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Targeted therapy for liver cancer: Current status and future directions

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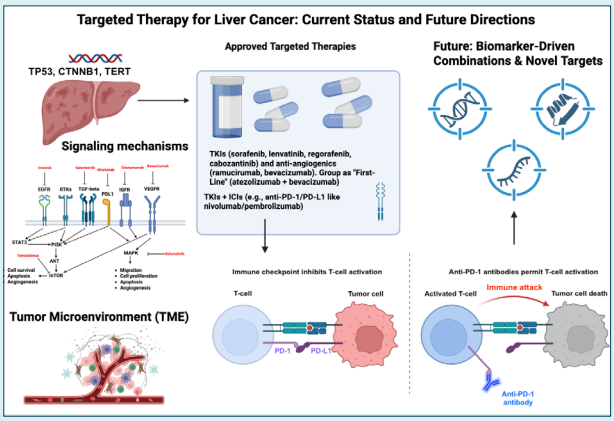
Abstract



Because of its intrinsic tumor heterogeneity, poor response to traditional chemotherapy, and lack of viable molecular targets, liver cancer mostly hepatocellular carcinoma (HCC) continues to be a major worldwide health concern. With a focus on molecular processes, resistance routes, and combination therapy approaches, this review provides a thorough analysis of the status and new advancements in targeted therapeutics for liver cancer. By blocking the mechanisms that lead to angiogenesis and tumor growth, first-line systemic treatments, such the multi-tyrosine kinase inhibitors (TKIs) lenvatinib and sorafenib, have shown moderate improvements in survival. However, their long-term efficacy is significantly reduced by intrinsic and acquired resistance, which is why second-line medications like regorafenib, cabozantinib, and ramucirumab are being studied. When combined with anti-VEGF treatments, parallel developments in immunotherapy, in particular immune checkpoint inhibitors (ICIs) such as atezolizumab and nivolumab, have shown promising outcomes. The review highlights the role of the tumor microenvironment, epigenetic regulators including EZH2 and HDACs, and key oncogenic drivers and aberrant signaling cascades in HCC, such as the Wnt/β-catenin, PI3K/AKT/mTOR, and RAS/RAF/MEK/ERK pathways. It also covers metabolic vulnerabilities, DNA damage response pathways, and new targets including FGFR4, AXL, and c-MET. To get around resistance mechanisms and improve therapeutic effectiveness, special attention is paid to logical combination treatments, which include combining targeted medicines with ICIs, irradiation, or synthetic lethality techniques. In the end, the review promotes the combination of dynamic molecular profiling and biomarker-driven precision medicine to enhance patient stratification, improve treatment decision-making, and provide long-lasting clinical effects. A strategic foundation for future advancements and individualized treatment of hepatocellular carcinoma is provided by this comprehensive synthesis.

Introduction

With an 18% 5-year survival rate, liver cancer is the fourth most prevalent cause of cancer-related mortality globally and the sixth most common kind of cancer overall.[1–3] Hepatocellular carcinoma (HCC) accounts for 90% of the cases. [4] Hepatitis B virus (HBV) infection is the major risk factor, accounting for 50% of HCC cases. [5] Hepatitis C virus (HCV) infection, long-term alcohol use, and non-alcoholic fatty liver disorders (NAFLD) are other causes.[6] Even if HBV vaccination and efficient HCV antivirals have reduced virus-related HCC, excessive alcohol use and the rising rates of obesity and diabetes in Western countries are the major causes of the overall increase in HCC incidence.[7] A complicated multistep process, the pathophysiology of HCC has a diverse mutational landscape and histological characteristics.[8–11] 80% of

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HCC cases have telomerase activation brought on by mutations or rearrangements in the TERT promoter.[9–12] The identification of important driver genes in HCC, such as TP53 (28–36%), CTNNB1 (17–37%), AXIN1 (4–14%), ARID1A (16.8%), and ARID2 (5.6%), has been made easier by next-generation sequencing. These genes are involved in controlling the cell cycle, Wnt/β-catenin signaling, and epigenetic changes.[13–15]

Nowadays, the primary cancer driver genes are still undetectable, and only 25% of individuals with HCC have at least one possible actionable mutation.[16] Unfortunately, hepatic resection and liver transplantation are the primary curative treatments for HCC since it does not respond to traditional chemotherapy.[17] Systemic treatments based on TKIs have improved treatment results for HCC since 2010. By blocking VEGFR2, sorafenib inhibits angiogenesis and the RAF-MEK-ERK signaling cascade,[18] It serves as a first-line treatment, although provides a survival advantage of about 2.8 months compared to placebo.[18] The phase 3 REFLECT study conducted in 2018 confirmed the effectiveness of lenvatinib, a TKI with enhanced inhibition of VEGF receptors and the FGFR family, revealing a small increase in median overall survival compared to sorafenib (13.6 vs. 12.3 months).[19] Some TKIs (regorafenib) are second-line treatments for advanced HCC[20] and cabozantinib[21]) and ramucirumab, a monoclonal antibody specific for VEGFR2[22], It has shown a particular advantage for individuals with elevated AFP serum levels after sorafenib's failure (REACH trial).[22]

Since 2017, novel treatments that target the microenvironment of liver tumors have surfaced. The FDA approved pembrolizumab and nivolumab, two PD-1-targeting immune checkpoint inhibitors (ICIs), as second-line treatments for advanced HCC; nevertheless, their overall survival benefits were not as great as those of sorafenib.[23,24] As a second-line treatment for advanced HCC, the FDA has authorized the combination of nivolumab and ipilimumab, a monoclonal antibody targeting CTLA-4.[25] Atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) were approved by the FDA in 2020 as a first-line treatment for advanced HCC after the phase 3 IMBRAVE-150 trial (NCT03434379) demonstrated better efficacy than sorafenib, with a median progression-free survival of 6.8 months as opposed to 4.3 months.[26] Even with these encouraging developments, only 20–30% of HCC patients benefit with immunotherapy, and there are still no trustworthy biomarkers to detect responders with certainty.[25,27] Ultimately, in order to create novel combination medicines that may inhibit tumor development and overcome immunotherapy resistance, a deeper understanding of the liver cancer microenvironment is needed. Finding response and resistance indicators is also crucial for improving patient selection and facilitating individualized treatment plans. An extensive examination of both established and new targeted treatments for liver cancer, including HCC, is provided in this study. It looks at resistance routes, important molecular factors, and new treatment approaches, including as combination regimens. In order to direct future efforts to improve clinical outcomes in the care of liver cancer, emphasis is put on translational advancements and the potential of precision medicine. The comprehensive workflow of liver cancer therapy was showed in Fig. 1.

Molecular pathogenesis of liver cancer

Genetic and epigenetic drivers (e.g., TP53, CTNNB1, TERT)

The development and spread of liver cancer are influenced by a complex interaction of environmental, genetic, and epigenetic variables. Genetic changes such point mutations, gene amplifications, promoter region modifications, and copy number variations often brought on by viral infections or long-term hepatotoxic insults are what drive hepatocarcinogenesis. Hepatocytes undergo metamorphosis as a result of these alterations, and HCC is often associated with abnormalities in important oncogenes and tumor suppressor genes.[9,28] Notably, frequent genetic changes in genes such CTNNB1, TERT, CDKN2A, SMARCA2, and HGF are linked to alcohol-related HCC. As one of the most frequent genetic events in liver cancer, TERT promoter mutations that result in telomerase reactivation are especially common among these, occurring in around 60% of cases.[29,30] Mutations in CTNNB1, which encodes β-catenin, and TP53, a crucial tumor suppressor, are often seen in HCC and are essential in interfering with apoptosis, cell cycle regulation, and Wnt/β-catenin signaling, which promotes unregulated proliferation and survival. These mutations establish different molecular subgroups of HCC and are usually mutually exclusive. Large, well-differentiated, cholestatic tumors with microtrabecular or pseudoglandular architecture and little inflammatory infiltrates are often seen in CTNNB1-mutant tumors. On the other hand, tumors with TP53 mutations are often poorly differentiated, compact, multinucleated, pleomorphic, and have a high rate of vascular invasion.[29] The development of liver cancer is also influenced by epigenetic changes, such as modifications to histones, DNA, and RNA.[31] While worldwide DNA hypomethylation may activate oncogenes and aid in the development of tumors, abnormal methylation of tumor suppressor gene promoters silences their production. Furthermore, by altering the chromatin architecture, histone modifications including methylation, phosphorylation, acetylation, ubiquitylation, and sumoylation control the expression of genes. Acetylation and methylation are two of them that have a special impact on chromatin remodeling and gene transcription regulation.[32] Gene expression in NAFLD and NASH is impacted by enzyme changes in histone

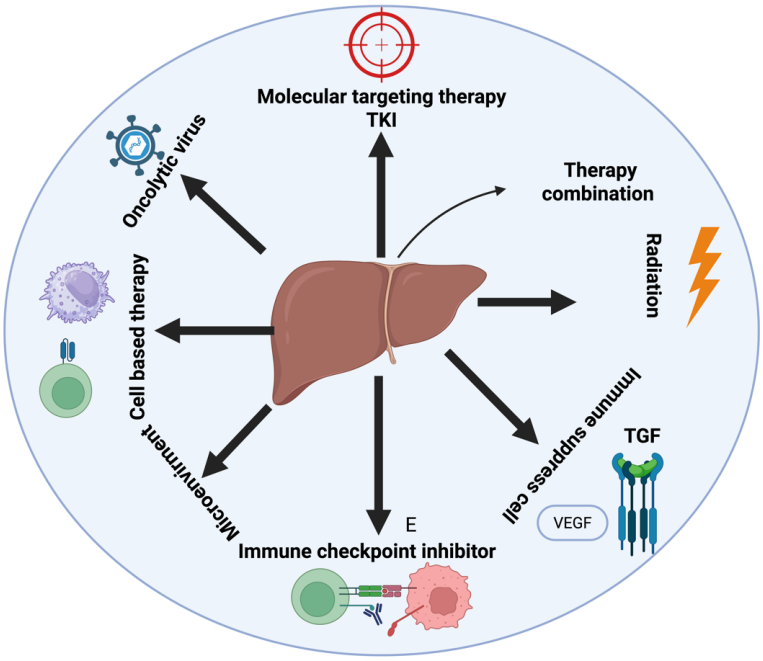

Fig. 1. Comprehensive therapeutic strategies for liver cancer. This figure illustrates a range of current and emerging therapeutic strategies for liver cancer, highlighting approaches that target both the tumor and its surrounding microenvironment. Key treatments include molecular targeting therapies such as TKIs, which block cancer-driving signaling pathways, and immune checkpoint inhibitors that restore T-cell function by blocking inhibitory pathways like PD-1/PD-L1. Additional strategies involve targeting immune suppressive cells to overcome tumor-induced immunosuppression, and radiation therapy to directly destroy cancer cells. Therapies aimed at modulating the tumor microenvironment, including inhibition of TGF-β and VEGF, are also shown to support anti-tumor immunity. Oncolytic virus therapy leverages viruses engineered to selectively infect and kill cancer cells, while cell-based therapies use immune cells like CAR-T or NK cells to directly target the tumor. The integration of these treatments through combination therapies is emphasized as a promising approach to enhance effectiveness and overcome therapeutic resistance in liver cancer.

acetylation and methylation, which may cause apoptosis, impaired hepatic metabolism, and an elevated risk of HCC. Genes are regulated by these epigenetic changes without changing the DNA sequence.

Signaling mechanisms that are aberrant

Wnt/β-catenin

During HCC formation, the Wnt/β-catenin cascade is crucial. Wnt ligands signal cell surface Frizzled receptors.[33,34] Genetic mutations or Wnt pathway dysregulation may accelerate HCC development. A protein complex consisting of GSK-3β, APC, and Axin phosphorylates β-catenin, causing proteasome degradation in the absence of Wnt ligands. GSK-3β activity is inhibited by Wnt ligands binding to Frizzled receptors, preventing β-catenin degradation.[34,35] This hinders β-catenin degradation and phosphorylation. Wnt activation causes it to enter the nucleus from the cytoplasm. This is made easier by APC and Axin destruction complex disruption. By binding to T-cell factor/lymphoid enhancer factor (TCF/LEF), stabilized β-catenin activates Wnt target gene transcription in the nucleus.[36] The β-catenin/TCF-LEF complex regulates gene expression crucial for cell survival, differentiation, and proliferation. In HCC, dysregulation of the Wnt/β-catenin pathway leads to unregulated activation of genes that promote angiogenesis, prevent apoptosis, and promote proliferation.

PI3K/AKT/mTOR

HCC development requires the signaling cascade of PI3K, Akt, and mTOR.[37] When IGF and EGF bind to their cell surface receptors, PI3K is activated. Activated PI3K phosphorylates PIP2 into PIP3.[38] PIP3 recruits and activates Akt as a second messenger. Akt is phosphorylated by PDK1 and mTORC2 after binding PIP3. Akt-induced TSC2 phosphorylation and inhibition activates mTORC1. Through phosphorylation of downstream effectors including p70S6K and 4E-BP1, mTORC1 regulates protein synthesis, metabolism, and cell proliferation.[39,40] These downstream effectors boost protein synthesis and cell division. PI3K/Akt/mTOR pathway dysregulation in HCC causes angiogenesis, metabolic reprogramming, uncontrolled cell proliferation, apoptosis resistance, and extended mTORC1 activation (Fig. 2).[41]

RAS/RAF/MEK/ERK

The RAS/RAF/MEK/ERK pathway affects cellular activities include differentiation, apoptosis, proliferation, and stress response. Its aberrant activation helps colon cancer, HCC, leukemia, and melanoma develop and advance.[42–47] External stimuli activate RAS proteins, small GTPases. Activated RAS causes RAF dimerization and activation in the RAS/RAF/MEK/ERK cascade. RAF phosphorylates MEK, which activates ERK, propagating the signal downstream.[48] P-ERK, the active form of

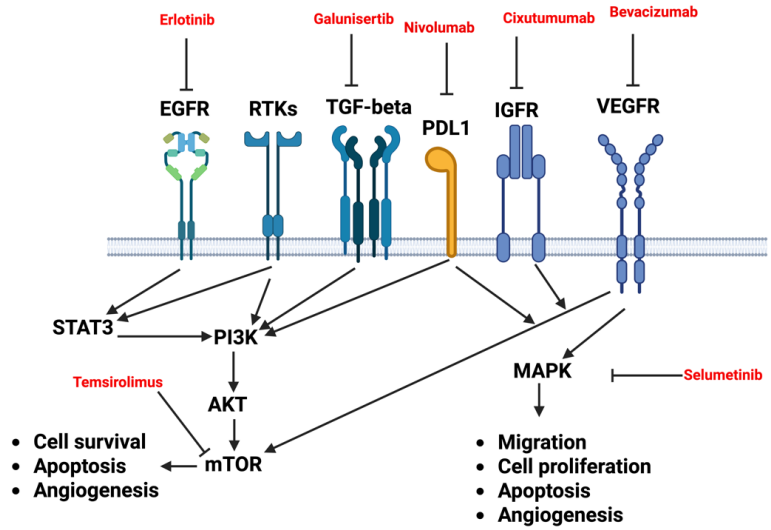

Fig. 2. In the management of unresectable hepatocellular carcinoma (HCC), several molecular targets have been identified for therapeutic intervention. Erlotinib exerts its antitumor effects by blocking epidermal growth factor receptor (EGFR) activity, which subsequently disrupts downstream signaling pathways, notably the STAT, PI3K/Akt, and mTOR axes, ultimately suppressing key oncogenic processes. Galunisertib, an inhibitor of the transforming growth factor-beta receptor (TGFβR), similarly impedes tumor progression by attenuating the PI3K/Akt/mTOR signaling cascade. Immune checkpoint modulation is achieved through agents such as nivolumab, which targets programmed death-ligand 1 (PD-L1), while cixutumumab and bevacizumab selectively inhibit the insulin-like growth factor receptor (IGFR) and vascular endothelial growth factor receptor (VEGFR), respectively. These agents disrupt tumor-promoting signals predominantly via the MAPK pathway. Additionally, temsirolimus and selumetinib act as direct inhibitors of mTOR and MAPK, respectively, offering targeted suppression of proliferative and survival mechanisms in recurrent HCC.

ERK, is a critical indicator of RAS/RAF/MEK/ERK signaling.[49] Around 30% of cancers are caused by RAS gene mutations, which overactivate RAS.[50–53] It has been widely proven that aberrant activation of this route in HCC tissues causes HCC, malignant transformation, and treatment resistance.[53,54] However, RAS mutations are rare and found in less than 5% of HCC patients, despite extensive signaling activity.[55]

JAK/STAT

Signal transduction via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway begins when cytokines, hormones, or growth factors bind to cell surface receptors.[33,56] When ligands interact with receptor-associated Janus kinases (JAKs), STAT3 and STAT5 tyrosine residues are phosphorylated. After phosphorylation, STATs form homo- or heterodimers in the nucleus. STAT dimers connect to STAT response elements (SREs) in target gene promoter regions to initiate transcription in the nucleus.[57,58] STAT binding to DNA controls targets gene transcription. Activated STATs govern cell differentiation, migration, apoptosis, and proliferation. JAK/STAT pathway dysregulation in HCC may cause uncontrollable cell proliferation and tumor growth. To prevent overactivation, STATs induce SSI-1 and SOCS1 synthesis. These negative regulators inhibit signaling by binding to phosphorylated JAKs and receptors.[59]

TGF-β

By downregulating pro-proliferative transcription factors such c-Myc, TGF-β promotes cell cycle arrest in HCC. The suppression is caused by the nuclear translocation of Smad3, E2F4 or E2F5, and RB-related protein p107. These elements halt c-Myc synthesis and the cell cycle.[60–62] Additionally, it modulates CDK inhibitors, which arrests G1.[63] To start the cell cycle, CDK2 binds to cyclin E and CDK4 or CDK6 to cyclin D.[64] TGF-β reduces the inhibitory effects of c-Myc on CDK inhibitors p21CIP1 and p15INK4B, leading to cell cycle arrest.[65–68] Rising ROS and Nox4 levels in well-differentiated HCC cells lead to increased p21CIP1 and p15INK4B expression, which is induced by TGF-β.[69] In addition to G1 phase arrest, TGF-β promotes G2 phase arrest in HCC-cells via activating Wee1 kinase and CDK inhibitors p21CIP1 and p27KIP.[70]

Tumor microenvironment (immune cells, angiogenesis, fibrosis)

Additionally, cancer cells depress the immune system in the tumor microenvironment (TME), especially when they interfere with T cell activity. One important immunomodulator, prostaglandin E2 (PGE2), influences T cells among other immune cells. Its release triggers the cyclooxygenase (COX) pathway, which has been linked to resistance to immunotherapy.[71,72] When β-catenin signaling is triggered in cancer cells, the accumulation of conventional DC1 is inhibited.[73] Furthermore, kynurenine, which is generated in excess by IDO1, tryptophan 2,3-dioxygenase, and adenosine, which comes from dead tumor cells, are immunosuppressive metabolites released by cancer cells. These metabolites alter the TME, as does the loss of essential amino acids needed for T cell activity. Together, they reduce anti-tumor immunity and help

malignancies evade the immune system.[74] By encouraging the development of regulatory T cells (Tregs), preventing the growth of stem-like memory T cells, and inducing a stromal response that keeps T cells out of the tumor microenvironment, TGF-β, which is generated by cancer cells, reduces anti-tumor immunity.[75–78] Notably, cancer cells have an independent defensive system that allows them to quickly fix membrane holes created by the deadly chemical perforin, which is produced by T cells. This defense mechanism shields the cancer cells from being killed by T cells.[79]

Tissue-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), and Tregs are among the immune and stromal cell subsets that influence immune evasion in the TME of HCC. Among these, CAFs are essential because they promote carcinogenesis in healthy epithelial cells and modify the extracellular matrix (ECM), especially collagen fibers. CAFs can provide tumor cells characteristics of stroma that increase their aggressiveness. They may circulate throughout the body and are derived from vascular cells, cancer cells, or activated mesenchymal stem cells in the bone marrow.

Human solid tumors have three main types of CAFs: antigen-presenting, inflammatory, and myofibroblastic CAFs.[80] Myofibroblastic CAFs release fibrosis-associated chemicals and ECM components that promote angiogenesis and tumor invasion. In the tumor microenvironment, they also inhibit CD8 T cells and other immune effector cells, which aids in immune evasion.[81–83] C-C motif chemokine ligand 2 (CCL2), CCL12, and IL-6 are secreted by inflammatory CAFs, which may have immunosuppressive effects.[84,85] Treg cell mobilization is triggered by antigen-presenting CAFs that express immune regulatory factors and MHC class II molecules.[86]

CAFs are essential for the TME, which can be used to slow the development of HCC and liver fibrosis and might be a novel target for treatment.[87,88] As a byproduct, CAF-produced IDO and PGE2 inhibit natural killer (NK) cells' production of TNF-α and IFN-γ, reducing their antitumor activity and promoting the growth of HCC.[87–89] Hepatic fibroblasts may be stimulated to release pro-inflammatory cytokines by bone morphogenetic protein 4 (BMP4) in HCC, which would improve their penetration into the tumor microenvironment. As a result, BMP4 plays a crucial role in controlling CAF activity and promotes tumor growth in HCC (Table 1).[89]

Current landscape of targeted therapies

Approved therapies

Tyrosine kinase inhibitors

TKIs are crucial for the treatment of advanced HCC, especially in individuals who cannot receive liver transplantation or surgery. TKIs provide a practical and efficient method of halting the course of the illness when taken orally as systemic treatments.

Dysregulated intracellular signaling, especially from the cell surface inward, is the primary driver of important events in HCC, including tumor cell proliferation, metabolism, angiogenesis, and metastasis. Growth factors and the receptor tyrosine kinases (RTKs) that correspond to them, such as fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), hepatocyte growth factor receptor (HGFR/MET), platelet-derived growth factor receptor (PDGFR), and epidermal growth factor receptor (EGFR), mediate this signaling.[100] Intracellular signaling cascades, namely the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways, are initiated when these receptors are activated by their corresponding growth factors. By encouraging cell division, survival, angiogenesis, and metastasis in HCC, these cascades drive tumor growth.[100]

TKIs are crucial for treating HCC because they block these pathways, which stops tumor development, angiogenesis, and metastasis.[101] This multi-targeted approach disrupts many signaling pathways that are necessary for the development and spread of tumors. TKIs have been shown in clinical studies to increase overall survival in patients with advanced HCC. VEGFR1-3, PDGFRβ, KIT, RET, FLT3, and downstream kinases RAF1 and BRAF are among the targets that are inhibited by sorafenib, the first licensed systemic treatment for HCC to show a survival benefit. [102] The therapeutic advantage of sorafenib in advanced HCC was shown by the phase III SHARP study, which had 602 patients with the disease and demonstrated a substantial improvement in median overall survival of 2.8 months when compared to placebo.[18,103] Sorafenib's effectiveness in treating advanced HCC in a variety of populations was further supported by the phase III ASIA-PACIFIC research, which included 226 HCC patients from the Asia-Pacific area and validated the survival advantages shown in the SHARP trial.[104] There was no statistically significant difference in overall survival between lenvatinib and sorafenib in the REFLECT trial, a randomized, open-label phase III research that included 1,492 HCC patients. However, lenvatinib was approved as a first-line therapy for advanced HCC since it demonstrated a higher progression-free survival.[105] Lenvatinib targets VEGFR1-3, PDGFRα/β, FGFR1-4, KIT, and RET and differs greatly from sorafenib in that it does not include the fluorine atoms that sorafenib does.[102] With the advent of more recent TKIs like as cabozantinib and regorafenib, the options for second-line treatment for advanced HCC have expanded, providing other approaches in the event that first-line therapy fails. Similar in structure to sorafenib, regorafenib has one extra fluorine atom, which increases its capacity to inhibit a greater variety of molecular targets implicated in the development of

Table 1. Important molecular pathways, elements, and their functions, benefits, and difficulties in the etiology and management of hepatocellular carcinoma

Pathway/Factor	Key components	Description	Function in HCC	Advantages	Challenges	References
Genetic drivers	TP53, CTNNB1, TERT, CDKN2A, SMARCA2, HGF	Tumor start and subtype development are driven by genetic changes in important oncogenes and tumor suppressor genes.	Modify survival, apoptosis, and the cell cycle; identify molecular subtypes	enables the possibility of targeted treatment and molecular categorization.	Tumor heterogeneity and several mutations remain undiagnosed.	9,90,91
Epigenetic alterations	Histone changes (acetylation, methylation), and DNA methylation	Epigenetic modifications impact tumor suppressor and oncogene activity by controlling gene expression without changing the DNA sequence.	Mute tumor suppressor genes, turn on carcinogens, and alter metabolism	reversible changes that epigenetic medications may target.	epigenetic plasticity, off-target toxicity, and global impacts.	92,93
Wnt/β-catenin	Frizzled, Wnt ligands, GSK-3β, APC, β-catenin, TCF/LEF	Abnormal activation of this canonical pathway, which is important in liver development, promotes immune evasion and proliferation.	Encourage resistance, angiogenesis, and proliferation via nuclear β-catenin	β-catenin inhibitors may target this subtype of HCC, which is immune-cold.	Complex regulation; direct inhibition of β-catenin is difficult.	94
PI3K/AKT/mTOR	PI3K, AKT, mTORC1/2, PIP2, PIP3, TSC2, 4E-BP1, p70S6K	Often dysregulated in HCC, this system is essential for metabolism, cell proliferation, and survival.	Promote resistance, protein synthesis, angiogenesis, and cell proliferation	mTOR inhibitors have a strong promise for treatment and are now in use.	development of resistance and impact on systemic metabolism.	95
RAS/RAF/MEK/ERK	RAS, RAF, MEK, ERK, LZTR1, CRL3 E3 ligase	LZTR1 regulates RAS activity by ubiquitination; the MAPK pathway is implicated in stress response and proliferation.	Drug resistance and proliferation are stimulated by ubiquitination via LZTR1.	Modulation of LZTR1 provides a new treatment strategy.	Uncertain regulatory mechanisms and a low mutation frequency.	96
JAK/STAT	JAKs, STAT3, STAT5, SOCS1, SSI-1	Overactivation of cytokine-mediated signaling accelerates the growth of tumors and regulates immune response and proliferation.	control immune signaling and proliferation; cancer is encouraged by dysregulation.	Drugs that block the JAK/STAT pathway are being developed.	Off-target effects are caused by broad immune functions.	97,98
TGF-β	Smad3, E2F4/5, p107, CDK2, CDK4/6, p21CIP1, p15INK4B, p27KIP1, Wee1	complex modulator of apoptosis, differentiation, and cell cycle arrest; dual function in tumor development and repression.	induce G1/G2 arrest, control transcription factors and CDKs, and encourage tumor suppression	TGF-β inhibitors have the ability to alter fibrosis and immunological responses.	Targeting is made more difficult by its dual function in tumor development and repression.	60
Tumor microenvironment	CAFs, TAMs, TANs, MDSCs, Tregs, PGE2, IDO1, adenosine, TGF-β	Tumor growth and immune escape are shaped by the intricate interactions of immune cells, fibroblasts, cytokines, and metabolic products.	alter fibrosis, angiogenesis, and immune evasion; CAFs and cytokines encourage the formation of tumors.	TME may be reshaped and immunological function restored by targeting CAFs or cytokines.	Extremely patient-specific and dynamic; difficult to successfully moderate.	99

tumors.[106] Cabozantinib is a dual inhibitor of VEGFR2 and the HGFR/MET, and it has a different chemical structure than sorafenib. It also targets RET, KIT, TIE2/TEK, and AXL, among other important receptors implicated in tumor development and angiogenesis.[107] Compared to traditional chemotherapy, new-generation TKIs often have better side-effect profiles, enhancing patient tolerance, adherence, and general quality of life. Their incorporation into treatment plans is still developing, especially when combined with immunotherapies, which have shown improved therapeutic effectiveness via mutually reinforcing processes. TKIs are being included to personalized medicine frameworks more often as our understanding of the pathophysiology of HCC grows. In order to provide more individualized and efficient treatments, ongoing biomarker research attempts to determine which individuals are most likely to benefit from certain TKIs. Altogether, TKIs have revolutionized the way that HCC is treated by providing strong therapeutic alternatives for a condition that is often discovered at an advanced stage. Their relevance in HCC treatment is only increasing because to their multi-targeted action and their involvement in combination therapies.

Anti-angiogenic agents

HCC is distinguished by its abundant vascularization. Antiangiogenic treatments are essential for managing the disease's severe stages. In 2007, sorafenib, an oral multikinase inhibitor that targets angiogenic pathways and RAS/RAF signaling, was authorized as the first therapy for advanced HCC worldwide. After demonstrating that

lenvatinib was not inferior to sorafenib in terms of overall survival in 2018, the European Medicines Agency (EMA) and the U.S. FDA approved it. ICIs have revolutionized the treatment of HCC and other cancers. For unresectable HCC, the standard of therapy now consists of bevacizumab, a monoclonal antibody that targets VEGF, and atezolizumab, a PD-L1 inhibitor. This change was brought about by the successful results of the IMbrave150 research and the FDA's subsequent approval of this treatment strategy.[26,108,109] Nevertheless, even while phase 3 trials of single-agent therapy in first- and second-line settings showed response rates of 15–20%,[24,25] as first-line monotherapies for patients with HCC, single-agent PD-1 inhibitors like pembrolizumab and nivolumab have not yet shown a discernible increase in overall survival. For HCC patients who did not react to sorafenib, regorafenib was the first authorized treatment in the second-line scenario. An oral multikinase inhibitor called cabotinib, which targets the MET, AXL, RET, FLT3, and VEGF receptors, was also authorized for use in patients who had previously had sorafenib treatment. Furthermore, the FDA expedited the approval of nivolumab and pembrolizumab and nivolumab plus ipilimumab (a CTLA-4 inhibitor) for patients with advanced HCC who had previously been exposed to sorafenib.[110,111] The FDA-approved was shown in Fig. 3.

A human IgG monoclonal antibody called Ramucirumab targets the extracellular domain of VEGFR-2. It has anticancer effects by preventing VEGFR-2 from binding to its major ligand, VEGF-A, which affects downstream signaling pathways and suppresses endothelial cell migration and proliferation.[112–118] When compared to a placebo, ramucirumab did not substantially increase overall survival, according to the REACH trial, the first randomized, double-blind, placebo-controlled phase 3 research assessing second-line therapy after sorafenib.[119] Ramucirumab had significant effectiveness in individuals with alpha-fetoprotein (AFP) levels higher than 400 ng/mL, according to a subgroup analysis of the REACH study. In light of these results, the REACH-2 study was carried out to compare ramucirumab with a placebo, particularly in patients who had advanced HCC and AFP levels more than 400 ng/mL after receiving sorafenib therapy.[22,120] Ramucirumab was adopted as a routine second-line treatment in this subgroup after the REACH-2 study showed that it gave patients with advanced HCC and increased AFP levels a survival benefit over placebo. Uncertainty surrounds the biological basis for the association between better ramucirumab outcomes and higher baseline AFP levels. AFP-high tumors may be more sensitive to VEGFR-2 inhibition because of increased VEGF signaling pathway activation and overexpression of VEGFB and placental growth factor (PGF), according to Robert et al.[121] Increased activation of VEGFR1 and decreased availability of VEGFR1 for VEGFA binding may result from overexpression of VEGFB and PGF in AFP-high tumors. By rerouting VEGFA to preferentially bind VEGFR2, this competitive displacement may improve VEGFR2-mediated signaling. This has led to the hypothesis that ramucirumab may reverse this change in AFP-high HCC by inhibiting VEGFR2, which would disrupt the enhanced VEGFA signaling cascade and provide a potential reason for its effectiveness in this patient subgroup. Ramucirumab is used as a follow-up therapy after other authorized regimens and after sorafenib in clinical settings when numerous systemic treatments are available for advanced HCC. In patients with advanced HCC, there is, however, little data on the clinical effectiveness and results of ramucirumab when administered after systemic treatments other than sorafenib.

FGFR inhibitors

HCC is one of many malignancies that have been shown to have changes in the fibroblast growth factor (FGF)/FGFR signaling axis, which is categorized under class IV receptors. The growth and spread of tumors are facilitated

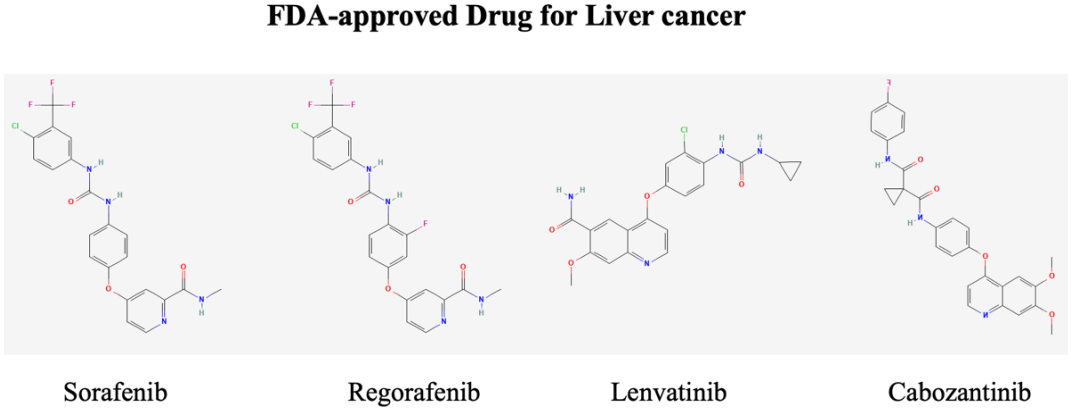

Fig. 3. FDA-approved drugs for liver cancer. This figure presents the chemical structures of four FDA-approved targeted therapies used in the treatment of liver cancer: Sorafenib, Regorafenib, Lenvatinib, and Cabozantinib. These agents are multi-kinase inhibitors that block various signaling pathways involved in tumor growth, angiogenesis, and metastasis. Their approval has significantly advanced systemic therapy options for hepatocellular carcinoma (HCC), offering improved survival outcomes for patients with advanced disease.

by the deregulation of this pathway, which is essential for controlling cell division, proliferation, and survival.[122,123] In fact, research has shown that at least one FGF8 subfamily member and/or one FGFR are upregulated in around 82% of HCC patients, suggesting that the FGF/FGFR signaling axis is often activated in hepatocarcinogenesis.[124]

While FGFR1 and FGFR2 are seldom elevated, FGFR3 and FGFR4 are the main fibroblast growth factor receptors that are overexpressed in HCC. Notably, for a number of years, FGFR3 isoforms have been suggested as attractive therapeutic targets for HCC, underscoring their potential use in focused therapy approaches.[125,126] Recently, FGFR4 was shown to represent an oncogenic driving pathway for patients with HCC,[127] furthermore validated by proteomic analysis.[128]

Along with FGF8, FGF17, and FGF18, FGF2 a soluble ligand that is normally undetectable in nonparenchymal cells or healthy liver tissue is markedly overexpressed in HCC. The genesis and progression of liver cancer are significantly influenced by FGF19 in particular. In HCC, members of the FGF1 subfamily are known to stimulate angiogenesis, invasiveness, and tumor cell proliferation mainly via autocrine signaling. Crucially, chronic liver disease also exhibits FGF1 and FGF2 expression, with greater levels corresponding to more advanced tumor stages.[129–132] The most researched of the FGFs is FGF2, and FGFR3 seems to have the most role in the development of HCC.[133,134] As mentioned earlier, an anti-FGF2 diabody has demonstrated promise as a treatment by preventing immunological evasion and metastasis. It showed promise in addressing important mechanisms of HCC progression by suppressing both anti-PD-L1 expression and the epithelial mesenchymal transition (EMT) in hepatoma cells.[135]

The primary binding sites of FGF8, FGF17, and FGF18 within the FGF8 subfamily are FGFR2, FGFR3, and FGFR4, respectively. The tumor progresses as a result of these ligands' active promotion of angiogenesis, malignancy, and cell proliferation in HCC via paracrine signaling.[124] Interestingly, FGF8 contributes to EGFR inhibitor resistance.[136]

On the other hand, it has been shown that the FGF19–FGFR4–KLB signaling axis plays a major factor in the development and spread of HCC. It is essential for controlling hepatocellular carcinoma cells' motility, invasion, EMT, survival, and proliferation.[129,137–144]

The main member of the FGF19 subfamily associated with liver cancer is FGF19, which is an endocrine hormone. Although the liver does not normally produce FGF19 under normal physiological settings, cirrhosis, hepatocellular carcinoma, and hepatitis C have all been linked to increased production of this protein.[129,145] Larger tumor sizes, more advanced disease stages, and early recurrence are also strongly associated with the protein level overexpression of FGF19 in HCC tissues.[129,146,147]

Many inhibitors that target the FGF/FGFR signaling pathway have been developed because of its crucial role in the development and progression of HCC. These include more recent, more selective FGFR4 inhibitors and early broad-spectrum pan-FGFR inhibitors, some of which are now undergoing Phase I/II clinical studies (NCT04194801 and NCT02508467).

Resistance mechanisms

Primary vs. acquired resistance

Drug resistance in the treatment of HCC is often divided into two categories: acquired and primary. Primary resistance is difficult to overcome since it occurs before treatment is started and is often an inherent feature of the tumor. On the other hand, acquired resistance develops gradually over the course of therapy and is a significant management problem for advanced HCC as it reduces the long-term efficacy of systemic medicines.[148,149] A focus of this study is the processes behind acquired resistance in HCC. Inhibition of apoptosis, dysregulated proliferation signaling pathways, altered drug transport, epigenetic modifications, changes in the TME, disruptions in drug metabolism, and enhanced DNA repair capacity are some of the contributing factors that have been identified by studies on sorafenib resistance.[150,151] Nevertheless, little is known about the major processes and molecular targets underlying lenvatinib resistance in HCC. Since lenvatinib was just recently introduced, there are currently no trustworthy indicators to predict therapy response, and no particular drugs have been created to combat resistance. This restriction prevents lenvatinib from reaching its full clinical potential as a systemic treatment for HCC. In order to improve therapy effectiveness, it is essential to look into the underlying processes of lenvatinib resistance and find new therapeutic targets.

Tumor heterogeneity

The presence of several cell subpopulations inside a single tumor or between tumors of the same histological type is referred to as tumor heterogeneity. These cell groupings have different phenotypic characteristics and genetic compositions, which may lead to different biological activities and treatment reactions.[152–154] Inter-tumoral heterogeneity, which describes variations across tumors from various people or between discrete tumor nodules within the same patient, is one way that tumor heterogeneity might appear at the population level. It may also manifest as intratumoral heterogeneity, in which a single tumor nodule contains a variety of cellular subpopulations,[155] Moreover, etiological heterogeneity refers to variations in cellular and molecular characteristics among HCCs originating from various causes for instance, tumors resulting from hepatitis virus infection may differ significantly from those associated with alcohol consumption. Finally, tumor heterogeneity can also occur over time and space, known as spatiotemporal

heterogeneity, where the tumor's characteristics change before and after treatment or across different tumor regions.[156,157] HCC is characterized by heterogeneity, which results in a variety of cellular, molecular, functional, and lineage characteristics. It is believed to result from a confluence of environmental factors and patient genetic variation. This variability is caused by a variety of factors, including as epigenetic changes, interactions within the TME, cancer cell development and reprogramming, genomic abnormalities, and the conversion of non-cancerous cells into malignant ones. These elements work together to drive clonal development, which gives the tumor its genetic, molecular, and functional variety.[158–160] The clinical difficulties of HCC are exacerbated by its complicated and multifactorial development, which also plays a major role in treatment resistance, tumor dormancy, and recurrence after first therapy. This variation makes therapeutic reactions more difficult and emphasizes the need for more individualized and flexible treatment plans.

EMT and cancer stem cell involvement

A network of transcription factors drives the EMT, which starts significant alterations in the structure and function of cells. Cells lose intercellular adhesion, epithelial polarity decreases, the cytoskeleton is rearranged, and basement membranes degrade during EMT and its opposite process, mesenchymal–epithelial transition (MET). EMT-associated transcription factors (EMT-TFs), which control gene expression to support the mesenchymal state, are essential to these changes. Depending on how they interact with elements of the signaling pathway, some EMT-TFs may change from being transcriptional repressors to activators. Mesenchymal–epithelial transition transcription factors (MET-TFs), on the other hand, support the maintenance of epithelial traits in both healthy and malignant cells. By inhibiting mesenchymal gene expression and establishing reciprocal inhibitory feedback loops with EMT-TFs, they preserve the equilibrium between mesenchymal and epithelial states.[161–165] A number of MET-TFs, including CDH1, ZO-1, and the genes encoding claudin-4 and claudin-5 (CLDN4 and CLDN5), actively stimulate the transcription of genes that produce proteins essential to epithelial lineage determination in addition to their regulatory roles. By directly promoting the expression of the structural and functional elements of epithelial cells, these substances aid in the reinforcement of epithelial identity.[166,167]

The complexity of the cellular transitions involved in EMT and MET is shown by these coordinated molecular events, underscoring the need of a thorough understanding of these processes in both healthy and pathological settings. EMT is mostly regulated by basic helix-loop-helix (bHLH) proteins including ZEB1 and ZEB2, as well as important transcription factors like Snail1 and Snail2 (also called Slug). Twist is another important participant that plays a major role in the activation and maintenance of the mesenchymal phenotype during EMT,[168,169] lymphoid enhancer binding factor 1 (LEF-1) may directly stimulate this member of the T cell factor (TCF) family.[170] In order to suppress the production of genes involved in cell-cell adhesion, such those producing E-cadherin, these transcription factors bind to their promoter regions. One of the main beginning events in the EMT process that propels the loss of epithelial qualities and the acquisition of mesenchymal traits is this targeted transcriptional repression. The exact control of EMT is largely dependent on the Snail family of transcriptional repressors. To inhibit the transcription of the CDH1 gene, Snail1 and Snail2 attach to its promoter region. E-cadherin, a crucial protein essential in maintaining epithelial cell–cell interaction, is encoded by CDH1, and its downregulation is a defining feature in the start of EMT.[171,172] Breast cancer phenotypes that are prone to metastases have been associated with nuclear accumulation of Snail1 and decreased expression of E-cadherin. This change is a result of increased EMT activity, which raises the invasiveness of the tumor and increases its potential for distant dissemination.[173] A strong correlation between Snail1 overexpression and the potential for metastasis has been suggested by the discovery that circulating tumor cells from patients with metastatic HCC express Snail1 at levels up to 20 times higher than those seen in patients with nonmetastatic HCC (Table 2).[173]

Emerging molecular targets

Novel RTKs and non-RTKs

c-MET, AXL, EGFR inhibitors

The most common primary liver cancer, HCC, varies significantly in both phenotype and molecular makeup. The critical roles that RTKs and non-RTKs play in promoting carcinogenic signaling pathways in HCC have been brought to light by developments in cancer genetics. Notably, because of their substantial role in tumor growth and potential for clinical intervention, c-MET, AXL, and EGFR have become important therapeutic targets.[184]

Hepatocyte growth factor (HGF) receptor c-MET is often overexpressed or aberrantly activated in a portion of HCC patients. Its dysregulation is linked to increased angiogenesis, aggressive tumor features, and treatment resistance. The proliferation, migration, and survival of tumor cells are enhanced by the activation of the HGF/c-MET signaling axis, which sets off downstream pathways including PI3K/AKT and RAS/MAPK.[185] Clinical studies have shown promising outcomes for targeted inhibition of c-MET with small-molecule inhibitors such as tivantinib, cabozantinib, and tepotinib, particularly in patients with elevated c-MET expression. Of them, cabozantinib has been approved to treat advanced HCC in individuals who have already had sorafenib therapy.[186]

Table 2. Detailed description of the causes, effectiveness, drawbacks, clinical state, and molecular precision techniques of targeted therapy for HCC

Therapy class	Description	Mechanism of action	Efficacy	Limitations & challenges	Clinical/ experimental status	References
TKI – Sorafenib	multikinase inhibitor that targets the pathways involved in tumor growth and angiogenesis.	PDGFR-β, RAF, KIT, RET, FLT3, VEGFR1-3, and others are excluded.	OS improved by 2.8 months during the SHARP trial.	Resistance, little advantage, frequent negative consequences	Approved (1st-line)	174–176
TKI – Lenvatinib	TKI that is multi-targeted and has more action than sorafenib.	VEGFR1-3, FGFR1-4, PDGFRα, KIT, and RET targets	REFLECT trial: superior PFS; not inferior to sorafenib	Lack of biomarkers, hypertension, and selective advantage	Approved (1st-line)	177,178
TKI – Regorafenib	utilized as a second-line therapy; structurally similar to sorafenib.	More extensive kinase inhibition compared to sorafenib	OS improved by 2.8 months after using sorafenib in the RESORCE study.	Only after using sorafenib, toxicity	Approved (2nd-line)	179
TKI – Cabozantinib	broad-spectrum dual MET and VEGFR2 inhibitor.	Inhibits MET, VEGFR2, RET, KIT, TIE2, AXL	Trial CELESTIAL: enhanced OS and PFS	High toxicity and consequences that are not intended	Approved (2nd-line)	180
Anti-VEGFR2 – Ramucirumab	In AFP-high HCC, a monoclonal antibody that blocks VEGFR-2 works well.	inhibits VEGFA-mediated angiogenesis by binding VEGFR-2.	REACH-2 is useful for patients whose AFP is more than 400 ng/mL.	Efficacy restricted to those with elevated AFP	Approved (AFP-high, 2nd-line)	181
ICI + Anti-VEGF – Atezolizumab + Bevacizumab	In advanced HCC, immunotherapy with anti-angiogenic medication is the first-line treatment.	Combination PD-L1 inhibitor and VEGF-A inhibitor	Better OS and PFS than Sorafenib with IMbrave150	Not appropriate for those who are at risk of bleeding	Approved (1st-line)	182
FGFR4 Inhibitors – FGF401, etc.	In HCC, experimental treatments inhibit FGF19–FGFR4 signaling.	targets the FGFR4-KLB-FGF19 axis, which is implicated in metastasis and proliferation.	FGF19-overexpressing HCC shows potential in phase I/II studies.	Resistance, toxicity, and restricted patient selection	Experimental (Phase I/II)	183

As a member of the TAM (TYRO3, AXL, MER) receptor tyrosine kinase family, AXL is essential for immunological escape, metastasis, EMT, and resistance to systemic therapy. Poor clinical outcomes and a reduced response to immune checkpoint medications are associated with elevated AXL expression in HCC. Therapeutic drugs like gilteritinib and bemcentinib are now being studied in conjunction with immunotherapies and targeted treatments to boost antitumor effectiveness and overcome drug resistance in order to counteract these effects.[187]

A fraction of HCC patients has EGFR dysregulation, which activates important signaling pathways such PI3K/AKT and RAS/RAF/MEK/ERK, hence promoting tumor development. In order to improve therapeutic outcomes, especially in patient groups defined by biomarkers, current research is investigating combination strategies, such as pairing EGFR blockade with ICIs or anti-angiogenic agents, even though EGFR inhibitors like erlotinib and gefitinib have demonstrated limited efficacy as monotherapies.[188]

In conclusion, there is a lot of therapeutic promise for HCC when c-MET, AXL, and EGFR are targeted. However, precision medicine techniques are necessary to properly achieve therapeutic advantages. These include the creation of logical combination therapy targeted at targeting tumor heterogeneity and overcoming resistance mechanisms, rigorous biomarker validation, and efficient patient classification.[184,186,188]

Dual/multikinase inhibitors

As of right now, the primary molecularly targeted treatment for advanced HCC is still sorafenib (Nexavar), a multikinase inhibitor that targets RAF serine/threonine kinases, VEGFR1-3, PDGFRβ, and elements of the RAS/RAF/MEK/ERK signaling cascade. An important turning point in the systemic treatment of HCC was reached in 2007 when a crucial clinical research revealed its survival advantage.[104,189] Sorafenib has been the accepted first-line systemic treatment for advanced HCC in individuals with maintained liver function ever since it was approved. However, the development of drug resistance, frequent treatment cessation owing to side effects, and a brief duration of response restrict its therapeutic value. Many attempts over the last ten years to find strong second-line treatments after sorafenib failure or create better first-line substitutes have mostly failed.[190] Regulatory bodies in Europe and Asia authorized lenvatinib (Lenvima), a multikinase inhibitor that targets VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT, as an alternate first-line treatment for patients with incurable HCC in 2018. The results of a multicenter, open-label, randomized phase 3 study (NCT01761266) that contrasted lenvatinib with sorafenib served as the basis for its approval. According to the trial, lenvatinib had a better safety profile and markedly

increased time to progression (TTP), progression-free survival (PFS), and overall response rate. Nonetheless, lenvatinib's overall survival (OS) was similar to that of sorafenib.[105] A structurally unique multikinase inhibitor, regorafenib (Stivarga) targets a variety of kinases linked to cancer. These include oncogenic receptor tyrosine kinases like KIT, RET, and RAF; stromal kinases like PDGFRβ and FGFR; and angiogenic kinases like VEGFR1-3 and TIE-2. Regorafenib's broad range of action enables it to disrupt many pathways implicated in the development, angiogenesis, and progression of tumors,[191,192] was authorized by the US FDA in April 2017 as a backup treatment for individuals who don't react to sorafenib therapy in the first place.[20] Another second-line multikinase inhibitor, cabotinib, targets RET, MET, AXL, KIT, and VEGFR1-3. In January 2019, the US FDA authorized it for use in HCC patients who have already been treated with sorafenib. The findings of a worldwide, randomized, placebo-controlled phase 3 study (NCT01908426) that showed clinical improvement in patients with unresectable HCC who had received one or two previous lines of treatment, including sorafenib, provided support for its approval.[21] As multikinase inhibitors, sorafenib, regorafenib, lenvatinib, and cabozantinib all work by inhibiting important protein kinases implicated in tumor angiogenesis (VEGFRs), oncogenic signaling (RAS, RAF, KIT, and RET), and metastasis PDGFR. Of them, regorafenib has a more favorable side effect profile and higher cytotoxic efficacy. It is not advised for people who are intolerant to sorafenib, nevertheless, because of its pharmacological resemblance to the drug[190]; for cabozantinib, dose reduction is a frequent concern.[193] Therefore, treating patients with HCC who do not respond to current multikinase inhibitors or who relapse after these treatments is dependent on the development of tailored medicines with new mechanisms of action. These developments may help close existing treatment gaps and enhance results for this difficult patient population.

In contrast to conventional HCC treatments like sorafenib, regorafenib, and lenvatinib, researchers have created a new dual FMS-like tyrosine kinase 3 (FLT3)/Aurora kinase (AURK) multikinase inhibitor, DBPR114 (also known as BPR1K871). DBPR114 specifically targets oncogenic receptor kinases such as FLT3, AURK, KIT, and RET, while other medicines mainly target angiogenic pathways VEGFRs and the RAS/RAF/MEK/ERK cascade. DBPR114 was first created to treat FLT3 internal tandem duplication (ITD)-positive acute myeloid leukemia (AML) and FLT3 wild-type AML. Its target specificity was demonstrated by the strong growth inhibition it showed in FLT3-mutant AML cells and the low activity it displayed in FLT3-negative leukemia cell lines.[194] Ten times less DBPR114 was needed to provide half-maximal growth inhibition (IC50) in FLT3-expressing AML cells than the well-known AURK inhibitors VX680 and barasertib, suggesting that DBPR114 is far more effective at targeting these leukemia cells.[194] In addition to its effectiveness in AML, DBPR114 has shown broad-spectrum anticancer action against a variety of solid tumor types, such as uterine sarcoma and malignancies of the colon, stomach, lung, and pancreas. DBPR114 shown its promise as a multipurpose anticancer drug by drastically reducing tumor volume in preclinical xenograft models, especially in colon and pancreatic malignancies.[194] Through mechanistic studies with HCT-116 colon cancer cells and MV4-11 leukemia cells, it was shown that DBPR114 efficiently regulates intracellular targets FLT3 and AURKA/B. Multinucleated cells accumulated after DBPR114 treatment, indicating a disruption of the mitotic checkpoint, mostly due to suppression of AURKB. This mitotic failure identifies a crucial mechanism via which DBPR114 inhibits cell division.[194] We looked at the possibility of using DBPR114 as a multikinase inhibitor to treat advanced HCC as a result of these results. We used six human HCC cell lines that closely resemble the genetic and histological features of actual HCC tumors in order to evaluate its therapeutic effectiveness. In order to find pharmacodynamic biomarkers that may be used as measures of target engagement and medication response, the effects of DBPR114 were examined at the cellular and molecular levels.[195]

HER2 in cholangiocarcinoma

HCC remains the primary focus of targeted therapy research in liver cancers, intrahepatic cholangiocarcinoma (ICC) represents another important entity with distinct molecular features. Among them, HER2 amplification and overexpression have emerged as actionable alterations in a subset of ICC patients. DNA-based sequencing was performed on 283 of the 304 ICC samples that were examined. There were 271 control samples in this cohort that did not have HER2 amplification and 12 samples that did. Single-nucleotide variations, minor insertions or deletions (InDels), frameshift mutations, splice site modifications, and multi-hit mutations were among the mutations that were categorized as either somatic synonymous or non-synonymous. The five genes with the highest frequency of mutations in the HER2-amplified group were TP53 (50%), TERT (42%), ATM (33%), NPM1 (24%), and NF1 (21%). The mutational landscape of the non-HER2 amplified group, on the other hand, was different; the most frequently changed genes were TP53 (34%), KRAS (25%), ARID1A (14%), NPM1 (13%), and PBRM1 (12%).[196] The mutation load was considerably lower in the non-HER2-amplified group than in the HER2-amplified group ($p = 0.03854$). Based on the findings of next-generation sequencing, we simultaneously analyzed samples from several HER2 IHC categories. Interestingly, the different HER2 IHC groups did not significantly vary in terms of total mutation load or mutational patterns.[196] Two of the 304 ICC samples that were examined had

mismatch repair (MMR) defects; they were both in the HER2 non-amplified group and both showed contemporaneous loss of MLH1 and PMS2 expression. The HER2-amplified group had a decreased prevalence of MMR changes, according to further analysis of mRNA expression for four MMR proteins and a comparison of mutation status in important MMR-related genes (MLH1, MLH3, MSH3, MSH6, PMS1, and PMS2). Remarkably, only one of the twelve HER2-amplified samples had an MSH6 mutation. Three HER2 point mutations were also found in the 283 analyzed samples by second-generation sequencing: HER2 p.S310F, p.R678Q, and p.Q711H.[196] ERBB2 amplification or overexpression occurs in a modest but meaningful subset of cholangiocarcinoma cases approximately 5 % in intrahepatic CCA and up to ~18–20 % in extrahepatic disease highlighting its potential as a therapeutic vulnerability.[197] Retrospective analyses indicate that responses to HER2-targeted therapies in CCA have generally been limited; for instance, trastuzumab-based treatments showed no objective responses in small cholangiocarcinoma cohorts, despite efficacy in gallbladder cancers (Tables S1, S2).[198,199] Prospective trials, however, are reshaping this narrative. Dual HER2 blockade with pertuzumab and trastuzumab achieved an objective response rate (ORR) of ~23 % in advanced biliary tract cancers, while the bispecific antibody zanidatamab (Ziihera) produced ORRs of ~40–52 % in later-phase studies with FDA accelerated approval in November 2024 for previously treated HER2-positive biliary tract cancer.[200,201] Additionally, the antibody–drug conjugate trastuzumab-deruxtecan (T-DxD) achieved ORRs around 36 % and robust disease control in phase II BTC cohorts.[199] In contrast, HER2 alterations are exceedingly rare in HCC, and HER2-targeted therapies have not been a focus in HCC treatment paradigms. Thus, HER2-positive CCA represents a distinct molecular subgroup amenable to precision therapy and underscores the heterogeneity between liver tumor types, with HER2 serving as a clinically impactful target in CCA but not in HCC. In comparison with HCC, where HER2 alterations are rare and not a major therapeutic focus, HER2 amplification in ICC highlights the heterogeneity of liver cancers and the need for subtype-specific targeted approaches. Thus, HER2-positive ICC represents a small but clinically relevant group of patients who may benefit from precision medicine strategies, making HER2 an emerging and distinct therapeutic target in cholangiocarcinoma.

Epigenetic targets

EZH2, HDACs, DNA methyltransferases

Methylation, phosphorylation, ubiquitination, and acetylation are the main conventional HPTMs linked to HCC.[202,203] Acetylation and methylation are two examples of histone post-translational modifications (HPTMs) that affect chromatin structure by controlling compaction and influencing the recruitment of transcription factors and chromatin remodeling complexes. HPTMs have direct influence on gene transcription via these methods. In addition to being crucial for the development and spread of tumors, they are also involved in key physiological functions including gene expression, DNA replication, and repair. One of the main epigenetic changes in cancer is the aberrant methylation of CpG islands, which compacts chromatin in promoter areas and causes transcriptional silence of genes.[204–206] Methyl-binding proteins (MBPs) like MeCP2 are drawn to CpG islands inside promoter regions when methyl groups are added by DNA methyltransferases (DNMTs). By acting as molecular "bridges," these MBPs draw histone methyltransferases (HMTs) and deacetylases (HDACs) to the location. While HMTs add restrictive methylation marks, such H3K9me3, which cause chromatin condensation, HDACs remove acetyl groups from histones. Gene expression is silenced by this densely packed chromatin structure, which prevents transcription factors from entering.[207] For example, when the p16 promoter region is hypermethylated, its gene expression is silenced, which hinders its vital role in controlling the cell cycle. Unchecked cell growth is made easier by this absence of regulation. These epigenetic modifications may serve as early indicators of the development of cancer as they often appear in the early phases of carcinogenesis and may also be seen in precancerous lesions.[208] Similarly, the cell's capacity to repair alkylated DNA lesions is reduced when the DNA repair gene MGMT (O6-methylguanine-DNA methyltransferase) is silenced. Because of the increased genomic instability brought on by this decline in DNA repair capabilities, mutations may flourish and cancer can be encouraged.[209–211]

Treatment for HCC may benefit from therapeutic strategies that target epigenetic changes. By preventing HDAC activity, HDAC inhibitors like panobinostat and belinostat may restore the expression of suppressed tumor suppressor genes, which in turn prevents angiogenesis and cell proliferation in HCC. Furthermore, by inhibiting EZH2 activity, GSK126, a histone methyltransferase inhibitor, lowers the restrictive H3K27me3 histone marks. By encouraging death in tumor cells and boosting immune cells' capacity to cause cytotoxicity, this reactivation of tumor suppressor gene expression improves anticancer responses.[212–215]

Role of non-coding RNAs (e.g., miRNAs, lncRNAs)

The enzymatic breakdown of double-stranded RNA is essential to the maturation and decay of RNA molecules.[215,216] MicroRNAs are single-stranded, tiny RNA molecules that are spontaneously produced by living organisms. They consist of around 22 nucleotides.[217] The miRBase database now contains 1,492 human miRNA sequences. miRNAs are essential for the post-

transcriptional control of gene expression, despite the fact that they do not have coding domains. They have a role in vital biological processes and have been linked to the development and spread of a number of illnesses, including cancer.[218] Within the nucleus, RNA polymerase II normally transcribes the miRNA gene, producing a main transcript called pri-miRNA. One or more hairpin structures that will subsequently be processed into mature miRNAs are present in this initial transcript, which typically has a length of one to four kilobases.[219] Monocistronic transcripts are those that express a single mature miRNA due to the presence of a single miRNA gene downstream of a promoter. In contrast, a single parent transcript that encodes many miRNA gene products gathered together is the source of polycistronic transcripts, such the miR-17-92 cluster. This makes it possible for many functionally related miRNAs to express themselves in unison from a single promoter.[220] About half of miRNA genes, sometimes referred to as intragenic miRNAs or mirtrons, are found in the introns of host genes that code for proteins and are believed to be co-regulated with the transcription of their host genes. MiRNAs present in intergenic areas, on the other hand, are probably transcribed separately, indicating that they operate as separate transcriptional units with unique regulatory factors.[221] Depending on where miRNAs are located in the genome, the percentage of regulatory alterations varies greatly. The main miRNA transcript (pri-miRNA) is processed into a shorter hairpin shape called precursor miRNA (pre-miRNA) in the nucleus by the microprocessor complex, which is made up of the DiGeorge syndrome critical region gene 8 (DGCR8) protein and the nuclease Drosha. Exportin-5 then carries this pre-miRNA, which is around 70 nucleotides long, to the cytoplasm. The pre-miRNA is converted into a mature miRNA–miRNA duplex of around 18–25 nucleotides by the enzyme Dicer once it is in the cytoplasm. This duplex is then ready to be incorporated into the RNA-induced silencing complex (RISC) to control gene expression.[222]

miRNAs have a dual role in carcinogenesis by interacting with a variety of molecular components in cancer and acting as both oncogenes and tumor suppressors. For instance, it has been shown that miR-429 slows the growth of endometrial cancer. By controlling the expression of DDX53, a gene linked to the advancement of cancer, it partially suppresses tumors and increases tumor cells' susceptibility to anticancer medications.[223] Overexpression of miR-21 and miR-125b is thought to be a biomarker for ovarian cancer. Furthermore, platinum resistance in ovarian cancer is caused by downregulation of miR-125b.[224] Another factor preventing cervical tumors is miR-1299. Cervical cancer has low expression of miR-1299, which is inhibited by KCNQ1OT1.[225] In thyroid cancer, miR-1284 suppresses tumor growth and spread while promoting apoptosis. By downregulating N-cadherin, a mesenchymal marker linked to enhanced cell mobility and invasiveness, and upregulating E-cadherin, a crucial epithelial marker that improves cell–cell adhesion, it suppresses the EMT.[226] More crucially, miRNAs may create feedback loops with their targets. For example, in breast tumors, the loop between PAX5 and miR-142 can change the expression levels of ZEB1 and DNMT1.[227] MiR-1290 and miR-29c-3p plasma levels are indicators for lung cancer.[228] Additionally, miR-629 inhibits LATS2 to promote prostate tumor development.[229] Because exosomes may transport miRNAs, they can also control the expression of miRNAs in human malignancies.[230] MiR-1180's downregulation of FXYD5 may prevent pancreatic tumor migration and metastasis.[231]

In human malignancies, long non-coding RNAs (lncRNAs) interact with a variety of molecular targets and impact important cellular functions. For example, it has been shown that lncRNA LITATS1 inhibits the EMT and encourages the breakdown of TβRI (TGF-β receptor I), which lowers the plasticity of cancer cells and restricts their ability to spread.[232] Another element that has been shown to slow the growth of breast cancer is LncRNA MIR17HG, which increases FAM135A levels by sponging miR-454-3p.[233] Like miRNAs, lncRNAs are primary regulators of miRNAs in cancer and may be concentrated in exosomes.[234] LINC01614 modulates the SLC31A1 gene, which has been implicated as a regulator of cuproptosis in breast tumors.[235] An adverse prognosis is mediated by the increased expression of HOTAIR in breast tumors, which interacts with miR-129-5p.[236] Thus, in human malignancies, including ovarian tumors, lncRNAs interact with a number of biological pathways.[237,238]

Metabolic pathways

Glutamine metabolism

A nonessential amino acid called glutamine is essential to the metabolism of HCC. It supports the fast development and multiplication of tumor cells by acting as a nitrogen donor for the production of nucleotides and amino acids and as a vital carbon source for anaplerosis, which replenishes intermediates in the tricarboxylic acid cycle.[239–241] It also makes a substantial contribution to other biosynthetic processes, such as lipid synthesis and the creation of anti-ROS glutathione/NADPH.[242] Notably, the overexpression of important transporters and enzymes that promote greater glutamine uptake and use is indicative of dysregulated glutamine metabolism in HCC. Overexpression of transporters like SLC38A1 and SLC1A5 (also called ASCT2) encourages the import of glutamine into cancer cells. Furthermore, increased amounts of glutaminase isoforms GLS1 and GLS2 contribute to the TCA cycle by promoting the conversion of glutamine into glutamate, which is then converted into alpha-ketoglutarate (α-KG).[243,244] Compared to GLS2, the isoform that is mostly expressed in normal hepatocytes,

GLS1 overexpression is especially noticeable in HCC. Glutaminases start the two-step deamination process that turns glutamine into α-KG. This metabolic change in glutaminolysis, which is often brought on by MYC activation, is linked to the development of tumors and has significant effects on patient outcomes, underscoring its potential as a target for therapy.[245,246]

The Wnt/β-catenin signaling system controls glutamine synthetase (GS), an essential enzyme in glutamine metabolism. Both a potential biomarker and a therapeutic target, elevated GS expression is connected to increased cell proliferation in HCC and has been related to a variety of prognostic outcomes, depending on the tumor environment. [247,248] In fact, new research points to a multifaceted function for GS in HCC, perhaps connected to tumor behavior and cellular differentiation.[249–251] Additionally, a number of downstream signaling pathways, most notably mTORC1, are impacted by the dysregulation of glutamine metabolism [252,253] and mTORC2–AKT–C-MYC,[254] The overexpression of GS and other changes in glutamine metabolism have a major impact on cellular bioenergetics and are linked to carcinogenic processes in HCC. These metabolic pathways are further modulated by the HGF signaling axis, underscoring the intricate interaction between growth factor signaling and metabolic reprogramming that propels the development of cancer.[255]

Lipid metabolism and fatty acid synthase

Stearoyl-CoA desaturase (SCD), fatty acid synthase (FASN), and arboxylase (ACC) are all changed in HCC.[256,257] FASN, for instance, has been connected to the development of tumors in HCC. It has been shown that FASN loss postpones the formation of tumors, a phenomenon linked to elevated sterol regulatory element-binding protein (SREBP) activity. Genes involved in cholesterol production and de novo lipogenesis (DNL) are upregulated as a result of this increased SREBP activity, indicating a compensatory metabolic response that might affect tumor behavior.[258] It has been shown that by inhibiting the NAD^+/Sirtuin 1 (SIRT1) signaling pathway, mitochondrial fission activation in HCC cells increases the acetylation of sterol regulatory element-binding protein 1 (SREBP1). Key enzymes involved in DNL, including as FASN, ACC, and elongation of very long chain fatty acid protein 6 (ELOVL6), are upregulated as a result of this increased acetylation, which stabilizes and activates SREBP1. These alterations promote the development and spread of tumors by causing lipid buildup and metabolic reprogramming.[259] The USP7/ZNF638 axis, which is linked to ubiquitination, selectively increases SREBP1c cleavage and activation as HCC advances. Important lipogenic enzymes such ACC, FASN, and SCD are upregulated as a result of this activation, which supports tumor growth and encourages lipid production.[260] Notably, fatty acid synthesis-related long non-coding RNA (FASRL), which is generated by upstream stimulatory factor 1 (USF1), interacts with ACC. In the end, this binding exacerbates the development of HCC by increasing fatty acid production and encouraging lipid buildup.[261] Furthermore, it has been shown that inhibiting ubiquitin-specific protease 22 (USP22) lowers HCC growth and suppresses de novo fatty acid production. ACC and ATP citrate lyase (ACLY), two important lipogenic enzymes, are downregulated as a result of the expression of peroxisome proliferator-activated receptor (PPAR), a transcription factor that controls lipid metabolism.[262] In HCC, ACLY, a strong modulator of Wnt/β-catenin signaling, is also crucial for controlling the stemness and metastasis of liver tumor-initiating cells.[263] According to lipidomic investigations, stearoyl-CoA desaturase 1 (SCD1) mediates the alterations in the lipid composition of HCC cells in response to matrix stiffness. Membrane fluidity is impacted by the ratio of monounsaturated fatty acids (MUFA) to saturated fatty acids (SFA), which is influenced by SCD1 expression. Increased cellular motility is made possible by this change in membrane characteristics, which also increases the invasive and metastatic potential of HCC cells.[264]

Hypoxia and HIF-1α signaling

The activation of pro-tumor signaling pathways and oncogenes is closely linked to the overexpression of important glycolytic enzymes in HCC cells. In HCC, hypoxia-inducible factor 1α (HIF-1α) plays a key role in controlling glycolysis, especially in hypoxic environments. It promotes greater glucose absorption and glycolytic flux to support tumor growth and survival by increasing the transcription of many glycolytic enzymes, most notably glucose transporter 1 (GLUT1) and hexokinase 2 (HK2).[265,266] One important transcription factor that helps cells adjust to hypoxic environments is HIF-1α, which is also crucial for controlling glycolysis in TAMs. Research has shown that pyruvate kinase M2 (PKM2) is phosphorylated during lipopolysaccharide (LPS) stimulation, which promotes the development of a nuclear PKM2/HIF-1α complex. In the HCC microenvironment, this complex interacts to the HIF-1α promoter, increasing its expression and boosting glycolytic activity in TAMs.[267] It is essential to block the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway since it is involved in the development of tumors and the advancement of cancer.[268] By controlling GLUT4 and HK2, the PI3K/Akt/mTOR signaling pathway, which is important for tumor growth, has also been linked to encouraging glycolysis in HCC cells.[269,270]

DNA damage response (DDR) targets

PARP inhibitors

DNA repair, damage tolerance, and cell-cycle checkpoint control are among the several processes that make up the DNA damage response (DDR) system. In the end,

this complex mechanism promotes cell survival by ensuring precise DNA replication and cell proliferation. The DDR pathway is essential for maintaining genomic integrity because it fixes different types of DNA damage. Chromosome fragmentation and gene loss may result from strand breaks brought on by nucleotide changes, single-strand breaks (SSBs), or double-strand breaks (DSBs). Reactive oxygen species (ROS), ionizing radiation, mechanical stress, and broken DNA replication forks are the main causes of DNA double-strand breaks.[271] The enzymes of the poly (ADP-ribose) polymerase (PARP) family, particularly PARP-1 and PARP-2, are crucial elements of the DDR. Their main responsibility is to identify SSBs and start the repair process. The recruitment and assembly of DNA repair complexes is facilitated by PARP enzymes, which swiftly relocate to the break sites and catalyze the attachment of ADP-ribose polymers to other proteins and themselves.

PARP-1 is essential for both the idea of synthetic lethality and the repair of DNA damage. DNA lesions like DSBs and SSBs trigger different repair pathways. DSBs are repaired by homologous recombination repair (HRR), while SSBs are repaired by base excision repair (BER). Cells turn to non-homologous end joining (NHEJ), an error-prone repair pathway that often causes genomic instability and cell death, when both BER and HRR are impaired, a state known as BRCAness. DNA-PKcs for the backup alternative end joining (ALT-EJ) and conventional NHEJ (C-NHEJ) pathways are important proteins in these processes. Targeting PARP-1, PARP inhibitors (PARPi) take advantage of flaws in cancers with low HR. PARP-1's activity depends on its functional domains, including the DNA binding domain (DBD) and automodification domain (AD). ROS, DNA repair proteins such as XRCC1, PALB2 (a BRCA2 partner), and RAD51 recombinase are additional significant players. Enzymes like TIP60, ATM, ATR, and checkpoint kinase 1 (CHEK1) also control cell cycle checkpoints and DNA damage signaling. While less precise than HRR, single strand annealing (SSA) also aids in DSB repair. Collectively, these mechanisms preserve the integrity of the genome, and their malfunction may be used therapeutically to create synthetic lethality, which kills cancer cells.[272]

ATR/CHK1 inhibitors in combination with TKIs

Significant heterogeneity and genetic instability are hallmarks of HCC, which often develops in the context of viral hepatitis infections, chronic inflammatory conditions, or liver metabolic dysfunctions. Because of the increased oxidative stress and ongoing DNA damage caused by these pathological circumstances, cancer cells are forced to rely significantly on DDR mechanisms in order to survive. The ATR (ataxia telangiectasia and Rad3-related) and CHK1 (checkpoint kinase 1) signaling axis are essential for these responses because they reduce replication stress, protect genomic integrity, and coordinate cell cycle checkpoints and DNA repair mechanisms. This increased dependence on ATR/CHK1 signaling is a major therapeutic weakness in HCC, especially in tumors with TP53 mutations. In order to sustain survival in the face of genomic insults, these mutations impair the G1/S checkpoint, causing the cancer cells to primarily depend on the ATR and CHK1 pathways to regulate cell cycle progression through the S and G2/M phases.[273] Critical cell cycle checkpoints are disrupted by inhibitors that target ATR and CHK1, which causes unrepaired DNA damage to accumulate, replication forks to collapse, and eventually apoptosis. However, the intrinsic variety of malignancies often limits their efficacy as stand-alone therapy. As a treatment strategy, combining ATR or CHK1 inhibitors with TKIs as lenvatinib or sorafenib has showed potential. TKIs increase replication stress and DNA damage while suppressing angiogenesis and signaling pathways that are critical for tumor development, such as RAF/MEK/ERK and PI3K/AKT. Increased cytotoxicity and tumor cell death are the results of this combination's dual attack on tumor cells, which overwhelms their DNA repair systems.[274,275]

TKIs and ATR inhibitors, such as berzosertib, have been shown in preclinical research to work in concert, as shown by increased levels of DNA damage markers like γH2AX, decreased cellular proliferation, and improved tumor growth suppression. Additionally, it has been shown that prexasertib and other inhibitors that target CHK1 enhance the therapeutic benefits of TKIs, particularly in hepatocellular carcinoma models that lack functional p53.[276] This strategy concurrently targets several oncogenic stress pathways, offering a viable path toward the development of more potent, biomarker-guided treatments for HCC. To evaluate the safety, tolerability, and effectiveness of various combination medicines, clinical research is now being conducted (Table 3).[277]

Combination strategies

Targeted therapy + immunotherapy

In order to overcome the drawbacks of single-agent treatments and improve patient outcomes, the combination of targeted therapy and immunotherapy has emerged as a novel approach to the treatment of HCC. Notably, one of the most successful strategies is the combination of TKIs and ICIs, which has shown promising outcomes in both clinical trials and laboratory studies.[301,302] By suppressing pathways including VEGFR, PDGFR, and other growth factors, TKIs, such as lenvatinib and sorafenib, mainly prevent tumor development by preventing angiogenesis and cell proliferation. TKIs have important immunomodulatory effects in addition to their direct anti-cancer activities. They aid in the normalization of the aberrant blood vessels in the TME, which promotes increased immune cell infiltration, especially cytotoxic $CD8^+$ T cells, while

Table 3. Describe the causes, benefits, difficulties, and current clinical status of new molecular targets and treatment drugs in HCC

Target / Pathway	Therapeutic agents	Description	Mechanism	Advantages	Challenges	Clinical/ experimental status	Ref.
c-MET	Tivantinib, Cabozantinib, Tepotinib	blocks angiogenesis and tumor development by targeting HGF/c-MET signaling.	inhibits MAPK and PI3K/AKT via c-MET	Cabotanzantinib is an authorized drug that is effective in c-MET-high malignancies.	Patient stratification is necessary because to resistance.	Others are in clinical studies; cabotanzantinib has been authorized.	278,279
AXL	Bemcentinib, Gilteritinib	targets the AXL receptor to prevent EMT and immune escape.	inhibits signals mediated by TAM receptors	Possible cooperation with immunotherapies	Limited as a monotherapy; requires confirmation of biomarkers	Clinical trials ongoing	280,281
EGFR	Erlotinib, Gefitinib	inhibits the proliferation and survival signals triggered by EGFR.	suppresses PI3K/AKT, RAS/ RAF/MEK/ERK	Combination tactics seem promising.	Ineffective monotherapy in individuals who were not chosen	Investigative in combination regimens	282,283
HER2 (ICC)	Trastuzumab (HER2 + ICC)	targets the subpopulation of HER2-amplified cholangiocarcinoma.	suppresses HER2 signaling	Individualized treatment for HER2 + ICC	Low rate of HER2 amplification; potential for resistance	Investigative; ICC HER2 screening	284
Multikinase Inhibitors	Sorafenib, Lenvatinib, Regorafenib, Cabozantinib	Block many kinases involved in metastasis, proliferation, and angiogenesis.	Inhibits VEGFRs, FGFRs, PDGFR, KIT, RET	Several approvals and a wider range of activities	adverse effects and agent cross-toxicity	All approved for HCC	285,286
FLT3/AURK (DBPR114)	DBPR114	A novel dual inhibitor created for AML is now being evaluated for solid tumors, such as HCC.	Inhibits FLT3, AURKA/B, KIT, RET	Strong preclinical activity and a distinct mechanism	Still in the early stages of development	Preclinical validation in HCC	287
EZH2	GSK126	restores tumor suppressor genes that have been silenced by inhibiting histone methylation.	targets H3K27me3 via inhibiting EZH2.	stimulates the immunological system and apoptosis	Effects that are not intended; intricacy of epigenetics	Preclinical and early clinical studies	288
HDACs	Panobinostat, Belinostat	HDAC inhibition prevents angiogenesis and reverses gene silencing.	reverses the deacetylation of histones	inhibits growth and increases immunological destruction	Cytotoxicity in healthy tissues; wide-ranging impact	Clinical stage	289,290
DNMTs	Decitabine, Azacitidine	inhibits DNA methylation to reactivate tumor suppressor genes that have been silenced.	Prevents DNMT-induced methylation of CpG	enhances the regulation of genomic expression	Systemic toxicity; requires the use of combinations	Clinical trials in solid tumors	291
miRNAs / lncRNAs	miR-21, miR-125b, HOTAIR (targeted via antisense approaches)	Drug resistance, apoptosis, metastasis, and gene expression are all influenced by non-coding RNAs.	mRNA post-transcriptional control	Antisense oligo targets; possibility for diagnosis	Delivery difficulties and issues with specificity	Experimental	292,293
Glutamine Metabolism	GLS1/2 inhibitors, GS modulators	Target the glutamine metabolism-dependent biosynthesis and tumor energy pathways.	inhibits the production of glutathione and α-KG	targets HCC's metabolic susceptibility	Typical tissue damage; metabolic adjustment	Preclinical models	294,295
Lipid Metabolism	FASN, ACC, SCD inhibitors	blocks the fatty acid production pathways that are essential for the development and spread of tumors.	interferes with membrane lipid remodeling and DNL	slows the growth of tumors and reverses EMT	Adaptation to tumors and off-target metabolic changes	Investigational drugs	256
HIF-1α / Hypoxia	PX-478, Digoxin	interferes with glycolysis and signaling brought on by hypoxia in the tumor microenvironment	prevents the induction of GLUT1, HK2, and VEGF	decreases glycolysis and angiogenesis	compensating for hypoxia; limited opportunity for treatment	Early trials ongoing	296,297
PARP (DDR)	Olaparib, Niraparib	prevents PARP enzymes from repairing DNA in cancers with BRCA mutations or HR deficiencies.	creates artificial lethality	Effective in cancers that have "BRCAness" or HR-deficient	Variable DDR state in HCC	Early clinical trials	298,299
ATR / CHK1 (DDR)	Berzosertib, Prexasertib (± TKIs)	blocks replication checkpoints, which increases DNA damage, particularly in p53-mutant HCC.	Replication stress response inhibition	TKI-synergistic; useful in high-genomic instability the HCC	Normal cell toxicity and the creation of biomarkers	Preclinical and clinical studies	300

also reducing the immunosuppressive environment produced by TAMs, Tregs, and MDSCs.[303,304] ICIs, which include anti-PD-1 medications like pembrolizumab and nivolumab and anti-PD-L1 medications like atezolizumab, work by reactivating worn-out T cells and enhancing the body's immune response against tumors. However, the immunosuppressive TME feature of HCC often reduces their efficacy as monotherapies. TKIs and ICIs work together to improve immune cell infiltration and decrease immunosuppressive factors in the TME, which strengthens and prolongs the immune response against cancer cells.[305] Fig. 4 presents the timeline of FDA-approved drugs and monoclonal antibodies for the treatment of HCC.

The effectiveness of this synergistic treatment approach is shown by the key IMbrave150 study. In patients with incurable HCC, the combination of bevacizumab (an anti-VEGF drug) and atezolizumab (an anti-PD-L1 antibody) produced significant survival benefits over sorafenib monotherapy in this phase III research. The combination raised the objective response rate (ORR), considerably extended the median OS and PFS, and finally established a new standard of therapy for this patient group.[306] Clinical studies like LEAP-002 are presently evaluating other combination treatments, such as lenvatinib with pembrolizumab. According to preliminary results, this regimen may increase treatment efficacy by taking advantage of lenvatinib's ability to reduce VEGF-driven immunosuppression. It also promotes dendritic cell maturation and improves antigen presentation, which increases the immune system's capacity to target tumors. In summary, ICIs and targeted treatments work in concert to treat HCC by reviving the immune system and restoring normal blood vessel function. Treatment techniques for advanced HCC have changed as a result of this combination approach, offering new hope for long-lasting therapeutic results and improved survival.[307,308] To get the most benefit, current clinical studies are concentrating on enhancing patient selection and optimizing biomarker-based strategies.[309–312]

Targeted therapy + locoregional therapy

Due in large part to the intricacy of the tumor microenvironment and the limited efficacy of single-modality methods in later stages, the combination of targeted therapies and locoregional treatments has become more popular in the management of HCC. For patients with intermediate to advanced HCC, locoregional treatments such as radiation and transarterial chemoembolization (TACE) are common; nevertheless, tumor-induced hypoxia, which stimulates angiogenesis, often reduces their efficacy. TKIs and mTOR/VEGF pathway inhibitors in particular are examples of targeted medicines that have complementing activities that may increase and prolong the therapeutic advantages of these localized treatments.[313–315]

TACE + TKIs

By administering chemotherapy directly to the tumor and cutting off its blood supply, TACE produces ischemic tumor necrosis. Tumor recurrence may result from the hypoxic circumstances that accompany TACE, which cause an increase in pro-angiogenic factors like VEGF. In order to effectively combat this compensatory angiogenesis, TKIs, such as sorafenib, lenvatinib, and apatinib, target VEGFR, PDGFR, and other survival pathways.[316] To assess its effectiveness, this therapy combination has been investigated in a number of clinical studies, such as SPACE and TACTICS.[305] TKI administration must be timed and sequenced precisely to optimize therapeutic efficacy, as the TACTICS study showed that starting

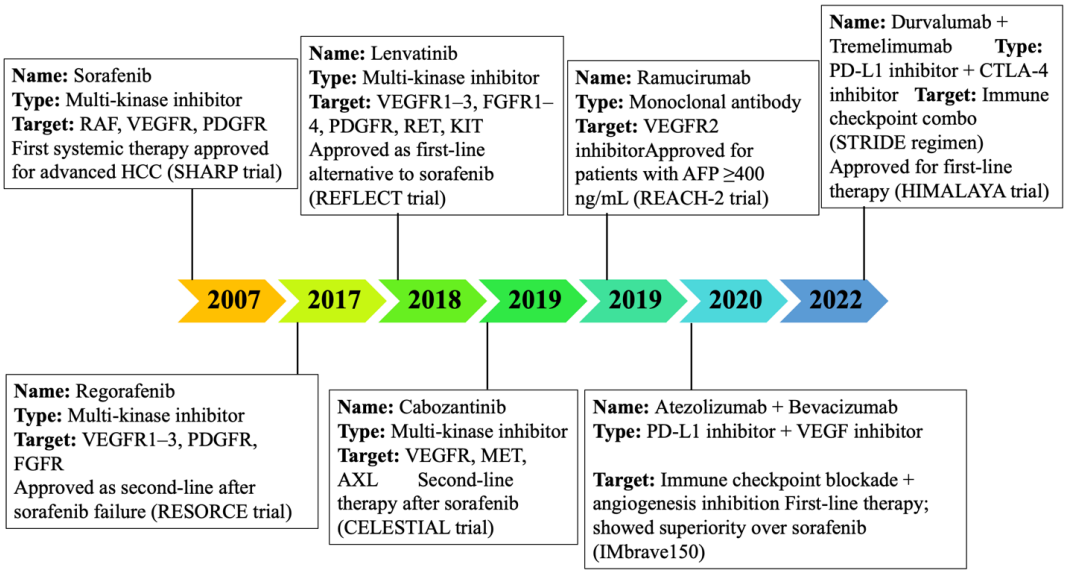

Fig. 4. Timeline overview of targeted therapies and immunotherapy combinations approved for advanced hepatocellular carcinoma (HCC).

sorafenib therapy prior to TACE significantly improved PFS.[317] Toxicology is still a problem despite encouraging outcomes, particularly hepatotoxicity and hand-foot skin responses.[318]

Radiotherapy + mTOR/VEGF inhibitors

Unresectable HCC is increasingly being treated with external beam radiation treatment, particularly stereotactic body radiation therapy (SBRT). Although radiation may trigger anti-tumor immune responses and damage DNA, its efficacy is often limited by the existence of hypoxic areas within the tumor and innate tumor resistance mechanisms.[319] By disrupting the development of the cell cycle and protein synthesis, medications such as everolimus that inhibit the mTOR pathway may make tumor cells more sensitive to radiation. Similarly, VEGF inhibitors like bevacizumab aid in the normalization of tumor blood vessels, which enhances oxygen supply and, in turn, the tumor's radiation sensitivity. These combination treatments may improve overall survival outcomes and increase local tumor control, according to preclinical studies and early-phase clinical trials.[320,321] All things considered, combining targeted medicines with locoregional therapy in HCC is a promising approach; nonetheless, successful clinical outcomes depend on patient classification, proper sequencing, and toxicity control.

Synthetic lethality and rational combinations

In cancer treatment, synthetic lethality a tactic in which the simultaneous disruption of two genes or pathways causes cell death whereas the damage of one gene or route alone is not lethal has become well-known.[322] Utilizing synthetic lethality offers a rational foundation for developing effective combination medicines, especially for patient subgroups identified by biomarkers, in HCC, which is characterized by genetic variation and treatment resistance.[323] A well-studied example focuses on the Wnt/β-catenin signaling system, which is abnormally triggered in around 30–40% of instances of HCC because of mutations in genes like AXIN1 or CTNNB1 (which encode β-catenin). These genetic changes provide serious treatment problems because they encourage immunological exclusion and lead to resistance to ICIs. By combining Wnt pathway inhibitors with additional targeted medicines or ICIs, synthetic lethality strategies seek to overcome this resistance. Particularly, in preclinical models of β-catenin-driven HCC, PORCN inhibitors, which prevent the production of Wnt ligands, and tankyrase inhibitors, which encourage β-catenin disintegration, have shown encouraging outcomes. Additionally, combining Wnt inhibitors with ICIs may change the immune milieu around the tumor, reviving immune surveillance in otherwise immunologically "cold" tumors.[324] Several additional strategic combinations that take advantage of weaknesses resulting from DNA damage repair (DDR) errors, epigenetic modifications, or connections between oncogenic signaling pathways are being studied in addition to targeting the Wnt pathway. PARP inhibitors, for example, may be used to specifically target hepatocellular carcinomas with homologous recombination repair deficits, such as those with BRCA mutations. The therapeutic effect is further enhanced when ATR or CHK1 inhibitors are added. Treatment regimens that combine particular inhibitors of these targets with anti-angiogenic drugs may also be beneficial for tumors displaying FGF19 amplification or MET pathway activation. The goal is to use synthetic lethality by concurrently inhibiting compensatory survival pathways.[325] The use of biomarker-driven patient selection is a crucial component that makes these synthetic lethality-based strategies successful. Comprehensive molecular profiling is essential to identify individuals with actionable genetic changes or particular pathway dependencies in order to successfully transfer these tactics into therapeutic benefit. In order to classify patients and adjust treatments appropriately, methods like liquid biopsies, next-generation sequencing (NGS), and transcriptome profiling are being used more and more. For example, people with TP53 mutations or deficiencies in DDR pathways may be good candidates for therapies that target DNA repair mechanisms, whereas those with β-catenin mutations may react well to Wnt pathway inhibitors.[326] Synthetic lethality has a lot of promise, but there are still a number of obstacles to overcome, including intratumoral heterogeneity, resistance that develops over time, and a lack of thorough clinical evidence on the toxicity and safety of combination treatments. However, the combination of synthetic lethality principles, accurate biomarker identification, and careful therapeutic design is gradually changing the way HCC is treated, opening the door to more accurate and successful oncology approaches in this historically challenging cancer (Table 4). [327]

Biomarkers and precision medicine

Precision medicine that is individualized for each patient is replacing traditional, one-size-fits-all methods to treating HCC as a result of the discovery of biomarkers. Generally speaking, biomarkers may be divided into two groups: prognostic indicators, which provide information on the overall course of the illness regardless of treatment, and predictive markers, which indicate the likelihood of responding to a specific therapy. Finding reliable biomarkers is particularly important for improving patient care because of the significant heterogeneity of HCC as well as issues including impaired liver function and common treatment resistance.[323] Techniques for liquid biopsies, particularly the measurement of circulating tumor DNA (ctDNA), have emerged as useful non-invasive ways to evaluate tumor activity in real time. ctDNA records genetic and epigenetic alterations

in HCC, including mutations in the TERT promoter, TP53, and CTNNB1, which can guide therapy decisions. Since ctDNA allows for more frequent sampling than traditional tissue biopsies, it is especially helpful for tracking the efficacy of treatments and identifying the emergence of resistance over time.[324] Because it provides comprehensive information on mutations, gene fusions, and copy number variations, tissue-based genomic profiling remains a fundamental component in cancer diagnoses. The use of comprehensive genomic panels that can identify actionable changes, like FGF19 amplification, MET overexpression, or deficiencies in DDR, is made easier by modern integrated platforms. This aids in the creation of individualized treatment regimens that are specific to the tumor biology of each patient.[337] HCC is rapidly being classified into several molecular subtypes using transcriptomic profiling, each of which has its own particular immunological and metabolic characteristics. In contrast to "CTNNB1-enriched" cancers, which often show resistance to immunotherapy, tumors categorized as belonging to the "immune class," which have inflammatory gene signatures, typically react positively to ICIs. More accurate sequencing and therapy combination customization are made possible by this molecular stratification. Utilizing multi-omics and clinical information, recent developments in artificial intelligence (AI) and machine learning (ML) are being incorporated into clinical practice to reveal intricate patterns. AI-powered models can predict treatment outcomes, help find new biomarkers, and stratify patients based on risk. These technologies have the potential to improve prognosis accuracy, provide dynamic, adaptive treatment options for HCC, and improve early detection.[338] Notwithstanding significant progress, a number of obstacles still exist, including the need for standardized biomarker testing procedures, securing regulatory clearances, and guaranteeing fair access to new technologies. However, by enabling individualized, biology-driven treatment approaches, biomarker-guided precision medicine has great promise to improve outcomes in HCC with further innovation and thorough validation (Table S3).[323]

Challenges in targeted therapy

Despite substantial advancements, the clinical efficacy of targeted treatments for HCC is still limited by major hurdles. Tumor heterogeneity is a major obstacle. It may be seen inside a single tumor, where many genetically different subclones coexist, as well as across tumors, which are molded by different underlying causes such as alcohol-related liver disease, viral hepatitis, or non-alcoholic steatohepatitis (NASH). Despite early encouraging results, this clonal diversity contributes to treatment resistance and illness recurrence.[339,340] One of the biggest challenges in treating HCC is drug resistance, which may be innate or develop with time. TKI effects are often circumvented by tumor cells via the activation of alternative signaling pathways such as PI3K/AKT, RAS/MAPK, or FGFR. Furthermore, resistance mechanisms are influenced by elements found in the tumor microenvironment, including hypoxia, immunological suppression, and increased angiogenesis. Additionally, prolonged treatment may cause EMT, which makes treatment more difficult and increases the tumor's capacity to spread.[341,342] The absence of proven predictive biomarkers for HCC is a serious obstacle to reaching treatment precision. Patients run the danger of obtaining inefficient medicines that may potentially cause needless toxicity if reliable

Table 4. Comprehensive review of combination approaches in HCC treatment, emphasizing the underlying clinical trial data, therapeutic advantages, difficulties, and processes

Combination strategy	Mechanism/Description	Advantages	Challenges	Clinical evidence	References
Targeted Therapy + Immunotherapy	mixes ICIs with TKIs to encourage vascular normalization, lower immunosuppression, and boost T cell infiltration.	Synergistic immune activation, improved response rates and survival, and a new standard of therapy for advanced HCC.	Predictive biomarker identification, immune-related adverse events, and toxicity control.	LEAP-002, IMbrave150, and continuing studies (such as lenvatinib with pembrolizumab)	[282,328]
Targeted Therapy + TACE	TACE causes ischemia necrosis; after TACE, TKIs inhibit VEGF-mediated rebound angiogenesis.	Prolonged PFS; effective in intermediate-stage HCC; inhibits post-TACE angiogenesis.	Risk of hepatotoxicity and HFS responses; timing and sequencing are crucial.	Current regional TACE-TKI trials, TACTICS, and SPACE	[329–331]
Targeted Therapy + Radiotherapy	Tumor DNA is damaged by radiation; mTOR/VEGF inhibitors promote oxygenation, which increases radiation sensitivity and the immune response.	enhanced local control, radiation sensitivity, and a combined effect on the immune system and tumor burden.	Immune suppression, cumulative toxicity, and the ideal dose/ radiation schedule.	Early-stage trials; SBRT/VEGF preclinical research	[332,333]
Synthetic Lethality-Based Combinations	utilizes synergistic drug pairings to selectively kill tumor cells by taking advantage of tumor-specific weaknesses (such as Wnt/β-catenin and DDR mutations).	Preclinical effectiveness in resistant and immune-excluded cancers is promising, as is precise targeting of mutation-defined subgroups.	toxicity profiles, inadequate clinical trial data, tumor heterogeneity, and biomarker validation.	Preclinical research; early-stage trials based on biomarkers (e.g., PARPi + ATRi, PORCN + ICIs)	[334–336]

genomic, transcriptomic, or proteomic indicators are not available to guide treatment decisions. This might eventually compromise the patients' quality of life as well as the overall value of the therapy. Considering that many patients with HCC also have underlying liver cirrhosis, toxicity is still a major issue. Systemic side effects, such as tiredness, hypertension, hemorrhage, hepatotoxicity, and gastrointestinal problems, are linked to medications such as TKIs and mTOR/VEGF inhibitors. These side effects sometimes call for dosage adjustments or even stopping treatment.[343,344] The high expenses of targeted medicines provide significant socioeconomic obstacles to access, especially in settings with limited resources. In the absence of accurate biomarker-guided patient selection, the cost burden of some therapies may be difficult to justify, since they only provide minor gains in survival. Furthermore, preclinical model limitations still make it difficult to successfully translate treatments.[345,346] The intricate human liver environment, including its architecture, fibrosis, immunological interactions, and tumor heterogeneity, is not well simulated by traditional two-dimensional cell cultures and mouse xenograft models . While more accurate representations are provided by sophisticated systems, such as humanized mouse models, three-dimensional co-culture models, and patient-derived organoids, these platforms still need standardization and broader usage to reach their full potential in drug discovery.[159,347] A comprehensive research strategy that incorporates integrative investigations, real-time molecular profiling, and adaptable clinical trial designs is needed to address these intricate problems. In order to develop tailored medicines for HCC that are not only efficient but also available and fair to all patients, such tactics are crucial.[348-349]

Future directions and innovative technologies

mRNA-based therapeutics and gene editing

Therapies based on messenger RNA (mRNA) are showing promise as a novel approach to the treatment of HCC. These systems use liver-optimized lipid nanoparticles (LNPs) to transport immune-activating cytokines or tumor suppressor genes, such p53 and PTEN, straight into cancer cells.[350] This technique lowers the danger of insertional mutagenesis since mRNA does not integrate into the host genome. Concurrently, developments in CRISPR-Cas9 gene editing are making it possible to precisely fix oncogenic mutations, such as those seen in patient-derived HCC models in the TP53, CTNNB1, and TERT promoter genes.[319,351] Modern gene-editing tools, such as base editors and prime editors, allow for accurate single-base changes without breaking double-strand DNA. Notwithstanding these advances, there are still significant obstacles that need to be addressed in order to effectively convert these strategies into therapeutic treatments, including obtaining targeted and effective delivery to hepatocytes, reducing side effects, and preventing innate immune system activation.[352,353]

Targeted protein degradation

Molecular glues and proteolysis targeting chimeras (PROTACs) are novel therapeutic strategies for focusing on proteins in HCC that have hitherto been regarded as "undruggable." Critical oncogenic drivers including β-catenin, c-MYC, and YAP/TAZ are preferentially degraded by these molecules via the ubiquitin-proteasome system.[354] PROTACs enable the permanent removal of disease-causing proteins, in contrast to conventional inhibitors that just stop protein function. This may lessen the chance of resistance developing and need a lower dose of medication.[355,356] In preclinical research, next-generation liver-targeted PROTACs have shown encouraging pharmacokinetic characteristics and significantly reduced systemic toxicity.[357] These PROTACs are engineered to effectively pass through the hepatic sinusoidal endothelium and specifically break down tumor-specific proteins. To optimize clinical potential, current efforts concentrate on boosting therapeutic efficacy, improving oral bioavailability, and improving tissue selectivity.[358]

Nanotechnology in targeted drug delivery

The liver's distinct vascular anatomy and receptor-mediated endocytosis processes are being exploited by sophisticated smart nanoparticles.[359] Highly selective tumor uptake is accomplished by functionalizing these nanocarriers with ligands that target receptors such as transferrin receptors, integrins, or the asialoglycoprotein receptor (ASGPR). In order to maximize drug concentration within the tumor and minimize systemic side effects, these nanoparticles are also designed to be stimuli-responsive, releasing their therapeutic payload in response to local triggers like acidic pH, increased enzymatic activity, or hypoxic conditions.[360] TKIs, chemotherapeutic medications, small interfering RNAs (siRNAs), immunomodulators, or imaging probes are just a few of the substances that may be loaded into these intelligent nanocarriers to create multipurpose theranostic platforms. Real-time monitoring of medication distribution and tumor response is made possible by this dual capacity, which enables customized dosage modifications and treatment plans that are best suited to the requirements of each patient.[361,362] Da et al developed a platelet membrane-coated nanocarrier co-loaded with anti-PD-1 antibody and Sorafenib (aPD-1-PLTM-HMSNs@Sora) for targeted delivery to HCC (Figs. 5 and 6). In vivo studies in H22 tumor-bearing mice demonstrated superior tumor suppression, with average tumor volumes reduced to 26.85% of controls. Immunofluorescence and histological analysis showed significant $CD8^+/CD4^+$ T cell infiltration and VEGF-A inhibition, while regulatory T cells were diminished.

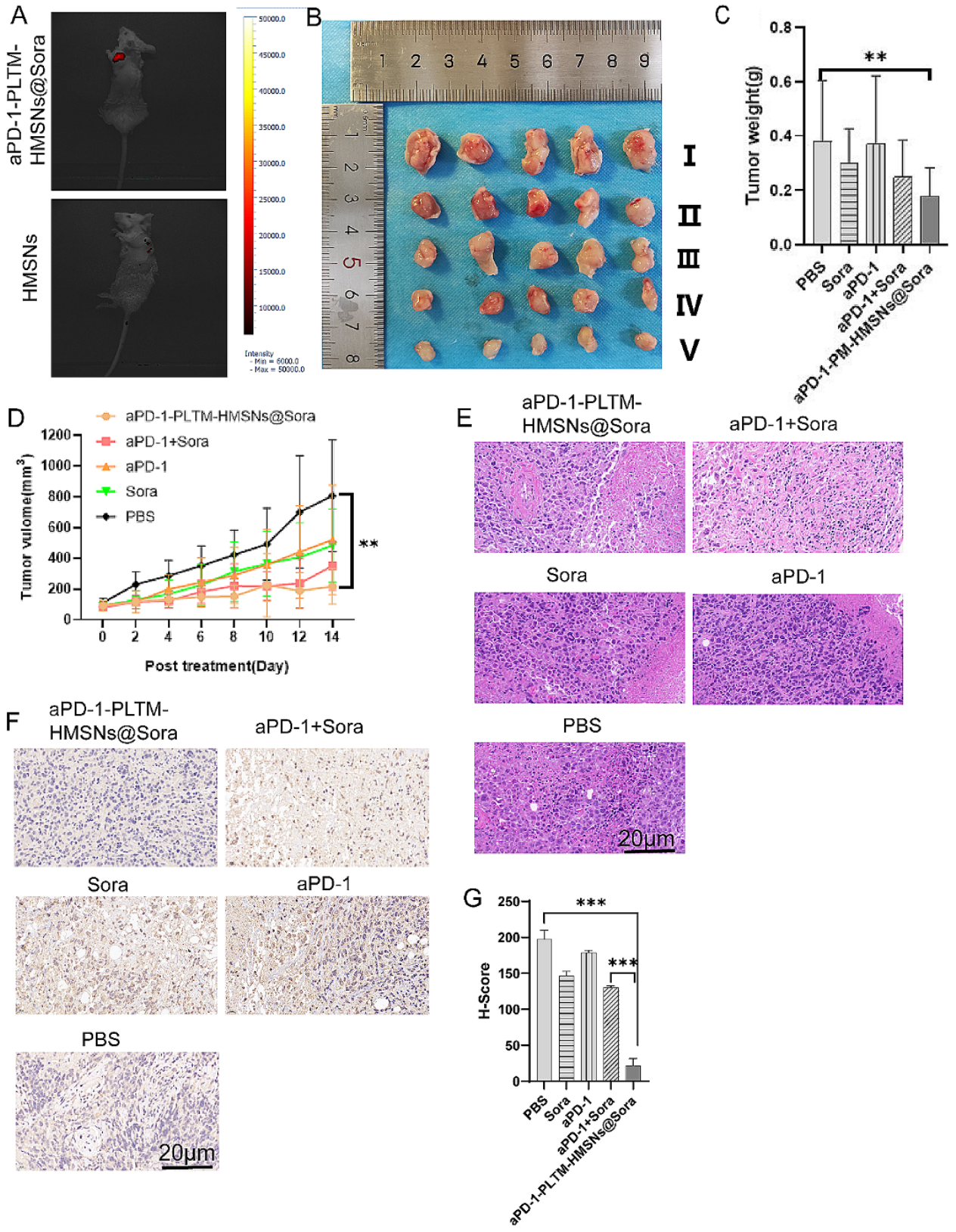

Fig. 5. Antitumor efficacy and immune activation induced by aPD-1-PLTM-HMSNs@Sora in hepatocellular carcinoma (HCC) models. Therapeutic efficacy of different treatment regimens in H22 tumor-bearing mice. (A) In vivo fluorescence imaging shows enhanced tumor targeting of Cy5.5-labeled aPD-1-PLTM-HMSNs@Sora compared to HMSNs alone. (B) Representative images of tumors harvested from five groups: I, PBS; II, Sorafenib (Sora); III, aPD-1; IV, aPD-1 + Sora; V, aPD-1-PLTM-HMSNs@Sora. (C) Tumor weight comparison among treatment groups. (D) Tumor growth curves over 14 days, showing the greatest inhibition in the aPD-1-PLTM-HMSNs@Sora group ($p < 0.01$). (E) H&E staining indicates more extensive tumor necrosis in the aPD-1-PLTM-HMSNs@Sora group. (F) Immunohistochemistry of VEGF-A expression across groups. (G) Quantitative H-score analysis of VEGF-A, with significant reduction in the aPD-1-PLTMHMSNs@Sora group (*$P < 0.001$).

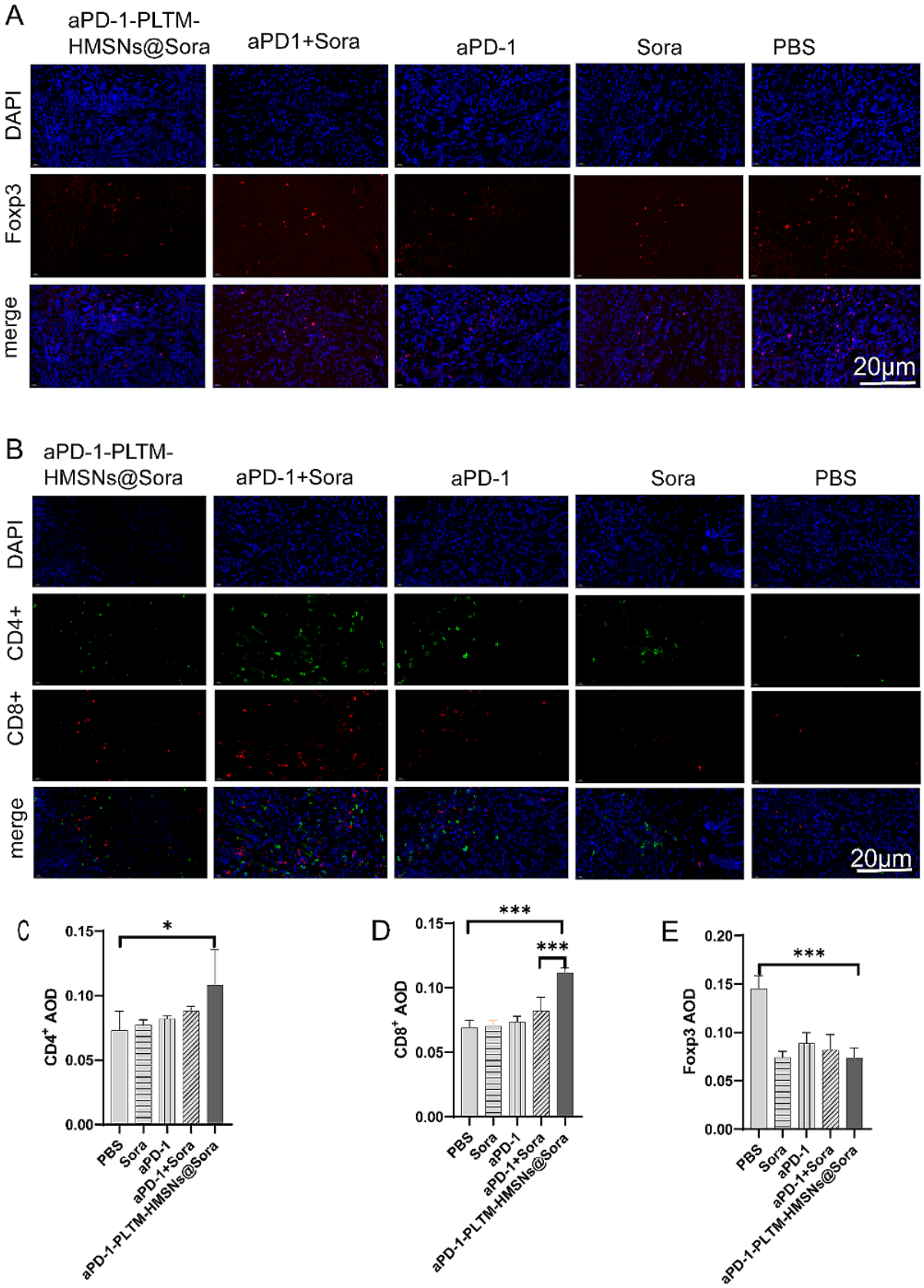

Fig. 6. aPD-1-PLTM-HMSNs@Sora enhances T cell–mediated immune response in HCC tumors.(A) Immunofluorescence staining for Foxp3⁺ regulatory T cells shows significant reduction in the aPD-1-PLTM-HMSNs@Sora group. (B) Increased infiltration of CD4⁺ and CD8⁺ T cells in tumors from aPD-1-PLTM-HMSNs@Sora-treated mice compared to other groups. (C–E) Quantification of CD4⁺ (C), CD8⁺ (D), and Foxp3⁺ (E) cells, revealing enhanced cytotoxic T cell infiltration and reduced immunosuppressive Tregs, indicating an immunostimulatory shift in the tumor microenvironment.

These results suggest potent synergistic antitumor activity through both direct cytotoxic and immunomodulatory mechanisms.[363]

Finally, we note that well-designed nanoparticles function effectively as passive delivery vehicles through the enhanced permeability and retention (EPR) effect inherent to the tumor microenvironment. Tumor vasculature is inherently leaky and characterized by poor lymphatic drainage, allowing nanoparticles typically 10–100 nm in size to selectively extravasate and accumulate in tumor tissue.[364,365] This passive targeting enables increased local drug concentration and reduced systemic side effects. Optimizing nanoparticle physicochemical properties including size, circulation half-life, and surface chemistry can further enhance EPR-mediated accumulation and therapeutic efficacy in solid tumors.

Organoids and patient-derived xenograft (PDX) models

Evaluation of individualized treatment is changing as a result of advancements in preclinical modeling. The histological characteristics and intratumoral heterogeneity of the original tissue are preserved in patient-derived organoids (PDOs), which are generated directly from individual HCC tumors. This fidelity speeds up the creation of specialized treatment plans by enabling quick in vitro testing of both individual drugs and specific combination therapies.[366] In order to more precisely replicate the intricate tumor microenvironment, recent developments have established techniques that co-culture autologous immune and stromal cells with PDOs. Better treatment choices are made possible by this improved model's increased predictive ability for evaluating immunotherapy responses.[367] Patient-derived xenograft (PDX) mice models faithfully mimic the stromal and genetic characteristics of the original tumors, allowing for thorough in vivo evaluation of medication effectiveness, the best course of therapy, and the emergence of resistance over time. These models are being used more and more in co-clinical trial settings, where knowledge from PDO and PDX research is used to inform stratification and customize therapy decisions alongside patient therapies.[368]

Conclusion and expert perspective

Recent developments in immunotherapy, biomarker discovery, and molecular oncology have significantly changed the treatment landscape for HCC[369-372] (Fig. 7). Among the groundbreaking advancements are ICIs like atezolizumab and nivolumab, as well as multi-targeted TKIs like sorafenib, lenvatinib, and cabozantinib. A novel therapy paradigm that includes strategies that target angiogenesis, immune evasion, and tumor growth simultaneously has been introduced by the clinical

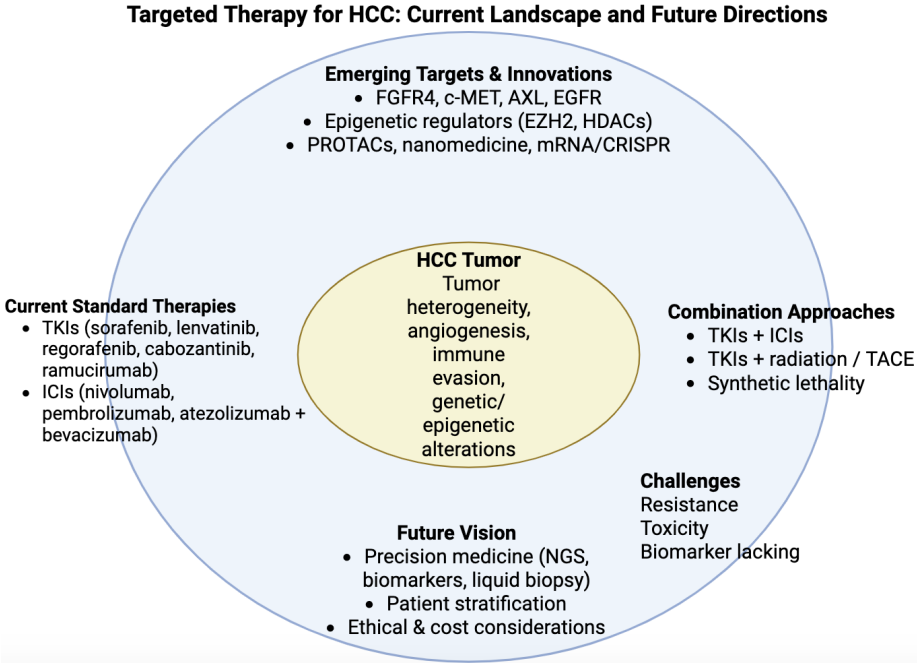

Fig. 7. Summary of Targeted Therapy for Hepatocellular Carcinoma (HCC): Current Landscape and Future Directions. This schematic illustrates the therapeutic framework for HCC. At the center lies the tumor, driven by heterogeneity, angiogenesis, and immune evasion. Surrounding layers represent: (i) **current standard therapies**, including tyrosine kinase inhibitors (sorafenib, lenvatinib, regorafenib, cabozantinib, ramucirumab) and immune checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab plus bevacizumab); (ii) **combination strategies**, such as TKIs with ICIs, TKIs with radiation or TACE, and synthetic lethality approaches, alongside key challenges of resistance, toxicity, and biomarker limitations; (iii) **emerging molecular targets and innovations**, including FGFR4, c-MET, AXL, EGFR, epigenetic regulators (EZH2, HDACs), and novel modalities such as PROTACs, nanomedicine, mRNA therapeutics, and CRISPR-based strategies; and (iv) the **future vision**, highlighting precision medicine guided by next-generation sequencing, liquid biopsy, dynamic biomarkers, and multidisciplinary collaboration. Together, these elements provide a strategic overview of current progress and future directions in the individualized treatment of liver cancer

Review Highlights

- Hepatocellular carcinoma (HCC) remains a major global health challenge with limited response to traditional chemotherapy, highlighting the need for targeted therapies focusing on key pathways like Wnt/β-catenin, PI3K/AKT/mTOR, and RAS/RAF/MEK/ERK.
- First-line TKIs such as sorafenib and lenvatinib offer modest survival benefits, while second-line options like regorafenib, cabozantinib, and ramucirumab address resistance, particularly in patients with high AFP levels.
- Immunotherapy advancements, including ICIs (e.g., atezolizumab + bevacizumab), show promise in 20–30% of patients, emphasizing the role of the tumor microenvironment and combination strategies to overcome resistance.
- Emerging targets like FGFR4, c-MET, AXL, and epigenetic regulators (e.g., EZH2, HDACs) offer new avenues for precision medicine, with a focus on biomarker-driven approaches for improved patient stratification.
- Future directions include rational combinations (e.g., TKIs + ICIs + radiation), synthetic lethality, and dynamic molecular profiling to enhance long-term efficacy and personalize HCC treatment.

integration of these drugs, which has also improved survival results for patients with advanced HCC.[373-375] Furthermore, a move toward more individualized treatment approaches has been fueled by a better understanding of oncogenic pathways, including as Wnt/β-catenin, PI3K/AKT/mTOR, FGFR4, and c-MET, as well as knowledge of the tumor microenvironment and epigenetic processes. Personalized targeted treatments have the potential to become the mainstay of HCC treatment in the future. Clinicians will be able to customize therapy to the specific biology of each patient's tumor by using NGS, liquid biopsy technologies, and transcriptome profiling to find actionable mutations in real time. However, strong interdisciplinary and translational research partnerships are essential to the development of precision medicine. To bridge the gap between laboratory findings and clinical application, it is essential to integrate molecular biology, clinical oncology, computer modeling, and pharmacological innovation. Additionally, the development of dynamic predictive biomarkers will improve combination regimens, ease the monitoring of treatment resistance, and improve patient selection. Policymakers and regulatory agencies must create flexible frameworks that strike a balance between strict safety and ethical scrutiny and the quick licensing of innovative treatments in order to maintain advancement in this quickly changing sector. The privacy of genetic data, fair access to customized treatments, informed consent in biomarker-driven trials, and the expense of new therapeutics are among the issues that need immediate attention. To preserve public confidence and promote sustainable innovation, ethical issues must be included into every step of the research and clinical implementation process. In conclusion, multimodal, tailored, and biomarker-guided techniques are the way of the future for treating liver cancer. An age of precision oncology for hepatocellular carcinoma is not only possible but also impending with sustained scientific advancement, multidisciplinary collaboration, and careful policy change.

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Ethical Approval
This article is a comprehensive review based on previously published studies and does not involve any original human or animal experimentation. Therefore, no ethical approval from an institutional review board or ethics committee was required. All referenced studies were assumed to have adhered to relevant ethical guidelines, including the Declaration of Helsinki where applicable.

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Supplementary files
Supplementary file 1 contains Table S1-S3.

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