

World Journal of *Gastroenterology*

World J Gastroenterol 2023 May 7; 29(17): 2515-2703



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Editorial Board Member of *World Journal of Gastroenterology*, Mohamad Amin Pourhoseingholi, PhD, Associate Professor, Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran 19835, Iran. aminphg@gmail.com

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The primary aim of *World Journal of Gastroenterology* (*WJG, World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJG* as 5.374; IF without journal self cites: 5.187; 5-year IF: 5.715; Journal Citation Indicator: 0.84; Ranking: 31 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2021 is 8.1 and Scopus CiteScore rank 2021: Gastroenterology is 18/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

May 7, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Current and novel approaches in the pharmacological treatment of hepatocellular carcinoma

Fernanda Villarruel-Melquiades, María Eugenia Mendoza-Garrido, Claudia M García-Cuellar, Yesennia Sánchez-Pérez, Julio Isael Pérez-Carreón, Javier Camacho

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bao YZ, China; Han J, China; Wang C, China

Received: December 27, 2022

Peer-review started: December 27, 2022

First decision: January 11, 2023

Revised: January 19, 2023

Accepted: April 11, 2023

Article in press: April 11, 2023

Published online: May 7, 2023



Fernanda Villarruel-Melquiades, Javier Camacho, Departamento de Farmacología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (CINVESTAV-IPN), Mexico City 07360, Mexico

María Eugenia Mendoza-Garrido, Departamento de Fisiología, Biofísica y Neurociencias, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (CINVESTAV-IPN), Mexico City 07360, Mexico

Claudia M García-Cuellar, Yesennia Sánchez-Pérez, Subdirección de Investigación Básica, Instituto Nacional de Cancerología (INCan), Mexico City 14080, Mexico

Julio Isael Pérez-Carreón, Instituto Nacional de Medicina Genómica, Instituto Nacional de Medicina Genómica (INMEGEN), Mexico City 14610, Mexico

Corresponding author: Javier Camacho, BSc, MSc, PhD, Research Scientist, Departamento de Farmacología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (CINVESTAV-IPN), Avenida Instituto Politécnico Nacional 2508, Mexico City 07360, Mexico. fcamacho@cinvestav.mx

Abstract

Hepatocellular carcinoma (HCC) is one of the most lethal malignant tumours worldwide. The mortality-to-incidence ratio is up to 91.6% in many countries, representing the third leading cause of cancer-related deaths. Systemic drugs, including the multikinase inhibitors sorafenib and lenvatinib, are first-line drugs used in HCC treatment. Unfortunately, these therapies are ineffective in most cases due to late diagnosis and the development of tumour resistance. Thus, novel pharmacological alternatives are urgently needed. For instance, immune checkpoint inhibitors have provided new approaches targeting cells of the immune system. Furthermore, monoclonal antibodies against programmed cell death-1 have shown benefits in HCC patients. In addition, drug combinations, including first-line treatment and immunotherapy, as well as drug repurposing, are promising novel therapeutic alternatives. Here, we review the current and novel pharmacological approaches to fight HCC. Preclinical studies, as well as approved and ongoing clinical trials for liver cancer treatment, are discussed. The pharmacological opportunities analysed here should lead to significant improvement in HCC therapy.

Key Words: Liver cancer; Systemic therapy; Immunotherapy; Drug repurposing; Drug combinations; Hepatocellular carcinoma

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Core Tip: Hepatocellular carcinoma (HCC) is one of the most lethal malignant tumours worldwide. Unfortunately, most HCC cases are diagnosed at an advanced stage, and "curative" options are not suggested for these patients. The best option is to start with drug therapy, with sorafenib and lenvatinib as the first-choice drugs. However, most patients do not respond to these treatments; therefore, new therapeutic strategies are urgently needed. Here, we review current potential and novel pharmacological approaches, including immunotherapy, drug combination, and drug repositioning, that should help to improve the prognosis of HCC patients.

Citation: Villarruel-Melquiades F, Mendoza-Garrido ME, García-Cuellar CM, Sánchez-Pérez Y, Pérez-Carreón JI, Camacho J. Current and novel approaches in the pharmacological treatment of hepatocellular carcinoma. *World J Gastroenterol* 2023; 29(17): 2571-2599

URL: <https://www.wjgnet.com/1007-9327/full/v29/i17/2571.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v29.i17.2571>

INTRODUCTION

Liver cancer ranks seventh in incidence and fourth in mortality worldwide. It is one of the malignancies with the highest mortality-to-incidence ratio, reaching up to 91.6%, according to the World Health Organization[1]. This cancer frequently occurs in association with chronic liver disease and is classified according to the cells of origin of the tumour. Hepatocellular carcinoma (HCC) is the most common, originating in hepatocytes and accounting for 75%-85% of all cases[2].

The main risk factors for developing HCC are chronic liver disease, such as non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, as well as hepatitis B (HBV) and C virus (HCV) infections[3]. In addition, some habits, including excessive alcohol consumption and smoking, are also considered major risk factors for developing HCC[2].

The most appropriate management in clinical practice depends on the stage of the disease. At an early or even intermediate stage, the treatment options currently available are surgical methods (liver resection and transplantation), locoregional therapy (radiofrequency ablation), and transarterial chemoembolization therapy[4]. The 5-year survival rate for patients at these stages is 14%, and only 30% can be subjected to curative treatment. Unfortunately, most diagnoses are made when HCC is at an advanced stage, and treatment options are no longer viable[5,6]; pharmacological therapy is suggested in these cases. Chemotherapy is a potential treatment for these patients, but the main disadvantage is that such agents target both cancer and healthy cells, leading to unwanted events that can even endanger the life of the patient. The use of chemotherapeutic agents in monotherapy is ineffective; therefore, more effective and directed drugs are urgently needed. A new generation of treatments called "targeted therapy" (also known as "systemic therapy") aims to specifically target some molecular features that provide malignant advantages to cancer cells while having low toxicity to non-cancerous cells[7,8]. Table 1 summarizes the recommended HCC management based on the Barcelona Clinic Liver Cancer strategy (BCLC), the most widely used liver cancer staging system. This system has five stages depending on disease extension, liver function, and performance status (Table 1)[9-11].

Systemic therapy is the standard treatment for advanced-stage disease (BCLC stage C). This type of treatment is classified into first- and second-line therapies, and its use in clinical practice depends on the individual patient characteristics. To date, many potential drug targets for the treatment of HCC have been investigated; the most critical targets are listed below and represented in Figure 1[8].

Growth factors and their receptors include vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), mesenchymal-epithelial transition factor (c-Met), insulin-like growth factor, and transforming growth factor α (TGF- α).

Intracellular signalling pathways include phosphoinositide 3-kinase (PI3K)/Akt/mechanistic target of rapamycin (mTOR), RAS/RAF/MEK/ERK, Janus kinase (JAK)/signal transducer and activator of transcription (STAT), and Wnt/ β -catenin and the Hedgehog pathway. There are also cell cycle regulators such as CDKs. Transcription factors include nuclear factor κ B (NF- κ B), activating protein-1 and cyclic AMP response element binding (CREB).

Table 1 Barcelona Clinic Liver Cancer staging system and treatment strategy

Stage	Very early stage (0)	Early stage (A)	Intermediate stage (B)	Advanced stage (C)	Terminal stage (D)
Characteristics	Single nodule < 2 cm, preserved liver function, ECOG PS 0	Single or 2-3 nodules < 3 cm, preserved liver function, ECOG PS 0	Multinodular, unresectable, preserved liver function, ECOG PS 0	Portal invasion/extrahepatic spread, preserved liver function, ECOG PS 1-2	Not transplantable HCC, end-stage liver function, ECOG PS 3-4
Treatment	Ablation, resection, transplant		Chemoembolization	Systemic therapy	Best supportive care
Survival	> 5 yr		> 2.5 yr	> 2 yr	3 mo

ECOG PS: Eastern Cooperative Oncology Group performance status; HCC: Hepatocellular carcinoma.

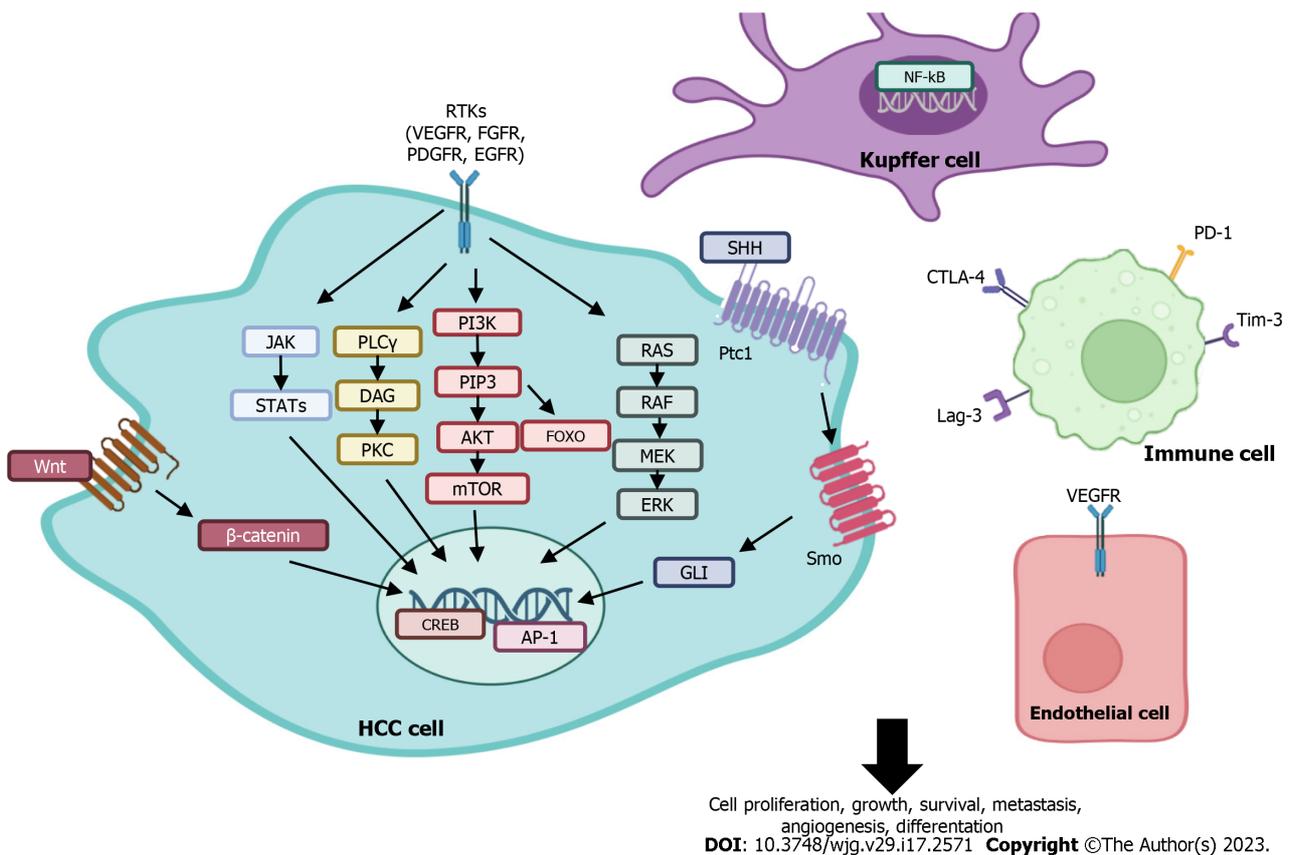


Figure 1 Critical signalling pathways involved in hepatocellular carcinoma progression. Systemic therapy primarily targets signalling pathways triggered by tyrosine kinase receptors expressed on tumour cells, which are known to play an essential role in liver carcinogenesis. However, Wnt/B-catenin and Smo (hedgehog pathway) signalling are also important components in liver cancer development. Furthermore, Kupffer cells, immune cells, and endothelial cells are part of the tumour microenvironment, and activation of critical signalling pathways in these cells may also contribute to cancer development. Indeed, the expression of immune checkpoint molecules (cytotoxic T-lymphocyte-associated protein 4, programmed cell death protein 1, Lag-3, Tim-3) on the surface of immune cells play an essential role in the development of hepatocellular carcinoma (discussed in the main text). RTK: Receptor tyrosine kinase; VEGFR: Vascular endothelial growth factor receptor; FGFR: Fibroblast growth factor receptor; PDGFR: Platelet-derived growth factor receptors; EGFR: Endothelial growth factor receptor; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; PLC γ : Phospholipase C- γ ; DAG: Diacylglycerol; PKC: Protein kinase C; PI3K: Phosphoinositide 3-kinase; PIP3: phosphatidylinositol 3,4,5-trisphosphate; mTOR: Mechanistic target of rapamycin; FOXO: Forkhead box O; AP-1: Activating protein-1; CREB: Cyclic AMP response element binding; NF- κ B: Nuclear factor κ B; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PD-1: Programmed cell death protein 1.

Next, first- and second-line systemic therapies approved for advanced HCC, as well as those drugs and targets under investigation for treating the disease, are described and discussed in detail and summarized in [Table 2](#).

Table 2 Summary of first and second-line drugs approved for the treatment of advanced hepatocellular carcinoma

Drug	Pharmacological target	Trial (NCT)	Treatment arm	Control arm
First-line				
Systemic therapy				
Sorafenib	VEGF 1-3, PDGF, KIT, FLT3, BRAF, RAF	SHARP (NCT00105443)	Sorafenib (400 mg twice daily)	Placebo
Lenvatinib	VEGFR1-3, FGFR 1-4, PDGR, RET and KIT	REFLECT (NCT01761266)	Lenvatinib (12 mg/day for bodyweight ≥ 60 kg or 8 mg/day for bodyweight < 60 kg)	Sorafenib (400 mg twice-daily in 28-d cycles)
Immunotherapy				
Atezolizumab plus bevacizumab	PD-L1, vEGF	IMbrave150 (NCT03434379)	1200 mg of atezolizumab plus 15 mg per kilogram of body weight of bevacizumab intravenously every 3 wk	Sorafenib (400 mg orally twice daily)
Tremelimumab plus durvalumab	CTLA-4, PD-L1	HIMALAYA (NCT03298451)	STRIDE: Tremelimumab plus durvalumab or durvalumab alone (300 mg, one dose of tremelimumab plus 1500 mg every 4 wk for durvalumab)	Sorafenib (400 mg orally twice daily)
Second-line ¹				
Systemic therapy				
Regorafenib	VEGFR 1-3, PDGFR, FGFR 1-2, RET, RAF	RESORCE (NCT01774344)	Regorafenib (160 mg once daily during weeks 1-3 of each 4-wk cycle)	Placebo
Cabozantinib	VEGFR 1-3, MET and AXL	CELESTIAL (NCT01908426)	Cabozantinib (60 mg once daily)	Placebo
Ramucirumab	VEGFR	REACH-2 (NCT02435433)	Ramucirumab 8 mg/kg intravenous ramucirumab every 2 wk	Placebo
Immunotherapy				
Nivolumab	PD-1	CheckMate-459 (NCT02576509)	Nivolumab (240 mg intravenously every 2 wk)	Sorafenib(400 mg orally twice daily)
Nivolumab plus ipilimumab	PD-1, CTLA-4	CheckMate-040 (NCT01658878)	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, administered every 3 wk (4 doses), followed by nivolumab 240 mg every 2 wk (arm A); nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, administered every 3 wk (4 doses), followed by nivolumab 240 mg every 2 wk (arm B); or nivolumab 3 mg/kg every 2 wk plus ipilimumab 1 mg/kg every 6 wk (arm C)	Placebo
Pembrolizumab	PD-1	KEYNOTE-240 (NCT02702401)	Pembrolizumab (200 mg intravenously every 3 wk for at least 35 cycles during approximately 2 yr)	Placebo

¹Eligible patients who had received previous treatment with sorafenib.

CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PD-1: Programmed cell death protein 1; VEGFR: Vascular endothelial growth factor receptor; FGFR: Fibroblast growth factor receptor; PDGFR: Platelet-derived growth factor receptors; OS: Overall survival; PFS: Progression-free survival; PD-L1: Programmed death ligand-1.

FIRST-LINE SYSTEMIC THERAPIES

Sorafenib

The need for new and better treatments for patients in advanced stages has led researchers to develop molecules to specifically target components of the carcinogenesis process. Sorafenib was the first oral multikinase inhibitor drug approved by the Food and Drug Administration (FDA) in 2007 to treat advanced HCC. *In vitro* experiments found that this drug inhibited HCC cell line growth and angiogenesis by inhibiting the RAF/MEK/ERK signalling pathway, as well as tyrosine and serine/threonine kinase receptors, including those for VEGF, PDGF, c-KIT, FLT3 and BRAF[12]. This drug is indicated in patients with preserved liver function who are not candidates for surgical or locoregional therapies and those with advanced tumours according to the BCLC classification and the Child-Pugh scale[9].

Sorafenib was the first drug to significantly improve the survival of patients with advanced HCC in the Asia-Pacific region. The median overall survival (OS) was 6.5 mo [95% confidence interval (CI): 5.56-7.56] in patients treated with sorafenib compared to 4.2 mo (3.75-5.46) in patients treated with placebo [13]. Similar results in terms of improved survival were observed in the SHARP clinical trial (ClinicalTrials.gov identifier: NCT00105443), a phase III, double-blind, placebo-controlled study that evaluated the effect of sorafenib on OS and time to symptomatic progression in patients diagnosed with advanced HCC. Here, the median OS was 10.7 mo in the sorafenib group and 7.9 mo in the placebo group. The most frequent adverse events in the sorafenib group were weight loss, diarrhoea, hypophosphataemia, and hand-foot skin reactions. Based on these trials, sorafenib became the first targeted therapy drug to be approved for the treatment of advanced HCC and has been the first-choice drug since its approval. Currently, the treatment of patients with sorafenib until significant radiographic progression and simultaneous treatment with regorafenib (discussed below) are recommended[9]. Unfortunately, only 30% of sorafenib users benefit, and within a short period of time, resistance to sorafenib often develops, rendering further use ineffective[14].

Lenvatinib

Following the approval of sorafenib, research led to the recognition of lenvatinib as another drug targeting important receptors and pathways in HCC. Lenvatinib is an oral receptor tyrosine kinase inhibitor and was approved in 2018 by the FDA as a first-line treatment for unresectable HCC[15]. VEGF receptor (VEGFR), FGF receptor (FGFR), PDGFR α , RET, and KIT[16,17] are among its therapeutic targets. In preclinical models, lenvatinib was shown to selectively inhibit the proliferation of human HCC cell lines and *in vivo* tumour growth in xenograft models[18]. The approval of this molecule was based on the REFLECT clinical trial (ClinicalTrials.gov identifier: NCT01761266), a phase III, multicentre, open-label, non-inferiority trial that evaluated the OS of patients diagnosed with advanced HCC treated with lenvatinib *vs* patients treated with sorafenib. Lenvatinib met non-inferiority criteria against sorafenib, as the median survival for lenvatinib was 13.6 mo (95%CI: 12.1-14.9) *vs* 12.3 mo for the sorafenib group [12.3 mo, 10.4-13.9; hazard ratio (HR): 0.92, 95%CI: 0.79-1.06][19]. The most common adverse events in the lenvatinib group in this study were diarrhoea, loss of appetite, and weight loss.

Atezolizumab plus bevacizumab

Atezolizumab is a monoclonal antibody that selectively targets programmed death ligand-1 (PD-L1) to reverse the suppression of T-cell activity[20]. Its activity was assessed through an assay that determined predictive correlates of response to this antibody in cancer patients. According to Herbst *et al*[20], who studied various types of cancer, responses were observed in patients with tumours expressing high levels of PD-L1, mainly when it was expressed on tumour-infiltrating immune cells[20].

Conversely, the monoclonal antibody bevacizumab interferes with angiogenesis and tumour growth by inhibiting VEGF activity[21]. Finn *et al*[22] demonstrated the potential of bevacizumab as a promising anti-VEGF treatment for liver cancer in preclinical trials. They evaluated the effect of this humanized antibody in an orthotopic mouse model of HCC using the Hep3B cell line and found that bevacizumab treatment significantly reduced tumour microvessel density and alpha-fetoprotein (AFP) levels and prolonged time to progression compared to the control group[22].

The combination of atezolizumab and bevacizumab is a therapeutic strategy aiming to simultaneously inhibit PD-L1 (atezolizumab) and VEGF (bevacizumab) signalling in patients with advanced HCC. This combination was evaluated in the Imbrave150 clinical trial (ClinicalTrials.gov identifier: NCT03434379), a global, open-label, phase III study that evaluated the effect of the combination of these two antibodies in patients with unresectable HCC against the effect of sorafenib as a single drug, resulting in improved OS and progression-free survival (PFS) for the combination group [67.2% (95%CI: 61.3-73.1) and 54.6% for the sorafenib group (95%CI: 45.2-64.0)][23]. A few years later, a longer follow-up of these patients was performed, reporting that the combination maintained the improvement in patients over the effect of sorafenib[24]. Accordingly, atezolizumab plus bevacizumab combination therapy was very recently approved by the FDA (2020) as the initial treatment for advanced HCC, adding a targeted drug combination to the first-line treatment strategies for these patients[25].

Tremelimumab plus durvalumab

In October 2022, the FDA approved the combination of tremelimumab plus durvalumab for treating

patients with unresectable HCC, which could form part of the first-line treatment for this cancer[26].

Tremelimumab is a fully human immunoglobulin G (IgG)2 monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), a receptor that inhibits T-cell activity[27]. Duffy *et al*[28] subjected patients diagnosed with HCC to a study evaluating the efficacy of treatment with tremelimumab plus an ablative procedure performed during week 6 (ClinicalTrials.gov identifier: NCT01853618). The authors observed that such a combination led to the accumulation of intratumoural CD8+ T-cells and suggested it as a potential new treatment for patients with advanced HCC[28]. In contrast, durvalumab is another human monoclonal antibody that binds to the PD-L1 protein and has been shown to be effective in liver cancer and in small-cell lung cancer, especially when used in combination with another therapeutic agent[29,30].

A phase I/II clinical trial (ClinicalTrials.gov identifier: NCT02519348) evaluated the safety and efficacy of monotherapy and combination treatment of tremelimumab plus durvalumab (300 mg and 1500 mg, respectively) in patients with HCC who had progressed on, were intolerant to, or refused sorafenib. The objective response rates (ORRs) were 24.0% (95%CI: 14.9-35.3) for the combination, 10.6% for durvalumab (5.4-18.1), and 7.2% (2.4-16.1) for tremelimumab, while the median OS was 18.7 (10.8-27.3), 13.6 (8.7-17.6), and 15.1 (11.3-20.5) months, respectively[31]. However, the clinical study that led to the approval of this combination was HIMALAYA (ClinicalTrials.gov identifier: NCT03298451), a phase III and global study with a heterogeneous population representative of HCC patients and no previous systemic treatment, which also evaluated the effect of durvalumab monotherapy and compared it to sorafenib. Here, the median OS was 16.43 mo for the combination (95%CI: 14.16-19.58), 16.56 mo (95%CI: 14.06-19.12) with durvalumab, and 13.77 mo (95%CI: 12.25-16.13) with sorafenib. The combination significantly improved OS over sorafenib, and durvalumab was not inferior to sorafenib in these patients, suggesting that it could be used as a first-line treatment[32].

SECOND-LINE SYSTEMIC THERAPIES AND IMMUNOTHERAPY

Although approximately 30% of patients receiving sorafenib show improvement, resistance to treatment can develop after prolonged use (approximately 6 mo), rendering it ineffective after this period[14]. Therefore, second-line treatments are indicated for patients who either have progressed on previous sorafenib or do not respond to it. Notably, to date, no clinical trials have evaluated second-line therapy after lenvatinib[33].

Regorafenib

Regorafenib is another oral multikinase inhibitor that primarily targets VEGFR, PDGF receptors, FGFR, RET, and RAF and, in preclinical trials, was shown to significantly inhibit liver tumour development [34]. In addition, it activates proteins involved in MAPK signalling, apoptosis, and autophagy[35]. The FDA approved this drug as a second-line treatment for patients who have already been treated with sorafenib. The safety and efficacy of this drug in humans were tested in a multinational, randomized, double-blind, placebo-controlled, phase III clinical trial (RESORCE, ClinicalTrials.gov identifier: NCT01774344), in which the median OS was 10.6 mo (95%CI: 9.1-12.1) for the regorafenib group *vs* 7.8 mo (6.3-8.8) in the placebo group[36]. The most common adverse events reported in this study were hypertension, hand-foot skin reactions, fatigue, and diarrhoea. Thus, because of the survival benefit of regorafenib in HCC patients unresponsive to sorafenib, it was approved by health agencies in several countries, including the United States, Japan, and China.

Cabozantinib

Cabozantinib is a multikinase inhibitor suppressor of tumour growth, metastasis, and angiogenesis that primarily targets VEGFR but also targets MET and AXL, which in addition to being implicated in HCC progression are involved in sorafenib resistance[37]. Initially, this drug showed clinical activity in a phase II study in previously untreated HCC patients and those with progression or no response to sorafenib, resulting in a median OS of 5.5 mo with no significant radiographic responses[38]. However, its approval was based on the results of the CELESTIAL clinical trial (ClinicalTrials.gov identifier: NCT01908426), a randomized, double-blind, phase III trial evaluating cabozantinib *vs* placebo in patients diagnosed with advanced HCC, in which cabozantinib demonstrated significant benefit over placebo in OS and tumour PFS. The median OS was 10.2 mo with cabozantinib and 8.0 mo with placebo (95%CI: 0.63-0.92). The median PFS was 5.2 mo with cabozantinib and 1.9 mo with placebo (95%CI: 0.36-0.52)[39]. In 2019, the FDA approved cabozantinib for treating patients with advanced HCC who were previously treated with sorafenib[40].

Interestingly, this drug is involved in tyrosine kinase inhibition and has also been reported to be an immunomodulator since some of its targets are involved in the immune response. Indeed, in combination with anti-programmed cell death protein 1 (PD-1) therapy, cabozantinib showed a greater antitumour effects than monotherapy or placebo in animal models of HCC. On its own, cabozantinib significantly increased neutrophil infiltration and reduced intratumoural CD8+ PD-1+ T-cell ratios, while the combination further stimulated this effect[41].

Ramucirumab

Ramucirumab is an antiangiogenic anti-VEGFR2 monoclonal antibody[42,43]. The efficacy of this drug was tested in the REACH clinical trial, a randomized, placebo-controlled, double-blind, multicentre, phase III trial (ClinicalTrials.gov identifier: NCT01140347). Here, ramucirumab was tested against placebo in patients diagnosed with advanced HCC who were previously treated with sorafenib and who experienced either progression or intolerance. The median OS for the ramucirumab group was 9.2 mo (95%CI: 8.0-10.6) *vs* 7.6 mo (6.0-9.3) for the placebo group (HR: 0.87; 95%CI: 0.72-1.05; *P* = 0.14). Consistent with these results, second-line treatment with ramucirumab did not significantly improve survival over placebo in patients with advanced HCC[44]. A follow-up trial, REACH-2, was a randomized, double-blind, placebo-controlled, phase III trial comparing ramucirumab *vs* placebo at a 2:1 ratio in the same population, but this time for a preselected population with AFP concentrations \geq 400 ng/mL. The median OS was 8.5 mo (95%CI: 7.0-10.6) *vs* 7.3 mo (5.4-9.1); HR: 0.71 (95%CI: 0.53-0.95; *P* = 0.0199) and PFS [2.8 mo (2.8-4.1) *vs* 1.6 mo (1.5-2.7); 0.452 (0.33-0.60); *P* < 0.0001] were significantly improved in the ramucirumab group compared with the placebo group. This trial showed improved OS with ramucirumab compared to placebo in patients with HCC and AFP concentrations of at least 400 ng/mL who had previously received sorafenib[45].

Very recently, the clinical relevance of rechallenge treatment with previously administered drugs was evaluated, with five consecutive patients with advanced HCC who received rechallenge treatment with lenvatinib and with failure after treatment with ramucirumab. Here, the radiological findings using the modified Response Evaluation Criteria in Solid Tumours showed stable disease in four patients and a partial response in one. This trial demonstrated that re-exposure to lenvatinib treatment after ramucirumab might be effective for treating advanced HCC[46].

IMMUNOTHERAPY

Unfortunately, cancer cells can develop resistance to systemic therapies. Thus, more and better drug treatments must be devised for these patients. Potential strategies include combination approaches and immunological therapy. In fact, immunotherapy has now been postulated as a possible therapeutic strategy to treat different types of cancer.

Cancer cells can escape the defence mechanisms of immune cells in the tumour microenvironment, thus avoiding detection and elimination by host lymphocytes by downregulating stimulatory immunoreceptors and stimulating inhibitory immunoreceptors. For example, in the case of T cells, tumour cells can modulate stimulatory activity by downregulating MHC-I on the surface. Conversely, inhibitory activity can be modulated by these cells through upregulation of PD-L1 on the surface[47-49]. Such molecules are known as immune checkpoints, which act as modulators of immune responses. These molecules can be used as pharmacological targets to generate various monoclonal antibodies that modulate their activity. Among the most studied immune receptors are PD-1, CTLA-4, LAG3, TIM3, TIGIT, and BTLA[49].

Immunotherapy has been shown to have significant efficacy in the treatment of different types of cancer, including HCC[50], making it an excellent option for patients with cancer progression or for whom systemic therapy with sorafenib was ineffective. Several immune checkpoint inhibitors that primarily target CTLA-4, PD-1, and its ligand PD-L1 have been tested to date. Some ICIs have also been approved by the FDA for the treatment of HCC. PD-L1, also called B7-H1 or CD274, is expressed in many cancer and immune cells and plays an essential role in blocking the "cancer immunity cycle" by binding to PD-1 and B7.1 (CD80), both of which are negative regulators of T-cell activation[51,52].

Antibody-based therapy is the main strategy designed to modulate the tumour immune response, but other cancer immunotherapeutic strategies, such as adoptive cell therapy, chimeric antigen receptor-modified immune cells, engineered cytokines, and therapeutic cancer vaccines, are still under development[53,54].

Nivolumab

Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor, inhibiting its interaction with PD-L1 and PD-L2 and restoring T-cell activity[55]. Nivolumab has been shown to be effective in several malignancies, including melanoma, renal Hodgki's lymphoma, lung cancer, and gastric cancer[56-60].

Nivolumab was evaluated in HCC patients in a study called CheckMate-040 (ClinicalTrials.gov identifier: NCT01658878), a phase I/II, open-label, non-comparative, multicentre trial that included patients with advanced HCC who either had also reported progression after treatment with sorafenib or were sorafenib naive. Patients received intravenous nivolumab 240 mg every 2 wk until unacceptable toxicity or disease progression occurred. In this study, nivolumab showed favourable clinical activity and safety with manageable toxicities, suggesting that it could be suitable for patients with advanced HCC[61].

Subsequently, the activity of nivolumab (240 mg intravenously every 2 wk) was compared to that of sorafenib (400 mg orally twice daily) in a randomized, open-label, phase III trial (CheckMate 459, ClinicalTrials.gov identifier: NCT02576509) until disease progression or unacceptable toxicity. OS was improved from 14.7 mo for sorafenib to 16.4 mo with nivolumab but did not reach statistical significance ($P = 0.0752$). In addition, there was no significant difference in PFS (3.7 *vs* 3.8 mo). The ORRs for nivolumab and sorafenib were 15% and 7%, respectively. Nivolumab showed relevant clinical activity and a favourable safety profile for patients with advanced HCC. However, nivolumab administered for the first time in these patients was not significantly better than sorafenib in terms of OS[62]. Thus, in September 2017, nivolumab was approved by the FDA as a second-line treatment for patients with advanced HCC. It is worth mentioning that this antibody has only been approved by this institution[63].

Recently, the effect of the combination of nivolumab plus ipilimumab, a fully human IgG1 monoclonal antibody that binds to CTLA-4 on T cells[64], was evaluated. The efficacy of this combination was tested in the CheckMate 040 study (ClinicalTrials.gov identifier: NCT01658878), a multicentre, open-label, multicohort, phase I/II study in which it was shown that the combination of nivolumab plus ipilimumab led to high OS rates and had a manageable safety profile[65]. Based on the results of this trial, in March 2020, the FDA approved the combination of nivolumab plus ipilimumab as a second-line treatment for patients with HCC who had been previously treated with sorafenib[66].

Pembrolizumab

Pembrolizumab is an anti-PD-1 monoclonal antibody that demonstrated clinical efficacy in patients with advanced HCC. This antibody was evaluated in a non-randomized, multicentre, open-label, phase II study in patients with BCLC B-C HCC pre-treated with sorafenib (ClinicalTrials.gov identifier: NCT02702414), and it showed antineoplastic activity with an ORR of 17% and a manageable safety profile[67]. Based on these results, in November 2018, the FDA granted accelerated approval to pembrolizumab for patients with HCC who had been previously treated with sorafenib[68]. A subsequent study was then conducted evaluating pembrolizumab in a randomized, double-blind, phase III study in patients with advanced HCC previously treated with sorafenib (KEYNOTE-240, ClinicalTrials.gov identifier: NCT02702401). Here, the median OS was 13.9 mo (95%CI: 11.6-16.0 mo) for pembrolizumab *vs* 10.6 mo (95%CI: 8.3-13.5 mo) for placebo (HR: 0.781; 95%CI: 0.611-0.998; $P = 0.0238$). The median PFS for pembrolizumab was 3.0 mo (95%CI: 2.8-4.1 mo) *vs* 2.8 mo (95%CI: 1.6 to 3.0 mo) for placebo[69].

Additionally, the KEYNOTE-394 trial (ClinicalTrials.gov identifier: NCT03062358), a randomized, double-blind, phase III study, evaluated the efficacy of pembrolizumab plus best supportive care *vs* placebo in Asian HCC patients as second-line therapy. Overall, the results were consistent with those seen in previous trials, further supporting the use of pembrolizumab in patients with advanced HCC. Here, the median OS was 14.6 mo (12.6-18.0) for pembrolizumab and 13.0 mo (10.5-15.1) for placebo (95%CI); furthermore, pembrolizumab showed significant improvement of PFS (HR: 0.74, 95%CI: 0.60-0.92, $P = 0.0032$)[70].

INNOVATIVE STRATEGIES FOR HCC TREATMENT

Drug combination and repurposing

Currently, monotherapies are ineffective in fighting cancer mainly due to the development of resistance of cancer cells to available drugs[71], and preclinical findings may not be replicated in patients. For instance, the monoclonal antibody bortezomib demonstrated promising antineoplastic activity in preclinical assays, but in humans, it did not show notable single-agent activity compared to sorafenib [72]. Thus, more and better treatment options are needed for these patients, and drug combinations are promising options. This strategy consists of simultaneously administering two or more drugs aimed at different cancer-specific drug targets and has shown significant benefits compared to monotherapy[73]. However, combining drugs must become a rational strategy that guarantees significant pharmacological responses, especially for those patients who either did not respond to current therapy or developed resistance.

Several tools have been developed for the identification of potentially useful drug combinations; these tools include dose-response matrices, RNA interference technology, and the wide adaptation of clustered regularly interspaced short palindromic repeats (CRISPR) systems, as well as more novel techniques such as patient-derived xenograft (PDX) models and *ex vivo* primary cell and organoid models[74]. For instance, Lim *et al*[75] used PDXs of HCC, PDX-derived organoids and a hybrid experimental-computational approach—namely, the quadratic phenotypic optimization platform—and found that the combination of the second-generation proteasome inhibitor ixazomib and the CDK inhibitor dinaciclib (Dina), which they tested *in vitro* and *in vivo*, is effective against HCC[75]. Another example of the usefulness of these strategies is CRISPR-Cas9 combinatorial screening, a technique that accelerated the discovery of combination treatment with the approved drug ifenprodil (an NMDA receptor antagonist) and sorafenib as a new therapeutic alternative for advanced HCC[76].

Therefore, implementing the abovementioned strategies should aid the discovery of potentially useful drug combinations. In this manner, medical staff may have different choices and establish a selection order more suitable for each HCC patient in a personalized manner[77,78].

Conversely, it is well known that the discovery of new molecules with pharmacological activity is a process with two main disadvantages: Time and cost. It takes at least 10 years to bring a new drug to the market, and the approximate cost ranges from \$314 million to \$2.8 billion[79]. Furthermore, in emergency situations such as cancer, the demand for effective treatments is extremely high, and additional strategies are required to obtain novel therapies in an expedited manner. Thanks to advances in pharmacology and genomics, several non-cancer drugs have been shown to have great potential for use in treating multiple cancers. Drug repurposing is a strategy that involves the discovery of already known drugs initially used to treat other diseases but with the potential to treat various malignancies. The main advantage of this approach is that it allows an accelerated and less costly process to identify new cancer treatments since it focuses on the selection of drugs already approved by relevant health institutions[80,81]. Some non-cancer drugs showing antineoplastic activity against HCC and with high repurposing potential are described below and summarized in Table 3.

One of the differences between repositioned drugs and existing drugs approved to treat HCC is that the latter target relatively few signalling pathways; in contrast, repositioned drugs have the enormous advantage of targeting a surprisingly wide variety of signalling pathways involved in liver carcinogenesis (Table 3). For instance, Nair *et al*[82] identified CDC20 as a marker of poor prognosis during the development of early and advanced HCC. Through molecular docking studies, it was determined that labetalol, a beta blocker, binds with high affinity to CDC20[82], suggesting that the effect of labetalol against the development of HCC should be tested. The same research group further investigated this possibility by *in vitro* cytotoxicity studies, in which labetalol significantly inhibited the growth of the HepG2 cell line[83]. Subsequent application of bioinformatics analysis tools to repositioned drugs provides an incredible advantage for the identification of unknown drug targets and signalling pathways potentially involved in liver carcinogenesis.

Antihistamines

Histamine exerts a variety of physiological activities *via* its G protein-coupled receptors, the activation of which has been associated with the progression of different types of cancer[84,85]. It is well known that histamine favours the development of different types of cancer, including liver cancer[86]. Accordingly, overexpression of the histamine H1 receptor (H1HR) is associated with HCC cell proliferation and metastasis by inducing cell cycle progression, lamellipodia production, matrix metalloprotease 2 (MMP2) production and inhibition of apoptosis. Furthermore, suppressing H1HR activity significantly inhibited tumour growth and metastasis in mouse xenograft models[86]. Interestingly, very recently, it was shown that antihistamine consumption is associated with a significant decrease in the developing of liver cancer in patients diagnosed with HBV, HCV or both viruses[87].

Astemizole

Ellegaard *et al*[88] analysed cohort studies and reported that the use of cationic amphiphilic antihistamines, including astemizole (an H1-antihistamine), was associated with a significant reduction in mortality in lung cancer patients[88]. It is worth mentioning that astemizole might affect cancer cell proliferation *via* different molecular mechanisms, including ion channels.

The ether α -go-go-1 (Eag1) potassium channel has been reported to play an important role in the development of several types of cancer, such as liver, cervical, breast, lung and colon cancer[89-93], suggesting that this channel is a potential early biomarker and drug target for these tumours[94]. Eag1 overexpression has been implicated in cell cycle progression and cancer cell proliferation[95], and inhibition of this channel has reduced tumour progression in both *in vitro* and *in vivo* assays in leukaemia and gastric cancer[86-97]. De Guadalupe Chávez-López *et al*[98] found that astemizole inhibited cell proliferation and induced apoptosis in human HCC cell lines[98]. In the same study using an HCC model induced by diethylnitrosamine (DEN) in mice, they found that astemizole inhibited tumour development and decreased Eag1 mRNA and protein levels[98].

Cytochrome P450 2J2 (CYP2J2) is implicated in the development of different types of cancer. In HCC, CYP2J2 is overexpressed, and its activity promotes cell proliferation[99-101]. Interestingly, astemizole and loratadine inhibit CYP2J2 activity[102]. Ellegaard *et al*[88] proposed the possibility that this drug targets this protein, which would partially explain the effect of reduced mortality in lung cancer patients [88].

TRPV2 is a calcium channel expressed in and associated with several types of cancer, including HCC progression. Both mRNA and protein levels of this channel are increased in well-differentiated HCC tumour tissue compared to undifferentiated tissue. There is a strong association between its expression and portal vein invasion. Van den Eynde *et al*[103] reported that TRPV2 is related to endometrial cancer progression and identified astemizole, loratadine, and clemizole as TRPV2 blockers, with loratadine being the most potent antagonist, leading to inhibition of cell proliferation and migration in *in vitro* assays in HEK293 cells[103].

Table 3 Identified drugs and their targets for drug repurposing in hepatocellular carcinoma

Drug	Original therapeutic indication	Molecular targets in HCC	Ref.
Antihistamines	Allergy	H1R-H4R, Eag1, CYP2J2, TRPV2, AP-1, NF-B	[88,91,96,98,102,103,105,109,111,113,115,116]
Raloxifene, bazedoxifene	Breast cancer (raloxifene), osteoporosis	ER-, ER-, GPER, IL-6R, aHR, NF-B, STAT3, PI3K/AKT, MAPK	[135-137,141,142]
Disulfiram	Alcoholism	NF-B, TGF- β , ROS-JNK	[149-151,157]
Clofazimine	Antimycobacterial used to treat leprosy	Wnt/-catenin pathway	[166-178]
Albendazole	Anthelmintic	Tubulin, ERK1/2-HIF-1 α -p300/CREB	[175]
Pimozide	Antipsychotic used to manage Tourette's Disorder	STAT3, Wnt/-catenin	[185,188]
Natamycin	Macrolide antifungal	PRDX1	[191]
Metformin	Glycemic control in type 2 diabetes mellitus	PI3K-mTOR pathway, AMPK	[200-202,206,207]
Valproate	Anticonvulsant	HDAC, Notch-1, MAPK pathway, -catenin pathway	[220,221,223]
Atorvastatin	Lower lipid levels and reduce the risk of cardiovascular disease	Mevalonate pathway	[231]
Celebrex	NSAID	COX-2, PNO1	[237,243]
Hydroxychloroquine	Antimalarial	Autophagy inhibition, TLR9 pathway	[247]

NSAID: Non-steroidal anti-inflammatory drug; mTOR: Mechanistic target of rapamycin; HCC: Hepatocellular carcinoma; NF-kB: Nuclear factor kB; AP-1: Activating protein-1; CYP2J2: Cytochrome P450 2J2; ER: Oestrogen receptor; IL-6R: Interleukin-6R; STAT3: Signal transducer and activator of transcription 3; PI3K: Phosphoinositide 3-kinase; TGF- β : Transforming growth factor- β ; PRDX1: Peroxiredoxin 1; HDAC: Histone deacetylase; aHR: Adjusted hazard ratio.

Loratadine

Loratadine is a second-generation antihistamine indicated for the treatment of allergic rhinitis and urticaria. It is a selective H1HR receptor antagonist[104]. Fritz *et al*[105,106] evaluated the effect of loratadine through retrospective studies in patients diagnosed with breast cancer and melanoma and found that loratadine use was associated with improved OS[105,106]. In patients diagnosed with lung cancer, a cohort study found that the use of loratadine or its metabolite desloratadine was associated with a significant reduction in mortality; the authors proposed that cancer-related changes in lysosomal membranes could favour the entry of these antihistamines[88,107]. To date, there has been scarce evidence studying the effect of loratadine in HCC. In a thesis from a few years ago, the cytotoxic effect of the combination of loratadine and cisplatin in HCC cell lines was evaluated; loratadine alone had a concentration-dependent cytotoxic effect on liver cancer cell lines, and the combination of loratadine with cisplatin had a synergistic effect[108]. The same thesis showed that loratadine alone and in combination also induced apoptosis and cell cycle arrest in the G2/M phase. Loratadine targets proteins that have been suggested to be involved in the development of HCC. As in the case of astemizole, loratadine might exert antineoplastic effects through H1HR antagonism, lysosomal membrane sensitization, TRPV2 calcium channel blockade and inhibition of CYP2J2 activity[86,88,102,103]. Furthermore, it has been reported that loratadine could exert anti-inflammatory activity by inhibiting the inflammatory response triggered by NF-kB signalling[109], an effect that reduces the levels of proinflammatory components, including interleukin (IL)-6 and tumour necrosis factor (TNF)- α . The effect of loratadine on HCC and its potential mechanisms of action deserve further investigation.

Deptropine

Deptropine is a first-generation H1HR antihistamine indicated to treat asthma[110]. This drug has activity against cancer cells. For example, *in vitro* assays in human liver cancer cells showed that, compared to the activity of other first- and second-generation antihistamines, deptropine was more potent in inhibiting cell proliferation and inducing autophagosome formation by significantly increasing the expression of light chain 3B-II. In mouse xenograft models, deptropine potently inhibited the tumour effect[111].

Cyproheptadine

This antihistamine is a potential anti-HCC agent. Feng *et al*[112] evaluated the activity of cyproheptadine in liver cancer cell viability and found that this drug had a potent inhibitory effect on cell proliferation through cell cycle arrest. Interestingly, a minimal cytotoxic effect was observed in healthy

hepatocytes[112]. Subsequently, a cohort study in Taiwanese patients at different stages of HCC compared patients who received cyproheptadine treatment and those who did not. The adjusted HR (aHR) of all-cause mortality significantly decreased in all stages in the patients who received palliative treatments with cyproheptadine use compared with those who received palliative treatments without cyproheptadine use (all $P < 0.0001$ and aHR = 0.76, 0.80, 0.66, and 0.66 for stages I, II, III, and IV, respectively). The authors suggested that cyproheptadine could improve survival in patients with HCC at any stage[113]. The same research group conducted a case report documenting that a 62-year-old woman with suspected advanced HCC and bone metastases showed disease remission after cyproheptadine monotherapy[114]. A dose of 4 mg of this drug three times daily for 17 mo reduced serum AFP concentrations from 17697.62 ng/mL to 4.3 ng/mL in only 3 mo. A liver biopsy performed two months after starting cyproheptadine treatment showed no malignancy. This outcome was previously observed in another case report in which two patients with HCC and lung metastases were treated with a combination of cyproheptadine plus thalidomide (it should be noted that the cyproheptadine prescription was indicated for skin itching). Computed tomography imaging showed complete remission of HCC in both patients after 6 mo and 6 wk of treatment[115].

A cohort study evaluated the efficacy of the combination of cyproheptadine with sorafenib compared to sorafenib alone in patients with advanced HCC. The median OS was 11 mo in the combination group (95%CI: 6.8-15.1 mo) and 4.8 mo in the sorafenib group (95%CI: 3.1-6.6 mo), while the median PFS time was 7.5 mo (95%CI: 5.1-10.0 mo) in the combination group compared with 1.7 mo (95%CI: 1.4-2.1 mo) in the sorafenib group[116].

Roles of other histamine receptors and antihistamines in HCC

Histamine 2 receptor: Histamine receptor 2 (H2HR) activation has an inhibitory effect on tumour progression in colorectal cancer; gene expression profiling studies in tumour samples from colorectal cancer patients described the elevated expression of this receptor, associated with improved OS outcomes[117]. In human liver cancer cells, H2HR activation leads to the inhibition of IL-6 expression and signalling, arresting cell proliferation[118]. In contrast, there is evidence that H2HR activation in HCC favours the expression of β -catenin and survivin, leading to cell survival[119]. Cimetidine, an H2 antihistamine, decreases intracellular cAMP concentrations, as well as EGF-induced cell proliferation and migration, and it has been suggested as an HCC chemopreventive agent[120]. Additionally, cimetidine treatment was shown to inhibit liver carcinogenesis in rats with DEN-induced HCC[121]. Recently, Crouchet *et al*[122] developed a system in human liver cells that models a clinical prognostic liver signature predicting long-term liver disease progression to HCC, and they identified nizatidine, an H2HR antihistamine, for the treatment of advanced liver disease and prevention of HCC[122].

Histamine 3 receptor: The H3HR receptor has been described to participate in the carcinogenesis of different types of cancer, including colorectal and pancreatic cancer[123,124]. In tumour tissues from HCC patients, H3HR was overexpressed and associated with poor prognosis, and its activation promoted the growth and metastasis of HCC cell lines by inducing lamellipodia formation[125,126]. Zhang *et al*[126] reported that H3HR activation favours HCC progression through an acceleration of the G1-S phase transition, inhibition of apoptosis, and activation of the AMPc/PKA/CREB signalling pathway to downregulate the expression of CDKN1A, a cyclin-dependent kinase inhibitor that has anti-oncogene activity[126]. Thus, the oncogenic role of H3HR might be antagonized as a potential therapy in HCC.

Histamine 4 receptor: Analysis of cancer genomic data from The Cancer Genome Atlas showed that the histamine H4 receptor (H4HR) is slightly but significantly overexpressed in human HCC tumour tissues compared to healthy tissue[84]. Furthermore, patients with increased H4HR protein expression in tumour cells also had increased tumour sizes and more metastasis compared to those with lower receptor expression, suggesting that H4HR levels could be used as a prognostic marker for liver cancer [127]. However, to date, there have been insufficient studies demonstrating the role of H4HR in HCC and its clinical relevance, so it is crucial to investigate its association with this cancer.

ESTROGEN RECEPTOR MODULATORS

According to the Global Cancer Observatory, liver cancer ranks fifth in incidence in men, while in women, it ranks ninth[1]. This fact has attracted the attention of researchers, who have argued that oestrogens explain this difference. Accordingly, oestrogens play a protective role against liver damage and prevent the development of HCC[128-130]. Epidemiological data have indicated that oestrogen deficiency in peri- and postmenopausal women increases the risk of developing liver damage and increases HCC incidence in postmenopausal women; in concordance, oestrogen treatment suppresses this phenomenon[131,132].

Both isoforms of the nuclear oestrogen receptor (ER), ER- α and ER- β , are involved in the development of liver cancer; however, the functions of ER- β have not yet been fully described. Both ER- α and ER- β are expressed in the liver under normal conditions, but their expression is modified during inflammatory

processes. Both are decreased in HCC patients compared to healthy tissue samples[133] and are believed to lose their function during disease progression; indeed, the ER- α isoform might even be considered a predictor of poor prognosis in HCC[128,134]. Conversely, Matsushima *et al*[135] reported that the selective oestrogen receptor modulators (SERMs) raloxifene and bazedoxifene inhibited HCC progression through their specific interaction with ER- β . They proposed that both drugs could activate the ER- β receptor in the liver, which through downstream signal transduction suppresses TGF-induced HCC cell migration *via* inhibition of Akt[135].

Raloxifene is indicated for the treatment of osteoporosis and is used for the treatment and prevention of breast cancer[136]. Raloxifene is a potent inhibitor of the IL-6/GP130 signalling pathway, which is involved in the process of oncogenesis of various cancers, including HCC[137]. This research group observed that raloxifene inhibited cell viability in human liver cancer cell lines. Furthermore, using an *in vivo* model, they also demonstrated that it could inhibit tumour growth.

Because liver cancer frequently develops in the context of chronic inflammatory liver disease, proinflammatory cytokines and immune cells play important roles in carcinogenesis. One of the most relevant cytokines in the development of HCC is IL-6; when overproduced, it has a strong effect on liver carcinogenesis, and its high expression is related to a high rate of metastasis and poor prognosis in HCC [138-140]. Naugler *et al*[141] reported in an animal model that oestrogen administration inhibited IL-6 secretion and significantly reduced DEN-induced injury in males[141]. When IL-6 binds to its receptor, it recruits JAK, leading to activation of STAT3, a transcription factor that favours proliferative processes, angiogenesis, invasion, *etc*[142]. In addition, ER- α could interact directly with NF- κ B and inhibit IL-6 secretion, and raloxifene could interact with ER- α and inhibit IL-6 secretion and thus tumour progression[142].

OTHER DRUGS

Disulfiram

Disulfiram is an FDA-approved drug from several years ago and has been extensively used in the treatment of alcoholism[143]. This drug has potential anticancer activity in different types of cancer, including lymphoma[144], breast cancer[145,146], and pancreatic cancer[147]. A phase II, multicentre, randomized, double-blind trial (ClinicalTrials.gov identifier: NCT00312819) evaluated the safety and efficacy of the combination of disulfiram with cisplatin and vinorelbine in patients diagnosed with lung cancer. Interestingly, a significant increase in survival was observed in patients given this combined treatment[148]. Intracellular copper (Cu) levels are significantly elevated in HCC cells and are associated with poor patient prognoses[149,150]. Surprisingly, the increase in Cu concentration might be harnessed for therapeutic use since disulfiram has Cu-dependent anticancer properties. Li *et al*[151] found that disulfiram inhibited the proliferation, migration, and invasion of liver cancer cells; interestingly, Cu enhanced this activity when combined with disulfiram; however, Cu alone did not [151]. In this regard, a phase I clinical trial determined the maximum tolerated dose of Cu administered with disulfiram in patients with liver cancer and found that 250 mg of daily Cu gluconate were well tolerated by these patients[152]. In the same study, temporary disease stabilization was observed in some patients, but there were no objective responses. Disulfiram can penetrate cancer cells and chelate intracellular Cu because Cu levels are elevated in many cancers. This action provides the advantage of specificity for cancer cells compared to healthy cells. Disulfiram might work as a Cu ionophore that induces oxidative stress by promoting reactive oxygen species (ROS) production, resulting in the inhibition of NF- κ B[151], a transcription factor involved in the regulation of inflammatory processes and the development of liver injury, as well as HCC progression[153,154]. Blocking NF- κ B signalling leads to an increase in ROS-induced toxicity and consequent cell apoptosis[155]. Furthermore, Thiery[156] found that inhibition of NF- κ B signalling also resulted in inhibition of liver cancer cell metastasis by reversing the epithelial-to-mesenchymal transition (EMT), an important process in cancer metastasis in which NF- κ B and TGF- β are important components[156]. Indeed, in this same study, disulfiram was found to inhibit TGF- β signalling. Interestingly, disulfiram plus Cu reversed EMT more effectively than disulfiram alone[151].

Most recently, Zhang *et al*[157] reported that disulfiram plus copper in combination with sorafenib resulted in increased anticancer activity against HCC under *in vitro* and *in vivo* conditions. Moreover, this combination synergistically inhibited the proliferation of human HCC cell lines and significantly increased autophagy and apoptosis compared to sorafenib alone. In addition, in a mouse orthotopic HCC xenograft model, the combination effectively inhibited tumour growth compared to the effect of sorafenib alone[157].

Clofazimine

The canonical Wnt/ β -catenin signalling pathway is a crucial component during embryonic development and normal adult homeostasis because it participates in processes such as cell differentiation, polarity, migration, and apoptosis[158]. However, abnormal activation of this pathway (especially of the transcription factor β -catenin) has been linked to cellular malignant transformation

and promotion of carcinogenesis, and it is present in many types of cancer, including HCC[159-161]. Notably, mutations in the *CTNNB1* gene, which codes for β -catenin, are the most frequent mutations during HCC[162,163]. Interestingly, clofazimine, an anti-leprosy agent, could be useful for treating Wnt-dependent cancers. For instance, it has been shown to be effective against triple-negative breast cancer, both *in vitro* and *in vivo*, through inhibition of Wnt/ β -catenin signalling[164,165]. Furthermore, Xu *et al* [166] demonstrated that clofazimine could effectively suppress HCC cell growth, inhibiting Wnt/ β -catenin canonical signalling[166]. This drug has been evaluated for some years, and the results have suggested that it might work successfully as an antitumour agent. For example, Van Rensburg *et al*[167] found that it inhibited HCC cell line proliferation *in vitro*[167]. In addition, in a phase II clinical trial in patients with unresectable or metastatic liver cancer, 600 mg of this drug were administered daily for two weeks, followed by a dose reduction to 400 mg until progression or death. In this trial, 13 of 30 treated patients had disease stability for up to 20 mo, and the median OS was 13 wk[168]. Furthermore, a phase II clinical trial evaluated the combination of clofazimine plus doxorubicin in patients diagnosed with HCC. Although no patients showed complete or partial response, this combination showed only mild toxic effects, and the authors recommended further studies involving this antileprosy agent[169]. Overall, these trials provided strong evidence to suggest that clofazimine might be useful in treating HCC.

Albendazole

Albendazole is an antiparasitic agent used to treat parenchymal neurocysticercosis and other helminth infections by blocking parasite microtubules, leading to the inhibition of glucose uptake and transport and, ultimately, cell death[170]. Interestingly, this drug has been reported to possess antitumour activity and has been studied in different malignancies, including liver, lung, breast, prostate, and colorectal cancers and melanoma[171-175]. Pourgholami *et al*[176] evaluated the effect of this drug in several liver cancer cell lines and in mouse xenograft models (human SKHEP-1 tumour growth in nude mice), reporting that the drug induced dose-dependent inhibition of [³H] thymidine incorporation in all the cell lines studied and a significant decrease in the number of SKHEP-1 cells significantly inhibiting tumour growth[176].

Pimozide

Pimozide is a dopamine receptor antagonist neuroleptic drug[177] that was approved by the FDA for the treatment of Tourette's syndrome and schizophrenia[178] and it has shown efficacy for the treatment of different types of cancer, such as breast cancer[179,180], prostate cancer[181], brain tumours[182], colorectal cancer[183], and chronic myelogenous leukaemia[184]. In liver cancer, pimozide effectively inhibited cell proliferation of HCC cell lines through disruption of Wnt/ β -catenin signalling and reduction of epithelial cell adhesion molecule expression, a marker of both liver stem cells[185] and HCC tumour-initiating cells[186,187]. Furthermore, Chen *et al*[188] found that pimozide was able to inhibit cell proliferation, migration, colony formation, and sphere formation *in vitro* in HCC cell lines and stem-like cells by suppressing STAT3 activity. Additionally, pimozide reduced the tumour burden in a xenograft model in nude mice[188]. Moreover, the same research group found that the antiproliferative effects of pimozide on HCC cell lines were reversible and in line with the involvement of cell quiescence and ROS production. Interestingly, pimozide combined with sorafenib synergistically inhibited HCC cell proliferation *in vitro*[188].

Natamycin

Natamycin is a natural polyene amphoteric macrolide antibiotic with antifungal properties[189]. It has been reported to significantly inhibit the proliferation of prostate cancer cells[190]. Conversely, An *et al* [191] found that natamycin induced apoptosis and inhibited the proliferation of HCC cells by triggering excessive ROS production through the downregulation of peroxiredoxin 1 (PRDX-1). Additionally, they found that the combination of natamycin plus sorafenib exerted a synergistic effect on cell growth suppression compared to the effect of monotherapy[191].

Dysregulation of cellular redox systems is a critical feature of many types of cancer. Increased ROS play a fundamental role in the tumour microenvironment, activating important signalling pathways in carcinogenesis, such as MAPK/ERK, JNK, and PI3K/AKT, and in turn activating NF- κ B, MMPs, and VEGF, consequently affecting angiogenesis, metastasis and cell survival in many types of cancer[192-194]. However, at significantly elevated ROS concentrations, cancer cells are able to develop antioxidant defence systems to maintain redox homeostasis and survive[195]. An example of this situation is the participation of the peroxiredoxin family, which consists of peroxidases that break down hydrogen peroxide, protecting the cancer cell from oxidative stress and consequently providing a survival advantage; thus, this family of enzymes are potential targets for tumour growth arrest and cancer therapy[196,197]. It is worth mentioning that the PRDX-1 isoform is the most abundant and positively regulated protein in different types of cancer, and its expression is associated with poor prognosis[198].

Valproic acid

Valproic acid is a drug that possesses anticonvulsant activity and is primarily indicated for the

treatment of epilepsy. However, it is also useful for treating migraine, bipolar disorder, anxiety, and psychiatric disorders[199]. The interest in testing the activity of this drug as an antineoplastic agent came from findings in human neuroblastoma models. This molecule was able to inhibit proliferation and induce differentiation of primitive neuroectodermal tumour cells *in vivo*, providing evidence for using valproic acid as a treatment for neuroblastoma patients[200]. Machado *et al*[201] reported the effect of this drug on human liver cancer cells both *in vitro* and *in vivo*. Valproic acid significantly inhibited cell proliferation in a dose-dependent manner, while in mouse xenograft models, it reduced tumour growth, in addition to negatively regulating Notch-1 mRNA levels[201]. Very recently, Bai *et al* [202] evaluated the effect of valproate in animal models of HCC in rats treated with DEN and found that this drug significantly reduced liver nodules and AFP levels, as well as other important liver enzymes, compared to rats treated with DEN alone. Additionally, valproate reduced inflammatory cytokines, such as TNF- α , IL-6, IL-1 β , NF- κ B and TGF- β 1, in liver tissue[202].

Lee *et al*[203] took advantage of the benefits of combination therapy to evaluate the effects of cytokine-induced killer (CIK) cells with valproic acid. CIK cells are *ex vivo* expanded T lymphocytes expressing natural killer and T-cell markers that are used as adjuvant therapy to reduce HCC recurrence, yet CIK cell monotherapy is insufficient to treat advanced HCC[203-205]. Therefore, this research group determined whether treatment with CIK cells and valproic acid synergized to inhibit tumour growth in mouse models of HCC. After seven days of the combined treatment, there was a synergistic effect on relative tumour volume in the animals since the relative tumour volume in control animals was significantly increased[206].

Additionally, Yu *et al*[207] implemented a therapeutic strategy in HCC cells *in vitro* and *in vivo* that consisted of testing the combined effect of valproic acid with proton and photon irradiation. Histone deacetylase (HDAC) inhibitors, including valproic acid, have shown promising results in the treatment of different cancers[208-210]. However, their use as monotherapy has not been satisfactory, so using them in combination with another therapy is an appealing strategy. HDAC inhibitors can sensitize human cancer cells to ionizing radiation[211], which is a therapeutic strategy for cancer[212]. In a study by Yu *et al*[207], valproic acid prolonged DNA damage and increased proton-induced apoptosis and ROS formation while suppressing the expression of nuclear factor erythroid 2-related factor 2, a transcription factor involved in cellular antioxidant regulation. In tumour xenograft models, valproic acid significantly enhanced tumour growth retardation[207]. In addition, An *et al*[213] reported that valproic acid could induce cellular senescence in HCC cells through its role as an HDAC inhibitor[213].

ONGOING CLINICAL TRIALS USING ONCOLOGY AND NON-ONCOLOGY DRUGS

Table 4 summarizes the ongoing clinical trials for HCC patients. Immunotherapy is currently positioned as the most innovative pharmacological strategy to treat different types of cancer, including liver cancer. In addition, it is interesting to note that most of the ongoing HCC clinical trials are evaluating the effects of combination therapy and that drug repurposing is gaining tremendous interest, as non-oncology molecules are now being tested. Next, the non-oncology drugs used in ongoing clinical trials (Tables 3 and 4) are discussed.

Metformin

This drug is commonly used for the treatment of type 2 diabetes and was approved by the FDA in 1994. Metformin lowers glucose levels and improves insulin sensitivity[214]. Surprisingly, metformin has been shown to have antineoplastic activity in different types of cancer[83,215]. It is one of the most successful non-cancer drugs used in oncology. Several clinical trials are currently investigating the therapeutic potential of this drug in various cancers, including breast, prostate, endometrial, and colorectal cancer[216-219]. In the case of liver cancer, metformin has gained interest as an antineoplastic agent, given the increased risk of developing liver cancer in diabetic patients. Meta-analyses have reported that metformin has a beneficial effect on the incidence and/or survival of patients with liver cancer. For example, Ma *et al*[220] reported the association between metformin use and improved survival in diabetic patients with liver cancer[220]. Afterwards, the same research group reported a meta-analysis of 19 studies in diabetic subjects and suggested that metformin use reduced the proportion of liver cancer by 48% compared to non-users[221]. At the molecular level, metformin reduces insulin levels, activating the PI3K-mTOR signalling pathway and inhibiting cell proliferation in cancers expressing the insulin receptor[222]. Other mechanisms include negative regulation of mTOR *via* AMPK activation[223].

Ongoing clinical trials in HCC patients are evaluating the use of metformin in combination with other molecules, such as vitamin C (ClinicalTrials.gov identifier: NCT04033107), statins (ClinicalTrials.gov identifier: NCT02819869) and Celebrex (ClinicalTrials.gov identifier: NCT03184493).

Statins (atorvastatin)

Statins are agents that decrease the level of low-density lipoprotein cholesterol in the blood. They are specific inhibitors of the mevalonate pathway through inhibition of the conversion of 3-hydroxy-3-

Table 4 Ongoing clinical trials involving monotherapy, drug combination and non-oncology drugs

Study title	NTC number	Study design	Drugs	Status
Monotherapy				
Study of Pembrolizumab (MK-3475) as Monotherapy in Participants With Advanced Hepatocellular Carcinoma (MK-3475-224/KEYNOTE-224)	NCT02702414	Phase II, non-randomized, parallel assignment, open label	Pembrolizumab	Active, not recruiting
An Investigational Immuno-therapy Study of Nivolumab Compared to Sorafenib as a First Treatment in Patients With Advanced Hepatocellular Carcinoma	NCT02576509	Phase III, randomized, parallel assignment, open label	Nivolumab. Sorafenib	Active, not recruiting
Exploratory Study on Combined Conversion Immuno-therapy for Liver Metastasis of MSS Type Initial Unresectable Colorectal Cancer Based on Gene Status	NCT05409417	Phase II, III, single group assignment, open label	Experimental drug	Recruiting
First-in-Human Safety, Tolerability and Antitumour Activity Study of MTL-CEBPA in Patients With Advanced Liver Cancer	NCT02716012	Phase I, non-randomized, parallel assignment, open label	MLT-CEBPA. Sorafenib (200 mg)	Active, not recruiting
Drug combination				
A Phase III, Open-Label, Randomized Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma (IMbrave150)	NCT03434379	Phase III, randomized, parallel assignment, open label	Atezolizumab. Bevacizumab. Sorafenib	Active, not recruiting
A Trial of Lenvatinib Plus Pembrolizumab in Participants With Hepatocellular Carcinoma	NCT03006926	Phase I, single group, open label	Lenvatinib. Pembrolizumab (200 mg)	Active, not recruiting
A Study of Durvalumab or Tremelimumab Monotherapy, or Durvalumab in Combination With Tremelimumab or Bevacizumab in Advanced Hepatocellular Carcinoma	NCT02519348	Phase II, randomized, parallel assignment, open label	Tremelimumab. Durvalumab. Bevacizumab	Active, not recruiting
Pembrolizumab With or Without Elbasvir/Grazoprevir and Ribavirin in Treating Patients With Advanced Refractory Liver Cancer	NCT02940496	Phase II, non-randomized, parallel assignment, open label	Elbasvir/Grazoprevir. Pembrolizumab. Ribavirin	Active, not recruiting
Clinical Recruitment of Patients With First-line Targeted Drug Resistance or Intolerance to Hepatocellular Cancer With PD-1 Inhibitor (Toripalimab, JS001) Detected on the NGS Platform Combined With Anlotinib	NCT05453383	Phase II, single group assignment, open label	Anlotinib. Toripalimab	Recruiting
TACE Combined With Camrelizumab and Apatinib in the Treatment of Advanced Liver Cancer	NCT05550025	Phase II, single group assignment, open label	Camrelizumab. Apatinib	Recruiting
IBR900 Cell Injection Combined With Lenvatinib or Bevacizumab in the Treatment of Advanced Primary Liver Cancer	NCT05411757	Phase I, single group assignment, open label	IBR900. Lenvatinib. Bevacizumab	Not recruiting yet
Trial to Evaluate the Safety of Talimogene Laherparepvec Injected Into Tumors Alone and in Combination With Systemic Pembrolizumab MK-3475-611/Keynote-611	NCT02509507	Phase I, II, non-randomized, sequential assignment, open label	Talimogene. Laherparepvec. Pembrolizumab	Active, not recruiting
HAIC Sequential TAE Combined With Lenvatinib and Tislelizumab in Unresectable HCC	NCT05532319	Phase II, single group assignment, open label	HAIC sequential TAE. Lenvatinib. Tislelizumab	Not recruiting yet
A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor	NCT04008797	Phase I, non-randomized, sequential assignment, open label	E7386. Lenvatinib	Recruiting
An Immuno-therapy Study to Evaluate the Effectiveness, Safety and Tolerability of Nivolumab or Nivolumab in Combination With Other Agents in Patients With Advanced Liver Cancer	NCT01658878	Phase I, II, parallel assignment, open label	Nivolumab. Sorafenib. Ipilimumab. Cabozantinib	Active, not recruiting
A Phase I Clinical Study of Recombinant Humanized Anti-BTLA Monoclonal Antibody (JS004) Injection Combined With Toripalimab Injection in Patients With Advanced Solid Tumors	NCT05427396	Phase I, single group assignment, open label	JS004. Toripalimab	Recruiting
mFOLFOX7 Plus Camrelizumab and Apatinib for Advanced HCC	NCT05412589	Phase II, single group assignment, open label	mFOLFOX7. Camrelizumab. Apatinib	Recruiting
Trial of PXS-5505 Combined With First Line Atezolizumab Plus Bevacizumab For Treating Patients With Unresectable Hepatocellular Carcinoma	NCT05109052	Phase II, III, single group assignment, open label	PXS-5505. Atezolizumab. Bevacizumab	Not recruiting yet

Combination of Regorafenib and Nivolumab in Unresectable Hepatocellular Carcinoma	NCT04310709	Phase II, single group assignment, open label	Regorafenib. Nivolumab	Recruiting
Phase Ib Trial of Infigratinib In Combination With Atezolizumab And Bevacizumab for The Second-Line Treatment of Advanced Cholangiocarcinoma With FGFR2 Fusion/Amplification	NCT05510427	Phase I, randomized, single group assignment, open label	Infigratinib. Atezolizumab. Bevacizumab	Recruiting
A Study of TAK-500 With or Without Pembrolizumab in Adults With Select Locally Advanced or Metastatic Solid Tumors	NCT05070247	Phase I, non-randomized, parallel assignment, open label	TAK-500. Pembrolizumab	Recruiting
A Study of Nivolumab and Relatlimab in Combination With Bevacizumab in Advanced Liver Cancer	NCT05337137	Phase I, II, randomized, parallel assignment, quadruple (participant care, provider, investigator, outcomes assessor)	Relatlimab. Nivolumab. Bevacizumab	Recruiting
Drug repurposing				
High Dose Vitamin C Combined With Metformin in the Treatment of Malignant Tumors	NCT04033107	Phase II, single group assignment, open label	Vitamin C. Metformin	Recruiting
Statin Combination Therapy in Patients Receiving Sorafenib for Advanced Hepatocellular Carcinoma	NCT03275376	Phase II, randomized, parallel assignment, Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Atorvastatin	Terminated
The Combination Effect of Statin Plus Metformin on Relapse-free	NCT02819869	Phase II, randomized, parallel assignment	Statin. Metformin	Terminated
Statin for Preventing Hepatocellular Carcinoma Recurrence After Curative Treatment	NCT03024684	Phase IV, randomized, parallel assignment, triple masking (Participant, Care Provider, Investigator)	Atorvastatin	Recruiting
Meclizine for Hepatocellular Carcinoma	NCT03253289	Phase I, single group assignment, open label	Meclizine	Recruiting
Celebrex and Metformin for Postoperative Hepatocellular Carcinoma	NCT03184493	Phase III, non-randomized, parallel assignment	Celebrex plus metformin	Recruiting
Sorafenib Induced Autophagy Using Hydroxychloroquine in Hepatocellular Cancer	NCT03037437	Phase II, non-randomized, parallel assignment, open label	Sorafenib. Hydroxy-chloroquine	Recruiting

PD-1: Programmed cell death protein 1; HCC: Hepatocellular carcinoma.

methylglutaryl coenzyme A into mevalonate, which is responsible for cholesterol synthesis[224]. Interestingly, mevalonate signalling is deregulated in several types of cancer and is also involved in the process of tumorigenesis[225,226], making it a potentially useful target for cancer treatment. Preclinical trials have demonstrated that statins can be used as antitumour agents in colorectal cancer[227-229]. It was suggested that statins might reduce the risk of developing HCC[230]. Kim *et al*[231] reported that atorvastatin inhibited the activation of YAP (*via* the mevalonate pathway) and AKT (*via* stabilization of the truncated retinoid X receptor alpha pathway), which are involved in cancer development[231].

Ongoing clinical trials are evaluating the effects of statins in patients with advanced HCC, such as a trial evaluating atorvastatin in patients receiving treatment with sorafenib (ClinicalTrials.gov identifier: NCT03275376) and a clinical trial studying two non-oncology drugs—statins and metformin—either alone or in combination (ClinicalTrials.gov identifier: NCT03024684).

Celebrex

Celebrex (celecoxib) is a cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drug indicated for the treatment of pain and inflammation caused by osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis[232]. Interestingly, celecoxib anticancer activity is presumed to occur by inhibiting COX-2[233-235] because this cyclooxygenase isoform is frequently expressed in many types of cancer and promotes carcinogenesis and resistance of cancer cells to chemotherapy[236]. Dai *et al*[237] found that celecoxib also targets the RNA-binding protein "" partner of NOB1"" (PNO1) and exerts antitumour activity through the AKT/mTOR pathway[237]. In addition, PNO1 has been reported to participate in the progression of lung, oesophageal, breast, bladder, and colorectal cancer[238-242]. Targeting PNO1 (which is overexpressed in HCC tissues) can inhibit cell apoptosis by promoting autophagy through the ERK/MAPK signalling pathway[243].

A clinical trial is currently ongoing to compare the effect of Celebrex alone, metformin alone, and the combination of both drugs in preventing HCC recurrence after hepatic resection (ClinicalTrials.gov identifier: NCT03184493). In preclinical trials, it was shown that the combination of the two *in vitro* and

in vivo inhibited HCC proliferation more effectively than the effect of each drug alone[244].

Hydroxychloroquine

Hydroxychloroquine is an antimalarial drug that has been evaluated as an antitumour agent in HCC and has even been used for the treatment of other cancers, either alone or in combination with other therapeutic agents[215,245]. This drug targets cancer cells and the tumour microenvironment; among its molecular mechanisms of action, it inhibits autophagosome-lysosome fusion and Toll-like receptor 9 (TLR9) signalling, along with TLR7, which are overexpressed in HCC and are involved in cell proliferation and inhibition of apoptosis[246]. Furthermore, Chen *et al*[247] reported that hydroxychloroquine and miRNA (hsa-miR-30a-5p) target and resensitize sorafenib-resistant HCC cells to sorafenib through impairment of autophagy and DNA damage by oxidative stress *via* the TLR9/SOD1/hsa-miR-30a-5p/Beclin-1 pathway[247]. Since one of the mechanisms of sorafenib resistance is the induction of autophagy, a prospective, phase II clinical trial is currently under way to evaluate the efficacy of sorafenib and hydroxychloroquine treatment in patients with advanced HCC (ClinicalTrials.gov identifier: NCT03037437).

PERSPECTIVES

The high mortality caused by liver cancer remains an important concern in oncology. Therefore, there is an urgent need to implement new therapeutic strategies to provide significant benefits in patients with advanced HCC.

Immunotherapy is a tool that has shown great promise in treating HCC. Nevertheless, it is necessary to continue developing immunotherapy agents, which increase understanding of the role of the immune response in the tumour and take advantage of this process.

In contrast, the use of combination therapy has shown very favourable results compared to the effect of monotherapy, reflected by the diversity of current clinical trials evaluating the impact of the combination of two or more agents in HCC. Drug combinations simultaneously targeting relevant signalling pathways in liver carcinogenesis provide at least four potential advantages: (1) Anticancer synergistic effects; (2) minimization of treatment resistance; (3) reduction of individual drug doses; and (4) the occurrence of minimal adverse events. These advantages should facilitate HCC treatment, making it extremely important to consider possible future drug combinations to achieve greater benefits for HCC patients.

Furthermore, growing evidence has supported that non-cancer drugs possess antineoplastic activity. In emergency situations such as cancer, drug repurposing can be a very useful strategy. Compared to the traditional process of developing new drugs, drug repurposing allows for the rapid and less costly discovery of new treatments, increasing the likelihood of success with the advantage that safety issues in humans have already been described. It is crucial to mention that drug repurposing does not replace the traditional process; both are extremely important. However, repurposing non-oncology drugs is an attractive strategy to obtain more treatment options for advanced HCC.

Simultaneously, implementing non-oncology drug repurposing and proposing combinations of non-oncology drugs with systemic therapy or immunotherapy are very attractive strategies to generate significant benefits in patients with unresectable HCC. In addition, new relevant signalling pathways, critical drug targets, and biomarkers of this cancer might be identified along the way, providing significant advantages for understanding liver carcinogenesis.

CONCLUSION

Currently, approved drug options for treating advanced HCC are limited, and the likelihood of generating resistance is high, making the use of novel pharmacological approaches urgent (Figure 2). Compared to monotherapy, this review demonstrated that combining therapies has resulted in more significant benefits for HCC patients. Furthermore, evidence has been provided indicating that several non-oncology drugs are potentially useful for the treatment of this cancer. In addition, immunotherapy has significant effects in some cases compared to current systemic therapy, making this approach, along with repositioning and combination therapy, promising for the pharmacological treatment of advanced liver cancer.

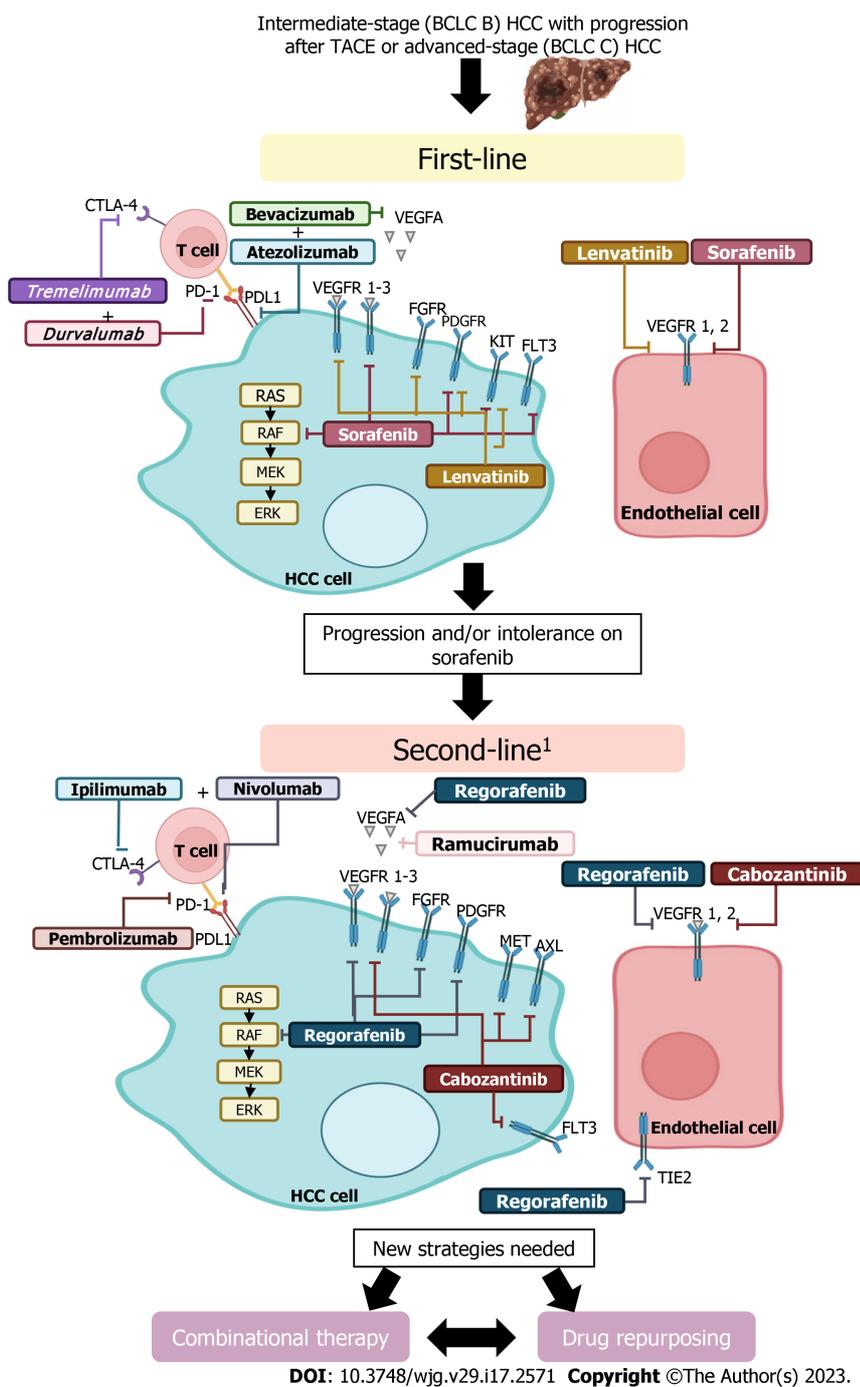


Figure 2 Pharmacological strategies for the treatment of advanced hepatocellular carcinoma. When a patient is diagnosed with hepatocellular carcinoma either intermediate (BCLC B) or advanced (BCLC C) stage, surgical and locoregional therapeutic options are no longer indicated. In these cases, the most appropriate treatment option is systemic therapy with first-line treatments with sorafenib and lenvatinib as the initial drugs. However, if the patient develops resistance to sorafenib or disease progression after therapy, treatment with second-line drugs indicated in the schedule is initiated. It is important to note that immunotherapy using monoclonal antibodies is already part of the current and approved drug options. Because current drug treatments are limited and monotherapy is ineffective, the implementation of combination and drug repositioning are two therapeutic strategies to achieve more and better treatments. ¹All agents require prior sorafenib use. BCLC: Barcelona Clinic Liver Cancer; TACE: Transarterial chemoembolization; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PD-1: Programmed cell death protein 1; VEGFR: Vascular endothelial growth factor receptor; FGFR: Fibroblast growth factor receptor; PDGFR: Platelet-derived growth factor receptors; HCC: Hepatocellular carcinoma.

FOOTNOTES

Author contributions: Villarruel-Melquiades F and Camacho J wrote the paper and made substantial contributions to conception of the manuscript; Mendoza-Garrido ME, García-Cuellar CM, Sánchez-Pérez Y and Pérez-Carreón JI made critical revisions related to important intellectual content of the manuscript; all authors read and approved the final version of the article to be published.

Supported by CONACyT Fellowship (FV-M), No. 787907.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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Country/Territory of origin: Mexico

ORCID number: María Eugenia Mendoza-Garrido 0000-0003-2037-0618; Claudia M García-Cuellar 0000-0001-8080-5797; Yesennia Sánchez-Pérez 0000-0003-0103-9188; Julio Isael Pérez-Carreón 0000-0001-9284-7775; Javier Camacho 0000-0002-8886-086X.

S-Editor: Fan JR

L-Editor: A

P-Editor: Zhao S

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