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HEPATITIS

Managing HCV DAA Failure: Now and Later

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Disclosures

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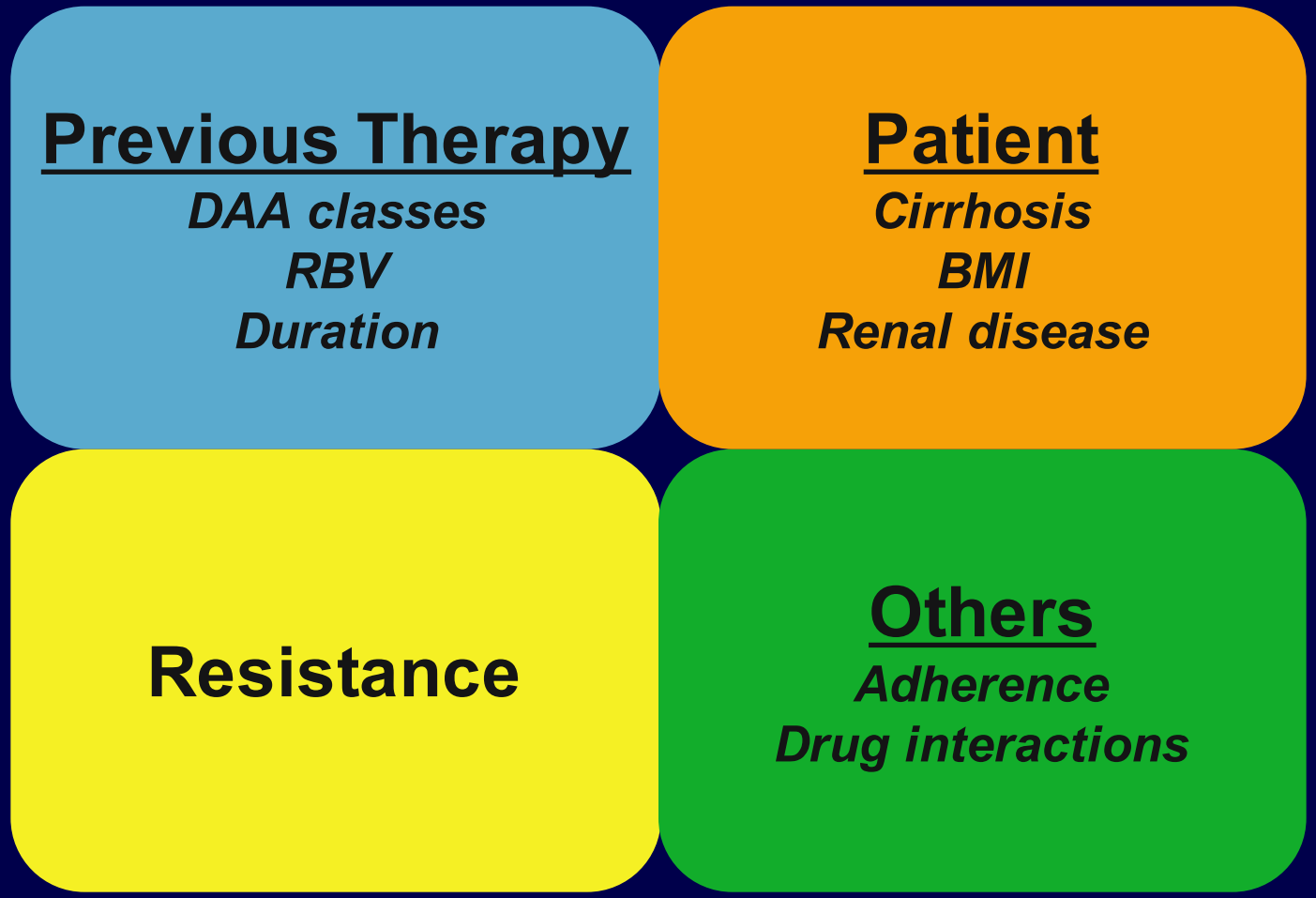
Considerations for DAA Regimen Failure



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Key Clinical Questions

- Should additional testing be done?
  - What is the role of resistance testing in retreatment?
- Can the pt take RBV?
- Should you wait and retreat once other treatment options are available?
  - What is the chance his/her liver disease will progress?
- What options are available to me (authorization considerations)?

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Case 1

- 59-yr-old black man with GT1a HCV, DM, GERD, and HTN, treated with pegIFN + RBV in 2009 (null response)
- Physical exam: BMI 32, no ascites, no edema, palmar erythema
- Cirrhosis confirmed by elastography in 2015 (22.6 kPa; IQR 11%)
- Treated in 2015 with LDV/SOF + RBV for 12 wks
  - Treatment Wk 4: HCV RNA < 15 IU/mL detected
  - Relapse at posttreatment Wk 4: HCV RNA 176,000 IU/mL
- Current medications: amlodipine, atorvastatin 40 mg, omeprazole 20 mg BID

Current Laboratory Parameter	Result
Platelets/mm^3	98,000
Albumin, g/dL	3.7
ALT, IU/L	47
AST, IU/L	56
Total bilirubin, mg/dL	0.9
INR	1.2
CTP	A5

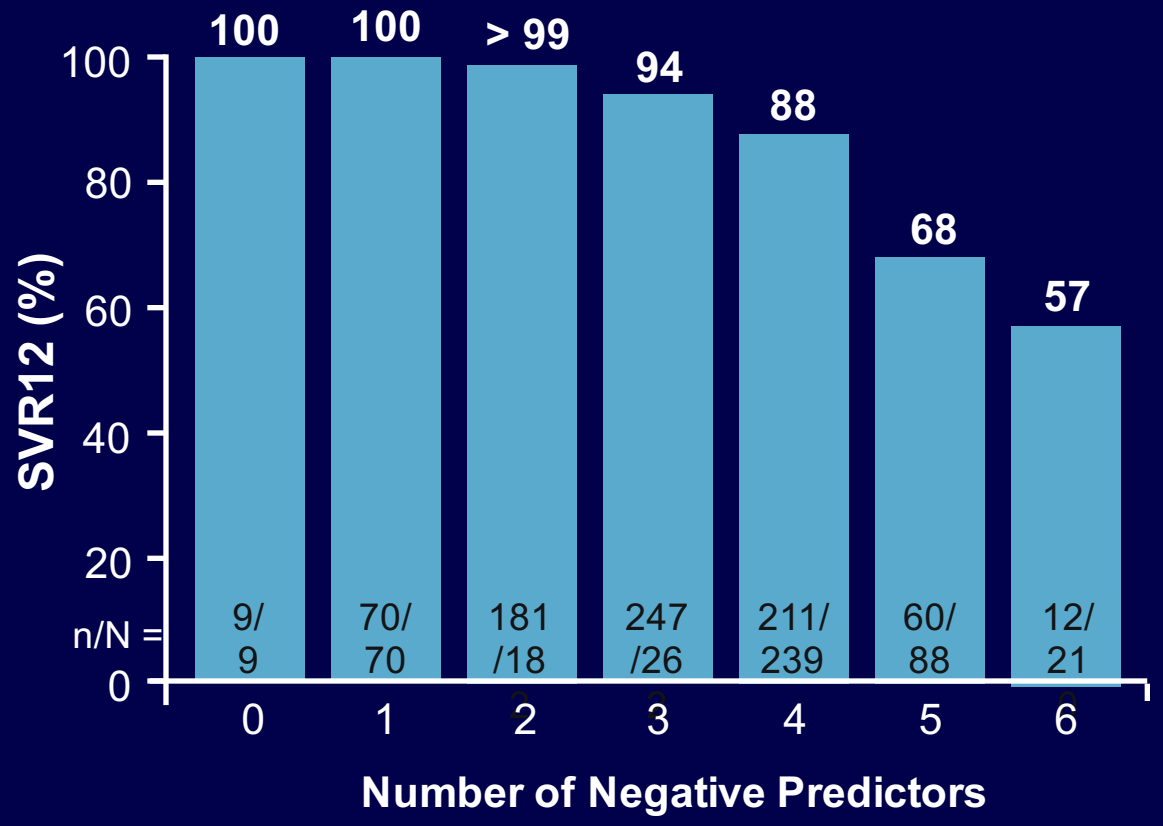
Slide credit: clinicaloptions.com

Was Our Pt Set up for Treatment Failure?

- Negative predictors in our pt:
  - Black race and male
  - Treatment experienced
  - High BMI, diabetes (?)
  - Cirrhosis with portal HTN
  - Drug–drug interaction: omeprazole 20 mg BID and LDV

Impact of Multiple Negative Predictors on Response

- Retrospective analysis of phase II/III studies of SOF + RBV ± pegIFN in pts with GT1-3 HCV (N = 871)



Negative Predictors:

- Treatment experienced
- Cirrhosis
- HCV RNA
- Male
- ≥ 75 kg
- IL28B non-CC
- NS5A RASs?

Foster GR, et al. EASL 2014. Abstract O66.

Slide credit: clinicaloptions.com

HCV TARGET: Predictors of HCV DAA Failure

- Prospective, observational cohort study of real-world clinical practice
  - N = 4099 pts with GT1 HCV treated with oral therapy including ≥ 2 DAAs
  - SVR: 93.7%; no SVR: 6.3%
- Factors independently associated with lack of SVR
  - Logistic linear regression: cirrhosis, time of treatment start
  - Multivariate logistic regression: cirrhosis, low albumin, low platelet count, high total bilirubin, male sex, older age
- Inverse probability weighting by propensity scores identified lower likelihood of SVR with SMV + SOF vs LDV/SOF or OBV/PTV/RTV + DSV (all ± RBV)
  - Limited data available on Q80K presence
- 19 of 22 pts retreated with LDV/SOF or OBV/PTV/RTV + DSV ± RBV achieved SVR

Sulkowski MS, et al. EASL 2017. Abstract SAT-229.

Slide credit: clinicaloptions.com

Key HCV Resistance Concepts

- HCV resistance-associated substitutions
  - Enriched in pts experiencing DAA treatment failure
  - Has an impact on treatment response in specific situations
- HCV resistance is NOT absolute
- Some pt characteristics are just as important as RASs
- Future regimens appear to obviate the need for most resistance testing

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Resistance Characteristics of HCV Antiviral Classes

Class	Antiviral Potency	GT Activity	Resistance Barrier	FDA Approvals
NS3 protease inhibitor[1]	+++ to ++++	1, 4 (± 2, 3, 6)	Low to high ↓	Simeprevir (2013) Paritaprevir (2014) Grazoprevir (2016) Voxilaprevir (2017*) Glecaprevir (2017*)
NS5B nucleotide[2]	++++	1-6	Very high	Sofosbuvir (2013) Uprifosbuvir (2018?*)
NS5B nonnucleoside[2]	++	1	Low	Dasabuvir (2014)
NS5A inhibitor[3]	++++	1, 4, 6 (± 2, 3)	Low to high ↓	Ledipasvir (2014) Daclatasvir (2015) Ombitasvir (2014) Elbasvir (2016) Velpatasvir (2016) Pibrentasvir (2017*) Ruzasvir (2018?*)

*Anticipated FDA approvals.

References in slidenotes.

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Resistance Testing Approaches

- Ultradeep or next-generation vs population (Sanger) sequencing
- What is broadly commercially available:
  - HCV GT1 NS3 and GT1 and GT3 NS5A drug resistance assays
    - NGS with 10% detection level reported (*LabCorp/Monogram Biosciences*)[1]
    - RT-PCR with DNA sequencing (*Quest Diagnostics*)[2]
- Both NS5A assays now available for GT1 and GT3 HCV
  - GT1 assays are subtype specific (1a vs 1b)

1. HCV NS5A Drug Resistance Assay Product Label. 2016.
2. Hepatitis C Viral RNA Genotype 1/3 NS3 and/or NS5 Drug Resistance Assay Product Labels. 2016.

Slide credit: clinicaloptions.com

Comparing RAS Types

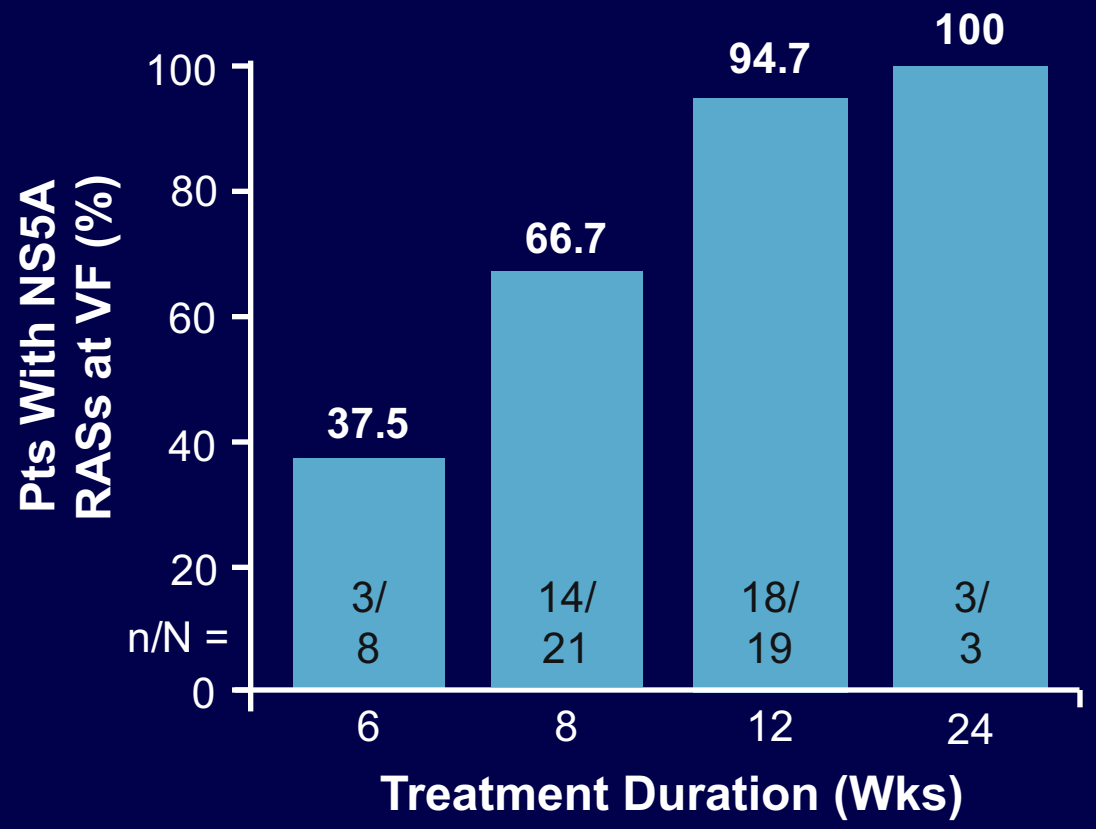
Characteristic	Baseline RASs	Selected RASs
Variants	Single	Multiple (with “linkage”)
Fold-change	Variable	High
Prevalence in viral population	Variable	High
Population	Any	Difficult to treat

Dvory-Sobol H, et al. EASL 2015. Abstract O059.
Cooper C, et al. Clin Infect Dis. 2016;63:528-531.

NS5A Resistance Selection Rate Upon Virologic Failure

- Varies by regimen and duration
- PI based:
  - EBR/GZR: 94%[1]
  - OBV/PTV/RTV + DSV: 68%[2]
- Nucleotide based:
  - LDV/SOF: 75%[3]
  - SOF/VEL: 93% (14/15; majority GT3)[4]
  - SOF/VEL/VOX (≤ 6 wks): 0% (n = 15)[5]
  - SOF + EBR/GZR (≤ 8 wks): 37% (n = 30)[6]

NS5A RAS Detection Among Pts With VF in LDV/SOF Phase II/III Trials[3]



References in slidenotes.

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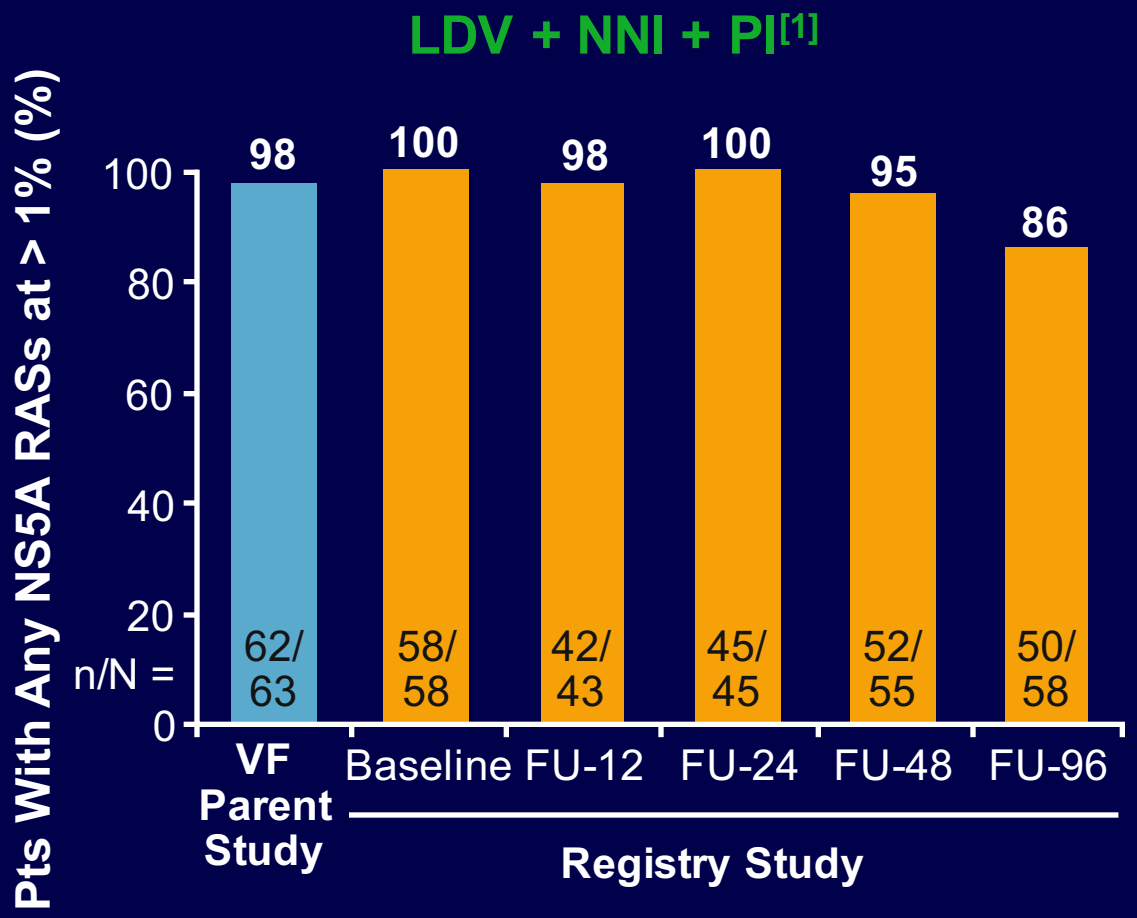
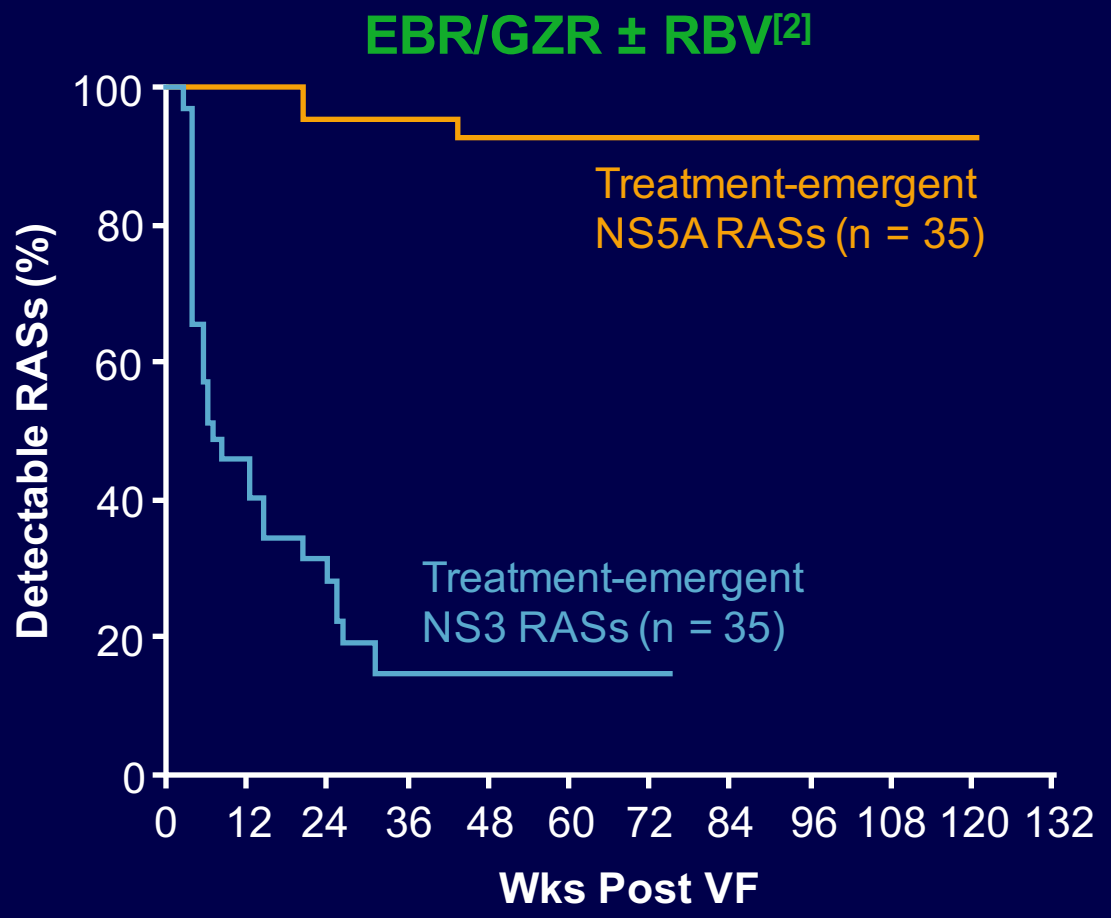
Durability of Treatment-Emergent NS5A RASs





1. Dvory-Sobol H, et al. EASL 2015. Abstract O059.
2. Lahser F, et al. AASLD 2016. Abstract 61.

Slide credit: clinicaloptions.com

Broad Cross-Resistance With "Early-Generation" NS5A Inhibitors

Fold Change	Genotype 1a				Genotype 1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H/N
Ledipasvir	20x	> 100x	> 100x/ > 100x	> 1000x/ > 10,000x		> 100x/--
Ombitasvir	> 1000x	> 100x	< 3x / > 100x	> 10,000x/ > 10,000x	< 10x	20x/50x
Daclatasvir	> 100x	> 1000x	> 100x/ > 1000x	> 1000x/ > 10,000x	< 10x	20x/50x
Elbasvir	20x	> 100x	> 10x / > 100x	> 1000x/ > 1000x	< 10x	> 100x/--
Velpatasvir	< 10x	< 3x	20x/50x	> 100x/ > 1000x	< 3x	< 3x/--
Pibrentasvir	< 3x	< 3x	< 3x	< 10x/< 10x	< 3x	< 3x/< 3x
Ruzasvir	< 10x	< 10x	< 10x	< 10x	< 10x	< 10x

References in slidenotes.

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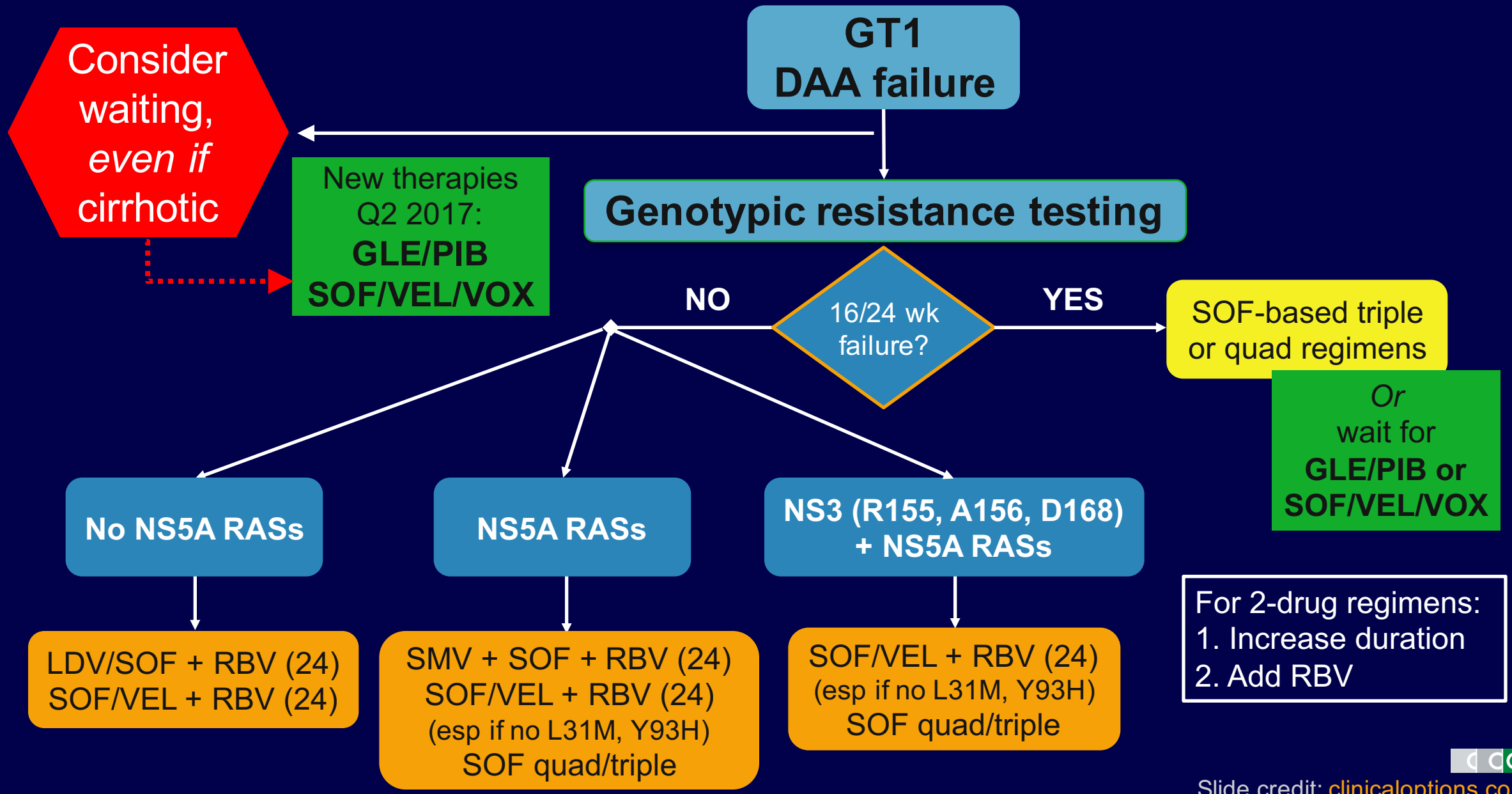
Back to Case 1

- 59-yr-old black man with GT1a HCV, DM, GERD, and HTN, treated with pegIFN/RBV in 2009 (null response)
- Physical exam: BMI 32, no ascites, no edema, palmar erythema
- Cirrhosis confirmed by elastography in 2015 (22.6 kPa; IQR 11%)
- Relapse after LDV/SOF + RBV for 12 wks in 2015
- Resistance test shows NS5A RASs: Q30H, Y93H
- Current medications: amlodipine, atorvastatin 40 mg, omeprazole 20 mg BID

Current Laboratory Parameter	Result
Platelets/mm^3	98,000
Albumin, g/dL	3.7
ALT, IU/L	47
AST, IU/L	56
Total bilirubin, mg/dL	0.9
INR	1.2
CTP	A5

Slide credit: clinicaloptions.com



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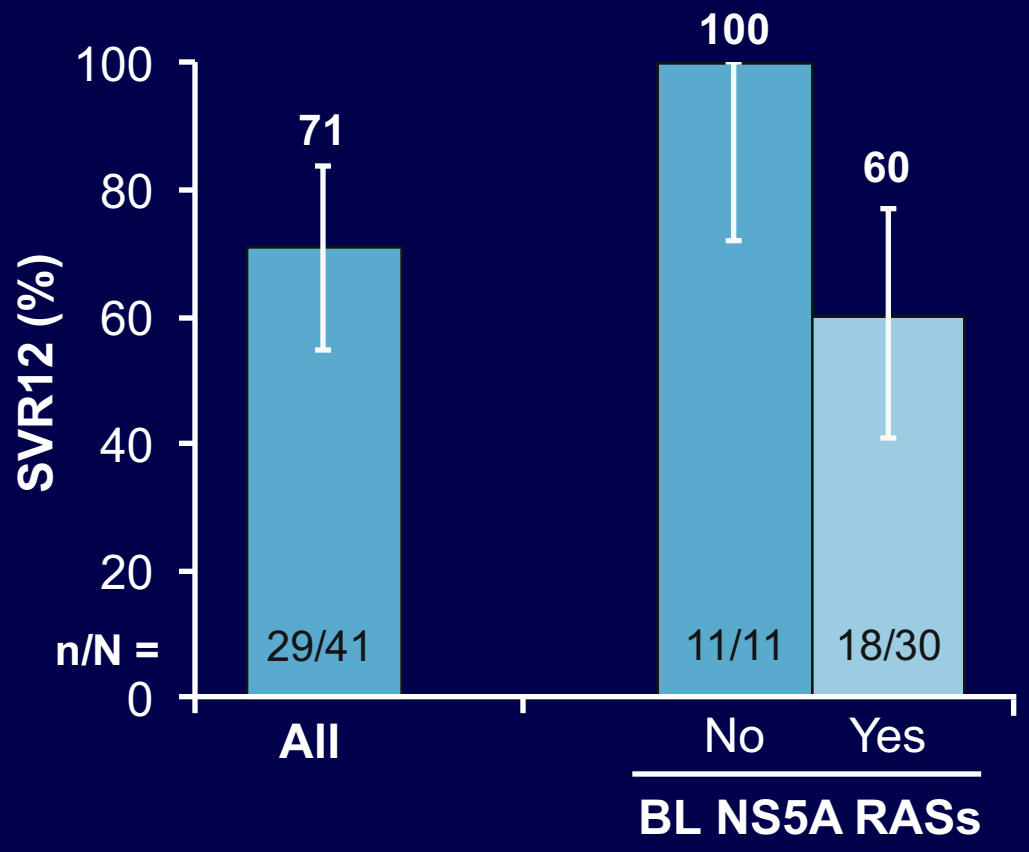
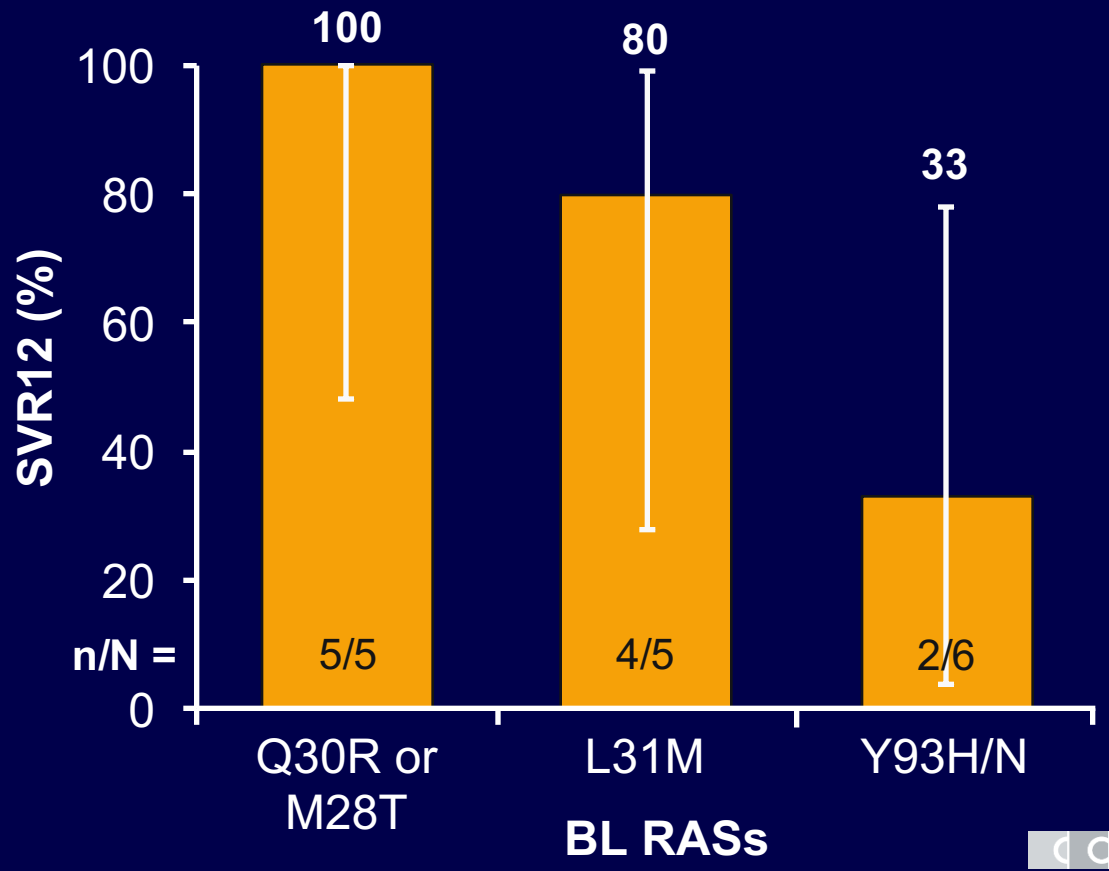
NS5A RASs Associated With Retreatment Failure With a Cross-Resistant Regimen

- 8-wk or 12-wk LDV/SOF-based treatment failures retreated with LDV/SOF for 24 wks (N = 41)





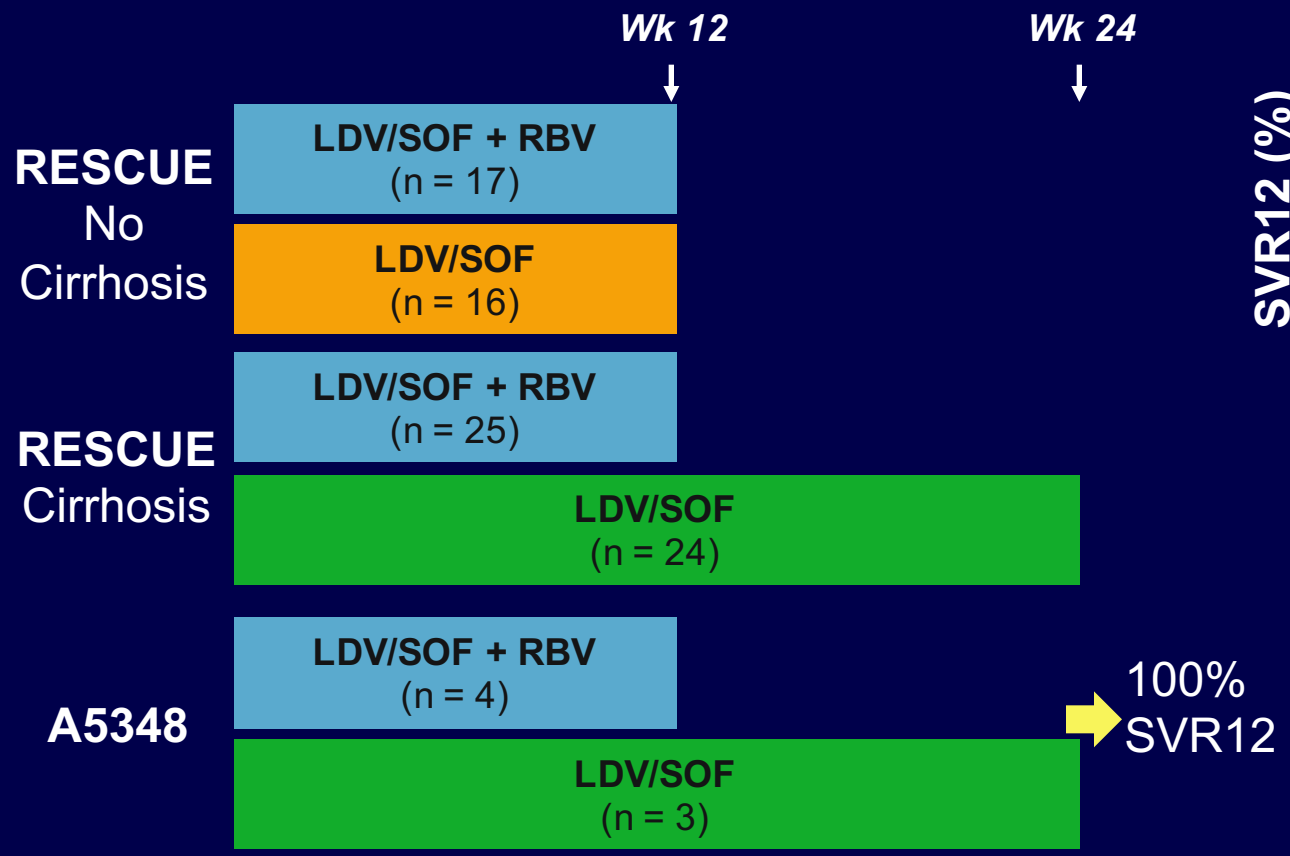
Lawitz E, et al. EASL 2015. Abstract O005.

Slide credit: clinicaloptions.com

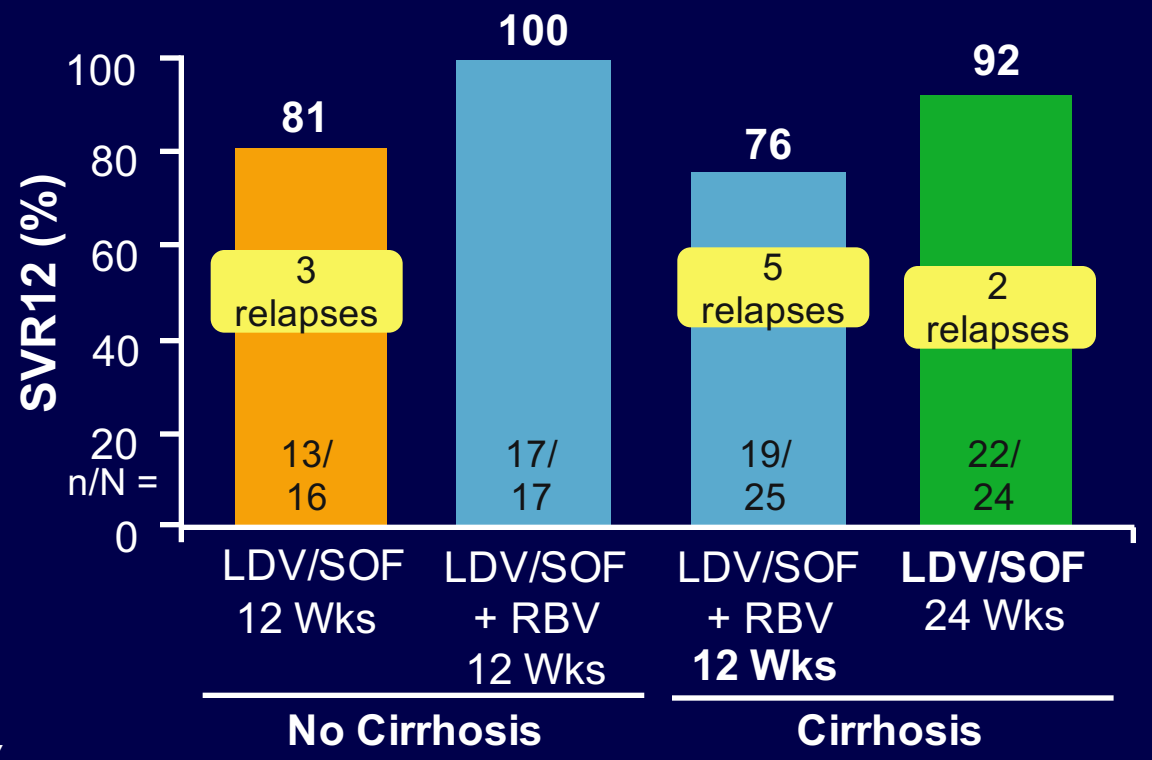
RESCUE/A5348: RBV and Longer Tx Duration for Overcoming Resistance, Optimizing Retreatment

Previous SOF Failure Without NS5A Exposure

37% (30/82) with previous SMV + SOF failure



RESCUE



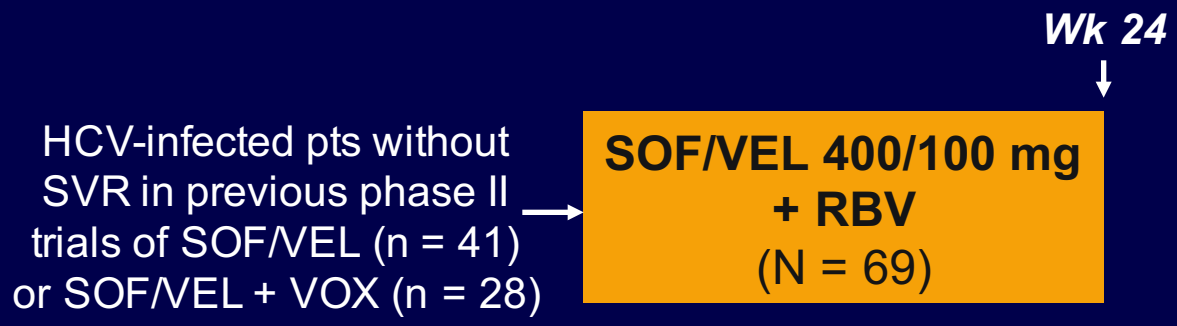
- 6/10 VFs SOF + SMV failures; 7/10 cirrhotic
- No impact of BL NS5A or NS5B RASs

Tam E, et al. EASL 2017. Abstract THU-265.

Slide credit: clinicaloptions.com

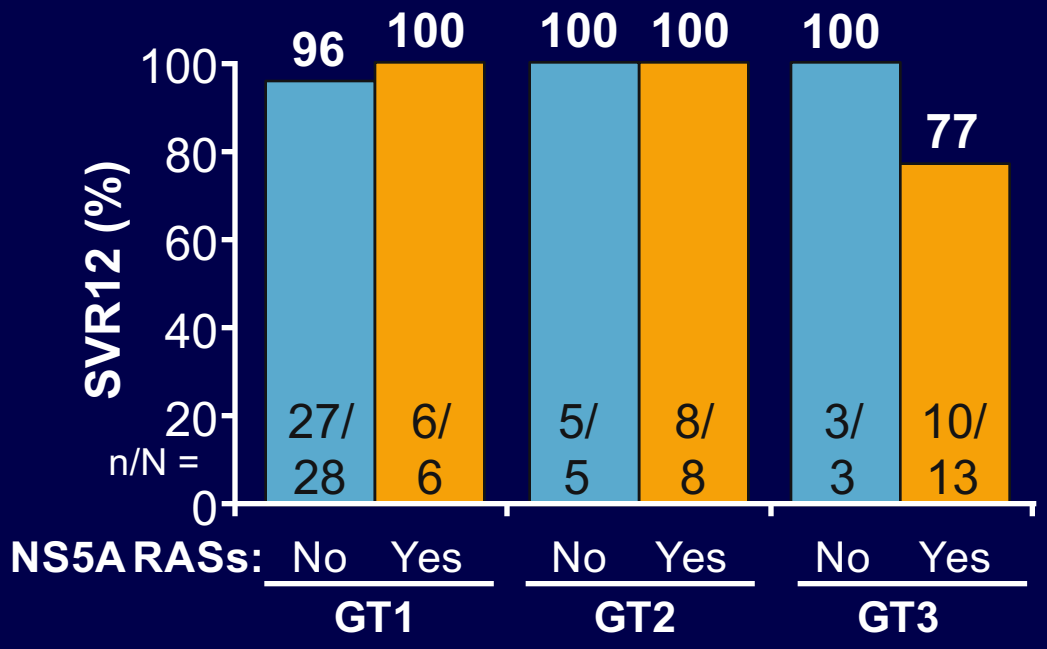
Roles of RBV and Longer Tx Duration in Overcoming Resistance, Optimizing Retreatment

- Single-arm trial



- Cirrhosis: 26%; previous relapse: 99%
- 20% GT2
- Only 18% of GT1 with NS5A RASs
- Previous treatment: 41% VEL 25 mg, 74% < 12 wks

- Overall SVR12: GT1 (n = 34): 97%; GT2 (n = 14): 91%; GT3 (n = 17): 76%



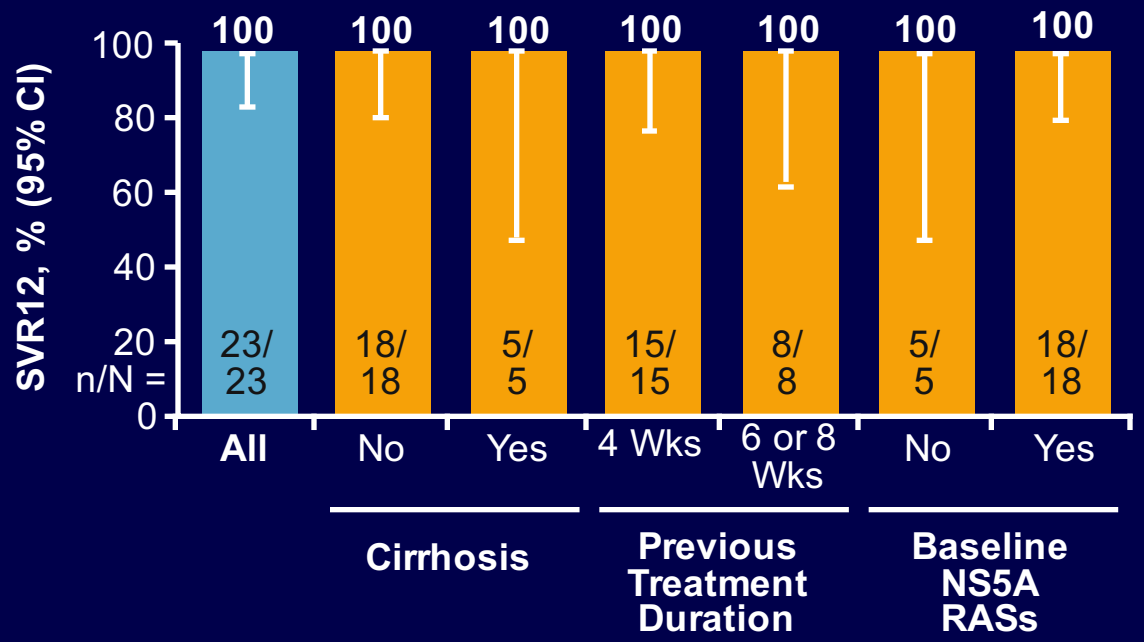
- 9/11 (82%) pts with GT3 HCV and Y93H achieved SVR12

Gane EJ, et al. EASL 2016. Abstract PS024.

Slide credit: clinicaloptions.com

Retreatment of Previous Short Duration SOF + EBR/GZR Failure

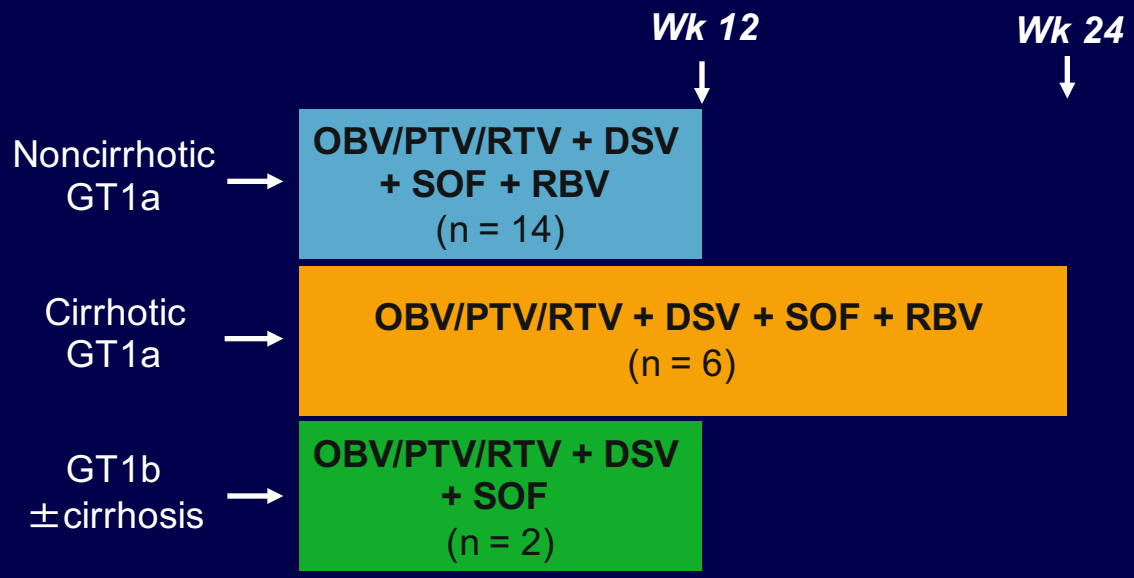
- 25 pts who experienced failure of short course SOF + EBR/GZR (4-8 wks)
  - 22 GT1a, 3 GT1b
    - 20 experienced failure with 4 wks
  - 5 (20%) cirrhosis
  - 80% with NS5A RASs
  - 52% NS3 RASs
  - 44% NS3/NS5A RASs
- Pts retreated with SOF + EBR/GZR + RBV for 12 wks
- 100% SVR12 (9/9) in pts with dual RASs

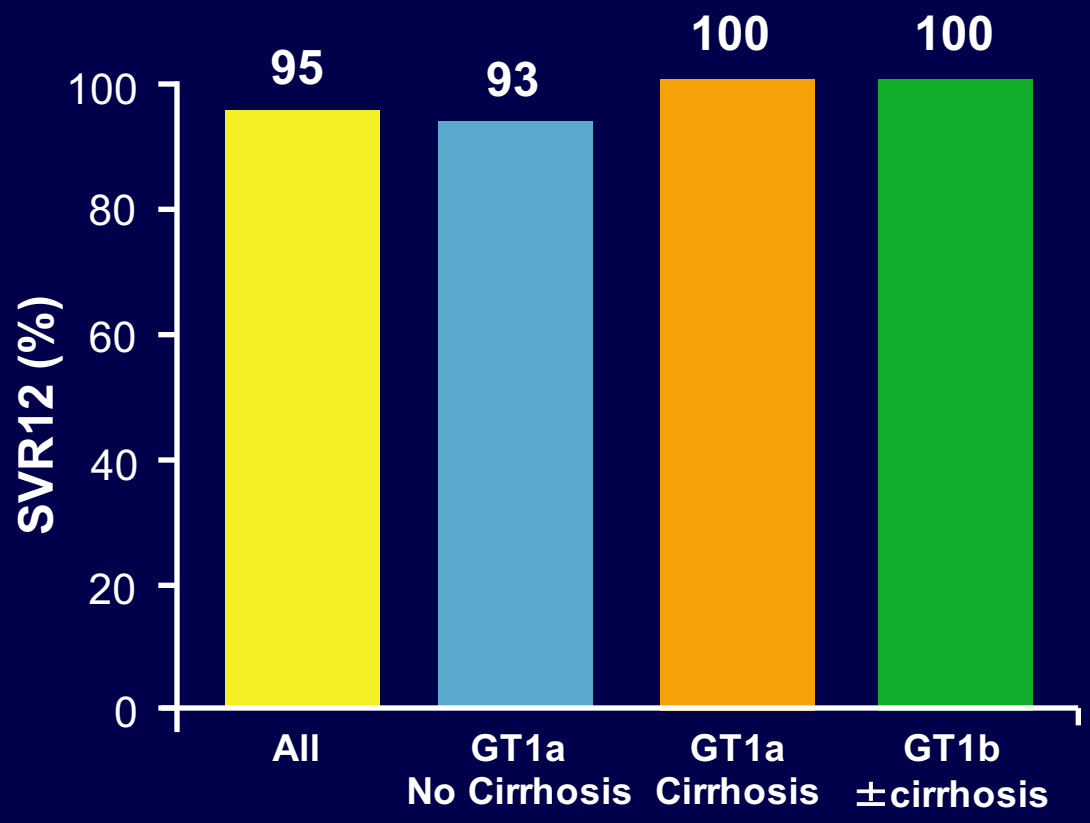


Lawitz E, et al. AASLD 2015. Abstract LB-12.

Slide credit: clinicaloptions.com

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





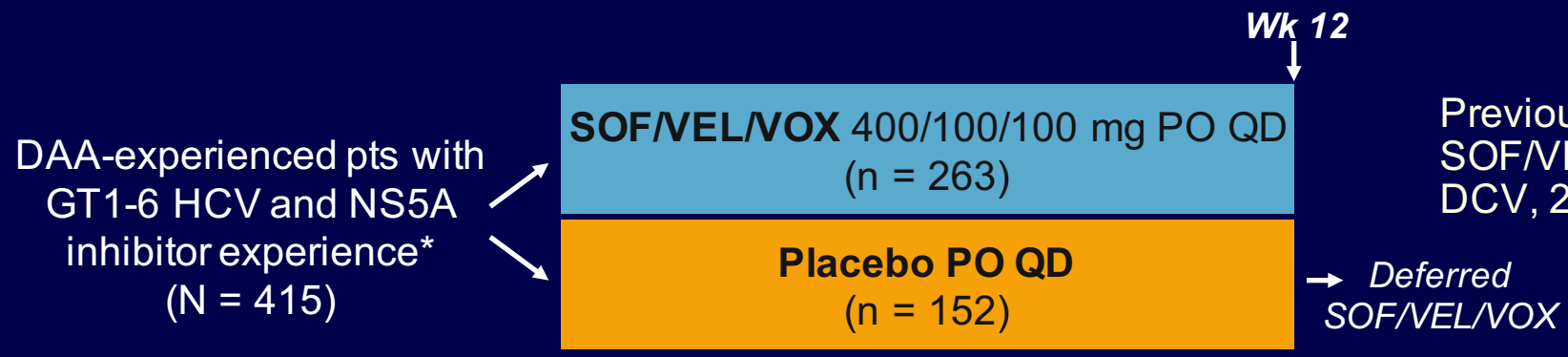
- Multicenter, open-label phase II study
- 14/20 GT1a had previous OBV/PTV/RTV + DSV failure; no previous LDV/SOF failure
- BL RASs: D168E/V (n = 5); Y93C/F/H (4); Q30E/H/R (n = 12)

Poordad F, et al. EASL 2016. Abstract SAT-156.

Slide credit: clinicaloptions.com

POLARIS-1, -4: SOF/VEL/VOX for 12 Wks After DAA Failure in GT1-6 HCV

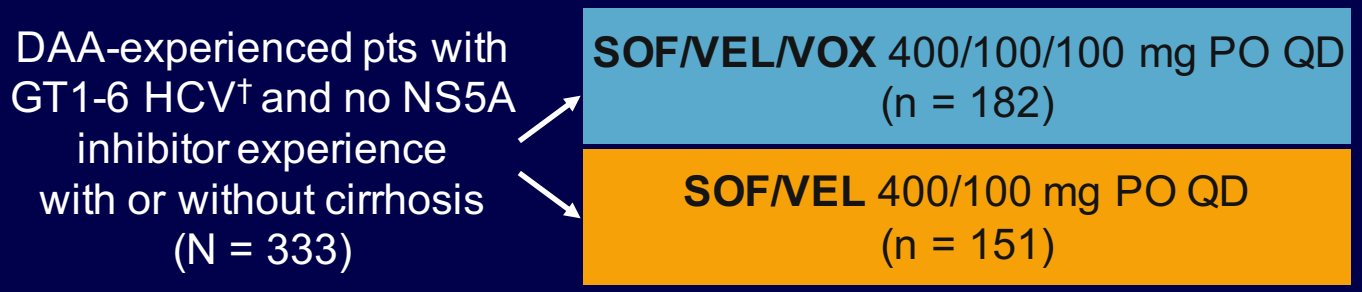
POLARIS-1: randomized, double-blind, placebo-controlled phase III trial[1]



Previous NS5A treatment in SOF/VEL/VOX group LDV, 51%; DCV, 27%; OBV, 11%; other, 13%

*Pts with GT1 HCV at screening equally randomized between arms; pts with GT2-6 HCV assigned to active treatment arm.

POLARIS-4: randomized, open-label, active-controlled phase III trial[2]



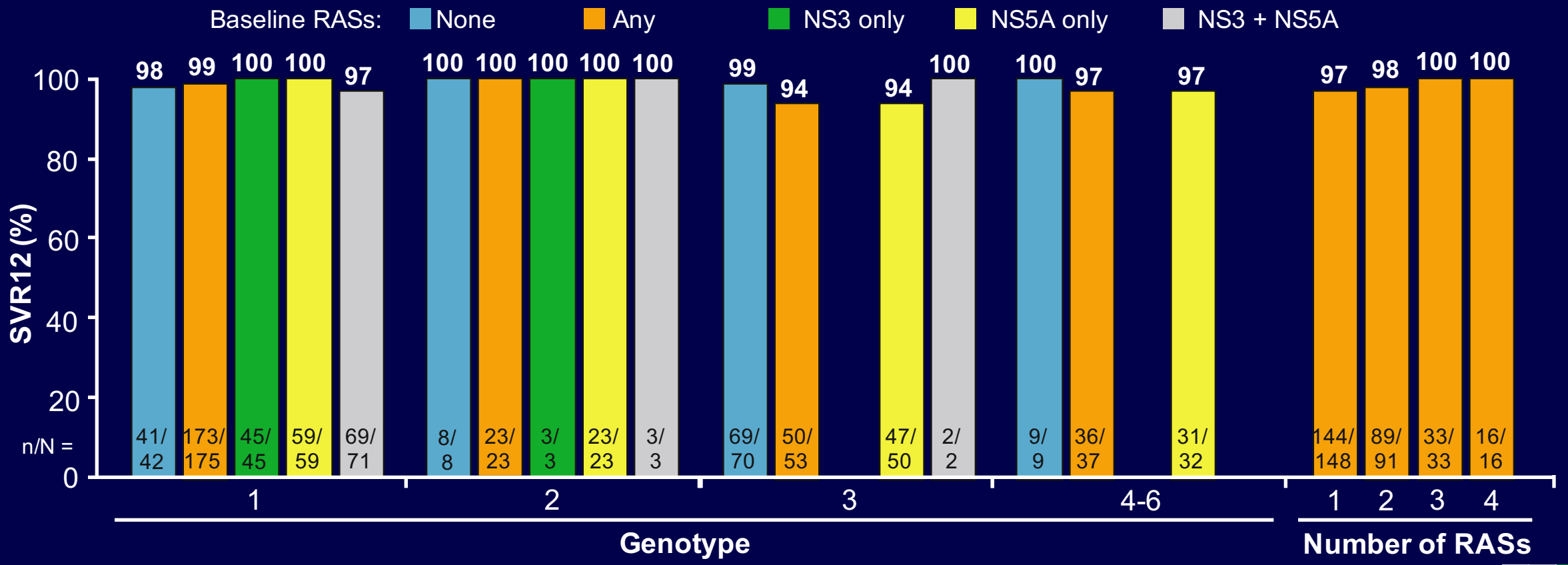
Previous HCV treatment: SOF, 69%; other NS5B inhibitor, 4%; SOF + SMV, 11%; other NS5B/NS3 inhibitor combinations, 14%

†Pts with GT1-3 HCV randomized 1:1 between arms. Pts with GT4-6 HCV assigned to SOF/VEL/VOX.

1. Bourlière M, et al. AASLD 2016. Abstract 194. 2. Zeuzem S, et al. AASLD 2016. Abstract 109.

POLARIS-1 and -4: Impact of Baseline RASs on 12-Wk SOF/VEL/VOX in DAA-Experienced Pts

- Integrated analysis of data from SOF/VEL/VOX arms of 2 phase III trials of DAA-experienced pts with (n = 263) and without (n = 182) previous NS5A inhibitors

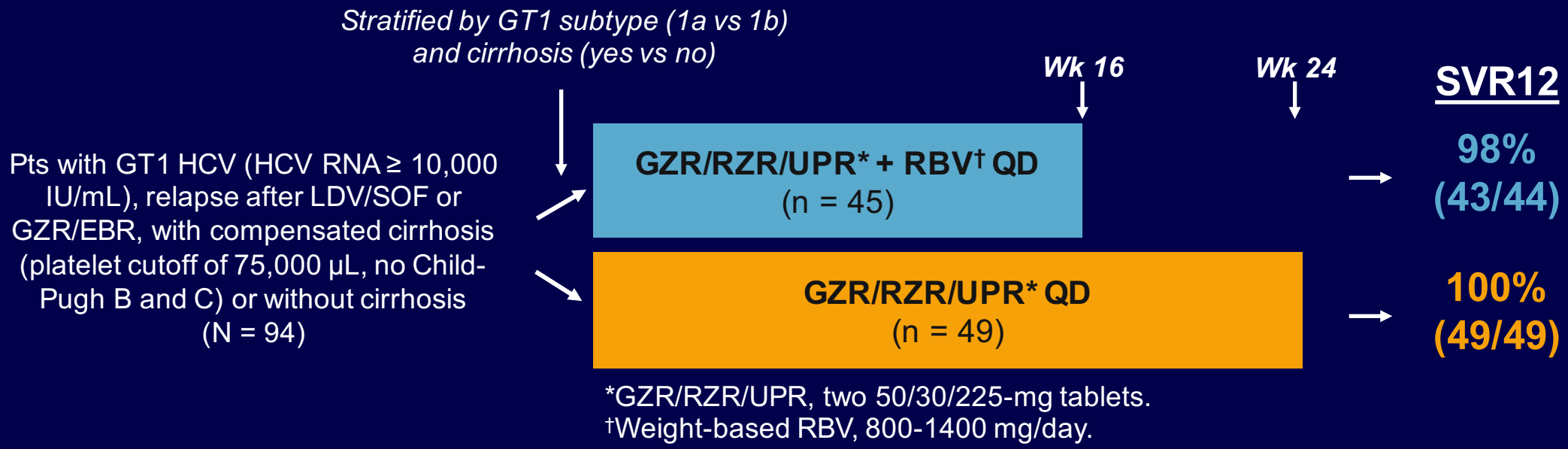


Sarrazin, et al. EASL 2017. Abstract THU-248.

Slide credit: clinicaloptions.com

C-SURGE: Grazoprevir/Ruzasvir/Uprifosbuvir for GT1 HCV Pts Who Relapsed on DAA Therapy

- Randomized, open-label phase II trial



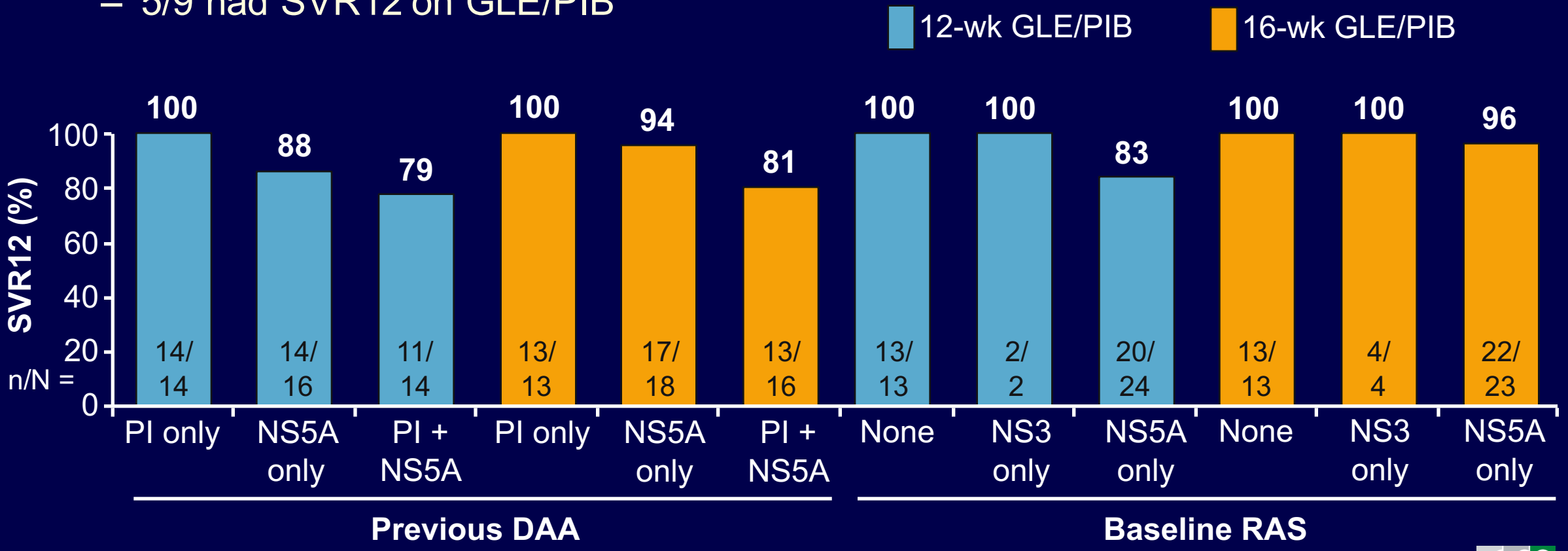
- Baseline characteristics
  - Noncirrhotic, 56%; compensated cirrhosis, 43%; unknown, 1%
  - **NS5A RASs, 84%; NS3 RASs, 65%; dual NS5A and NS3 RASs, 55%**

Wedemeyer H, et al. EASL 2017. Abstract PS-159.

Slide credit: clinicaloptions.com

MAGELLAN-1: Glecaprevir/Pibrentasvir in GT1 or 4 HCV With Previous DAA Failure

- Of pts with NS3 and NS5a RASs, 9/9 had previous failure with PI + NS5A
  - 5/9 had SVR12 on GLE/PIB



Poordad F, et al. EASL 2017. Abstract PS-156.

Slide credit: clinicaloptions.com

Back to the Original Case: While Waiting for New Therapies . . .

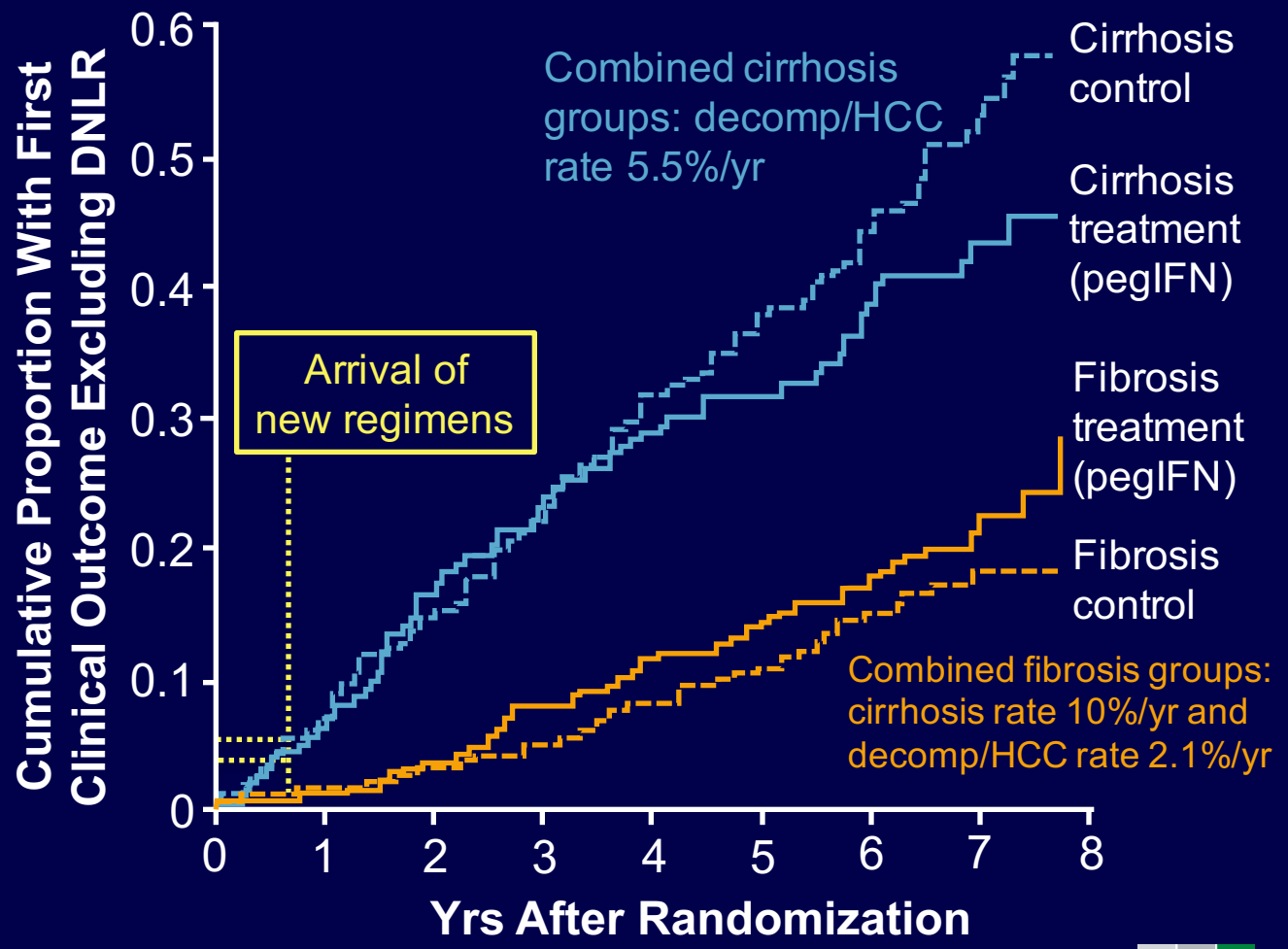
- Pt gains 25 lbs over 3 wks; wife reports pt intermittently confused
- Admitted: new ascites, edema, and encephalopathy
  - U/S shows no masses; tap without evidence of SBP
  - Responds to diuretics, Na+ restriction, and lactulose
  - EGD with grade 2 varices, banded
  - CTP B9, MELD 17

- Black man with GT1a HCV and cirrhosis
- Previous pegIFN/RBV null response, relapse after LDV/SOF + RBV 12 wks
- Dual NS5A RASs: Q30H, Y93H

Slide credit: clinicaloptions.com

Progression of Liver Disease and Decompensation

- Lower baseline platelet count associated with higher incidence of decompensation/ HCC
  - < 100,000/mm^3: 7.9%
  - ≥ 200,000/mm^3: 1.3%



Dienstag JL, et al. Hepatology. 2011;54:396-405.

Slide credit: clinicaloptions.com

Key Considerations for Genotype 1/4 Decompensated Cirrhosis

- Treatment options are more limited than for pts without cirrhosis or with compensated cirrhosis
  - SVR rates are generally lower
- **Protease inhibitors are not recommended for CPT B or C**
- Continuing role for ribavirin
  - Low dose for CPT C; weight-based for CPT B with SOF/VEL
- Extend duration to 24 wks if RBV ineligible

AASLD/IDSA. HCV guidance. April 2017.

Slide credit: clinicaloptions.com

AASLD/IDSA Guidance for Pts With GT1 HCV and Decompensated Cirrhosis

- Refer to experienced HCV provider (ideally liver transplant center)

GT1 Population	DCV + SOF	LDV/SOF	SOF/VEL
RBV eligible	12 wks + low-dose RBV*	12 wks + low-dose RBV*	12 wks + RBV (weight based for CPT B; low dose* for CPT C)
RBV ineligible	24 wks	24 wks	24 wks

*Initial dose: 600 mg/day, increase as tolerated.

AASLD/IDSA. HCV guidance. April 2017.

Slide credit: clinicaloptions.com

AASLD/IDSA Guidance for Pts With GT1 HCV and Decompensated Cirrhosis

- Refer to experienced HCV provider (ideally liver transplant center)

GT1 Population	DCV + SOF	LDV/SOF	SOF/VEL
RBV eligible	12 wks + low-dose RBV*	12 wks + low-dose RBV*	12 wks + RBV (weight based for CPT B; low dose* for CPT C)
RBV ineligible	24 wks	24 wks	24 wks

*Initial dose: 600 mg/day, increase as tolerated.

But our case pt has experienced NS5A inhibitor failure and has NS5A RASs

AASLD/IDSA. HCV guidance. April 2017.

Slide credit: clinicaloptions.com

Case 2

- 52-yr-old Hispanic woman with GT3 HCV, F3 fibrosis based on elastography in 2015 (10.8 kPa, IQR 17%)
  - Relapsed after DCV + SOF for 12 wks in 2015

Current Laboratory Parameter	Result
Platelets/mm^3	156,000
Albumin, g/dL	3.9
ALT, IU/L	52
AST, IU/L	45
INR	1.0
NS5A RASs	Y93H

Slide credit: clinicaloptions.com

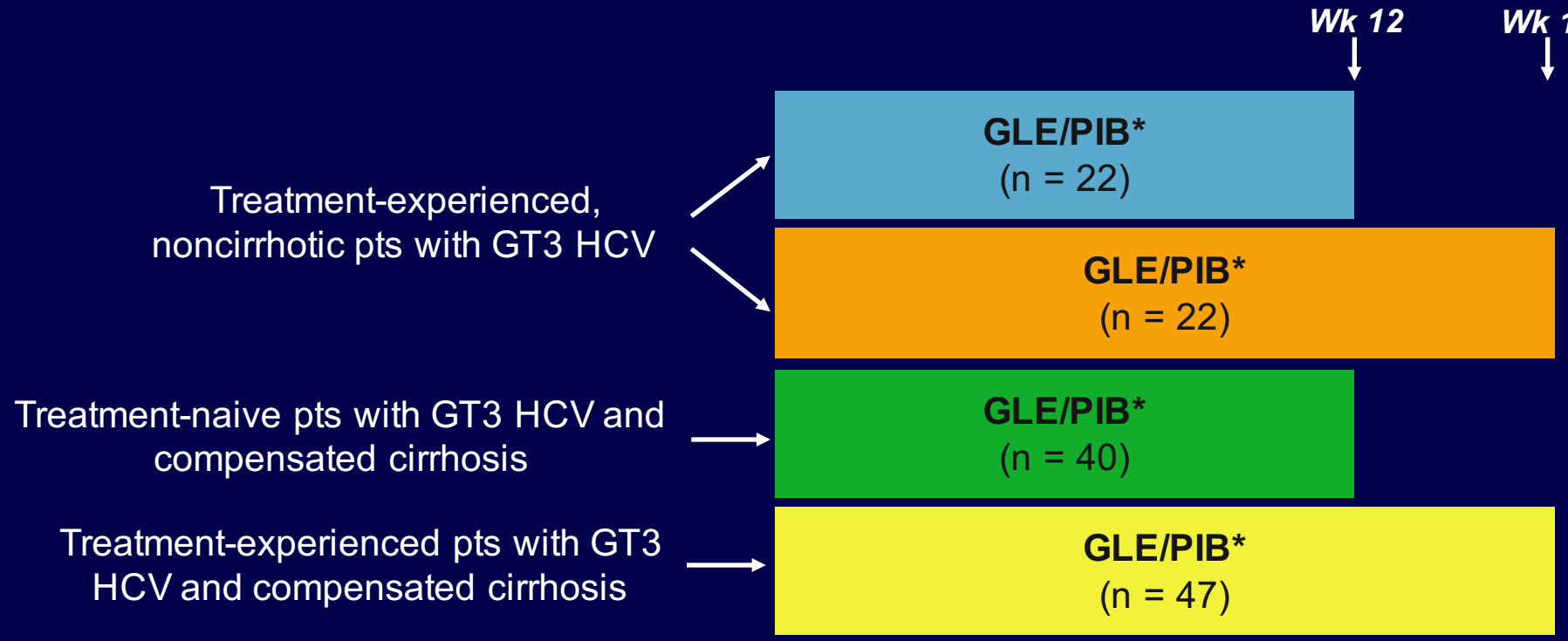
Retreatment of GT3 With Previous NS5A Inhibitor Failure

- Retreatment after failure of 4-12 wks of SOF/VEL[1]
  - SOF/VEL + RBV for 24 wks
  - SVR12 in GT3: 76% (13/17)
    - With NS5A RASs: 77%
    - Without NS5A RASs: 100%
- POLARIS 1: SOF/VEL/VOX for 12 wks after NS5A failure[2,3]
  - SVR12 in GT3: 95% (74/78)
    - With RASs: 94% (50/53)
    - Without RASs: 99% (69/70)
  - 4/6 viral relapses were GT3

1. Gane EJ, et al. EASL 2016. Abstract PS024. 2. Bourlière M, et al. AASLD 2016. Abstract 194. 3. Sarrazin C, et al. EASL 2017. Abstract THU-248.

SURVEYOR-II, Part 3: GLE/PIB for Pts With GT3 HCV ± Cirrhosis

- Partially randomized, open-label phase II trial (N = 131)
  - Previous treatment experience: IFN or pegIFN ± RBV or SOF + RBV ± pegIFN

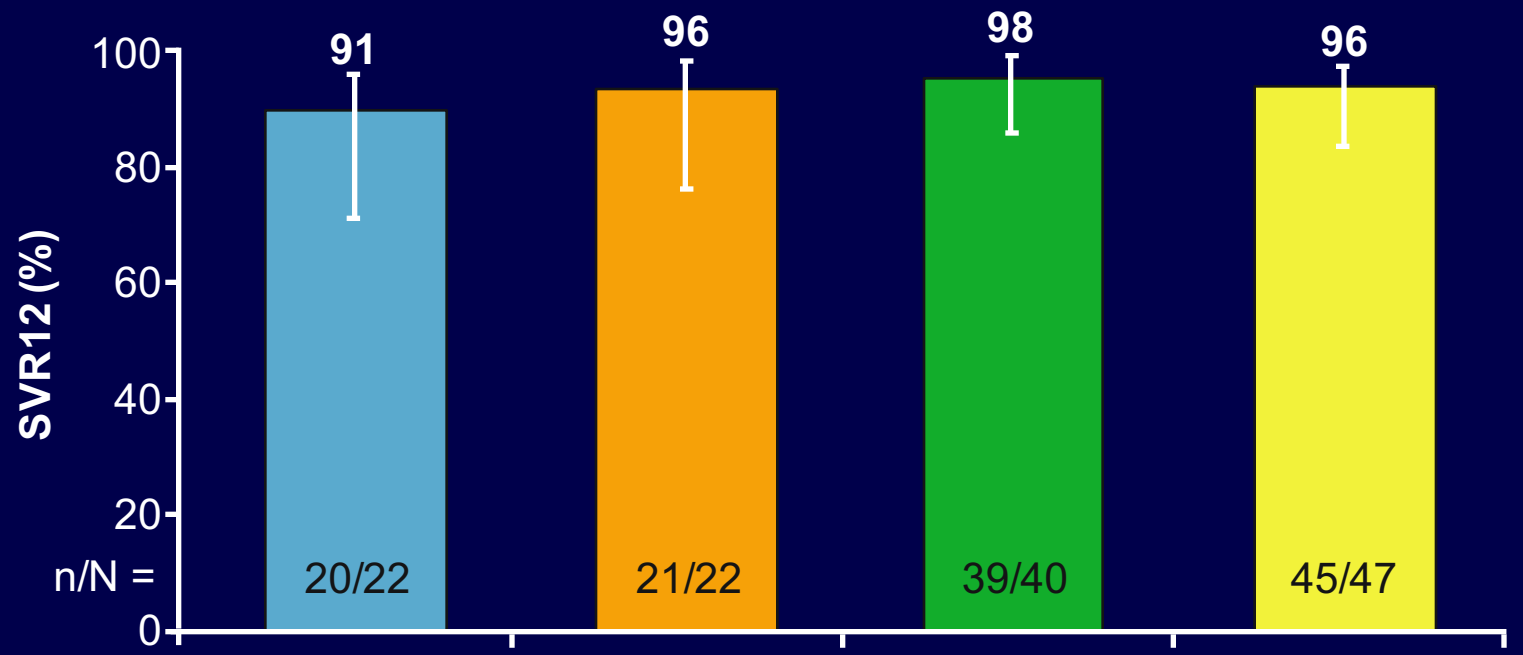


*Dosing: GLE/PIB given as 3 coformulated 100/40-mg tablets QD for a total dose of 300/120 mg.

Wyles DL, et al. AASLD 2016. Abstract 113.

Slide credit: clinicaloptions.com

SURVEYOR-II, Part 3: SVR12 Rates With GLE/PIB for Pts With GT3 HCV ± Cirrhosis



Tx Wks	12	16	12	16
Cirrhosis	-	-	+	+
Tx Experienced	+	+	-	+
Breakthrough	0	0	0	1
Relapse	2	1	0	1
LTFU	0	0	1	0

Wyles DL, et al. AASLD 2016. Abstract 113.

Slide credit: clinicaloptions.com

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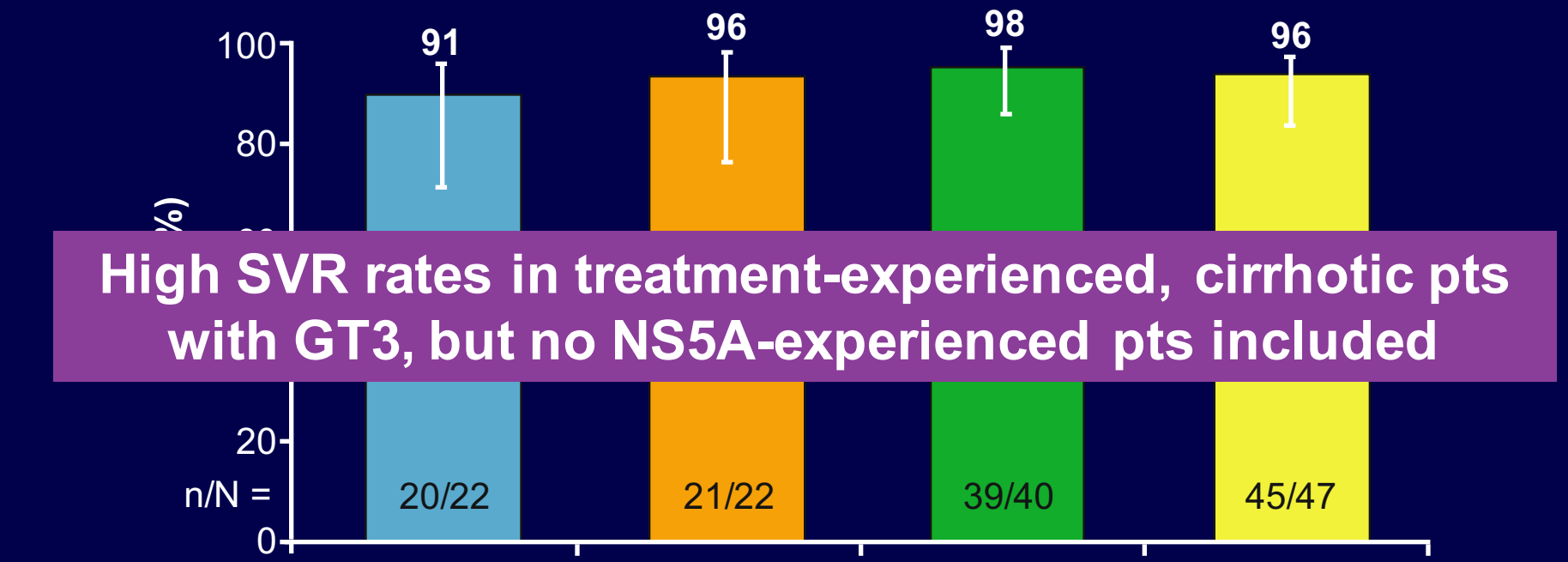

High SVR rates in treatment-experienced, cirrhotic pts with GT3, but no NS5A-experienced pts included

Tx Wks	12	16	12	16
Cirrhosis	-	-	+	+
Tx Experienced	+	+	-	+
Breakthrough	0	0	0	1
Relapse	2	1	0	1
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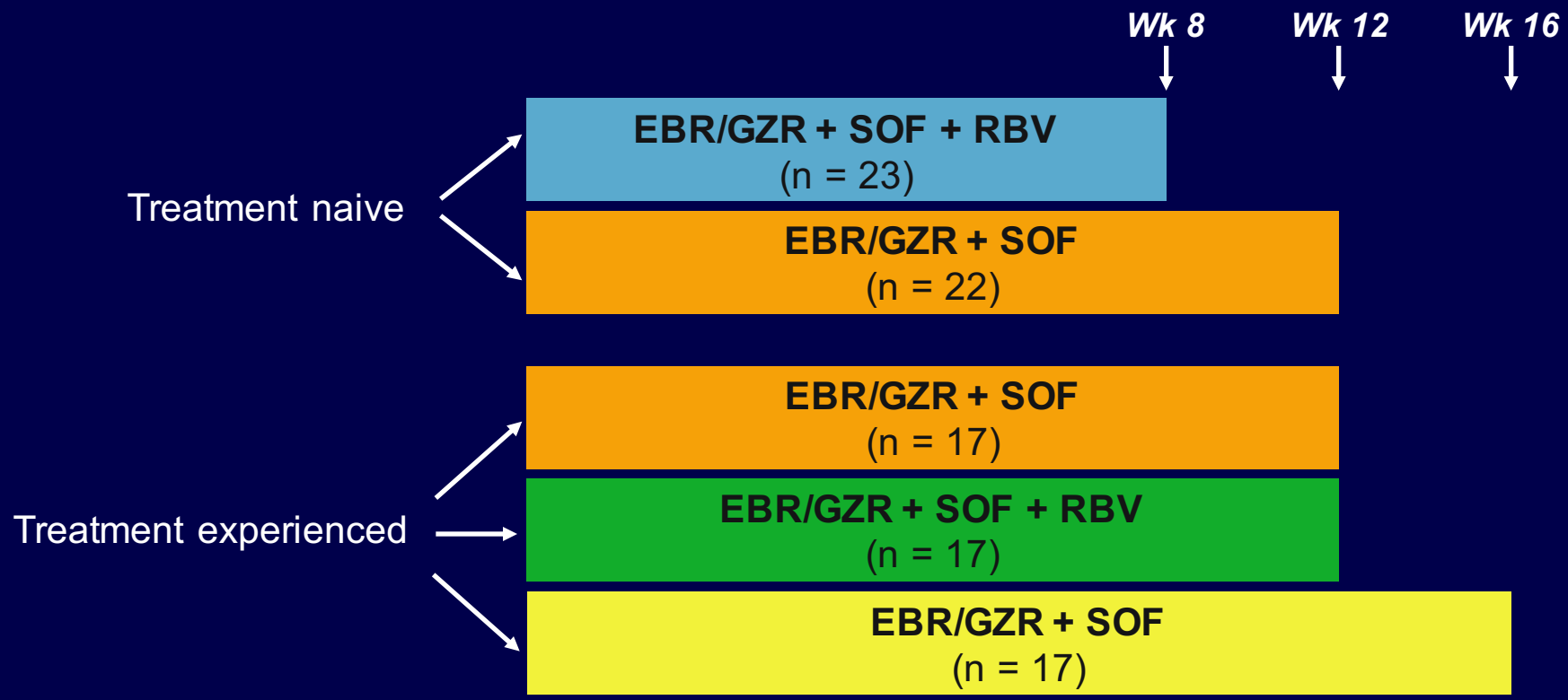
C-ISLE: EBR/GZR + SOF ± RBV for GT3 HCV in Pts With Compensated Cirrhosis

- Randomized, open-label phase II trial for pts with GT3 HCV infection and compensated cirrhosis; treatment experience included pegIFN/RBV



Foster GR, et al. AALSD 2016. Abstract 74.

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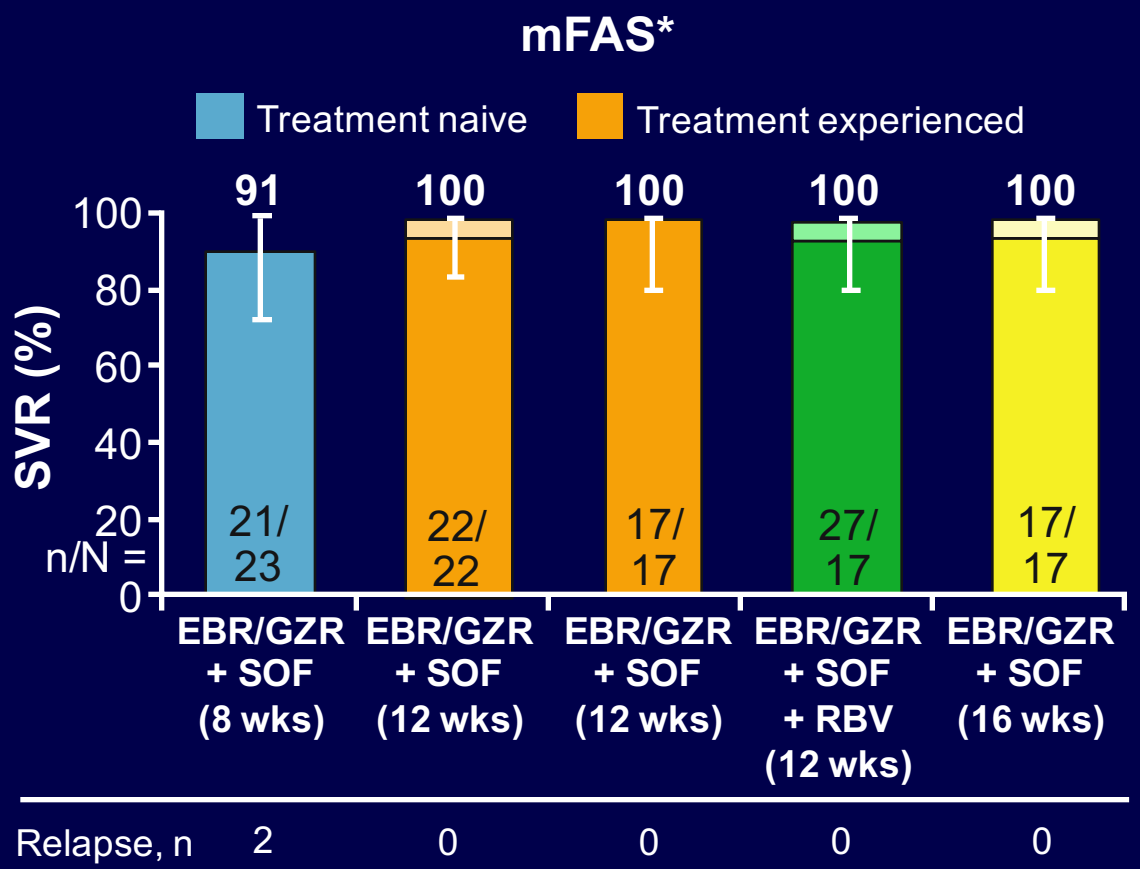
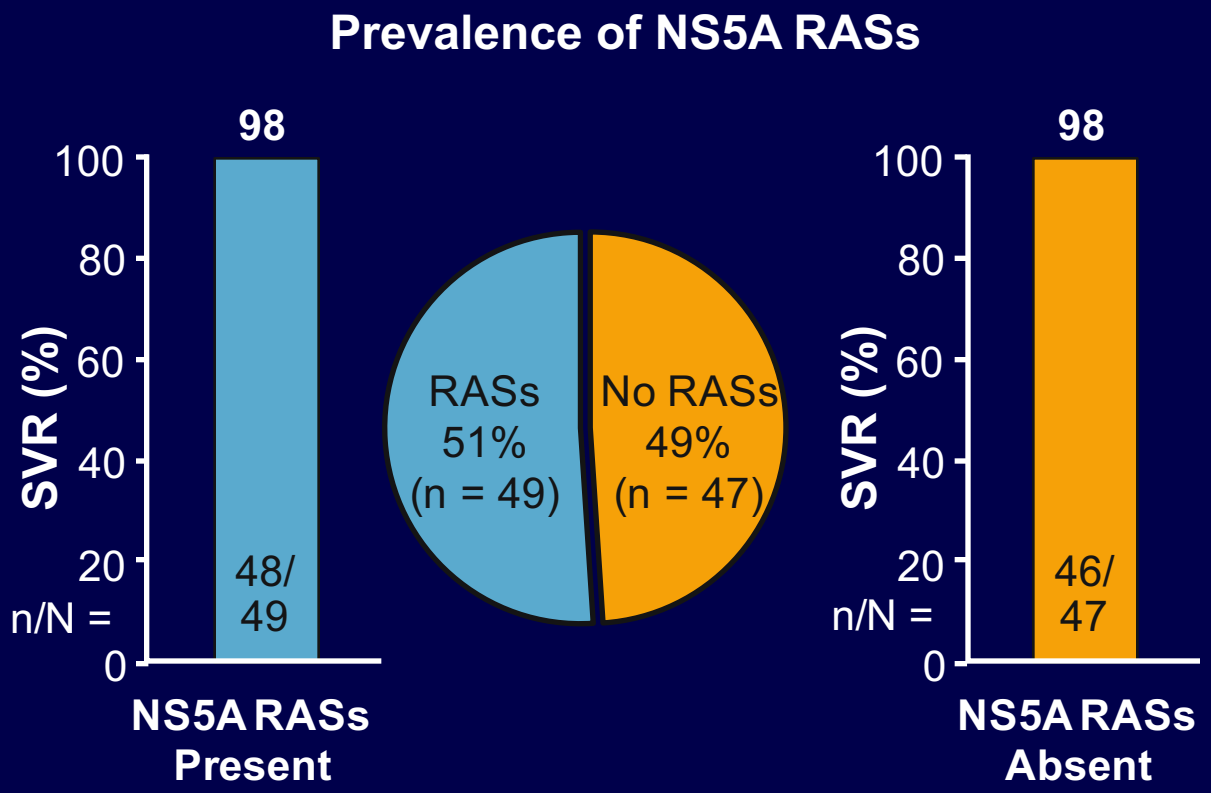
C-ISLE: SVR With EBR/GZR + SOF ± RBV for GT3 HCV in Pts With Compensated Cirrhosis



*Modified full analysis set excludes discontinuations not related to study drugs. 3 pts discontinued for administrative reasons.



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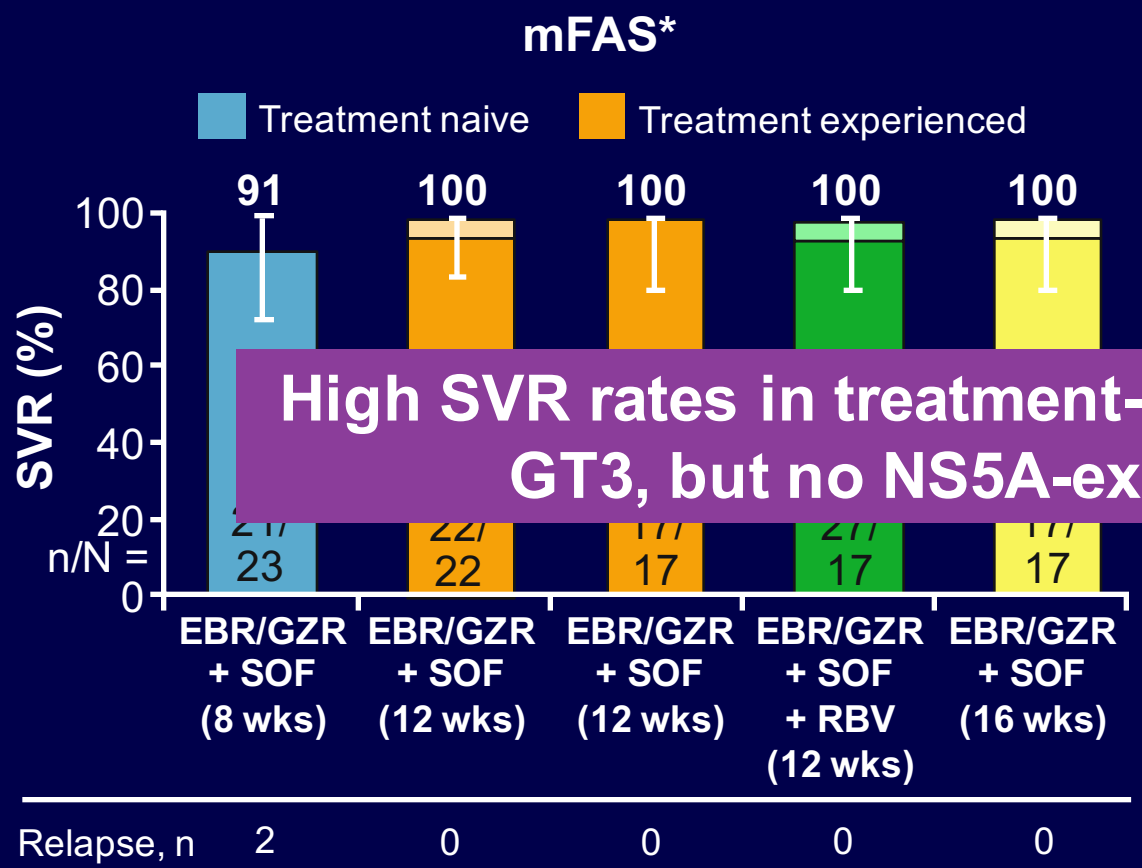

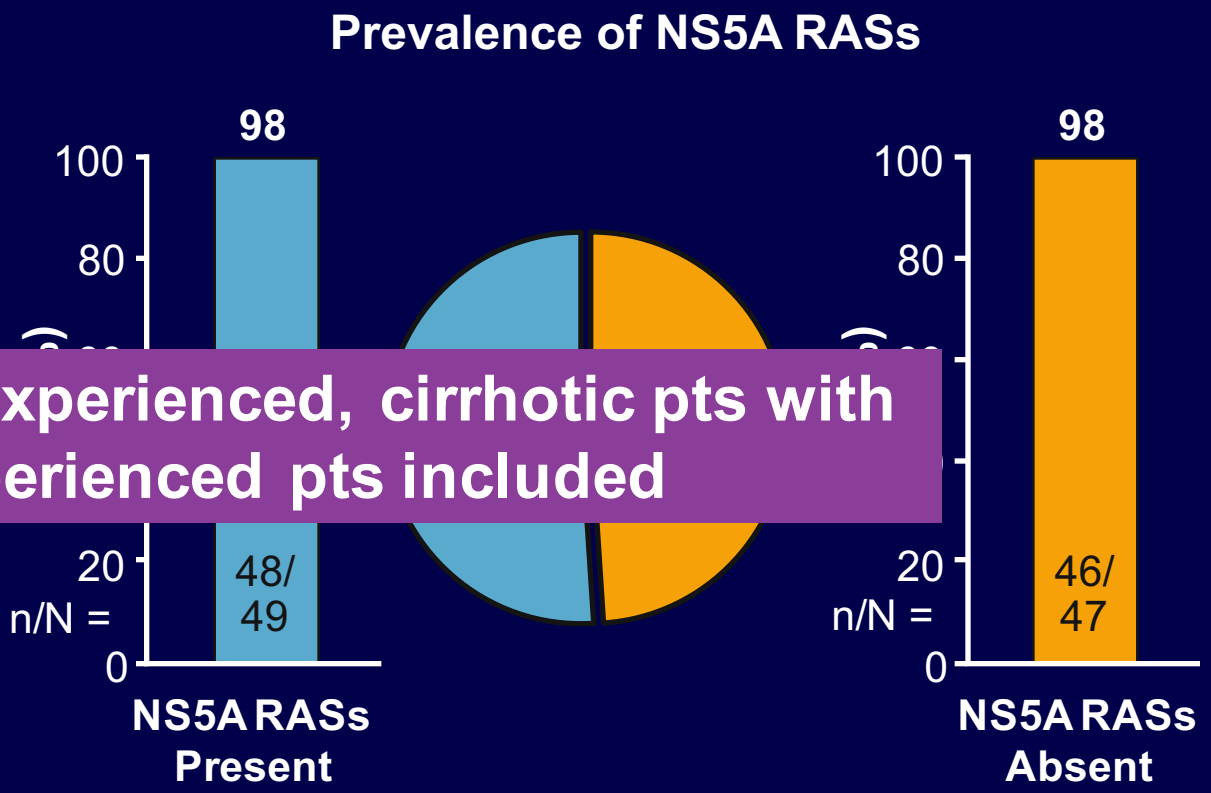

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