Updates in Hepatocellular Carcinoma

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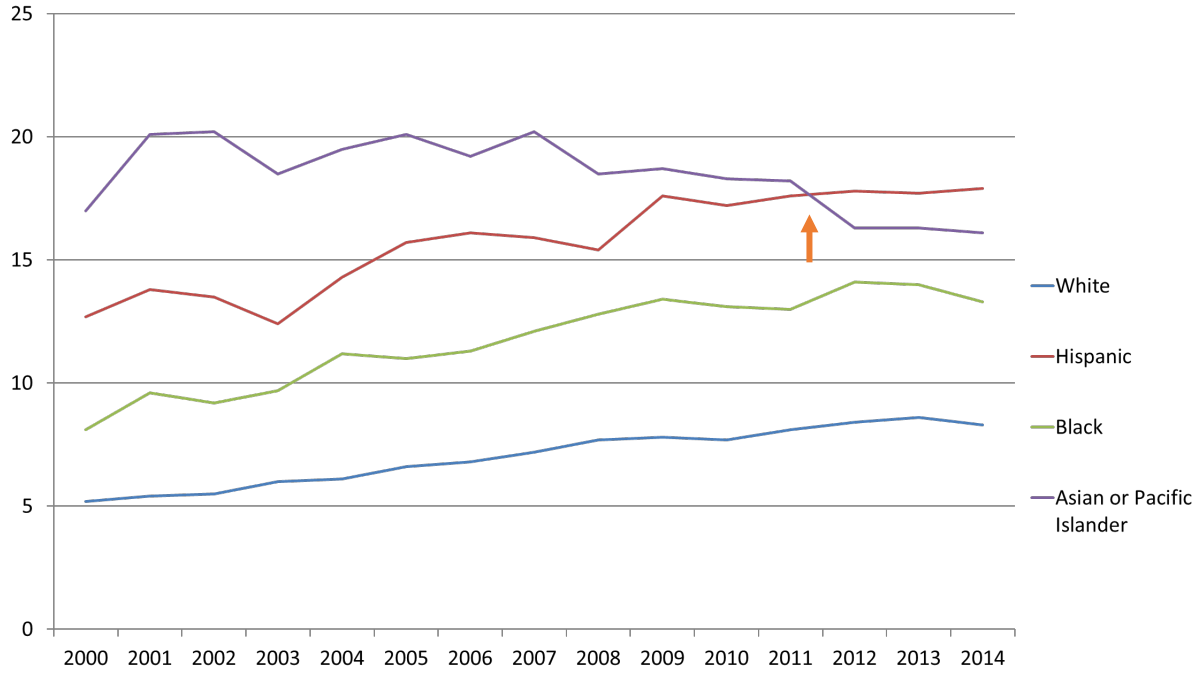
HCC and epidemiology

HCC and ethnicity: Analysis of the SEERS database (2000-2014)

- SEERS: a US population-based cancer registry

In 2012, HCC incidence overtook Asians to become the race/ethnic group with the highest HCC incidence in the USA



Hispanics and HCC

- SEER registry
- Hispanics account for 20% of

all HCC in US

- Only 38% were within MILAN at time of diagnosis regardless of sex or insurance
- The older a patient is, the more likelihood to present outside MILAN

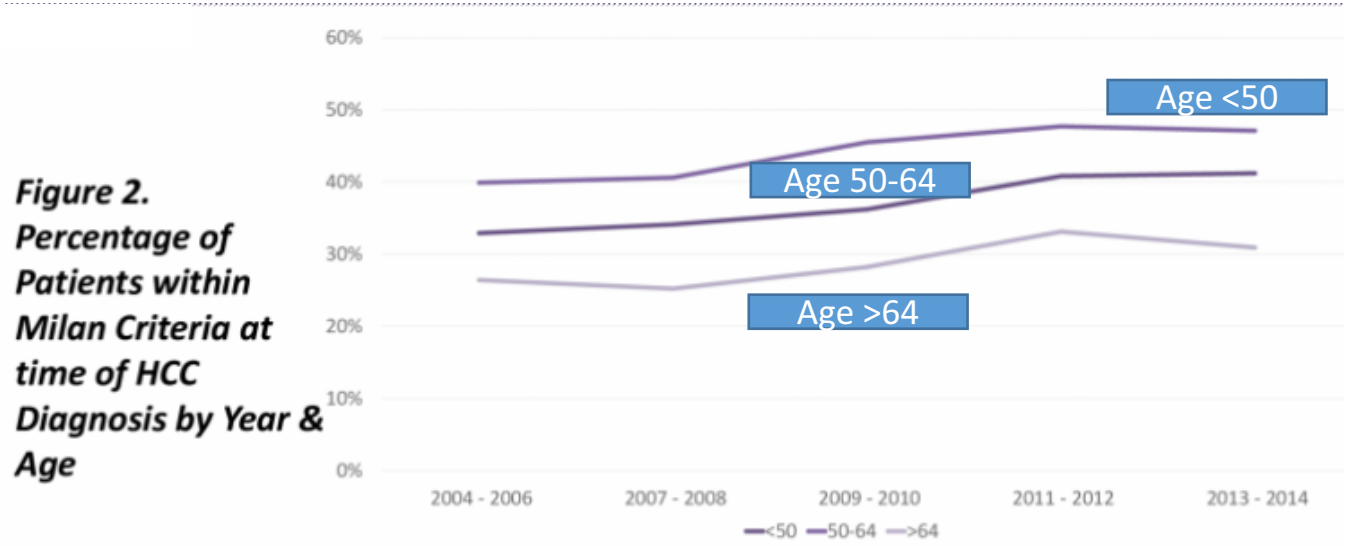
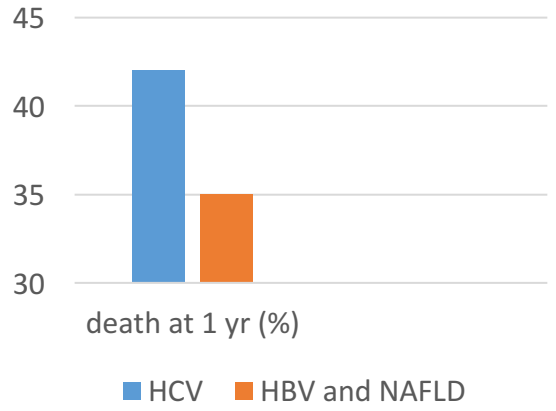


Figure 2. Percentage of Patients within Milan Criteria at time of HCC Diagnosis by Year & Age

Liver Diseases and HCC

- Data from the Office of Statewide Health Planning and Development (2005-13) database which incudes all hospital admission in CA (>38 million population)
- 13,735 HCC and 371,161 controls without HCC

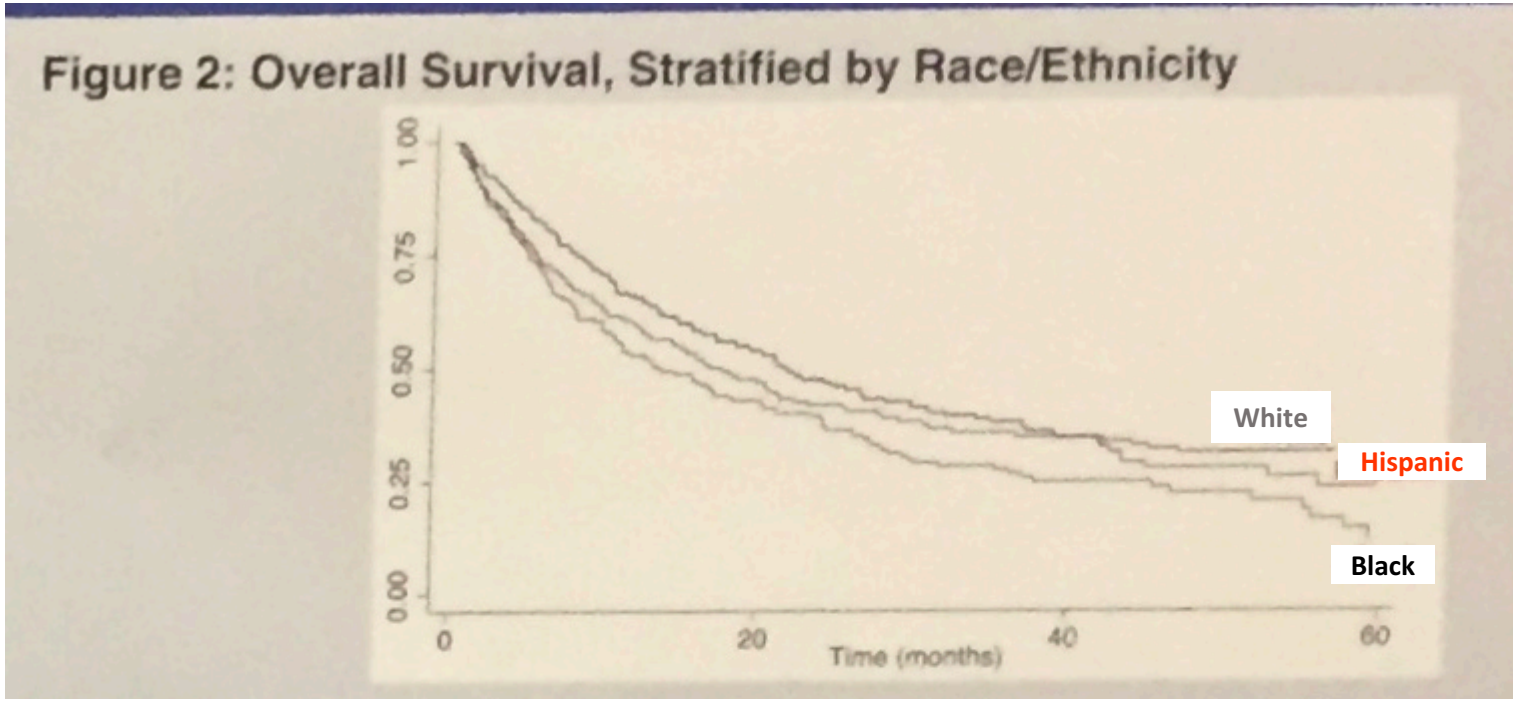
HCC cohort (n=13735)	33% HCV (n=4576)	11% HBV (n=1538)	2.4% NAFLD (n=333)	5% Other liver disease (n=691)	37% More than one liver disease (n=5032)	11 % ALD (n=1565)
OR of HCC (95% CI)	4.52 (4.24-4.81)	6.87 (6.28-7.51)	0.64 (0.57-0.72)	2.91 (2.63-3.21)	4.62 (4.34-4.92)	Reference
HR of 1-year	1.24 (P<0.05)	0.85 (P>0.05)	1.30 (P>0.05)	1.66 (P<0.05)	1.51 (P<0.05)	Reference
mortality (P value)					HCV/ALD HCV/HBV	



Having HCV is associated with ~5x increased odd of having HCC and
24% more likely to die within 1 year of HCC diagnosis compared to ALD

Racial impact on HCC

- 2008-2016
- UT Southwestern



Blacks have worst overall survival than Whites despite similar tumor stage and receipt of curative treatment

Rich N et al. Abs 1367. AASLD 2017

Racial impact and Predictors of overall survival

Table 3: Patient-level Predictors of Overall Survival (n=699)

Variable	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Median Survival (month
Race/Ethnicity*			
White	1.00	1.00	14.3
Black	1.43 (1.14 – 1.80)	**1.35 (1.05 – 1.72)**	10.7
Hispanic	1.20 (0.94 – 1.53)	0.96 (0.74 – 1.25)	12.4
Age > 60 years	0.99 (0.82 – 1.19)	1.11 (0.90 – 1.37)	11.9 vs. 12.5
Female sex	0.83 (0.66 – 1.03)	0.84 (0.66 – 1.07)	14.5 vs. 11.5
Child Pugh Class			
Child A	1.00	1.00	16.4
Child B	1.84 (1.53 – 2.22)	**1.73 (1.41 – 2.12)**	7.7
Health System			
Safety-net	1.00	1.00	11.1
Tertiary Care	0.75 (0.61 – 0.91)	**0.76 (0.60 – 0.96)**	15.4
Tumor Stage			
BCLC 0/A	1.00	1.00	21.5
BCLC B	2.71 (2.11 – 3.49)	**2.19 (1.67 – 2.89)**	10.7
BCLC C	6.85 (5.50 – 8.53)	**6.11 (4.76 – 7.86)**	4.1
Curative Treatment	0.33 (0.25 – 0.43)	**0.59 (0.43 – 0.81)**	21.1 vs. 9.5

‡ Excluded BCLC stage D patients ineligible for treatment beyond best supportive care, * HR adjusted for BCLC stage, Child Pugh scor
and receipt of curative therapy

HBV and HCC

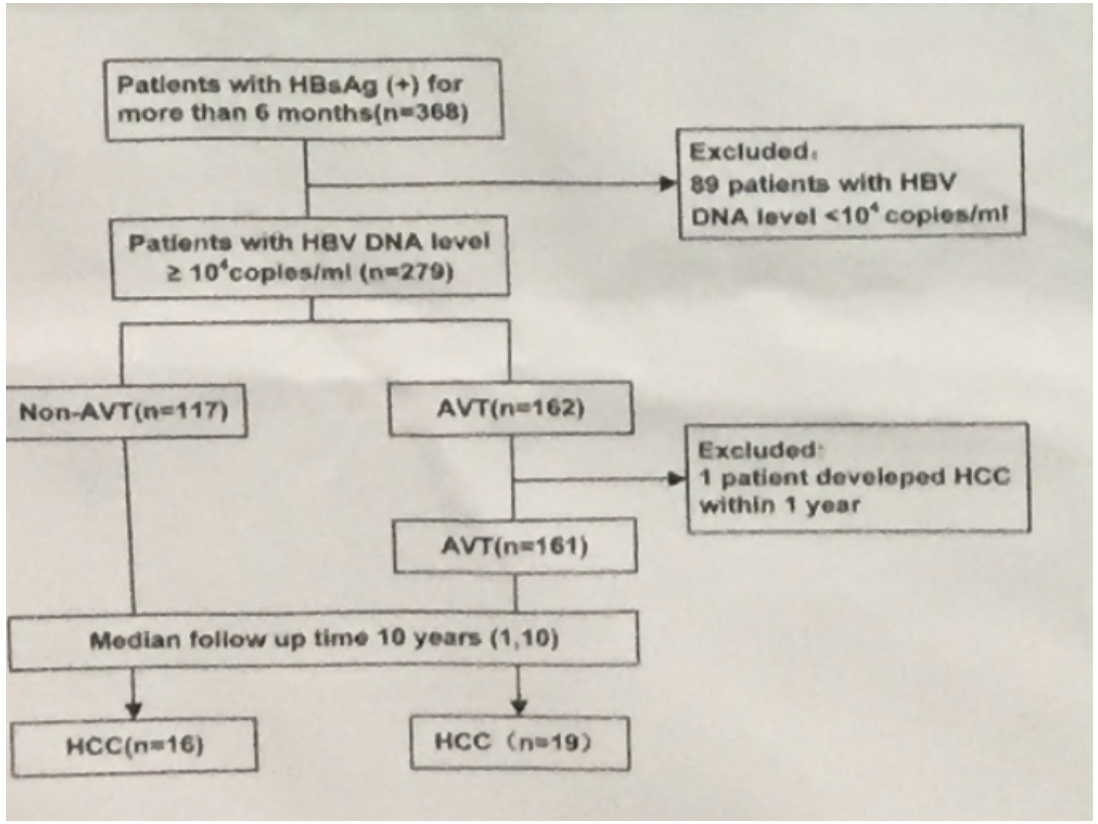
HBV and HCC- 10 yrs follow-up

- Prospective Chinese study
- 2004-2014
- Adefovir vs no Rx

- mean age 40.3, male 69.4%, e-Ag pos 55.8%, cirrhosis 24.8%

- f/u: q6 M

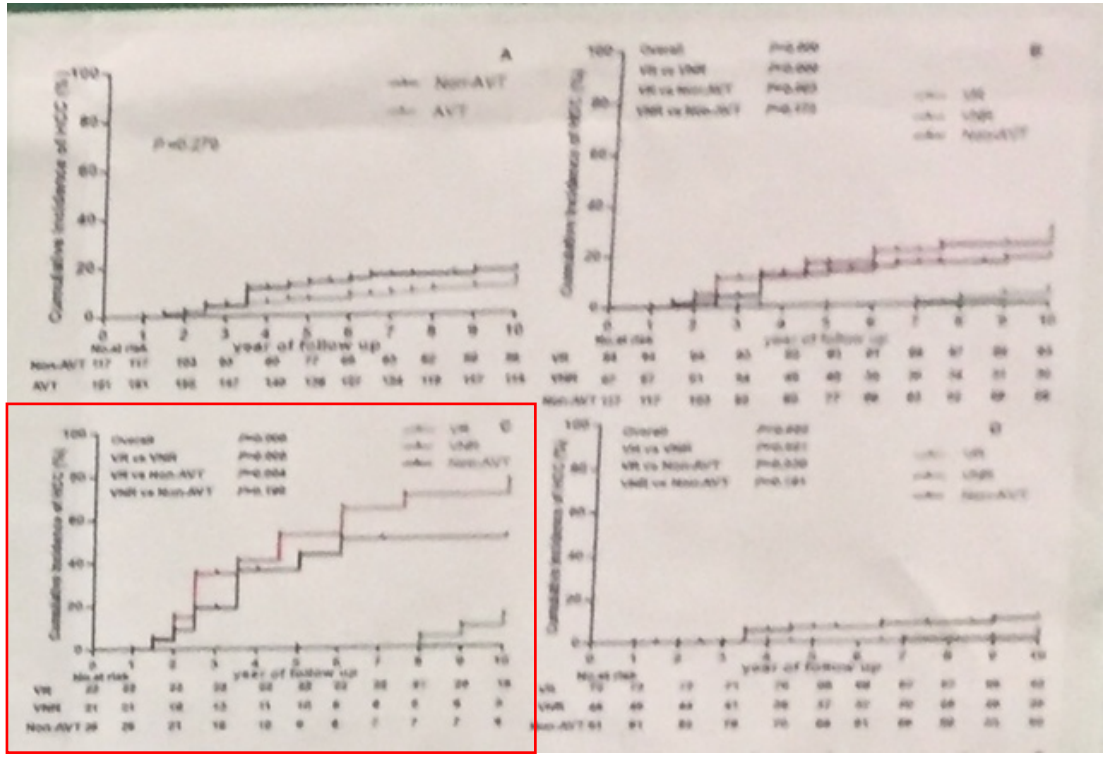
- End point: development if HCC



HBV and HCC- 10 yrs follow-up

- 10 yr incidence of HCC
  - Cirrhosis
    - ADV VR vs no response: 14.29% vs 76.3% p<0.001
  - Non cirrhotics: VR vs control: 1.49 vs. 9.98 p 0.03

Effective viral suppression reduces the risk of HCC development



HCC risk modifiers

Aspirin and risk of HCC in patients with compensated alcoholic cirrhosis

973 Korean patients

Aspirin	Non-aspirin
222	751

Mean age 54.4+/-11.4

133 patients developed HCC (13.6%)

Aspirin use: HR 0.63 (0.47-0.85) p 0.002

Aspirin therapy was not associated with increased bleeding risk (p 0.126)

Aspirin use ≥ 90 days decreased risk of HCC without increasing bleeding risk

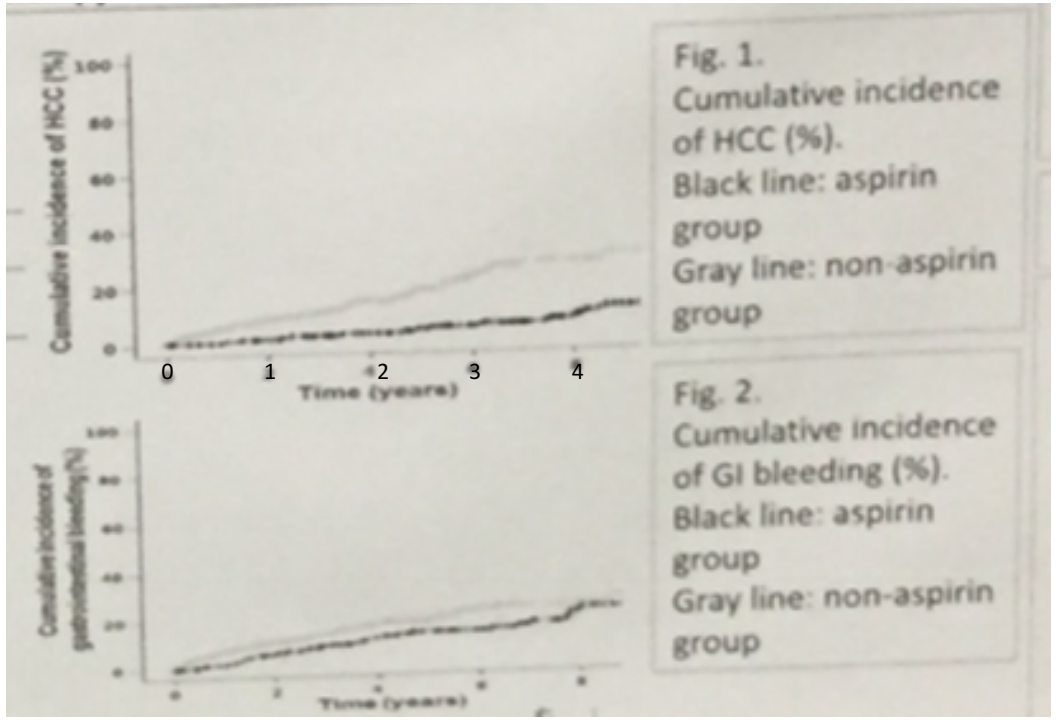


Fig. 1.
Cumulative incidence of HCC (%).
Black line: aspirin group
Gray line: non-aspirin group

Fig. 2.
Cumulative incidence of GI bleeding (%).
Black line: aspirin group
Gray line: non-aspirin group

Lee M et al. Abs 1348. AASLD 2017

Statin and HCC in NAFLD

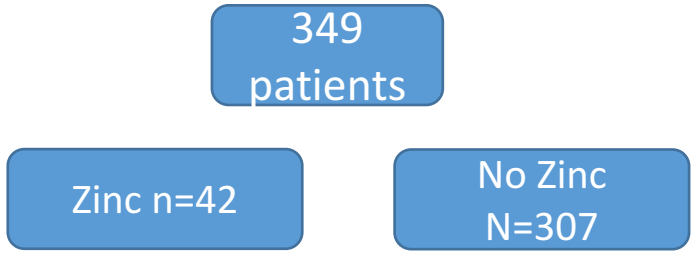
- 34 NAFLD cirrhosis vs 68 NAFLD control
- 2002-2016
- Matched for baseline: age, sex, Caucasians, age at Dx of HCC
- Screening q6 months

UNIVARIATE ANALYSIS		
Variable	**Odds Ratio and 95% CI**	**P Value**
Statin Use and HCC (Protective)	0.35 (0.13-0.91)	0.03
Metformin Use (Trend Protective)	0.44 (0.18- 1.06)	0.07
Aspirin Use (Trend Protective)	0.49 (0.21- 1.13)	0.09
Hypertension (Increased Risk HCC)	5.25 (1.93-14.3)	0.001
MULTIVARIATE ANALYSIS (Only significant data points shown)		
Statin Use (PROTECTIVE)	0.35 (0.13-0.91)	0.03

- BMI, DM-2, A1C, vit D supplementation albumin level (p NS)
- Univariates: aspirin, metformin, statin →lower HCC; HTN ->higher risk of HCC
- Multivariate: only statin →decrease risk of HCC development (OR 0.35, p 0.03)
- Visceral adiposity on CT at baseline tends to be higher in HCC than controls (p 0.45)

Zinc and liver cancer

- Zinc decreases reactive oxygen species
- Retrospective analysis of 349 patients who were cured from HCV with DAA (G1/2=279/70)
- ZnSO4: ZN 60-120 mg/d
- Male/female: 145/204
- Mean age: 67+/-11.8 yrs (17091)
- PLT 14.4+/- 5.9/ml
- AFP 15+/-33.5
- Follow-up 10.9+/-4.7 months



Zinc and HCC: Results

- 11 patients developed HCC
- Cumulative incidence rate at 1 yr: 3.23%
- Zinc concentration was higher at any one time (before DAA, end of DAA and at SVR12) in the no-HCC group compared to HCC group ($p<0.01$)
- At time of presentation: no HCC developed in the Zinc group

Multivariate analysis: low serum zinc <65 mg/dl ($p=0.0015$) at the end of DAA therapy is a risk factor of HCC development

Hosui A et al. Abs 1372. AASLD 2017

Vitamin D and NAFLD-HCC

- Nested case controlled study from a cohort of NAFLD patients with compensated liver diseases
- 2002-2016: 34 NAFLD vs. 34 control
- Similar DM rates
- HCC screening q6 months

Lower vit D level, lower albumin level and higher fasting glucose are associated with increased risk of HCC development

	NAFLD	Control	P
N	34	34	
Mean age (yrs)	63.8	66.5	>0.05
Vit D (ng/ml)	22.7	34.1	0.05
Albumin	3.2	3.7	0.002
Fasting glucose (mg/dl)	157	119	0.02
BMI	35	32.1	0.10
Aspirin use	26/334	12/34	0.001
Statin use	29/34	6/34	0.0001

Community vs. tertiary care center

- 2008-2016 UT southwestern
- Still low rate of surveillance
- Higher likelihood of receiving curative therapy at tertiary center 46.4% vs. 23.3%
  - Within MILAN: 75% vs. 50%

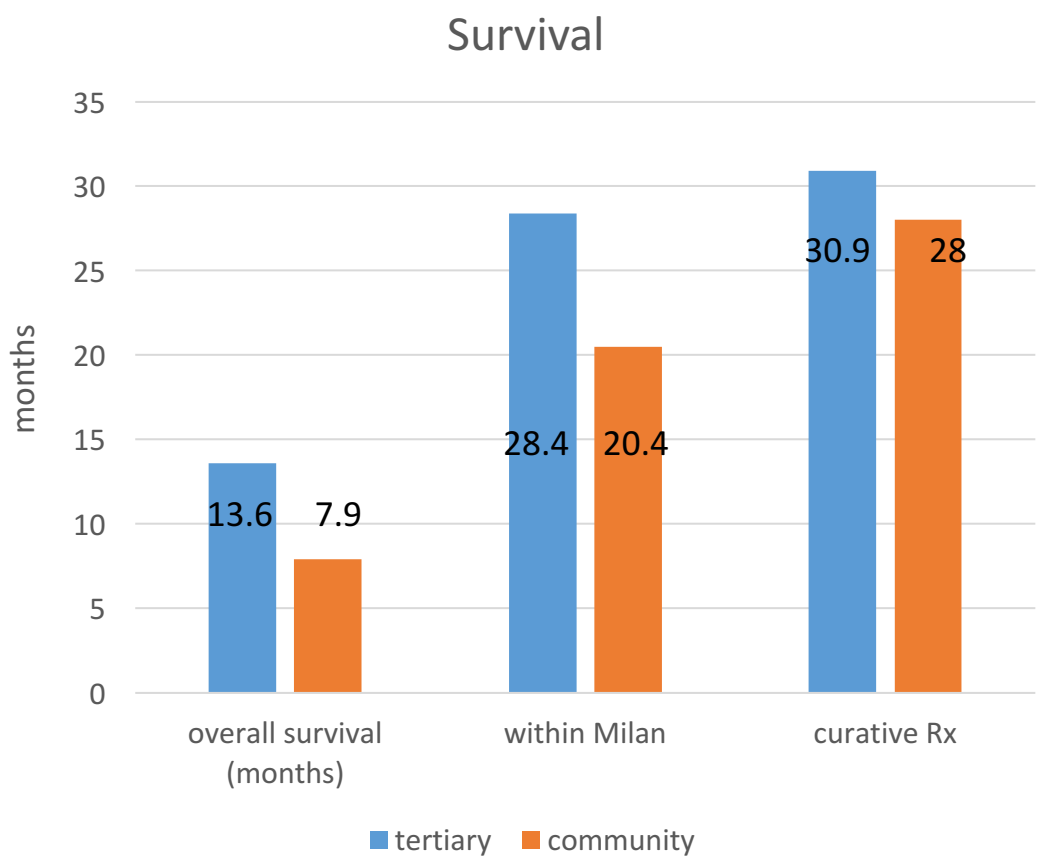
Table 1. Patient Clinical and Tumor Characteristics by Hospital System (n=966)

	Safety-Net Hospital (n=680)	Tertiary-Care Referral Center (n=286)	*p*-value
Mean age (years)	58.0 ± 8.6	63.4 ± 10.9	<0.001
Race/ethnicity			<0.001
Non-Hispanic White	163 (24.0)	166 (58.3)	
Black	248 (36.5)	52 (18.3)	
Hispanic	215 (31.6)	52 (18.3)	
Insurance status			<0.001
Uninsured/Medicaid	539 (79.3)	24 (8.4)	
Insured	141 (20.7)	262 (91.6)	
Child-Pugh Class			0.006
Child A	298 (43.8)	155 (54.4)	
Child B	275 (40.4)	100 (35.1)	
Child C	107 (15.7)	30 (10.5)	
Seen by hepatologist in year prior to HCC diagnosis (%)	148 (21.8)	109 (38.3)	<0.001
Surveillance detected (%)	225 (34.3)	134 (48.7)	<0.001
Within Milan criteria (%)	276 (40.7)	143 (50.5)	0.005
BCLC stage			0.001
BCLC 0/A	264 (39.0)	131 (46.5)	
BCLC B	93 (13.7)	54 (19.2)	
BCLC C	176 (26.0)	62 (22.0)	
BCLC D	144 (21.3)	35 (12.4)	

- Overall, 155 (23.3%) safety-net hospital patients underwent curative treatment compared to 128 (46.4%) of patients at the tertiary care referral center (p<0.001).
- Among those within Milan criteria, 137 (50%) safety-net hospital patients underwent curative treatment compared to 105 (75.0%) of patients at the tertiary care referral center (p<0.001).

Rich N et al. Abs 1356. AASLD 2017

HCC: Community vs. tertiary



Even when diagnosed at an early stage, HCC patients at community centers are less likely to undergo curative therapy

Overall survival was significantly worse in community HCC patients compared to HCC tertiary patients

Rich N et al. Abs 1356. AASLD 2017

DAA and HCC

ANRS HEPATHER: HCV DAA Therapy and Risk of Mortality, HCC, and Decompensated Cirrhosis

- Multicenter observational cohort study assessing short-term effects of DAAs on mortality, HCC, and DC risk in pts with HCV (N = 9295)
  - Median follow-up: 24 mos
- **DAA treatment associated with decreased risk of death vs no DAA treatment**

Event, n (%)	DAA Treatment (n = 6460)*	No DAA Treatment (n = 2835)†	aHR (95% CI)
All-cause death	90 (1.4)	78 (2.8)	**0.65 (0.45-0.95); *P* = .0258**
▪ Liver related	NR	NR	0.68 (0.36-1.29)
▪ Nonliver related	NR	NR	0.75 (0.43-1.31)
HCC	164 (2.5)	57 (2.0)	1.19 (0.85-1.66); *P* = .3178
DC	77 (1.2)	35 (1.2)	0.90 (0.58-1.41); *P* = .6533

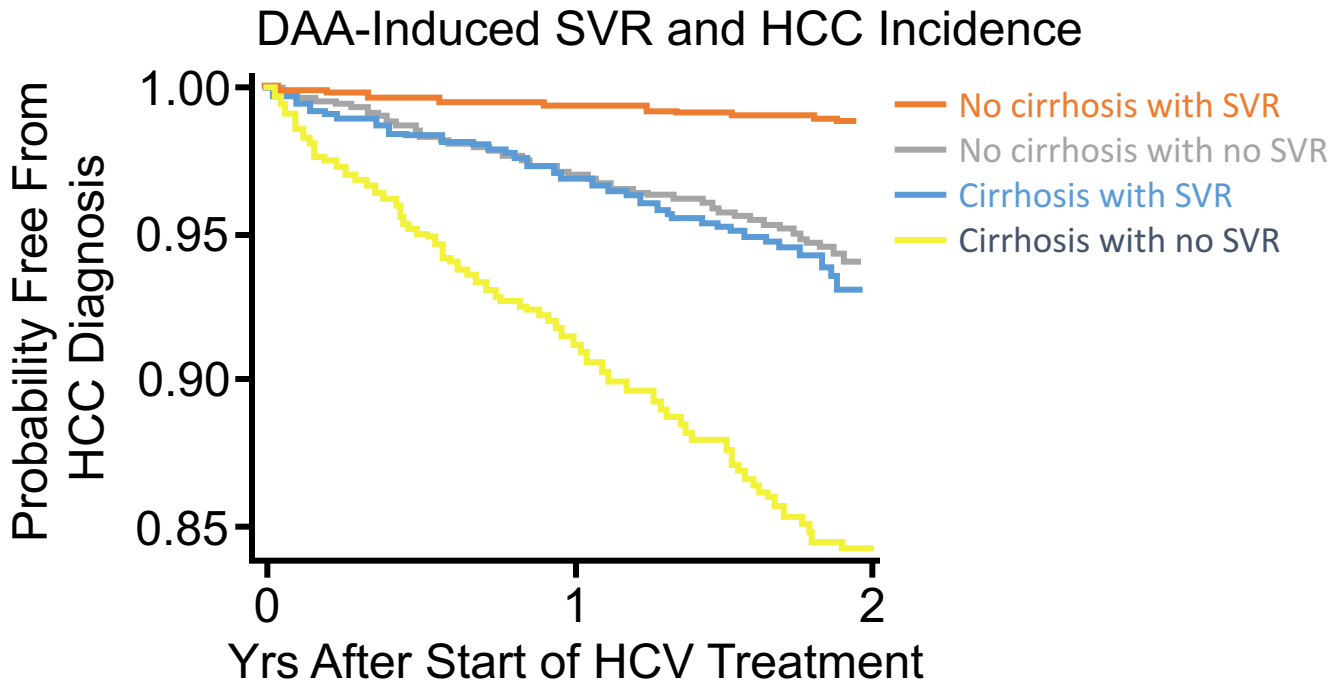
Effect of DAAs quantified with weighted Cox proportional hazards models adjusted for confounding via IPTW. IPTW scores derived from covariates associated with DAA, including age, sex, cirrhosis, and treatment experience.
*8482 person-yrs. †10040 person-yrs.

Carrat F, et al. AASLD 2017. Abstract LB-28.

DAA Therapy and HCC Risk in Large VA Cohort

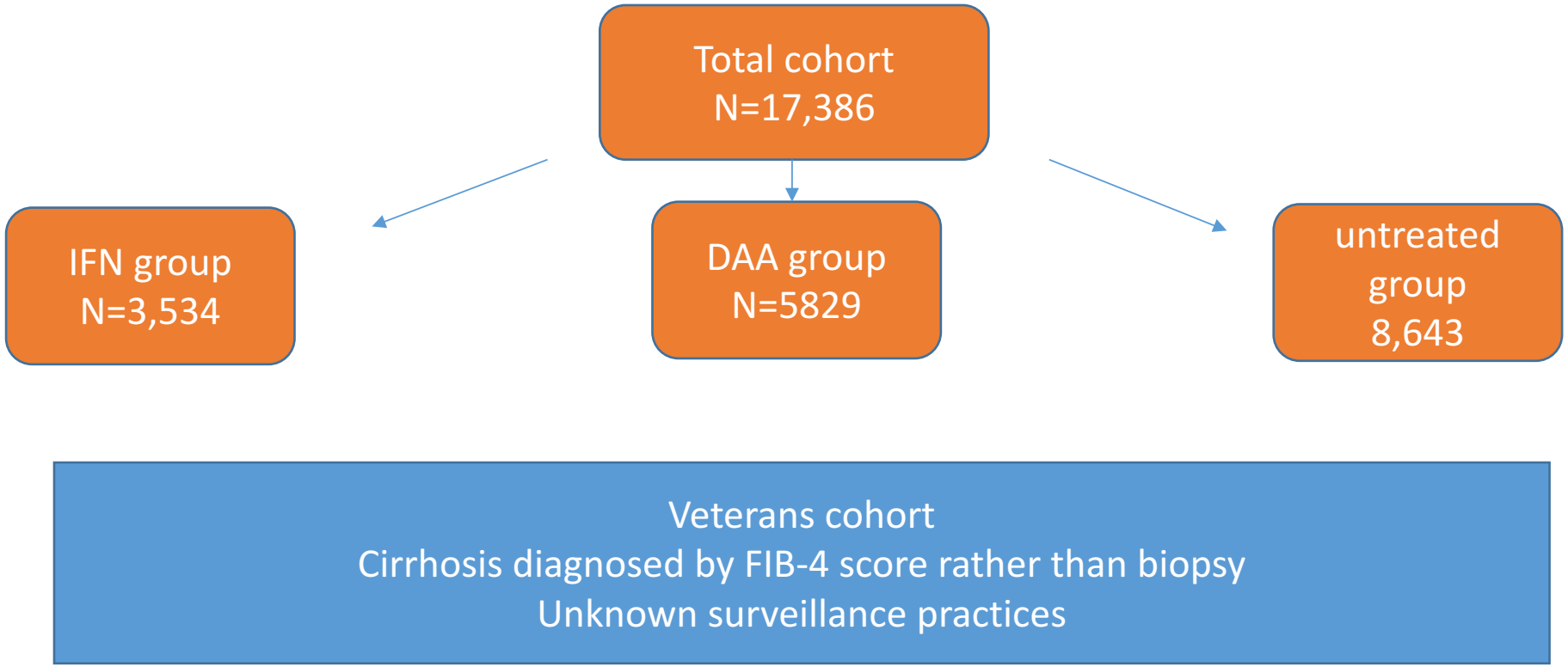
- Retrospective cohort study assessing the relationship between SVR and HCC risk in pts with HCV in the VA healthcare system receiving antiviral therapy 1999-2015 (N = 62,354)
  - 58% received IFN-only therapy, 35% received DAA-only therapy
- **SVR with DAA regimen associated with 71% decrease in HCC risk**

Regimen	HCC/100 PY	aHR
IFN only		
▪ SVR	0.28	0.32
▪ No SVR	1.07	
DAA + IFN		
▪ SVR	0.6	0.48
▪ No SVR	1.73	
DAA only		
▪ SVR	0.92	0.29
▪ No SVR	5.2	



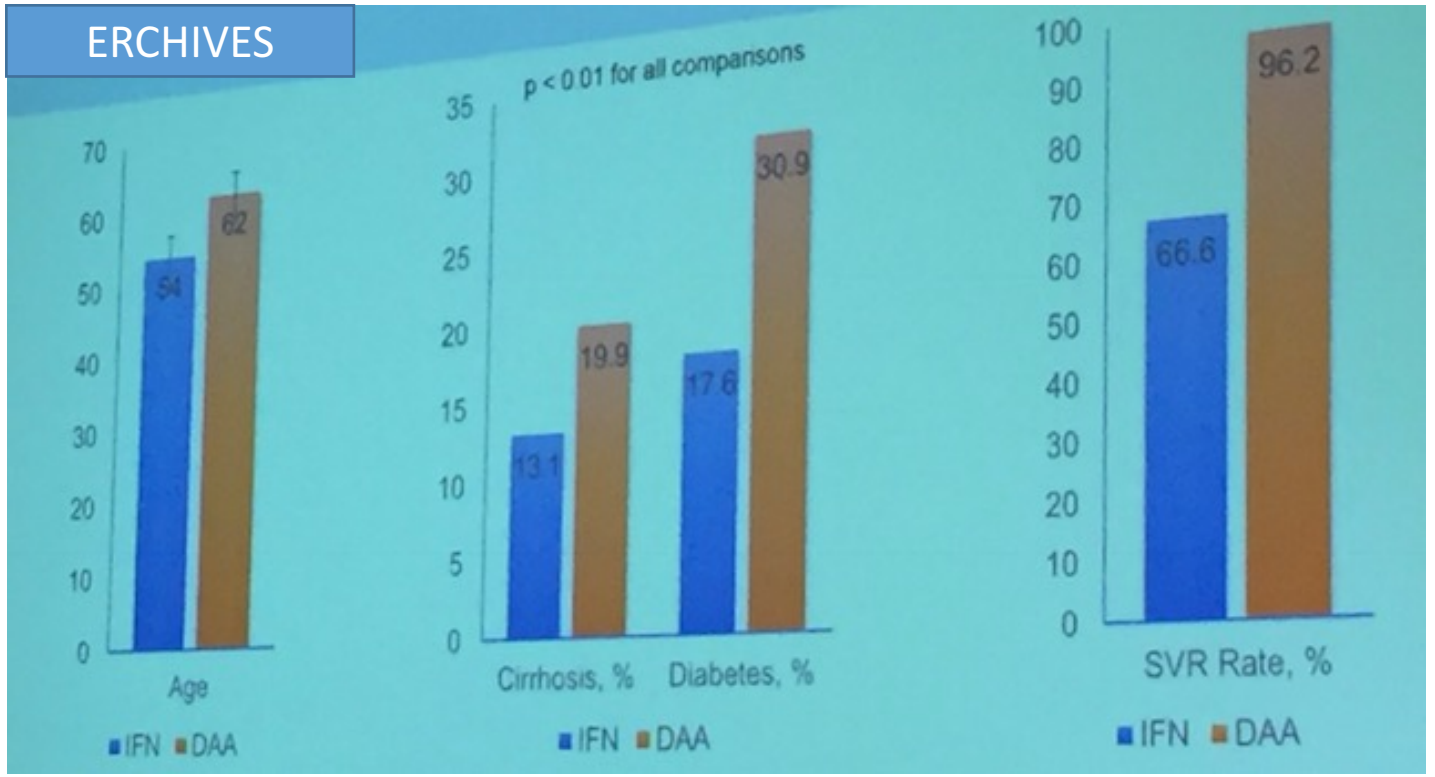
Ioannou G, et al. AASLD 2017. Abstract 142.

ERCHIVES: de novo HCC and IFN or DAA



Li D, et al, Abs 228. AASLD 2017.

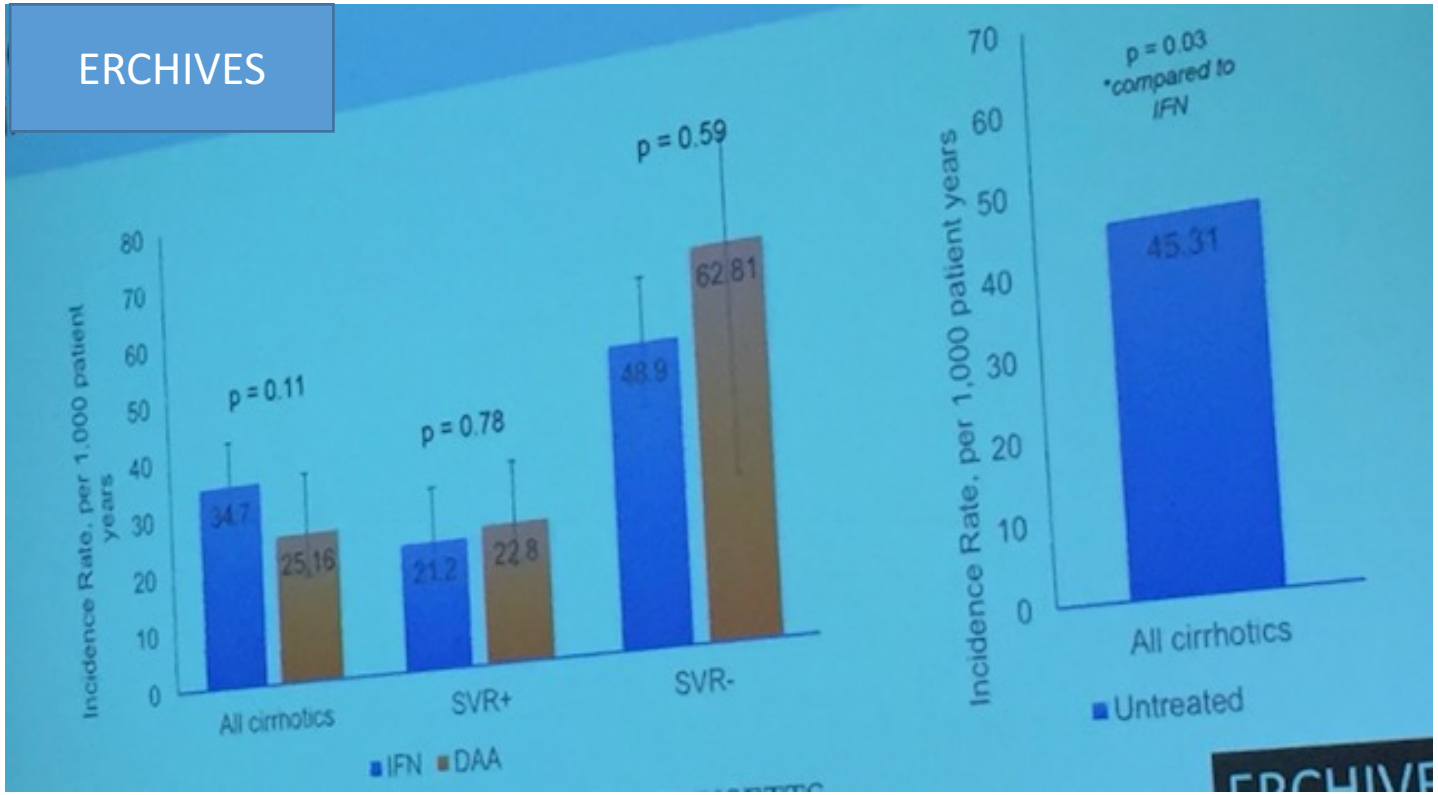
ERCHIVES: baseline risks for HCC development



DAA patients have higher baseline risks for HCC development

Li D, et al, Abs 228. AASLD 2017.

HCC incidence between IFN and DAA treated cirrhotics

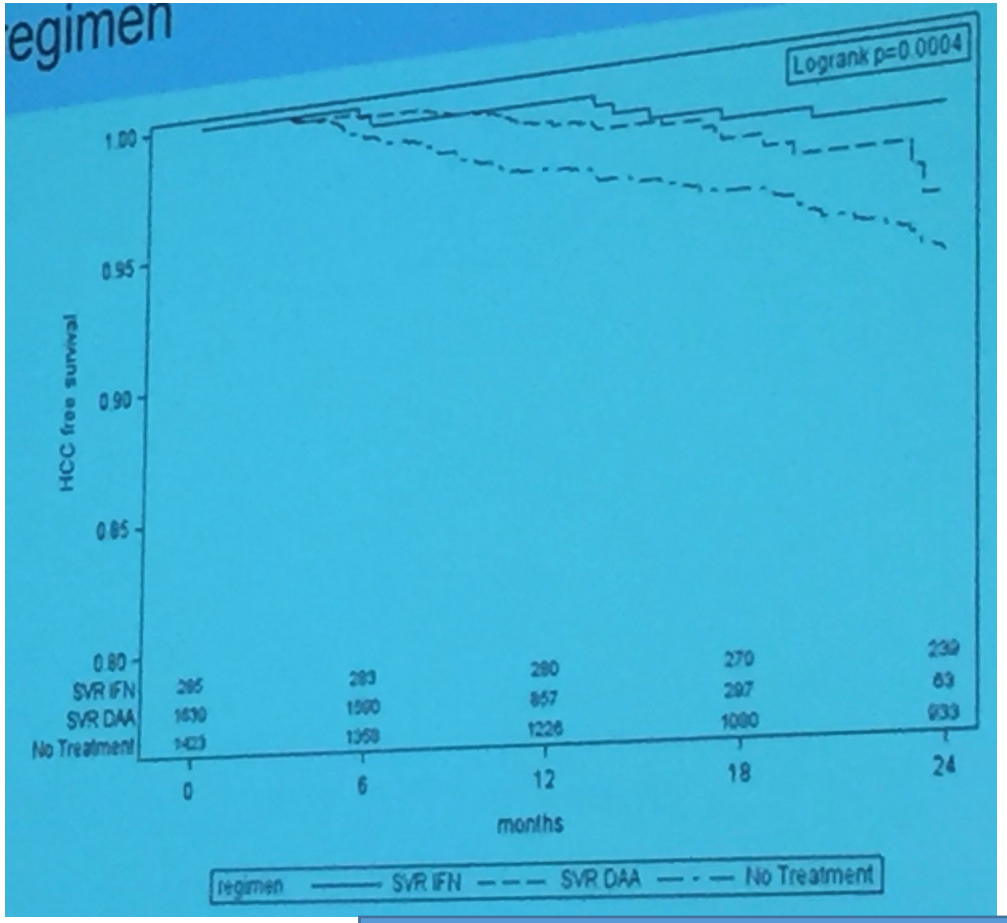


Similar rates of HCC incidence between Ifn and DAA treated cirrhotics

Li D, et al, Abs 228. AASLD 2017.

Li D, et al, Abs 228. AASLD 2017.

ERCHIVES: no increased risk of HCC with DAA



	Hazards ratio	95% CI
Age, per 10 year increase	1.76	1.26, 2.46
Male sex	1.34	0.32, 5.62
Diabetes	1.01	0.67, 1.50
Body mass index, per 1 unit increase	0.98	0.95, 1.01
Alcohol abuse history	1.27	0.85, 1.89
Statin use (baseline onwards)	0.50	0.31, 0.80
AFP >20 (vs. <=20)	4.10	2.75, 6.10
Treatment Regimen		
PEG/RBV(comparator)	1	--
Any DAA	1.07	0.55, 2.08
Attainment of SVR	0.66	0.42, 0.98

Patients who achieved SVR have similar HCC-free survival
DAAs are not associated with increased HCC risk

DAA and HCC-another VA analysis

- Backus D et al. Abs 78
  - Impact of sustained virologic response with direct-acting antiviral treatment on mortality and hepatocellular carcinoma
  - VA HCV cohort
  - LDV/SOF based regimen: ~60%

Incident HCC Rates in ACLD Patients	*No SVR (n = 871)*		*With SVR (n = 13,153)*		*Risk Reduction, %*
	1-Yr HCC, n	*1-Yr HCC Rate, % (95% CI)*	*1-Yr HCC, n*	*1-Yr HCC Rate, % (95% CI)*	*Risk Reduction, %*
All patients	67	9.4 (7.4-11.9)	210	1.9 (1.7-2.2)	79.8*

DAA and HCC recurrence

- 191 patients who received DAA with h/o HCC
- 87 had recurrence of HCC
  - DAA vs DAA-untreated patients: 42.5% VS. 53.5% (P=0.15)
  - Adjusting for BCLS stage and HCC treatment:
    - DAA was not associated with recurrence:OR 0.66 (0.35-1.22)
  - Median time to recurrence: 364 days
    - DAA-Treated vs non treated: 223 d vs. 554 d
  - Recurrence pattern:
    - Unifocal 60%, >3 lesions: 15..3%, vascular invasion 3.5%, metastases 8.1%
  - Higher disease control rate in DAA treated patients (83.8% vs 66.0%, p=0.02)

DAA is associated with shorter time to recurrence

HCC recurrence after curative therapy and DAA therapy

- 163 Japanese patients with h/o HCC (M/F=96/67, median age 74 (49-87)
- DAA treatment:2014-2016: SVR12 92%
- MRI and CT confirmed absence of HCC prior to DAA
- Median time to HCC development: 3.9 yrs (0.03-18.8 yrs)

- 78 patients developed HCC recurrence
- Recurrence rate at 1 and 2 yrs: 38% and 54.5%

Early DAA therapy decreases HCC recurrence

Risk factors for early recurrence	
AFP-L3	**HR**
AFP-L3 >15%	3.08 (p=0.0004)
DCP > 40	2 (p=0.057)
#of HCC Rx: >3 vs 1	2.25 (p=0.005)
# HCC Rx: 2 vs 1	1.32 (p=0.42)
Interval between the last HCC Rx and start of DAA > 2yrs	0.34 (p=0.009)

Minami T et al. Abs 1421. AASLD 2017

Markers of HCC progression

- 1407: osteopontin predicts recurrence
- 1353: High expression of miR-196a is associated with progression of HCC
- 1371: AFP

- High serum HMGB1 (high mobility group box 1) at week 4 after sorafenib therapy is a poor prognostic factor. (Ono A et al. Abs 1426, AASLD 2017)
- High level of sCTLA-4 (>10) is associated with HCC recurrence after curative RFA in Chinese patients (Teng W et al. Abs 1434. AASLD 2017)

AFP, AFP-L3 and DCP: Caucasians Abs 1409

- 604 VA patients (Aug 2014-May 2017)
- No prior HCC
- Surveillance every 6 months (U/S +AFP)
- 30 patients developed HCC
  - 26 patients had complete data
    - Mean age 63.5, 98% men
    - HCV 71%, etoh 57%, NAFLD 20%
    - At Dx: HCC 2.2 cmm (SD 1.1)
    - 1 nodule (15), 2 nodules (6), ≥3 nodules (5)

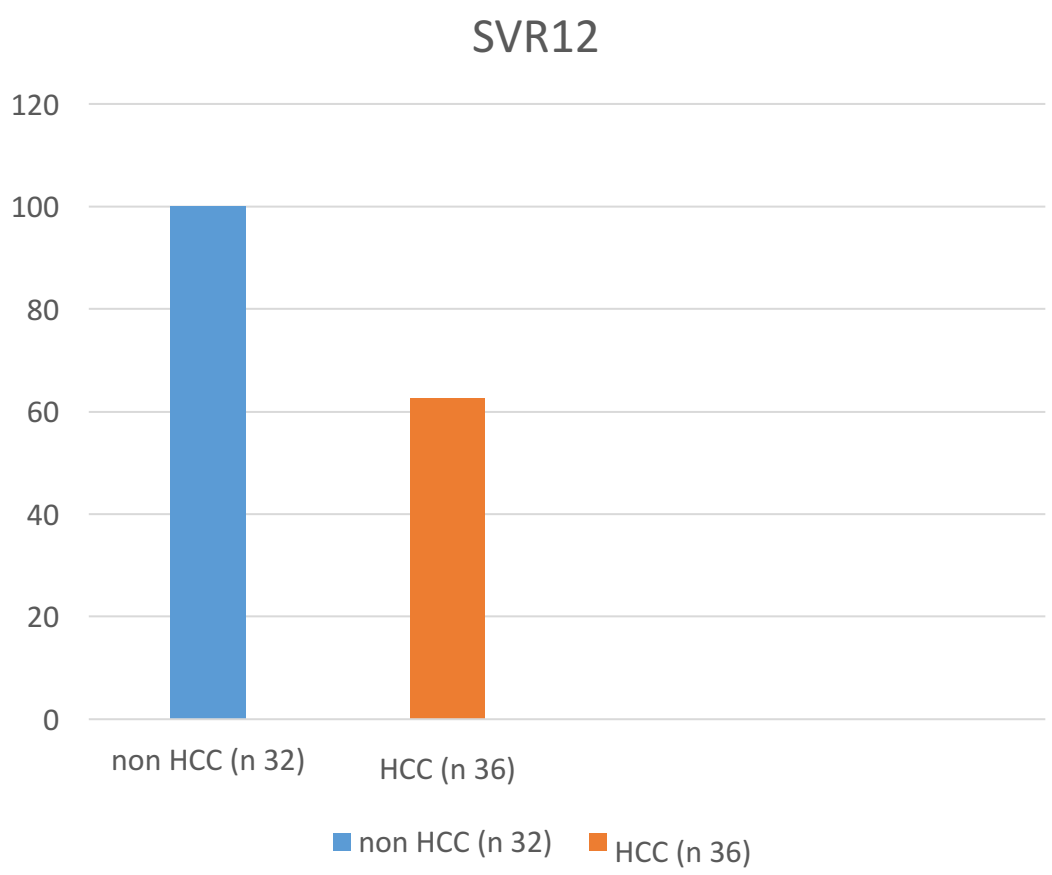
Improved sensitivity but increased false positive results

.	HCC within 6 months (Cases: 21, Controls: 543)		HCC within 12 months (Cases: 26, Controls: 543)		HCC within 24 months (Cases: 26, Controls: 543)	
	Sensitivity †	FPR‡	Sensitivity †	FPR‡	Sensitivity †	FPR‡
AFP>20 ng/mL	24%	6%	31%	5%	31%	5%
AFP-L3%>10%	38%	5%	42%	5%	42%	4%
DCP>2 ng/mL	48%	11%	42%	11%	46%	11%
Either: AFP>20 ng/mL, AFP-L3%>7% or DCP>0.48 ng/mL	62%	20%	69%	19%	69%	18%
GALAD> -0.63	81%	28%	85%	27%	85%	27%

†Sensitivity=probability of <1 positive screen 6, 12 or 24months before HCC diagnosis
‡FPR=probability of a positive screen in control patients or in cases more than 6, 12 or 24months prior to diagnosis

HCC and SVR

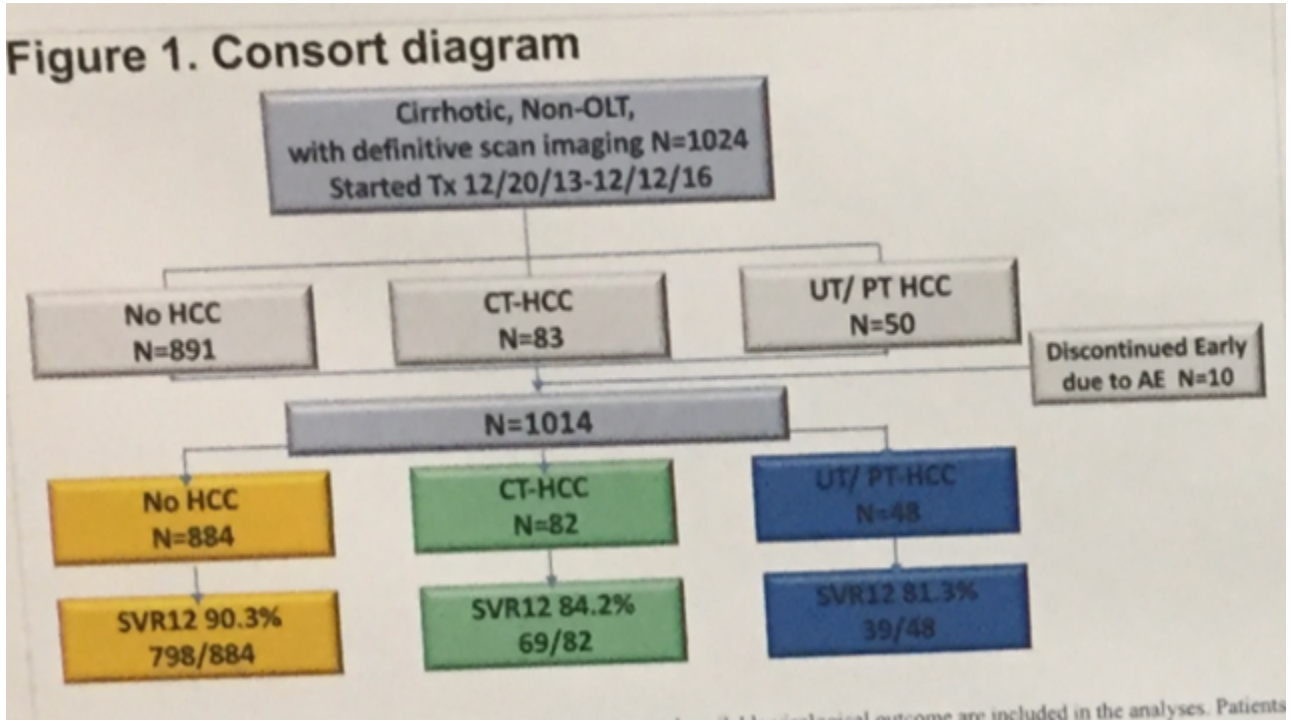
HCC lowers SVR



- DAA +/- RVN
- HCC: cirrhosis 100%
- Non HCC: cirrhosis 40%
- AST, ALT, AP, INR, PLT, ALB, CR, APRI, FIB4, MELD, Rx experience status were not statistically significant

Nguyen K, El-Kabany et al. Abs1041. AASLD 2017

Impact of HCC treatment on SVR-HCV TARGET



Decreased SVR rates to <90% in presence of HCC

UT/PT: untreated/Partially treated
CT: completely treated

SVR: DAA therapy and HCC: HCV-TARGET

- Of 759 patients, 178 had HCC
  - 109 with completely treated HCC prior to DAA (CT-HCC)
  - 69 with or with partially treated HCC at time of DAA (UT-PT HCC)
- DAA: 93% SOF based and 7% PI based
- Presence of HCC at baseline:
  - OR of SVR: 0.53 (0.37-0.78)
- No effect on SVR in HCC groups
  CT-HCC vs. UT-PT HCC

	CT-HCC	UT-PT HCC
SVR12 (%)	78	72
OR	0.575 (0.38-1.51)	

Presence of HCC is associated with reduced odds of SVR but no difference in those with completely treated HCC vs untreated or partially treated HCC

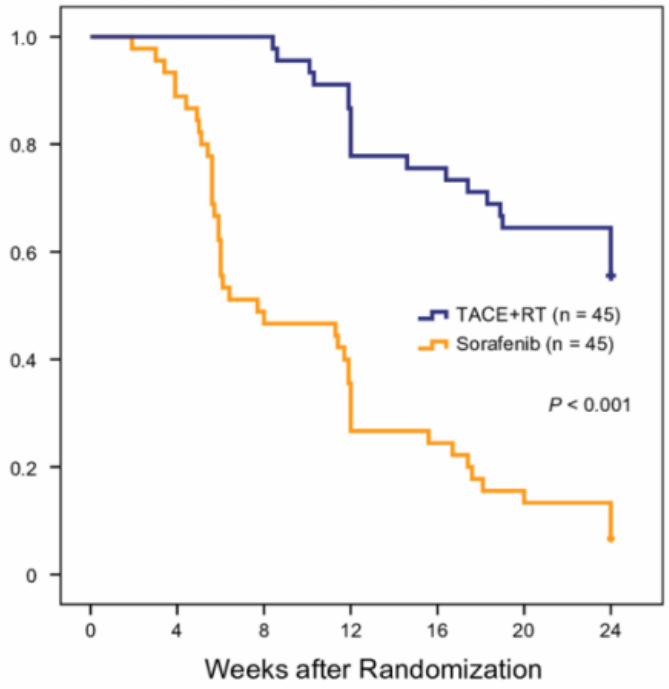
HCC therapies

sorafenib vs. TACE + external beam radiotherapy in HCC with vascular invasion

START trial: 7/2013-10/2016 (phase 2)

Randomized 1:1

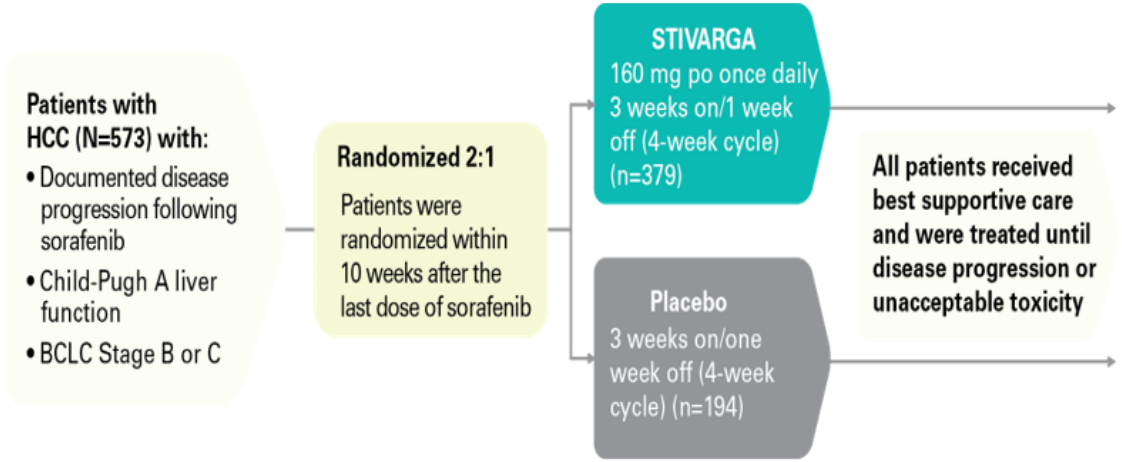
PFS rates within 24 weeks

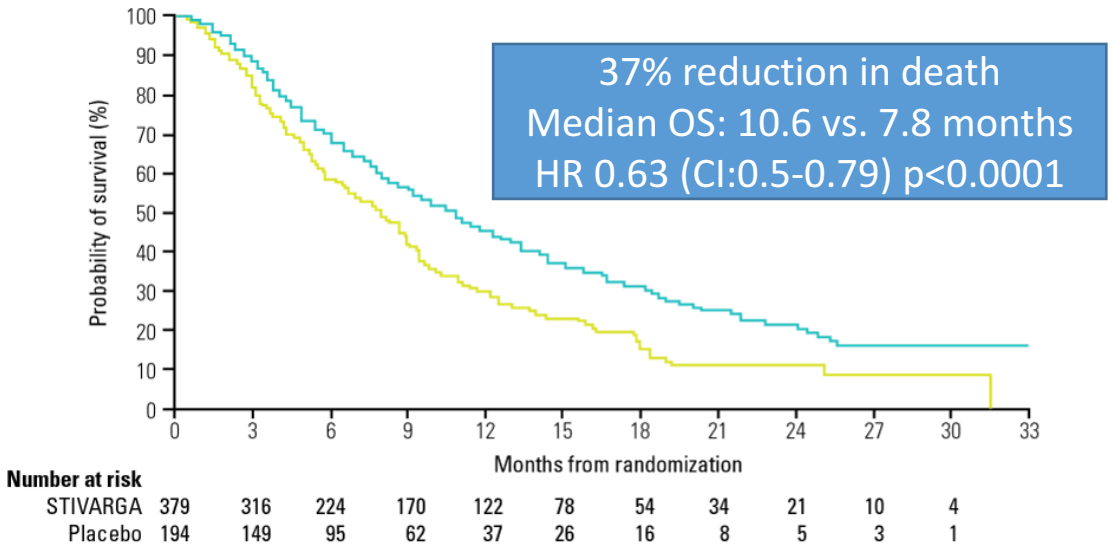


Outcome	Sorafenib (n = 45)	TACE+RT (n = 45)
At 12 weeks		
Radiologic response rate, n (%)	2 (4.4%)	13 (28.9%)
Complete Response	0	0
Partial Response	2 (4.4%)	13 (28.9%)
Stable Disease	10 (22.2%)	23 (51.1%)
Progressive Disease	25 (55.6%)	9 (20.0%)
Not evaluable*	8 (17.8%)	0
Progression-free survival rate,†‡ % (95% CI)	26.7% (16.4 – 43.3)	77.8% (66.5 – 90.9)

Yoon S et al. Abs 1360. AASLD 2017

Regorafenib





37% reduction in death
Median OS: 10.6 vs. 7.8 months
HR 0.63 (CI:0.5-0.79) p<0.0001

REG is a multikinase inhibitor targeting tumor angiogenesis, tumor immunity, proliferation and metastasis

Side effects occurred within the first 4 weeks of therapy

Table 1. TEAEs reported in ≥30% of patients in either treatment group at any grade

	Regorafenib (n=374)				Placebo (n=193)			
		Grade				Grade		
TEAE, %	Any		3	4	Any		3	4
HFSR	53	14%	13	NA	8	4%	1	NA
Diarrhea	42	11%	3	0	15	7%	0	0
Fatigue	41	11%	9	NA	32	16%	5	NA
Hypertension	31	18%	15	<1	6	3%	5	0
Anorexia	31	8%	3	0	15	7%	2	0

HFSR, hand–foot skin reaction; NA, not applicable; TEAE, treatment-emergent adverse event.

Bruix J et al. Lancet.2017;389:56-66
Merle P et al. Abs 1354. AASLD 2017

Lenvatinib

REFLECT STUDY (phase 3)

-Unresectable HCC (n=954)
-No prior systemic Rx
-BCLC stage B or C

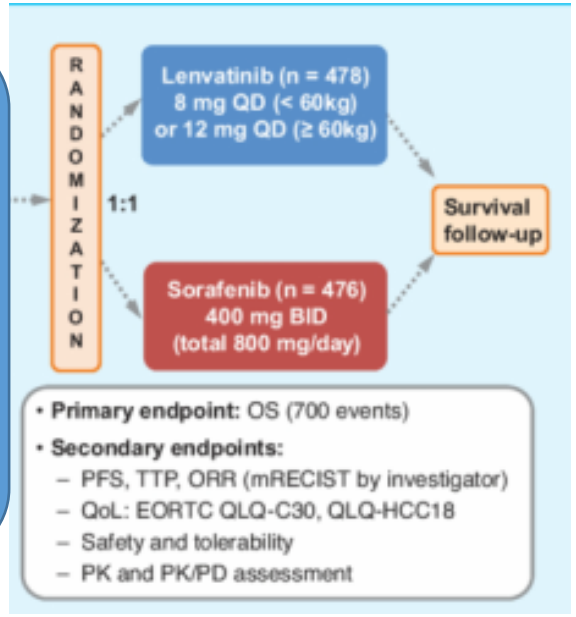


Table 1. Efficacy outcomes

Efficacy outcome median (95% CI)	Overall Population		Asia-Pacific Population	
	Lenvatinib (n = 259)	Sorafenib (n = 244)	Lenvatinib (n = 218)	Sorafenib (n = 208)
OS, months	13.4 (11.6–14.6)	10.2 (8.6–12.4)	13.1 (10.9–14.4)	9.4 (8.0–11.1)
HR (95% CI)	0.83 (0.68–1.02)		0.82 (0.66–1.02)	
PFS, months	7.3 (5.6–9.1)	3.6 (2.6–3.6)	7.4 (5.5–9.2)	3.5 (2.0–3.6)
HR (95% CI)	0.62 (0.50–0.75)		0.58 (0.46–0.71)	
TTP, months	7.6 (6.6–9.2)	3.6 (3.4–3.7)	9.1 (5.8–9.2)	3.6 (2.4–3.6)
HR (95% CI)	0.58 (0.47–0.72)		0.56 (0.44–0.70)	
ORR, %	20.8 (15.9–25.8)	8.2 (4.8–11.6)	21.1 (15.7–26.5)	8.7 (4.8–12.5)
OR (95% CI)	3.15 (1.80–5.53)		2.88 (1.60–5.19)	

CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

LEN is a inhibitor of growth factor receptors 1-3, fibroblast growth factor receptors 1-4, derived growth factor receptor α, and KIT

Han KH et al. Abs 1382. AASLD 2017

Conclusions

- HCC in Hispanics is rising
  - ?association with NAFLD
- We still need to do better job at screening for HCC
- The myth of DAA and de-novo HCC is settled
- HCC decreases SVR12
- Chemoprevention: aspirin, Zinc, vitamin D
- New approved therapies for HCC
- Markers for HCC progression in development