Real-world evidence in hepatocellular carcinoma

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Abstract
Real-world evidence includes all health-related information, such as electronic health records, insurance claims, pharmacy records and wearables that are obtained outside of clinical trials. These data can provide critical insights into the natural history of disease and evaluate the safety and effectiveness of treatment regimens used in clinical practice. Real-world data have been applied to varying degrees by global regulatory agencies to inform and expedite many phases of drug development and help refine the use of therapeutic regimens after marketing, especially in populations that are under-represented in registration trials. For the management of hepatocellular carcinoma, early detection provides the best chance for curative therapies, whose success has been evaluated in numerous cohorts. The availability of novel systemic therapies, including kinase inhibitors and immunotherapies, has provided new treatment options and improved survival in patients with advanced stage hepatocellular carcinoma. Real-world longitudinal observational studies can help understand the long-term safety and effectiveness of these agents.

KEYWORDS
hepatocellular carcinoma, real-world data, real-world evidence

1 SOURCES AND ROLES OF REAL-WORLD DATA

Real-world data (RWD) may be obtained from a variety of sources, such as registries or observational studies, pragmatic trials (ie trials designed to more closely reflect usual clinical practice vs a traditional clinical trial), insurance claims, prescriptions, electronic health records and hospital chargemaster data.1 Other newer sources of data may include those obtained from social media or wearables such as smart watches (Figure 1).

Real-world evidence (RWE) has regularly filled the gap that exists between evidence generated from clinical trials and the use of approved medications in usual clinical practice.2-4 Real-world data have been used to inform multiple phases of drug development, including preclinical development, identification of unmet needs, development of product profiles and clinical trial designs by informing patient characteristics and comorbid conditions, frequently used concomitant medications and treatment paradigms, and the feasibility of inclusion and exclusion criteria planned for the clinical study, as well as by providing detailed information on the natural history of disease.1 Perhaps RWE’s most widely recognized contributions are in the post-authorization space by supporting label expansion for approved medicinal products and to fulfill post-authorization requirements including long-term safety. Real-world evidence has also played a critical role in improving the understanding of treatment effectiveness and safety in expanded patient populations that were under-represented in registration trials.5

A more complete picture of a patient’s journey may be obtained from disease-specific registries. These longitudinal observational studies differ from traditional clinical trials, which have narrowly selected patient populations to answer specific clinical questions and support ultimate approval with regulatory agencies.6 Observational
studies collect data from patients treated in usual clinical practice and may include either a retrospective look-back period and/or a prospective longitudinal period. These studies can inform clinicians about the optimal use of medicinal products in the real world, such as in specific populations for which information may be lacking from clinical trials, such as those with certain comorbid diseases, severe disease, different races or older age, as well as provide long-term safety data.\textsuperscript{6}

2 | REGULATORY VIEW OF REAL-WORLD DATA AND REAL-WORLD EVIDENCE

The 21st Century Cures Act of 2016 was designed to accelerate the development of new drugs and more quickly and efficiently make these therapies available to patients in the United States (US).\textsuperscript{7} Pursuant to this act, the Food and Drug Administration (FDA) released a framework in 2018 for the evaluation of the use of real-world evidence for supporting either a new indication of a previously approved drug or to meet post-market regulatory requirements.\textsuperscript{8} This framework defines real-world data (RWD) as ‘data relating to patient health status and/or the delivery of health care routinely collected’ outside of clinical trials, and real-world evidence (RWE) as the ‘clinical evidence regarding the usage and potential benefits or risks of a medicinal product derived from the analysis of RWD’.\textsuperscript{7} Thus, RWD may contribute information directly related to the safety and effectiveness of a medicinal product or contribute to the design and efficiency of a planned traditional clinical study (eg feasibility, inclusion/exclusion criteria, selection of geographical regions, etc).\textsuperscript{1}

Of note, the FDA regularly uses RWE to monitor the safety of medicinal products approved in the US via the Sentinel System. The full system was officially launched in 2016 and consists of administrative claims data and electronic health record data.\textsuperscript{9} The Sentinel System

Key points
- Real-world evidence can be used to fill gaps between data generated from traditional clinical trials and the use of approved medicines in clinical practice.
- There are many sources of real-world data, ranging from electronic health records and claims data to observational longitudinal cohort studies. The latter can be used for the assessment of long-term safety of approved medicines, populations that were under-represented in clinical trials and the natural history of disease in a real-world setting.
- Real-world evidence continues to play an important role in understanding disease progression in hepatocellular carcinoma, and the safety and effectiveness of approved therapies and treatment paradigms.

![Real-World Evidence](image)

**FIGURE 1** Real-world evidence informs the drug development process from the early discovery phases through post-market surveillance. Adapted from Galson and Simon (2016)\textsuperscript{1}
has been used to assess post-market safety, patterns of medication use including use in specific subpopulations and to determine the impact of medical countermeasures in public health emergencies.9

In Europe, a Heads of Medicines Agencies/European Medicines Agency (EMA) Joint Task Force on Big Data was established in 2017. Subsequent published reports have addressed both RWD and, in a final report released on January 2020, made recommendations for the use and implementation of big data.10,11 As described by the Joint Task Force, 'big data' includes RWD sources such as electronic health records, registry data and claims data, among others. The EMA has conducted numerous studies using RWD. Real-world data have also been accepted by other regulatory authorities, such as Health Canada and Japan's Pharmaceuticals and Medicinal Devices Agency (PDMA), to support the approval of new applications or line extensions. Moreover, Health Canada released guiding principles for regulatory decision-making related to RWE.12,13 According to the study by Bolisli et al, in most instances, the EMA, FDA, Health Canada and the PDMA used RWD as a control or historical control group or as supportive data to validate findings, and these data were generally utilized to support the development of products for rare diseases, where there was an unmet medical need or where a traditional randomized controlled trial was not feasible.12

3 | REAL-WORLD EVIDENCE IN HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is increasingly responsible for a significant number of deaths and is currently a fourth leading cause of cancer-related deaths worldwide.14 Unfortunately, the incidence of HCC is rising in areas such as the US, partly because of the high number of patients with advanced hepatitis C virus (HCV) infection, and in addition to an increasing number of patients with NAFLD.15-17 Despite advances in therapies for HCC in recent years, studies are generally limited to phase 2 and 3 trials with strict inclusion and exclusion criteria, thus lacking generalizability to usual clinical practice. A summary of evidence from traditional registry clinical trials used in the approval of new therapies, as well as observational cohort studies used for the surveillance of disease progression are described below.

4 | INCIDENCE AND SURVEILLANCE

Multiple HCC cohort studies have been performed in a variety of geographical regions throughout the world. One large European study using electronic health records data to determine new diagnoses of advanced liver disease included primary care data from the European Medical Information Framework Network, specifically from the United Kingdom, the Netherlands, Italy and Spain, which included over 18 million adults, 136,703 with a diagnosis of nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH). These RWD were used to identify the most frequently observed comorbidities observed in the NAFLD/NASH group compared to matched controls (diabetes, hypertension and obesity), as well as a baseline diagnosis of diabetes as a strong predictor of a diagnosis of HCC or cirrhosis.18

Another study, the Hepatocellular Carcinoma Early Detection Strategy study, is a multicentre National Cancer Institute Early Detection Research Network initiative to establish a large biorepository and database on patients who are considered at risk for the development of HCC. As of 2018, this database includes 1482 participants with cirrhosis and without HCC at enrolment and should provide a valuable opportunity to examine the incidence of HCC in this population as well as to study potential biomarkers.19

Projections and determining the odds of survival are important in the management and treatment of patients with HCC. Cohort studies in both Denmark and the US examining the progression of HCC over a 12-year and 6-year period, respectively, both showed an increased incidence of HCC over time.20,21 However, it cannot be determined whether this was related to an increase in the prevalence of liver diseases, or an awareness of HCC screening in clinical practice. The increased incidence of HCC has escalated the importance of examining the likelihood of survival and potential mitigating factors. Surveillance of liver cancer has been shown to lead to earlier detection and a better chance of receiving curative treatment.22 A cohort study in Italy from 1999 to 2010 using 320 HCC patients with a new diagnosis of HCC showed that patients with Barcelona Clinic Liver Cancer (BCLC) stage D at baseline had a 1-year survival of less than 5%.23 These findings confirm the importance of early detection and subsequent treatment of HCC globally.

One area of interest in patients with HCC is the impact of racial/ethnic minorities and socio-economic status on mortality. As reviewed by Rich et al, HCC disproportionately affects disadvantaged populations in the US, including racial and ethnic minorities, with African Americans having lower odds of detection of HCC at an early stage and overall survival than Caucasians. Others noted that HCC is often clustered geographically in areas with low socio-economic status. These disparities affect the prevention, early detection and outcomes of HCC.24-27

5 | LOCOREGIONAL THERAPIES AND SURGICAL RESECTION FOR EARLY STAGE HCC

Clinical guidelines recommend the use of locoregional therapies and surgical resection for the management of early or moderately advanced HCC.28,29 Numerous real-world cohort studies have examined the impact of locoregional therapies and/or surgical resection on early stage HCC, and several examples are discussed below.30-32 In a retrospective Australian study of patients with BCLC 0/A, those treated with curative intent had better overall survival and recurrence-free survival than patients receiving transarterial chemoembolization (TACE).30 A study from Thailand showed that approximately one third of patients across all stages of HCC had first-line treatment that deviated from recommended treatment guidelines,
which regularly influenced their survival. A study by the Liver Cancer Study Group of Japan showed that use of surgical resection in patients with HCC was associated with significantly lower risks of both death and recurrence in patients with early or moderately advanced HCC. While resection can be beneficial to some patients, survival is influenced by disease severity. A study in Germany showed that the overall survival of patients undergoing resection was 34 ± 23 months with the 1-, 3- and 5-year overall survival rates decreasing from 82.9% to 41.8% and 13.7% respectively.

6 | SYSTEMIC TREATMENT FOR HCC

Until recently, therapeutic options were limited and the prognosis for patients with advanced HCC was poor. Sorafenib, an oral multikinase inhibitor approved by the FDA in 2007, was the first agent for the treatment of inoperable HCC that demonstrated a modestly better survival than with placebo. Subsequently, numerous other systemic and immunotherapeutic agents, such as regorafenib, lenvatinib, ramucirumab, nivolumab, pembrolizumab, and combinations such as nivolumab/ipilimumab and atezolizumab/bevacizumab, have been approved based on compelling phase 2 and phase 3 studies and provide additional potential benefits for patients with advanced HCC (Table 1).

Evidence for approval of these therapies was mainly obtained from traditional clinical trials and thus restricted to stringent inclusion and exclusion criteria limiting the overall generalizability of the study population to patients presenting with HCC in clinical practice. Real-world evidence from registries and cohort studies can provide additional confidence in the effectiveness and safety of these medications in expanded patient populations and represents a natural evolution in research in HCC management.

Numerous real-world studies have shown the efficacy of sorafenib. A prospective multicentre clinical study from 2009 to 2014 examined overall survival with sorafenib treatment in 13 centres in Japan. Results from this study showed that sorafenib could be administered as a long-term treatment for patients with advanced HCC. The utility of sorafenib has been shown across patients with HCC, including the elderly. An international observational study examined 5598 patients from 2007 to 2018 to test the influence of age on overall survival. Sorafenib was shown to be effective in an elderly population (>75 years of age). A combination of TACE and sorafenib led to an improvement in survival rates with a reduced mortality of 26%.

Regorafenib is an oral multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis and tumour immunity. A randomized, double-blind, parallel-group phase 3 clinical trial was conducted in 21 countries in adults with HCC who tolerated sorafenib and progressed. A total of 567 patients began treatment (374 receiving regorafenib; 193 placebo) resulting in 10.6 and 7.8 months median survival respectively. This treatment strategy has been used in patients in whom disease progresses during sorafenib treatment and has been shown to provide benefits to survival in HCC patients. The use of regorafenib meets a previously unmet need for treatment options in patients with HCC by prolonging overall survival, progression-free survival and time to progression.

Nivolumab is an immunotherapy that inhibits programmed death receptor-1 (PD-1) used as a second-line systemic treatment in HCC patients who have been treated with, or are intolerant to, sorafenib. Nivolumab treatment resulted in durable responses at all dose levels with a 6-month OS rate of 72%. Nivolumab was originally tested in patients with advanced HCC with or without prior exposure and was found to result in a prolonged tumour response. An observational study confirmed the safety and efficacy of nivolumab across various lines of therapy. The use of immune checkpoint inhibitors (ICI) in advanced HCC has been shown to be a comparable to that in HCC patients with Child-Pugh A cirrhosis.

Lenvatinib has been shown to be an effective second-line therapy in a number of real-world settings. Atezolizumab-bevacizumab,
7 | DIRECT-ACTING ANTIVIRALS AND THE RISK OF HCC RECURRENCE

It is well established that patients with cirrhosis who are cured of hepatitis C have a continued risk of developing HCC and that ongoing surveillance for the development of HCC is warranted. Unexpectedly, reports of an increased risk of recurrent HCC after successful direct-acting antiviral (DAA) therapy in those with a complete tumour response to treatment raised concerns of the association of DAA therapy with an increased risk of early HCC recurrence. A report by Reig et al (2016) concluded that patients treated with DAs had an unexpected, increased risk of early HCC recurrence, which sparked numerous questions. Additional studies have been published both supporting and refuting findings from the Reig study. Singal and colleagues conducted a large retrospective study in North America that evaluated the impact of DAA therapy in nearly 800 patients after a complete response to therapy for HCC. There was no difference in early recurrence or in the pattern of recurrence between those treated with DAs and those without DAA therapy for hepatitis C. The EMA required all marketing authorization holders of DAs to perform a prospective study of DAA treatment among patients with previously treated HCC. Thus, the DAA-PASS international, observational study, a substudy of TARGET-HCC described below, was designed to investigate the impact of exposure to DAs on early recurrence of HCC in adult HCV-infected participants following successful HCC treatment (NCT03707080).

8 | TARGET-HCC

TARGET-HCC is an ongoing, longitudinal observational cohort of adult patients with a diagnosis of HCC who are receiving standard care at academic and community sites across the US and Europe. TARGET-HCC was designed to better understand the natural course of the disease, the utilization of available therapies, interventions, concomitant medications and outcomes in patients managed for HCC in usual clinical practice. Patients are enrolled at a variety of site types such as those with specialties in gastroenterology/hepatoLOGY, hepatobiliary/transplant surgery and oncology. Clinical data are obtained directly from the electronic medical record, thus allowing a detailed review and centralized abstraction of data from a complete record including clinical narratives, laboratory assessments, concomitant medications, therapies, procedures, imaging and pathology reports. Patient-reported outcome measures and health-related quality of life questionnaires are assessed throughout the study, and blood samples are obtained for future analysis. Key disease stage indicators assessed include BCLC tumour staging and Milan criteria; cirrhosis status, defined by biopsy and/or clinical criteria; and Child-Pugh status, which is derived from clinical data abstracted from records.

Over 1800 patients have been enrolled in TARGET-HCC with a wide range of disease severities and patient characteristics from 67 sites in the US and Europe. Patients are mostly Caucasian men with a median age of 64. The most common aetiology of liver disease is HCV infection, followed by NAFLD/NASH, alcohol-related liver disease and hepatitis B, and most patients have cirrhosis including decompensated cirrhosis in over 70%. At diagnosis, most patients with available tumour staging were BCLC stage A and over half were within the Milan criteria. Most patients received locoregional therapy for HCC.

### TABLE 2 Initial therapy for HCC according to BCLC staging at time of diagnosis for patients enrolled in TARGET-HCC (from Cabrera et al) 61

| Summary        | BCLC 0 (N = 146) | BCLC A (N = 774) | BCLC B (N = 187) | BCLC C (N = 91) | BCLC D (N = 67) | All patients (N = 1421) |
|----------------|------------------|------------------|------------------|----------------|----------------|------------------------|
| Total Subjects | 126              | 696              | 166              | 70             | 46             | 1246                   |
| Locoregional Therapy | 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                     |

Note: Initial HCC therapies include any treatments taken on the first date of treatment for each patient.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; TACE, Transarterial chemoembolization.
therapies as the initial treatment, while fewer had surgery or systemic therapies, probably because of earlier stage disease in these patients, who were mostly recruited from hepatology sites (Table 2).41

Patients enrolled in TARGET-HCC are being longitudinally followed to evaluate disease progression or regression in relation to serial locoregional and systemic therapies, as well as long-term outcomes.

9 | CONCLUSIONS

The use of RWE contributes valuable information to numerous areas including the assessment of the applicability of current therapies to broad populations with characteristics that may have been underrepresented in registration trials, the optimization of treatment effectiveness in subpopulations and the long-term safety of regimens used in clinical practice. As new therapies and treatment modalities become available, HCC registries with carefully curated data can be used to provide a rapid assessment of the safety and effectiveness of these new therapeutic regimens and to continuously evaluate the impact of shifting treatment paradigms on long-term outcomes.

DISCLOSURES

Drs. Mospan and Morris are employees of Target RWE. Dr Fried is Chief Medical Officer for TARGET RWE and receives personal fees and is a stockholder in the company.

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