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Strategic drug sequencing in hepatocellular carcinoma in the era of chemo-diversity: maximizing the therapeutic benefit of lenvatinib

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The emergence of systemic therapies has ushered in an era of chemo-diversity for hepatocellular carcinoma, in which drug sequencing is pivotal for maximizing outcomes. Among available agents, lenvatinib is notable for its potent anti-angiogenic and immunomodulatory properties. This review proposes a structured building-block strategy for optimizing sequential drug therapy, conceptualizing each treatment line as a block that contributes cumulatively to survival, and grounding the discussion in clinical insights from lenvatinib administration. We comprehensively evaluated clinical trials, preclinical investigations, and real-world data to identify actionable approaches that enhance tolerability and prolong progression-free survival, with a particular focus on mitigating adverse events, optimizing dosing schedules, and integrating with transarterial therapies. Five refinements emerge as central to maximizing therapeutic benefit: early detection and classification of adverse events, use of supportive agents such as L-carnitine and branched-chain amino acids, structured telephone follow-up, optimization of dosing schedules, including weekend-off regimens, and strategic combination with transarterial therapy. In addition, rationale-based sequencing and clinically relevant switching criteria that extend beyond RECIST are summarized. Collectively, these measures increase the height of each therapeutic block, thereby contributing to cumulative survival within the building-block strategy. In the current era of chemo-diversity, lenvatinib remains a cornerstone agent when accompanied by these clinical refinements. The review provides a practical and conceptual framework for enhancing efficacy through structured sequencing, proactive adverse-event mitigation, and synergistic locoregional strategies, with broad applicability to real-world clinical practice. **(J Liver Cancer 2026;26:83-92)**

Keywords: Hepatocellular carcinoma; Lenvatinib; Drug-sequential therapy

INTRODUCTION

For decades, the mainstay of treatments for hepatocellular carcinoma (HCC) has consisted of locoregional therapies, such as hepatic resection, ablation, transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and radiation therapy.[1-3] However, the treatment paradigm has undergone a profound transformation over the past decade.[4] With the approval of key agents, including sorafenib, lenvatinib, cabozantinib, atezolizumab plus bevacizumab, and durvalumab plus tremelimumab, systemic therapy has become central to the management of unresectable HCC, marking the arrival of the era of chemo-diversity.[2,5]

Systemic agents in this era can be broadly categorized into two classes.[6,7] One group consists of anti-angiogenic agents, which suppress tumor vascularization. This includes sorafenib, lenvatinib, regorafenib, ramucirumab, and cabozantinib.[8] The other group comprises immune checkpoint inhibitors (ICIs) used in combination with immunotherapy, which promote immune-mediated tumor destruction. They have increasingly assumed central

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roles in first-line therapy.[9,10]

While combination immunotherapies have become the preferred initial option in many cases, anti-angiogenic agents continue to play a vital role due to their robust anti-tumor effects and compatibility with sequential drug therapy.[2] Among these, lenvatinib, which was approved in 2018 based on the REFLECT trial, has garnered increasing clinical interest.[11] Lenvatinib inhibits not only vascular endothelial growth factor receptors (VEGFR) but also fibroblast growth factor receptors. In addition to its potent anti-angiogenic activity, lenvatinib has recently gained attention for its immunomodulatory effects, including the ability to promote an immune-permissive tumor microenvironment.[12] These effects are characterized by increased infiltration of cytotoxic T lymphocytes and a reduction in regulatory T cells, which together enhance anti-tumor immunity.[13,14]

In the era of chemo-diversity, the dominant strategy for long-term disease control is drug-sequential therapy, which is defined as the strategic, stepwise administration of systemic agents aimed at prolonging disease control and maximizing overall survival (OS). To conceptualize this approach, we propose the building-block strategy (Fig. 1). In this concept, each block represents a line of therapy, such as first-line, second-line, and beyond, and the height of each block corresponds to the progression-free survival (PFS) achieved with that agent. The cumulative height of these therapeutic blocks ultimately represents the total survival time of the patient. Therefore, optimizing each block directly contributes to improving OS.

Three principles are essential in this building-block strategy: 1) maximize the height of each block. To prolong the PFS of each agent, it is essential to understand its unique adverse event (AE) profile and to establish appropriate management strategies. This includes the development of AE management protocols, the use of supportive medications, and adjustments to dosing schedules and regimens as necessary. These measures help maintain treatment adherence and maximize therapeutic benefit. 2) Understand the shape of each block. Each agent has distinct pharmacodynamics, mechanisms of action, and clinical behaviors. Understanding these characteristics, the shape of each block, enables rational sequencing. This knowledge also facilitates the identification of the most appropriate next-line therapy, ensuring that the treatment tower can be built higher with stability. 3) Preserve the foundation. To build a therapeutic tower, a stable foundation is indispensable. In HCC, this foundation is liver function. Most patients with HCC have underlying liver disease, including chronic hepatitis or cirrhosis. If hepatic reserve is compromised, continuation of systemic therapy becomes difficult, regardless of

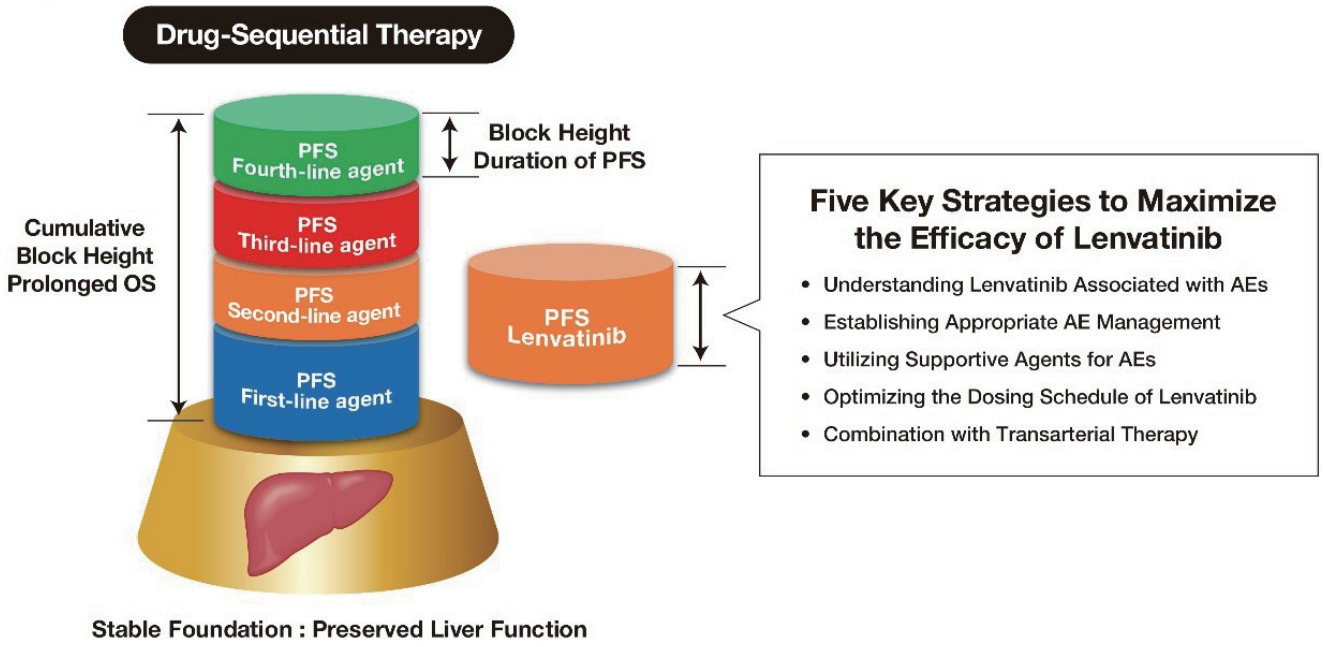

Figure 1. Conceptual model of the building-block strategy for maximizing overall survival (OS) in treatments for hepatocellular carcinoma. Each block represents the progression-free survival (PFS) achieved by a single-line agent. By preserving liver function as the foundation, sequential therapies can be layered to extend OS cumulatively. Refinements to maximize the efficacy of lenvatinib, including the management of adverse events (AEs), provision of appropriate supportive care, optimization of the dose schedule, and combination with transarterial therapy, enhance the effectiveness of first-line treatment.

the efficacy of individual agents. Therefore, preserving liver function is essential to enable and sustain effective drug-sequential therapy.

In this review, we focus on strategies to optimize the use of lenvatinib within this building-block strategy, including efforts to prolong PFS, maintain tolerability, incorporate locoregional therapies when appropriate, and position lenvatinib effectively within drug-sequential therapy. To this end, we present five key refinements that may enhance the efficacy of lenvatinib: 1) understanding lenvatinib-related AEs, 2) establishing effective AE management strategies, 3) employing appropriate supportive agents for AE, 4) optimizing the dosing schedule, and 5) considering combination with transarterial therapy when clinically appropriate. These refinements are discussed in detail in the subsequent sections of this review.

ADVERSE EVENTS ASSOCIATED WITH LENVATINIB: KNOW THE ENEMY TO WIN

Clinical and real-world profiles of lenvatinib-related adverse events

To maximize the efficacy of systemic therapy, it is essential to understand AEs, which often lead to treatment discontinuation. While AE profiles from clinical trials provide standardized information, they must be interpreted in conjunction with real-world data to capture actual tolerability in daily practice.

In the phase III REFLECT trial, which demonstrated the non-inferiority of lenvatinib to sorafenib, common AEs included hypertension (42%), decreased appetite (34%), and weight loss (31%).[11] Hypertension of grade 3 or higher occurred in 23% of cases. We previously reported a real-world analysis of 177 patients with unresectable HCC treated with lenvatinib.[15] The most frequent AEs of any grade were hypertension (53.1%), appetite loss (52.5%), fatigue (50.8%), and proteinuria (37.9%). AE onset timing varied: hypertension typically appeared early (median 4 days), whereas fatigue emerged later (median 30 days). Understanding these patterns enables timely management and supports treatment adherence.

The prognostic implications of AEs differ by type. Our analysis suggested that hypertension and hand-foot skin reaction were associated with more favorable outcomes, potentially reflecting pharmacodynamic response. In contrast, appetite loss was associated with a poorer prognosis and reduced tolerance. Distinguishing beneficial from harmful AEs is therefore essential.

A particular concern is discontinuation of lenvatinib due to severe AEs (DLSAE), which significantly worsens survival. In our cohort, the median OS was 12.8 months in patients with DLSAE, whereas it was not reached in those without. Appetite loss and fatigue contributed to the development of DLSAE, underscoring the importance of early detection and intervention to maintain therapy.

A clear understanding of lenvatinib-related AEs, including their frequency, timing, and clinical relevance, is essential for developing effective management strategies. Recognizing and addressing these events at the appropriate time contributes to durable treatment continuity.

Mechanisms underlying the adverse events of lenvatinib: the role of vascular endothelial growth factor in vascular homeostasis

A deeper understanding of the mechanisms behind lenvatinib-related AEs can help refine clinical management strategies. While vascular endothelial growth factor (VEGF) signaling is well known for its role in tumor angiogenesis, it is also crucial for maintaining normal vascular structures and physiological homeostasis.[16]

In a pivotal preclinical study, Yang et al.[17] demonstrated that blocking VEGF or VEGFR in healthy mice results in a range of systemic vascular alterations. Histological and functional analyses revealed that VEGF inhibition induced vascular regression, endothelial apoptosis, and increased tissue hypoxia even in non-tumorous organs. These changes were most pronounced in endocrine and metabolically active tissues, such as the thyroid, adrenal gland, pancreatic islets, and kidney glomeruli.

These findings suggest that VEGF/VEGFR pathways are not only critical for neovascularization but also indispensable for the structural and functional maintenance of normal vasculature. The vascular fragility induced by VEGF blockade provides a mechanistic explanation for several clinically observed AEs associated with lenvatinib, including hypertension, proteinuria, hypothyroidism, and gastrointestinal toxicities.

This pathophysiological insight supports the notion that many on-target AEs of anti-angiogenic therapy reflect collateral vascular injury in non-cancerous tissues. A comprehensive understanding of these mechanisms is crucial for predicting toxicity patterns and developing preventive strategies during lenvatinib therapy.

Know the enemy to formulate an appropriate strategy

AEs are not merely obstacles to systemic therapy but also critical clues that inform clinical strategy. A comprehensive understand-

ing of their frequency, timing, severity, prognostic relevance, and underlying mechanisms enables clinicians to distinguish between those that may be manageable and those that threaten treatment continuity.

By recognizing these differences, clinicians can formulate appropriate and individualized management plans. In this context, understanding the complex and diverse spectrum of lenvatinib-related AEs represents the first step in building effective strategies that ensure both treatment durability and tolerability. Based on these insights, the following section addresses practical measures to mitigate AEs and to support long-term lenvatinib administration.

STRATEGIES TO MAXIMIZE THE PFS OF LENVATINIB

To maximize the therapeutic potential of lenvatinib, clinicians must delicately balance its potent antitumor activity against the risk of treatment-limiting AEs, which can compromise both adherence and quality of life. This therapeutic trade-off resembles a balance scale, with efficacy and tolerability counterbalancing one another (Fig. 2). Maintaining this equilibrium is pivotal for achieving sustained administration and PFS. Clinical strategies to support this objective include the use of supportive agents, optimization of dosing and schedule, structured follow-up systems, and combination with transarterial therapy.

Supportive therapy to reduce adverse events

Fatigue remains one of the most prevalent and dose-limiting AEs associated with lenvatinib. Among various supportive measures, L-carnitine supplementation has shown clinical efficacy in ameliorating this symptom. Mechanistically, lenvatinib inhibits the organic cation transporter OCTN2 (SLC22A5), which mediates carnitine uptake critical for mitochondrial β-oxidation.[18] Based on this mechanism, Okubo et al.[19] reported secondary carnitine deficiency in 15% of patients receiving lenvatinib, reflected by an elevated acylcarnitine-to-free carnitine ratio measured on days 14-28 of treatment. In patients with grade 2 or higher fatigue, oral levocarnitine supplementation (1,500 mg/day) improved symptoms, as assessed by the Brief Fatigue Inventory (BFI).[19]

We previously demonstrated that branched-chain amino acid

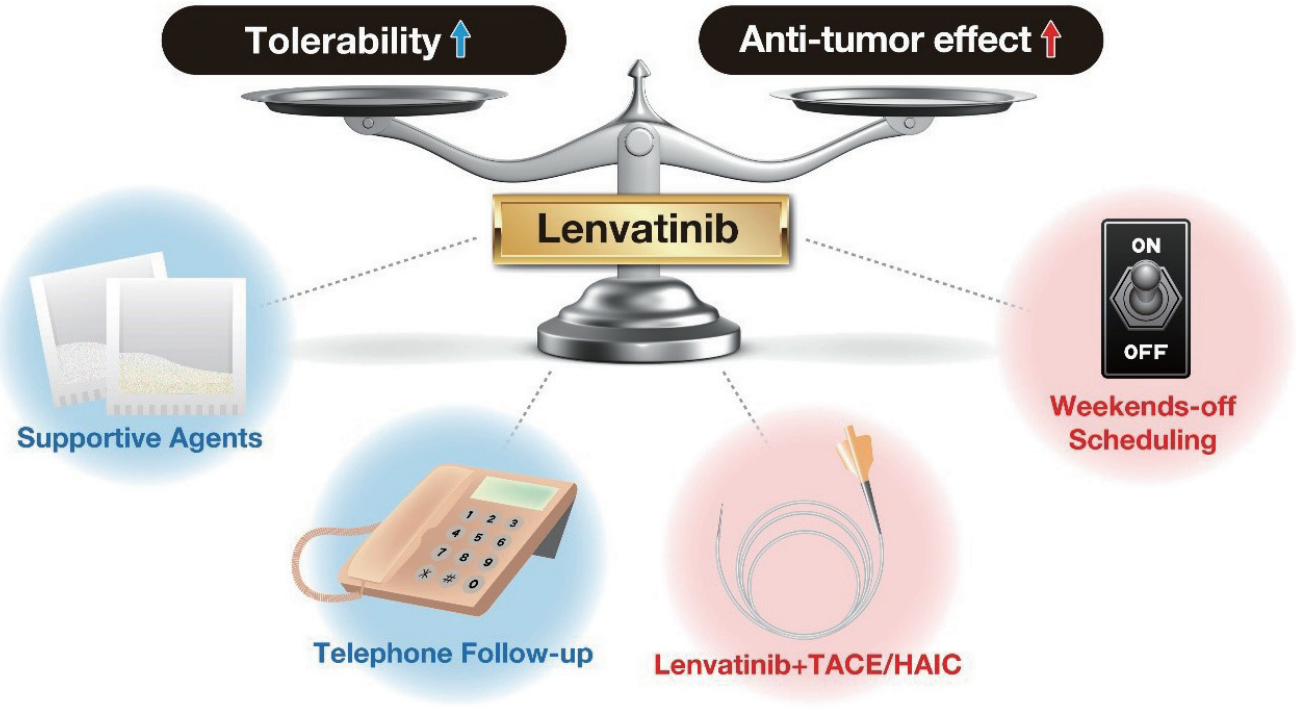

Figure 2. Practical strategies to sustain lenvatinib therapy and maximize its effectiveness. This figure summarizes the clinical strategies that support long-term administration of lenvatinib and enhance its anti-tumor effect. These include the use of supportive agents, telephone follow-up, weekends-off schedule, and combination with transarterial therapy, all of which contribute to improved tolerability and prolonged treatment duration. Transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) contribute to enhancing treatment continuity and efficacy.

(BCAA) supplementation was independently associated with a reduced incidence of grade 2 or higher fatigue among patients receiving lenvatinib.[20] BCAAs may contribute to preserved physical function and energy metabolism, thereby facilitating the continuation of systemic therapy.

Collectively, these findings support an integrative supportive care approach to mitigate fatigue and nutritional decline, which in turn may enhance the tolerability and long-term administration of lenvatinib, ultimately improving PFS in clinical practice.

Telephone follow-up: a simple but effective strategy to sustain lenvatinib therapy

Sustaining treatment continuity is critical to maximizing the PFS benefit of lenvatinib. Beyond pharmacologic interventions, structured patient support systems are instrumental. One pragmatic and cost-effective approach involves telephone follow-up by healthcare professionals.

A multicenter retrospective study of 132 patients with unresectable HCC demonstrated that pharmacist-led telephone follow-up significantly improved treatment continuity.[21] Patients receiving regular calls had longer treatment durations (median, 10.4 vs. 4.1 months) and superior PFS (6.1 vs. 3.7 months, P=0.001). This intervention was associated with fewer AE-related discontinuations and lower rates of self-withdrawal.

This low-cost strategy enables early AE detection, promotes adherence, and facilitates timely dose adjustments. Particularly in real-world settings with limited in-person access, structured telephone follow-up represents a scalable and effective tool to reinforce the durability and success of lenvatinib therapy.

Optimization of dosing schedule

The pharmacokinetic and pharmacodynamic profile of lenvatinib underscores the importance of schedule optimization. A phase I study by Ikeda et al.[22] demonstrated that lenvatinib reaches its peak plasma concentration (Cmax) within 1 to 4 hour(s) and exhibits a prolonged half-life of 28-34 hours. Notably, a dose reduction from 12 to 8 mg resulted in a 48% decline in Cmax, which may compromise efficacy. Thus, strategies to maintain drug exposure while mitigating AEs are necessary.

The weekends-off regimen, involving 5 consecutive days of administration followed by a 2-day break, has been investigated.[23] In a multicenter study, this regimen improved disease control rate (19.2% to 61.5%), extended treatment duration (3.0 to 7.9 months), and improved OS (9.0 to 14.5 months, P=0.025). Grade ≥3 AEs declined from 76.9% to 38.5%, and 66.7% of patients maintained therapy without further dose reduction. Relative dose intensity was sustained at approximately 71%.

Preclinical models have demonstrated that VEGF receptor blockade induces vascular regression in normal tissues, which is partially reversible during treatment breaks. This supports the rationale for intermittent dosing to allow recovery in non-tumor vasculature while maintaining anti-angiogenic effects in tumors.

Similar benefits of intermittent dosing have been observed in differentiated thyroid carcinoma, where drug holidays preserved dose intensity and minimized intolerable AEs.[24]

Notably, the weekends-off method is not the sole strategy. Any pre-planned, flexible dosing schedule tailored to liver function, AE profiles, and patient preferences can be considered. Clinicians should avoid rigid adherence to uniform patterns.

Overall, personalized dosing schedules that balance tolerability and efficacy can extend treatment duration, reduce AE burden, and optimize PFS, in line with the building-block strategy.

COMBINATION WITH TRANSARTERIAL THERAPY: MUTUAL COMPLEMENTATION AND TWO THERAPEUTIC GOALS

Targeting diverse tumor vasculature: pharmacological and physical complementation

Tumor angiogenesis in HCC is classically characterized by sprouting angiogenesis, a VEGF-dependent process that forms the basis of most anti-angiogenic strategies. However, accumulating evidence suggests that tumors employ diverse vascularization mechanisms beyond sprouting angiogenesis, including vasculogenesis, vascular mimicry, and, notably, vessel co-option.[25,26]

In vessel co-option, tumor cells hijack pre-existing host vessels in the surrounding liver tissue, bypassing the need for new vessel formation. This VEGF-independent vascularization mechanism has been implicated in resistance to VEGF-targeted therapies such as tyrosine kinase inhibitors.

Kuczynski and Kerbel[27] reported that vessel co-option plays a significant role in mediating resistance to sorafenib, and this likely extends to lenvatinib as well. Lenvatinib exerts pharmacological vascular inhibition by blocking the VEGF and fibroblast growth factor (FGF) signaling pathways; however, it may not sufficiently eliminate co-opted vessels in peritumoral regions. As a result, residual blood flow around the tumor may persist despite VEGF blockade. On the other hand, TACE induces physical vascular occlusion by embolizing tumor-feeding arteries, directly

depriving tumors of blood supply. However, TACE has its own limitations: 1) oncological issues: limited efficacy in multifocal, poorly vascularized, or aggressive tumors, and 2) technical issues: procedural difficulty due to complex vascular anatomy or diffuse arterial supply.

Given these limitations, lenvatinib and TACE can be viewed as mutually reinforcing therapies. Pharmacological and physical vascular targeting, when combined, enable a more comprehensive disruption of the tumor blood supply, thereby overcoming the limitations of each approach when used alone.

This combined modality serves two main therapeutic goals: 1) To achieve a complete response: enhancing TACE efficacy through vascular remodeling and synergistic effects, and 2) to prolong disease control: alternating lenvatinib with transarterial therapy to enable long-term administration.

To achieve complete response: lenvatinib priming followed by TACE

Sequential lenvatinib followed by TACE has shown high efficacy in achieving tumor responses. In the TACTICS-L trial, this approach achieved a complete response (CR) rate of 67.7% and an objective response rate (ORR) of 88.7%, including in TACE-unsuitable patients.[28] Subgroup analyses confirmed consistent benefit across tumor types and criteria.

The scheduled LEN-TACE strategy demonstrated similar outcomes, particularly in patients meeting the up-to-seven criteria.[29] A preclinical study by Tachiiri et al.[30,31] found that vascular remodeling occurs within 4 days of lenvatinib initiation, supporting short priming durations. This sequential approach offers a rational treatment pathway for intermediate-stage HCC, especially for patients initially ineligible for transarterial therapy.

Prolonging disease control and enabling long-term administration of lenvatinib

Long-term lenvatinib use is often hindered by AE-driven dose reductions, compromising efficacy. Alternating therapy with TACE or HAIC can preserve disease control during dose attenuation or breaks.

We previously reported that alternating lenvatinib with TACE or HAIC significantly extended OS and treatment continuation rates.[32] This was further supported by improved outcomes in advanced-stage HCC when intrahepatic control was maintained.[33]

In Barcelona Clinic Liver Cancer (BCLC) stage C HCC, alternating therapy doubled OS compared to monotherapy (23.1 vs. 11.6 months, P=0.002).[34] The LAUNCH trial also validated this strategy, with improved OS (17.8 vs. 11.5 months), PFS (10.6 vs. 6.4 months), and ORR (54.1% vs. 25.0%) for the combination group.[35]

Together, these findings support the use of alternating transarterial therapy as a key component of the building-block strategy to extend systemic treatment, preserve intrahepatic control, and improve survival in patients with intermediate to advanced HCC.

CHALLENGES IN THE ERA OF CHEMO-DIVERSITY

The era of chemo-diversity has brought a substantial expansion of treatment options for HCC, including molecular-targeted agents and ICIs. However, this diversity has also introduced new challenges for clinical decision-making, especially in determining the optimal sequencing and appropriate timing for switching therapies. Given the limited head-to-head clinical comparisons, treatment choices often rely not on empirical evidence, but on mechanistic rationale and tumor biology.

This chapter addresses two critical issues: 1) optimal drug sequencing: where to begin, where to go: exploring sequencing strategies based on fundamental biological rationale, and 2) when to switch therapy? Beyond Response Evaluation Criteria in Solid Tumors (RECIST) criteria: discussing optimal switching points beyond conventional definitions of disease progression.

Optimal drug sequencing: where to begin, where to go

The growing diversity of systemic therapies has made it increasingly difficult to determine the optimal sequence of agents for HCC. Clinicians are frequently confronted with the question of what the most appropriate next-line agent should be, particularly following the failure of first-line treatments involving ICIs.

As therapeutic options expand, the number of potential sequencing permutations increases exponentially. Attempting to evaluate all these combinations through prospective clinical trials is neither practical nor feasible, given the immense logistical, financial, and ethical burdens such studies would entail.

Therefore, it is crucial to establish a mechanistic rationale based on preclinical research to predict how a tumor's molecular and microenvironmental characteristics may be altered by exposure to a given agent. This understanding enables clinicians to logically select the most appropriate subsequent therapy that effectively targets the transformed tumor environment. In this context, such mechanistic insight corresponds to understanding the shape of

each block in the building-block strategy (Fig. 3). By characterizing the tumor-altering effects of each agent, clinicians can determine which therapeutic block to place next, thereby constructing a rational sequence that may ultimately lead to an ideal drug-sequential therapy adapted to the evolving biology of HCC. Through this approach, the blocks can be stacked more stably and to greater height, maximizing therapeutic continuity and long-term efficacy.

For example, lenvatinib has been shown to exert strong immunomodulatory effects by inhibiting FGF signaling.[8,13,14,36] These include the reduction of regulatory T cells and the enhancement of CD8-positive T cell infiltration, both of which contribute to a more immune-permissive tumor microenvironment. This rationale is supported by clinical observations demonstrating that lenvatinib appears to retain efficacy following the failure of ICIs, with superior outcomes compared to sorafenib in this setting.[37,38] Additionally, it has been reported that lenvatinib treatment can lead to the activation of the hepatocyte growth factor-c-MET signaling pathway.[39-41] This activation may be a result of feedback mechanisms triggered by the inhibition of FGF signaling, and could potentially contribute to acquired resistance. Based on this rationale, the subsequent use of cabozantinib, a multi-kinase inhibitor that targets c-MET, may serve as the next logical block in the treatment sequence, providing a mechanistically informed and potentially effective strategy.

While lenvatinib serves as a representative example, this strategy should not be limited to a single agent. Similar mechanistic rationales must be developed for other molecular-targeted agents and immunotherapies, enabling personalized sequencing decisions across the whole therapeutic landscape of HCC.

When to switch therapy? Beyond RECIST

In current clinical practice, the timing for transitioning to the next systemic therapy is typically guided by disease progression, as defined by the RECIST or modified RECIST (mRECIST) criteria. However, whether this conventional milestone represents the optimal handoff point in a carefully planned drug-sequential therapy remains uncertain. In fact, determining the most appropriate timing for therapeutic transition is a newly emerging challenge in the era of chemo-diversity, particularly when aiming to build the most effective treatment sequence.

RECIST defines progressive disease (PD) as a 20% or greater increase in tumor burden from the nadir, and switching therapy at this point is a common clinical practice. However, there are additional timepoints that may warrant treatment modification based on clinical judgment. These include 1) biological progression despite radiological stable disease, such as rising tumor markers, 2) a 20% increase in tumor size from the nadir, corresponding to RECIST-defined PD, 3) a 20% increase in tumor size from baseline, and 4) radiological PD with preserved liver function and clinical stability, where continued therapy may still be appropriate (beyond RECIST-PD).

Ultimately, the key question is whether the chosen switching point will lead to improved overall patient survival. In this context, we previously reported that during treatment with atezolizumab plus bevacizumab, tumor markers and radiological assessments do not always align.[42] The study highlighted that tumor

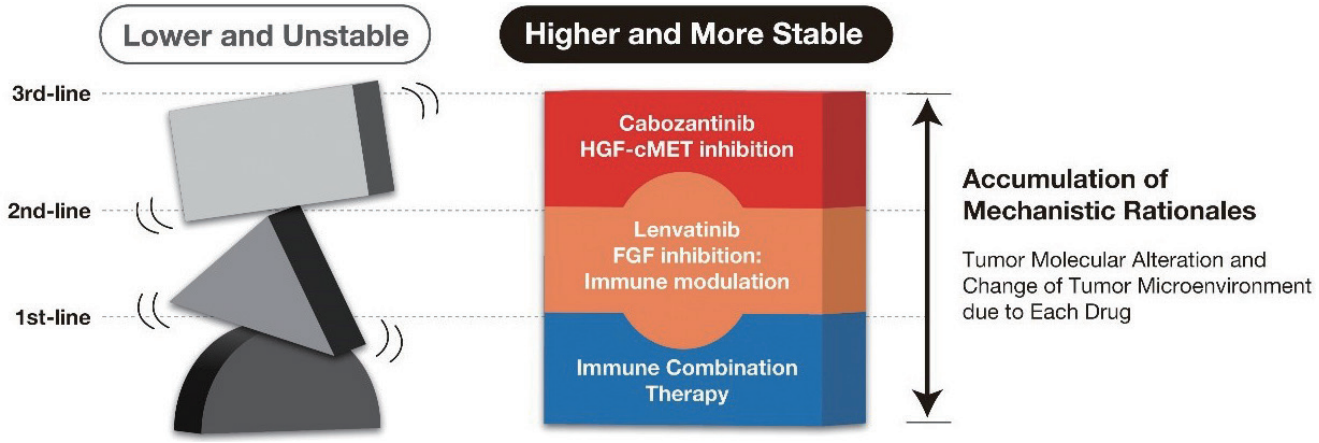

Figure 3. Transarterial therapy as a complementary approach to lenvatinib. Transarterial therapy complements lenvatinib both pharmacologically and physically, contributing to tumor control and long-term tolerability. This combined approach includes lenvatinib priming followed by transarterial chemoembolization (TACE) to achieve a complete response, and alternating strategies to extend disease control and enable prolonged lenvatinib administration. HGF, hepatocyte growth factor; FGF, fibroblast growth factor.

markers may suggest early progression not yet captured by imaging, underscoring their value in treatment decision-making.

The optimal timing for switching therapy has yet to be defined (Fig. 4). For now, when faced with radiological stability but rising tumor markers, one practical approach is to bring forward the following scheduled imaging assessment. This allows clinicians to avoid missing the ideal switching window, ensuring that the subsequent therapy can be initiated at a time when its full benefit can still be realized. While this strategy is based on clinical experience rather than high-level evidence, it may serve as a valuable interim measure until more robust prospective data become available.

Lenvatinib as second-line therapy after immunotherapy

Lenvatinib was initially approved as a first-line therapy; however, its use as a second-line treatment after immunotherapy has recently gained attention.[43] Several clinical reports indicate that, in the post-immunotherapy setting, lenvatinib maintains a median PFS of approximately 4 to 6 months, and the objective response rate by mRECIST is about 30-40%, suggesting preserved antitumor activity as second-line therapy.[37,44] Lenvatinib's distinctive signal-transduction inhibition profile plausibly supports this activity. After atezolizumab plus bevacizumab, VEGF-A is neutralized by bevacizumab, whereas VEGF receptors themselves remain uninhibited. Because VEGF-A belongs to a ligand family that also includes VEGF-B, VEGF-C, and VEGF-D, signaling via alternative ligands may contribute to bevacizumab resistance.[45] By inhibiting multiple VEGF receptors, lenvatinib can counter ligand-driven stimulation at the receptor level. Moreover, VEGF blockade is known to be accompanied by compensatory FGF-driven angiogenesis; therefore, dual inhibition of the VEGF and FGF pathways by lenvatinib is mechanistically meaningful.[46] As noted earlier, lenvatinib also exerts immunomodulatory effects, which may enhance its second-line activity after immunotherapy.[13]

Regarding adverse events in the second-line setting, to our knowledge, there are no studies directly comparing the incidence rates of first- and second-line treatments. In a recent report, however, the spectrum, frequency, and grades of adverse events with

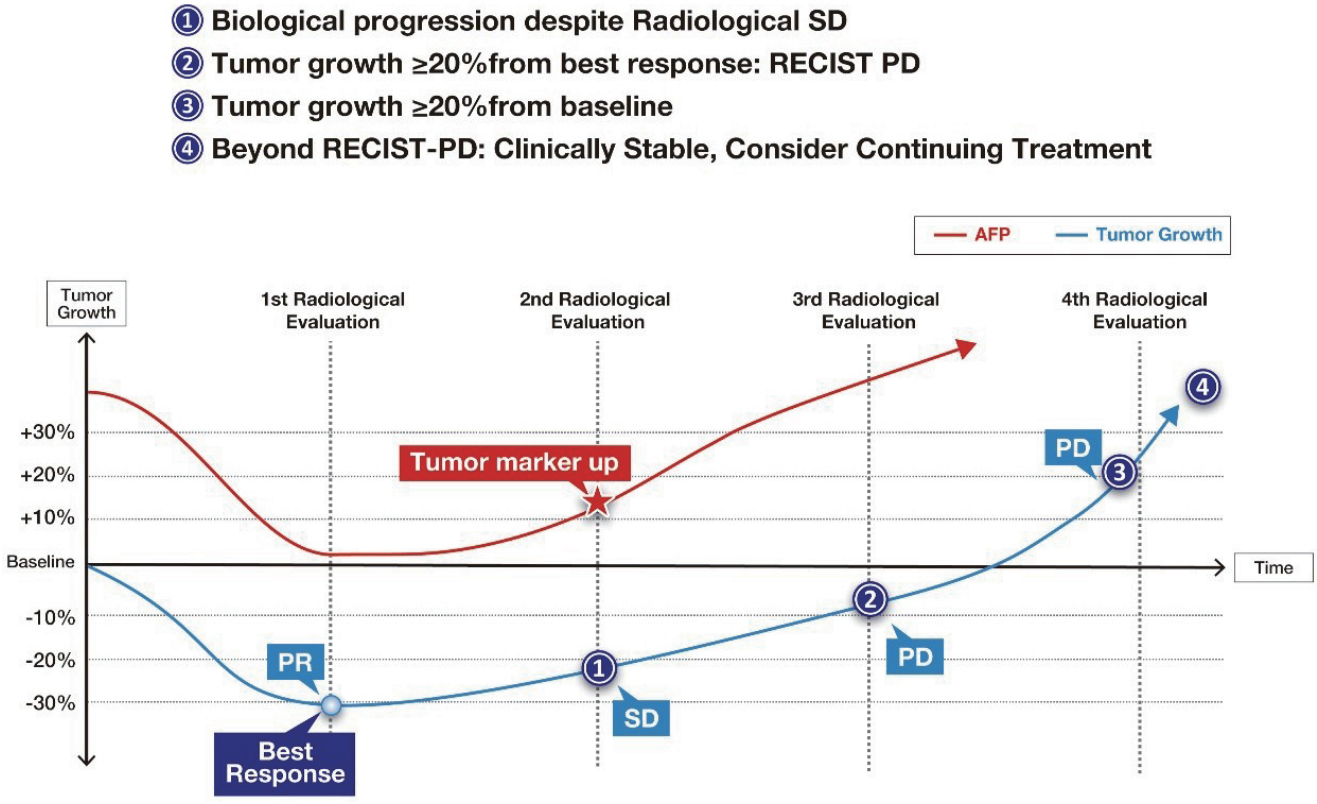

Figure 4. Time course and treatment decision beyond Response Evaluation Criteria in Solid Tumors (RECIST). This figure illustrates four key clinical scenarios relevant to treatment decisions beyond the RECIST criteria. These include biological progression despite stable disease, tumor growth of 20% or more from the best response, progression by 20% or more from baseline as defined by RECIST, and continuation of post-progression treatment in patients who remain clinically stable. SD, stable disease; PD, progressive disease; AFP, alpha-fetoprotein; PR, partial response.

second-line lenvatinib did not show significant deviations from established experience.[37] Nonetheless, as outlined in Sections 4.1 and 4.2, a timely transition to second-line therapy is essential. Prolonged use of first-line regimens may lead to deterioration of liver function and anti-VEGF-related AEs, such as proteinuria, which can hinder the initiation of lenvatinib at an appropriate dose and may necessitate early dose reductions or interruptions due to reduced tolerability. Therefore, when lenvatinib is employed as second-line therapy, the practical measures described in this review to maximize its effect should be fully implemented to enable sustained administration.

CONCLUSION

Lenvatinib represents one of the key agents in the building-block strategy for HCC in the era of chemo-diversity. Drug efficacy and value are not fully captured by clinical trials alone. Only after regulatory approval and real-world application do their true potentials become evident.

As demonstrated throughout this review, a multifaceted approach that maximizes both tolerability and antitumor efficacy, by understanding agent-specific adverse events and implementing appropriate clinical strategies, is essential to fully realize patient benefit.

This review highlights practical strategies to optimize the therapeutic efficacy of lenvatinib, providing insights that can be directly applied to real-world clinical care.

Ultimately, such efforts enable each building block to be stacked higher, more stably, and more precisely, thereby contributing to meaningful improvements in patient prognosis.

In this process, clinicians must continually strive to maintain a balance for their patients, striking an appropriate equilibrium between therapeutic efficacy and safety, as well as between disease control and quality of life.

Conflicts of Interests

HI has received honoraria (lecture fees) from Eisai Co., Ltd. and Chugai Pharmaceutical Co., Ltd., and research funding from Eisai Co., Ltd. SS has received honoraria (lecture fees) from Eisai Co., Ltd., Chugai Pharmaceutical Co., Ltd., and AstraZeneca K.K. TK has received honoraria (lecture fees) from ASKA Pharmaceutical Co., Ltd., Taisho Pharmaceutical Co., Ltd., Kowa Company, Ltd., AbbVie GK., Eisai Co., Ltd., EA Pharma Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Sumitomo Pharma Co., Ltd., Novo Nordisk Pharma Ltd., Otsuka Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K. The other authors declare no conflicts of interest relevant to this work.

Ethics Statement

This review article is fully based on articles which have already been published and did not involve additional patient participants. Therefore, IRB approval is not necessary.

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REFERENCES

1. Goh MJ, Sinn DH, Kim JM, Lee MW, Hyun DH, Yu JI, et al. Clinical practice guideline and real-life practice in hepatocellular carcinoma: a Korean perspective. Clin Mol Hepatol 2023;29:197-205.
2. Hwang SY, Danpanichkul P, Agopian V, Mehta N, Parikh ND, Abou-Alfa GK, et al. Hepatocellular carcinoma: updates on epidemiology, surveillance, diagnosis and treatment. Clin Mol Hepatol 2025;31(Suppl):S228-S254.
3. Koga H, Iwamoto H, Suzuki H, Shimose S, Nakano M, Kawaguchi T. Clinical practice guidelines and real-life practice in hepatocellular carcinoma: a Japanese perspective. Clin Mol Hepatol 2023;29:242-251.
4. Cho Y, Kim BH, Park JW. Overview of Asian clinical practice guidelines for the management of hepatocellular carcinoma: an Asian perspective comparison. Clin Mol Hepatol 2023;29:252-262.
5. Ogasawara S, Ooka Y, Koroki K, Maruta S, Kanzaki H, Kanayama K, et al. Switching to systemic therapy after locoregional treatment failure: definition and best timing. Clin Mol Hepatol 2020;26:155-162.
6. Yoon SM. Novel paradigm in the treatment of hepatocellular carcinoma: anticipating breakthroughs with particle therapy. Clin Mol Hepatol 2023;29:977-979.
7. Suzuki H, Mishra S, Paul S, Hoshida Y. Molecular and immune landscape of hepatocellular carcinoma for therapeutic development. J Liver Cancer 2025;25:9-18.
8. Chan LL, Chan SL. The evolving role of lenvatinib at the new era of first-line hepatocellular carcinoma treatment. Clin Mol Hepatol 2023;29:909-923.
9. Kudo M. Durvalumab plus tremelimumab: a novel combination immunotherapy for unresectable hepatocellular carcinoma. Liver Cancer 2022;11:87-93.
10. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab

plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-1905.
11. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173.
12. Hussein Z, Mizuo H, Hayato S, Namiki M, Shumaker R. Clinical pharmacokinetic and pharmacodynamic profile of lenvatinib, an orally active, small-molecule, multitargeted tyrosine kinase inhibitor. Eur J Drug Metab Pharmacokinet 2017;42:903-914.
13. Suzuki H, Iwamoto H, Tanaka T, Sakaue T, Imamura Y, Masuda A, et al. Fibroblast growth factor inhibition by molecular-targeted agents mitigates immunosuppressive tissue microenvironment in hepatocellular carcinoma. Hepatol Int 2024;18:610-622.
14. Yamada T, Fujiwara N, Kubota N, Matsushita Y, Nakatsuka T, Kurosaki S, et al. Lenvatinib recruits cytotoxic GZMK+CD8 T cells in hepatocellular carcinoma. Hepatol Commun 2023;7:e0209.
15. Shimose S, Iwamoto H, Niizeki T, Shirono T, Noda Y, Kamachi N, et al. Clinical significance of adverse events for patients with unresectable hepatocellular carcinoma treated with lenvatinib: a multicenter retrospective study. Cancers (Basel) 2020;12:1867.
16. Lazarus A, Keshet E. Vascular endothelial growth factor and vascular homeostasis. Proc Am Thorac Soc 2011;8:508-511.
17. Yang Y, Zhang Y, Cao Z, Ji H, Yang X, Iwamoto H, et al. Anti-VEGF- and anti-VEGF receptor-induced vascular alteration in mouse healthy tissues. Proc Natl Acad Sci U S A 2013;110:12018-12023.
18. Jing Z, Okubo H, Morishige JI, Xu P, Hasan N, Nagata N, et al. Lenvatinib causes reduced expression of carnitine/organic cation transporter 2 and carnitine deficiency in the skeletal muscle of rats. Toxicol Lett 2022;366:17-25.
19. Okubo H, Ando H, Ishizuka K, Kitagawa R, Okubo S, Saito H, et al. Carnitine insufficiency is associated with fatigue during lenvatinib treatment in patients with hepatocellular carcinoma. PLoS One 2020;15:e0229772.
20. Shimose S, Koya S, Kawaguchi T, Hirota K, Yoshio S, Niizeki T, et al. Impact of branched-chain amino acids and frailty on the management of lenvatinib-related fatigue in patients with hepatocellular carcinoma. Clin Mol Hepatol 2021;27:616-619.
21. Tsumura S, Shimose S, Niizeki T, Kuboyama E, Iwamoto H, Tanaka M, et al. Telephone follow-up contributes to improving adherence and treatment duration in patients with hepatocellular carcinoma treated with lenvatinib. J Gastroenterol Hepatol 2023;38:1140-1147.
22. Ikeda M, Okusaka T, Mitsunaga S, Ueno H, Tamai T, Suzuki T, et al. Safety and pharmacokinetics of lenvatinib in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2016;22:1385-1394.
23. Iwamoto H, Suzuki H, Shimose S, Niizeki T, Nakano M, Shirono T, et al. Weekends-off lenvatinib for unresectable hepatocellular carcinoma improves therapeutic response and tolerability toward adverse events. Cancers (Basel) 2020;12:1010.
24. Matsuyama C, Enokida T, Ueda Y, Suzuki S, Fujisawa T, Ito K, et al. Planned drug holidays during treatment with lenvatinib for radioiodine-refractory differentiated thyroid cancer: a retrospective study. Front Oncol 2023;13:1139659.
25. Dudley AC, Griffioen AW. Pathological angiogenesis: mechanisms and therapeutic strategies. Angiogenesis 2023;26:313-347.
26. Ribatti D, Annese T, Tamma R. Vascular co-option in resistance to anti-angiogenic therapy. Front Oncol 2023;13:1323350.
27. Kuczynski EA, Kerbel RS. Implications of vessel co-option in sorafenib-resistant hepatocellular carcinoma. Chin J Cancer 2016;35:97.
28. Kudo M, Ueshima K, Saeki I, Ishikawa T, Inaba Y, Morimoto N, et al. A phase 2, prospective, multicenter, single-arm trial of transarterial chemoembolization therapy in combination strategy with lenvatinib in patients with unresectable intermediate-stage hepatocellular carcinoma: TACTICS-L trial. Liver Cancer 2023;13:99-112.
29. Shimose S, Niizeki T, Iwamoto H, Tanaka M, Moriyama E, Shirono T, et al. Efficacy and safety of lenvatinib-transcatheter arterial chemoembolization sequential therapy for hepatocellular carcinoma within the up-to-seven criteria. Hepatol Res 2025;55:1015-1025.
30. Tachiiri T, Minamiguchi K, Taiji R, Sato T, Toyoda S, Matsumoto T, et al. Effects of short-term lenvatinib administration prior to transarterial chemoembolization for hepatocellular carcinoma. Cancers (Basel) 2024;16:1624.
31. Tachiiri T, Nishiofuku H, Maeda S, Sato T, Toyoda S, Matsumoto T, et al. Vascular normalization caused by short-term lenvatinib could enhance transarterial chemoembolization in hepatocellular carcinoma. Curr Oncol 2023;30:4779-4786.
32. Shimose S, Iwamoto H, Tanaka M, Niizeki T, Shirono T, Noda Y, et al. Alternating lenvatinib and trans-arterial therapy prolongs overall survival in patients with inter-mediate stage hepatocellular carcinoma: a propensity score matching study. Cancers (Basel) 2021;13:160.
33. Jung SM, Jang JW, You CR, Yoo SH, Kwon JH, Bae SH, et al. Role of intrahepatic tumor control in the prognosis of patients with hepatocellular carcinoma and extrahepatic metastases. J Gastroenterol Hepatol 2012;27:684-689.
34. Shimose S, Iwamoto H, Niizeki T, Tanaka M, Shirono T, Moriyama E, et al. Efficacy of lenvatinib combined with transcatheter intra-arterial therapies for patients with advanced-stage of hepatocellular carcinoma: a propensity score matching. Int J Mol Sci 2023;24:13715.
35. Peng Z, Fan W, Zhu B, Wang G, Sun J, Xiao C, et al. Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: a phase III, randomized clinical trial (LAUNCH). J Clin Oncol 2023;41:117-127.
36. Yamauchi M, Ono A, Amioka K, Fujii Y, Nakahara H, Teraoka Y, et al. Lenvatinib activates anti-tumor immunity by suppressing immunoinhibitory infiltrates in the tumor microenvironment of advanced hepatocellular carcinoma. Commun Med (Lond) 2023;3:152.
37. Cheon J, Shimose S, Kim HD, Niizeki T, Ryu MH, Shirono T, et al. Lenvatinib versus sorafenib as second-line therapy following progression on atezolizumab-bevacizumab in patients with unresectable hepatocellular carcinoma: a multicenter retrospective study from Korea and Japan. J Cancer Res Clin Oncol 2025;151:52.
38. Persano M, Casadei-Gardini A, Tada T, Suda G, Shimose S, Kudo M, et al. Lenvatinib versus sorafenib second-line therapy in patients with hepatocellular carcinoma progressed to atezolizumab plus bevacizumab: a retrospective real-world study. Oncology 2025;103:456-468.
39. Han JE, Kim SS, Cheong JY, Eun JW. Uncovering the MET-TRIB3-FOXO1 axis: a novel target in MET-driven hepatocellular carcinoma: Editorial on "MET promotes hepatocellular carcinoma development through the promotion of TRIB3-mediated FOXO1 degradation". Clin Mol Hepatol 2026;32:436-438.
40. Wang T, Rao D, Fu C, Sun Z, Luo Y, Lu J, et al. MET promotes hepatocellular carcinoma development through the promotion of TRIB3-mediated FOXO1 degradation. Clin Mol Hepatol 2025;31:1032-1057.
41. Buttell A, Qiu W. The action and resistance mechanisms of lenvatinib in liver cancer. Mol Carcinog 2023;62:1918-1934.
42. Iwamoto H, Shimose S, Niizeki T, Koga H, Torimura T. Clinical significance of the discrepancy between radiological findings and biochemical responses in atezolizumab plus bevacizumab for hepatocellular carcinoma. Clin Mol Hepatol 2022;28:575-579.
43. Vogel A, Saborowski A, Rimassa L, El-Khoueiry A. Navigating second-line therapy after immunotherapy in advanced HCC. JHEP Rep 2025;8:101630.
44. Aoki T, Kudo M, Ueshima K, Morita M, Chishina H, Takita M, et al. Exploratory analysis of lenvatinib therapy in patients with unresectable hepatocellular carcinoma who have failed prior PD-1/PD-L1 checkpoint blockade. Cancers (Basel) 2020;12:3048.
45. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669-676.
46. Abdullah SE, Perez-Soler R. Mechanisms of resistance to vascular endothelial growth factor blockade. Cancer 2012;118:3455-3467.