

3RD

OPTIMIZE

USING DAAS IN PATIENTS WITH CIRRHOSIS
AND LIVER RECIPIENTS

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Treating hepatitis C infection in decompensated patients on waiting list

Dr Audrey Coilly
Centre Hepato-Biliaire
Paul Brousse hospital
Villejuif, France



Disclosures

Advisory Boards and/or consultancy

Audrey COILLY

AbbVie, Astellas, BMS, Gilead, Janssen, Novartis



WHY TREATING BEFORE LIVER TRANSPLANTATION?



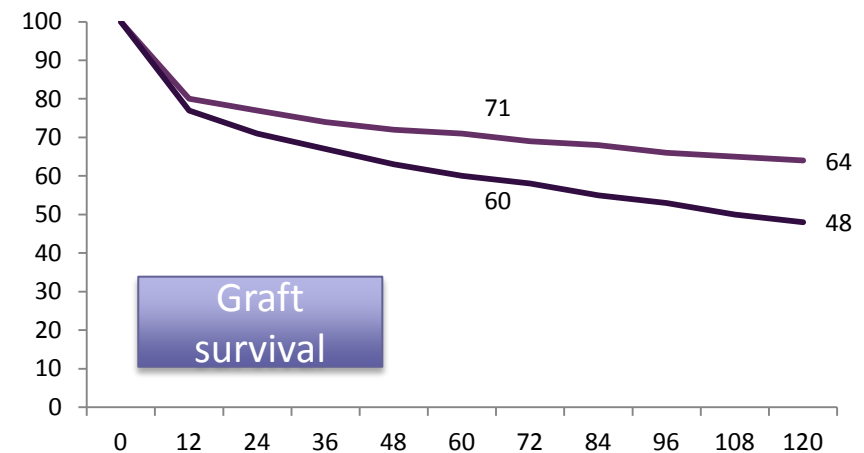
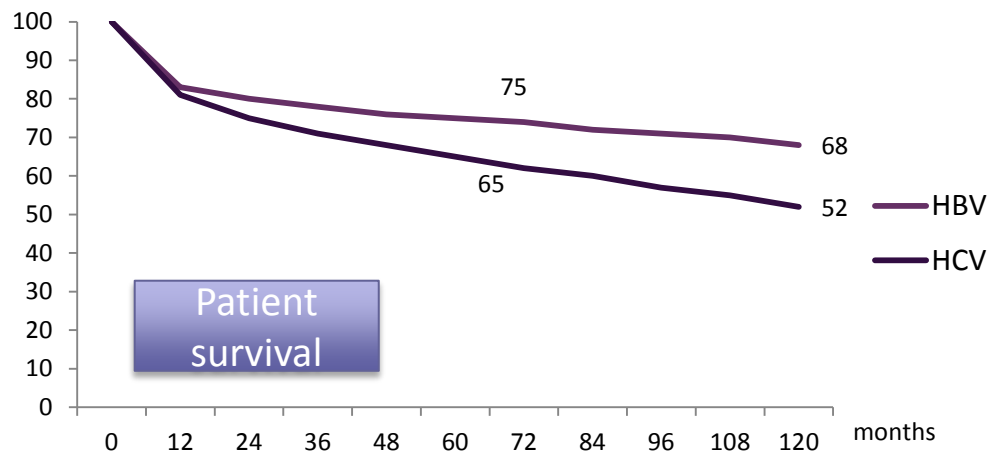
WHY TREATING BEFORE LIVER TRANSPLANTATION?

1) Avoid HCV recurrence



HCV recurrence: a major issue

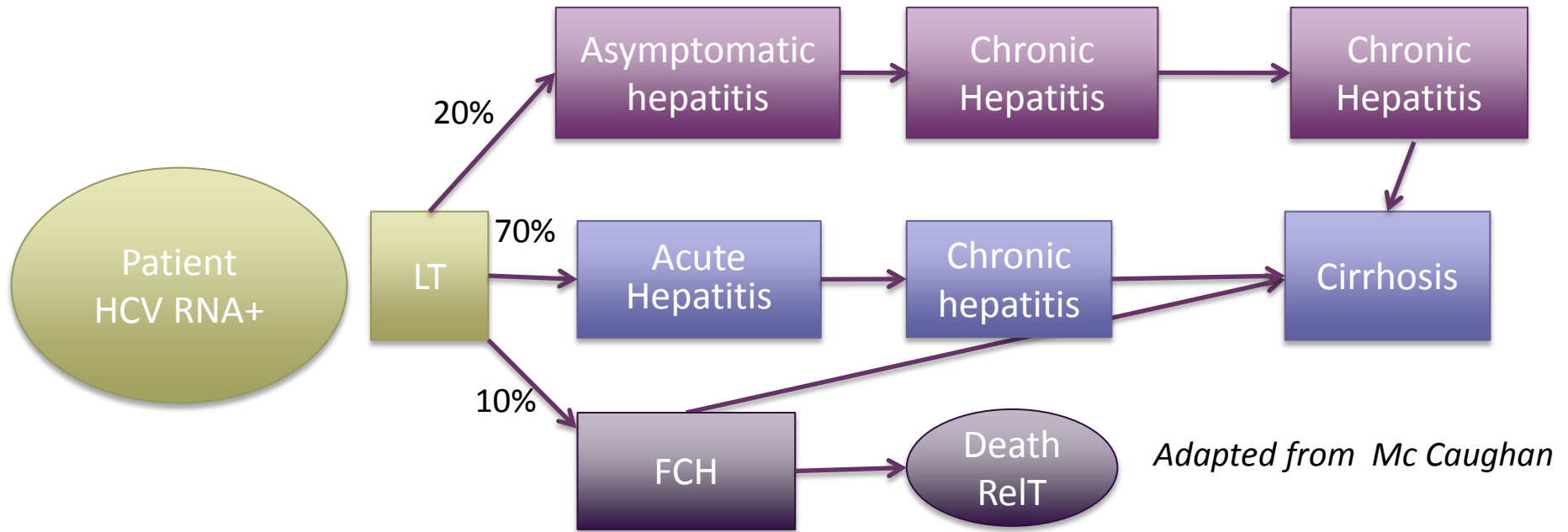
- HCV recurrence used to be a major issue during 2 decades



ELTR, n=19,335 patients,
global log-rank $p < 0.001$



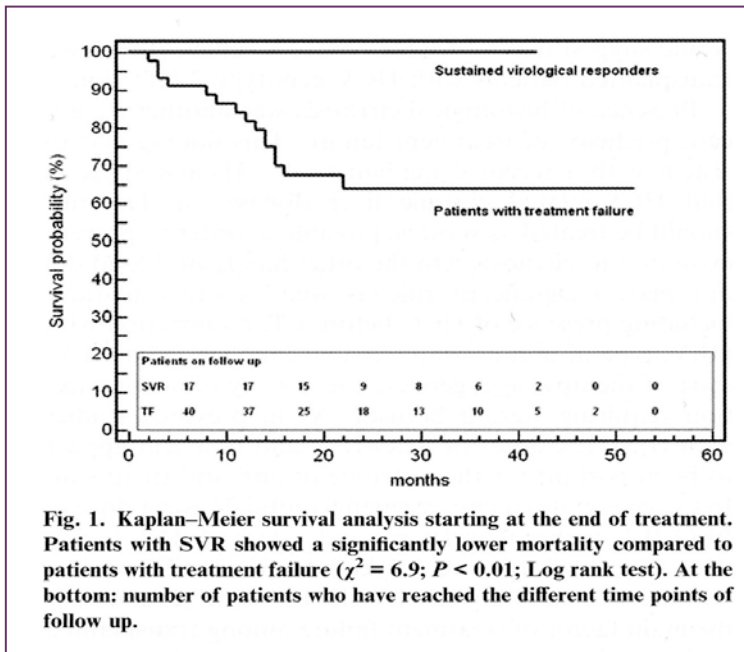
HCV recurrence affects all patients



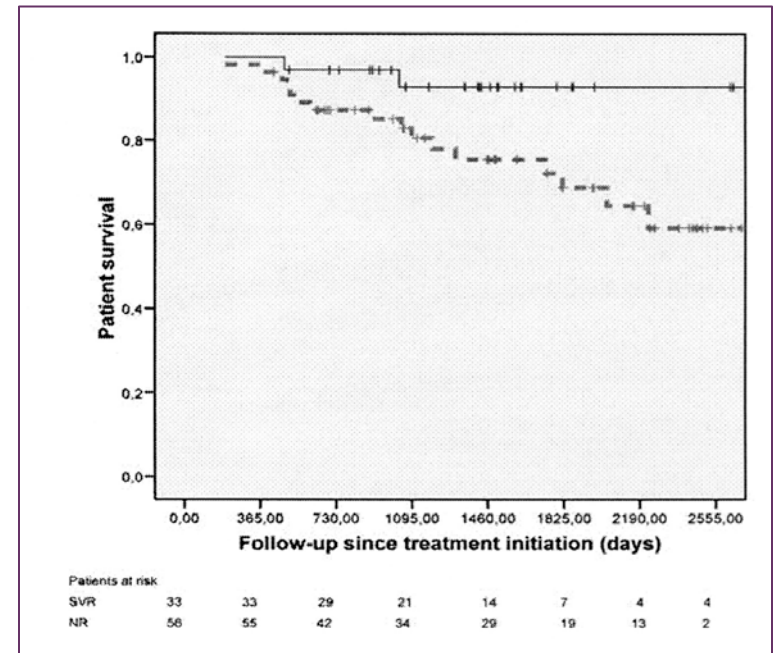
- Five years post-LT, 30% of LT patients have a cirrhosis on the graft



Only chance: To achieve SVR



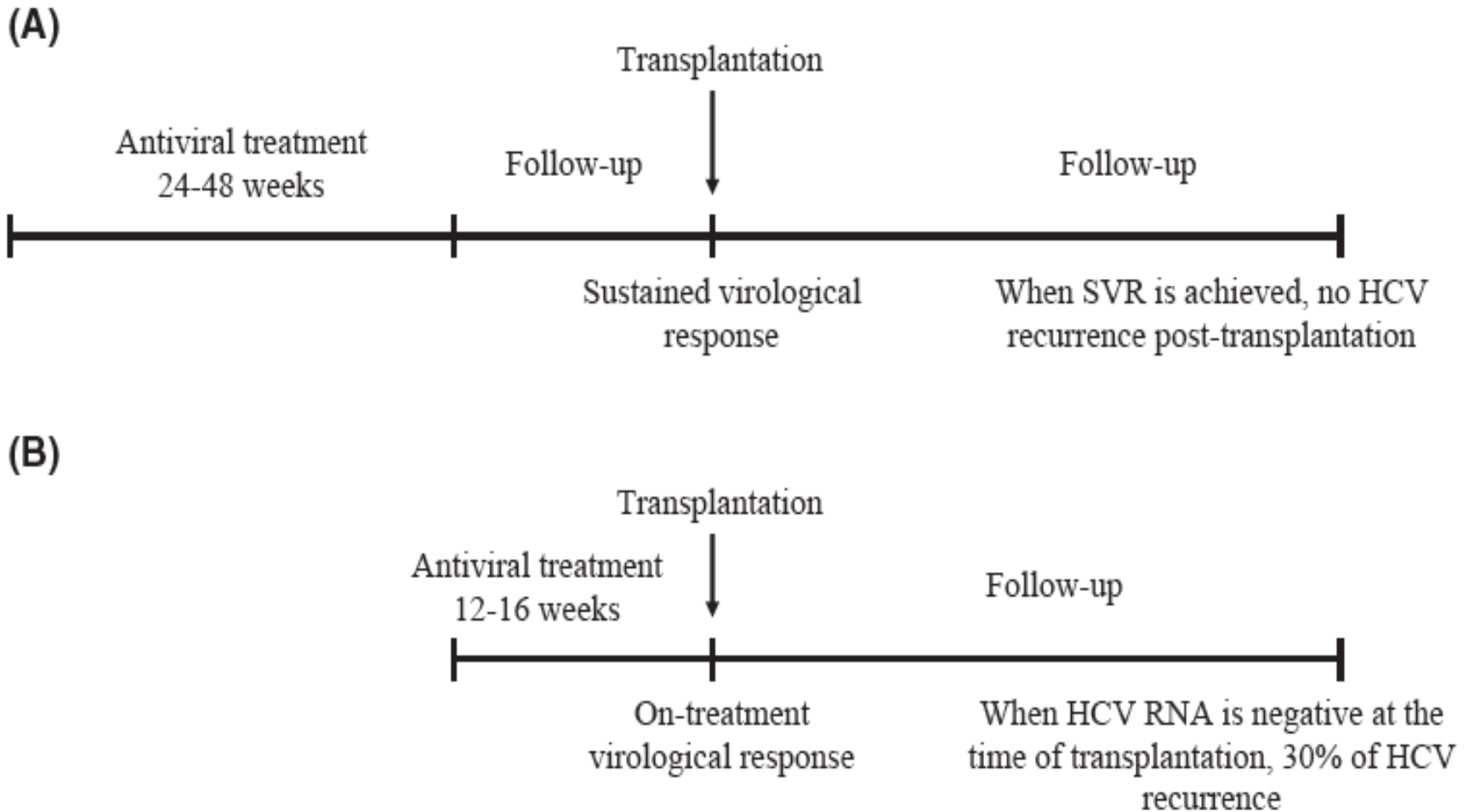
Piciotto
J Hepatol 2007



Berenguer
AJT 2008



Strategies of treatment before LT



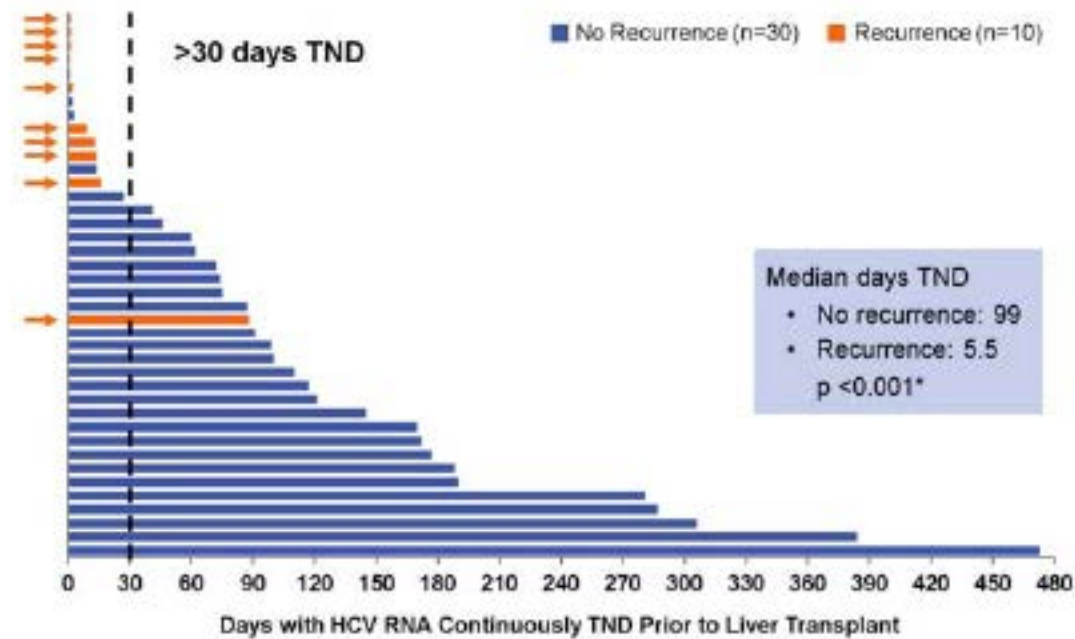
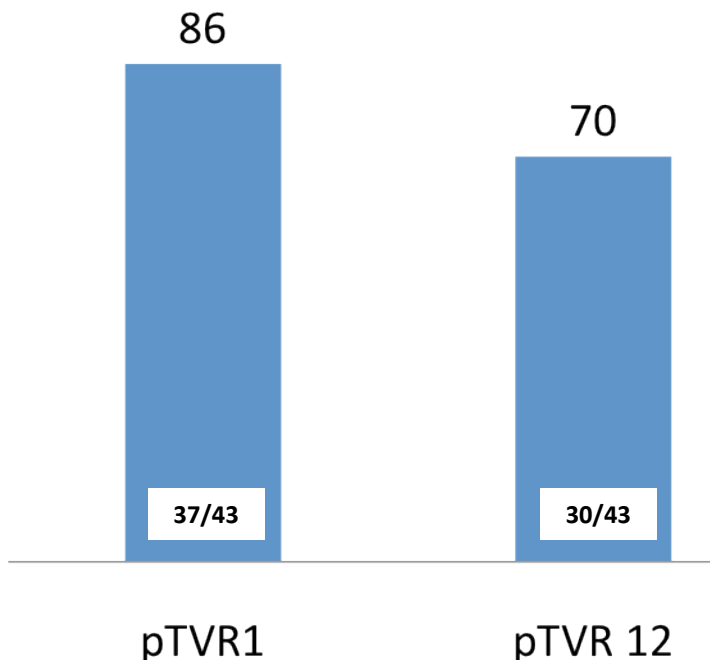


Decrease recurrence when HCV RNA negative before LT

SOF+RBV

24Wks or more

PreLT – Low MELD score



*Wilcoxon rank sum test.



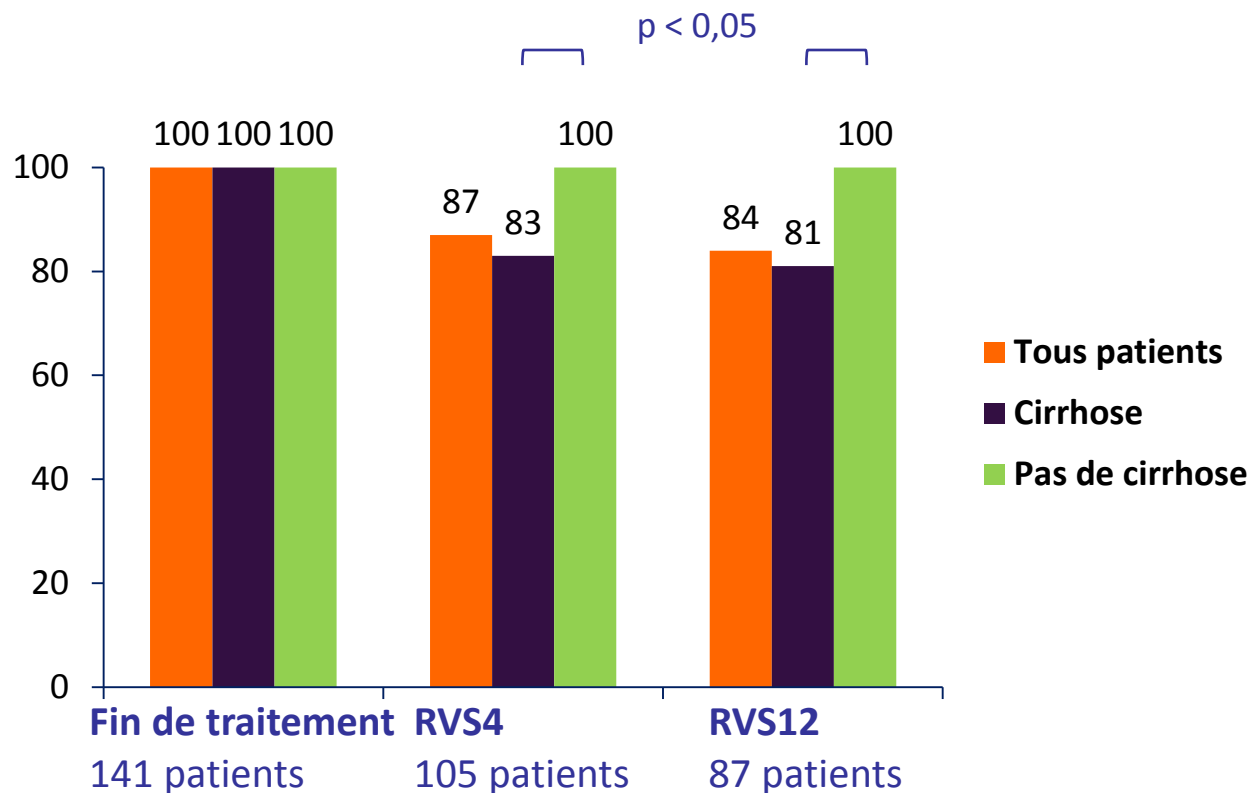
WHY TREATING BEFORE LIVER TRANSPLANTATION?

- 1) Avoid HCV recurrence
- 2) Remarkable data with new DAA in cirrhotic patients



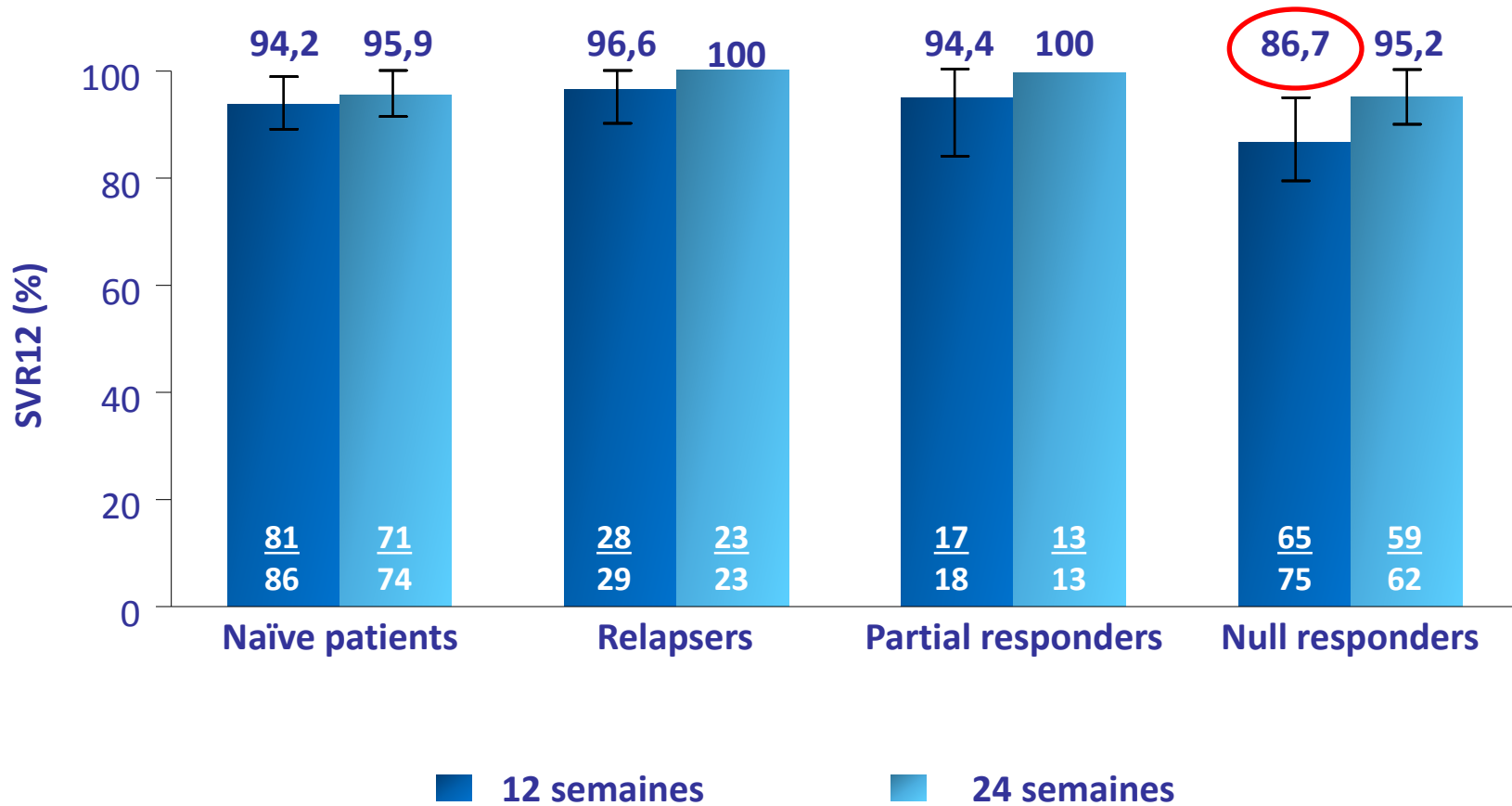
SOFO+SIME+/-RBV before LT

- 3 centres in USA n=147, G1
 - 12 weeks of treatment (20 patients with RBV)
- Genotype 1a (70 %), Cirrhosis (78 %), IL-28 non CC (79 %)
- Median MELD score was 12 (7-17)





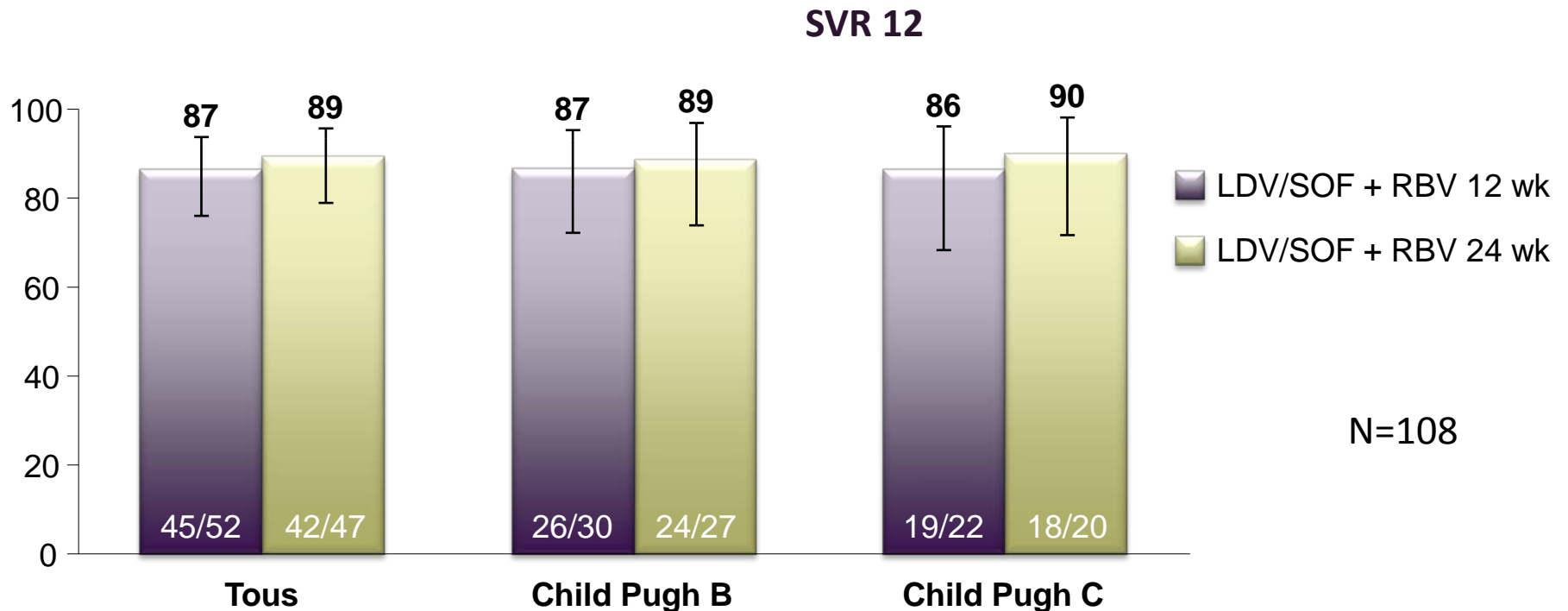
ABT-450/r/Ombitasvir + Dasabuvir + RBV in G1 cirrhotic patients





Decompensated cirrhotic patients

G1-4





WHY TREATING BEFORE LIVER TRANSPLANTATION?

- 1) Avoid HCV recurrence
- 2) Remarkable data with new DAA in cirrhotic patients
- 3) Avoid liver transplantation?



SOFO+RBV: Liver function improvement

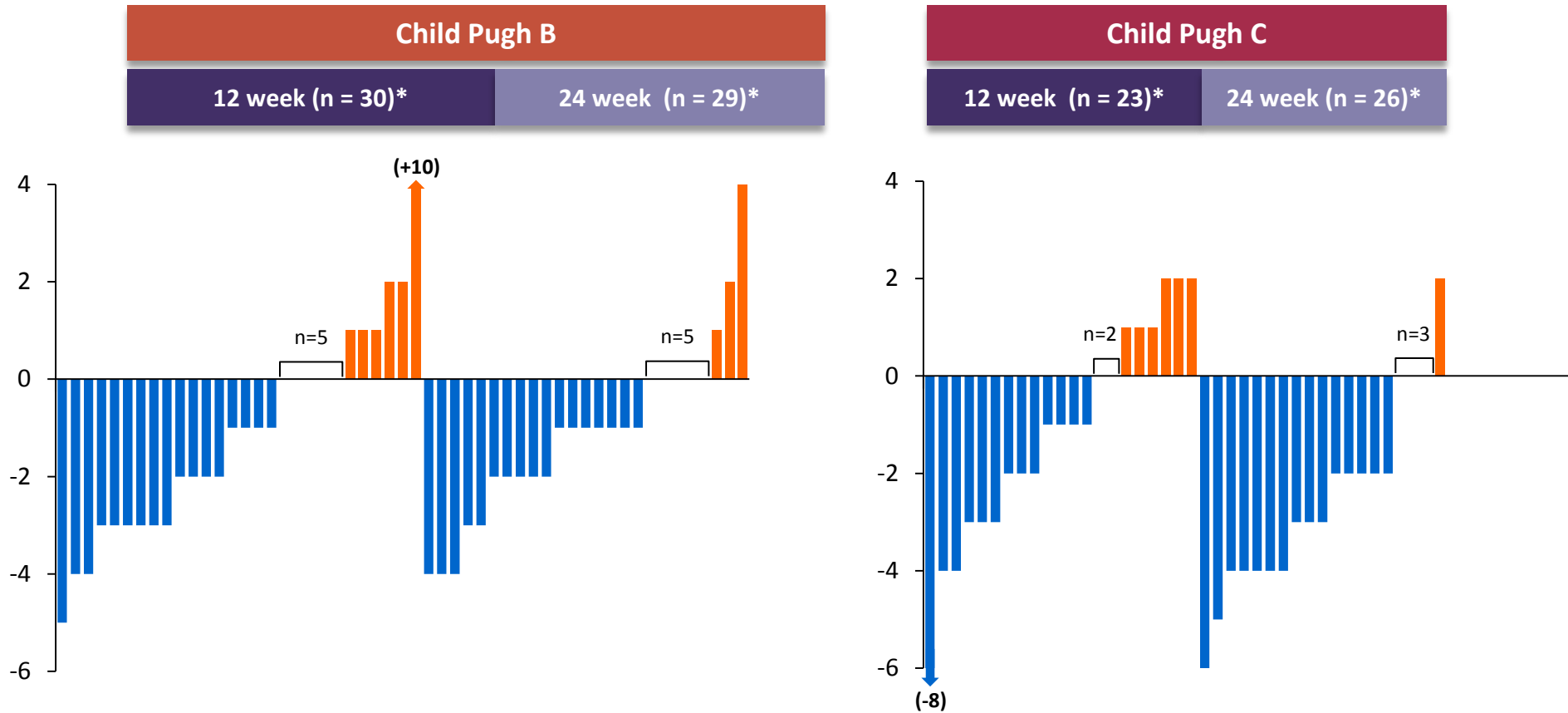
- 50 patients with oesophageal varices, gradient > 6mmHg
- Treated with SOF + RBV 24 weeks : interim analysis

	Ascites		Hepatic encephalopathy	
	SOF + RBV (n=25)	Control (n=25)	SOF + RBV (n=25)	Control (n=25)
Baseline	6	9	5	2
Week 12	5	8	3	3
Week 24	0	7	0	4



SOFO+LEDI+RBV: Liver function improvement

Variation in MELD score 4 weeks after treatment discontinuation



*Missing data: n = 2 CP B 12 week ; n = 4 CP B 24 week ; n = 2 CP C 12 week ; n = 7 CP C week



Patient With Decompensated Hepatitis C Virus-Related Cirrhosis Delisted for Liver Transplantation After Successful Sofosbuvir-Based Treatment

Evolution of clinical and biological parameters after the initiation of therapy with sofosbuvir and ribavirin

Parameter	Antviral treatment						Week 12 after treatment
	Day 1	Week 4	Week 8	Week 12	Week 16	Week 24	
Prothrombin time (seconds)	1,58	1,76	1,65	1,58	1,58	1,67	1,60
Albumin (g/l)	23,6	24,2	25,6	28,2	29,7	28,9	31,6
Total bilirubin ($\mu\text{mol/l}$)	53	48	65	56	49	48	21
Aspartate aminotransferase (IU/l)	138	48	39	40	37	35	32
Alanine aminotransferase (IU/l)	72	31	30	26	21	21	25
HCV RNA (IU/ml)	53	50	< 12	< 12	< 12	< 12	< 12
Ascites	Yes, refractory	Yes, refractory	Yes, treated	Yes, treated	No, treated	No, untreated	No, untreated
Hepatic encephalopathy	Yes	Yes	No	No	No	No	No
Child-Pugh score	C12	C12	C10	B9	B7	B7	A6
Model for end-stage liver disease score	16	17	17	16	16	16	12



**WHY NOT TREATING BEFORE LIVER
TRANSPLANTATION?**



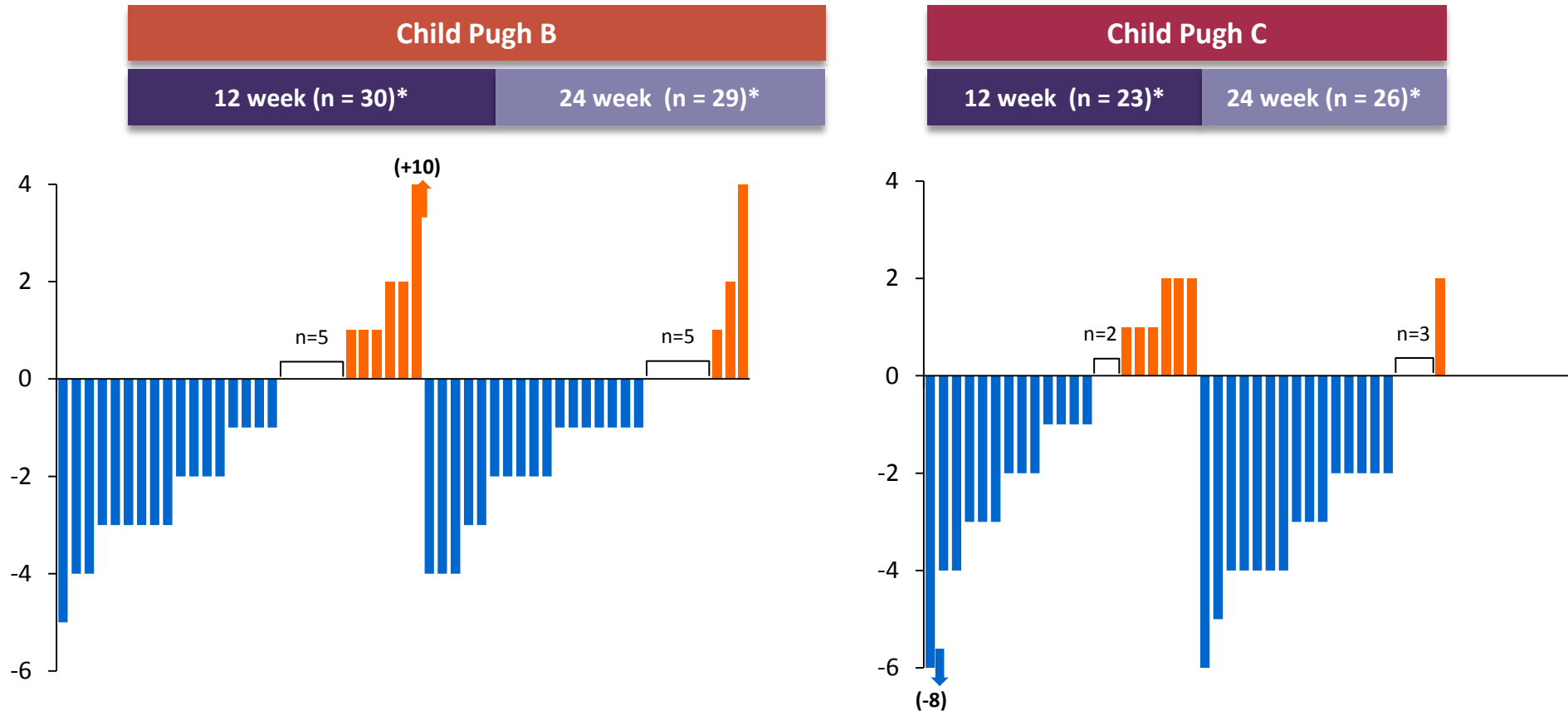
WHY NOT TREATING BEFORE LIVER TRANSPLANTATION?

1) Disadvantage patients on waiting list



SOFO+LEDI+RBV: Liver function improvement: enough?

Variation in MELD score 4 weeks after treatment discontinuation



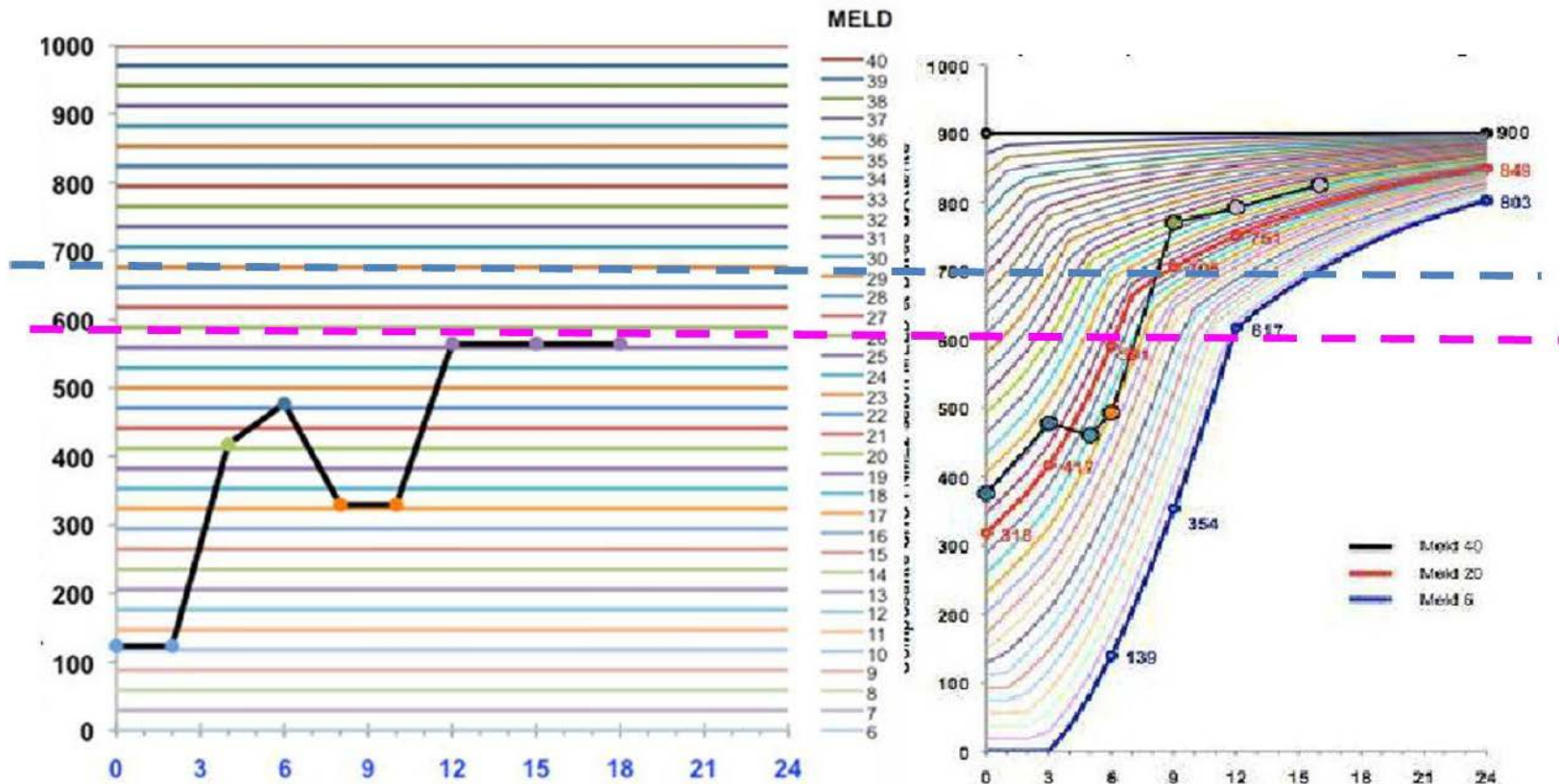
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System allocation based on MELD score

Cirrhosis
Sickest first

HCC
Time

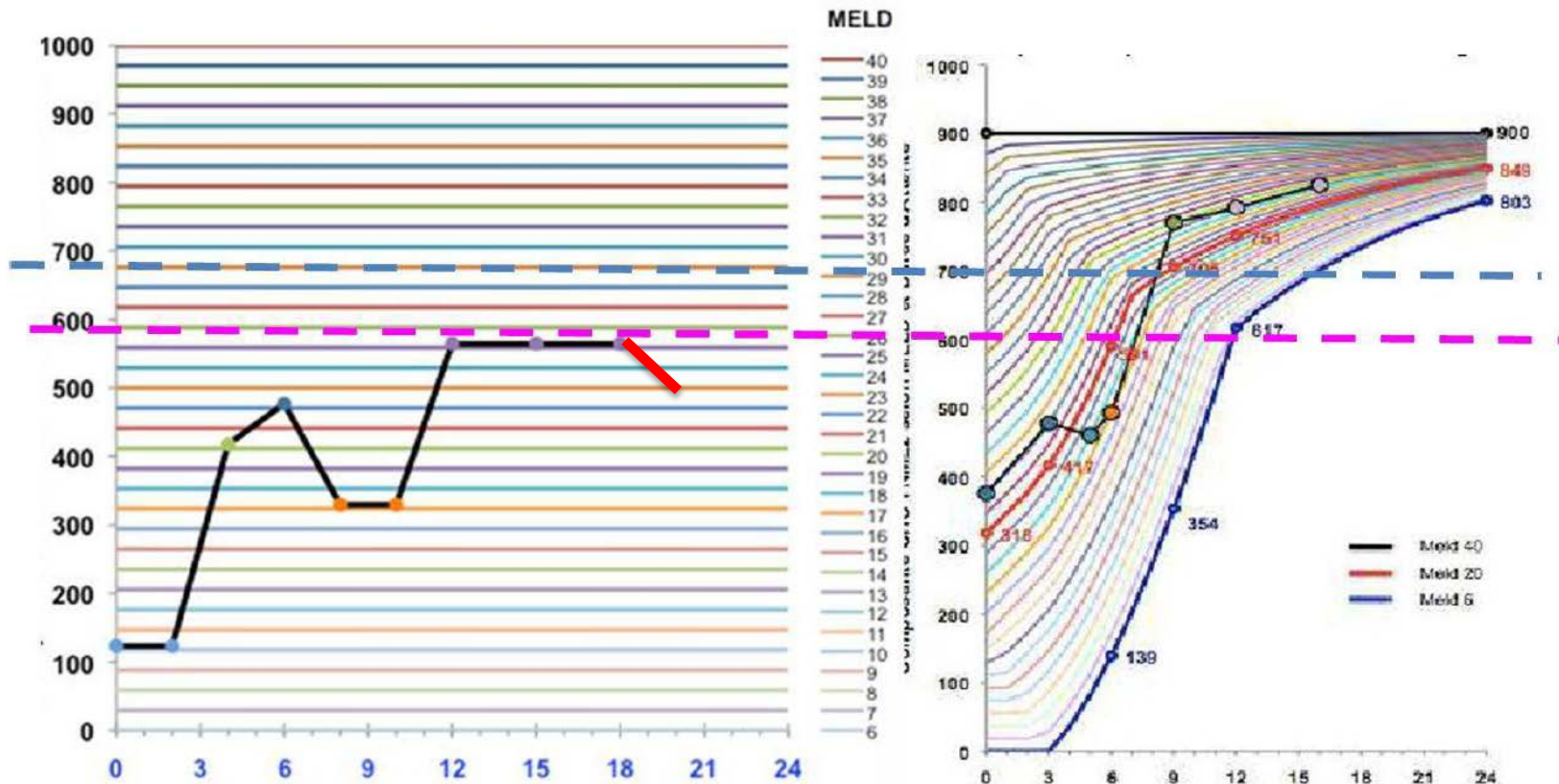




System allocation based on MELD score

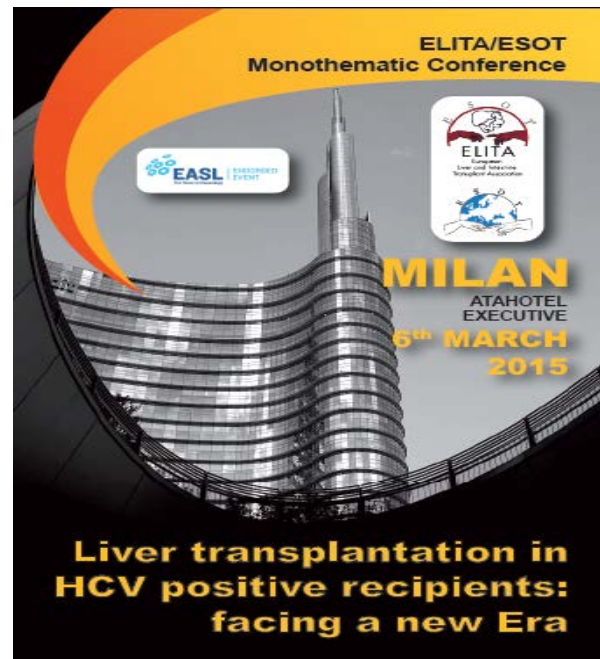
Cirrhosis
Sickest first

HCC
Time





Real-life experience in 9 European centres



	N° pts	MELD <18 at start	N° inactivated for improvement (MELD at start)	N° transplanted /waiting for LT (MELD at start)
9 centres en Europes	95	57/95 (60%)	20/95 (21%)	41/95 (43%)



WHY NOT TREATING BEFORE LIVER TRANSPLANTATION?

- 1) Disadvantage patients on waiting list
- 2) Safety concerns



**NO DATA FOR PATIENTS WITH MELD
SCORE >20**



What needs to be taken into account?

Pharmacokinetic changes according to liver function

	Liver impairment			Avoid
	Mild	Moderate	Severe	
SMV ¹		+ 2.44	+ 5.22	Child C?
SOF ²		+ 1.26	+ 1.43	
LDV ³	No adjustment			
ABT-450/r ⁴	- 0.71	+ 1.62	+ 10.23	Child C
Ombitasvir ⁴	+ 0.92	+ 0.70	+ 0.45	
Dasabuvir ⁴	+ 1.17	+ 0.84	+ 4.19	Child C?
Asunaprevir ⁴	- 0.79	+ 9.8	+ 32	Child B/C
DCV ⁵	- 0.57	- 0.62	- 0.64	

1. Ouwerkerk-Mahadeva S, et al. AASLD 2013. Oral #65;
 2. Gilead Sciences Europe. SOVALDI (sofosbuvir), Summary of Product Characteristics, January 2014; 3. German P, et al. AASLD. 2013. Oral #52; 4. Khatri A, et al. AASLD. 2012. Oral #66; 5. Bifano M, et al. AASLD. 2011. Oral #78.

ABT-450/r, asunaprevir, daclatasvir, dasabuvir, ledipasvir and ombitasvir are investigational agents and not approved for use in HCV by the EMA



WHY NOT TREATING BEFORE LIVER TRANSPLANTATION?

- 1) Disadvantage patients on waiting list
- 2) Safety concerns
- 3) Remarkable data to treat HCV recurrence

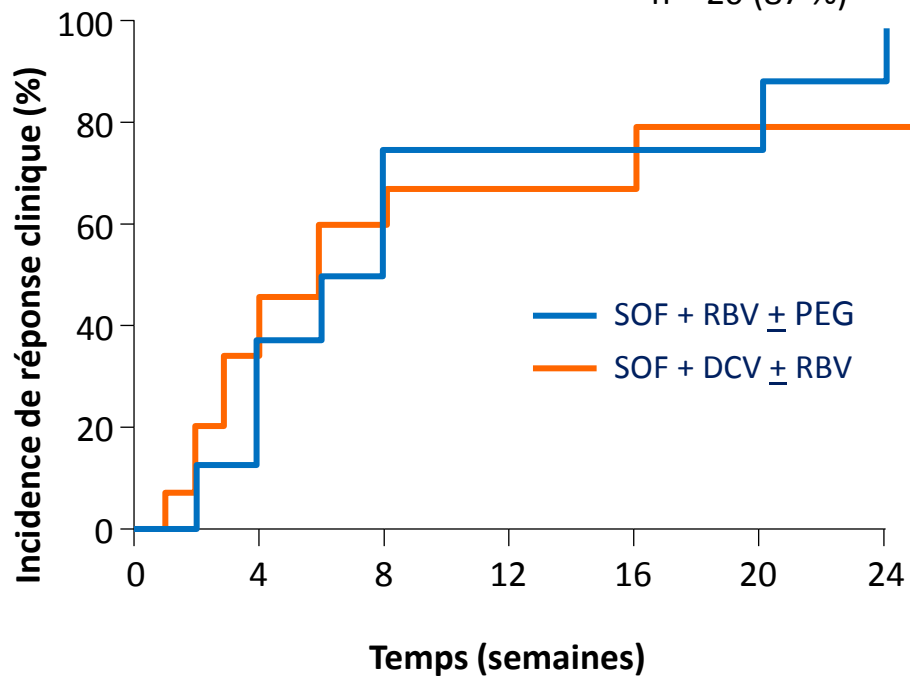


ANRS CO23 CUPILT: FCH

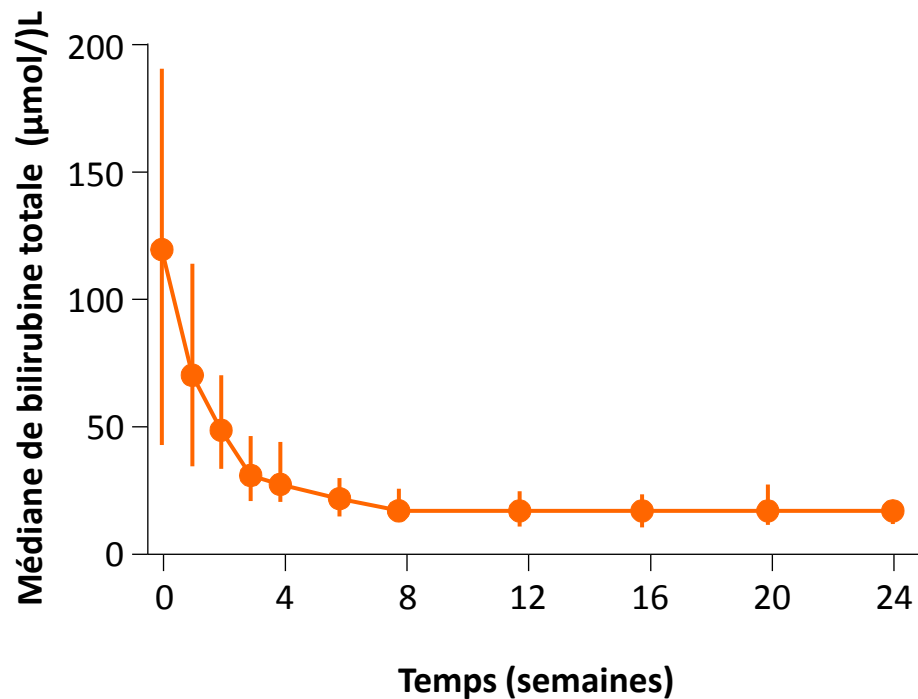
- Multicentric, prospective cohort study

Clinical response at 24 weeks

n = 20 (87 %)



Bilirubinemia at 24 weeks

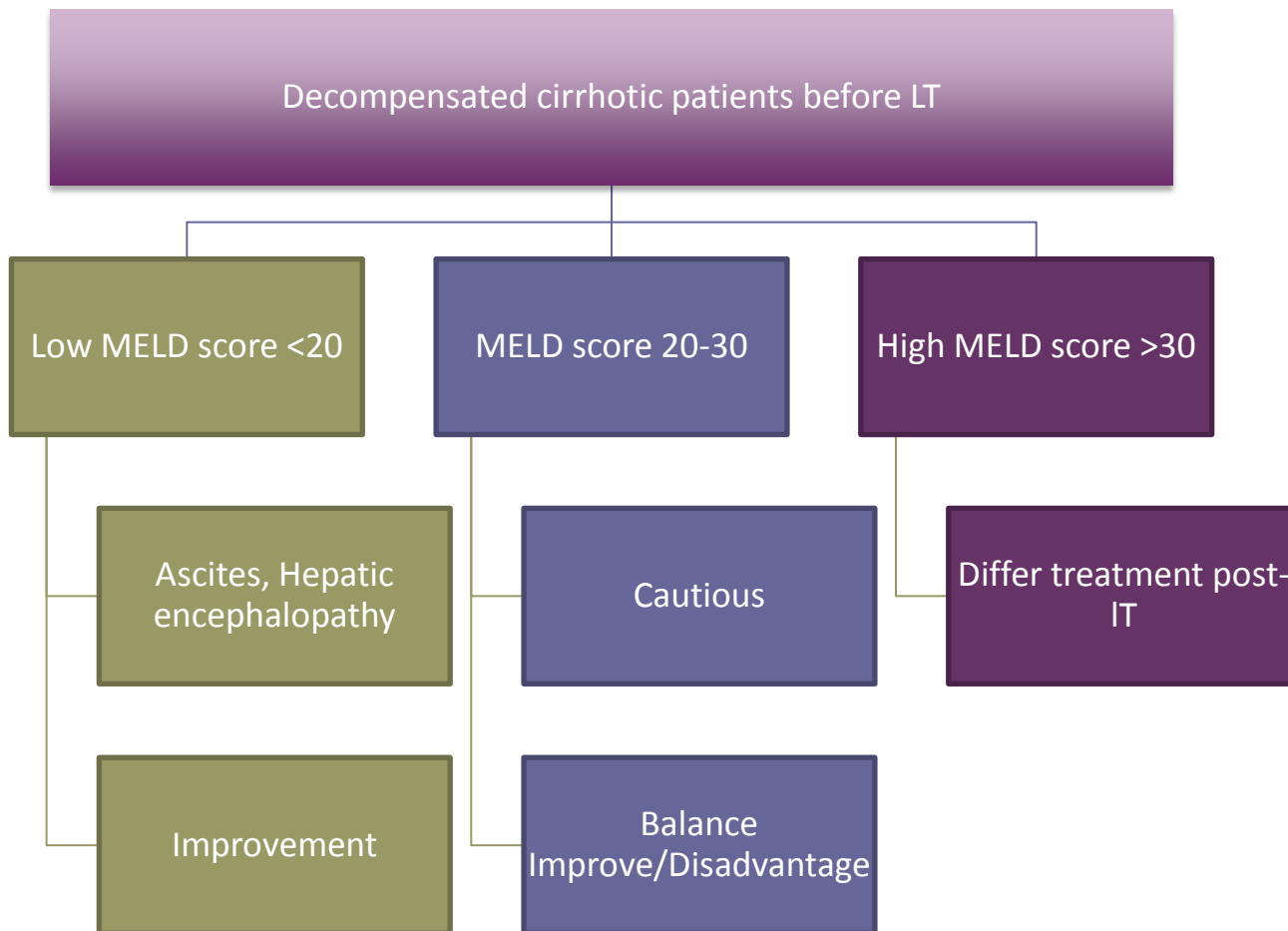




FINALLY, WHAT TO DO?



Suggestion...





Conclusion

- The field of liver transplantation in HCV Patients is moving dramatically with IFN-free anti-HCV regimen
- A lot of opening questions: when to treat? Delisting?

POUR

Avoid HCV recurrence

Improvement of liver function

Avoid LT

CONTRE

Safety?

Risk to disadvantage patients when system allocation is based on MELD

Easy to treat after LT

- The survival after transplantation for HCV infection will improve dramatically