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Research Article

Multitarget Therapeutic Strategies for Hepatocellular Carcinoma: From Molecular Rationale to Clinical Integration

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Abstract

Recent advances in the molecular characterization of hepatocellular carcinoma (HCC) have shifted therapeutic strategies from single-agent interventions toward multitarget drug approaches that simultaneously inhibit oncogenic signaling, angiogenesis, immune evasion, and tumor microenvironment remodeling. The substantial molecular heterogeneity of HCC, coupled with intrinsic and acquired drug resistance, has limited the long-term efficacy of conventional monotherapies, creating a strong rationale for combination and multitarget therapeutic regimens. This narrative review summarizes recent developments in multitarget treatment strategies for HCC, focusing on the integration of multikinase inhibitors, immune checkpoint inhibitors, anti-angiogenic agents, epigenetic modulators, and emerging molecularly targeted therapies. Particular emphasis is placed on the biological mechanisms underlying therapeutic synergy, including coordinated inhibition of VEGF, RAF/MEK/ERK, PI3K/AKT/mTOR, Wnt/β-catenin, MET, FGFR, and immune checkpoint pathways. The review also discusses evolving biomarker-guided patient stratification, mechanisms of resistance, and the influence of the tumor immune microenvironment on treatment response. Emerging approaches involving bispecific antibodies, antibody–drug conjugates, adoptive cellular therapies, and rational combinations with locoregional interventions are highlighted as promising components of future multimodal treatment paradigms. Although multitarget therapies have significantly improved survival outcomes in selected patients, challenges remain regarding optimal sequencing, toxicity management, resistance prevention, and personalized treatment selection. Continued integration of molecular profiling, translational research, and precision oncology is expected to facilitate the development of individualized multitarget therapeutic strategies, ultimately improving clinical outcomes for patients with hepatocellular carcinoma.

Keywords: HCC, RTK, PD-L1, CTLA-4, FGFR4

Introduction

Hepatocellular carcinoma (HCC) remains one of the most formidable challenges in contemporary oncology, representing the third leading cause of cancer-related mortality worldwide. The disease burden is particularly pronounced in East Asia and regions with high prevalence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, though its incidence continues to rise globally in parallel with the metabolic syndrome epidemic. Despite substantial advances in screening, surveillance, and therapeutic interventions, the prognosis for patients with advanced-stage HCC remains dismal, with 5-year survival rates below 12% [1,2].

The therapeutic landscape of advanced HCC has undergone a remarkable transformation over the past two decades. The approval of sorafenib in 2007 as the first molecularly targeted agent for HCC represented a paradigm shift, establishing systemic therapy as a viable option for patients with unresectable disease. This milestone was followed by a succession of multikinase inhibitors (MKIs),

including lenvatinib, regorafenib, cabozantinib, and ramucirumab, each demonstrating modest but meaningful survival benefits in carefully selected patient populations. More recently, the emergence of immune checkpoint inhibitors (ICIs) and their integration with anti-angiogenic agents has fundamentally altered the standard of care, with combinations such as atezolizumab–bevacizumab and durvalumab–tremelimumab now established as first-line treatment options [1,3,4].

However, the clinical reality of HCC management remains sobering. Despite the proliferation of therapeutic options, objective response rates in advanced disease rarely exceed 30%, and the majority of patients either fail to respond to initial therapy or develop acquired resistance within months. This therapeutic attrition reflects the extraordinary molecular heterogeneity intrinsic to HCC-a malignancy characterized by diverse oncogenic drivers, complex signaling network redundancies, and a profoundly immunosuppressive tumor microenvironment (TME).

The recognition that HCC is not a single disease but a constellation of molecularly distinct subtypes has driven the evolution from single-agent interventions toward multitarget and combination therapeutic strategies. The conceptual foundation of this approach rests on the premise that simultaneous inhibition of multiple oncogenic pathways can overcome compensatory signaling, prevent or delay resistance emergence, and exploit synergistic vulnerabilities that are inaccessible to monotherapies. This is particularly relevant for HCC, where the convergence of angiogenesis, immune evasion, and aberrant proliferative signaling creates interdependent vulnerabilities that can be rationally co-targeted [4,5].

This narrative review provides a comprehensive synthesis of recent developments in multitarget therapeutic strategies for HCC. We examine the molecular rationale underlying combination approaches, critically evaluate clinical evidence for current regimens, explore mechanisms of therapeutic resistance, and discuss emerging strategies that promise to further refine and personalize HCC treatment. The review concludes with perspectives on remaining challenges and future directions for integrating molecular profiling and precision oncology principles into the clinical management of this complex malignancy [5,6].

Molecular Landscape of HCC: A Foundation for Multitarget Therapy

Hallmark Signaling Pathways in Hepatocarcinogenesis

The molecular pathogenesis of HCC is driven by the dysregulation of multiple interconnected signaling pathways that collectively orchestrate malignant transformation, proliferation, survival, angiogenesis, and metastasis. Understanding these pathways is essential for rational design of multitarget therapeutic strategies. RAF/MEK/ERK (MAPK) Pathway. The mitogen-activated protein kinase (MAPK) cascade represents a central oncogenic driver in HCC, frequently activated through upstream receptor tyrosine kinase (RTK) signaling or downstream mutations in RAS and RAF family members. Aberrant MAPK signaling promotes uncontrolled proliferation, survival, and metabolic reprogramming. Multikinase inhibitors with activity against RAF and downstream effectors have been a cornerstone of HCC therapy since sorafenib's approval [7,8].

PI3K/AKT/mTOR Pathway. The phosphoinositide 3-kinase (PI3K) axis is hyperactivated in approximately 30-50% of HCC cases through various mechanisms including PTEN loss, PIK3CA mutations, and RTK cross-talk. This pathway integrates growth factor signaling with cellular metabolism, survival, and protein synthesis. mTOR inhibitors and dual PI3K/mTOR inhibitors have been explored in clinical trials, though their efficacy as monotherapies has been limited. Wnt/β-Catenin Signaling. Aberrant Wnt/β-catenin signaling, present in 20-40% of HCC, is among the most common molecular alterations. CTNNB1 mutations and AXIN1 inactivation lead to constitutive β-catenin accumulation, driving proliferation and stemness. Importantly, β-catenin activation has been associated with immune exclusion and resistance to checkpoint inhibitors, highlighting its role in immune evasion [8].

VEGF/VEGFR Signaling. Vascular endothelial growth factor (VEGF) pathway dysregulation is universal in HCC, reflecting the highly vascular nature of this tumor. Hypoxia, driven by rapid tumor growth and inadequate vascularization, upregulates VEGF expression, promoting angiogenesis, vascular permeability, and immunosuppression. VEGFR-targeting MKIs and anti-VEGF monoclonal antibodies (bevacizumab) form the backbone of contemporary combination regimens [8,9].

MET/HGF Pathway. The MET receptor tyrosine kinase and its ligand hepatocyte growth factor (HGF) are frequently overexpressed in HCC and correlate with aggressive tumor behavior and poor prognosis. MET activation promotes epithelial-mesenchymal transition (EMT), invasion, and therapeutic resistance. Cabozantinib, which targets MET alongside VEGFR and AXL, demonstrates efficacy in HCC, particularly in sorafenib-refractory disease [10].

FGFR/FGF Signaling. The fibroblast growth factor 19 (FGF19)-FGFR4 axis has emerged as a critical oncogenic pathway in a subset of HCC. FGF19 gene amplification occurs in up to 20% of HCC and is associated with adverse prognostic factors including high alpha-fetoprotein (AFP), microvascular invasion, and increased recurrence risk. The FGF19-FGFR4 axis activates downstream MAPK and PI3K/AKT signaling, promoting proliferation and apoptosis resistance. Importantly, FGF19 overexpression also upregulates PD-L1 in the TME, linking this pathway to immune evasion [11].

Epigenetic Dysregulation. Beyond genetic alterations, HCC is characterized by profound epigenetic reprogramming involving histone modifications, DNA methylation, and chromatin remodeling. Epigenetic regulators including EZH2 and histone deacetylases (HDACs) are frequently overexpressed, contributing to aberrant gene expression patterns that sustain malignancy and immune evasion. Epigenetic modulators represent an emerging therapeutic frontier, with the potential to resensitize tumors to conventional therapies and alter the immune landscape [12].

Molecular Heterogeneity and Implications for Therapy

Perhaps the most significant barrier to effective HCC therapy is the extraordinary molecular heterogeneity that exists both betwe-

en patients (inter-tumor heterogeneity) and within individual tumors (intra-tumor heterogeneity). Inter-tumor Heterogeneity. HCC comprises distinct molecular subclasses defined by transcriptomic profiling. These subtypes-typically categorized as proliferation versus non-proliferation classes-exhibit divergent biology, clinical behavior, and therapeutic vulnerabilities. Proliferation-class tumors are characterized by activation of cell cycle pathways, mTOR signaling, and oncogenic transcription factors; they tend to occur in HBV-associated HCC and may be more sensitive to certain targeted agents. Non-proliferation tumors often exhibit CTNNB1 mutations and resemble hepatocyte-like differentiation, with a less aggressive clinical course but potential resistance to checkpoint inhibitors [13,14].

Intra-tumor Heterogeneity. Single-cell sequencing and spatial transcriptomics studies have revealed remarkable cellular diversity within individual HCC tumors. Distinct subpopulations of malignant cells coexist within the same tumor, exhibiting differential metabolic programming, proliferative capacity, and drug sensitivity. This phenomenon is evident in studies where multiple nodules from the same patient demonstrate disparate treatment responses-one nodule showing necrosis after lenvatinib therapy while another exhibits intrinsic resistance [15,16]. The concept of cellular state plasticity has emerged as a key driver of intra-tumor heterogeneity and therapeutic resistance. Tumor cells can undergo dynamic transitions between different differentiation states, enabling adaptation to therapeutic pressure. This plasticity is governed by transcriptional regulators including the FOXM1/CEBPB axis, which functions as a master switch controlling developmental heterogeneity. Targeting this axis can restore tumor homogeneity and resensitize cells to therapy [16].

The Tumor Immune Microenvironment: A Therapeutic Nexus

The HCC TME is characterized by profound immunosuppression, maintained through multiple overlapping mechanisms that create formidable barriers to effective anti-tumor immunity. Immune Cell Composition. The HCC immune infiltrate is dominated by immunosuppressive cell populations including regulatory T cells (Tregs), tumor-associated macrophages (TAMs) with M2-like polarization, and myeloid-derived suppressor cells (MDSCs). CD14+ monocytes with suppressive function have been identified as enriched in HCC patients, particularly those with poorer liver function (Child-Pugh B), and are associated with unfavorable immunotherapy outcomes. These cells exhibit upregulation of TGFβ and Wnt/β-catenin signaling, angiogenesis, EMT, and hypoxia pathways [17,18].

Immune Evasion Mechanisms. HCC cells employ diverse strategies to evade immune surveillance. PD-L1 upregulation-driven by oncogenic signaling such as FGF19-FGFR4 or VEGF-promotes T-cell exhaustion and dysfunction. The immunosuppressive cytokine milieu, featuring TGFβ, IL-10, and VEGF, further dampens effector T-cell responses. Importantly, distinct HCC subtypes exhibit differential immune landscapes, with β-catenin-activated tumors characterized by immune exclusion and resistance to checkpoint inhibitors [18].

Liver Function and Immunotherapy. The relationship between liver function and immunotherapy outcomes is particularly relevant in HCC. Patients with worse liver function (Child-Pugh B) demonstrate enrichment of immunosuppressive CD14+ monocytes and downregulation of IFNα/IFNγ pathways in T cells, correlating with lower response rates and shorter survival. This underscores the interplay between underlying liver disease and therapeutic efficacy, highlighting the need for careful patient selection [18,19].

Multikinase Inhibitors: The Foundational Therapeutic Platform

Evolution of MKI Therapy in HCC

Multikinase inhibitors have served as the cornerstone of systemic therapy for advanced HCC since sorafenib's landmark approval. These agents, by virtue of their ability to simultaneously target multiple RTKs and their downstream effectors, offer a multitarget approach to oncogenic pathway inhibition. Sorafenib. As the first FDA-approved systemic therapy for HCC, sorafenib established the proof-of-concept that molecularly targeted therapy could improve survival in advanced disease. Sorafenib inhibits RAF kinases (CRAF, BRAF, mutant BRAF) and multiple RTKs including VEGFR-1/2/3, PDGFRβ, c-KIT, and FLT-3. The SHARP trial demonstrated a median overall survival (OS) of 10.7 months versus 7.9 months for placebo, establishing sorafenib as the standard of care for a decade [19].

Lenvatinib. The non-inferiority of lenvatinib compared to sorafenib in the REFLECT trial established an alternative first-line option. Lenvatinib exhibits a distinct kinase inhibition profile, targeting VEGFR1-3, FGFR1-4, PDGFRα, c-KIT, and RET. Notably, lenvatinib's activity against FGFR1-4 distinguishes it from sorafenib and may provide additional anti-tumor efficacy in FGF-driven tumors [19].

Second-Line Agents. The recognition that patients progressing on sorafenib might benefit from sequential therapy led to the approval of several second-line MKIs. Regorafenib, which targets VEGFR1-3, TIE-2, PDGFR, FGFR, c-KIT, RET, RAF, and p38, demonstrated improved OS in the RESORCE trial. Cabozantinib, with its unique activity against MET and AXL in addition to VEGFR2, showed efficacy in sorafenib-refractory patients. Ramucirumab, a VEGFR2 monoclonal antibody rather than a TKI, demonstrated survival benefit in patients with AFP ≥400 ng/mL [19].

Beyond First-Line: Sequencing and Resistance

Despite the expansion of MKI options, long-term efficacy is limited by intrinsic and acquired resistance. Real-world data indicate that less than half of patients benefit from MKI therapy, with OS extension of less than six months. Over 70% of patients fail to achieve objective response to lenvatinib, and approximately 80% show only tumor stabilization or progression in real-world cohorts [20]. Mechanisms of MKI resistance are multifaceted. Activation of compensatory signaling pathways-including MET, EGFR, and FGFR upregulation-can circumvent VEGFR inhibition. Metabolic reprogramming, particularly shifts in glycolysis and fatty acid metabolism, contributes to resistance through altered bioenergetics and redox homeostasis. Epithelial-mesenchymal transition and enhanced

stemness properties enable tumor cells to evade drug effects and persist in a therapy-resistant state [20,21]. Biomarker identification for MKI resistance has emerged as a critical priority. Single-cell sequencing studies have identified upregulated genes including PCK1 and ALDH1A1 that are significantly associated with lenvatinib resistance, offering potential predictive biomarkers for treatment selection. Additionally, adrenomedullin (ADM) has been identified as a driver of TACE and sorafenib cross-resistance through immune microenvironment remodeling [22.23].

Immune Checkpoint Inhibitors: Reshaping the Immunotherapeutic Landscape

From Monotherapy to Combination

The success of ICIs across multiple cancer types generated substantial interest in HCC, given the immunogenic nature of chronic hepatitis-driven malignancies. The anti-PD-1 agents nivolumab and pembrolizumab initially demonstrated promising response rates in early-phase trials, leading to accelerated approvals. However, subsequent phase III trials failed to meet their primary endpoints, underscoring the limitations of ICI monotherapy in HCC (24). The recognition that VEGF-mediated immunosuppression represents a major barrier to ICI efficacy provided the rationale for combining anti-angiogenic agents with checkpoint inhibitors. VEGF promotes immune evasion through multiple mechanisms: inhibition of dendritic cell maturation, suppression of T-cell infiltration and function, expansion of MDSCs and Tregs, and upregulation of checkpoint molecules on endothelial and immune cells. By normalizing the vasculature and reducing immunosuppression, anti-angiogenic agents can potentiate ICI activity [24.26].

Established Combination Regimens

Atezolizumab–Bevacizumab. The IMbrave150 trial established atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGF) as the first-line standard of care for advanced HCC. This combination demonstrated superior OS and PFS compared to sorafenib, representing the first regimen to outperform sorafenib in a phase III trial. The hazard ratio for OS was 0.58, and PFS was 0.59, establishing the combination as a new benchmark. Durvalumab–Tremelimumab. The HIMALAYA trial evaluated the combination of durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4) in the STRIDE regimen (Single Tremelimumab Regular Interval Durvalumab). The STRIDE regimen demonstrated superior OS compared to sorafenib, providing an alternative first-line option. This regimen offers distinct advantages including the absence of anti-VEGF-related toxicity, making it preferable for patients with bleeding risk or other contraindications to bevacizumab. TKI–ICI Combinations. Multiple phase III trials have evaluated MKI–ICI combinations in HCC. The CARES-310 study demonstrated improved PFS and OS for camrelizumab (anti-PD-1) plus rivoceranib (VEGFR2 TKI) compared to sorafenib, supporting this combination as an additional first-line option. However, other trials have yielded more nuanced results: the LEAP-002 study of pembrolizumab plus lenvatinib did not meet its pre-specified superiority endpoint versus lenvatinib alone. The COSMIC-312 trial of cabozantinib plus atezolizumab showed improved PFS but no significant OS improvement compared to sorafenib, though subgroup analyses suggested benefit in HBV-associated HCC [27].

Sequencing Considerations: Priming Strategies

An emerging concept in HCC immunotherapy is the potential benefit of "priming" the tumor microenvironment with ICI before initiating anti-angiogenic therapy. Preclinical studies demonstrated that initial PD-1 blockade can exert angioprotective effects, reducing vascular permeability and enhancing subsequent response to MKI therapy. This phenomenon is dependent on CD8+ T cells and suggests that the order of therapy administration may affect outcomes. Clinical data support this concept: HCC patients receiving sorafenib after initial PD-1 blockade showed superior outcomes including 12% objective response rate and median OS of 12.1 months. While these findings require prospective validation, they suggest that sequencing strategies could optimize therapeutic benefit (27).

Emerging Targeted Approaches

FGFR4 Inhibitors: Targeting a Defined Molecular Subset

The FGF19-FGFR4 axis represents one of the most promising emerging therapeutic targets in HCC, given its role in driving oncogenesis in a defined molecular subset . Selective FGFR4 inhibitors, in contrast to pan-FGFR inhibitors, offer the potential for targeted efficacy while avoiding the dose-limiting hyperphosphatemia associated with FGFR1-3 inhibition [27]. Selective FGFR4 Inhibitors. Several irreversible covalent FGFR4 inhibitors have entered clinical development. BLU-9931, the first selective FGFR4 inhibitor, demonstrated potent activity in preclinical models. Subsequent agents including FGF401 and irpagratinib (ABSK-011) have advanced to clinical trials. Phase I data for irpagratinib showed an objective response rate of 43.5% in FGF19-positive HCC, increasing to 55.6% when combined with atezolizumab.

Combination Strategies. The rationale for combining FGFR4 inhibitors with MKIs or ICIs is compelling. MKIs have activity against the FGF19-FGFR4 axis, and combination with selective FGFR4 inhibitors may provide more complete pathway inhibition. Moreover, FGF19 overexpression upregulates PD-L1 in the TME, providing a mechanistic rationale for FGFR4 inhibitor–ICI combinations. Early clinical data for these combinations show encouraging activity. Biomarker Development. FGF19 serves as a potential predictive biomarker for FGFR4 inhibitor sensitivity. Approximately 20% of HCC tumors exhibit FGF19 gene amplification, with higher prevalence in certain geographic regions. Integrating FGF19 status into patient selection strategies could identify those most likely to benefit from FGFR4-directed therapy [27,28].

Epigenetic Modulators

The recognition of epigenetic dysregulation as a driver of HCC pathogenesis has spurred interest in epigenetic-targeting agents. EZH2, the catalytic subunit of the PRC2 complex that mediates histone H3K27 methylation, is frequently overexpressed in HCC and promotes proliferation, invasion, and stemness. EZH2 inhibitors

have shown preclinical activity, with potential to reverse immune evasion and synergize with ICIs. HDAC inhibitors represent another class of epigenetic modulators under investigation. By altering chromatin accessibility and gene expression, HDAC inhibitors can modulate the immune microenvironment, increase antigen presentation, and sensitize tumors to immunotherapy. However, clinical development of HDAC inhibitors in HCC has been limited by toxicity concerns and modest single-agent activity [29-31].

Novel Approaches: RNAi-Based Therapy

The recognition of FOXM1 as a master regulator of cell-state plasticity and therapeutic resistance has led to the development of novel RNA interference-based therapeutics. FOXM1 drives developmental heterogeneity in HCC, promoting therapeutic resistance through activation of drug resistance genes and immune evasion. A GalNAc-conjugated, chemically modified siRNA targeting hepatic FOXM1 has been developed and demonstrated potent antitumor efficacy with favorable tolerability in preclinical models. This approach leverages the hepatic delivery specificity of GalNAc conjugation to enable targeted gene silencing. By restoring tumor developmental homogeneity and re-exposing tumor cells to immune surveillance, FOXM1 siRNA represents an innovative strategy for overcoming therapeutic resistance [32-34].

Rationale and Mechanisms of Combination Therapy

Biological Synergy: Beyond Simple Addition

The success of combination regimens in HCC stems from their ability to exploit biological synergy at multiple levels. VEGF Inhibition and Immune Enhancement. The synergy between anti-angiogenic agents and ICIs is perhaps the best-characterized example. VEGF is a central node connecting angiogenesis and immunosuppression. VEGF inhibition reduces Treg and MDSC accumulation, normalizes the vasculature to enhance T-cell infiltration, and decreases PD-L1 expression. These effects create a more permissive immune microenvironment for checkpoint inhibition [35,36]. Multi-Node Pathway Targeting. By inhibiting multiple nodes within interconnected signaling networks, combinations can overcome compensatory pathway activation that limits monotherapy efficacy. For example, simultaneous inhibition of VEGF, MET, and AXL (as with cabozantinib) may be more effective than targeting any single pathway, particularly in tumors with redundant RTK signaling. Tumor Microenvironment Remodeling. Combinations can exert effects on diverse TME components-including tumor cells, endothelial cells, immune cells, and fibroblasts-that extend beyond the direct actions of individual agents. This broad-based TME remodeling can transform an immunosuppressive “cold” tumor into an immune-permissive “hot” phenotype [36-37].

Clinical Evidence for Synergy

The clinical data for combination regimens demonstrate compelling evidence for synergy. The OS and PFS improvements observed with atezolizumab–bevacizumab exceed what would be predicted from the sum of the individual effects of each agent. Similar synergy is observed with TKI-ICI combinations, though the degree of benefit appears to vary based on the specific agents and patient population. Subgroup analyses have revealed important insights into which patients derive most benefit. In COSMIC-312, patients with HBV etiology showed significantly greater PFS and OS improvement with cabozantinib–atezolizumab versus sorafenib (HR for OS 0.63), whereas HCV and non-viral etiologies showed less pronounced benefit. This suggests that viral etiology may influence immune contexture and response to combination immunotherapy [37].

Mechanisms of Resistance and Strategies to Overcome

Primary Resistance

A substantial proportion of HCC patients derive no benefit from first-line systemic therapy, reflecting primary resistance. Mechanisms underlying primary resistance include: Molecular Drivers. Activation of β-catenin signaling is associated with immune exclusion and resistance to ICIs. Tumors with CTNNB1 mutations exhibit reduced T-cell infiltration and decreased expression of immune-related genes, rendering them less responsive to checkpoint inhibition. Microenvironmental Barriers. The immunosuppressive TME, characterized by abundant Tregs, MDSCs, and TAMs, can prevent effective T-cell activation even in the presence of immune checkpoint inhibition. Enrichment of immunosuppressive CD14+ monocytes correlates with poor outcomes. Metabolic Barriers. Metabolic reprogramming-including dysregulated glycolysis, fatty acid oxidation, and redox homeostasis-can limit immune cell function and promote tumor survival despite therapy (38,39).

Acquired Resistance

Even patients who initially respond to therapy invariably develop acquired resistance. Mechanisms include:

Oncogenic Pathway Reactivation. Upregulation of alternative RTKs-including MET, EGFR, and FGFR-can circumvent MKI-mediated inhibition. FGF19 overexpression, for example, can drive resistance to VEGF-targeting therapies through alternative angiogenic signaling.

Immunological Evasion. Loss of antigen presentation, upregulation of alternative checkpoint molecules (e.g., LAG-3, TIM-3), and recruitment of immunosuppressive cell populations can enable immune escape. Cell-State Plasticity. Dynamic transitions between cellular states, driven by transcriptional regulators like FOXM1, enable therapy adaptation. As tumors evolve under therapeutic pressure, they may activate developmental programs that confer resistance. Epigenetic Reprogramming. Changes in chromatin state and gene expression patterns can establish therapy-resistant phenotypes that persist even after drug withdrawal [38,39].

Strategies to Overcome Resistance

Rational Combinations. Targeting multiple resistance mechanisms simultaneously-for example, combining VEGFR inhibition with MET or FGFR inhibition-can prevent pathway reactivation.

Biomarker-Guided Selection. Identifying patients most likely to respond through molecular profiling can avoid ineffective therapy. Biomarkers including FGF19 amplification, β-catenin mutation status, and immune gene expression signatures hold promise for patient stratification. Sequencing Strategies. Optimal sequencing of therapies may mitigate resistance. Data suggesting benefit from PD-1 blockade followed by MKI therapy provides one example. Sequential therapy with different agents may allow tumors to evolve away from one resistance mechanism while remaining susceptible to another. Epigenetic Reprogramming. Agents that alter the epigenetic landscape may resensitize tumors to therapy. HDAC inhibitors and EZH2 inhibitors, by reversing therapy-associated epigenetic changes, could restore therapeutic vulnerability [40].

Biomarker-Guided Patient Stratification

Predictive Biomarkers for Current Therapies

Alpha-Fetoprotein (AFP). AFP ≥400 ng/mL defines a subset of HCC patients with distinct biology and therapeutic considerations. Ramucirumab is specifically indicated for patients with elevated AFP based on the REACH-2 trial. Elevated AFP also identifies a subset that may have unique responses to TKI-ICI combinations. Molecular Subtypes. Transcriptomic subclassification identifies proliferation versus non-proliferation tumors with different sensitivities to therapies. Proliferation-class tumors may be more responsive to mTOR inhibitors and certain MKIs, whereas non-proliferation tumors may benefit from immune-based approaches. Immune Gene Signatures. Immune-related gene expression signatures can predict response to ICIs. Tumors with "hot" immune phenotypes-characterized by CD8+ T-cell infiltration, interferon signaling, and low immunosuppressive cell content-are more likely to benefit from checkpoint inhibition. Viral Etiology. HBV-associated HCC may have distinct immune contextures and responses to therapy. COSMIC-312 demonstrated that HBV patients derived significant benefit from cabozantinib–atezolizumab, whereas other etiologies did not [41,42].

Emerging Biomarkers

FGF19. As the target for FGFR4 inhibitors, FGF19 amplification serves as a direct predictive biomarker. Approximately 20% of HCC patients harbor FGF19 amplification, identifying those who may benefit from selective FGFR4 inhibition. Resistance Biomarkers. PCK1 and ALDH1A1 have been identified as biomarkers of inherent lenvatinib resistance through single-cell sequencing. These markers could identify patients unlikely to benefit from lenvatinib, enabling early switching to alternative therapies [42,43]. Microenvironment Biomarkers. CD14+ monocyte enrichment predicts poor immunotherapy outcomes. Assessment of immune cell composition could guide treatment selection, favoring alternative strategies for patients with immunosuppressive phenotypes. Cell-State Plasticity Markers. Transcriptional signatures reflecting developmental heterogeneity may identify tumors at risk of therapeutic resistance. Targeting the FOXM1/CEBPB axis in these tumors could restore sensitivity [42,44].

Integration into Clinical Practice

Biomarker-driven therapy selection remains an aspirational goal in HCC, with limited prospective validation. Challenges include:

- Sample Availability: Obtaining adequate tumor tissue for comprehensive molecular profiling can be challenging in HCC, particularly in advanced disease.
- Intra-tumor Heterogeneity: Molecular profiling of a single biopsy may not capture the full spectrum of tumor heterogeneity.
- Dynamic Changes: Biomarker status may evolve over time and with treatment, requiring repeat assessment.
- Validation: Most biomarkers require prospective validation in clinical trials before routine clinical use [44].

Future Directions and Emerging Approaches

Bispecific Antibodies and ADCs

The development of bispecific antibodies targeting two antigens simultaneously holds promise for improving therapeutic specificity and efficacy. In HCC, bispecific antibodies targeting PD-1 and other checkpoint molecules (e.g., LAG-3, TIM-3) could provide enhanced immune activation. Antibody-drug conjugates (ADCs) targeting HCC-enriched antigens-such as glypican-3 (GPC3)-offer the potential for selective delivery of cytotoxic payloads to tumor cells [44].

Adoptive Cellular Therapies

Chimeric antigen receptor (CAR)-T cell therapy, which has revolutionized the treatment of hematologic malignancies, is being explored in HCC. GPC3-targeting CAR-T cells have shown early promise, though challenges including limited T-cell persistence, tumor antigen heterogeneity, and the immunosuppressive TME remain significant barriers. TCR-engineered T cells targeting HCC-specific neoantigens represent another frontier [44].

Rational Combinations with Locoregional Therapies

The integration of systemic therapies with locoregional interventions-including transarterial chemoembolization (TACE), radioembolization, and ablation-offers opportunities for multimodal disease control. TACE, for example, induces tumor necrosis and inflammatory responses that may enhance systemic therapy efficacy by releasing tumor antigens and altering the immune microenvironment. However, ADM-driven resistance mechanisms may limit the durability of TACE responses, highlighting the need for combination strategies [44].

Personalized Combination Therapy

The ultimate goal of precision oncology is the selection of individualized therapy based on comprehensive molecular profiling. In HCC, this entails:

- Genomic and Transcriptomic Profiling: Identifying actionable mutations, amplifications, and gene expression signatures.

- Immune Profiling: Characterizing the TME composition, immune checkpoint expression, and immune gene signatures.
- Microenvironment Assessment: Evaluating vascular density, hypoxia, and fibrosis that may influence drug delivery and efficacy.
- Dynamic Monitoring: Tracking tumor evolution and resistance emergence through liquid biopsies and non-invasive imaging (44).

Challenges and Unresolved Questions

Optimal Sequencing of Therapies

With multiple effective regimens now available, determining the optimal sequence of therapies is a critical clinical challenge. Should patients receive ICI-based combinations upfront, or should MKIs be preferred in certain subsets? Does prior TKI therapy compromise or enhance subsequent ICI efficacy? Does sequencing affect resistance mechanisms and subsequent treatment options? These questions require prospective investigation [44,45].

Toxicity Management

Combination therapies inevitably increase toxicity burden. TKI-ICI combinations are associated with substantial treatment-emergent adverse events, with grade 3-4 events observed in 60-80% of patients. Dose reductions are frequent, potentially compromising efficacy. Strategies for toxicity prevention, early detection, and management are essential [45].

Patient Selection Across Liver Function

The landmark trials for combination therapy have predominantly enrolled patients with well-preserved liver function (Child-Pugh A). However, many HCC patients present with impaired liver function (Child-Pugh B or C), limiting their eligibility for evidence-based therapies. Whether combination regimens can be safely and effectively administered in patients with worse liver function is unknown, though preliminary data suggest distinct immune landscapes in this population [45].

Treatment of Non-viral HCC

The rising incidence of non-alcoholic fatty liver disease (NAFLD)-associated HCC introduces additional complexity. NAFLD-HCC exhibits distinct biology, including different mutational profiles, immune environments, and possibly differential responses to therapy. Many clinical trials have predominantly enrolled viral hepatitis patients, limiting generalizability to NAFLD-HCC. Specific studies in this growing population are urgently needed [45,46].

Economic and Access Considerations

Multitarget therapy regimens are costly, placing substantial economic burdens on healthcare systems and patients. In resource-limited settings, access to novel agents may be restricted. Ensuring equitable access while managing healthcare costs represents a significant challenge [46].

Conclusions

The therapeutic landscape of hepatocellular carcinoma has undergone a remarkable transformation, evolving from single-agent interventions to sophisticated multitarget and combination regimens that exploit biological synergy across multiple interconnected pathways. The recognition that HCC is a molecularly heterogeneous disease-characterized by redundant signaling networks, profound immunosuppression, and dynamic cellular state transitions-has established a compelling rationale for therapeutic strategies that address multiple vulnerabilities simultaneously [46]. Current standards of care, including atezolizumab–bevacizumab and durvalumab–tremelimumab, demonstrate the power of combining immune checkpoint inhibition with anti-angiogenic approaches. Multikinase inhibitors remain foundational agents, both as monotherapies and in combination with immunotherapies. Emerging targeted approaches-including selective FGFR4 inhibitors, epigenetic modulators, and RNAi-based therapeutics-promise to further expand the therapeutic armamentarium and enable more precise patient selection [47].

Yet significant challenges remain. Primary and acquired resistance limit long-term efficacy in the majority of patients. The molecular complexity of HCC, coupled with intra-tumor heterogeneity, demands comprehensive biomarker strategies to guide therapy selection and monitor response. Optimal sequencing, toxicity management, and integration with locoregional interventions represent active areas of investigation that will refine treatment paradigms [47,48].

The path forward lies in personalized medicine-the integration of molecular profiling, immune characterization, and clinical parameters to select the optimal multitarget strategy for each patient. Continued investment in translational research, biomarker discovery, and innovative clinical trial designs will be essential to realize this vision. As we deepen our understanding of HCC biology and refine our therapeutic approaches, the prospect of durable disease control and improved survival for patients with this challenging malignancy grows increasingly attainable [48].

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