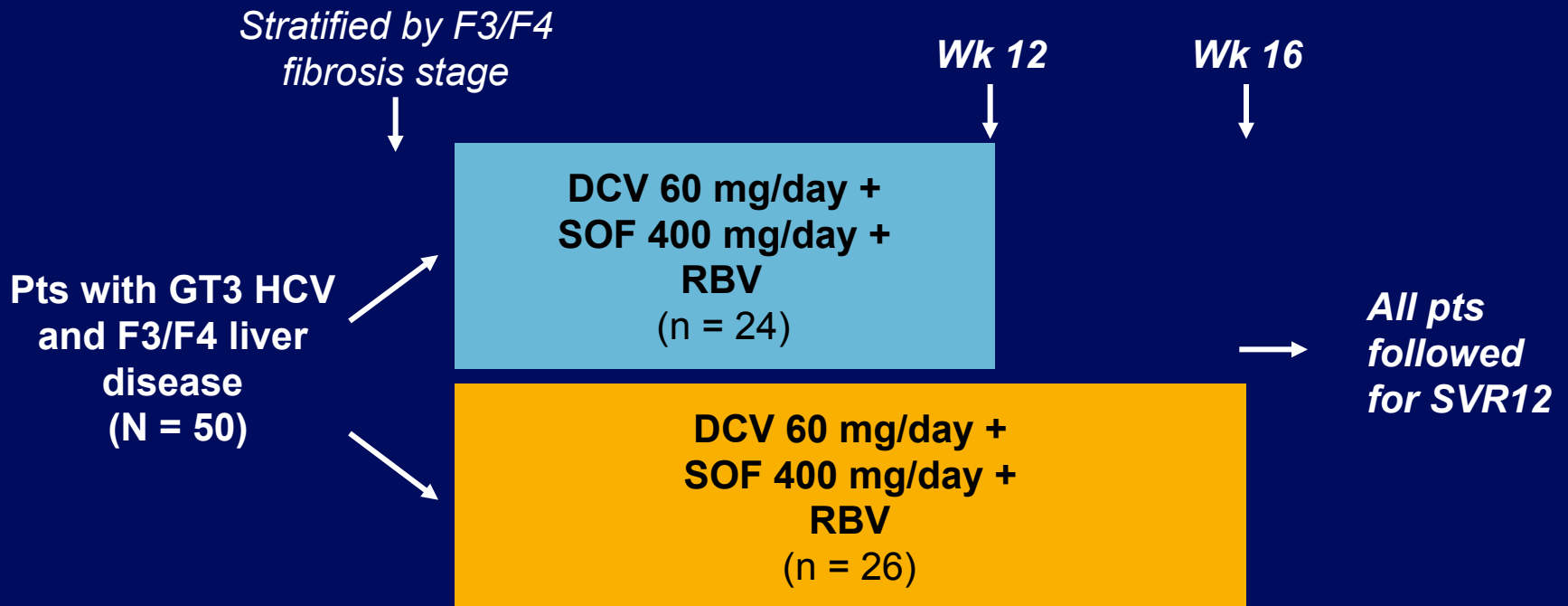


Factors Associated With Lower SVR Rate	P Value
Platelet count < 100K/mL	< .001
Cirrhosis	< .001
Prescribing outside of FDA-approved labeling*	< .001
Male sex	.008

*149/1685 pts treated outside of FDA-approved labeling.

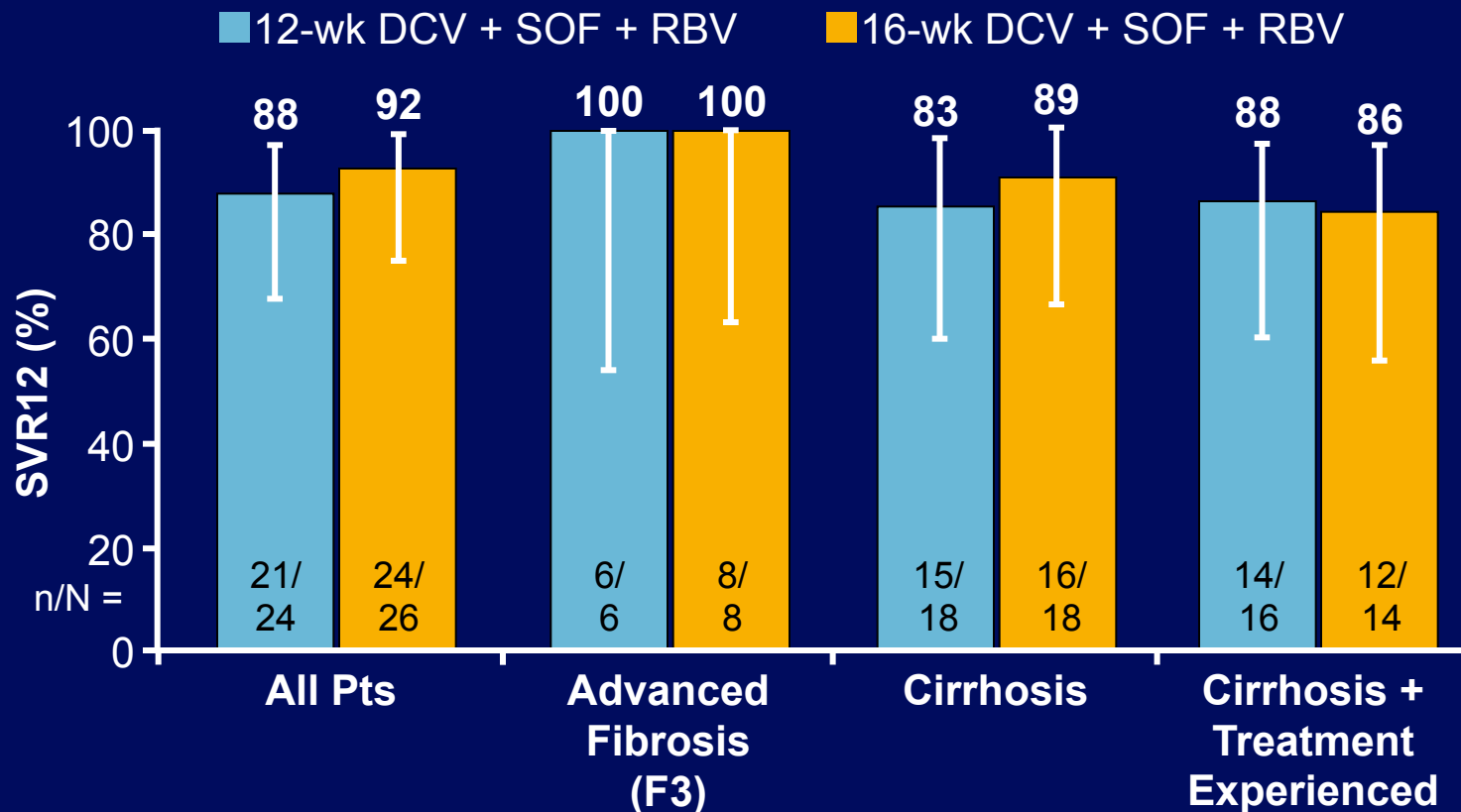
ALLY-3+: DCV + SOF + RBV in Pts With GT3 HCV and Advanced Liver Disease

- Open-label, randomized phase IIIb study
 - Primary endpoint: SVR12



ALLY-3+: Virologic Efficacy

- No virologic failures or AE-related discontinuations



ALLY-3+: Safety/Tolerability

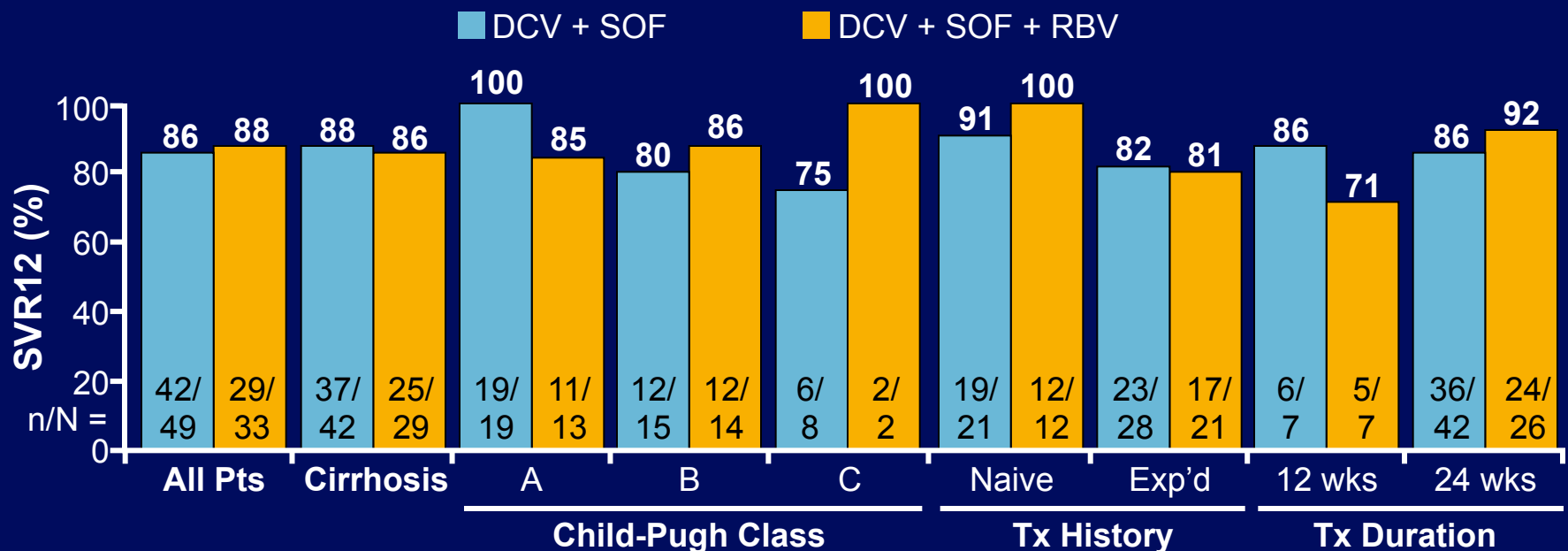
- No discontinuations or deaths deemed Tx-related

Safety Outcome, %	DCV + SOF + RBV Overall (N = 50)	DCV + SOF + RBV 12 Wks (n = 24)	DCV + SOF + RBV 16 Wks (n = 26)
Any AE	94	96	92
Serious AEs	10	8	12
Death	2	4	0
Discontinuation for AEs	0	0	0
RBV dose reduction	12	8	15
AEs in ≥ 20% pts in any arm			
▪ Insomnia	30	33	27
▪ Fatigue	26	25	27
▪ Headache	24	29	19
▪ Irritability	14	21	8
Grade 3 lab abnormalities			
▪ Hemoglobin < 9.0 g/dL or decrease ≥ 4.5 g/dL	2	0	4
▪ TBI > 2.5 x ULN	4	4	4



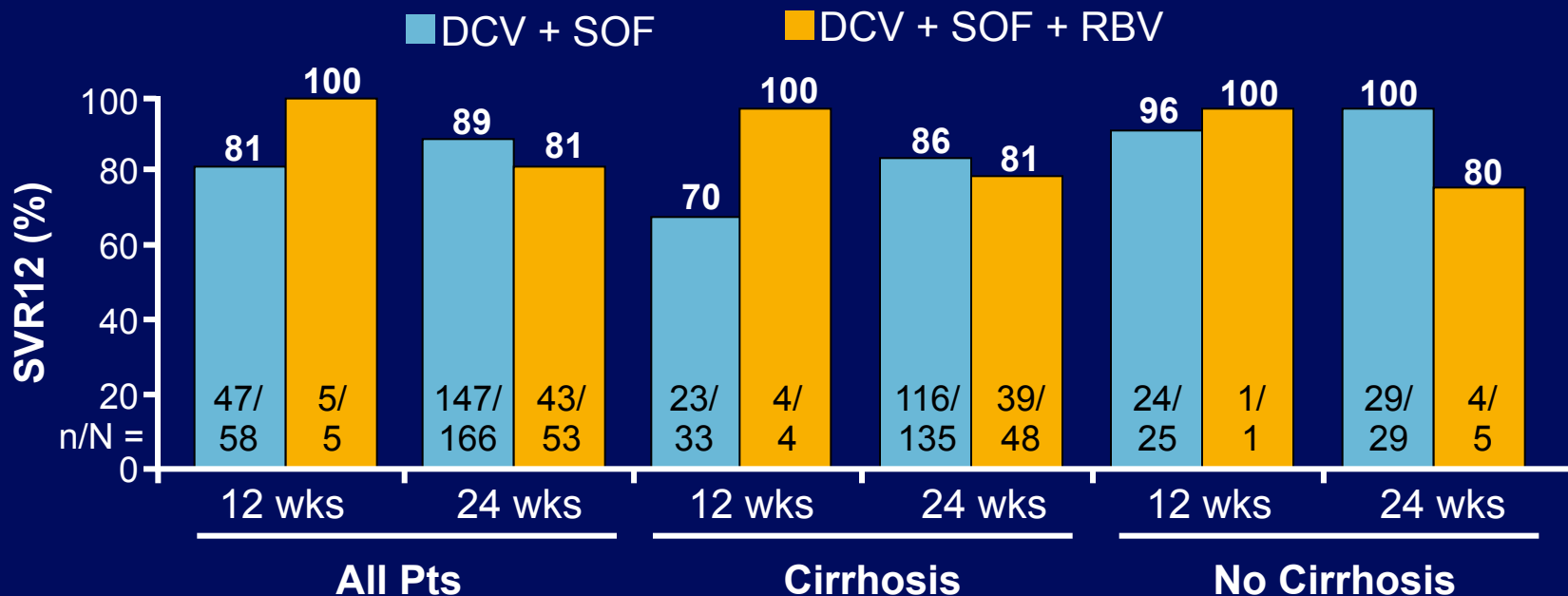
Interim Analysis: Daclatasvir + Sofosbuvir ± RBV in GT3 HCV in European CUP

- Pts treated with DCV 60 mg + SOF 400 mg QD for 24 wks; RBV added or duration shortened to 12 wks per physician discretion
- Most common AEs: fatigue, nausea, anemia
 - Tx-related serious AEs (n = 1 each): pancytopenia, HE, HCC, circulatory collapse

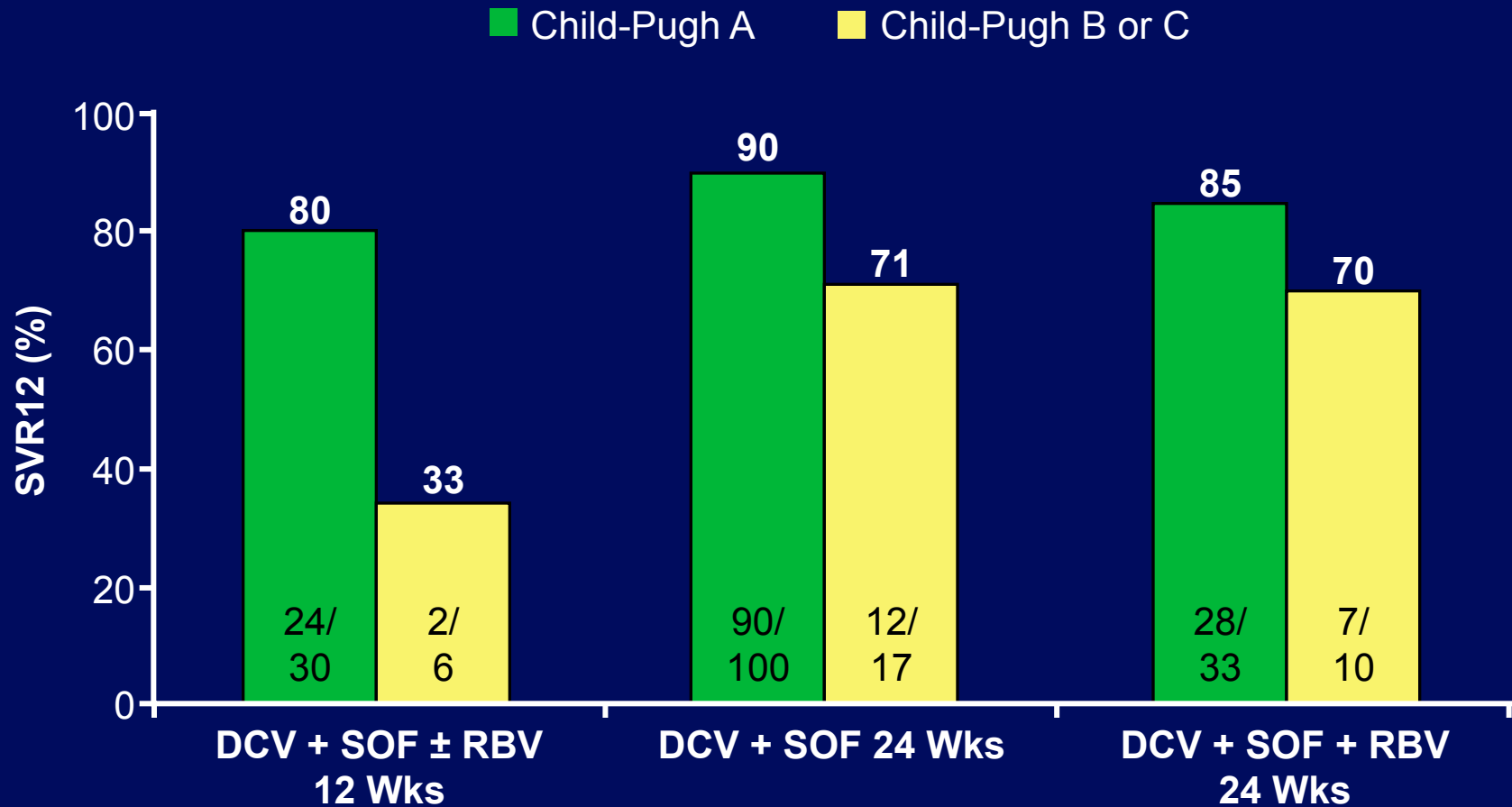


Interim Analysis: Daclatasvir + Sofosbuvir ± RBV in GT3 HCV in French CUP

- Pts treated with DCV 60 mg + SOF 400 mg QD for 24 wks; RBV added or duration shortened to 12 wks per physician discretion
- Most common AEs: asthenia, sleep disorder, headache
 - Tx-related serious AEs (n = 1 each): hepatic decompensation, allergic dermatitis



Interim Analysis of French CUP: SVR12 by Child-Pugh Score



SLAM-C: Sofosbuvir + Ledipasvir or Simeprevir for Acute HCV Infection

- Randomized, open-label, prospective pilot study
 - N = 29 pts with acute HCV infection at 6 drug rehabilitation centers (NYC)
- Group A (n = 14)
 - LDV/SOF 90/400 mg QD for 4 wks
- Group B (n = 15)
 - SOF 400 mg + SMV 150 mg QD for 8 wks

Outcome, % (n/N)	LDV/SOF for 4 Wks (n = 14)	SOF + SMV for 8 Wks (n = 15)
SVR12		
▪ All pts	100 (14/14)	87 (13/15)
▪ Per protocol*	100 (14/14)	100 (13/13)
Retention through 20 wks	93 (13/14)	87 (13/15)

*Excludes pts lost to follow-up or who discontinued for nonvirologic reasons.

HCC Risk Remains High After SVR With PegIFN ± RBV

- Retrospective VA cohort study of HCV-infected pts treated with pegIFN ± RBV from 1999-2009 (N = 22,028)
- HCC incidence rate 3.27/1000 PY with SVR vs 13.2/1000 PY without SVR (HR: 0.358)

Predictor of HCC Following SVR*	HR (95% CI)	P Value
Cirrhosis at time of SVR	4.45 (2.53-7.82)	< .0001
Age at SVR, yrs (vs younger than 55 yrs)		
▪ 55-64	2.40 (1.53-3.77)	.0002
▪ 65 or older	4.69 (2.04-10.78)	.0003
Diabetes	2.07 (1.35-3.20)	.0010
HCV GT (vs GT1)		
▪ 2	0.56 (0.32-1.01)	.0522
▪ 3	1.91 (1.14-3.18)	.0131

*Cox proportional hazards model adjusted for competing risk of death.



HCV Treatment Options Expected in the Near Future



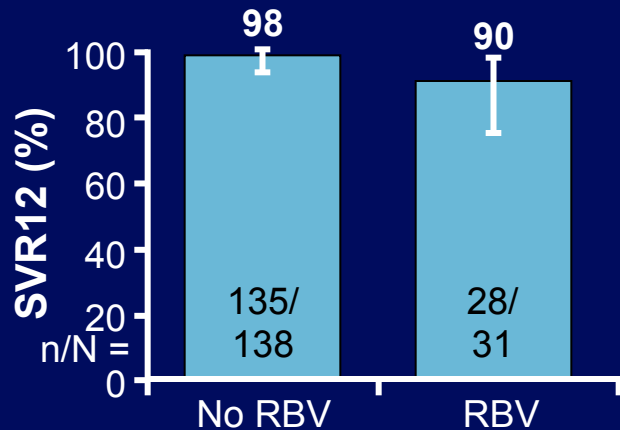
Elbasvir/Grazoprevir in Compensated Cirrhosis: Pooled Analysis of Ph II/III Data

- Includes pts with Child-Pugh A cirrhosis and GT1, 4, or 6 HCV who received elbasvir/grazoprevir ± RBV in phase II/III trials
 - Treatment-naive pts treated for 12 wks (n = 169)
 - Treatment-experienced pts treated for 12, 16, or 18 wks (n = 233)
 - FAS: all randomized pts who received ≥ 1 dose of drug
 - Modified FAS: FAS, excluding pts who discontinued for reasons unrelated to study drug

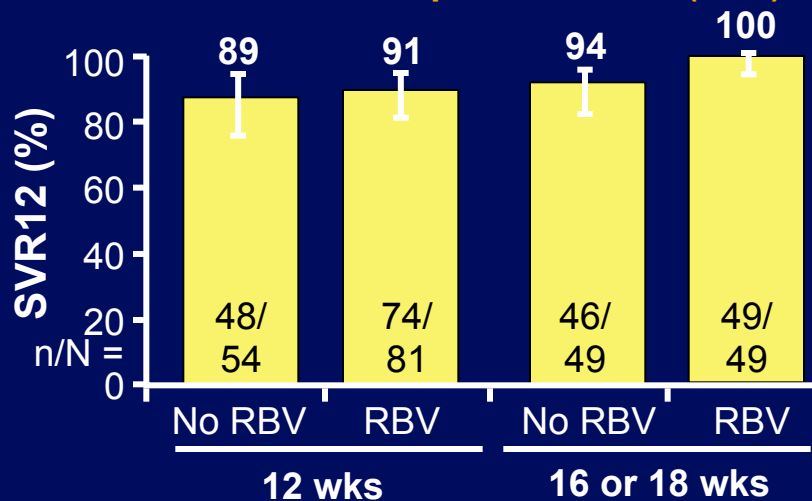
HCV Genotype, n (%)	Pts (N = 402)
1a	219 (54.5)
1b	152 (37.8)
1 other	5 (1.2)
4	23 (5.7)
6	3 (0.8)

Elbasvir/Grazoprevir in Compensated Cirrhosis: SVR12

Treatment Naive Pts; 12 Wks (FAS)



Treatment Experienced Pts (FAS)



- Treatment-naive pts:** SVR12 rates similar regardless of RBV use, HCV subtype in FAS and regardless of platelets, cirrhosis determination method, *FibroScan* score in mFAS
 - SVR12 rate range across subgroups treated without RBV: 96% to 100%
- Previous relapsers (mFAS):** SVR12 rates not affected by treatment duration or RBV use
- Previous nonresponders (mFAS):** SVR12 rates lower with 12-wk, no RBV vs 16/18-wk, + RBV treatment
 - GT1: 92% vs 100%
 - GT4: 67% vs 100%



Elbasvir/Grazoprevir in Compensated Cirrhosis: Safety

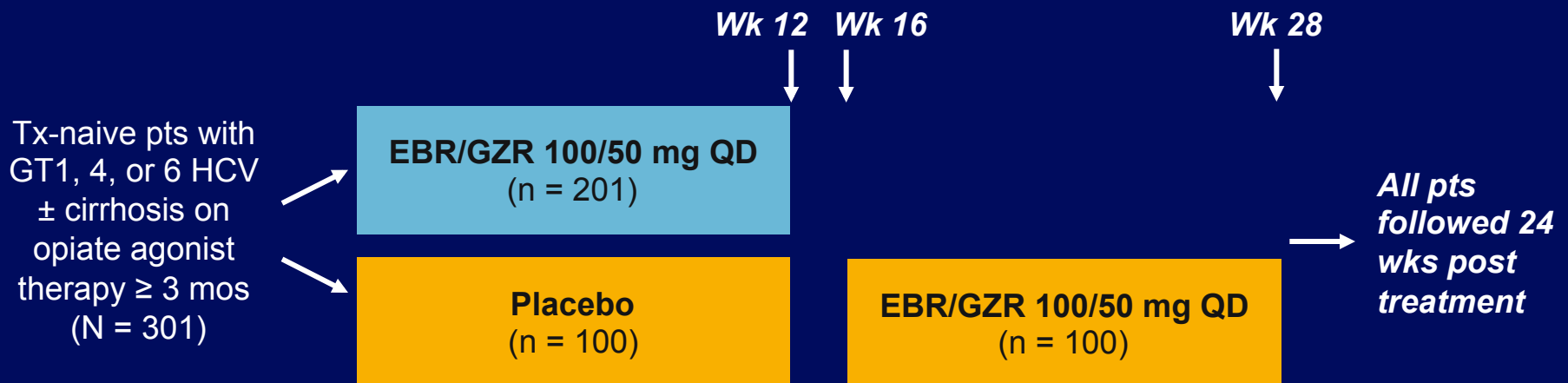
Safety Outcome (FAS), %	Elbasvir/Grazoprevir (n = 264)	Elbasvir/Grazoprevir + RBV (n = 193)
Drug-related AE	42.0	73.1
Serious AE	3.0	3.1
Serious drug-related AE	0.4	0
Discontinuation for AE	0.4	2.1
Discontinuation for lab abnormality*	0.4	0
Death†	0.4	0.5
AEs in > 10% pts		
▪ Fatigue	15.2	30.6
▪ Headache	16.7	20.7
▪ Nausea	4.2	13.5

*ALT elevation with increased eosinophils. †Coronary artery disease (n = 1), car accident (n = 1).



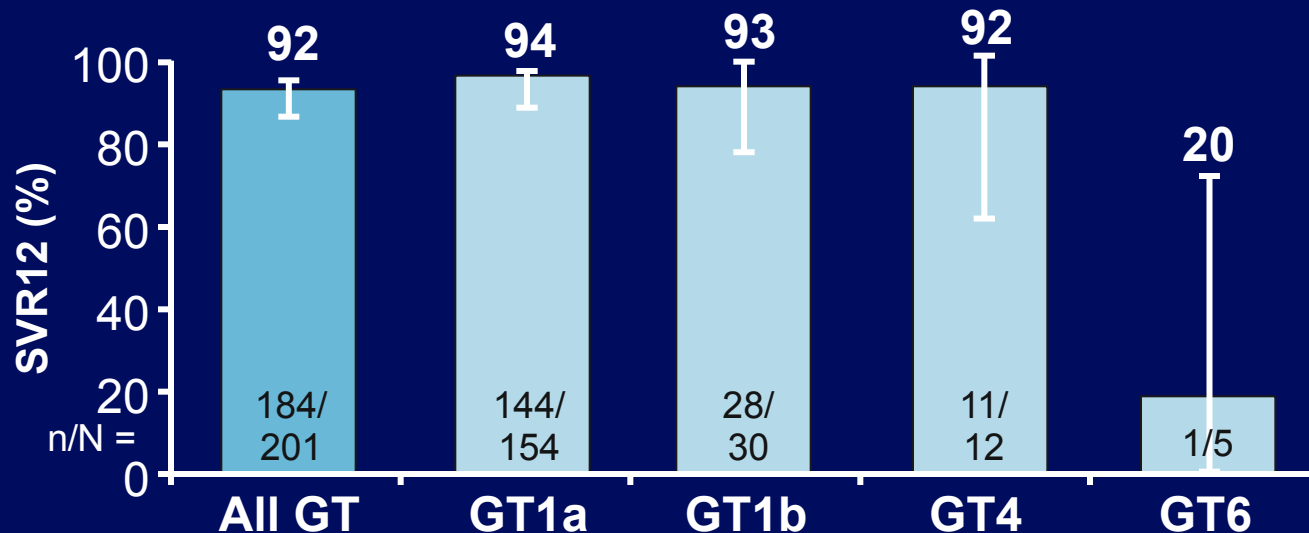
C-EDGE CO-STAR: Elbasvir/Grazoprevir for GT1, 4, or 6 HCV in PWID

- Randomized, double-blind, placebo-controlled phase III study in PWID on opiate agonist therapy
 - Primary endpoint: SVR12 in immediate treatment arm
 - Study unblinded at Wk 12



C-EDGE CO-STAR: SVR12

- High HCV treatment adherence rate, despite ongoing drug use
 - ~ 60% of pts had positive urine test for at least 1 of 8 drug classes (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, propoxyphene) throughout 12 wks EBR/GZR tx
 - 96% to 97% pts had ≤ 3 missed doses during 12-wk EBR/GZR
- 5 pts without SVR had evidence of HCV reinfection (by phylogenetics)



ASTRAL-1, -2, -3, -4 Trials: Sofosbuvir/Velpatasvir FDC ± RBV in GT1-6 HCV

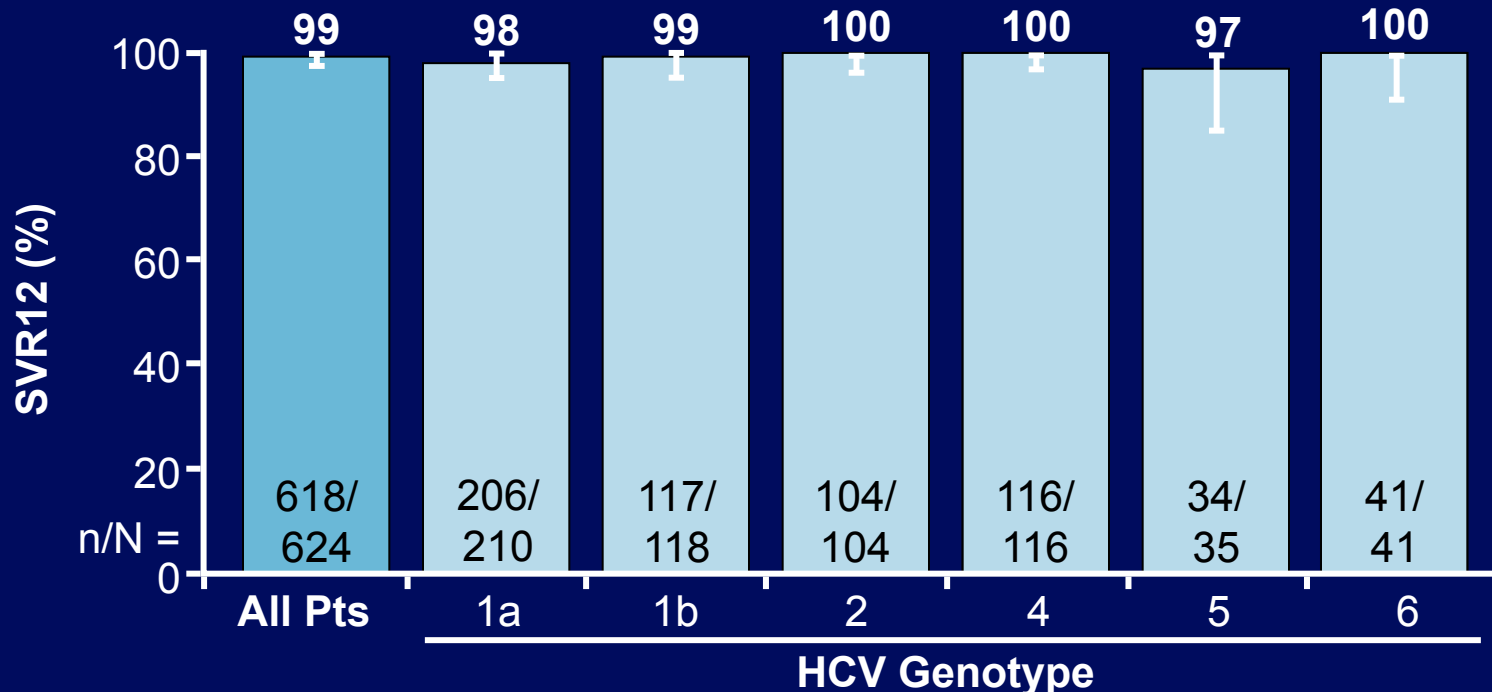
- Multicenter, randomized phase III trials in Tx-naive and Tx-experienced pts



1. Feld JJ, et al. AASLD 2015. Abstract LB-2. 2. Sulkowski MS, et al. AASLD 2015. Abstract 205. 3. Mangia A, et al. AASLD 2015. Abstract 249. 4. Charlton MR, et al. AASLD 2015. Abstract LB-13.

ASTRAL-1: SVR12 With Sofosbuvir/Velpatasvir in GT1, 2, 4, 5, 6 HCV

- Double-blind, placebo-controlled trial
 - All pts with GT5 HCV allocated to active Tx because few pts in this group (n = 35)
 - Key baseline characteristics: cirrhosis 19%; Tx exp'd 32%; BL NS5A RAVs 42%
- No impact of cirrhosis, Tx experience, BL NS5A RAVs on SVR rates



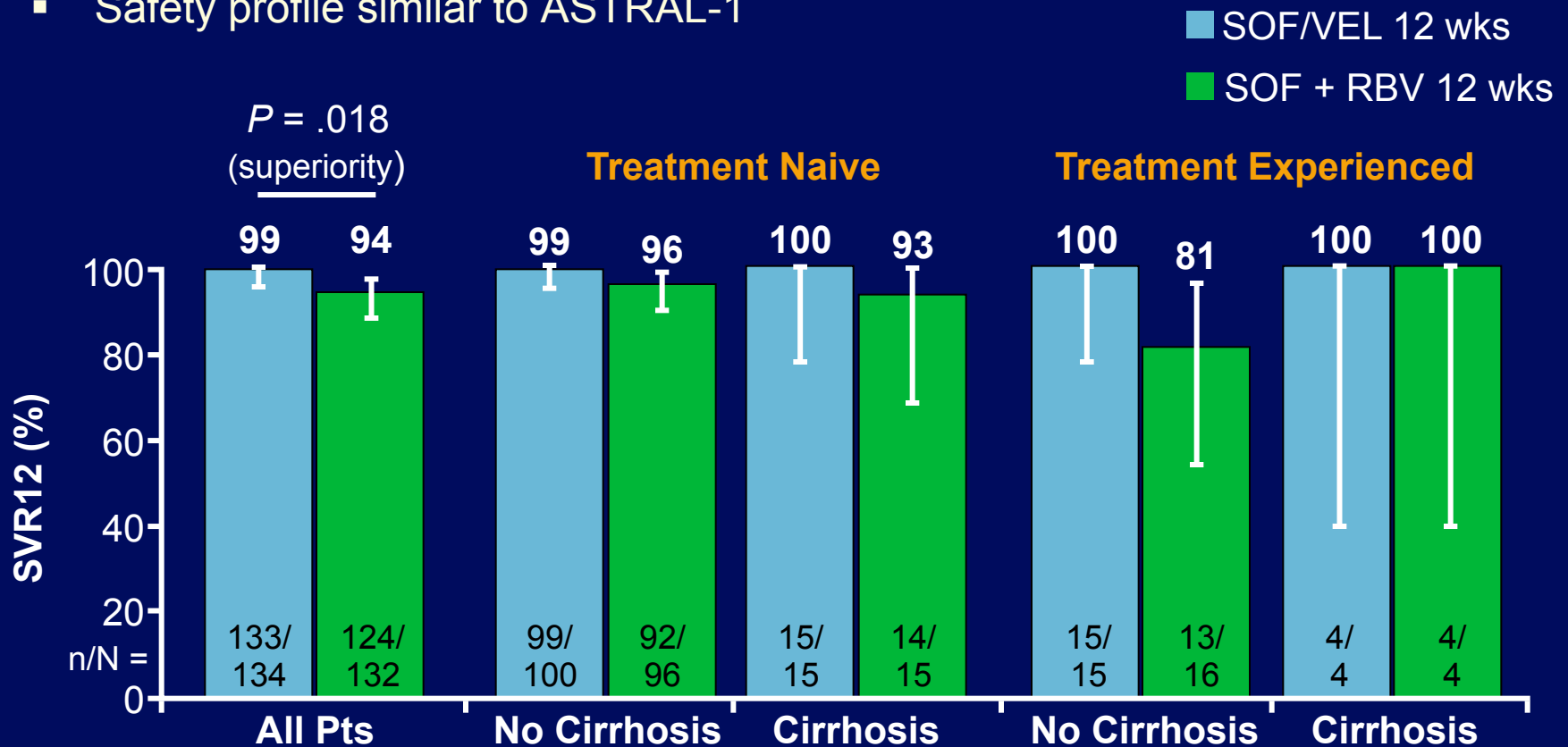
ASTRAL-1: Safety of Sofosbuvir/ Velpatasvir in GT1, 2, 4, 5, 6 HCV

Safety Outcome, %	Placebo 12 Wks (n = 116)	Sofosbuvir/Velpatasvir 12 Wks (n = 624)
Any AE	77	78
Grade 3/4 AE	< 1	3
Serious AE	0	2
Discontinuation for AE	2	< 1
Death	0	< 1*
Laboratory abnormalities		
▪ Grade 3/4	12	7
▪ Hemoglobin < 10 g/dL	0	< 1
AEs in ≥ 10% pts		
▪ Headache	28	29
▪ Fatigue	20	20
▪ Nasopharyngitis	10	13
▪ Nausea	11	12

*1 pt died during sleep 8 days after Tx completion; deemed by investigator to be unrelated to study drug.

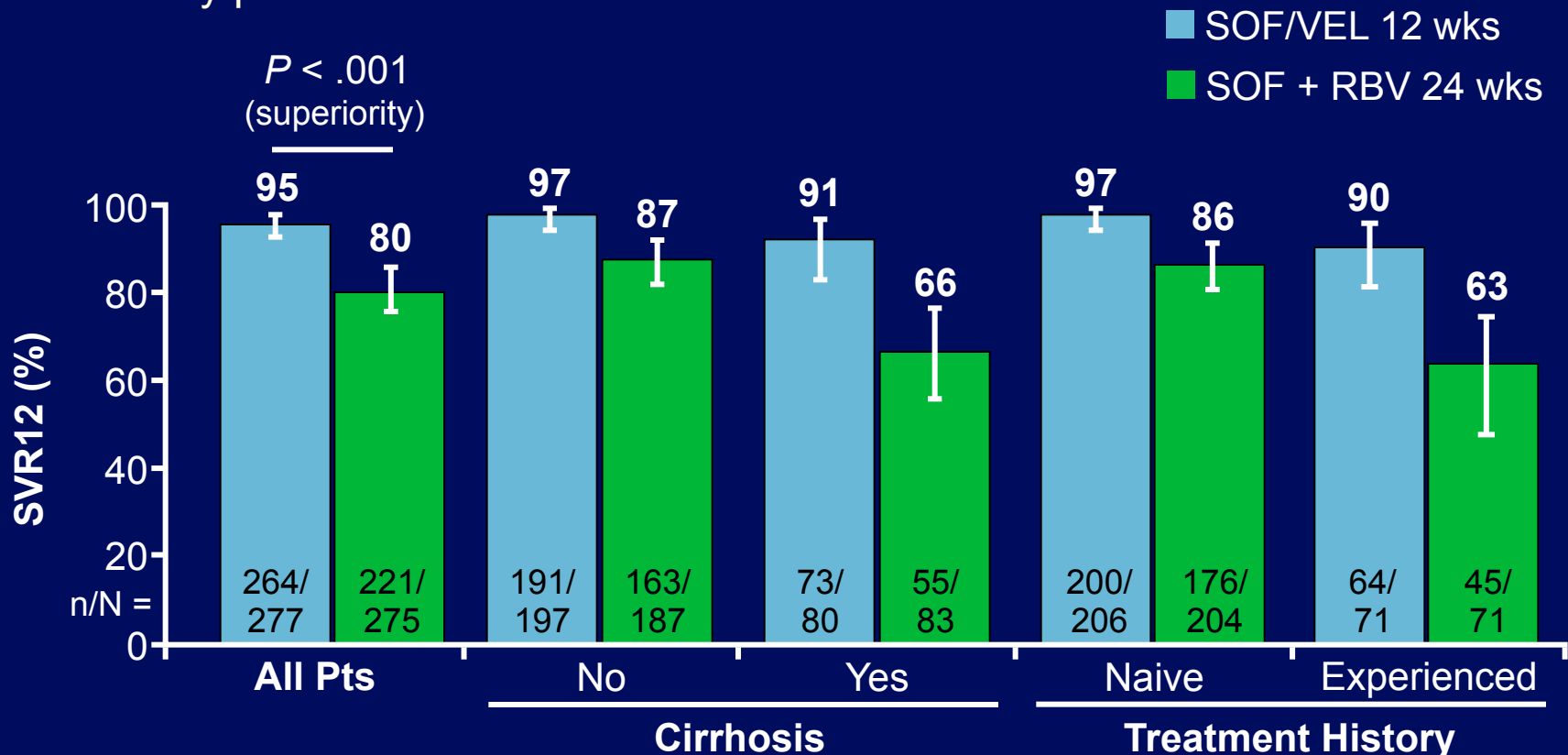
ASTRAL-2 Open-Label Trial: SVR12, Safety With Sofosbuvir/Velpatasvir in GT2 HCV

- No impact of BL NS5A RAVs on SVR rates
- Safety profile similar to ASTRAL-1



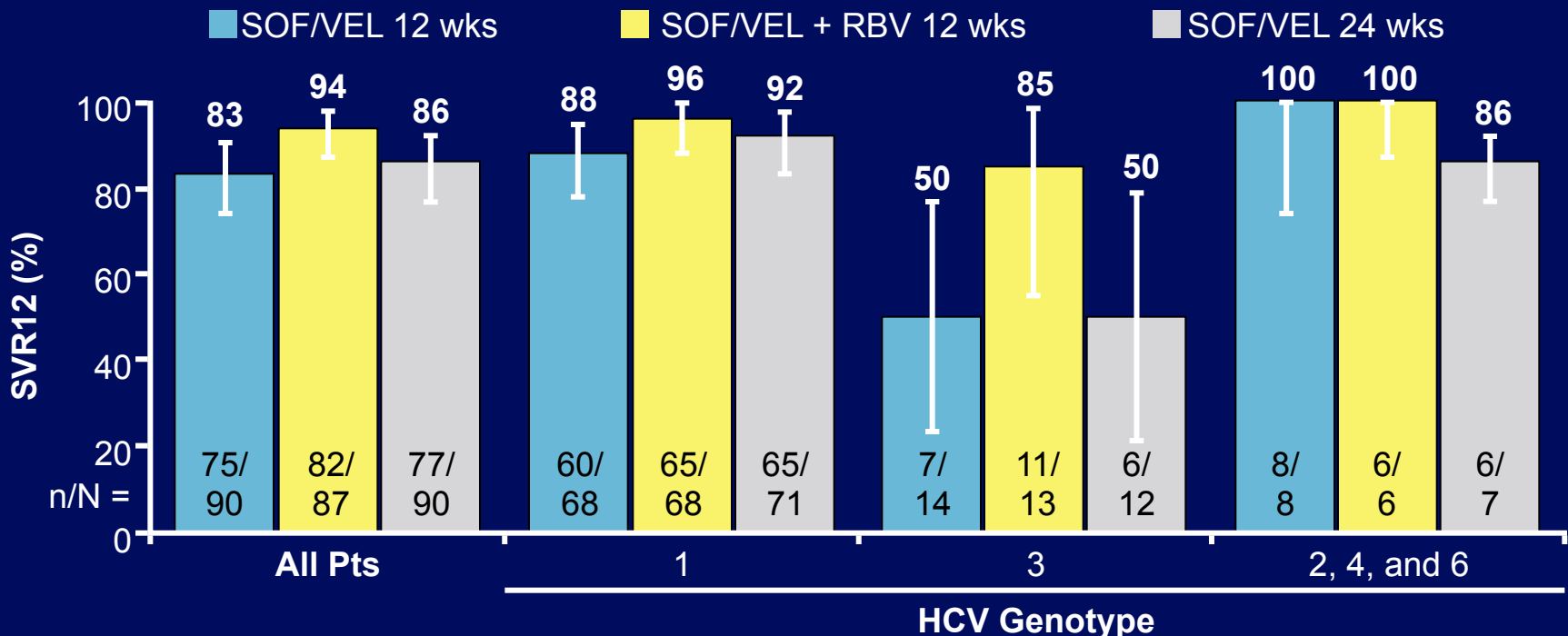
ASTRAL-3 Open-Label Trial: SVR12, Safety With Sofosbuvir/Velpatasvir in GT3 HCV

- SVR12 rate numerically lower with vs without BL NS5A RAVs (88% vs 97%)
- Safety profile similar to ASTRAL-1



ASTRAL-4: Sofosbuvir/Velpatasvir in Decompensated Cirrhosis

- Open-label trial; HCC and liver transplantation excluded
- In pts with BL MELD > 15, SVR12, score improved in 84%, worsened in 8%; in pts with BL MELD < 15, SVR12, score improved in 52%, worsened in 27%
- AEs consistent with advanced liver disease and RBV toxicity

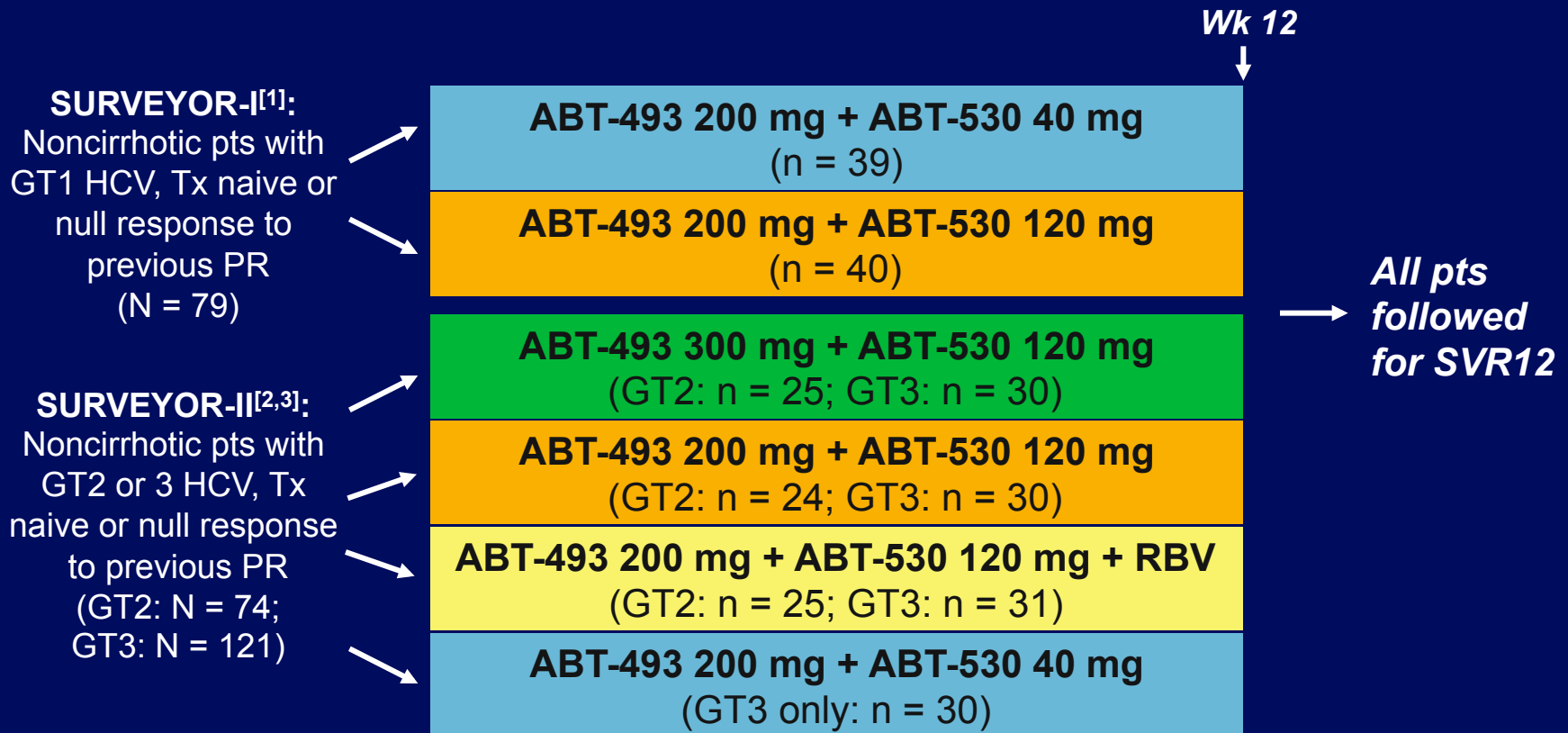


Potential Future HCV Therapies



SURVEYOR-I and -II: ABT-493 + ABT-530 ± RBV for GT1, 2, or 3 HCV

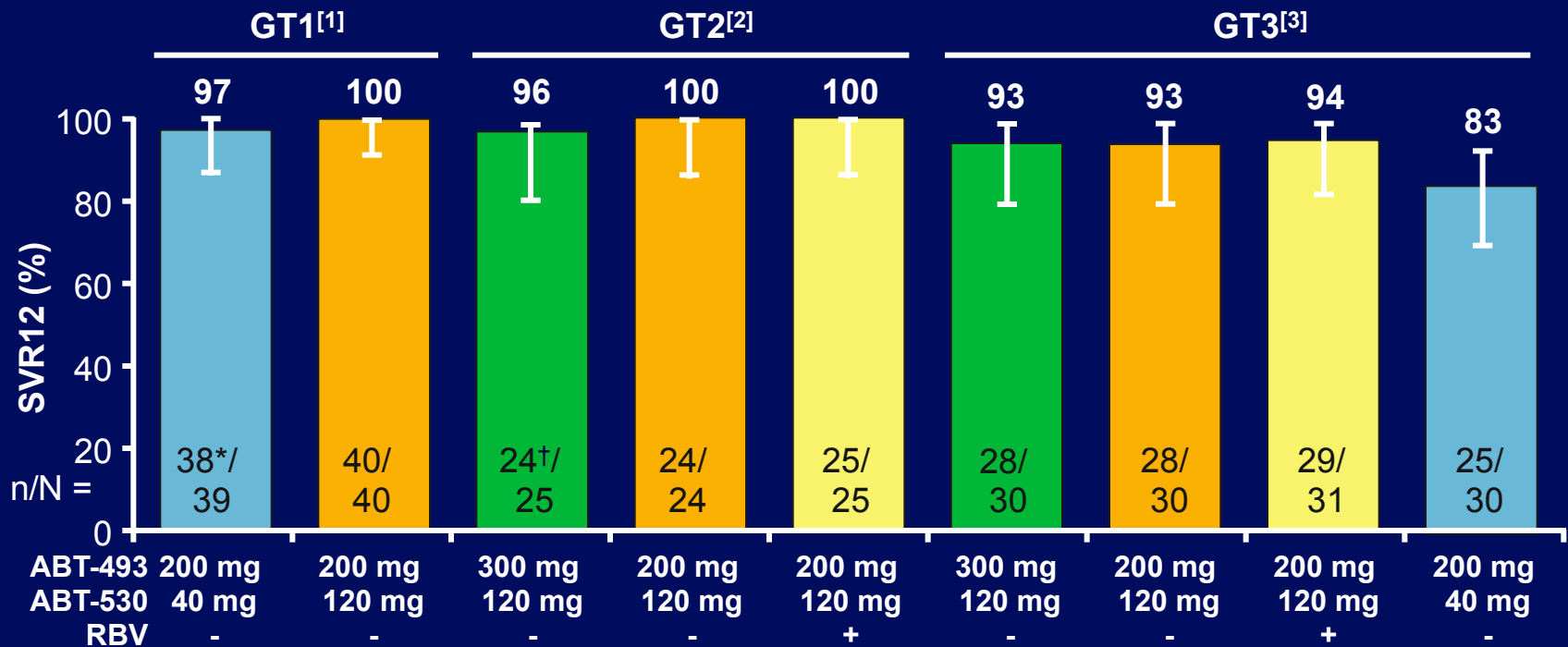
- Multicenter, open-label, dose-ranging phase II studies
 - Primary endpoint: SVR12



1. Poordad F, et al. AASLD 2015. Abstract 41. 2. Wyles D, et al. AASLD 2015. Abstract 250. 3. Kwo P, et al. AASLD 2015. Abstract 248.

SURVEYOR-I and -II: SVR12 (ITT) With ABT-493 + ABT-530 ± RBV

- GT1 or 2: SVR12 achieved by all pts with BL NS3 or NS5A resistance
- Most AEs mild, most frequent AEs fatigue, nausea, diarrhea, headache
 - For GT1 and 2: no tx-related serious AEs, no discontinuations for AE



*Viral relapse in 1 pt with GT1a HCV; NS5A Q30K + H58D emerged at relapse. [†]1 pt lost to follow-up after 2-wk Tx.

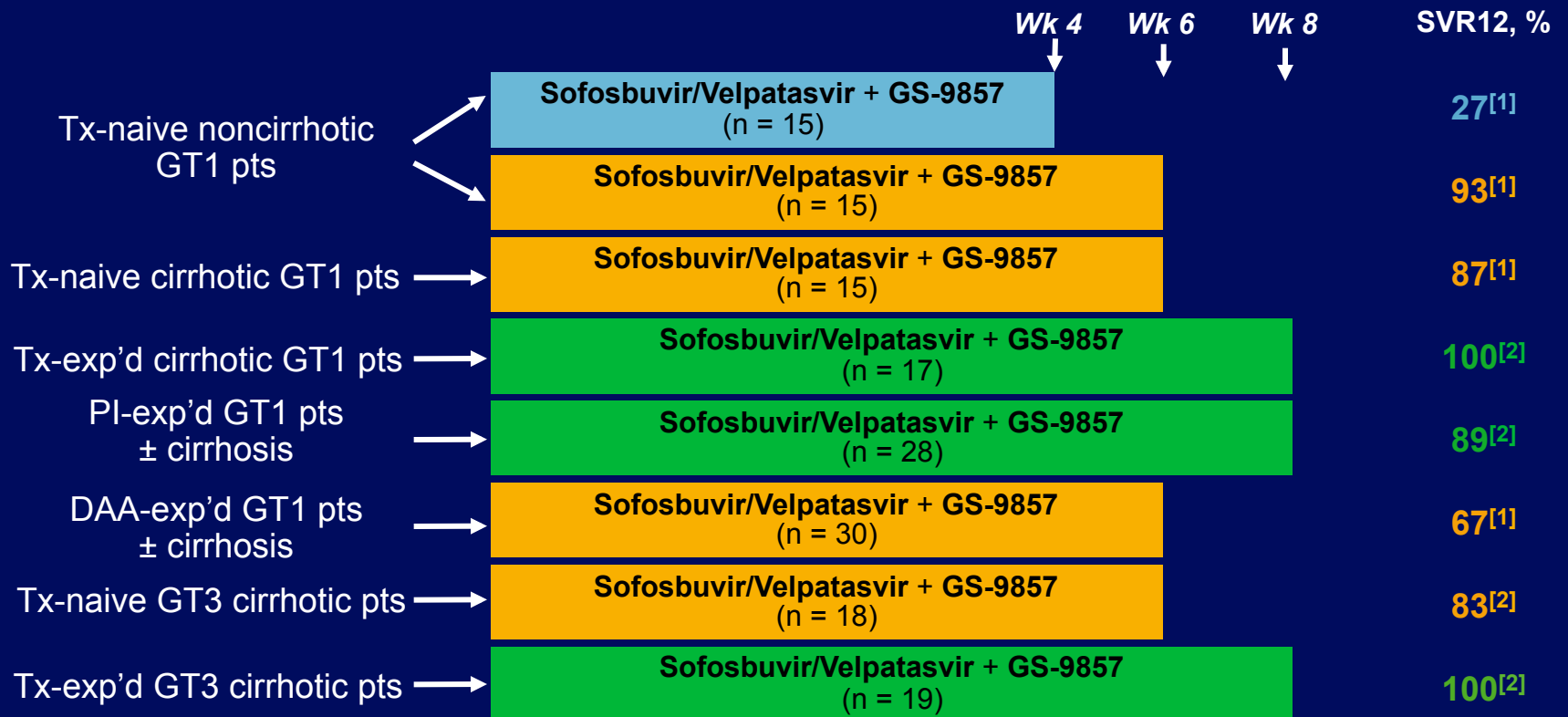
1. Poordad F, et al. AASLD 2015. Abstract 41. 2. Wyles D, et al. AASLD 2015. Abstract 250. 3. Kwo P, et al. AASLD 2015. Abstract 248. Reproduced with permission.



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Short-Duration Sofosbuvir/Velpatasvir + GS-9857 in Pts With GT1 or 3 HCV

- Single-center, nonrandomized, open-label phase II trial



SOF/VEL 400 mg/100 mg FDC QD; GS-9857 100 mg QD

1. Gane EJ, et al. EASL 2015. Abstract LP-03.
 2. Gane EJ, et al. AASLD 2015. Abstract 38.



Sofosbuvir/Velpatasvir + GS-9857 in GT1 or 3 HCV: Safety and Resistance

- SVR rates decreased in the presence of NS5A (90% vs 95% without) and NS3 (88% vs 96% without) RAVs at baseline
- Most frequent AEs were headache, fatigue, nausea, diarrhea, and URTI

Safety Outcome, %	SOF/VEL + GS-9857 Duration			
	8 wks	8 wks	6 wks	8 wks
	GT1, TE, Cirrhosis (n = 17)	GT1, PI Exp' d ± Cirrhosis (n = 28)	GT3, TN, Cirrhosis (n = 18)	GT3, TE, Cirrhosis (n = 19)
Any AE	88	79	83	79
Grade 3/4 AE	0	0	0	0
Serious AE*	0	4	0	11
D/c due to AE	0	0	0	0
Death	0	0	0	0
Grade 3/4 lab abnormalities	12	7	11	21

*Included atrial fibrillation (n = 1), HCC (n = 1), and bladder cancer (n = 1); all deemed unrelated to study treatment.



HCV Retreatment After DAA Failure



SYNERGY: LDV/SOF for GT1 HCV After Failure of 4-6 Wks' LDV/SOF-Based Tx

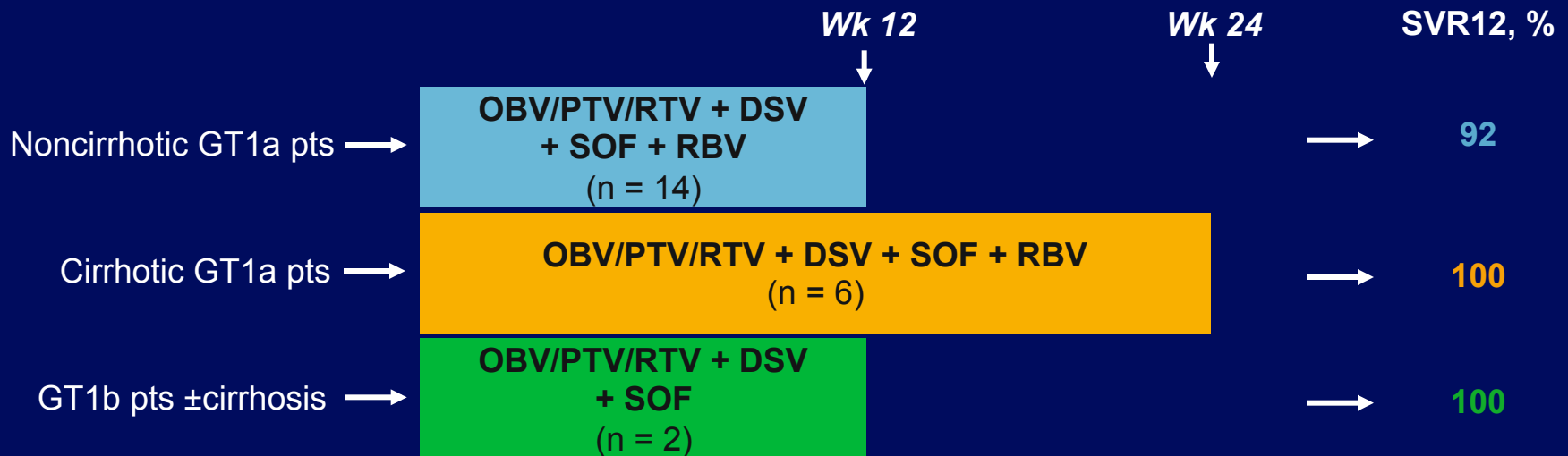
- Current analysis includes noncirrhotic pts with GT1 HCV who experienced failure (all viral relapse) of first-line therapy on any of 3 other trial arms:
 - LDV/SOF + GS-9669 for 6 wks, LDV/SOF + GS-9451 for 4 wks, or LDV/SOF + GS-9451 + GS-9669 for 4 wks



SVR12 in Pts With NS5A RAVs, % (n/N)	Pts (N = 34)
ITT	90 (26/29)
Per protocol	96 (26/27)

QUARTZ-I: OBV/PTV/RTV + DSV + SOF ± RBV for DAA-Exp'd Pts With GT1 HCV

- Multicenter, open-label, phase II study
 - Previous Tx: 73% OBV/PTV/RTV ± DSV; 9% TPV + PR; 9% SOF + RBV or SOF + PR; 4.5% SMV + SOF; 4.5% SMV + samatasvir + RBV
- Majority of AEs mild to moderate
 - 2 serious AEs not related to study drugs (pneumonia and cellulitis)
 - 1 grade 3 ALT elevation resolved by EOT without treatment interruption



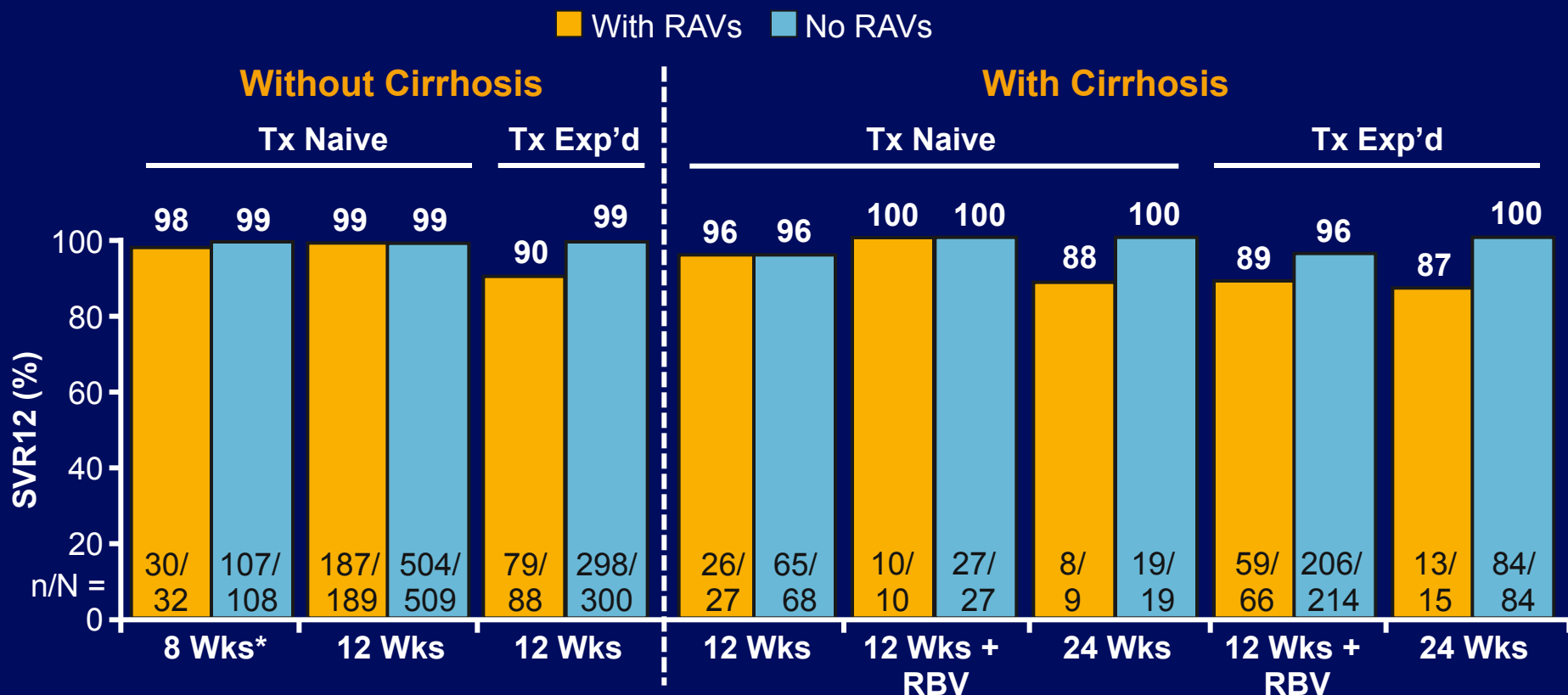
OBV/PTV/RTV 25/150/100 mg QD + DSV 250 mg BID; SOF 400 mg QD; weight-based RBV.

Effect of Drug Resistance on HCV Treatment Efficacy



Effect of BL NS5A RAVs on Ledipasvir/Sofosbuvir Efficacy in GT1 HCV

- Deep sequencing of baseline samples obtained from 1566 pts treated with guideline-based LDV/SOF regimens in clinical trials



*HCV RNA < 6 million IU/mL.

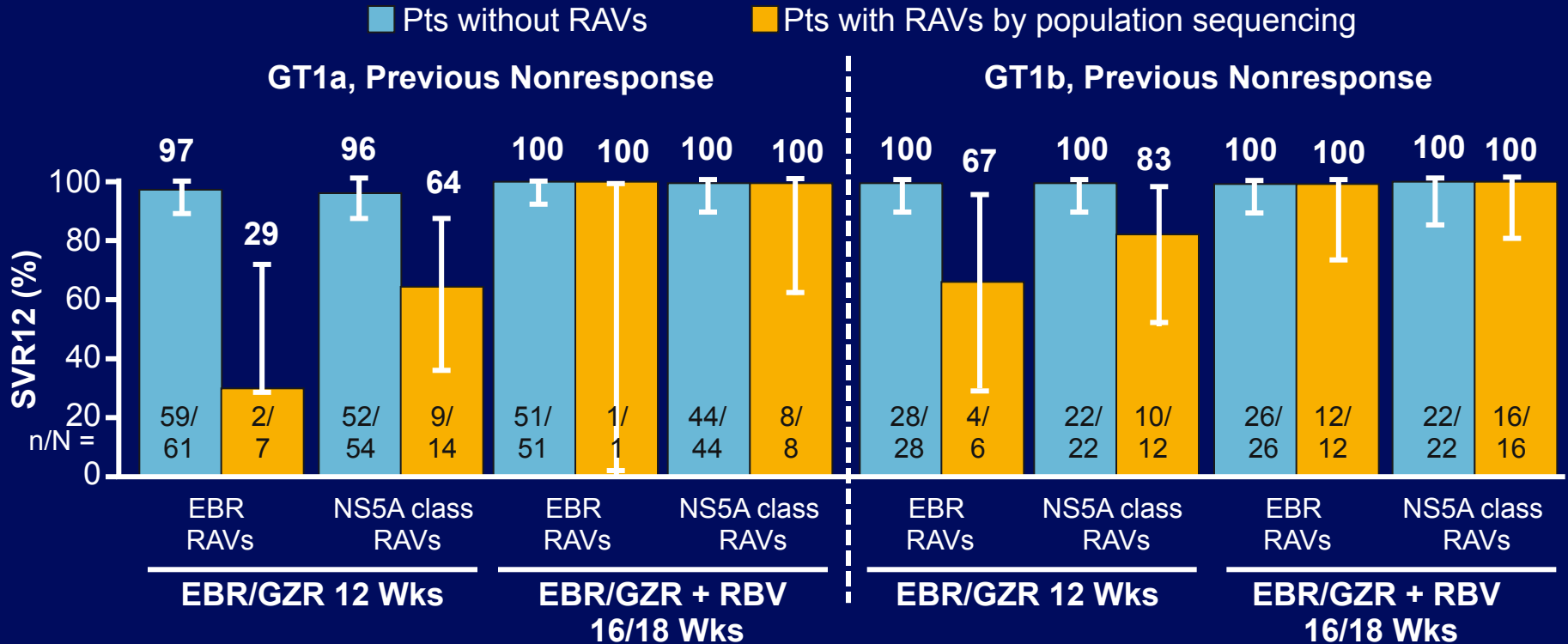


Effect of BL NS5A RAVs on Elbasvir/ Grazoprevir Efficacy in GT1 HCV

- Analysis included Tx-naive or PR-exp'd pts with GT1a or GT1b HCV treated with EBR/GZR-based regimens in phase II/III trials
 - Pts who did not achieve SVR12 for nonvirologic reasons and pts without baseline resistance analysis excluded
- Evaluated NS5A class RAVs and EBR-specific RAVs (= subset of NS5A class RAVs)
- Baseline prevalence by population sequencing
 - NS5A class RAVs: 15% to 42%
 - EBR-specific RAVs
 - Tx naive or previous relapse to PR: 5% to 17%
 - Previous nonresponse to PR: 2% to 32%

SVR12 With Elbasvir/Grazoprevir in GT1 HCV With vs Without Baseline NS5A RAVs

- Tx-naive or previous relapse, EBR/GZR for 12 wks
 - GT1b: high SVR12 rates (98% to 100%) regardless of EBR or NS5A class RAVs
 - GT1a: SVR12 rates lower with EBR (58%) or NS5A class (86%) RAVs vs no RAVs (98%)



HCV Treatment in Patients With Renal Dysfunction



RUBY-1: OBV/PTV/RTV + DSV ± RBV in Tx-naive, Noncirrhotic GT1 Pts With CKD

- Multicenter, open-label phase IIIb study

Tx-naive,
noncirrhotic GT1 pts
with eGFR
< 30 mL/min/1.73m²
(N = 20)



*RBV dosed at 200 mg QD and managed as follows: RBV dosed 4 hrs before hemodialysis in hemodialysis pts; wkly Hb assessment in Mo 1 and then Wks 6, 8, 12; RBV suspended in pts with > 2 g/dL decline in Hb in < 4 wks or Hb < 10 g/dL; RBV dosing resumed at clinician's discretion if Hb normalized.

- Key baseline characteristics
 - F3 fibrosis: 20%; eGFR 15-30: 30%; eGFR < 15 or on dialysis: 70%
- 2 pts without SVR12: 1 relapsed, 1 died of LV systolic dysfunction, cardiac arrest after treatment completion
- 69% of pts with GT1a required RBV dose reduction for anemia
 - No discontinuations for anemia
- No cases of grade 3 or higher ALT elevations

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