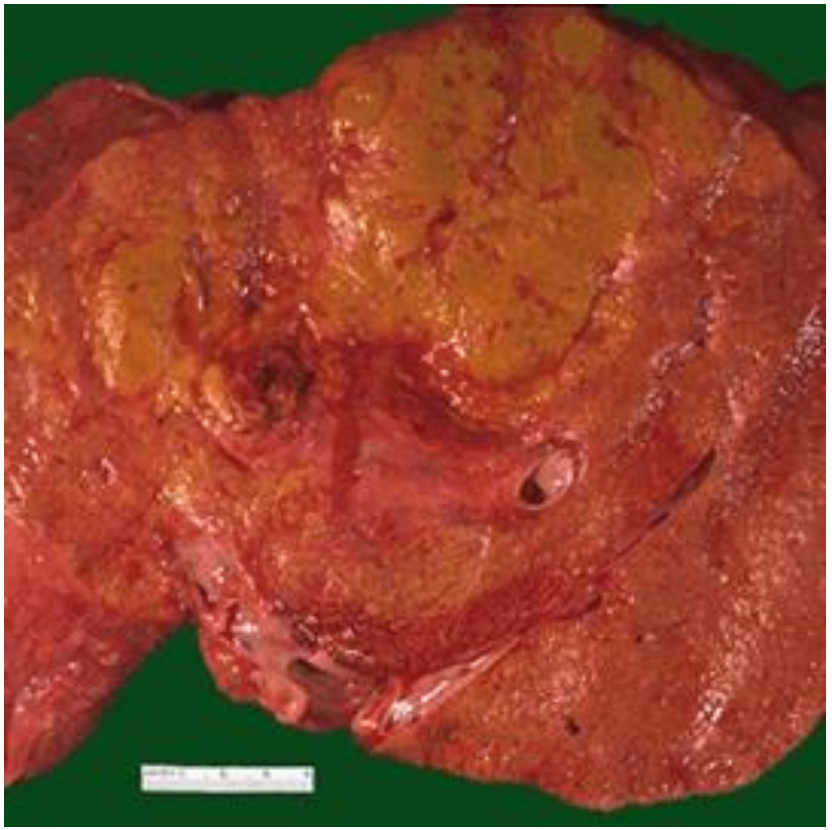
Leids Universitair
Medisch Centrum

Diagnostic evaluation and treatment of Hepatocellular carcinoma

DLW 2018



Minneke J. Coenraad

Maag, Darm en Leverziekten

LEIDEN

No disclosures

Outline HCC

Epidemiology and risk factors for HCC

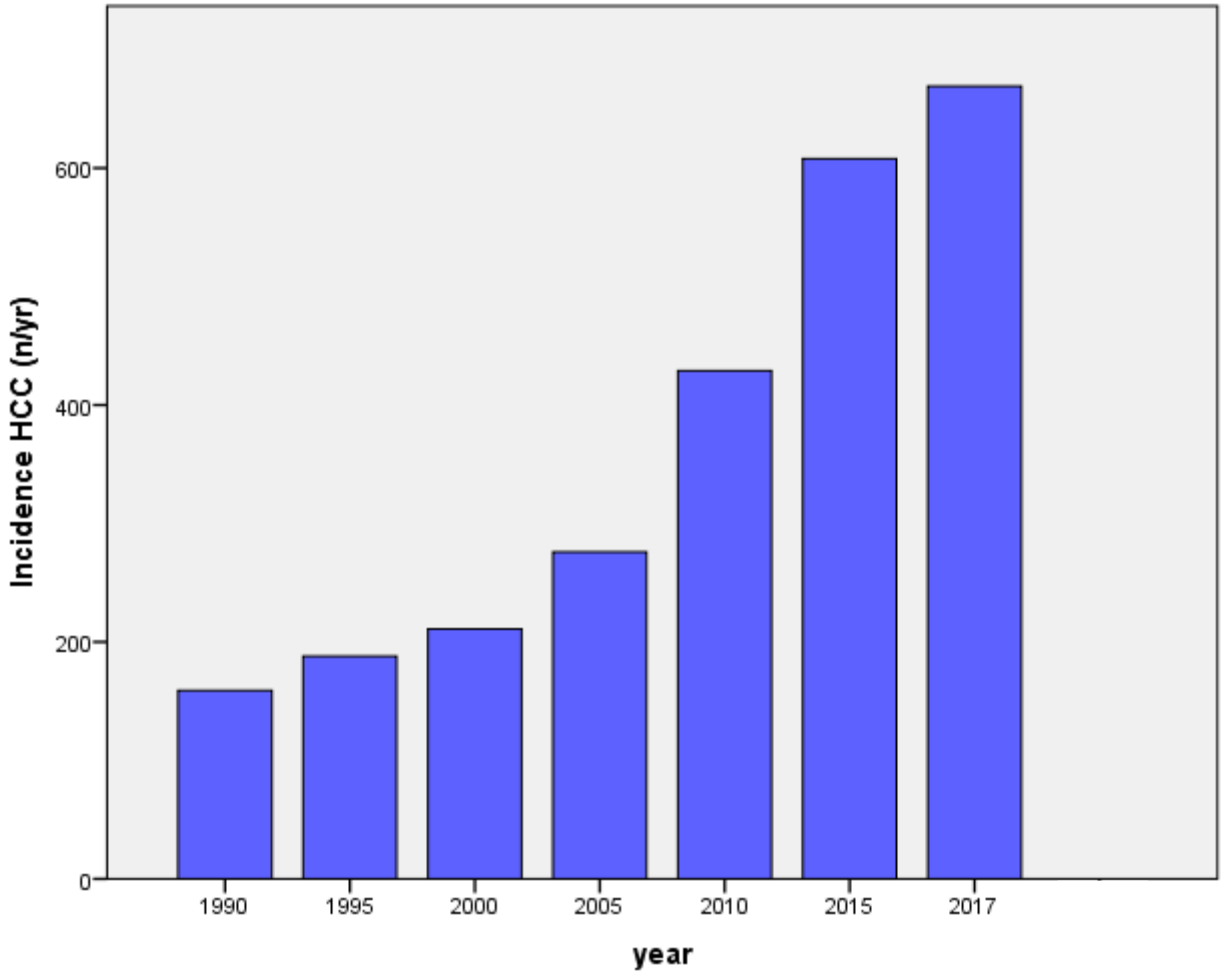
Noncirrhotic HCC: risk factors and prognosis

Is surveillance indicated?

Role of biopsy in diagnostic algorithm for suspected HCC

Evolving treatment cirrhotic HCC

Rising incidence of HCC



Risk of HCC depends on cause, ethnicity/region, stage of fibrosis/ cirrhosis

Hepatocellular carcinoma

Cirrhosis is key risk factor for HCC development

- Prevalence of cirrhosis among patients with HCC 85%-95%
- HCC incidence rate in patients with cirrhosis 2%-4% per year

Geographical distribution of main risk factors for HCC worldwide

Geographic area	**Risk factors**		**Alcohol**	**Others**
	HCV(%)	**HBV(%)**	**(%)**	**(%)**
Europe	60-70	10-15	20	10
North America	50-60	20	20	10 (NASH)
Asia and Africa	20	70	10	10

Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: results from a large cohort in the Netherlands

	Total group	Cirrhosis	No cirrhosis	P-value*
Patient number	1221 (100)	983 (81)	238 (19)	
Male sex	936 (77)	779 (79)	157 (66)	**<0.001**
Age at HCC diagnosis	63 (8–91)	63 (8–91)	65 (11–88)	0.514
BMI [mean (SD)]	26.7 (5.0)	27.1 (5.0)	25.4 (4.7)	**<0.001**
Etiology				**<0.001**
Alcohol	349 (29)	312 (32)	37 (16)	
Chronic viral hepatitis				
HBV	197 (16)	162 (16)	35 (15)	
HCV	249 (20)	236 (24)	13 (6)	
Coinfection	19 (2)	18 (2)	1 (<1)	
Hemochromatosis	37 (3)	29 (3)	8 (3)	
NAFLD	181 (15)	114 (12)	67 (28)	
Others	43 (3)	39 (4)	4 (2)	
No risk factors known	146 (12)	73 (7)	73 (30)	
ALT (U/l)	47 (4–1193)	49 (4–1193)	39 (8–712)	**<0.001**
AST (U/l)	66 (14–8678)	71 (15–8678)	46 (14–1344)	**<0.001**
Albumin	38 (13–62)	37 (13–58)	43 (18–62)	**<0.001**
Platelets	146 (8–985)	125 (8–985)	259 (62–724)	**<0.001**
INR	1.1 (0.8–2.9)	1.2 (0.8–2.9)	1.0 (0.8–1.8)	**<0.001**
PT	13.9 (9.7–36.7)	14.3 (10.0–36.2)	12.3 (9.7–36.7)	**<0.001**
APRI	1.6 (0.1–304)	2.0 (0.1–304)	0.6 (0.1–32)	**<0.001**
MELD score	9 (6–33)	10 (6–33)	7 (6–29)	**<0.001**

Results indicate numbers and, between brackets, percentages. Continuous variables reported as medians and, between brackets, ranges unless otherwise indicated. Significant *P*-values are in bold.

ALT, alanine transaminase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransaminase; coinfection, HBV + HCV infection; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model For End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; PT, prothrombin time.

*P-value applies to the 'cirrhosis' versus 'no cirrhosis' groups.

Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: results from a large cohort in the Netherlands

	Total group	Cirrhosis	No cirrhosis	*P*-value[a]
Patient number	1221 (100)	983 (81)	238 (19)	
Number of lesions				**<0.001**
1	632 (52)	473 (48)	159 (67)	
2	152 (12)	132 (14)	20 (8)	
3	68 (6)	63 (6)	5 (2)	
Multifocal/diffuse	369 (30)	315 (32)	54 (23)	
Tumor size (cm)	5 (1–26)	4 (1–26)	8 (1–26)	**<0.001**
BCLC stage				**<0.001**
0	75 (6)	72 (7)	3 (1)	
A	345 (28)	301 (31)	44 (18)	
B	406 (33)	274 (28)	132 (56)	
C	299 (25)	247 (25)	52 (22)	
D	96 (8)	89 (9)	7 (3)	
α-Fetoprotein (μg/l)	29 (1–2.7×10^6)	35 (1–1.8×10^6)	10 (1–2.7×10^6)	**<0.001**
Treatments				**<0.001**
Surgical therapy	341 (28)	215 (22)	126 (53)	
Resection	214 (18)	95 (10)	119 (50)	
Transplantation	120 (10)	116 (12)	4 (2)	
Both	6 (<1)	4 (<1)	2 (1)	
RFA[b]	149 (12)	145 (15)	4 (2)	
TACE/TARE[c]	207 (17)	176 (18)	31 (13)	
Systemic therapy	118 (10)	85 (8)	33 (14)	
Best supportive care	351 (29)	314 (32)	36 (15)	
Unknown	55 (4)	48 (5)	8 (3)	

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[a]*P*-value applies to 'cirrhosis' versus 'no cirrhosis' groups.
[b]Thirteen patients received RFA and subsequently TACE with more than 1 month interval.
[c]In 31 patients a combination of TACE and RFA within a 1 month interval was performed as initial therapy.

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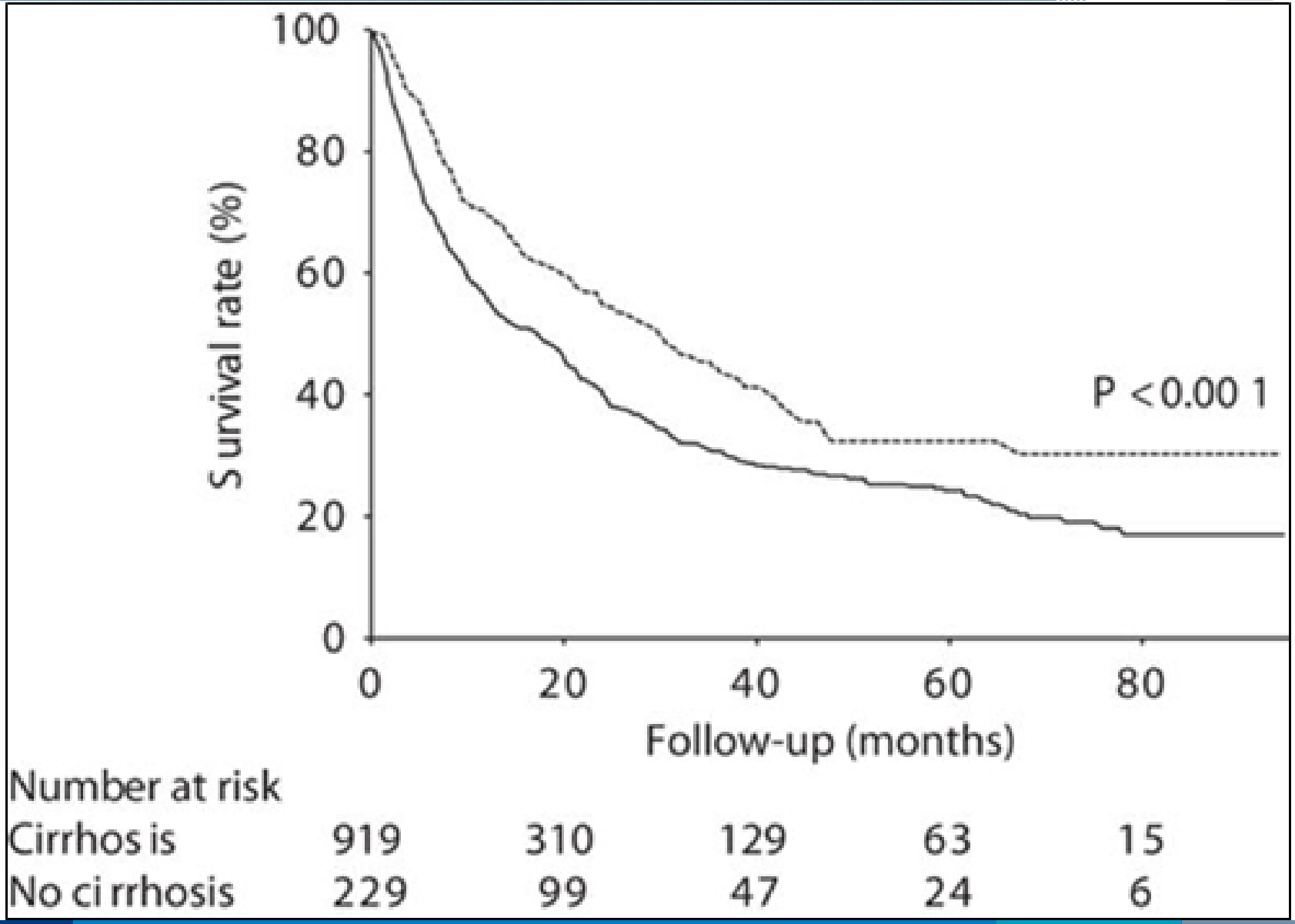
Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: results from a large cohort in the Netherlands



Case

Female 58 yr

HCV genotype 1A, non response to peginterferon/ ribavirin

Child Pugh A cirrhosis, MELD 6

Q: Surveillance for HCC?

YES

NO

Case

Male, 66 yr

Diabetes mellitus, hypertension

NASH cirrhosis, Child Pugh B, MELD 8

Q: Surveillance for HCC?

YES

NO

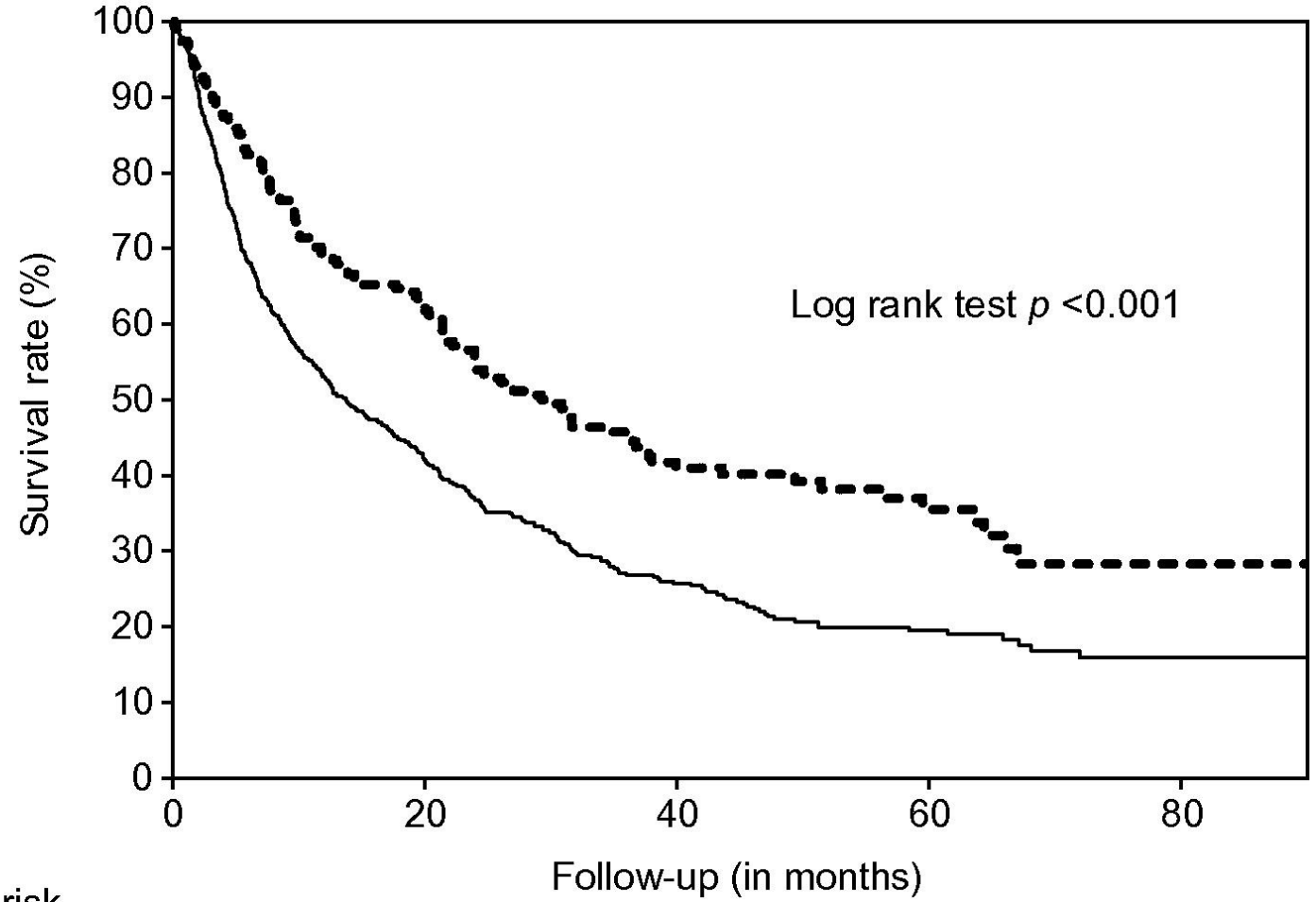
Surveillance for hepatocellular carcinoma is associated with increased survival: Results from a large cohort in NL

Retrospective analysis

Patients with HCC in 2005-2012 from five Dutch academic centers

	Surveillance 295 (27%)	**Non surveillance 779 (73%)**
Cirrhosis	286 (97%)	460 (60%)
Viral hepatitis	179 (61%)	214 (27%)
NAFLD	22 (7%)	154 (20%)
BCLC 0/A	179 (61%)	163 (21%)
Surgical treatment	101 (34%)	199 (25%)

Surveillance for hepatocellular carcinoma is associated with increased survival: Results from a large cohort in NL



Number at risk					
Surveillance:	279	123	57	24	6
Non-surveillance:	720	216	86	43	8

HCC surveillance guidelines

EASL EORTC guideline 2012

- Cirrhosis Child Pugh A and B and CP-C awaiting LT
- HCV F3 fibrosis
- Active HBV infection or with positive family history HCC

Nederlandse richtlijn 2013

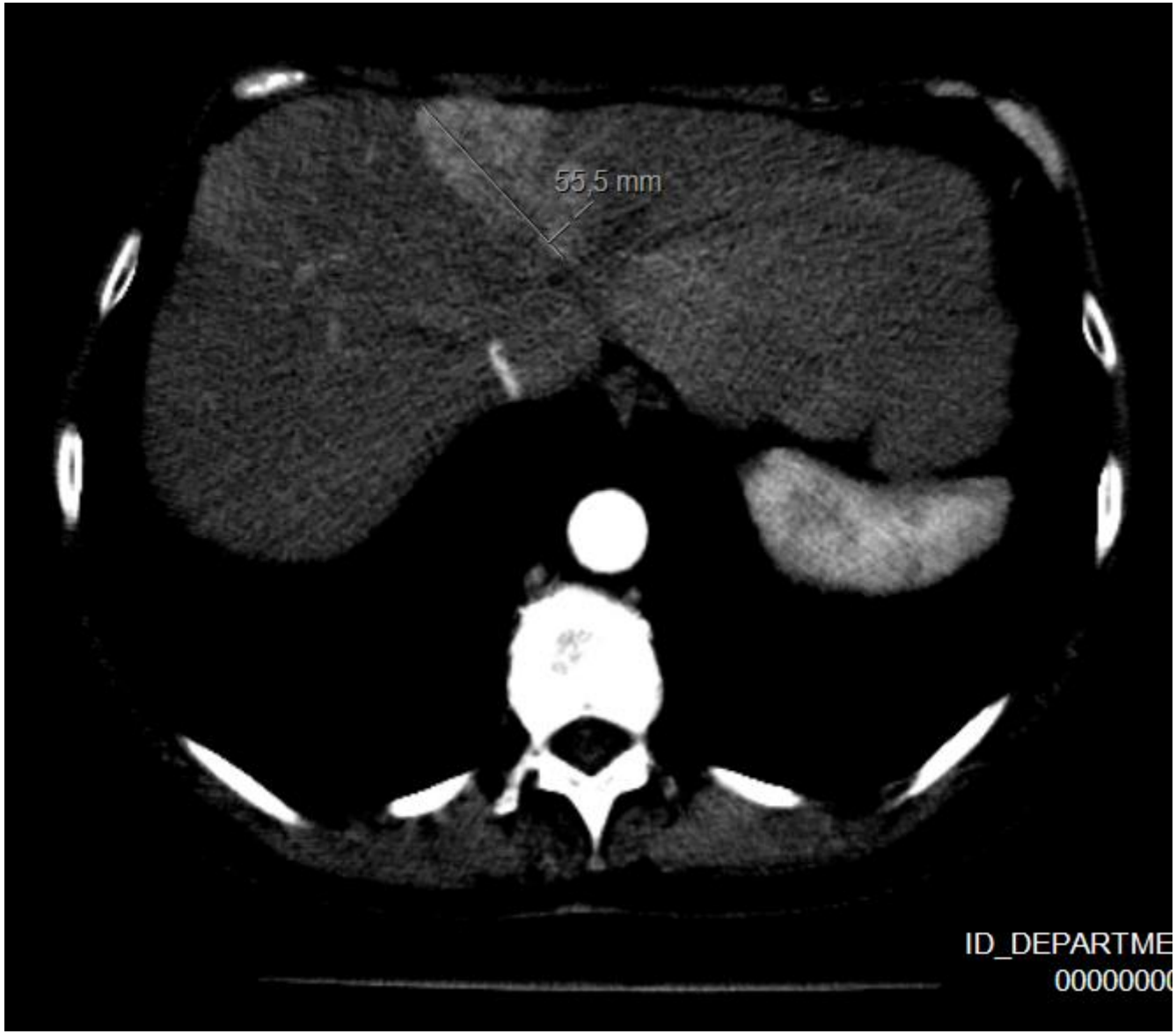
- Cirrhosis due to HBV, HCV, ALD, hemochromatosis, PBC
- Active HBV infection or with positive family history HCC

AASLD guideline 2018

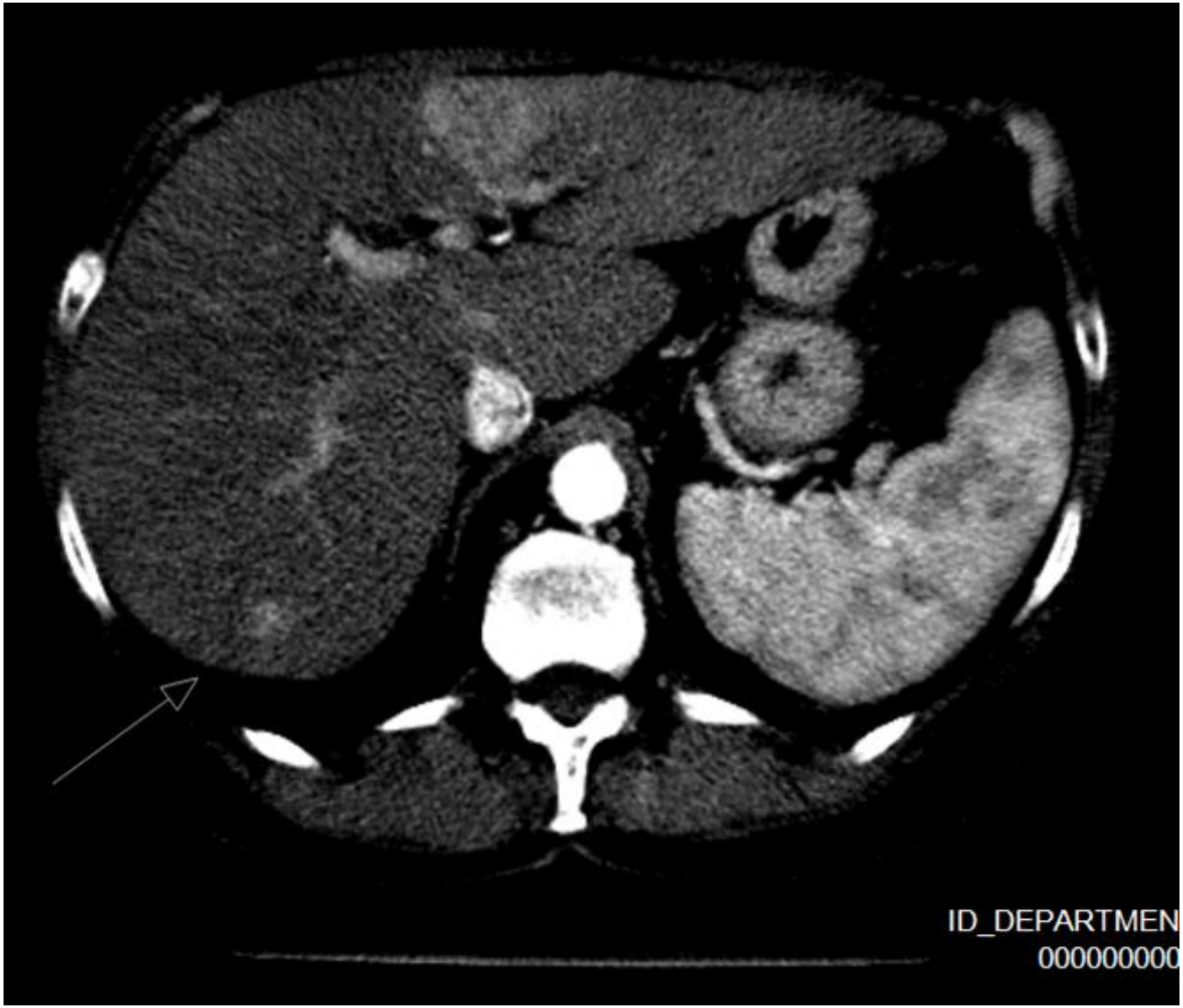
- Cirrhosis Child Pugh A and B and CP-C awaiting LT

improvement in survival, higher early-stage HCC detection

Back to case



Case



Liver biopsy indicated for diagnosis?

Yes

No

Diagnostic evaluation in cirrhosis and suspected HCC

Until 2000 diagnosis based on biopsy despite limitations

- Feasibility due to location
- Risk of complications (bleeding or needle-track seeding)
- Sampling error, especially in very small lesions

2001, expert panel reported non-invasive criteria for HCC

Recommendation #2 AASLD 2018

The AASLD recommends diagnostic evaluation for HCC with either multiphasic CT or multiphasic MRI because of similar diagnostic performance

Adults with cirrhosis with indeterminate nodule

AASLD HCC guideline 2018:

Substantial proportion of 1- to 2-cm indeterminate nodules are nonmalignant histologically and unlikely to progress to HCC during follow-up

The AASLD suggests against routine biopsy of every indeterminate nodule

Several options: follow-up imaging, alternative modality imaging or biopsy

Individualized diagnostic workup based on:

- clinical context
- imaging findings
- feasibility of biopsy
- institutional expertise

Biopsy in expert centres in potentially curable patients

Back to case

Female 58 yr

HCV cirrhosis Child Pugh A, MELD 6

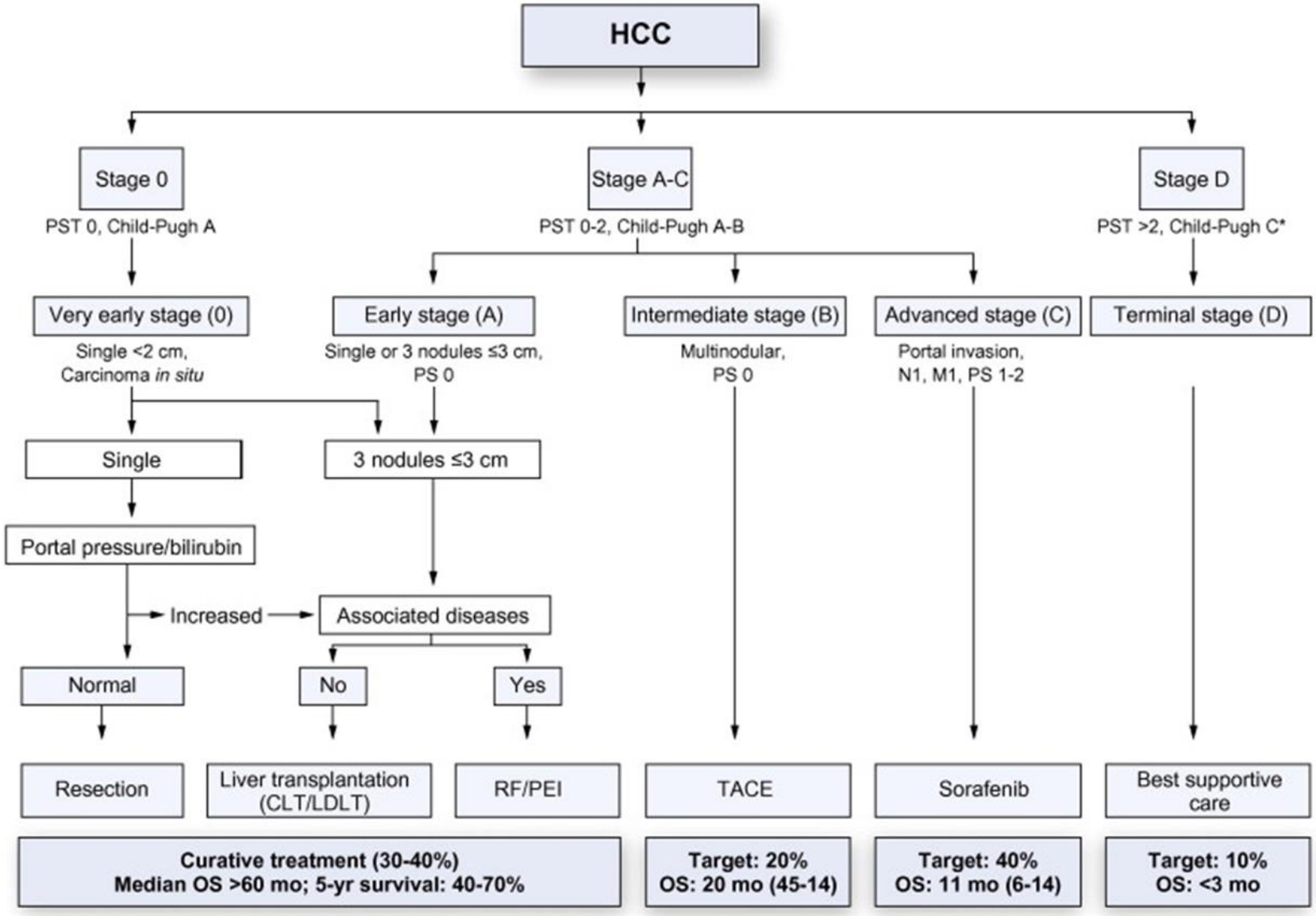
Multifocal bilobar HCC

ECOG performance status 0

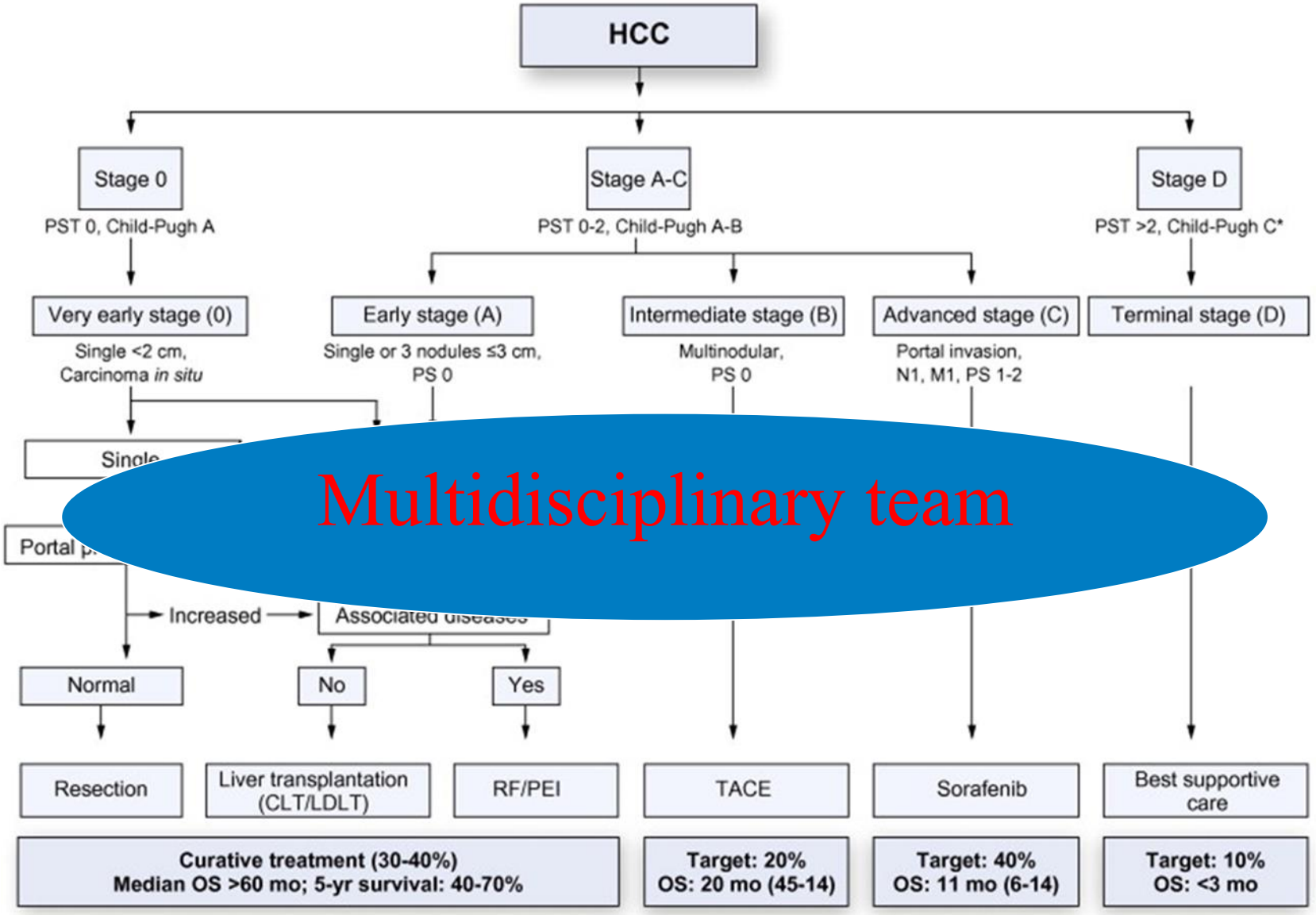
Stage?

Treatment?

BCLC staging system



BCLC staging system



Evolving field of HCC treatment: Early stage HCC

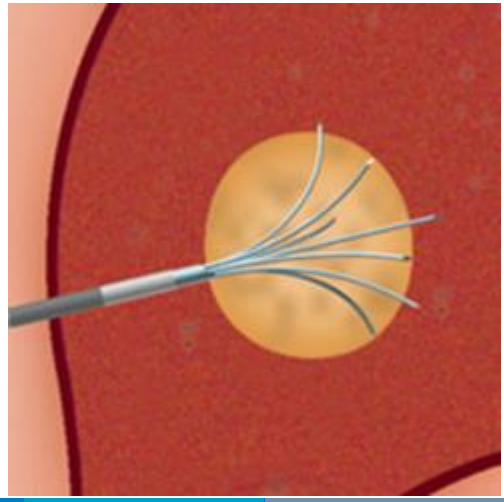
Recommendation #4 AASLD 2018

Adults with Child-Pugh class A cirrhosis and resectable T1 or T2 HCC undergo resection over radiofrequency ablation

2 RCTs: resection vs RFA in 578 patients with early stage HCC

overall survival HR 0.56; 95% CI, 0.40-0.78

2-year survival HR, 0.38; 95% CI, 0.17-0.84



Ann Surg 2010;252:903-912, J Hepatol 2012;57:794-802.

Evolving field: Intermediate stage HCC

Recommendation #8 AASLD 2018

Patients beyond the Milan criteria (T3) should be considered for liver transplantation after successful downstaging into the Milan Criteria

The Milan criteria currently benchmark for selection in Eurotransplant

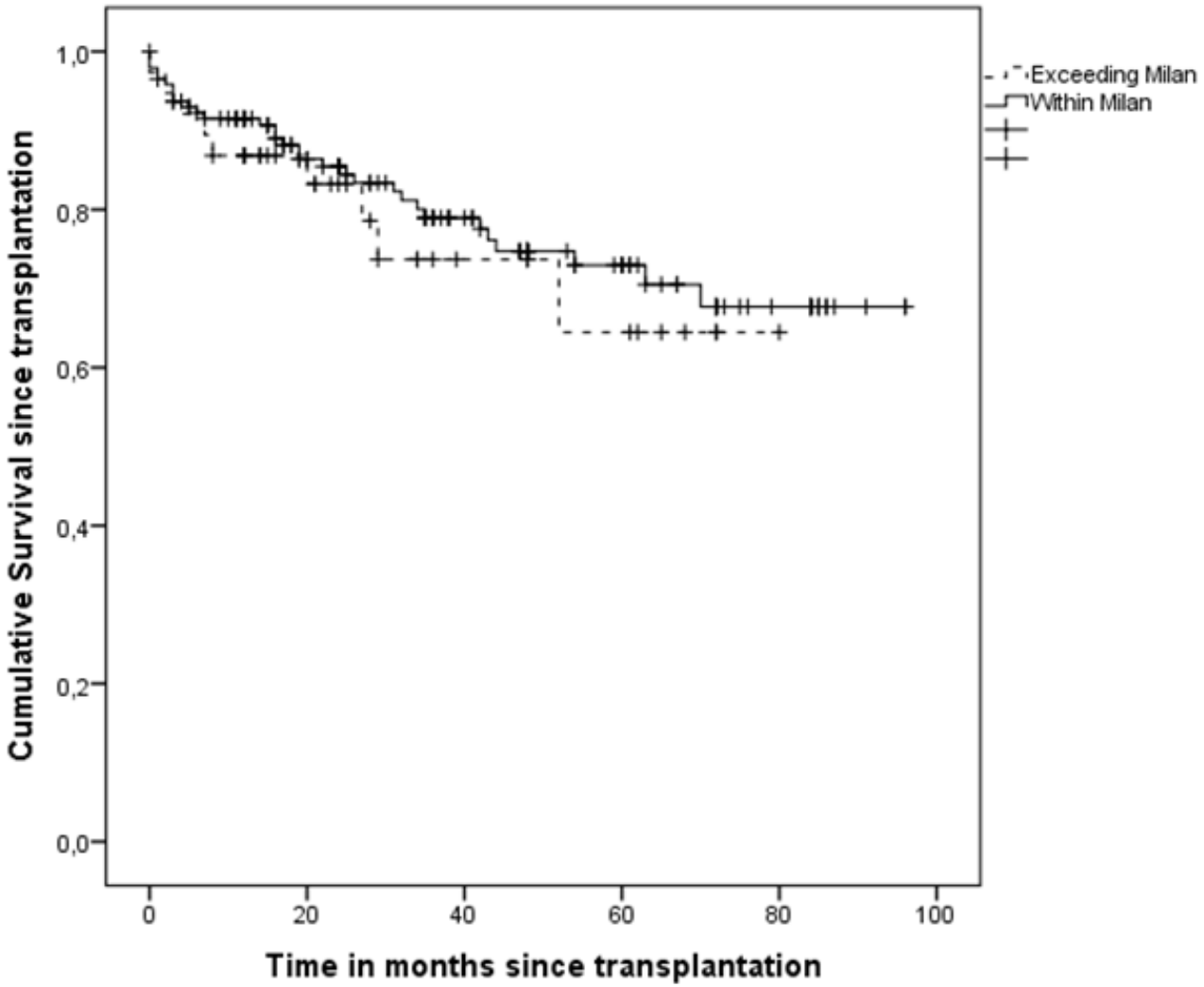
- 5 yr overall survival rate 70%
- Recurrence rate after liver transplantation 8-12%

The role of downstaging of hepatocellular carcinoma before liver transplantation in The Netherlands

Variable median (IQR)/ number (%)	Total cohort (n=230)	Within Milan at diagnosis (n= 183)	Exceeding Milan at diagnosis (n=47)
Age (y)	59 (52-63)	59 (53-63)	58 (50-63)
Male gender	181 (78%)	145 (79%)	34 (79%)
Cirrhosis present	220 (94%)	176 (96%)	41 (87%)
Etiology HCV HBV ALD Other	79 (34%) 31 (13%) 70 (30%) 50 (33%)	61 (33%) 25 (14%) 57 (31%) 40 (22%)	17 (36%) 6 (13%) 11 (23%) 13 (28%)
AFP concentration	15 (5-105)	12 (5-101)	23 (8-221)
No of tumors 1 2 3 4	145 (63%) 56 (24%) 19 (8%) 8 (4%)	126 (69%) 43 (24%) 12 (7%)	20 (43%) 11 (23%) 6 (13%) 8 (17%)
Diameter largest nodule (mm)	24 (17-34)	22 (16-28)	52 (35-65)
Neoadjuvant LRT before LT	190 (81%)	145 (79%)	42 (89%)

Coenraad et al. on behalf of LOL Manuscript in preparation

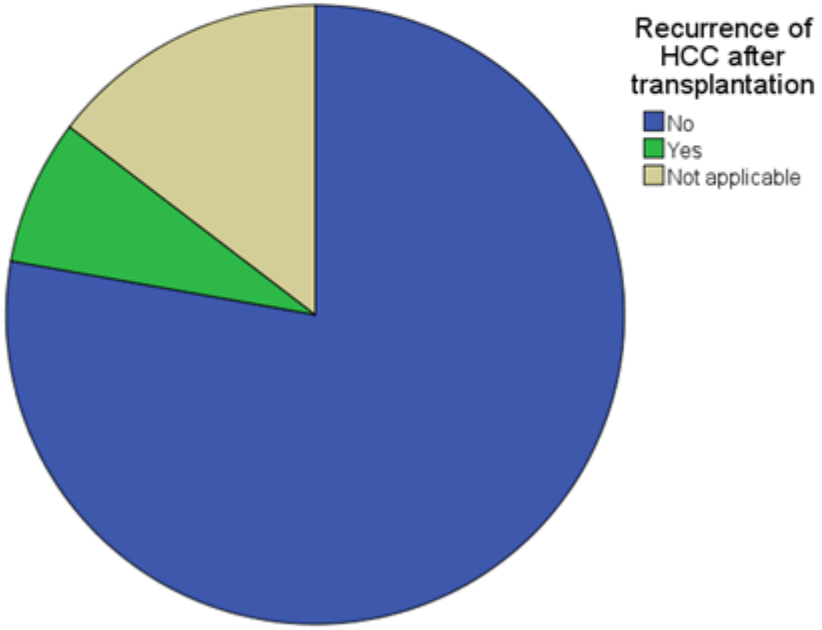
Survival after liver transplantation



Recurrence of HCC after LT

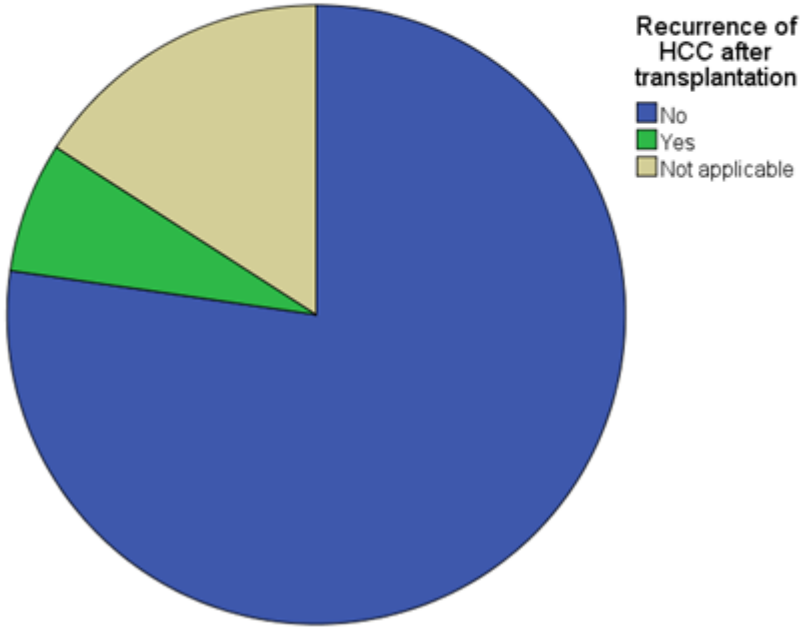
Within Milan criteria

13/145 (8.9%)



Exceeding Milan criteria

3/38 (7.8%)



Back to case: BCLC Intermediate stage HCC

April 2015 underwent whole liver TransArterial RadioEmbolisation (TARE) using Yttium90 microspheres

July 2015 Fulfilled Milan criteria, RF ablation of small residual HCC lesion

November 2015 within Milan criteria: screening for liver transplantation

National audit: registration at Wait List for transplantation

10-10-2016 Orthotopic LT
PA explant: Cirrhosis, in segm 4 reactive changes and embolisation material, no vital HCC

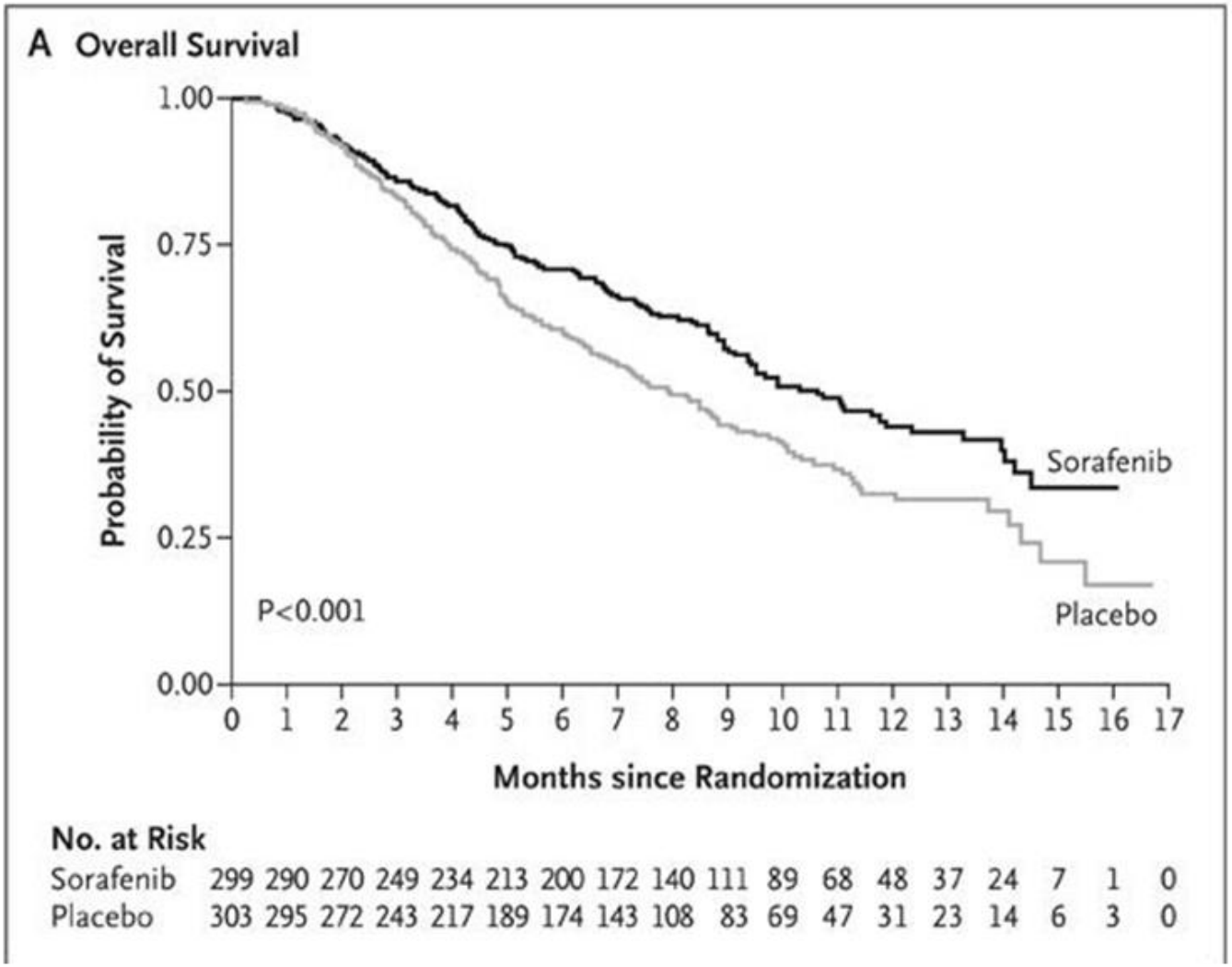
April 2018 Alive, good QOL, no sign of tumor recurrence

Advanced stage HCC

Recommendation #10 AASLD 2018

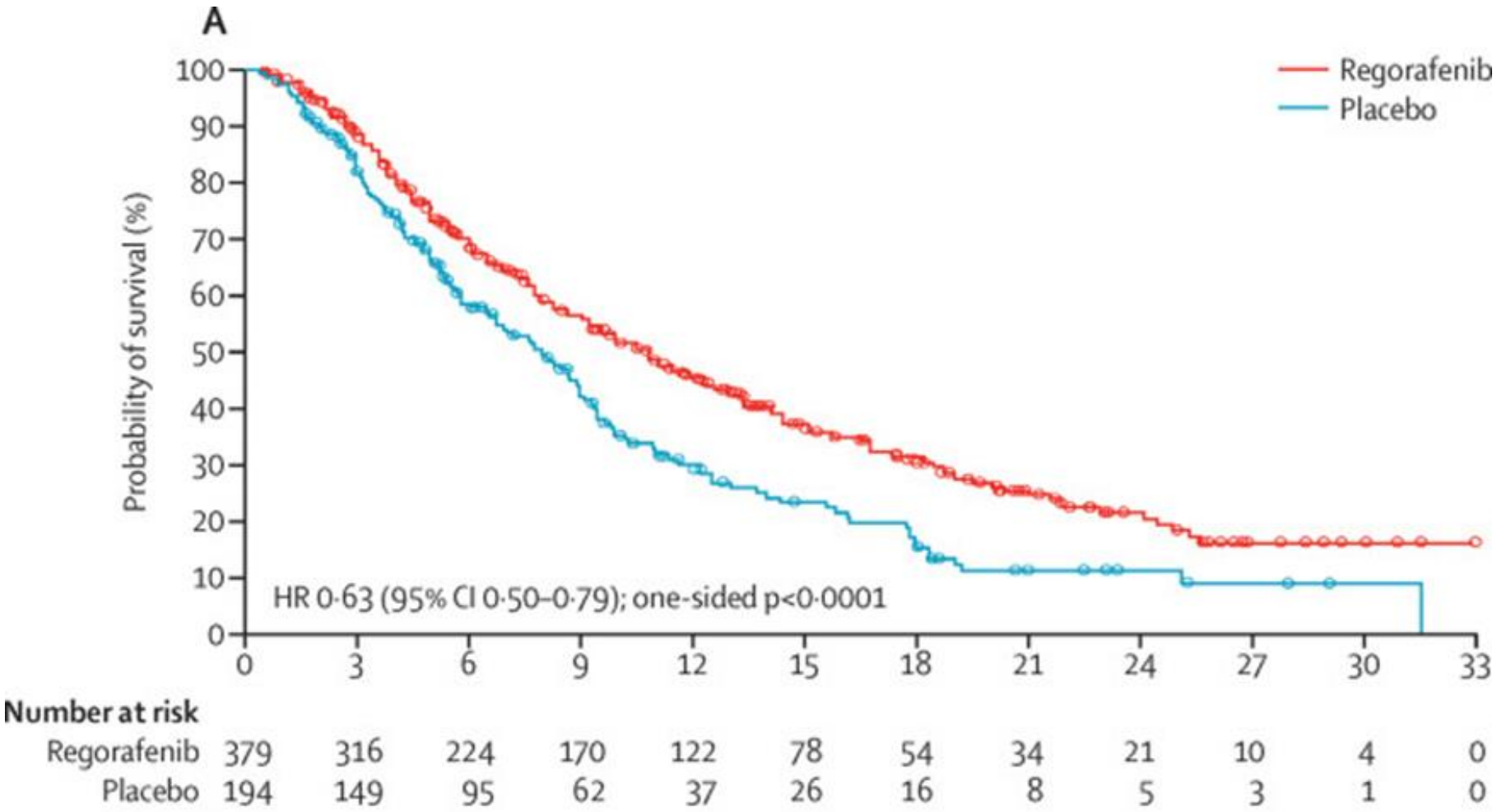
The AASLD recommends the use of systemic therapy over no therapy for patients with Child-Pugh class A cirrhosis or well-selected patients with Child-Pugh class B cirrhosis plus advanced HCC with macrovascular invasion and/or metastatic disease.

Sorafenib in advanced hepatocellular carcinoma



Llovet, NEJM 2008

Regorafenib for patients with HCC who progressed on sorafenib treatment (RESORCE): a phase 3 trial



Future in advanced HCC: immune checkpoint inhibitors?

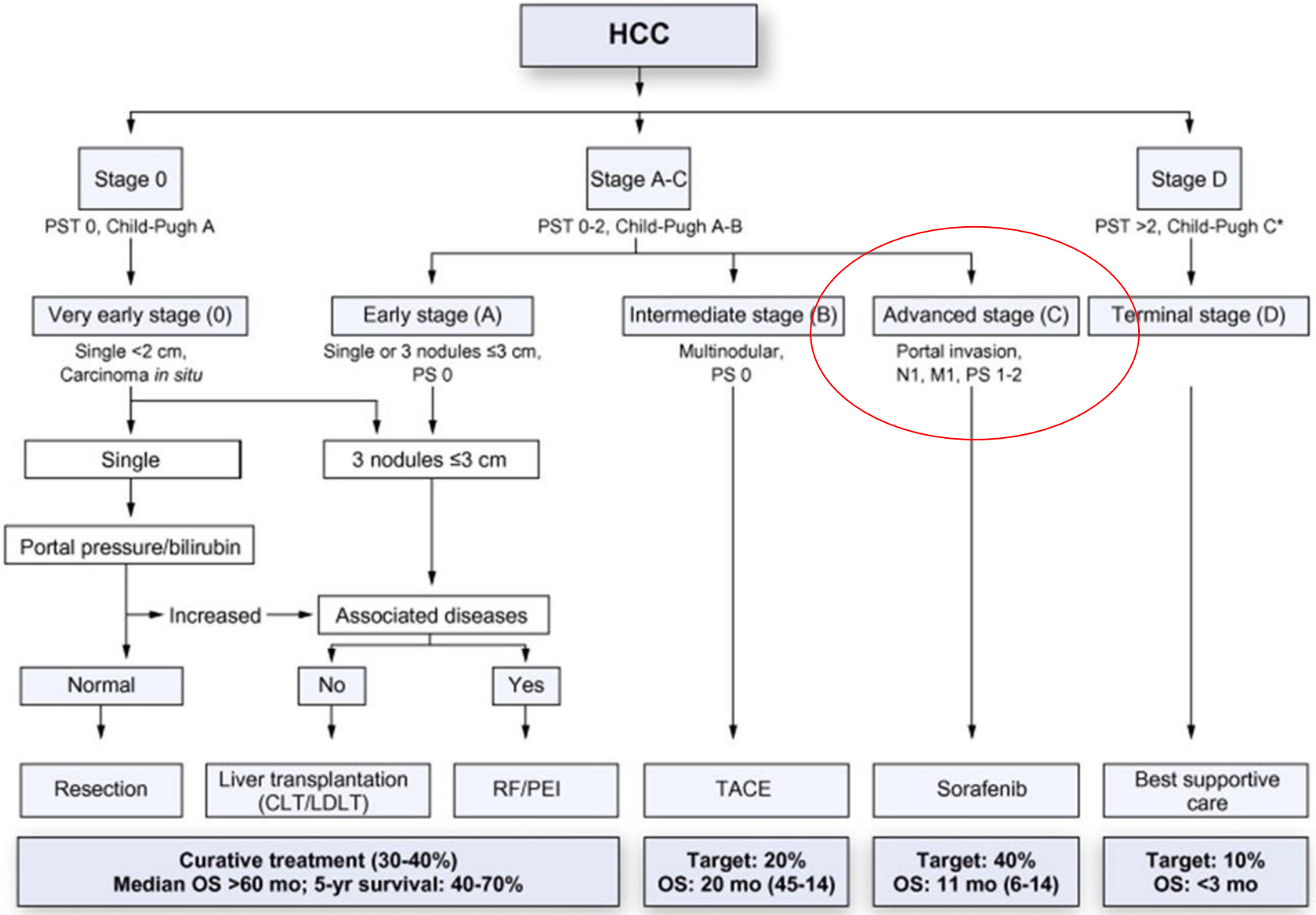
Immune checkpoint affects immune system functioning; can be stimulatory or inhibitory

Tumors can use checkpoints to protect from immune system

Checkpoint therapy blocking inhibitory checkpoints can restore immune cell function

- Tremelimumab (human monoclonal AB against cytotoxic T-lymphocyte-associated protein CTLA-4)
- Pembrolizumab (humanized PD-1 receptor inhibitor)
- Nivolumab (human PD-1 receptor inhibitor) Check Mate 040

Patients with advanced HCC need a personalized management: A lesson from clinical practice (ITA.LI.CA)



Giannini et al, Hepatology 2018; 67: 1784

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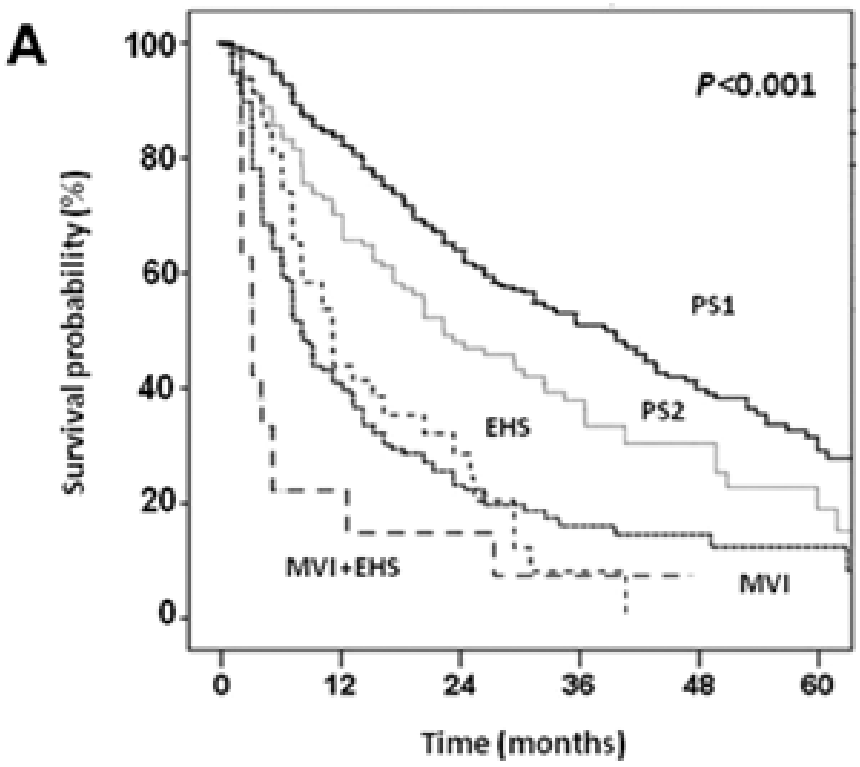
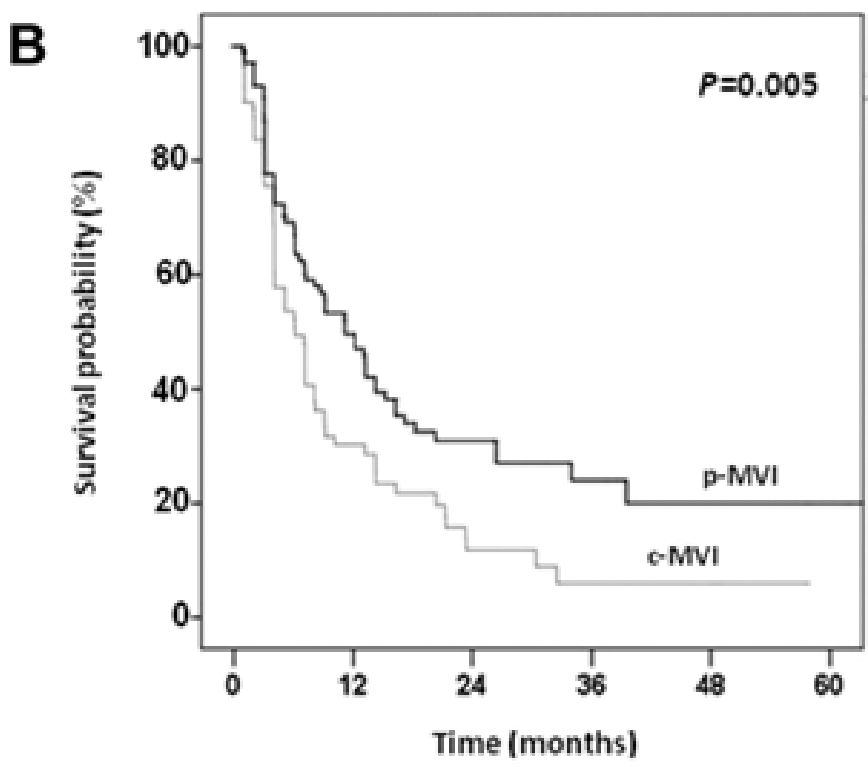


Patients at risk:

PS1	385	269	171	103	55	24
PS2	146	77	43	25	11	4
MVI	224	66	27	11	6	3
EHS	69	17	8	2		
MVI+EHS	29	2	1			



Patients at risk:

p-MVI	108	39	19	8	8	8
c-MVI	86	17	6	1	1	1

Giannini et al, Hepatology 2018; 67: 1784

Patients with advanced HCC need a personalized management: A lesson from clinical practice (ITA.LI.CA)

Table 3. Treatment Distribution in the Various BCLC C Subclasses

	PS1	**PS2**	**MVI**	**EHS**
	n = 385 (46.1)	**n = 146 (17.5)**	**n = 224 (26.8)**	**n = 51 (6.1)**
Liver transplant	10 (2.6)	1 (0.7)	—	—
Resection	29 (7.5)	7 (4.8)	23 (10.3)	2 (3.9)
Ablation	114 (29.6)	35 (24.0)	4 (1.8)	1 (2.0)
TA(C)E	133 (34.5)	25 (17.1)	11 (4.9)	7 (13.7)
TARE	3 (0.8)	—	10 (4.5)	2 (3.9)
Sorafenib	14 (3.6)	12 (8.2)	88 (39.3)	19 (37.3)
BSC	71 (18.4)	61 (41.8)	72 (32.1)	15 (29.4)

Conclusions

Rising incidence of HCC also in The Netherlands

20% of HCC in noncirrhotic patients

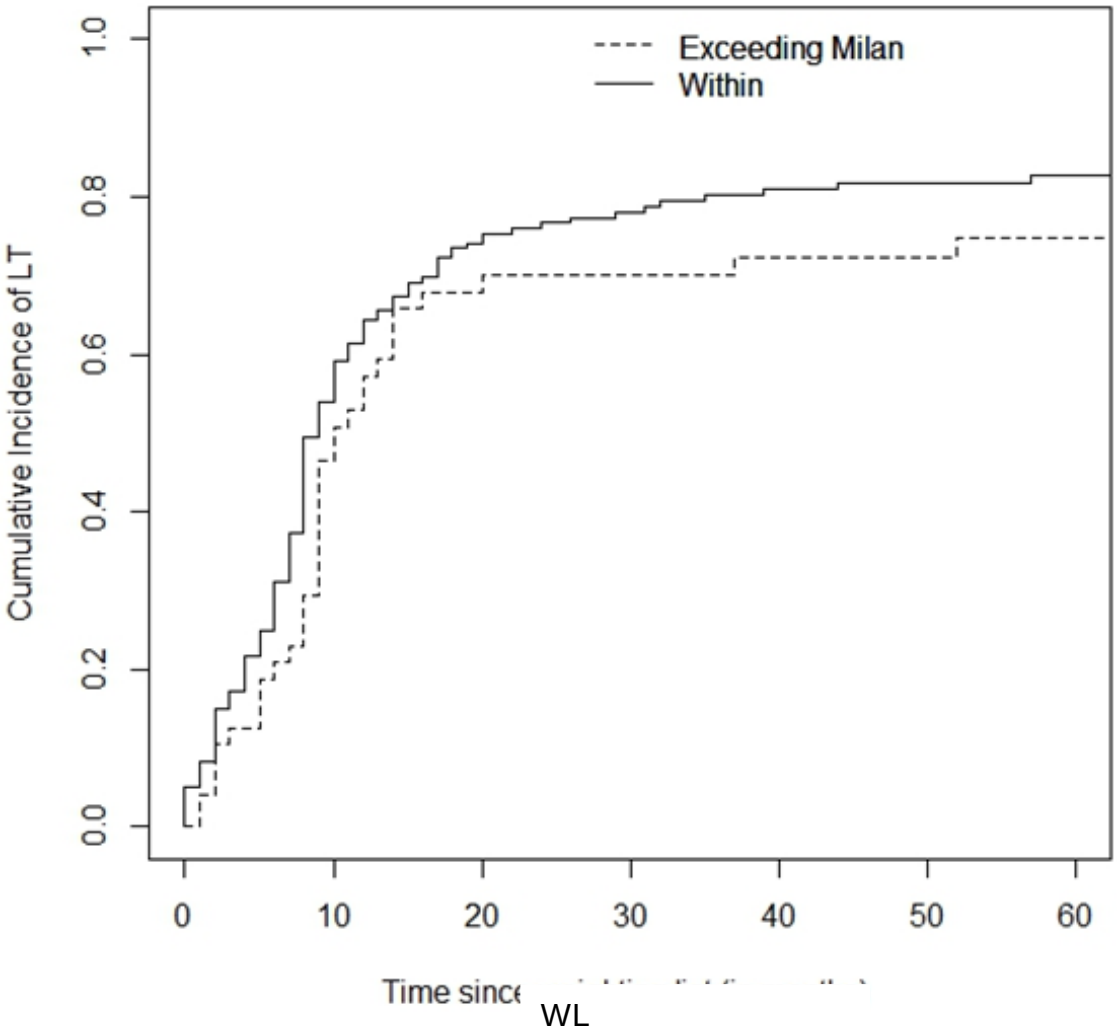
Surveillance by 6 months-interval ultrasound in cirrhotic patients

Tumor biopsy in expert centres in potentially curable patients

Multidisciplinary approach for HCC treatment

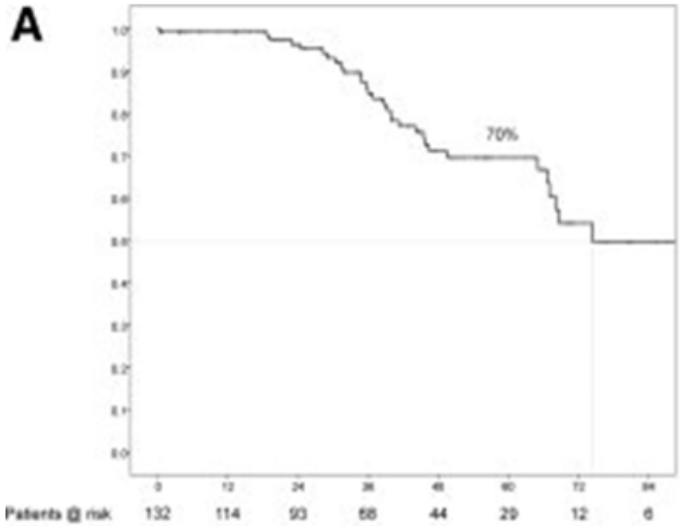
Evolving treatment cirrhotic HCC: from '*one size fits all* ' to more personalized approach

Cumulative incidence of liver transplantation

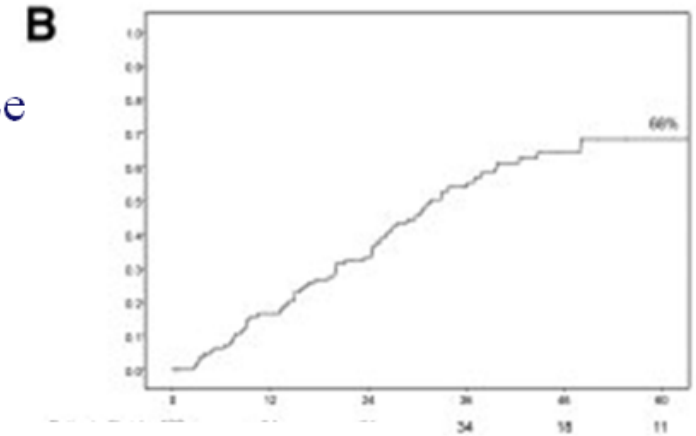


Resection of HCC < 2 cm: results from 2 Western centers

Overall survival

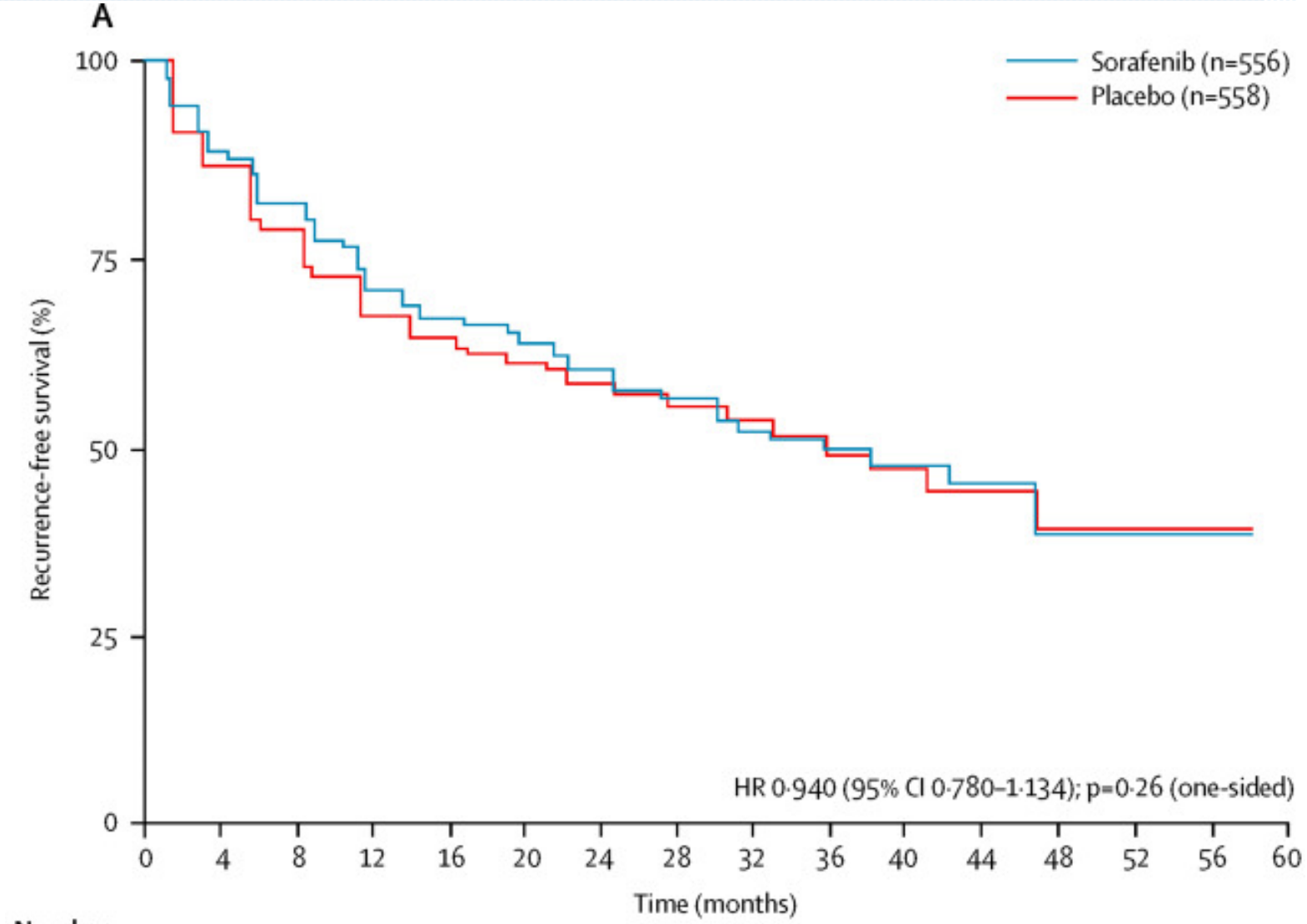


Time to recurrence



Roayaie and Mazzaferro, Hepatology 2013

Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3 trial



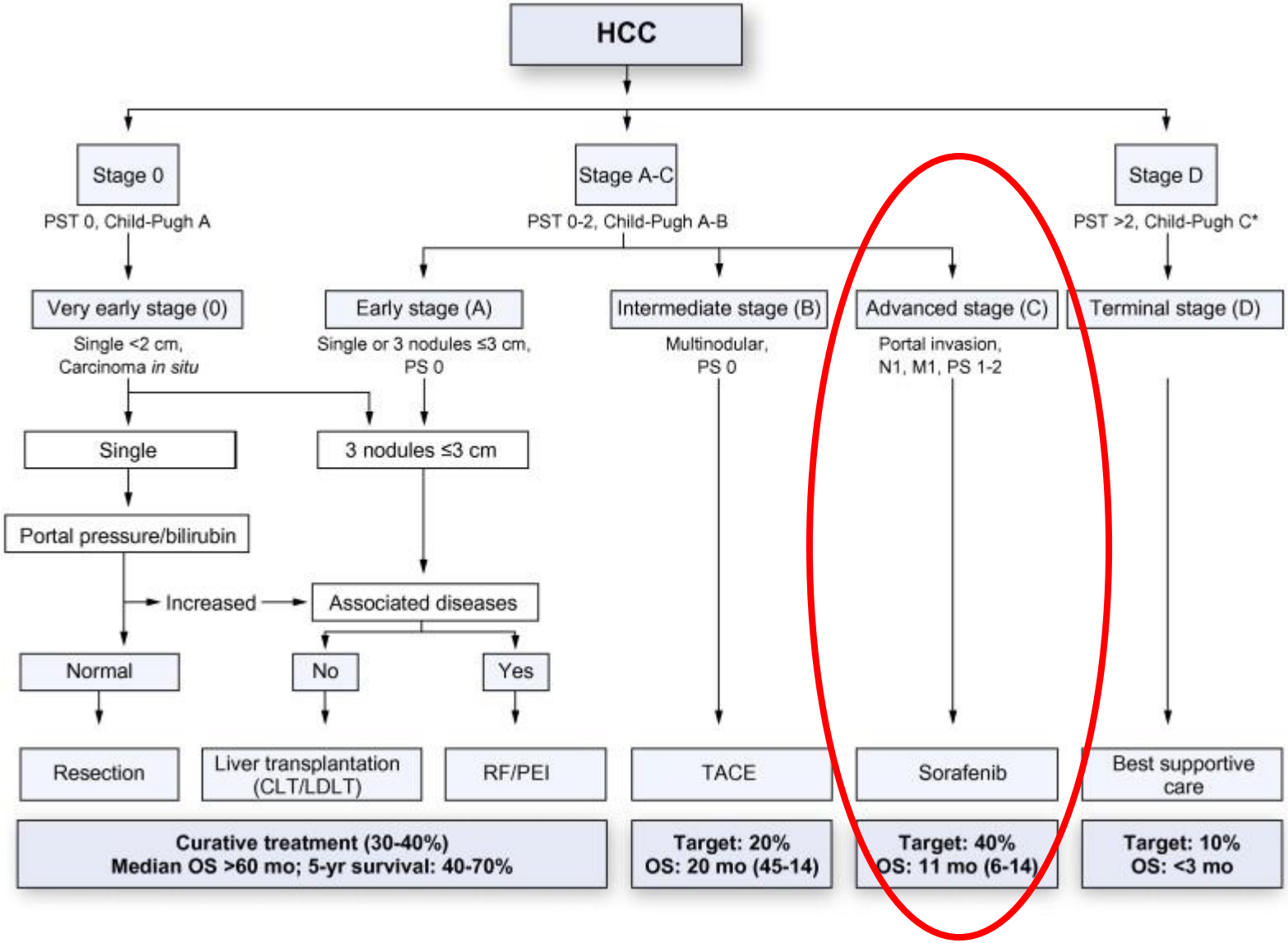
Lancet Oncol 2015

10. SHOULD ADULTS WITH CHILD-PUGH CLASS A/B CIRRHOSIS AND ADVANCED HCC WITH MACROVASCULAR INVASION AND/OR METASTATIC DISEASE BE TREATED WITH SYSTEMIC THERAPY OR LRT OR NO THERAPY?

Recommendation

10. The AASLD recommends the use of systemic therapy over no therapy for patients with Child-Pugh class A cirrhosis or well-selected patients with Child-Pugh class B cirrhosis plus advanced HCC with macrovascular invasion and/or metastatic disease.

Outline


HCC
Stage 0
PST 0, Child-Pugh A
Stage A-C
PST 0-2, Child-Pugh A-B
Stage D
PST >2, Child-Pugh C*
Very early stage (0)
Single <2 cm, Carcinoma in situ
Early stage (A)
Single or 3 nodules ≤3 cm, PS 0
Intermediate stage (B)
Multinodular, PS 0
Advanced stage (C)
Portal invasion, N1, M1, PS 1-2
Terminal stage (D)
Single
3 nodules ≤3 cm
Portal pressure/bilirubin
Increased
Associated diseases
Normal
No
Yes
Resection
Liver transplantation (CLT/LDLT)
RF/PEI
TACE
Sorafenib
Best supportive care
Curative treatment (30-40%)
Median OS >60 mo; 5-yr survival: 40-70%
Target: 20%
OS: 20 mo (45-14)
Target: 40%
OS: 11 mo (6-14)
Target: 10%
OS: <3 mo

Leids Universitair Medisch Centrum

ADVANCED STAGE HCC: combined locoregional and systemic therapy superior?

Sorafenib with vs without cTACE in pts with advanced HCC; results from a multicenter, open label, phase III RCT

Background: Standard of care in advanced stage HCC: first-line sorafenib therapy

Aim: Phase III trial evaluating effect of SOR +/- Transarterial chemoembolisation

Methods:

Multicenter RCT in 339 patients from 13 hospitals in South Korea

Sorafenib + TACE versus Sorafenib alone

Follow-up until progression or unacceptable toxicities

Sorafenib with vs without cTACE in pts with advanced HCC; results from a multicenter, open label, phase III RCT

	SOR + TACE	SOR	HR	P
Median overall survival	12.8 mo	10.8 mo	0.91 (95% CI 0.69-1.21)	p=0.290
Time to progression	5.3 mo	3.5 mo	0.67 (0.53-0.85)	P=0.0028
SAE	33.3%	19.8%		0.006
Grade ≥3 SAE ↑ALAT ↑bilirubin Ascites	 20.3% 11.8% 11.8%	 3.6% 3.0% 4.2%		 <0.05

Conclusions:

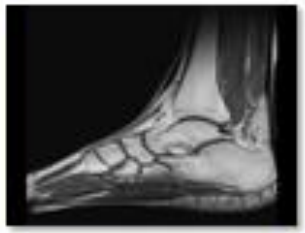
Combined TACE + sorafenib therapy did not improve OS in advanced stage HCC

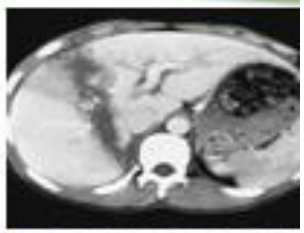
The SORAMIC trial palliative cohort: an Investigator Initiated Trial

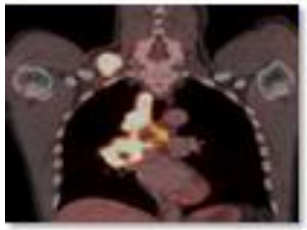
JENS RICKE FOR THE SORAMIC STUDY GROUP

Funded by SIRTeX Bayer HealthCare

Sponsored by Universität Magdeburg

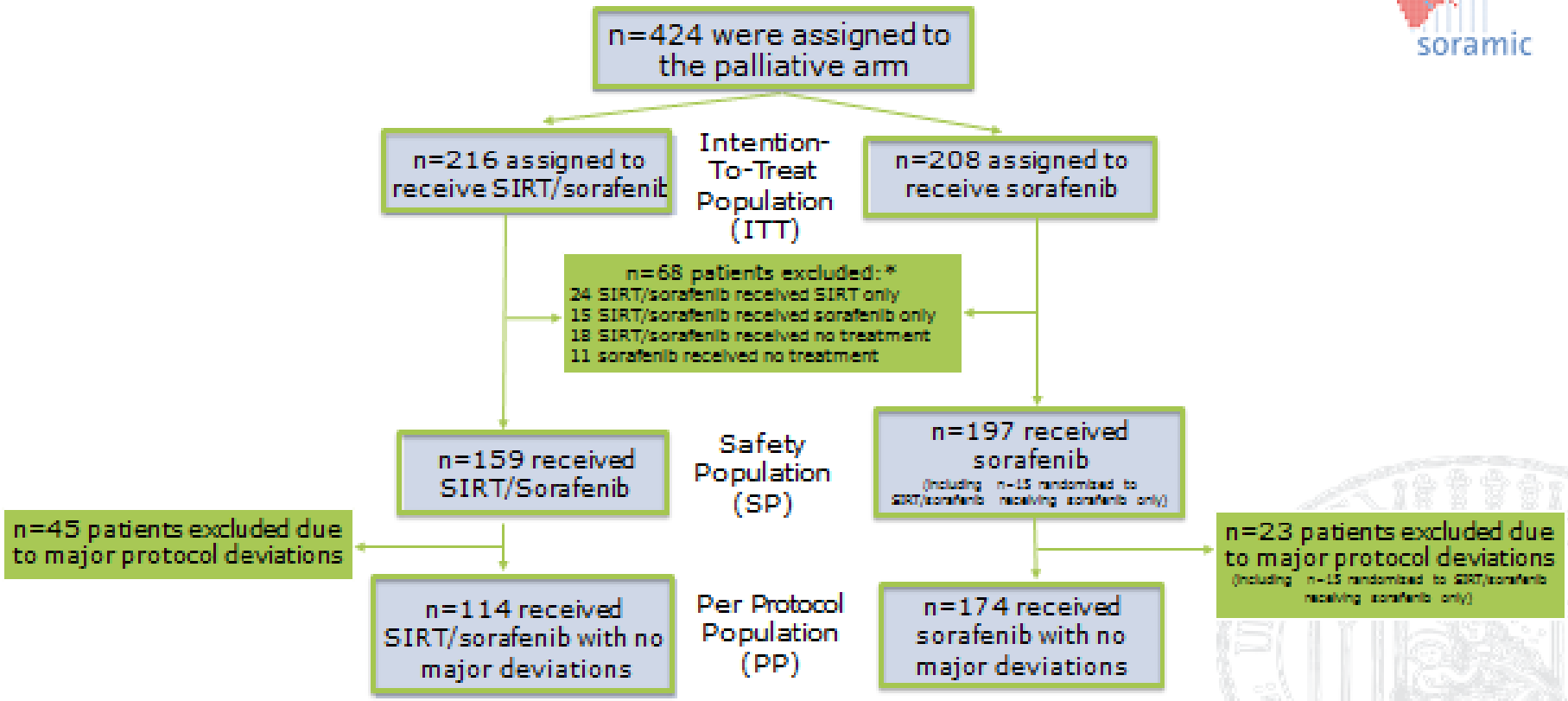






PATIENT FLOW

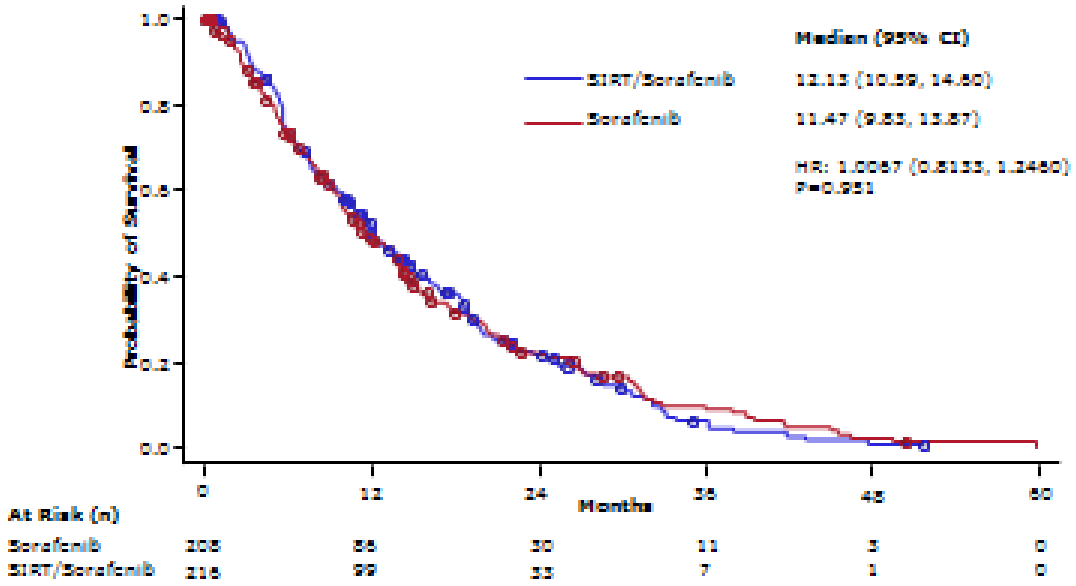
BCLC B and C patients



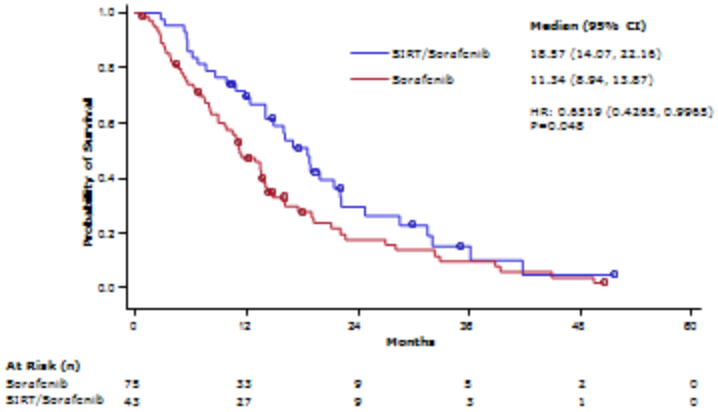
*Two sites, recruiting 38 patients, experienced major compliance issues despite diligent follow-up to implement corrective action. The data from these sites could not be recovered. The compliance issues were reported to the national authorities.

KLINIKUM DER UNIVERSITÄT MÜNCHEN*
KLINIK UND POLIKLINIK FÜR RADIOLOGIE

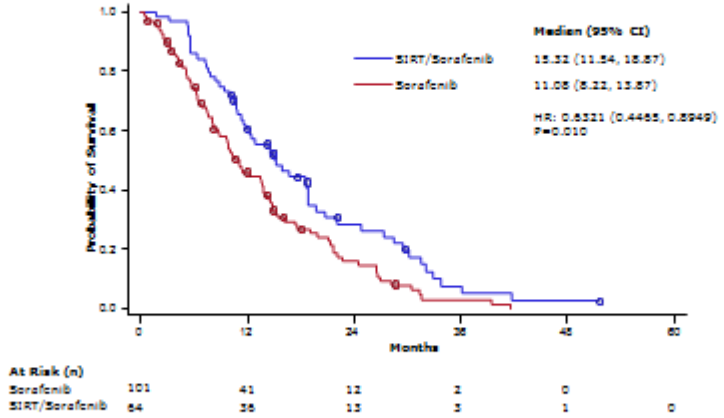
OVERALL SURVIVAL: SIRT/SORAFENIB VS SORAFENIB
(INTENT-TO-TREAT POPULATION)



OVERALL SURVIVAL: PATIENTS <65 YEARS OF AGE (PER PROTOCOL POPULATION)



OVERALL SURVIVAL: PATIENTS WITH NON-ALCOHOLIC AETIOLOGY (PER PROTOCOL POPULATION)



SUMMARY OF STUDY RESULTS PALLIATION STUDY

- The addition of SIRT to the sorafenib treatment regimen did not result in a significant improvement in survival compared to sorafenib alone
- The safety and toxicity of the SIRT/sorafenib combination was similar to sorafenib alone
- Subgroup analyses (hypothesis generating) suggest a clinical benefit for:
  - *non-cirrhotics*
  - *patients presenting with non-alcoholic aetiology*
  - *younger patients*

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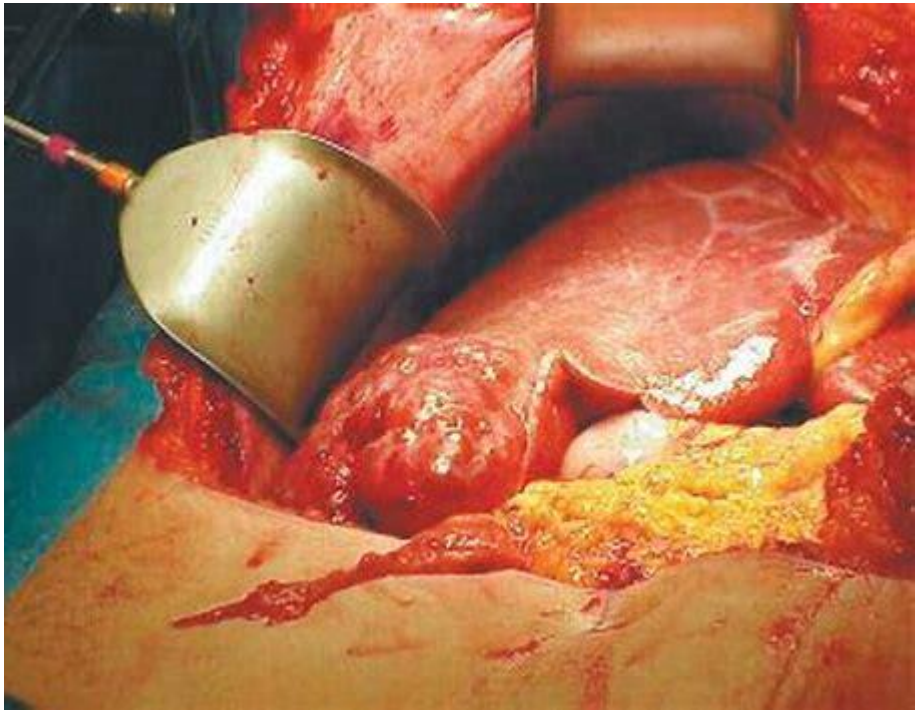
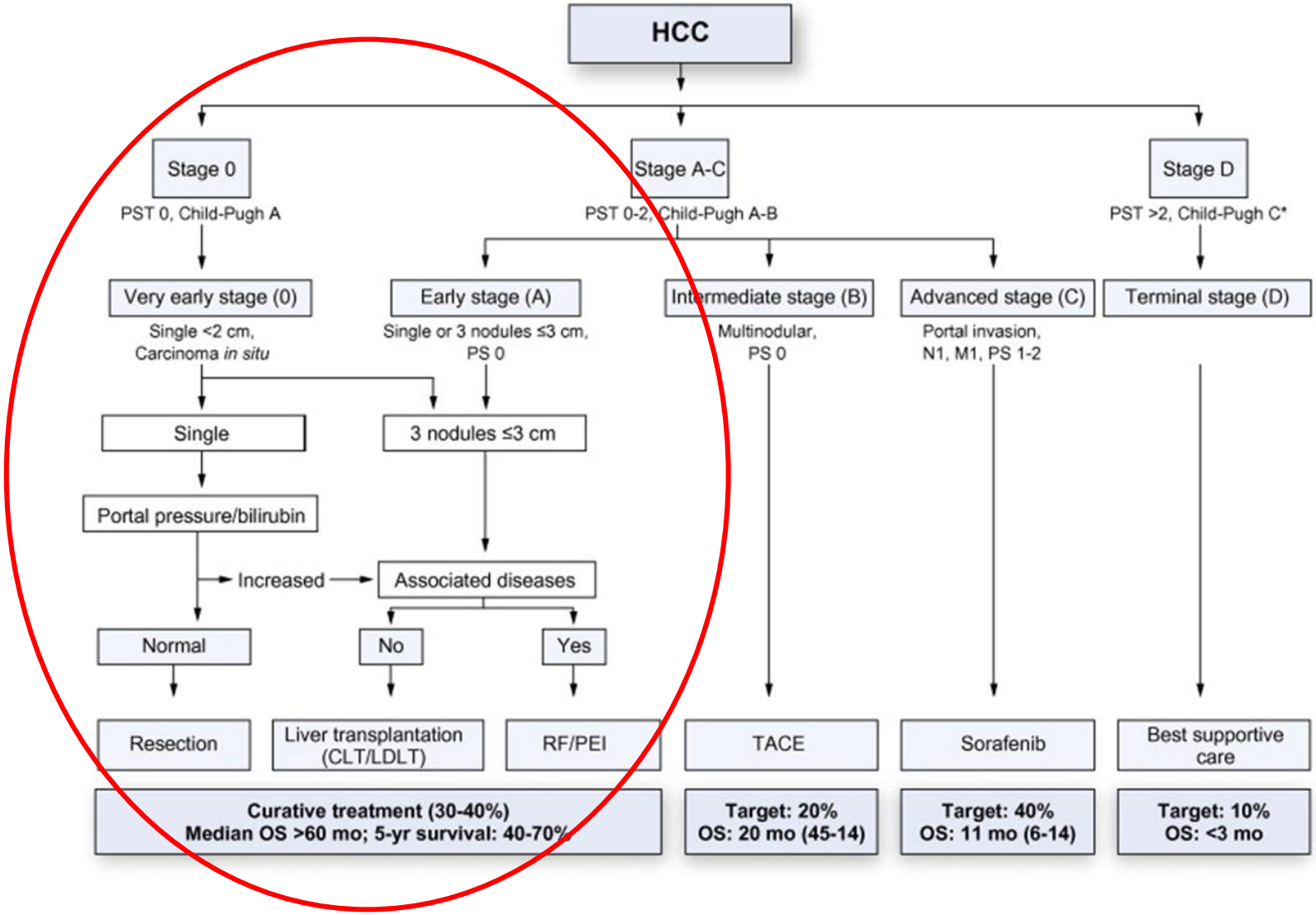
Medisch Centrum

Early stage HCC: adjuvant immunotherapy in HCC patients eligible for curative treatment




HCC
Stage 0
PST 0, Child-Pugh A
Stage A-C
PST 0-2, Child-Pugh A-B
Stage D
PST >2, Child-Pugh C*
Very early stage (0)
Single <2 cm,
Carcinoma in situ
Early stage (A)
Single or 3 nodules ≤3 cm,
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Portal invasion,
N1, M1, PS 1-2
Terminal stage (D)
Single
3 nodules ≤3 cm
Portal pressure/bilirubin
Increased
Associated diseases
Normal
No
Yes
Resection
Liver transplantation (CLT/LDLT)
RF/PEI
TACE
Sorafenib
Best supportive care
Curative treatment (30-40%)
Median OS >60 mo; 5-yr survival: 40-70%
Target: 20%
OS: 20 mo (45-14)
Target: 40%
OS: 11 mo (6-14)
Target: 10%
OS: <3 mo

Sustained Efficacy of Adjuvant Immunotherapy with Cytokine-Induced Killer Cells for HCC

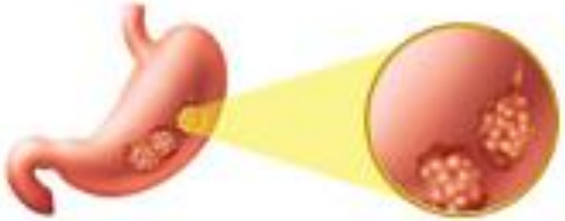
An Extended Follow-up Study of a RCT

Jeong-Hoon Lee M.D. | Ph.D.

Department of Internal Medicine and Liver Research Institute
Seoul National University College of Medicine, Seoul, Korea

GC녹십자

Early HCC (*vs.* **EGC**): early recurrence of the tumor

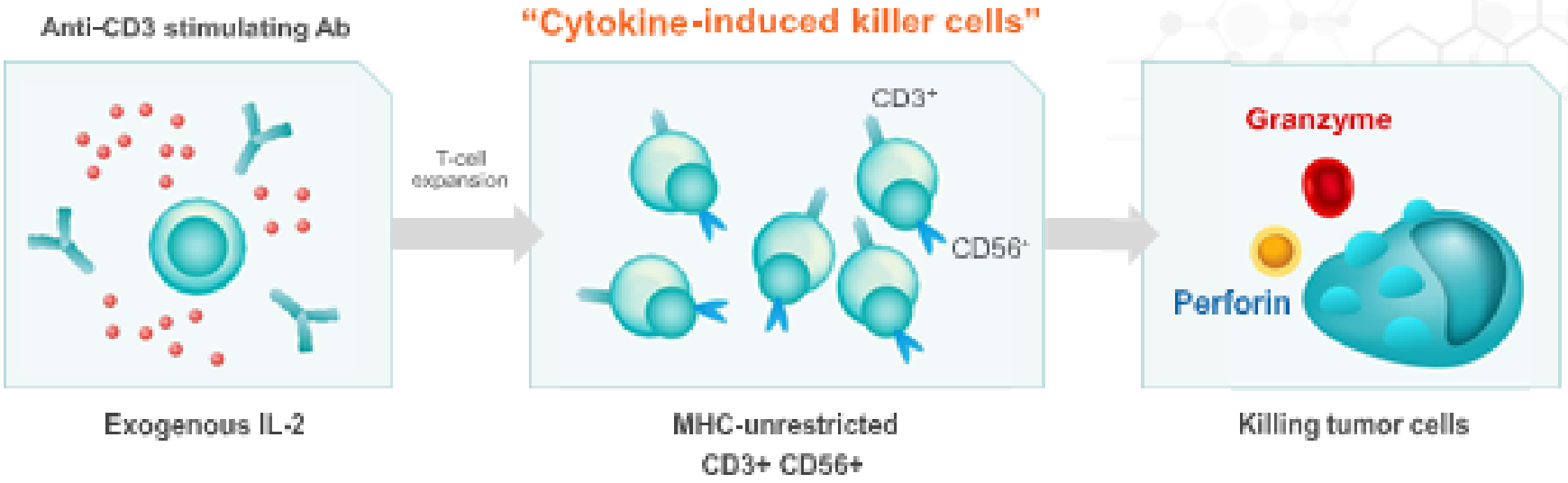
HCC	EGC
	
after curative treatment (resection, RFA, or PEI)	**after curative resection**
5 YSR: 76.1%	5 YSR: >90% (mucosal tumor, ~ 100%; submucosal tumor, 80-90%)
5 yr RFS: **29.1%**	5 yr RFS: **97.8%**
Cho EJ et al. Clin Cancer Res. 2013;19:4218-27.	Youn HG et al. Ann Surg Oncol. 2010;17:448-54.

No adjuvant therapy proven to reduce the risk of HCC recurrence

CIK cells

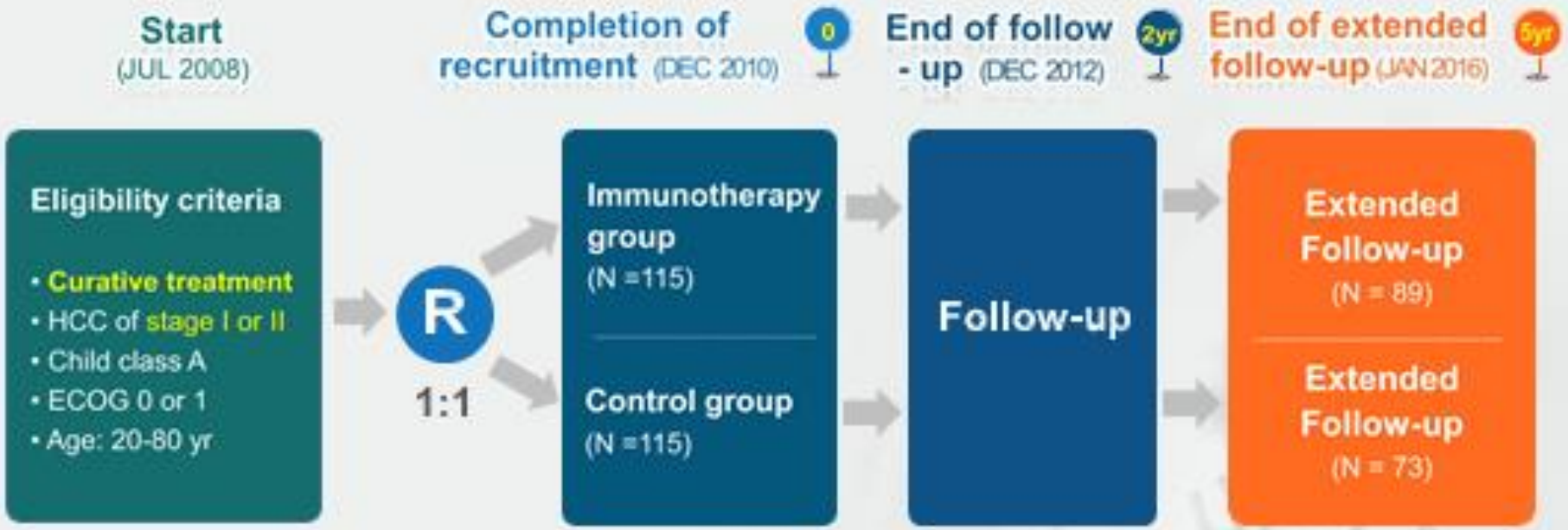
Cytokine-induced killer (CIK) cells

ex vivo expanded autologous **T cells** (with anti-CD3 mAb, IL-2)
with **NK cell** functions (non-MHC-restricted)



Extended Follow-up Study: Study Design

ClinicalTrials.gov number: NCT01890291



* Median follow-up duration: 68.5 months (IQR, 45.0-82.2)

← Original study: 38.0 months

Primary endpoint: RFS
Secondary endpoints: OS, cancer-specific survival

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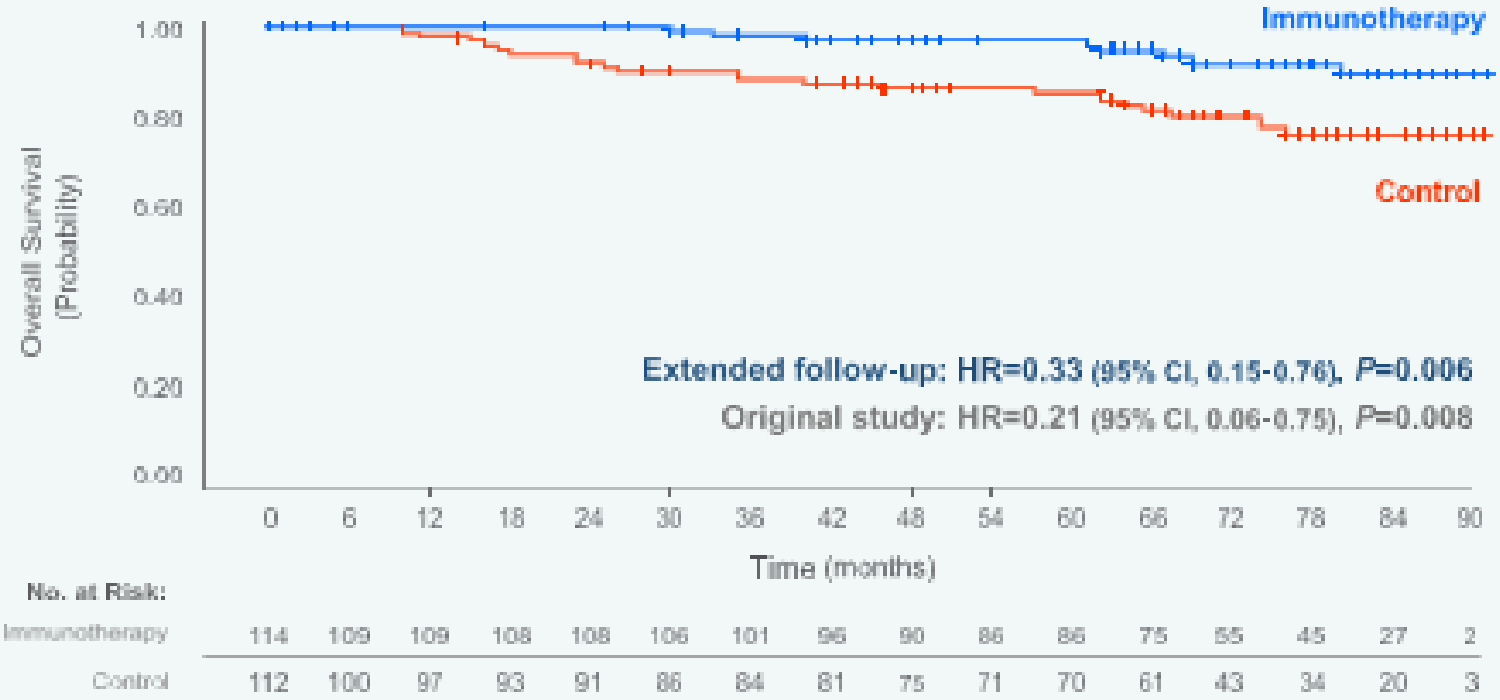
Baseline Characteristics

Results

Variable	Immunotherapy (n = 114)	Control (n = 112)	P Value
Sex, male, N (%)	**95** (83.3)	**91** (81.3)	**0.68**
Age, years, mean (SE)	**55.4** (8.2)	**56.4** (10.6)	**0.41**
Treatment modality, N (%)			**0.06**
PEI	**13** (11.4)	**4** (3.6)	
RFA	**69** (60.5)	**70** (62.5)	
Surgical resection	**32** (28.1)	**38** (33.9)	
HCC stage, N (%)			**0.67**
Stage I	**98** (86.0)	**94** (83.9)	
Stage II	**16** (14.0)	**18** (16.1)	
Size of HCC, cm, median (IQR)	**1.8** (1.4–2.3)	**2.3** (1.5–3.1)	**0.03**
Cirrhosis, N (%)	**76** (66.7)	**70** (62.5)	**0.51**
Platelet, $\times 10^3/mm^3$, median (IQR)	**117** (92–158)	**141** (118–166)	**0.01**

Overall Survival



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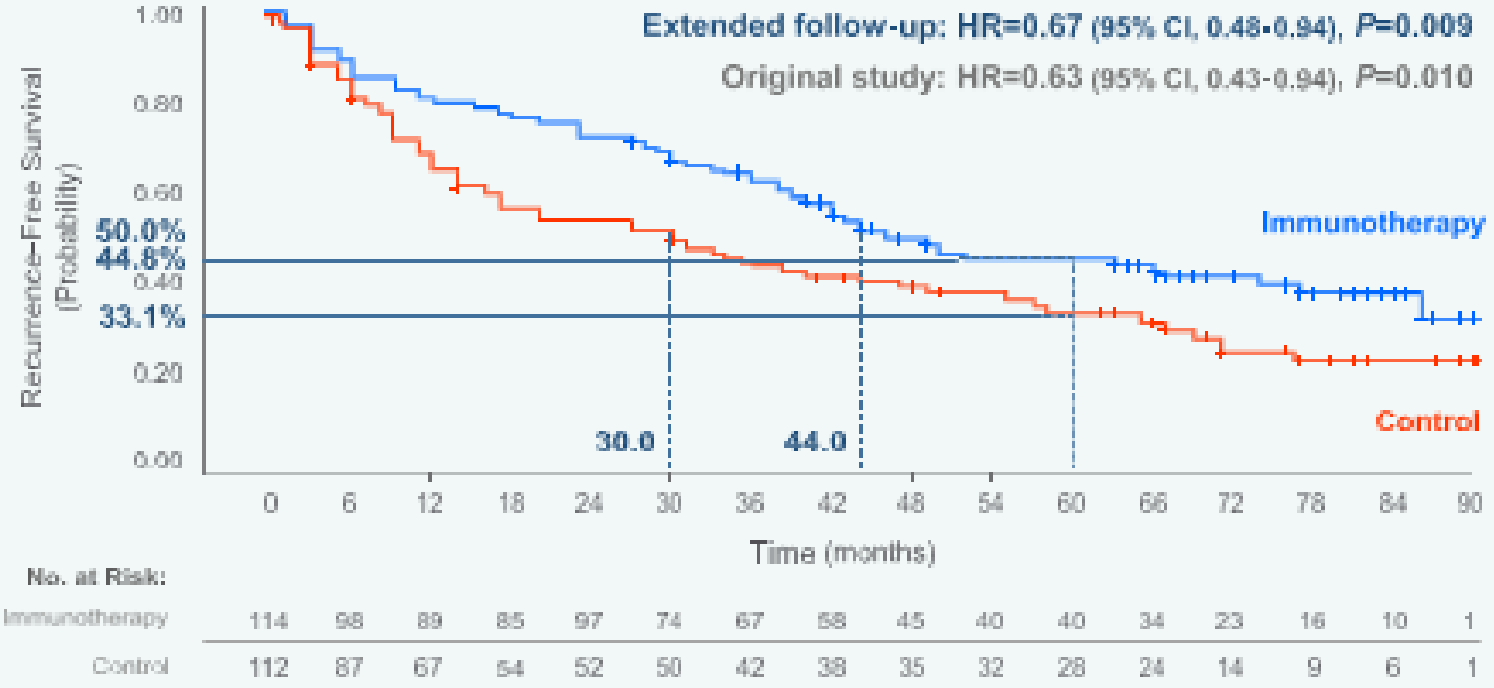
Recurrence-Free Survival



Median RFS: 44.0 mo vs 30.0 mo

5-YR RFS rate: 44.8% vs 33.1%

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Summary

Adjuvant autologous CIK cell immunotherapy

▲ RFS, OS, and cancer-specific survival

Sustained during an extended follow-up period

- ▼ 33% risk of recurrence or death
- ▼ 67% risk of overall death

CIK cells might have a prolonged antitumor activity

- Long-lasting memory T cells
- Memory NK cells
- CIK cells itself as a terminally differentiated memory T cells

Recommendations for the management of women with suspected hepatocellular adenoma&childbearing potential

Aim: assess accuracy of diagnostics of liver lesion in women with childbearing potential

Methods: Pregnancy and Liver adenoma Management (PALM) study, multicenter prospective cohort study

Results:
57 women with suspected hepatocellular adenomas
median size 25 mm
CE-MRI confirmed HCA 48/57 (84%); 9/57 (16%) Focal Nodular Hyperplasia

Conclusion:
Large proportion of childbearing women suspected of having HCA appears to have FNH. State of art imaging warranted

Original Study: Adverse Events

	Immunotherapy (n=115)				Control (n=115)			
	All AE		TEAE		All AE		*P* value	
Adverse events	**Any grade**	Grade 3 or 4	**Any grade**	Grade 3 or 4	**Any grade**	Grade 3 or 4	**Any grade**	Grade 3 or 4
Overall	71 (62%)	7 (6%)	40 (35%)	0	47 (41%)	4 (4%)	.002	.35
Vomiting	3 (3%)	0	1 (1%)	0	3 (3%)	1 (1%)	1.00	1.00
Chills	10 (9%)	0	9 (8%)	0	0	0	.001	NA
Fatigue	11 (10%)	0	3 (3%)	0	3 (3%)	0	.03	NA
Pyrexia	13 (11%)	0	10 (9%)	0	0	0	<.001	NA
URI	7 (6%)	0	0	0	3 (3%)	0	.20	NA
Headache	3 (3%)	0	2 (2%)	0	1 (1%)	1 (1%)	.62	1.00
Productive cough	6 (5%)	0	0	0	0	0	.03	NA

But, no difference in serious AE (7.8% *vs* 3.5%, P=0.15)

Lee JH et al. Gastroenterology 2015;148:1383-91. 11

KEY PATIENT SELECTION CRITERIA PALLIATION STUDY

Inclusion criteria:

- Child Pugh A through B7
- BCLC B (not eligible for TACE per investigator decision) and C
- Prior resection (transplant excluded) or vascular (PEI, TAE, TACE, RFA) procedures permitted
  - *Post TACE/TAE: >3 months interval and revascularization present*
  - *Extra-hepatic disease (excluding pulmonary metastases) permitted*

Exclusion criteria:

- Bilirubin above 1.5 times the upper limit of the normal range
- Hepato-pulmonary shunt leading to a lung dose >30 Gy
- any previous external beam radiation therapy to the liver
- previous therapy with monodonal antibodies