Cirrhotic and/or experienced patients

Philippe Sogni

Paris-Descartes University, INSERM U-1016 and
Hepatology unit, Cochin hospital, Paris; France

Philippe Sogni – Disclosures

- Board, workshop participations or meeting invitations: Gilead, Bristol-Myers Squibb, Schering-Plough / MSD, Roche, Janssen, Mayoly-Spindler

- Sub-investigator in HCV trials: Bristol-Myers Squibb, Roche, Schering-Plough / MSD, Gilead, Boehringer Ingelheim, Tibotec, Vertex, Janssen.

CASE 1

Mr. M.

- Male, 56 y.o.
- Weight 83 kg / size 176 cm (BMI = 27 kg/m^2)
- General good condition
- Diabetes treated with metformine
- Tobacco = 0, alcohol = 1 to 3 units/d actually
- HCV + since a long time (IVDU in 80's) but never explored
- He comes to see you because he heard about new treatments for HCV

Mr. M. (2)

- Palpation of the liver: lower edge hard
- Hb 14.8 g/dl; platelets 90,000; leukocytes 5,500
- ASAT 2xN; ALAT 3xN; gGT 3xN; bilirubin 17 µmol/L
- INR 1.4; albumin 29 g/L; creatinin 90 µmol/L
- Glucose 1.3 g/L, glycated Hb 7.3%
- US: hyper-echogenicity of the liver, liver dysmorphy, spleen upper limit, no ascites, no portal vein thrombosis
- FibroScan™ 19.3 kPa (IQR 1.9)
- HCV genotype 1b; HCV viral load 6.2 log UI/mL
- HBsAg –, antiHBs +, antiHBc + and HIV –

Mr. M.
Q1: Do you think that?

A. Mr M. has a liver cirrhosis due to HCV and I treat and follow him as recommended
B. He has a liver cirrhosis due to HCV, metabolic syndrome and alcohol, and I treat and follow him as recommended
C. I'm not convinced for the diagnosis of cirrhosis and I propose a liver biopsy
D. I'm convinced but he has a multifactorial liver disease and I propose a liver biopsy to try to understand

Mr. M.
A1: Do you think that?

A. Mr M. has a liver cirrhosis due to HCV and I treat and follow him as recommended

B. He has a liver cirrhosis due to HCV, metabolic syndrome and alcohol, and I treat and follow him as recommended

C. I'm not convinced for the diagnosis of cirrhosis and I propose a liver biopsy

D. I'm convinced but he has a multifactorial liver disease and I propose a liver biopsy to try to understand

He has a liver cirrhosis due to HCV, metabolic syndrome and alcohol, and I treat and follow him as recommended

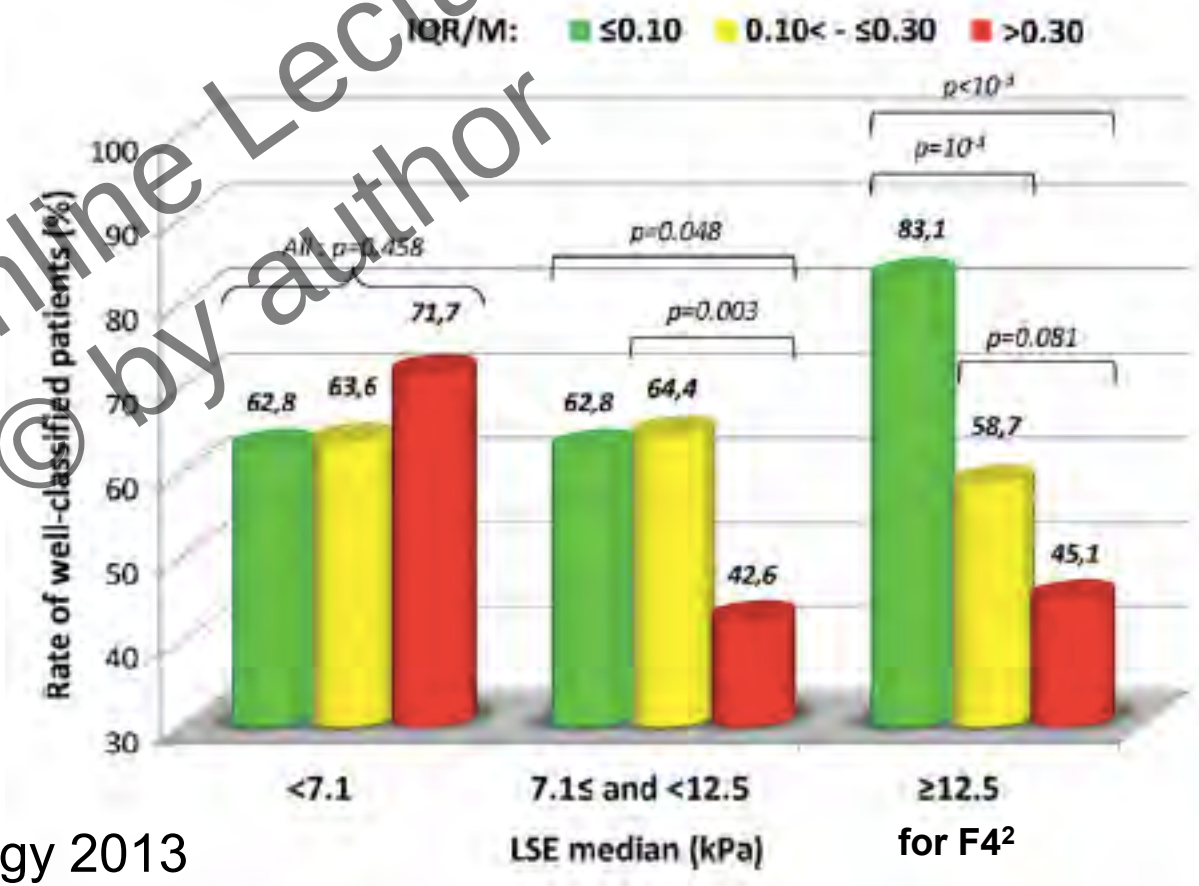
- Cirrhosis: association of clinical, platelets, INR, US and FibroScan™ results

➢ Cirrhosis Child-Pugh A6 / MELD Score 10

Evaluation with FibroScan™ Rate of well classified patients[1]

- 1,165 patients with chronic liver disease from 19 French centers
- All patients had Liver Biopsy and LSE with FibroScan™

Mr. M.:
LS = 19.3 kPa
IQR = 1.9
IQR / M = 0.10



[1]Boursier J et al. Hepatology 2013
[2]Castera L et al. Gastroenterology 2005

LSE: Liver Stiffness Evaluation

Mr. M. (3)

Upper digestive endoscopy: no esophageal varices, gastritis

Alcohol	Metabolic syndrome	HCV
Stop !	• Optimized treatment of the diabetes • Check arterial pressure, cholesterol, triglycerides… • Physical exercise • Decrease weight • Cardio-vascular evaluation • …	Treatment

➔ Follow-up every 6 months: clinical, biological and US

Mr. M.
Q2: How I treat him for HCV?

A. I treat him with PegIFN + RBV
B. I treat him with PegIFN + RBV + telaprevir
C. I treat him with PegIFN + RBV + boceprevir
D. I think that he has a too severe liver disease to be treated with PegIFN + RBV telaprevir or boceprevir

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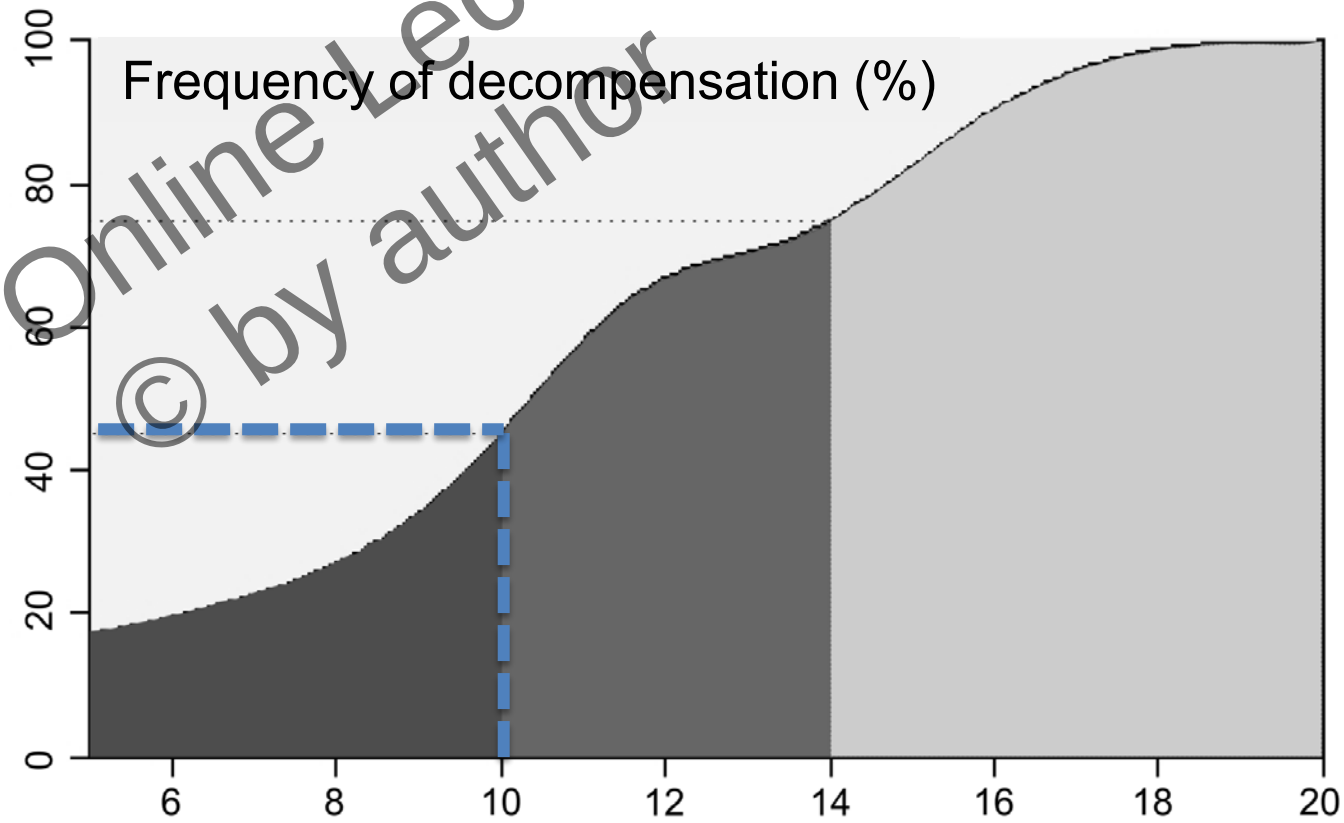
Liver decompensation during anti-viral treatment in patients with HCV cirrhosis

- 68 patients with HCV-associated liver cirrhosis (MELD score 9.2 2.7)
- PegIFN + RBV: SVR in 26.5% and hepatic decompensation in 36.8%

Univariate analysis
- MELD
- Bilirubin
- Platelets
- Albumin
- Leukocytes

Multivariate analysis
- MELD



Dultz G et al. PlosOne 2013

Liver decompensation during anti-viral treatment in patients with HCV cirrhosis

- **ANRS CO20-CUPIC cohort (ClinicalTrials.gov NCT01514890)**
- HCV-G1 Child-Pugh A cirrhotic experienced IFN-based treatment patients
- Patients treated with PegIFN + RBV + TVR or PegIFN+RBV+BOC

Factors associated with death or severe complication (mutivariate analysis)

Factors	Platelet count >100,000/mm³	Platelet count ≤100,000/mm³
Serum albumin		
≥35 g/L	3.4% (10/298)	4.3% (3/69)
<35 g/L	7.1% (2/28)	44.1% (15/34)

Fontaine H et al. EASL 2013 / Hezode C et al. J Hepatol 2013

Mr. M. (4)

Treated Mr M. with PegIFN+RBV or PegIFN+RBV+TVR or PegIFN+RBV+BOC

Risk of SAEs ≈ 45%

- **SVR with PegIFN+RBV** **33 – 38%[1,2]**
- **SVR with PegIFN+RBV+TVR** **62%[1]**
- **SVR with PegIFN+RBV+BOC** **41 – 52%[2]**

[1]Jacobson IM et al. N Engl J Med 2011 (phase 3: naïve HCV-1 F4 patients)
[2]Poordad F et al. N Engl J Med 2011 (phase 3: naïve HCV-1 F3-F4 patients)

Mr. M. (5)

- If I want to treat Mr M. with IFN-based regimen ➔ Evaluate for Liver Transplantation

- If not ➔ try with DAAs (or wait for DAAs)

Mr. M. – Take Home Messages

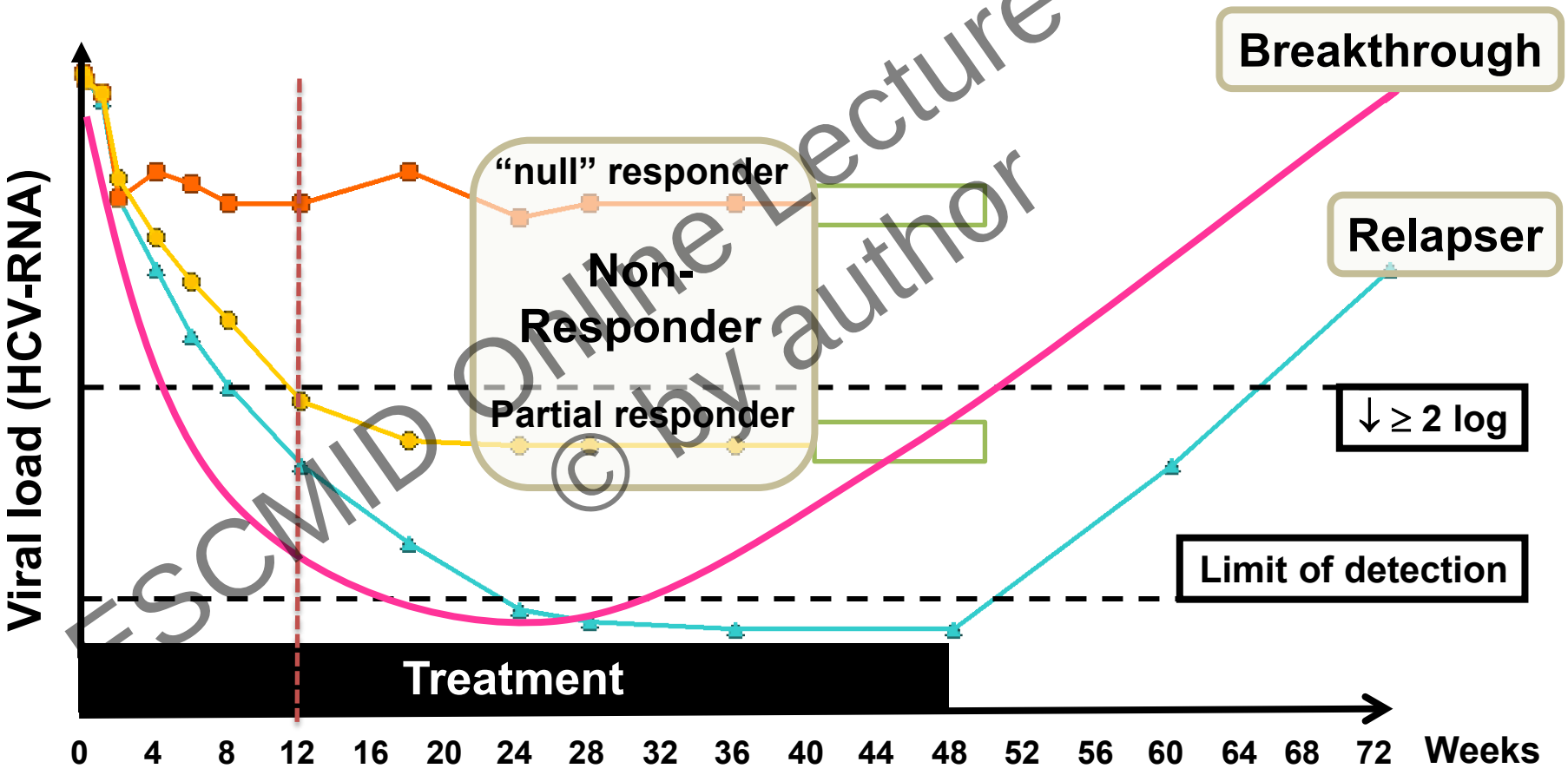
1. Evaluate carefully the severity of liver cirrhosis
2. To treat now or to wait for new molecules is a difficult question at this time
3. Treatment of cirrhotic patients with IFN-based therapy is at risk (MELD / platelets / albumin…)
4. Evaluate patients for Liver Transplantation if you want to treat cirrhotics with IFN-based therapy?
5. Take into account other causes of liver disease than viral infection, like alcohol or metabolic syndrome

CASE 2

Mrs. F.

- Female, 62 y.o.
- Weight 58 kg / size 155 cm (BMI = 24 kg/m^2)
- General good condition
- Cholesterol: treatment with simvastatine
- Tobacco = 0, alcohol = 0
- HCV +; genotype 1a (transfusion hepatitis)
- HBsAg –, antiHBs +, antiHBc – (vaccıne) and HIV –
- PegIFN + RBV (2009): null responder
- Liver Biopsy (2011): A1-F3
- ALAT 2xN; liver US normal; no argument for cirrhosis

Failures of treatment



Mrs. F.

Q1: You want to retreat her with PegIFN+RBV What is the success rate expected?

A. 5 %
B. 10 %
C. 15 %
D. 20 %
E. 30 %

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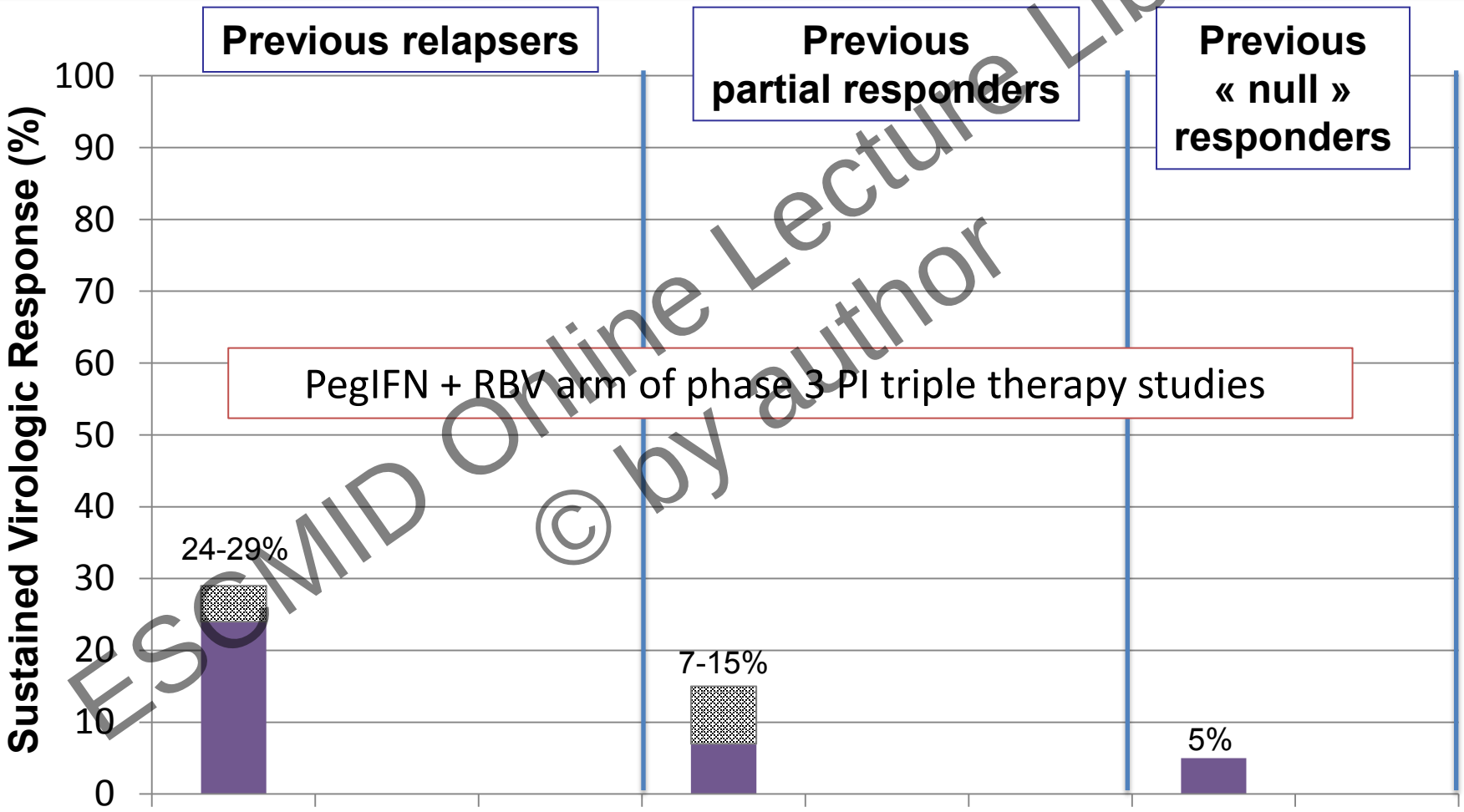
Re-treatment with PegIFN + RBV



Bacon BR et al. N Engl J Med 2011 / Zeuzem S et al. N Engl J Med 2011

Mrs. F.

Q2: You want to retreat her with PegIFN+RBV+TVR. What is the success rate expected?

A. 5 %
B. 10 %
C. 15 %
D. 20 %
E. 30 %

Mrs. F.

A2: You want to retreat her with PegIFN+RBV+TVR. What is the success rate expected?

A. 5 %
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C. 15 %
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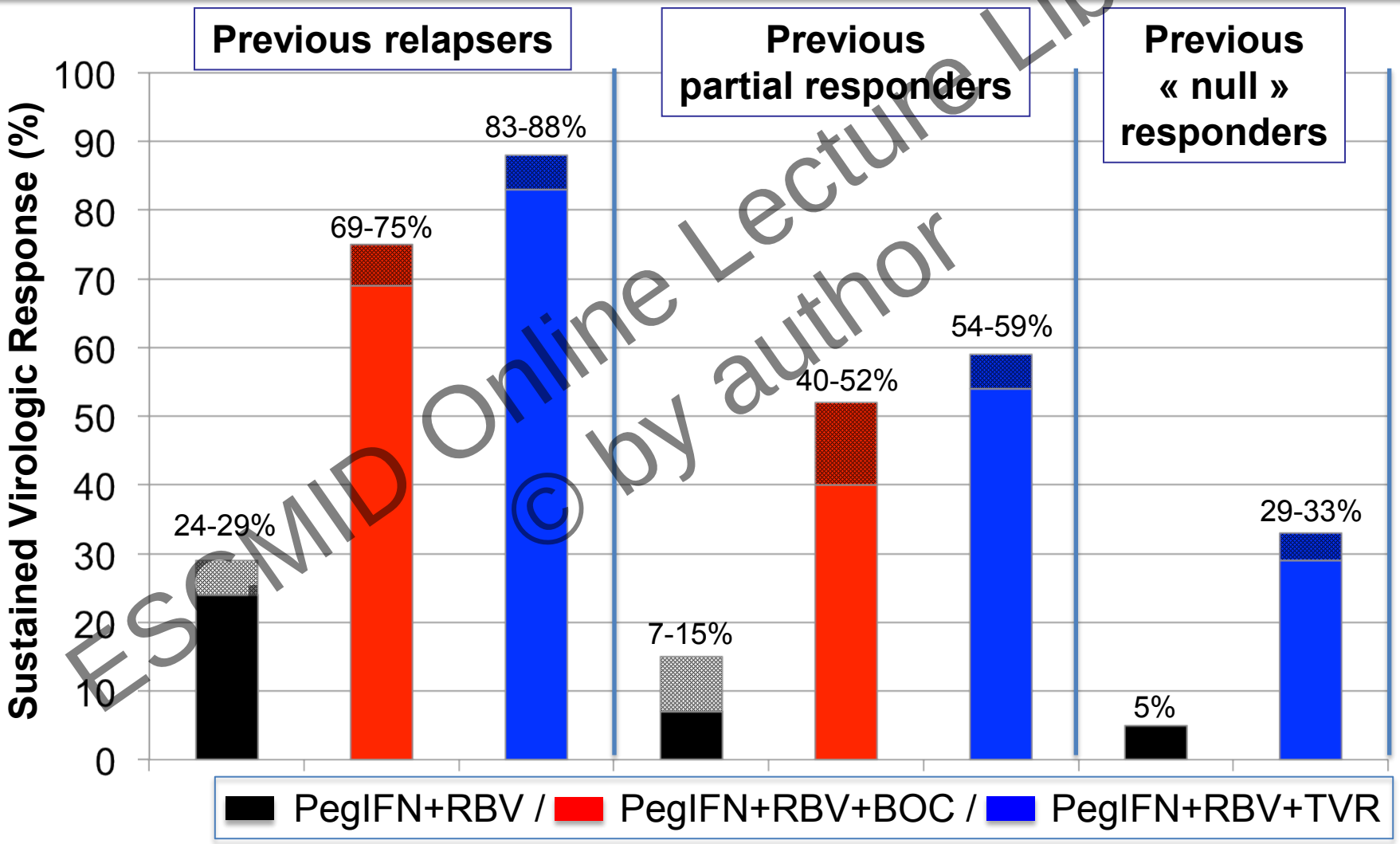
Re-treatment with PegIFN + RBV ± PI

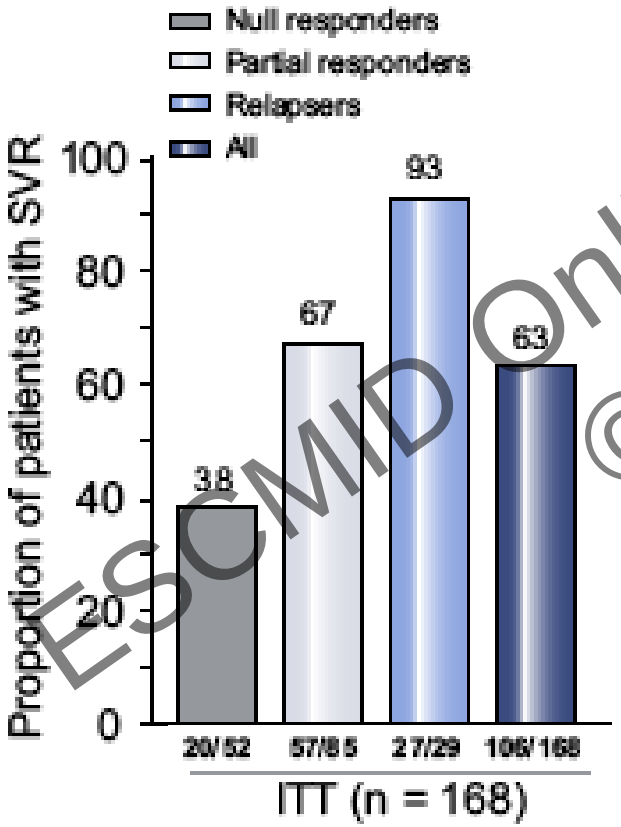


Bacon BR et al. N Engl J Med 2011 / Zeuzem S et al. N Engl J Med 2011

Treatment of PegIFN + RBV + BOC or TVR in experienced patients

PegIFN + RBV + BOC

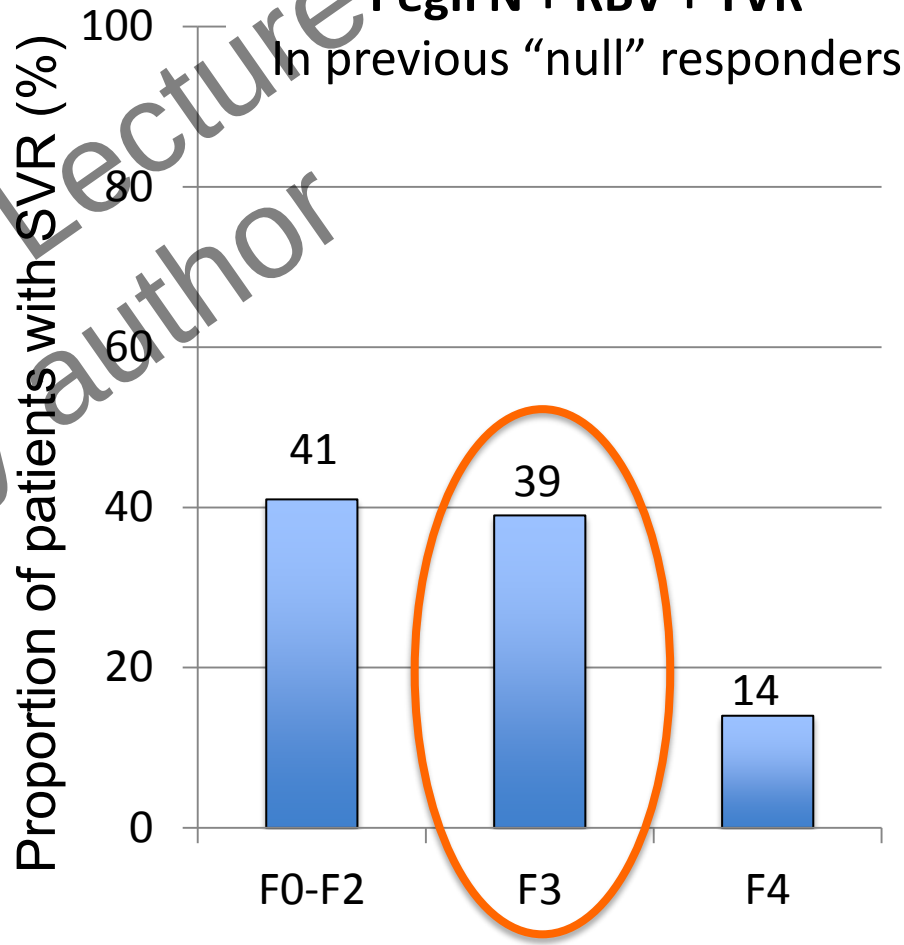
Relation with previous failure



Vierling JM et al.
J Hepatol 2014 (in press)

PegIFN + RBV + TVR

In previous "null" responders



Zeuzem S et al.
N Engl J Med 2011

Mrs. F. (2)

- You have explain her the expected success rate of a retreatment with PegIFN + RBV PI
- She had experienced a lot of secondary effects with the first treatment and she don't want to be retreated with IFN-based regimen
- She looks on internet and asks you that a lot of new molecules arrive

Mrs. F.

Q3: She asks you that a lot of new molecules arrive. What is your response?

A. Its true and you can do that right now
B. Its true but the first step possible for her in Feb 2014, is to combine 1 new DAA and PegIFN + RBV
C. Its true but in Feb 2014, it depends of the availability of each new DAA in each european country

Mrs. F.

A3: She asks you that a lot of new molecules arrive. What is your response?

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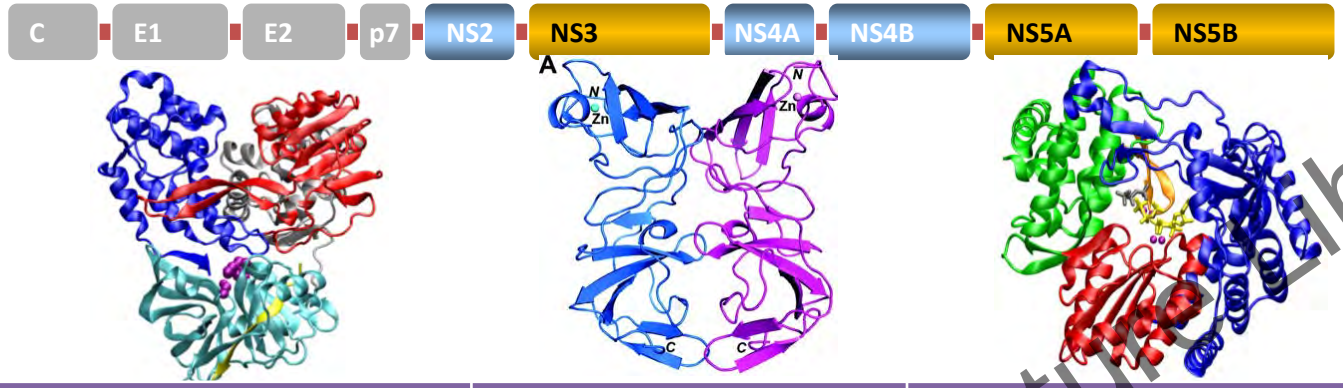
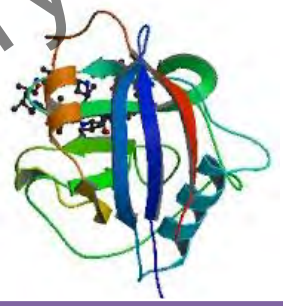
Viral targets

Host targets





NS3/4A Protease Inhibitors	NS5A Replication Complex Inhibitor	NS5B Nucleos(t)ide or non-nucleos(t)ide Inhibitors	Cyclophilin A
The NS3/4A serine protease is essential for post-translational processing of HCV polyproteins	Multifunctional membrane-associated phosphoprotein essential component of the HCV-RNA replication complex[2]	NS5B is an HCV-specific, RNA-dependent RNA polymerase[1]	Host protein involved in HCV replication through interaction with NS5A and the HCV polymerase[4]
Boceprevir Telaprevir MK 7009 (Vaniprevir), BI-201335 (Faldaprevir), TMC-435 (Simeprevir), ABT-450/r, Asunaprevir, Danoprevir/r, GS-9451, ACH-1625, MK-5172	**Daclatasvir (BMS 790052) GS-5885 ABT-267** PPI-668	Nucleos(t)ide analogue **Sofosbuvir (GS-7977), Mericitabine (RG 7128)**, IDX-184* Non-nucleoside analogue **BI-207127, ABT-333, Tegobuvir (GS9190)**, ABT-072, BMS-791325, Setrobuvir, VX-222, Filibuvir	Alisporivir** SCY-635
• Poor/no activity against GT3 • Low-to-medium barrier to resistance • Extensive cross-resistance • QD, BID or TID dosing • Potential for CYP-mediated DDIs	• Picomolar activity against multiple GTs *in vitro* • Low-to-medium barrier to resistance • QD dosing • Potential for CYP-mediated DDIs	• Broad GT coverage • High barrier to resistance • QD or BID dosing • Limited potential for CYP-mediated DDIs	• Most are GT/subtype specific[1] • Low barrier to resistance[1] • QD or BID dosing[8] • Limited potential for CYP-mediated DDIs[9]	• Broad GT coverage *in vitro* • Limited resistance data available • BID/QD dosing • Potential for CYP-mediated DDIs

Pol, Corouge & Sogni. Ther Adv Infect Dis 2014

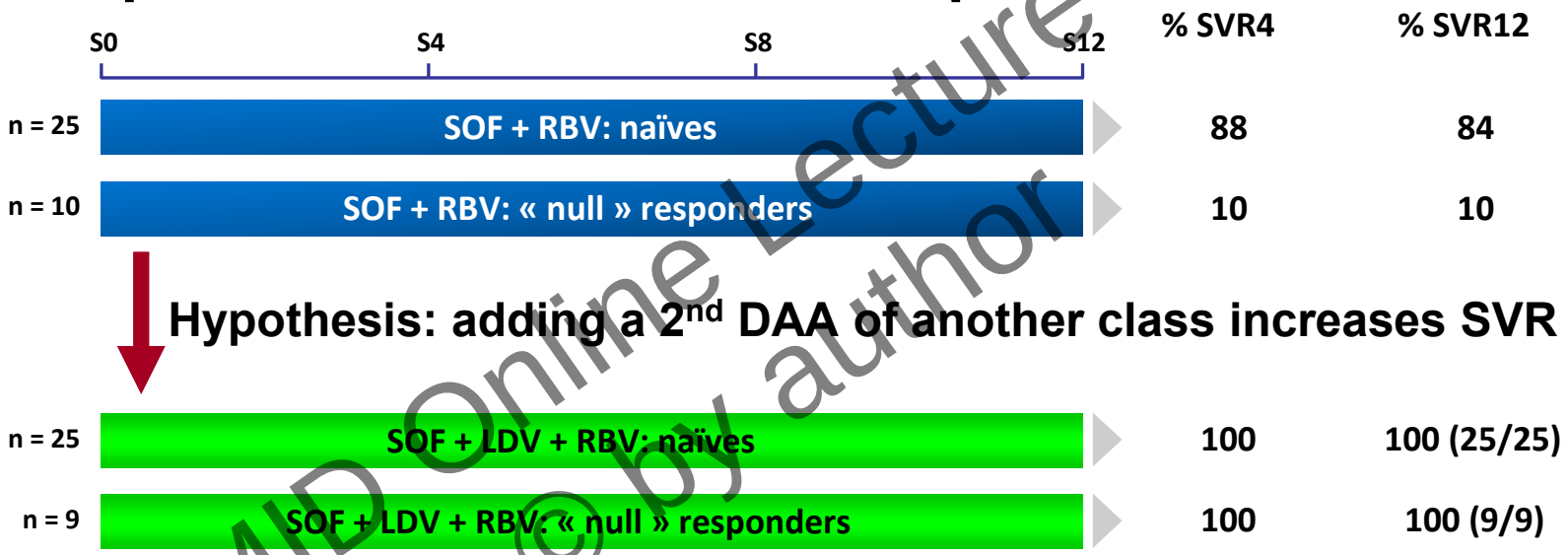
Results of phase 2 and 3 studies evaluating Sofosbuvir for GT1 patients

Patient population	Treatment	Sub-group	SVR12
Naïve (NEUTRINO[1])	SOF + PegIFN + RBV 12 weeks	Global	90%
		GT 1a	92%
		GT 1b	83%
		Cirrhosis	80%
Naïve HIV-HCV co-infected (PHOTON-1[2])	SOF + RBV 24 weeks	Global	76%
		GT 1a	82%
		GT 1b	54%
		Cirrhosis	60%
Naïve (QUANTUM[3] & 11-1-025g[4])	SOF + RBV 24 weeks	Global	65%
		GT 1a	69%
		GT 1b	53%
		Cirrhosis	36%

[1]Lawitz E et al. N Engl J Med 2013 / [2]Sulkowski MS et al. AASLD 2013
[3]Lalezari JP et al. EASL 2013 /[4]unpublished

Without IFN: need for DAAs combination

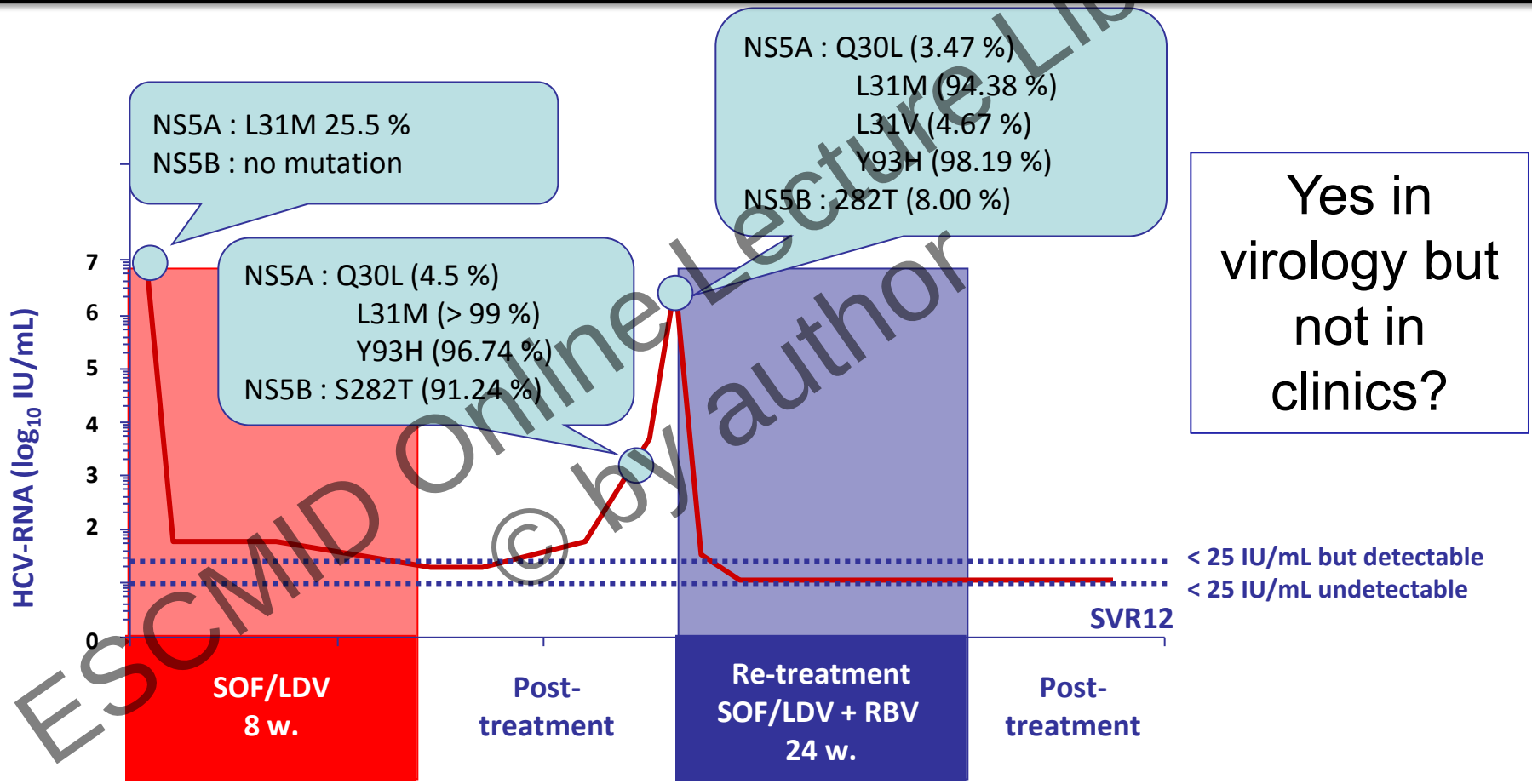
GT1 patients: naïve or "null" responders



SOF (Sofosbuvir): Polymerase Inhibitor (nucleosidique)
LDV (Ledipasvir): NS5A Inhibitor

Gane EJ et al. EASL 2013

“rescue” therapy after relapse
Resistance or not?

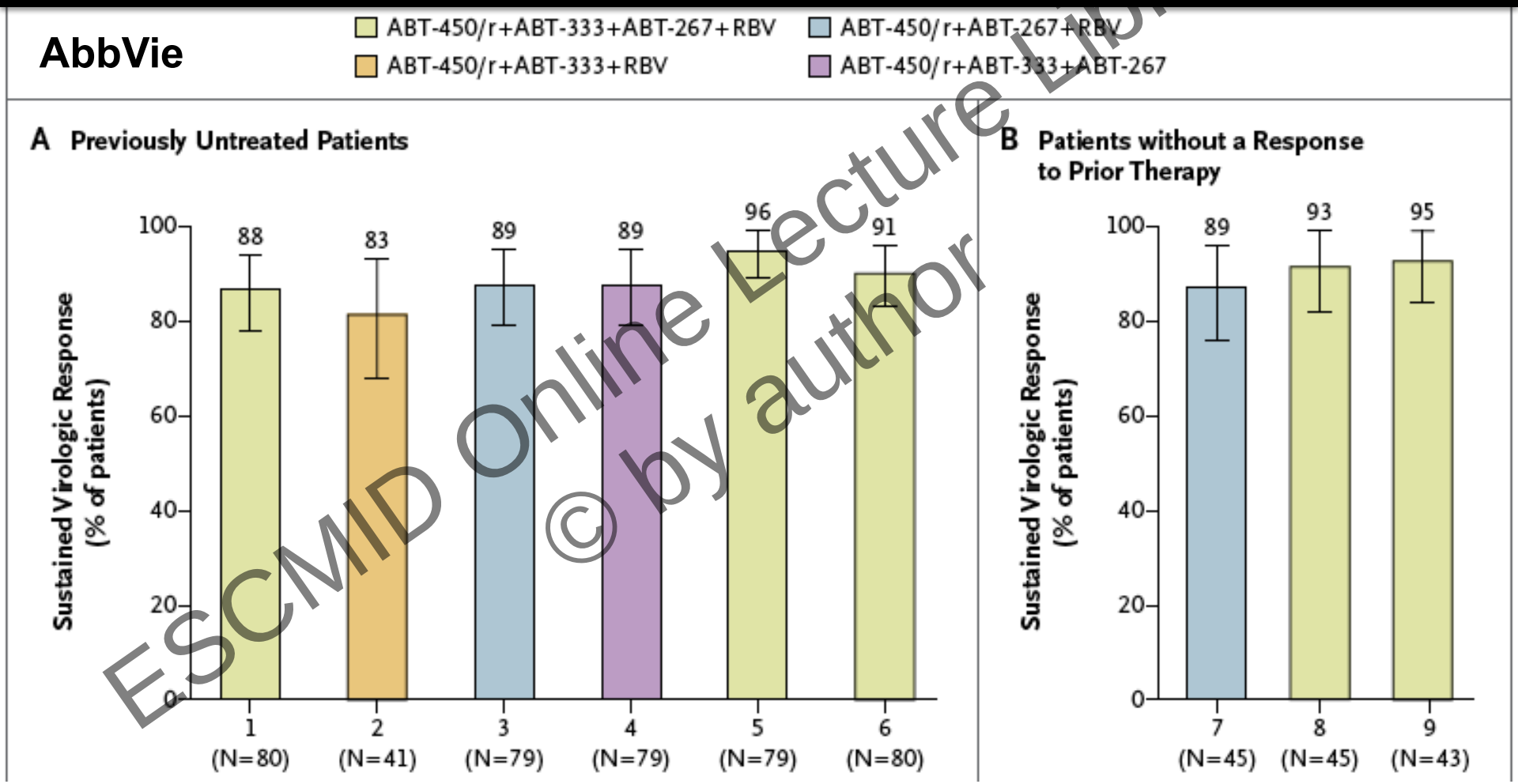


Yes in virology but not in clinics?

SOF (Sofosbuvir): Polymerase Inhibitor
LDV (Ledipasvir): NS5A Inhibitor

Lawitz E et al. AASLD 2013

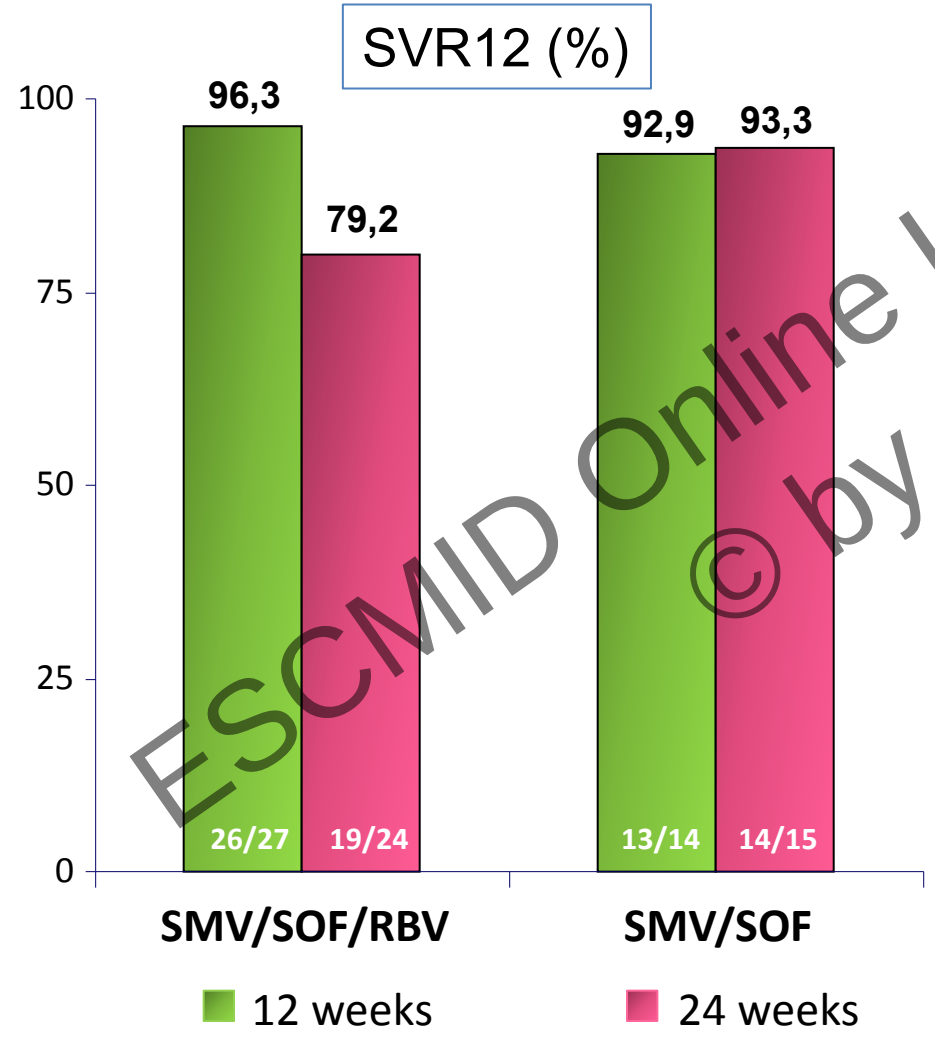
Combination of DAAs in GT1 patients



Kowdley KV et al. N Engl J Med 2014

ABT-450: Protease Inhibitor
ABT-333: Polymerase Inhibitor
ABT-267: NS5A Inhibitor

Combination of DAAs in GT1 “null” responders (COSMOS study)



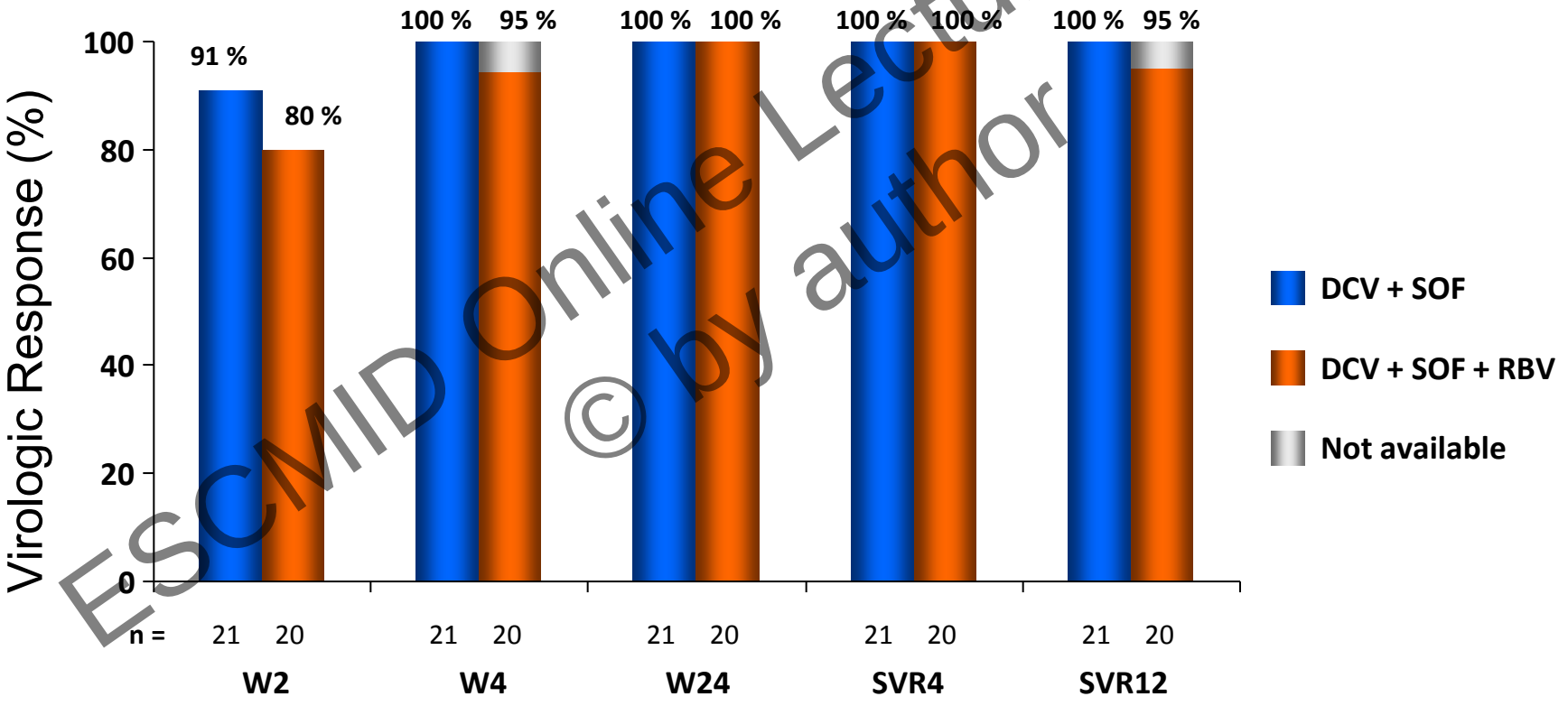
Sofosbuvir + Simeprevir RBV
Treatment during 12 or 24 weeks
Patients “null” responders (n=80)
- METAVIR F0-F2
- 78 % GT 1a (50% Q80K)

SVR12 for GT1a with Q80K: 89 %
Patients without SVR:
- 3 relapses: all GT1a with Q80K
- 4 premature stop
- 1 death but with SVR4

Sofosbuvir: Polymerase Inhibitor
Simeprevir: Protease Inhibitor

Combination of DAAs in triple therapy TVR or BOC failures

Sofosbuvir + Daclatasvir RBV for 24 weeks



Sulkowski MS et al. N Engl J Med 2014

Sofosbuvir: Polymerase Inhibitor
Daclatasvir: NS5A Inhibitor

European Medicines Agency (EMEA)

16/01/2014 Sovaldi -EMEA/H/C/002798

- Sovaldi treatment should be initiated and monitored by a physician experienced in the management of patients with chronic hepatitis C
- The recommended dose is one 400 mg tablet, taken orally, once daily with food
- Sovaldi should be used in combination with other medicinal products

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf

European Medicines Agency (EMEA)
16/01/2014 Sovaldi -EMEA/H/C/002798

Patient population[a]	Treatment	Duration
GT 1, 4, 5 or 6	Sovaldi + PegIFN + RBV	12 weeks[b]
	Sovaldi + RBV in patients ineligible or intolerant to IFN	24 weeks
GT 2	Sovaldi + RBV	12 weeks[b]
GT 3	Sovaldi + PegIFN + RBV	12 weeks[b]
	Sovaldi + RBV	24 weeks
Patient awaiting liver transplantation	Sovaldi + RBV	Until transplantation

[a] Includes patients co-infected with HIV

[b] Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peginterferon alfa and ribavirin therapy).

European Medicines Agency (EMEA)
16/01/2014 Sovaldi -EMEA/H/C/002798

- Availability of Sovaldi in European countries (Feb 2014)
  - France
  - Germany
  - Netherlands
  - United Kingdom

Up-to-date European recommendations i.e. German recommendations

Treatment Experienced Patients with PegIFN + RBV

Genotype	Recommended	Alternative	Not recommended
1, 4-6	SOF + PegIFN + RBV x 12 weeks, but no data available, higher SVR rates expected than with BOC or TVR, tx only for patients with urgent medical need or patient wish	Waiting for all-oral regimens: - SOF + SMV + RBV x 12 weeks - SOF + DCV + RBV x 12 weeks	TVR or BOC based regimen
2	SOF + RBV x 12 weeks	Treatment expansion to 24 weeks possible in patients with negative predictive factors	
3	SOF + PegIFN + RBV x 12 weeks	SOF + RBV x 24 weeks	

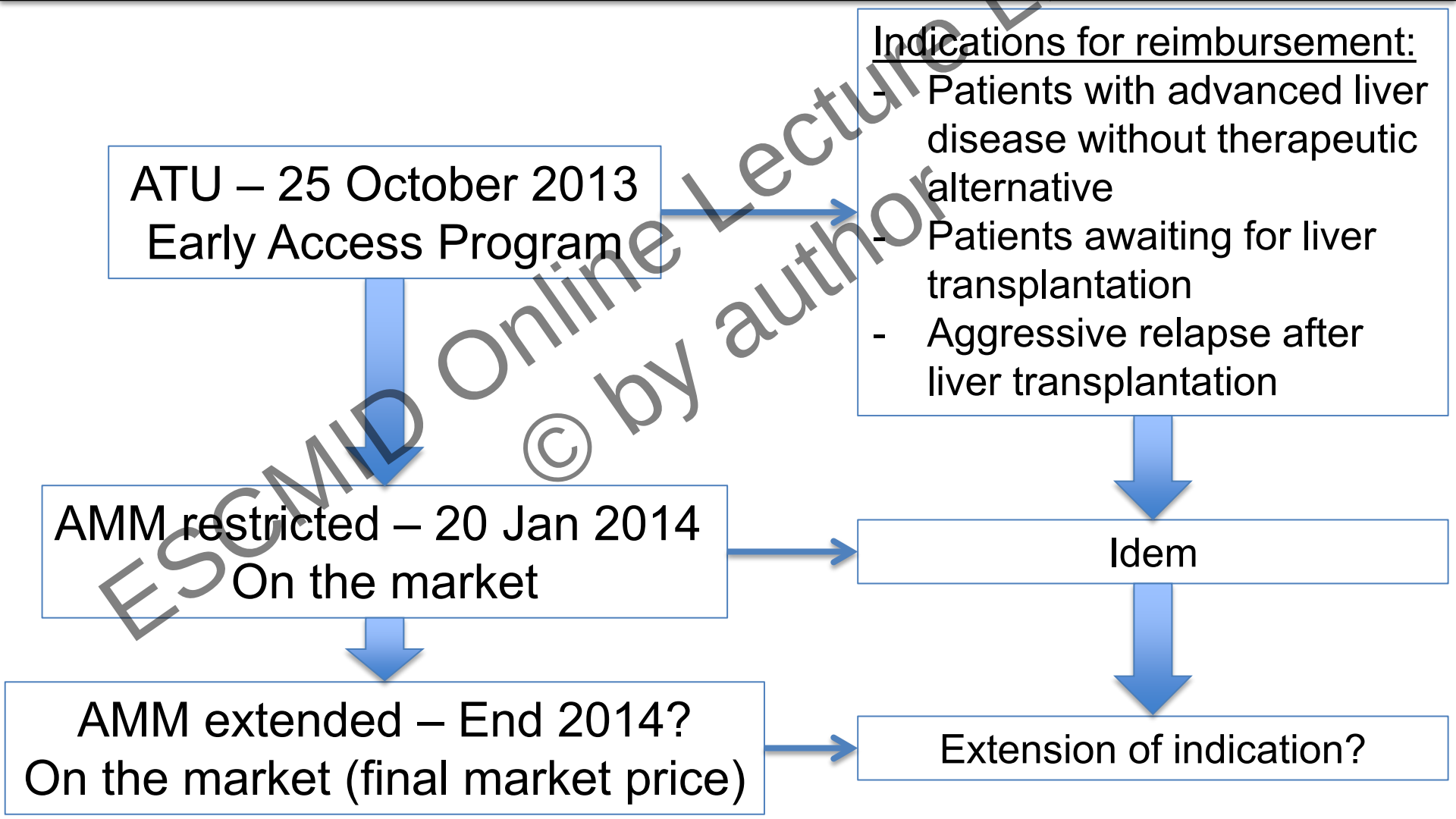
http://www.leberhilfe.org/tl_files/lh_org_download/Allgemeines/2014_Empfehlung_Therapie_HCV_nach_Zulassung_Sofosbuvir.pdf

Up-to-date European recommendations i.e. German recommendations

Genotype	[illegible]	Alternative	[illegible]
Treatment Experienced Patients – Triple therapy failure with BOC or TVR			
1	SOF + PegIFN/RBV for 12 weeks. No data available for SOF + PegIFN + RBV in this population and must avoid the potential of Sofosbuvir monotherapy in patients who have failed TVR or BOC triple therapy	Waiting for all-oral regimens: - SOF + DCV + RBV x 24 weeks	
Interferon intolerant Patients			
1, 4-6	SOF + RBV x 12 weeks	Combining SOF + SMV (or DCV can be considered after approval)	SOF + TVR or BOC

http://www.leberhilfe.org/tl_files/lh_org_download/Allgemeines/2014_Empfehlung_Therapie_HCV_nach_Zulassung_Sofosbuvir.pdf

National Procedures
i.e. French approval for Sovaldi



National Procedures (Feb 2014) i.e. French approval for new DAAs

SOFOSBUVIR Polymerase Inhibitor	SIMEPREVIR Protease Inhibitor	DACLATASVIR NS5A inhibitor
On the market	Early Access Program	Early Access Program
<u>Indication for reimbursement</u> - Patients with advanced liver disease without therapeutic alternative - Patients awaiting for liver transplantation - Aggressive relapse after liver transplantation	<u>Indication for availability</u> Genotype 4 cirrhotic patients with PegIFN + RBV	<u>Indication for availability</u> Decompensated cirrhotic patients in association

Take Home Messages-1
Future rules with new DAAs?

1. For genotype 2 patients (naïve/experienced, cirrhotic or not), the association Sofosbuvir + RBV 12 (24?) weeks is sufficient
2. For other genotypes, the first possibility is to combine 1 DAAs (Sofosbuvir or Simeprevir) and PegIFN + RBV
3. For other genotypes, if you want to avoid IFN, you have to combine 2 or 3 DAAs
4. If you combine 2 or 3 DAAs, you have to choose each DAA in a different class of viral target

Take Home Messages-2
Future rules with new DAAs?

1. In case of triple therapy failure including telaprevir or boceprevir, avoid retreatment with new PI (Simeprevir, Asunaprevir, BT450…) or test for resistance (?)
2. If you use Simeprevir in patients with genotype 1a (naïve or not), you have to test for the Q80K mutation
3. Treatment failure with DAA (Sofosbuvir only?) is not always in relation with resistance
4. Especially for the PI class (Telaprevir, Boceprevir, Simeprevir, Asunaprevir, BT450…), you have to check for drug-drug interactions