Received: 22 November 2021 | Revised: 29 March 2022 | Accepted: 4 April 2022

DOI: 10.1002/hep.32527

ORIGINAL ARTICLE

Racial and ethnic disparities in early treatment with immunotherapy for advanced HCC in the United States

Joseph C. Ahn[1] | Marie Lauzon[2] | Michael Luu[2] | Mazen Noureddin[3,4] | Walid Ayoub[3,4] | Alexander Kuo[3,4] | Vinay Sundaram[3,4] | Kambiz Kosari[3,5,6] | Nicholas Nissen[3,5,6] | Jun Gong[5] | Andrew Hendifar[5] | Lewis R. Roberts[1] | Ghassan K. Abou-Alfa[7,8] | Amit G. Singal[9,10] | Ju Dong Yang[3,4,5]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA

[2]Biostatistics and Bioinformatics Research Center, Cedars-Sinai Medical Center, Los Angeles, California, USA

[3]Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, California, USA

[4]Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, California, USA

[5]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA

[6]Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, California, USA

[7]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA

[8]Department of Medicine, Weill Medical College at Cornell University, New York, New York, USA

[9]Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, Texas, USA

[10]Division of Digestive and Liver Diseases, UT Southwestern Medical Center, Dallas, Texas, USA

Correspondence
Ju Dong Yang, Karsh Division of Gastroenterology and Hepatology, Department of Medicine, Cedars Sinai Medical Center at 8900 Beverly Blvd., Los Angeles, CA 90048, USA.
Email: judong.yang@cshs.org

Abstract

Background and Aims: Immunotherapy has emerged as an effective treatment for patients with advanced-stage HCC. We aimed to investigate the efficacy of immunotherapy for advanced HCC in a nationwide cohort and racial and ethnic disparities in access to immunotherapy.

Approach and Results: We used the US National Cancer Database to identify patients with tumor-node-metastasis stage 3 or 4 HCC between 2017 and 2018. We performed multivariable Cox regression to identify factors associated with overall survival (OS) and logistic regression to identify factors associated with receipt of immunotherapy. Of the 3,990 patients treated for advanced HCC, 3,248 (81.4%) patients received chemotherapy and 742 (18.6%) patients received immunotherapy as a first-line treatment. Immunotherapy was associated with improved OS compared with chemotherapy (adjusted HR: 0.76, 95% CI: 0.65–0.88) after adjusting for covariates. There were racial and ethnic disparities in access to immunotherapy, with Hispanic (adjusted OR [aOR]: 0.63, 95% CI: 0.46–0.83) and Black patients (aOR: 0.71, 95% CI: 0.54–0.89) less likely to receive immunotherapy compared with White patients. There was a significant interaction between race-ethnicity and facility type, with higher disparity observed in nonacademic centers (interaction p = 0.004).

Conclusions: Immunotherapy was associated with improved OS compared with chemotherapy in advanced HCC. There are significant disparities in early access to immunotherapy, likely due to differential access to clinical trials and experimental therapies. A comprehensive approach to monitoring and eliminating racial-ethnic disparities in the management of advanced HCC is urgently needed.

Abbreviations: AFP, alpha-fetoprotein; aHR, adjusted HR; aOR, adjusted OR; CTLA-4, cytotoxic T lymphocyte-associated protein 4; FDA, US Food and Drug Administration; ICPI, immune checkpoint inhibitor; MELD, model for end-stage liver disease; NCDB, national cancer center database; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; RR, relative risk; TNM, tumor/node/metastasis.

INTRODUCTION

HCC is an aggressive primary liver cancer that develops in patients with chronic liver disease and is a leading cause of global cancer mortality.[1] Patients diagnosed with early-stage HCC may achieve favorable long-term survival from curative treatments such as ablation, resection, or liver transplantation. On the other hand, patients who have large tumor burden, vascular invasion, or extrahepatic metastasis have poor outcomes.[2] Nevertheless, decades of research and several recent positive phase 3 clinical trials have led to substantial progress in the systemic treatment of patients with advanced HCC.[3]

The first breakthrough came with the advent of molecularly targeted chemotherapy agents in the family of oral multityrosine kinase inhibitors. In 2007, sorafenib was approved as the first-line treatment for patients with Child-Pugh A cirrhosis and unresectable or metastatic HCC.[4] Since 2017, another multityrosine kinase inhibitor, lenvatinib, has been approved as an additional first-line treatment,[5] and two additional multityrosine kinase inhibitors (cabozantinib and regorafenib) and a VEGF receptor 2 inhibitor (ramucirumab) have been approved as second-line treatments.[6–8] However, none of the molecularly targeted chemotherapy agents have demonstrated significantly improved survival compared with sorafenib.

In recent years, immunotherapy using immune checkpoint inhibitors targeting programmed cell death-1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T lymphocyte–associated protein 4 (CTLA-4) have revolutionized the treatment of many cancers, with HCC being no exception.[9] The anti-PD-1 antibody, pembrolizumab, was approved as a second-line agent for patients with advanced HCC after open-label, single-arm phase 2 trial demonstrated durable responses in 15%–20% of patients.[10] In 2020, the combination of the anti-PDL1 antibody atezolizumab and the anti-VEGF antibody bevacizumab was found to be superior to sorafenib in a phase 3, randomized controlled trial and was approved as the first-line treatment for advanced HCC.[11] Other combination therapies are being evaluated and awaiting further data to be reported.[12–14]

Historically, racial and ethnic minorities have been underrepresented in clinical trials and experimental treatments for cancer.[15] As with other therapies, there is also a concern for potential racial-ethnic disparities in early access to immunotherapy among patients with HCC in the United States. With the emergence of immunotherapy as a highly promising new treatment in patients with advanced HCC, it is important to investigate potential disparities and ensure that patients have equitable access to these highly effective but expensive new drugs. Therefore, the aims of this study were to investigate the efficacy of immunotherapy for advanced HCC in a large nationwide cohort as well as racial and ethnic disparity in access to immunotherapy.

METHODS

Database

We conducted a retrospective cohort study using the National Cancer Database (NCDB). The NCDB is a large, nationwide clinical oncology database sponsored by the American College of Surgeons and the American Cancer Society. The NCDB is comprised of hospital registry data from over 1,500 U.S. facilities accredited by the Commission on Cancer, which represents more than 70% of newly diagnosed cancer cases and 34 million historical records.[11]

Patients and variables

All patients diagnosed with HCC between January 1, 2017, and December 31, 2018, were identified by the NCDB. The diagnosis of HCC was based on the International Classification of Diseases–Oncology 3rd Edition code C22.0 and the histology codes 8170-8175. We only included patients who met the definition of stage 3 or 4 HCC according to the American Joint Committee on Cancer tumor-node-metastasis (TNM) classification system and received systemic treatment as a first-line treatment.[16] Patients with missing treatment information and those who were not treated with immunotherapy or chemotherapy as first-line treatment were excluded. NCDB does not provide detailed information on the specific immunotherapy and chemotherapy regimens. NCDB classifies multityrosine kinase inhibitors as chemotherapy and immune checkpoint inhibitor as immunotherapy. In this study, patients who received both chemotherapy and immunotherapy as first-line treatment were classified as the immunotherapy group.

Covariates including demographics, socioeconomic status, medical comorbidities, treatment facility, treatment region, as well as liver and HCC-specific clinical variables including Model for End-Stage Liver Disease (MELD) score, method of diagnosis, tumor size, and alpha-fetoprotein (AFP) category were captured for all patients. Demographic information included patients' age, sex, and race-ethnicity. Categories of socioeconomic status included insurance status, median income level, educational level, and living environment. Medical comorbidities were graded by the Charlson/Deyo Comorbidity Index. Treating facilities were classified into academic (> 500 new cancer diagnoses annually and at least four postgraduate training programs), comprehensive community (> 500 new cancer diagnoses annually), integrated network (no minimum

caseload; joint venture with multiple facilities, at least one of which is a hospital; and a commission on cancer-accredited cancer program), and community (100–500 new cancer diagnoses annually). The treating facilities were also classified by to their geographic regions within the United States (Northeast, Midwest, South, and West).

Statistical analysis

Baseline demographic and clinical characteristics were summarized using standard descriptive measures, then compared by treatment group using the Welch's t-test, Mann-Whitney Wilcoxon test, or Pearson's chi-square test where appropriate. Survival probabilities were estimated using the Kaplan-Meier method and compared using the log-rank test. Median follow-up was estimated using the reverse Kaplan-Meier method.[17] Time-to-event was defined as the time from HCC diagnosis to death, with patients otherwise censored at date of last follow-up. To identify factors associated with overall survival (OS), univariate and multivariable Cox proportional hazards regression was performed for patients diagnosed in 2017, as follow-up survival data are not available for patients diagnosed in 2018. The proportional hazards assumption was assessed visually using the scaled Schoenfeld residuals and quantitatively using the goodness-of-fit test as described by Grambsch and Therneau.[18] Univariate and multivariable logistic regression was used to test the association between race-ethnicity and the receipt of immunotherapy over chemotherapy. Interactions between race-ethnicity and other covariates were tested by including an interaction term in the multivariable logistic regression model. The chained equation approach for multiple imputation was used[19] to account for missing data in the NCDB. Cirrhosis was not added in the main regression analysis due to a high proportion of missing data (90%), although we performed a secondary analysis after adding the cirrhosis variable with missing data imputation in the multivariable model. Subgroup analysis was performed to demonstrate the impact of immunotherapy and chemotherapy combination on OS. All statistical analyses were performed using R statistical software (version 4.0.5; R Foundation, Vienna, Austria) with two-sided tests and a significance level of 0.05.

RESULTS

Patient characteristics

Table 1 summarizes the baseline characteristics for the 3,990 patients with advanced HCC who received systemic treatments for advanced HCC in 2017 and 2018. There were 3,248 (81.4%) patients treated with chemotherapy and 742 (18.6%) patients treated with immunotherapy. During the study period, the annual proportion of patients receiving immunotherapy increased from 14.2% in 2017 to 23.0% in 2018. The two treatment groups had similar age and sex distributions, with median age of 64 years and male predominance. Compared to patients treated with chemotherapy, patients treated with immunotherapy had higher proportions of White (66.6% vs. 61.9%) and Asian (10.3% vs. 7.9%) patients and lower proportions of Hispanic (9.1% vs. 12.4%) and Black patients (14.0% vs. 17.8%) ($p < 0.001$). In addition, higher proportions of patients treated with immunotherapy belonged to the highest income quartile (34.5% vs. 27.7%, $p = 0.001$) and lived in neighborhoods with high average education levels (21.2% vs. 14.9%, $p = 0.002$).

Compared with patients in the chemotherapy group, a higher proportion of the immunotherapy group was treated at academic centers (55.1% vs. 45.8%, $p < 0.001$) and in the Northeast (29.6% vs. 19.8%, $p < 0.001$). Patients treated with immunotherapy had larger tumor sizes (median 8.0 cm vs. 7.5 cm, $p = 0.012$). There were no significant differences in the Charlson Comorbidity Index, diagnosis method, MELD score, cirrhosis, or AFP category between the two groups.

Factors associated with OS

Patients who were diagnosed in 2017 (total = 2020, 1732 chemotherapy vs. 288 immunotherapy) were included in the survival analysis. Over a median follow-up of 6.8 months, the median OS for the entire cohort was 7.6 months. One-year and 2-year survival estimates were 30.8% and 11.4%, respectively. Median [interquartile range] follow-up times among those who were censored were similar between the immunotherapy (22.6 [14.2, 26.5]) and chemotherapy (19.1 [8.3, 26.7]) groups. Patients who received immunotherapy had higher OS compared with patients who received systemic treatment at 1 year (39.9% vs. 29.3%) and 2 years (13.5% vs. 11.0%) (Figure 1). In multivariable Cox regression analysis (Table 2), receipt of immunotherapy was independently associated with improved OS (adjusted HR [aHR]: 0.76, 95% CI: 0.65–0.88) compared with chemotherapy. After the addition of cirrhosis status, immunotherapy continued to be associated with improved OS (aHR: 0.76, 95% CI: 0.65–0.89). Among the immunotherapy group, 303 (40.8%) patients received combination therapy and 439 patients (59.2%) received immunotherapy alone. Both combination treatment (aHR: 0.72, 95% CI: 0.58–0.89) and immunotherapy alone (aHR: 0.79, 95% CI: 0.65–0.97) were associated

TABLE 1 Baseline characteristics of patients with advanced HCC

Characteristics		[ALL] *N = 3,990*	Chemotherapy *N = 3,248*	Immunotherapy *N = 742*	*p*
Mean age (SD)		64.2 (9.87)	64.3 (9.70)	63.8 (10.6)	0.283
Sex	Male	3,245 (81.3%)	2,645 (81.4%)	600 (80.9%)	0.758
	Female	745 (18.7%)	603 (18.6%)	142 (19.1%)	
Race	White	2,449 (62.7%)	1,965 (61.9%)	484 (66.6%)	0.001
	Hispanic	460 (11.8%)	394 (12.4%)	66 (9.08%)	
	Black	668 (17.1%)	566 (17.8%)	102 (14.0%)	
	Asian + others	327 (8.38%)	252 (7.93%)	75 (10.3%)	
Insurance status	Uninsured	155 (3.93%)	131 (4.08%)	24 (3.27%)	0.691
	Private	1,201 (30.4%)	969 (30.2%)	232 (31.7%)	
	Medicaid/Medicare	2,513 (63.7%)	2,050 (63.8%)	463 (63.2%)	
	Other	77 (1.95%)	63 (1.96%)	14 (1.91%)	
Median income	< $40,227	832 (25.4%)	702 (26.5%)	130 (20.9%)	0.001
	$40,227–$50,353	765 (23.4%)	612 (23.1%)	153 (24.6%)	
	$50,354–$63,332	725 (22.2%)	601 (22.7%)	124 (20.0%)	
	$63,333 +	949 (29.0%)	735 (27.7%)	214 (34.5%)	
Without high school degree	≥ 17.6%	998 (30.4%)	816 (30.7%)	182 (29.2%)	0.002
	10.9%–17.5%	950 (29.0%)	786 (29.6%)	164 (26.3%)	
	6.3%–10.8%	802 (24.5%)	657 (24.7%)	145 (23.3%)	
	< 6.3%	529 (16.1%)	397 (14.9%)	132 (21.2%)	
Urban/rural	Metro	3,319 (85.7%)	2,708 (85.5%)	611 (86.3%)	0.759
	Urban	495 (12.8%)	407 (12.9%)	88 (12.4%)	
	Rural	60 (1.55%)	51 (1.61%)	9 (1.27%)	
Facility type	Academic	1,861 (47.5%)	1,464 (45.8%)	397 (55.1%)	< 0.001
	Community cancer program	222 (5.67%)	193 (6.04%)	29 (4.03%)	
	Comprehensive cancer program	1,227 (31.3%)	1,016 (31.8%)	211 (29.3%)	
	Integrated network	607 (15.5%)	524 (16.4%)	83 (11.5%)	
Region	Northeast	845 (21.6%)	632 (19.8%)	213 (29.6%)	< 0.001
	Midwest	802 (20.5%)	696 (21.8%)	106 (14.7%)	
	South	1,610 (41.1%)	1,338 (41.9%)	272 (37.8%)	
	West	660 (16.8%)	531 (16.6%)	129 (17.9%)	
Charlson Comorbidity Index	0 or 1	2,861 (71.7%)	2,307 (71.0%)	554 (74.7%)	0.062
	2	426 (10.7%)	347 (10.7%)	79 (10.6%)	
	≥ 3	703 (17.6%)	594 (18.3%)	109 (14.7%)	
Diagnosis method	Cytology or histology	2,546 (63.8%)	2,054 (63.2%)	492 (66.3%)	0.127
	Clinical diagnosis	1,444 (36.2%)	1,194 (36.8%)	250 (33.7%)	
AFP	Negative	297 (16.7%)	254 (16.7%)	43 (16.7%)	1.000
	Positive	1,485 (83.3%)	1,271 (83.3%)	214 (83.3%)	
Median MELD [IQR]	11.0 [8.47; 16.2]	10.9 [8.47; 15.8]	11.6 [8.48; 17.6]	0.164	
Cirrhosis	No	87 (21.1%)	72 (20.1%)	15 (27.8%)	0.268
	Yes	325 (78.9%)	286 (79.9%)	39 (72.2%)	
Median tumor size, cm [IQR]	7.50 [4.90; 11.1]	7.50 [4.80; 11.0]	8.00 [5.10; 11.9]	0.012	

Abbreviations: AFP, alpha-fetoprotein; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; NA, not applicable.

with improved OS compared with chemotherapy, although the aHR was numerically lower in the combination group. Other factors associated with poor OS include nonacademic facility type, higher Charlson Comorbidity Index, increased AFP, higher MELD score, and larger tumor size.

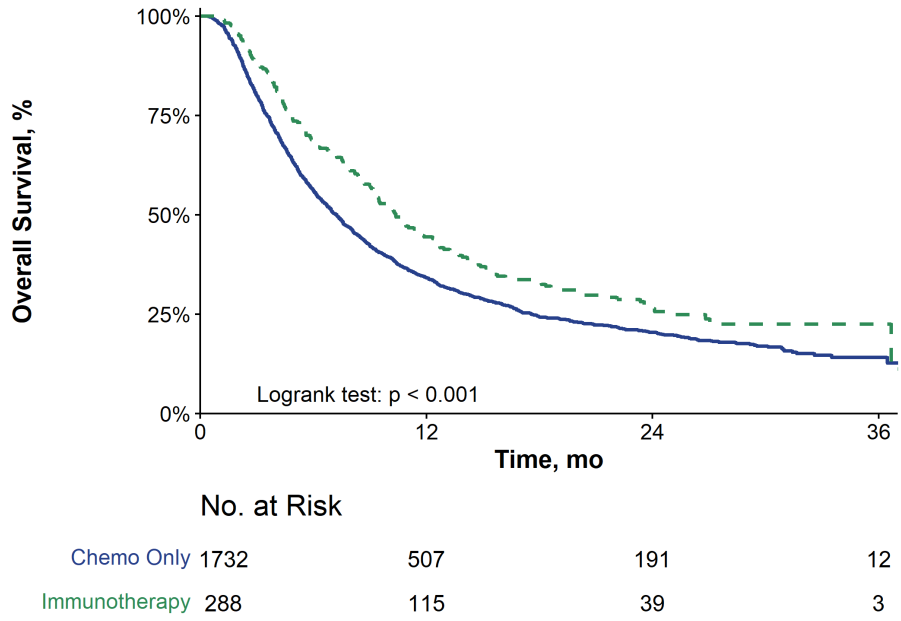

FIGURE 1 Overall survival estimates of patients with advanced-stage HCC treated with immunotherapy versus chemotherapy

Factors associated with receipt of immunotherapy as a first-line treatment

Table 3 displays the results of logistic regression on the factors associated with receiving immunotherapy instead of chemotherapy. All 3,990 subjects (3,248 chemotherapy vs. 742 immunotherapy) were included in the analysis. Race-ethnicity was one of the strongest predictors of receiving immunotherapy: Hispanic (adjusted OR [aOR]: 0.63, 95% CI: 0.46–0.83) and Black patients (aOR: 0.71, 95% CI: 0.54–0.89) were significantly less likely to receive immunotherapy compared with White patients. In contrast, there were no significant differences in treatment choice by socioeconomic status or education measures.

Type and region of treatment site showed a strong association with receipt of immunotherapy. Compared with patients treated at academic centers, those treated at community cancer programs (aOR: 0.56, 95% CI: 0.36–0.82), comprehensive community cancer programs (aOR: 0.77, 95% CI: 0.62–0.92), and integrated networks (aOR: 0.62, 95% CI: 0.48–0.80) were significantly less likely to receive immunotherapy. In addition, patients treated in the Midwest (aOR: 0.45, 95% CI: 0.36–0.61) and the South (aOR: 0.67, 95% CI: 0.57–0.87) were less likely to receive immunotherapy compared with patients treated in the Northeast. In terms of clinical variables, patients with Charlson Comorbidity Index of 3 or higher were less likely to receive immunotherapy compared to those with Charlson Comorbidity Index of 0 or 1 (aOR: 0.76, 95% CI: 0.59–0.94). While diagnosis method, MELD score, and AFP were not associated with receipt of immunotherapy, larger tumor size was associated with a higher likelihood of receiving immunotherapy (aOR: 1.01, 95% CI: 1.004–1.03).

Finally, we tested the interaction between race-ethnicity and other factors for association with receipt of immunotherapy. While there was no significant interaction between race-ethnicity with socioeconomic status (e.g., medical insurance, median income, education), there was a significant interaction between race-ethnicity with facility type, with higher racial and ethnic disparities observed in nonacademic centers than academic centers (interaction $p = 0.004$) (Table 4).

DISCUSSION

Our study provides an analysis of large-scale nationwide data demonstrating race-ethnicity-specific early use and efficacy of immunotherapy in patients with advanced HCC, with several important findings to be highlighted. Our study confirmed the efficacy of immunotherapy by demonstrating improved OS among a large nationwide cohort of patients who received immunotherapy versus chemotherapy. While chemotherapy remained the most common treatment received by patients with advanced HCC, the proportion of patients receiving immunotherapy increased by about 10% between 2017 and 2018. With the recent approval of atezolizumab-bevacizumab combination as first-line therapy for patients with advanced HCC, this trend of increased use of immunotherapy will likely continue to accelerate, given its superior efficacy. In addition, we discovered significant disparities in early access to immunotherapy, with lower use among Black and Hispanic patients compared with White patients.

TABLE 2 Factors associated with overall survival among patients with advanced HCC

	Univariate		Multivariable	
Characteristics	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age (10-year change)	1.009 (0.959–1.061)	0.734	1.015 (0.957–1.076)	0.627
Sex_Male (reference)	(reference)		(reference)	
Sex_Female	0.999 (0.877–1.138)	0.985	1.006 (0.881–1.149)	0.930
Race_White (reference)	(reference)		(reference)	
Race_Hispanic	0.897 (0.757–1.063)	0.210	0.949 (0.791–1.139)	0.575
Race_Black	1.039 (0.902–1.197)	0.596	1.049 (0.901–1.220)	0.539
Race_Asian + Others	1.018 (0.844–1.228)	0.850	1.092 (0.893–1.337)	0.391
Uninsured (Refence)	(reference)		(reference)	
Private insurance	0.933 (0.703–1.239)	0.631	0.995 (0.744–1.331)	0.974
Medicaid/Medicare insurance	0.899 (0.681–1.185)	0.450	0.965 (0.723–1.287)	0.808
Other insurance	0.690 (0.418–1.140)	0.148	0.715 (0.427–1.197)	0.202
Median income < $40,227 (reference)	(reference)		(reference)	
Median income $40,227–$50,353	1.040 (0.878–1.232)	0.649	1.016 (0.835–1.237)	0.870
Median income $50,354–$63,332	1.007 (0.858–1.182)	0.933	0.959 (0.782–1.176)	0.686
Median income $63,333+	1.019 (0.884–1.174)	0.799	1.055 (0.840–1.324)	0.647
Without high school degree ≥ 17.6% (reference)	(reference)		(reference)	
Without high school degree 10.9%–17.5%	1.121 (0.973–1.291)	0.114	1.110 (0.931–1.325)	0.246
Without high school degree 6.3%–10.8%	1.024 (0.885–1.186)	0.748	0.994 (0.811–1.219)	0.954
Without high school degree < 6.3%	1.061 (0.889–1.267)	0.509	1.020 (0.786–1.323)	0.881
Metro (reference)	(reference)		(reference)	
Urban	1.140 (0.979–1.327)	0.092	1.113 (0.946–1.310)	0.198
Rural	1.094 (0.747–1.602)	0.644	1.121 (0.759–1.657)	0.566
Facility_Academic (reference)	(reference)		(reference)	
Facility_Community Cancer Program	1.524 (1.226–1.894)	< 0.001	1.453 (1.160–1.820)	0.001
Facility_Comprehensive Community Cancer Program	1.329 (1.182–1.494)	< 0.001	1.341 (1.186–1.516)	< 0.001
Facility_Integrated Network	1.264 (1.086–1.471)	0.002	1.238 (1.060–1.447)	0.007
Region_Northeast (reference)	(reference)		(reference)	
Region_Midwest	1.204 (1.027–1.411)	0.022	1.142 (0.961–1.357)	0.132
Region_South	1.131 (0.985–1.299)	0.082	1.072 (0.925–1.241)	0.357
Region_West	1.129 (0.953–1.338)	0.161	1.054 (0.881–1.262)	0.563
Charlson Index 0 or 1 (reference)	(reference)		(reference)	
Charlson Index 2	1.054 (0.894–1.243)	0.533	1.091 (0.922–1.289)	0.310
Charlson Index 3	1.170 (1.026–1.334)	0.019	1.215 (1.060–1.392)	0.005
Diagnosis_Cytology (reference)	(reference)		(reference)	
Diagnosis_Clinical	0.964 (0.868–1.071)	0.499	0.962 (0.862–1.074)	0.494
AFP_Normal (reference)	(reference)		(reference)	
AFP_Elevated	1.332 (1.153–1.539)	< 0.001	1.309 (1.126–1.522)	< 0.001
MELD score (10-unit change)	1.099 (1.019–1.185)	0.014	1.086 (1.008–1.171)	0.030
Tumor size	1.010 (1.004–1.016)	0.001	1.011 (1.005–1.017)	< 0.001
Treatment_Chemotherapy (reference)	(reference)		(reference)	
Treatment_Immunotherapy	0.759 (0.654–0.881)	< 0.001	0.756 (0.649–0.881)	< 0.001

The advent of immune checkpoint inhibitors (ICPIs) has transformed the treatment for numerous types of cancers including HCC.[20] The first study of ICPIs in patients with advanced HCC was reported in 2013, when tremelimumab, a monoclonal antibody against CTLA-4, showed significant antitumor and antiviral effects in

TABLE 3 Factors associated with immunotherapy treatment among patients with advanced HCC

	Univariate		Multivariable	
Characteristics	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age (10-year change)	0.955 (0.881–1.035)	0.256	0.915 (0.835–0.998)	0.051
Sex_Male (reference)	(reference)		(reference)	
Sex_Female	1.038 (0.845–1.269)	0.718	1.093 (0.885–1.344)	0.404
Race_White (reference)	(reference)		(reference)	
Race_Hispanic	0.684 (0.523–0.907)	0.007	0.625 (0.458–0.829)	0.002
Black	0.731 (0.572–0.910)	0.008	0.706 (0.541–0.893)	0.006
Race_Asian + others	1.190 (0.906–1.568)	0.213	0.994 (0.732–1.317)	0.970
Uninsured (reference)	(reference)		(reference)	
Private insurance	1.312 (0.861–2.157)	0.244	1.075 (0.691–1.768)	0.762
Medicaid/Medicare insurance	1.236 (0.816–1.999)	0.352	1.125 (0.731–1.849)	0.618
Other insurance	1.218 (0.585–2.515)	0.593	1.076 (0.502–2.241)	0.847
Median income < $40,227 (reference)	(reference)		(reference)	
Median income $40,227–$50,353	1.274 (0.968–1.554)	0.045	1.248 (0.939–1.567)	0.090
Median income $50,354–$63,332	1.116 (0.893–1.451)	0.377	1.052 (0.848–1.487)	0.723
Median income $63,333+	1.472 (1.236–1.914)	< 0.001	1.133 (0.935–1.739)	0.427
Without high school degree ≥ 17.6% (reference)	(reference)		(reference)	
Without high school degree 10.9%–17.5%	0.943 (0.759–1.159)	0.586	0.896 (0.688–1.099)	0.361
Without high school degree 6.3%–10.8%	1.009 (0.769–1.194)	0.936	0.929 (0.639–1.114)	0.603
Without high school degree < 6.3%	1.400 (1.138–1.813)	0.005	1.258 (0.834–1.599)	0.166
Metro (reference)	(reference)		(reference)	
Urban	0.941 (0.730–1.185)	0.621	1.015 (0.802–1.351)	0.908
Rural	0.766 (0.343–1.451)	0.463	0.865 (0.405–1.771)	0.697
Facility_Academic (reference)	(reference)		(reference)	
Facility_Community Cancer Program	0.566 (0.371–0.828)	0.005	0.562 (0.360–0.817)	0.006
Facility_Comprehensive Community Cancer Program	0.770 (0.637–0.918)	0.005	0.766 (0.624–0.918)	0.007
Facility_Integrated Network	0.587 (0.459–0.760)	< 0.001	0.617 (0.477–0.801)	< 0.001
Region_Northeast (reference)	(reference)		(reference)	
Region_Midwest	0.453 (0.356–0.591)	< 0.001	0.454 (0.357–0.607)	< 0.001
Region_South	0.610 (0.511–0.763)	< 0.001	0.672 (0.568–0.869)	< 0.001
Region_West	0.727 (0.576–0.941)	0.011	0.807 (0.641–1.075)	0.105
Charlson Index 0 or 1 (reference)	(reference)		(reference)	
Charlson Index 2	0.948 (0.726–1.225)	0.689	1.004 (0.761–1.297)	0.979
Charlson Index 3	0.764 (0.608–0.953)	0.019	0.763 (0.593–0.940)	0.021
Diagnosis_Cytology (reference)	(reference)		(reference)	
Diagnosis_Clinical	0.874 (0.738–1.033)	0.117	0.856 (0.709–1.007)	0.083
AFP_Normal (Reference)	(reference)		(reference)	
AFP_Elevated	0.849 (0.754–1.143)	0.122	0.869 (0.799–1.217)	0.202
MELD (10 units change)	1.043 (0.972–1.178)	0.393	1.079 (1.008–1.228)	0.130
Tumor size	1.015 (1.006–1.027)	0.005	1.014 (1.004–1.026)	0.012

patients with HCC and chronic HCV infection.[21] Within the past few years, efficacy and safety of two anti-PD-1 antibodies, nivolumab and pembrolizumab, were proven in patients with advanced HCC.[10,22–24] Several combinations of PD-1/PDL-1 inhibitors with CTLA-4 inhibitors, VEGF inhibitor, or multikinase inhibitors have shown promising results.[25–29] with the recent approval of the atezolizumab-bevacizumab combination

TABLE 4 Association between race-ethnicity and immunotherapy receipt stratified by facility type

	Academic center			Nonacademic center		
Whites (Ref)	**aOR**	**95% CI**	***p***	**aOR**	**95% CI**	***p***
Hispanics	0.68	0.37–1.25	0.550	0.58	0.29–1.17	0.274
Blacks	0.97	0.59–1.58	0.999	0.48	0.24–0.95	0.023
Asian/Others	1.48	0.82–2.67	0.465	0.58	0.26–1.30	0.451

Abbreviation: aOR, adjusted OR.

treatment as a first-line treatment for patients with advanced HCC.[28] Our retrospective analysis of close to 4,000 patients from the NCDB showed that receipt of immunotherapy over chemotherapy was independently associated with improved survival. These are meaningful large-scale nationwide data outside of individual clinical trials, which confirms the effectiveness of immunotherapy compared with chemotherapy. Moreover, multiple studies have shown immunotherapy to be relatively well-tolerated with an acceptable side-effect profile and quality of life compared with sorafenib. With many other phase 3 trials underway testing various combinations between ICPIs and tyrosine kinase inhibitors, the role of immunotherapy in patients with advanced HCC will continue to evolve and become individualized according to patient characteristics and tolerability.[9]

Despite the positive results showing the overall efficacy of immunotherapy in patients with advanced HCC, our study also highlights significant racial and ethnic disparities in early access to immunotherapy, more notable in the nonacademic cancer centers. It is known that health care disparities can emerge or worsen with discoveries of more effective approaches to cancer treatment such as immunotherapy.[30] Racial and ethnic minorities experience significant barriers in access to clinical trials and experimental therapies. For example, a study of 310 clinical trials conducted between 2003 and 2016 showed that Black and Hispanic patients were less likely to enroll in clinical trials for breast, colorectal, lung, pancreas, prostate, and renal cell carcinoma and melanoma.[31] A more recent study with the National Cancer Institute's Clinical Data Update System between 2000 and 2019 showed persistent underrepresentation of Black and Hispanic patients in breast, colorectal, lung, and prostate cancer clinical trials, although disparity has decreased in recent years.[32] The barriers could arise at multiple levels.[15] At a system level, racial and ethnic minorities are more likely to be underinsured and receive their care at underresourced hospital systems with limited offers for clinical trials or experimental drugs.[33] Studies have reported that implicit bias among physicians has an impact on interactions with racial and ethnic minority patients, and that some physicians are hesitant to discuss clinical trials or experimental treatments with Black patients because they believe that Black patients will be resistant or less likely to comply with the recommended treatments.[34,35] Conversely, racial and ethnic minority patients and their family members may also hold negative attitudes and mistrust toward clinical trials and experimental treatments, which affects their willingness to participate.[36,37] A recent study among a cohort of patients with HCC highlighted high proportions of medical mistrust, health literacy, and transportation barriers among Black and Hispanic patients compared with White patients.[38] At an interpersonal level, racial and ethnic differences in the quality of communication between health care professionals and patients exist, with or without language barriers. A linguistic analysis of encounters between oncologists and Black patients has shown that the visit times were overall shorter compared to the visits with White patients, the topic of clinical trials was less frequently mentioned, and even when clinical trials were mentioned, less time was spent discussing them.[39]

Racial and ethnic disparities in HCC treatment have been well-described before the advent of immunotherapy.[40,41] A retrospective study of patients in two large urban health systems showed that Hispanic patients (OR: 0.75, 95% CI 0.55–1.00) and Black patients (OR: 0.74, 95% CI 0.56–0.98) were significantly less likely to be diagnosed with early-stage HCC compared with White patients, likely due to decreased access to HCC surveillance.[42] Another large retrospective study of patients with early-stage HCC using the Surveillance, Epidemiology, and End Results database suggested that Black patients were less likely to receive liver transplantation (relative risk [RR]: 0.54, 95% CI 0.36–0.79), and Hispanic patients were less likely to receive resection (RR: 0.47, 95% CI 0.30–0.74) or ablation (RR: 0.63, 95% CI 0.48–0.82) compared with White patients.[43] Another recent study of 359 patients with HCC showed that Black and Hispanic patients were significantly less likely to receive any form of treatment for HCC compared with White patients (50% vs. 45.3% vs. 15.2%, $p < 0.001$), and Black patients had a significantly higher risk of mortality compared with White patients (HR: 1.87, 95% CI 1.06–3.28).[44,45] In light of such significant racial and ethnic disparities in early access to immunotherapy during the years before US Food and Drug Administration (FDA) approval or clinical trial participation, a comprehensive approach

involving all stakeholders will be needed to eliminate disparities in access to clinical trials and novel experimental treatment, and make it an available option for patients with advanced HCC across all demographic and socioeconomic backgrounds across the United States. A multilevel, team-based approach designed to eliminate biases and mistrust, and to facilitate effective communications with minority patients, will be critical.

The strength of our study includes the use of a large, nationwide sample that provides valuable data on the use of immunotherapy in patients with advanced HCC. While most clinical trials limit their participants to those with well-preserved liver function (Child-Pugh A cirrhosis), more than half of the patients in our study had MELD scores greater than 10, indicating the inclusion of patients with hepatic dysfunction. Furthermore, our study highlighted significant racial/ethnic, socioeconomic, and regional disparities in access to immunotherapy, which could be a surrogate for clinical trial participation and early access to novel experimental therapy.

Our study also must be interpreted in the context of its limitations related to its study design and data source. This was a retrospective study of a large cancer-focused database that is limited to patients treated at the participating institutions. Some of the pertinent clinical data such as patients' Child-Pugh class, Barcelona Clinic Liver Cancer staging, and etiology of liver disease were not available, although we did have information on patients' MELD scores, AFP, and tumor sizes. Because NCDB groups Medicare and Medicaid under the same umbrella of government-sponsored insurances, we could not assess the difference in outcomes between patients with Medicare versus Medicaid, although the two may represent very different patient populations. As our study period was limited to years 2017 and 2018, with follow-up OS information available in patients diagnosed in 2017, we had a relatively small sample size for subgroup analysis. We do not have detailed information on the specific immunotherapy and chemotherapy regimens used at individual levels. As immunotherapy received FDA approval as first-line therapy in advanced HCC in May 2020, patients in our cohort received immunotherapy via a clinical trial setting or off-label use as an experimental treatment. NCDB does not provide information on whether immunotherapy was administered under clinical trial participation. We believe that a significant portion of patients may have received immunotherapy as an off-label use outside of clinical trials, as our cohort had shorter OS than what has been reported in previous clinical trials. However, the proportion of clinical trial participants was likely different between immunotherapy and chemotherapy groups, which could have introduced selection bias.

Considering that immunotherapy obtained FDA approval as a first-line treatment for HCC in 2020, use of immunotherapy is projected to greatly increase over the next several years. Therefore, additional ongoing assessments will be needed to more clearly elucidate the national trends in immunotherapy use, race-ethnicity specific disparities in immunotherapy access, and patient outcomes in this new era of HCC treatment.

Immunotherapy is associated with improved survival compared with chemotherapy in patients with advanced HCC. Although the use of immunotherapy for treatment of advanced HCC will likely increase, significant disparities in access to immunotherapy need to be further investigated in future studies. Our results also suggest a significant disparity in early access to clinical trials and novel experimental therapies. A comprehensive approach to monitoring and eliminating racial-ethnic disparities in the management of advanced HCC is urgently needed.

DISCLOSURE

Dr. Yang provides a consulting service for Eisai, Exact Sciences, and Gilead. Dr. Singal has been on advisory boards and served as a consultant for Genentech, Bayer, Eisai, BMS, Exelixis, AstraZeneca, and TARGET RWE. No other potential conflicts of interest relevant to this article exist. Dr. Abou-Alfa received institutional research support from Arcus, Agios, Astra Zeneca, BioNtech, BMS, Celgene, Flatiron, Genentech/Roche, Genoscience, Incyte, Polaris, Puma, QED, Silenseed and Yiviva, and consulting support fromAdicet, Alnylam, Astra Zeneca, Autem, Bayer, Beigene, Berry Genomics, Celgene, Cend, CytomX, Eisai, Eli Lilly, Exelixis, Flatiron, Genentech/Roche, Genoscience, Helio, Incyte, Ipsen, Legend Biotech, Merck, Nerviano, QED, Redhill, Rafael, Servier, Silenseed, Sobi, Surface Oncology, Therabionics, Vector, and Yiviva. Dr. Gong serves a consulting/advisory role for EMD Serono, Elsevier, Exelixis, QED Therapeutics, Natera, Basilea, HalioDx, Eisai, Janssen, Astellas, and Amgen.

CONFLICT OF INTEREST

Dr. Abou-Alfa received research support from Arcus, Astra Zeneca, BioNtech, BMS, Celgene, Flatiron, Genentech/Roche, Genoscience, Incyte, Polaris, Puma, QED, Silenseed and Yiviva, and consulting support from Adicet, Alnylam, Astra Zeneca, Autem, Beigene, Berry Genomics, Boehringer Ingelheim, Celgene, Cend, CytomX, Eisai, Eli Lilly, Exelixis, Flatiron, Genentech/Roche, Genoscience, Helio, Helsinn, Incyte, Ipsen, Merck, Nerviano, Newbridge, Novartis, QED, Redhill, Rafael, Servier, Silenseed, Sobi, Vector and Yiviva, and has a patent submission PCT/US2014/031545 filed on March 24, 2014, and priority application Serial No. 61/804,907 (filed March 25, 2013).

Dr. Singal consults for Genentech, AstraZeneca, Bayer, Eisai, Exelixis, BMS, and TARGET RWE.

Dr. Hendifar consults and received grants from Ipsen, Novartis, and Merck.

Dr. Yang consults for Exact Sciences and Eisai.

Dr. Roberts advises and received grants from Bayer, Exact Sciences, and Gilead Sciences. He consults for AstraZeneca, MJH Life Sciences, Pontifax, Novartis Venture Fund, Roche Laboratories, and Global Life Science. He advises GRAIL, Tavec, QED Therapeutics, Genentech, Envision, Eisai, Hepion, and Lynx Group. He received grants from Ariad, BTG International/ Boston Scientific, Fujifilm, TARGET PharmaSolutions, Glycotest, and RedHill.

Dr. Noureddin owns stock and received grants from Viking. He owns stock in Aneatos and Rivus Pharma. He consults for and received grants from Gilead, Pfizer, and Madrigal. He consults for 89 Bio, Altimmune, cohBar, Cytodyn, Intercept, Novo Nordisk, Blade, EchoSens, Fractyl, NorthSea, Perspectum, Terns, Siemens, and Roche Diagnostic. He received grants from Allergan, BMS, Galmed, Galectin, Genfit, Conatus, Enanta, Novartis, Shire, and Zydus.

Dr. Sundaram consults for Saol. He is on the speakers' bureau for Gilead and AbbVie.

AUTHOR CONTRIBUTIONS

Study concept: Ju Dong Yang. *Data extraction, statistical analysis, and generation of tables and figures:* Marie Lauzon and Michael Luu. *Data interpretation:* All authors. *Manuscript draft:* Joseph C. Ahn, under Ju Dong Yang's supervision. *Manuscript revisions and critical review for important intellectual content:* Mazen Noureddin, Walid Ayoub, Alexander Kuo, Vinay Sundaram, Kambiz Kosari, Nicholas Nissen, Jun Gong, Andrew Hendifar, Shelly C. Lu, Lewis R. Roberts, Ghassan K. Abou-Alfa, and Amit G. Singal. All authors approved the final version to be published.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available in the National Cancer Database. https://www.facs.org/quality-programs/cancer/ncdb.

ORCID

Joseph C. Ahn https://orcid.org/0000-0001-6994-2870
Vinay Sundaram https://orcid.org/0000-0002-1450-7756
Amit G. Singal https://orcid.org/0000-0002-1172-3971
Ju Dong Yang https://orcid.org/0000-0001-7834-9825

REFERENCES

1. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 2017;3:524–548.
2. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol. 2006;44:723–731.
3. Yang JD, Heimbach JK. New advances in the diagnosis and management of hepatocellular carcinoma. BMJ. 2020;371:m3544.
4. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378–390.
5. Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163–73.
6. Abou-Alfa GK, Meyer T, Cheng A-L, El-Khoueiry AB, Rimassa L, Ryoo B-Y, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med. 2018;379:54–63.
7. Bruix J, Qin S, Merle P, Granito A, Huang Y-H, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389:56–66.
8. Zhu AX, Kang Y-K, Yen C-J, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20:282–96.
9. Sangro B, Sarobe P, Hervás-Stubbs S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2021;18:525–43.
10. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19:940–52.
11. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382:1894–905.
12. Rimassa L, Cheng A, Braiteh F, Benzaghou F, Hazra S, Borgman A, Sinha R, et al. P-238 - Phase 3 (COSMIC-312) study of cabozantinib in combination with atezolizumab vs sorafenib in patients with advanced hepatocellular carcinoma (aHCC) who have not received previous systemic anticancer therapy. Ann Oncol. 2019;30:iv65–iv66.
13. Llovet JM, Kudo M, Cheng A-L, Finn RS, Galle PR, Kaneko S, et al. Lenvatinib (len) plus pembrolizumab (pembro) for the first-line treatment of patients (pts) with advanced hepatocellular carcinoma (HCC): phase 3 LEAP-002 study. J Clin Oncol. 2019;37:TPS4152.
14. Abou-Alfa GK, Chan SL, Furuse J, Galle PR, Kelley RK, Qin S, et al. A randomized, multicenter phase 3 study of durvalumab (D) and tremelimumab (T) as first-line treatment in patients with unresectable hepatocellular carcinoma (HCC): HIMALAYA study. J Clin Oncol. 2018;36:TPS4144.
15. Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. Cancer Control J Moffitt Cancer Center. 2016;23:327–37.
16. Benson AB, D'Angelica MI, Abbott DE, Anaya DA, Anders R, Are C, et al. Hepatobiliary cancers, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19:541–65.
17. Moore D. Applied survival analysis using R. New York, NY: Springer; 2016. https://doi.org/10.1007/978-3-319-31245-3
18. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81:515–26.

19. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30:377–99.
20. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359:1350-1355.
21. Sangro B, Gomez-Martin C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol. 2013;59:81–8.
22. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389:2492–502.
23. Yau T, Park JW, Finn RS, Cheng A-L, Mathurin P, Edeline J, et al. LBA38_PR - CheckMate 459: a randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). Ann Oncol. 2019;30:v874–v875.
24. Finn RS, Ryoo B-Y, Merle P, Kudo M, Bouattour M, Lim HY, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. J Clin Oncol. 2019;38:193–202.
25. Yau T, Kang Y-K, Kim T-Y, El-Khoueiry AB, Santoro A, Sangro B, et al. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): results from CheckMate 040. J Clin Oncol. 2019;37:4012.
26. Kelley RK, Sangro B, Harris WP, Ikeda M, Okusaka T, Kang Y-K, et al. Efficacy, tolerability, and biologic activity of a novel regimen of tremelimumab (T) in combination with durvalumab (D) for patients (pts) with advanced hepatocellular carcinoma (aHCC). J Clin Oncol. 2020;38:4508.
27. Zhu AX, Finn RS, Ikeda M, Sung MW, Baron AD, Kudo M, et al. A phase Ib study of lenvatinib (LEN) plus pembrolizumab (PEMBRO) in unresectable hepatocellular carcinoma (uHCC). J Clin Oncol. 2020;38:4519.
28. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382:1894–905.
29. Kelley RK, Sangro B, Harris W, Ikeda M, Okusaka T, Kang Y-K, et al. Safety, efficacy, and pharmacodynamics of tremelimumab plus durvalumab for patients with unresectable hepatocellular carcinoma: randomized expansion of a phase I/II study. J Clin Oncol. 2021;39:2991–3001.
30. Osarogiagbon RU, Sineshaw HM, Unger JM, Acuña-Villaorduña A, Goel S. Immune-based cancer treatment: addressing disparities in access and outcomes. Am Soc Clin Oncol Educ Book. 2021;66–78.
31. Duma N, Vera Aguilera J, Paludo J, Haddox CL, Gonzalez Velez M, Wang Y, et al. Representation of minorities and women in oncology clinical trials: review of the past 14 years. J Oncol Pract. 2018;14:e1–e10.
32. Javier-DesLoges J, Nelson TJ, Murphy JD, McKay RR, Pan E, Parsons JK, et al. Disparities and trends in the participation of minorities, women, and the elderly in breast, colorectal, lung, and prostate cancer clinical trials. Cancer. 2022;128:770–7.
33. Diehl KM, Green EM, Weinberg A, Frederick WA, Holmes DR, Green B, et al. Features associated with successful recruitment of diverse patients onto cancer clinical trials: report from the American College of Surgeons Oncology Group. Ann Surg Oncol. 2011;18:3544–50.
34. Moskowitz GB, Stone J, Childs A. Implicit stereotyping and medical decisions: unconscious stereotype activation in practitioners' thoughts about African Americans. Am J Public Health. 2012;102:996–1001.
35. Sabin JA, Rivara FP, Greenwald AG. Physician implicit attitudes and stereotypes about race and quality of medical care. Med Care. 2008;46:678–85.
36. Rivers D, August EM, Sehovic I, Lee Green B, Quinn GP. A systematic review of the factors influencing African Americans' participation in cancer clinical trials. Contemp Clin Trials. 2013;35:13–32.
37. Ford JG, Howerton MW, Lai GY, Gary TL, Bolen S, Gibbons MC, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer. 2008;112:228–42.
38. Schoenberger H, Rich NE, Jones P, Yekkaluri S, Yopp A, Singal AG, Arroyo A, et al. Racial and ethnic disparities in barriers to care in patients with hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2021 Dec 26. https://doi.org/10.1016/j.cgh.2021.12.027. [Epub ahead of print].
39. Eggly S, Barton E, Winckles A, Penner LA, Albrecht TL. A disparity of words: racial differences in oncologist-patient communication about clinical trials. Health Expect. 2015;18:1316–26.
40. Guo A, Pomenti S, Wattacheril J. Health disparities in screening, diagnosis, and treatment of hepatocellular carcinoma. Clin Liv Dis. 2021;17:353–8.
41. Rich NE, Carr C, Yopp AC, Marrero JA, Singal AG. Racial and ethnic disparities in survival among patients with hepatocellular carcinoma in the United States: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2022;20:e267–e288.
42. Rich NE, Hester C, Odewole M, Murphy CC, Parikh ND, Marrero JA, et al. Racial and ethnic differences in presentation and outcomes of hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2019;17:551–9.
43. Peters NA, Javed AA, He J, Wolfgang CL, Weiss MJ. Association of socioeconomics, surgical therapy, and survival of early stage hepatocellular carcinoma. J Surg Res. 2017;210:253–60.
44. Barzi A, Zhou K, Wang S, Dodge JL, El-Khoueiry A, Setiawan VW. Etiology and outcomes of hepatocellular carcinoma in an ethnically diverse population: the multiethnic cohort. Cancers. 2021;13:3476.
45. Barzi A, Zhou K, Wang S, Dodge JL, El-Khoueiry A, Setiawan VW. Etiology and outcomes of hepatocellular carcinoma in an ethnically diverse population: the multiethnic cohort. Cancers. 2021;13:3476.

How to cite this article: Ahn JC, Lauzon M, Luu M, Noureddin M, Ayoub W, Kuo A, Racial and ethnic disparities in early treatment with immunotherapy for advanced HCC in the United States. Hepatology. 2022;76:1649–1659. https://doi.org/10.1002/hep.32527