Treatment of Hep C in liver transplant candidates and recipients in the DAA era: recommendations from the 2015 and 2016 ELITA/ESOT monothematic conferences

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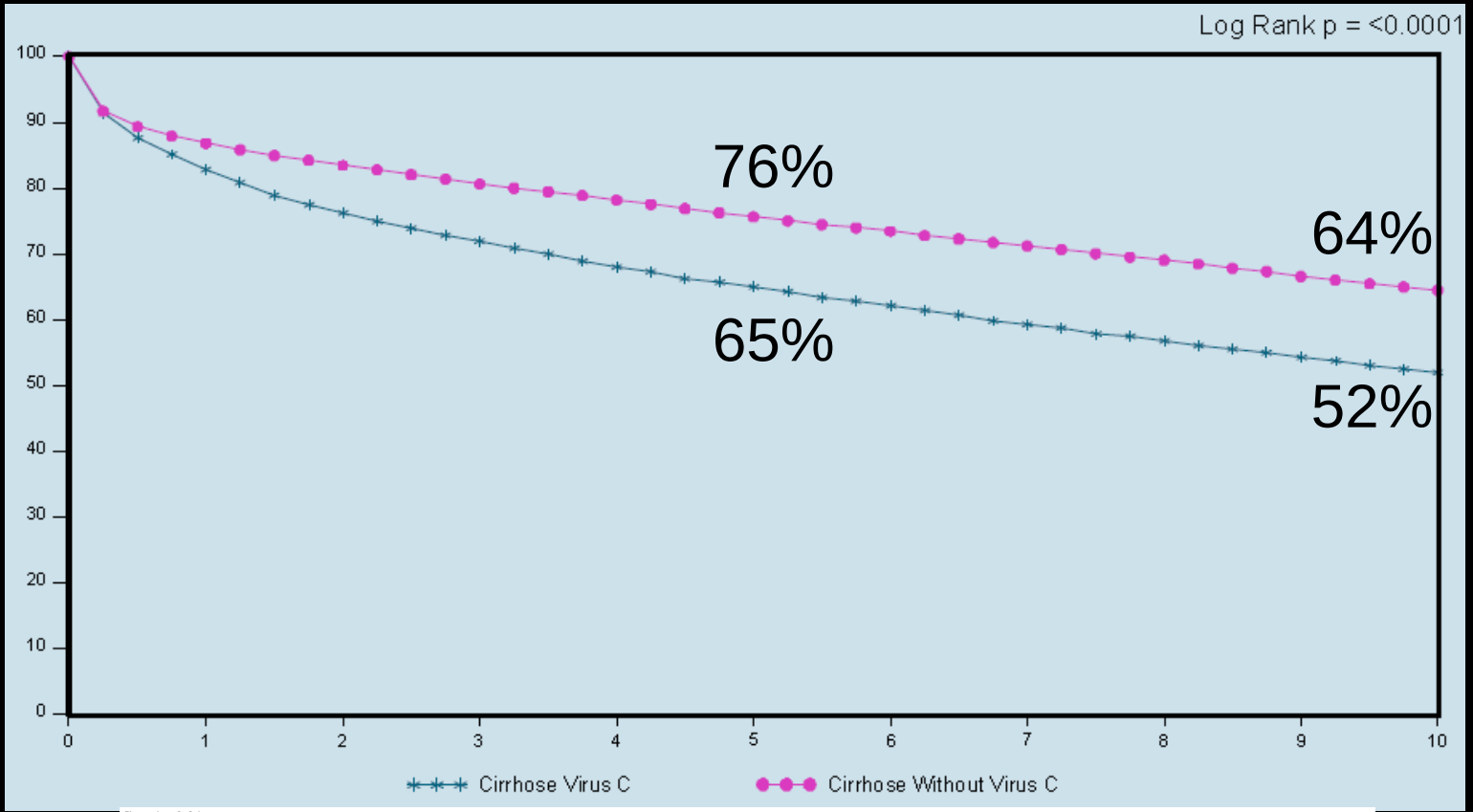
Disclosures

- No disclosures for this presentation
- Chair of ELITA

Patient Survival after LT for HCV Compared to Other cirrhotic indications

50,602 Adult Recipents

January 2000 – December 2013



Survival %

Cirrhose_etiology C versus not C	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Cirrhose	83%	76%	72%	68%	65%	62%	59%	57%	54%	52%
	87%	83%	81%	78%	76%	73%	71%	69%	67%	64%

Number of exposed patients

	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Cirrhose	16324	11259	9081	7526	6228	5174	4211	3333	2494	1797	1223
	34278	23732	19815	16715	14039	11608	9571	7598	5844	4293	2976

Two different strategies to face HCV recurrence

To Prevent HCV recurrence
To Avoid LT?

Treatment of HCV recurrence

To prevent
- de novo fibrosis/cirrhosis
- Renal function impairment ?
- Post LT diabetes ?

To improve survival

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Luca Saverio Belli
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Main pre LT issues

1- What is the impact of pre LT DAA on prevention of HCV recurrence post-LT ?

2- **What is the impact of DAAs on liver function and delisting pre transplant ?**

3- **Who should be treated or not treated before LT among decompensated cirrhotics/among pts listed for HCC**

4- How safe are DAA when used in decompensated cirrhosis

5- How to take into account drug to drug interactions and frequent renal impairment in LT candidates and recipients ?

Achieving SVR in a CTP C patient listed for transplantation MELD Purgatory

Christophe Duvoux
Henri Mondor Hospital
Paris Est-University

Clinical case

- 52-yr old man
- HCV Cirrhosis diagnosed in October 2014
  - Medical history
    - Past: transient drug abuse; withdrawn for 20 yrs; smoking
    - Recently :
      - » Hepatic Encephalopathy : 3 episodes over 2 months,
      - » grade II to III leading to admission in a 2dary care hospital
  - Physical examination : T°: 36°9; BP: 108/65, 90/mn
    - Weight : 90kg/ 1m77 ;
    - Jaundice and mild oedema
    - Tense ascites
    - Asterixis

Clinical case cont…

Initial Treatment

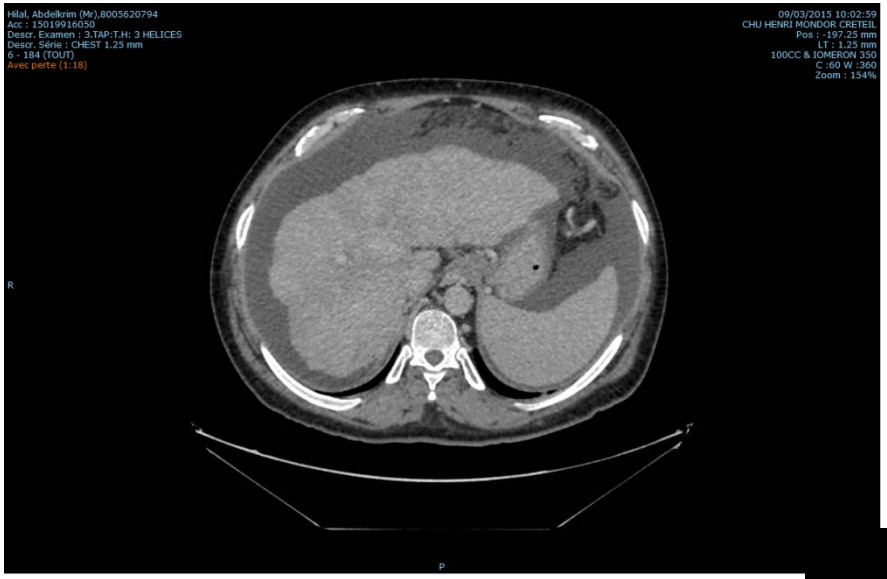
- Large volume paracentesis:
  - -8L followed by 6L /2weeks
- Lactulose
- Cautious reintroduction of diuretics
- Spironolactone : 75 mg/d
- Furosemide : 80 mg/d
- Propranolol 40 mg/bid

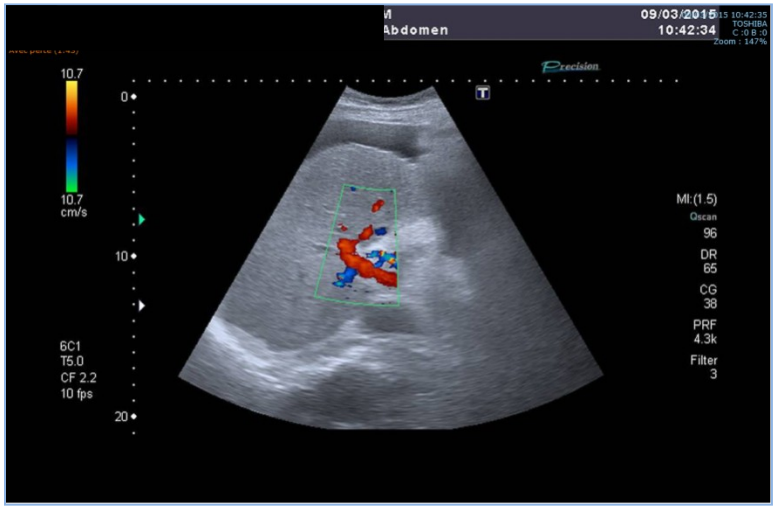
→ Referred in December 2015 to our Institution to consider liver transplantation

Clinical case ongoing…

- HCV genotype : 1a, naive
- HCV viral load : 5.54 log
- MELD score : 22
- Child Pugh score : C 10-11
- Blood type : O+
- Pre-operative work-up :
  - HIV negative, HBs Ag/HBs Ab : -/-, CMV+
  - No contra-indication to liver transplantation

Pre transplant imaging





How to manage this patient ?

- TIPS contra-indicated
- Listed for LT on January 6th, 2015
  - Lactulose ✉ Rifaximin
  - Diuretics + paracentesis

- Other options ?

✉ Would you consider treatment with DAA ?

Goals of pre LT treatement.
ELITA 2015/2016 guidelines

Prevent HCV recurrence
Post-transplant

Consider probability
of achieving SVR
and subsequent liver function
Improvement delisting ?

Factors to be taken into account in the decision making process before DAA treatment in decompensated cirrhosis. ELITA 2015/2016 guidelines

- Avoid futile DAA treatment
- Consider safety issues
- Consider probabilty of achieving SVR and subsequent liver function improvement
- Anticipate MELD purgatory

2015 ELITA Practical Guidelines on the use of DAAs in Liver transplant candidates and recipients

Recommendations

R15. Based on current studies and practice, pre LT DAA treatment is not recommended in patients with high MELD scores (> 25) because of their poor prognosis due to a significant risk of death either pre and post-LT, unknown probability of improvement, and rapid access to LT. In these patients the option of post LT treatment with DAAs is preferable (expert opinion).

R16. In Child-Pugh B patients the probability clinical improvement and regression of signs of decompensation makes DAA treatment before LT a reasonable option as some of these patients can be delisted.

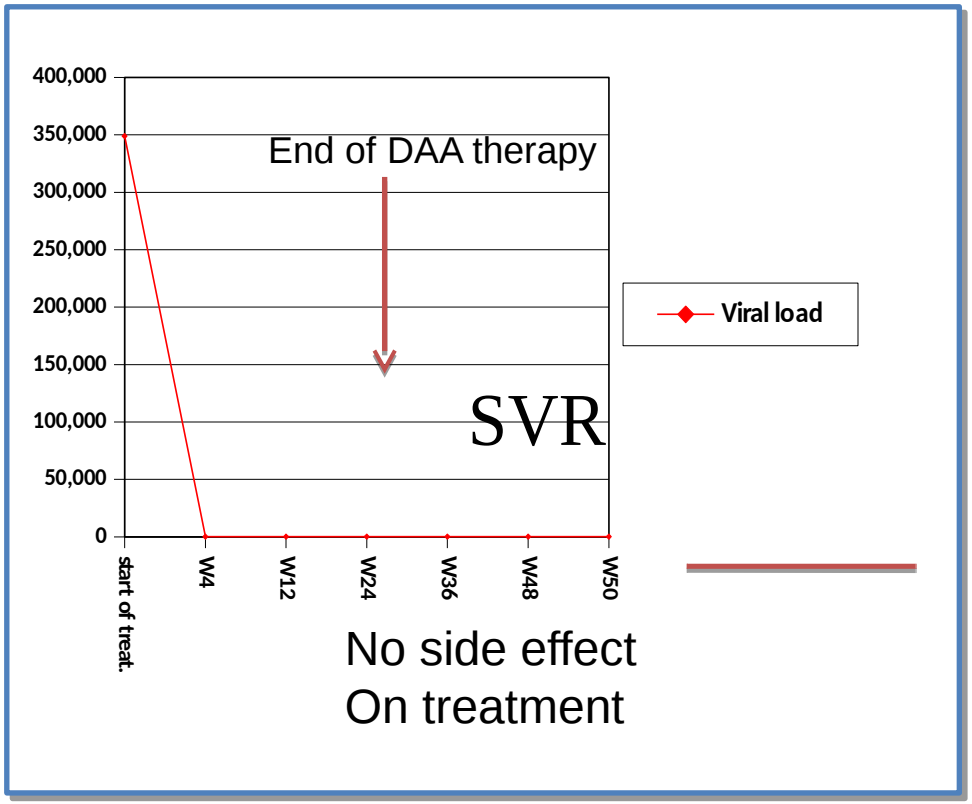
R17. In Child-Pugh C patients with a MELD <25, an improvement of either Child-Pugh score or MELD by 2-3 points can be achieved in 20 to 40% of the cases. However this improvement may not be sufficient to achieve delisting and again may limit access to LT. The decision whether to treat these patients should therefore be cautious, making sure that it will not be detrimental to the patient. (B2)

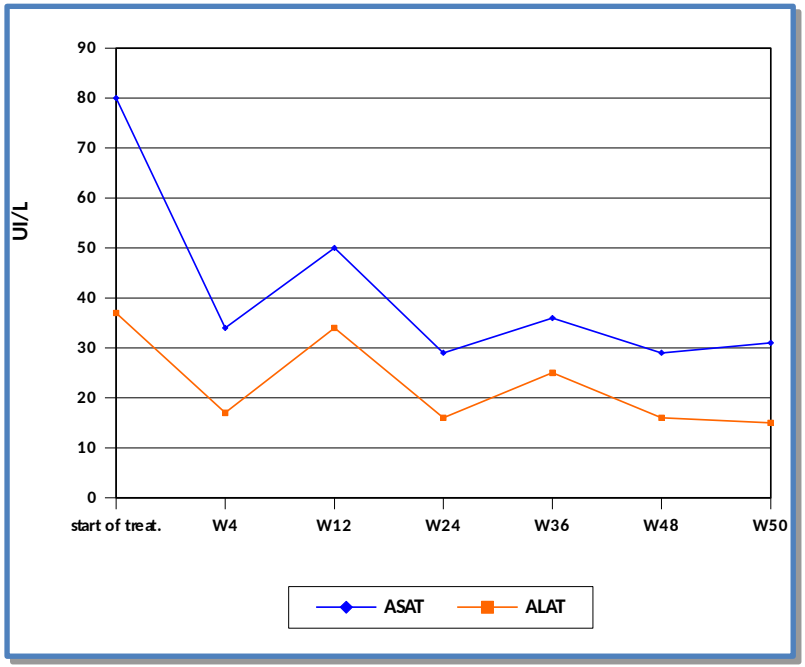
R18 Further studies are required to determine possible predictors of delisting and cut-offs of MELD score beyond which DAA would be detrimental for the patients. (expert opinion

Consider anti-viral treatment in our patient ?

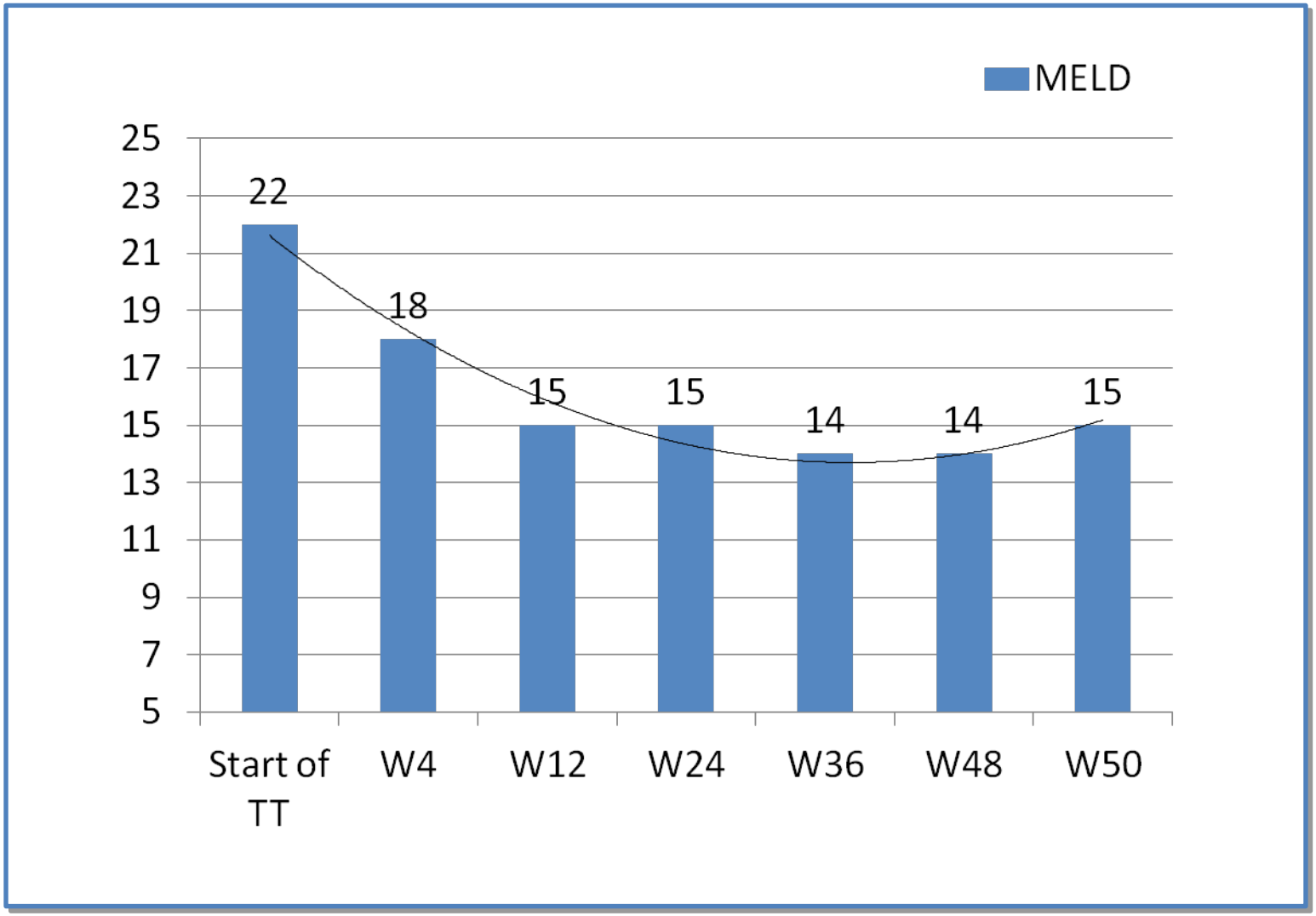
- Sofosbuvir : 400 mg /d
- → Ledipasvir: 90 mg /d

Follow-up : HCV viral load and transaminases

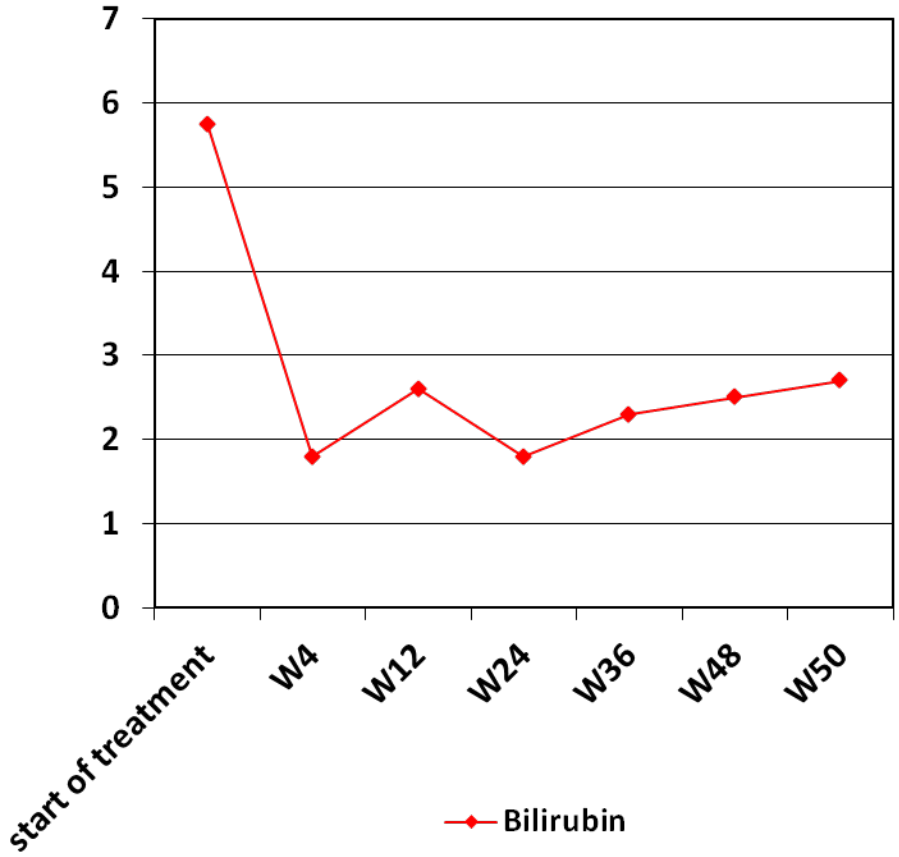


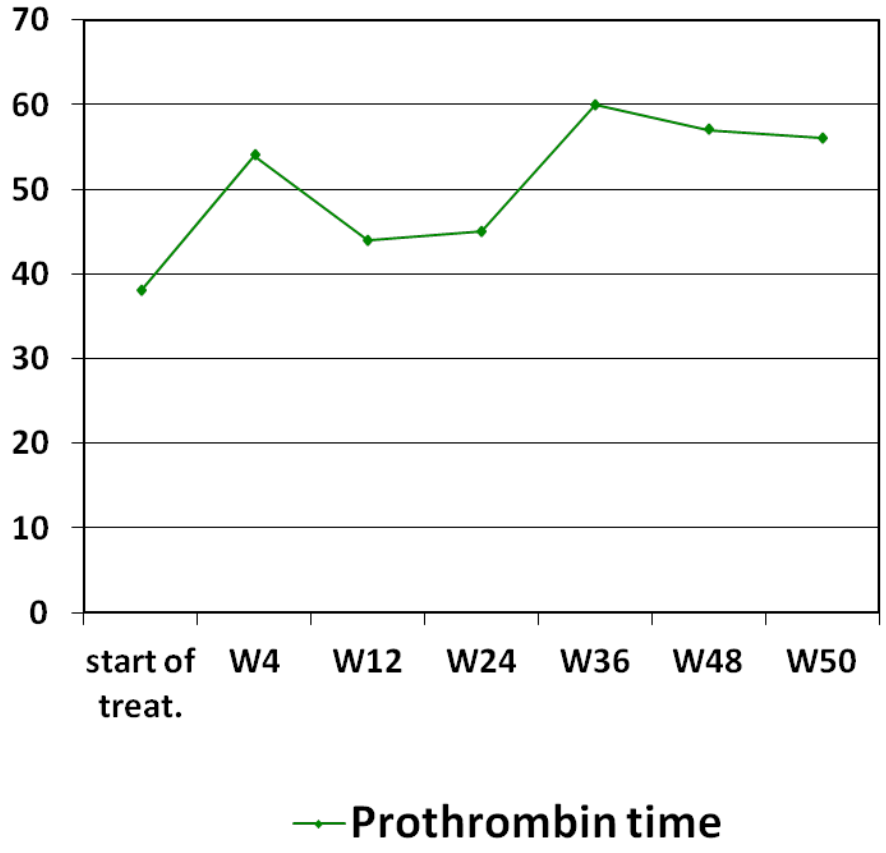


Evolution of MELD on the wait list

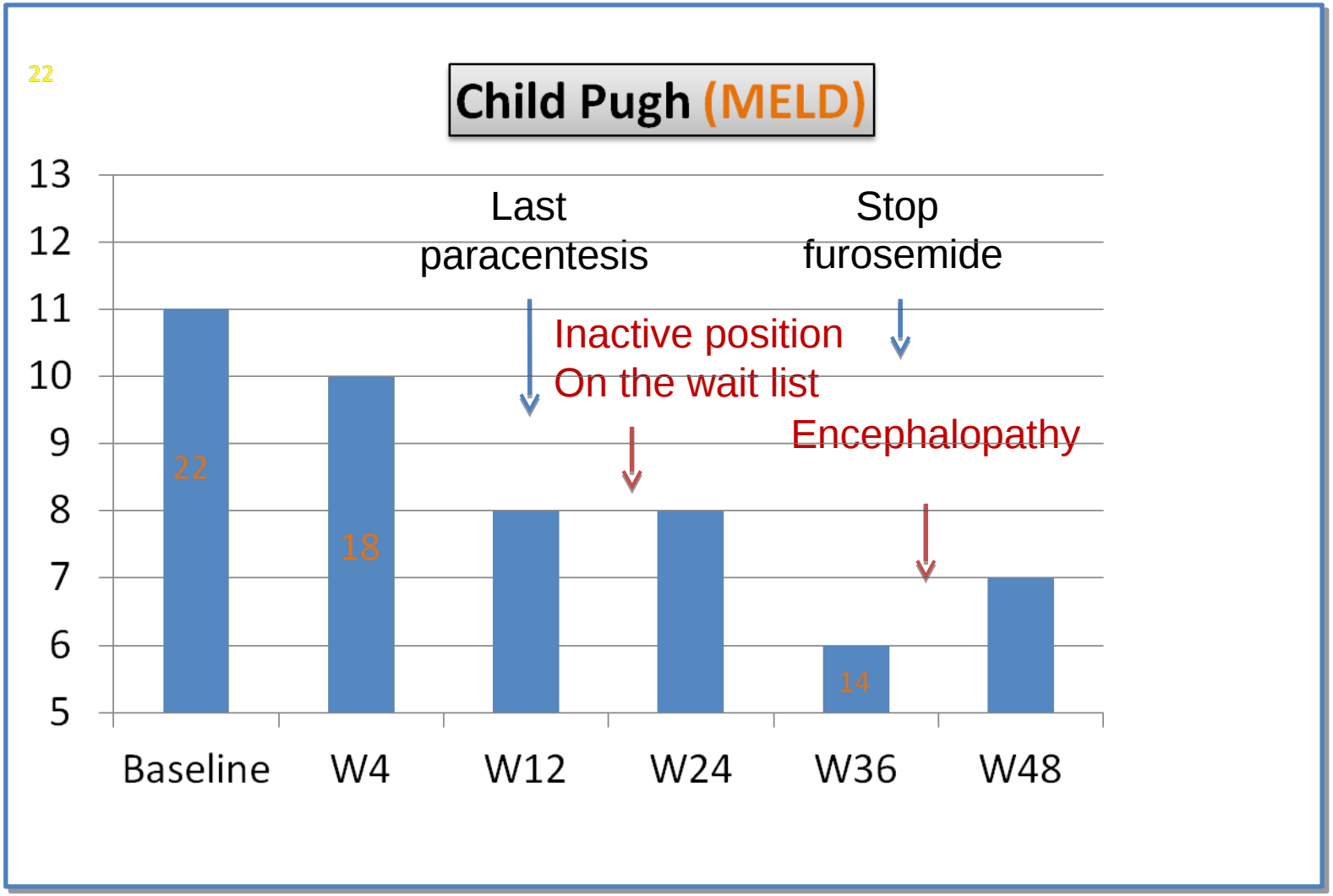


Behind MELD...

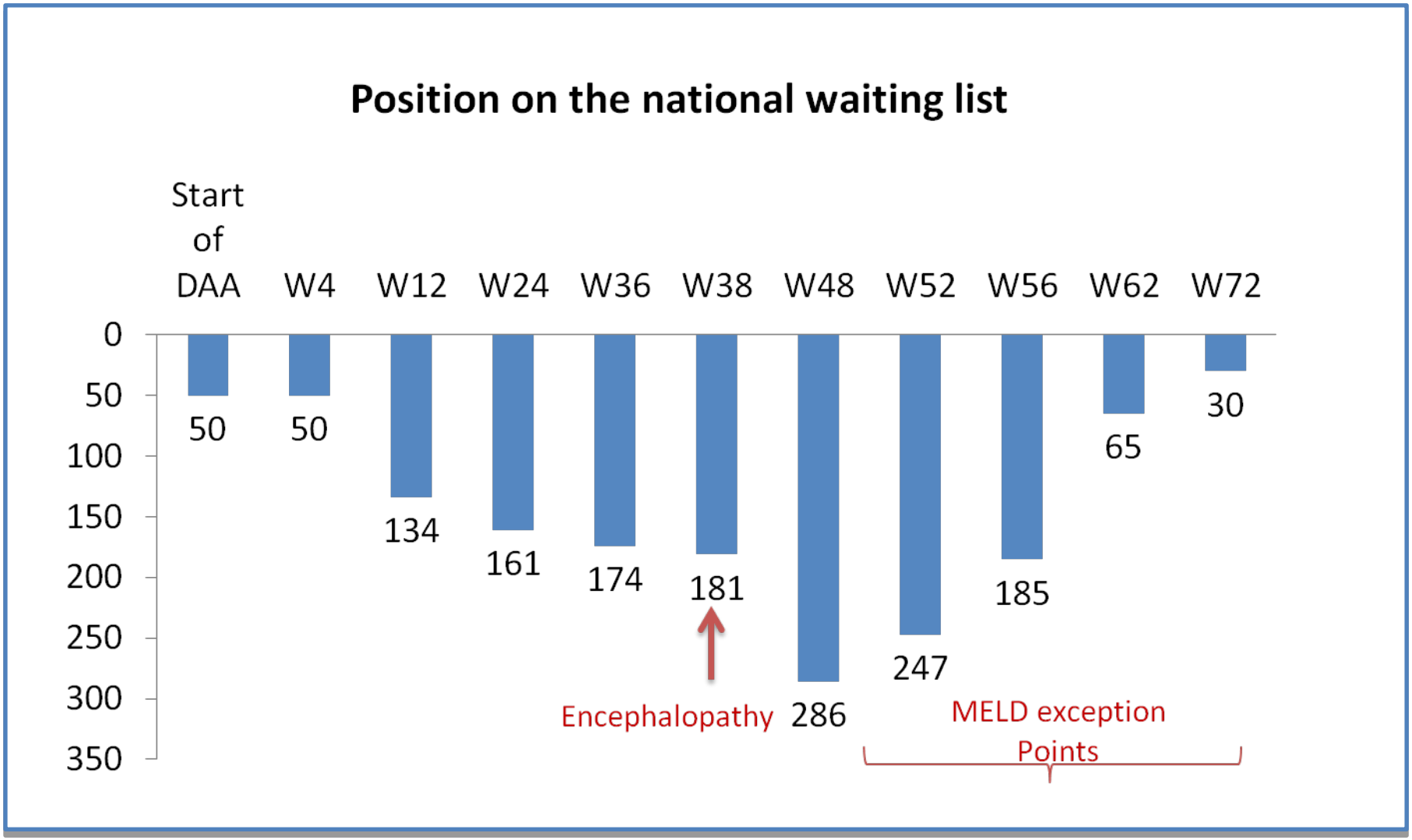

7
6
5
4
3
2
1
0
start of treatment
W4
W12
W24
W36
W48
W50
Bilirubin


70
60
50
40
30
20
10
0
start of treat.
W4
W12
W24
W36
W48
W50
Prothrombin time

Follow-up : Child-Pugh score

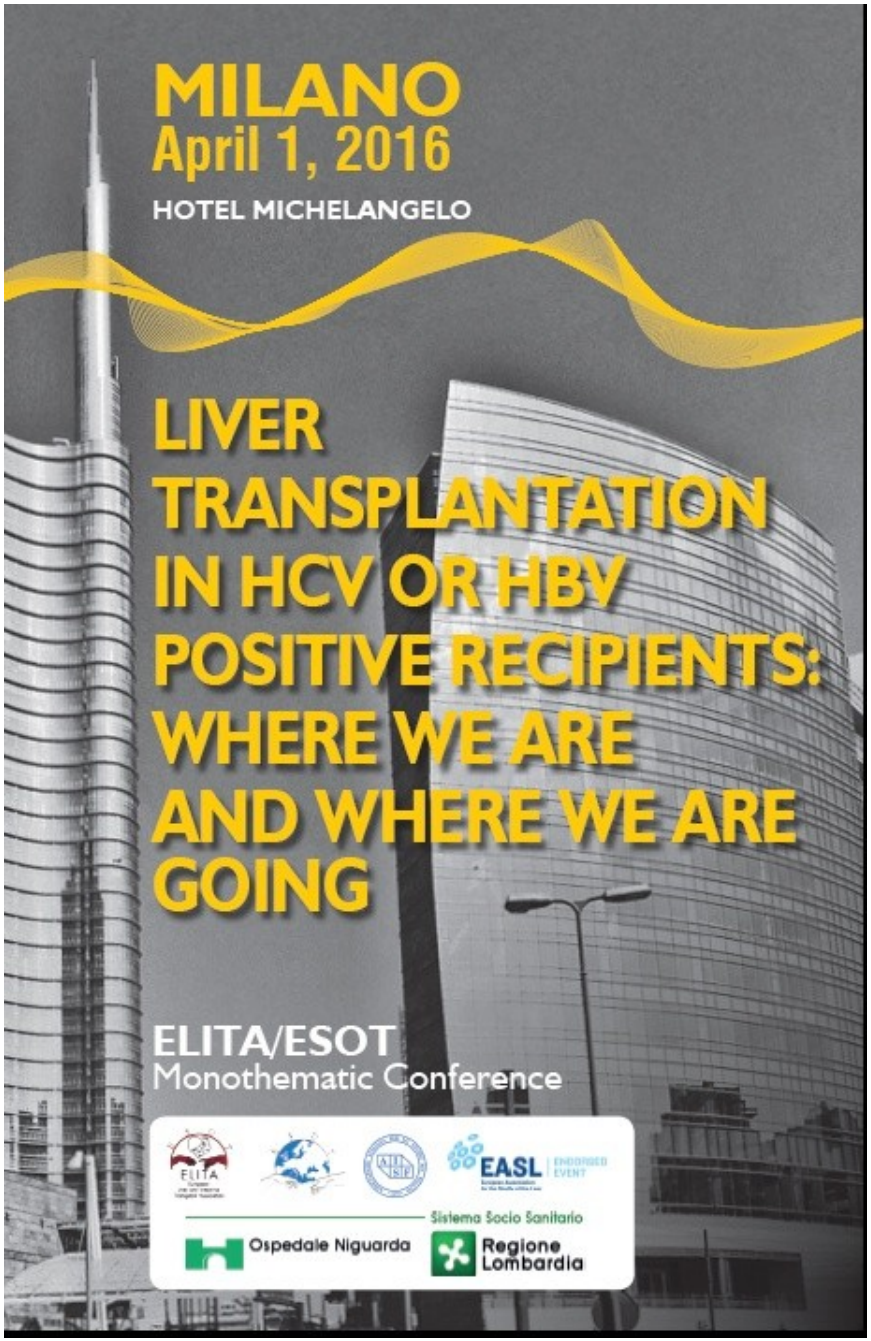


Impact of MELD improvement on position on the wait list : MELD purgatory



5 questions raised by this clinical case to take into account in the decision to treat or not

- What is the probability of getting SVR in advanced de-compensated cirrhotics ?
- Is there a chance of being inactivated and further delisted during the waiting phase after DAA therapy ?
- Impact of the Meld purgatory
  - On risk of death, on chance to be transplanted
- Are there any reliable predictors of MELD improvement, inactivation and delisting ?
- How long may last improvement after DAA therapy ?


MILANO
April 1, 2016
HOTEL MICHELANGELO
LIVER TRANSPLANTATION IN HCV OR HBV POSITIVE RECIPIENTS: WHERE WE ARE AND WHERE WE ARE GOING
ELITA/ESOT
Monothematic Conference
EASL
ENDORSED EVENT
Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

Impact of direct anti-viral agents on inactivation/de-listing of liver transplant candidates listed for decompensated C cirrhosis: a European study

Christophe Duvoux, Marina Berenguer, Paolo Cortesi, Mario Strazzabosco, Susanne-Rasoul Rockenschaub, Silvia Martini, Cristina Morelli, Francesca Donato, Riccardo Volpes, Georges-Philippe Pageaux, Audrey Coilly, Stefano Fagiuoli, Giuliana Amaddeo, Giovanni Perricone, Carmen Vinaixa, Gabriela Berlakovich, Rita Facchetti, Wojciech Polak, Paolo Muiesan and Luca S Belli

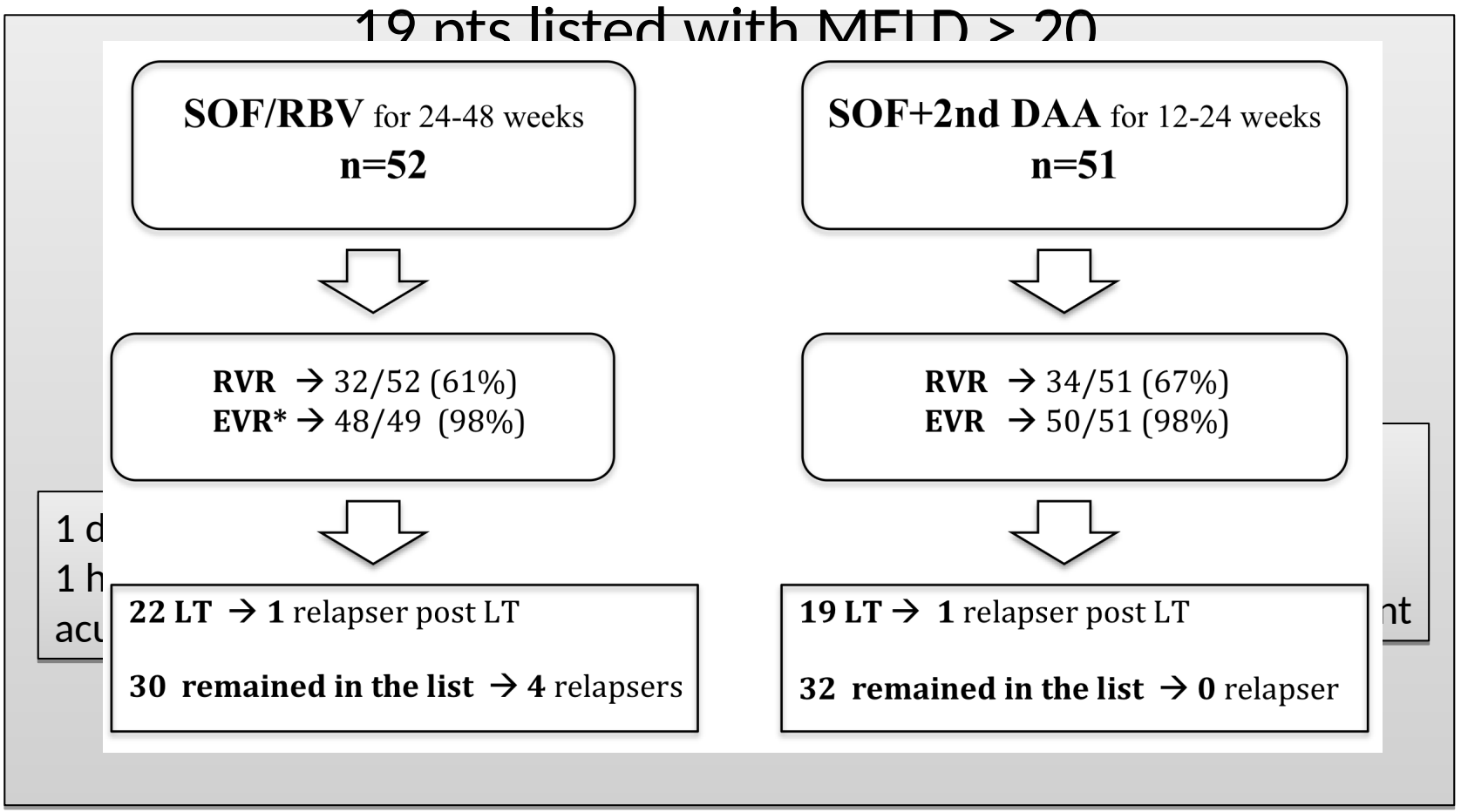
for the European Liver and Intestine Association (ELITA)

Baseline characteristics of treated patients (N=103)

Variables		Values
Age	Median (Range)	54 (37-71)
Male	N (%)	70 (68.0)
MELD	Median (Range)	16 (6-31)
MELD classes, N (%)	<16	51 (49.5)
	16-20	38 (36.9)
	>20	14 (13.6)
Child-Pugh	Median (Range)	10 (7-13)
Child-Pugh classes, N (%)	A 5-6	0
	B 7-9	46 (44.6)
	C 10-14	57 (55.3)
Ascites, N (%)	None	15 (14.6)
	Medically controlled	61 (59.2)
	Medically uncontrolled	27 (26.2)
Encephalopathy, N (%)	None	54 (52.4)
	Medically controlled	48 (46.6)
	Medically uncontrolled	1 (1.0)

MELD, Mayo-model for End stage Liver Disease; DAAs, Direct Acting Antivirals; SOF, Sofosbuvur; RBV, Ribavirin; LDV, Ledipasvir; DCV, Daclatasvir; SMV, Simeprevir

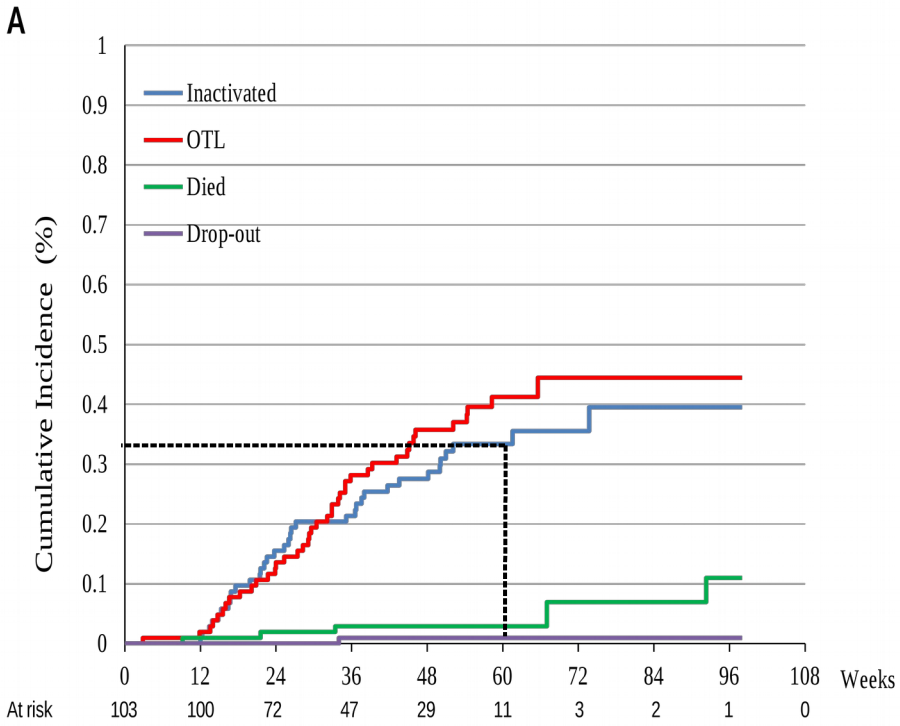
Virological Efficacy

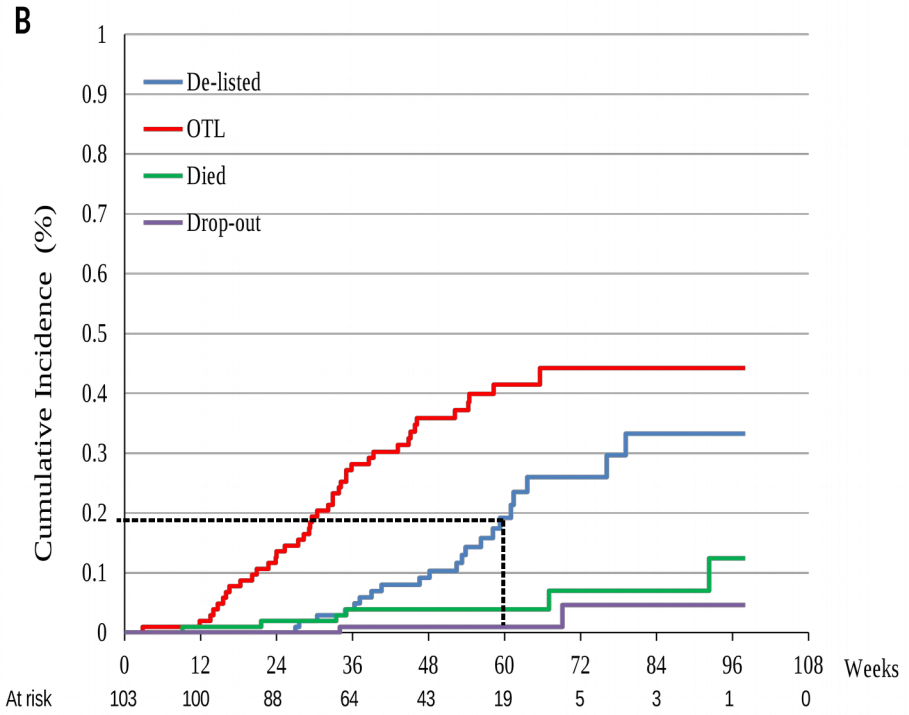


Competing risk analysis of “treated patients”

Inactivated

Delisted





ELITA study: submitted for publication to J Hepatol

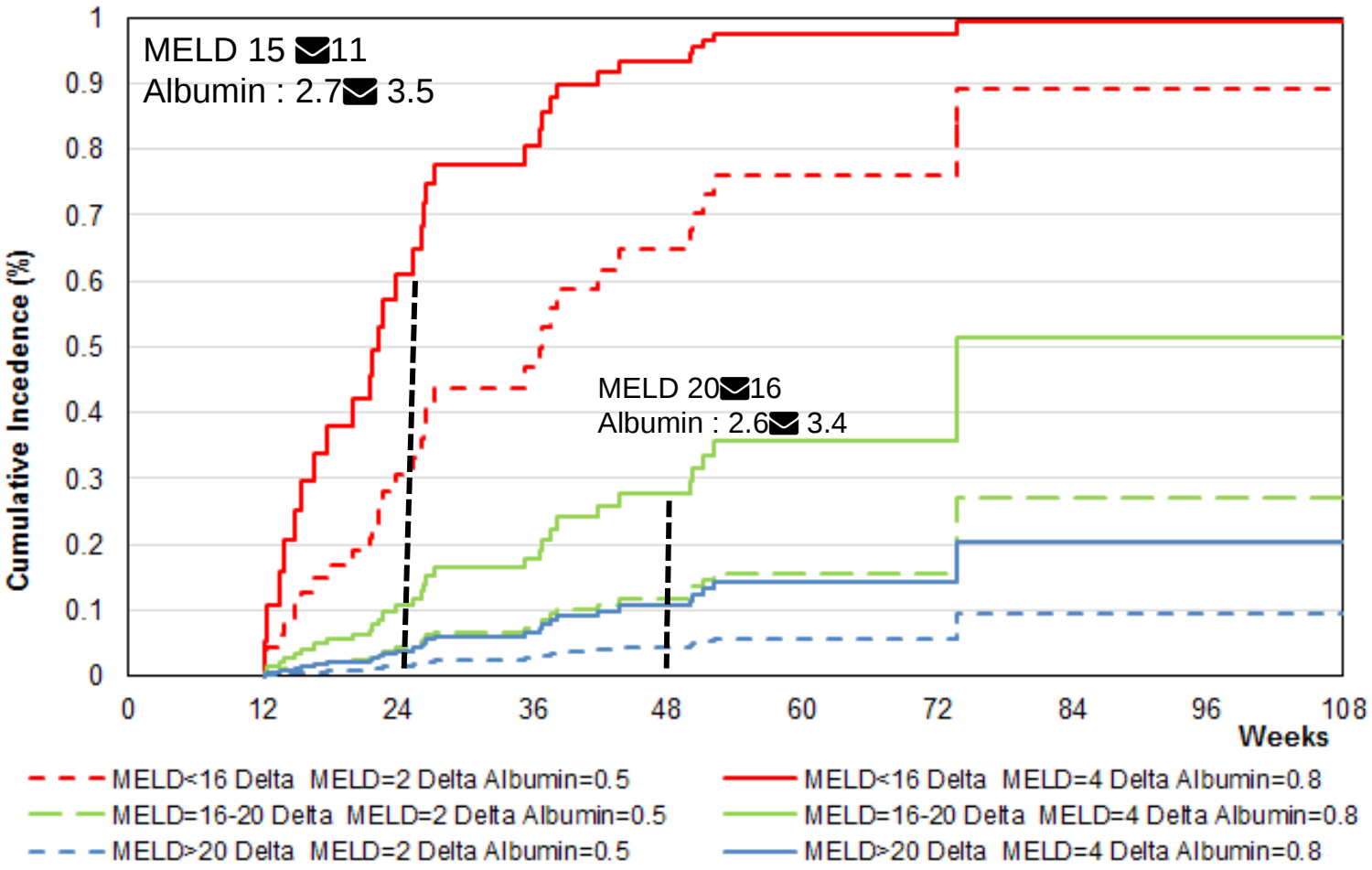
Predictors of inactivation

Table 3. Competing risk analyses of inactivation from list: multivariable model.

Variable	Category	HR (IC95%)	p-value
Delta MELD at 12 weeks	c.v.	1.349 (1.2-1.516)	<.0001
MELD at baseline	<16	1	ref
	16-20	0.12 (0.036-0.396)	0.0005
	>20	0.042 (0.013-0.138)	<.0001
Delta Albumin at 12 weeks	c.v.	0.307 (0.13-0.724)	0.0069

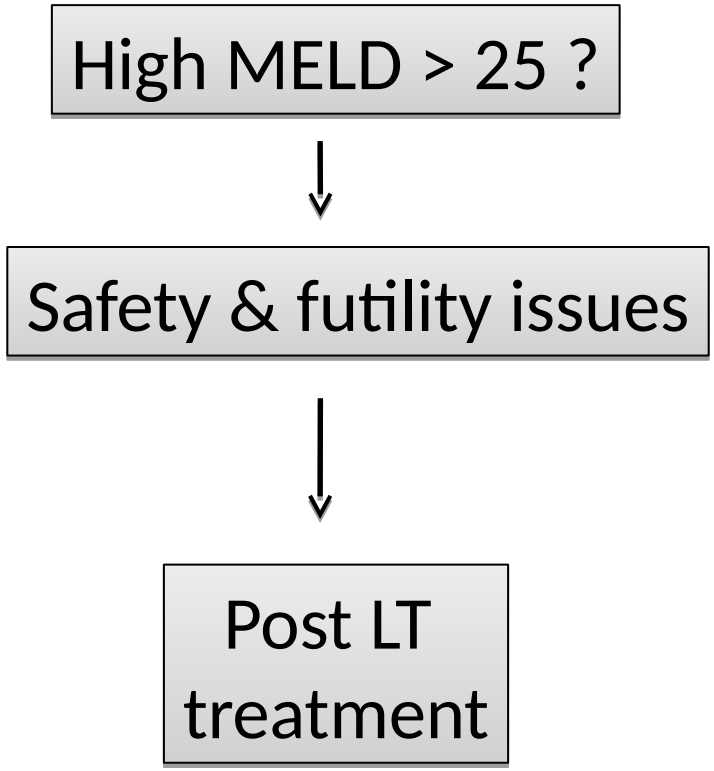
c.v. = continuous variable

Estimated cumulative incidence of inactivation based baseline MELD, 12w Delta MELD and 12w Delta albumin.



Decision to treat or not a de-compensated Child C cirrhotic waiting for LT is difficult

Multidisciplinary approach

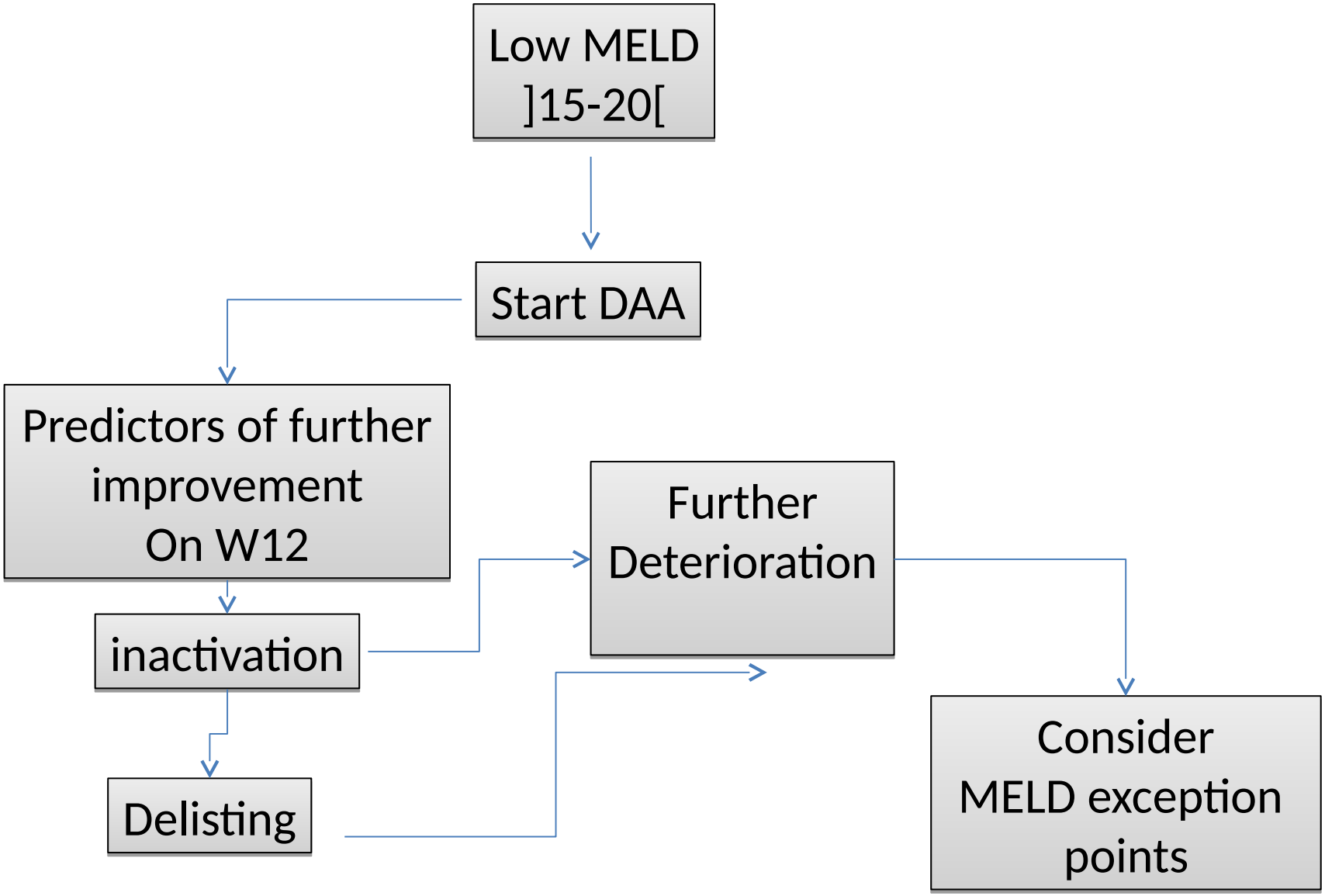


Decision to treat or not a de-compensated Child C cirrhotic waiting for LT is difficult

When not to treat ?
Which MELD cut –off ?

ELITA 2016 consensus meeting
Expert opinion : MELD 20
Final decision : 22 ?

Decision to treat or not a de-compensated Child C cirrhotic waiting for LT is difficult



2016 ELITA Recommendations pre final

13. Based on current studies and practice, pre LT DAA treatment is not recommended in patients with high MELD scores (> 25) because of their poor prognosis with a significant risk of death either pre and post-LT, unknown probability of improvement,
rapid access to LT and safety issues. In these patients the option of post LT treatment with DAAs is preferable (expert opinion).

14- patients with baseline MELD <16 (typically Child-Pugh B). They have a high chance (35%) to be delisted [C1] due to clinical improvement. The probability of regression of signs of decompensation makes DAA treatment before LT a reasonable option. These patients should therefore be treated while listed (B1)

15 - Patients with baseline MELD between 16 and 20 (typically Child-Pugh C). They have a lower but significant chance to be delisted of about 15 [C2] %. Treatment should be encouraged followed by a prognostic evaluation on week 12 of treatment. Patients with the highest probability of being delisted can be identified by taking into account the extent of albumin and a MELD change after 12 weeks of DAA therapy (figure Paolo) and should be considered for inactivation and further delisting. Patients with no significant improvement in MELD and albumin should be maintained on the wait list. (B1).

16 Patients with baseline MELD between 21 and 25 (typically advanced Child-Pugh C). They may show a limited MELD improvement which is not sufficient to lead to delisting and which possibly hampers the access to LT (purgatory). However some patients may still undergo a significant improvement in liver function (figure) (B1). For such patients a case by case multidisciplinary decision is advised. In patients in whom DAA prove easy to manage (normal renal function, no expected DDI), DAA treatment can be considered. The same strategy as in recommendation 12 is subsequently recommended, depending on the magnitude of MELD/albumin improvement. (B1)

17 In the case of a modest improvement of MELD not consistent with delisting, patients should be maintained on the wait list with their baseline MELD as assessed before DAA therapy to counteract the MELD purgatory effect. Such a MELD exception rule should be implemented after agreement of OSOs. (Expert opinion)

Main issues

1- What is the impact of pre LT DAA on prevention of HCV recurrence post-LT ?

2- What is the impact of DAAs on liver function and delisting pre transplant ?

3- Who should be treated or not treated before LT among decompensated cirrhotics/among pts listed for HCC

4- **How safe are DAA when used in decompensated cirrhosis**

5 -**How to take into account drug to drug interactions and frequent renal impairment in LT candidates and recipients** ?

Which compound ? DAA PK in Cirrhotics

Table 3. Pharmacokinetics (change in AUC) of DAAs in hepatic impairment (graded according to CTP score) and recommendation.

Drug	CTP A (5-6 points)	CTP B (7-9 points)	CTP C (≥10 points)
Sofosbuvir [38,108]	NR	NPD	NPD
Simeprevir [109]†	NR	NR	AUC x 3
Daclatasvir [110, 111]¥	NR	NR	NR
Asunaprevir [112]	NR	AUC x 9.8	AUC x 32
Ledipasvir [113]	NR	NR	NR
ABT-450/r [114]§	NR	NR	AUC x 11
Dasabuvir [114]	NR	NR	NR
Ombitasvir [114]	NR	NR	NR
MK-8742 [103]	NR	NR	NPD
MK-5172 [103]	NR	NR	NPD

NR, dose adjustment not required; NPD, no pharmacokinetic data or studies

Gamballi J Hepatol 2014

Pre LT Recommendations

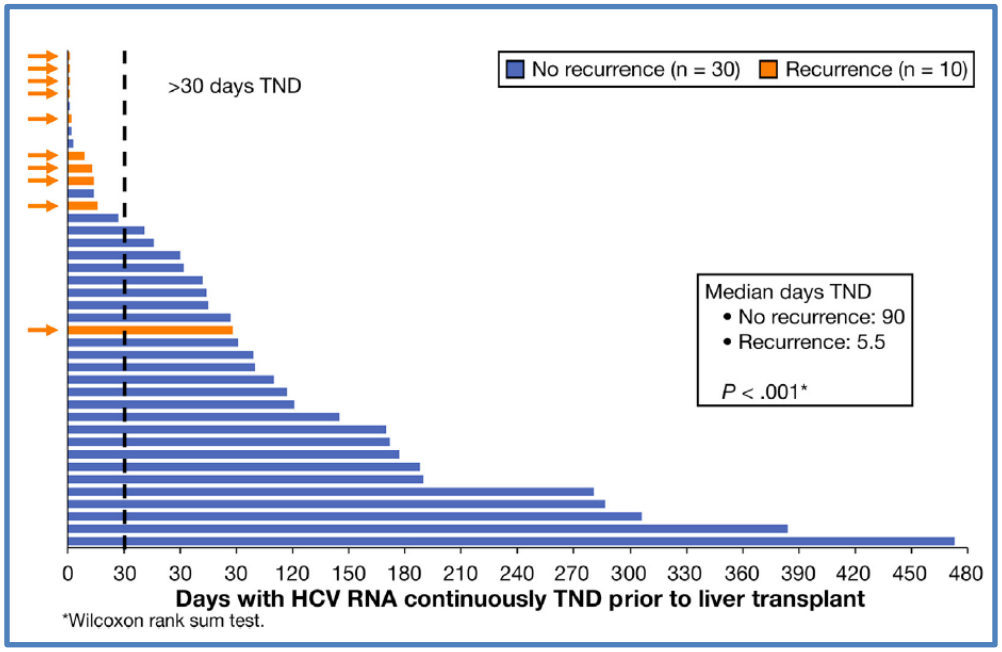
- **1. Sofosbuvir, ledipasvir,and daclatasvir can be used in patients with cirrhosis with no need of dose adjustment, whatever the liver impairment** (A1).
- **2. The 3D combo (Paritaprevir/r, ombitasvir, dasabuvir), the 2D combo (Paritaprevir/r, ombitasvir) should not be used in patients with decompensated cirrhosis** (Child-Pugh B and C). **Simeprevir is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and should be avoided in Child-Pugh C (A1).** The 3D, 2D combo, Simeprevir and Grazoprevir/Elbasvir can be safely used in patients with compensated cirrhosis (Child-Pugh A)(B1).
- **3. Sofosbuvir requires dose adjustment in case of eGFR< 30 mL/min** (every other day) and in patients on hemodialysis (B2). <u>In case severe kidney impairment, treatment with Sofosbuvir is preferably administered after LT</u>
- 4**. Careful evaluation of Drug Drug interactions** with antiretrovirals and other concomitant treatments is mandatory before starting any anti HCV treatment. Discussion of interactions with a pharmacologist or hospital pharmacist with the help of international websites (www.hepcdruginteractions.com) is encouraged (expert opinion).

1- What is the impact of pre LT DAA on prevention of HCV recurrence post-LT ?

61 HCC-HCV LT candidates receiving SOF+RBV before LT
43 pts (70%) with HCV RNA negative at LT

Table 2. Post-Transplant Virologic Response by Visit for Patients With HCV-RNA Level Less Than the LLOQ at the Last Measurement Before Liver Transplantation

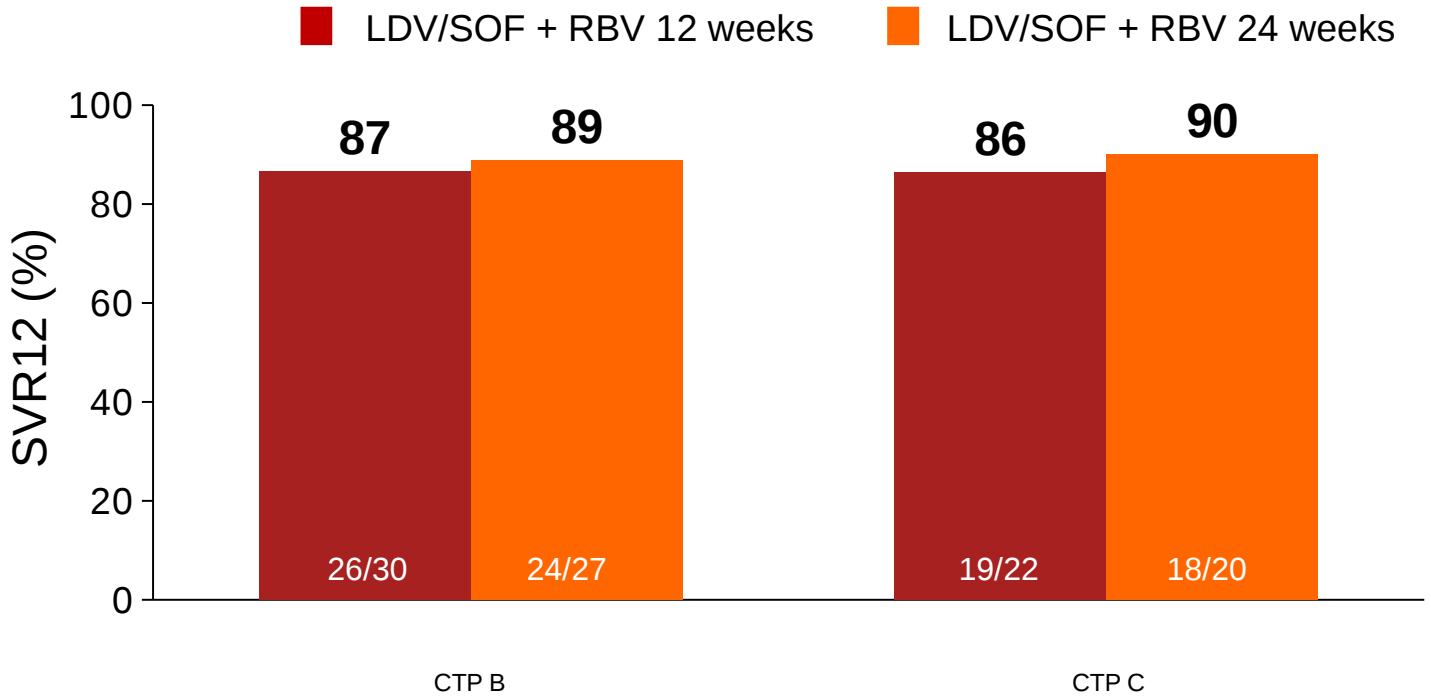
	Sofosbuvir-ribavirin for ≥12 weeks (N = 32)	Sofosbuvir-ribavirin for any duration (N = 43)
Post-transplant week 1		
<LLOQ, n/N (%)	28 (88%)	37 (86%)
90% CI	74%–96%	74%–94%
Post-transplant week 2		
<LLOQ, n/N (%)	26 (81%)	35 (81%)
90% CI	66%–92%	69%–90%
Post-transplant week 4		
<LLOQ, n/N (%)	24 (75%)	31 (72%)
90% CI	59%–87%	59%–83%
Post-transplant week 8		
<LLOQ, n/N (%)	24 (75%)	31 (72%)
90% CI	59%–87%	59%–83%
Post-transplant week 12		
<LLOQ, n/N (%)	24 (75%)	30 (70%)
90% CI	59%–87%	56%–81%



Curry et al. Gastroenterology 2015

SOLAR-1: LDV/SOF + RBV in Decompensated Cirrhosis

Prospective, multicentre study of 12 or 24 weeks of LDV/SOF + RBV in TN and TE HCV GT 1 and 4 patients with CTP B (N=59) or CTP C (N=49) clinically decompensated cirrhosis



SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Virological response was associated with improvements in bilirubin, albumin, MELD and CTP scores in both CTP class B and C patients

LDV/SOF + RBV for 12 weeks is not an EMA-recommended treatment regimen;
Error bars represent 90% confidence intervals;
TE: treatment-experienced; TN: treatment-naïve

Flamm S, et al. AASLD 2014; Oral #239.

Pre LT Recommendations.

5. Virological response after DAA therapy is very high, in the order of 90%, in patients with compensated cirrhosis (Child-Pugh A) and high, in the order of 80%, in those with decompensated cirrhosis (Child-Pugh B-C) and is not influenced by HIV coinfection: therefore DAA therapy can be considered in patients who are listed for LT (A1).

6. Since patients with advanced liver disease (Child-Pugh B and C) are at risk of dying before LT and their chances to receive a graft increase with their priority on the waiting list, the duration of DAA treatment should be as short as possible. Therefore, DAA combinations achieving a SVR in 12 weeks should be preferred. (A2)

7. For listed patients with Child-Pugh A cirrhosis, HCV-RNA clearance of at least 1 month duration seems to be a reliable virological end point to proceed with LT with a low risk (<5%) of viral recurrence after LT. Whether the same virological end point also holds true for patients with decompensated cirrhosis needs to be confirmed. (expert opinion)

Pre LT Recommendations.

8. First line treatment options for listed patients according to specific genotypes are the following:

- - **Genotype 1/4**. **SOF/LDV/RBV or SOF/DCV/RBV for 12 weeks** are associated with SVR12 rates in the order of 90% in patients with compensated cirrhosis (Child-Pugh A), and of 80%in those with decompensated cirrhosis (Child-Pugh B and C) and should be considered the first line option in listed patients with decompensated cirrhosis(A1). If patients do not tolerate RBV the duration of treatment can be extended up to LT or for a maximum of 24 weeks. SOF/SIM +/-RBV and 2D and 3D for 12 weeks should be considered equally valuable options in Child-Pugh A patients.
- - **Genotype 2**. **SOF/DCV for 12 weeks** is the preferred regimen in any listed patient infected with genotype 2 due to its short duration. SOF/RBV for up to 20 weeks is a possible effective alternative.
- **- Genotype 3**. **SOF/DCV+/-RBV for up to 12 weeks** achieve the highest SVR12 both in compensated (Child-Pugh A) and decompensated cirrhosis (Child-Pugh B).
  - ✉ SOF + Velpastasvir in a close future
- - Genotype 5-6. The same regimens suggested for genotype 1 or 4 should be used for genotypes and 6 although data are limited (B1).

Aim of DAA treatment in HCC patients

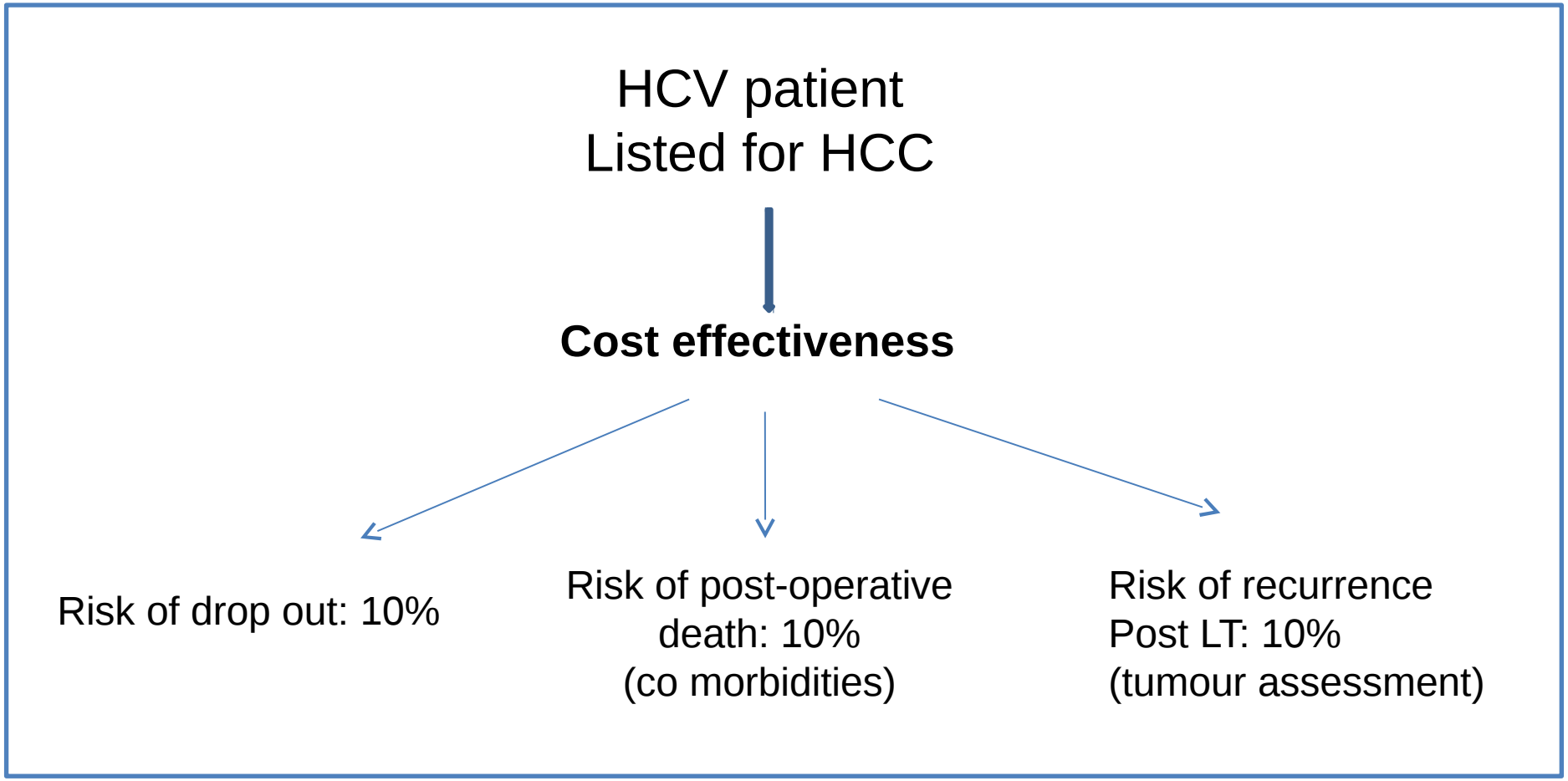
Median MELD 12

- To prevent post transplant HCV recurrence

In patients amenable to « curative » bridging therapy with long waiting time

- To prevent liver function deterioration and HCC recurrence ?

Factors to be taken into account in the decision making process Before DAA treatment in HCC candidates



✉ Avoid futile DAA treatment

Decision making algorithm (proposal)

Listing → Observation period

↓

Evaluation after 1rst bridge therapy

Low risk group

- Milan criteria
& AFP level < 1000
or AFP score ≤2
- Response to bridge therapy according to UCSF criteria
- Compensated cirrhosis
- Waiting time > 3 months

↓

Proceed with DAA treatment Pre LT

High risk patients

- Increased AFP during waiting perod
- Partial response or progression on bridge therapy
- Down staging procedure
- short waiting time
- Decompensated cirrhosis

↓

No drop out

✉ **Proceed with LT**

→ **Explant pathology** →

<u>Post LT treatment</u> depending on clinical situation And risk of HCC recurrence

Après Transplantation ?

- Les points clés
  - Schémas de traitement et efficacité similaire au contexte de patients non transplantés si le traitement est débuté avant le stade de cirrhose
    - Recommandation : traiter le plus tôt possible sans prendre en compte le stade de fibrose
  - Prendre en compte les interactions médicamenteuses (SIM, 3 D): ✉ SOF/LEDI ou SOF/DAC +/- riba
  - Prendre en compte la fonction rénale (Cl < 30 mL/mn) (SOF)
  - Prendre en compte les différents traitements à visée cardio-vasculaires
  - Attention à la clairance virale qui s'accompagne d'une accélération du métabolisme des CNI