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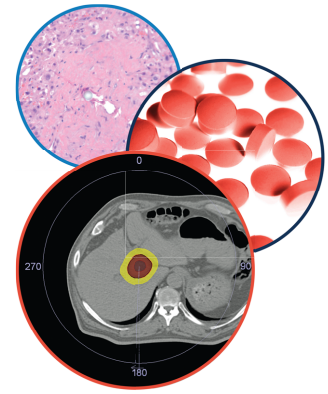

Hepatic Oncology

Clinical outcomes by Child-Pugh Class in patients with advanced hepatocellular carcinoma in a community oncology setting

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Aim: Many pivotal trials in advanced hepatocellular carcinoma (HCC) require participants to have Child-Pugh A disease. However, many patients in real-world practice are Child-Pugh B or C. This study examined treatment patterns and clinical outcomes in patients with advanced HCC treated with first-line systemic therapy. **Materials & methods:** In this retrospective study, patients with HCC treated with first-line systemic therapy (2010–2017) were identified from US Oncology Network records. Outcomes included overall survival and progression-free survival, by Child-Pugh Class and prior liver-directed therapy. **Results:** Of 352 patients, 78.7% were Child-Pugh A or B, 96.6% received first-line sorafenib, and 33.8% received first-line-prior liver-directed therapy. Survival outcomes were similar for Child-Pugh A or B, and longer after first-line prior liver-directed therapy. **Conclusion:** First-line systemic therapy is beneficial in patients with Child-Pugh A or B, and after first-line prior liver-directed therapy. These findings may help position systemic therapy in the community setting.

First draft submitted: 20 March 2023; Accepted for publication: 13 July 2023; Published online: 9 August 2023

Keywords: Child-Pugh class • clinical outcomes • hepatocellular carcinoma • real-world evidence • systemic therapy • treatment patterns

Hepatocellular carcinoma (HCC) is associated with a poor prognosis (overall 5-year survival rate of ~19.6% and an advanced-stage 5-year survival rate of 2.5%). The highest proportion of cases involve localized disease (44%), followed by regional (27%) and distant (18%) [1].

Patients upon diagnosis are evaluated for suitability of resection, liver transplant, or ablation for curative purposes. However, for patients diagnosed with unresectable and/or metastatic HCC, systemic therapies, locoregional therapies, best supportive care, or enrollment in a clinical trial are recommended [2].

The leading risk factors are related to cirrhosis from any etiology. These risk factors include viral hepatitis, non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), heavy alcohol consumption, genetic hemochromatosis, autoimmune liver disease, and alpha-1-antitrypsin deficiency [2,3]. Other risk factors include cigarette smoking and aflatoxin exposure [3]. Patients with HCC are more likely to be older, with mean ages at diagnosis of 69, 65 and 62 years in Japan, Europe, and North America, respectively, while in China and South Korea they were 52 and 59 years, respectively [4], and in parts of Africa it was 45 years [5]. The disease is approximately threefold more likely to occur in men [4,6,7].

To determine treatment options, the extent of HCC, the functional status of the liver, underlying liver disease, and the general health of the patient must be considered. Child-Pugh (CP) scoring assesses severity of liver disease in terms of grade of hepatic encephalopathy, degree of ascites, serum albumin and bilirubin levels, and prothrombin time. Each variable is graded on a point system, with the total points used to assign a grade of A, B or C, in order of increasing severity; higher scores indicate poorer operative risk [8].

Future Medicine

The landscape for advanced HCC treatment has changed over the last 4–5 years. The current standard-of-care first-line (1L) systemic therapies for HCC include atezolizumab + bevacizumab and lenvatinib monotherapy, in addition to sorafenib monotherapy. Sorafenib, a multi-tyrosine kinase inhibitor (multi-TKI), was the standard of care for advanced stage HCC for 10 years, from 2007 to 2017; the US FDA approval in 2007 was supported by the SHARP clinical trial. Most patients in SHARP had CP Class A and Barcelona Clinic Liver Cancer (BCLC) stage C status [9,10]. Lenvatinib was approved by the FDA for unresectable HCC on August 2018, based on its non-inferiority to sorafenib in the first-line setting in the REFLECT trial. Patients had CP A and BCLC stage B or stage C status [11,12]. Atezolizumab (an anti-PD-L1 checkpoint inhibitor immune-oncology [IO] therapy) + bevacizumab (human VEGF-2 antagonist) received FDA approval in May 2020 for unresectable/metastatic HCC, on the basis of IMbrave150; trial patients had CP A status [13,14]. Tremelimumab (anti-cytotoxic T-lymphocyte-associated antigen 4 IO therapy) + durvalumab (anti-PD-L1 IO therapy) was approved by the FDA for unresectable HCC on the basis of HIMALAYA where participants also had CP A status [15,16]. The National Comprehensive Cancer Network (NCCN) guidelines give a Category 1 recommendation for sorafenib for patients with CP Class A or B7, although the guidelines caution about a lack of safety data for CP Class B or C status. The NCCN guidelines give Category 1 recommendations for atezolizumab + bevacizumab and for lenvatinib monotherapy for patients with CP Class A only, and for tremelimumab + durvalumab for all patients [17].

The NCCN guideline-recommended second-line (2L) treatments include nivolumab and ipilumumab, pembrolizumab, regorafenib, cabozantinib, and ramucirumab. In September 2017, the FDA granted accelerated approval to nivolumab, an anti-PD-1 checkpoint inhibitor IO therapy for patients with advanced HCC previously treated with sorafenib, based on the results from the CheckMate-040 trial, however in April 2021, continued accelerated approval was not received after the phase 3 clinical trial, CheckMate-459 (NCT02576509), failed to meet the primary end point for overall survival (OS) [18,19]. Regorafenib, a multi-TKI, was approved in April 2017 for advanced HCC in patients who had disease progression following treatment with sorafenib. Approval was based on the results from the RESORCE trial, in which the patients had CP A and BCLC stage B or C HCC [20,21]. Another multi-TKI, cabozantinib, was approved by the FDA in 2019 for patients with CP A status who have progressed on or after sorafenib, on the basis of the CELESTIAL trial. Ramucirumab, a VEGF-2 antagonist, was approved by the FDA in May 2019 for patients with alpha fetoprotein of ≥400 ng/mL who have progressed on sorafenib, on the basis of REACH-2; patients had CP Class A and BCLC stage B or C status [22,23].

The treatment and management of patients with HCC are based on the characteristics of the underlying liver disease and the general health of the patient [2]. Given the complexity of treating HCC and the changing landscape of treatment options, this study was performed to help physicians to understand the characteristics and outcomes in patients with advanced HCC with and without a history of liver targeted therapies and varying risk staging.

The objectives of this study were to gain an understanding of patient profiles and select clinical outcomes among patients with advanced HCC treated with 1L systemic therapy when sorafenib was the only FDA-approved systemic therapy in the US community oncology setting. Giving the expanding treatment options for HCC, this study may help us to better position systemic treatment in the community setting.

Materials & methods

Study design & data sources

A retrospective, observational, descriptive study was performed to investigate US adult patients with advanced HCC who initiated 1L systemic treatment between 1 January 2010 and 31 December 2017 and were followed through 30 April 2018 or until date of last record. Patients were from practices in The US Oncology Network that utilize the iKnowMed™ electronic health record (iKM EHR). The US Oncology Network is affiliated with approximately 1400 physicians in more than 480 sites of care across 25 states in the US, representing approximately 12% of US patients newly diagnosed with cancer. Data were obtained via programmatic database abstraction from the EHR. Vital status was confirmed with data from the Social Security Death Index (SSDI). Data for BCLC staging at initial diagnosis and at the time of systemic therapy, as well as data for prior liver-directed HCC therapy, were obtained via chart review.

Patients enrolled in the study were diagnosed with HCC at any time and initiating a 1L systemic therapy during 01 January 2010 and 31 December 2017 (first date of treatment = index event). They were also ≥18 years of age at initial diagnosis of HCC and with ≥2 visits after the index event during the study period at a US Oncology Network site utilizing the full EHR capabilities of iKM. Patients were excluded if they were enrolled in clinical

trials at any time during the study period or had another documented primary cancer diagnosis prior to or during the study period.

The study protocol was subjected to a privacy review and did not require informed patient consent, because data were deidentified. McKesson received an exemption and waiver of informed consent and authorization from the US Oncology Inc. Institutional Review Board.

Outcomes of interest

The following outcomes were investigated: baseline demographics and clinical characteristics, treatment patterns (prior liver-directed HCC therapies, time to treatment failure [TTF], time to next treatment [TTNT], reasons for discontinuation), best overall response (BOR), OS, and progression-free survival (PFS). TTF, BOR, PFS, and OS were stratified by risk (CP score) and 1L-prior liver-directed HCC therapy. TTF was defined as the interval from the initiation of 1L treatment until discontinuation of treatment for any reason or censoring. TTNT was calculated from the end of 1L treatment to the initiation of 2L treatment. BOR was calculated according to physician-assessed response information in progress notes from patient charts, and not by Response Evaluation Criteria in Solid Tumors (RECIST) imaging criteria. OS was defined as the interval between initiation of 1L treatment and the date of death as documented in the SSDI or the iKM EHR database. PFS was defined as the interval from the initiation of 1L treatment until the earliest date of physician-noted progression or death.

CP scoring assesses severity of liver disease in order to determine operative risk. Each variable is graded on a point system, from 1–3. Total points are used to assign a grade of A, B, or C: A = 5–6 points (good operative risk), B = 7–9 points (moderate operative risk), and C = 10–15 points (poor operative risk). Bilirubin is scored as 1–3 points for <2 mg/dl, 2–3 mg/dl, and >3 mg/dl, respectively. Albumin is scored as 1–3 points for >3.5 g/dl, 2.8–3.5 g/dl, and <2.8 g/dl, respectively. Prothrombin time is scored as 1–3 points for <4 seconds prolonged (<1.7 international normalized ratio [INR]), 4–6 seconds (1.7–2.3 INR), and >6 seconds (>2.3 INR), respectively. Ascites is scored as 1–3 points for none, mild, and for severe. Hepatic encephalopathy is scored as 1–3 points for none, Grades I-II, and Grades III-IV, respectively. In this study, ascites and hepatic encephalopathy were imputed as not present when the conditions were not documented in patient charts.

Statistical analysis

Demographic, clinical, and treatment characteristics were analysed with descriptive statistics. Chi-square testing was performed to assess associations between categorical variables when patient counts for single cells within the results tables were greater than or equal to 5. When the distribution could not be assumed to be Chi-square, Fisher's exact test was performed. Depending on normality, ANOVA/t-tests or Kruskal-Wallis tests were used to analyze associations between continuous variables. An alpha level of 0.05 was considered the primary criterion for statistical significance. Time-to-event outcomes of TTF, PFS and OS were assessed using the Kaplan-Meier method and stratified by CP risk categories at initial diagnosis. Patients who did not experience the event during the study period were censored.

Results

Within The US Oncology Network, 7,153 patients were selected with a documented diagnosis of "liver cancer" in the iKM EHR database and ≥2 visits within The US Oncology Network, and who were ≥18 years old at their first diagnosis of liver cancer. Among them, 4,238 were receiving systemic therapy for HCC within the study period. After excluding patients enrolled in clinical trials during the study period, with other documented concomitant cancer diagnoses prior to or during the study period, and those with no documentation of 1L treatment in structured data, 1,015 were selected. Among these, 484 were randomly selected for chart review. Finally, 352 patients were selected upon selection criteria confirmation.

Patient characteristics

Among the overall study population, the median age was 64.0 years, 47.7% were aged 65 years or older, 77.3% were male, 63.1% were White, and 72.2% received treatment in the South (Table 1). CP scores at initial HCC diagnosis were available or able to be determined for 88.1% of patients (CP Class A: 42.6%; CP Class B: 36.1%; CP Class C: 9.4%; CP Class unknown: 11.9%).

Among the overall study population, 23.3% had American Joint Committee on Cancer (AJCC) [24] Stage III and 28.7% had AJCC Stage IV disease, 70.2% had Eastern Cooperative Oncology Group performance status

Table 1. Demographic and clinical characteristics for patients with HCC stratified by Child-Pugh class at initial diagnosis.

Variable	Overall, n (%)	Child-Pugh class at initial diagnosis				p-value
		Class A, n (%)	Class B, n (%)	Class C, n (%)	Unknown, n (%)	
Total patient count	352	150 (42.6)	127 (36.1)	33 (9.4)	42 (11.9)	
Age at diagnosis (years)						0.0032
Patients with available data	352	150	127	33	42	
Mean (SD), years	64.9 (10.4)	66.3 (10.1)	63.7 (10.1)	61.3 (11.0)	66.9 (10.8)	
Median (Min, Max), years	64.0 (22.0, 91.3)	65.8 (33.6, 90.2)	62.6 (33.2, 91.3)	58.9 (43.8, 87.9)	66.8 (22.0, 85.4)	
Age group						0.0216
<65 years	184 (52.3)	67 (44.7)	77 (60.6)	23 (69.7)	17 (40.5)	
>75 years	62 (17.6)	28 (18.7)	21 (16.5)	4 (12.1)	9 (21.4)	
≥65–75 years	106 (30.1)	55 (36.7)	29 (22.8)	6 (18.2)	16 (38.1)	
Sex						0.3061
Female	80 (22.7)	39 (26.0)	26 (20.5)	5 (15.2)	10 (23.8)	
Male	272 (77.3)	111 (74.0)	101 (79.5)	28 (84.8)	32 (76.2)	
Race						0.8755
White	222 (63.1)	87 (58.0)	82 (64.6)	24 (72.7)	29 (69.0)	
Black or African–American	29 (8.2)	12 (8.0)	12 (9.4)	2 (6.1)	3 (7.1)	
Unknown	101 (28.7)	51 (34.0)	33 (26.0)	7 (21.2)	10 (23.8)	
Ethnicity						0.0263
Hispanic or Latino	78 (22.2)	25 (16.7)	33 (26.0)	11 (33.3)	9 (21.4)	
Not Hispanic or Latino	195 (55.4)	96 (64.0)	61 (48.0)	17 (51.5)	21 (50.0)	
Unknown	79 (22.4)	29 (19.3)	33 (26.0)	5 (15.2)	12 (28.6)	
Practice region						0.4023
South	254 (72.2)	97 (64.7)	95 (74.8)	25 (75.8)	37 (88.1)	
West	51 (14.5)	27 (18.0)	14 (11.0)	6 (18.2)	4 (9.5)	
Midwest	33 (9.4)	18 (12.0)	13 (10.2)	1 (3.0)	1 (2.4)	
Northeast	14 (4.0)	8 (5.3)	5 (3.9)	1 (3.0)	0	
Stage at initial diagnosis						0.5841
I	26 (7.4)	11 (7.3)	10 (7.9)	1 (3.0)	4 (9.5)	
II	44 (12.5)	14 (9.3)	18 (14.2)	6 (18.2)	6 (14.3)	
IIIA	48 (13.6)	23 (15.3)	11 (8.7)	9 (27.3)	5 (11.9)	
IIIB	28 (8.0)	8 (5.3)	11 (8.7)	3 (9.1)	6 (14.3)	
IIIC	6 (1.7)	2 (1.3)	1 (0.8)	1 (3.0)	2 (4.8)	
IV	32 (9.1)	14 (9.3)	13 (10.2)	3 (9.1)	2 (4.8)	
IVA	29 (8.2)	12 (8.0)	11 (8.7)	3 (9.1)	3 (7.1)	
IVB	40 (11.4)	18 (12.0)	16 (12.6)	2 (6.1)	4 (9.5)	
Unknown	99 (28.1)	48 (32.0)	36 (28.3)	5 (15.2)	10 (23.8)	
ECOG						0.0020
0	39 (11.1)	23 (15.3)	12 (9.4)	0	4 (9.5)	
1	208 (59.1)	94 (62.7)	69 (54.3)	19 (57.6)	26 (61.9)	
2	53 (15.1)	16 (10.7)	25 (19.7)	5 (15.2)	7 (16.7)	
3+	12 (3.4)	2 (1.3)	3 (2.4)	5 (15.2)	2 (4.8)	
Not documented	40 (11.4)	15 (10.0)	18 (14.2)	4 (12.1)	3 (7.1)	
Metastatic status						1.0000
No	302 (85.8)	128 (85.3)	109 (85.8)	29 (87.9)	36 (85.7)	
Yes	50 (14.2)	22 (14.7)	18 (14.2)	4 (12.1)	6 (14.3)	
Cirrhosis						0.0002
Yes	252 (71.6)	95 (63.3)	105 (82.7)	29 (87.9)	23 (54.8)	
Not documented	100 (28.4)	55 (36.7)	22 (17.3)	4 (12.1)	19 (45.2)	

ECOG: Eastern Cooperative Oncology Group; HCC: Hepatocellular carcinoma; INR: International normalized ratio; SD: Standard deviation.

Table 1. Demographic and clinical characteristics for patients with HCC stratified by Child-Pugh class at initial diagnosis (cont.).

Variable	Overall, n (%)	Child-Pugh class at initial diagnosis				p-value
		Class A, n (%)	Class B, n (%)	Class C, n (%)	Unknown, n (%)	
Hepatitis B						0.0414
Yes	35 (9.9)	21 (14.0)	11 (8.7)	0	3 (7.1)	
Not documented	317 (90.1)	129 (86.0)	116 (91.3)	33 (100)	39 (92.9)	
Hepatitis C						0.0795
Yes	165 (46.9)	63 (42.0)	66 (52.0)	20 (60.6)	16 (38.1)	
Not documented	187 (53.1)	87 (58.0)	61 (48.0)	13 (39.4)	26 (61.9)	
Encephalopathy						<0.0001
None/absent	285 (81.0)	141 (94.0)	93 (73.2)	13 (39.4)	38 (90.5)	
Mild/moderate	60 (17.0)	8 (5.3)	32 (25.2)	16 (48.5)	4 (9.5)	
Severe	7 (2.0)	1 (0.7)	2 (1.6)	4 (12.1)	0	
Ascites						<0.0001
None/absent	168 (47.7)	109 (72.7)	31 (24.4)	3 (9.1)	25 (59.5)	
Mild/slight	123 (34.9)	34 (22.7)	65 (51.2)	11 (33.3)	13 (31.0)	
Moderate/severe	61 (17.3)	7 (4.7)	31 (24.4)	19 (57.6)	4 (9.5)	
Non-alcoholic fatty liver disease/steatohepatitis						
Not documented	352 (100)	150 (100)	127 (100)	33 (100)	42 (100)	
Cholangitis (acute)						
Not documented	352 (100)	150 (100)	127 (100)	33 (100)	42 (100)	
Barcelona Clinic Liver Cancer stage						<0.0001
A	11 (3.1)	7 (4.7)	4 (3.2)	0	0	
B	15 (4.3)	9 (6.0)	6 (4.7)	0	0	
C	224 (63.6)	119 (79.3)	105 (82.7)	0	0	
D	40 (11.4)	2 (1.3)	3 (2.4)	33 (100)	2 (4.8)	
Unknown	62 (17.6)	13 (8.7)	9 (7.1)	0	40 (95.2)	
Presence of portal vein invasion/tumor thrombosis						0.9301
No	57 (16.2)	24 (16.0)	22 (17.3)	5 (15.2)	6 (14.3)	
Yes	137 (38.9)	57 (38.0)	51 (40.2)	15 (45.5)	14 (33.3)	
Not documented	158 (44.9)	69 (46.0)	54 (42.5)	13 (39.4)	22 (52.4)	
Albumin (g/dl)						<0.0001
Patients with available data	352	150	127	33	42	
Mean (SD)	3.3 (0.7)	3.6 (0.5)	3.0 (0.6)	2.7 (0.7)	3.5 (0.6)	
Median (Min, Max)	3.3 (0.8, 5.0)	3.6 (2.3, 5.0)	3.1 (0.8, 4.6)	2.6 (1.8, 4.3)	3.6 (1.8, 4.7)	
Prothrombin time (s)						<0.0001
Patients with available data	254	128	98	25	3	
Mean (SD)	14.0 (4.1)	13.1 (3.5)	14.3 (4.1)	17.3 (5.7)	15.2 (1.0)	
Median (Min, Max)	13.2 (7.2, 38.5)	12.5 (7.2, 38.5)	13.2 (8.9, 36.7)	15.4 (10.4, 32.0)	15.2 (14.3, 16.2)	
INR						<0.0001
Patients with available data	281	145	109	27	0	
Mean (SD)	1.2 (0.3)	1.1 (0.2)	1.3 (0.4)	1.5 (0.6)	. (.)	
Median (min, max)	1.1 (0.8, 4.7)	1.1 (0.8, 2.2)	1.2 (0.9, 4.7)	1.4 (0.9, 3.0)	. (.,.)	
Bilirubin (mg/dl)						<0.0001
Patients with available data	351	150	127	33	41	
Mean (SD)	1.4 (1.4)	1.0 (1.0)	1.7 (1.5)	2.6 (2.0)	0.8 (0.4)	
Median (Min, Max)	1.0 (0.1, 11.1)	0.8 (0.2, 11.1)	1.3 (0.1, 9.8)	2.1 (0.5, 7.5)	0.7 (0.2, 2.1)	
Alpha-fetoprotein (ng/dl)						0.5288
Patients with available data	341	147	124	30	40	

ECOG: Eastern Cooperative Oncology Group; HCC: Hepatocellular carcinoma; INR: International normalized ratio; SD: Standard deviation.

10.2217/hep-2023-0002

Table 1. Demographic and clinical characteristics for patients with HCC stratified by Child-Pugh class at initial diagnosis (cont.).

Variable	Overall, n (%)	Child-Pugh class at initial diagnosis				p-value
		Class A, n (%)	Class B, n (%)	Class C, n (%)	Unknown, n (%)	
Mean (SD)	17270.7 (129980.7)	21796.6 (162577.5)	8307.6 (39301.5)	9299.3 (30821.3)	34402.1 (205135.9)	
Median (Min, Max)	167.0 (0.7, 1935166)	110.0 (0.7, 1935166)	184.1 (2.4, 391800.0)	136.5 (1.1, 156040.0)	209.0 (1.0, 1299000)	
Number of liver nodes						0.3611
Patients with available data	328	140	117	31	40	
Mean (SD)	1.9 (1.6)	1.9 (1.6)	2.0 (1.5)	1.7 (1.2)	2.2 (2.1)	
Median (Min, Max)	1.0 (1.0, 13.0)	1.0 (1.0, 10.0)	2.0 (1.0, 13.0)	1.0 (1.0, 5.0)	1.0 (1.0, 10.0)	

ECOG: Eastern Cooperative Oncology Group; HCC: Hepatocellular carcinoma; INR: International normalized ratio; SD: Standard deviation.

Table 2. Most common first-line to second-line treatment sequences for patients with hepatocellular carcinoma.

1L regimen	2L regimen	HCC patients (n = 72), n (%)
Sorafenib	Nivolumab	27 (37.5)
Sorafenib	Regorafenib	17 (23.6)
Sorafenib	Capecitabine	5 (6.9)
Sorafenib	Gemcitabine + oxaliplatin	3 (4.2)
Sorafenib	Pembrolizumab	3 (4.2)
Sorafenib	Doxorubicin	2 (2.8)
Sorafenib	Sorafenib + doxorubicin	2 (2.8)
Bevacizumab	Gemcitabine + oxaliplatin	1 (1.4)
Carboplatin + etoposide	Etoposide	1 (1.4)
Doxorubicin	Gemcitabine	1 (1.4)

1L: First-line; 2L: Second-line; HCC: Hepatocellular carcinoma.

(ECOG PS) of 0–1, and 14.2% had metastatic disease (Table 1). Cirrhosis was documented in 71.6% of the overall study population and was highest among patients with CP Class C at diagnosis (87.9% compared with 63.3% in Class A, 82.7% in Class B, and 54.8% in Class unknown patients, p = 0.0002). Hepatitis B was observed in 9.9% of patients overall (Class A, 14.0%; Class B, 8.7%; Class C 0.0%; Class unknown, 7.1%; p = 0.0414), and hepatitis C was observed in 46.9% of patients (Class A, 42.0%; Class B, 52.0%; Class C 60.6%; Class unknown, 38.1%; p = 0.0795). Alpha-1-antitrypsin deficiency, portal hypertension, hemochromatosis, NAFLD/ NASH, and cholangitis were not documented for any patients in all classes. Portal vein/tumor thrombosis was present in 38.9%, although it was not documented for 44.9%. The majority of patients had BCLC stage C disease (63.6%).

Treatment patterns

Nearly all patients (96.6%) in the overall study population received sorafenib as 1L treatment. Among those patients with available data, the mean (SD) starting dose for 1L sorafenib was 601.8 mg overall, 600.0 mg (214.5; n = 81) among CP Class A, 596.4 mg (223.0; n = 112) among CP Class B, 570.6 mg (215.4; n = 34) among CP Class C, and 618.2 mg (214.3; n = 110) among those with unknown CP class. The most common 1L–2L sequences were sorafenib to nivolumab (37.5%), followed by sorafenib to regorafenib (23.6%) and sorafenib to capecitabine (6.9%) (Table 2).

A total of 119 patients underwent liver-targeted therapies prior to initiation of 1L systemic therapy (Table 3). The most common procedure was transcatheter arterial chemoembolization (TACE) or TACE with drug eluting beads - doxorubicin (20.5%, n = 72 of the overall study population), followed by radioembolization (9.9%, n = 35 of the overall study population), and radiofrequency ablation (5.4%, n = 19 of the overall study population). In this cohort of patients, TACE was the frontline therapy in 20.7% (n = 31) among CP Class A, 20.5% (n = 26) among CP Class B, 24.2% (n = 8) among CP Class C, and 16.7% (n = 7) among those with unknown CP class. Radioembolization was observed in 14.0% (n = 21), 7.9% (n = 10), 3.0% (n = 1), and 7.1% (n = 3) among the respective cohorts. Radiofrequency ablation was observed in 6.7% (n = 10), 3.2% (n = 4), 6.1% (n = 2), and 7.1% (n = 3) among the respective cohorts. Microwave and transarterial embolization were observed among 1.7%

Table 3. Treatment characteristics of patients with hepatocellular carcinoma, stratified by Child-Pugh class at initial diagnosis.

Variable	Overall, n (%)	Child-Pugh class at initial diagnosis			
		Class A, n (%)	Class B, n (%)	Class C, n (%)	Unknown, n (%)
Treatments prior to diagnosis					
Total patient count	352	150	127	33	42
Liver transplantation	1 (100)	1 (100)	0	0	0
Number of prior non-systemic treatments for HCC					
Patients with available data	4	2	1	0	1
Mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (-)	–	1.0 (-)
Median (Min, Max)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	–	1.0 (1.0, 1.0)
TACE or TACE with drug eluting beads - doxorubicin	1 (0.3)	0	0	0	1 (2.4)
Radioembolization	2 (0.6)	1 (0.7)	1 (0.8)	0	0
Other therapy	1 (0.3)	1 (0.7)	0	0	0
Treatments prior to 1L initiation					
Total patient count	352	150	127	33	42
Surgical resection	23 (100)	12 (100)	5 (100)	1 (100)	5 (100)
Liver transplantation	6 (100)	4 (100)	2 (100)	0	0
Number of prior liver-targeted treatments for HCC					
Patients with available data	119	59	38	9	13
Mean (SD)	1.7 (0.9)	1.8 (1.0)	1.7 (0.8)	2.1 (1.4)	1.3 (0.9)
Median (Min, Max)	1.0 (1.0, 5.0)	1.0 (1.0, 5.0)	2.0 (1.0, 4.0)	2.0 (1.0, 5.0)	1.0 (1.0, 4.0)
Radiofrequency ablation	19 (5.4)	10 (6.7)	4 (3.2)	2 (6.1)	3 (7.1)
Microwave	6 (1.7)	2 (1.3)	4 (3.2)	0	0
Transarterial embolization	4 (1.1)	1 (0.7)	3 (2.4)	0	0
TACE or TACE with drug eluting beads - doxorubicin	72 (20.5)	31 (20.7)	26 (20.5)	8 (24.2)	7 (16.7)
Radioembolization	35 (9.9)	21 (14.0)	10 (7.9)	1 (3.0)	3 (7.1)
Other Therapy	10 (2.8)	7 (4.7)	2 (1.6)	1 (3.0)	0

1L: First-line; HCC: Hepatocellular carcinoma; SD: Standard deviation; TACE: Transcatheter arterial chemoembolization.

(n = 6) and 1.1% (n = 4) of the overall study population, respectively, but were only observed among patients in the CP Class A and B cohorts: microwave among 1.3% (n = 2) and 3.2% (n = 4) of the respective cohorts, and transarterial embolization among 0.7% (n = 1) and 2.4% (n = 3) of the respective cohorts. The most common reasons for discontinuing 1L treatment among the overall study population were disease progression (43.2%), toxicity (18.2%), and other (16.2%). Patient preference was the reason for 1.4%, and death was the reason for 8.0%. Disease progression was the most common reason among all CP classes except Class C, where toxicity (26.5%) was the most common reason, although disease progression was the second most common reason (23.5%) (Table 4).

In the overall study population, the median TTNT was 1.5 months (95% CI: 1.1–2.4) and was 2.0 months (95% CI: 1.1–3.0) in the CP Class A, 0.9 months (95% CI: 0.6–2.0) in Class B, 2.6 (95% CI: 0.9–4.5) months in Class C, and 1.3 (95% CI: 0.5–3.9) months in the unknown cohort (Figure 1A).

In the overall study population, the median TTF was 3.0 months (95% CI: 2.7–3.5). At 12 months, 8.7% of patients were still on treatment. Median TTF ranged from 2.2 months (95% CI: 1.2–3.2) in the Class C cohort to 3.9 months (95% CI: 2.7–5.0) in the Class Unknown cohort (Figure 1B).

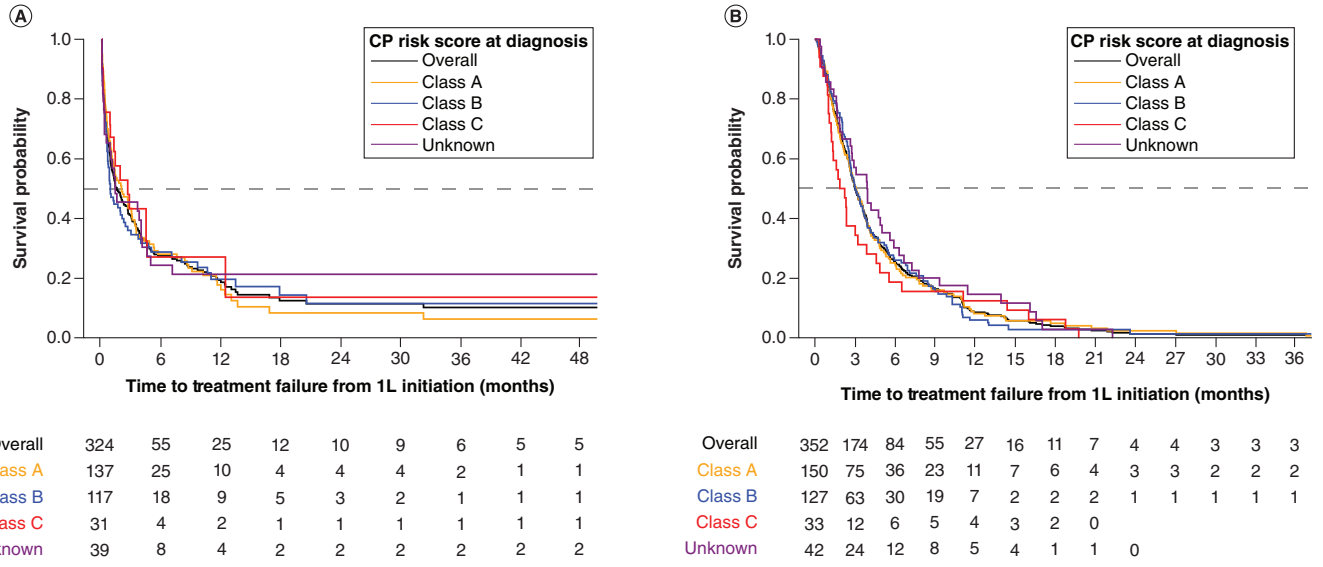
Clinical outcomes

The most common response to 1L treatment in the overall population was progressive disease (36.9%), followed by response not otherwise specified (which includes physician-noted partial response and physician descriptions of improvement and responding disease; 21.9%). Complete response was observed in 4.0% of patients. Response profiles were similar across the CP class cohorts. Progressive disease was the most common response in all cohorts except for Class C, where not evaluated was the most common response (Table 5).

Table 4. Reasons for discontinuation of first-line treatment among patients with hepatocellular carcinoma.

Reasons for 1L treatment discontinuation	Overall (n = 352), n (%)	Child-Pugh (CP) risk score at 1L initiation			
		Class A (n = 84), n (%)	Class B (n = 118), n (%)	Class C (n = 34), n (%)	Unknown (n = 116), n (%)
Progression	152 (43.2)	40 (47.6)	52 (44.1)	8 (23.5)	52 (44.8)
Toxicity	64 (18.2)	17 (20.2)	17 (14.4)	9 (26.5)	21 (18.1)
Death	28 (8.0)	3 (3.6)	9 (7.6)	6 (17.6)	10 (8.6)
Decline in performance status	13 (3.7)	3 (3.6)	7 (5.9)	1 (2.9)	2 (1.7)
Patient preference	5 (1.4)	3 (3.6)	1 (0.8)	0	1 (0.9)
Physician preference	4 (1.1)	1 (1.2)	1 (0.8)	1 (2.9)	1 (0.9)
Financial/insurance	3 (0.9)	0	0	0	3 (2.6)
Other	57 (16.2)	10 (11.9)	24 (20.3)	8 (23.5)	15 (12.9)
Not documented	2 (0.6)	1 (1.2)	1 (0.8)	0	0
Ongoing	24 (6.8)	6 (7.1)	6 (5.1)	1 (2.9)	11 (9.5)
Patients entering hospice care after 1L discontinuation but no 2L	124 (48.4)	21 (35.0)	42 (45.7)	12 (42.9)	49 (64.5)

1L: First-line; 2L: Second-line; HCC: Hepatocellular carcinoma.



Child pugh class at initial diagnosis					
Statistic	Overall	Class A	Class B	Class C	Unknown
N	324	137	117	31	39
Events, n (%)	218 (67.3)	97 (70.8)	75 (64.1)	18 (58.1)	28 (71.8)
Mean (SE) months	6.6 (0.7)	6.0 (1.0)	5.3 (0.8)	4.6 (1.1)	2.9 (0.5)
Median (95% CI) months	1.5 (1.1, 2.4)	2.0 (1.1, 3.0)	0.9 (0.6, 2.0)	2.6 (0.9, 4.5)	1.3 (0.5, 3.9)
Q1, Q3	0.3, 8.3	0.5, 8.5	0.3, 9.6	0.8, 12.4	0.3, 4.9

Child pugh class at initial diagnosis					
Statistic	Overall	Class A	Class B	Class C	Unknown
N	352	150	127	33	42
Events, n (%)	337 (95.7)	145 (96.7)	120 (94.5)	32 (97.0)	40 (95.2)
Mean (SE) months	5.3 (0.4)	5.6 (0.8)	5.2 (0.7)	4.3 (1.0)	5.7 (0.9)
Median (95% CI) months	3.0 (2.7, 3.5)	3.1 (2.6, 3.6)	3.0 (2.6, 3.7)	2.2 (1.2, 3.2)	3.9 (2.7, 5.0)
Q1, Q3	1.6, 6.1	1.4, 6.0	1.9, 6.8	1.1, 4.9	1.7, 7.3

Figure 1. Kaplan-Meier estimates: time to next treatment (A) and time to treatment failure (B) from initiation of 1L treatment stratified by Child-Pugh Class at initial diagnosis.
CI: Confidence interval; SE: Standard error; TTF: Time to treatment failure; TTNT: Time to next treatment.

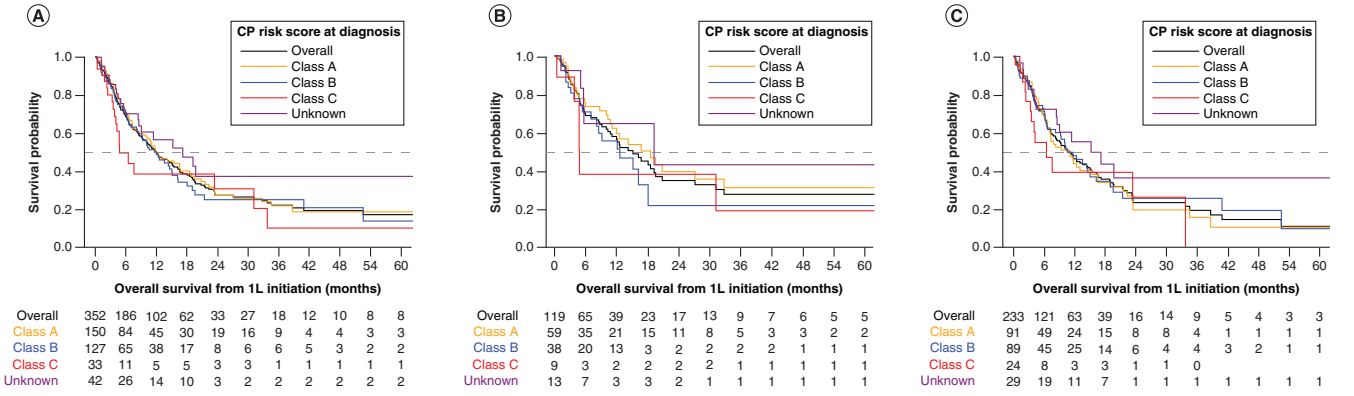
In the overall study population, the median OS from the initiation of 1L treatment was 12.0 months (95% CI: 10.1–15.1). Figure 2A shows the median OS and probability of survival among CP Classes A, B, C and unknown.

Patients who received liver-targeted treatments before initiation of 1L therapy had a median OS of 15.1 months (95% CI: 10.3–19.5). Figure 2B shows the median OS and probability of survival among CP Classes A, B, C, and

Table 5. Response to first-line treatment for patients stratified by Child-Pugh class at first line initiation.

Best overall response to 1L treatment (physician assessed)	Overall, n (%)	Child-Pugh class at 1L initiation				
		Class A, n (%)	Class B, n (%)	Class C, n (%)	Unknown, n (%)	p-value
Complete response	14 (4.0)	2 (2.4)	2 (1.7)	1 (2.9)	9 (7.8)	
Response not otherwise specified	77 (21.9)	17 (20.2)	24 (20.3)	7 (20.6)	29 (25.0)	
Stable disease	31 (8.8)	9 (10.7)	6 (5.1)	1 (2.9)	15 (12.9)	
Mixed response	6 (1.7)	1 (1.2)	1 (0.8)	0	4 (3.4)	
Progressive disease	130 (36.9)	38 (45.2)	45 (38.1)	7 (20.6)	40 (34.5)	
Not evaluated	94 (26.7)	17 (20.2)	40 (33.9)	18 (52.9)	19 (16.4)	

1L: First-line.



Child pugh class at initial diagnosis					
Statistic	Overall	Class A	Class B	Class C	Unknown
N	352	150	127	33	42
Events, n (%)	190 (54.0)	84 (56.0)	67 (52.8)	19 (57.6)	20 (47.6)
Mean (SE) months	26.4 (2.5)	27.2 (3.7)	19.4 (2.3)	14.3 (2.9)	13.2 (1.2)
Median (95% CI) months	12.0 (10.1, 15.1)	12.0 (9.4, 16.7)	12.1 (8.5, 15.1)	4.8 (3.8, 31.1)	17.2 (8.4, –)
Q1, Q3	4.8, 32.7	5.0, 32.7	4.9, 40.9	3.5, 31.1	5.6, –
Survival probability (%) (95% CI)					
6-month	69.1 (63.6, 73.9)	71.1 (62.6, 78.1)	71.0 (61.6, 78.5)	49.7 (30.1, 66.6)	70.3 (53.6, 82.0)
12-month	49.8 (43.6, 55.6)	50.0 (40.6, 58.7)	50.1 (39.6, 59.7)	38.7 (19.5, 57.6)	56.7 (38.6, 71.3)
18-month	38.8 (32.4, 45.1)	40.3 (30.7, 49.6)	34.4 (23.9, 45.1)	38.7 (19.5, 57.6)	47.6 (28.9, 64.1)
24-month	27.5 (21.3, 34.2)	27.4 (18.4, 37.2)	25.2 (15.0, 36.7)	30.9 (12.4, 51.7)	37.5 (19.3, 55.7)
36-month	22.3 (16.0, 29.3)	22.0 (13.4, 32.0)	25.2 (15.0, 36.7)	10.3 (0.8, 34.7)	37.5 (19.3, 55.7)
48-month	19.5 (13.2, 26.8)	18.8 (10.1, 29.6)	21.0 (10.6, 33.8)	10.3 (0.8, 34.7)	37.5 (19.3, 55.7)

Child pugh class at initial diagnosis					
Statistic	Overall	Class A	Class B	Class C	Unknown
N	119	59	38	9	13
Events, n (%)	58 (48.7)	28 (47.5)	19 (50.0)	6 (66.7)	5 (38.5)
Mean (SE) months	17.1 (1.3)	18.5 (1.9)	11.3 (1.2)	14.2 (5.2)	14.0 (2.4)
Median (95% CI) months	15.1 (10.3, 19.5)	18.5 (10.7, 32.7)	12.6 (7.0, 18.0)	4.8 (0.4, –)	19.2 (5.0, –)
Q1, Q3	5.0, –	5.9, –	4.9, 18.0	4.7, 31.1	5.6, –
Survival probability (%) (95% CI)					
6-month	68.8 (58.9, 76.8)	73.5 (59.3, 83.4)	70.7 (52.1, 83.2)	38.1 (8.9, 68.0)	64.6 (30.6, 85.1)
12-month	56.5 (45.7, 65.8)	59.5 (44.1, 71.9)	55.6 (36.1, 71.2)	38.1 (8.9, 68.0)	64.6 (30.6, 85.1)
18-month	45.0 (33.7, 55.7)	50.3 (34.3, 64.3)	32.6 (13.5, 53.5)	38.1 (8.9, 68.0)	64.6 (30.6, 85.1)
24-month	34.8 (23.5, 46.4)	39.5 (23.6, 55.0)	21.8 (5.0, 46.1)	38.1 (8.9, 68.0)	43.1 (8.3, 75.2)
36-month	27.6 (16.7, 39.7)	31.1 (16.0, 47.6)	21.8 (5.0, 46.1)	19.0 (1.1, 54.1)	43.1 (8.3, 75.2)

Child pugh class at initial diagnosis					
Statistic	Overall	Class A	Class B	Class C	Unknown
N	233	91	89	24	29
Events, n (%)	132 (56.7)	56 (61.5)	48 (53.9)	13 (54.2)	15 (51.7)
Mean (SE) months	22.2 (2.9)	20.6 (4.1)	19.2 (2.7)	14.2 (3.5)	12.9 (1.4)
Median (95% CI) months	10.9 (8.3, 14.4)	10.9 (7.2, 15.4)	10.6 (6.7, 15.0)	6.5 (3.4, 33.7)	15.2 (8.4, –)
Q1, Q3	4.3, 23.4	5.0, 23.2	4.4, 40.9	3.4, 33.7	4.5, –
Survival probability (%) (95% CI)					
6-month	69.2 (62.4, 75.0)	69.6 (58.2, 78.4)	71.1 (59.7, 79.9)	54.8 (30.8, 73.6)	72.2 (52.1, 85.0)
12-month	46.2 (38.7, 53.5)	43.7 (31.8, 55.0)	47.9 (35.4, 59.3)	39.2 (16.3, 61.6)	55.2 (34.2, 71.9)
18-month	35.6 (28.0, 43.2)	33.8 (22.3, 45.7)	34.5 (22.2, 47.0)	39.2 (16.3, 61.6)	43.5 (22.5, 62.7)
24-month	23.3 (15.9, 31.4)	19.4 (9.8, 31.5)	25.5 (13.9, 38.8)	26.1 (5.8, 53.1)	36.2 (15.9, 57.0)
36-month	19.2 (11.7, 28.0)	15.5 (6.4, 28.2)	25.5 (13.9, 38.8)	–	36.2 (15.9, 57.0)
48-month	14.4 (7.2, 23.9)	10.4 (2.6, 24.4)	19.1 (7.3, 35.1)	–	36.2 (15.9, 57.0)

Figure 2. Overall survival from 1L treatment initiation stratified by Child-Pugh Class at initial diagnosis (A) overall (B) among patients with prior liver-targeted treatments and (C) without prior liver-targeted treatments.
CI: Confidence interval; CP: Child-Pugh; SE: Standard error.

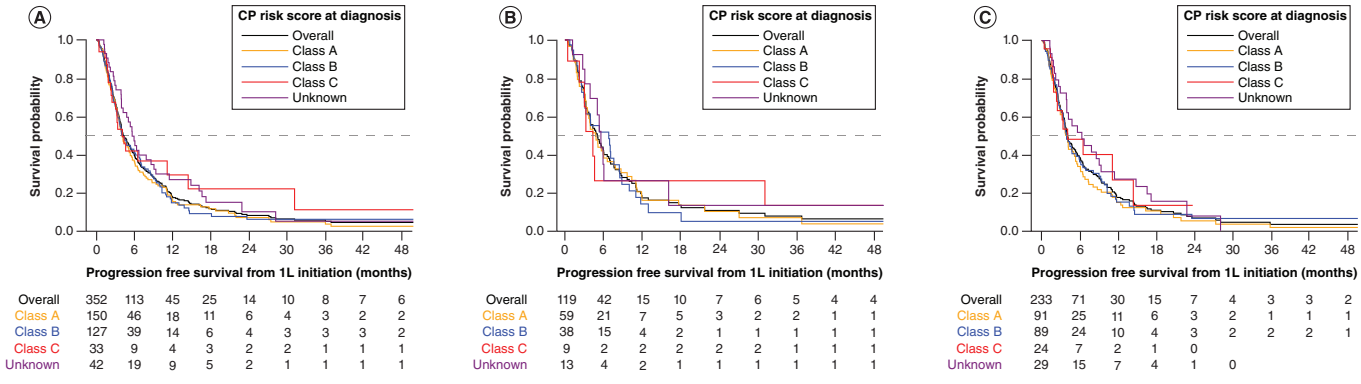
unknown. Patients who did not receive liver-targeted therapies before initiation of 1L therapy had a median OS of 10.9 months (95% CI: 8.3–14.4). Figure 2C shows the median OS and probability of survival among CP Classes A, B, C, and unknown.

In the overall study population, the median PFS from initiation of 1L treatment was 4.2 months (95% CI: 3.9–5.1). Figure 3A shows the median PFS and probability of PFS across CP Classes A, B, C and unknown.

Patients who received liver-targeted treatments before initiation of 1L treatment had a median PFS of 5.0 months (95% CI: 3.9–6.0). Figure 3b shows the median PFS and probability of PFS across CP Classes A, B, C and unknown. Patients who did not receive liver-targeted therapies before initiation of 1L treatment had a median PFS of 4.1 months (95% CI: 3.6–5.0). Figure 3c shows the median PFS and probability of PFS across CP Classes A, B, C and unknown.

Discussion

In this retrospective study of patients receiving 1L treatment for advanced HCC in a large network of community-based oncology practices, most patients received 1L sorafenib regardless of liver disease severity. TTF was numerically



Child pugh class at initial diagnosis					
Statistic	Overall	Class A	Class B	Class C	Unknown
N	352	150	127	33	42
Events, n (%)	286 (81.3)	129 (86.0)	100 (78.7)	21 (63.6)	36 (85.7)
Mean (SE)	10.3 (1.2)	8.7 (1.4)	6.8 (0.6)	10.5 (2.5)	9.3 (1.4)
Median (95% CI)	4.2 (3.9, 5.1)	4.1 (3.5, 5.1)	4.1 (3.4, 5.9)	4.1 (2.5, 11.1)	5.6 (3.9, 8.6)
Q1, Q3	2.4, 10.0	2.2, 9.4	2.4, 9.9	2.2, 14.4	3.1, 14.8
PFS probability (%) (95% CI)					
6-month	39.5 (34.1, 44.8)	36.2 (28.2, 44.2)	40.7 (31.6, 49.6)	41.7 (23.7, 58.9)	47.0 (31.4, 61.2)
12-month	17.3 (13.2, 21.9)	15.2 (9.6, 22.0)	14.6 (8.5, 22.2)	29.2 (12.0, 49.0)	26.7 (14.2, 41.0)
18-month	11.6 (8.0, 15.8)	11.5 (6.5, 17.9)	8.9 (4.0, 16.2)	21.9 (6.7, 42.7)	14.9 (5.7, 28.2)
24-month	8.0 (4.9, 11.9)	6.9 (3.0, 12.8)	5.9 (2.1, 12.7)	21.9 (6.7, 42.7)	9.9 (2.4, 24.0)
36-month	4.9 (2.5, 8.5)	3.4 (1.0, 8.6)	5.9 (2.1, 12.7)	11.0 (1.0, 34.9)	5.0 (0.4, 19.0)
48-month	4.3 (2.0, 7.8)	2.3 (0.5, 7.1)	5.9 (2.1, 12.7)	11.0 (1.0, 34.9)	5.0 (0.4, 19.0)

Child pugh class at initial diagnosis					
Statistic	Overall	Class A	Class B	Class C	Unknown
N	119	59	38	9	13
Events, n (%)	96 (80.7)	49 (83.1)	30 (78.9)	7 (77.8)	10 (76.9)
Mean (SE)	8.7 (1.0)	8.6 (1.4)	6.7 (0.9)	10.3 (4.7)	7.4 (1.6)
Median (95% CI)	5.0 (3.9, 6.0)	4.8 (3.5, 6.6)	6.8 (3.0, 8.4)	4.3 (0.4, 31.0)	5.6 (3.1, 16.1)
Q1, Q3	2.8, 10.4	2.6, 11.0	2.6, 8.8	3.0, 31.0	3.9, 16.1
PFS probability (%) (95% CI)					
6-month	41.7 (32.3, 50.8)	39.8 (26.8, 52.4)	51.5 (33.8, 66.6)	25.9 (3.9, 57.0)	34.6 (10.9, 60.2)
12-month	16.9 (10.3, 25.0)	15.7 (7.2, 27.0)	13.7 (4.4, 28.3)	25.9 (3.9, 57.0)	26.0 (6.3, 51.7)
18-month	13.1 (7.2, 20.8)	13.0 (5.4, 24.2)	9.2 (1.9, 23.6)	25.9 (3.9, 57.0)	13.0 (0.9, 41.0)
24-month	10.3 (5.0, 17.8)	9.8 (3.1, 21.1)	4.6 (0.4, 18.3)	25.9 (3.9, 57.0)	13.0 (0.9, 41.0)
36-month	7.4 (3.0, 14.5)	6.5 (1.4, 17.5)	4.6 (0.4, 18.3)	13.0 (0.7, 43.3)	13.0 (0.9, 41.0)
48-month	5.9 (2.1, 12.7)	3.3 (0.3, 13.6)	4.6 (0.4, 18.3)	13.0 (0.7, 43.3)	13.0 (0.9, 41.0)

Child pugh class at initial diagnosis					
Statistic	Overall	Class A	Class B	Class C	Unknown
N	233	91	89	24	29
Events, n (%)	190 (81.5)	80 (87.9)	70 (78.7)	14 (58.3)	26 (89.7)
Mean (SE)	9.4 (1.4)	7.8 (1.6)	6.7 (0.8)	7.0 (1.3)	9.4 (1.6)
Median (95% CI)	4.1 (3.6, 5.0)	4.1 (3.3, 5.2)	3.9 (3.4, 5.4)	4.1 (1.9, 14.4)	6.3 (3.9, 9.3)
Q1, Q3	2.2, 9.9	2.0, 7.4	2.4, 9.9	1.9, 14.4	2.9, 14.8
PFS probability (%) (95% CI)					
6-month	38.4 (31.8, 44.9)	33.8 (23.9, 44.0)	36.2 (25.8, 46.7)	48.1 (25.9, 67.2)	51.7 (32.5, 67.9)
12-month	17.5 (12.5, 23.3)	14.9 (8.0, 23.7)	15.1 (7.9, 24.4)	26.7 (6.2, 53.5)	27.2 (12.6, 44.0)
18-month	10.8 (6.7, 16.0)	10.4 (4.7, 18.7)	8.6 (3.1, 17.7)	13.4 (0.9, 42.1)	15.5 (5.0, 31.3)
24-month	6.7 (3.4, 11.6)	5.2 (1.5, 12.6)	6.5 (1.9, 15.2)	–	7.8 (0.8, 26.1)
36-month	3.4 (1.0, 8.0)	1.7 (0.2, 8.0)	6.5 (1.9, 15.2)	–	–

Figure 3. Progression-free survival from 1L treatment initiation stratified by Child-Pugh Class at initial diagnosis (A) overall (B) among patients with prior liver-targeted treatments and (C) without prior liver-targeted treatments.
CI: Confidence interval; CP: Child-Pugh; PFS: Progression-free survival; SE: Standard error.

similar across CP classes A and B, and survival outcomes were numerically similar across CP classes A and B except when analyzing the subset of patients who received prior liver-directed treatments. Treatment discontinuation due to toxicity was slightly lower among patients with CP Class B liver disease. These real-world data suggest that efficacy and safety of sorafenib are similar in patients with CP Classes A and B.

This study showed some similarities in demographic and clinical characteristics with other real-world studies. Mean and median ages in other real-world studies ranged from 55–73 years, 75%–92% were male, and most had ECOG PS of 0–1 [25–27]. Several studies included patients with BCLC stage B or C disease as well as A [26,28,29], in contrast with clinical trials, which included patients with CP A or B7 [10,19,21]. Proportions of patients with CP Class A (36%–76%), Class B (20%–44%), and Class C (3%–15%) varied widely across real-world studies [26–30].

Our study also showed some similarities in treatment patterns with other real-world studies. In our study, the median TTF for the CP Class A, B, and C cohorts were 3.1 months, 3.0 months, and 2.2 months respectively. In a multinational registry study (GIDEON – Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) including 2,708 patients with HCC treated with sorafenib, 73% had CP A, 25% had B, and 3% had C. Median durations of sorafenib treatment for the respective cohorts were 17.6 weeks (4 months), 9.9 weeks (2.3 months), and 5.6 weeks (1.3 months) [26]. In a single-center retrospective study of 241 patients, the median duration of sorafenib treatment was 2.6 months (interquartile ratio 0.92–78) [31]. Bonafede *et al.*, in a review of a claims database including patients who received 1L sorafenib for HCC (n = 1,125), found that the median duration of treatment was 3.0 months [32].

The most common 2L treatments following sorafenib were nivolumab (37.5%), regorafenib (23.6%), and capecitabine (6.9%); other real-world studies have demonstrated the effectiveness of these therapies when used as 2L treatments following sorafenib. In another real-world study, survival of 23 patients with advanced HCC who received nivolumab after 1L sorafenib treatment was shown to relate with CP score at the start of treatment; CP Class A at initiation of nivolumab was associated with superior OS (p = 0.014) [33]. Experience of treatment sequencing from sorafenib to regorafenib in the real-world setting has also been reported with an increase in OS and tolerable safety profile, similar to that observed in clinical trials [34–36]. The use of capecitabine as a 2L treatment option likely reflects the study period, when no standard treatment options were available. However, capecitabine was well tolerated and antitumor activity was reported in a retrospective analysis of patients with HCC following prior sorafenib treatment [37,38].

Sorafenib is one of the recommended systemic therapies for CP Class A disease according to the NCCN guidelines [2]. However, our study population also included patients with Class B disease (36.1%), Class C (9.4%), and unknown class disease (11.9%), in addition to 42.6% having CP Class A disease. In the GIDEON registry study (Marrero *et al.*), in which 73% had CP A, 25% had B, and 3% had C, there were similar types and incidence of adverse events (AEs) across CP classes A and B (17% and 21%, respectively), and most AE were within the first 4 weeks of treatment for all CP classes. Marrero *et al.* also found that discontinuation of sorafenib associated with treatment-related AEs was comparable in patients with CP A versus B disease; the most common types of AEs leading to sorafenib discontinuation were hand-foot skin reactions (4%) in patients with CP A, and liver dysfunction (6%) in patients with CP B [26]. The results of that study suggest that sorafenib could provide a treatment option in select patients with CP Class B as well as Class A disease, bearing in mind the need for patient evaluation.

Notably, except for TACE, it appeared that liver-targeted therapies were found among higher proportions of patients with less severe disease as assessed by CP status. Radioembolization and radiofrequency ablation were observed most often among those with CP A status. NCCN guidelines recommend locoregional therapy for patients for whom surgical curative treatments are not indicated, or as bridging treatment to prepare patients for liver transplantation [2]. The NCCN guidelines in particular recommend ablative treatments for smaller tumors (ie, $\leq$3 cm) located such that ablation is possible, and TACE is among the treatments to consider for all tumors regardless of location including limited portal vein invasion, and including unresectable or inoperable tumors [2]. In this study, 38.0%, 40.2%, 45.5%, and 33.3% of patients in the respective CP cohorts had portal vein invasion/tumor thrombus; however, the study did not determine if those patients received TACE or not.

In our study, we observed descriptively that patients with liver-targeted therapies prior to 1L treatment had longer OS and PFS compared with patients without liver-targeted therapies prior to 1L treatment. Our study was descriptive and thus did not compare outcomes in the two groups. Existing literature indicates that locoregional HCC therapies, such as ablation, may provide synergistic effects with subsequent systemic therapies that can improve prognoses for advanced HCC [39,40]. In this study, the improved OS and PFS in patients with liver targeted therapies prior to 1L may therefore be due to effects of prior liver-targeted therapy on tumor biology or preserving liver function. Among 352 patients, 119 patients received TACE before 1L initiation. These patients had a longer OS and PFS from 1L initiation to the end of the study observation period, compared with those patients who did not receive TACE before 1L initiation.

Strengths & limitations

There are several limitations to the study. First, while CP scoring is used to assess patient's liver reserve and is a strong predictor for survival, the CP score is not often documented by the treating oncologist. The BCLC staging system is the most comprehensive to date and is considered the standard for assessing prognosis for HCC at the time of diagnosis, according to the EASL-EORTC clinical practice guidelines [41,42]. In addition to tumor characteristics (size, number, vascular invasion, vascular invasion, nodal spread, extrahepatic metastases) and liver function (CP, portal hypertension), BCLC staging includes the general health of the patient (ECOG-PS) and symptoms to enable the physician to recommend the most appropriate treatment. Importantly, BCLC is evolving with new knowledge about disease characterization and the availability of new treatment options [41,43]. However, in this dataset, BCLC stage was not documented in a portion of cases. Second, certain variables in CP may not be available across clinical practices. For example, INR/prothrombin times are assessed by hepatologists and primary care physicians but not necessarily by oncologists. Due to a lack of data, 12% of the overall study population were classified as CP Class Unknown, limiting conclusions about the relationship of CP class with their treatment patterns and outcomes. Other variables may be subjectively assessed (ie, ascites and encephalopathy), and these were not documented for at least 90% of the study population, although they were imputed when not available in patient charts. Still other variables in CP scoring have arbitrary cut-off points for albumin, bilirubin and prothrombin categories that may group together patients with otherwise wide variations in disease severity. Third, most patients with HCC had CP Class A disease but may still have had varying levels of liver dysfunction not measured by CP, such as portal hypertension [2]. Of note, portal hypertension, NAFLD and NASH were not documented for any of the patients in this study, further limiting assessment of liver disease severity.

To address these limitations, other scoring systems relying only on objectively measured variables (ie, albumin and bilirubin concentrations) have been assessed and validated in clinical trial patients, such as the Albumin-Bilirubin Score (ALBI). This finer categorization of patient characteristics can help to improve treatment decision

making [44,45]. Future studies may consider including other scoring systems, such as ALBI, which were unable to be accounted for during the time period of the current study.

The data source and study design, also generate additional limitations to consider when drawing conclusions from the study results. First, as a retrospective, observational EHR study, limitations include potential missing or incomplete data. The BOR calculation in this study was limited to information obtained from patient charts, similar to other real-world studies in this area. Second, data on services provided outside of US Oncology Network practices was not available. Third, EHR data are recorded for clinical care, not for research, which may result in data errors of omission and commission; some variables of interest were not always available for the entire study population. Fourth, generalizability may be limited due to the location distribution of US Oncology Network practices and their use of evidence-based guidelines. Additionally, as the data source was not set up to provide detail at patient level, outcomes, such as quality of life (QoL), were not adequately available for evaluation; QoL assessment in such a population may be of interest for further research. Similarly, dose reductions or treatment interruptions were not captured in our study and such data may be of interest for future studies.

At the same time, our study has several strengths. Although CP scores were not routinely reported in patient records, after imputation methods, CP scores were available for 88% of patients. Further, the study population showed similar demographic and clinical characteristics to several other real-world studies of patients with BCLC stage A, B or C disease [26,28,29]. In addition, use of the EHR data in our study represents usual care in a large network of community oncology practices. Given these strengths, these data can be used to report real-world findings that are more representative of typical patients with HCC.

Conclusion

In this study, approximately half of patients with HCC initiating 1L systemic therapy in the community oncology setting had CP Class B and C disease, and approximately one third underwent liver-directed therapies prior to 1L. The data show that CP Class B patients may have a similar OS and PFS benefit from systemic therapy compared with CP Class A patients receiving sorafenib in the 1L setting for advanced HCC, underlining the benefit of systemic therapy in CP Class B patients. Future clinical trials allowing for the inclusion of CP Class B patients may be warranted to establish benefit more clearly for new, more recently approved, agents in this patient group with high unmet need.

Summary points

- Hepatocellular carcinoma (HCC) is associated with poor prognosis.
- Child-Pugh (CP) scoring is used to assess the severity of liver disease and is taken into consideration in the management of patients with HCC.
- Clinical trials are often limited as they only include patients with CP Class A, and hence may not reflect real-world populations.
- This retrospective, observational, descriptive study, conducted in the US community oncology setting, assessed clinical outcomes among treated patients with advanced HCC who had received no previous systemic therapy when sorafenib was the only US Food and Drug Administration -approved systemic therapy.
- The majority of patients who received sorafenib had CP Class A/B.
- Survival outcomes were numerically similar across patients with CP Class A/B; however, a longer overall survival was reported in the subset of patients who received prior liver-directed treatments.
- Treatment discontinuation due to toxicity was slightly lower among patients with CP Class B liver disease than those with Class A.
- These real-world data suggest that efficacy and safety of sorafenib are similar in patients with CP Class A or B.

Author contributions

AA: conception and design of the study; analysis and interpretation of data; administrative, technical, or material support. NF: conception and design of the study; analysis and interpretation of data; administrative, technical, or material support; study supervision. BS: conception and design of the study; analysis and interpretation of data; administrative, technical, or material support; study supervision. TP: data acquisition; analysis and interpretation of data. YW: analysis and interpretation of data. SP: conception and design of the study; analysis and interpretation of data; study supervision. ARH: conception and design of the study; analysis and interpretation of data; study supervision.

Financial & competing interests disclosure

This study was funded by AstraZeneca. A Aly was an employee of and held stock in AstraZeneca at the time of the study, and is an employee of and holds stock in Novo Nordisk. N Fulcher is an employee of McKesson Life Sciences. B Seal was an employee of AstraZeneca at the time of the study and holds stock in AstraZeneca. T Pham was an employee of and a held stock in McKesson Life Sciences at the time of the study, is an employee of and holds stock in Deciphera Pharmaceuticals, and holds stock in MacroGenics. Y Wang is an employee of and holds stock in McKesson Life Sciences. S Paulson reports holding stock in Actinium, Aptose, Alexion Pharmaceuticals, Lyn Health, and Stromatis Pharma; receiving Honoraria from Cardinal Health; a consulting or advisory role for AADi, Advanced Accelerator Applications, Amgen, Astellas Pharma, Bristol Myers Squibb, Eisai, EMD Serono, Exelixis, Incyte, Ipsen, Lilly Pharmaceuticals, Mirati, Hutchinson, Pfizer, QED Therapeutics, and Stromatis Pharma; receiving speakers' bureau from Ideo Oncology; receiving research funding (to institution) from AstraZeneca, Bayer, Bristol Myers Squibb, Camurus, Deciphera, Exelixis, G1 Therapeutics, Hutchinson, Incyte, Innovative Cellular Therapeutics, Ipsen, Lilly Pharmaceuticals, Merck, Nucana, Relay Therapeutics, Seattle Genetics, Sotio, Taiho Pharmaceutical, Tempus, and Zentalis; and receiving travel expenses from Pfizer. AR He reports no conflicts of interest. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editorial assistance was provided by E McLachlan and A Briggs on behalf of CMC Connect, a division of IPG Health Medical Communications, and was funded by AstraZeneca in accordance with Good Publication Practice (GPP 2022) guidelines (Ann Intern Med 2022).

Ethical conduct of research

The study protocol was subjected to a privacy review and did not require informed patient consent, because data were deidentified. McKesson received an exemption and waiver of informed consent and authorization from the US Oncology Inc. Institutional Review Board.

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