MEDIZINISCHE KLINIK 1
des Klinikums
der Johann Wolfgang Goethe-Universität
Frankfurt am Main

UNIVERSITÄTS KLINIKUM FRANKFURT

Hepatitis C: Difficult-to-treat Patients

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Disclosures

Advisory boards: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept, Janssen, Merck Sharp & Dohme
Speaker: AbbVie, Gilead Sciences,
Merck Sharp & Dohme

Less Difficult-to-treat patients in the DAA era

Special Populations	IFN era	DAA era*
Compensated liver cirrhosis	+	-
Compensated liver cirrhosis and HCC	+	?
Decompensated liver cirrhosis	N/A	(+)
Decompensated liver cirrhosis and HCC	N/A	(+)
Post-transplant	+	(+)
DAA-failure patients (RAS)	N/A	- / (+)
ESRD, hemodialysis	+	- / (+)
Cryoglobulinemia, vasculitis, etc.	+	-
HCV/HIV coinfection	+	-
Elderly patients	+	-
Children	+	-
PWID	+	-
Patients with psychiatric diseases	+	-
African American patients	+	-

* drug-drug interactions must still be considered

HCV treatment of patients with decompensated cirrhosis (without HCC)

Consensus Statement for Treatment of Patients with Decompensated Cirrhosis

Recommendation 2.1

We suggest that HCV-infected patients with decompensated cirrhosis with CTP Class B and/or MELD less than 20 on the waiting list for liver transplantation, who are without refractory portal hypertensive symptoms or other conditions requiring more immediate transplantation, should be treated with antiviral therapy.

Recommendation 2.2

We suggest that HCV-infected patients with advanced decompensated cirrhosis (MELD 30) or those who are expected to undergo liver transplantation within 3 months should not undergo antiviral therapy.

Recommendation 2.3

We suggest that HCV-infected patients with decompensated cirrhosis with intermediate MELD scores and/or low MELD scores but refractory portal hypertensive complications who are on the waiting list be offered treatment with antiviral therapy selectively.

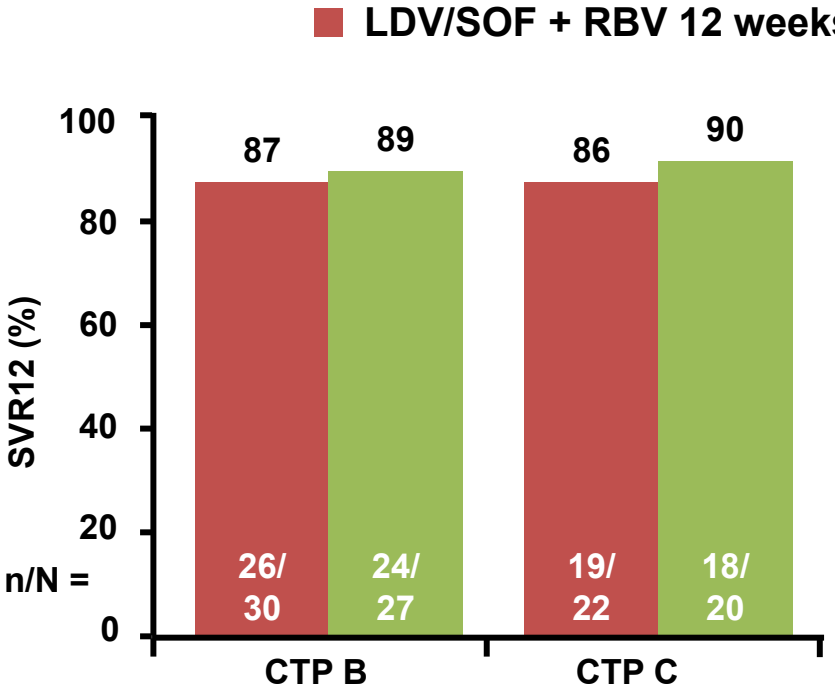
Terrault et al., International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Candidates. Transplantation 2017; 101: 945-955

Clinical Trials in Patients with Decompensated Liver Cirrhosis

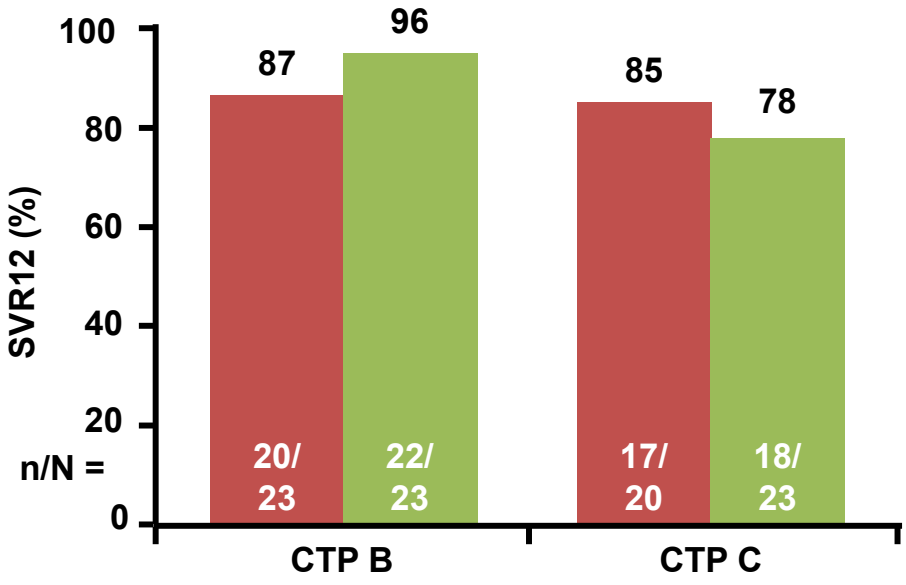
	HCV-1	HCV-2	HCV-3	HCV-4	HCV-5	HCV-6
Sofosbuvir + Ledipasvir	SOLAR-1 & -2					
Sofosbuvir + Valpatasvir	ASTRAL-4					
Sofosbuvir + Daclatasvir	ALLY-1					
Sofosbuvir + Simeprevir	NS3/4A protease Inhibitors and non-nucleosidic polymerase inhibitors **Contraindicated** in patients with decompensated liver cirrhosis					
Paritaprevir/r + Ombitasvir ± Dasabuvir ± RBV						
Grazoprevir + Elbasvir						
Glecaprevir + Pibrentasvir						
Triple Therapies	x	x	x	x	x	x

SOLAR-1 and SOLAR-2: LDV/SOF + RBV in GT 1 or 4 with Decompensated Cirrhosis

Comparable Efficacy (SVR12) Between SOLAR-1 and SOLAR-2 Studies



SOLAR-1: GT 1 and 4



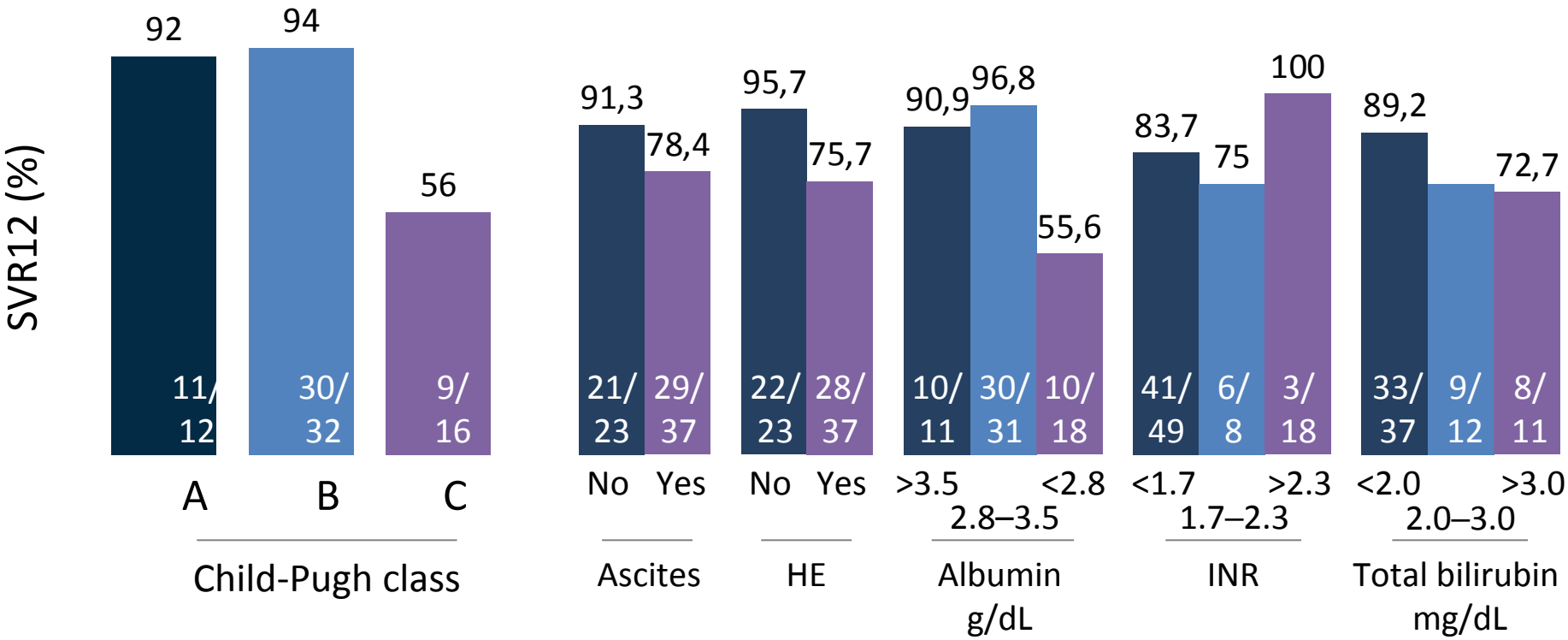
SOLAR-2: GT 1

Charlton M, et al., Gastroenterology 2015;149:649-59
Manns M, et al., Lancet Infect Dis 2016;16:685-97

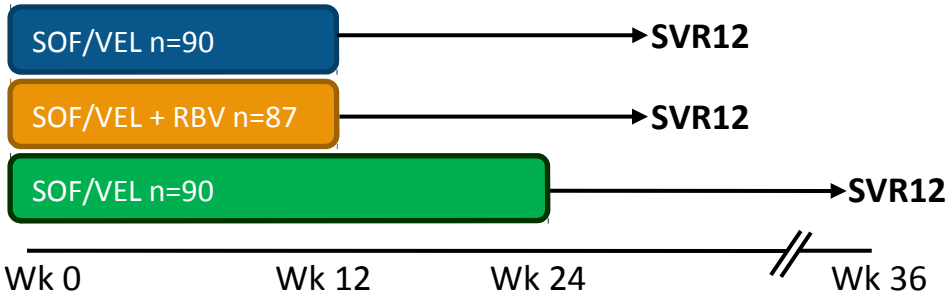
ALLY-1: DCV, SOF + RBV (600 mg) for HCV Patients with Advanced Cirrhosis or Post-LTX Recurrence

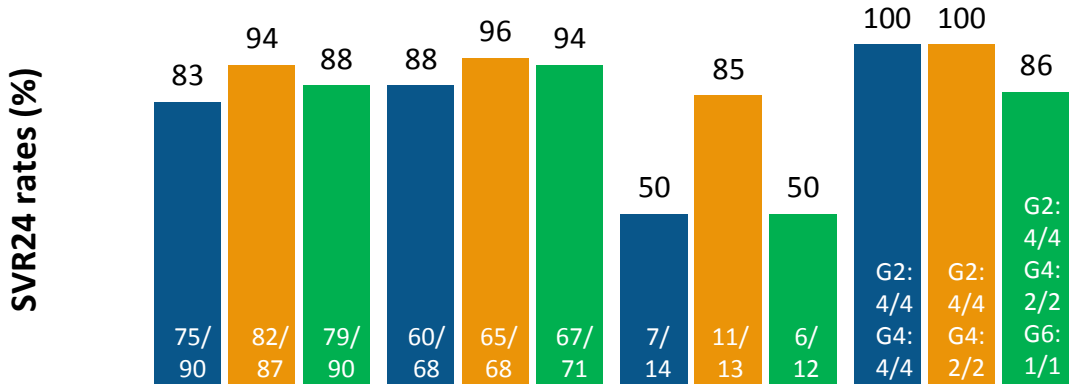
<u>Primary end point</u>: SVR12 in GT1 82% (advanced cirrhosis) and 95% (post-transplant)

SVR12 by Child-Pugh class: Advanced cirrhosis cohort, all genotypes



ASTRAL-4: SOF/VEL for HCV in Patients with Decompensated Cirrhosis

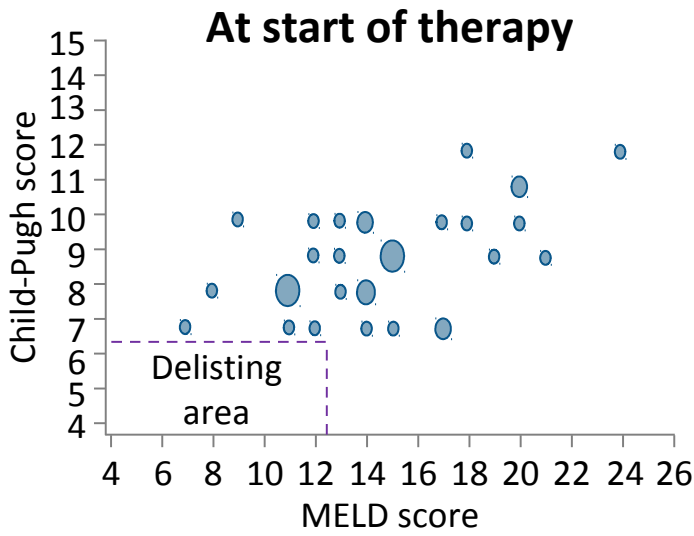


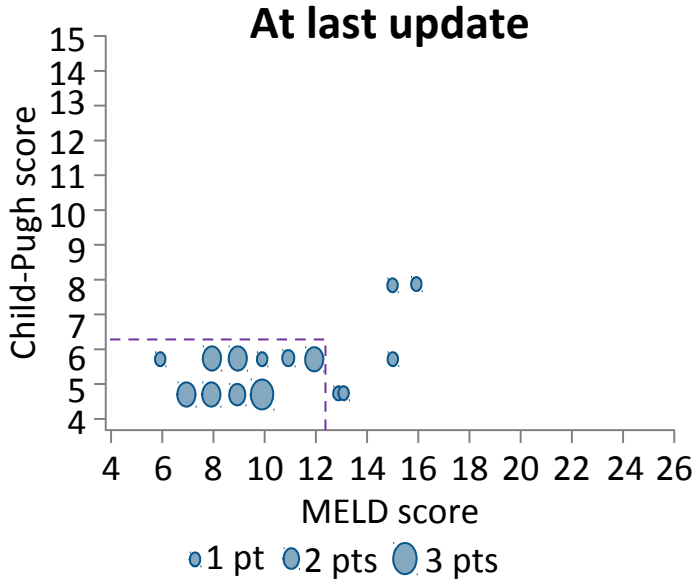


BT	-	1	1	-	-	-	-	1	1	-	-	-
Relapse	11	2	7	5	1	3	6	1	4	-	-	-
LTFU	1	-	1	1	-	1	-	-	-	-	-	-
Death	3	2	2	2	2	-	1	-	1	-	-	1

Delisting of liver transplant candidates with chronic HCV infection after viral eradication: Outcome after delisting

Variable	HR	95% CI	p-value
Δ MELD at 12 wks	1.315	1.181–1.464	<0.0001
BL MELD			
<16	Ref		
16–20	0.176	0.075–0.41	<0.0001
>20	0.094	0.029–0.305	<0.0001





HCV treatment in patients with compensated cirrhosis and HCC

Consensus Statement for Treatment of Pts with Compensated Cirrhosis and HCC

Recommendation 1.1

We suggest that waitlisted HCV-infected patients with compensated cirrhosis and HCC be treated with antiviral therapy.

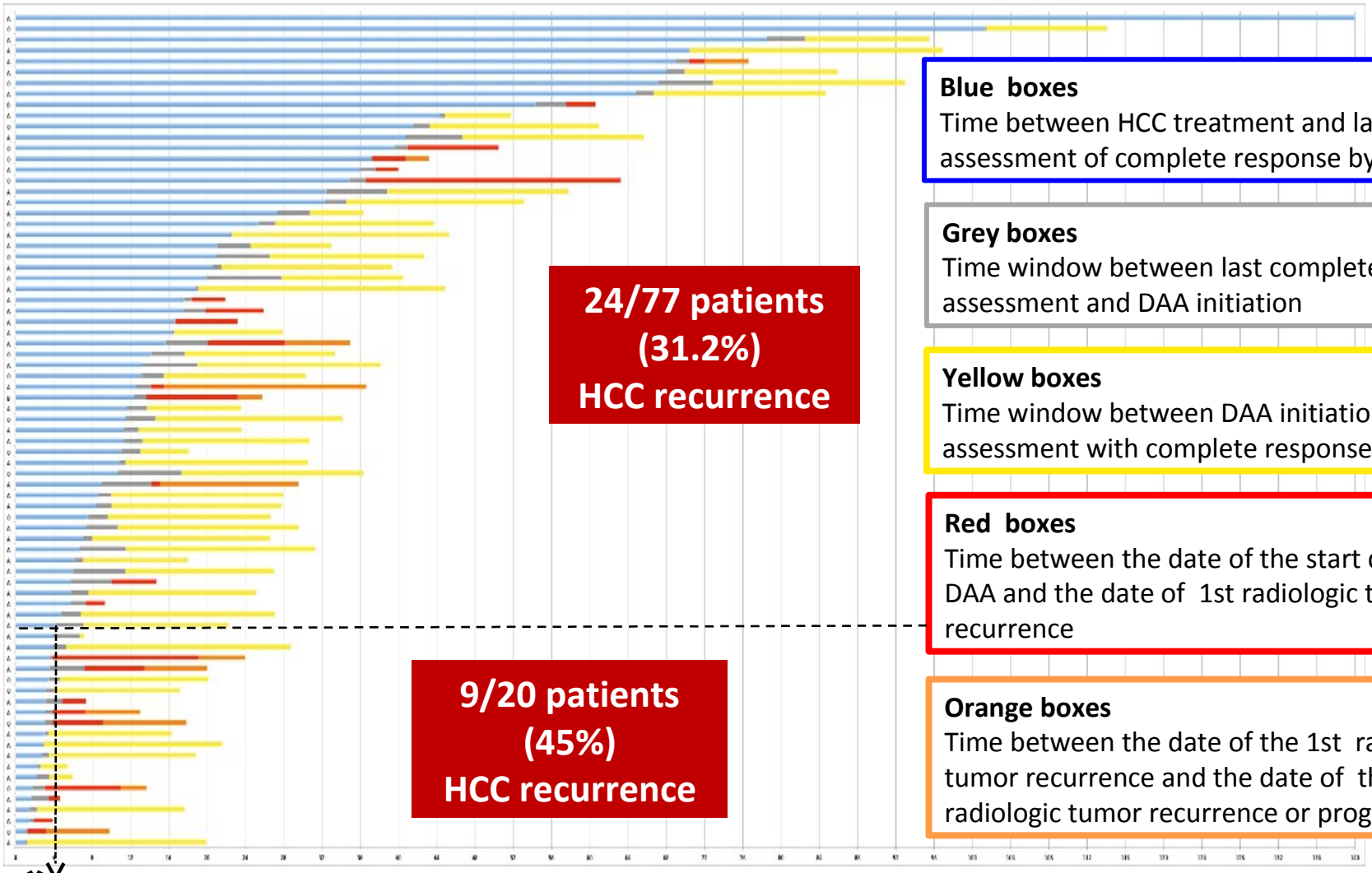
Technical Remarks:

- Anticipated time to LT
- Access to living donor LT
- Availability of anti-HCV-positive donors
- Waitlist drop-off rates for HCC progression
- Access to and costs of antiviral therapy
- Sufficient time to complete treatment is recommended
- Undetectable HCV RNA for at least 30 days pre-LT

Treatment of HCV in patients with successfully treated HCC may result in the unintended consequence of aggressive HCC recurrence

Terrault et al., International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Candidates. Transplantation 2017; 101: 945-955

Tumor recurrence after tx for HCV pts with previously treated HCC discloses a more aggressive pattern and faster HCC growth



Blue boxes
Time between HCC treatment and last assessment of complete response by imaging

Grey boxes
Time window between last complete response assessment and DAA initiation

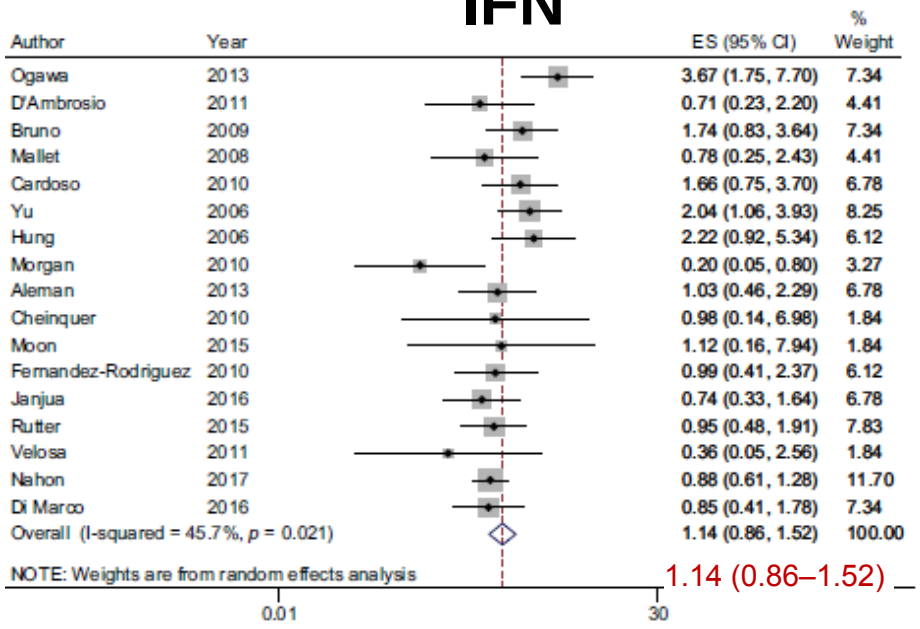
Yellow boxes
Time window between DAA initiation and last assessment with complete response

Red boxes
Time between the date of the start dose of DAA and the date of 1st radiologic tumor recurrence

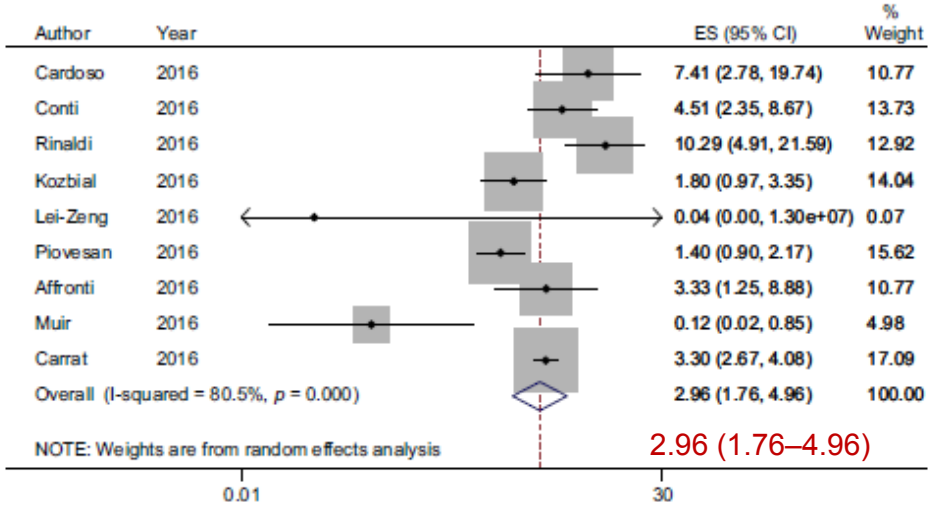
Orange boxes
Time between the date of the 1st radiologic tumor recurrence and the date of the 2nd radiologic tumor recurrence or progression

A meta-analysis of the risk of HCC occurrence following SVR to IFN or DAAs

IFN



DAA



Meta regression of HCC occurrence

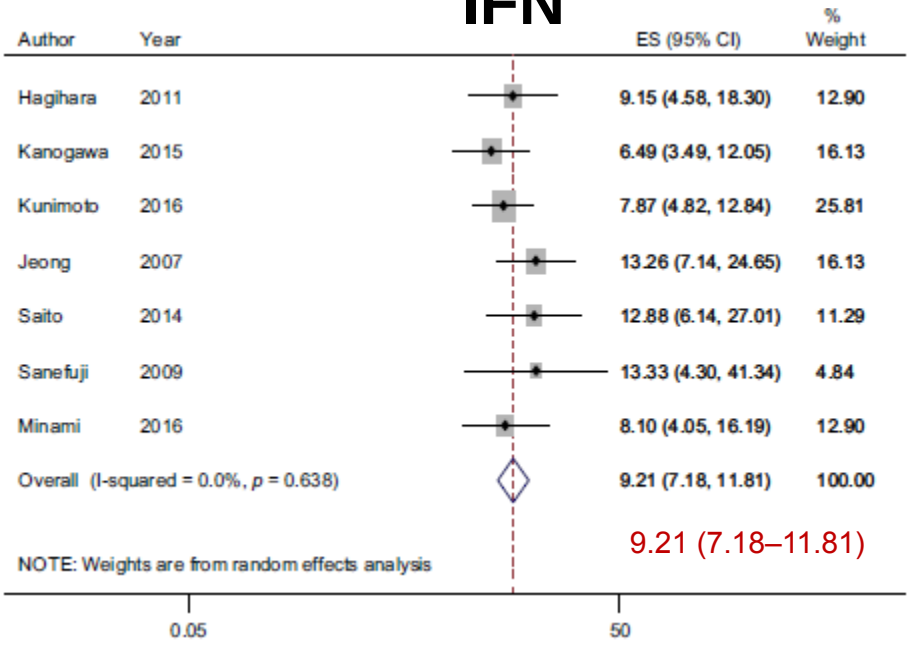
	Unadjusted RR	Adjusted RR	95% CI	P-value
Average follow-up	0.88	0.75	0.56–0.99	0.04
Average age	1.11	1.06	0.99–1.14	0.12
DAA treatment	2.77	0.68	0.18–2.55	0.56

Waziry R, et al. J Hepatol 2017;67:1204–12

RR: risk ratio

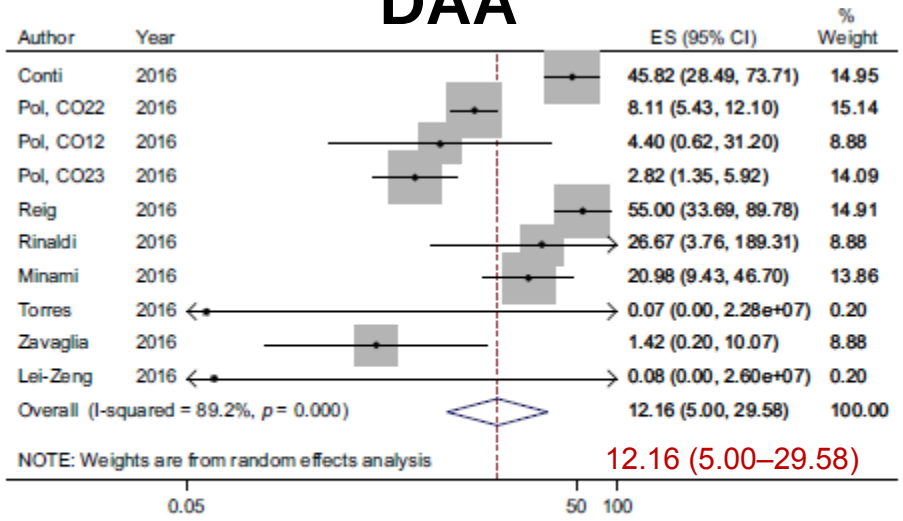
A meta-analysis of the risk of HCC recurrence following SVR to IFN or DAAs

IFN



HCC recurrence rate (/100 PY)

DAA



HCC recurrence rate (/100 person-years)

Meta regression of HCC reccurrence

	Unadjusted RR	Adjusted RR	95% CI	P-value
Average follow-up	0.86	0.79	0.55–1.15	0.19
Average age	1.11	1.11	0.96–1.27	0.14
DAA treatment	1.36	0.62	0.11–3.45	0.56

Waziry R, et al. J Hepatol 2017;67:1204–12

Management of patients with decompensated cirrhosis and HCC

Consensus Statement for Management of Patients with Decompensated Cirrhosis and HCC

- *Recommendation 3.1*
  We suggest that HCV-infected patients with decompensated cirrhosis and HCC, who are not expected to undergo liver transplantation within a short time (3-6 months), should be treated with antiviral therapy.
- *Recommendation 3.2*
  We suggest that HCV-infected patients with decompensated cirrhosis and HCC, who are expected to undergo liver transplantation within a short time (3-6 months), should not be treated with antiviral therapy.

Paucity of data, therefore pragmatic approach

Primary benefit is prevention of waitlist drop off due to worsening decompensation,

Potentially lower SVR rates

Potentially more aggressive tumor growth

Terrault et al., International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Candidates. Transplantation 2017; 101: 945-955

Impact of HCV therapy on the mortality of hepatitis C patients awaiting liver transplantation

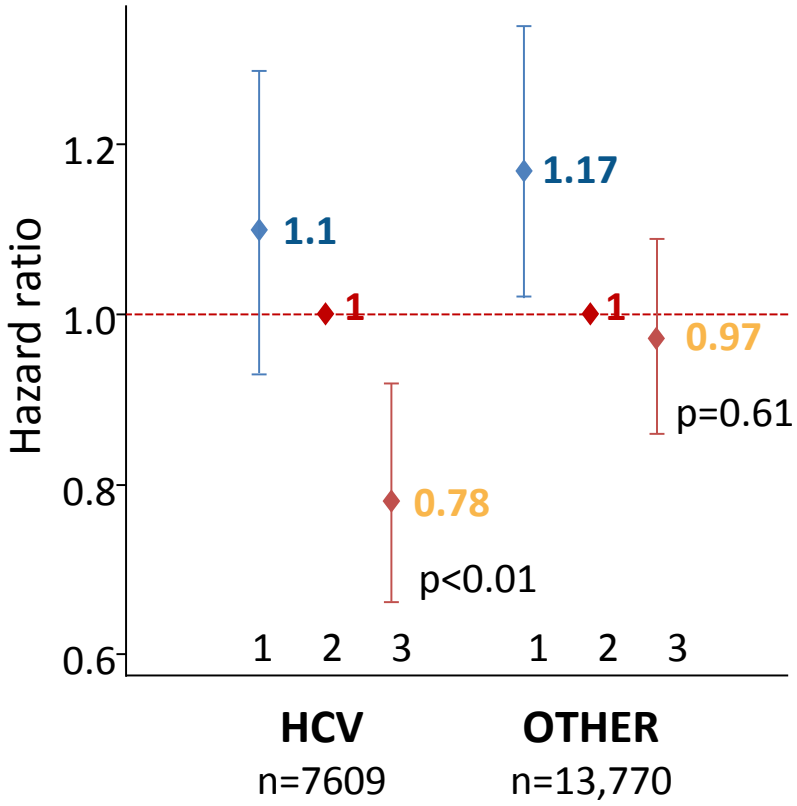
Decreasing mortality in hepatitis C patients awaiting liver transplantation in the DAA era

Baseline characteristics

Chronic HCV, by cohort (N=7609)

	Cohort 1: 2004 n=2410	Cohort 2: 2009 n=2416	Cohort 3: 2014 n=2783	p-value
Age, years (IQR)	52 (48–57)	55 (51–59)	58 (54–62)	<0.01
Male, n (%)	1549 (64.3)	1607 (66.5)	1807 (64.9)	0.242
HCC, n (%)	391 (16.2)	429 (17.8)	404 (14.5)	<0.01
MELD score (IQR)	13 (11–16)	13 (10–16)	14 (11–17)	<0.01
Status at 1 year after start date, n (%)				
Alive	1544 (64.1)	1525 (63.1)	1768 (63.5)	
Transplanted	515 (21.4)	512 (21.2)	520 (18.7)	
Died	285 (11.8)	277 (11.5)	319 (11.5)	
Withdrawn	66 (2.7)	102 (4.2)	176 (6.3)	

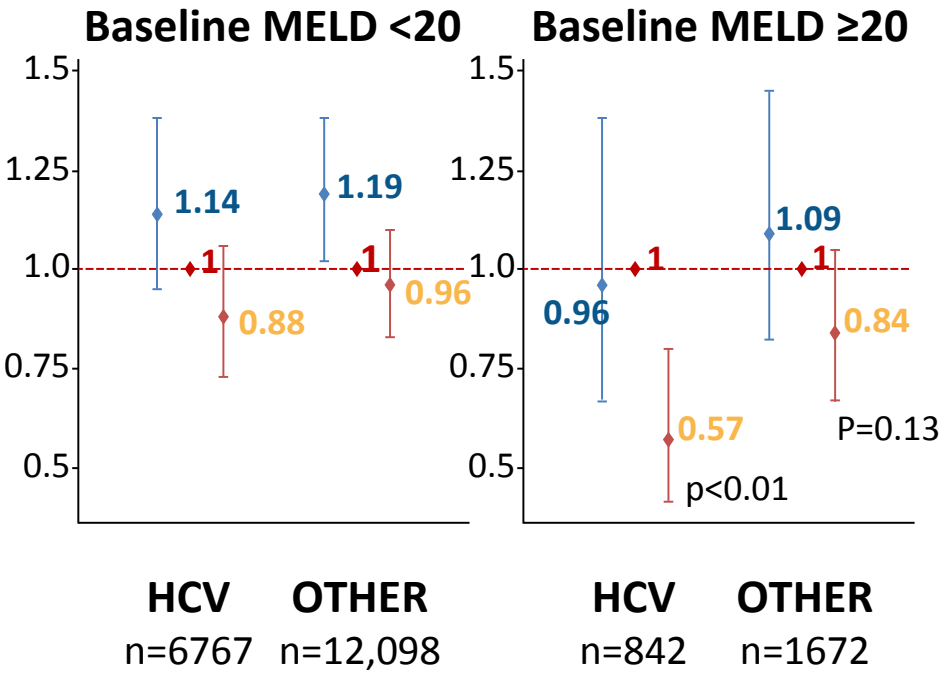
12-month survival in liver transplant waitlist registrants



Kim D, et al. AASLD 2016, Boston. #55

Decreasing mortality in hepatitis C patients awaiting liver transplantation in the DAA era

Multivariable cox proportional hazards regression:
12-month survival in liver transplant waitlist registrants



- For non-HCV patients, mortality has not changed in Cohort 2014 compared to Cohort 2009 (adjusted HR=0.97, p=0.61)
- For HCV patients, risk of death 22% lower in Cohort 2014 compared to Cohort 2009 after adjusting for age & MELD
- Improved survival for HCV Cohort 2014 driven by patients with baseline MELD ≥20

Kim D, et al. AASLD 2016, Boston. #55

Pre/peri-transplant HCV RNA negativization reduces early allograft dysfunction (EAD) in hepatitis C recipients

- Early allograft graft dysfunction (EAD) post-OLT assessed in 603 HCV-infected patients receiving a cadaveric organ
- 77/603 were HCV RNA negative (16 patients on DAA therapy)
- 54.4% developed EAD (Olthoff's definition) and had poorer outcomes chiefly due to graft loss

Multivariable analysis of risk factors for EAD

	Odds ratio	95% CI	p
MELD score at LT >25	2.25	1.30–3.98	0.004
MELD score at LT 15–25	1.61	1.11–2.33	0.012
HCV RNA positive at LT	1.75	1.02–3.04	0.043
Macro steatosis ≥30%	10.70	2.83–70.35	0.002
Cold ischemia time ≥8 h	2.38	1.69–3.38	<0.001

- Clearing HCV pre-OLT improves outcomes
- Donor factors (steatosis) & cold ischemia time play a major role

Martini S, et al. et al. AASLD 2016, Boston. #26

Management of HCV in the post-liver transplant recipient with recurrent hepatitis C

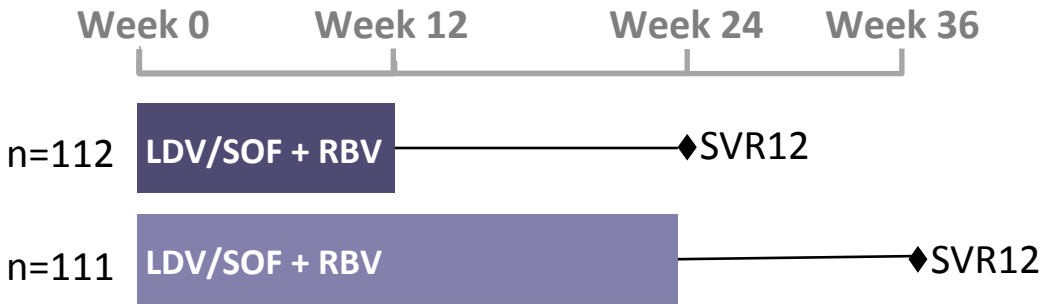
Consensus Statement on Hepatitis C Management in Liver Transplant Recipients

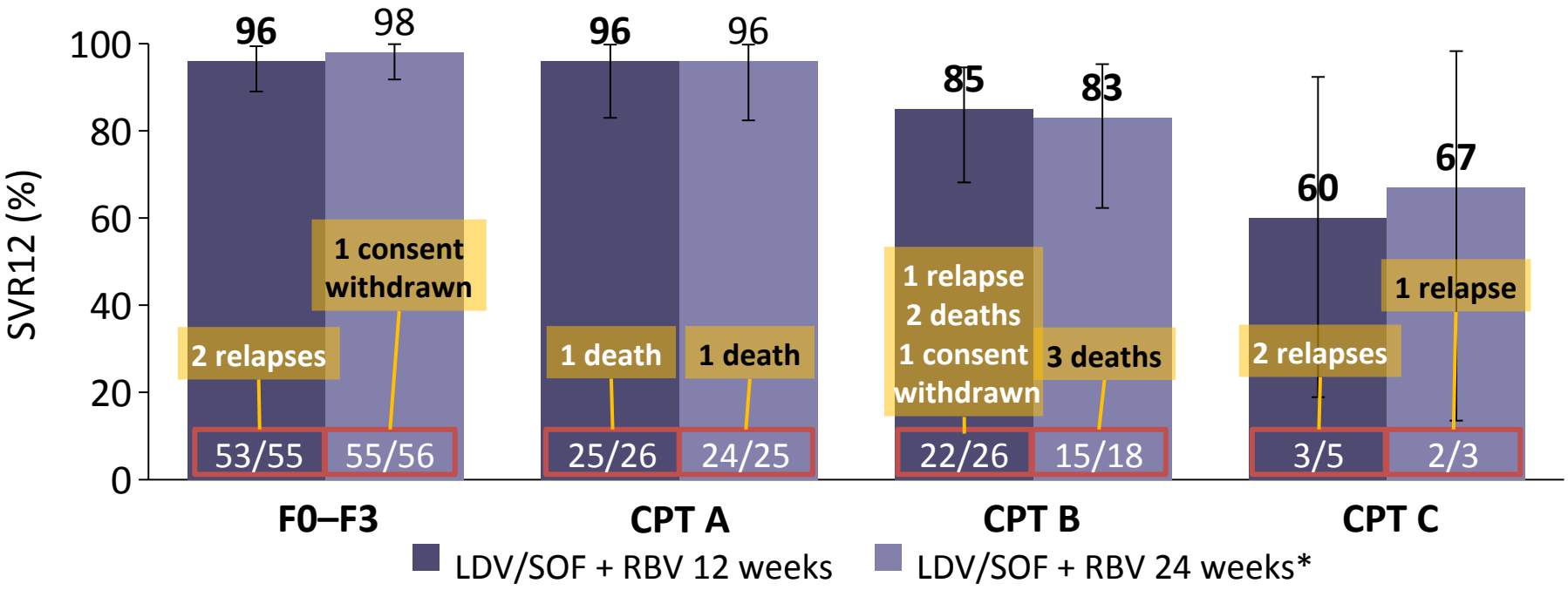
- *Recommendation 1.1*
  We recommend that all liver transplant recipients with recurrent hepatitis C receive treatment with oral DAA therapy.
- *Recommendation 1.2*
  We suggest that antiviral therapy be undertaken once the patient is clinically stable rather than waiting until significant disease is documented.
- *Recommendation 2.1*
  We recommend that liver transplant recipients with recurrent hepatitis C and cirrhosis (compensated and decompensated) receive treatment with combination DAA therapy
- *Recommendation 2.2*
  We recommend that HCV-positive liver transplant recipients with decompensated cirrhosis be considered for retransplantation, if suitable.
- *Recommendation 3.1*
  We recommend that patients with severe cholestatic recurrent hepatitis C after liver transplantation be treated with combination DAA therapy.

Terrault et al., International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Recipients. Transplantation 2017; 101: 956-967

LDV/SOF + RBV for the Treatment of HCV in Pts with Post-transplant Recurrence (SOLAR-1)

- G1 or 4, treatment-naive or -experienced





*8 CPT B 24-week and 1 CPT C 24-week pts had not reached the Wk 12 post-Tx visit

Charlton M, et al., Gastroenterology 2015;149:649-59

Conclusions

- Broad treatment indications in patients with HCV and (de)compensated cirrhosis, pre- and post-transplant
- Decompensated cirrhosis: Sofosbuvir +NS5A-inhibitor
- Protease and non-nucleosidic polymerase inhibitors are contraindicated in patients with decompensated liver cirrhosis
- Safety of DAAs in these populations not yet fully defined – thorough surveillance during therapy
- Consider drug-drug interactions, in particular immunosuppressants in transplanted patients
- Timing of DAA treatment under discussion in patients with chronic hepatitis C and HCC treated with curative intention
- Patients with HCV-associated liver disease should disappear in the transplant setting