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MEETING SUMMARY
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IMMUNE THERAPY IN HEPATOCELLULAR CARCINOMA

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YEARLY AGE-ADJUSTED INCIDENCE RATES OF HCC IN UNITED STATES BETWEEN 2000 AND 2012 BY RACE AND ETHNICITY

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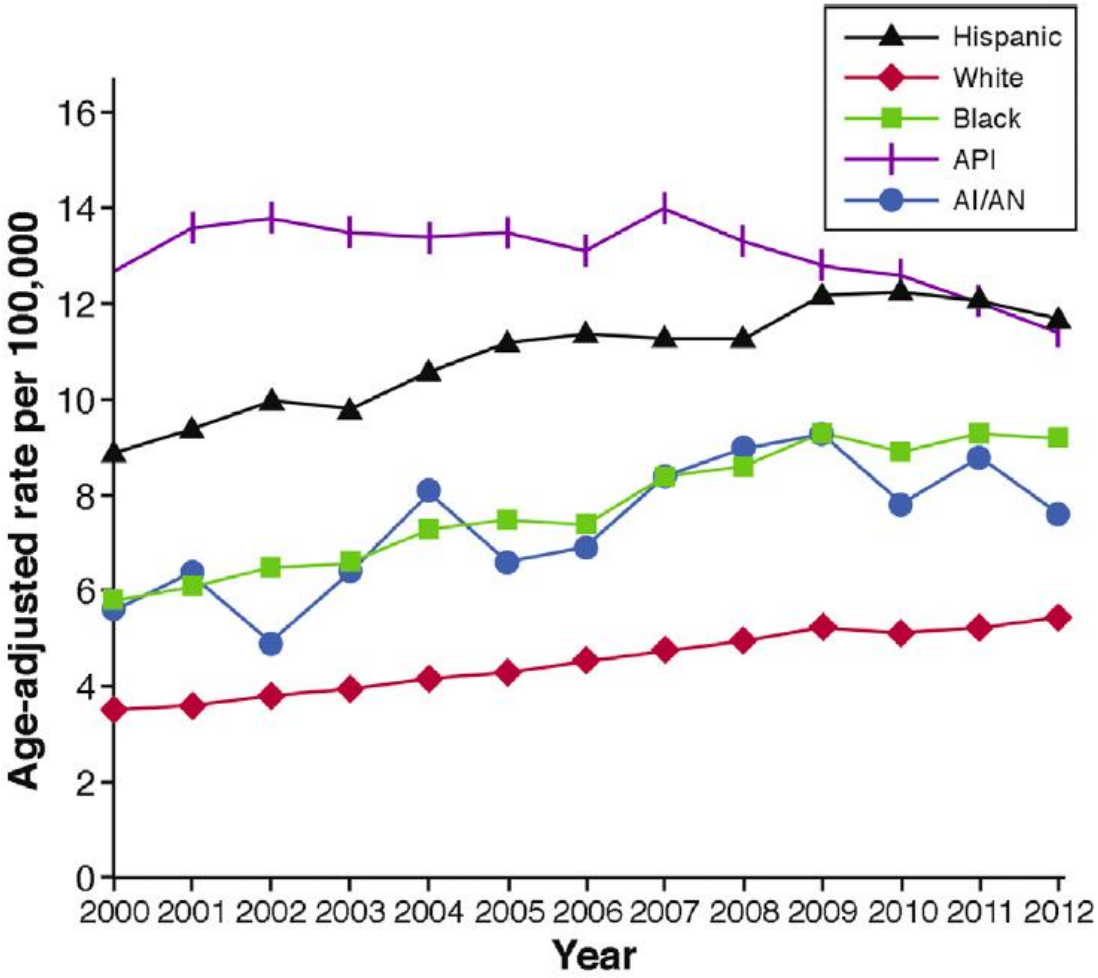
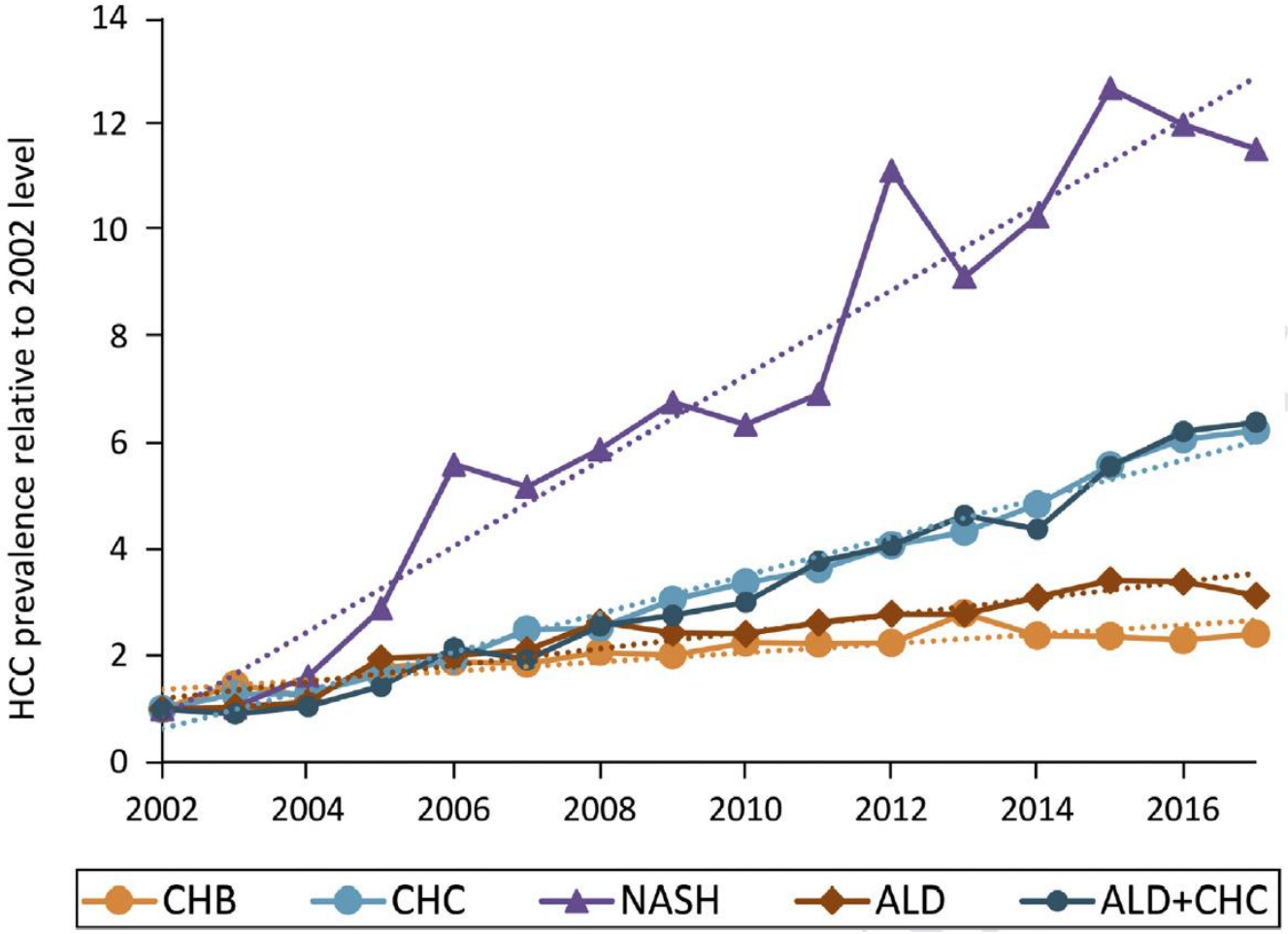


AI/AN, American Indian or Alaska Native; API, Asian Pacific Islander; HCC, hepatocellular carcinoma

Kulik L, El-Serag HB. Gastroenterology. 2019;156:477-491

PREVALENCE OF HCC IN WAITLISTED CANDIDATES BY ETIOLOGY



ALD, alcoholic liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis

Younossi Z, et al. Clin Gastroenterol Hepatol. 2019;17:748-755.e3

IMMUNE-CHECKPOINT MOLECULES TURN ON THE LIGHT SWITCH AND ALLOW IMMUNE RESPONSES AGAINST HCC

OFF ON

HCC, hepatocellular carcinoma

FDA-APPROVED SYSTEMIC THERAPIES FOR HCC

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Sequence	Agent	Mechanism of Action
First-Line Therapy	Sorafenib	Multi-kinase inhibitor acting through inhibition of the serine-threonine kinases Raf-1 and B-Raf, VEGF receptors 1-3 and PDGF receptor
	Lenvatinib	Multi-kinase inhibitor, targeting VEGF receptors 1-3, FGF receptors 1-4, PDGF receptor α, RET, and KIT
Second-Line Therapy	Regorafenib	Multi-kinase inhibitor, targeting VEGF receptors 1-3, KIT, RET, B-Raf and PDGF receptor
	Cabozantinib	Multi-kinase inhibitor, targeting VEGF receptors 1-3, MET, AXL, RET, KIT, and FLT3
	Ramucirumab	Recombinant human monoclonal antibody which binds to VEGF receptor 2, blocking endothelial proliferation
	Nivolumab	Inhibitor of PD-1, a receptor expressed on the surface of T-cells allowing for increased immune response against tumour cells
	Pembrolizumab	Inhibitor of PD-1, a receptor expressed on the surface of T-cells allowing for increased immune response against tumour cells

B-Raf, v-raf murine sarcoma viral oncogene homolog B; FDA, Food and Drug Administration; FGF, fibroblast growth factor; FLT3, fms-related tyrosine kinase 3; HCC, hepatocellular carcinoma; KIT, v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog; MET, met proto-oncogene; PD-1, programmed cell death protein 1; PDGF, platelet-derived growth factor; Raf-1, v-raf-1 murine leukaemia viral oncogene homolog 1; RET, rearranged during transfection; VEGF, vascular endothelial growth factor

Winters A, et al. Clin Liver Dis. 2019 (in press)

CLINICAL-TRIAL EXPERIENCE WITH IMMUNE-CHECKPOINT INHIBITORS IN HCC

CHECKMATE-040

CHECKMATE 040: EFFICACY, HEPATIC SAFETY, AND BIOMARKERS OF NIVOLUMAB + IPILIMUMAB COMBINATION THERAPY IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

Sangro B, et al. AASLD 2019 Abstract #200

METHODS

- **Phase 1/2 study** randomising sorafenib-treated patients with advanced HCC to:
  A. Nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3W – 4 doses → nivolumab 240 mg Q2W
  B. Nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W – 4 doses → nivolumab 240 mg Q2W
  C. Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W

- Treatment continued until intolerable toxicity or disease progression

- **Primary endpoints**
  - Safety and tolerability (investigator assessed using NCI CTCAE v4.0)
  - ORR and DoR (investigator assessment per RECIST v1.1)
  - OS

CTCAE, Common Terminology Criteria for Adverse Events; DoR, duration of response; HCC, hepatocellular carcinoma; NCI, National Cancer Institute; ORR, overall response rate; OS, overall survival; QxW, every x weeks; RECIST, Response Evaluation Criteria in Solid Tumours

1. Sangro B, et al. AASLD 2019 Abstract #200. 2. https://clinicaltrials.gov/ct2/show/NCT01658878. Accessed 15 November 2019.

RESULTS

N = 148	Arm A (NIVO1 + IPI3 Q3W)	Arm B (NIVO3 + IPI3 Q3W)	Arm C (NIVO3 Q2W + IPI1 Q6W)
Median follow-up	28 months		
Efficacy			
ORR, %	32	31	31
CR, n	4	3	0
Median OS, months	22.8	12.5	12.7
Safety			
Hepatic TRAEs of any grade, %			
Abnormal liver-function tests	39	37	21
Increased blood bilirubin	6	0	4
Hepatic IMAEs, n/N (%)	10/49 (20)	6/49 (12)	3/48 (6)
Resolved, n/N (%)	9/10 (90)	5/6 (83)	2/3 (67)
Median time to onset, weeks (range)	5.6 (3.1-17.9)	8.1 (1.1-12.7)	5.9 (3.6-8.6)
Median time to resolution, weeks (range)	6.6 (0.4-58.7)	7.9 (1.6-16.0)	6.1 (3.9-88.6+)

CR, complete response; IMAE, immune-mediated adverse event; IPI, ipilimumab; NIVO, nivolumab; ORR, overall response rate; OS, overall survival; QxW, every x weeks; RECIST, Response Evaluation Criteria in Solid Tumours; TRAE, treatment-related adverse event

Sangro B, et al. AASLD 2019 Abstract #200

AUTHORS' CONCLUSIONS

- **Nivolumab + ipilimumab** led to **durable response** in sorafenib-treated patients
  - Each treatment arm had an ORR twice that of nivolumab monotherapy
- The safety profile was acceptable and included **manageable hepatic IMAEs**
- The **favourable risk-benefit profile** observed warrants **further investigation** in patients with HCC
- Suggests **combination therapy** may play an important role in the treatment of advanced HCC
- Median **overall survival** substantially increased with combination therapy, but at a costs of greater adverse events

HCC, hepatocellular carcinoma; ORR, overall response rate
Sangro B, et al. AASLD 2019 Abstract #200

REAL-WORLD EXPERIENCE WITH IMMUNE-CHECKPOINT INHIBITORS IN HCC

REAL-WORLD EXPERIENCE OF NIVOLUMAB THERAPY FOR ADVANCED HEPATOCELLULAR CARCINOMA IN TAIWAN: EARLY REDUCTION OF SERUM ALPHA-FETOPROTEIN ASSOCIATED WITH THERAPEUTIC RESPONSE AND OVERALL SURVIVAL

Lin C-C, et al. AASLD 2019 Abstract #871

AIMS AND METHODS

- **Retrospective study** of 102 patients with advanced HCC (excluding Child-Pugh class C) who received nivolumab between August 2015 and December 2018
  - Age (60.6 ± 11.2 years), male (77.5%), ECOG PS >0 (52.9%), Child-Pugh A/B (82.3%/16.7%), HBV (66.7%), HCV (23.5%), EHS (63.7%), MVI (53.9%), BCLC stage B/C (12.8%/87.3%), and AFP >20 ng/mL (74.5%) before nivolumab treatment
  - 42 (41.2%) patients had not received any systemic treatment
- **Aim**
  - to report the real-world experience of nivolumab for the treatment of HCC in Taiwan
  - to evaluate the AFP response with nivolumab

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MVI, macrovascular invasion; RECIST, Response Evaluation Criteria in Solid Tumours

Lin C-C, et al. AASLD 2019 Abstract #871

RESULTS

Efficacy	N = 102
Response[a], %	
Overall response rate	17.6
Disease control rate	48.0
CR	2.9
PR	14.7
SD	30.4
PD	28.4
No image evaluation	23.5
Median duration of response, months	19.4
Median time to progression, months	3.0 ± 0.4
Median progression-free survival, months	4.2 ± 1.2
Median OS, months	11.4 ± 3.0

- 35 patients (34.3%) had **early AFP response**[b]
  - Early AFP responders vs non-early AFP responders had a
    - higher image response rate (40.0% vs 6.0%; *P*<0.001)
    - better OS (median: NR vs 8.3 months; *P*=0.006)
  - Early AFP response was independently associated with
    - therapeutic image response (*P*<0.001; OR: 9.294; 95% CI, 2.685-32.167)
    - better OS (*P*=0.001; HR: 0.292; 95% CI, 0.141-0.604)

[a] Image response was reviewed by an independent radiologist according to RECIST v1.1 criteria
[b] Early AFP response was defined as a baseline AFP level >20 ng/mL and >20% decrease from baseline within the first 3 months after starting nivolumab

AFP, α-fetoprotein; CI, confidence interval; CR, complete response; HR, hazard ratio; NR, not reached; OR, odds ratio; OS, overall survival PD, progressive disease; PR, partial response; SD, stable disease

Lin C-C, et al. AASLD 2019 Abstract #871

AUTHORS' CONCLUSIONS

- **Real-world experience** with nivolumab for advanced HCC in this HBV-predominant Chinese patient population **mirrors clinical trial efficacy**

- **Early AFP response** was associated with a higher therapeutic response and a better OS

AFP, α-fetoprotein; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; OS, overall survival

Lin C-C, et al. AASLD 2019 Abstract #871

NIVOLUMAB IN THE MANAGEMENT OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH ADVANCED CIRRHOSIS: A REAL-LIFE EXPERIENCE FROM INDIA

Arora V, et al. AASLD 2019, Abstract #872

BACKGROUND AND METHODS

- **Background**
  - Real-life experience with nivolumab in the management of HCC is scarce, especially in patients with advanced liver disease from India
  - Most patients have been treated in clinical trials investigating nivolumab in Child-Pugh class A or early B patients in the BCLC-B stage
- This **retrospective study** included patients with HCC treated with nivolumab at the ILBS, New Delhi, India, with:
  - age 18-75 years
  - AST/ALT <5 × ULN
  - progression on or intolerance to sorafenib
  - macrovascular invasion
  - performance status ≥1
  - not amenable to liver transplantation or resection or loco-regional therapy

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; ILBS, Institute of Liver and Biliary Sciences; HCC, hepatocellular carcinoma; ULN, upper limit of normal

Arora V, et al. AASLD 2019 Abstract #872

RESULTS

- **35 patients** with HCC were included
  - Viral hepatitis (48.6%) and NASH (42.9%) were the predominant aetiologies for cirrhosis
  - Child-Pugh classes were A (28.6%), B (54.3%) and C (17.1%)
  - Mean MELD was 14.14 ± 3.21
  - BCLC stage B (22.8%) and C (77.2%)
- Dosage of **nivolumab** was 3 mg/kg in all patient groups
  - The median number of cycles administered was 5 (2-12)
- **Prior treatment**
  - TACE or RFA: 17 (48.6%) patients
  - Sorafenib: 19 (54.3%) patients
- The mean **AFP value** was log 5.96 ± 3.14 ng/mL
  - A significant reduction by log 3.1 was noted in responders vs non-responders ($P<0.001$)

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; MELD, Model For End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization

Arora V, et al. AASLD 2019: Abstract #872

RESULTS *(CONTINUED)*

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- **Response**
  - CR in 1 patient (2.8%)
  - PR in 8 patients (22.8%)
  - SD in 10 patients (28.6%)
- 39 **AEs** were noted
  - None required discontinuation of nivolumab
- No significant differences between sorafenib-exposed vs sorafenib-naïve patients and patients with viral hepatitis-related HCC vs other aetiologies
- Median follow-up after therapy completion was 120 days
  - 1/9 responders died (11.1%)
  - 13/26 non-responders died (53.8%; p=0.01)

AE, adverse event; CR, complete response; HCC, hepatocellular carcinoma; PR, partial response; SD, stable disease

Arora V, et al. AASLD 2019 Abstract #872

AUTHORS' CONCLUSIONS

- Nivolumab treatment is **safe and clinically efficacious** even in patients with advanced cirrhosis, compromised performance status and inoperable HCC
- Nivolumab reduced **AFP levels** and reduced or stabilised the **tumour burden**
- Patients with advanced liver disease and HCC **require further prospective evaluation** of the efficacy of nivolumab

AFP, α-fetoprotein; HCC, hepatocellular carcinoma

Arora V, et al. AASLD 2019 Abstract #872

REGORAFENIB VERSUS NIVOLUMAB FOR HEPATOCELLULAR CARCINOMA PATIENTS WHO EXPERIENCED SORAFENIB TREATMENT FAILURE: A PROPENSITY SCORE ANALYSIS

Lee C-H, et al. AASLD 2019 Abstract #331

AIMS AND METHODS

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- **Retrospective analysis** of 151 patients with HCC who received regorafenib (n=103) or nivolumab (n=48) after sorafenib treatment failure

- **Aim**: to compare the efficacy of regorafenib and nivolumab in HCC patients who have failed sorafenib treatment

HCC, hepatocellular carcinoma

Lee C-H, et al. AASLD 2019 Abstract #331

RESULTS

- **Median OS**
  - Regorafenib: 6.4 months (95% CI, 2.4–10.4)
  - Nivolumab: 5.9 months (95% CI, 3.7–8.1) (log-rank *P*=0.82)

- After **adjusting for baseline characteristics**, patients treated with nivolumab showed **significantly longer OS** vs patients treated with regorafenib (aHR: 0.48; 95% CI, 0.25-0.91; *P*=0.03)
  - Baseline characteristics included the levels of ALP, AST, and MoRAL score [=11xsqrt(PIVKA) + 2xsqrt(AFP)], Child-Pugh class and the presence of clinically significant portal hypertension

AFP, α-fetoprotein; ALP, alkaline phosphatase; AST, aspartate aminotransferase; aHR, adjusted hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; MoRAL, Model of Recurrence After Liver Transplant; OS, overall survival; PIVKA, prothrombin induced by vitamin K absence

Lee C-H, et al. AASLD 2019 Abstract #331

AUTHORS' CONCLUSIONS

- **Improved OS** was demonstrated in patients who were treated with nivolumab vs patients who were treated with regorafenib after rigorous adjustment for baseline demographic and clinical characteristics

OS, overall survival

Lee C-H, et al. AASLD 2019 Abstract #331

CLINICAL INTERPRETATION

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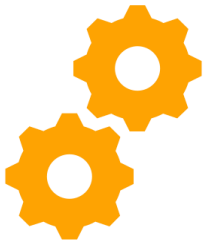
Real-life experiences confirm efficacy and safety of immune mediators like nivolumab in the treatment of HCC

These data **suggest a role for on-treatment assessment of AFP values** to predict treatment response



Clinical trials are needed to confirm the **optimal treatment sequence** for individual patient groups

AFP, α-fetoprotein; HCC, hepatocellular carcinoma

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