OXFORD

Real-world Treatment Patterns and Reasons for Therapy Selection in Patients with Advanced Hepatocellular Carcinoma in US Oncology Practices

Andrew J. Klink[1,*], Landon Z. Marshall[1], Abdalla Aly[2], Brian Seal[2], Marcus J. Healey[2], Bruce Feinberg[1]

[1]Cardinal Health, Dublin, OH, USA
[2]AstraZeneca, Gaithersburg, MD, USA
*Corresponding author: Andrew J. Klink, PhD, MPH, Cardinal Health, 7000 Cardinal Place, Dublin, OH 43017, USA. Email: andrew.klink@cardinalhealth.com

Abstract

Background: The treatment landscape for advanced hepatocellular carcinoma (aHCC) is rapidly expanding beyond tyrosine kinase inhibitors (TKIs) in the first-line (1L) setting, with multiple TKIs and immune-checkpoint inhibitors (ICIs) now being evaluated in combination. Real-world evidence describing current treatment patterns and reasons for 1L and 2L treatment selection in aHCC is sparse.

Patients and Methods: A retrospective cohort study with a cross-sectional survey element was conducted using Cardinal Health's Oncology Provider Extended Network. U.S. medical oncologists identified adult aHCC patients initiating 1L systemic therapy between January 1, 2017 and July 31, 2019 and abstracted data from patient medical records. Data included provider characteristics, patient demographics and clinical characteristics, treatment regimens, and physician rationale for treatment regimen choice.

Results: A total of 44 medical oncologists provided data on 284 aHCC patients. The median age at 1L initiation was 61.5 years, and the majority were male (78%) and white (66%). Nearly half (47%) initiated 1L treatment in 2019, 34% were ECOG performance status 2+, and 63% were Child-Pugh Class B/C. Among the 284 aHCC patients, TKIs were used by 94% of patients in the 1L setting, comprised predominantly of sorafenib (54%) and lenvatinib (38%). ICIs were most common among the 90 patients (66%) who received 2L treatment.

Conclusion: In the community-oncology practice setting, nearly all aHCC patients received sorafenib or lenvatinib in the 1L setting, while the majority of patients received an ICI in the 2L setting. With recent ICI approvals in aHCC, this marks the beginning of an increased use of ICIs in the 1L setting.

Key words: carcinoma; hepatocellular; immune checkpoint inhibitors; liver neoplasms; humans; atezolizumab; bevacizumab.

Implications for Practice

We aimed to understand real-world management and treatment of advanced HCC, with a particular focus on reasons for selecting first- and second-line therapy. Recent evidence demonstrated the efficacy and safety of the immune checkpoint inhibitor combination atezolizumab/bevacizumab, which is now a recommended first-line regimen. With the rapidly changing armamentarium of treatment options in first and second line, oncologists must select the optimal treatment and sequence to manage and treat patients with advanced HCC within a value-based care framework.

Introduction

Liver cancers comprise the sixth leading cause of cancer deaths in the United States with a 5-year relative survival rate of 18%.[1] Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver with an estimated incidence of 5.84 per 100,000.[2,3] Cirrhosis, hepatitis B and C, alcoholic liver disease, non-alcoholic steatohepatitis, and metabolic syndrome are common risk factors for HCC development.[3]

Management of HCC requires a multidisciplinary collaboration between oncologists, hepatologists, interventional radiologists, and supportive care specialists to manage and treat tumor burden and hepatic dysfunction, which often coexist

due to underlying chronic liver disease. Curative treatment options such as surgical resection, ablation, or liver transplant are available for select HCC patients at early stages; however, many patients are initially diagnosed with late-stage disease due to the relatively asymptomatic nature of the disease.[4] In this later stage setting, there are significant unmet needs for patients with advanced HCC (aHCC, commonly referred to as unresectable HCC.[5]

Since 2017, multiple systemic treatment regimens have been approved by the U.S. Food and Drug Administration (FDA) in the first-line (1L) and second-line (2L) settings for patients with aHCC. In April 2017, regorafenib became the first liver cancer treatment approved (in 2L) since sorafenib in 2007 (in

1L).[6] Numerous FDA approvals have followed: accelerated approval for nivolumab in 2L[7] (September 2017) (although the FDA recently voted to oppose maintaining the accelerated approval for nivolumab), lenvatinib in 1L[8] (August 2018), accelerated approval for pembrolizumab in 2L[9] (November 2018), cabozantinib in 2L[10] (January 2019), ramucirumab in 2L[11] (May 2019), accelerated approval for nivolumab plus ipilimumab in 2L[12] (March 2020), and atezolizumab plus bevacizumab in 1L[13] (May 2020). In this often difficult-to-treat population, many factors influence treatment choice and treatment sequencing, which can include tumor-related characteristics (eg, alpha-fetoprotein [AFP] >400 ng/mL, extrahepatic spread), clinical presentation (eg, Child-Pugh [CP] score), physician preference (eg, perceived risk/benefit), patient preference (eg, route of administration, quality of life), and financial considerations (eg, out-of-pocket cost).[14]

The National Comprehensive Cancer Network (NCCN) gives a category 1 recommendation to treatment with sorafenib, lenvatinib, or atezolizumab plus bevacizumab in the 1L setting.[14] Subsequent treatments of regorafenib or cabozantinib (oral tyrosine kinase inhibitor [TKI] therapies) have category 1 recommendations by the NCCN in the 2L setting. Additionally, ramucirumab has an NCCN category 1 recommendation as subsequent therapy among patients with serum AFP greater than 400 ng/mL.[1] Immune checkpoint inhibitors (ICIs) are recommended as 2L or subsequent-line therapy with category 2A recommendations (nivolumab, nivolumab plus ipilimumab) or a category 2B recommendation (pembrolizumab).

The HCC treatment paradigm continues to evolve with multiple oral TKIs and ICIs now being evaluated in combination.[15] The approval of atezolizumab plus bevacizumab as a new option in the 1L treatment of aHCC likely marks the beginning of a shift in ICI use earlier in the treatment of aHCC.[13,16] Ongoing research efforts investigating combination therapies involving ICIs such as durvalumab plus tremelimumab,[17] cabozantinib plus atezolizumab,[18] and pembrolizumab plus lenvatinib[19] will likely introduce further variation in the sequence of treatments. The increasing incidence of aHCC and its etiological relationship to alcohol consumption, hepatitis B and C virus, as well as diabetes-induced liver disease is of interest as it may have implications for the expanding availability of therapeutics with the different mechanisms of action.[20] Currently, there is a dearth of data characterizing treatment patterns based on recent FDA drug approvals and guideline recommendations in real-world clinical practice. Treatment patterns, sequencing, and reasons for 1L and 2L treatment selection in aHCC are neither well understood nor adequately described. This study aimed to describe real-world treatment patterns and physicians' reasons for treatment selection among patients with aHCC. The primary objective was to describe systemic therapy patterns (eg, regimens received, duration of therapy, dose, dose adjustment, the reason for dose adjustment, the reason for discontinuation), byline of therapy (ie, 1L, 2L).

Methods

A retrospective cohort study with a cross-sectional survey element was conducted using Cardinal Health's Oncology Provider Extended Network (OPEN). This network consists of over 7000 active physicians across the United States with specialties in medical oncology or hematology; approximately 800 comprise the real-world research community.

Data were collected from patient medical records and abstracted into an electronic case report form (eCRF) by medical oncologists who treated and/or managed the patients included in this study. The same medical oncologists provided responses when asked what other regimens were considered and reasons for not selecting other regimens after consideration. Patient-level data included provider characteristics (eg, practice setting, specialty, practice experience), patient demographics and clinical characteristics (eg, age, gender, primary payer, ECOG-PS, CP score, disease characteristics (AFP level, BCLC stage), treatment regimens (eg, drug regimens, dates of initiation/discontinuation), and rationale for treatment regimen choice (according to physician opinion).

Patients included in the study had a histologically confirmed diagnosis of HCC, were 18 years or older at initial diagnosis of HCC, initiated 1L systemic therapy for aHCC between January 1, 2017 and July 31, 2019 and received treatment for at least 2 months (unless the patient died within 2 months of treatment initiation). Data were abstracted between March 1, 2020 and April 6, 2020. Patients with a diagnosis of any other malignancy (except for non-melanoma skin cancer and primary liver cancer) or with prior history of or awaiting liver transplantation were excluded from the study. Medical oncologists abstracted data on consecutive patients within their electronic medical records, beginning with the earliest patient meeting study selection criteria.

Participating medical oncologists were blinded to the study sponsor and vice versa. The eCRF and study protocol was submitted to the Western Institutional Review Board, a centralized, independent review board, and determined exempt from full review, and a waiver of informed consent was granted.

Data were summarized descriptively using counts and frequencies for dichotomous and categorical variables, while measures of centrality (mean, median) and spread (minimum, maximum, standard deviation [SD], interquartile range [IQR], as appropriate) were used for continuous variables. Treatment regimens were summarized according to the specific regimen for each line of therapy. Reasons for not using a regimen after consideration were expressed as a proportion of all aHCC patients. Statistical analyses were performed using the Statistical Analysis Software (SAS software version 9.4, SAS Institute Inc., Cary, NC).

Results

A total of 44 medical oncologists (Table 1) provided data on 284 aHCC patients (Table 2). Oncologists from small (23%, *n* = 10), medium (23%, *n* = 10), and large (25%, *n* = 11) community practices were evenly represented, and another 18% reported an affiliation with an academic center. Participating oncologists had a median of 16 years in practice and managed a median of 10 HCC patients in the year before data collection. Nearly 14% of oncologists practiced in rural settings, and the remainder were in urban (43%, *n* = 19) and suburban (43%, *n* = 19) settings. All 4 U.S. regions were represented, with the South representing the greatest proportion of oncologists (41%).

Median age at 1L initiation was 61.5 years (Table 2). The majority of patients (78%, *n* = 221) were male and white (66%, *n* = 187). Over one-third of patients had commercial

Table 1. Provider characteristics.

Provider characteristics	N = 44
Primary practice setting (*n*, %)	
Solo practitioner	3 (6.8%)
Small, private, community practice	10 (22.7%)
Medium-sized, private, community practice	10 (22.7%)
Large, private, community practice	11 (25.0%)
Community practice owned by an academic center/Academic medical center	8 (18.2%)
Affiliated teaching hospital	1 (2.3%)
VA/military hospital/DoD	1 (2.3%)
Specialty (*n*, %)	
Medical oncology	11 (25.0%)
Hematology/Oncology	29 (65.9%)
Medical oncology, Hematology/Oncology	4 (9.1%)
Years in practice (median, IQR)	16 (14-22)
Practice setting (*n*, %)	
Urban	19 (43.2%)
Suburban	19 (43.2%)
Rural	6 (13.6%)
Practice setting (*n*, %)	
Northeast	10 (22.7%)
Midwest	9 (20.5%)
South	18 (40.9%)
West	7 (15.9%)
Number of HCC patients managed in past year (median, IQR)	10 (6-20)

Notes: Small, 2-5 physicians; medium, 6-10 physicians; large, >10 physicians.
Missing or unknown data, if any, are reported per variable.
Abbreviations: DoD, Department of Defense; HCC, hepatocellular carcinoma; IQR, interquartile range (25th and 75th percentile reported); VA, Veterans Affairs.

insurance (37%, *n* = 106), and 22% (*n* = 62) and 19% (*n* = 53) had Medicare or Medicare Advantage/Supplemental, respectively. Nearly half (47%, *n* = 134) initiated 1L treatment in 2019, and 30% (*n* = 84) and 23% (*n* = 66) initiated 1L treatment in 2018 and 2017, respectively. Approximately one-third (34%, *n* = 97) were ECOG-PS 2+, and the majority were CP Class B/C (63%, *n* = 178). Before 1L therapy initiation, conventional transarterial chemoembolization (TACE) was used among 21% (*n* = 60) of patients, while interventional radiologists were involved in the treatment of 40% (*n* = 113) of patients. Supplementary Table 1 provides patient characteristics by 1L and 2L regimen.

Among the 284 aHCC patients, TKIs were the most common 1L treatment (94%, *n* = 266) (**Table 3**), predominantly comprised of sorafenib (55.3%, *n* = 157) and lenvatinib (38.4%, *n* = 109). Among the 90 patients who received 2L treatment during the study period, ICIs were the most common (65.6%, *n* = 59), followed by TKIs received by 34% of 2L patients. The 5 therapies most commonly received by patients in the 2L setting were the following: nivolumab (52.2%, *n* = 47), regorafenib (14.4%, *n* = 13), pembrolizumab (14.4%, *n* = 13), lenvatinib (10.0%, *n* = 9), and cabozantinib (8.9%, *n* = 8).

It is important to note that ICIs for aHCC were approved in 2020 and, before this time, were used only in clinical trial settings.[21] At the time of 1L decision making (**Supplementary Figure 1A**), sorafenib was used in 55.3% (*n* = 157) of patients (considered in 80.6%, *n* = 229; not used in 25.4%, *n* = 72).

At the time of 2L decision making (**Supplementary Figure 1B**), the top 3 regimens used were nivolumab (considered in 57.8% (*n* = 52); used in 52.2%, (*n* = 47); not used in 5.6%, *n* = 5%), pembrolizumab (considered in 21.1% (*n* = 19); used in 14.4% (*n* = 13); not used in 6.7%, *n* = 6), and regorafenib (considered in 16.7% (*n* = 15); used in 14.4% (*n* = 13); not used in 2.2% *n* = 2). **Supplementary Table 2** presents reasons for using TKI and ICI therapies and reasons for not using TKI and ICI therapies by regimen type and line of therapy.

Discussion

The rapidly expanding arsenal of treatments for aHCC is likely to increase variation in the treatment of this disease as physicians utilize novel agents in both monotherapy and in combination. Understanding the evolving patterns of care and the rationale behind the choice of treatment sequence is foundational in a value-based care delivery model. This was the basis for the methodology of selecting real-world data (RWD) collected by the treating medical oncologist coupled with their perceptions around treatment selection to construct the real-world evidence (RWE) around the management of aHCC.

The study cohort is largely representative of patients having metastatic disease (78%, *n* = 109) with poor prognostic factors such as moderate/higher tumor burden (49%, *n* = 139), portal vein thrombosis (36%, *n* = 102), cirrhosis (52%, *n* = 149), American Joint Committee on Cancer (AJCC) Stage IVB (65%, *n* = 85), CP Class B/C (63%, *n* = 178), BCLC Stage C or D (86%, *n* = 216), and ECOG-PS ≥2 (34%, *n* = 97). This population differs from aHCC clinical trial populations and recent RWE cohorts. For example, the phase III KEYNOTE-240 trial consisted of patients with a median age of 67 years, ECOG-PS 0/1, and CP Class A (99.6%).[22] In the phase III REFLECT trial (1L lenvatinib vs 1L sorafenib), mean age was 61 years, all patients were ECOG-PS 0/1 and CP Class A/B, 80% were BCLC Stage C, and 61% had extrahepatic spread.[23] Additionally, a recently published (2020) retrospective database study using IBM MarketScan, a healthcare database comprised of claims from large employers, managed care organizations, hospitals, EMR providers, Medicare, and Medicaid[24] described aHCC treatment patterns whereby 1L consisted mostly of sorafenib (77%) and 2L consisted mostly of systemic chemotherapy (49%) among a younger aHCC population (median age 62 years) with less than half of patients having cirrhosis (44%) between January 1, 2008 to September 20, 2015.[25] Analyses of the patterns of care in the current study demonstrate that few patients (38%) received locoregional therapy before 1L treatment, TKIs were the dominant 1L regimen choice, and ICIs were the preferred choice for the majority of patients receiving 2L therapy. The identification period of the current study predated the approval of atezolizumab plus bevacizumab based on the open-label, phase III IMbrave150 study, which moved ICI-based treatment into 1L.[16] Atezolizumab plus bevacizumab resulted in improved overall survival (OS) and progression-free survival compared with sorafenib, which was previously the standard for 1L treatment of patients with unresectable

Table 2. Baseline patient demographics and clinical characteristics.

Patient demographics	Overall cohort *N* = 284
Patient age at 1L treatment initiation, years (median, IQR)	61.5 (55.0-68.0)
Male gender (*n*, %)	221 (77.8%)
Race/Ethnicity (*n*, %)	
White	187 (65.8%)
Asian	40 (14.1%)
Black/African American	49 (17.3%)
American Indian or Alaska Native	3 (1.1%)
Hispanic	5 (1.8%)
Payer at time of 1L treatment[a] (*n*, %)	
Medicare	62 (21.8%)
Medicare Advantage/Supplemental	53 (18.7%)
Medicaid	60 (21.1%)
Commercial	104 (36.6%)
Self-pay	4 (1.4%)
Military health insurance	10 (3.5%)
Year of 1L treatment (*n*, %)	
2017	66 (23.2%)
2018	84 (29.6%)
2019	134 (47.2%)
Follow-up from initiation of 1L treatment, months (median, IQR)	8.1 (6.0-12.7)
Disposition at time of data collection (*n*, %)	
Currently receiving therapy	157 (55.3%)
Under observation	8 (2.8%)
Receiving palliative treatment only and/or referred to hospice	12 (4.2%)
Deceased	106 (37.3%)
Unknown, lost to follow up	1 (0.4%)
American Joint Committee of Cancer stage (*n*, %)	
Stage II	6 (4.6%)
Stage IIIA	8 (6.1%)
Stage IIIB	8 (6.1%)
Stage IVA	24 (18.3%)
Stage IVB	85 (64.9%)
Unknown/not reported	153 (53.9%)
Eastern Cooperative Oncology Group Performance Status at initiation of 1L (*n*, %)	
0/1	187 (65.8%)
≥2	97 (34.1%)
Child-Pugh score (*n*, %)	
Class A	106 (37.3%)
Class B	132 (46.5%)
Class C	46 (16.2%)
Barcelona Clinic Liver Cancer stage/classification (*n*, %)	
0	2 (0.8%)
A	25 (10.0%)
B	8 (3.2%)
C	210 (83.7%)
D	6 (2.4%)
Unknown/not reported	33 (11.6%)
Extensive liver tumor burden (*n*, %)	
<10%	13 (4.6%)
>10%-25%	132 (46.5%)
>25%-50%	102 (35.9%)
>50%	37 (13.0%)

Table 2. Continued

Patient demographics	Overall cohort *N* = 284
Albumin-bilirubin grade (*n*, %)	
1	17 (6.0%)
2	169 (59.5%)
3	98 (34.5%)
Alpha-fetoprotein level (*n*, %)	
<400	166 (58.5%)
Ascites (*n*, %)	124 (43.7%)
Extra hepatic spread (*n*, %)	221 (77.8%)
Portal vein invasion (*n*, %)	103 (36.3%)
Risk factors (*n*, %)	
History of smoking	177 (62.3%)
History of alcohol use disorder/excessive alcohol intake	160 (56.3%)
Obesity	51 (18.0%)
Hepatitis B infection (active or resolved)	41 (14.4%)
Active	24 (8.5%)
Resolved	17 (6.0%)
Hepatitis C infection (active or resolved)	99 (34.9%)
Active	41 (14.4%)
Resolved	58 (20.4%)
Disease-related comorbidities (*n*, %)	
Diabetes with chronic complications	19 (6.7%)
Diabetes without chronic complications	45 (15.8%)
Dyslipidemia	61 (21.5%)
Liver disease—mild	68 (23.9%)
Liver disease—moderate or severe	32 (11.3%)
Hepatic cirrhosis	149 (52.5%)
Hepatic fibrosis	7 (2.5%)
Comorbidity indicators (*n*, %)	
Cardiovascular disease	85 (29.9%)
Cerebrovascular disease	7 (2.5%)
Chronic pulmonary disease	60 (21.1%)
Congestive heart failure	18 (6.3%)
Connective tissue disease	6 (2.1%)
Dementia	2 (0.7%)
Hypertension	143 (50.4%)
Myocardial infarction	13 (4.6%)
Peptic ulcer disease	20 (7.0%)
Peripheral vascular disease	10 (3.5%)
Renal disease	24 (8.5%)
Rheumatologic disorders	6 (2.1%)
Thromboembolic events (arterial or venous)	6 (2.1%)
Therapies before 1L (*n*, %)	
Conventional TACE	60 (21.1%)
Ablation	20 (7.0%)
TARE	11 (3.9%)
TAE	6 (2.1%)
DEB-TACE	5 (1.8%)
Resection	7 (2.5%)
Interventional radiologist involved in care	113 (39.8%)

[a]Not mutually exclusive. Disease-related comorbidities were collected in 2 separate sets. One related to Charlson Comorbidity Index (CCI) and the other HCC specific.

Missing or unknown data, if any, are reported per variable. Missing or unknown data are indicated here by labels of "unknown, lost to follow-up" or "unknown, not reported."

Abbreviations: 1L, first-line therapy; DEB-TACE, drug-eluting bead transarterial chemoembolization; IQR, interquartile range (25th and 75th percentile reported); TACE, transarterial chemoembolization; TAE, transarterial embolization.

Table 3. First-line (1L) and second-line (2L) treatment patterns by year of treatment initiation.

	Overall	Year of treatment initiation		
		2017	2018	2019
1L treatment regimen (*n* = 284)				
TKIs	266 (93.7%)	60 (90.9%)	76 (90.5%)	130 (97.0%)
Sorafenib	157 (55.3%)	59 (89.4%)	50 (59.5%)	48 (35.8%)
Lenvatinib	109 (38.4%)	2 (3.0%)	27 (32.1%)	80 (59.7%)
Cabozantinib	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Regorafenib	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
ICIs	14 (4.9%)	4 (6.1%)	6 (7.1%)	4 (3.0%)
Nivolumab	12 (4.2%)	3 (4.5%)	7 (8.3%)	2 (1.5%)
Pembrolizumab	2 (0.7%)	2 (3.0%)	0 (0.0%)	0 (0.0%)
Other	4 (1.4%)	0 (0.0%)	2 (2.4%)	2 (1.5%)
2L treatment regimen (*n* = 90)				
TKIs	31 (34.4%)	14 (48.3%)	12 (30.0%)	5 (23.8%)
Sorafenib	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lenvatinib	9 (10.0%)	4 (13.8%)	5 (12.5%)	0 (0.0%)
Cabozantinib	8 (8.9%)	1 (3.4%)	4 (10.0%)	3 (14.3%)
Regorafenib	13 (14.4%)	8 (27.6%)	3 (7.5%)	2 (9.5%)
ICIs	59 (65.6%)	15 (51.7%)	28 (70.0%)	16 (76.2%)
Nivolumab	47 (52.2%)	12 (41.4%)	23 (57.5%)	12 (57.1%)
Pembrolizumab	13 (14.4%)	3 (10.3%)	6 (15.0%)	4 (19.0%)

Percentages may not total 100 due to rounding.
Missing or unknown data, if any, are reported per variable.
Abbreviations: 1L, first-line; 2L, second-line; ICI, immune-checkpoint inhibitor; TKI, tyrosine kinase inhibitor.

HCC.[16] Findings from the IMbrave150 study, which required screening endoscopy to assess for and treat varices before study initiation to reduce bleeding risk, showed meaningful clinical benefits across multiple subgroups of aHCC patients (i.e., hepatitis B virus negative or hepatitis C virus negative, Asian and non-Asian). However, the treatment benefits remain unknown for aHCC populations with poor prognosis such as patients with compromised liver function and/or ECOG-PS ≥2. This is only the beginning of a shift to 1L ICI use, as the extent of ongoing research of ICIs in combination with other agents is likely to make the aHCC treatment landscape highly dynamic in the coming years.[26] Understanding patterns of care and the provider perceptions behind those patterns may provide valuable insights in the continuing evolution of aHCC management.

Our findings suggest that physician decision making is multifaceted when selecting among the expanding arsenal of available treatment options. Efficacy, safety, and quality of evidence were consistently cited as reasons for both 1L sorafenib and lenvatinib use. Only a small percentage of patients (11%) received lenvatinib in 1L citing affordability as a reason for its use. Despite nivolumab as the dominant 2L regimen, cabozantinib and pembrolizumab were also considered for 62% and 67% of 2L nivolumab patients, respectively. Consistent with reasons associated with the dominant 1L regimens, efficacy and safety were reasons for nivolumab use among a majority of patients. Interestingly, patient choice as a reason for regimen use increased from the 1L setting (8% and 6% of 1L sorafenib and lenvatinib patients) to the 2L setting (15% of 2L nivolumab patients).

The role of ICIs, particularly in the 1L setting, is being elucidated as the aHCC treatment paradigm continues to evolve. Several trials investigating various treatment regimens (e.g., ICI plus locoregional therapy, ICI in combination with TKI or other ICI) are ongoing across all HCC stages.[27-32] While the current study did not focus on clinical outcomes, the following studies provide valuable context for the treatment landscape of HCC. A systematic review of ICIs found them to be safe and effective against unresectable HCC[33] while another systematic review found immunotherapies to be less effective in nonviral etiologies of HCC.[34] In studies conducted in Asia, ICIs were associated with promising efficacy, tolerable toxicity,[35] and improved (OS).[36] A German study found prolonged median OS in patients treated with multiple, sequential therapies after progression or intolerance to sorafenib,[37] and an international study found PD-1-targeted immunotherapies nivolumab or pembrolizumab had promising efficacy and safety.[34,38] In studies conducted in Asia, ICIs were associated with promising efficacy, tolerable toxicity,[35] and improved (OS).[36] A German study found prolonged median OS in patients treated with multiple, sequential therapies after progression or intolerance to sorafenib,[37] and an international study found PD-1-targeted immunotherapies nivolumab or pembrolizumab had promising efficacy and safety.[38] Evidence of positive clinical benefits from these studies is likely to impact treatment patterns, treatment guideline recommendations, and future treatment choices. In this study, few patients initiated 1L ICI monotherapy, yet ICI therapy was the 2L treatment choice for a majority of patients continuing to 2L therapy. Additional evidence is needed to identify predictive biomarkers of treatment response and to further examine how these outcomes change as combination therapies of 2 or more agents are approved and used earlier in systemic therapy for aHCC

Limitations of this research are largely those inherent to the retrospective, observational research. Selection bias, data entry errors, including errors of omission or commission, and recall bias when abstracting patient data are possible. The brief review period of 2017-2019 also represents a limitation considering the approval of several agents for aHCC in 2019 and onwards. The study also did not include data regarding treatment response and adverse events. The limited availability of staging information may have been driven by informal staging within community oncology settings. Data abstraction performed by the treating physician minimized any interpretation of the data requested from the patient medical record. Furthermore, the reasons for treatment choice are best collected directly from the treating physician.

Observational studies, when compared with clinical trials, often differ in their representation of patients with poor prognosis; trials tend to include healthier patients, while real-world cohorts tend to include a broader spectrum of severity, including those who would not have met strict trial inclusion criteria. This phenomenon was observed in the current study, as highlighted by the notable incidences of cirrhotic liver disease, extrahepatic spread, patients of Asian and African American race, and public U.S. healthcare payers (ie, Medicaid, Medicare). Furthermore, one-third of the patients had portal vein tumor thrombosis, which reflects more aggressive disease, worse hepatic function, treatment intolerance, and increased morbidity, when compared with published aHCC trial populations. These poor prognostic characteristics may have influenced physician choice in treatment selection. The ASCO Guidelines on the systemic treatment of aHCC published in December 2020 are available for physicians to guide treatment and care.[39]

Conclusions

The current study describes HCC treatment patterns, from 2017 to 2019, particularly those of aHCC patients with poor prognosis in the community-oncology setting. During the study period ending in 2019, sorafenib and lenvatinib were the dominant 1L therapy choices, while ICIs were mostly used in the 2L setting. This prescribing practice is likely to change as results of several ongoing 1L trials of other ICI combinations become available and additional efficacy and toxicity data in patient subgroups become available. As new regimen approvals are on the horizon, particularly involving ICIs, future studies should further describe treatment sequencing and associated outcomes, characterize the reasons associated with therapy selection, and elucidate the current clinical burden associated with aHCC in the real-world setting.

Supplementary Data

Supplementary material is available at *The Oncologist* online.

Funding

Conflict of Interest

Author Contributions

Conception/design: A.J.K., L.Z.M., B.S., M.J.H., and B.F. **Provision of study material or patients:** A.J.K., L.Z.M., B.S., M.J.H., and B.F. **Collection and/or assembly of data:** A.J.K., L.Z.M., B.S., M.J.H., and B.F. **Data analysis and interpretation:** A.J.K., L.Z.M., B.S., M.J.H., and B.F. **Manuscript writing:** A.J.K., L.Z.M., B.S., M.J.H., and B.F. **Final approval of manuscript:** A.J.K., L.Z.M., B.S., M.J.H., and B.F.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. American Cancer Society. Cancer statistics center: liver and intrahepatic bile duct at a glance. https://cancerstatisticscenter. Cancer.Org/#!/cancer-site/liver%20and%20intrahepatic%20 bile%20duct. Accessed November 11, 2020.
2. Shiels MS, O'Brien TR. Recent decline in hepatocellular carcinoma rates in the United States. *Gastroenterology*. 2020;158(5):1503-1505.e2.
3. National Organization for Rare Disorders (NORD). Hepatocellular carcinoma (HCC). https://rarediseases.Org/physician-guide/ hepatocellular-carcinoma-hcc/. Accessed November 12, 2020.
4. ASCO Cancer.net. ASCO answers liver cancer. https://www.Cancer. Net/sites/cancer.Net/files/asco_answers_liver.Pdf. Accessed November 12, 2020.
5. Bupathi M, Kaseb A, Meric-Bernstam F, Naing A. Hepatocellular carcinoma: Where there is unmet need. *Mol Oncol*. 2015;9(8):1501-1509.
6. U.S. Food & Drug Administration. FDA expands approved use of stivarga to treat liver cancer. April 27, 2017. https://www.Fda.Gov/ news-events/press-announcements/fda-expands-approved-use-stivarga-treat-liver-cancer. Accessed November 10, 2020.
7. U.S. Food & Drug Administration. FDA grants accelerated approval to nivolumab for HCC previously treated with sorafenib. September 22, 2017. https://www.Fda.Gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-hcc-previously-treated-sorafenib#:~:Text=on%20september%20 22%2c%202017%2c%20the,been%20previously%20tre-ated%20with%20sorafenib. Accessed November 10, 2020.
8. U.S. Food & Drug Administration. FDA approves lenvatinib for unresectable hepatocellular carcinoma. August 16, 2018. https:// www.Fda.Gov/drugs/resources-information-approved-drugs/ fda-approves-lenvatinib-unresectable-hepatocellular-carcinoma. Accessed November 10, 2020.
9. U.S. Food & Drug Administration. FDA grants accelerated approval to pembrolizumab for hepatocellular carcinoma. November 9, 2018. https://www.Fda.Gov/drugs/fda-grants-accelerated-approval-pembrolizumab-hepatocellular-carcinoma. Accessed November 10, 2020.
10. U.S. Food & Drug Administration. FDA approves cabozantinib for hepatocellular carcinoma. January 14, 2019. https://www.Fda. Gov/drugs/fda-approves-cabozantinib-hepatocellular-carcinoma. Accessed November 10, 2020.
11. U.S. Food & Drug Administration. FDA approves ramucirumab for hepatocellular carcinoma. May 10, 2019. https://www.Fda.Gov/drugs/

resources-information-approved-drugs/fda-approves-ramucirumab-hepatocellular-carcinoma. Accessed November 10, 2020.

12. U.S. Food & Drug Administration. FDA grants accelerated approval to nivolumab and ipilimumab combination for hepatocellular carcinoma. March 10, 2020. https://www.Fda.Gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma. Accessed November 10, 2020.

13. U.S. Food & Drug Administration. FDA approves atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma. May 29, 2020. https://www.Fda.Gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-plus-bevacizumab-unresectable-hepatocellular-carcinoma. Accessed November 10, 2020.

14. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Hepatobiliary cancers, v5.2020. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.

15. Bteich F, Di Bisceglie AM. Current and future systemic therapies for hepatocellular carcinoma. *Gastroenterol Hepatol (N Y)*. 2019;15(5):266-272.

16. Finn RS, Qin S, Ikeda M, et al; IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894-1905.

17. Abou-Alfa GK, Chan SL, Furuse J, 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-TPS4144.

18. Kelley RK, W Oliver J, Hazra S, et al. Cabozantinib in combination with atezolizumab versus sorafenib in treatment-naive advanced hepatocellular carcinoma: COSMIC-312 Phase III study design. *Future Oncol*. 2020;16(21):1525-1536.

19. Finn RS, Ryoo BY, Merle P, et al; KEYNOTE-240 investigators. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol*. 2020;38(3):193-202.

20. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol*. 2019;16(10):589-604.

21. Romero D. Combination set to transform HCC therapy. *Nat Rev Clin Oncol*. 2020;17(7):389.

22. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. *J Clin Oncol*. 2020;38(26):2960-2970.

23. Kudo M, Finn RS, Qin S, 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(10126):1163-1173.

24. IBM Watson health: IBM marketscan research databases for life sciences researchers. https://www.Ibm.Com/downloads/cas/owzwj0qo. Accessed November 3, 2021.

25. Bonafede MM, Korytowsky B, Singh P, et al. Treatment patterns and economic burden by lines of therapy among patients with advanced hepatocellular carcinoma treated with systemic cancer therapy. *J Gastrointest Cancer*. 2020;51(1):217-226.

26. Shek D, Read SA, Nagrial A, et al. Immune-checkpoint inhibitors for advanced hepatocellular carcinoma: a synopsis of response rates. *Oncologist*. 2021;26(7):e1216-e1225.

27. ClinicalTrials.gov. Bethesda M. National library of medicine (US). Identifier nct03847428, assess efficacy and safety of durvalumab alone or combined with bevacizumab in high risk of recurrence HCC patients after curative treatment [emerald-2]. https://clinicaltrials.Gov/ct2/show/nct03847428. Accessed January 12, 2021.

28. ClinicalTrials.gov. Bethesda M. National library of medicine (us). Identifier nct04268888, nivolumab in combination with TACE/TAE for patients with intermediate stage HCC [TACE-3]. https://clinicaltrials.Gov/ct2/show/nct04268888. Accessed January 12, 2021.

29. ClinicalTrials.gov. Bethesda M. National library of medicine (US). Identifier nct04340193, a study of nivolumab and ipilimumab in combination with transarterial chemoembolization (TACE) in participants with intermediate stage liver cancer [checkmate 74w]. https://clinicaltrials.Gov/ct2/show/nct04340193. Accessed January 12, 2021.

30. ClinicalTrials.gov. Bethesda M. National library of medicine (US). Identifier nct03006926, a trial of lenvatinib plus pembrolizumab in participants with hepatocellular carcinoma. https://clinicaltrials.Gov/ct2/show/nct03006926. Accessed on January 12, 2021.

31. ClinicalTrials.gov. Bethesda M. National library of medicine (us). Identifier nct03713593, safety and efficacy of lenvatinib (e7080/mk-7902) in combination with pembrolizumab (mk-3475) versus lenvatinib as first-line therapy in participants with advanced hepatocellular carcinoma (mk-7902-002/e7080-g000-311/leap-002). https://clinicaltrials.Gov/ct2/show/nct03713593. Accessed January 12, 2021.

32. ClinicalTrials.gov. Bethesda M. National library of medicine (us). Identifier nct03298451, study of durvalumab and tremelimumab as first-line treatment in patients with advanced hepatocellular carcinoma (himalaya). https://clinicaltrials.Gov/ct2/show/nct03298451. Accessed January 12, 2021.

33. Ziogas IA, Evangeliou AP, Giannis D, et al. The role of immunotherapy in hepatocellular carcinoma: a systematic review and pooled analysis of 2,402 patients. *Oncologist*. 2021;26(6):e1036-e1049.

34. Haber PK, Puigvehi M, Castet F, et al. Evidence-based management of hepatocellular carcinoma: systematic review and meta-analysis of randomized controlled trials (2002-2020). *Gastroenterology*. 2021;161(3):879-898.

35. Xie D, Sun Q, Wang X, et al. Immune checkpoint inhibitor plus tyrosine kinase inhibitor for unresectable hepatocellular carcinoma in the real world. *Ann Transl Med*. 2021;9(8):652.

36. Tsai HM, Han MZ, Lin YJ, et al. Real-world outcome of immune checkpoint inhibitors for advanced hepatocellular carcinoma with macrovascular tumor thrombosis. *Cancer Immunol Immunother*. 2021;70(7):1929-1937.

37. von Felden J, Karkmann K, Ittrich H, et al. Sequential systemic treatment in advanced hepatocellular carcinoma is able to prolong median survival to more than 3 years in a selected real-world cohort. *Visc Med*. 2021;37(2):87-93.

38. Scheiner B, Kirstein MM, Hucke F, et al. Programmed cell death protein-1 (PD-1)-targeted immunotherapy in advanced hepatocellular carcinoma: efficacy and safety data from an international multicentre real-world cohort. *Aliment Pharmacol Ther*. 2019;49(10):1323-1333.

39. Gordan JD, Kennedy EB, Abou-Alfa GK, et al. systemic therapy for advanced hepatocellular carcinoma: ASCO guideline. *J Clin Oncol*. 2020;38(36):4317-4345.