CASE REPORT

Exploration of Personalized Treatment for Advanced Hepatocellular Carcinoma: Combination Therapy of Selinexor, Palbociclib, and Pembrolizumab with Umbilical Cord Blood NK Cells

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ABSTRACT

Objective • To report the efficacy and safety of combination therapy with selinexor, palbociclib, pembrolizumab, and umbilical cord blood NK cells for advanced hepatocellular carcinoma (HCC).Advanced HCC has a poor prognosis and limited effective treatment options. Exploring personalized combination treatment strategies is critically important for improving outcomes in patients with advanced HCC. This study aims to provide preliminary evaluation of the clinical effectiveness and safety of this combination regimen in this high-risk population, and lay the groundwork for larger studies to bring more treatment choices to patients with advanced HCC.

Methods • A 67-year-old male patient with advanced HCC and multiple metastases was treated with palbociclib 75mg on days 1-14 of a 28-day cycle, pembrolizumab 200mg intravenous infusion, selinexor 40mg weekly, and umbilical cord blood NK cell (12×109 cells) infusion on days 1, 14, 28 and 42. Imaging examinations and tumor marker detection were performed before and after two cycles of treatment to evaluate response.

Results • After two cycles of combination treatment, follow-up PET-CT showed partial response with the liver tumors reduced in size by approximately 60%, lung metastases reduced by approximately 90%, and FDG uptake decreased more than 90% in lymph nodes and bone metastases. The AFP level decreased compared to baseline. Liver function tests including albumin, bilirubin and prothrombin time improved. The patient's performance status also improved from ECOG 2 to ECOG 1.

Conclusions • This case report describes preliminary signals that the combination of selinexor, palbociclib, pembrolizumab, and umbilical cord blood NK cells may warrant further investigation for the treatment of advanced HCC. Objective response was observed based on standardized response criteria. However, due to the limitations of a single-arm case study design, definitive conclusions cannot be drawn regarding the efficacy or safety profile of this personalized combination approach. Larger and more robust clinical trials are needed to fully validate if this treatment strategy can achieve clinical benefit for advanced HCC. Future studies should aim to elucidate potential biomarkers that may help identify patients most likely to respond to this combination regimen. Exploring optimal patient selection criteria could also help maximize clinical benefit. Further research is warranted to continue exploring precision medicine combinations involving immunotherapy, targeted agents and cellular therapies for advanced HCC. (*Altern Ther Health Med.* [E-pub ahead of print.])

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CASE INTRODUCTION

A 67-year-old male patient presented with a one-year history of malignant liver cancer, four months of fatigue, and lower back pain. Medical history: In November 2021, the patient was diagnosed with a malignant liver tumor by abdominal CT enhancement due to right upper abdominal pain. After interventional and targeted therapy, the tumor continued to progress. He was admitted to our department on August 31, 2022 for further treatment. Past medical history: The patient had a history of hypertension for more than 30 years and had been taking sustained-release nifedipine tablets 30 mg/day, with good blood pressure control. He had also been diagnosed with type 2 diabetes for

Figure 1. Hepatocyte focal necrosis with rare peripheral cell dysplasia.

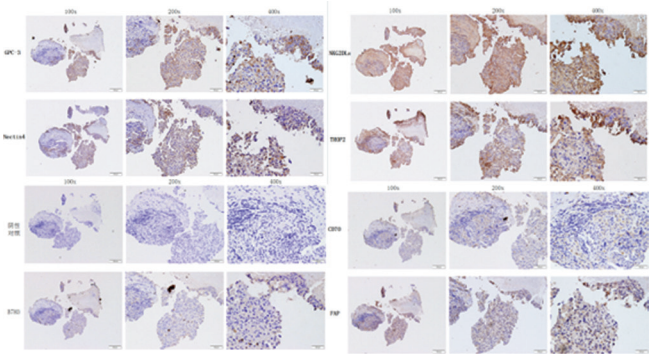
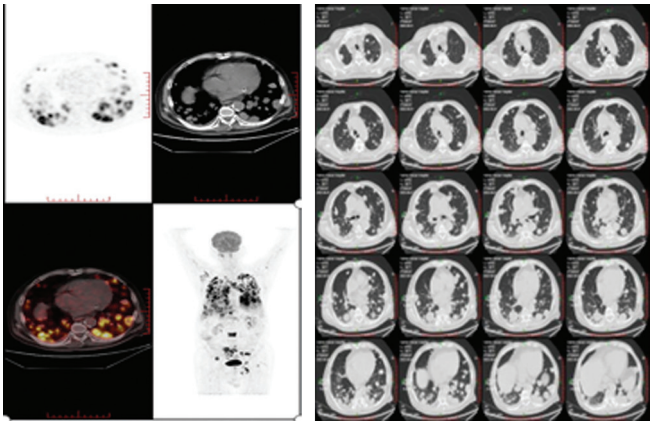


Table 1. Detection of tumor-associated gene mutations

Mutation test	Test Result	Category	Clinical Significance
KDR (VEGFR2)	Positive	High sensitivity to sorafenib, regorafenib, and sunitinib	
CCND1	Positive	High sensitivity to abemaciclib, palbociclib, and ribociclib	
Tumor Mutation Burden (TMB)	Positive	Predictive marker for immunotherapy efficacy	High benefit from immunotherapy drugs such as pembrolizumab
CTNNB1 Mutation	Positive	Negative correlation with treatment efficacy	Positive mutation suggests poor treatment efficacy
CCNDA, FGF3, FGF4, and FGF19 Amplification	Positive	Treatment-related disease progression	Amplification positivity is associated with disease progression

Note: CCND1 gene has an increased copy number and is sensitive to CDK4/6 inhibitors (Palbociclib, Ribociclib, Abemaciclib).

Figure 2. After liver cancer treatment, the liver S6 huge mass, considering the local inactivity after tumor treatment; 2. Multiple round slightly low-density foci in the liver, consider liver cancer subfoci or metastases; 3. Multiple nodules and masses of varying size in both lungs, consider multiple lung metastases in both lungs; 4. Multiple small and enlarged lymph nodes in the mediastinum, double hilar and right diaphragmatic angle area, consider lymph node metastasis; 5. Multiple small lymph nodes parathoracic parathoracic segment, paragastric cardia, hepatic portal area and retroperitoneum, do not exclude metastasis; 6. Multiple increased bone density throughout the body, consider bone metastasis.



15 years and had been treated with subcutaneous injection of Menoductal insulin 22iu three times a day and acarbose tablets 50 mg tid to control blood sugar. He denied a history of coronary heart disease, chronic hepatitis B, and other diseases. Physical examination: The patient had a normal nutritional status, clear consciousness, poor mental state, no liver palms, no spider nevi, no yellowing or bleeding points on the skin, mucous membranes, or sclera, right upper abdominal tenderness, no superficial varicose veins on the abdominal wall, abdominal distension, liver palpable below the rib, about 3 cm below the rib, with irregular margins, hard texture, and tenderness, no spleen palpable below the rib, no ascites, and no edema in either lower limbs. Imaging examination: Liver MRI showed a mass in the right posterior lobe of the liver and multiple nodular lesions in the liver, suggesting liver cancer with multiple intrahepatic metastases or primary liver cancer.

Initial Treatment Course

The patient underwent liver tissue puncture on November 22, 2021, due to abdominal pain: focal necrosis with slight cell dysplasia was observed around the lesion. Immunohistochemistry (Figure 1): Dysplastic cells were positive for CD34 (vascular+), negative for alpha-fetoprotein, positive for Ki-67 (20%), positive for GPC-3, positive for CD10 and P53, and positive for CK8/18 but negative for CK19. Combined with immunohistochemistry, hepatocellular carcinoma was considered. On November 18, 2021, the patient underwent hepatic arterial interventional chemotherapy embolization, injection of pembrolizumab, and treatment with Palbociclib, which resulted in severe oral mucosal injury. The liver tumor progression was evaluated in March 2022. On June 12, 2022, the patient received treatment with atezolizumab in combination with bevacizumab, completing four cycles of treatment. In July 2022, the patient was re-examined by CT due to general weakness and lower back pain, which revealed liver cancer with lung and systemic bone metastases. Molecular testing was performed in August 2022 (Table 1).

Secondary Treatment Course

The patient was admitted to our department for liver cancer treatment on August 31, 2022. Upon admission, the patient had normal nutrition, clear consciousness, poor mental state, no liver palms, no spider nevi, and no yellowing or bleeding points on the skin, mucous membranes, or sclera. The patient had right upper abdominal pain, no superficial venous varices on the abdominal wall, abdominal distension, a hard liver edge irregular in shape with tenderness, and no palpable spleen edge or ascites. The lower limbs were not swollen. The auxiliary examination showed that the abnormal prothrombin assay was greater than 3000, and the AFP was greater than 2000 ng/mL. The whole-body PET-CT (Figure 2) showed: 1. After liver cancer treatment, a huge S6 liver mass was observed, but no abnormal radioactive concentration was seen on PET, suggesting local inactivity

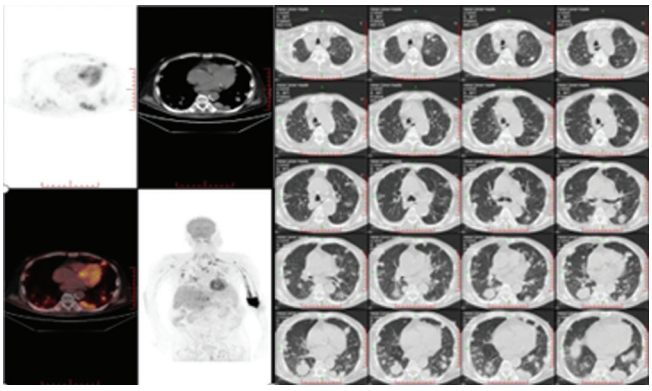
after tumor treatment; 2. Multiple round, slightly low-density lesions were observed in the liver, with abnormal radioactive concentration on PET, suggesting liver cancer sub-nodules or metastatic tumors; 3. Multiple nodules and masses of varying sizes were observed in the lungs, with abnormal radioactive concentration on PET, suggesting multiple lung metastatic tumors; 4. Multiple small and enlarged lymph nodes were observed in the mediastinum, bilateral pulmonary hilum, and right hilar region, with mild to moderate abnormal radioactive concentration on PET, suggesting lymph node metastasis; 5. Multiple bone density increased lesions were observed in the whole body, with mild to moderate abnormal radioactive concentration on PET, suggesting multiple metastatic bone lesions. Then he was treated with Palbociclib, pembrolizumab,Selinexor and received umbilical cord blood NK cell infusion therapy. (see Table 2)

A follow-up whole-body PET-CT on October 26, 2022 (Figure 3) showed: 1. The right lobe liver mass remained unchanged, with no metabolic activity; 2. The left lobe liver mass showed a local increase in blurred radioactive uptake, suggesting liver cancer sub-nodules or metastatic tumors, but with reduced size and metabolism compared to before; 3. Multiple solid nodules and masses in the lungs showed abnormal radioactive concentration on PET, suggesting lung metastatic tumors but with reduced size and metabolism compared to before; 4. Multiple slightly enlarged lymph nodes in the hepatic portal area and hepatogastric ligament showed mild radioactive concentration on PET, and multiple lymph nodes in the mediastinum showed varying degrees of abnormal radioactive concentration on PET, suggesting lymph node metastasis but with reduced size and metabolism compared to before; 5. Multiple bone density increased lesions were observed in the whole body, with mild to moderate abnormal radioactive concentration on PET, suggesting multiple bone metastatic lesions, but with reduced size and metabolism compared to before. The initial positive findings after two treatment cycles informed the decision to continue with the combination regimen. Specifically, the partial response seen on imaging with reductions in both liver and metastatic lesions, along with decreasing AFP levels and improved performance status, demonstrated early signs of clinical benefit. This supported maintaining the personalized combination as the primary treatment approach for this patient.

Table 2. Treatment regimen and schedule

Drug	Dose	Schedule
Palbociclib	75mg PO daily	Days 1-14 of 28-day cycle
Pembrolizumab	200mg IV infusion	Every 3 weeks
Selinexor	40mg PO weekly	
Umbilical cord blood NK cells	$12x10^9$ cells IV infusion	Days 1, 14, 28, 42

Figure 3. 1. Changes after comprehensive treatment of liver cancer, abnormal density mass in the right lobe of the liver, same as before; 2. The local area of vague radioactive uptake increased in the left lobe of the liver, considering the liver cancer subfoci or metastases, significantly reduced, reduced, and metabolism decreased compared with before; 3. Multiple solid nodules and masses in both lungs, considering lung metastases, significantly reduced and reduced compared with before; 4. Lymph nodes with slightly larger lymph nodes in the portal area and hepatogastric space, multiple swollen lymph nodes in the mediastinum, considering lymph node metastasis, it is reduced and reduced compared with the previous one, and metabolism is reduced; 5. Multiple bone density increase in the whole body, consider multiple bone metastases, the scope of lesions is reduced compared with before, and metabolism is reduced.



DISCUSSION

Primary liver cancer is one of the most common cancers globally and is highly malignant. Surgery is the main treatment for early primary liver cancer, but some patients are prone to recurrence and metastasis after surgery. Liver cancer has a hidden onset, lacks specific symptoms, and is difficult to detect in the early stages. Most patients present with advanced-stage disease at diagnosis, preventing the opportunity for surgical resection, which greatly affects survival and prognosis. In recent years, there have been new advances in the treatment of advanced liver cancer, especially in the fields of cellular immunotherapy and targeted drugs. The emergence of various new drugs has brought hope to patients with advanced liver cancer and improved survival outcomes. Combination regimens harnessing multiple mechanisms hold promise to address HCC's heterogeneity and overcome resistance seen with single agents. This case provides a glimpse into the potential of personalized combination approaches for advanced HCC. It describes achieving an objective response through a novel multi-pronged regimen tailored to the patient's molecular profile and prior treatment history. The combination of selinexor, palbociclib, pembrolizumab and NK cells was chosen based on several factors in this patient's case. Molecular testing found mutations suggesting sensitivity to CDK4/6 inhibition, which provided the rationale for inclusion of palbociclib. The patient had also progressed on prior immunotherapy, highlighting the need to enhance response. Preclinical evidence shows selinexor can increase immune checkpoint expression and the activity of pembrolizumab. Additionally, umbilical cord blood NK cells were selected to provide cellular immunity given their potential role in HCC. Together,

these agents were intended to act synergistically based on their distinct mechanisms - blocking tumor growth through immune-mediated, targeted and cellular approaches. This personalized selection of drugs and cellular therapy aimed to address the molecular profile and treatment history characteristics of this patient's advanced HCC.

This case report provides preliminary evidence that the combination treatment may achieve partial response in this patient with advanced HCC, but more patients and longer follow-ups are needed to better evaluate its efficacy and safety, as only a single case is reported. It also indicates the combination therapy resulted in partial response based on imaging, tumor marker, and improvement in liver function tests and performance status in this patient with advanced HCC.

Umbilical Cord Blood NK Cells

NK cells are the third type of lymphocytes, in addition to T cells and B cells. They are not only related to anti-tumor, anti-viral infections, and immune regulation but also involved in hypersensitivity reactions and autoimmune diseases. They are the core cells of the innate immune system. Currently, studies are showing that the number of NK cells in tumor tissues is related to the survival and prognosis of patients with primary liver cancer.[1] In patients with advanced primary liver cancer, a certain number of NK cells have impaired function.[2] The impaired NK cells are associated with an increased regulatory T cell subpopulation and bone marrow-derived suppressor cells, thereby reducing the anti-tumor immune response.[3] An article published in the Journal of Modern Oncology showed that the ORR of NK cell therapy for liver cancer patients was 14.3%, the disease control rate (DCR) was 71.4%. No serious adverse reactions were observed in patients after treatment. Whether NK cells can have a lasting effect in tumor patients depends mainly on the support of cytokines such as IL-2 and IL-15. Umbilical cord blood NK cells (UCB-NK) have lower cytotoxicity compared to peripheral blood NK (PB-NK) cells.[18] Non-modified UCB-derived NK cells are a feasible method for treating tumors.[19]

UCB-NK cells can be expanded over 10 000 times from a single donor through proliferation and differentiation, and can be stored as a "ready-to-use" product, which is convenient for multiple infusions. The low immunogenicity of UCB-NK cells can prevent adverse reactions after repeated PB-NK infusions. UCB-NK cells have low KIR levels, which support their effective killing of MHC class I-expressing tumor cells. Non-modified UCB-NK cells have been used in multiple clinical trials, all focused on hematological malignancies, including as maintenance therapy after chemotherapy and as a "bridging" strategy in combination with autologous hematopoietic stem cell transplantation or UCB stem cell transplantation. The results of three clinical trials have been published, and the results are encouraging.[20-22] In addition, UCB-NK cells have shown excellent results in *in vitro* experiments in solid tumors. Overall, although there are still many challenges to be addressed in NK cell therapy, researchers have made some innovations accordingly. From a clinical trial perspective, NK cell therapy has shown great potential in treating solid tumors and is expected to become a new direction for tumor cell immunotherapy following CAR-T therapy.[23]

Immune checkpoint inhibitor therapy

In recent years, immune checkpoint inhibitors have made great progress in the treatment of liver cancer. Among them, combination with anti-angiogenic therapy is more common, but the efficacy is still inconsistent. The IMbrave150 trial showed that the combination of atezolizumab and bevacizumab can significantly improve the overall survival and progression-free survival of patients with unresectable hepatocellular carcinoma, and has a good safety profile.[24] However, the results of the CheckMate 459 trial showed that the combination of lenvatinib and pembrolizumab did not significantly improve overall survival in patients with unresectable hepatocellular carcinoma, but significantly improved progression-free survival and had good safety.[25] In addition, the DEDUCTIVE trial investigated the efficacy and safety of the combination of tivozanib and PD-L1 inhibitor durvalumab in patients with unresectable hepatocellular carcinoma, and the results showed good tolerability and efficacy in untreated patients.[26] The results of the RATIONALE 301 trial showed that the combination therapy of toripalimab and sorafenib significantly improved overall survival (median OS 10.4 months vs. 7.3 months) and progression-free survival (median PFS 4.1 months vs. 1.8 months) compared with sorafenib monotherapy as first-line treatment for unresectable hepatocellular carcinoma, and had good safety.[27] However, the treatment difficulty for patients who fail and progress after immune checkpoint inhibitor therapy will become more prominent.

The weakening, loss, and mutation of targets such as PD-L1 and CTLA-4 are major factors in immune checkpoint inhibitor resistance. Preclinical studies have found that selinexor can increase the expression of PD-1 and CTLA-4 on the surface of normal white blood cells by more than 2 times and induce PD-L1 expression in multiple tumor cell lines.[5] selinexor alone or in combination with immune checkpoint inhibitors can improve the immune microenvironment and increase the number of T cells and NK cells.[4] When combined with PD-1, PD-L1, or CTLA-4 antibodies, selinexor significantly reduced tumor growth rate in mice carrying homologous B16F10 melanoma tumors.[5] Similar results were obtained in a mouse homologous renal cell carcinoma model treated with selinexor and PD-1 antibodies.[4] In a mouse T-cell lymphoma EL4 tumor model experiment, the combination of selinexor and PD-L1 antibodies significantly inhibited tumor growth, and the combination therapy increased the density and cytotoxic activity of CD8+ T cells in tumor tissue, suggesting the clinical potential of selinexor in combination with PD-1 for the treatment of T-cell lymphoma. A phase Ib study of selinexor in combination with pembrolizumab for melanoma patients reported that among 25 subjects, 3 achieved complete

response (CR, 13%), 6 achieved partial response (PR, 26%), and 10 achieved stable disease (SD, 43%). Adverse events (AEs) were mainly nausea, vomiting, and anemia, and 3 subjects withdrew from the study due to AEs, indicating good tolerability of the combination therapy.[6] In addition, in clinical practice, several R/R ENKTL subjects with central nervous system infiltration who had previously received multiple-line treatments, including PD-1/PD-L1 antibodies were treated with selinexor in combination with anti-PD-1 antibodies (including toripalimab), and the combination therapy showed good safety and tolerability, as well as encouraging preliminary efficacy.

Selective XPO-1 inhibitor (Selinexor)

Nuclear export receptor exportin-1 (XPO1, CRM1) mediates the export of proteins containing leucine-rich nuclear export signals (NES) from the nucleus to the cytoplasm, and is therefore essential for the survival of cancer cells.[7,8] Studies have found that Selinexor is a promising drug that can be used alone or in combination with other anticancer drugs for non-hematologic malignancies, and has shown certain efficacy.[9] Its safety and efficacy have been demonstrated in multiple clinical trials. The use of Selinexor alone or in combination with other anticancer drugs has been shown to inhibit tumor growth, promote cell apoptosis, and enhance the sensitivity of tumor cells to chemotherapy.[29] XPO-1 is overexpressed in HCC, and Selinexor has anti-proliferative activity in liver cancer cells *in vitro* and in xenograft models.[10] It has also been found that Selinexor in combination with PD-1 has excellent anti-tumor activity.[5]Preclinical studies have found that Selinexor can increase the expression of PD-1 and CTLA-4 on white blood cells and induce PD-L1 expression in tumor cells. Selinexor alone or in combination with immune checkpoint inhibitors can improve the immune microenvironment and increase T and NK cell numbers. When combined with PD-1, PD-L1, or CTLA-4 antibodies, Selinexor significantly reduced tumor growth in mouse models. Currently, there is limited research on Selinexor for the treatment of advanced liver cancer, and a retrospective clinical trial showed that Selinexor in combination with chemotherapy resulted in disease stabilization in 7 out of 14 treated patients (including 5 with liver/bile duct cancer).[28] The study of this drug provides new treatment methods and means for the field of cancer treatment. Therefore, the options for drugs to treat advanced liver cancer are relatively limited, and Selinexor is a promising clinical candidate for HCC.

CDK4/6 inhibitors

One of the most basic biological characteristics of malignant tumors is the malignant transformation and uncontrolled proliferation of tumor cells caused by cell cycle regulation disorder. CDK4/6 inhibitors restore the cell cycle by selectively inhibiting cyclin-dependent kinases 4 and 6 (CDK4/6), and block cell proliferation in various tumor cells, including breast cancer. In recent years, the combination of CDK4/6 inhibitors and endocrine therapy has been considered the most important advance in MBC, and palbociclib was the first CDK4/6 inhibitor to enter clinical use.[11] Preclinical studies suggest CDK4/6 inhibitors can enhance antigen presentation and upregulate cytokines in the tumor microenvironment.[30] They have also been shown to promote PD-L1 expression, suggesting a rationale for combining with anti-PD-L1 therapy. CDK4/6 inhibitors may enhance tumor immunogenicity and promote anti-tumor immunity when used with immunotherapy. Others have shown that CDK4/6 inhibitors can also regulate the mitotic kinase signaling pathway, induce senescence, and promote anti-tumor immunity,[12,13] providing a basis for combination with immunotherapy drugs. In particular, by inhibiting the Rb-E2F axis, CDK4/6 inhibitors can enhance antigen presentation.[14] CDK4/6 inhibitors can inhibit immunosuppressive regulatory T cells (Tregs) and enhance effector T cell responses by upregulating cytokine (IL-2) levels in the tumor microenvironment.[15] It has been reported that the cyclin D-CDK4 complex plays a role in reducing PD-L1 expression; therefore, CDK4/6 inhibitors can promote PD-L1 expression, leading to tumor immune escape.[16,17] CDK4/6 inhibitors can enhance the expression and release of tumor-associated antigens in tumor cells and promote the activation of antigen-presenting cells, thereby enhancing tumor immune recognition and clearance. These studies suggest that CDK4/6 inhibitors show combinatorial benefits when used in combination with anti-PD-L1 therapy. The tumor-related gene detection report in this case suggested the detection of drug-related gene mutations, high expression of CCND1, sensitivity to CDK4/6 inhibitors (palbociclib, ribociclib), and a high TMB level. Combining the above principles, the excellent efficacy of CDK4/6 inhibitors combined with pembrolizumab in this patient can be explained to some extent.

In summary, personalized treatment for advanced hepatocellular carcinoma (HCC) is an emerging field that holds great promise for the future. The significant tumor heterogeneity of HCC has made it challenging to develop a standard treatment regimen. However, with the advancement of precision medicine, targeted therapies based on genetic and molecular characteristics of individual tumors have become increasingly important. The combination of different treatments, such as CDK4/6 inhibitors with endocrine therapy or anti-PD-L1 therapy, has demonstrated synergistic effects in improving treatment outcomes. Furthermore, the use of NK cell therapy has shown promising results in clinical trials and may become a new direction for HCC treatment.

Looking ahead, the future direction of research will focus on the selection of drugs with different mechanisms of action and targets and the combination of these drugs to block multiple signaling pathways and inhibit tumor growth. The integration of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, will enable a more comprehensive understanding of the molecular mechanisms underlying HCC and facilitate the development

of personalized treatment strategies. With the increasing recognition of the heterogeneity of advanced HCC, the treatment model will ultimately move towards personalized treatment. Challenges and opportunities coexist, and we should attach great importance to and actively participate in relevant clinical research to continuously explore ways to improve the treatment efficacy of advanced HCC.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

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AUTHOR CONTRIBUTIONS

Xiang Wang and Jing Zhang contributed equally to this work. XW, JZ and YT designed the study and performed the experiments, YL and YW collected the data, RW, YC and CC analyzed the data, XW, JZ and YT prepared the manuscript. All authors read and approved the final manuscript.

ETHICAL COMPLIANCE

This study was approved by the ethics committee of Hainan Cancer Hospital, Signed written informed consents were obtained from the patients and/or guardians.

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