Original Article

# A retrospective database analysis to understand treatment patterns and outcomes of intermediate and advanced hepatocellular carcinoma in Alberta, Canada (A-CAPTAIN study)

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**Background:** With the emergence of new systemic therapies there has been a substantial change in treatment options for hepatocellular carcinoma (HCC). The aim of this study was to assess treatment patterns and outcomes in real-world Canadian HCC patients with intermediate and advanced stage disease who have received systemic treatments prior to 2021.

**Methods:** All HCC patients with intermediate or advanced disease who received at least one dose of systemic therapy between January 1, 2008 to December 31, 2020 in the Canadian province of Alberta were included. Patient characteristics, treatment patterns, overall survival (OS), real-world progression-free survival (rwPFS), clinician-assessed response rates (RRs), and reasons for treatment discontinuation were retrospectively analyzed in all patients.

**Results:** Of the 321 total patients included, 33 (10%) were intermediate and 288 (90%) were advanced stage. With respect to intermediate and advanced HCC patients, most were Eastern Cooperative Oncology Group (ECOG) 0–1 (94%, 85%, respectively) and Child-Pugh A (82% for both). For intermediate and advanced patients, RRs to first-line systemic therapy were 13% and 19%, median rwPFS was 7.4 and 4.2 months, and median OS was 13.5 and 10.9 months, respectively.

**Conclusions:** This study characterized the systemic treatment patterns and outcomes of intermediate and advanced HCC patients treated prior to 2021 and can serve as a baseline for future comparison with HCC patients who predominantly receive first-line immunotherapy.

**Keywords:** Hepatocellular carcinoma (HCC); advanced stage; intermediate stage

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## Introduction

Hepatocellular carcinoma (HCC) is one of the most common and deadly cancers worldwide, being the third leading cause of cancer death according to the World Health Organization (1,2). In Canada, it was estimated that approximately 3,500 people were diagnosed with liver cancer in 2022 and that there would be at least 1,650 liver cancer deaths (3,4). The incidence is increasing and may be partially attributed to immigration from regions where exposure to liver cancer risk factors, such as hepatitis B virus (HBV) and hepatitis C virus (HCV), are more common (3,4). Other factors may include increasing rates of alcohol related liver cirrhosis and fatty liver disease in Canadians over time (5).

Although the best outcomes are often seen after surgical

resection or transplant, most patients are not eligible for these curative strategies as they are diagnosed at a later stage in their disease with limited survival (6-8). Systemic treatment options have evolved and changed the paradigm of advanced HCC treatment with the introduction of immunotherapy-based regimens (9-13). The IMbrave150 trial showed that atezolizumab with bevacizumab improved overall survival (OS) compared to sorafenib in advanced HCC patients, and more specifically median survival for atezolizumab with bevacizumab was 19.2 months after a median follow-up of 17.6 months (12). The HIMALAYA trial showed that durvalumab with tremelimumab improved OS compared to sorafenib with a median survival of 16.4 months after a median follow-up of 49.12 months and a long-term 4-year survival of 25.2% (13). Both of these immunotherapy combinations are now considered first-line standard of care options in treatment of advanced HCC.

With the development of more effective systemic therapy options, there is increasing debate regarding whether to start systemic therapy earlier in patients with intermediate stage HCC. Historically, intermediate stage HCC patients have been treated with transarterial chemo-embolization (TACE) (14). However, there is significant heterogeneity within this group and the outcomes with TACE can be variable (14). In addition, there is a risk of deterioration of liver function after repeated TACE treatments. This can result in patients becoming ineligible for systemic therapies which have been shown to significantly improve their survival (15-18). With emerging therapies for HCC, the treatment patterns are expected to shift in terms of sequencing, varied use of agents in each line of therapy, and also earlier use of systemic therapies.

The Barcelona Clinic Liver Cancer (BCLC) staging system is widely used to estimate prognosis and inform management decisions for patients with HCC. In this scoring system patients with intermediate stage disease are classified as BCLC B stage and patients with advanced disease are classified as BCLC C stage. While this staging system has been previously validated and shown to perform well in predicting survival, it has not been well assessed in patients with intermediate and advanced disease in the era where systemic therapy is widely used (19-22).

To assess unmet needs in HCC, this study aimed to assess real-world treatment patterns and outcomes in Canadian patients with intermediate and advanced stage HCC who received systemic treatment prior to 2021. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-692/rc).

**Highlight box**

**Key findings**

- Systemic treatment patterns and outcomes of intermediate and advanced Canadian hepatocellular carcinoma (HCC) patients appeared to be comparable, with a possible trend towards better progression-free survival and overall survival in intermediate stage patients.

**What is known and what is new?**

- Systemic treatment options have evolved and changed the paradigm of advanced HCC treatment with the introduction of immunotherapy-based regimens. With the development of more effective systemic therapy options, there is increasing debate regarding whether to start systemic therapy earlier in patients with intermediate stage HCC.
- This study characterized the systemic treatment patterns and outcomes of intermediate and advanced HCC patients treated prior to 2021 in Canada. Use of systemic treatment in intermediate stage HCC appeared to cause similar outcomes than when used in advanced stage.

**What is the implication, and what should change now?**

- This study may serve as baseline data for any future research of HCC patients receiving immunotherapy-based treatments as first-line standard of care. Additional studies examining earlier use of systemic therapy in intermediate stage HCC patients should be considered.

## Methods

### *Study design*

We conducted a retrospective observational cohort study using real-world data available from all cancer centres in the province of Alberta, Canada. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Health Research Ethics Board of Alberta, Cancer Committee (HREBA.CC-22-0113). Patient consent was waived due to the fact the study was a population-based retrospective analysis.

The provincial cancer care pharmacy database was used to identify all HCC patients who had received systemic treatment for HCC in Alberta, Canada between January 1, 2008 to December 31, 2020. Subsequently, the electronic medical records were examined to determine demographic and clinical characteristics, treatment patterns, and clinical outcomes up to December 31, 2021. The data was collected

for each patient until death or last available follow-up note as recorded in the patient chart.

### *Study population*

Patients diagnosed with either intermediate or advanced stage HCC and treated with at least one dose of systemic therapy from January 1, 2008 to December 31, 2020 were included in this study. Intermediate stage HCC was defined by the BCLC staging system where intermediate stage (stage B) patients have multinodular disease and preserved liver function. In our study, we did not use the Eastern Cooperative Oncology Group (ECOG) performance status (PS) criteria to define BCLC B patients. This is in agreement with other authors who have also criticized the use of PS in BCLC staging (23). Advanced stage HCC (stage C) was defined by the BCLC staging system as patients with portal invasion and/or extrahepatic spread with preserved liver function and ECOG performance status 0–2. Patients could have presented with *de novo* intermediate or advanced disease or progressed to these stages from an earlier stage at diagnosis and were assigned to the respective cohort based on the stage at which they first received systemic therapy. HCC patients treated in blinded placebo-controlled clinical trials were excluded from this study as information related to the specific drug received on trial would not be known.

### *Data collection*

Demographics, tumour-related characteristics and previous localized and systemic treatment data were extracted from individual patient electronic medical records that cover 17 cancer centres (2 tertiary centers, 4 regional and 11 community centers) covering the 4.5 million residents of Alberta.

### *Outcomes*

OS and real-world progression-free survival (rwPFS) were the primary outcomes of interest for this study. OS was calculated in months from the start date of first-line systemic therapy to date of death or censored at last follow-up, whichever occurred first. rwPFS was calculated in months from the start of first-line systemic therapy to date of disease progression or death, whichever occurred first. Patients who were not known to have progressed or died were censored as of the date of their last follow-up. Secondary outcomes of interest included: clinical response rate (RR), treatment duration (date of systemic therapy start until date of last dose) and time from diagnosis to first-line treatment initiation. Clinical RR was determined by reviewing the treating oncologists' notes and imaging results. It was not possible to have all the imaging reviewed to assess response according to RECIST 1.1 or mRECIST criteria as this is not standard of care reporting by radiologists in Alberta.

### *Statistical analysis*

Descriptive statistics were used to summarize baseline patient characteristics and treatment patterns. Continuous variables were summarized using means, standard deviations, medians, interquartile ranges, minimums, and maximums. Categorical variables were summarized using counts and proportions. For time-to-event outcomes, the survival function and median survival [along with the corresponding 95% confidence intervals (Cis)] were estimated using the Kaplan-Meier methods. The results were reported for the overall cohort, and where appropriate, were reported separately for the intermediate and advanced cohorts.

## Results

### *Patient population*

A total of 321 patients were identified and met the inclusion criteria of this study. Of these, 33 (10%) were intermediate stage, while 288 (90%) were advanced stage. Demographic and clinical characteristics are shown in *Table 1*. Median age was 66 and 63 years old for the intermediate and advanced stage groups, respectively. Most patients were male (91% and 80%) and the most common etiology of liver disease was alcohol (36%) for intermediate stage and hepatitis C (42%) for advanced stage. Most patients were ECOG 0–1 (94% and 85%) and albumin-bilirubin (ALBI) grade 1 or 2 (97% and 95%) for the intermediate and advanced stage groups respectively. In both groups, 82% were Child-Pugh before the start of first-line treatment. Prior treatments included: TACE (33% and 30%), TARE (6% and 8%), liver resection (24% and 17%) and stereotactic body radiotherapy (SBRT) (15% and 4%), respectively.

### *Treatment outcomes and characteristics*

Median follow-up was 13.5 months for the intermediate and

**Table 1** Demographic and clinical characteristics of patients

| Characteristics | Overall (n=321) | BCLC B/intermediate stage (n=33) | BCLC C/advanced stage (n=288) |
|---|---|---|---|
| Median age (years) | 64 | 66 | 63 |
| Gender | | | |
| Male | 261 [81] | 30 [91] | 231 [80] |
| Female | 60 [19] | 3 [9] | 57 [20] |
| Ethnicity | | | |
| East-Asian | 61 [19] | 3 [9] | 58 [20] |
| Non-East-Asian | 259 [81] | 29 [88] | 230 [80] |
| Unknown | 1 [0.3] | 1 [3] | 0 [0] |
| Etiology of liver disease | | | |
| Alcohol | 84 [26] | 12 [36] | 72 [25] |
| Hepatitis C | 132 [41] | 11 [33] | 121 [42] |
| Hepatitis B | 73 [23] | 5 [15] | 68 [24] |
| NASH | 40 [12.5] | 8 [24] | 32 [11] |
| Previous localized treatment | | | |
| TACE | 96 [30] | 11 [33] | 85 [30] |
| TARE | 26 [8] | 2 [6] | 24 [8] |
| SBRT | 17 [5] | 5 [15] | 12 [4] |
| Liver resection | 58 [18] | 8 [24] | 50 [17] |
| Liver transplant | 19 [6] | 0 [0] | 19 [7] |
| ECOG performance status | | | |
| ECOG 0 | 89 [28] | 17 [52] | 72 [25] |
| ECOG 1 | 188 [59] | 14 [42] | 174 [60] |
| ECOG 2 | 39 [12] | 2 [6] | 37 [13] |
| ECOG 3 | 1 [0.3] | 0 [0] | 0 [0] |
| Child-Pugh class | | | |
| A | 263 [82] | 27 [82] | 236 [82] |
| B | 49 [15] | 6 [18] | 43 [15] |
| ALBI grade | | | |
| Grade 1–2 | 306 [95] | 32 [97] | 274 [95] |
| Grade 3 | 10 [3] | 1 [3] | 9 [3] |
| Involvement of liver | | | |
| <50% | 234 [73] | 27 [82] | 207 [72] |
| ≥50% | 86 [27] | 6 [18] | 80 [28] |

Data are presented as n [%]. ALBI, Albumin-to-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; NASH, non-alcoholic steatohepatitis; SBRT, stereotactic body radiotherapy; TACE, trans-arterial chemoembolization; TARE, trans-arterial radioembolization.

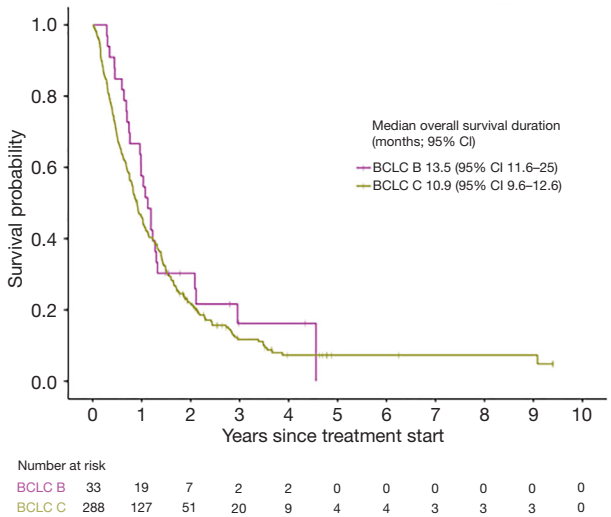


**Figure 1** Kaplan-Meier curves for overall survival according to stage (BCLC B/intermediate and BCLC C/advanced) at treatment initiation. BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval.

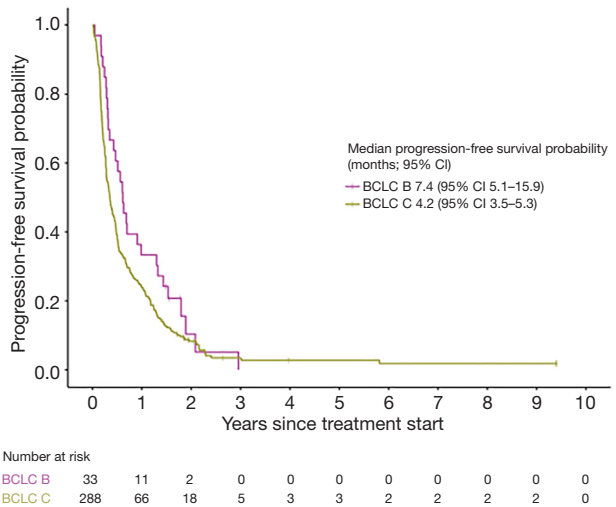


**Figure 2** Kaplan-Meier curves for progression-free survival according to stage (BCLC B/intermediate and BCLC C/advanced) at treatment initiation. BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval.

10.0 months for advanced stage patients, respectively.

For the overall population, clinical RR was 20% with first line treatment. For patients with intermediate stage disease RR was 15% and 20% for advanced stage.

Median OS was 11.1 months (95% CI: 9.9–12.9) for all patients, 13.5 months for intermediate stage (95% CI: 11.6–25) and 10.9 months (95% CI: 9.6–12.6) for advanced stage patients (*Figure 1*).

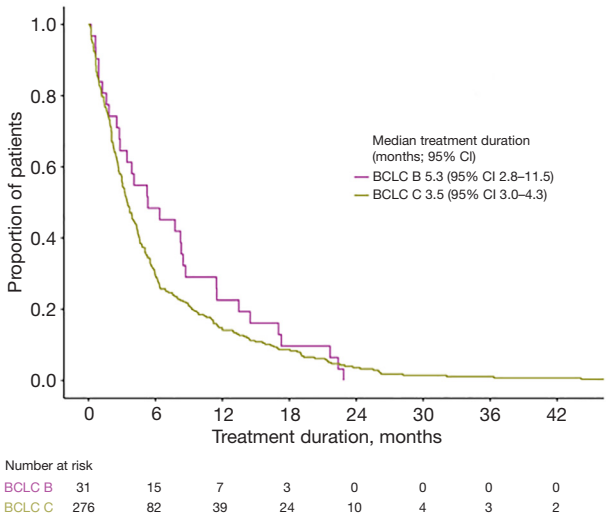


**Figure 3** Kaplan-Meier curves for treatment duration according to stage (BCLC B/intermediate and BCLC C/advanced) at treatment initiation. BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval.

Median rwPFS was 4.9 months (95% CI: 4.1–5.8) for the overall population, 7.4 months (95% CI: 5.1–15.9) for intermediate stage and 4.2 months (95% CI: 3.5–5.3) for advanced stage patients (*Figure 2*).

Median time from diagnosis to systemic treatment initiation was 11.5 months (95% CI: 6.3–21.3) and 10.4 months (95% CI: 8.5–13.0), for intermediate and advanced stage patients, respectively. Median systemic treatment duration was 5.3 months (95% CI: 2.8–11.5) and 3.5 months (95% CI: 3.0–4.3), respectively (*Figure 3*).

The specific first-line systemic treatments received are summarized in *Table 2*. The most common first-line systemic treatments received were: sorafenib (76% for intermediate stage, 80% for advanced stage) and lenvatinib (21%, 13%, respectively). Atezolizumab and bevacizumab were used only in 3% and 3.5% of the intermediate and advanced stage patients, respectively. Other first-line treatments were used in 6% of the overall population and included: nivolumab, durvalumab + tremelimumab and durvalumab monotherapy.

The physician's notes indicated an intention to bridge to transplant in 6% of the intermediate stage and 2% of the advanced stage patients.

**Table 2** First-line treatments received and reasons for discontinuation

| | Overall (n=321) | BCLC B/intermediate stage (n=33) | BCLC C/advanced stage (n=288) |
|---|---|---|---|
| First-line treatment | | | |
| Sorafenib | 255 [79] | 25 [76] | 230 [80] |
| Lenvatinib | 45 [14] | 7 [21] | 38 [13] |
| Atezolizumab + bevacizumab | 11 [3] | 1 [3] | 10 [3.5] |
| Others | 6 [2] | 0 [0] | 6 [2] |
| Reason for discontinuation | | | |
| Progression | 181 [56] | 17 [52] | 164 [57] |
| Toxicity | 88 [27] | 8 [24] | 80 [28] |
| Patient choice | 19 [6] | 4 [12] | 15 [5] |
| Death | 22 [7] | 1 [3] | 21 [7] |

Data are presented as n [%]. BCLC, Barcelona Clinic Liver Cancer.

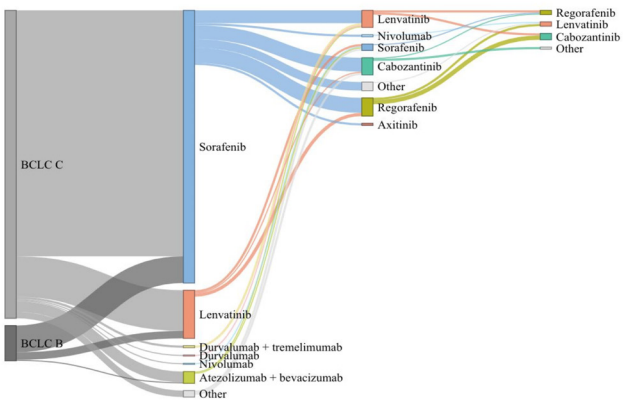


**Figure 4** Sankey diagram of systemic treatment by stage (BCLC B/intermediate and BCLC C/advanced) and each successive treatment line. BCLC, Barcelona Clinic Liver Cancer.

Treatment discontinuation was mostly due to progression (52% and 57%), followed by toxicity (24% and 28%). Patient choice accounted for 12% and 5% of the reasons for discontinuation.

*Figure 4* contains a Sankey diagram showing the systemic therapy regimens received for each intermediate and advanced stage as well as successive treatment lines. Approximately 30% of the intermediate stage and 28% of advanced stage patients received second-line treatment and 3% and 6% of these patients received third line treatment, respectively. In the second line, most common systemic therapy drugs for intermediate and advanced stage patients were: lenvatinib (40%, 26%), cabozantinib (30%, 24%) and regorafenib (10%, 26%). In the third line, the most common agent used for intermediate stage patients was cabozantinib (100%) and for advanced stage patients, regorafenib (33%). After systemic therapy, approximately 12% of the intermediate stage patients and 8% of the advanced stage patients underwent subsequent locoregional treatments.

After discontinuation of systemic treatment, 45% of intermediate stage patients were classified as Child-Pugh A, 45% Child-Pugh B and 10% Child-Pugh C. For the advanced stage patients, 52% remained Child-Pugh A, while 39% were Child-Pugh B and 9% deteriorated to Child-Pugh C. ALBI score remained grade 1 or 2 in 58% of the BCLC B patients and 74% of the BCLC C.

## Discussion

This study descriptively summarized the clinical characteristics, treatment patterns and outcomes of patients with intermediate and advanced unresectable HCC who received systemic treatment in Alberta, Canada between January 1, 2008 to December 31, 2020.

The cohorts were comprised of 10% (n=33/321) intermediate stage patients relative to 90% (n=288/331) with advanced disease. We note that in the SHARP, REFLECT, IMbrave150 and HIMALAYA trials 15–21% of the patients had intermediate stage disease (9-13). One

possible explanation for this lower percentage is that in the real world systemic therapy was not initiated for intermediate stage HCC patients even when they were ineligible or refractory to TACE. Subsequently, a large proportion of patients would have deterioration in their liver function to Child-Pugh B or worse, making them ineligible for systemic therapy. This would be supported by the results of the OPTIMIS study of TACE and sorafenib treatment (24). It may be the case that previously sorafenib was regarded as a treatment with little efficacy and patients with intermediate HCC continued to receive TACE even when they were ineligible until they progressed to advanced disease or had poor liver function. Since 2018, systemic treatments with higher RR and PFS have become available in Alberta such as lenvatinib (available in August 2018), atezolizumab + bevacizumab (June 2020) and durvalumab + tremelimumab (November 2023). It is possible that if this study was repeated in patients treated in 2018 or later that there would likely be a larger proportion of intermediate stage patients, closer to what was seen in the previously mentioned clinical trials. It is also important to note that most of this patient cohort was treated with first-line sorafenib or lenvatinib and not atezolizumab + bevacizumab as the latter was not available in Alberta until June 2020.

The OS and rwPFS estimates for the overall study population within our study were relatively low compared to more recent outcomes reported in the REFLECT, IMbrave150 and HIMALAYA clinical trials (10-13). This is expected as 79% of the patients in this study received sorafenib as first-line treatment with the majority being treated in the sorafenib era from 2008–2018 when lenvatinib and immunotherapy were not used to treat HCC in Canada. The median OS of 11.1 months in this patient population, however, does closely resemble the median OS of 10.7 months seen in the SHARP trial (9).

Although our study was not powered for a formal comparison of survival between BCLC B and C groups, median OS was numerically higher for BCLC B compared to BCLC C patients (13.5 *vs.* 10.9 months) and the survival curves also support a trend of the BCLC B patients having better survival. This would have been expected as the BCLC staging system has been previously validated to predict survival. It is interesting to note that there was also a strong trend towards improved rwPFS on first-line treatment within the intermediate stage patients compared to advanced stage patients. The median rwPFS was 7.4 months for intermediate stage patients and 4.2 months for advanced stage. This raises the question of whether systemic therapy prolongs rwPFS to a greater degree in intermediate stage patients compared to the advanced stage and whether systemic therapy should be started more frequently before HCC patients are found to have advanced disease. A prospective trial to validate this observation of improved PFS when systemic therapy is started in earlier stage disease could confirm this observed trend.

Intermediate stage HCC patients are considered to be a heterogenous group and optimal management is frequently debated in multidisciplinary tumour board meetings. Universally accepted international guidelines for treating intermediate stage HCC do not exist, however, there are regional guidelines, such as the APPLE (Asia-Pacific Primary Liver Cancer Expert) Consensus Statements, and also national guidelines, such as the Canadian clinical consensus statement on establishing roles of locoregional and systemic therapies for the treatment of intermediate stage HCC (25,26). While most guidelines suggest TACE as the main therapeutic option for intermediate stage patients (21,25,26), some patients with a lower burden of disease may be considered for liver transplantation while those with a higher burden of disease may be considered for systemic therapy (21,25-27). In our study, only 33% of the intermediate stage and 30% of the advanced stage patients received TACE previously, indicating that the vast majority were TACE ineligible at diagnosis.

With emerging therapies for HCC, treatment patterns are expected to shift in terms of sequencing and agents used in each line of therapy. Although treatment-related morbidity is usually low with liver-limited therapies, multiple and repeat procedures can lead to several complications including pancreatitis, cholecystitis and liver failure (28,29). Several studies reported liver function deterioration after treatment with TACE, especially for patients with large tumor burden (15-18). Historically, it was common to use and repeat TACE as much as possible with less emphasis on liver function preservation due to limited effective systemic therapy options (24). However, HCC first-line treatment landscape has greatly improved in the past years, and patients now can achieve higher RRs and larger survival benefit (9-13). As such, clinical trials in HCC are now examining whether improvements in efficacy outcomes can be made by starting systemic therapy in TACE eligible patients. Strategies being explored include combining TACE with immunotherapy-based regiments (30,31) and starting treatment with systemic therapy only in TACE-eligible patients (32). For the TACE-ineligible patients, another strategy being investigated is the use

 

of combination systemic treatment with the objective of downstaging to allow for curative intent treatments (33). The use of combination systemic treatment in the study showed a curative conversion rate up to 30%.

The present study has several limitations that are common with observational studies utilizing real-world data. Firstly, this study only included a small sample size of intermediate stage patients relative to the advanced stage cohort. Due to the retrospective nature of the study the size of the intermediate stage group could not be increased. As a result, any trends observed in this group may have limited generalizability. Also, ECOG performance status was not used as criteria to define BCLC B. In real world practice, performance status, such as being ECOG 2, is often not used as an absolute contraindication for surgery or other localized treatments. ECOG performance status is also a subjective and physician-dependent criteria and other authors have criticize the use of ECOG performance status in BCLC staging (23). In addition, this study only captured patients who received systemic treatment and excluded intermediate or advanced stage HCC patients who were treated with only localized treatments or supportive care alone. For intermediate stage patients there may have been selection bias, as patients with Child-Pugh A6 liver function may have been preferentially started on systemic therapy given the lack of systemic therapy funding for Child-Pugh B patients in Alberta. We also note that this study focused solely on HCC patients treated in Alberta, and generalizability to other populations, particularly with different treatment patterns or causes of underlying liver disease, may be limited.

## Conclusions

Overall, this study characterized the systemic treatment patterns and outcomes of intermediate and advanced HCC patients in Alberta, Canada prior to 2021, a time when tyrosine kinase inhibitors were typically used as first-line systemic treatment. Additional studies examining earlier use of systemic therapy in intermediate stage HCC patients should be considered. This study may also serve as baseline data for any future research of HCC patients receiving immunotherapy-based treatments as first-line standard of care.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-692/rc

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Health Research Ethics Board of Alberta, Cancer Committee (HREBA.CC-22-0113). Patient consent was waived due to the fact the study was a population-based retrospective analysis.

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