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First-line Treatment Selection for Advanced Hepatocellular Carcinoma

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Introduction

The treatment landscape of advanced/unresectable hepatocellular carcinoma (uHCC) has rapidly evolved since 2018. Over recent years, various systemic therapies and treatment approaches have been explored. Systemic therapy has primarily relied on tyrosine kinase inhibitors (TKIs); however, immune checkpoint inhibitors (ICIs) have more recently entered the realm of the treatment armamentarium.

Overview

First-line Treatment

TKI Monotherapy

The first therapeutic intervention that demonstrated improved survival rates in uHCC was sorafenib. The SHARP trial demonstrated overall survival (OS) improvements for sorafenib as compared to placebo (10.7 vs. 7.9 months) (hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.55-0.87; p<0.001).[1] In the decade following sorafenib's approval, numerous trials assessing systemic treatments for uHCC failed. In 2018, lenvatinib, another TKI, exhibited comparable OS to sorafenib in the non-inferiority REFLECT study (13.6 vs. 12.3 months), leading to lenvatinib's approval as an alternative option to sorafenib in the first-line setting. Interestingly, all other endpoints, including progression-free survival (PFS) (HR: 0.66; 95% CI: 0.57-0.77) and objective response rate (ORR) (OR 3.34; 95% CI: 2.17–5.14), and the adverse event profile, favoured lenvatinib.[2]

ICI-based combination therapy

The Phase III IMbrave150 trial compared atezolizumab plus bevacizumab with sorafenib, enrolling 501 previously untreated patients with advanced uHCC and well-compensated cirrhosis (Child-Pugh class A). Patients had to have baseline esophagogastroduodenoscopy (EGD) within six months before inclusion, with appropriate variceal disease management.[3] In their most recent analysis[4], combination therapy showed significantly improved median OS (19.2 vs. 13.4 months, HR: 0.66; 95% CI: 0.52-0.85). The ORR was three times higher for the combination therapy than sorafenib (30% vs. 11%). At 18 months, 51% of patients with uHCC receiving combination therapy continued to have a response, whereas the rate for sorafenib was 22%. Both groups experienced similar rates of treatment-related grade 3 or 4 adverse events (43% vs. 46%).

The HIMALAYA trial enrolled patients with uHCC and randomized them to receive either a single dose of the anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody tremelimumab alongside regular doses of the anti-programmed cell death ligand 1 (PD-L1) monoclonal antibody durvalumab, durvalumab monotherapy, or sorafenib. Durvalumab monotherapy was found to be non-inferior to sorafenib. Moreover, the primary analysis revealed a significant improvement in OS with tremelimumab plus durvalumab compared to sorafenib (16.4 vs. 13.8 months, HR: 0.78; 96% CI 0.65–0.93). From the perspective of ORR, the dual immunotherapy arm was superior to sorafenib (20.1% vs. 5.1%). At 4 years of follow-up, the incidence of serious treatment-related adverse events was 17.5% and 9.6% for patients in the combination immunotherapy and sorafenib groups, respectively.[5,6]

First-line treatment options continue to broaden. The Phase III CheckMate-9DW trial, assessing nivolumab plus ipilimumab for first-line therapy in uHCC carcinoma without prior systemic therapy, has successfully met its primary endpoint by demonstrating an OS advantage compared to the investigator's TKI choice (sorafenib or lenvatinib). Recently presented results have reflected improvement in ORR and median duration

of response as well.[7] Rate of treatment-related toxicity was consistent with previously reported data in combination ICI therapy.

Treatment selection

First-line Treatment

Immunotherapy-based combination therapy has shifted the landscape of uHCC management in the last decade. However, the approach

Agent(s)	Schedule	OS	PFS	Toxicity profile	Special considerations
Sorafenib[1]	Oral, twice daily	10.7 vs. 7.9 months	5.5 vs. 2.8 months	• Diarrhea • Hand-foot syndrome • Hypertension	In our opinion can be used as a later line therapy
Lenvatinib[2]	Oral, daily	13.6 vs. 12.3 months	7.4 vs. 3.7 months	• Hypertension	
Atezolizumab plus bevacizumab[3,4]	Intravenous, 21-day cycle	19.2 vs. 13.4 months	6.9 vs. 4.3 months	• Grade 3/4 TRAEs 43% • Incidence of upper gastrointestinal bleeding 7%	• Patients with MVI were included • Highest ORR (30%) • Pre-treatment EGD recommended for all patients
Tremelimumab/ durvalumab[5,6]	• Intravenous, tremelimumab x1, • Durvalumab every 28 days	16.4 vs. 13.7 months	3.8 vs. 4.1 months	• Grade 3/4 immune-mediated TRAEs 12.6%	• Longest follow-up data (4 years) • DOR 22.3 months
Nivolumab plus ipilimumab[7]	Intravenous, combination every 21 days for 4 cycles then maintenance Nivolumab every 28 days for maximum of 2 years	23.7 vs. 20.6 months	NA	• Grade 3/4 immune-mediated TRAEs 41%	• Highest ORR (36%) • DOR 30.4 months

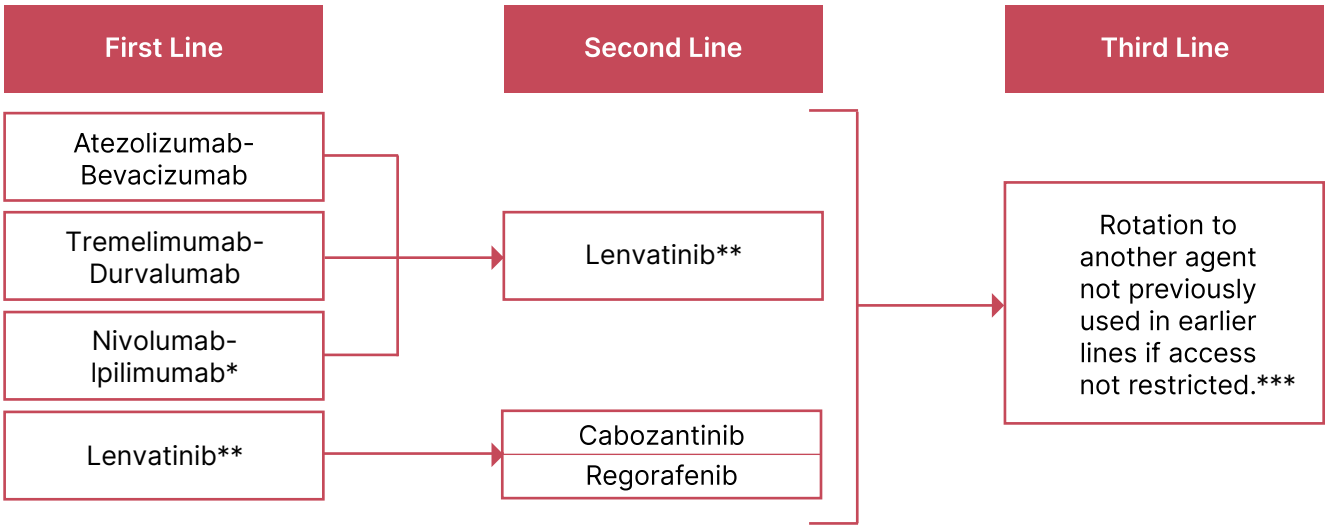
Table 1. Key factors in the treatment selection for patients with uHCC in the first-line setting; *courtesy of Zainab Al Maqrashi, MD, MSc and Brandon M. Meyers, MD, MSc, FRCPC*
Abbreviations: DOR: duration of response; **EGD:** esophagogastroduodenoscopy; **MVI:** microvascular invasion; **ORR:** objective response rate; **OS:** overall survival; **PFS:** progression-free survival; **TRAE:** treatment-related adverse events; **uHCC:** advanced/unresectable hepatocellular carcinoma.

to selecting first-line therapy is a complex, multifaced decision due to the lack of head-to-head comparison between different regimens and reliance on cross-trial comparisons **(Table 1)**.

First, factors related to accessibility, route of administration, and treatment convenience will prove valuable in therapy selection, especially from the patient's perspective. However, the data would indicate that patients suitable to receive ICI should receive one in the first-line setting due to the magnitude of benefit in OS, and in the Canadian landscape that ICI can only be given in the first-line setting.

Second, there are disease-related factors to be considered, including pre-existing unfavourable tumour biology, such as hepatic reserve, the burden of metastatic disease, and locoregional vascular invasion. In the IMbrave150 trial, 39.9% of the study population had microvascular invasion (MVI) prior to randomization.[3] A subsequent subgroup analysis revealed that the OS advantage was observed across all subgroups, irrespective of MVI status.[4] Post-hoc exploratory analyses on patients in the IMbrave150 trial with high-risk MVI (defined by the presence of a tumour thrombus in the main trunk and/or contralateral portal vein) was performed. Initial observations indicated that the advantages of combining atezolizumab plus bevacizumab for this subset of patients were comparable across various efficacy measures. Nevertheless, statistical significance was not attained, probably due to the limited number of subjects.[8] On the other hand, there are no data on patients with main portal invasion using other first-line therapies post the SHARP era, who are typically excluded from trials. However, other therapies are in use in high-risk MVI with appropriate screening EGD on the basis that the risk of bleeding is both therapy-dependent and related to disease characteristics (e.g. MVI, prior varices, or low platelets).[9]

Third, screening for contraindications for immunotherapy (e.g. active autoimmune conditions or liver transplantation) and anti-angiogenic therapy (e.g. recent thrombotic events, high bleeding risk, or uncontrolled hypertension) should be performed carefully and should include assessment for potential drug-drug interactions. An area of interest is the safety of atezolizumab plus bevacizumab in terms of bleeding risk. In line with the pivotal trial selection criteria, we recommend baseline EGD wherever feasible. Recognizing accessibility challenges in rural and community centres, a careful risk-benefit discussion should be carried out with the patient with the aim to complete the screening study within 1-2 cycles of therapy initiation and perhaps hold bevacizumab until screening is completed in high-risk patients.



* Pending Health Canada/CADTH approval; ** If intolerant, Sorafenib; *** In most jurisdictions in Canada, therapy beyond second line is not funded, however, these agents could be used if accessible or paid out of pocket; Sorafenib can be used if no other options available.

Figure 1. Current provisionally funded systemic therapies for advanced/unresectable hepatocellular carcinoma; *courtesy of Zainab Al Maqrashi, MD, MSc and Brandon M. Meyers, MD, MSc, FRCPC*

Fourth, the predictability of the toxicity profile, its patterns, and its possible impact on quality of life (QoL) should be prioritized in the shared decision-making with patients. In the REFLECT study, patients on lenvatinib had lower dermatological toxicity and alopecia rates than those on sorafenib. However, this was accompanied by higher rates of Grade 3 or 4 drug-induced hypertension[2]. We suggest hypertension is the more easily managed toxicity, with less impact on QoL. In an independent examination of patient-reported outcome measures derived from the IMbrave150 trial, individuals treated with atezolizumab plus bevacizumab exhibited notably extended intervals before experiencing a decline in median time to QoL deterioration, physical functioning, and role functioning. Furthermore, this treatment was associated with a diminished likelihood of deterioration in disease-related symptoms when contrasted with sorafenib monotherapy.[10] These findings underscore the importance of incorporating these parameters in care planning. In our opinion, lenvatinib is the TKI of choice in the first-line setting compared to sorafenib based on its efficacy and toxicity profile. Deciding between ICI combinations is more challenging and comes down to a physician-patient discussion regarding risks and benefits.

Later Lines of Treatment

Treatment choices after progression on initial therapy should be guided by prior systemic therapy, established clinically meaningful advantages, predicted tolerability based on potential treatment-related adverse events, hepatic reserve, and functional status. **Figure 1** shows the currently provisionally funded systemic therapies for uHCC.

TKI have been well-studied post-progression on sorafenib. The placebo-controlled RESORCE trial suggested a benefit for regorafenib in this clinical setting in terms of the median OS (10.6 vs. 7.8 months, HR: 0.63; 95% CI: 0.50-0.79) and ORR (11% vs. 4%),[11] and mandated that enrolled patients be sorafenib tolerant (≥400 mg daily for at least 21 of the 28 days before discontinuation). Cabozantinib, another TKI, was studied in the Phase III CELESTIAL trial after prior sorafenib therapy in first- or second-line treatment, and demonstrated superiority in OS and PFS over placebo.[12] Adverse events related to both drugs in their respective trials have been consistent with earlier TKI reports with no new safety signals. Selection between the two drugs should be based on matching the patient's profile with the potential toxicity.

Subsequent lines of treatment in the era of new combination therapies are less well-defined as there are currently no Phase III data to support second-line treatment after first-line ICI-based therapy. Practically speaking, TKIs are used post-progression on ICIs, as supported by the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN) guidelines with consideration for ICI monotherapy or combination treatment, depending on accessibility and the patient's profile.[13-15] Owing to the individual differences in the targeted cellular proteins and signaling pathways between different TKIs, in the event of tumour progression, rotation to another agent not previously trialed in the first or second line is recommended.[16]

Future Directions

With the rapid evolution in the management of uHCC after the introduction of ICIs, multiple areas for exploration remain. There is a paucity of prospective evidence looking at predictive biological markers of response, and whether the underlying disease etiology is a factor. Moreover, whether the observed therapeutic benefits can be extended in patients with an intermediate functional status (Eastern Cooperative Oncology Group [ECOG][2] and borderline hepatic reserve (Child-Pugh B) remains unclear.

In second-line therapy, the ideal regimen after immunotherapy remains undefined, and further guidance from randomized clinical trials is awaited.

Based on the current guidelines, ICIs are contraindicated in solid organ transplant recipients, which limits treatment options for patients with recurrent uHCC post-transplant. The circumstances might evolve in the future.

There is a growing interest in solidifying the role of combination ablative local interventions alongside standard-of-care systemic therapy for managing uHCC, pending further maturation of evidence to guide clinical decision-making. Radioembolization with Yttrium-90 (90Y), in addition to sorafenib, did not offer any OS advantage in uHCC.[17] In comparison, the recently published LAUNCH trial examining the role of transarterial chemoembolization (TACE) in addition to lenvatinib in previously untreated patients with uHCC showed improved PFS and

OS in the experimental arm, with an observed benefit across different high local disease risk groups, such as tumour multiplicity, existing portal vein tumour thrombus, and tumours ≥5 cm.[18] On the other hand, in an attempt to examine non-invasive interventions, the NRG/RTOG 1112 study evaluated stereotactic body radiation therapy (SBRT) followed by sorafenib versus sorafenib monotherapy in patients with uHCC, of whom 74% had MVI. Due to changes in the standard of care in HCC, the accrual was prematurely closed. Based on preliminary reports, the SBRT arm experienced improved OS and PFS, with improvements in the QoL at 6 months post-treatment initiation.[19] In the EMERALD-1 study, embolization candidates among patients with uHCC were randomized to TACE combined with durvalumab with or without bevacizumab. Early results have shown improved PFS alongside an ORR of 43.6% in the triple intervention arm compared to 29.6% in the TACE only arm. The OS data is not available yet.[20] This trial reflects an attempt at expanding the role of ICI-based systemic therapy in addition to locoregional management in intermediate-stage disease. Full publications from these trials and others in the pipeline are awaited.

Conclusion

The last decade has witnessed significant improvements in systemic therapy for uHCC in addition to the established option of sorafenib with the introduction of lenvatinib and ICI-based combination options, including atezolizumab plus bevacizumab and tremelimumab plus durvalumab. Locally approved second-line options encompass TKIs, such as regorafenib and cabozantinib. The selection of therapy depends on individualized treatment goals and the patient's profile.

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