Survival of Trial-Like and Non–Trial-Like Patients With Immunotherapy in Advanced Hepatocellular Carcinoma in Real World: A Collaborative Multicenter Indian Study (IMHEP)

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ABSTRACT

PURPOSE Immune checkpoint inhibitors (ICIs) is the initial line of management in advanced hepatocellular carcinoma (HCC), but survivals in the real world are not known.

MATERIALS AND METHODS A retrospective study of patients with advanced HCC receiving ICIs (as first-line therapy or as later lines of therapy) across 11 Indian institutions was conducted. Patients were divided into either cohort 1 (trial-like receiving ICI as first-line therapy), with a Child Pugh score (CTP) of ≤6, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1, and no VP4 (main portal vein thrombosis [MPVT]) or cohort 2 (trial unlike) who did not satisfy at least one of the above criteria. The primary end point was 12-month overall survival (OS).

RESULTS Between January 2017 and January 2022, 133 patient data were analyzed. The presence of MPVT was seen in 33 patients (25%). The ICIs used were atezolizumab-bevacizumab, nivolumab, and pembrolizumab in 89 (66%), 44 (33%), and one (1%) patients, respectively. With a median follow-up of 13.8 months, the 12-month OS for the entire cohort was 33.4% (95% CI, 23.6 to 43.2). Patients in cohort 1 (n = 31) had a significantly improved OS compared with patients in cohort 2 (n = 102; 12-month OS, 57.9% [95% CI, 38.5 to 77.3] *v* 24% [95% CI, 13.4 to 34.6]; $P = .005$). Patients with CTP A as compared with CTP B (9.7 *v* 4.3 months; $P < .001$) and an ECOG PS of 0/1 as compared with a PS of ≥2 (8.7 *v* 7.2 months; $P = .04$) and without MPVT (9.4 *v* 4.0; $P < .001$) had superior survivals.

CONCLUSION Patients with advanced HCC in the real world, trial-like have survivals in consonance with trial data, whereas patients with features excluding them from trials, such as main portal vein thrombosis, poor ECOG PS, and child Pugh B status, have markedly inferior survivals, despite good tolerance to immunotherapy.

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BACKGROUND

Treatment modalities in advanced hepatocellular carcinoma (HCC) have undergone a marked change over the past decade in terms of available systemic therapeutic options. The advent of atezolizumab-bevacizumab and the STRIDE regimen (tremelimumab 300 mg single dose and durvalumab 1,500 mg once every 4 weeks) as first-line options have improved outcomes compared with sorafenib.[1,2] The increased response rates and downstaging with newer tyrosine kinase inhibitors (TKIs) like lenvatinib as well as relatively well-tolerated nature of immunotherapeutic agents have resulted in expanding indications in clinical practice, that is, use beyond Child Pugh A status, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2, and concurrent use with liver-directed therapy.[3]

While clinical trials have specific and usually strict criteria for inclusion, wider indications are generally considered in clinical practice. This may result in efficacy and tolerance that may not be commensurate with that seen in seminal clinical trials. In addition, a majority of published data with immunotherapeutic agents has concentrated on outcomes when used as first-line therapy. A significant proportion of patients might have received immunotherapy post-treatment with sorafenib or lenvatinib as

CONTEXT

Key Objective

Do patients receiving immunotherapy for advanced hepatocellular carcinoma (HCC) in the real-world scenario satisfy strict inclusion criteria as enunciated in seminal clinical trials? What are the survival outcomes in trial-unlike patients?

Knowledge Generated

Approximately 75% of Indian patients receiving immunotherapy for advanced HCC in the study have a high proportion of characteristics such as Child Pugh score (CTP) B, main portal vein thrombosis, and an Eastern Cooperative Oncology Group performance status of ≥2, and this is at variance from patients in major clinical trials. Patients with characteristics similar to patients in clinical trials have survival outcomes in line with those seen in trials, whereas those with adverse baseline parameters at baseline have inferior survivals.

Relevance

While immunotherapy is the standard of care in fit patients with advanced HCC, expectations in terms of survival need to be tempered in patients who have adverse prognostic factors.

immunotherapeutic agents gained later approvals with emergence of newer data. Thus, data on the efficacy of immunotherapeutic agents in patients with advanced HCC in the real-world nontrial scenario are scarce. With this background, we conducted a study wherein patients who would fit into standard trial criteria were compared with patients who did not satisfy trial criteria with regard to the usage of immunotherapy in patients with unresectable HCC.

MATERIALS AND METHODS

Patient Selection

The Immunotherapy in advanced Hepatocellular Carcinoma (IMHEP) was a collaborative study between 11 institutions in India and aimed to evaluate the survivals of patients with advanced HCC who were treated with immunotherapeutic agents. The investigators evaluated retrospective data collected from across 11 centers for patients with HCC who had been treated between January 2017 and January 2022. Patients included in the study satisfied the following criteria: radiologically or histologically confirmed unresectable HCC; received at least one dose of immune checkpoint inhibitors (ICIs) as first-line therapy or during later lines of therapy; had at least one follow-up visit documenting response post-administration of the therapy, and had documented dates of starting and cessation of ICIs. The patients who did not receive immunotherapeutic agents were not included in the study.

Clinical Data Collection

Data were collected via a clinical record form designed on Google forms (Google, Mountain View, CA), which were distributed online for anonymized patient data entry. Data collected were demographic and clinical variables, disease-specific data including the Barcelona clinic liver cancer (BCLC) staging, details of ICIs administered, adverse events, and oncologic outcomes. The oncologic outcomes evaluated were progression-free survival (PFS), overall survival (OS), and adverse event rates.

Ethics and Consent

The initial approval for the study was obtained from the Institutional Ethics Committee at Tata Memorial Hospital (TMH; IEC418), after which ethical clearance was obtained by the other collaborating institutions over the next 6 months. The approval included the requirement of a short telephonic consent for patient data accrued in TMH as part of ethics committee requirements. Data collection and handling were conducted as per the ethical guidelines of the Declaration of Helsinki.

Statistics

Data were analyzed using IBM SPSS version 20 (Armonk, NY). Descriptive statistics such as median, frequency, and percentage were used to summarize the categorical variables. Patients in the study were divided into two cohorts—cohort 1 (trial like), which included patients receiving ICIs as first-line therapy without previous systemic therapy, with a Child-Pugh score (CTP) of ≤6, an ECOG PS of 0 or 1, and the absence of main portal vein thrombosis (MPVT; VP4), and cohort 2 (trial-unlike), which included patients who did not satisfy at least one of the above criteria. The primary end point of the study was OS, which was calculated from the date of starting ICIs to the date of death or loss of follow-up, whichever was earlier. The secondary end point was progression-free survival (PFS), which was calculated from the date of diagnosis of starting ICIs to the date of progression, loss to follow-up, or death, whichever was earlier. Survival analysis was performed using Kaplan-Meier estimates, and the log-rank test was used for bivariate comparisons. Prognostic factors with a P value of ≤.05 on

univariate analysis were considered as significant and evaluated for multivariate analysis.

RESULTS

Baseline Characteristics

A total of 149 patients had their data entered, of which data were found to be adequate for the analysis for 133 patients (Table 1). The median age of patients was 61 years (range, 17-87), a majority of patients had BCLC status (81%), and nonalcoholic steatohepatitis (NASH) was the most common etiology of HCC (34%). Portal vein thrombosis was seen in 52% of patients.

Atezolizumab-bevacizumab was the most commonly used ICI (66%), with 65% of patients receiving ICI as the first line of systemic therapy. Nivolumab was used in 33% of patients, whereas pembrolizumab was used in a single

TABLE 1. Baseline Characteristics of All Patients, Trial-Like and Trial-Unlike Cohorts

Characteristic	Entire Study Cohort	Trial-Like (n = 31)	Trial-Unlike (n = 102)
Age, years, median, (range)	61 (17-87)	60 (44-87)	61 (17-85)
Male sex, No. (%)	116 (87)	31 (100)	85 (83)
Etiology, No. (%)			
Hepatitis B–related	36 (27)	8 (26)	28 (28)
Hepatitis C–related	15 (11)	4 (13)	11 (11)
Alcohol-related	11 (8)	2 (7)	9 (9)
NASH	45 (34)	10 (32)	35 (35)
Cryptogenic	26 (20)	7 (22)	19 (19)
Child-Pugh score, No. (%)			
A	84 (63)	31 (100)	53 (52)
B7	24 (18)	0	24 (24)
B8-9	25 (19)	0	25 (25)
BCLC stage, No. (%)			
B	19 (14)	3 (10)	16 (16)
C	107 (81)	28 (90)	80 (79)
D	7 (5)	0	6 (6)
ECOG performance status, No. (%)			
0	25 (19)	10 (32)	15 (15)
1	78 (59)	21 (68)	57 (56)
2	28 (21)	0	28 (28)
3	2 (2)	0	2 (2)
Presence of background cirrhosis, No. (%)	74 (56)	13 (42)	61 (60)
Presence of baseline esophageal varices, No. (%)	60 (45)	13 (42)	47 (46)
Presence of portal vein thrombosis, No. (%)	69 (52)	12 (39)	57 (57)
Main portal vein thrombosis	33 (25)	0	33 (33)
Branch portal vein thrombosis	36 (27)	12 (39)	24 (24)
Absence of portal vein thrombosis	64 (48)	27 (61)	0
Extrahepatic disease, No. (%)	44 (33)	14 (45)	30 (30)
Raised AFP levels (>upper limit of normal), No. (%)	102 (77)	26 (84)	76 (75)
Use of previous systemic therapy	46 (35)	0	46 (45)
Lenvatinib	27 (20)		27 (27)
Sorafenib	16 (12)		16 (16)
Regorafenib	2 (2)		2(2)
Atezolizumab-bevacizumab	1 (1)		1 (1)
Immunotherapeutic agent used, No. (%)			
Atezolizumab-bevacizumab	88 (66)	28 (90)	60 (59)
Nivolumab	44 (33)	3 (10)	41 (40)
Pembrolizumab	1 (1)	0	1 (1)
Use of concurrent liver-directed therapy, No. (%)	10 (8)	2 (7)	8 (8)

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona clinic liver cancer; ECOG, Eastern Cooperative Oncology Group; NASH, nonalcoholic steatohepatitis.

patient. Thirty-one patients (23%) were classified as trial-like (cohort 1), whereas the remaining 102 patients (77%) were classified as trial-unlike (cohort 2).

Primary End Point and Survival

With a median follow-up of 13.8 months (95% CI, 10.8 to 15.2), 73 patients had died resulting in a median OS, 12-month OS, and 2-year OS for the entire cohort of 8.2 months (95% CI, 6.1 to 10.2), 33.4% (95% CI, 23.6 to 43.2), and 28.2% (95% CI, 18.2 to 38.2), respectively. Sixteen patients continued to be on ICIs at the time of data cutoff. The median PFS for the entire cohort was 3.5 months (95% CI, 3 to 3.9). After cessation of immunotherapy, 27 patients (20%) received further cancer-directed therapy.

With regard to the primary end point of the study, trial-like patients (n = 31) had a statistically improved OS compared with trial-unlike patients (n = 102; median OS not reached, 12-month OS 57.9% [95% CI, 38.5 to 77.3] *v* 7.6 months, 12-month OS 24% [95% CI, 13.4 to 34.6]; *P* = .005; Fig 1). However, statistically significant differences between the trial-like and trial-unlike cohort were not noted in terms of PFS (4.3 months [95% CI, 0.1 to 8.5] *v* 3.5 months [95% CI, 3.2 to 3.7]; *P* = .13).

On univariate analysis of factors that had an effect on OS, patients with CTP A and CTP B7 status compared with CTP B8/9 status (9.7 months [95% CI, 6.7 to 12.6] *v* 8.6 months [95% CI, 2.5 to 14.7] *v* 4 months [95% CI, 1.9 to 6.0]; *P* < .001), BCLC B compared with BCLC C and D (not reached *v* 7.1 months [95% CI, 5.3 to 8.9]; *P* = .014), and an ECOG PS of 0/1 compared with an ECOG PS of 2/3 (8.7 months [95% CI, 5.7 to 11.6] *v* 7.1 months [95% CI, 2.6 to 11.6]; *P* = .038) had statistically superior OS, whereas the presence of main portal vein thrombosis compared with patients with branch vein or no portal vein thrombosis (4 months [95% CI, 2.2 to 5.8] *v* 8.6 months [95% CI, 5.9 to 11.3] *v* 9.7 months [95% CI, 6.4 to 12.9]; *P* = .001) predicted for inferior OS. The presence of NASH compared with other etiologies (7.6 months [95% CI, 4.4 to 10.8] *v* 8.4 months [95% CI, 6.5 to 10.3]), extrahepatic disease compared with liver limited disease (7.1 months [95% CI, 4.6 to 9.7] *v* 8.6 months [95% CI, 6.7 to 10.5]; *P* = .87), and raised alpha-fetoprotein (AFP) versus AFP within normal limits (8 months [95% CI, 5.7 to 10.3] *v* 9.4 months [95% CI, 5.7 to 13.1]; *P* = .659) did not result in statistically significant differences in OS. On multivariate analysis of factors significant on univariate analysis, CTP A and CTP B7 status compared with CTP B8/9 status (hazard ratio [HR], 0.567 [95% CI, 0.343 to 0.938]; *P* = .027) continued to predict for superior OS, whereas the presence of main portal vein thrombosis compared with branch vein or no portal vein thrombosis (HR, 2.006 [95% CI, 1.154 to 3.487]; *P* = .014) predicted for inferior OS. However, BCLC B compared with BCLC C and D (HR, 0.403 [95% CI, 0.161 to 1.007]; *P* = .052) and an ECOG PS of 0/1 compared with the ECOG PS of 2/3 (HR, 0.763 [95% CI, 0.450 to 1.292]; *P* = .314) did not maintain statistical significance on multivariate analysis. In the trial-unlike cohort (n = 102), 56 patients had received ICIs as first-line therapy, whereas 46 patients have received ICIs after previous treatment with a TKI. The OS in these two subsets was 6.5 months (95% CI, 3.3 to 9.7) and 8.4 months (95% CI, 5.6 to 11.3), respectively.

Treatment-Related Adverse Events

Among the 113 patients who had stopped ICIs, the most common reasons for cessation were disease progression, liver decompensation, and immune-related adverse event in 47%, 11%, and 3% of patients, respectively. The cause of treatment cessation was not ascertained in 20% of patients, whereas 8% of patients were lost to follow-up.

Treatment-related adverse events were seen in 92% of patients, with the most common adverse events being fatigue (51%), nausea and vomiting (22%), immune-related hypothyroidism (6%), non–hypothyroid immune-related

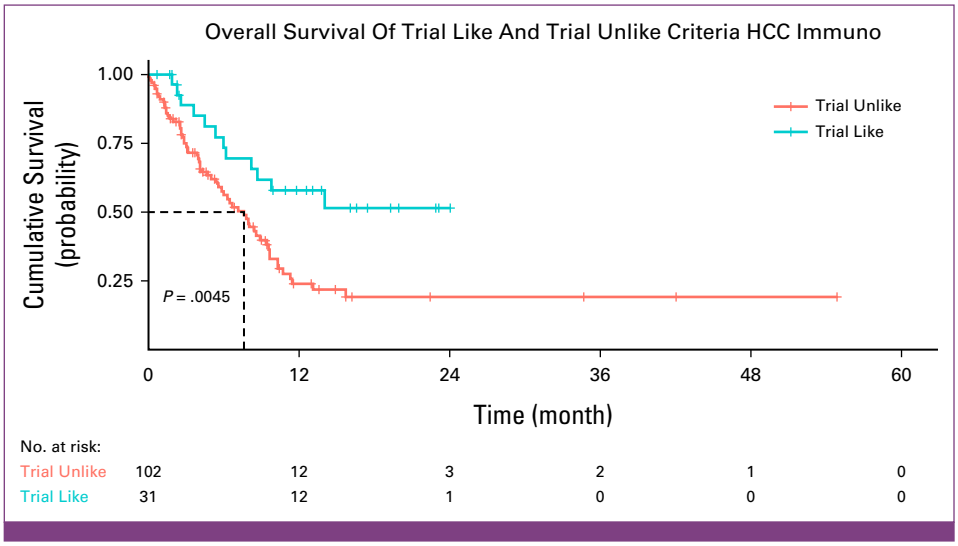

FIG 1. OS of trial-like and trial-unlike criteria. OS, overall survival.

endocrine dysfunction (4%), fever (4%), and immune-related arthralgia (2%).

DISCUSSION

The current study provides an insight into the practice of using ICIs in advanced HCC in the real world and suggests that while patients having similar characteristics to those evaluated in trials have survivals on expected lines, patients not fitting into trial criteria have markedly inferior survival outcomes.

While sorafenib was the single approved systemic therapeutic agent for the management of advanced HCC for almost a decade, the availability of newer TKIs such as lenvatinib and cabozantinib and immunotherapeutic agents has significantly increased treatment options and improved survivals in advanced HCC.[1-4] The OS has improved from <12 months to approximately 24 months if sequencing of treatment options is feasible. Before the seminal results of improved survival with atezolizumab-bevacizumab and the STRIDE regimen compared with sorafenib, initial results with nivolumab and pembrolizumab were also encouraging.[5-7] However, while the later studies comparing both nivolumab and pembrolizumab with sorafenib failed to achieve their primary end points, these agents were used in clinical practice because of the initial paucity of treatment options in advanced HCC.

The majority of patients (77%) in the study did not satisfy criteria used for inclusion in major phase III studies, and this may reflect the prevalence of such patients in clinical practice. The criteria used in the study to classify patients as trial-like have one important caveat—patients with MPVT were not included although they were not excluded from the IMBRAVE-150 study with atezolizumab-bevacizumab or the CHECKMATE 459 study with nivolumab. However, the HIMALAYA study evaluating the STRIDE regimen and the KEYNOTE-240 study with pembrolizumab did not include patients with MPVT in the trial.[2,8] Considering the lack of uniformity, the limited proportion of patients with MPVT in the seminal studies, and the marked negative prognostic impact of MPVT on outcomes, the decision to exclude patients with MPVT from the trial-like cohort was taken by the investigators. Besides this point of variance, a majority of patients in the trial-like cohort had baseline characteristics similar to those seen in the IMBRAVE150 and Himalaya trials. Another variance with the use of ICIs in this study was that a significant proportion of patients (35%) received ICIs as second-line therapy. This is a reflection of the initial enthusiasm with nivolumab as second-line therapy in advanced HCC and the later emergence of atezolizumab-bevacizumab as a frontline therapeutic option compared with TKIs like sorafenib or lenvatinib.

The survivals seen with patients in this study supply information on patients who otherwise would have been candidates for clinical trials and outliers for whom large-scale prospective phase trials do not currently exist or may not exist in the future as well. Patients who satisfied clinical trial criteria and had BCLC B status had OS, which was commensurate with data from seminal trials. Two recently published retrospective studies, evaluating 66 and 190 patients, respectively, also suggest that patients in the real world who had characteristics similar to those in the seminal trials had equivalent survivals with atezolizumab-bevacizumab.[9,10] The aforementioned retrospective data along with the results of the current study are reassuring as there were very limited patients from India in the seminal trials. More importantly, the results clearly indicate that patients with baseline adverse factors such as a CTP B of 8-9, an ECOG of PS ≥2, and MPVT do not perform well with ICIs, as has already been seen with other systemic therapeutic agents.[11-14] The seminal trials and the aforementioned retrospective studies with atezolizumab-bevacizumab have included very few patients with these criteria although the previously mentioned German retrospective study and a recently published study from India briefly commented on the guarded outcomes in patients with Child Pugh B and Child Pugh C status.[9,15] The presence of MPVT appears to be a particularly strong negative prognostic indicator even in comparison with the presence of branched vein thrombosis, and likely different additional therapeutic strategies are required to tackle this aggressive subset of advanced HCC. Patients with CTP B7 are usually considered for treatment in clinical practice, and the current data, within the confines of small numbers, suggest reasonable outcomes with ICIs in these patients. However, the use of ICIs in these outlier patients per se entails guarded outcomes in terms of expected survivals, and expectations from ICIs should be tempered in these situations as opposed to the outcomes seen in fit patients.

There is increasing literature with regard to lesser efficacy of ICIs in NASH-related HCC because of limitation of antitumor surveillance by the hepatic milieu in NASH.[16] This has been suggested by recently published real-world evidence as well.[10] However, the current study did not identify any such difference in terms of etiology and treatment with ICIs. The lack of such a signal is possibly due to the small numbers in the current study.

In the trial-unlike patients, patients who received ICIs as first-line or second-line therapy had numerically similar survivals although a statistical comparison between these two cohorts was not performed. This suggests that baseline high-risk variables such as ECOG PS, MPVT, and CTP status are the drivers of outcomes in these patients, and while ICIs can be used in such populations, survival outcomes are limited. However, the well-tolerated nature of ICIs allows easier administration even in pretreated patients, and thus, ICIs can be considered in this scenario. ICIs were well-tolerated in this study. While 92% of patients had some adverse event, only 3% of patients had treatment-related adverse events as a documented reason for cessation of ICIs.

The study benefits from being multi-institutional in nature and throwing light on subsets of advanced HCC populations not commonly evaluated in clinical trials. However, multiple

caveats with the study need to be highlighted. Three different ICIs agents have been used in patients, and they have differential efficacy and adverse event profiles. Comparing and contrasting outcomes in treatment-naïve and pretreated patients as evaluated in the current study are not ideal, although reflective of treatment in clinical practice. In regions where atezolizumab-bevacizumab or the STRIDE regimen is mandatorily funded via insurance, there will be limited applicability of the findings of the current study. The results are predominantly applicable in patients from regions where logistic constraints exist with regard to the use of ICIs as first-line systemic therapy. A significant proportion of patients did not have documented reasons for cessation of ICIs, and it is possible that cessation because of immunotherapy-related adverse events would be higher than the percentages noted.

In conclusion, the current study in a real-world scenario of patients receiving ICIs suggests that well-selected trial-like patients with advanced HCC have survivals in consonance with those seen in clinical trials, whereas trial-unlike patients with adverse characteristics such as main portal vein thrombosis, a ECOG PS of ≥2, and CTP B status have markedly inferior outcomes and the use of ICIs in such scenarios should be a calculated decision. Despite having a significant proportion of patients outside trial criteria, ICIs is very well tolerated with a small proportion of patients requiring treatment cessation because of immunotherapy-related adverse events.

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