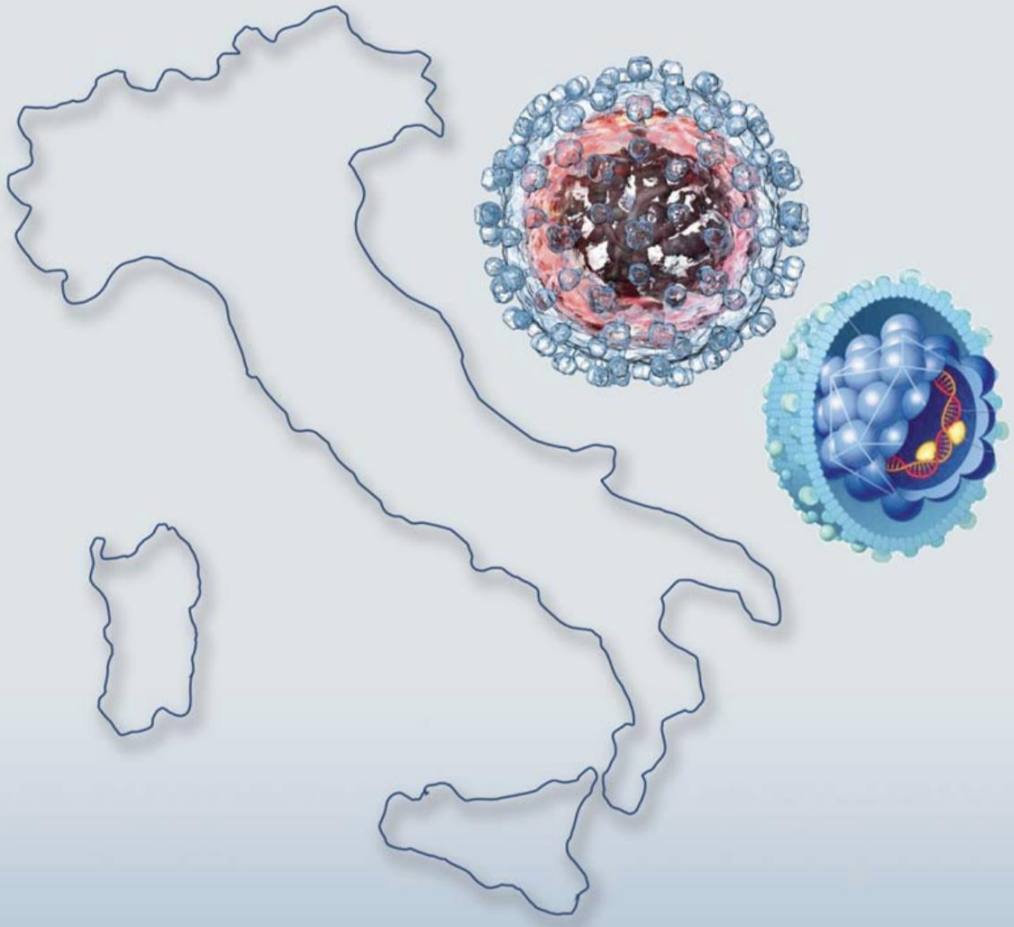
PITER
Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali

SIMIT
Società Italiana di Malattie Infettive e Tropicali

THE PITER MEETING



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Rome, 7 May 2019

UNIVERSITÀ DEGLI STUDI DI PALERMO

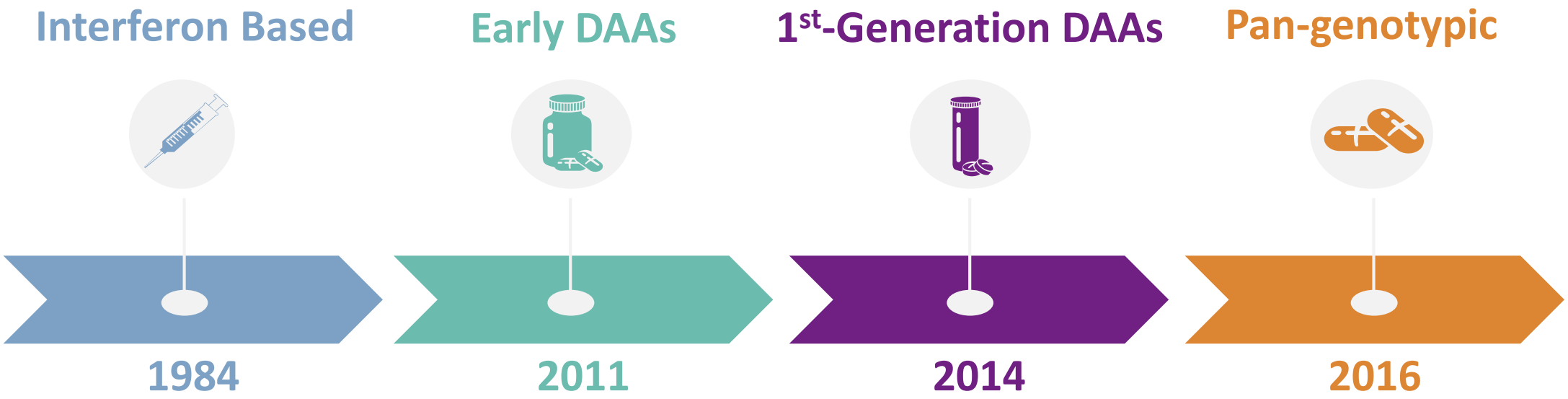
UNIPA2018

promise
Dipartimento di **Pro**mozione della Salute, **M**aterno-Infantile, Medicina **I**nterna e **S**pecialistica di **E**ccellenza "G. D'Alessandro"

HCV treatment: state of the art and future challenges

Antonio Craxì

HCV cure rate has evolved substantially over the past 30 years



Interferon Based (1984)	Early DAAs (2011)	1st-Generation DAAs (2014)	Pan-genotypic (2016)
SVR: 50%	SVR: 60%	SVR: 85%	SVR: 99% (including retx)
Applicability: 30%	Applicability: 25%	Applicability: 80%	Applicability: 99%
CURE: 15%	CURE: 15%	CURE: 68%	CURE: 98%

1. Pawlotsky JM, *et al. J Hepatol* 2016; **62**:S87–99;
2. Manns M, *et al. Nat Rev Dis Primers* 2017; **3**:1–19.

8–12-Week Pan-genotypic Regimens Are Recommended for Most Patients*

EASL Guidelines

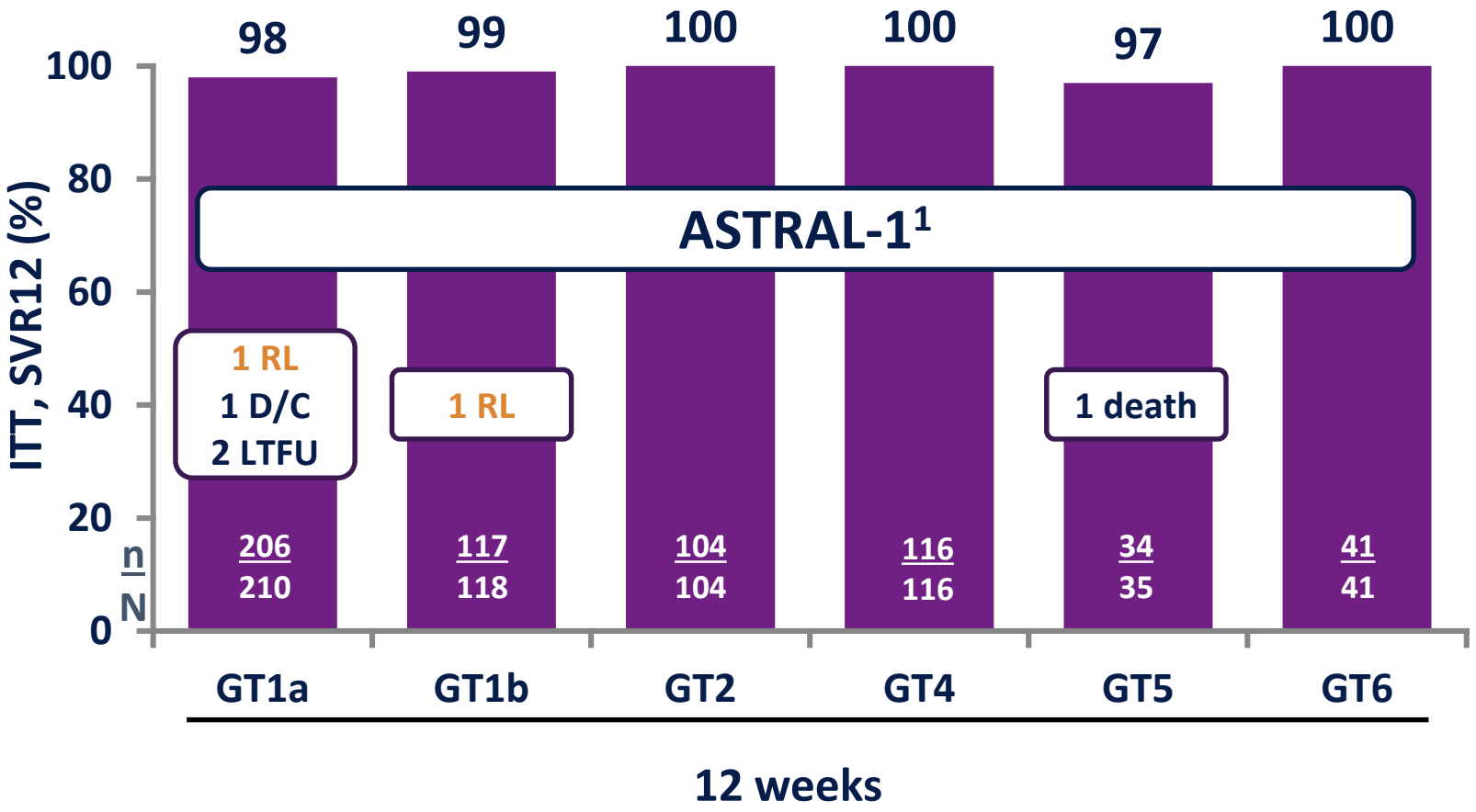
Patients	Prior Treatment Experience	Without Cirrhosis			With Compensated Cirrhosis		
		SOF/VEL	G/P	SOF/VEL/ VOX	SOF/VEL	G/P	SOF/VEL/ VOX
Genotype 1	Treatment naive	12 wk	8 wk	No	12 wk	12 wk	No
	Treatment experienced†	12 wk	8 wk	No	12 wk	12 wk	No
Genotype 2	Treatment naive	12 wk	8 wk	No	12 wk	12 wk	No
	Treatment experienced†	12 wk	8 wk	No	12 wk	12 wk	No
Genotype 3	Treatment naive	12 wk	8 wk	No	No	12 wk	12 wk
	Treatment experienced†	12 wk	12 wk	No	No	16 wk	12 wk
Genotype 4, 5, 6	Treatment naive	12 wk	8 wk	No	12 wk	12 wk	No
	Treatment experienced†	12 wk	8 wk	No	12 wk	12 wk	No

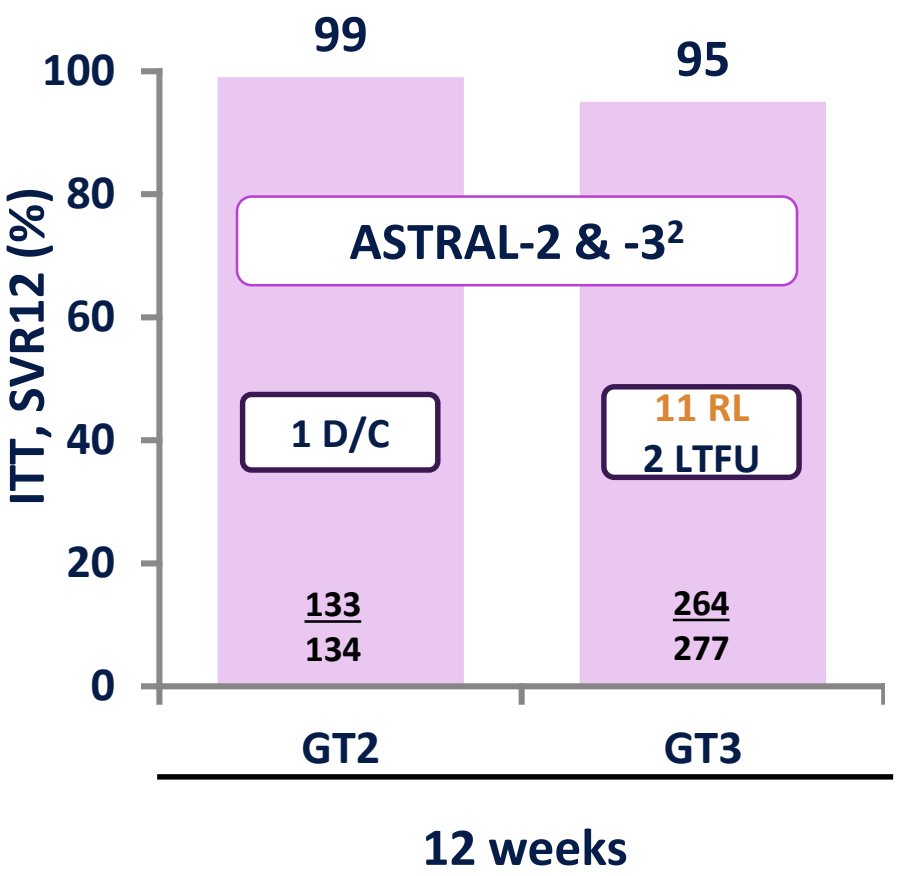
IFN-free, RBV-free, DAA-based regimens must be used (A1)‡

wk, weeks.
* Treatment naive or treatment experienced; † Treatment experienced to pegIFN + RBV ± SOF or SOF + RBV;
‡ In HCV-infected patients ± compensated cirrhosis, including treatment-naïve and treatment-experienced (previously treated with pegIFN + RBV ± SOF or SOF + RBV) patients due to their virological efficacy, ease of use, safety and tolerability.

EASL Recommendations on Treatment of Hepatitis C 2018. *J Hepatol* 2018; **69:**461–511.

ASTRAL-1, -2, -3: SOF/VEL for 12 Weeks in GT1–6 Treatment-Naive and -Experienced* Patients with and without Cirrhosis

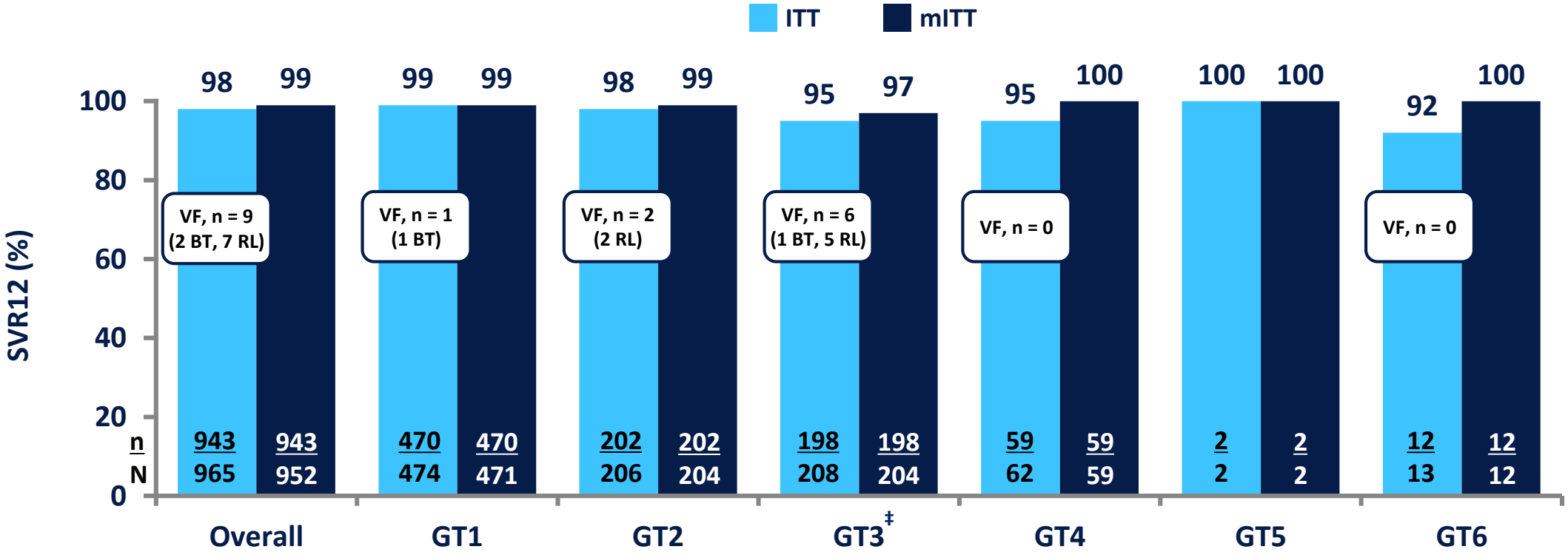




* Patients treated with pegIFN/RBV ± protease inhibitor or IFN ± RBV.
D/C, discontinuation; LTFU, lost to follow-up; RL, relapse.

1. Feld JJ, *et al. N Engl J Med* 2015; **373:**2599–2607;
2. Foster GR, *et al. N Engl J Med* 2015; **373:**2608–2617.

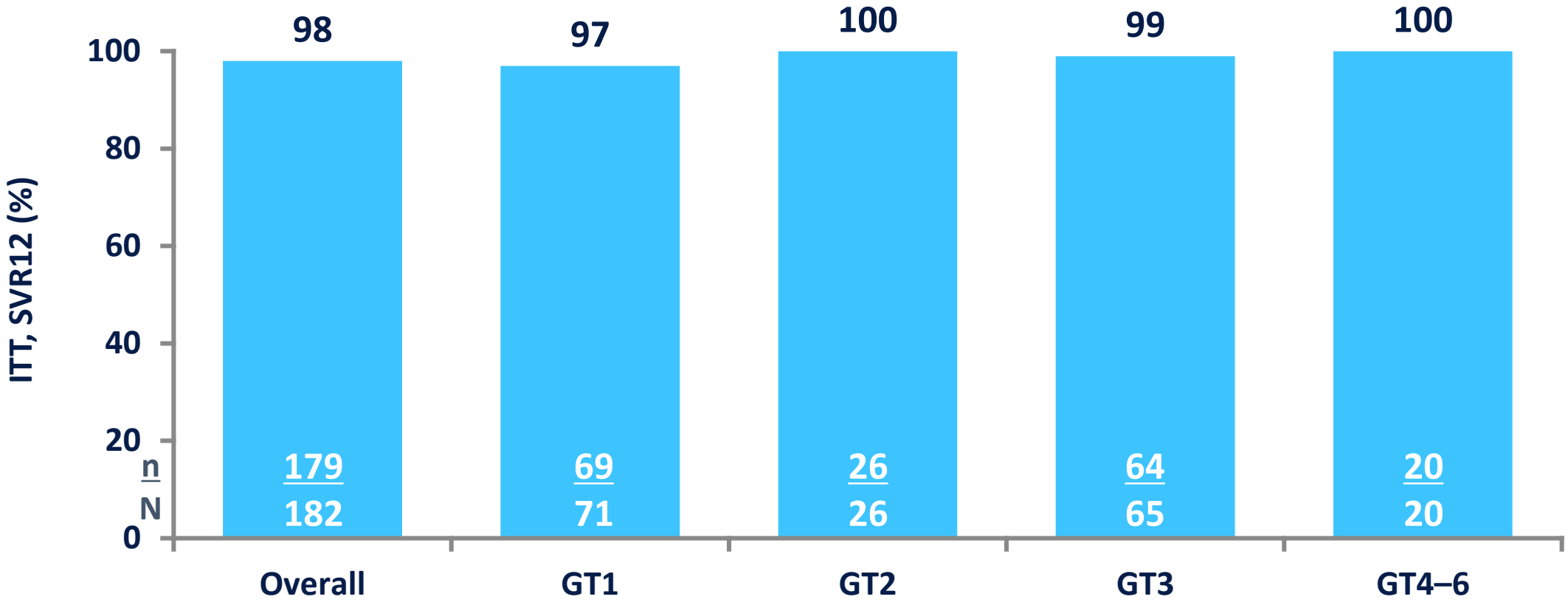
Integrated Efficacy Analysis:* G/P for 8 Weeks in GT1–6 Treatment-Naive and PRS-Experienced† Patients without Cirrhosis



* Pooled SVR12 data from arms of nine phase 2 or 3 clinical trials (EXPEDITION-2; EXPEDITION-4; ENDURANCE 1, 2, 3 and 4; SURVEYOR-I Part 2; SURVEYOR–II Parts 1 and 2; and SURVEYOR-II Part 4 studies);
† Treatment experienced to pegIFN + RBV ± SOF; ‡ All GT3 patients were treatment naive.
BT, breakthrough; RL, relapse; VF, virologic failure.

Puoti M, *et al. J Hepatol* 2018; **69:**293–300.

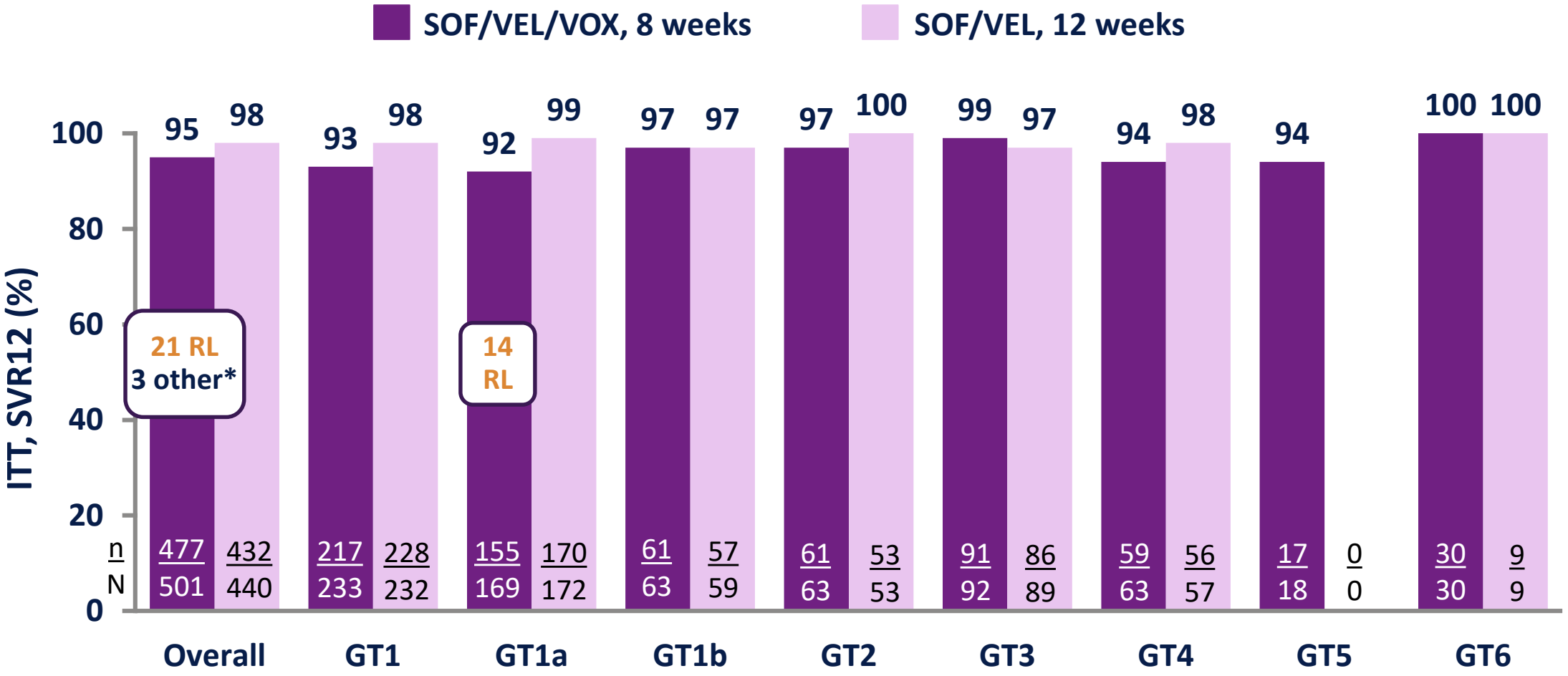
Integrated Efficacy Analysis:* G/P for 12 Weeks in GT1–6 Treatment-Naive Patients with Cirrhosis



* ITT SVR12 data from the pooled resistance analysis of G/P from phase 2 and 3 clinical studies (SURVEYOR-1 and -2; ENDURANCE-1–4; EXPEDITION-1 and -4).

Krishnan P, *et al. J Hepatol* 2017; **66**(Suppl):S500 (poster presentation FRI-205).

POLARIS-2: SOF/VEL/VOX for 8 Weeks in DAA-Naive HCV-Infected Patients with and without Cirrhosis



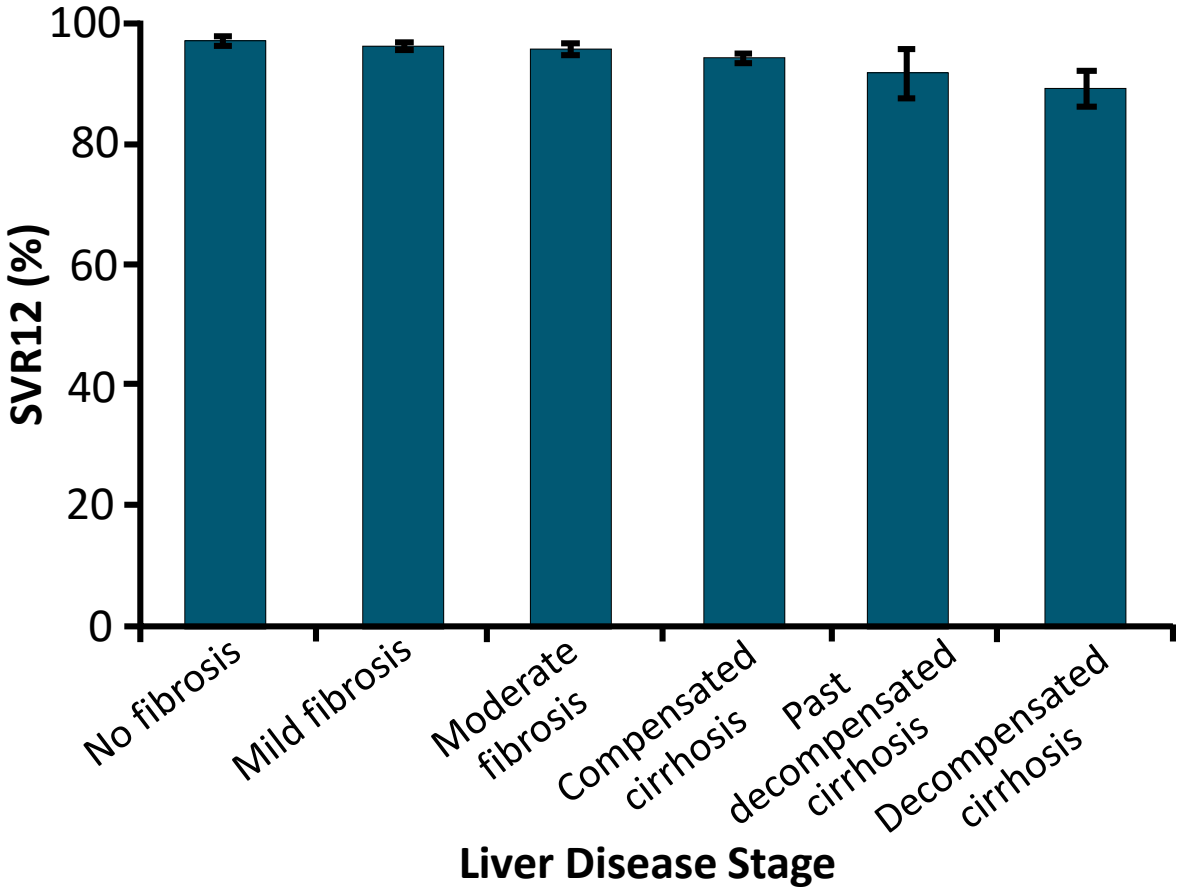
In GT1a patients without cirrhosis, response was influenced by baseline HCV RNA ≥ 800,000 IU/mL, BMI ≥ 30 kg/m^2, Q80K/L/R RAS, IL28B non-CC

* "Other" includes patients with missing data and those that discontinued treatment prior to virologic suppression.

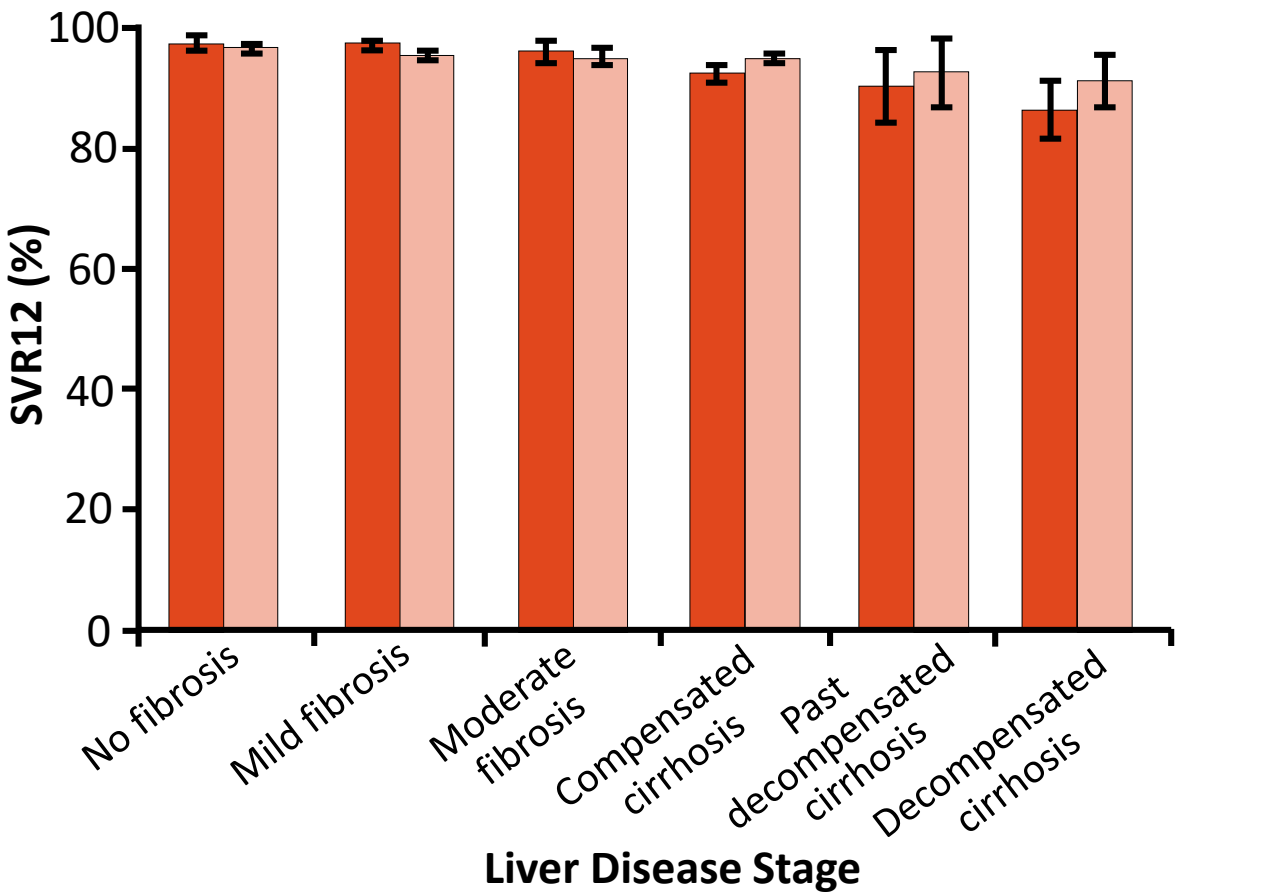
1. Jacobson IM, *et al. Gastroenterology* 2017; **153:**113–122;
2. Vosevi EU Summary of Product Characteristics (accessed March 2018).

English Hepatitis C Registry: SVR12

- SVR12 for **all patients**: 95.59%

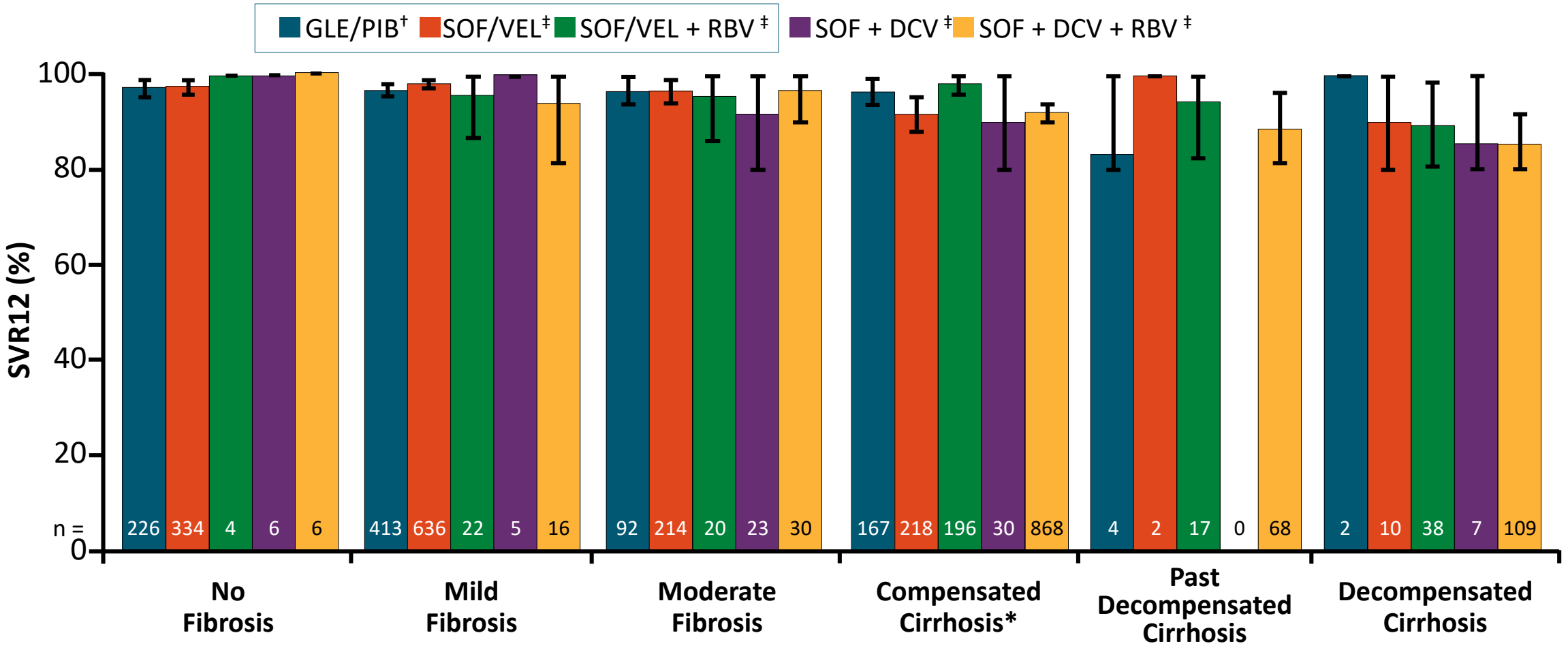


- SVR12 for **GT3 patients**: 95.04%



Drysdale. EASL 2019. Abstr LB-07.

English Hepatitis C Registry: SVR12 in GT3 by Regimen and Severity of Liver Disease



*SVR significantly improved with SOF/VEL + RBV vs SOF/VEL or SOF + DCV + RBV in this subgroup.

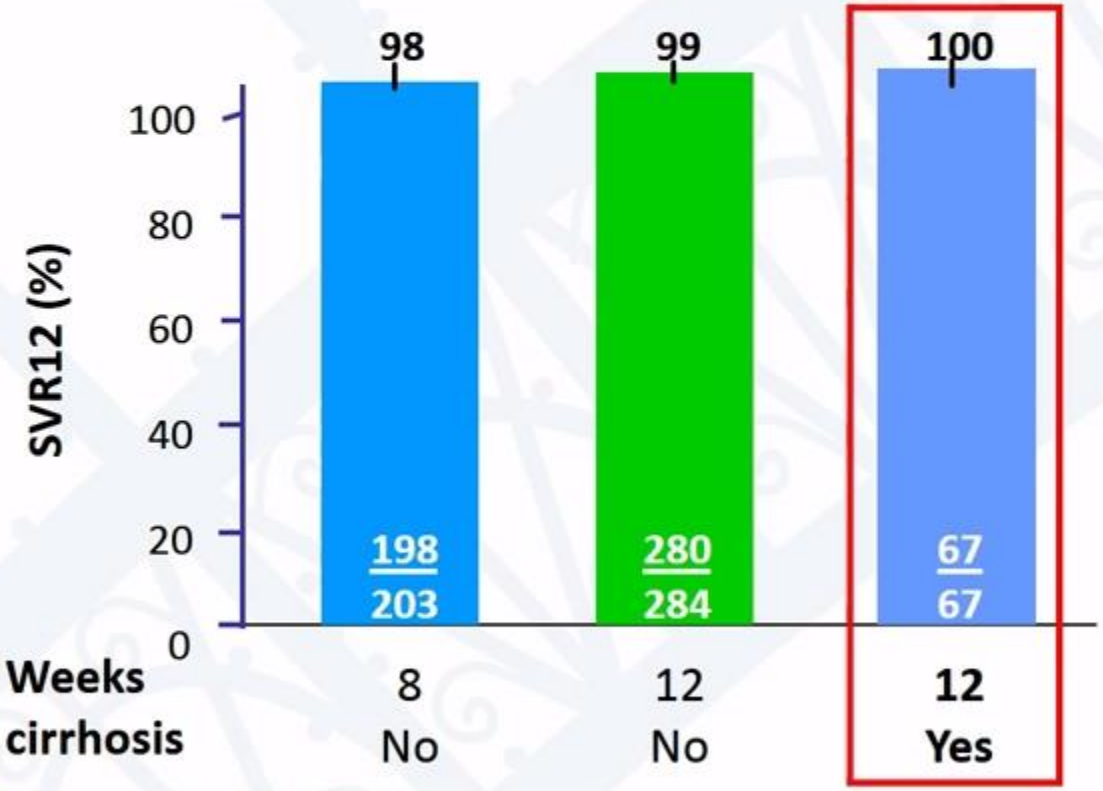
†8 wks if no, mild, or moderate fibrosis; 12 wks if compensated cirrhosis. ‡12 wks if no, mild, or moderate fibrosis.

Drysdale. EASL 2019. Abstr LB-07.

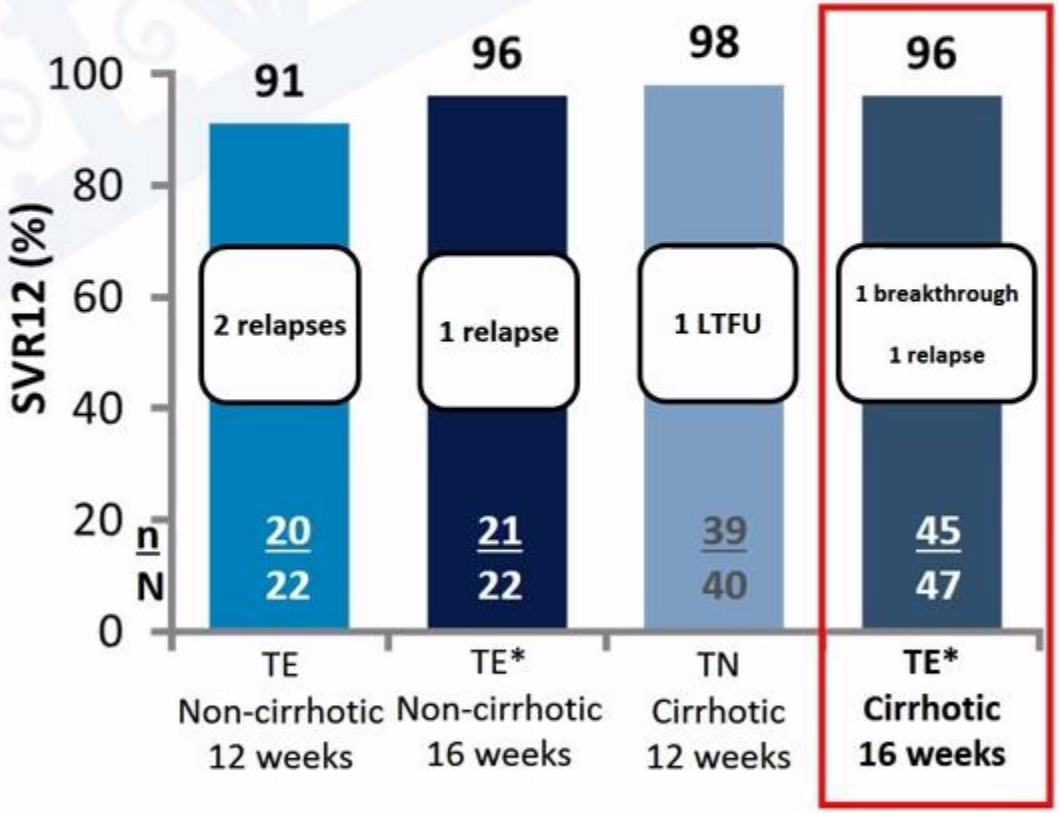
Difficult-to-treat patients: any left?

GLE/PBR for 12 or 16 weeks in genotype 3 patients with compensated cirrhosis

Pooled analysis 7 phase 2/3 trials: Naïve patients



SURVEYOR-II, Part 3



*Includes SOF-experienced patients

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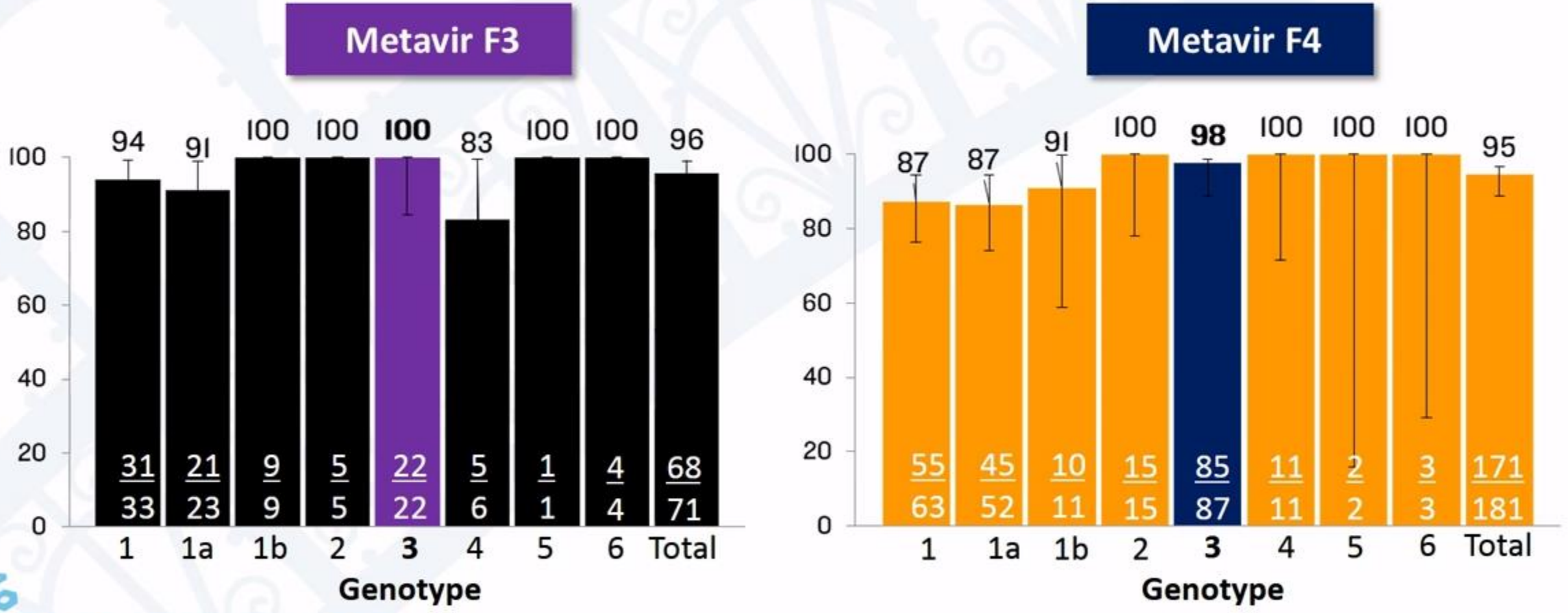
Flamm S, et al. AASLD 2017, Abs. 62

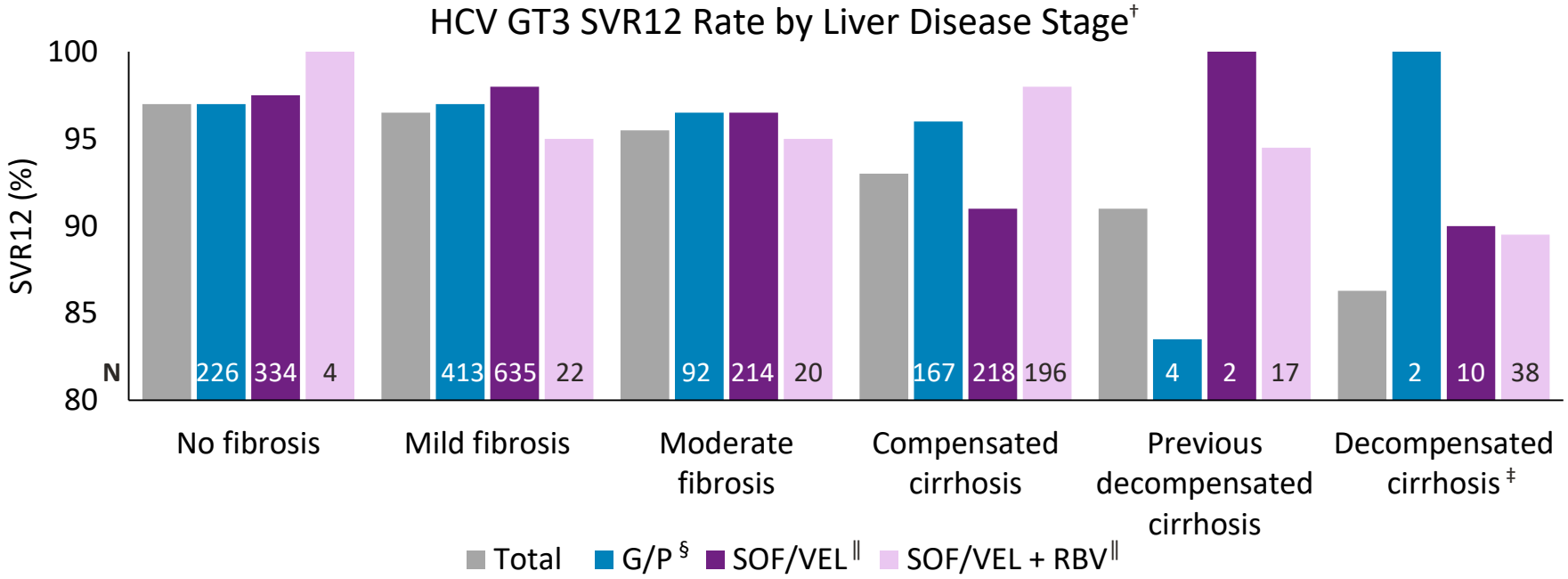
Wyles DL, et al. Hepatology 2017 Sep 19

POLARIS-2, and 3 (integrated efficacy analysis): SOF/VEL/VOX for 8 weeks in DAA-naïve patients



Effectiveness of Therapy in 16,756 DAA Treated People in England: High Response Rates in GT3 HCV Infection Regardless of Degree of Fibrosis, But RBV Improves Response in Cirrhosis

Meta-analysis of the England Hepatitis C Treatment Registry to determine the effects of liver disease stage on patient outcomes when using different DAA regimens to treat HCV GT3 (N=16,756*)



Overall PP SVR12 rate was 96% in all GTs

In patients with HCV GT3 SVR12 rate was 95%

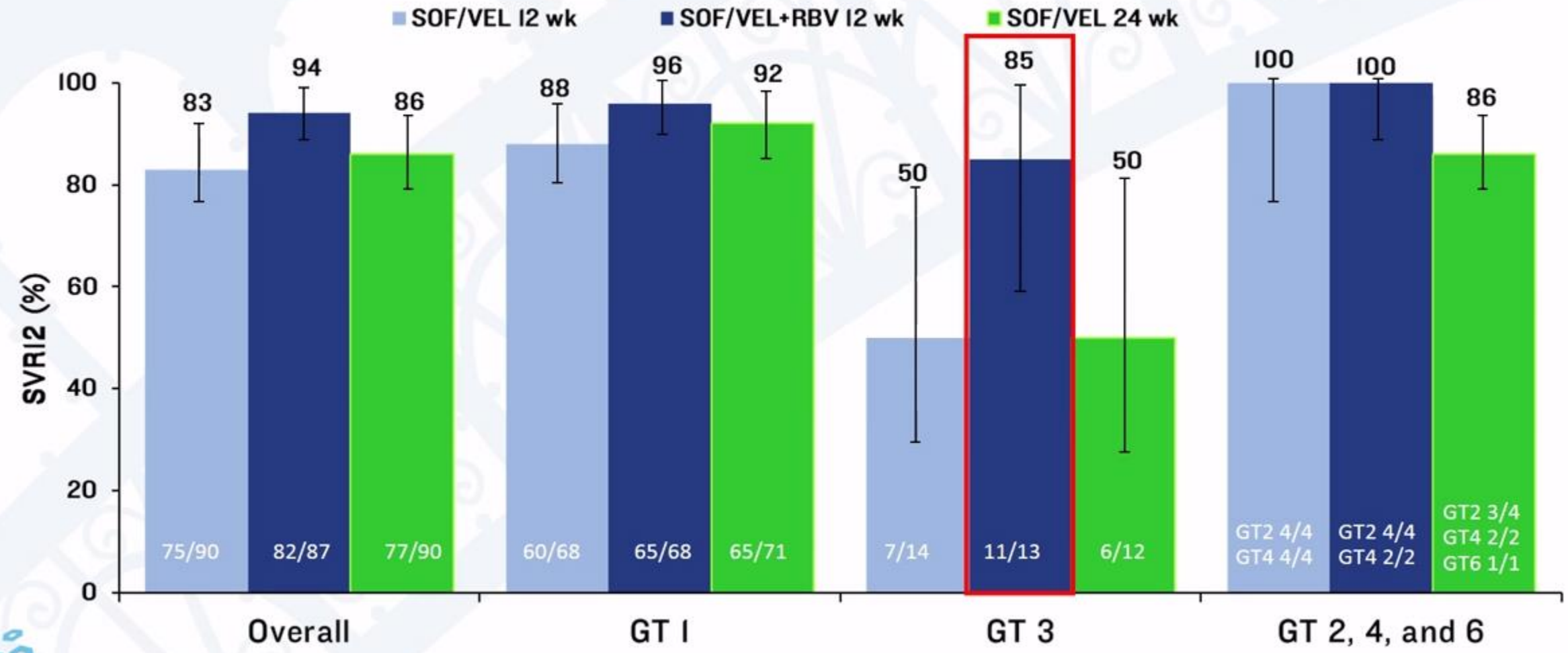
High SVR rates with 12 weeks of G/P were achieved in patients with GT3 and compensated cirrhosis

8 weeks of G/P and 12 weeks of SOF/VEL in patients with HCV GT3 and moderate fibrosis have similar efficacy. Addition of RBV to SOF/VEL significantly increases efficacy in patients with HCV GT3 and compensated cirrhosis

*Patients who received a valid treatment; †Graphical data has been estimated from the provided source presentation but no exact numbers are available; ‡ G/P is contraindicated in patients with severe hepatic impairment (Child-Pugh C); § Treatment durations with G/P were 8 weeks in patients with no fibrosis, mild fibrosis or moderate fibrosis and 12 weeks in patients with compensated cirrhosis, past decompensated cirrhosis or decompensated cirrhosis; ‖ Treatment durations were 12 weeks with SOF/VEL ± RBV for all stages of liver disease.

Drysdale K, *et al.* EASL 2019; oral presentation (LB-07).

ASTRAL-4: SOF/VEL in patients with decompensated cirrhosis



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Curry MP, et al. N Engl J Med 2015;373:2618–28

Genotype 3 with cirrhosis

EASL 2018 recommandations

Patients	Glecaprevir Pibrentasvir	Sofosbuvir Velpatasvir Voxilaprevir	Sofosbuvir Velpatasvir RBV
Genotype 3 Naïve Compensated cirrhosis	12 weeks	12 weeks	No
Genotype 3 Treatment-experienced Compensated cirrhosis	16 weeks	12 weeks	No
Genotype 3 Decompensated cirrhosis	No	No	12 weeks

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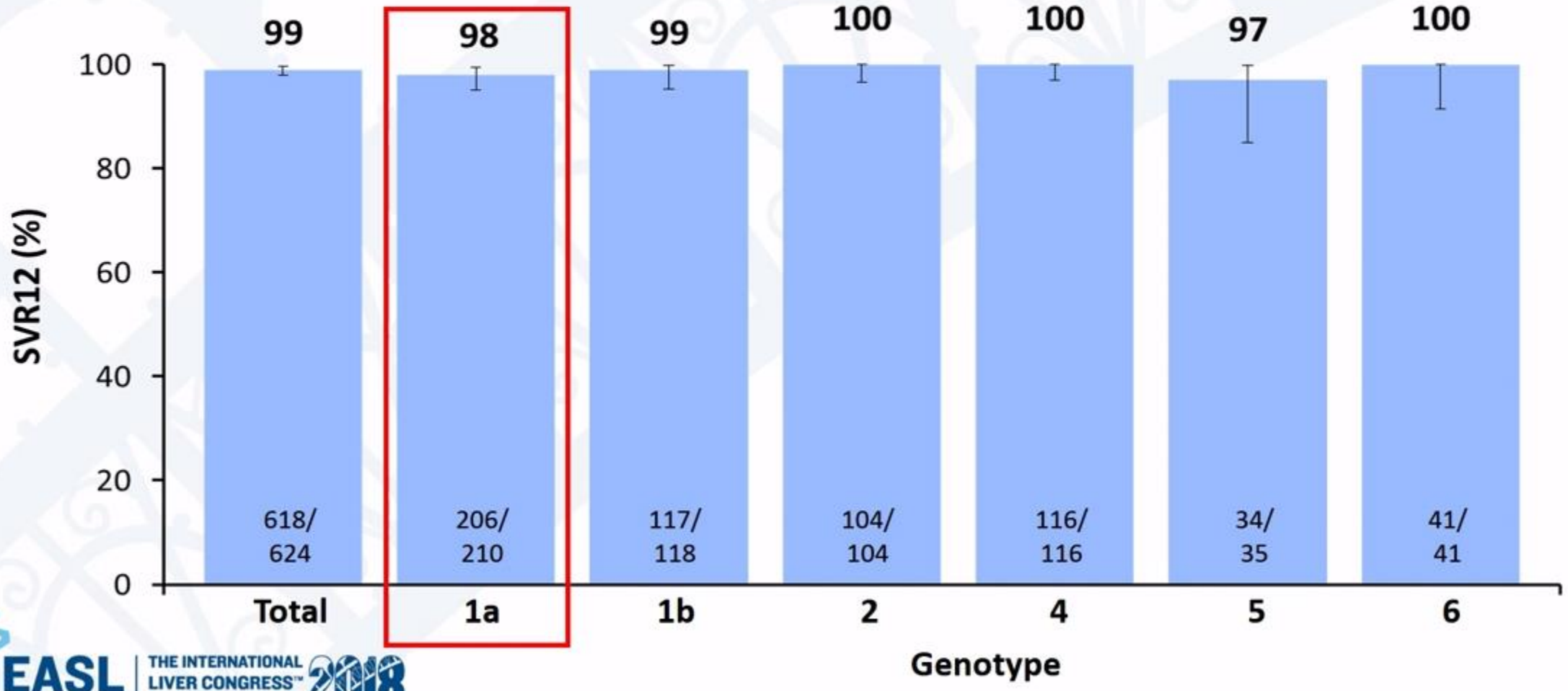
www.hep-druginteractions.org
Smartphone App HEP iChart

Genotype 1a P/R experienced with cirrhosis

ASTRAL-1: SOF/VEL FOR 12 weeks. No impact of genotype

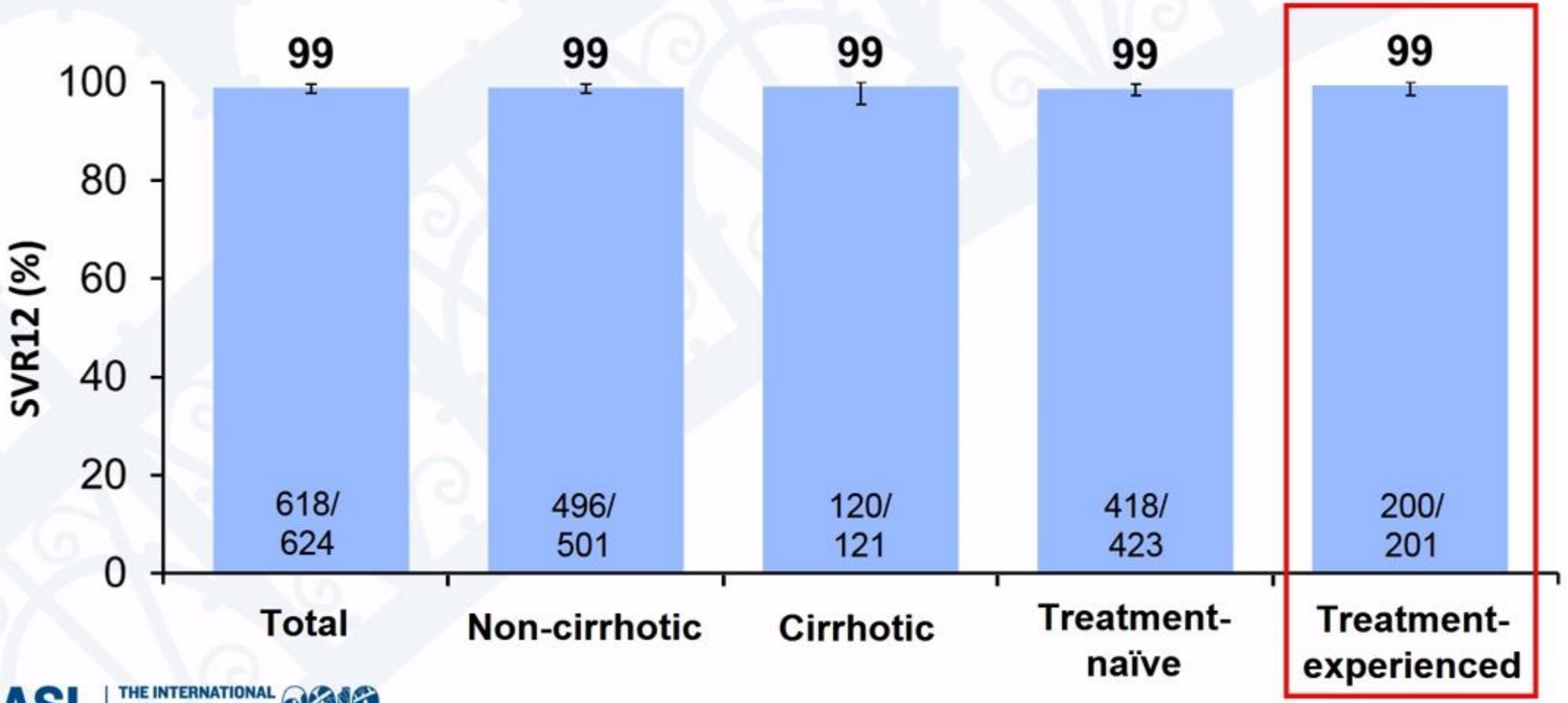


EASL The Home of Hepatology | THE INTERNATIONAL LIVER CONGRESS™ 2018

Feld JJ, et al. N Engl J Med 2015;373:2599–607

Genotype 1a P/R experienced with cirrhosis

ASTRAL-1: SOF/VEL FOR 12 weeks. No impact of cirrhosis and patient status



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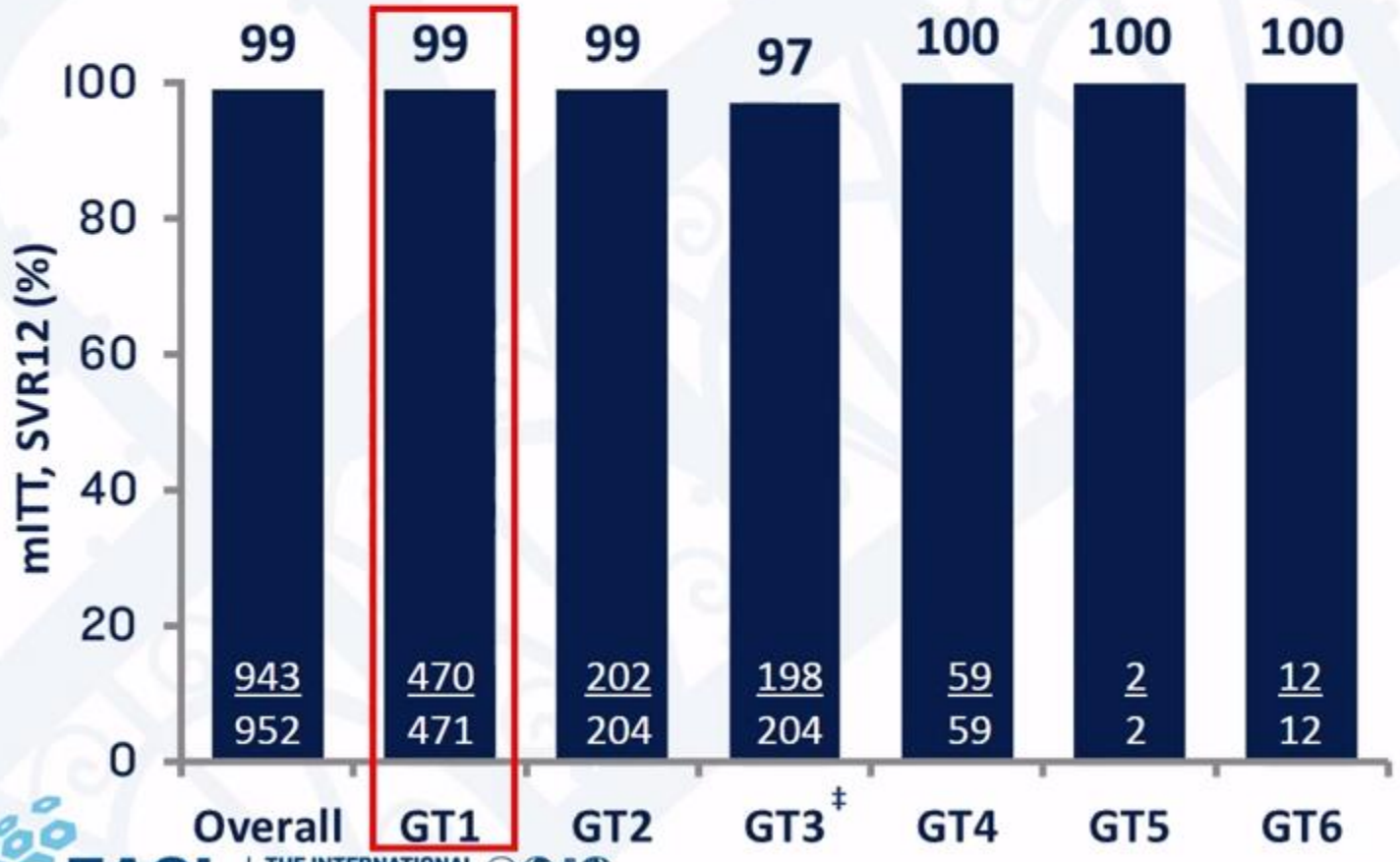
Feld JJ, et al. N Engl J Med 2015;373:2599–607

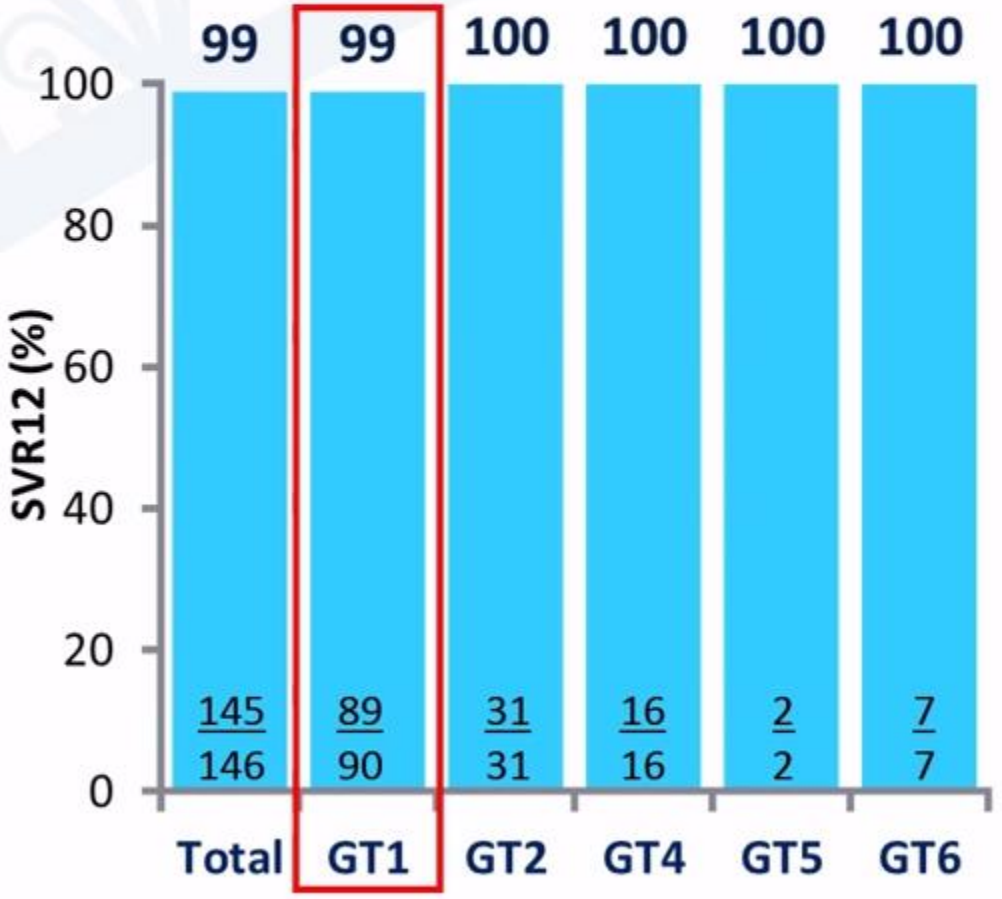
Genotype 1a P/R experienced with cirrhosis

Glecaprevir/Pibrentasvir for 8 or 12 weeks

Integrated analysis: G/P for 8 Weeks in treatment-naive and -experienced* patients without cirrhosis



EXPEDITION-I: G/P for 12 weeks in naïve or treatment-experienced patients with compensated cirrhosis



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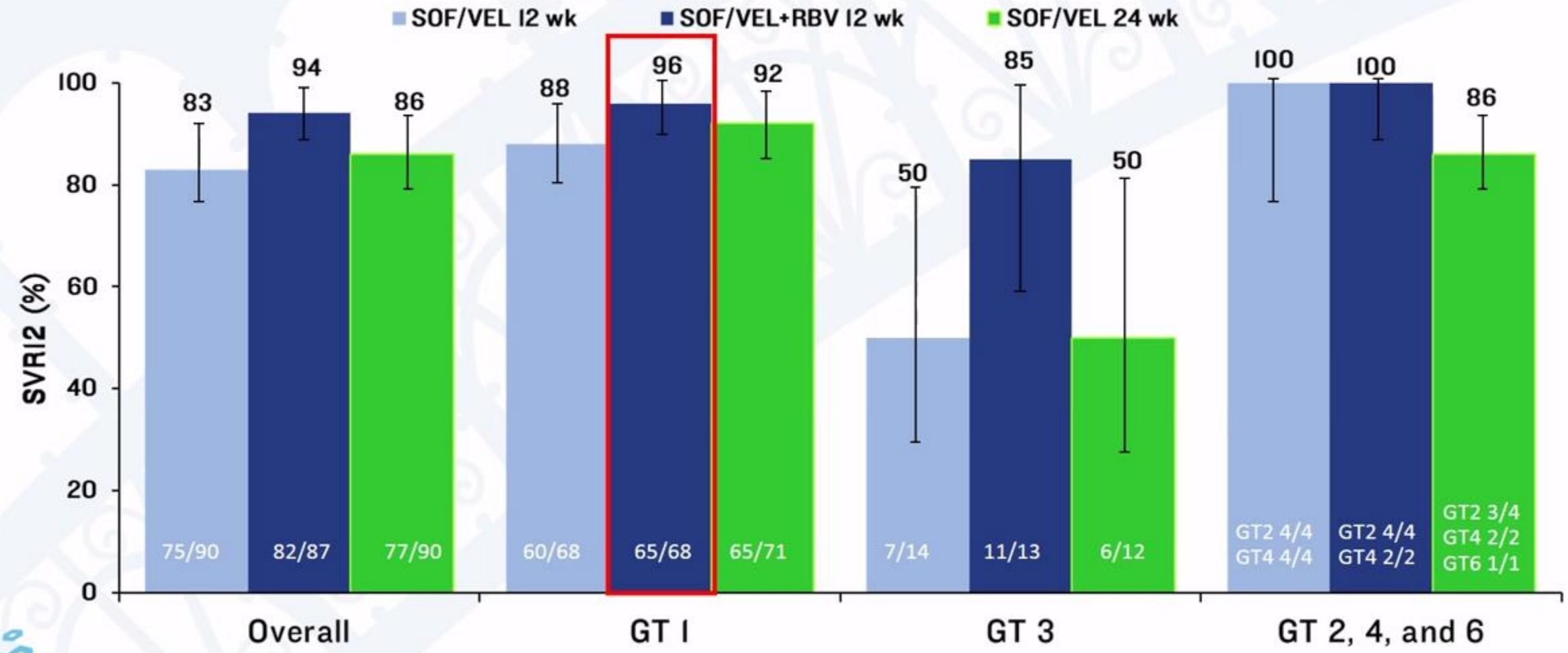
* Includes patients with prior SOF use (8-week G/P, n = 7)
‡ All GT3 patients were treatment naive

Puoti M, et al. J Hepatol 2018 Mar 15)

Forns X, et al. Lancet Infect Dis 2017;17:1062-8

Genotype 1a P/R experienced with cirrhosis

ASTRAL-4: SOF/VEL in patients with decompensated cirrhosis



EASL The Home of Hepatology | THE INTERNATIONAL LIVER CONGRESS™ 2018

Curry MP, et al. N Engl J Med 2015;373:2618–28

Genotype 1a P/R experienced with cirrhosis

EASL 2018 recommandations

Patients	Glecaprevir Pibrentasvir	Sofosbuvir Velpatasvir
Genotype 1a PR treatment-experienced	8 weeks (no cirrhosis) 12 weeks (cirrhosis)	12 weeks
Genotype 1a HCV RNA >800.000 IU/mL	8 weeks (no cirrhosis) 12 weeks (cirrhosis)	12 weeks
Genotype 1 Decompensated cirrhosis	No	12 weeks + RBV*

*SOF/LDV + RBV 12 weeks if SOF/VEL not available

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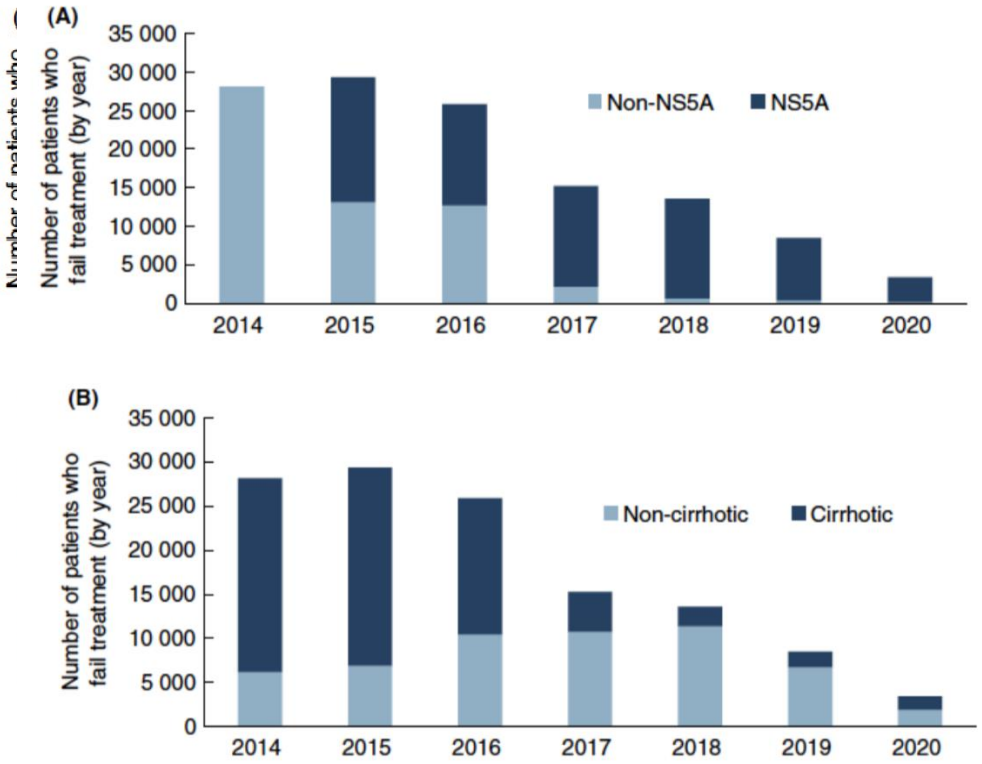
Difficult-to-treat patients: any left?

When next-generation NS5A inhibitors are available, the group of difficult-to-treat patients is limited:

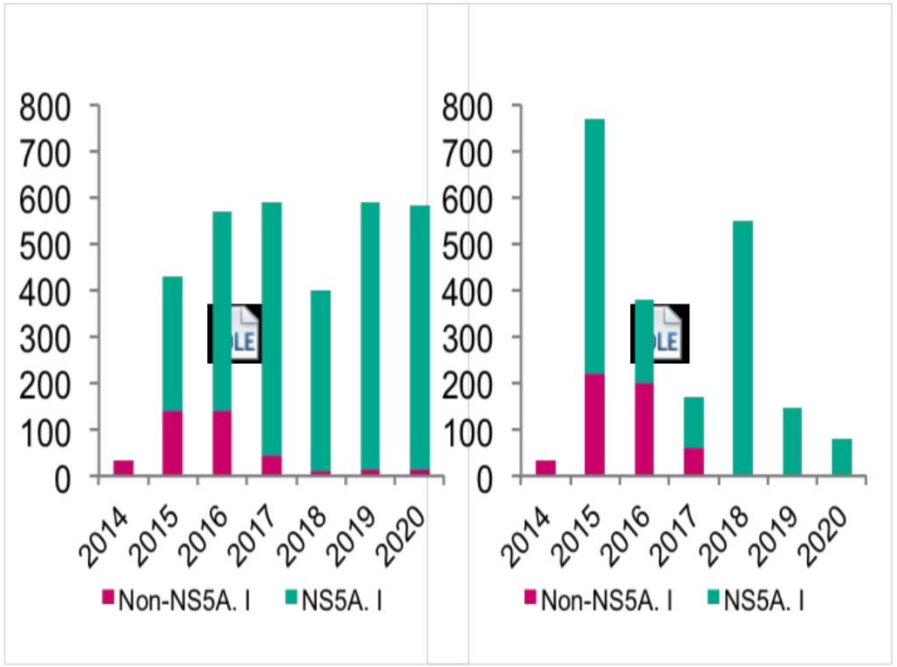
- Genotype 3 patients with compensated cirrhosis are easy-to-treat with SOF/VEL/VOX for 12 weeks or G/P for 12 or 16 weeks
- Genotype 1a PR treatment-experienced patients, or genotype 1a patients with HCV RNA higher than 800.000 IU/mL are easy-to-treat with SOF/VEL for 12 weeks or G/P for 8 to 12 weeks
- Genotype 1 patients with Child-Pugh B cirrhosis are easy-to-treat with SOF/VEL + RBV for 12 weeks
- However, genotype 3 patients with Child-Pugh B decompensated cirrhosis and all patients with Child-Pugh C cirrhosis remain difficult-to-treat

Do RASs still have an impact on efficacy in the pan-genotypic era?

Framework of DAAs failure in 2020



Number of patients who failed DAAs regimen with or without NS5A.I in France, between 2014 and 2020



124,000 patients will be DAA failure in USA
47,000 patients will be DAAs failure in 5 European country.
Since 2015, near all patients will be NS5A failure

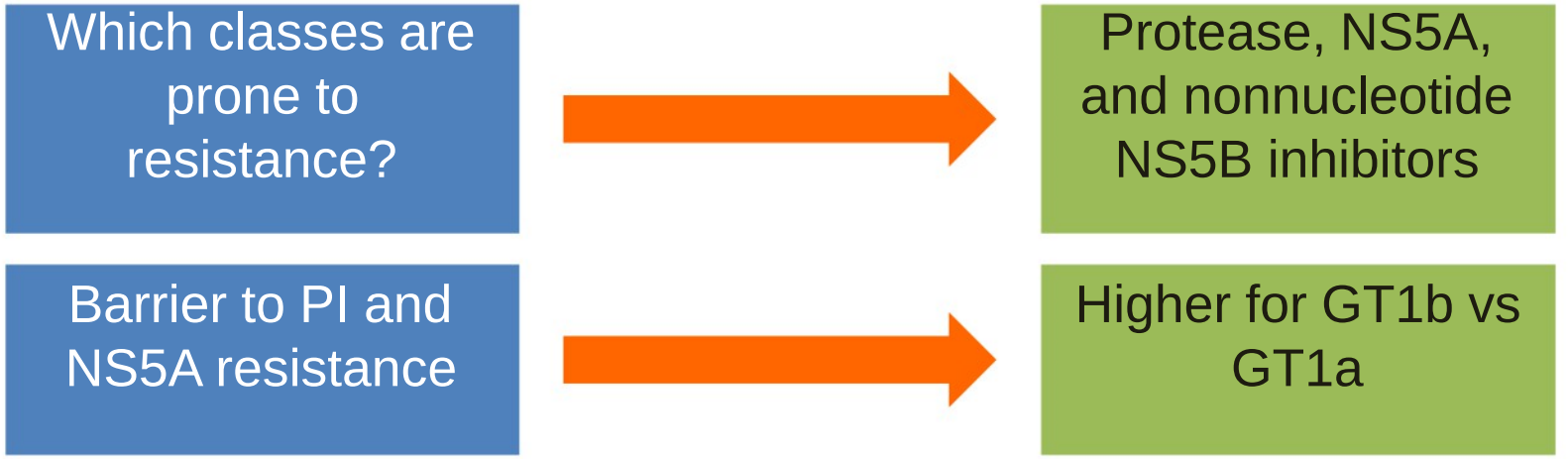
Chhatwal J et al. Aliment Pharmacol Ther 2018; 47: 1023-1031
Chhatwal J et al., EASL 2017 abstr. FRI-233

Reasons for DAAs failure

- **Treatment regimen**
  - Specific DAAs (intrinsic barrier for specific HCV strains)
  - Duration of treatment , adherence to treatment
  - Ribavirin
- **Cirrhosis**
  - Hepatic sanctuaries with low drug exposure due to distorted liver architecture and portal shunting of drug-rich blood
- Host innate immunity
  - IFN-lambda-4/IL-28B
- **Resistance associated substitutions**
  - Burden of liver infection (% hepatocytes infected estimated by HCV RNA level)
  - Specific RASs present and their impact on selected DAAs
  - Proportion of hepatocytes infected with HCV with RASs (estimated by % of the circulating population)

Courtesy from Mark Sulkoswsi

Resistance Considerations



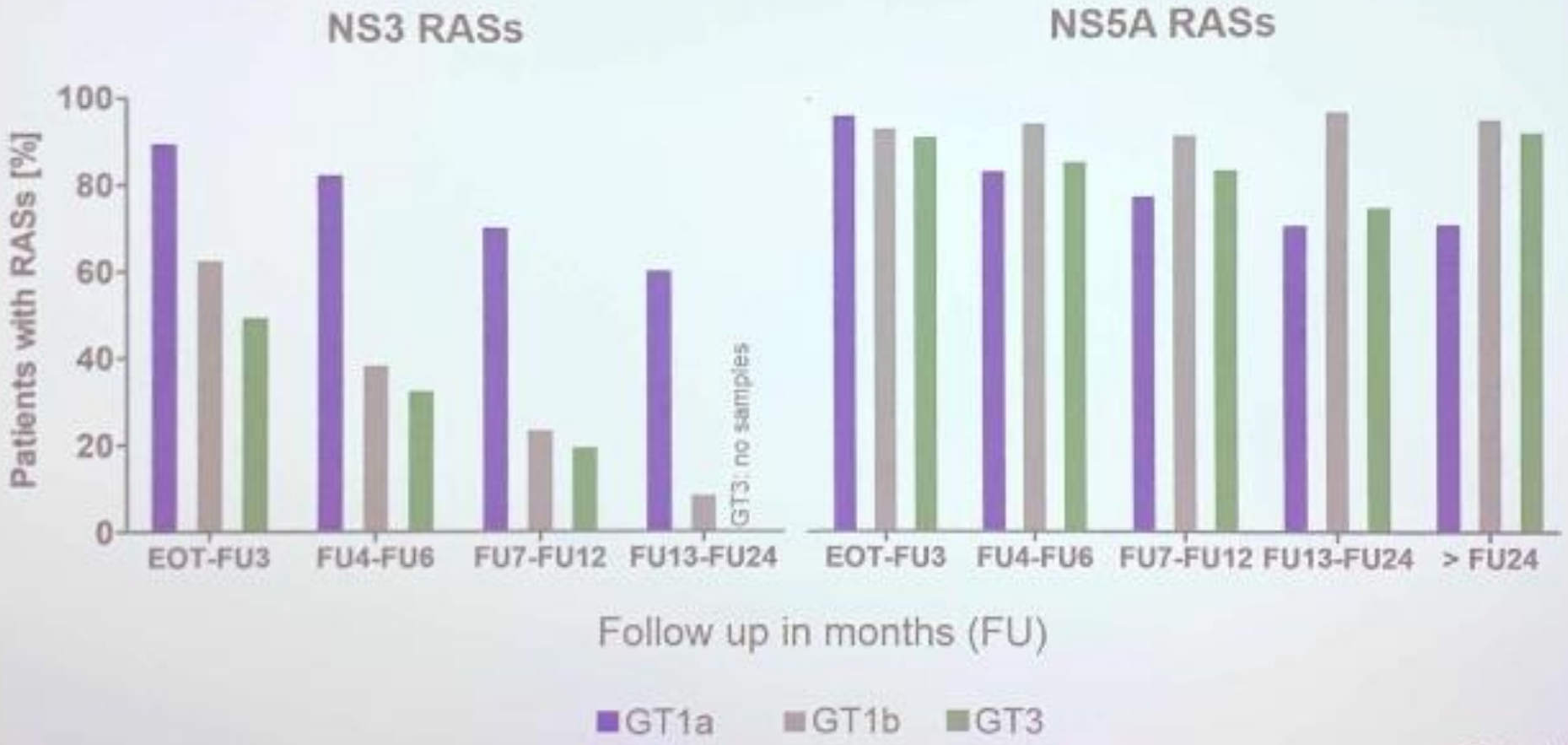
- **Most patients with failure of current DAAs have emergent resistance-associated substitutions (RASs)**
  - NS5A RASs persist much longer than PI RASs
- 15% of patients have baseline NS5A RASs with variable effects on GT1a response
- Second-generation drugs designed to cover RASs

Importance of resistance

Presence and long term kinetics of RASs

GT1/GT3 cohort (n=570 DAA failures, sequential samples of n=166 patients)

documented sampling time after end of treatment (EOT), mean follow-up (FU): 8.8 months (0.2 – 56.0)



Dietz et al., PS179, EASL 2019

Retreatment of DAA failures

- Retreatment strategy depends on initial regimen

Recommendations	Grade of evidence	Grade of recommendation
After failure of PEG-IFNα + RBV, SOF + PEG-IFNα/RBV or SOF + RBV • Retreat according to recommendations for TE patients, by HCV genotype	A	1
HCV resistance testing after failure of any DAA-based regimen (excluding regimens with SOF as the only DAA) is a useful guide to retreatment	B	2
After failure of DAA (PI and/or NS5A inhibitor)-containing regimen		
• First-line retreatment		
– SOF/VEL/VOX for 12 weeks (without cirrhosis/with compensated cirrhosis)	A	1
– SOF/VEL + RBV* for 24 weeks (decompensated cirrhosis)	B	2
• Patients with predictors of poor response, SOF + GLE/PIB for 12 weeks: – Advanced liver disease – Multiple courses of DAA-based treatment – Complex NS5A RAS profile	B	2
• Very difficult-to-cure patients:† SOF/VEL/VOX + RBV or SOF + GLE/PIB + RBV for 12 weeks or for 16 or 24 weeks	C	2

*Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or ≥75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance;
†Patients with NS5A RASs who failed twice to achieve SVR after a combination regimen including a PI and/or an NS5A inhibitor
EASL CPG HCV. J Hepatol 2018;69:461–511.

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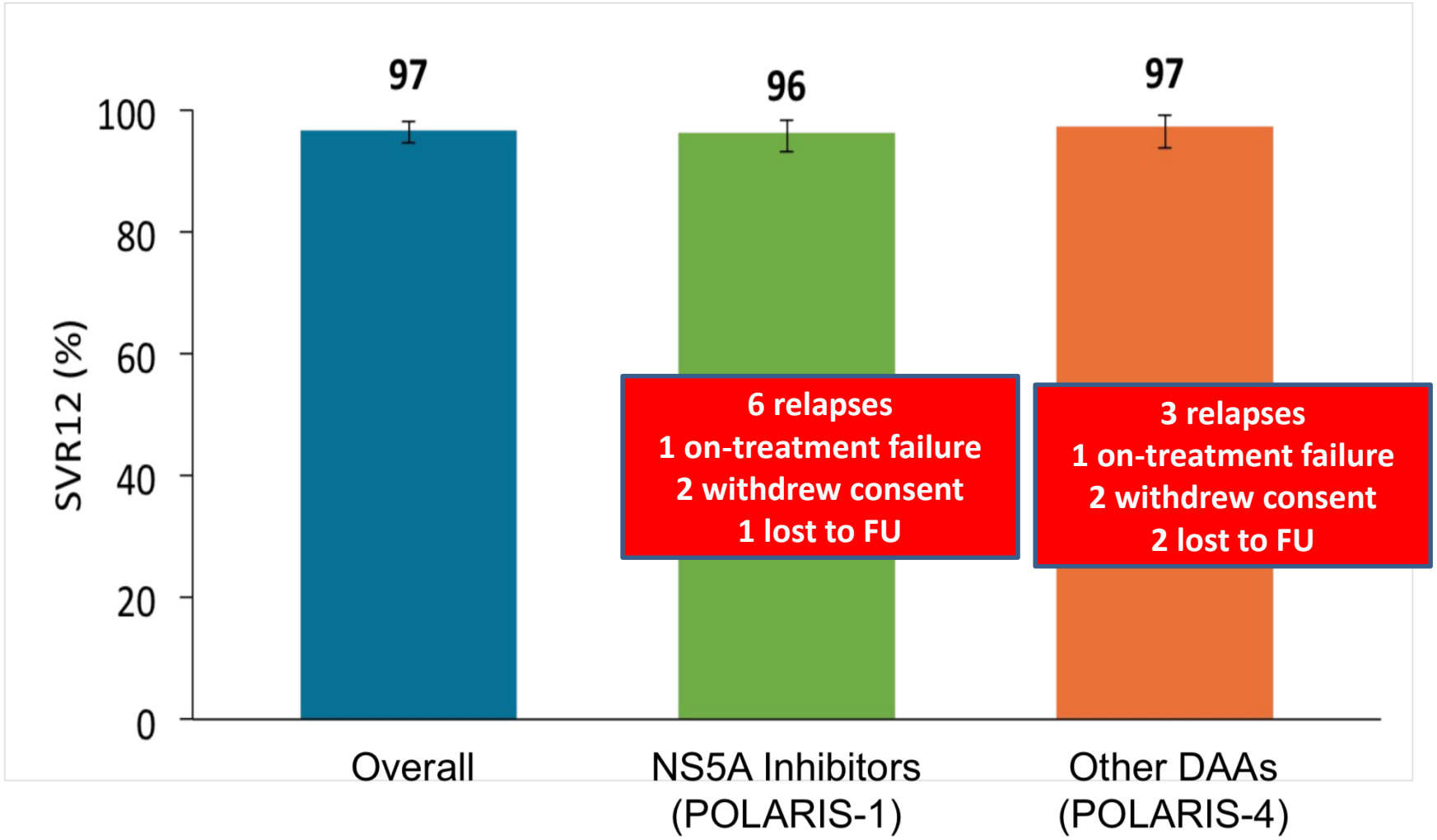
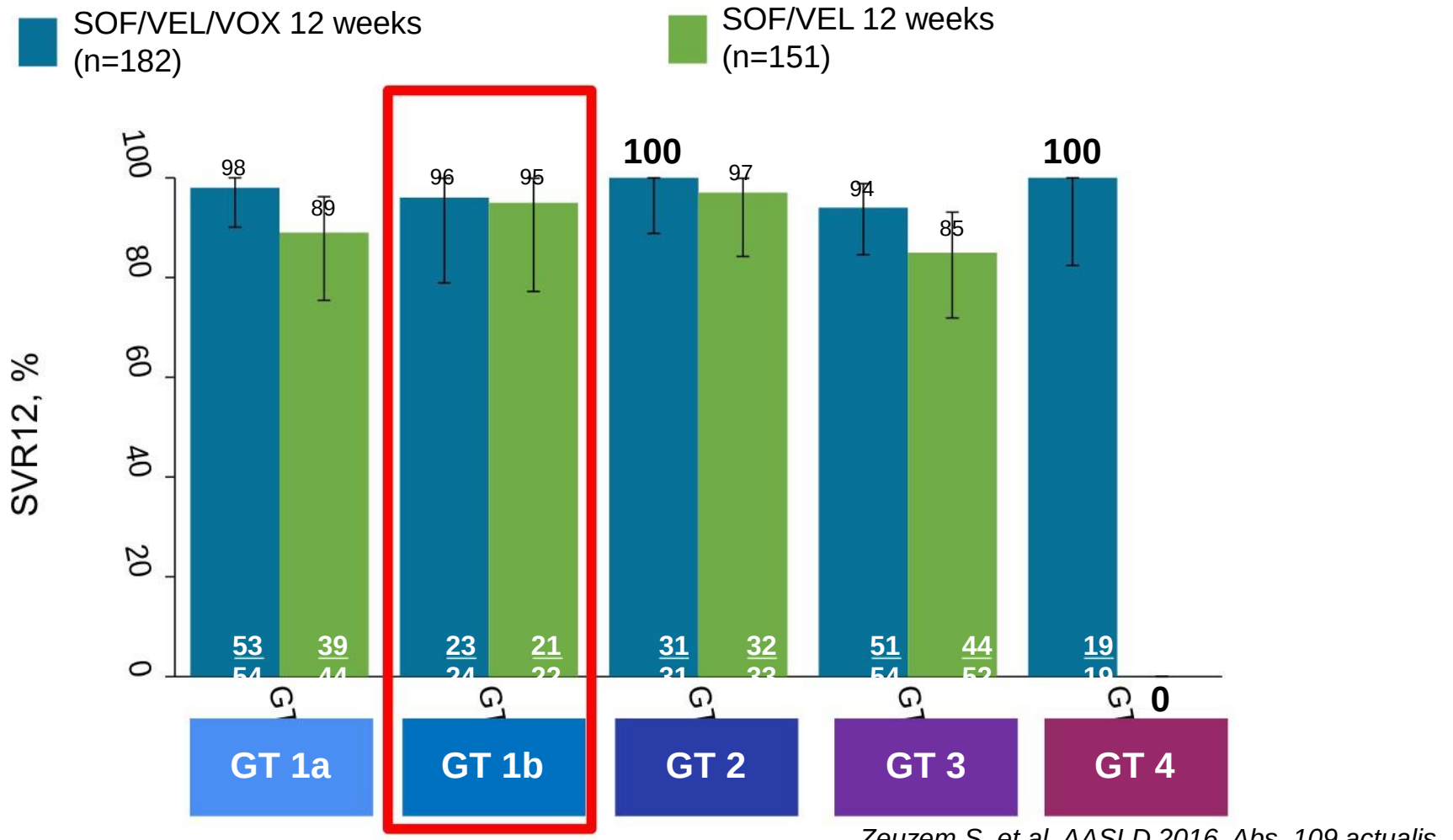
SOF/VEL/VOX 12 weeks in DAA-experienced Patients



Bourliere M, ….,Zeuzem S et al. NEJM 2017; 376: 2134-214

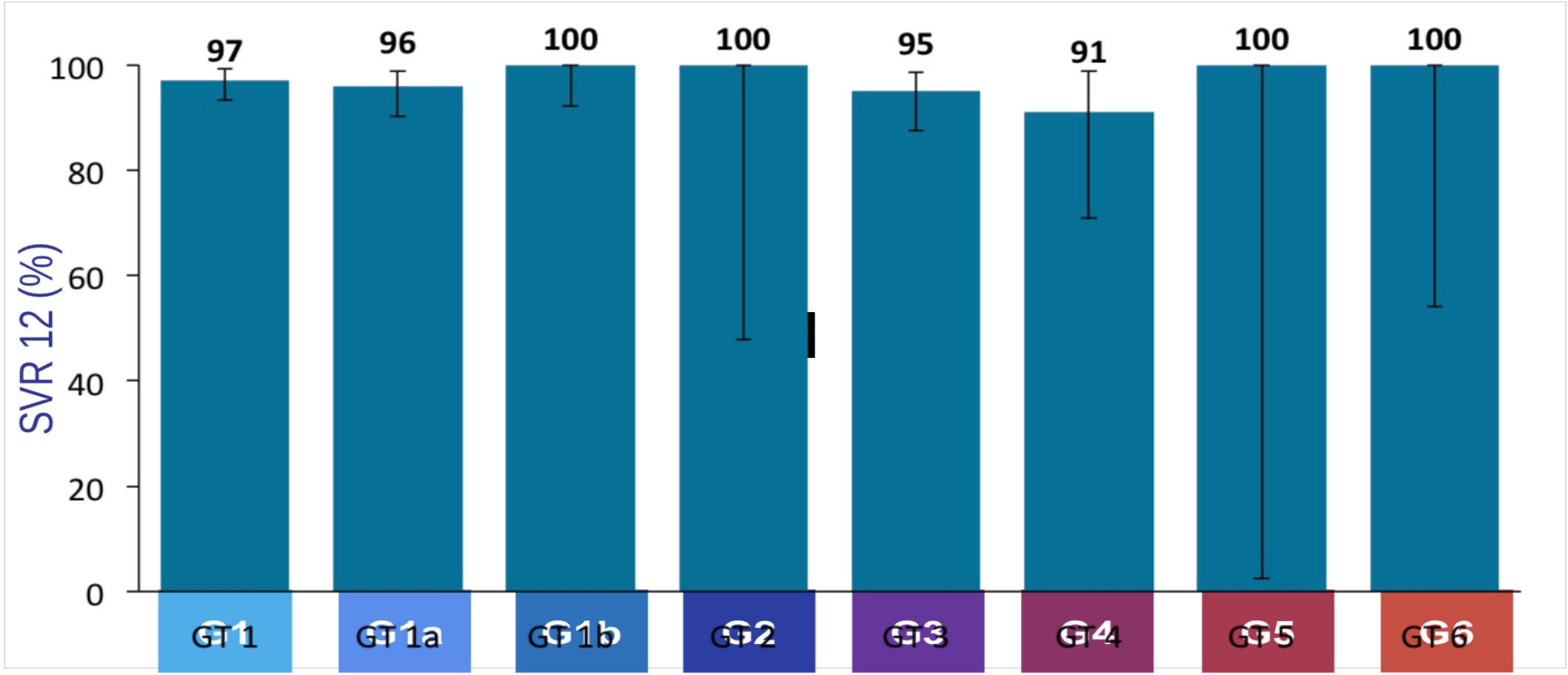
Sofosbuvir/velpatasvir/voxilaprevir versus sofosbuvir/velpatasvir in G1-6 patients who failed DAAs regimen without NS5A.I



Zeuzem S, et al. AASLD 2016, Abs. 109 actualis

Bourliere M,...,Zeuzem S et al. NEJM 2017; 376: 2134-214

sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in patients who failed DAAs regimen with NS5A.I



➔ **6 patients relapse (1 G1a, 4 G3 and 1 G4) all F4**

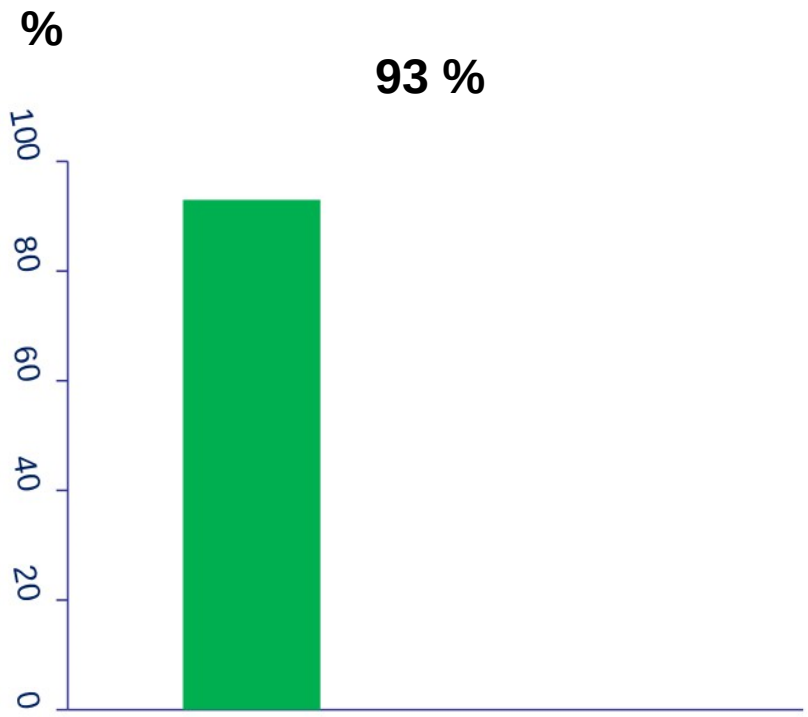
Bourliere M et al. NEJM 2017; 376: 2134-2146

SOF/VEL/VOX in patients who failed GLE/PIB

- 14 patients who failed Glecaprevir/pibrentasvir regimen were retreated with SOF/VEL/VOX 12 weeks

Patients charateristics

	n = 14
Cirrhosis	**7 (50 %)**
Genotype 1a	**5 (36 %)**
Cirrhosis	2/5
Relapsers	5/5
Genotype 3	**9 (64 %)**
Cirrhosis	5/9
Relapsers	7/9
Breakthrough	2/9
RAS at baseline	**12 (86 %)**
NS5A	5 (36 %)
NS3	1 (7 %)
NS5A +NS3	6 (43 %)
None	2 (14 %)

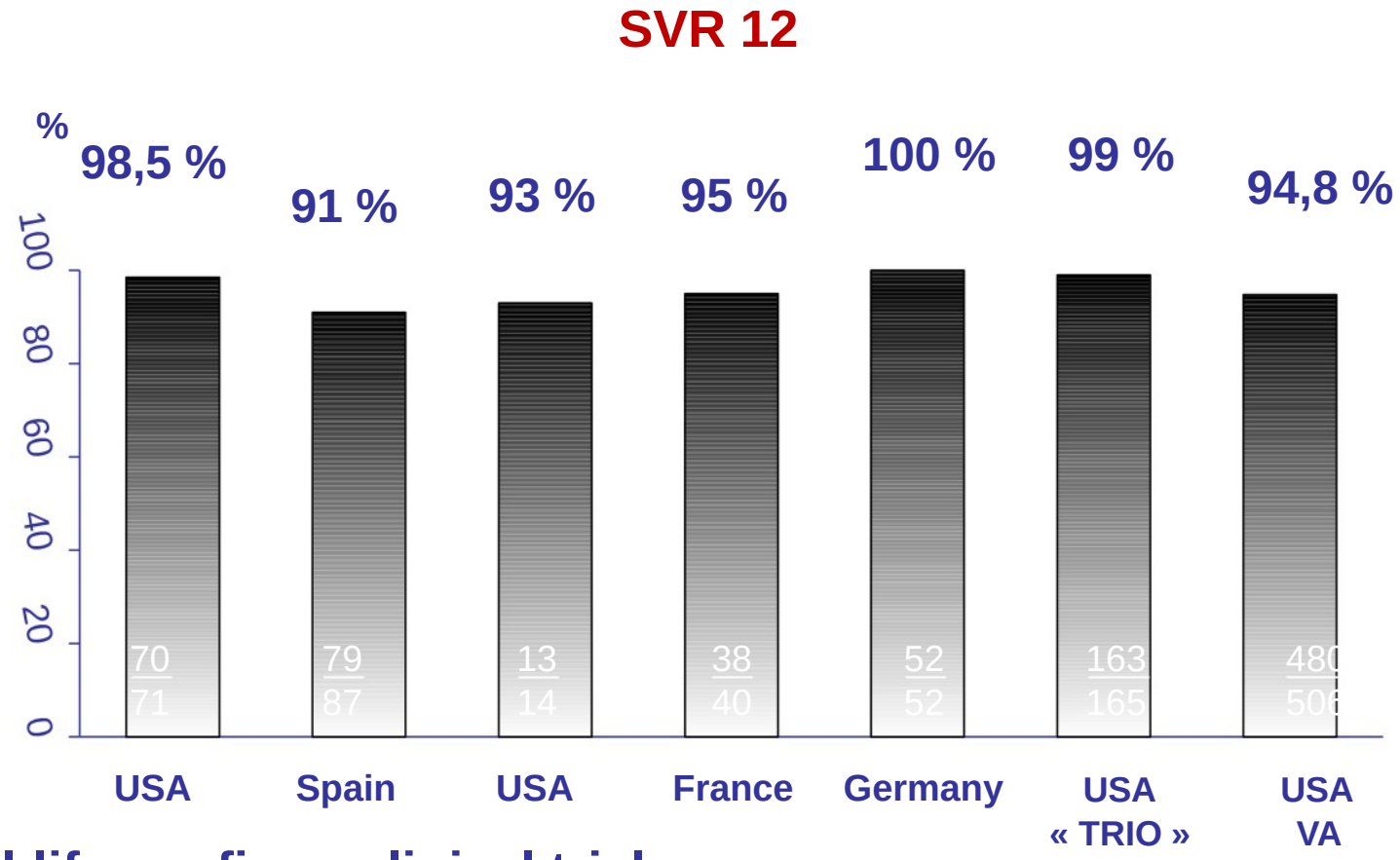


1 woman HCV GT3 without cirrhosis and initial RAS A30K relapse at 4 weeks

- **SOF/VEL/VOX achieve high SVR in G/P failure**

Pearlman B et al., AASLD 2018, Abs. 607

SOF/VEL/VOX in DAAs failures « real-life data »

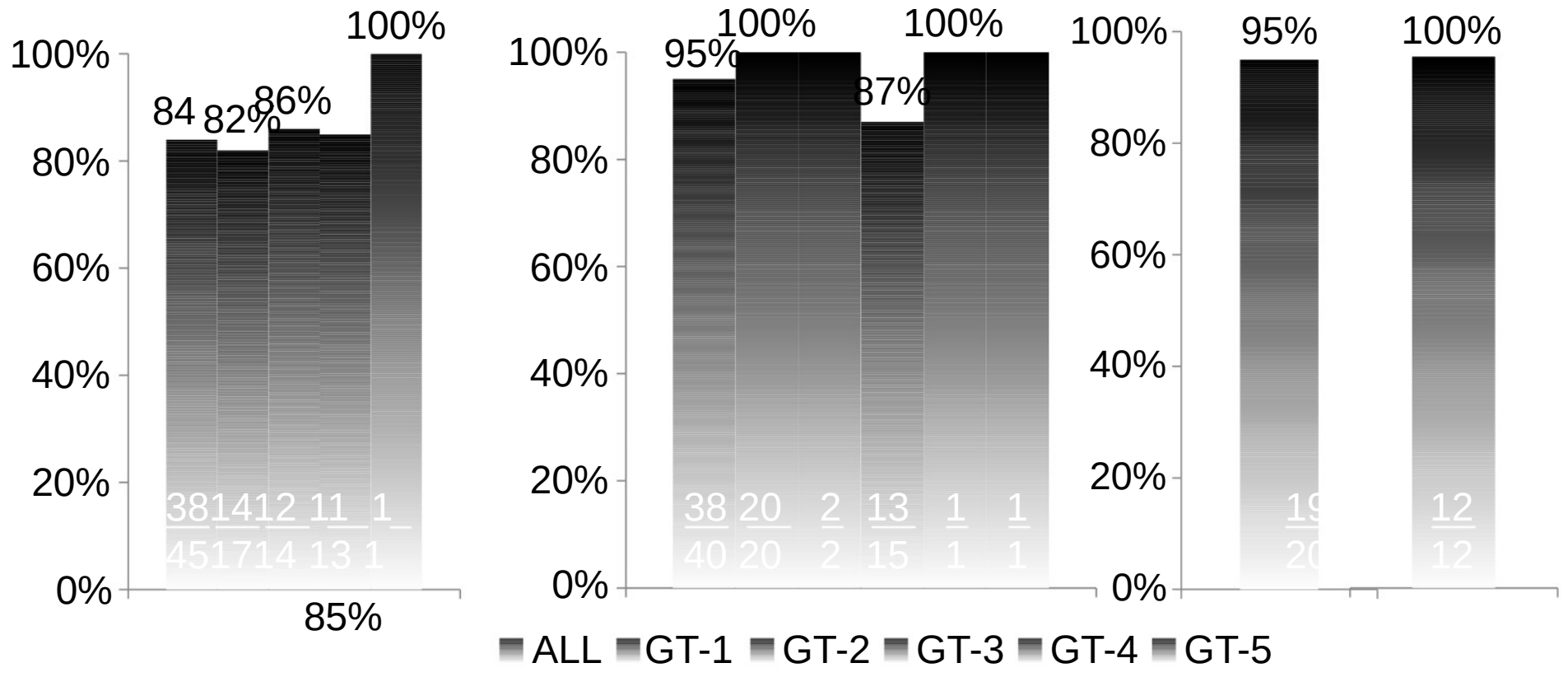


- Real-life confirms clinical trials

Covert E et al. AASLD 2018, Abs. 583
Llaneras J et al. AASLD 2018, Abs. 683
earlman B et al. AASLD 2018, Abs. 607

Hézode C et al. AASLD 2018, Abs. 629
Vermehren J et al. AASLD 2018, Abs. 676
Bacon B et al. AASLD 2018, Abs. 706
Belperio PS et al., AASLD 2018, Abs. 227

SOF/VEL/VOX in patients who failed SOF/VEL is there an issue ?



USA - VA cohort

Belperio PS, et al. AASLD 2018, Abs. 227

POLARIS 1-4

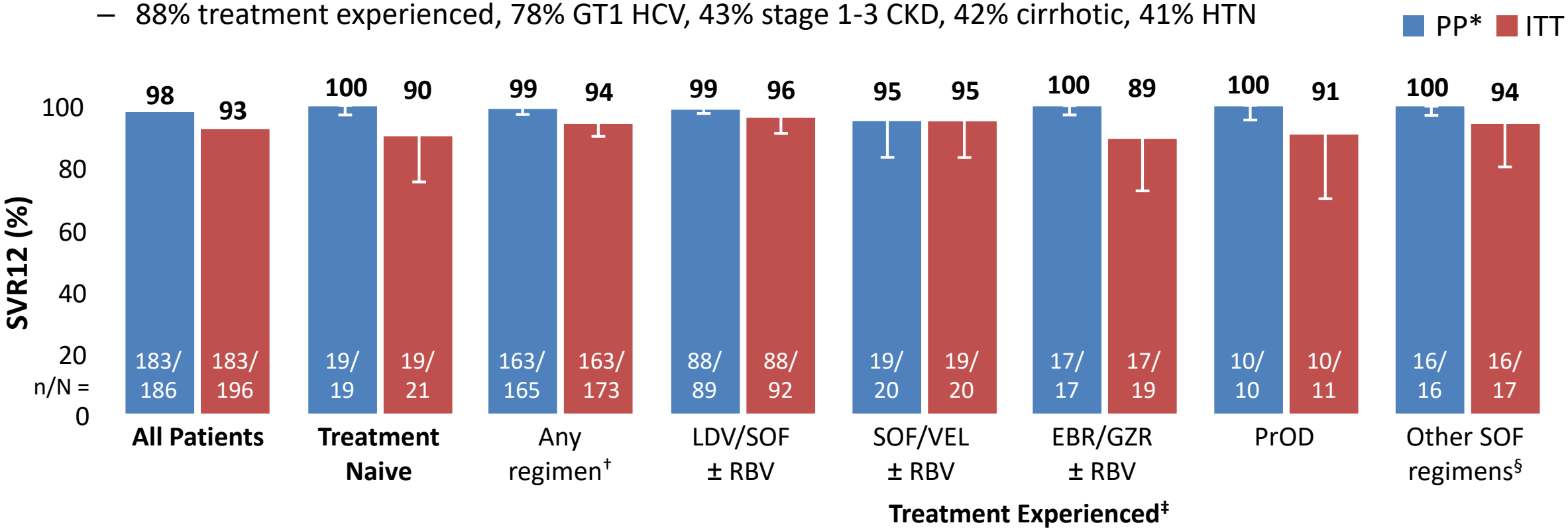
Ruane P et al; GHS 2018
Bourliere M et al NEJM 2017

USA Germany TRIO

Bacon B, et al AASLD 2018, Abs. 706
Vermehren J, et al AASLD 2018, Abs. 676

TRIO Network: SOF/VEL/VOX Efficacy in US Practice

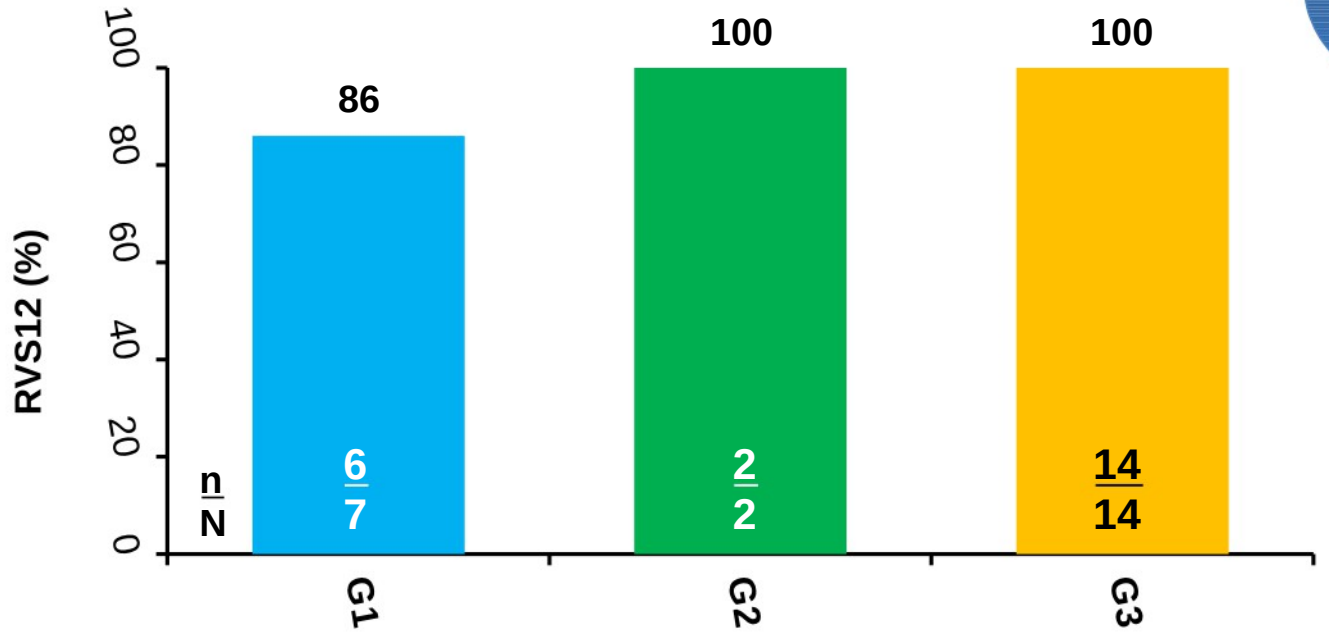
- Real-world data from providers and specialty pharmacies in the TRIO Health disease management program on SOF/VEL/VOX for 12 wks initiated between July 2017 and April 2018 (N = 196)
  - 88% treatment experienced, 78% GT1 HCV, 43% stage 1-3 CKD, 42% cirrhotic, 41% HTN



*Primary endpoint. †One patient with prior GLE/PIB achieved SVR. ‡Regimens prior to SOF/VEL/VOX.
§Includes DCV + SOF (n = 10), SOF + RBV (n = 6), PegIFN + SOF + RBV (n = 1).
Bacon. EASL 2019. Abstr THU-116. Reproduced with permission.

Sofosbuvir plus glecaprevir/pibrentasvir in G/P failure

SVR-12 according to genotype



SVR-12
96%

1 relapse patient

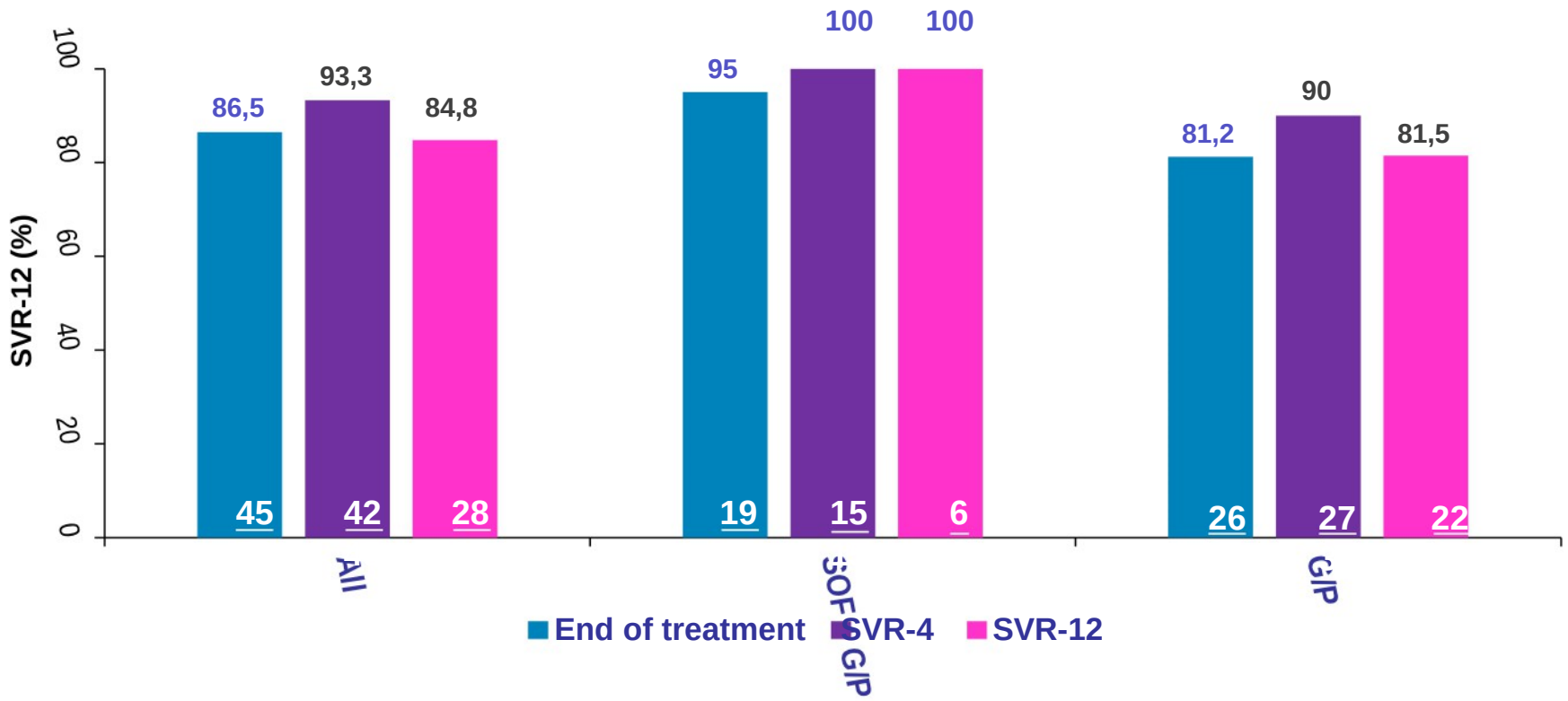
- GT-1a
- Compensated cirrhosis
- Failure to SOF/LDV then to G/P

SOF +G/P +RBV for 16 weeks is an option for GT-3 who have failed previous treatment with G/P

Wyles D et al, EASL 2018, Abs. PS-04

Sofosbuvir plus glecaprevir/pibrentasvir in DAAs failure (French ATU)

Virological response



SOF + G/P treatment for 12 weeks is a therapeutic option in DAAs failures

de Lédinghen V. et al. EASL 2018, Abs. THU-29

Approach to persons with HCV failure

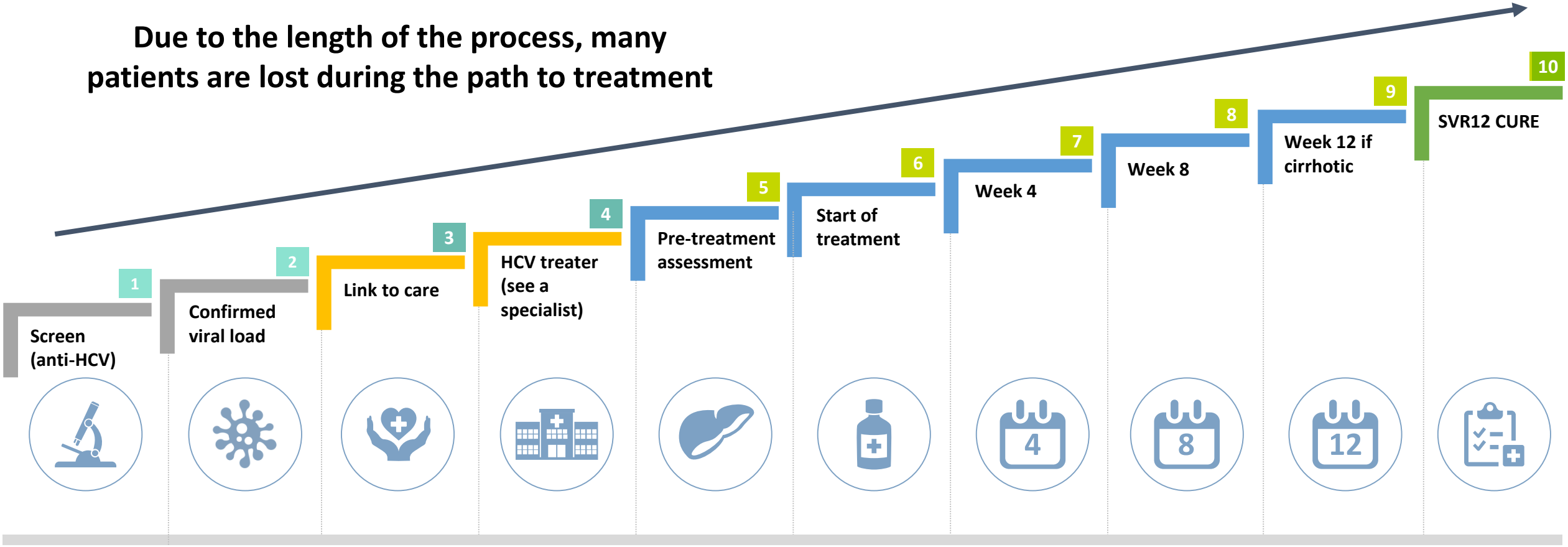
- Consider re-infection as a cause of recurrent viremia
- Assess adherence/persistence prior regimen
- Reassess genotype
- Assess liver disease stage: No cirrhosis, cirrhosis CTP A or B/C
- No cirrhosis and single DAA failure
  - Retreat with least two DAAs predicted to be active based on prior DAA use or directly use triple regimen for 12w (SOF/VEL/VOX or SOF+G/P)
  - RAS testing not compulsory
- Cirrhosis or prior therapy with both NS5A and NS3 inhibitor
  - RAS testing recommended
  - Use only triple regimens SOF/VEL/VOX or SOF+G/P
  - (if liver functions allows use of a PI….)
  - Consider Ribavirin and extended duration (16 or 24w)

Approach to persons with 2nd line DAA failure

- **2nd-line DAA failures are rare**
- **Patients with multiple negative treatment predictors**
- **No approved / validated re-treatment options**
- **Strategies for DAA-retreatment**
  - select DAAs according to viral resistance testing
  - multiple targeting regimens only (PI + NS5A + SOF)
  - extend treatment duration to 16 – 24 weeks
  - add Ribavirin

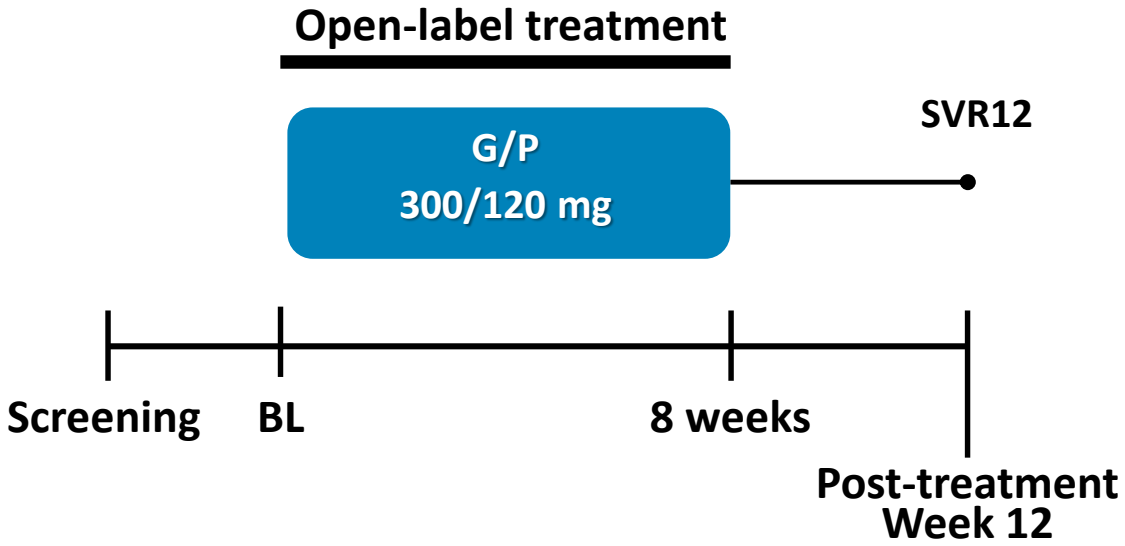
The HCV Care Cascade Involves Several Steps

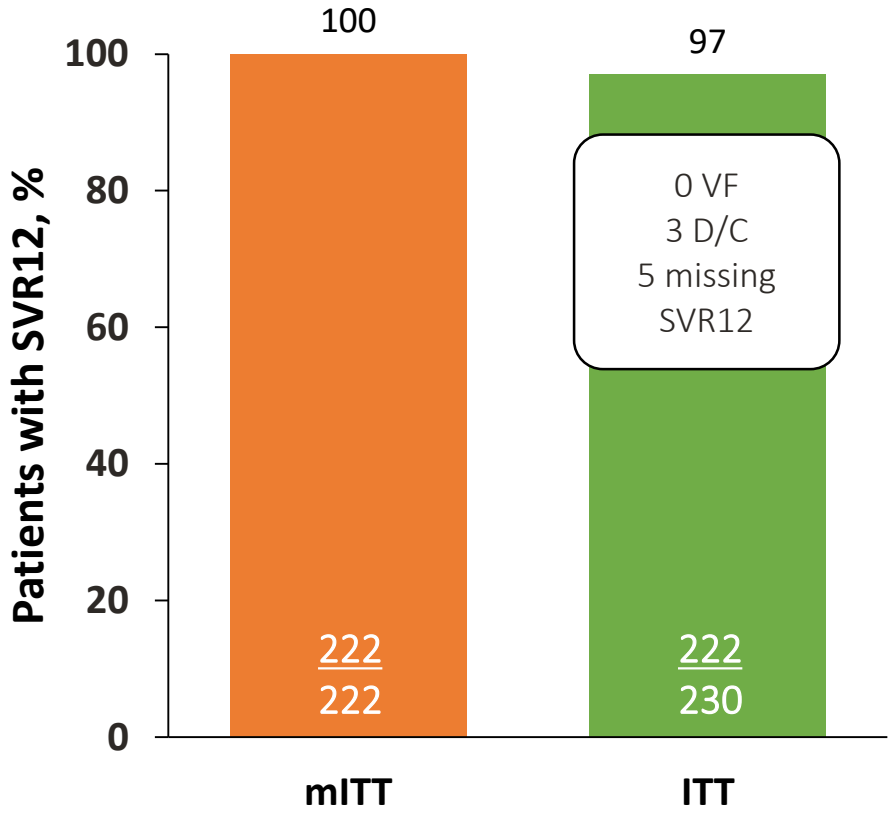
Due to the length of the process, many patients are lost during the path to treatment



APRI Test Is a Reliable, Non-invasive Method

Phase 3, open-label, single-arm, randomized, multicenter study to evaluate the safety and efficacy of 8 weeks of G/P in 230 treatment-naive adults with chronic HCV GT1–6 infection and APRI ≤ 1



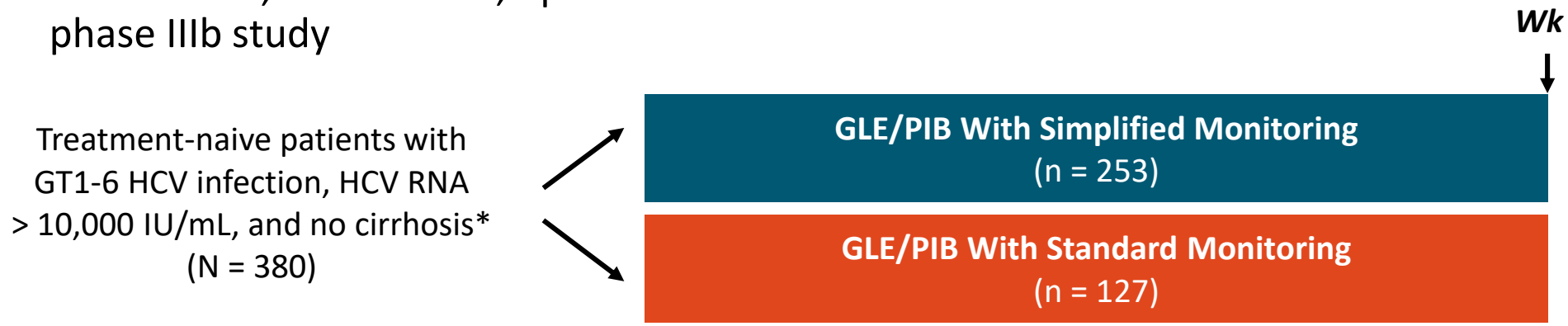


APRI, aspartate aminotransferase to platelet ratio index; BL, baseline; D/C, discontinuation; VF, virologic failure.

Fontana RJ, *et al. Hepatology* 2018; **68:**388A–389A (poster presentation #653).

SMART-C: Monitoring During GLE/PIB in Treatment-Naive Patients With GT1-6 HCV Infection

- Multicenter, randomized, open-label phase IIIb study



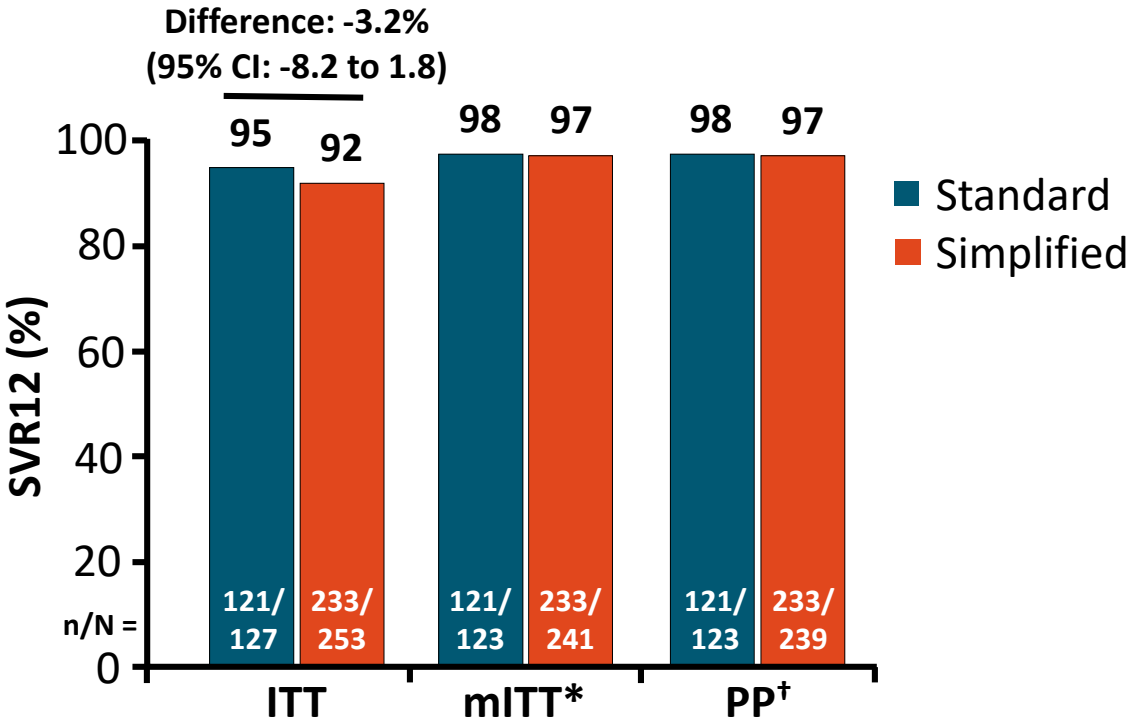
AEs and adherence assessed by study nurse via phone contact at Wks 4 and 8 in all patients. GLE/PIB dosed orally at 300/120 mg QD.
*Exclusion criteria: anticipated poor adherence, IDU within past 6 mos, positive urine drug screen.

- **Simplified monitoring:** Medication dispensed at BL; no on-treatment clinic visits
- **Standard monitoring:** Medication dispensed at BL and Wk 4; clinic visits with physician, study nurse, and pathology at Wks 4 and 8

- **Primary endpoint:** SVR12 in ITT population (6% noninferiority margin)
- **Secondary endpoints:** SVR12 in mITT and PP populations, adherence by Wk 20 pill count, treatment discontinuation and completion, safety

Dore. EASL 2019. Abstr PS-178.

SMART-C: Efficacy and Safety



*Excludes death (n = 1), LTFU (n = 14), or missing HCV RNA (n = 1).
†Excludes discontinuation (n = 2) in addition to mITT exclusions.

- VF: 2 (1.6%) standard vs 6 (2.4%) simplified
- Adherence > 95%: 98% standard vs 96% simplified

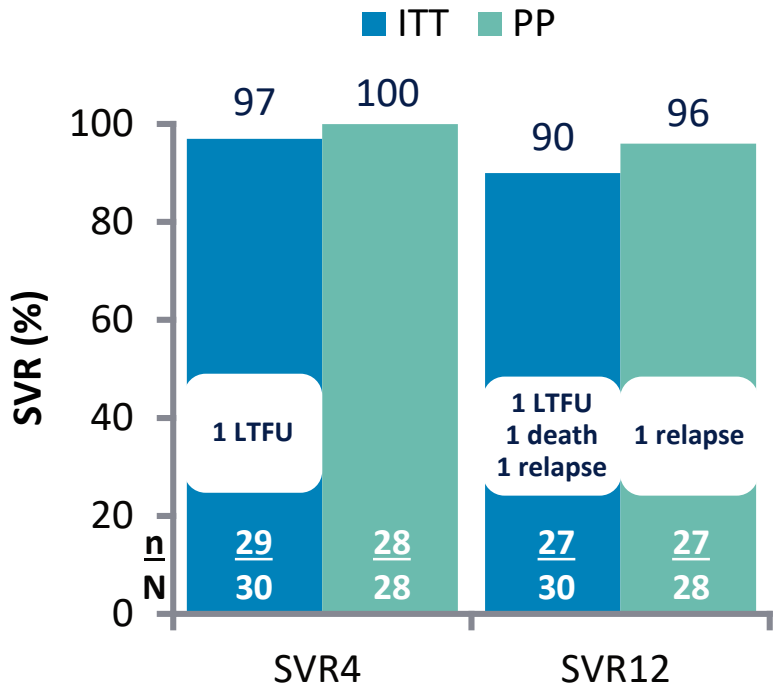
Treatment-Emergent AEs, n (%)	Standard (n = 127)	Simplified (n = 253)
AEs	70 (55)	133 (53)
▪ Grade 1/2	69 (54)	131 (52)
▪ Grade 3	1 (0.8)	2 (0.8)
▪ Grade 4	0	0
Common AEs (> 5%)		
▪ Fatigue	30 (14)	52 (15)
▪ Headache	26 (12)	43 (13)
▪ Nausea	25 (12)	17 (5)
Serious AEs	0	3 (1.2)
Unscheduled visits		
▪ On treatment	3 (2)	11 (4)
▪ Total	8 (6)	20 (8)

Dore. EASL 2019. Abstr PS-178. Reproduced with permission.

Shortened Duration Pan-genotypic Therapy with G/P for 6 Weeks among People with Acute and Recent HCV Infection

Open-label study to assess the efficacy of G/P for 6 weeks in patients with acute and recent HCV infection* in Australia, New Zealand, and England (N = 30)

Baseline Characteristics, n (%)	ITT population (N = 30)
Male	30 (100)
MSM	26 (87)
HIV/HCV co-infection	23 (77)
History of IDU	14 (47)
HCV re-infection	4 (13)
HCV GT	
1	24 (80)
2	1 (3)
3	2 (7)
4	3 (10)



- 1 patient with acute GT1a HCV had virologic failure, confirmed as relapse on sequencing
- Patient had baseline HCV RNA level of ~8 $\log_{10}$ IU/mL

There was one treatment-emergent SAE† and no treatment-related SAEs

Short-duration 6-week G/P treatment was highly effective among HIV-positive and HIV-negative individuals with acute and recent HCV infection

* Recent infection defined as HCV infection of < 12 months' duration with a first positive anti-HCV antibody and/or HCV RNA within 6 months of enrollment and either acute clinical hepatitis within the past 12 months (jaundice or ALT > 10 × upper limit of normal) or documented anti-HCV antibody seroconversion within 18 months; † Neutropenia on day 1, resolved on treatment without intervention.
LTFU, lost to follow-up; MSM, men who have sex with men; PP, per protocol; VF, virologic failure.

Martinello M, *et al.* EASL 2019; poster presentation (THU-157).

Simply does not necessarily means EASY