How to optimize treatment in G3 patients ?

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Disclosures

- I have received funding from Abbvie, Aptalis, Bayer, BMS, Gilead, Mayoly Spindler, Merck

Case Presentation (1)

- Man born in 1955, caucasian
- Intravenous drug use : 1974-1977
- Diagnosis of HCV G3a in 1995
  - systematic check-up proposed by public health insurance
- Alcohol: 40 units per week
- 76 kg / 175 cm
- Liver biopsy #1 in 1996: METAVIR A3F2, steatosis 80%

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- Intravenous drug use : 1974-1977
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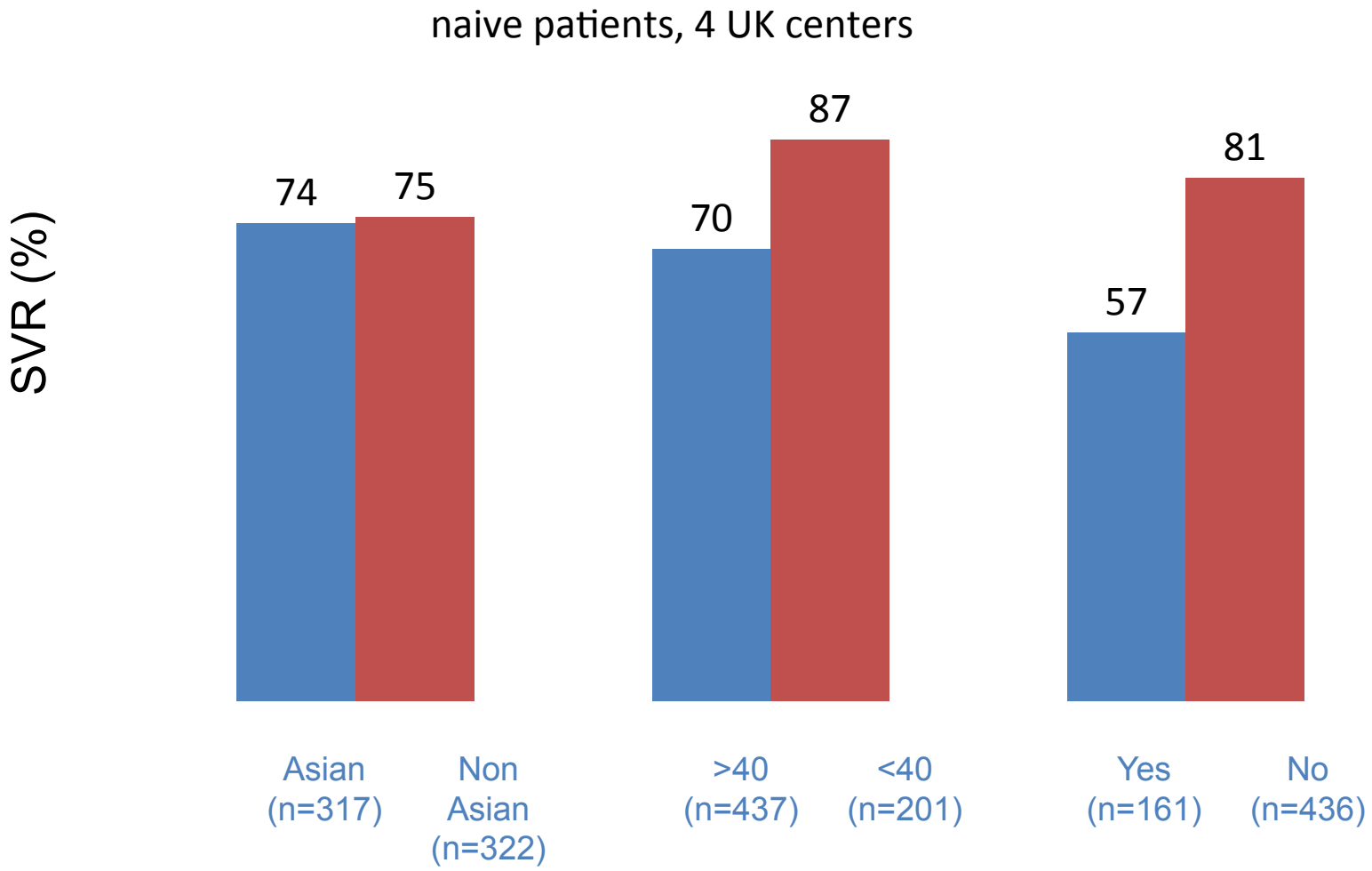
- Alcohol: 40 units per week
- 76 kg / 175 cm
- Liver biopsy #1 in 1996: METAVIR A3F2, steatosis 80%
- Treatment #1 in 1997: standard IFN
  - No effect on ALT, poor tolerance
  - Discontinuation after 3 months
- Liver biopsy #2 in 2001: METAVIR A2F2, steatosis 30%
- Treatment #2 in 2002: PEG-IFN α-2b + RBV (1000 mg/d)
  - Hb: 16,4 g/dL → 8,3 g/dL
  - Discontinuation after 3 weeks
- Reduction of alcohol consumption: 15 units per week

PEG-IFN + RBV 24 weeks (n = 639)

GT3

Naive



Shoeb D, et al. Eur J Gastroenterol Hepatol 2014;23:747-53. (slide: G Foster, PHC 2015)

Case Presentation (2)

- Treatment #3 (2006-2007): PEG-IFN α-2a + RBV
  - Progressive increase of RBV dose to 800 mg/d
  - Hb: 16,3 g/dL → 10,2 g/dL (no use of EPO)
  - Duration 48 weeks
  - HCV RNA undetectable at W12 → relapse
- FibroScan 14,5 kPa in 2008 (AST 119 IU/L, ALT 281 IU/L)
- FibroScan 17,5 kPa in 2011 (AST 103 IU/L, ALT 207 IU/L)
- Treatment #4 (2011): PEG-IFN α-2a 90 µg/week (maintenance*)
  - No effect on ALT: discontinuation after 24 weeks
- Stop alcohol in 2011

Di Bisceglie AM et al. HALT-C trial, NEJM 2008;359:2429-41.

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- Marked asthenia, no diabetes, 80 kg / 175 cm

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Question (1)

In january 2014 (7th PHC),

what would have been your recommendation ?

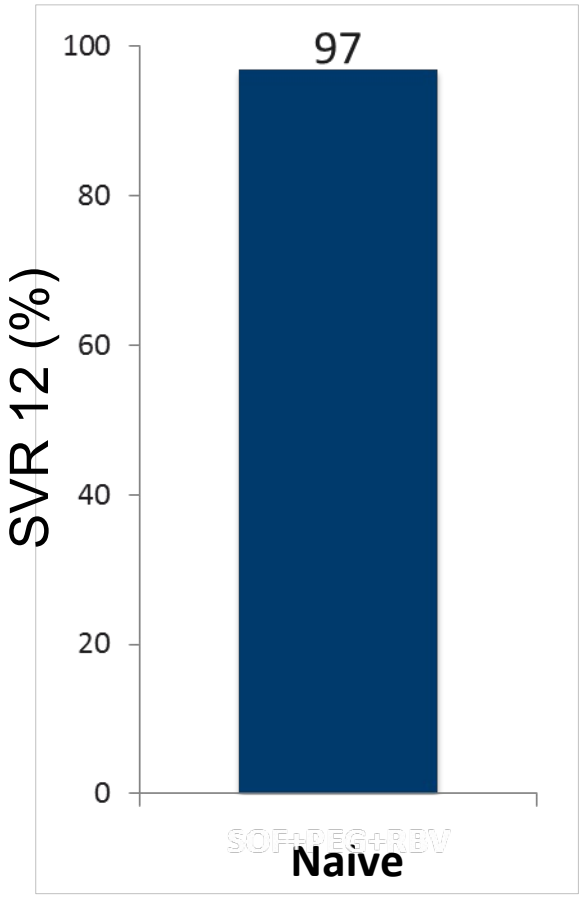
1. Carefull follow-up and HCC screening and wait for new DAA combination
2. Treatment using Sofosbuvir, PEG-IFN, and RBV for 12 weeks
3. Treatment using Sofosbuvir and RBV for 12 weeks
4. Treatment using Sofosbuvir and RBV for 24 weeks

Sofosbuvir + PEG-IFN +RBV 12 weeks

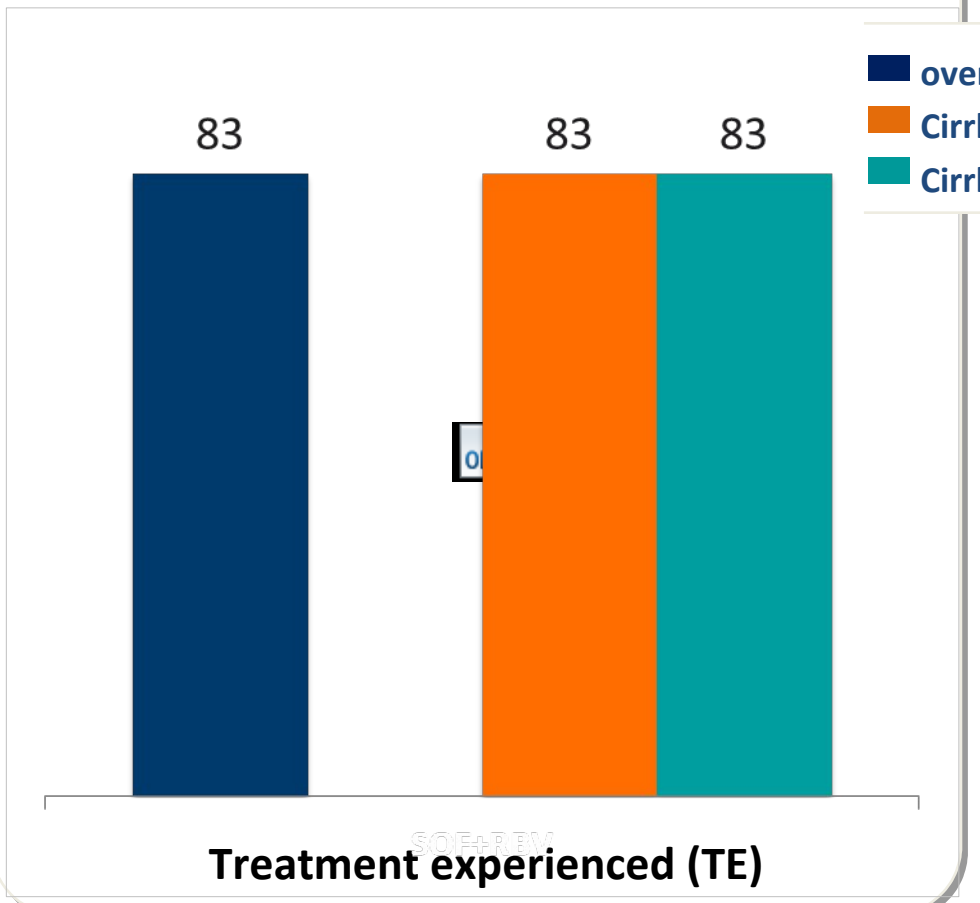
GT3

Naive or TE

ELECTRON & PROTON



LONESTAR-2

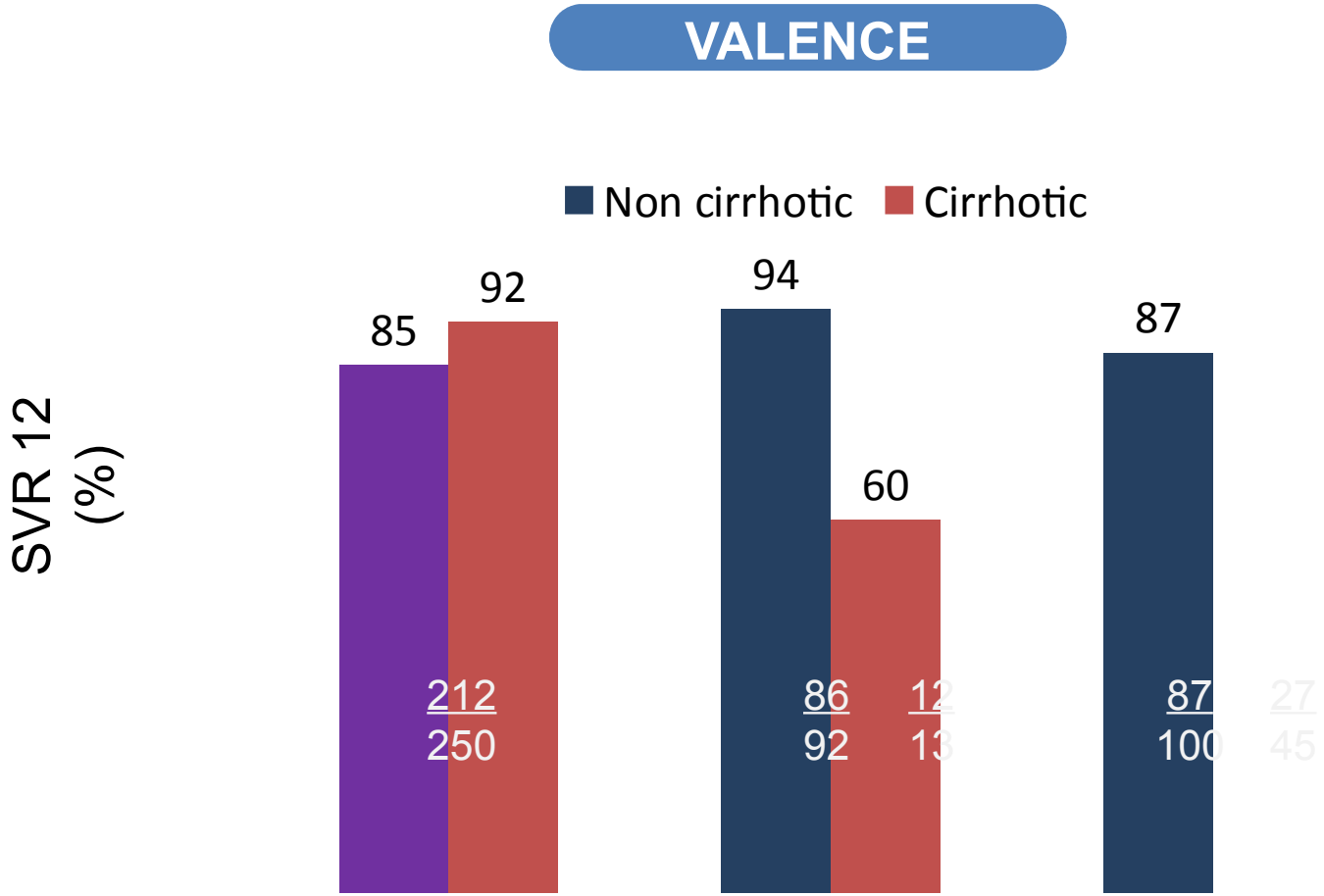


Gane EJ *et al.* CROI 2013 Lalezari J *et al*. EASL 2011 Lawitz E *et al*. AASLD 2013
Lawitz E et al. Hepatology 2015;61:769-75

SOF + RBV 24 weeks

GT3

Naive & TE



Zeuzem S et al. N Engl J Med 2014;370:1993-2001.

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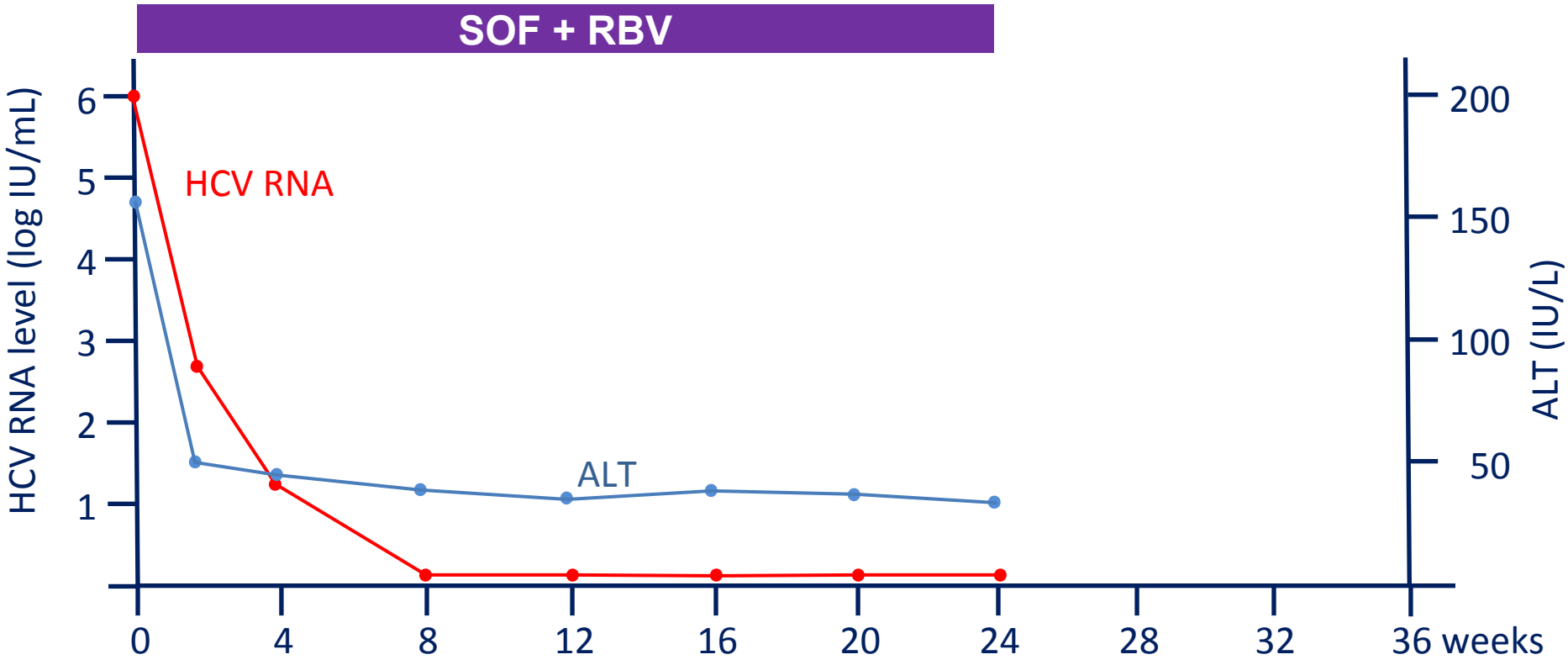
Case Presentation (3)

- Treatment #5 (2014): SOF + RBV
  - Hb: 16,1 g/dL → 9,2 g/dL (no use of EPO)
  - RBV dose 1000 mg/d → 600 → 800 mg/d (difficult to maintain)
  - Duration 24 weeks (january to june)



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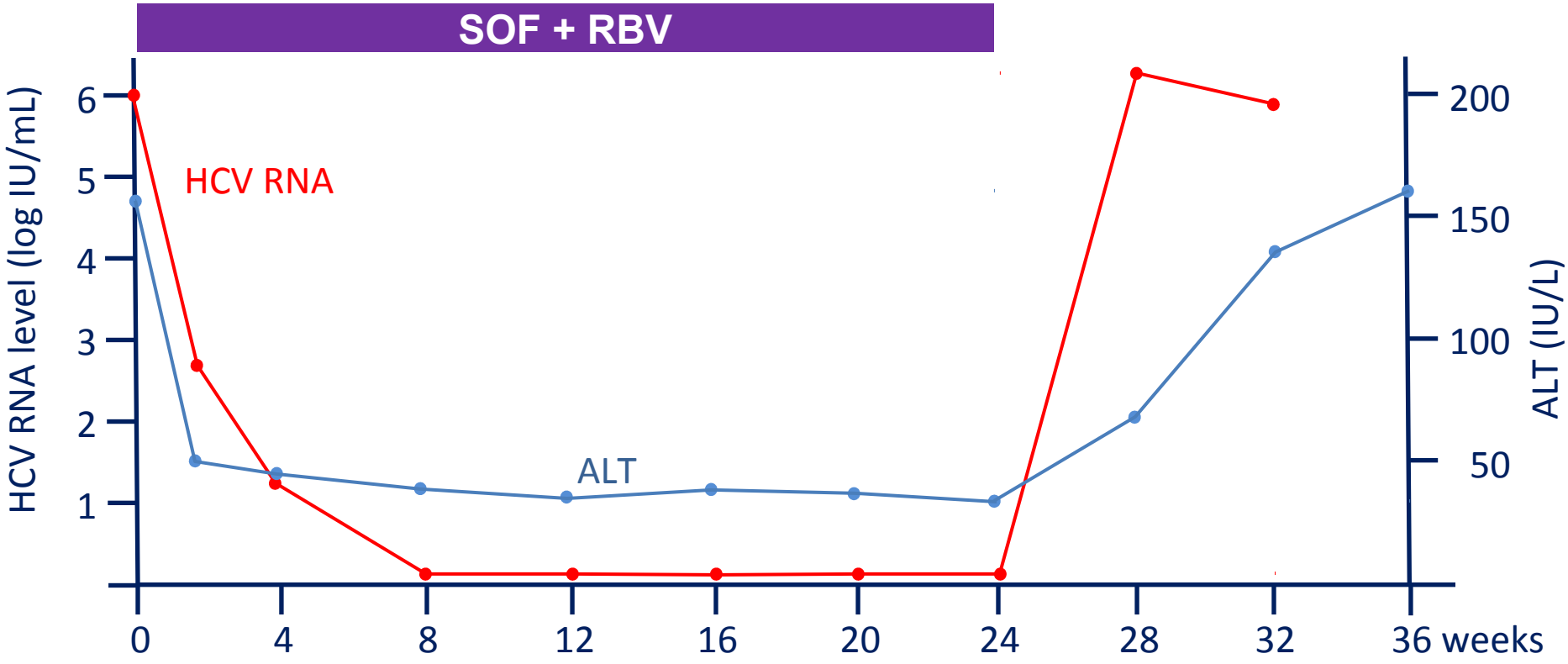


- Man, 59 yo
- FibroScan 34,3 kPa in 2013
- AST 106 IU/L, ALT 196 IU/L
- Liver biopsy #3 in 2013: METAVIR A3F3, steatosis 15%
- Hepatic dysmorphy (US), no oesopageal varice
- Marked asthenia, no diabetes, 80 kg / 175 cm

- Relapse after 24 weeks of SOF + RBV

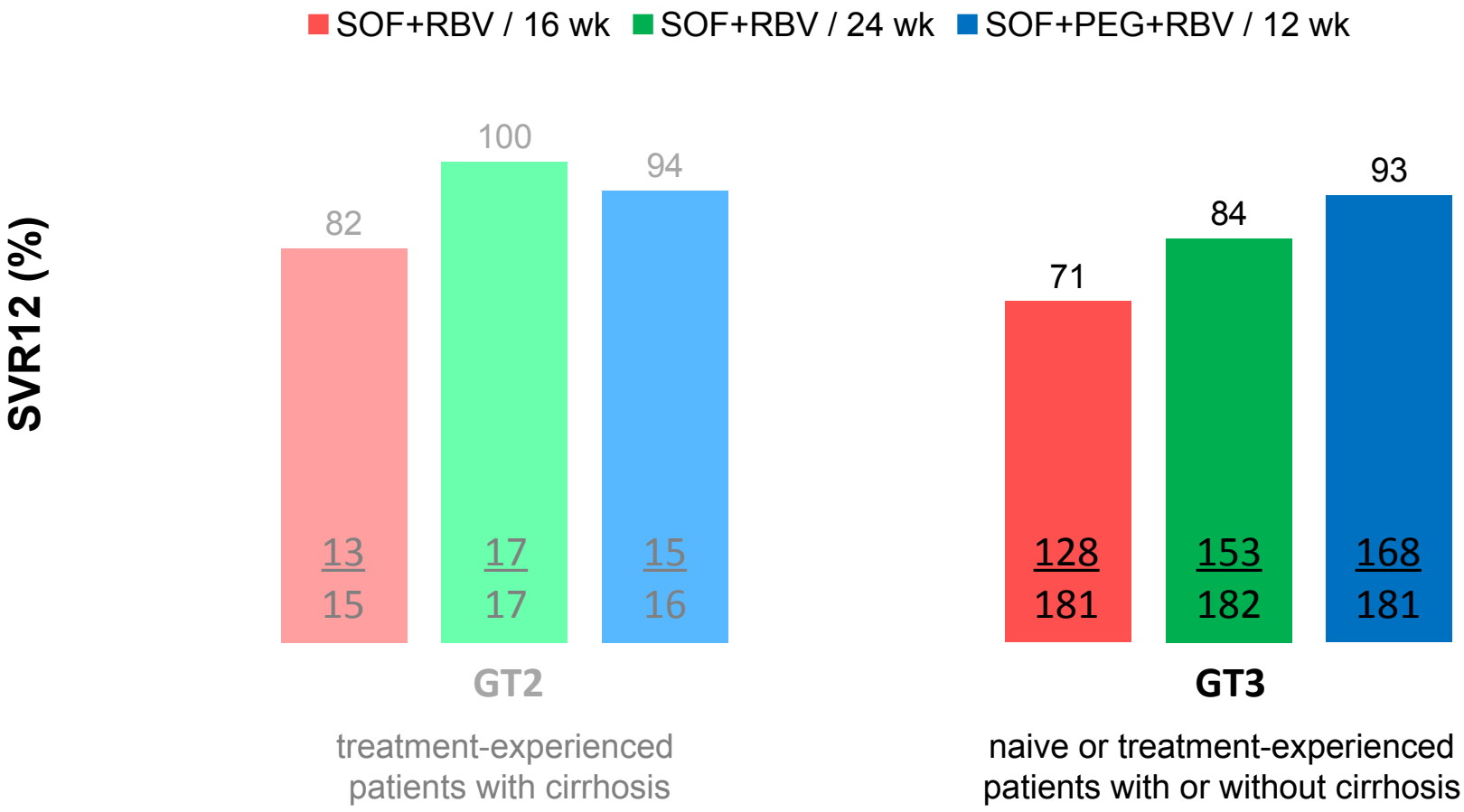
Why did the treatment fail ?

Sofosbuvir + RBV ± PEG-IFN

GT2 & GT3

Naive or TE

BOSON



Key baseline characteristics: 92% GT3, ~ 38% *IL28B* CC, ~ 53% previously treated, ~ 37% with cirrhosis

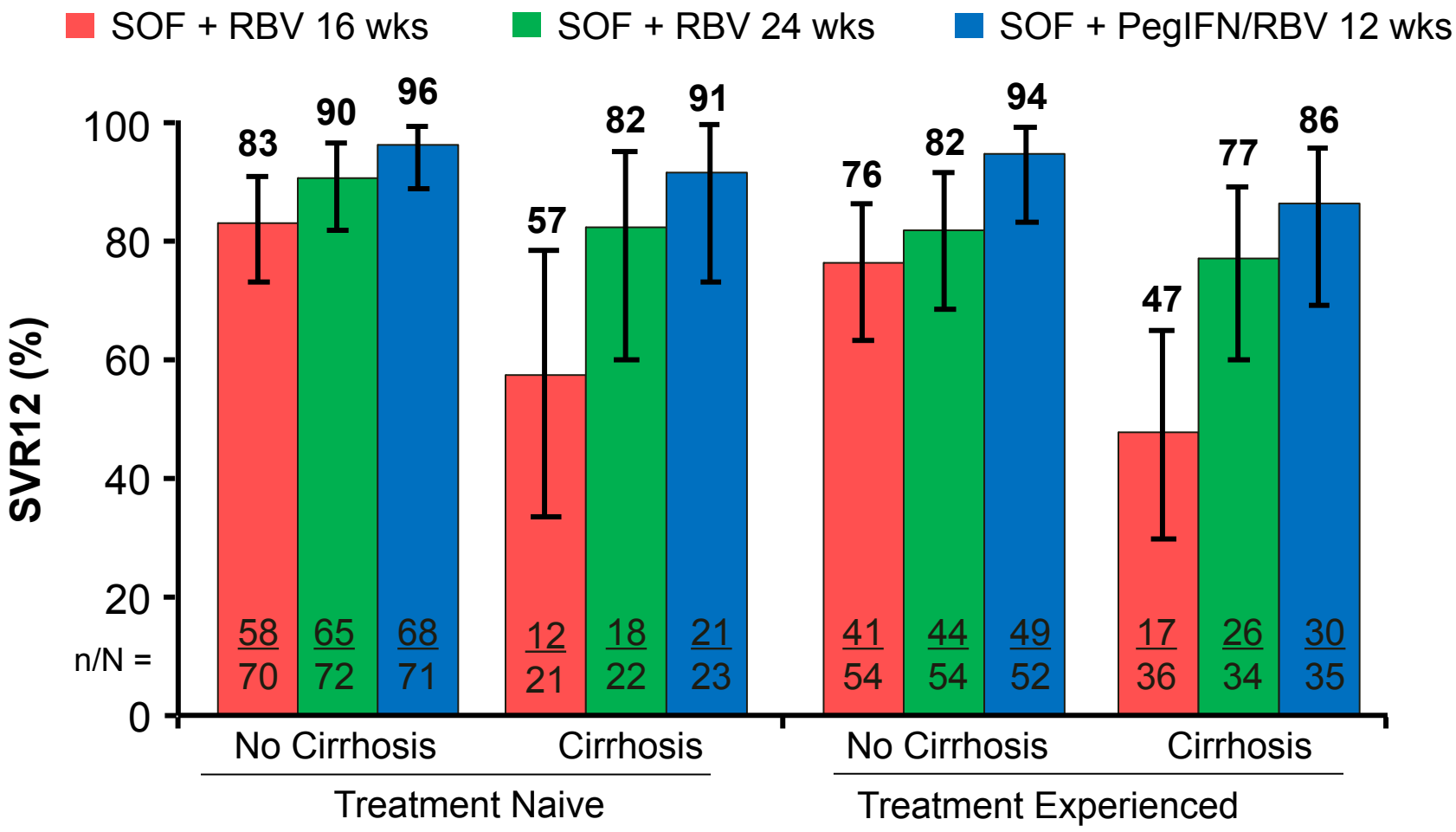
Foster GR, et al. Gastroenterology 2015;149:1462-70 *(presented at EASL 2015, abs LO5)*

Sofosbuvir + RBV ± PEG-IFN

GT3

Naive or TE

BOSON



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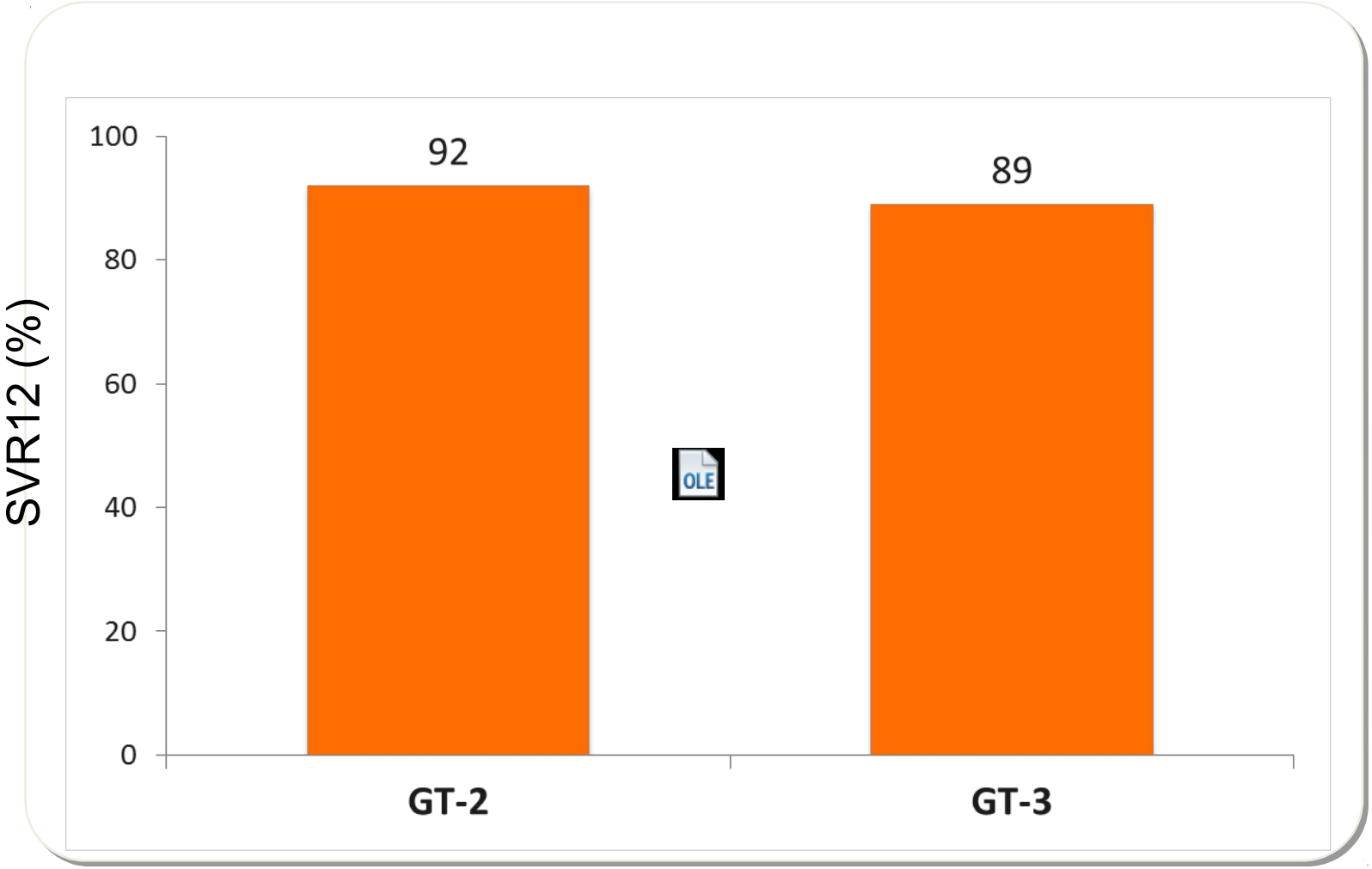
Sofosbuvir + Daclatasvir ± RBV 24 weeks

GT2-3

Naive



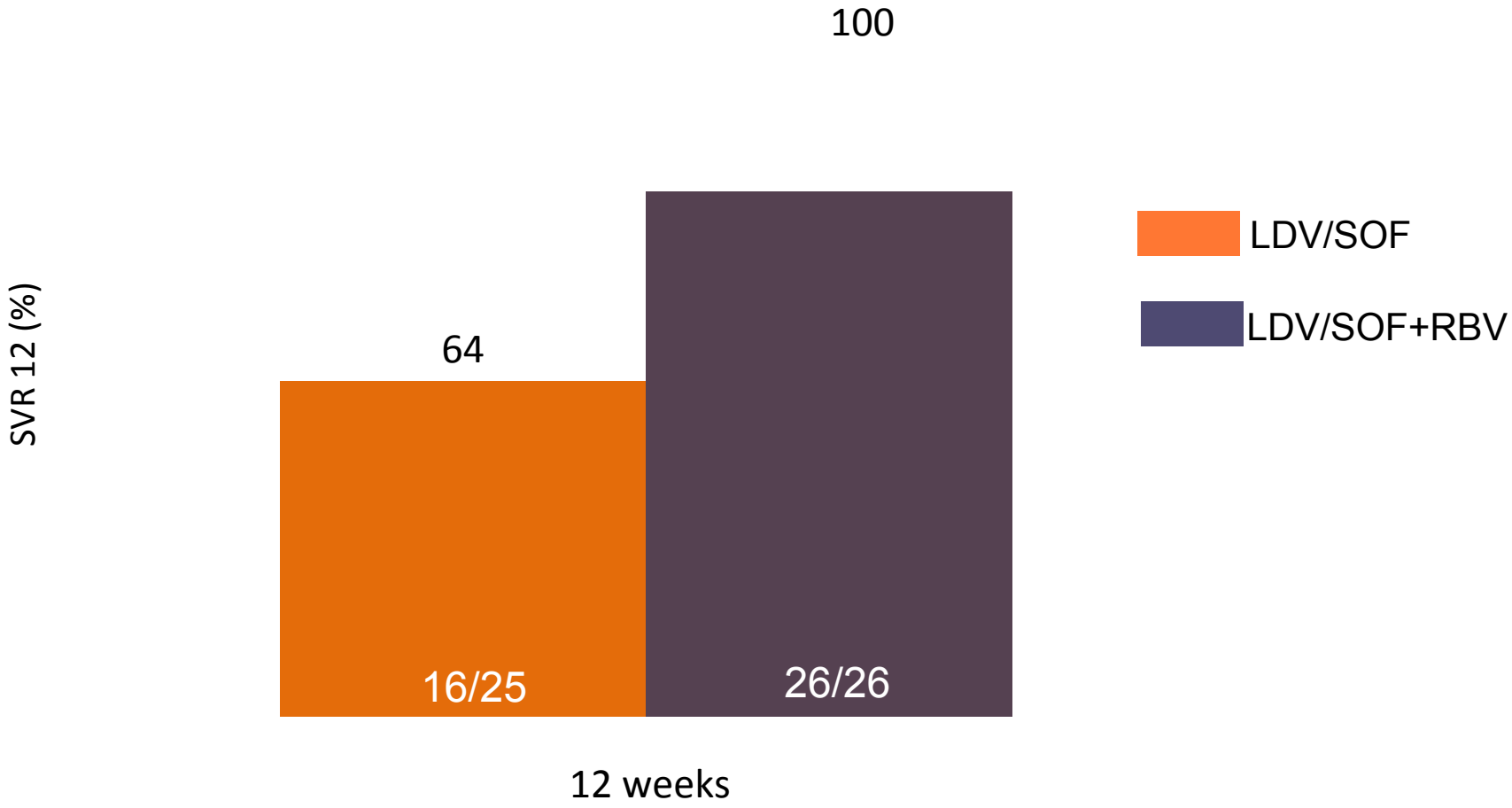
Sulkowski MS *et al*. N Engl J Med. 2014;370:211-21.

Sofosbuvir + Ledipasvir ± RBV

GT3

Naive

ELECTRON 2



Gane EJ, EASL 2014

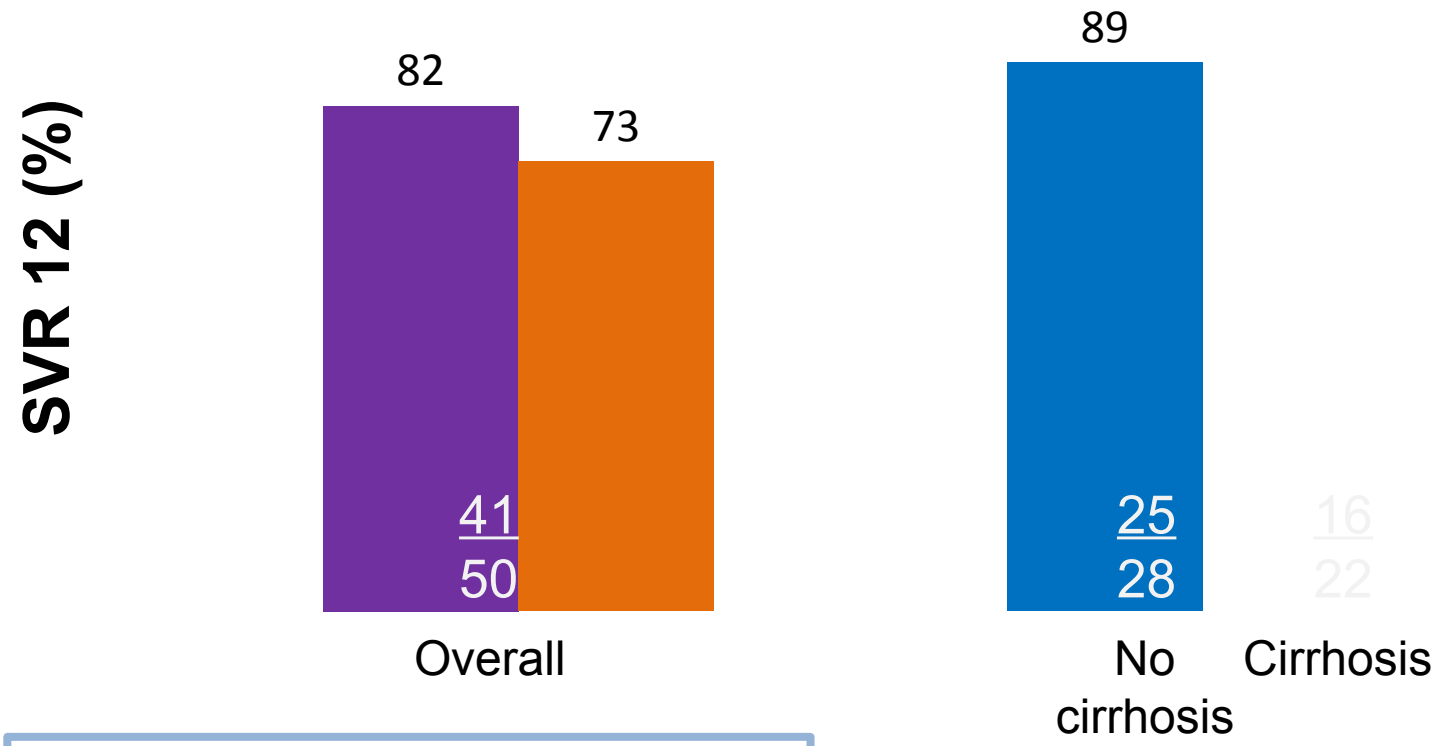
Gane EJ et al. Gastroenterology 2015;149:1454-1461.

Ledispasvir + Sofosbuvir + RBV 12 Weeks

GT3

TE

Two-center, open label study



Hemoglobin < 10 g/dL: 2 patients (4%)
Hemoglobin < 8.5 g/dL: 0

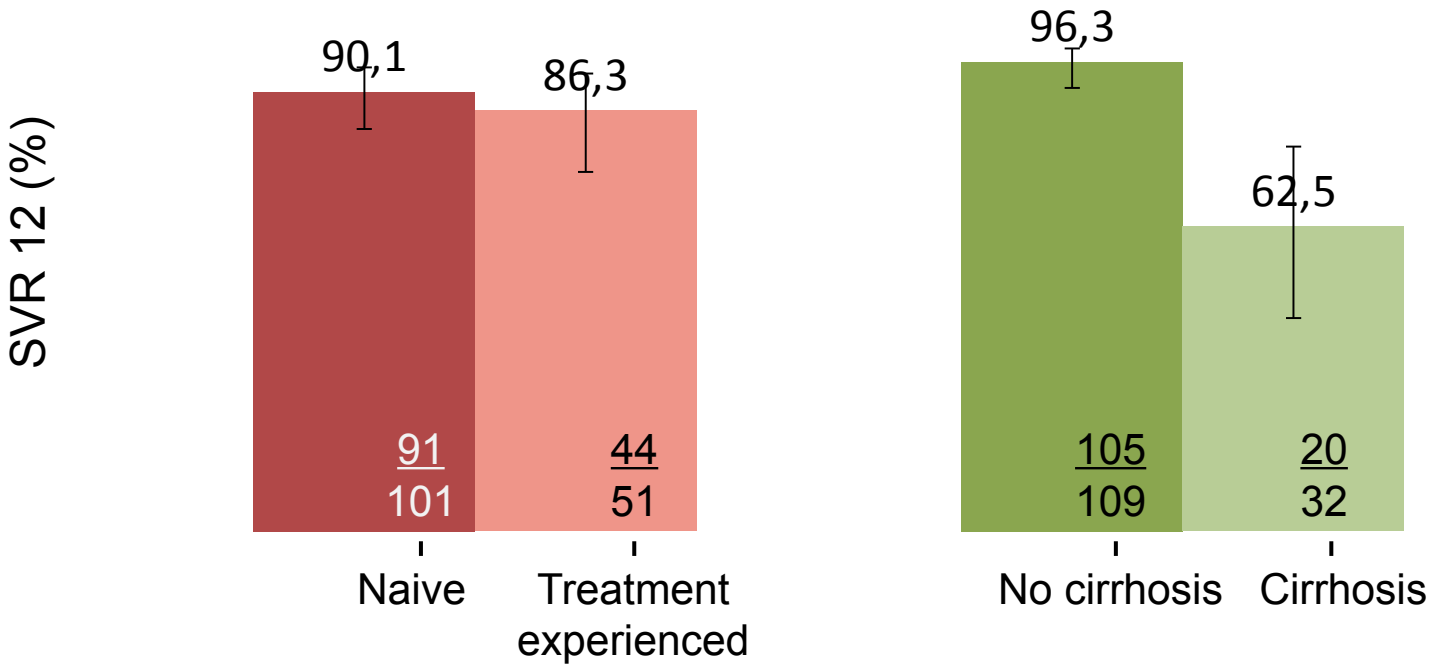
Gane EJ, AASLD 2014, Poster LB-11
Gane EJ et al. Gastroenterology 2015;149:1454-1461

Sofosbuvir + Daclatasvir 12 weeks

GT3

Naive or TE

ALLY 3

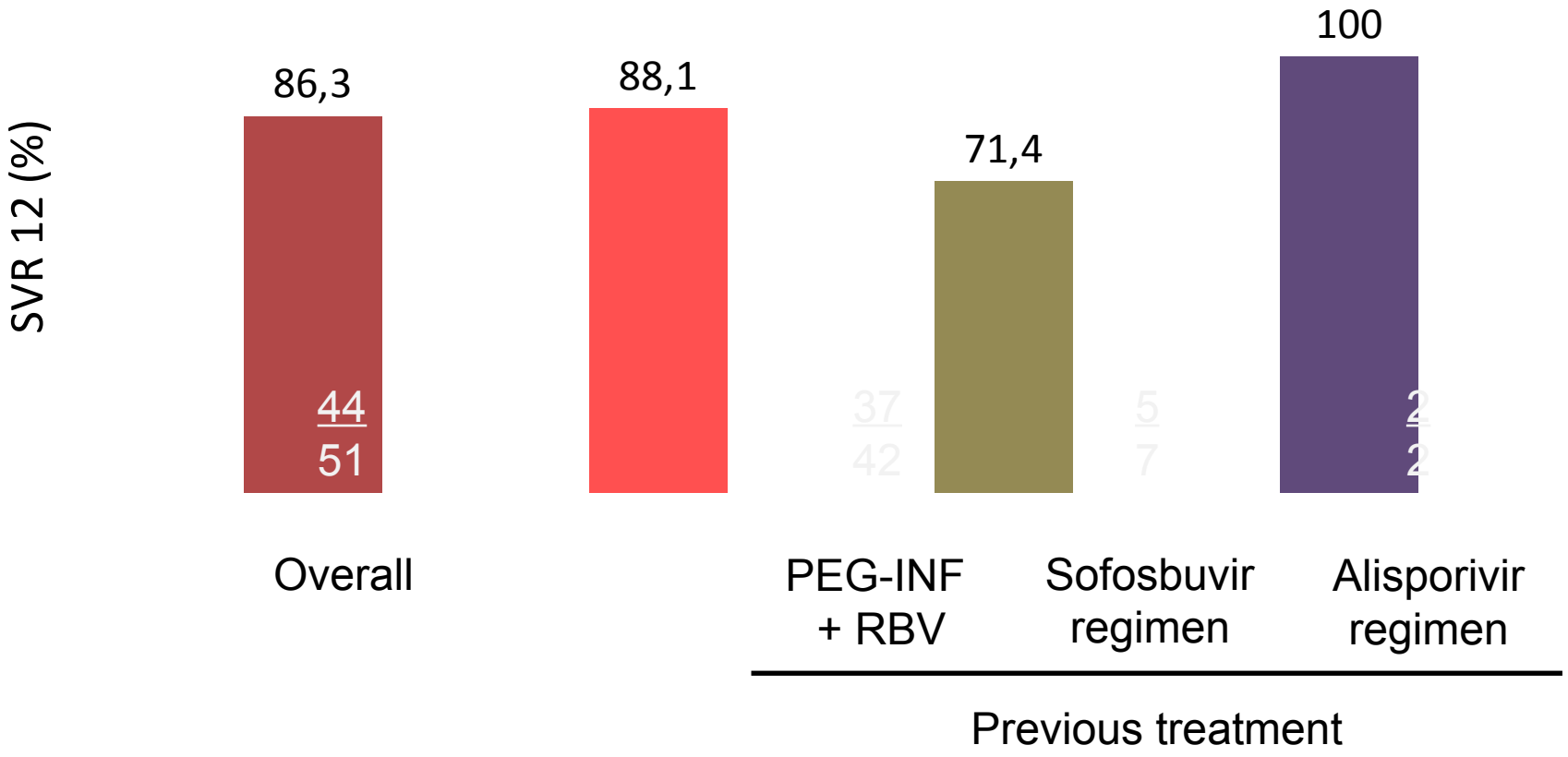


Nelson DR, AASLD 2014

Nelson DR et al. Hepatology 2015;61:1127-35.

Sofosbuvir + Daclatasvir 12 weeks

ALLY 3: treatment experienced patients



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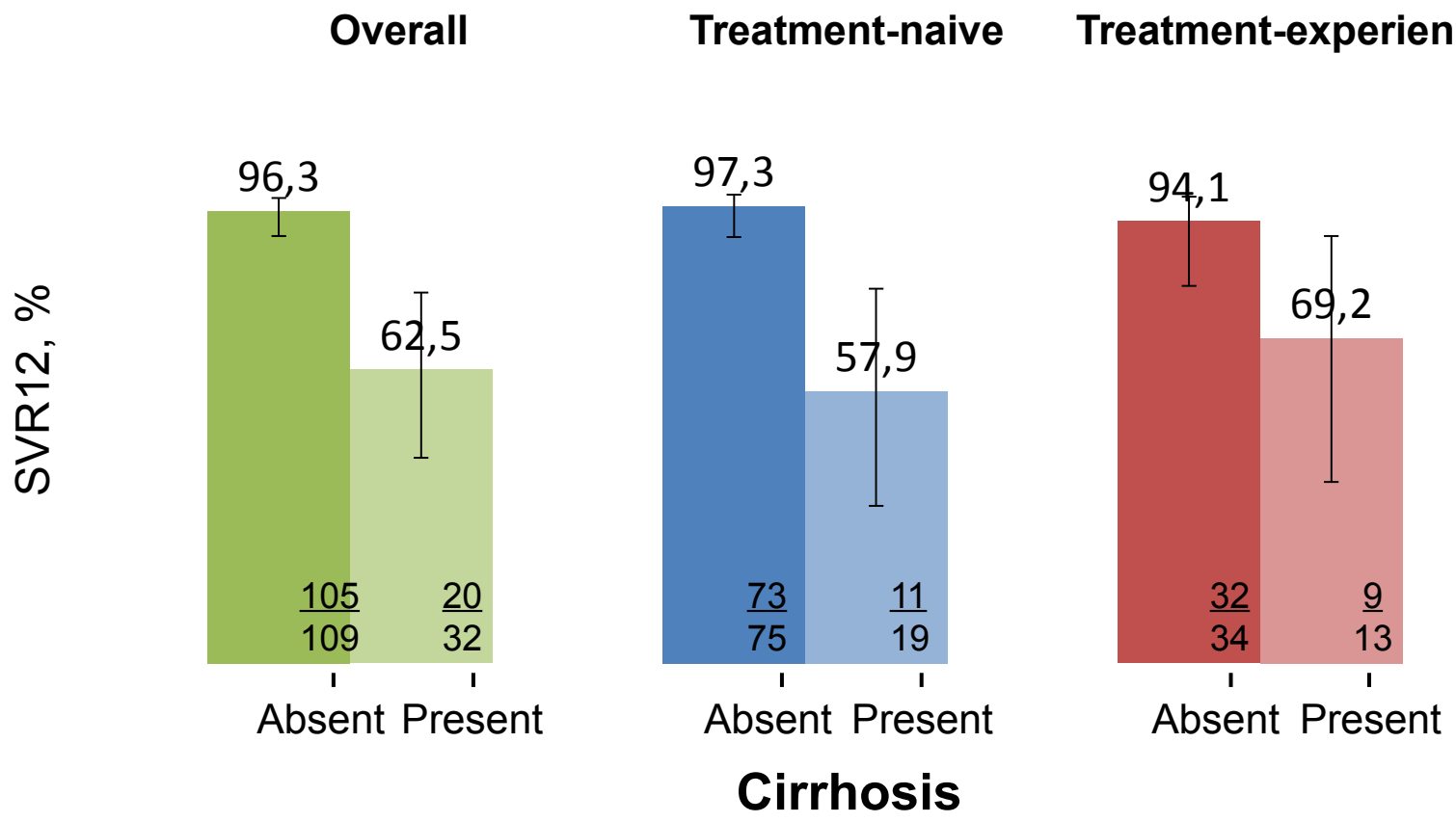

Among cirrhotic patients, 34% (11/32) had baseline platelet < 100,000/mm3

Nelson DR, AASLD 2014

Nelson DR et al. Hepatology 2015;61:1127-35.

French experts recommendations (january 2015)

AFEF

Génotype 3	Traitement	Durée (semaines)	Preuve
Cirrhose			
Naif	Sofosbuvir + Daclatasvir *	24	B
	Sofosbuvir + Ledipasvir + ribavirine	24	C
	Sofosbuvir + interféron pégylé + ribavirine	12	B
Echec PEG-Ribavirine	Sofosbuvir + Daclatasvir + ribavirine	24	C
	Sofosbuvir + Ledipasvir + ribavirine	24	C
	Sofosbuvir + interféron pégylé + ribavirine	12	B
Echec Sofosbuvir + ribavirine	Sofosbuvir + Daclatasvir + ribavirine	24	C
	Sofosbuvir + Ledipasvir + ribavirine	24	C
	Sofosbuvir + interféron pégylé + ribavirine	12	B
Echec Sofosbuvir + Daclatasvir ou Ledipasvir	Avis d'expert recommandé		
Cirrhose décompensée			
Naif & échec PEG-Ribavirine	Sofosbuvir + Daclatasvir + ribavirine	24	C
	Sofosbuvir + Ledipasvir + ribavirine	24	C
Fibrose F2F3			
Naif & échec PEG-Ribavirine	Sofosbuvir + ribavirine	24	A
	Sofosbuvir + Daclatasvir	12	B
	Sofosbuvir + Ledipasvir + ribavirine	12	B

* L'adjonction de ribavirine peut être discutée au cas par cas.

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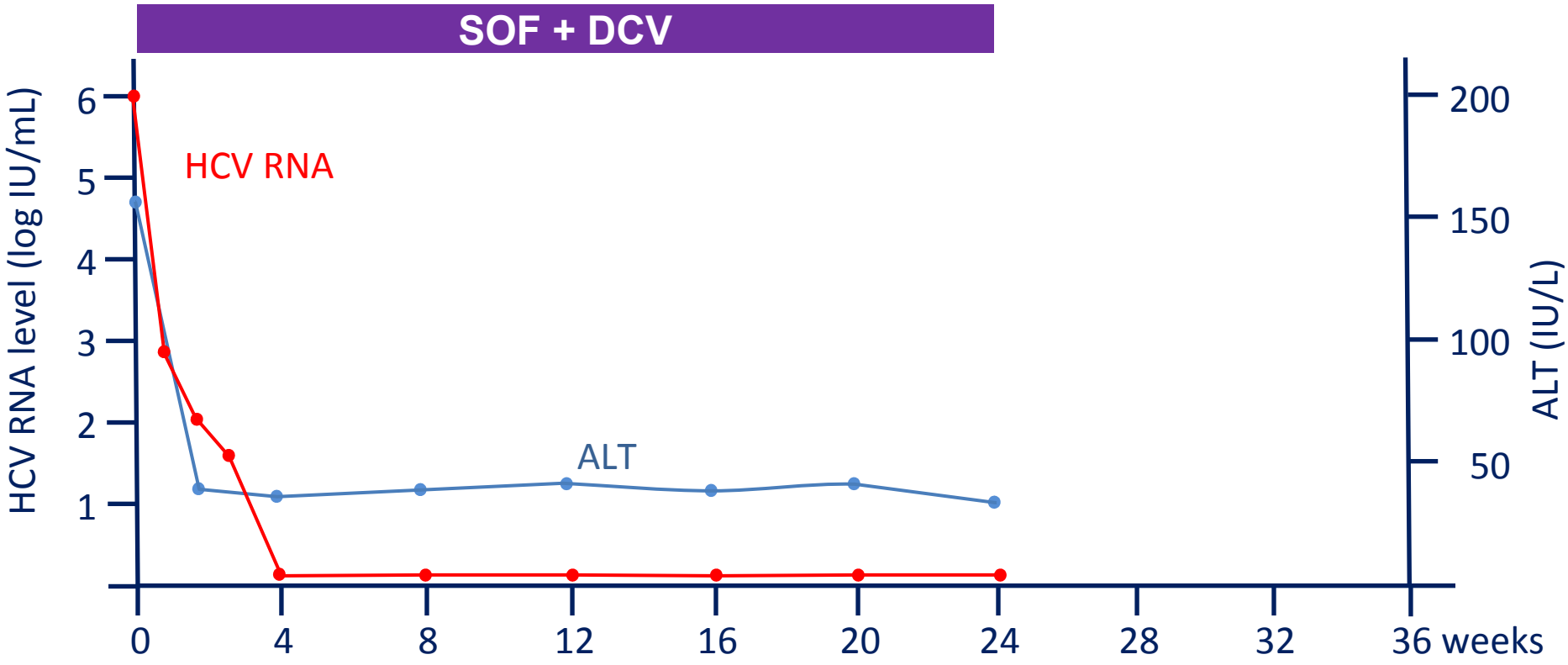
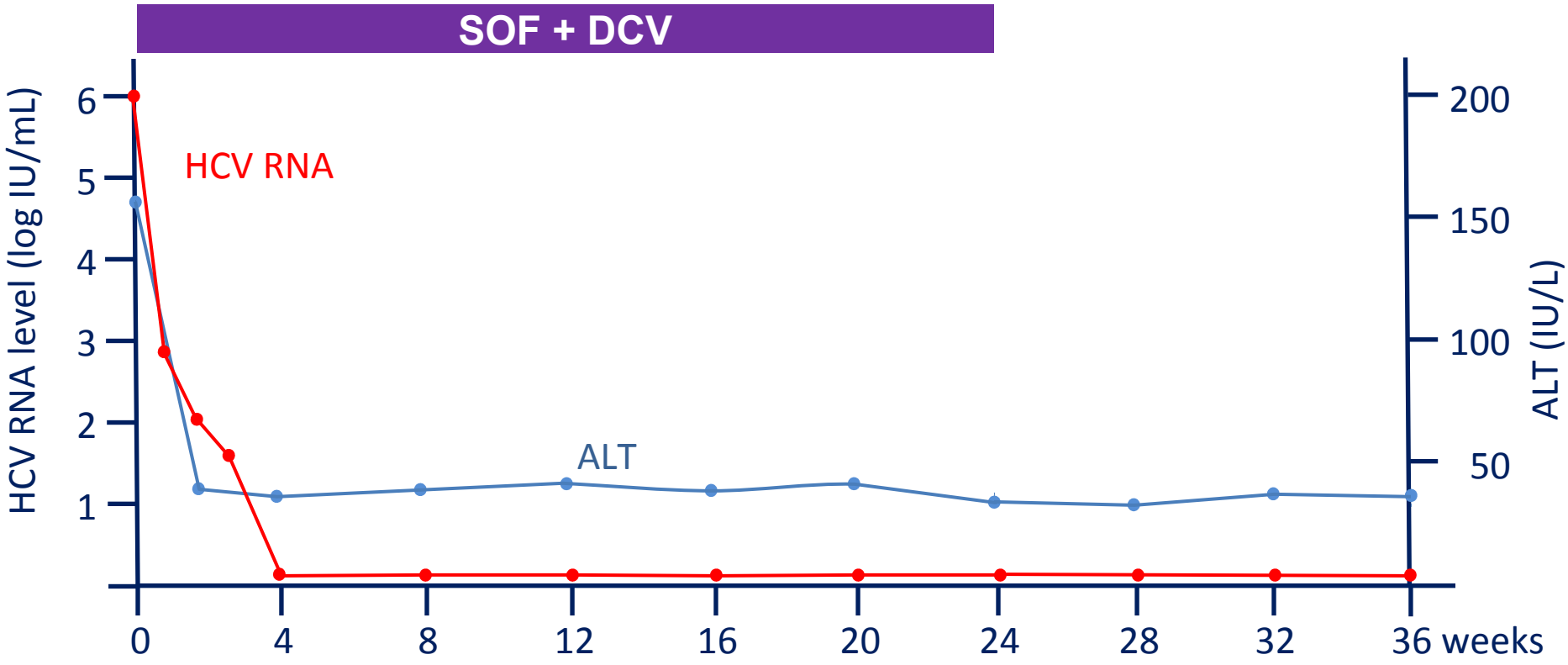
Case Presentation (5)

- Treatment #6 (2015): SOF + DCV
  - Duration 24 weeks (february to august)



Case Presentation (6)

- Treatment #6 (2015): SOF + DCV 24 weeks (february to august)
- FibroScan 19,6 kPa in december 2015
- AST 26 UI/L, ALT 40 UI/L, GGT 111 UI/L (December 2015)
- No more fatigue



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- Relapse after 24 weeks of SOF + RBV

- SVR after 24 weeks of SOF + DCV

Why did the treatment work ?

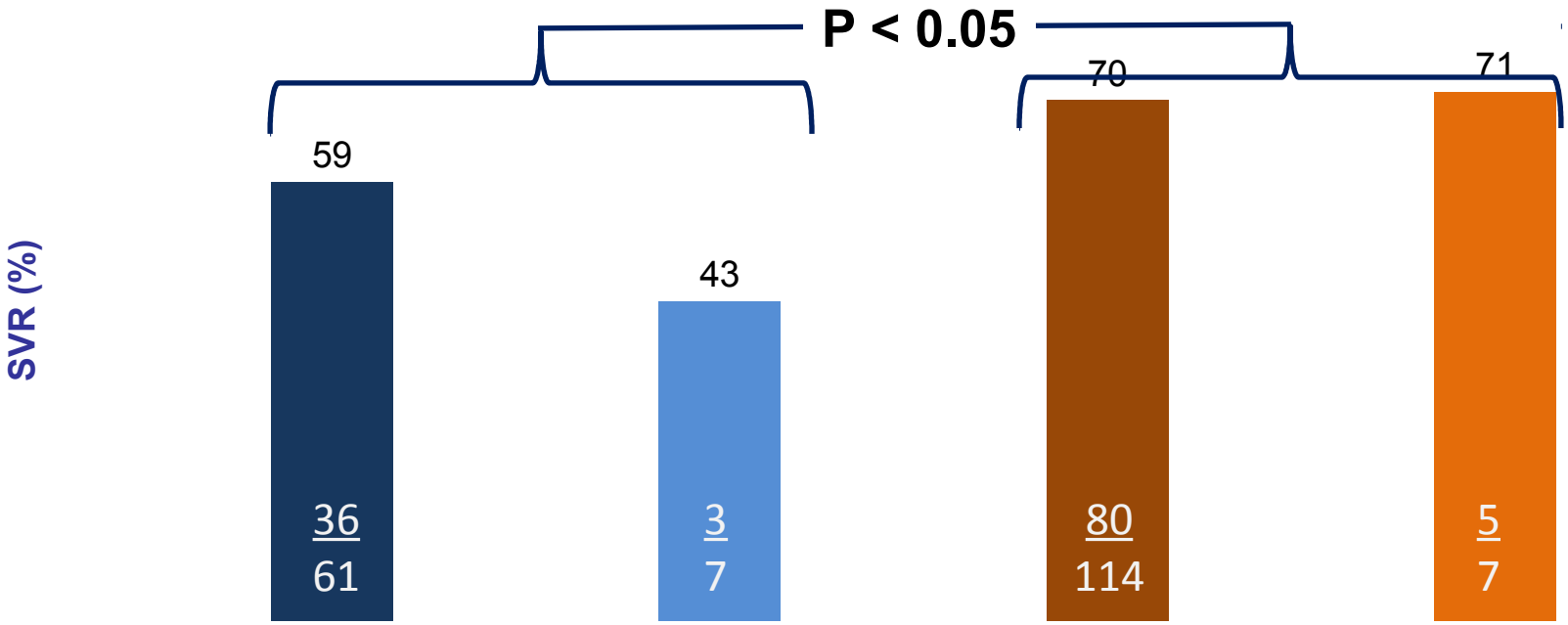
Sofosbuvir + Ledipasvir ± RBV
Sofosbuvir + Daclatasvir ± RBV

GT3

Naïve / TE

Observational cohort of NHSE (UK)

- At physician's discretion, patients received SOF + LDV or DCV ± RBV
- Decompensated cirrhosis (CP B: 64%; CP C: 13%)
- **Treatment duration 12 weeks**



Foster GR, et al. EASL 2015. Abstract O002

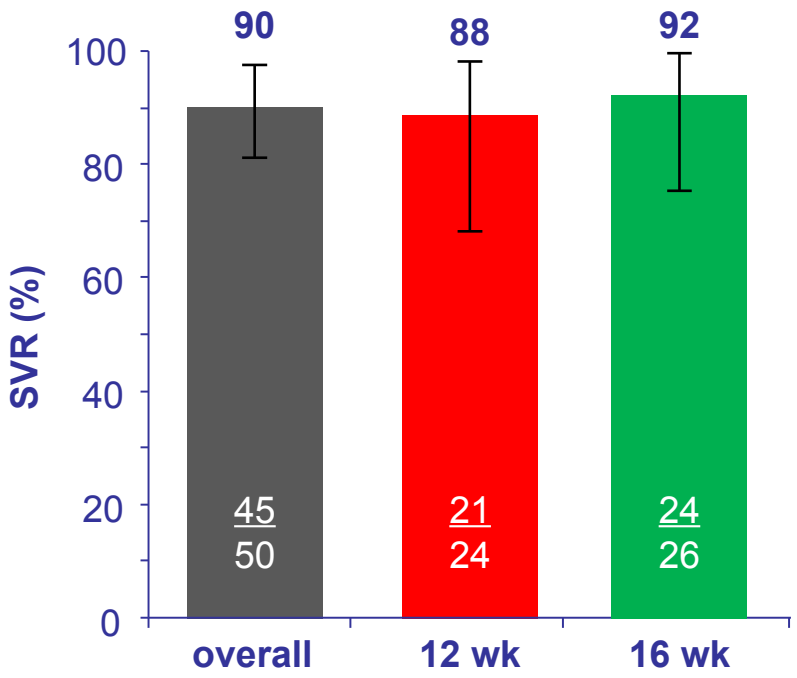
Sofosbuvir + Daclatasvir + RBV

GT3

Naïve / TE

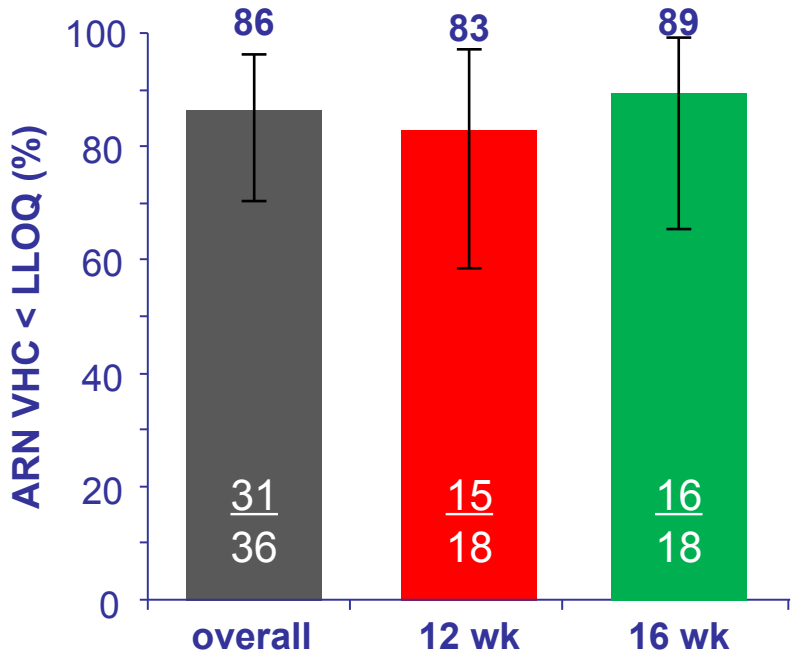
ALLY-3+

All patients (F3 and compensated F4)



Breakthrough	0	0	0
Relapse	4	2	2
Death	1	1	0

Compensated F4



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Leroy V, AASLD 2015, Abs. LB3

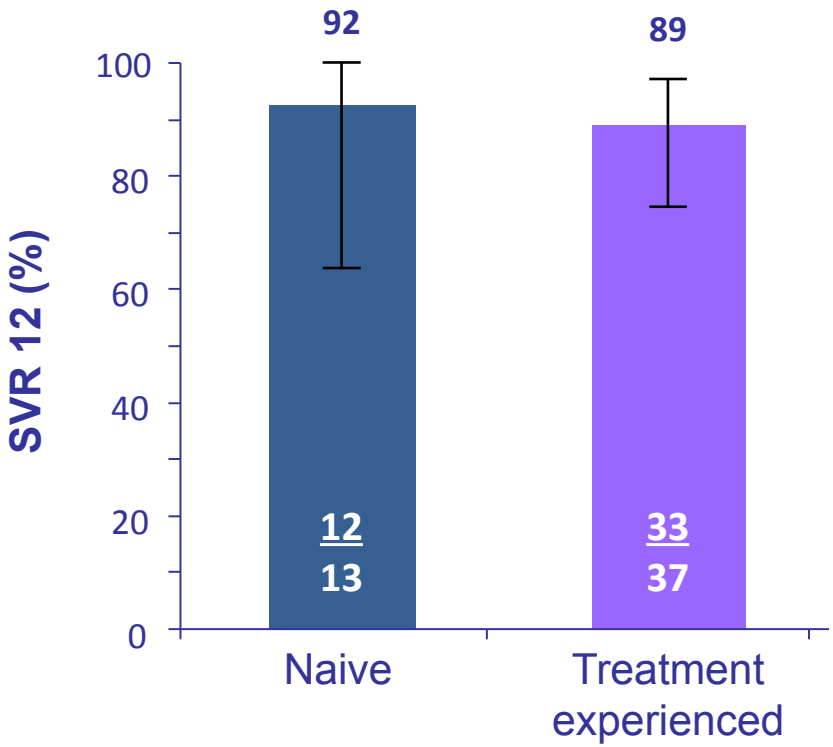
Sofosbuvir + Daclatasvir + RBV

GT3

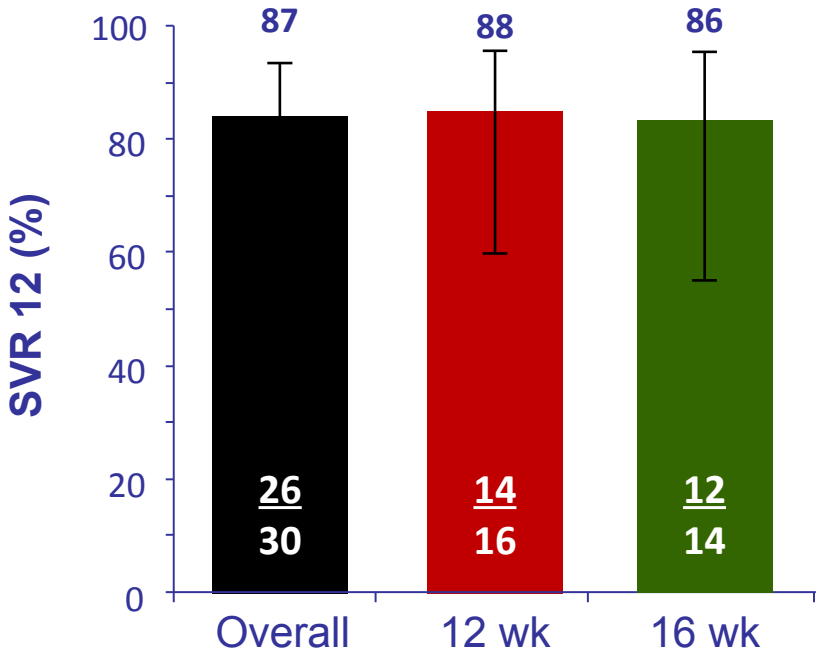
Naïve / TE

ALLY-3+

All patients



F4 treatment experienced



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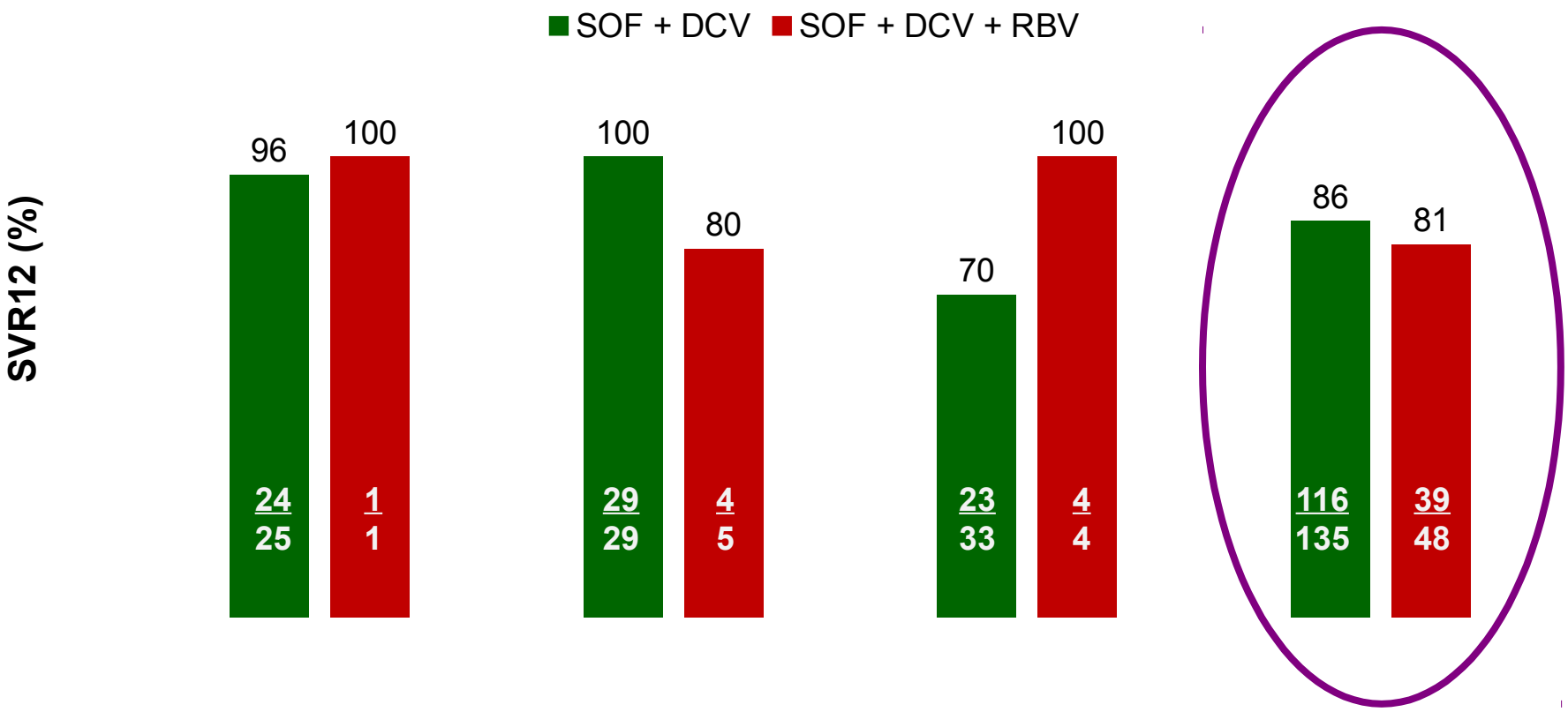
Sofosbuvir + Daclatasvir ± RBV

GT3

Naive or TE

French Early Access Program

- 284/ 561 patients (completed therapy with SVR12 data)
- Baseline characteristics: Male: 75%, F4: 79%, F3: 15%, Previously treated: 73%, Liver Transp: 8.5%



Hézode C, AASLD 2015, Abs. 206

No difference regarding RBV use

Sofosbuvir + Daclatasvir ± RBV

GT3

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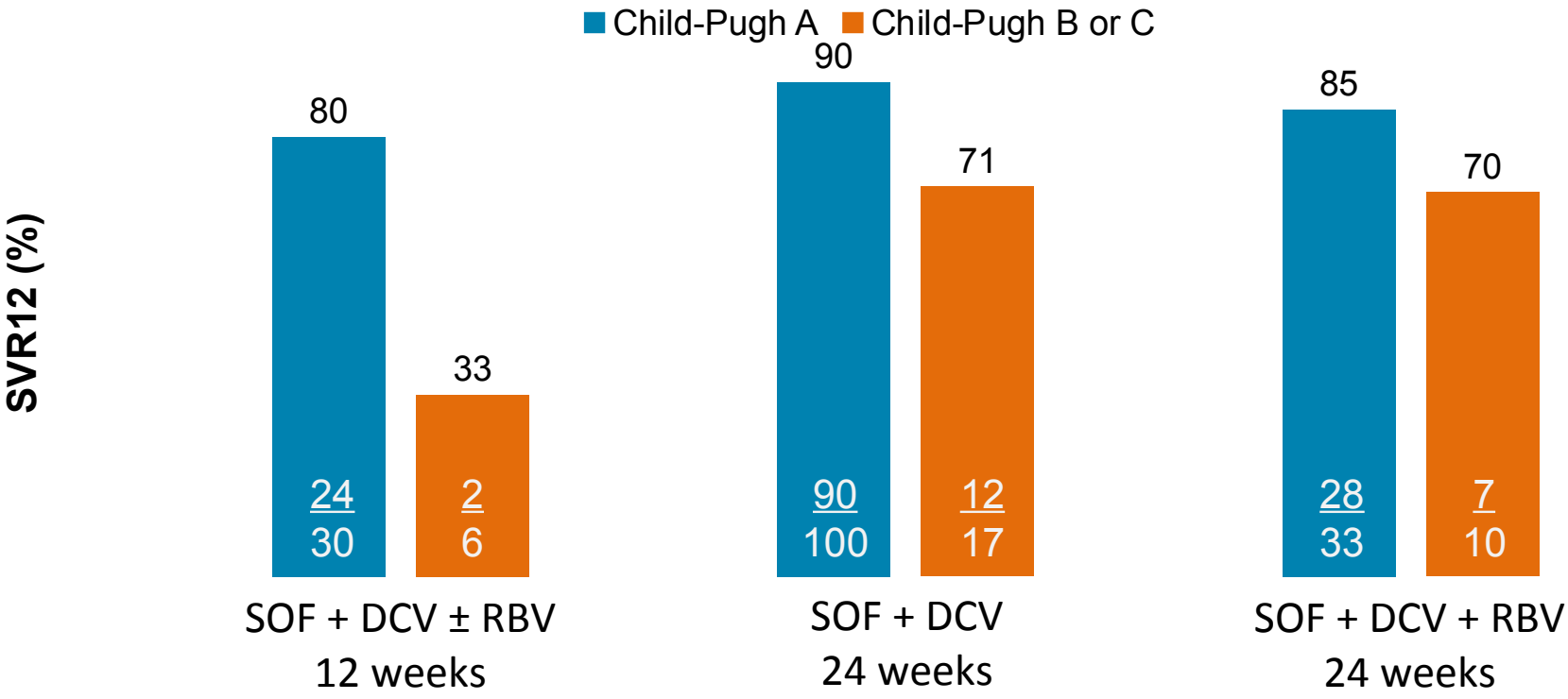


24 wk: No difference regarding RBV use

Hézode C, AASLD 2015, Abs. 206

Next generation DAAs for HCV GT3

Next generation DAAs for HCV GT3

Near Future (2016)

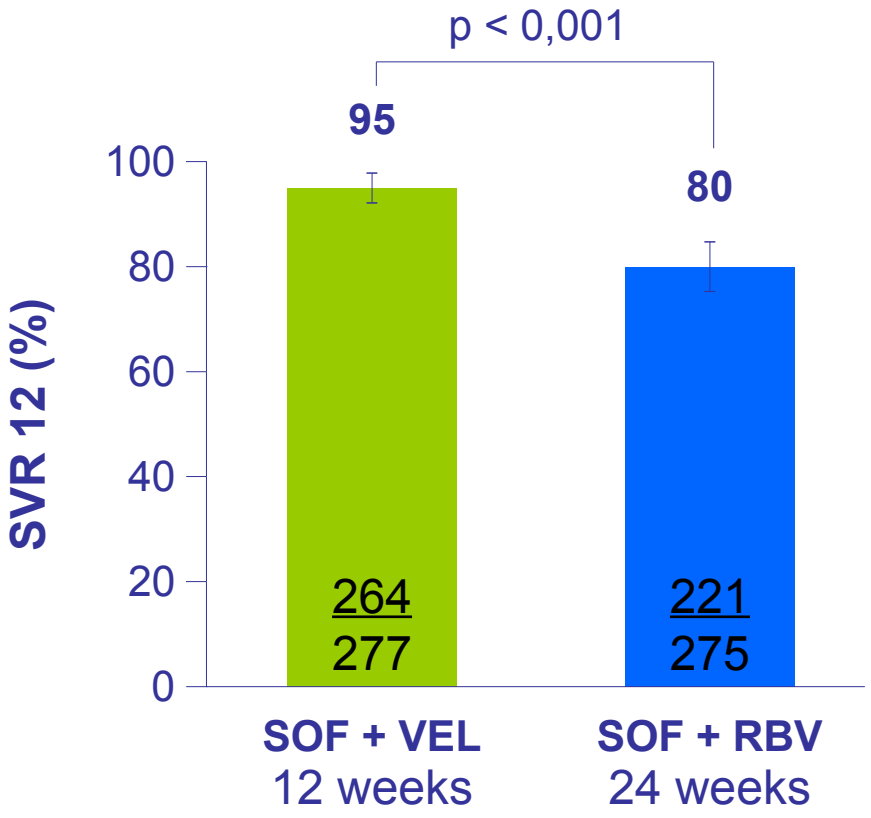
Sofosbuvir + Velpatasvir
Sofosbuvir + RBV

GT3

Naive or TE

ASTRAL 3

- Cirrhosis: 30%
- Treatment-experienced: 26%



Foster GR et al. N Engl J Med 2015;373:2608-17.

Sofosbuvir + Velpatasvir
Sofosbuvir + RBV

GT3

Naive or TE

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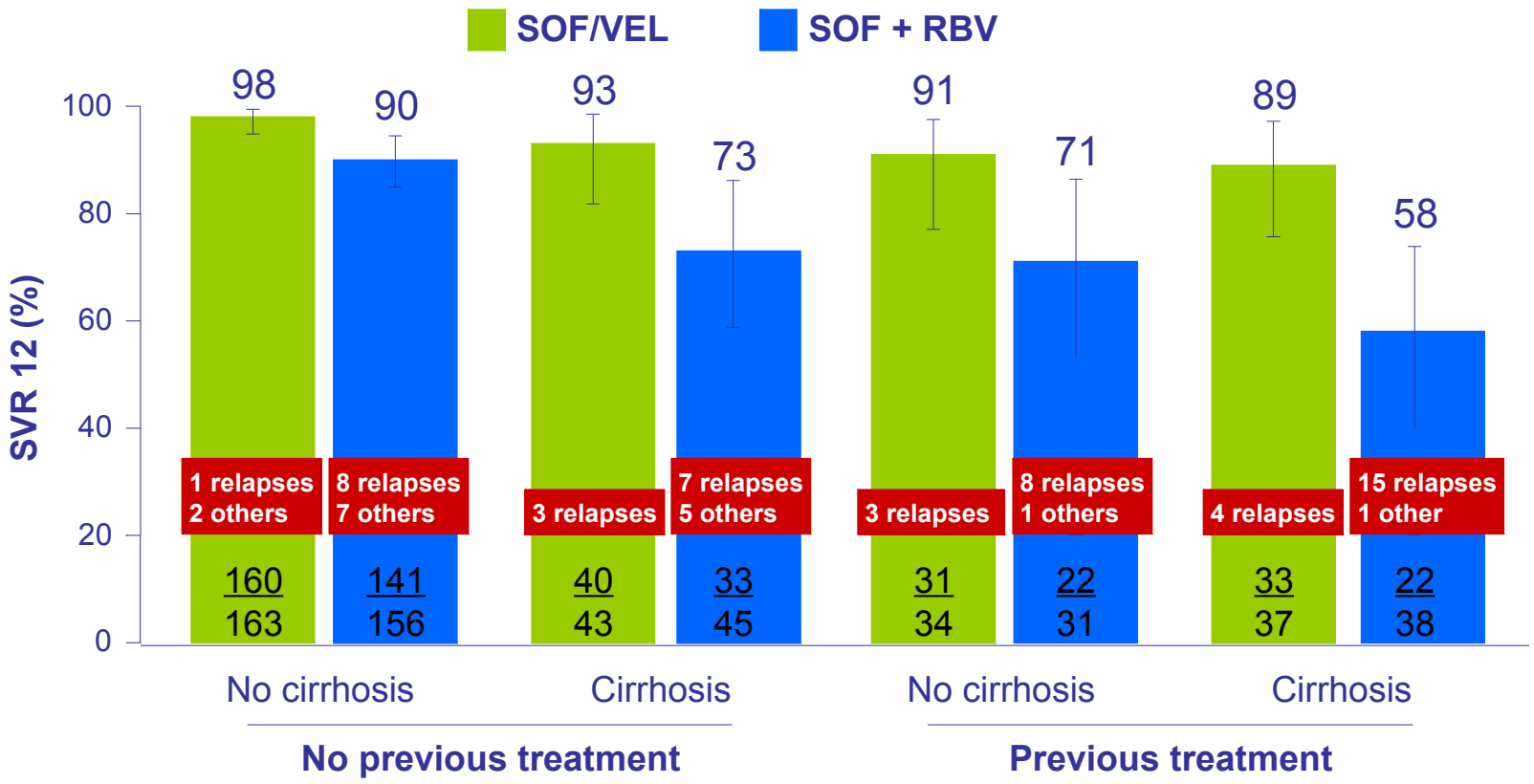

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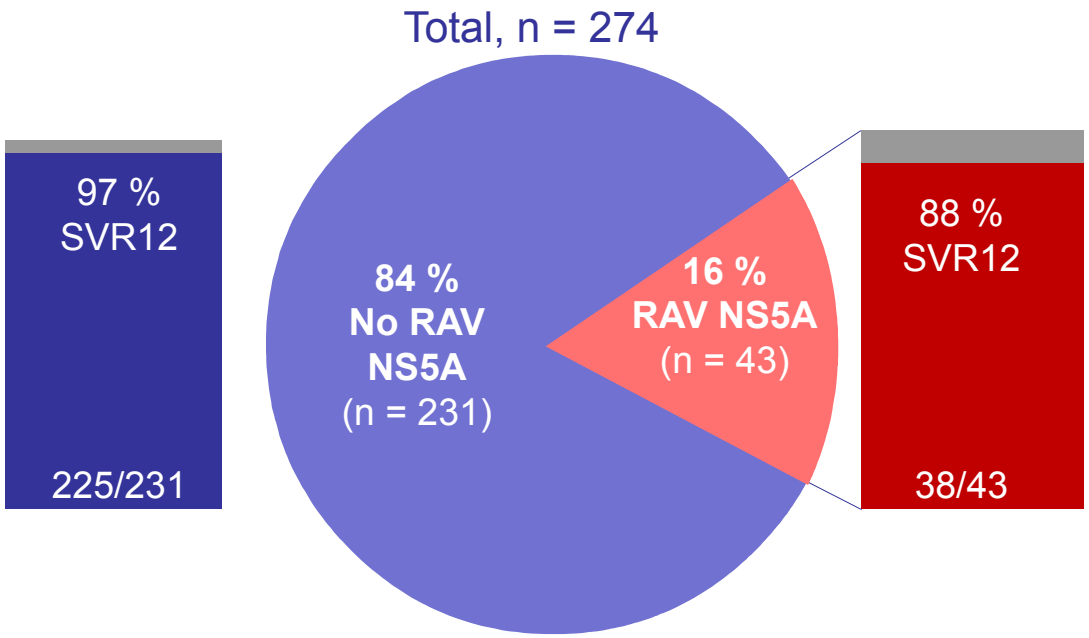
Sofosbuvir + RBV

GT3

Naive or TE

ASTRAL 3



SVR 12 : 84 % (21/25) in patients with Y93H mutation

Foster GR et al. N Engl J Med 2015;373:2608-17.

Next generation DAAs for HCV GT3

In the long term (2017 and after)

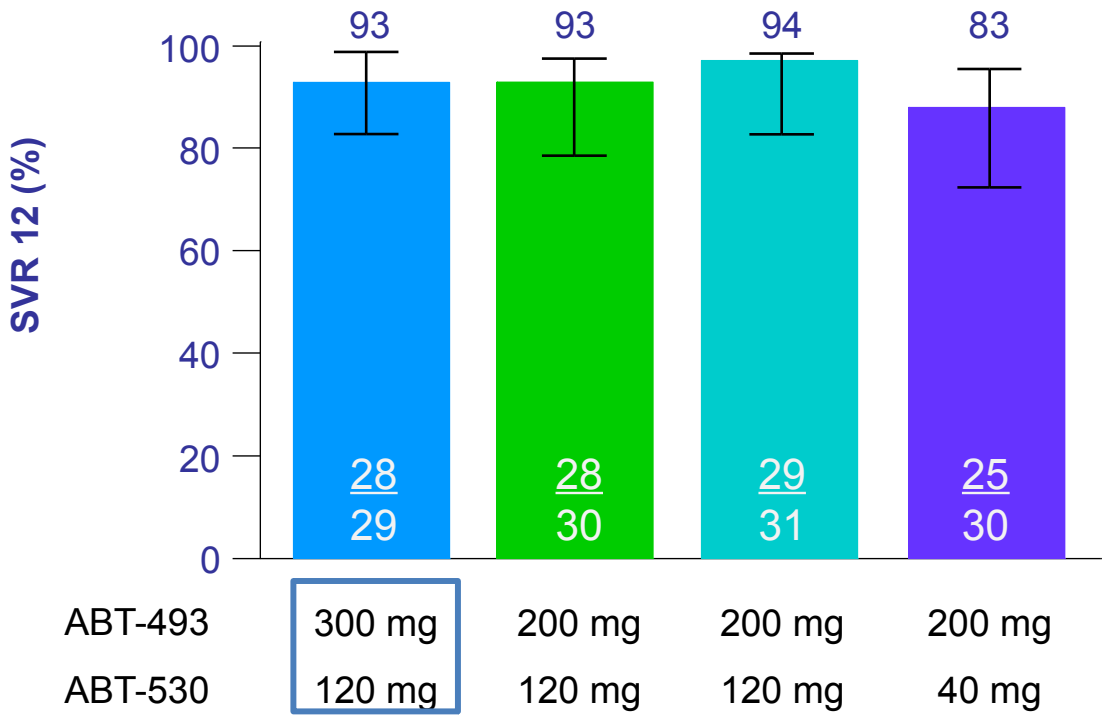
ABT-493 + ABT-530 12 weeks

GT3

Naive or TE

SURVEYOR 2

- ABT 493 : NS3/4A protease pangenotypic inhibitor
- ABT 530 : NS5A pangenotypic inhibitor
- Treatment naive: 90-93%, non cirrhotic

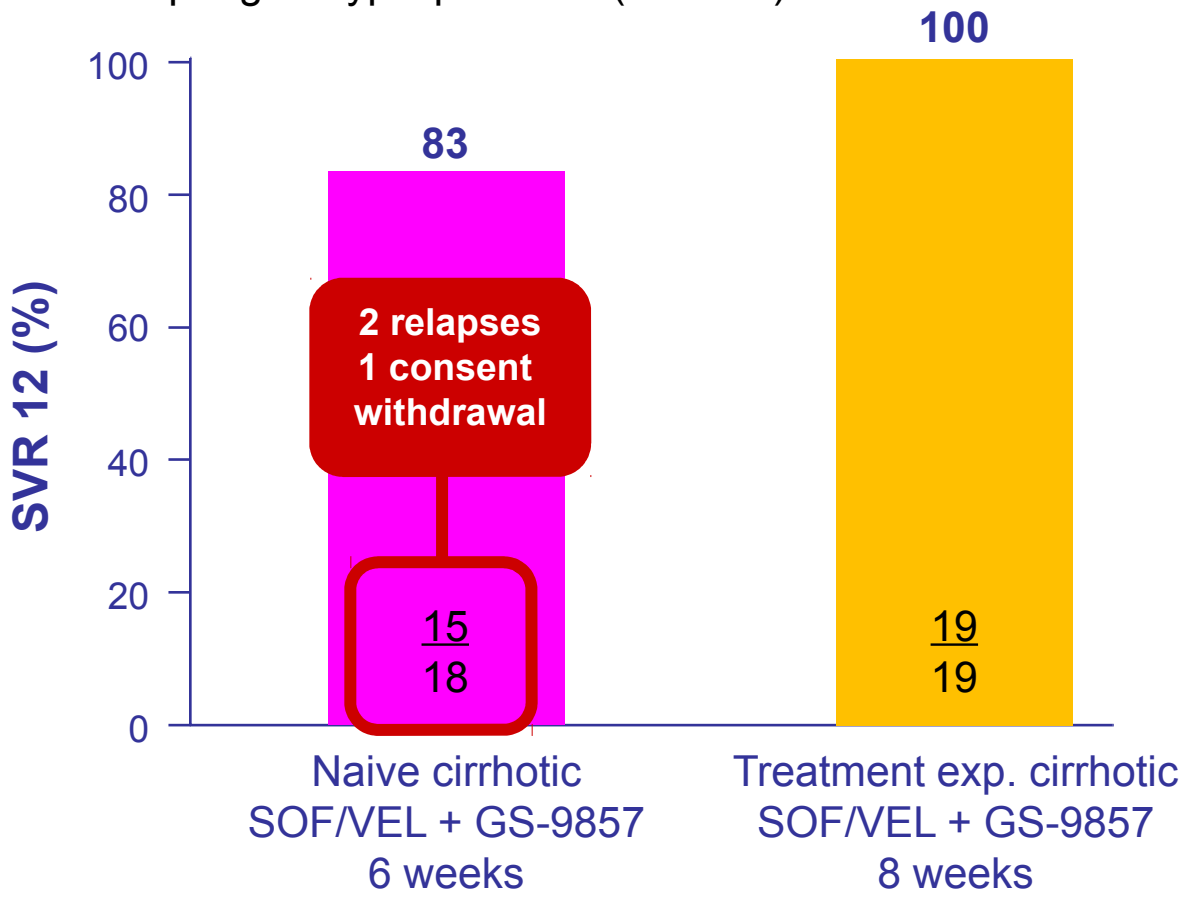


Kwo P, AASLD 2015, Abs. 248

SOF/VEL + GS-9857

LEPTON

- GS-9857: pangenotypic protease (NS3/4A) inhibitor



Gane EJ, AASLD 2015, Abs. 38

Grazoprevir + Elbasvir ± RBV
Grazoprevir + MK-8404 + MK-3682

GT3

Naïve

C-CREST 1 & 2A

- GZR/EBR ± RBV 12 weeks

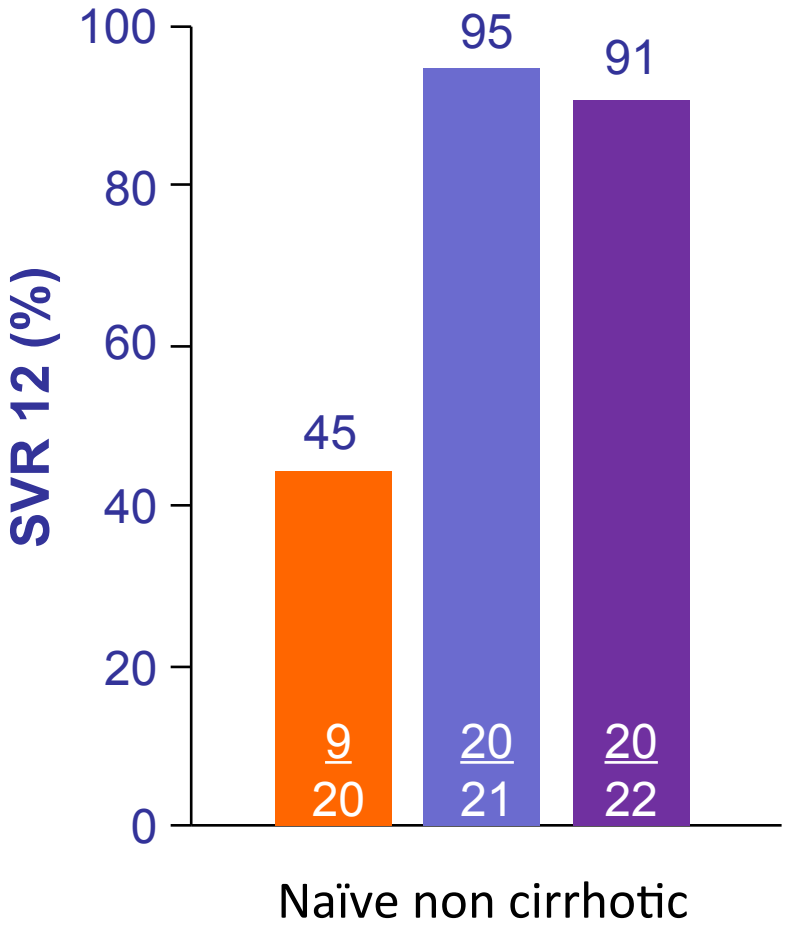
  Grazoprevir (GZR): protease inhibitor
  Elbasvir (EBR): NS5A inhibitor

- GZR/MK-8408/MK-3682 (300 mg) 8 weeks

  Grazoprevir (GZR): protease inhibitor
  MK-8404: NS5A inhibitor
  MK-3682: NS5B inhibitor

- GZR/MK-8408/MK-3682 (450 mg) 8 weeks

  Grazoprevir (GZR): protease inhibitor
  MK-8404: NS5A inhibitor
  MK-3682: NS5B inhibitor



Gane EJ, AASLD 2015, Abs. LB15

Question (3)

In january 2017 (10th PHC),

what will be your recommendation in a patient

who relapse after 24 weeks SOF + RBV treatment ?

1. Carefull follow-up and HCC screening and wait for new triple DAAs combination (such as GZR + MK-8408 + MK-3682 or SOF/VEL + GS-3682)
2. Treatment using Sofosbuvir + Daclastasvir for 24 weeks
3. Treatment using Sofosbuvir + Velpatasvir for 12 weeks
4. Treatment using Grazoprevir + Elbasvir + ribavirin for 12 weeks

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Conclusion

2 situations

- GT3 without cirrhosis: easy to cure
- GT3 with cirrhosis: difficult to manage
  - Extending therapy to 24 weeks may be an option
  - RBV may play a role

Sub-optimal treatment must be avoid (SOF + RBV, SOF/LDV + RBV)

- Which combination in january 2016 ?
  - Without cirrhosis:
    - SOF + DCV 12 weeks
  - With cirrhosis:
    - SOF + DCV ± RBV 24 weeks
    - SOF + PEG-IFN + RBV 12 weeks (compensated)
    - SOF + DCV + RBV 16 weeks (compensated)


THANK YOU
FOR YOUR ATTENTION