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Authors

Cabrera, Roniel
Singal, Amit G
Colombo, Massimo
et al.

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A Real-World Observational Cohort of Patients with Hepatocellular Carcinoma: Design and Rationale for TARGET-HCC

Roniel Cabrera,[1] Amit G. Singal,[2] Massimo Colombo,[3] R. Kate Kelley,[4] Hannah Lee,[5] Andrea R. Mospan ,[6] Tim Meyer,[7] Pippa Newell,[8] Neehar D. Parikh,[9] Bruno Sangro,[10] K. Rajender Reddy ,[11] Stephanie Watkins,[6] Richard C. Zink,[6] and Adrian M. Di Bisceglie[12]

This study describes the design of the TARGET-hepatocellular carcinoma (HCC) cohort and descriptive characteristics of the patient population at diagnosis among those who were enrolled in the cohort across academic and community clinical centers. TARGET-HCC is a 5-year, longitudinal, observational cohort of patients with HCC receiving care in usual clinical practice. Redacted clinical information, obtained from medical records, captures the natural history and management of the disease, including the safety and efficacy of treatment interventions used in usual clinical practice. Patients can complete patient-reported outcome measures and provide biological specimens for future translational studies. The TARGET-HCC study includes adults with histologic, cytologic, or radiologic diagnosis of HCC from academic and community centers in both the United States and Europe. A total of 1,841 participants were enrolled between January 9, 2017, and July 23, 2019, at 67 sites in the United States and Europe. To date, the most common liver disease etiology in the cohort continues to be hepatitis C, although nearly half had a nonviral etiology, including alcohol-related liver disease or nonalcoholic steatohepatitis. Most included patients were diagnosed at an early stage (Barcelona Clinic Liver Cancer Stage [BCLC] 0/A), but only approximately one third underwent curative treatment. Systemic therapy has been used in 7.3% of enrolled patients, including 45.7% of those with BCLC stage C tumors. ***Conclusion:*** **Overall, the TARGET-HCC cohort allows for the assessment of patient characteristics and investigation of new treatment paradigms and sequencing with existing agents as well as novel regimens for HCC. (*Hepatology Communications* 2021;5:538-547).**

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths worldwide and projected to exceed more than 1 million deaths per year by 2030.[1] Most cases of HCC occur in the setting of chronic liver diseases, including chronic hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-related liver disease, or nonalcoholic fatty liver disease (NAFLD).[2,3] In the United States, Canada, and parts of Europe, HCC is one of the only cancers with increasing incidence and mortality, largely due to a high prevalence of advanced chronic HCV infection and the rising number of patients with NAFLD.[4-6] Given the nature of patients having two concomitant diseases, they may present with symptoms of cancer and/or signs of liver dysfunction, making the clinical management inherently complex and multidisciplinary.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; EMR, electronic medical record; FDA, U.S. Food and Drug Administration; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LRT, local-regional therapy; NAFLD, nonalcoholic fatty liver disease; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; TACE, transarterial chemoembolization.

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Although several staging systems for HCC have been proposed, the most commonly used and endorsed by clinical practice guidelines is the Barcelona Clinic Liver Cancer (BCLC) system.[7,8] The BCLC system incorporates several factors that have been shown to impact HCC prognosis: tumor burden, degree of liver dysfunction, and Eastern Cooperative Oncology Group (ECOG) performance status. Tumor stage is one of the strongest drivers of HCC prognosis, with marked differences in survival between those detected at an early stage and those detected at intermediate or advanced stages, highlighting the importance of HCC screening among patients who are at risk.[9] Patients with early stage HCC (BCLC 0/A) can achieve 5-year survival rates exceeding 60% with potentially curative therapies, including surgical resection, liver transplantation, and local ablative therapies. In contrast, patients with intermediate-stage HCC (BCLC stage B) are typically offered local-regional treatments to slow tumor progression and can achieve a median survival of approximately 2 years; those with advanced stage HCC (BCLC stage C) are typically treated with systemic therapies with median survival of 1-2 years.

There have been significant medical advances in the past several years, with numerous new approvals for systemic agents in the last 3 years. The tyrosine kinase inhibitor sorafenib was the first systemic therapy approved for unresectable advanced HCC in 2008 and remained the only available systemic therapy for a decade.[10] However, recent phase 3 trials have led to the approval of lenvatinib in the first line and regorafenib, cabozantinib, and ramucirumab in the second line.[11-14] Immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab, ipilimumab + nivolumab) demonstrated high objective response rates in phase 2 clinical trials, leading to accelerated U.S. Food and Drug Administration (FDA) approval in the United States, although these agents are not approved in other countries following negative phase 3 trials.[15-17] Most recently, the combination of atezolizumab and bevacizumab has demonstrated superior survival to sorafenib in the first-line setting and will likely be used to a great extent.[18]

The efficacy of therapeutic interventions for HCC in these select populations, however, may not reflect effectiveness when these same therapies are

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ARTICLE INFORMATION:

From the [1]University of Florida, Gainesville, FL, USA; [2]University of Texas Southwestern Medical Center, Dallas, TX, USA; [3]Center for Translational Research in Liver Disease, Humanitas Hospital, Rozzano, Italy; [4]University of California San Francisco, San Francisco, CA, USA; [5]Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, Richmond, VA, USA; [6]Target RWE, Durham, NC, USA; [7]Royal Free Hospital and University College London Cancer Institute, University College London, London, United Kingdom; [8]The Oregon Clinic, Portland, OR, USA; [9]Division of Internal Medicine, University of Michigan, Ann Arbor, MI, USA; [10]Department of Internal Medicine, Clinica Universidad de Navarra, Madrid, Spain; [11]Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [12]Division of Gastroenterology and Hepatology, St. Louis University, St. Louis, MO, USA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Andrea R. Mospan, Ph.D.
Target RWE
2520 Meridian Parkway, Suite 105
Durham, NC 27713
E-mail: amospan@targetrwe.com
Tel.: +1-984-234-0268 ext. 207

applied to patients who may have varying degrees of liver dysfunction, compliance with treatment interventions, and comorbid disease.[19] Patients enrolled in phase 2 and phase 3 trials represent a highly selected group of patients with HCC who are not fully represented of the HCC population as a whole. Furthermore, these patients are followed in high-volume specialist centers with regimented trial protocols and nursing support, which may not reflect how therapies are delivered in clinical practice. In addition, the majority of clinical trial data focus on a homogeneous population of patients receiving first- or second-line therapy; there are limited data on systemic therapies administered sequentially after the first- or second-line context. Therefore, evaluation of real-world use and outcomes of these therapies are essential to understand their effectiveness in clinical practice.

With the changing landscape in liver-directed as well as systemic treatments for patients with HCC, TARGET-HCC provides clinical information on the overall use, safety, and effectiveness of these interventions in real-world clinical practice. The aim of this work is to describe both the design of the TARGET-HCC cohort as well as descriptive characteristics of the patient population at diagnosis among those who were enrolled in the cohort between January 9, 2017, and July 23, 2019.

Patients and Methods

OVERVIEW AND COHORT

TARGET-HCC is an ongoing, longitudinal, observational cohort of patients receiving medical care for HCC in usual clinical practice across both academic institutions and community practice sites in both the United States and Europe (Fig. 1). The primary aims of TARGET-HCC are to define the natural history of HCC and to estimate the association between therapeutic interventions for HCC and subsequent health outcomes in a real-world setting. Secondary aims include i) evaluation of the impact of HCC treatment interventions and concomitant medications on comorbid conditions and liver function and patient-reported outcome (PRO) measures during the natural course of HCC and management with health-related quality of life questionnaires and ii) establishing a Biorepository Specimen Bank. Exploratory aims include investigation of optimal type, duration, and sequence/combination of treatment interventions for HCC used in

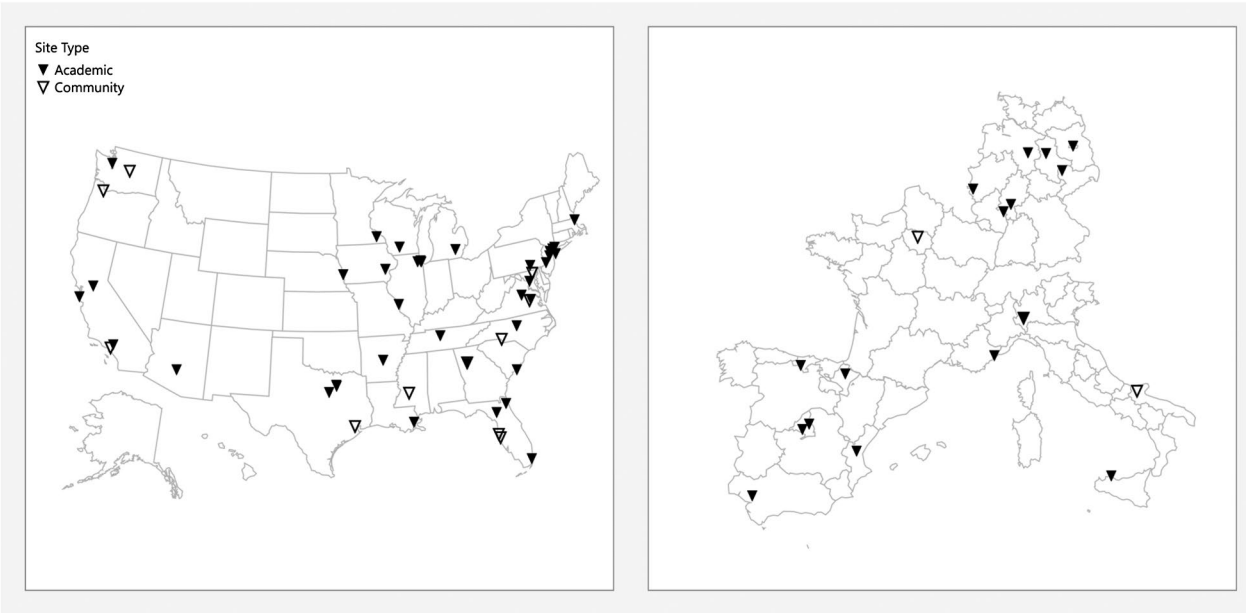

FIG. 1. TARGET-HCC sites in the United States and Europe. Maps illustrating the location of sites in the United States and Europe participating in TARGET-HCC; 84% of sites are located in the academic setting, 16% of sites are located in the community setting.

usual clinical practice; performing biomarker analyses to identify potential markers predictive of response patterns or side effect profiles; and generating hypotheses that may lead to further investigations regarding natural course and treatment of HCC.

The cohort included any patient ≥18 years old with a histologic/cytologic or radiologic diagnosis of HCC being managed in clinical practice. Patients with mixed HCC-cholangiocarcinoma and those who participated in prior clinical trials or other observational studies were included. Participating sites include academic and community clinical centers specializing in gastroenterology/hepatology, hepatobiliary/transplant surgery, interventional radiology, radiation oncology, or medical oncology. While enrollment was initially consecutive, targeted enrollment of select subpopulations that are historically underrepresented in randomized trials was implemented (e.g., Child B/C cirrhosis and/or advanced HCC).

Approvals from central and/or local institutional review boards and ethics committees were obtained before subject recruitment and enrollment. All participants signed written informed consent for participation.

ASCERTAINMENT OF CLINICAL INFORMATION

All data from enrollment sites in the United States were collected, processed, and stored centrally through an electronic data capture system by sponsor personnel or a designee in a similar manner to described methods.[20] All data from enrollment sites in Europe were collected and entered by local site personnel. Electronic checks, source data verification, and clinical monitoring to ensure entered data are accurate relative to source documents were performed. Data management activities, such as query management and coding of terms using the Medical Dictionary for Regulatory Activities or World Health Organization drug dictionaries, were performed by Target RWE. Longitudinal timelines for extraction of clinical information from the electronic medical record (EMR), completion of PROs, and collection of biospecimens are provided in Table 1.

EMR

At the date of enrollment, patients agreeing to participate provided access to their medical records for 3 years before enrollment and 5 years prospectively after enrollment. Clinical information from the EMRs, including clinical narratives, laboratory results, pathology reports, and imaging data, were uploaded into a secured database at 3-month intervals from enrollment during the first year and every 6 months thereafter. Clinical information of interest abstracted from medical records included comorbid conditions, medication use, hospital events, laboratory values, imaging results, biopsy results, and receipt of any treatments.

PRO Surveys

At enrollment, patients who consented to participate in TARGET-HCC completed the Alcohol Use Disorders Identification Test: self-report version (AUDIT). Patients in the United States at participating sites also had the option of completing several additional PRO surveys that were collected at enrollment, 3 months for the first year, and every 6 months thereafter during the longitudinal follow-up period. The PROs included the PRO Measurement Information System (PROMIS) Pain Interference-Short Form 8a, PROMIS Emotional Distress-Depression-Short Form 8a, PROMIS Fatigue-Short Form 8a, and the PROMIS Cancer Bank.[21] All instruments were validated and available in English and Spanish.

Biorepository Samples

Participants enrolled in TARGET-HCC at participating sites in the United States were invited to participate in the Biorepository Specimen Bank. Collection of blood samples for biomarker and DNA assays and tissue samples for biomarker assays was optional. Collected samples were stored and may be leveraged for research purposes to evaluate biomarkers across the Cancer Continuum for HCC, including early detection, diagnosis, prognosis, treatment selection, and treatment response.

OPERATIONAL DEFINITIONS OF DISEASE SEVERITY

Tumor Staging

Tumor stage, as determined by imaging reports at diagnosis, was categorized using the BCLC staging

TABLE 1. TIME AND EVENTS SCHEDULE

Assessment	Screening and Enrollment*	Month 0†	Follow-Up: Month 1 to 12‡	Follow-Up: Month 13 to 60§	End of Observation‖
Informed consent¶,#	X				
Demographic data	X				
AUDIT self-report	X**				
HRQoL, PROs††	X		X	X	X
Blood samples‡‡,##	X‡‡	X§§			
Tissue samples‖‖	X				
Expedited SAE reporting by sponsor¶¶			X	X	X
Study and medical records submission##,***,†††	X##	X##	X***	X***	X***

*Enrollment is the date of consent.
†Retrospective records from enrollment to 3 years prior.
‡Subsequent records every 3 months ± 1 month.
§Subsequent records every 6 months ± 2 months.
‖Month 60 but may be earlier if participant discontinues prematurely.
¶Study procedures are completed at or before regularly scheduled clinic visits.
#Participant can withdraw her/his consent at any time after she/he is enrolled in the study.
**The AUDIT self-report can be completed any time as soon as possible after enrollment.
††Optional web-based PRO surveys will be completed as soon as possible after enrollment and every 3 months (±1 month up to month 12) and every 6 months (±2 months from month 13 to month 60). Participants receive links to online surveys by e-mail.
‡‡Optional blood samples are collected as soon as possible after enrollment.
§§Optional blood samples are collected when feasible at each HCC progression, at the start of a new treatment intervention, and then ~3 to 6 months after the start of a new treatment intervention.
‖‖Optional paraffin-embedded slides of tumor or liver tissue are submitted to the sponsor or designee when tissue remains after tumor or liver biopsy or after liver surgery or transplant.
¶¶Expedited SAE reporting by the sponsor will begin for SAEs that occur from the time of enrollment until the end of observation. SAEs may be collected in the retrospective 3 years but will not be reported. Additionally, investigators may voluntarily report any SAE to the sponsor.
##Up to 3 years of medical record data are submitted following screening/enrollment.
***During follow-up, medical records data are submitted for up to 5 years: every 3 months (±1 month up to month 12) and every 6 months (±2 months from month 13 to month 60). The first submission during follow-up is ~3 months following the month-0 submission.
†††Additional "unscheduled" medical records submissions/entry may be requested as needed.
Abbreviations: HRQoL, health-related quality of life; SAE, serious adverse event.

system, as defined by American Association for the Study of Liver Diseases guidelines.[7,22] Of note, patients with ECOG performance stage 1 were classified as BCLC A or B based on tumor burden. Patients were classified as BCLC stage C if they had evidence of extrahepatic spread, any vascular invasion, or ECOG status >1. Tumor burden was also classified using the Milan criteria, the most common criteria for liver transplantation in the United States.[23]

Etiology and Degree of Liver Dysfunction

The diagnosis of cirrhosis was based on fibrosis stage per biopsy or clinical manifestations in the presence of HCC (nodular liver, ascites, splenomegaly, varices, and/or thrombocytopenia) (Supporting Table S1). Child-Pugh status was derived from a combination of clinical notes, pharmacy data, imaging reports, and laboratory data, adapted from a previous report (Supporting Table S2).[24] Etiologies were derived from abstracted data from the EMR.

Performance Status

Patient ability to perform activities of daily living was assessed using the ECOG performance status, as ascertained from the medical record.[25] If performance status was missing from medical records, it was assumed to be 0-1 unless the patient was referred for hospice.

STATISTICAL ANALYSIS

Categorical variables are presented as frequency and percentage of nonmissing values, and continuous

variables are presented as median and range of available values. Patient and disease characteristics, including cirrhosis, Child-Pugh class, and staging criteria, were calculated at the time of diagnosis. Initial therapies included any treatments taken on the first date of treatment for each patient. Treatments included local-regional therapies (LRTs), surgeries, radiation, and systemic therapies. Data were analyzed using SAS software version 9.4.

Results

A total of 1,841 patients with HCC were enrolled in the cohort between January 9, 2017, and July 23, 2019. Patients were recruited from a total of 50 sites across the United States and 17 sites in Europe (Fig. 1). Most sites (83.6%, n = 56) were academic centers, with 16.4% (n = 11) being community practice; most patients (74.6%, n = 1,373) were recruited by gastroenterology or hepatology services (Supporting Table S3). There was geographic heterogeneity, with 68.0% of U.S. sites located in large central metropolitan areas, 16.0% in medium metropolitan areas, and 16.0% in either large fringe or small metropolitan areas.

Imaging was available for tumor staging at the time of diagnosis for 1,421/1,841 (77.2%) participants. This cohort was predominantly (73.8%, n = 1,001) white, and 52.5% (n = 746) were between 40 and 64 years of age; the median age was 64 years, and 76.8% (n = 1,090) of patients were men. HCV infection was the most common liver disease etiology, occurring in 60.5% (n = 859) of patients, whereas 23.7% (n = 337) had alcohol-related liver disease, 290 (20.4%) had NAFLD, and 188 (13.2%) had a history of nonalcoholic steatohepatitis. There was no documented etiology in the medical record for 98 patients (6.9%). Most patients (88.3%, n = 1,255) were cirrhotic, and 59.0% (n = 708) of those with cirrhosis were Child-Pugh class A (Table 2).

All patients without available staging information had been diagnosed with HCC in the distant past. Of those patients, 54.5% (n = 774) were BCLC stage A, 13.2% (n = 187) were BCLC B, and 11.1% (n = 158) were BCLC stages C or D. Staging was unable to be determined for 11.0% (n = 156) of patients. Similarly, over half (57.0%, n = 810) of enrolled patients with HCC were inside Milan criteria (Table 2).

Initial HCC treatments are summarized overall and by BCLC stage in Table 3. The majority of patients received LRTs (76.6%, n = 955), with 13.7% (n = 171) undergoing surgical resection and 0.3% (n = 4) undergoing liver transplantation as their initial therapy. Overall, 29.6% (n = 421) of patients underwent curative treatment, with 13.7% (n = 171) having undergone resection, 19.7% (n = 246) local ablative therapy, and 0.3% (n = 4) liver transplantation. The most common treatment was transarterial chemoembolization (TACE), which was used in 40.4% (n = 503) of patients. Among advanced patients, 45.7% (n = 32) of BCLC C and 10.9% (n = 5) of BCLC D received systemic therapies. For patients with stage BCLC D, 64 of the 67 (95.5%) patients had Child-Pugh class C cirrhosis. The most common first-line systemic therapy was sorafenib (data not shown), although there was increased use of alternative agents after FDA approval in 2017 and later. Among 94 systemic therapies as first line for 91 participants, 73% were treated with sorafenib, 9.6% with nivolumab, and 6.4% with lenvatinib. Other treatments were used in fewer than 1% of participants. Among 91 subjects who used systemic therapies as first line, 80 (88%) had cirrhosis. Overall, 311 participants had more than one TACE procedure and 100 patients had more than 1 radio frequency ablation.

Discussion

TARGET-HCC is an international, longitudinal, observational cohort study conducted across international academic and community sites and multidisciplinary points of care to create a real-world view of the natural history and clinical management of patients with HCC. Presently, over 1,800 patients with HCC have been enrolled across 67 sites from the United States and Europe and will be followed over a 5-year period during their clinical management. The cohort provides a repository of clinical information on the disease course of HCC in which to evaluate safety and effectiveness of current and future therapies, patient and provider characteristics associated with treatment patterns, and clinical profiles regarding the management of treatment-emergent adverse events.

One of the main objectives of TARGET-HCC is to ascertain information about critical populations

TABLE 2. PATIENT AND DISEASE CHARACTERISTICS AT DIAGNOSIS*

Summary	All Patients (n = 1,421)
Patient characteristics	
Age at diagnosis, years†	
median (n)	64.0 (1,420)
Q1-Q3 (IQR)	59.0-69.0 (10.0)
Minimum-maximum	18.0-90.0
Age in years at diagnosis by category, n (%)	
n	1,420
18-39	14 (1.0%)
40-64	746 (52.5%)
≥65	660 (46.5%)
Not available	1
Sex, n (%)	
n	1,420
Female	330 (23.2%)
Male	1,090 (76.8%)
Not available	1
Race, n (%)	
n	1,356
White	1,001 (73.8%)
Black or African American	261 (19.2%)
Asian	60 (4.4%)
American Indian or Alaska Native	5 (0.4%)
Native Hawaiian or other Pacific Islander	3 (0.2%)
Other	26 (1.9%)
Not available	65
Ethnicity, n (%)	
n	1,348
Hispanic or Latino	148 (11.0%)
Not Hispanic or Latino	1,192 (88.4%)
Other	8 (0.6%)
Not available	73
Diabetes, n (%)‡	
n	1,421
Yes	476 (33.5%)
Disease characteristics	
Etiologies, n (%)§	
HCV	859 (60.5%)
HBV	126 (8.9%)
NAFLD/NASH	478 (33.6%)
Autoimmune hepatitis	15 (1.1%)
Primary biliary cholangitis	15 (1.1%)
Alcohol-related liver disease	337 (23.7%)
Other	17 (1.2%)
No etiologies	98 (6.9%)
Cirrhosis, n (%)‖	
n	1,421
Yes	1,255 (88.3%)
Decompensated cirrhosis, n (%)‖	
n	1,255
Yes	901 (71.8%)
Child-Pugh class, n (%)‖	
n	1,201
A	708 (59.0%)
B	427 (35.6%)
C	66 (5.5%)
Not available	54
BCLC staging, n (%)	
n	1,421
0	146 (10.3%)
A	774 (54.5%)
B	187 (13.2%)
C	91 (6.4%)
D	67 (4.7%)
Indeterminate	156 (11.0%)
Milan criteria, n (%)	
n	1,421
Inside	810 (57.0%)
Outside	428 (30.1%)
Indeterminate	183 (12.9%)
Modified Milan criteria, n (%)	
n	1,421
Inside Milan	810 (57.0%)
Outside Milan, no extrahepatic spread or vascular invasion	330 (23.2%)
Outside Milan, no extrahepatic spread, vascular invasion present	81 (5.7%)
Outside Milan, extrahepatic spread present	17 (1.2%)
Indeterminate	183 (12.9%)

*Includes only those participants with tumor staging available at time of diagnosis.
†Age calculated based on year of diagnosis minus birth year.
‡Diabetes is determined from the medical history.
§Patients can have more than one etiology, and data reflect that available at any time during the study. Hepatitis B and C are determined from the medical history, positive laboratory results, or medications indicated for the disease through diagnosis. NAFLD, primary biliary cholangitis, and autoimmune hepatitis are determined from the medical history. History of alcohol abuse is determined from the medical history or an AUDIT score ≥7 at the time of enrollment.
‖Decompensated cirrhosis and Child-Pugh for patients only with cirrhosis.
Abbreviation: NASH, nonalcoholic steatohepatitis.

who are excluded in clinical trials and to improve the understanding of the risks and benefits associated with each of the treatment approaches in these

TABLE 3. INITIAL HCC THERAPIES*

Summary	BCLC 0 (n = 146)	BCLC A (n = 774)	BCLC B (n = 187)	BCLC C (n = 91)	BCLC D (n = 67)	All Patients (n = 1,421)
Total subjects	126	696	166	70	46	1,246
LRT	105 (83.3%)	547 (78.6%)	144 (86.7%)	27 (38.6%)	37 (80.4%)	955 (76.6%)
Ablation	53 (42.1%)	144 (20.7%)	17 (10.2%)	1 (1.4%)	8 (17.4%)	246 (19.7%)
Embolization	52 (41.3%)	406 (58.3%)	127 (76.5%)	24 (34.3%)	29 (63.0%)	708 (56.8%)
TACE	38 (30.2%)	292 (42.0%)	89 (53.6%)	9 (12.9%)	23 (50.0%)	503 (40.4%)
Radioembolization	13 (10.3%)	106 (15.2%)	38 (22.9%)	17 (24.3%)	5 (10.9%)	195 (15.7%)
Other	1 (0.8%)	8 (1.1%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	12 (1.0%)
Surgery	18 (14.3%)	111 (15.9%)	8 (4.8%)	4 (5.7%)	1 (2.2%)	175 (14.0%)
Transplant	0 (0.0%)	2 (0.3%)	1 (0.6%)	0 (0.0%)	1 (2.2%)	4 (0.3%)
Resection	18 (14.3%)	109 (15.7%)	7 (4.2%)	4 (5.7%)	0 (0.0%)	171 (13.7%)
Radiation	1 (0.8%)	27 (3.9%)	0 (0.0%)	7 (10.0%)	3 (6.5%)	39 (3.1%)
Systemic	6 (4.8%)	18 (2.6%)	16 (9.6%)	32 (45.7%)	5 (10.9%)	91 (7.3%)
Not available	20	78	21	21	21	175

*Includes any treatments taken on the first date of treatment for each patient.

underrepresented subgroups. Importantly, these data will address gaps in knowledge of the clinical effectiveness of interventions and will help to validate optimal treatment algorithms. As regulatory authorities approve new medications, a database of this size can serve to monitor for drug-related adverse events; examine effectiveness outcomes according to sequence of treatments; and provide valuable post-marketing surveillance of newly approved medications mandated by regulatory agencies. Beyond measuring clinical effectiveness, this real-world observational study will also collect and interpret outcomes from patients' perspectives, including PROs, health-related quality of life, hospitalization, and other adverse events that will generate greater value care for all stakeholders.[26]

The strengths of the TARGET-HCC cohort are its large study population, the ascertainment of the entire spectrum of current and future therapies across all stages of HCC, and its real-world setting. The international observational study design enables clinical information to be collected from patients treated under local standards of care. Patients participating in the cohort receive care in diverse health care settings, including academic and community settings in both the United States and Europe; 68% of patients are receiving care in large urban metropolitan cities with over 1 million inhabitants.

All diagnostic procedures, treatments, sequences of treatments, management of the disease, and resource use ascertained from the medical record follow each clinic's local standard or care without being dictated by enrollment in the study protocol. This granularity in the assessment of treatment and subsequent outcomes in usual clinical practice encompasses a wider range of therapeutic decisions compared with the defined limits on therapy required by investigational study protocols. The real-world nature of the study highlights how treatment patterns in clinical practice can also vary from guideline recommendations. These variations are observed when the study cohort is categorized by the initial therapies received. For example, selected patients with limited multifocal disease or vascular invasion can be treated with resection. Similarly, there are some providers who use systemic therapy as bridging therapy for patients undergoing liver transplant. By classifying patients by their initial therapies, liver transplant appears to be underrepresented, with only 4 patients listed as having undergone transplant. However, the patients who would have received liver transplant are under the respective bridging therapy received while awaiting liver transplant. The 4 patients who are listed as having undergone transplant did not receive any bridging therapy. Decisions and outcomes made in real-world conditions are likely to be more widely applicable to clinical practice than those from restrictive interventional studies.

A limitation of the TARGET-HCC cohort is the relatively small proportion of patients with advanced disease receiving systemic therapy at the time of reporting; this is likely related to patient recruitment primarily at gastroenterology/hepatology rather than

oncology sites where a greater proportion of patients with advanced disease would be expected. During the planned follow-up period of TARGET-HCC, it is anticipated that a substantial proportion of the earlier stage patients will experience recurrent and/or progressive disease requiring systemic therapy.

Among all participants, a small percentage of them (12.3%) did not receive any therapies, and of these slightly more than half were patients with decompensated cirrhosis. Due to the retrospective nature of the cohort, we were unable to determine if the other untreated patients were related to patient choice, change in status (e.g., worsening liver dysfunction), or provider choice. However, this small proportion is similar to what has been described in other comparable cohorts. Another limitation is the lack of inclusion of Asian sites and a corresponding underrepresentation of patients with HBV as the underlying etiology of liver disease. Nonetheless, the TARGET-HCC Western demographic is relevant in representing the fastest rising causes of HCC death, including HCV and NAFLD.

TARGET-HCC is a longitudinal cohort using standardized practices to ascertain and monitor clinical information from the medical record to increase the efficiency of performing clinical research while ensuring collection of detailed safety and effectiveness data on patients being managed for HCC. TARGET-HCC engages community and academic practice providers as partners in the research to ensure rapid translation of research findings into improvement in health care quality and outcomes. The availability of an established cohesive cohort allows for the investigation of new treatment paradigms with existing agents as well as future therapeutics for HCC.

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