2020 VIRTUAL GI AND LIVER SYMPOSIUM

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Update: HCC Abstracts from AASLD/EASL

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Disclosure

- Consultant/Advisory board for Exact Sciences and Gilead Sciences

Digital Liver Meeting/ILC 2020

- HCC epidemiology & risk factor
- HCC biomarker
- HCC treatment

Rural-Urban disparities in HCC Incidence

- Incidence of HCC increased over the past 3 decades in the US
- More recent study showed overall incidence rates of HCC started declining
- Rural-urban disparities were seen in other cancers including colon cancer, but not known in HCC.
- Aim to investigate the rural-urban disparity in HCC incidene rates using North American Association of Central Cancer Registries

Gainey et al. Liver meeting #136

Rural-Urban disparities in HCC Incidence

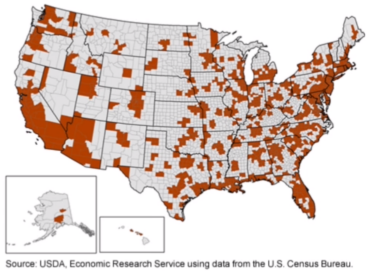
North American Association of Central Cancer Registries (NAACCR)

- 93% of US population

USDA Rural-Urban Continuum Code

- Based on population size and proximity to metropolitan area

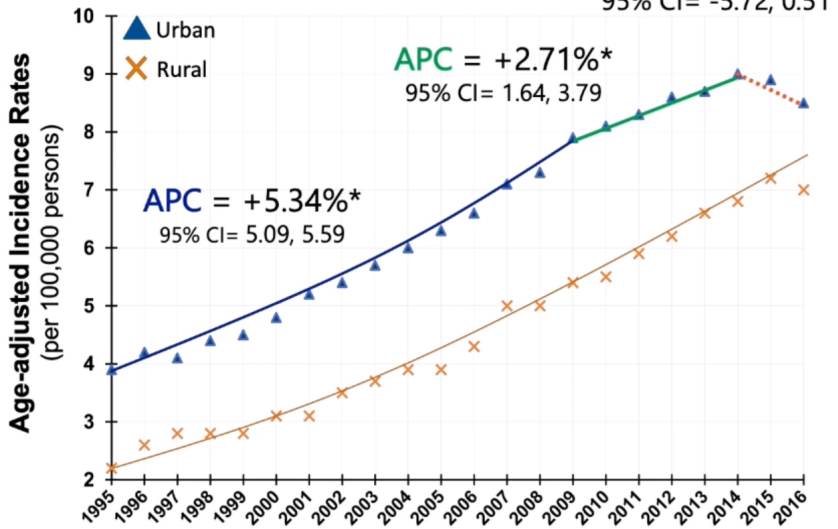
USDA 2013
metro/nonmetro counties



HCC age-adjusted incidence trends, 1995-2016

By rural/urban status

Since 2009, the rise in urban incidence has slowed



Conclusion
There was a striking rural-urban disparity in HCC incidence trend

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Black race and HCV-HCC

- Black patients with HCC have higher mortality
- Black patients with HBV can develop HCC at an earlier age in non-cirrhotic liver
- Black patients with HCV may develop HCC in non-cirrhotic liver
- Aim to compare the difference in liver dysfunction and tumor extent at HCC diagnosis between Black vs. non Black patients

Black race and HCV-HCC

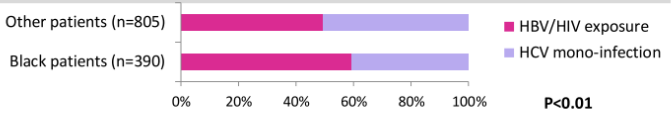
Single center
Retrospective cohort study
2003-2018

All HCC patients with HCV (N=1,195)

Racial and ethnic data on the study population

All patients	Black patients n=390	Other patients n=805	p value
Tumor size (cm), median (IQR)	3.5 (2.2-6.2)	3.1 (2.1-5.1)	<0.01
Number of tumors, median (IQR)	1 (1-3)	1 (1-2)	0.03
Gross vascular invasion	82 (21.2%)	147 (18.3%)	<0.01
Metastasis	40 (10.6%)	53 (7.1%)	<0.01
Within Milan Criteria at diagnosis	206 (53.0%)	475 (59.1%)	0.04
MELD score at diagnosis	9 (7-14)	10 (7-16)	0.02
CHILD PUGH at diagnosis A	270 (69.4%)	466 (58.5%)	
CHILD PUGH at diagnosis B	96 (24.7%)	231 (28.9%)	<0.01
CHILD PUGH at diagnosis C	23 (5.9%)	103 (12.9%)	
FIB-4 score at diagnosis	4.66 (2.94-7.52)	6.54 (3.99-10.53)	<0.01
FIB-4 < 3.25	122 (31.3%)	143 (17.8%)	<0.01
Platelet (10^3/uL)	144 (100-202)	105 (69-155)	<0.01
Bilirubin (mg/dL)	0.9 (0.6-1.5)	1.2 (0.7-2.2)	<0.01
INR	1.2 (1.1-1.4)	1.1 (1.0-1.3)	<0.01

All patients: HBV/HIV exposure



HCV Mono-infection	Black patients n=117	Other patients n=313	p value
Tumor size (cm), median (IQR)	3.5 (2.1-5.8)	2.9 (2.1-4.8)	0.19
FIB-4 score < 3.25	31 (26.5%)	57 (18.2%)	0.05
MELD score, median (IQR)	5.6 (3.2-8.1)	6.6 (4.1-10.6)	0.01
Platelets (10^3/mm^3), median (IQR)	135 (100-196)	99 (67-144)	<0.01
Bilirubin (mg/dL), median (IQR)	1.1 (0.6-1.7)	1.2 (0.7-2.3)	0.03
INR median (IQR)	1.1 (1-1.3)	1.2 (1.1-1.4)	0.02
Within Milan Criteria at diagnosis	61 (52.1%)	195 (62.3%)	0.05

Conclusion

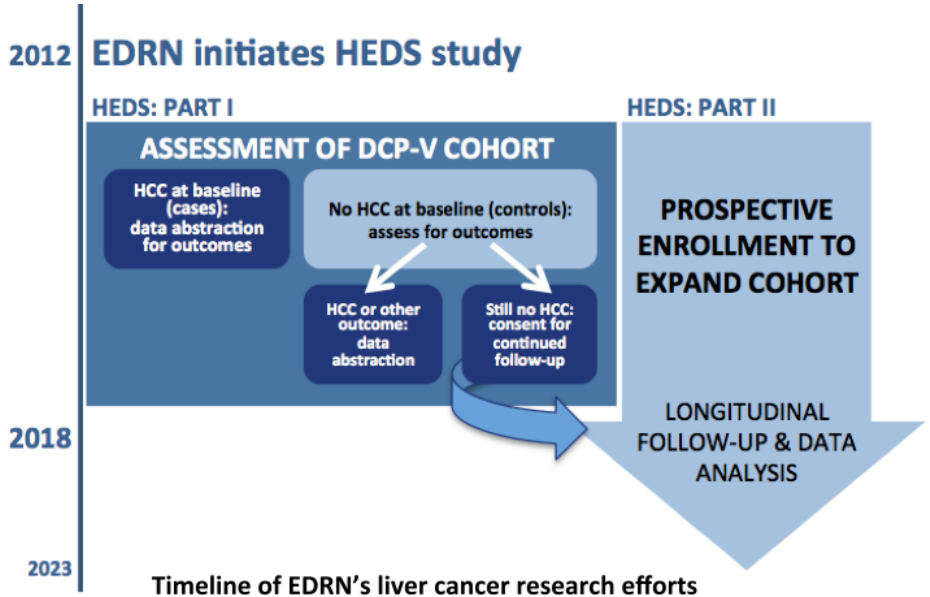
Black HCC patients

- present with larger tumors and less fibrotic liver
- may need different surveillance recommendation

Shaltiel et al. Liver meeting #1053

HCC early detection strategy (HEDS) study

- First multicenter (8 centers) prospective phase 3 biomarker cohort in the US
- NIH Early Detection Research Network (EDRN)
- Aim to prospectively assess the incidence of HCC and determine predictors of HCC in cirrhosis patients



Timeline of EDRN's liver cancer research efforts
EDRN: Early Detection Research Network
DCP-V: Des-carboxy Prothrombin Validation Study

Reddy et al. Liver meeting #1057

HCC early detection strategy (HEDS) study

	Non-HCC controls (n=1472)	HCC cases (n=87)	Total (n=1559)	P value
Male, n (%)	**781 (53.1)**	**65 (74.7)**	**846 (54.3)**	**<0.0001**
BMI (kg/m2)				
Median (25th percentile, 75th percentile	**30.0 (26.3, 35.0)**	**33.0 (27.8, 37.1)**	**30.1 (26.3, 35.1)**	**<0.01 (nonpar)**
Min, max	**12.3, 85.0**	**18.1, 48.3**	**12.3, 85.0**	**<0.05 (ttest)**
Race, n (%)				
White or Caucasian	1236 (85.6)	72 (82.8)	1308 (85.4)	0.23
Black or African-American	98 (6.8)	7 (8.0)	105 (6.9)	
Asian	32 (2.2)	0 (0.0)	32 (2.1)	
Other	78 (5.4)	8 (9.2)	86 (5.6)	
Ethnicity, n (%)				
Hispanic or Latino	153 (10.5)	8 (9.3)	161 (10.4)	0.86
Age (y)				
Median (25th percentile, 75th percentile	60 (54, 65)	62 (56, 66)	60 (54, 65)	0.03 (nonpar)
Min, max	**18, 87**	**29, 77**	**18, 87**	**<0.05 (ttest)**
Etiology of liver disease, n (%)				
History of HCV infection	614 (41.7)	44 (50.6)	658 (42.2)	0.12
Treated for HCV	430 (80.2)	33 (89.2)	463 (80.8)	0.28
SVR achieved	187 (48.3)	15 (53.6)	202 (48.7)	0.70
SVR achieved with DAA therapy	74 (67.3)	6 (85.7)	80 (68.4)	0.43
SVR achieved vs no SVR or untreated	187 (37.9)	15 (46.9)	202 (38.5)	0.35
HBV infection	37 (2.5)	2 (2.3)	39 (2.5)	1.00
HBV therapy exposed	23 (63.9)	1 (50.0)	24 (63.2)	1.00
NASH	322 (21.9)	15 (17.2)	337 (21.6)	0.35
Alcoholic Liver Disease	303 (20.6)	22 (25.3)	325 (20.8)	0.28
Autoimmune hepatitis	88 (6.0)	2 (2.3)	90 (5.8)	0.24
Cholestatic liver disease (PBC,PSC)	111 (7.5)	5 (5.8)	116 (7.4)	0.68
Other (Hemochromatosis, Wilson's, etc)	96 (6.5)	6 (6.9)	102 (6.5)	0.83
Alcohol use, n current (%)	146 (10.1)	9 (10.5)	155 (10.1)	0.86
Tobacco use, n (%)	817 (55.7)	60 (69.0)	877 (56.5)	0.02
Medications of interest, n ever taken (%)				
Statins	367 (25.6)	23 (26.7)	390 (25.7)	0.80
Metformin	194 (23.8)	10 (25.6)	204 (23.9)	0.85

- After median follow up of 3 years, 87 developed HCC with incidence rate of 2.7% per year
- 55 early, 20 intermediate-advanced, and 12 unknown stage

Predictor	Complete Data Models			
	Sig. Predictors From Full Set†	Stepwise Selection	Forward Selection	Backward Elimination
Female	0.36 (0.21, 0.63)	0.34 (0.20, 0.59)	0.33 (0.20, 0.57)	0.34 (0.20, 0.59)
Age (per 5 year change)	1.22 (1.05, 1.41)	1.18 (1.02, 1.36)	1.18 (1.03, 1.37)	1.18 (1.02, 1.36)
Log(BMI)	**4.30 (1.38, 13.5)**	**4.34 (1.43, 13.1)**	**3.90 (1.27, 11.9)**	**4.34 (1.43, 13.1)**
Log(AFP)	1.45 (1.06, 2.00)	1.60 (1.22, 2.12)	1.59 (1.20, 2.10)	1.60 (1.22, 2.12)
Albumin	NS	0.57 (0.38, 0.86)	0.58 (0.39, 0.88)	0.57 (0.38, 0.86)
Family Hist. of HCC or Liver Disease	NS	—	1.67 (0.99 2.82)	—
Esophageal Varices	NS	1.80 (1.10, 2.96)	1.72 (1.04, 2.84)	1.80 (1.10, 2.96)

Conclusion

- 2.7% incidence rate of HCC
- Male sex, older age, higher BMI and AFP were independent predictors of HCC

Reddy et al. Liver meeting #1057

Carvedilol and risk of HCC in the US

Carvedilol (Coreg)

- Alpha 1 and nonselective Betablocker
- Primary prophylaxis for esophageal variceal bleeding
- Decreased GI, GU and lung cancer

Aim

- To study the association between Coreg and HCC in cirrhosis patients

Method

- Cerner Health Fact database
- Propensity score matching
- Logistic regression analysis

Results

- 124,361 cirrhosis pts
- 9% Coreg, 9% Propranolol, and 5% for nadolol
- Incidence of HCC
  - 1.74% (carvedilol) vs.
  - 4.32% (propranolol) vs.
  - 4.33% (nadolol) vs.
  - 4.35% (no beta-blocker)

Carvedilol and risk of HCC in the US

Disease Groups	Medication	Before matching		After matching		Before matching		After matching	
		Univariate analysis OR (95% CI)	P value	Univariate analysis OR (95% CI)	P value	Multivariate analysis OR (95% CI)	P value	Multivariate analysis OR (95% CI)	P value
Cirrhosis (n= 124,361)	no beta-blockers (n=95,943)	Reference		Reference		Reference		Reference	
	Carvedilol (n=11,574)	0.39 (0.34 - 0.45)	<0.001*	0.37 (0.32 - 0.43)	<0.001*	0.37 (0.32 - 0.43)	<0.001*	0.40 (0.34 - 0.47)	<0.001*
	Propranolol (n=11,100)	0.99 (0.90 - 1.09)	0.898	0.95 (0.85 - 1.06)	0.368	0.90 (0.81 – 0.99)	0.030*	0.89 (0.79 -0.99)	0.041 *
	Nadolol (n=5,744)	1.00 (0.87 - 1.14)	0.955	0.95 (0.82 - 1.11)	0.499	0.91 (0.80 - 1.04)	0.166	0.88 (0.75 - 1.03)	0.111
Cirrhosis with complications (n=68,346)	no beta-blockers (n=47,172)	Reference				Reference			
	Carvedilol (n=6,254)	0.35 (0.30 - 0.41)	<0.001*	0.33 (0.28 - 0.40)	<0.001*	0.32 (0.27 - 0.38)	<0.001*	0.33 (0.27 -0.40)	<0.001*
	Propranolol (n=9,682)	0.68 (0.62 - 0.76)	<0.001*	0.68 (0.61- 0.76)	<0.001*	0.63 (0.57 - 0.70)	<0.001*	0.64 (0.57 - 0.71)	<0.001*
	Nadolol (n=5,238)	0.64 (0.56 - 0.73)	<0.001*	0.64 (0.55 - 0.74)	<0.001*	0.60 (0.53 - 0.69)	<0.001*	0.60 (0.52 - 0.70)	<0.001*
Cirrhosis without complications (n=56,015)	no beta-blockers (n=48,771)	Reference				Reference			
	Carvedilol (n=5,320)	0.43 (0.32 - 0.58)	<0.001*	0.36 (0.26 - 0.50)	<0.001*	0.42 (0.31 - 0.58)	<0.001*	0.45 (0.31 – 0.65)	<0.001*
	Propranolol (n=1,418)	0.51 (0.30 - 0.87)	0.014*	0.49 (0.27 - 0.88)	0.016 *	0.53 (0.31 – 0.91)	0.021*	0.50 (0.28 -0.91)	0.024*
	Nadolol (n=506)	1.25 (0.70 - 2.23)	0.446	1.04 (0.52 -2.12)	0.904	1.24 (0.69 - 2.21)	0.476	1.13 (0.54 - 2.33)	0.750
Cirrhosis with ascites (n = 41,564)	no beta-blockers (n=27,413)	Reference				Reference			
	Carvedilol (n=4,342)	0.27 (0.22 - 0.33)	<0.001*	0.26 (0.21 - 0.32)	<0.001*	0.25 (0.20 - 0.31)	<0.001*	0.27 (0.21 - 0.34)	<0.001*
	Propranolol (n=6,320)	0.69 (0.62 - 0.78)	<0.001*	0.65 (0.58 - 0.73)	<0.001*	0.59 (0.53 - 0.66)	<0.001*	0.57 (0.51 - 0.65)	<0.001*
	Nadolol (n=3,489)	0.68 (0.58 - 0.78)	<0.001*	0.68 (0.58 -0.81)	<0.001*	0.59 (0.51 - 0.69)	<0.001*	0.60 (0.51 - 0.72)	<0.001*
Cirrhosis with varices (n=32,999)	no beta-blockers (n=20,440)	Reference				Reference			
	Carvedilol (n=1,768)	0.46 (0.37 - 0.58)	<0.001*	0.48 (0.37 - 0.62)	<0.001*	0.37 (0.29 - 0.47)	<0.001*	0.44 (0.33 0.58)	<0.001*
	Propranolol (n=6,924)	0.59 (0.52 - 0.66)	<0.001*	0.57 (0.51 - 0.64)	<0.001*	0.55 (0.49 - 0.62)	<0.001*	0.54 (0.48 - 0.61)	<0.001*
	Nadolol (n=3,867)	0.5 (0.46 -)	<0.001*	0.54 (0.46 0.63)	<0.001*	0.51 (0.43 - 0.59)	<0.001*	0.51 (0.43 - 0.61)	<0.001*

Conclusion

- Carvedilol was associated with lower risk of HCC compared to other nonselective betablocker and no betablocker.
- RCT is needed.

Wijarnpreecha et al. Liver meeting #1037

Elecsys PIVKA-II and AFP for HCC detection

PIVKA-II

- Normal hepatocytes post-translationally carboxylate prothrombin precursors before secretion.
- DCP is a secreted non-carboxylated immature form of prothrombin.
- Unconverted glutamic acid residues are due to an absence in many HCC cells of vit. K dependent carboxylase.
- Potential serum based marker for early stage HCC detection

Aim

- To investigate clinical performance of PIVKA-II for detection of HCC using Elecsys PIVKA-II immunoassay

Method

Multicenter prospective study from 5 countries (China, Japan, Germany, Thailand and Japan)

Chan et al. Liver meeting #1124

Elecsys PIVKA-II and AFP for HCC detection

Table 1. Participant demographics and clinical characteristics

Characteristic	All (N=376)	Control (n=208)	HCC (n=168)
Mean ± SD age, years	56.95 ± 12.42	52.18 ± 12.27	62.86 ± 9.82
Male, n (%)	267 (71.0)	126 (60.6)	141 (83.9)
Race, n (%)			
Asian	170 (45.2)	99 (47.6)	71 (42.3)
White	196 (52.1)	101 (48.6)	95 (56.6)
Black or African American	3 (0.8)	3 (1.4)	0
Other	1 (0.3)	0	1 (0.6)
Missing	6 (1.6)	5 (2.4)	1 (0.6)
Disease etiology, n (%)			
Cirrhosis	218 (58.0)	79 (38.0)	139 (82.7)
HBV	86 (22.9)	72 (34.6)	14 (8.3)
HCV	30 (8.0)	27 (13.0)	3 (1.8)
NASH	31 (8.2)	30 (14.4)	1 (0.6)
ALD	2 (0.5)	0	2 (1.2)
Other	9 (2.4)	0	9 (5.4)
BCLC stage, n (%)			
0	–	–	10 (6.0)
A	–	–	67 (39.9)
B	–	–	26 (15.5)
C	–	–	57 (33.9)
D	–	–	8 (4.8)

Figure 2. ROC plot of Elecsys PIVKA-II for discriminating between HCC patients and disease controls, overall and by etiology group

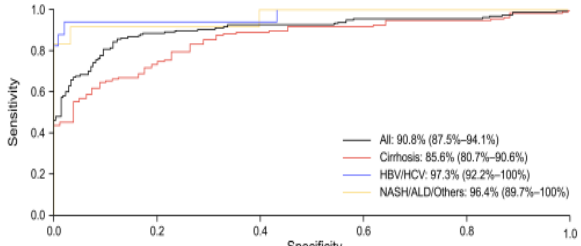


Figure 1. Distribution of PIVKA-II and AFP according to HCC BCLC disease stage

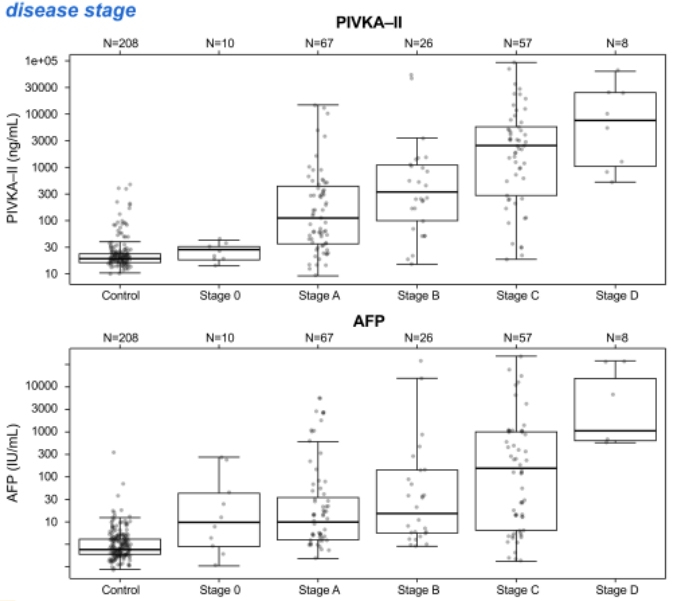


Table 3. Clinical performance of Elecsys PIVKA-II and Elecsys AFP assays by HCC BCLC stage

Assay (cut-off)	Metric, % (95% confidence interval)	HCC BCLC stage: Early (n=77)	Late (n=91)	Overall (n=168)
PIVKA-II (28.4 ng/mL)	Sensitivity	77.9 (67.0–86.6)	94.5 (87.6–98.2)	86.9 (80.8–91.6)
	Specificity	83.7 (77.9–88.4)	83.7 (77.9–88.4)	83.7 (77.9–88.4)
AFP (20 ng/mL)	Sensitivity	36.4 (25.7–48.1)	64.8 (54.1–74.6)	51.8 (44.0–59.5)
	Specificity	98.1 (95.1–99.5)	98.1 (95.1–99.5)	98.1 (95.1–99.5)

Combination of 2 markers
- 92% sensitivity
- 82% specificity

Conclusion
- Elecsys PIVKA-II and AFP are good blood based marker for HCC detection
- Combining AFP and PIVKA-II may further increase diagnostic performance

Chan et al. Liver meeting #1124

AFP-L3 and DCP predict waitlist Dropout

AFP L3 and DCP

- Elevated AFP is associated with increased waitlist dropout.
- AFP L3 and DCP play a role in HCC detection, but their ability to detect LT waitlist drop out is unknown.

Aim

- To evaluate the correlation between three biomarkers (AFP, AFP-L3, DCP) and LT waitlist dropout

Method

- Prospective single center cohort study from UCSF since July 2017
- Three marker levels were measured at the time of listing for OLT

AFP-L3 and DCP predict waitlist Dropout

Table 1. Demographic and Clinical Characteristics (N=258)	
Age (median, years)	63.2 (IQR 58.1-66.7)
Women	63 (24%)
Median number of HCC lesions at diagnosis	1 (IQR 1-2)
Median total tumor diameter at listing with MELD exception or before LRT (cm)	3.0 (IQR 2.2-4.6)
Tumor stage (worst classification)	
Milan criteria	210 (81%)
Downstaging	40 (15%)
All-comers	8 (3%)
LRT ever received	248 (96%)
Median number of LRT treatments	2 (IQR 1-3)
Median AFP pre-listing (ng/mL)	7.0 (IQR 3.4-21.5)
Median AFP-L3 pre-listing (%)	7.8 (IQR 0-13.4)
Median DCP pre-listing (ng/mL)	1 (IQR 0-3.9)

Cumulative incidence of waitlist dropout at 1 year – 18.1%

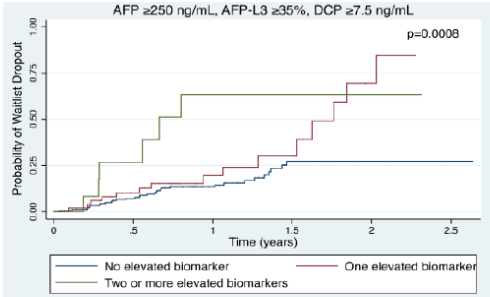
Cumulative incidence of LT at 1 year – 30.9%

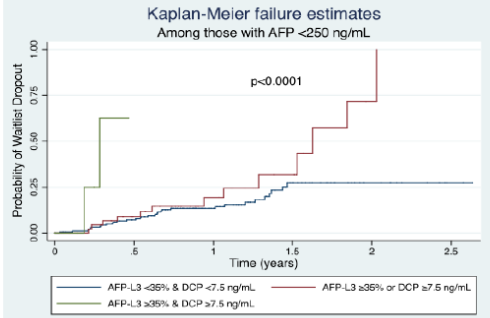
Table 2. Clinical Characteristics of those who received LT versus those who experienced waitlist dropout	LT (N=111)	Dropout (N=53)	p-value
Median total tumor diameter at listing with MELD exception/before LRT (cm)	3.1 (IQR 2.2-4.7)	2.8 (IQR 2.2-4.6)	0.55
Tumor stage (worst classification)			
Milan criteria	93 (84%)	39 (74%)	0.09
Downstaging	13 (12%)	13 (24%)	
All-comers	5 (4%)	1 (2%)	
Median MELD at listing	11 (IQR 8-16)	11 (IQR 8-15)	0.61
Time from initial diagnosis to listing (days)	184 (87-296)	234 (103-451)	0.10
AFP pre-listing ≥250 ng/mL	**3 (3%)**	**6 (11%)**	**0.02**
AFP-L3 pre-listing ≥35%	9 (8%)	8 (15%)	0.17
DCP pre-listing ≥7.5 ng/mL	26 (23%)	14 (26%)	0.68

Table 3. Univariate Analysis of Features Associated with Waitlist Dropout	Univariate OR (95% CI)	p-value
AFP pre-listing ≥250 ng/mL	**4.23 (1.31-13.72)**	**0.02**
AFP-L3 pre-listing ≥35%	**2.25 (0.90-5.64)**	**0.08**
DCP pre-listing ≥7.5 ng/mL	**1.94 (0.95-3.98)**	**0.07**
Total tumor diameter at diagnosis	0.97 (0.84-1.13)	0.73
Tumor stage at diagnosis		
Milan criteria	1	
Beyond Milan criteria	1.80 (0.88-3.68)	0.10
Number of local regional therapy treatments		0.51
0	1.42 (0.26-7.71)	
1	1	
2	1.34 (0.56-3.21)	
3	1.69 (0.65-4.39)	
≥4	2.19 (0.89-5.38)	
TACE (none vs. any)	**2.41 (1.03-5.65)**	**0.04**
RFA (none vs. any)	1.43 (0.78-2.64)	0.25
Y90 (none vs. any)	0.71 (0.32-1.55)	0.39
Ever downstaged		
No	1	
Yes	1.78 (0.83-3.77)	0.13
Time to listing after diagnosis		
≤1 year	1	
>1 year	**2.31 (1.19-4.46)**	**0.01**

P<0.1 in bold

Table 4. Multivariable Adjusted Logistic Regression of Features Associated with Waitlist Dropout	Adjusted OR (95% CI)	p-value
AFP pre-listing ≥250 ng/mL	**3.70 (1.03-13.33)**	**0.04**
AFP-L3 pre-listing ≥35%	1.29 (0.46-3.65)	0.63
DCP pre-listing ≥7.5 ng/mL	**2.12 (1.00-4.53)**	**0.05**
Time to listing >1 year	**2.36 (1.19-4.69)**	**0.01**
TACE (none vs. any)	2.21 (0.91-5.33)	0.08





Conclusion

- AFP ≥250 ng/mL and DCP ≥7.5 ng/mL prior to LT listing were predictors of waitlist dropout
- Among those with AFP <250 ng/mL, either AFP-L3 ≥35% or DCP ≥7.5 ng/mL were associated with increased risk of waitlist dropout, thus adding prognostic value to AFP alone

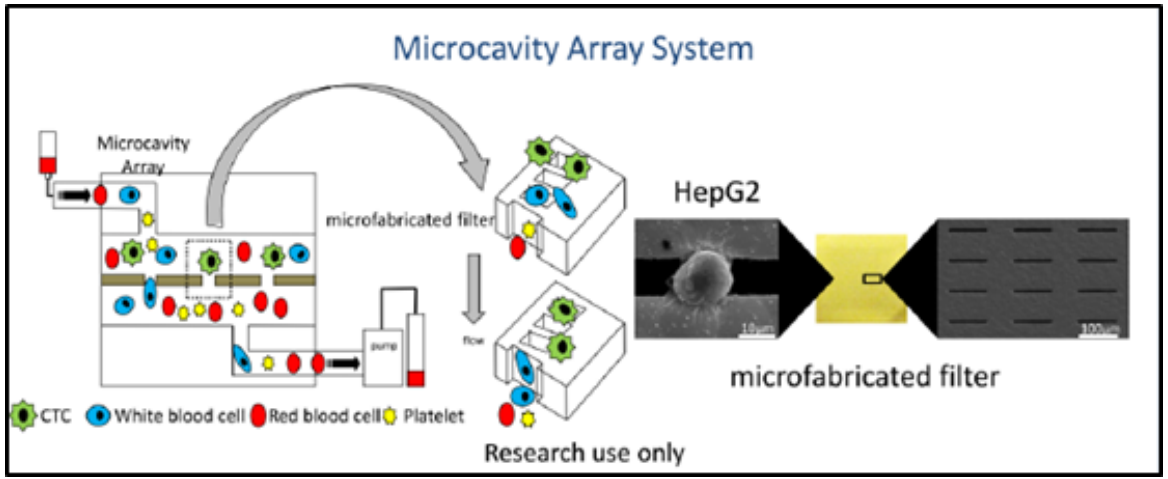
CTCs predict HCC outcome

Circulating tumor cells (CTCs)

- Cancer cells entering in blood circulation
- One of the most studied liquid biopsy tools
- Potential to monitor tumor progression and predicting clinical outcome

Microcavitary array

- Novel CTC isolation platform
- Filter based isolation technology based on physical properties (size and deformability of CTCs)
- Confirm CTC based on positivity for cytokeratin, DAPI positivity and CD45 negativity
- Downstream mRNA



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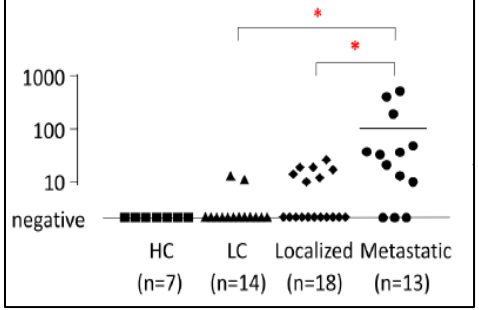
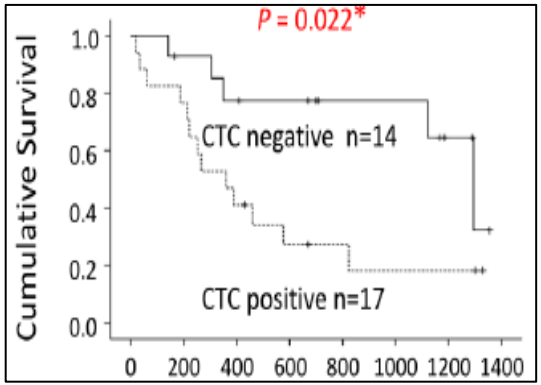
CTCs predict HCC outcome

Characteristics of Patients

	LC n=14	Localized n=18	Metastatic n=13
Sex, M/F	8/6	16/2	9/4
Age, ±SD, years	70.6±10.4	72.6±10.5	67.0±16.2
Platelets, ±SD, $\times 10^4/\mu L$	11.1±6.0	12.8±5.2	15.7±8.6
ALT, ±SD, U/mL	24.9±12.7	28.1±15.3	35.8±20.5
Etiology, n			
HBV/HCV/Alclhol/Others	0/3/6/5	3/8/5/2	4/5/2/2
AFP, ±SD, ng/mL	4.8±2.2	210.4±842.1	42716.7±68304.4
Tumor size, ±SD, mm		27.8±22.0	49.8±27.9
Tumor number, ±SD, n		2.4±1.8	7.6±3.2

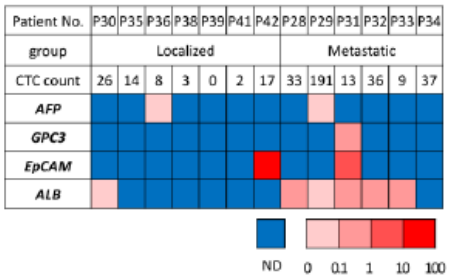
CTC Count

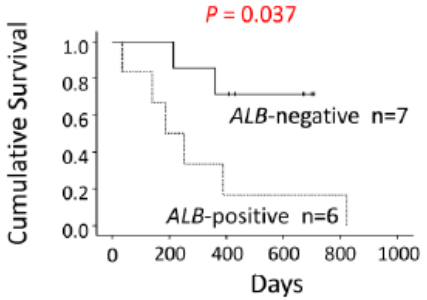




mRNA Detection in HCC Patients

Relative mRNA expression from CTCs





Conclusion

- The MCA system can isolate CTC with downstream gene expression analysis
- Patient with CTCs, particularly those with ALB gene expression are at higher risk of mortality

Takahashi et al. Liver meeting #1143

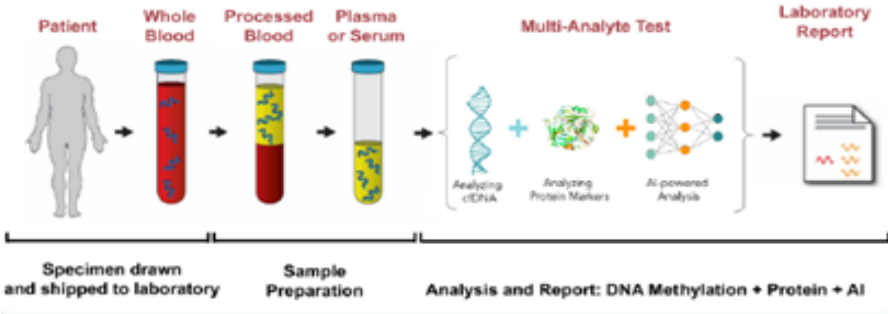
CtDNA methylation for HCC diagnosis

Circulating tumor DNA (CtDNA)

- Tumor DNA released in circulation from necrotic/proliferating cancer cells
- Liquid biopsy to monitor tumor DNA in peripheral blood
- Methylation of DNA is cancer and organ specific, useful for detecting HCC

Method

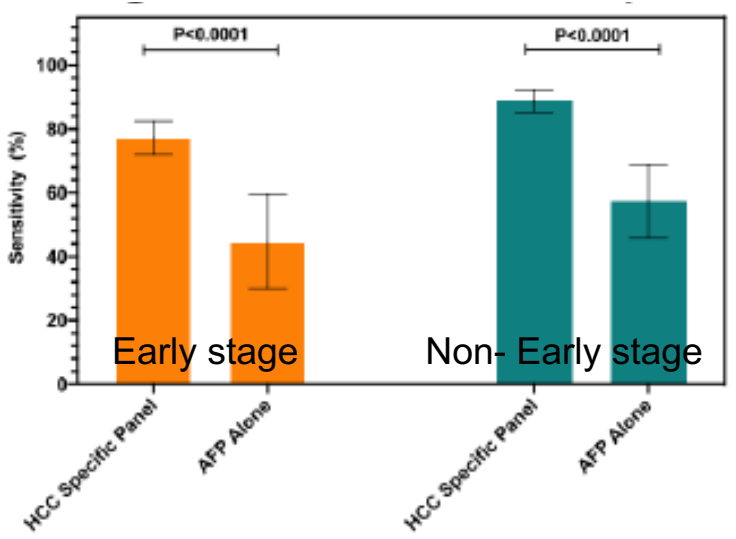
- ctDNA methylation marker+ AFP + age/sex in 631 subject with HCC (n=291), healthy control (n=340)
- ddPCR to measure ctDNA methylation
- Machine learning algorithm to build a diagnostic model

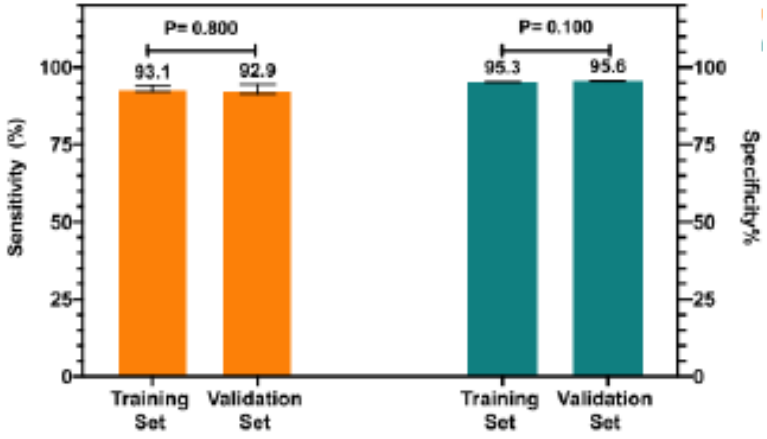


Roy et al. Liver meeting #1136

Ct DNA methylation for HCC diagnosis

	HCC						Normal Healthy
	Stage I	Stage II	Stage III	Stage IV	Unstaged	Overall	
No of participants	34	42	117	72	26	291	340
QC Failed	1	2	3	2	2	10	46
No of subjects used for analysis	33	40	114	70	24	281	294
Age, (Median, IQR)	54 [45-62]	60 [49-65]	55 [43-63]	48 [44-59]	56 [37-64]	54 [45-63]	46 [37-55]
Gender N (% of Male)	31 (93.9%)	31 (77.5%)	90 (76.9%)	55 (78.6%)	23 (95.8%)	230 (81.9%)	132 (44.9%)





Conclusion

Model combining ctDNA methylation, AFP, age, and sex have great potential for early stage HCC detection

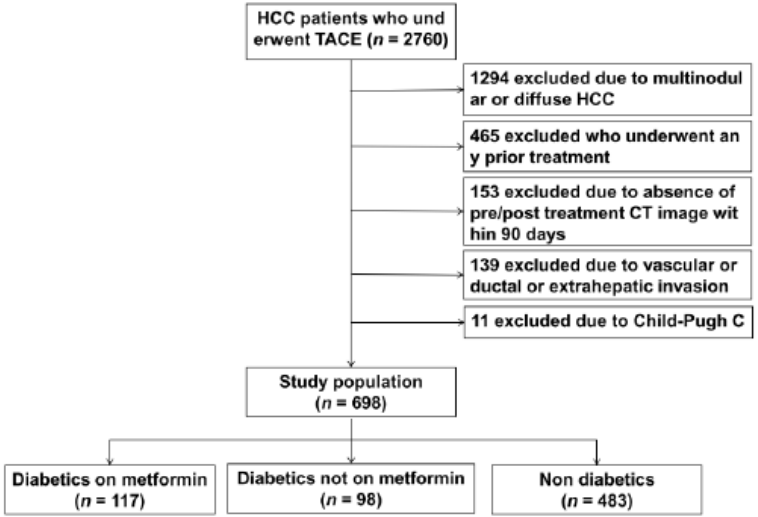
Roy et al. Liver meeting #1136

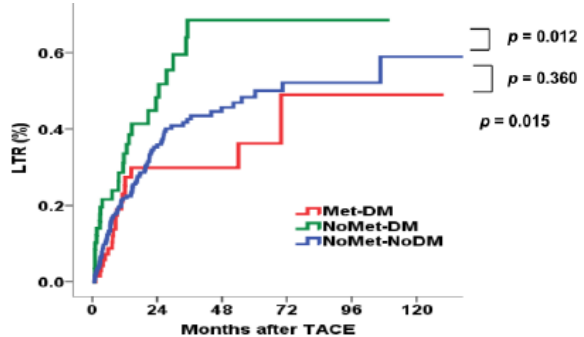
Metformin enhances antitumor effect of TACE

- Metformin decreases the risk of HCC in patients with cirrhosis
- In vitro data suggested that metformin may enhance anticancer effect of cytotoxic drug and radiotherapy in HCC cells
- Aim to investigate whether metformin enhances the therapeutic efficacy of TACE in patients with HCC
- Method
  - Single center retrospective study who underwent TACE between 2003 and 2020
  - Treatment naïve single nodule HCC
  - Logistic regression to determine predictor of treatment response
  - Cox regression to determine predictor of local tumor recurrence among diabetics

Jung et al. Liver meeting #1158

Metformin enhances antitumor effect of TACE





Predictor of tumor response

	Univariate		Multivariate	
Variables	OR(95% CI)	*P* value	OR(95% CI)	*P* value
Metformin use	2.133 (1.265-3.599)	0.005	4.895 (1.449-16.531)	0.011

Predictor of tumor recurrence

	Univariate		Multivariate	
Variables	OR(95% CI)	*P* value	OR(95% CI)	*P* value
Metformin use	0.479 (0.266-0.862)	0.014	0.334 (0.164-0.682)	0.003

Conclusion

Metformin enhances antitumor efficacy of TACE
RCT is warranted to confirm this observation

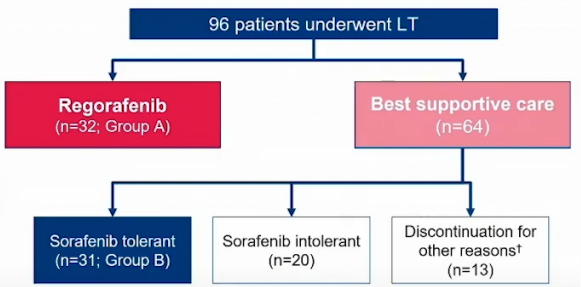
Jung et al. Liver meeting #1158

Regorafenib improves survival in post OLT recurrent HCC

- Regorafenib is a multikinase inhibitor, approved second line treatment for advanced HCC
- Regorafenib is safe and well tolerated in post OLT patient with recurrent HCC who failed sorafenib
- Aim to investigate OS with regorafenib vs. best supportive care in post OLT recurrent HCC patients after sorafenib discontinuation
- Method
  - Retrospective multicenter cohort study
  - Primary end point: OS from sorafenib discontinuation

Iavarone et al. ILC #150

Regorafenib improves survival in post OLT recurrent HCC



- Since sorafenib start
  - Median survival for the whole cohort: 19.3 months (13.4–25.1)

Parameter	Group A regorafenib Sorafenib tolerant (n=32)	Group B best supportive care Sorafenib tolerant (n=31)	p-value
Clinical and demographic features at sorafenib discontinuation were similar			
mTORi treatment, %	63	81	0.11
Sorafenib 800 mg, %	41	23	0.12
Sorafenib duration, months, median (range)	11.1 (0.7–76.7)	7.8 (0.9–96.3)	0.65
ECOG-PS 0–1, %	100	90	0.29
Tumour burden,* %	50	55	0.85
Alpha-fetoprotein, ng/mL, median (range)	134 (1–209,630)	1,044 (1–88,950)	0.83
Findings at follow-up since sorafenib discontinuation			
Median follow-up, months (range)	12.3 (0.6–42.2)	4.5 (0.0–22.3)	**0.0006**
Median overall survival,† months (95% CI)	14 (10–18)	4.5 (24–66)	**<0.005**
Median overall survival from sorafenib start, months (95% CI)	32.6 (18–46)	14.3 (7–21)	**0.001**

Conclusion

Regorafenib is a safe and effective second line option after sorafenib progression in patients with HCC recurrence after OLT

Pembrolizumab and HBV and HCV replication

Pembrolizumab

- PD-1 blocking antibody, approved for advanced HCC as a second line treatment
  - KEYNOTE-224 study: Single arm phase 2 study
  - KEYNOTE-240: Phase 3 RCT
- Limited information on HBV, HCV kinetics in HCC patients receiving immunotherapy

Objective

- To evaluate changes in viral hepatitis dynamics and flare in HCC patients receiving pembrolizumab

Method

- HBV and HCV patients enrolled in KEYNOTE-224 and 240
- Viral hepatitis flare defined by >1 log increase postbaseline and >1000 IU/mL viral load with a concurrent ALT elevation within 7 days of a viral load increase.

Chan et al. Liver meeting #1148

Pembrolizumab and HBV and HCV replication

Keynote 224, 240 trial of 517 HCCs

Pembrolizumab
- 80 HBsAg (+)
- 86 HBcAb (+) HBsAg (-)

Placebo
- 29 HBsAg (+)
- 29 HBcAb (+) &HBsAg (-)

Pembrolizumab
- 56 HCV RNA(+)
- 40 HCV RNA (-) HCVAb (+)

Placebo
- 21 HCV RNA(+)
- 18 HCV RNA (-) HCVAb (+)

Figure 2. Changes in HBV Viral Load and ALT Levels During Treatment in Patients With Active HBV Infection[a]

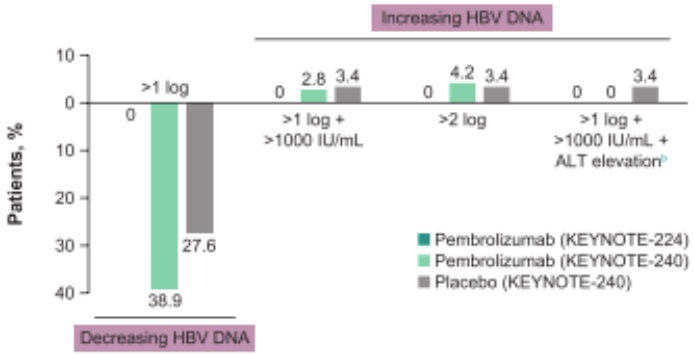
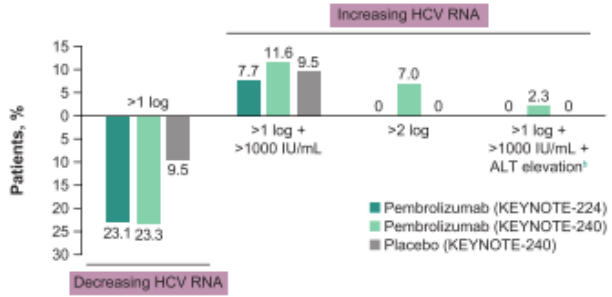


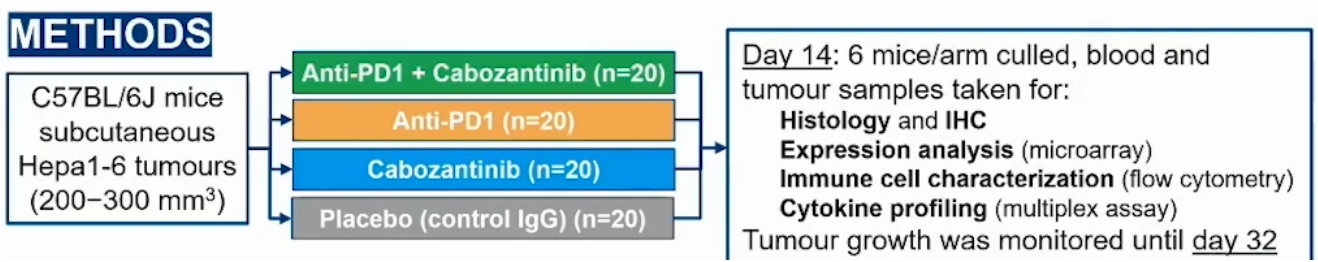
Figure 3. Changes in HCV Viral Load and ALT Levels During Treatment With Pembrolizumab or Placebo in Patients With Active HCV Infection[a]



Chan et al. Liver meeting #1148

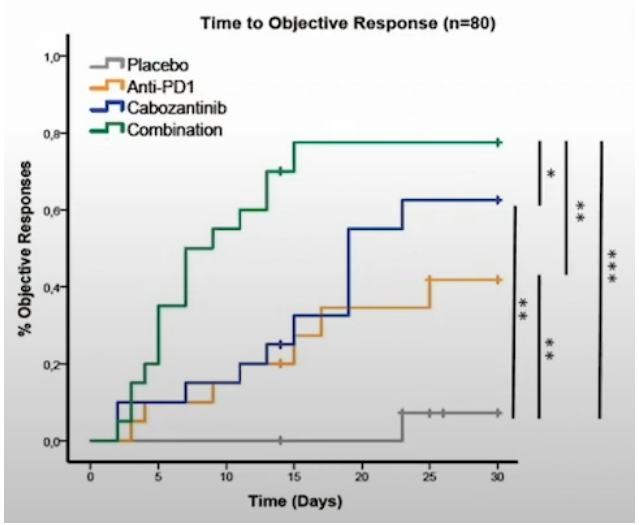
Cabozantinib modulates activity of immunotherapy

- Immune check point inhibitors are effective for HCC but only effective in about 20%
- Cabozantinib is a TKI with potential immune modulatory activity that can enhance the efficacy of immunotherapy
- Aim to assess the antitumor effect and mechanism of action of cabozantinib in combination with anti-PD1 treatment in immunocompetent murine HCC model



Willoughby et al, ILC 2020

Cabozantinib modulate activity of immunotherapy



Histologic and molecular efficacy

- Higher necrosis, reduced angiogenesis

Enhanced anti-tumor immunity

- Activation of anti-tumor immunity pathway
- Reduction of PD1+CD8+ T cells by flow cytometry

Systemic immunity

- Increase in circulating T lymphocytes
- Increase in circulating memory/effector T cell

Conclusion

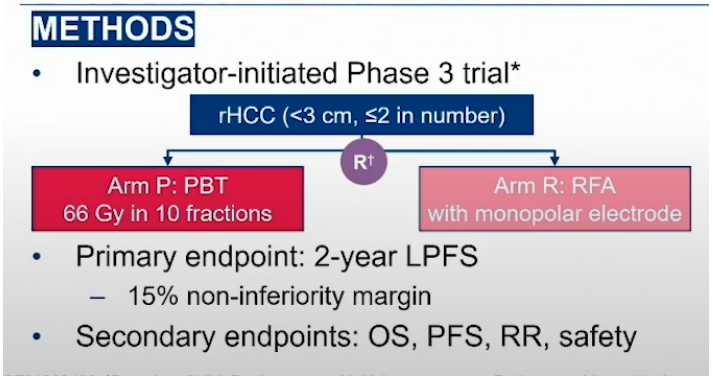
Cabozantinib enhances anti-PD1 anti-tumor efficacy and had beneficial immunomodulatory activity in HCC model supporting further investigation into the combination treatment

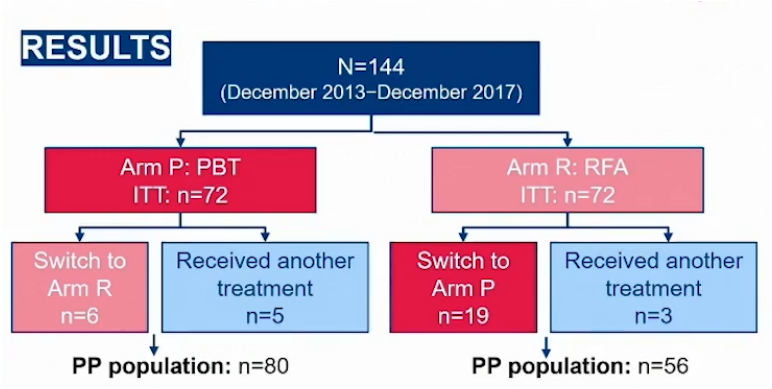
Proton beam treatment for HCC: Phase 3 RCT

Proton beam treatment (PBT)

- More accurate targeting of tumors
- Lower radiation exposure for normal tissue, reducing short- and long-term side effects, such as the development of new cancers
- Promising local tumor control and safety in phase 2 trial

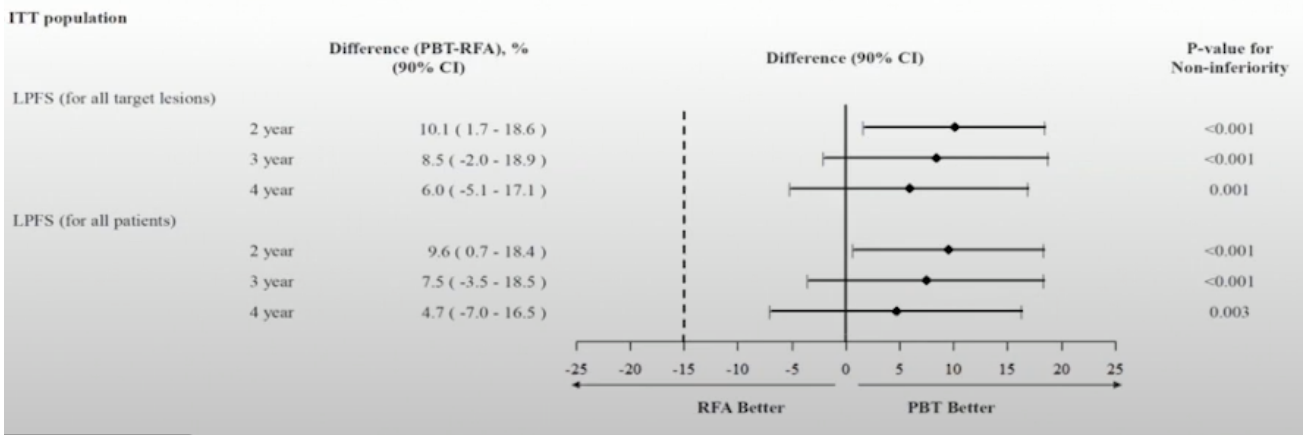
Aim to evaluate the effect of PBT vs RFA in patients with recurrent HCC





Park et al, ILC #07

Proton beam treatment for HCC: Phase 3 RCT



Safety

- No Grade 4 AEs or mortality
- Most common any-grade AEs:
  - **PBT**
    - Radiation pneumonitis: 32.5% pts
    - Leukocyte count decrease: 23.8% pts
  - **RFA**
    - ALT increase: 96.4% pts
    - Abdominal pain: 30.4% pts

Conclusion

PBT is non-inferior to RFA in terms of LPFS in recurrent HCC

Park et al, ILC #07

Thank you

Questions

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Question 1

High BMI is a risk factor for HCC in patients with cirrhosis

- 1. True
- 2. False

Question 2

Pembrolizumab increases the risk of HBV or HCV flare

- True
- False

Question 3

What is the recent incidence trend of HCC in the rural part of the US?

- It continues to increase
- It continues to decrease
- It plateaued recently and started trending down
- It plateaued recently and started trending up