KING'S HEALTH PARTNERS

Antiviral therapy in compensated cirrhosis and liver transplant
who knows…the state of play ?

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PHC Workshop Jan 2014

Disclosures: there is no middle ground…

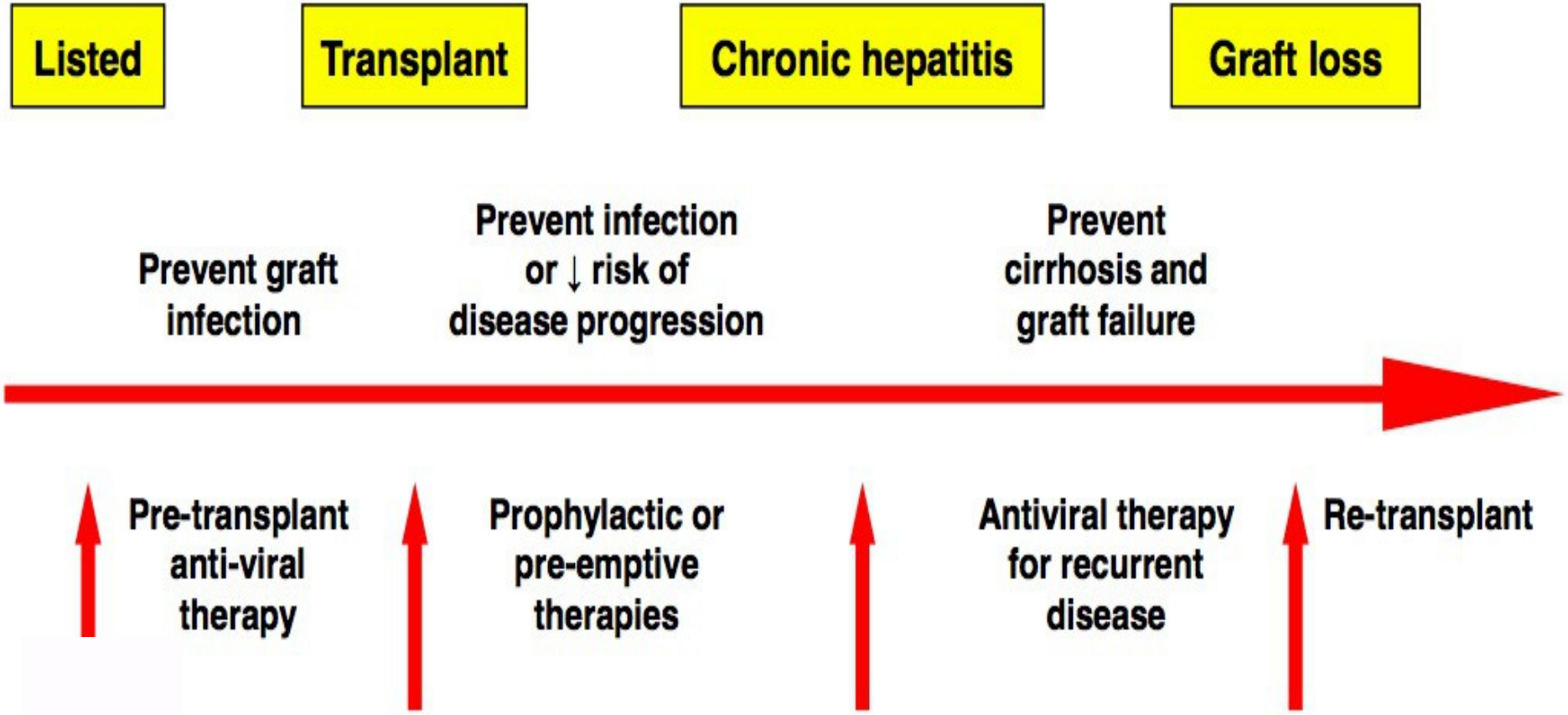
- Pharma support:

Janssen/ MSD/ Gilead/ BMS/ GSK/ Novartis/ Roche/ AbbVie/ Astellas

- This is a two-sided conversation…
- Spectrum in audience
- Personal opinion as a Clinician
- I will take the '*Why not*' viewpoint

If you risk nothing you risk everything…

Opportunities to treat HCV in patients undergoing liver transplantation

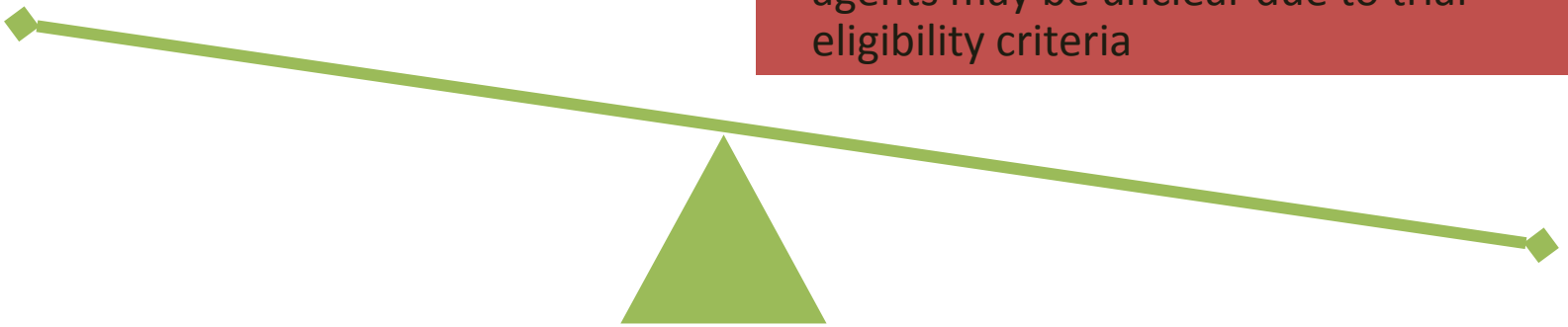


Biggins SW, Terrault NA. Infect Dis Clin N Am 2006; 20:155

Severity of Disease Increases Need for HCV Therapy but Also Impairs Response

- May not need immediate treatment
- BUT
  - Easier to treat
  - High likelihood of response

- Greater need for treatment
- BUT
  - Response may be impaired
- Perhaps more effective options in future, but efficacy of some investigational agents may be unclear due to trial eligibility criteria



Mild disease

Advanced disease/ cirrhosis

How not to do it - 2011

Male, 44 years, Caucasian

Cirrhosis . Previously listed for OLT in US but recompensated

2 previous treatments courses with Peg Interferon and Ribavirin – Relapser

Genotype 1A

Baseline HCV RNA – 385,000 IU/ml

IL 28B genotype CT

Well compensated pre treatment

Viral Response and Tolerability

TW 1 - 16 HCV RNA - < 15 IU/ml

Tolerates treatment reasonably well

Completes 12 weeks of Telaprevir with no major problems

Tolerability

TW16

Bili 53

Alb 32

AST 468/ALT 181

ALP 215, GGT 1902

PLTs 20

INR 1.05

Minimal jaundice, no HE, weight stable, felt reasonable

Tolerability

TW17 (5 days later)

Bili 124 (Conjugated 93)

Alb 32

AST 269

ALP 236, GGT 1719

PLTs 42

INR 1.1

Ascites?

Tolerability

US – small- moderate ascites

Ammonia - 62

No Drugs/ETOH/concurrent illness

Viral screen negative (Hep A,B,C,E, CMV/EBV/HSV)

Autoantibodies and Immunoglobulins normal

Sodium and renal function normal

Develops chest infection – Rx antibiotics (bili – 180)

Sudden bereavement – needs to go to USA

Back from US Feb 2012

Bili 26
Alb 39
AST 36
ALP 104, GGT 216
PLTs 201
INR 1.13
HCV RNA < 15 iu/ml initially
No ascites on repeat US
CT – no decompensation
Chest infection resolved

Mr HA

- 65 year old, G4
- 12 yrs post LT (x2)– Boujoun
- Treated Peg/riba IGD (HCV rna –ve) salvaged by AKB
- BR 89 alb 30
- Meld 12
- Rx on list -LADR full dose RNA at week 8 – 3 months
- iMeld 42 ascites +/- encephalopathy
- LITU x2

- Negative RNA till 8 weeks post

Grp B+ DBD – 14 months

Was transplantation an extension of antiviral Rx?

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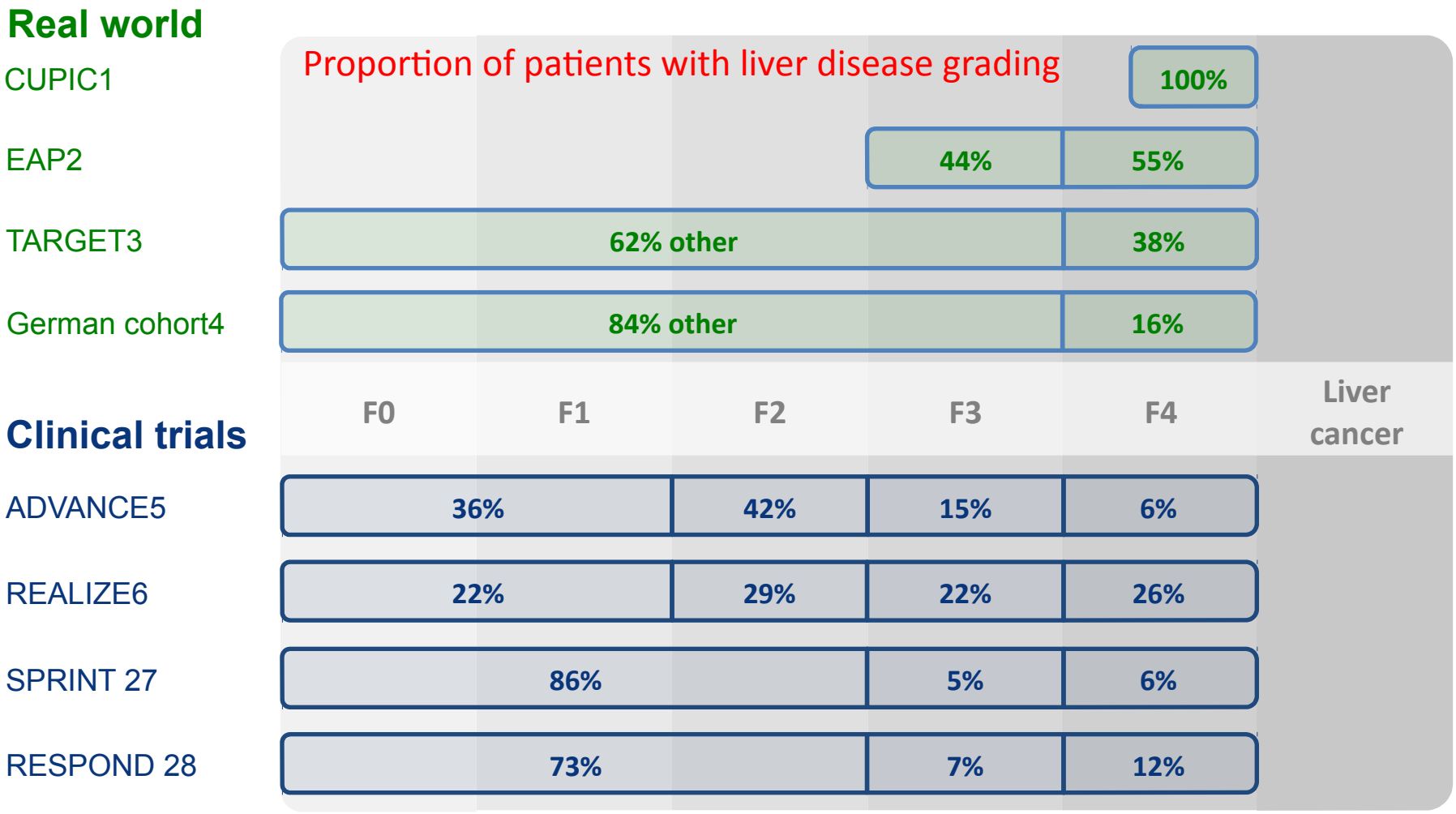
Treating patients with DAAs in the real world



1. Hézode C, et al. J Hepatol. 2013;59:434–41; 2. Colombo M, et al. AASLD: 2012. LB-15
3. Fried M, et al. EASL 2013: Abstract 818; 4. Berg T, et al. EASL 2013: Abstract 793
5. Jacobson I, et al. N Eng J Med 2011;364:2405–16; 6. Zeuzem S, et al. N Eng J Med 2011;364:2417–28
7. Poordad F, et al. N Eng J Med 2011;364:1195–206; 8. Bacon BR, et al. N Eng J Med 2011;164:1207–17

Albumin and MELD Score Predict Decompensation in Patients with HCV Cirrhosis and Thrombocytopenia on Interferon Therapy: Analysis from the ENABLE Studies

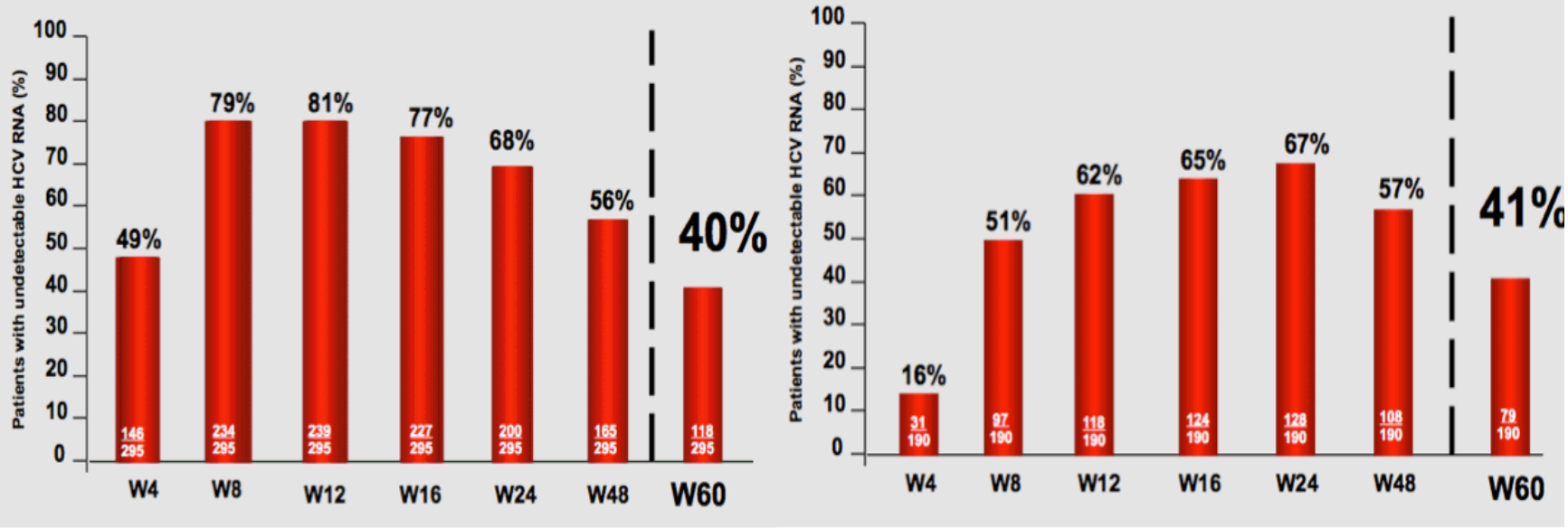
Nezam Afdhal[1], Edoardo G Giannini[2], Samuel Sigal[3], Stuart Gordon[4], Gregory T Everson[5], Abdullah MS Al-Osaimi[6], Geoffrey M Dusheiko[7], Teresa Casanovas[8], Norbert Brau[9], Sandra Y Vasey[10], Malini Iyengar[10], Ulla Forssen[10], Fiona Campbell[11], Dickens Theodore[12]

Table 3. Adverse Events Suggestive of Hepatic Decompensation by Baseline MELD Score

Number of patients (%)	Baseline MELD Score <10		Baseline MELD Score ≥10	
	Eltrombopag + AVT (N=541)	Placebo + AVT (N=264)	Eltrombopag + AVT (N=400)	Placebo + AVT (N=213)
Any event	**38 (7)**	**11 (4)**	**85 (21)**	**24 (11)**
Ascites	13 (2)	2 (<1)	41 (10)	12 (6)
Hepatocellular carcinoma	12 (2)	3 (1)	15 (4)	9 (4)
Death	6 (1)	2 (<1)	16 (4)	5 (2)
Hepatic encephalopathy	7 (1)	1 (<1)	16 (4)	3 (1)
Variceal hemorrhage	4 (<1)	3 (1)	9 (2)	1 (<1)
Other decompensation events	3 (<1)	0	12 (3)	1 (<1)
Spontaneous bacterial peritonitis	0	0	7 (2)	2 (<1)

AVT, antiviral therapy; MELD, model for end-stage liver disease.

CUPIC study: efficacy



- 15–20% less than what you would expect according to phase three results and the baseline characteristics
- Moderate but still reasonable efficacy

CUPIC: safety overview at Week 60

Outcomes, %	TVR N=299	BOC N=212
Serious adverse event	53.8	44.3
Premature discontinuations due to serious adverse events	23.8	17.5
Death, n (%)	8 (2.7)	3 (1.4)
Infections (grade 3/4)	9.7	2.4
Hepatic decompensation	4.7	4.2
EPO use	56.5	56.1
Transfusion	17.7	11.8
RBV dose reduction	27.8	23.6

Hézode C, et al. Presented at AFEF 2013

CUPIC: SVR12 and the risk of occurrence of severe complications*

		Platelets count ≤100,000/mm3	Platelets count >100,000/mm3
Albumin <35 g/L	N	**37**	**31**
	Complications, n (%)	**19 (51.4)**	**5 (16.1)**
	SVR12, n (%)	**10 (27.0)**	**9 (29.0)**
Albumin ≥35 g/L	N	**74**	**306**
	Complications, n (%)	**9 (12.2)**	**19 (6.2)**
	SVR12, n (%)	**27 (36.5)**	**168 (54.9)**

*Missing data for 63 patients
Severe complications include death, hospitalisation and hepatic decompensation

Hézode C, et al. Presented at AFEF 2013

Protease-Inhibitor (PI) Triple Therapy in Mildly Decompensated Cirrhotics

- Aims: To assess responses and safety of triple therapy in mildly decompensated (CP≥6) cirrhotics.

- Methods: Two-center retrospective cohort of all CP≥6 cirrhotics treated with (P/R) with telaprevir (70%) or boceprevir (30%) since PI approval.

- For safety outcomes, all compensated cirrhotics (CP=5) treated with TT during the same time period were used for comparison.

- 61 patients (median age 60yrs, 28% female, 66% G1A, 19% IL28B-CC, 28% previous null/partial responders) with mildly decompensated cirrhosis: CP 6 (range 6-11), MELD 10 (range 6-20] were followed for median 174days (IQR: 92-332) from start of PI (N=31 evaluable for SVR12)

Saxena V et al, et al. AASLD 2013. Abstract 1969

Protease-Inhibitor (PI) Triple Therapy in Mildly Decompensated Cirrhotics

- RVR in 35%,
- EOTR in 60% (28/47)
- SVR12 in 35% (11/31).

- In univariate analysis, SVR12 was associated with:
  - IL28B-CC, treatment naïve/relapse status, RVR, lower baseline total bilirubin and higher baseline platelet count.

- Negative predictive value for SVR:

  bilirubin (>1.8) 100%,

  baseline platelets (<100) 78%

  lack of RVR 83%

Saxena V et al, et al. AASLD 2013. Abstract 1969

Protease-Inhibitor (PI) Triple Therapy in Mildly Decompensated Cirrhotics

- Compared to cirrhotics with CP=5 (n=45), CP≥6 pts required more:
  - P/R dose reductions (48% vs 94%),
  - GCSF use (20% vs 44%),
  - eltrombopag use (4% vs 34%)
  - transfusions (7% vs 21%)
- 20 (33%) CP≥6 pts stopped TT early due to adverse events (15%) and due to virologic failure (18%).
- 50% (10/20) experienced decompensation (MELD increased ≥2) in the CP≥6 group vs 15% (2/13) in CP=5 group

Saxena V et al, et al. AASLD 2013. Abstract 1969

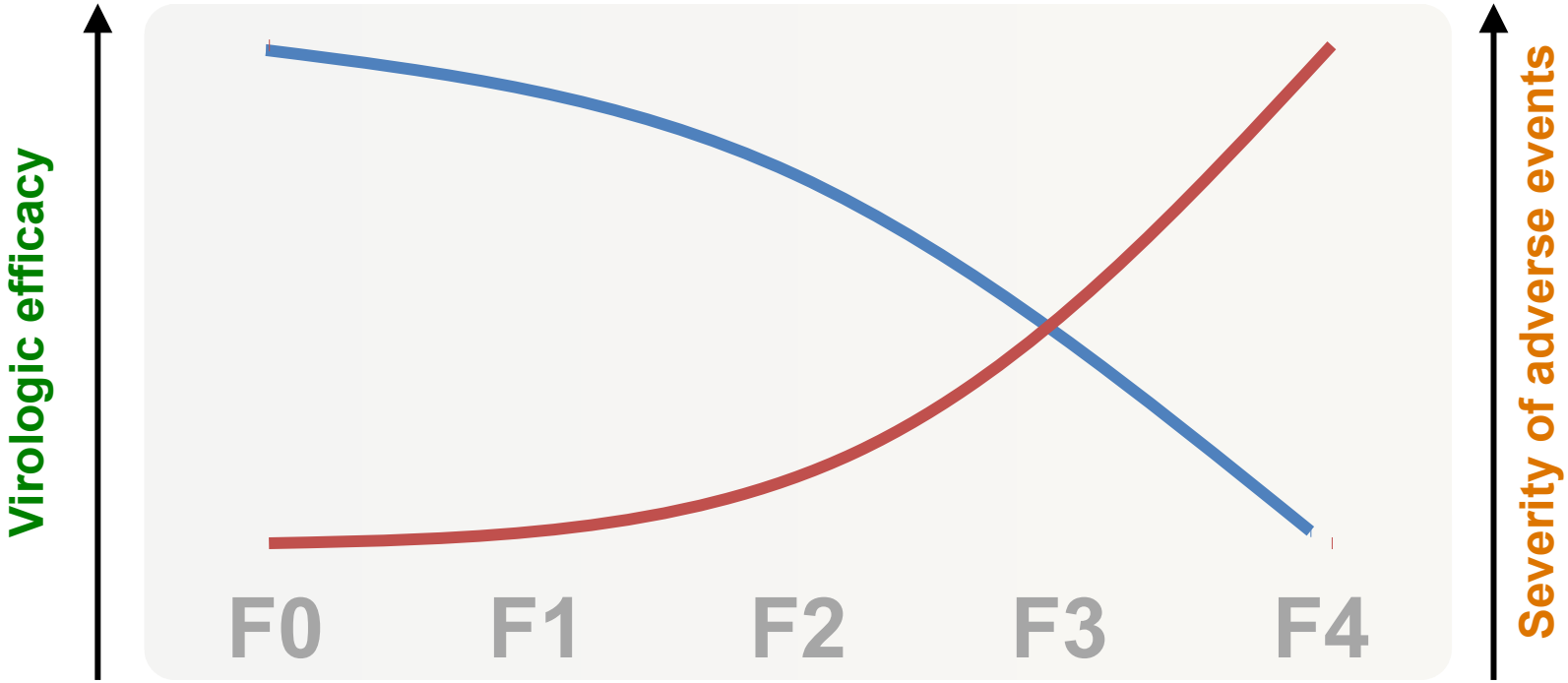
Protease-Inhibitor (PI) Triple Therapy in Mildly Decompensated Cirrhotics

Conclusions

- Low SVR rates (35%)
- High stopping rate (33%)
- 50% decompensate further after early stopping
- Modest benefit and significant risk
- Urgent need for alternative therapies

Saxena V et al, et al. AASLD 2013. Abstract 1969

Safety worsens in advanced liver disease



High Early Response Rates with Protease Inhibitor Triple Therapy in a Multicenter Cohort of HCV-Infected Patients Awaiting Liver Transplantation (Verna EC et al)

- 8 (29%) have undergone LT

Verna et al AASLD 2012

MELD at LT, median (range) **Laboratory** **UNOS**	 **10 (7-18)** **29 (18-35)**	CTP Class (%) A B C	 3 (38) 5 (63) 0 (0)
HCC (%)	**7 (88)**	**Previous Rx (%)**	**6 (75)**
LDLT (%)	**2 (25)**	**IL28B CC/CT/Unk**	**2/4/2**
Lead-in (%)	**3 (38%)**	**TPV as PI (%)**	**8 (100)**
Weeks on Rx prior to LT, median (range) **Total time** **Time on triple therapy**			 **19 (3-46)** **16 (3-46)**
Weeks follow-up post-LT, median (range)			**12 (5-23)**

Results: Transplanted Patients

	At LT	Week 2	Week 4	Week 8	Week 12
Total N	8	8	8	7	6
Positive	1	2	2	1	1
<LLOQ*, Detected	0	0	0	0	0
<LLOD**	7	6	6	6	5
% <LLOD**	86%	75%	75%	86%	83%

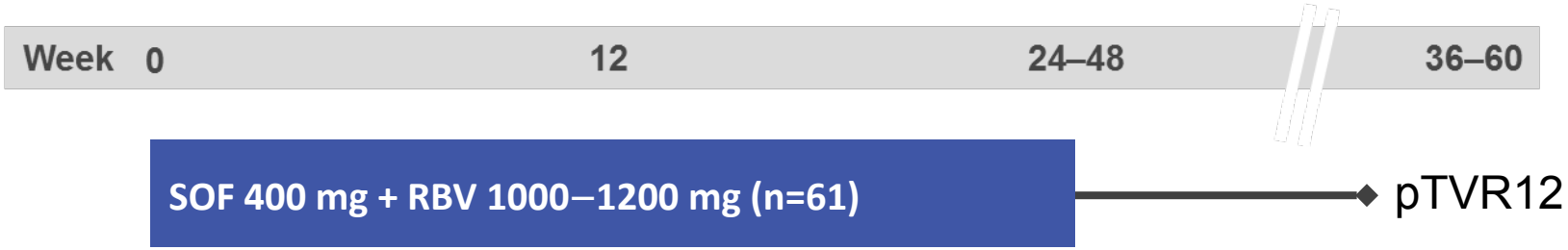
Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection After Liver Transplantation

Michael P. Curry1, Xavier Forns2, Raymond Chung3, Norah Terrault4, Robert Brown Jr5, Jonathan M. Fenkel6, Fredric Gordon7, Jacqueline O'Leary8, Alexander Kuo9, Thomas Schiano10, Gregory Everson11, Eugene Schiff12, Alex Befeler13, John G. McHutchison14, William T. Symonds14, Jill Denning14, Lindsay McNair14, Sarah Arterburn14, Dilip Moonka15 Edward Gane16, Nezam Afdhal1

1Beth Israel Deaconess Medical Center, Boston, MA; 2The Liver Unit, Barcelona, Spain; 3Massachusetts General Hospital, Boston, MA; 4University of California, San Francisco, CA; 5Columbia University, New York, NY; 6Thomas Jefferson University Hospital, Philadelphia, PA; 7Lahey Clinic, Burlington, MA; 8Baylor University Medical Center,, Dallas, TX; 9University of California, San Diego, La Jolla, CA; 10Mount Sinai School of Medicine, New York, NY; 11University of Colorado, Denver, CO; 12University of Miami, Miami, FL; 13St Louis University, St. Louis, MO; 14Gilead Sciences, Inc., Foster City, CA; 15Henry Ford Health System, Detroit, MI; 16Auckland City Hospital, Auckland, New Zealand

AASLD 2013, Washington, DC

Study Design



Patient population

- DDLT candidates with HCV and HCC meeting MILAN criteria
- MELD exception for HCC
- CPT ≤7

Enrollment at 16 sites

- 8 UNOS regions
- 2 international sites

61 patients enrolled

Original protocol: until LT or up to 24 weeks of treatment

- Amendment: extend treatment duration to 48 weeks or LT

Baseline Characteristics

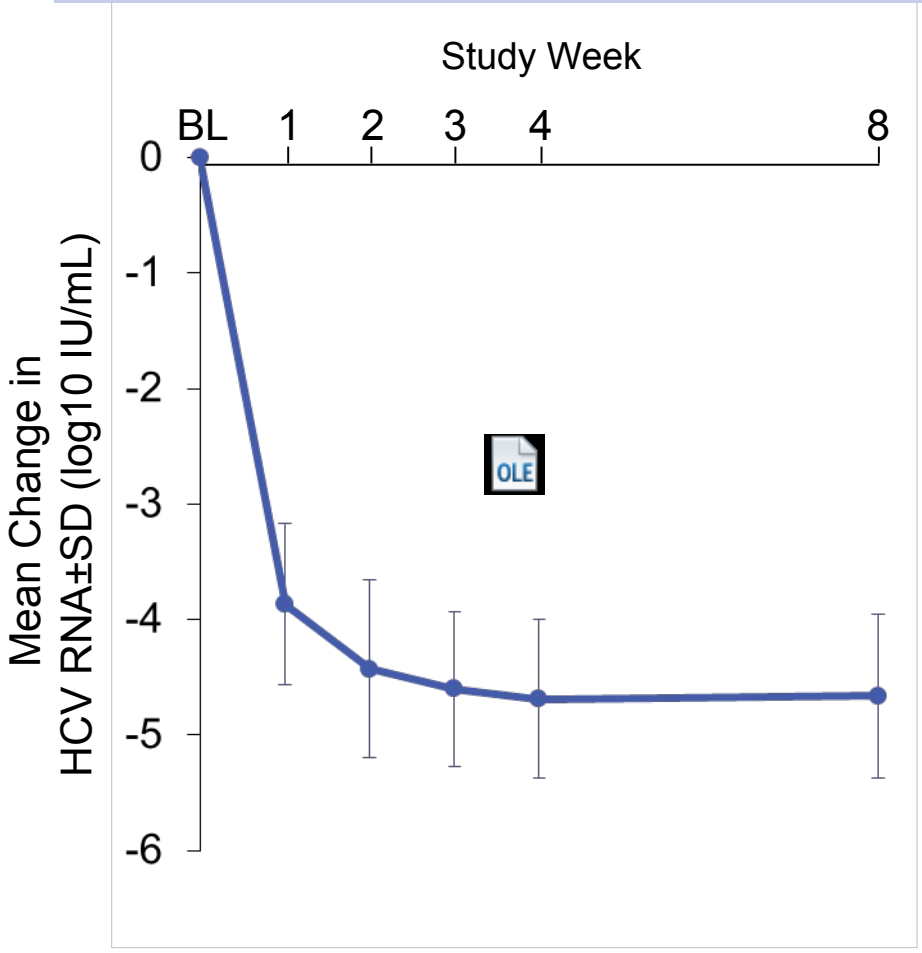
	SOF + RBV (n=61)
Male, n (%)	49 (80)
Median age, y (range)	59 (46-73)
White, n (%)	55 (90)
BMI <30 kg/m2, n (%)	43 (70)
HCV RNA >6 log10 IU/mL, n (%)	41 (67)
Genotype, n (%) 1a 1b 2 3a 4	 24 (39) 21 (34) 8 (13) 7 (12) 1 (2)
Non-CC allele, n (%)	47/60 (78)
CTP score, n (%) 5 6 7 8	 26 (43) 18 (30) 14 (23) 3 (5)
Median MELD score, (range)	8 (6-14)
Prior HCV treatment, n (%)	46 (75)

Patient Disposition

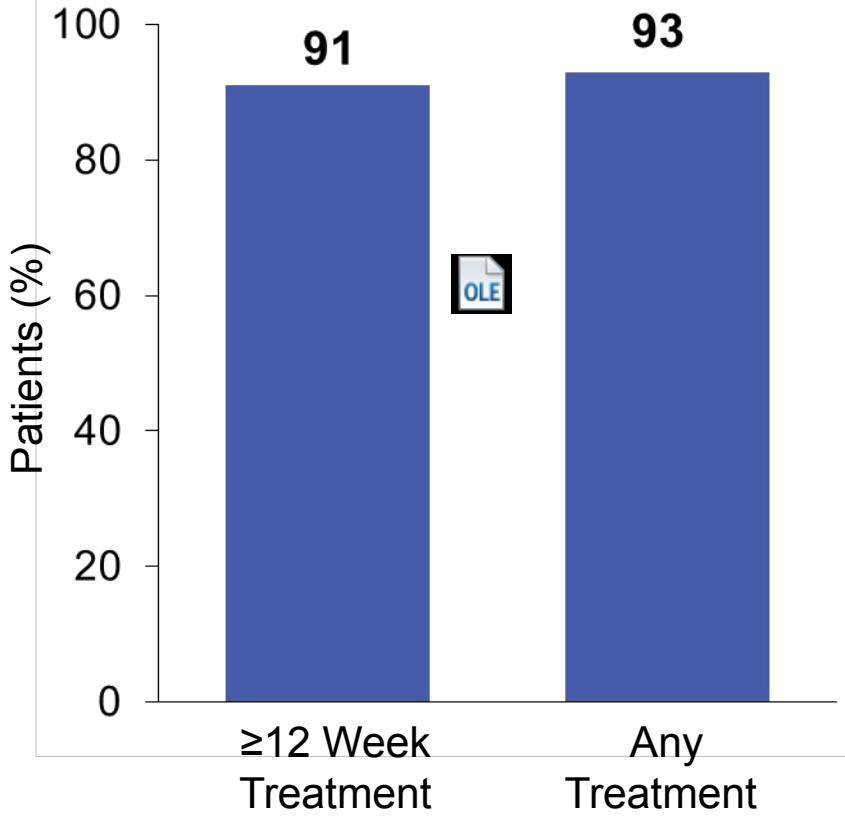
	SOF+ RBV n=61
Patients receiving a liver transplant with HCV RNA <LLOQ	41
Remaining on treatment	1
Post treatment, awaiting transplant	4
Discontinued treatment	10
HCC progression	2
HCV RNA >LLOQ at transplant	3

Results: On-Treatment Viral Response

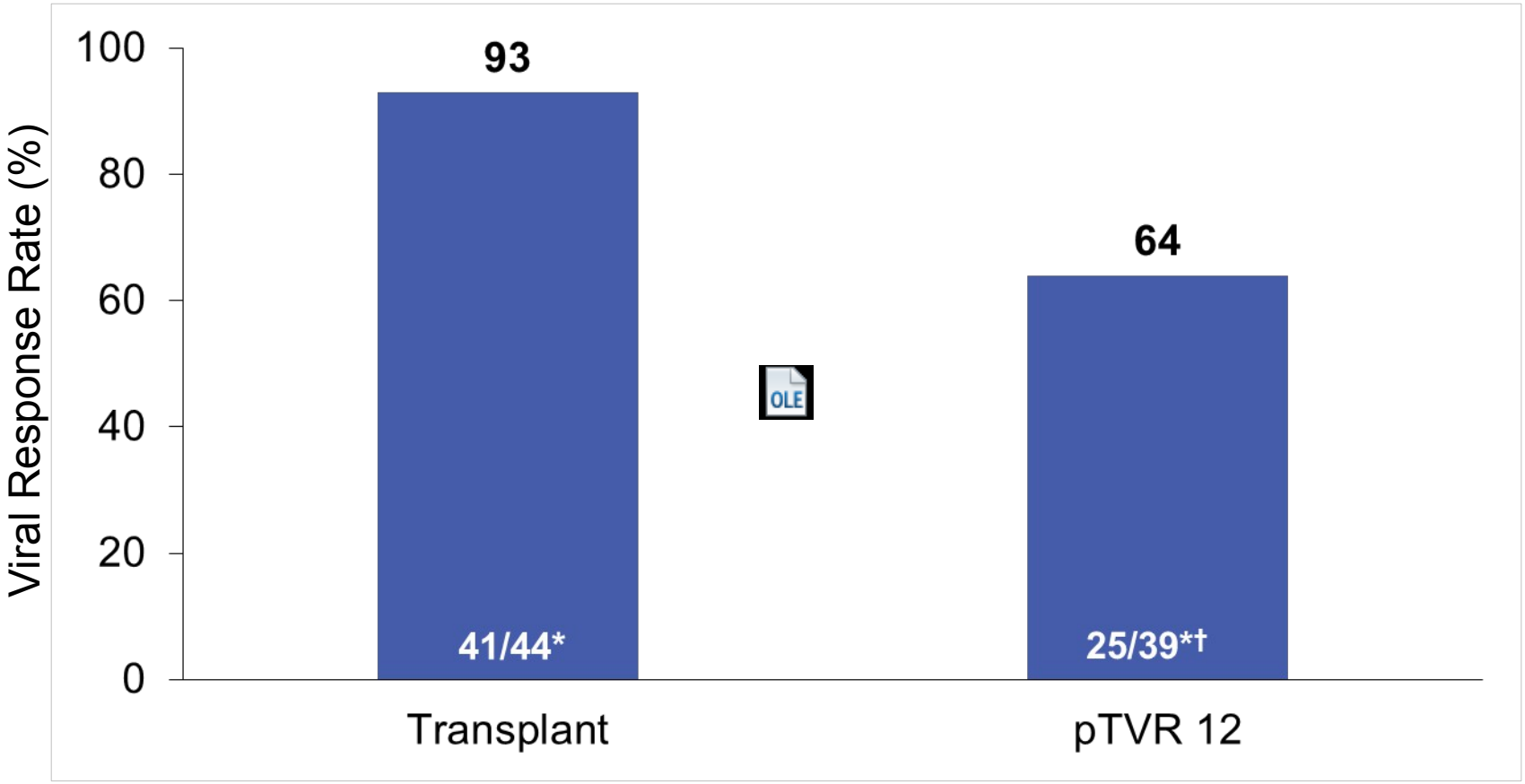
HCV RNA Change from Baseline (n=61)



HCV RNA <LLOQ at Transplant



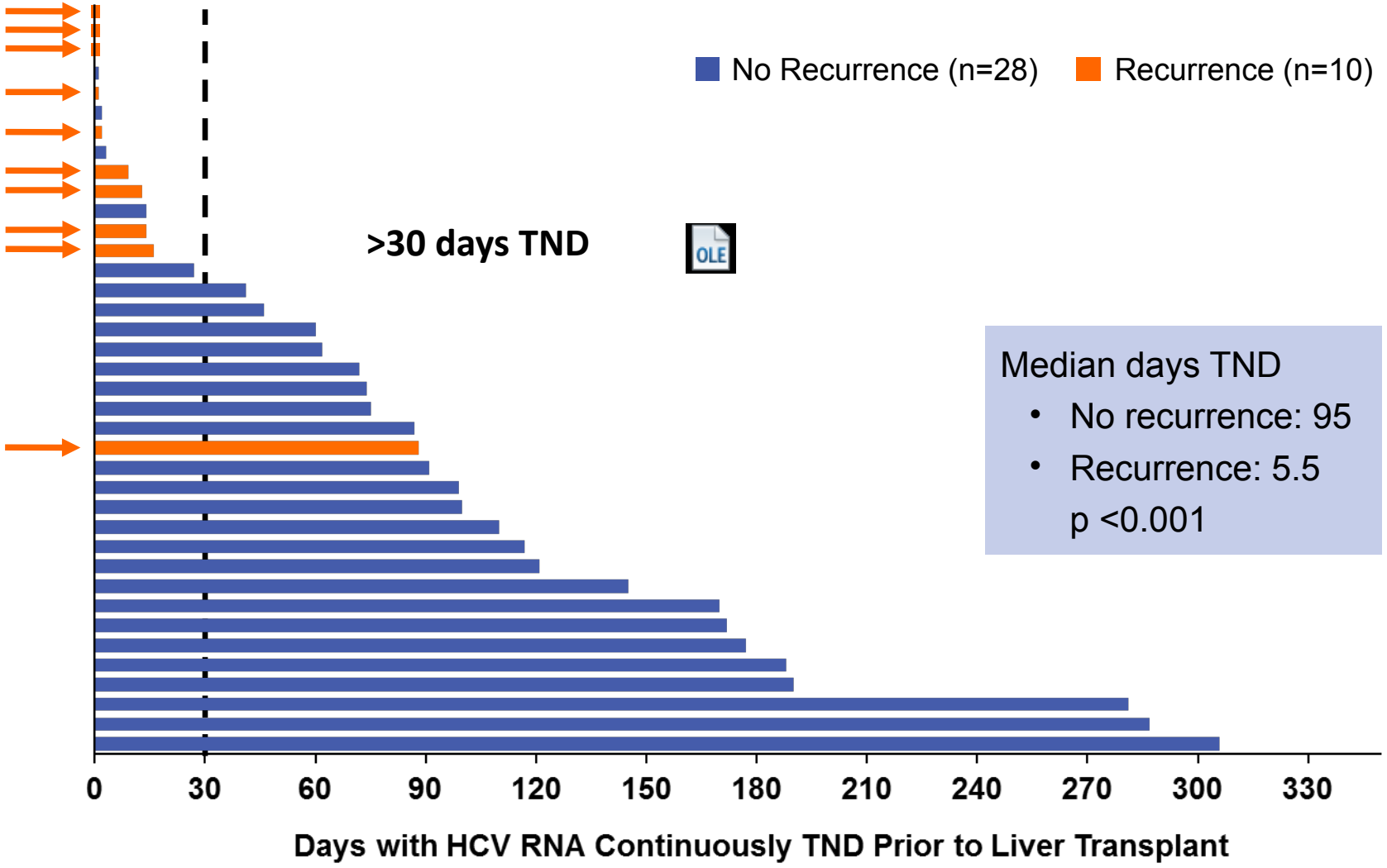
Results: Post-Transplant Virologic Response



*3 subjects were >LLOQ at transplant.

†1 subject has not reached pTVR12, 1 subject LTFU at Week 8 post transplant.

Days Continuously TND Prior to Transplant: No Recurrence vs Recurrence in GT 1–4



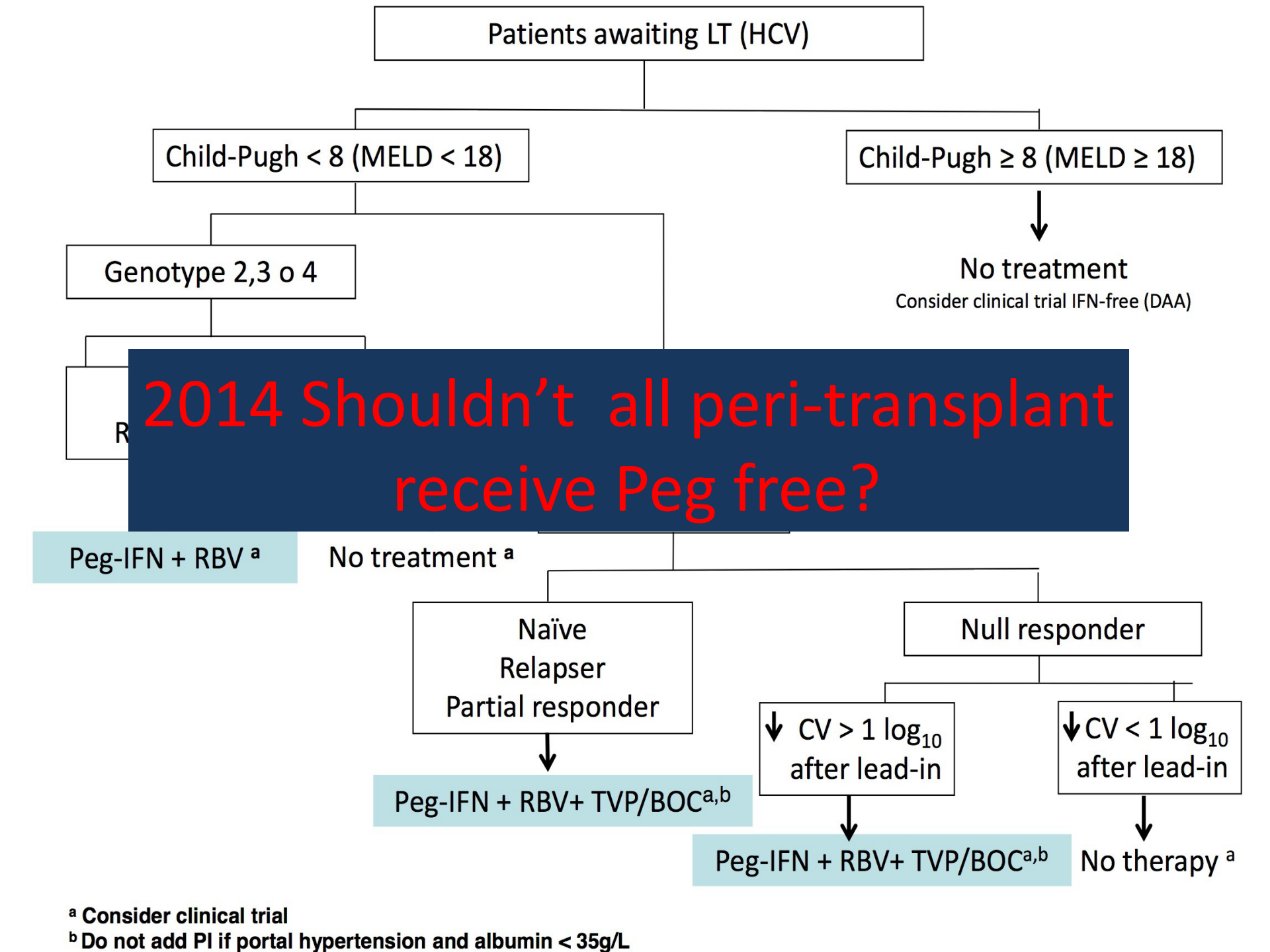
Results: Adverse Events

n (%)	SOF + RBV (N=61)
SAEs*	11 (18)
Deaths	
Pre transplant	2 (3)
Post transplant	3 (5)
AEs leading to DC of study treatment	2 (3)
AEs in ≥10% of patients	
Fatigue	23 (38)
Anemia	14 (23)
Headache	14 (23)
Nausea	10 (16)
Rash	9 (15)
Dyspnea	7 (11)
Insomnia	7 (11)

*No SAEs were deemed related to SOF.

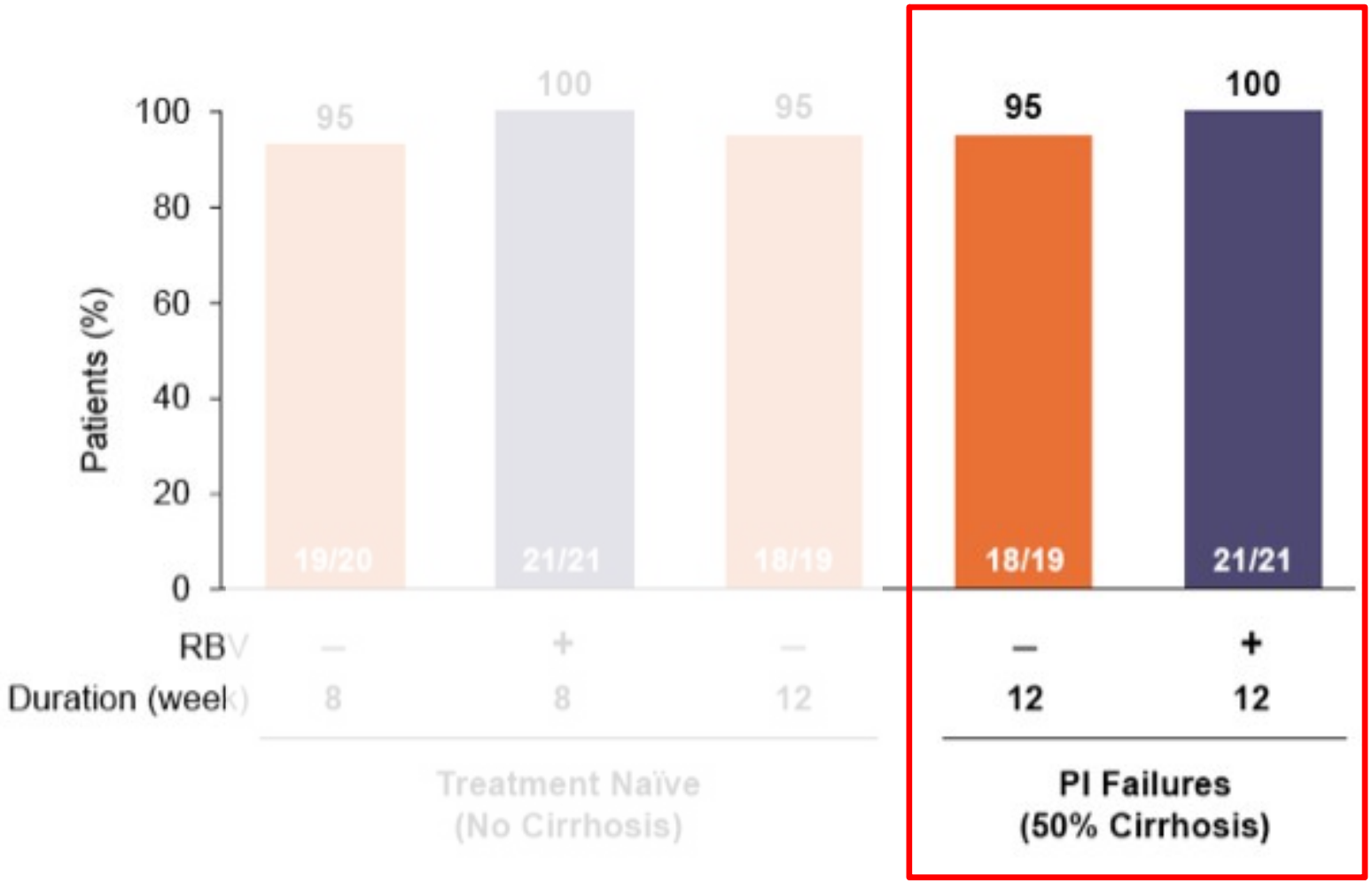
Conclusions

- SOF + RBV treatment prior to transplantation prevented HCV recurrence in the majority (64%) of patients who were HCV RNA <LLOQ at transplant
- The number of consecutive days with HCV RNA TND prior to transplant appears to be the strongest predictor of pTVR
- On treatment HCV RNA suppression was rapid and similar to other patient populations on SOF regimens
- Treatment with SOF + RBV was generally safe and well tolerated

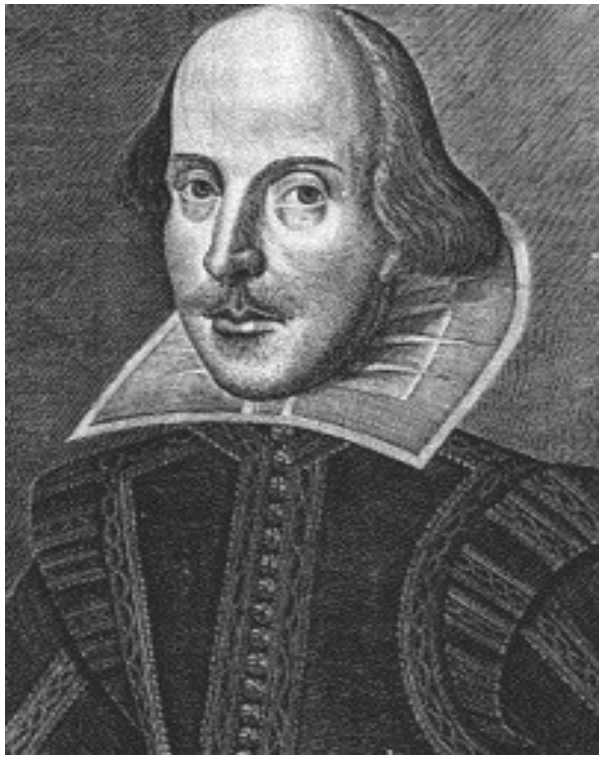


[a] Consider clinical trial
[b] Do not add PI if portal hypertension and albumin < 35g/L

SVR12



Lawitz E et al. AASLD 2013: Abstract 215



There is a tide in the affairs of men, which, taken at the flood, leads on to fortune…’

William Shakespeare

EASL & ILTS London 2014

Thought:

‘He who strives to utmost, for him there is salvation…’

Johann Wolfgang von Goethe (1749-1832)