9th Paris Hepatitis Conference

Paris, 12 January 2016

Treatment of hepatocellular carcinoma: beyond international guidelines

Massimo Colombo

Chairman Department of Liver, Kidney, Lung and Bone Marrow Units and Organ Transplant
Head Division of Gastroenterology and Hepatology
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
University of Milan
Milan, Italy

Financial Disclosures

Grant and research support: BMS, Gilead Science

Advisory committees: Merck, Roche, Novartis, Bayer, BMS, Gilead Science, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck, GSK, GenSpera

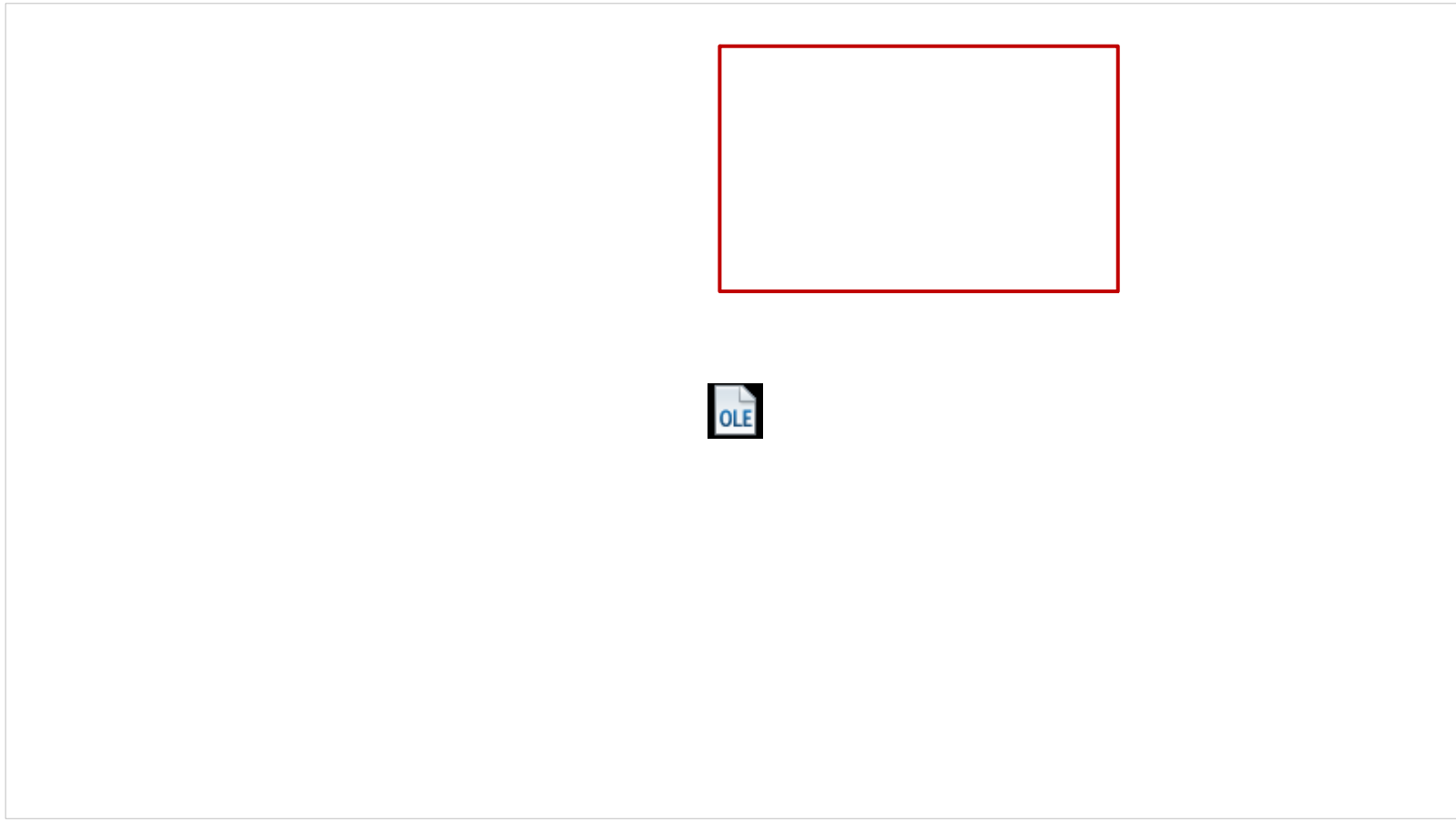
Speaking and teaching: Tibotec, Roche, Novartis, Bayer, BMS, Gilead Science, Vertex, Merck, Janssen

Treatment of Hepatocellular Carcinoma Beyond International Guidelines

Outline

- Loss of survival benefits in patients treated outside recommendations.
- Local ablation of early cancer is more cost effective than limited resection.
- Can resection in patients with portal hypertension be facilitated by DAAs?
- Can sorafenib therapy scale up in advanced cirrhosis following DAA therapy?
- Reconsidering non transplant therapeutic options in the era of donor shortage.

Evidence and Recommendation for HCC Therapies, 2011



EASL–EORTC CPG: Management of Hepatocellular Carcinoma, J Hepatol. 2012;56:908-43

Adherence to AASLD Recommendations in the Treatment of HCC. A Study in Milan

Reasons for withdrawing from recommendations	Total (No.370)	BCLC A (No. 251)	BCLC B (No. 66)	BCLC C (No. 53)
Impaired liver function	17 (5%)	0	7 (11%)	10 (19%)
Strategic localization and/or vascular invasion	53 (14%)	19 (8%)	21 (32%)	7 (13%)
Co-morbidities	33 (9%)	28 (11%)	2 (3%)	9 (17%)

Sangiovanni et al submitted

Adherence to AASLD Recommendations in the Treatment of HCC. A Study in Milan

- January 2007 to December 2011, 370 de novo HCCs (295 upon surveillance)
- All treated by a MDT according to AASLD criteria
- Overall yearly mortality: 11.5%. 9.8% adherent vs 16.6% non adherent (P=.0042)
- BCLC A (n=251, 81% adherent). Overall yearly mortality: 5.9%. 5.1% adherent vs 10.3% non adherent (P=.0056)
- Multivariate: OS predicted by AASLD adherence (HR 2.1,CI :1.1-4.3), tumor size, ascites.

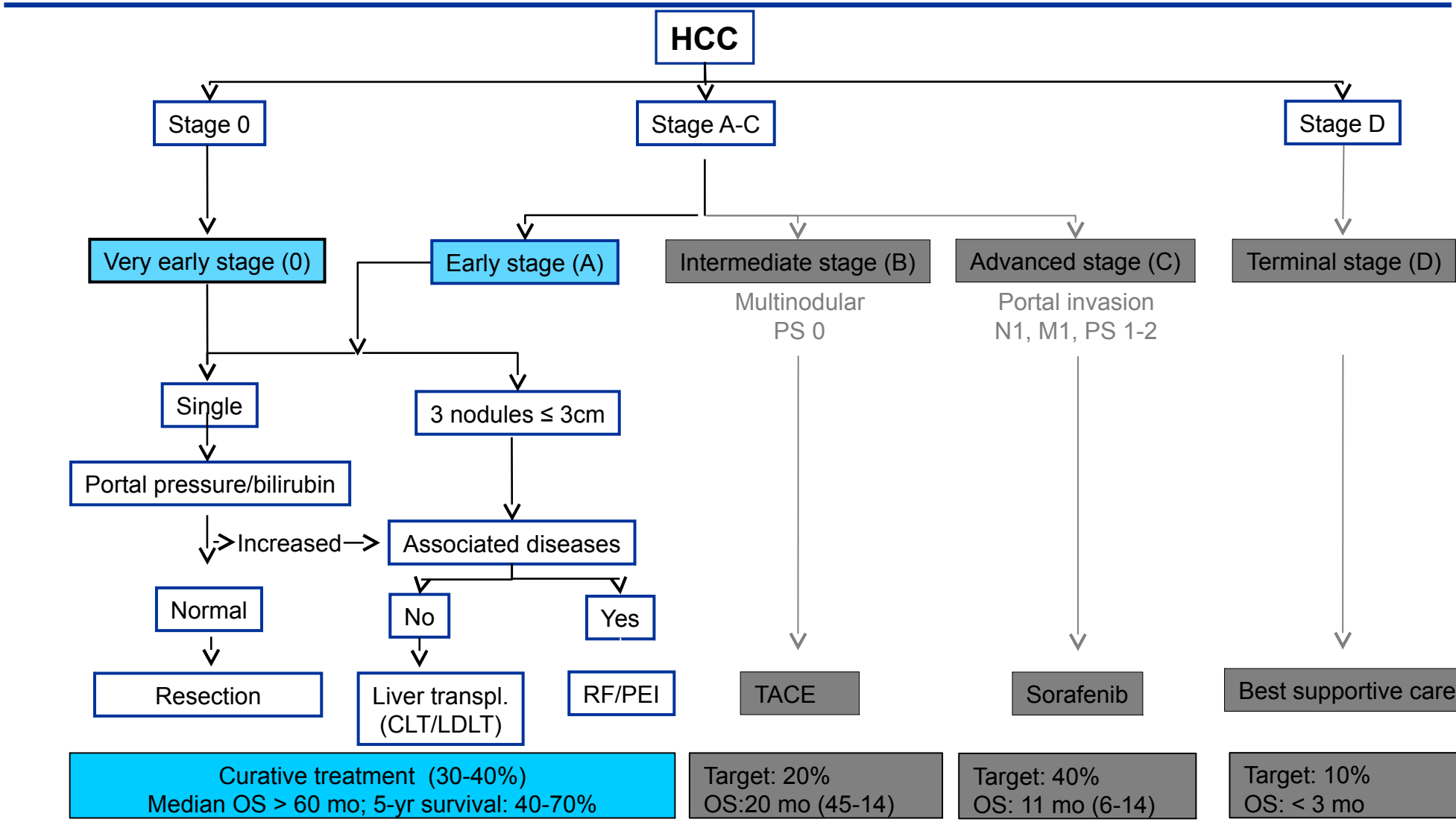
Sangiovanni et al, submitted

Treatment of Hepatocellular Carcinoma Beyond International Guidelines

Outline

- Loss of survival benef ts in patients treated outside recommendations.
- Local ablation of early cancer is more cost effective than limited resection.
- Can resection in patients with portal hypertension be facilitated by DAAs?
- Can sorafenib therapy scale up in advanced cirrhosis following DAA therapy?
- Reconsidering non transplant therapeutic options in the era of donor shortage.

EASL: BCLC Staging System and Treatment Strategy



EASL–EORTC CPG: Management of Hepatocellular Carcinoma, J Hepatol. 2012;56:908-43

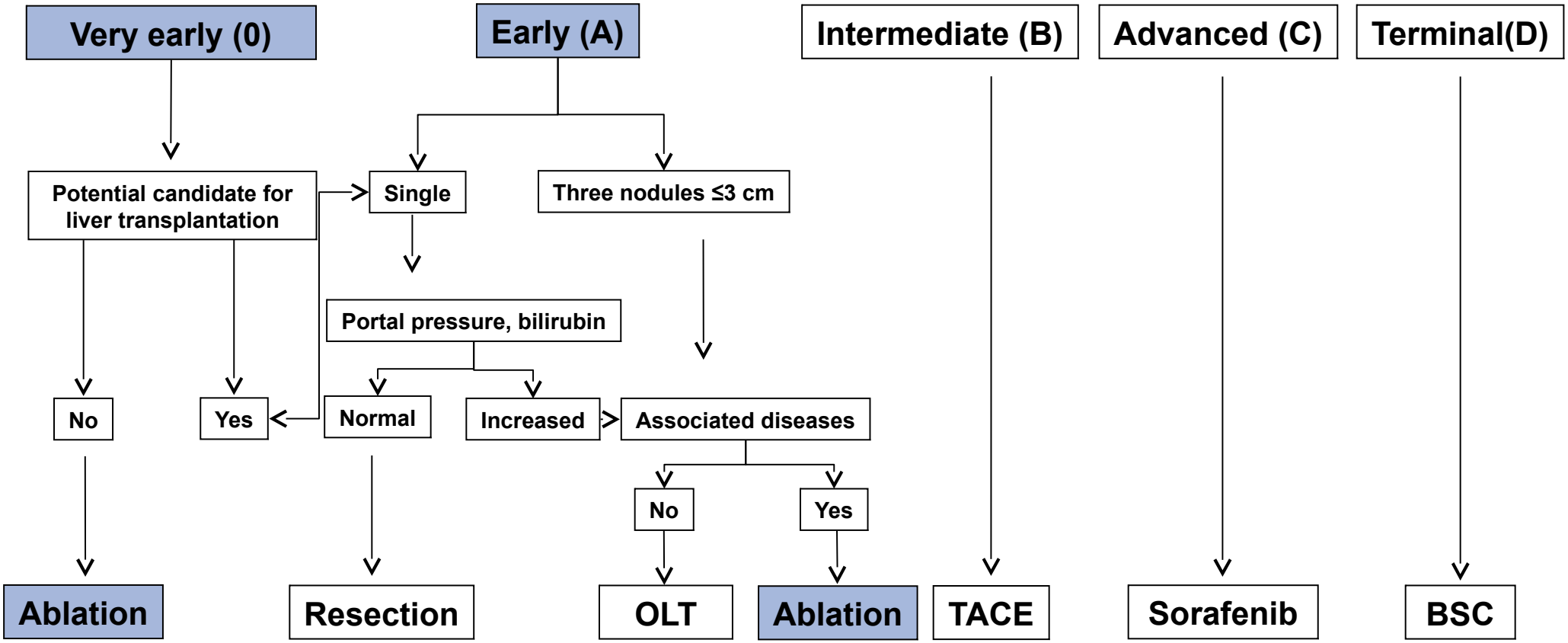
Review Three-yr Survival Following Resection or RFA of HCC in Child Pugh A Cirrhosis

Tumor	HR		RFA		Meta-analysis		
	No. of patients	Pooled estimate (%)	No. of patients	Pooled estimate (%)	Results (95% CI)	*p* value	I^2
Single, ≤2 cm	1265/1361	89.4 (73.2-98.7)	1411/1477			0.949	91
Single, ≤3 cm	480/551	86.2		6-83.2)	1.11 (1.03-1.19)	0.004	47
Single		7-86.9)	105/188	56.5 (47.9-64.9)	1.22 (1.06-1.42)	0.007	0
Two-three, ≤3 cm	37/55	66.4 (50.7-80.4)	86/122	65.1 (35.3-89.5)	1.03 (0.69-1.52)	0.886	55

Radiofrequency is more cost-effective than resection in very early HCC and 2-3 nodules 3 cm

Cucchetti et al, J Hepatol 2013;59:300-7

The Founders of BCLC. Staging and Treatment Strategy



Forner et al, Lancet 2012;379:1245-55

Treatment of Hepatocellular Carcinoma Beyond International Guidelines

Outline

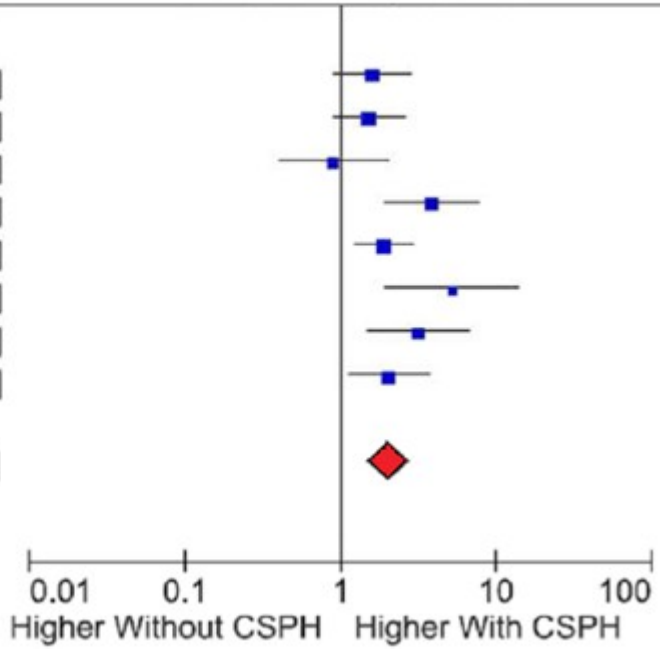
- Loss of survival benef ts in patients treated outside recommendations.
- Local ablation of early cancer is more cost effective than limited resection.
- Can resection in patients with portal hypertension be facilitated by DAAs?
- Can sorafenib therapy scale up in advanced cirrhosis following DAA therapy?
- Reconsidering non transplant therapeutic options in the era of donor shortage.

Portal Hypertension and Hepatic Resection for Small HCC
A Meta-analysis, 5-year Mortality

Study or Subgroup	With PH Events	With PH Total	Without PH Events	Without PH Total	Weight	Odds Ratio M-H, Random, 95% CI
Capussotti 2006	70	99	71	118	14.2%	1.60 [0.90, 2.82]
Cucchetti 2009	43	89	58	152	15.2%	1.51 [0.89, 2.57]
Giannini 2013	23	44	28	51	9.7%	0.90 [0.40, 2.02]
Hidaka2012	33	48	47	129	11.4%	3.84 [1.89, 7.79]
Ishizawa 2008	65	136	82	250	17.8%	1.88 [1.22, 2.88]
Llovet 1999	27	42	9	35	7.4%	5.20 [1.94, 13.94]
Ruzzenente2011	24	44	25	91	10.6%	3.17 [1.49, 6.71]
Santambrogio 2013	33	63	56	160	13.7%	2.04 [1.13, 3.69]
Total (95% CI)		**565**		**986**	**100.0%**	**2.07 [1.51, 2.84]**
Total events	318		376			

Heterogeneity: Tau² = 0.10; Chi² = 13.80, df = 7 (P = 0.05); I² = 49%

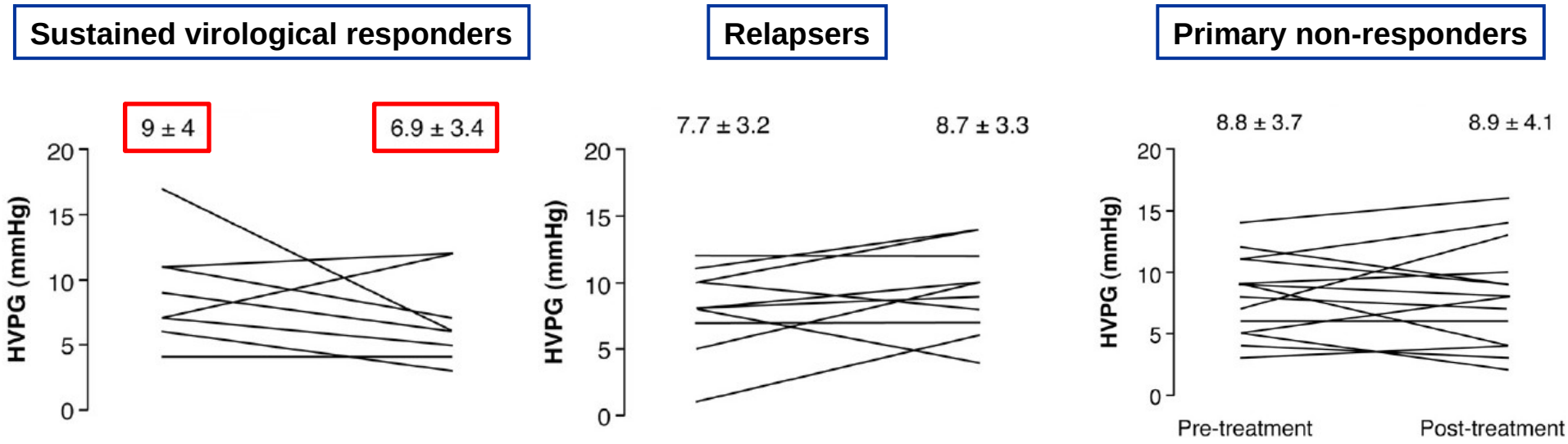
Test for overall effect: Z = 4.51 (P < 0.00001)



Berzigotti et al, Hepatology. 2015;61:526-36.

Effect of SVR to P+R on Hepatic Venous Pressure Gradient in HCV Cirrhosis

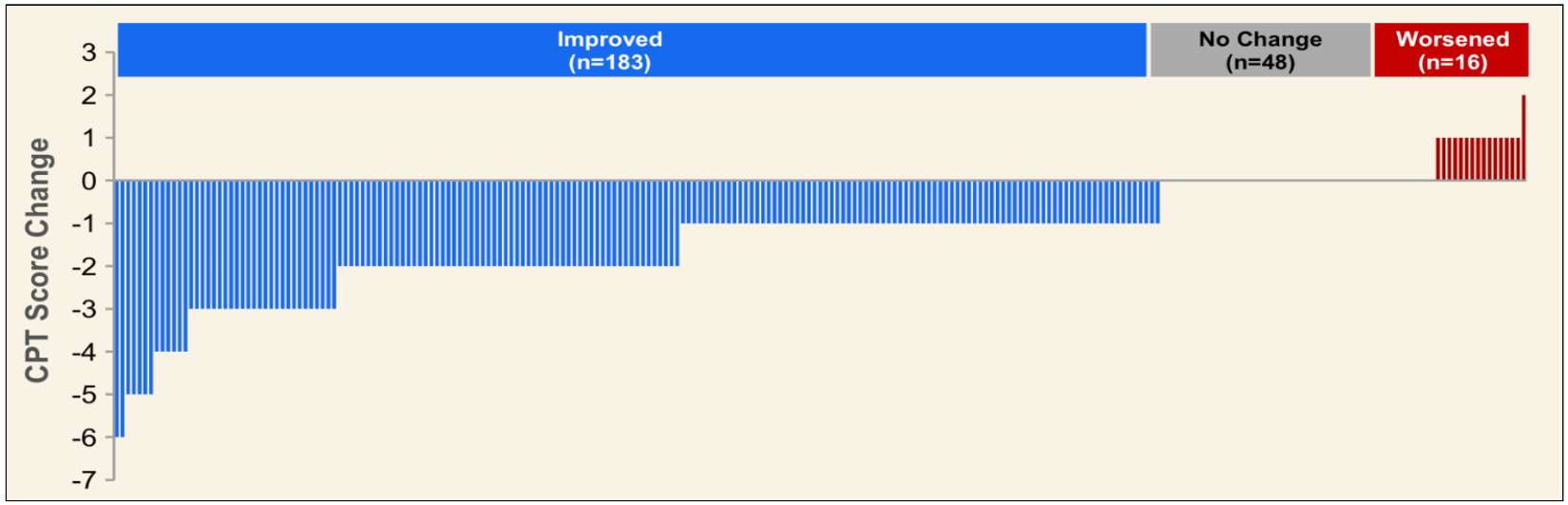
A study in Melbourne of 47 patients with cirrhosis treated with P+R



Signif cant association between 20% HVPG decline, histological response and SVR

Roberts S et al, Clin Gastroenterol Hepatol 2007;5:932-7

CPT Score Change from Baseline to FU-24 in CPT B/C Patients Who Achieved SVR12 to DAA Therapy



- **CPT B patients (n=187)** **40% (72/180) improved to CPT A**

  58% (104/180) had no change in CPT class

- **CPT C patients (n=77)** **12% (8/67) improved to CPT A**

  64% (43/67) improved to CPT B

  24% (16/67) had no change in CPT class

Gane et al, AASLD 2015

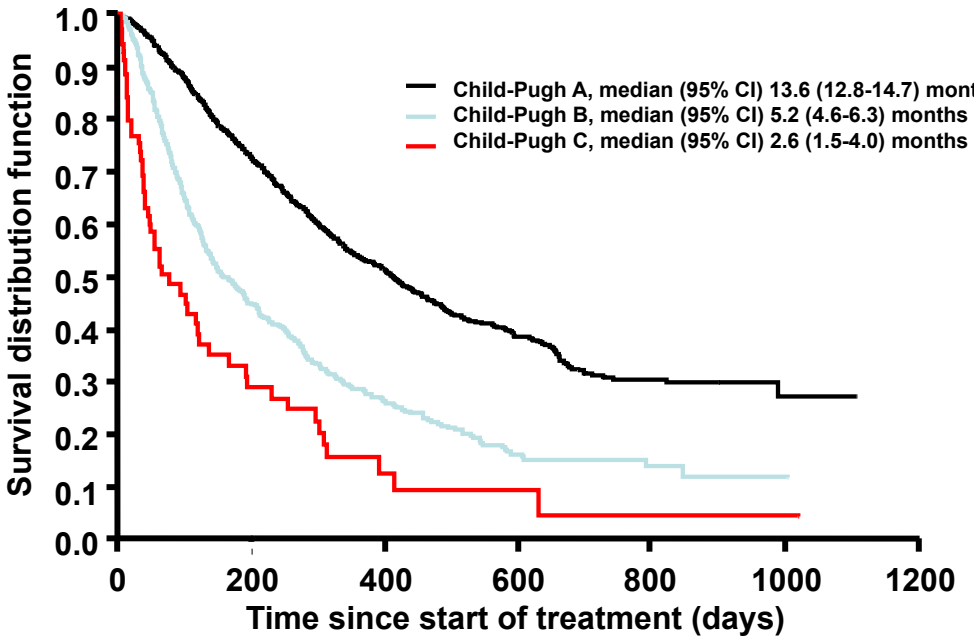
Treatment of Hepatocellular Carcinoma Beyond International Guidelines

Outline

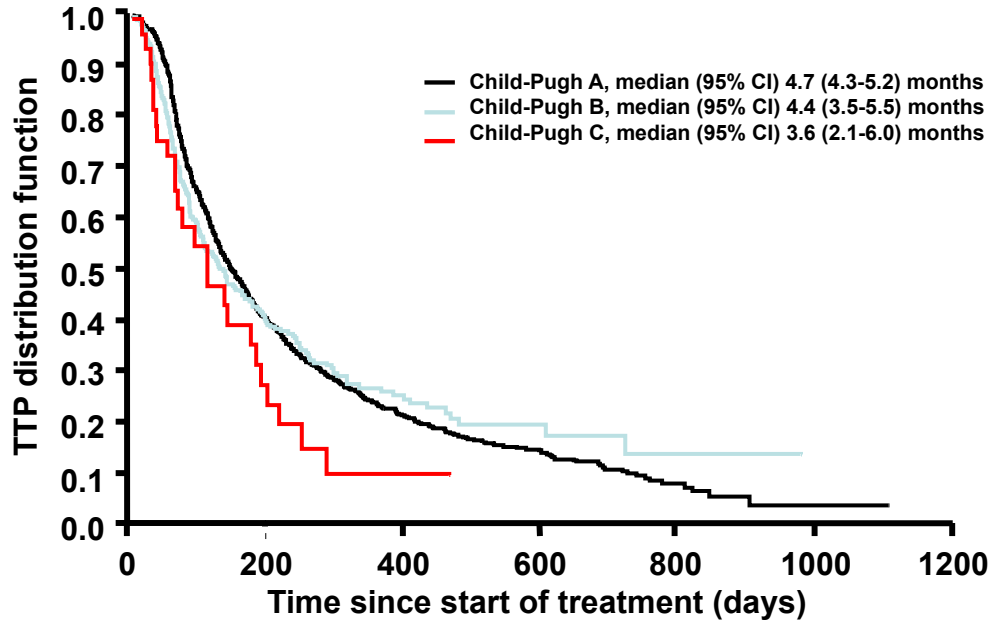
- Loss of survival benef ts in patients treated outside recommendations.
- Local ablation of early cancer is more cost effective than limited resection.
- Can resection in patients with portal hypertension be facilitated by DAAs?
- Can sorafenib therapy scale up in advanced cirrhosis following DAA therapy?
- Reconsidering non transplant therapeutic options in the era of donor shortage.

GIDEON: Treatment Outcome by Child-Pugh Status (3213 Patients, ITT)

Overall survival

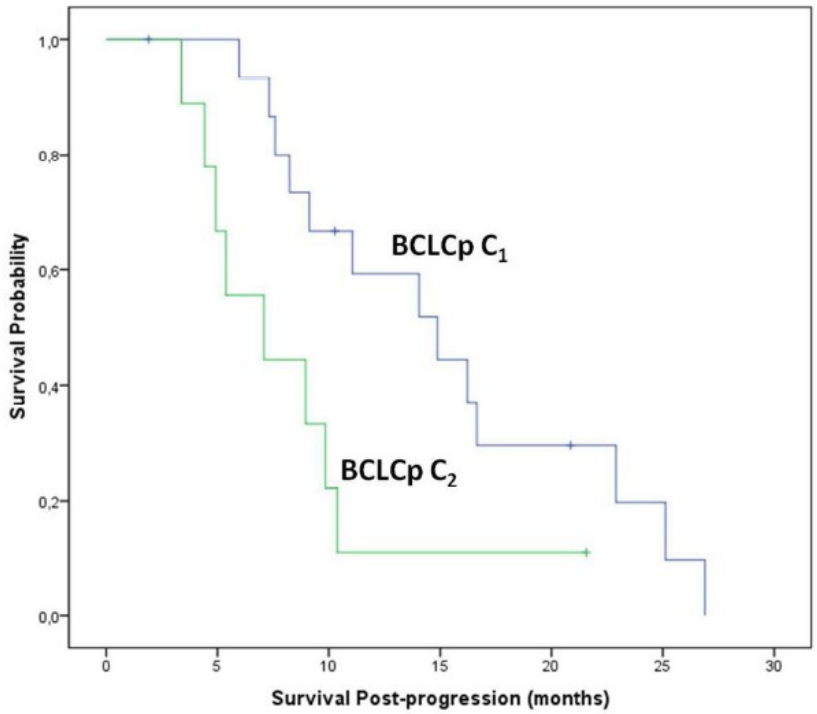


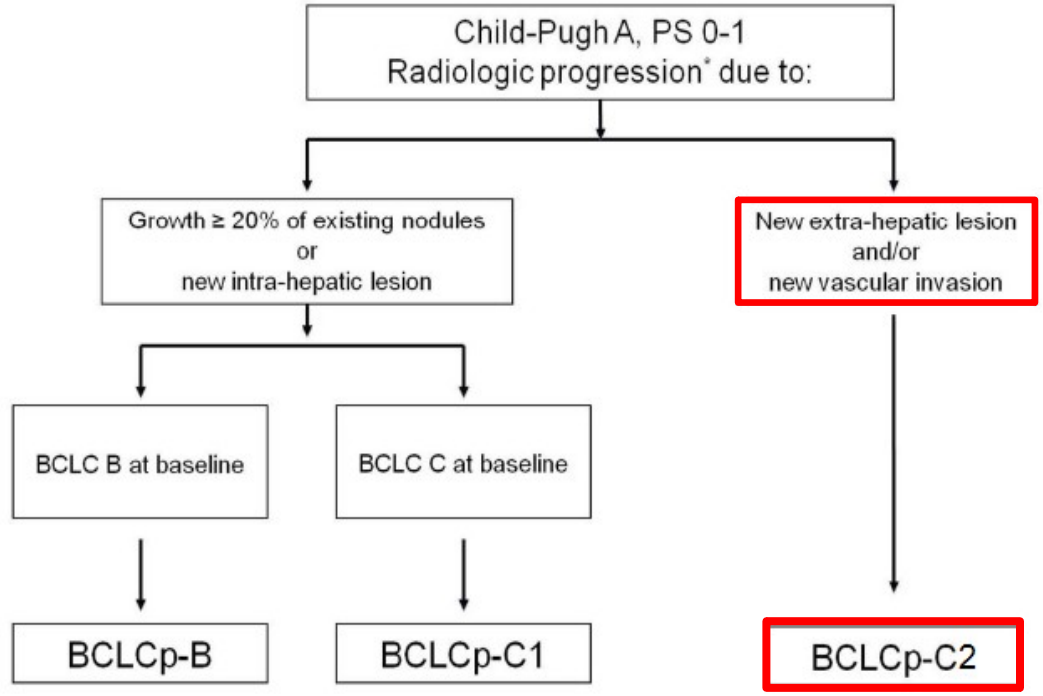
Time to tumor progression



Marrero J, ASCO 2013 abs # 4126.

Post-progression Survival of Patients with Advanced HCC. Rationale for Second Line Trial Design





BCLCp C1: Patients BCLC-C under sorafenib treatment with progression due to growth of existing nodules or new intra-hepatic sites.

BCLCp C2: Patients BCLC-C under sorafenib treatment with progression due to new extra-hepatic lesion and/or vascular invasion.

Reig M et al, Hepatology. 2013;58:2023-31.

Treatment of Hepatocellular Carcinoma Beyond International Guidelines

Outline

- Loss of survival benef ts in patients treated outside recommendations.
- Local ablation of early cancer is more cost effective than limited resection.
- Can resection in patients with portal hypertension be facilitated by DAAs?
- Can sorafenib therapy scale up in advanced cirrhosis following DAA therapy?
- Reconsidering non transplant therapeutic options in the era of donor shortage.

Drivers of Organ Allocation for Liver Transplantation in Patients with Cirrhosis vs HCC

Urgency	Focused on pretransplant risk of dying: patients with worse outcome on the waiting list are given higher priority for transplantation (based on Child-Pugh or MELD score)
Utility	Based on maximisation of post-transplant outcome, takes into account donor and recipient characteristics: mainly used for HCC since the MELD score poorly predicts post-transplant outcome in HCC due to the absence of donor factors and lack of predicting tumour progression while waiting
Benefit	Calculated by subtracting to the survival achieved with LT the survival obtained without LT. Ranks patients according to the net survival benefit that they would derive from transplantation and maximise the lifetime gained through transplantation. If applied to HCC without adjustments, it may prioritise patients at highest risk or recurrence.

Modified by Bruix et al, Gut 2014;63:844-55

Surgical Resection for HCC: Moving from What Can Be Done to What is Worth to Be Done

Drivers of Treatment Selection	In favor of Transplantation	In favor of Resection	In favor of Ablation
Patient			
• Age	≤ 70 years	≤ 75 years	no limit
• Performance Status	any grade (high MELD)	0	0
• Comorbidities	No	no / minor	major
Tumor			
• Size	single ≤ 5 cm	≥ 3 cm	≤ 3 cm
• Number	up to 3 nodules ≤ 3 cm	single	up to 3 nodules
• Location within liver	any site	peripheral / exophytic	central, far from vessels, bile tract and viscera
• Vascular invasion (branch / segment)	absent	not relevant by some	absent
• Satellites	not counted when < 1 cm	not relevant only in anatomic resections	absent
• AFP	< 1,000 ng/ml	the lower the better	any level
• Perceived anti-tumor efficacy	very high	high	high
Liver disease			
• Cirrhosis	yes	no	yes
• Portal hypertension	any	absent / mild	any
• Bilirubin (NV ≤ 1 mg/dl)	any	normal	normal / ≤ 2 x nv
• MELD score	any	very low	low

Modified from Romagnoli et al, Hepatology 2015 in press