THE LATEST DEVELOPMENTS IN SYSTEMIC TREATMENT FOR HEPATOCELLULAR CARCINOMA.

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Annotation

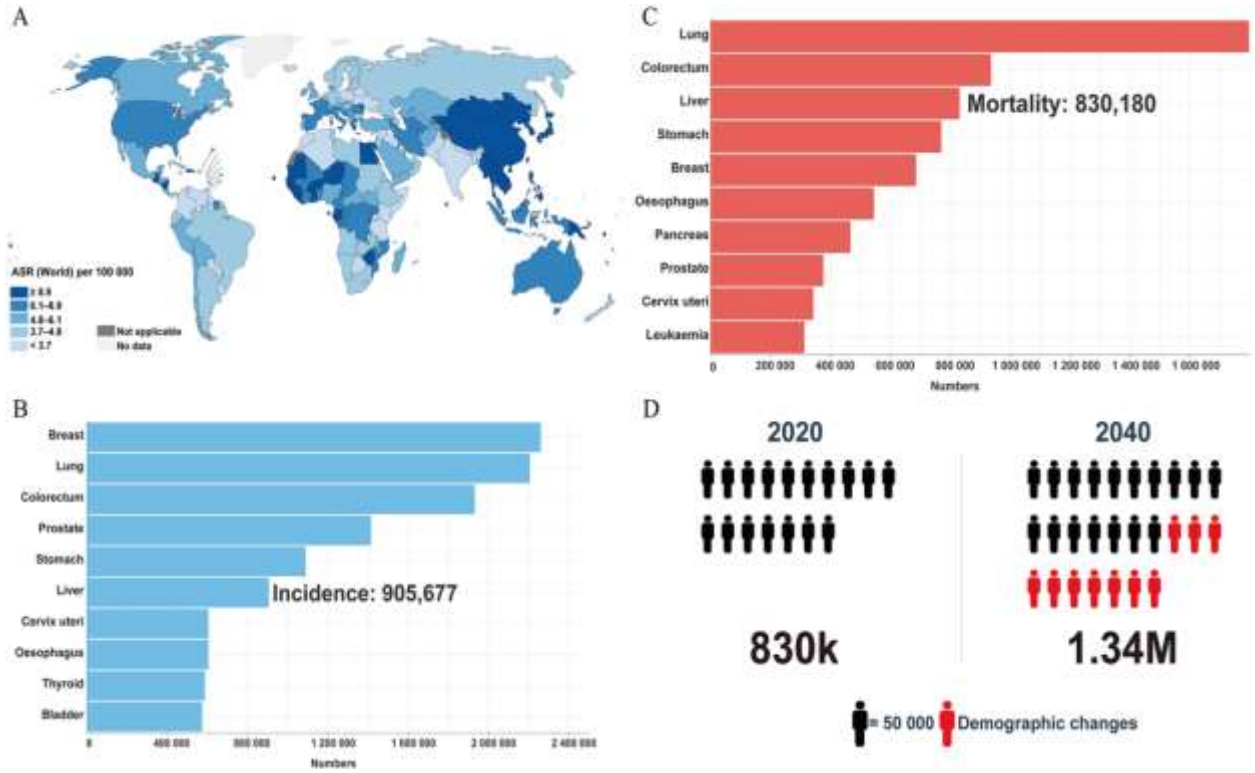
Hepatocellular carcinoma (HCC) stands as one of the most prevalent and deadly malignant tumors globally. Treatment options for advanced HCC are currently limited, with systemic approaches, particularly involving conventional cytotoxic drugs, often proving ineffective. For more than a decade, sorafenib has stood as the sole clinically proven systemic drug for treating advanced HCC. Nevertheless, the treatment landscape for advanced HCC has undergone significant transformation in the past three years, owing to the rapid advancements in molecular targeted therapies. The integration of immune checkpoint therapies into HCC treatment protocols is now underway, and their combination with molecular targeted therapy is emerging as a promising strategy to bolster the immune response. This review provides a comprehensive summary of the development and progress of molecular targeted agents and immunotherapies in the context of HCC.

Background

Globally, liver cancers are projected to rank sixth in terms of incident cases and become the third leading cause of cancer-related deaths in 2020, with an estimated 905,677 new cases and 830,180 deaths annually (Fig. 1A-C) [1]. According to World Health Organization estimates, more than 1.3 million individuals are expected to succumb to liver cancer by 2040 (Fig. 1D) [2]. Hepatocellular carcinoma (HCC) constitutes the predominant tumor among all primary liver cancers, making up 75%-85% of cases [3]. Typically, HCC is diagnosed at an advanced stage, and there are limited effective treatment options for such cases [4]. Palliative treatment at an advanced stage yields a median post-diagnostic survival ranging from 6 to 12 months [5]. Systemic treatments hold potential benefits for patients with advanced-stage HCC [6].

Before 2007, patients diagnosed with advanced-stage disease or those progressing to advanced stages after failed prior treatments had limited effective options [7]. Sorafenib emerged as a milestone, being the first and sole systemic drug endorsed by the U.S. Food and Drug Administration (FDA) as the standard treatment for advanced HCC from 2007 to 2016. However, significant progress over the last three years has resulted in the FDA approval of additional molecular targeted drugs and several immune checkpoint inhibitors (ICIs),

expanding the therapeutic arsenal for advanced HCC (Tables 1, 2, and 3). Notably, the successful combination of atezolizumab and bevacizumab represents a pivotal shift in the first-line treatment of HCC (GO30140, NCT NCT02715531) [8]. Presently, systemic therapy for advanced HCC encompasses molecular targeted therapy, immune checkpoint inhibitors, or a combination of both (Fig. 2).



Worldwide Epidemiology of Liver Cancer in 2020. Data source: GLOBOCAN 2020 (http://gco.iarc.fr/). (**A**) The estimated age-standardized incidences of liver cancer worldwide in 2020. (**B**) Bar charts of the estimated number of incident cases worldwide. (**C**) Bar charts of the estimated number of deaths worldwide. (**D**) WHO estimated the number of deaths from liver cancer from 2020 to 2040.

Table 1 Clinical trials of molecular targeted therapy for advanced HCC

Drug	Setting	Name/ID	Phase	Target	Results	Approval Status
Sorafenib	1st	SHARP	III	Multikinases	mOS 10.7 vs. 7.9 months (HR 0.69, p<0.001)	First-line, 2008
		NCT00492752	III		mOS 6.5 vs. 4.2 months (HR 0.68, p=0.014)	/
Lenvatini	1st	REFLECT	III	Multikin	mOS 13.6 vs.	First-line,

Drug	Setting	Name/ID	Phase	Target	Results	Approval Status
b				ases	12.3 months (compared to sorafenib, HR 0.92)	2018
Erlotinib	1st	SEARCH	III	EGFR	mOS 9.5 vs. 8.5 months (compared to sorafenib)	/
Brivanib	1st	BRISK-FL	III	VEGFR, PDGFR, FGFR	mOS 9.5 vs. 9.9 months (compared to sorafenib)	/
Sunitinib	1st	NCT0069 9374	III	VEGFR, PDGFR	mOS 7.9 vs. 10.2 months (compared to sorafenib)	/
Linifanib	1st	NCT0100 9593	III	VEGFR, PDGFR	mOS 9.1 vs. 9.8 months	/
Everolimus	2nd	EVOLVE-1	III	mTOR	mOS 7.6 vs. 7.3 months	/
Tivantinib	2nd	NCT0175 5767	III	c-MET	mOS 8.4 vs. 9.1 months	/
Regorafenib	2nd	RESORCE	III	Multikinases	mOS 10.6 vs. 7.8 months (HR 0.63, p<0.001)	Second-line, 2017
Cabozantinib	2nd	CELESTIAL	III	Multikinases	mOS 10.2 vs. 8 months (HR 0.76, p=0.005)	Second-line, 2019
Ramucirumab	2nd	REACH-2	III	VEGFR2	mOS 8.5 vs. 7.3 months (HR 0.71, p=0.0199)	Second-line, 2019
Tepotinib	1st	NCT0198	Ib/II	c-MET	mTTP 2.9 vs.	/

Drug	Setting	Name/ID	Phase	Target	Results	Approval Status
		8493			1.4 months (compared to sorafenib, HR 0.42, p=0.0043)	
	2nd	NCT02115373	Ib/II		RP2D 500mg, 12-week PFS 63.3% ($p < 0.0001$)	/
Capmatinib	1st	NCT01737827	II	c-MET	/	/
Fisogatinib (BLU554)	1st/2nd	NCT02508467	I	FGFR4	/	/
Roblitinib (FGF401)	/	NCT02325739	I/II	FGFR4	/	/
H3B-6527	2nd	NCT02834780	I	FGFR4	/	/
Tivozanib	1st	NCT01835223	I/II	Multikinases	ORR 21%, mPFS 6 months, mOS 9 months, did not proceed to stage 2	/
Donafenib	1st	ZGDH3	III	Multikinases	mOS 12.1 vs. 10.3 mo (compared to sorafenib, HR 0.831, p=0.0363)	/
Apatinib	2nd	AHELP	III	Multikinases	mOS 8.7 vs. 6.8 mo (HR 0.785, p=0.0476)	/

Abbreviations: *ORR* objective response rate, *mOS* median overall survival, *mPFS* median progression-free survival, *mTTP* median time to progression, *RP2D* recommended phase 2 dose

Table 2 ICI monotherapy for advanced HCC

ICI	Setting	Target	Phase	Name/NCT No.	Results	Approval Status
Tremelimumab	1st/2nd	CTLA-4	II	NCT01008358	/	/
Durvalumab	1st/2nd	PD-L1	I/II	NCT01693562	/	/
	2nd		III	NCT03847428	/	/
Avelumab	2nd	PD-L1	II	NCT03389126	ORR 10%, DCR 73.3%, mTTP 4.4 months, mOS 14.2 months	/
Nivolumab	2nd	PD-1	I/II	CheckMate-040	ORR 20%, mPFS 4.0 months	Conditional second-line, 2017
	1st		III	CheckMate-459	ORR 15%, mPFS 16.4 months	/
Pembrolizumab	1st/2nd	PD-1	II	KEYNOTE-224	ORR 17%, mOS 12.9 months,	Conditional second-line, 2018

ICI	Setting	Target	Phase	Name/NCT No.	Results	Approval Status
					mPFS 4.9 months, mTTP 4.9 months	
					1st setting: ORR 16%, DCR 57%, mOS 17 months	/
	2nd		III	KEYNOTE-240	ORR 18.3%, DCR 61.9%, mOS 13.9 months, mPFS 3.3 months	/
	2nd		III	KEYNOTE-394	/	/
	2nd		III	KEYNOTE-937	/	/
Tislelizumab	1st	PD-1	III	RATIONALE-301	/	/
Camrelizumab	2nd	PD-1	II	NCT02989922	ORR 14.7%, 6-month OS 74.4%	/

Abbreviations: *DCR* disease control rate, *ORR* objective response rate, *mOS* median overall survival, *mPFS* median progression-free survival, *mTTP* median time to progression

Table 3 ICI combination therapy for advanced HCC

Regimen	Setting	Phase	Name/NCT No.	Results	Approval Status
ICI + MKI					
Nivolumab + Ipilimumab	2nd	I/II	CheckMate-040	ORR 32%, DCR 54%, mOS 22.2 months	Conditional second-line, 2020
	1st	III	CheckMate-9DW	/	/
Nivolumab + Sorafenib	1st	II	NCT03439891	/	/
Nivolumab + Lenvatinib	1st	Ib	NCT03418922	/	/
Nivolumab + BMS986253	1st	II	NCT04050462	/	/
Nivolumab + Mogamulizumab	2nd	I/II	NCT02705105	/	/
Nivolumab + Galunisertib	2nd	Ib/II	NCT02423343	/	/
Nivolumab + Relatlimab	2nd	II	NCT04567615	/	/
Nivolumab + Cabozantinib	neoadjuvant	Ib	CaboNivo/NCT03299946	/	/
Pembrolizumab + Regorafenib	1st	Ib	NCT03347292	/	/
Pembrolizumab + Lenvatinib	1st	Ib	KEYNOTE524/NCT03006926	ORR 46%, mPFS 9.3	/

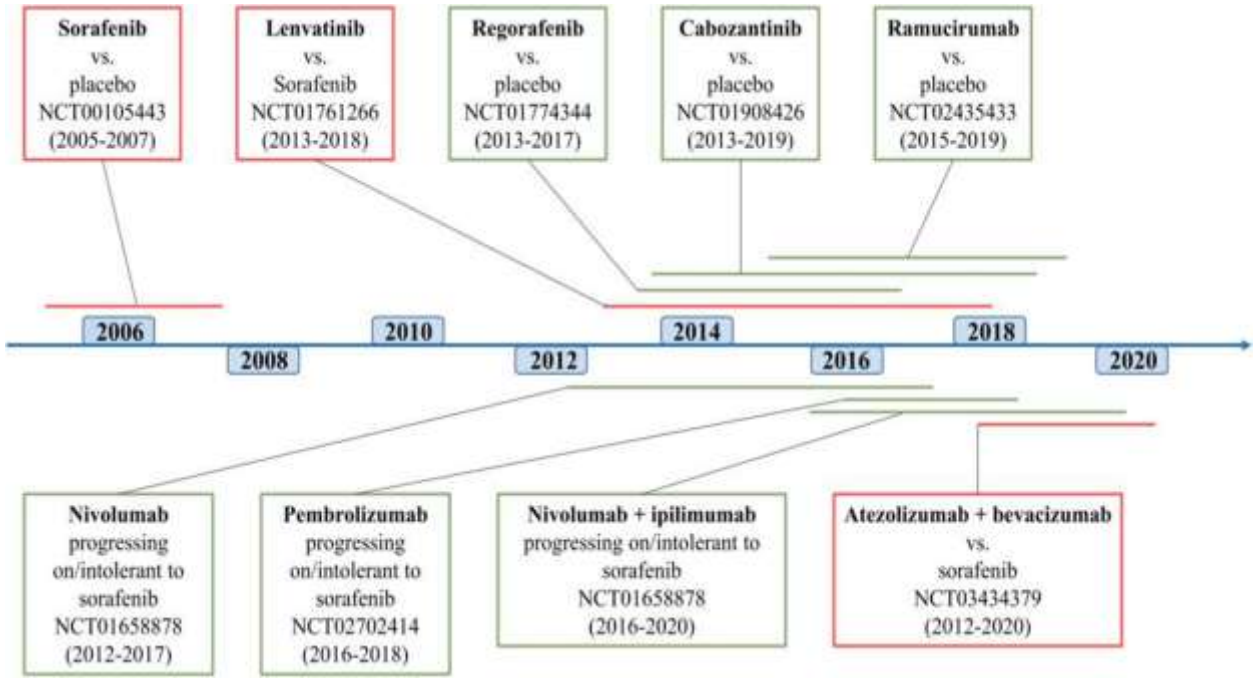
Regimen	Setting	Phase	Name/NCT No.	Results	Approval Status
				months, mOS 22 months	
	1st	III	LEAP-002/NCT03713593	/	/
Atezolizumab + Bevacizumab	1st	Ib	GO30140	ORR 36%, mPFS 5.6 vs. 3.4 months (compared to atezolizumab monotherapy, *p*= 0.011)	/
	1st	III	IMbrave150	ORR 29.8%, mOS 19.2 vs. 13.4 months (compared to sorafenib, HR 0.66, *p*= 0.0009)	First-line treatment, 2020
Atezolizumab + Cabozantinib	1st	III	COSMIC-312/NCT03755791	/	/
Avelumab + Axitinib	1st	I	NCT03289533	ORR 31.8%, mPFS 3.8	/

Regimen	Setting	Phase	Name/NCT No.	Results	Approval Status
				months	
Avelumab + Regorafenib	2nd	I/II	REGOMUNE/ NCT03475953	/	/
Durvalumab + Cabozantinib	2nd	Ib	NCT03539822 (CAMILLA)	/	/
Durvalumab + Ramucirumab	2nd	I	NCT02572687	/	/
Durvalumab + tivozanib	1st	Ib/ II	DEDUCTIVE/ NCT03970616	Ib: 2 of 7 achieving PR	/
Camrelizumab + Apatinib	1st	I	NCT02942329	ORR 50%, mPFS 5.8 months	/
	2nd	II	RESCUE/ NCT03463876	/	/
	1st	III	NCT03764293	/	/
Emibetuzumab + amucirumab	2nd	I/II	NCT02082210	/	/
ICI + ICI					
IBI310 + Sintilimab	1st	III	NCT04720716	/	/
Durvalumab + Tremelimumab	1st/2nd	I/II	NCT02519348	ORR 24%, mOS 18.7 months	/
	1st	III	HIMALAYA/ NCT03298451	/	/

Regimen	Setting	Phase	Name/NCT No.	Results	Approval Status
			1		

Abbreviations: *ICI* immune checkpoint inhibitor, *MKI* multikinase inhibitor, *ORR* objective response rate, *mOS* median overall survival, *mPFS* median progression-free survival, *mTTP* median time to progression, *PR* partial response

Fig. 2



Currently approved drugs for advanced HCC and timeline of pivotal clinical trials. The lines along the timeline indicate the time from the actual study start to FDA approval. The red boxes represent first-line therapies, and the green boxes represent second-line therapies.

Agents approved by the FDA

Molecular targeted therapies

In recent decades, progress in molecular cell biology has significantly enhanced our understanding of the molecular mechanisms underlying tumorigenesis and its progression. This knowledge has opened avenues for the development of innovative molecular targeted agents aimed at inhibiting molecular abnormalities, offering promising approaches to cancer treatment [9]. Currently, molecular targeted therapy primarily revolves around the use of tyrosine kinase inhibitors (TKIs) and/or monoclonal antibodies.

Sorafenib

Sorafenib functions as an oral tyrosine kinase inhibitor (TKI) targeting angiogenesis and proliferation pathways in tumors. It accomplishes this by obstructing vascular endothelial growth factor receptor (VEGFR) 1–3, platelet-derived growth factor receptor (PDGFR) β-pathways, and Raf-MEK-ERK signaling, all integral to the pathogenesis of hepatocellular carcinoma (HCC) (Fig. 4) [11, 12].

The SHARP trial results, presented at ASCO 2007, showcased sorafenib's efficacy against HCC, with significantly prolonged overall survival (OS) in the sorafenib treatment group compared

to the placebo group (median OS 10.7 vs. 7.9 months, hazard ratio [HR]=0.69; 95% confidence interval [CI], 0.55–0.87; p<0.0001). While time to symptomatic progression showed no significant difference, the sorafenib group exhibited improved median time to radiologic progression and a higher disease-control rate (P<0.001 and P=0.002, respectively). Adverse effects in the sorafenib group included diarrhea, weight loss, hand-foot skin reactions, alopecia, anorexia, and voice changes, surpassing those in the placebo group (P<0.001). Notably, 97% of the trial participants were assessed as Child-Pugh liver function class A. Consequently, sorafenib gained U.S. FDA approval in November 2007 as the first-line standard treatment for advanced HCC.

Despite its notable survival benefits, sorafenib faces challenges such as disease progression post-dosage adjustments or discontinuation due to adverse events. Furthermore, 27% of patients in the SHARP trial showed no initial response to sorafenib, indicating significant resistance, both primary and acquired. In patients permanently discontinuing sorafenib, the median post-sorafenib survival was a mere 4.1 months, associated with factors like liver decompensation, performance status (PS), tumor progression, and extrahepatic tumor spread. Subsequent phase III trials exploring various drugs as first-line or second-line treatments failed to surpass sorafenib's efficacy, maintaining its status as the sole effective first-line option for over a decade. However, lenvatinib, a small molecule inhibitor targeting VEGFR 1–3, fibroblast growth factor receptor (FGFR) 1–4, PDGFRα, KIT, and RET, emerged as a non-inferior alternative to sorafenib in overall survival (mOS, 13.6 vs. 12.3 months, HR=0.92, 95% CI, 0.79–1.06) based on the REFLECT trial (NCT01761266). Lenvatinib's superiority was demonstrated in secondary efficacy endpoints, including prolonged progression-free survival, time to progression, and a better objective response rate. As a result, the U.S. FDA approved lenvatinib for first-line treatment in advanced HCC on August 16, 2018.

Regorafenib

Regorafenib, an oral inhibitor, targets numerous angiogenic and tumorigenic kinases, including VEGFR1–3, tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2), PDGFRβ, FGFR1, B-RAF, RET, and KIT (Fig. 4) [27]. Its potential for broader antiangiogenic activity is attributed to the combined blockade of the VEGFR2 and TIE2 pathways. This synergy was demonstrated in a preclinical study by Tsai and Lee, where the combination of anti-TIE2 and sorafenib led to increased overall survival in a melanoma model [28].

On April 27, 2017, the U.S. FDA expanded the indication for regorafenib as a second-line treatment for advanced HCC patients previously treated with sorafenib [29]. Approval was based on the RESORCE trial (NCT01774344), a randomized, placebo-controlled international phase III trial assessing the safety and efficacy of regorafenib in HCC patients progressing during sorafenib treatment. Regorafenib exhibited longer overall survival compared to placebo (mOS, 10.6 vs. 7.8 months, HR=0.63, p<0.0001) and prolonged progression-free survival and time to progression by mRECIST (mPFS 3.1 vs. 1.5 months, HR=0.46, p<0.0001; mTTP was 3.2 vs. 1.5 months, HR=0.44, p<0.0001). The regorafenib group demonstrated an objective response rate (ORR) of 11% versus 4% in the placebo group (p=0.0047), and the disease control rate (DCR) was 65% versus 35% (p<0.0001). Notably, the RESORCE trial focused on patients who had progressed on prior sorafenib treatment, and the efficacy of regorafenib in sorafenib-intolerant patients has yet to be determined.

Additional analyses from the RESORCE trial suggested that regorafenib might offer clinical benefits regardless of the latest sorafenib dose or the time to progression after previous sorafenib treatment. Moreover, the occurrence of adverse events (AEs) appeared independent of the last sorafenib dose. Currently, multiple clinical trials are underway to evaluate the efficacy of regorafenib in combination with immune checkpoint inhibitors (Table 3).

Cabozantinib

Cabozantinib, a small-molecule tyrosine kinase inhibitor targeting MET and VEGFR 1-3, RET, KIT, AXL, and FLT3, all implicated in tumor pathogenesis, exhibits notable antitumor activity in hepatocellular carcinoma (HCC) through dual inhibition of MET and VEGFR2 (Fig. 4) [32, 33].

In the international, phase III double-blinded CELESTIAL trial (NCT01908426), 773 patients who had progressed on no more than two prior systemic treatments, including sorafenib, were randomized to receive cabozantinib or placebo. The primary endpoint of the trial demonstrated a significant improvement in overall survival (mOS 10.2 vs. 8.0 months, HR=0.76, p=0.005). Secondary efficacy endpoints indicated that cabozantinib significantly enhanced progression-free survival and objective response rate according to RECIST v1.1 (mPFS 5.2 vs. 1.9 months, HR=0.44, p<0.001; ORR 4% vs. <1%, p=0.009). Notably, 68% of patients in the cabozantinib group and 36% in the placebo group experienced grade 3 or 4 adverse events [34]. Consequently, on January 14, 2019, the U.S. FDA granted approval for cabozantinib for patients with HCC who had previously received sorafenib treatment [35]. Ongoing trials are evaluating combinations of cabozantinib with immune checkpoint inhibitors (ICIs) such as nivolumab and atezolizumab (Table 3).

In the CELESTIAL trial, 27% of patients (192) had received two previous systemic anticancer drugs, making cabozantinib a third-line therapy. Within this subgroup, overall survival was not significantly different (mOS 8.6 months vs. 8.6 months). However, cabozantinib demonstrated improved progression-free survival (mPFS 3.7 vs. 1.9 months, HR=0.58, 95% CI, 0.41-0.83), suggesting its potential as a viable third-line option for advanced HCC patients [34].

Ramucirumab

Ramucirumab, a humanized recombinant IgG1 monoclonal antibody, selectively binds to VEGFR-2, effectively preventing the activation of the VEGF pathway (Fig. 4) [36]. In a phase II trial, ramucirumab demonstrated anti-tumor activity in advanced HCC [37]. A subsequent prospective study, the REACH trial (NCT01140347), focused on ramucirumab as a treatment for the progression of advanced HCC while on sorafenib. The results indicated that ramucirumab did not lead to a significant improvement in overall survival (mOS 9.2 vs. 7.6 months, HR=0.87, p=0.14). However, in a subgroup with high baseline α-fetoprotein (AFP) concentrations (≥ 400 ng/mL), ramucirumab significantly prolonged overall survival, with a median OS of 7.8 months vs. 4.2 months (HR=0.674, p=0.006) [38].

Building on this finding, the biomarker-driven REACH-2 trial (NCT02435433) was conducted, assessing ramucirumab versus placebo in advanced HCC patients with elevated AFP levels (≥400 ng/mL) who had received prior sorafenib treatment. The primary endpoint of the REACH-2 trial demonstrated that, compared to the placebo group, overall survival was longer in the ramucirumab group (mOS 8.5 vs. 7.3 months, HR=0.71, p=0.0199). Ramucirumab also increased progression-free survival (mPFS 2.8 vs. 1.6 months, HR=0.452, p<0.0001), time to radiographic progression (mTTP 3.0 vs. 1.6 months, HR=0.427, p<0.0001), and disease

control rate (59.9% vs. 38.9%, p=0.0006). REACH-2 marked the first successful phase III trial screening for therapeutic candidates using biomarkers among patients with advanced HCC [39].

Based on these compelling results, on May 10, 2019, the U.S. FDA granted authorization for ramucirumab as a second-line treatment for HCC patients whose AFP levels were no less than 400 ng/mL [40].

Monotherapy with immune checkpoint inhibitors

The success of anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibodies in blocking immune checkpoints among advanced melanoma patients has instilled hope for the immunotherapy of various tumors. Hepatocellular carcinoma (HCC) often develops amidst chronic liver inflammation, potentially making it immunogenic [41]. Typically, immune tolerance in HCC is attributed to factors like myeloid-derived suppressor cells (MDSCs), alterations in immune checkpoint molecules (such as CTLA-4 and programmed cell death protein-1 [PD-1]), and an increase in T-regulatory cells (Tregs) [42].

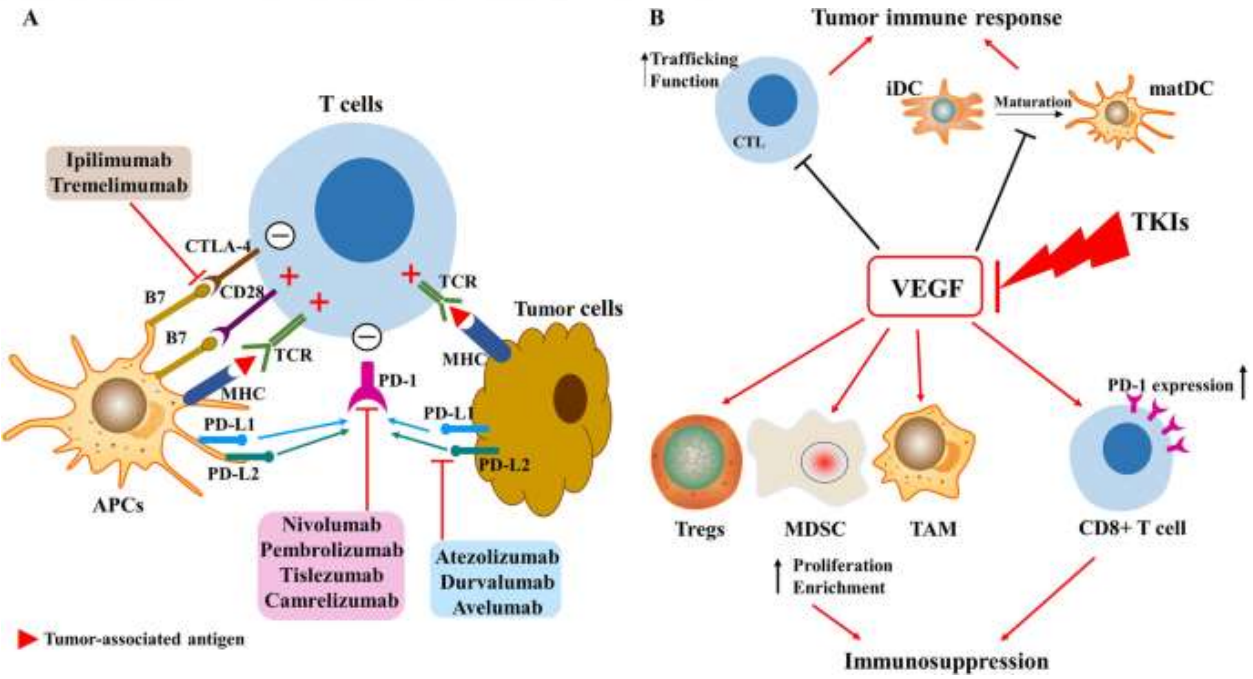
The initial indication that immune checkpoint inhibitors (ICIs) could have a significant impact on HCC treatment emerged from a phase II trial assessing the safety and antitumor activity of tremelimumab, a CTLA-4 blockade. This trial supported further investigations in patients with advanced HCC, particularly those with HCV-induced cirrhosis [43] (Table 2). Furthermore, several other clinical trials exploring ICI monotherapy for HCC have been conducted (Table 2).

Nivolumab

Nivolumab, a monoclonal antibody, acts by blocking the PD-1 signaling pathway (Figs. 3 and 4), thereby restoring anti-tumor immune activity. It has received authorization from the U.S. FDA for use in various tumors such as melanoma, non-small cell lung cancer (NSCLC), and kidney cancer [44].

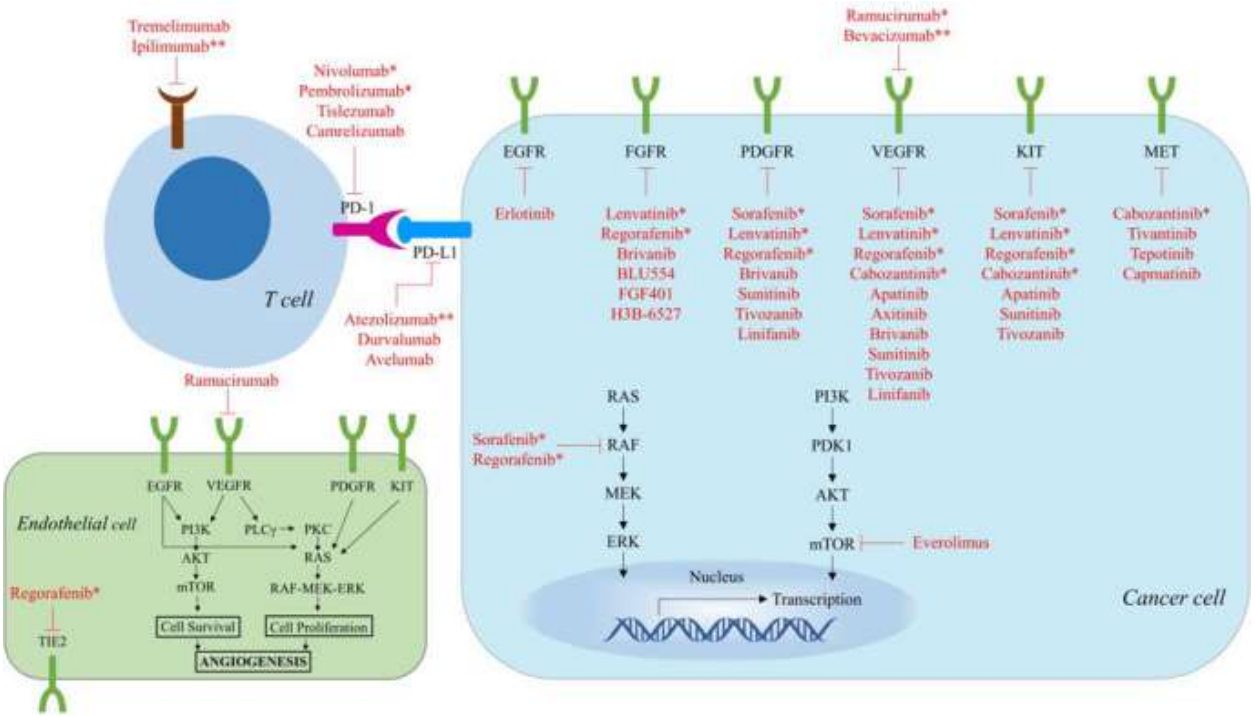
The CheckMate 040 trial (NCT01658878), a noncomparative phase I/II study, was designed to assess the safety and efficacy of nivolumab in advanced HCC patients. The trial involved escalating and expanding the dose of the medication, with prior sorafenib use permitted. Safety and tolerability were primary endpoints for the dose-escalation phase (n=48), while the dose-expansion phase (n=214) focused on the objective response rate (ORR). In the dose-escalation phase, the safety profile of nivolumab was evaluated, and the medication was well-tolerated: 25% of patients (12 of 48) experienced grade 3 or 4 treatment-related adverse events (TRAEs), and the incidence of TRAEs appeared to be dose-independent. In the dose-expansion phase, the ORR was 20% (42 of 214 patients, 95% CI, 15-26), with thirty-nine partial responses and three complete responses. The median duration of response was 9.9 months, and the median progression-free survival (mPFS) was 4.0 months (95% CI, 2.9-5.4). A majority of patients (57%) had their disease under control, with most disease stabilizations lasting for at least 6 months. Among untreated patients who were not previously treated with sorafenib, the ORR was 23%, and the nine-month overall survival rate was 82%, supporting further investigation of nivolumab as a first-line therapy for advanced HCC patients [45]. Based on the ORR and durable objective responses, the U.S. FDA accelerated the approval of nivolumab on September 22, 2017, for the treatment of HCC patients who were initially treated with sorafenib [46].

Fig 3.



Mechanism of combination therapies. (A) Complementary mechanisms of PD-1/PD-L1 and CTLA-4 inhibitors. Presentation of tumor-associated antigen by the major histocompatibility complex (MHC) expressed by APCs results in the release of an activation signal in combination with a co-stimulatory signal via the B7-CD28 pathway, leading to activation of T cells in the lymph node; B7 also binds to CTLA-4 with a higher affinity than that of CD28, in which case T cells cannot be activated. PD-1 on T cells inhibits antigen-specific T cell activation by interacting with its ligands PD-L1 and PD-L2. Immune escape is induced through the PD-1/PD-L1 axis, as well as the B7/CTLA-4 axis. This figure was adapted from Kudo, et al. [44]. (B) VEGF modulates the immunosuppressive TME, and TKIs restore this suppressive effect. Red arrows represent promotion effects. APCs, antigen presenting cells; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T-lymphocyte antigen 4; iDC, immature dendritic cell; matDC, mature dendritic cell; MDSCs, myeloid-derived stem cells; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; TAMs, tumor-associated macrophages; TME, tumor microenvironment; Tregs, regulatory T cells.

Fig 4.



Signaling pathways and molecular targeted therapies for HCC. * represents monotherapies approved by the FDA, ** represents agents as a component of combination therapy approved by the FDA. This figure was modified from Mossenta, et al. [10]. Note: This is an open access article distributed under the Creative Commons Attribution License that permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (CC BY 4.0)

Another research team conducted a randomized and multicenter phase III study (CheckMate 459; NCT02576509) to investigate the first-line treatment for advanced HCC patients, comparing nivolumab to sorafenib. The data from this study were presented at the 2019 Congress of the European Society for Medical Oncology (ESMO). The primary endpoint, overall survival (OS), did not reach statistical significance, with a median OS of 16.4 months in the nivolumab group and 14.7 months in the sorafenib group (HR=0.85, p=0.0752). Notably, patients receiving nivolumab exhibited a higher complete response rate (ORR, 15% vs. 7%, respectively). Adverse events of grade 3/4 were observed in 22% of patients (81 individuals) in the nivolumab group and 46% of patients (179 individuals) in the sorafenib group [47]. While these findings may not currently impact the standard treatment approach, they provide valuable insights suggesting that immunotherapy may have a potential role in the first-line treatment for advanced HCC.

Pembrolizumab

Pembrolizumab, a monoclonal antibody that blocks PD-1 (Figs. 3 and 4), has exhibited potent anti-tumor activity and tolerable safety profiles in various cancers [48]. Its efficacy and safety in advanced HCC patients were assessed in a nonrandomized, multicenter phase II trial known as KEYNOTE-224 (NCT02702414). The trial revealed that out of 104 patients, 18 (17%, 95% CI, 11–26) displayed an objective response according to RECIST v1.1, with 1 (1%) achieving a complete response and 17 (16%) achieving a partial response. The median response duration was not reached (range 3.1–14.6+ months), while both median time to progression (mTTP) and median progression-free survival (mPFS) were 4.9 months. The

median overall survival (mOS) was 12.9 months (95% CI, 9.7–15.5), and 54% of responding patients had response durations exceeding 12 months [49]. Based on these findings, pembrolizumab received accelerated approval from the U.S. FDA on November 9, 2018, for HCC patients progressing on sorafenib [50].

Subsequently, at the 2021 ASCO Gastrointestinal Cancer conference, results from the KEYNOTE-224 cohort 2 were reported. This cohort enrolled patients with advanced HCC without prior systemic therapy, showing an objective response rate (ORR) of 16% (95% CI, 7-29), disease control rate (DCR) of 57% (0 CR, 16% PR, 41% SD), mPFS of 4 months (95% CI, 2-6), and mOS of 17 months (95% CI, 8-NA). These results demonstrated durable anti-tumor activity and promising overall survival with pembrolizumab monotherapy, supporting further evaluation as a first-line treatment for advanced HCC [51].

Following KEYNOTE-224, a double-blind, randomized, phase III study (KEYNOTE-240; NCT02702401) was conducted to further assess the safety and efficacy of pembrolizumab. Updated results presented at the 2021 ASCO GI Conference indicated that mOS was 13.9 vs. 10.6 months compared to placebo (HR=0.771, 95% CI 0.617–0.964), mPFS was 3.3 vs. 2.8 months compared to placebo (HR=0.703, 95% CI 0.559–0.885), ORR was 18.3% for the pembrolizumab group and 4.4% for the placebo group, DCR was 61.9% vs. 53.3% compared to placebo, and median time to progression (TTP) was 4.0 vs. 2.8 months [52]. KEYNOTE-240 reaffirmed the clinical activity of pembrolizumab, supporting its accelerated FDA approval. Two other phase III trials evaluating pembrolizumab as second-line therapy are ongoing (KEYNOTE-394 and KEYNOTE-937, Table 2). Furthermore, pembrolizumab combined with molecular targeted drugs is being evaluated in several phase I/II trials (Table 3).

Combination therapy

To achieve a more favorable therapeutic response rate compared to immune checkpoint inhibitor (ICI) monotherapy, researchers are developing combination therapies based on ICIs for cancer treatment. In 2018, Larkin et al. discovered, through the CheckMate067 trial, that the combination of nivolumab and ipilimumab (a CTLA-4 inhibitor) was more effective than monotherapy in patients with advanced melanoma [53]. Potential mechanisms for this combination therapy include: 1) blocking the CTLA-4 pathway in lymph nodes, which increases the activation and proliferation of T cells, leading to CD8+ T cell infiltration; 2) blocking the PD-1/PD-L1 pathway, which not only maintains the killing capacity of cytotoxic T lymphocytes (CTLs) [44] but also enhances the ability of antigen-presenting cells to present tumor-associated antigens; and 3) due to the high expression of CTLA-4 and PD-1 on Tregs, the combination of these two inhibitors indirectly reduces the immunosuppressive tumor microenvironment (TME) (Fig. 3A) [54].

Another area of interest is the combination of tyrosine kinase inhibitors (TKIs) with ICIs. It's noteworthy that molecular targeted agents (such as sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab) with beneficial effects on survival in HCC patients all share the same characteristic—anti-angiogenesis. This underscores the importance of this hallmark in cancer treatment [55]. The restoration of tumor vascular function may enhance the efficacy of other drugs (e.g., ICIs) that can be used in combination with anti-angiogenic molecules to eliminate tumor cells [56, 57]. TKIs with antiangiogenic activity exert immunomodulatory effects on the tumor microenvironment (TME) [58], including promoting dendritic cell (DC)

maturation [59], enhancing T cell trafficking and function [10], and reversing the hypoxia-induced immunosuppressive effect in tissues [60] (Fig. 3B).

Nivolumab + Ipilimumab

Combining nivolumab with ipilimumab, as discussed earlier, leverages the synergistic effects of PD-1 and CTLA-4 inhibitors to enhance the anti-tumor immune response through distinct yet complementary mechanisms affecting different signaling pathways. This combination has demonstrated efficacy across various tumors, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, and mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer [61,62,63,64].

In cohort 4 of the CheckMate 040 trial (NCT01658878), 50 patients were administered four doses of nivolumab (1 mg/kg) combined with ipilimumab (3 mg/kg) every three weeks, followed by 240 mg of nivolumab every two weeks (arm A). The dosage regimen of arm A exhibited a favorable safety profile, a promising objective response rate (ORR), and a durable response. According to RECIST v1.1, the ORR was 32%, including four complete responses and twelve partial responses. The median response duration was 17.5 months (4.6–30.5+ months), with 31% of responses lasting over 24 months. Based on these results, on March 10th, 2020, the dosage regimen of arm A received accelerated approval for advanced HCC patients who had progressed on sorafenib treatment [65] (Table 3).

Recently, the 44-month follow-up results from CheckMate 040 were presented at the 2021 ASCO GI Conference. The median overall survival (mOS) was 22.2 months in arm A. The 24-month OS rate improved to 46% (95% CI, 32–59), and the 36-month OS rate was 42% (95% CI, 28–55). The ORR remained at 32%, and the median response duration continued at 17.5 months (5–47+ months) in arm A. The disease control rate (DCR) was higher in arm A than in arms B and C (54%, 43%, 49%, respectively). Nivolumab + ipilimumab as a second-line treatment continued to demonstrate clinical responses and long-term survival benefits [66].

Atezolizumab + Bevacizumab

Atezolizumab is an IgG1 monoclonal antibody that specifically binds to PD-L1, interrupting its interaction with PD-1 and thereby reversing T cell suppression. Bevacizumab, a humanized anti-VEGF monoclonal antibody, is known for its ability to suppress angiogenesis and tumor development in HCC, demonstrating ORRs of 13% and 14% in single-agent phase II trials for advanced HCC.

The combination of atezolizumab and bevacizumab has shown a tolerable safety profile and efficacy in treating unresectable HCC patients in the GO30140 trial (NCT02715531). This combination emerged as a promising treatment and has been compared with sorafenib in a global, open-label, phase III trial known as IMbrave 150 (NCT03434379). The results from the efficacy phase of the trial revealed that the atezolizumab + bevacizumab group had significantly longer overall survival (OS) and progression-free survival (PFS) compared to the sorafenib group. The estimated 6-month and 12-month survival rates were 84.8% and 67.2%, respectively, for the combination group, versus 72.2% and 54.6% for the sorafenib group. The median OS could not be evaluated (NE) in the atezolizumab + bevacizumab group versus 13.2 months in the sorafenib group (HR=0.58, $p<0.001$). The estimated median PFS was 6.8 months and 4.3 months, respectively (HR=0.59, $p<0.001$).

The objective response rates were also statistically significant, with the atezolizumab + bevacizumab group showing higher response rates compared to the sorafenib group according to RECIST v1.1 and mRECIST. The most common adverse events (AEs) affecting

more than 20% of patients in the atezolizumab + bevacizumab group were hypertension (29.8%), fatigue (20.4%), and proteinuria (20.1%). On May 29, 2020, the U.S. FDA approved atezolizumab in combination with bevacizumab as a first-line treatment for advanced HCC patients based on the safety and efficacy demonstrated in IMbrave 150.

At the 2021 ASCO Gastrointestinal Cancer Symposium, an updated OS analysis for IMbrave 150 was presented by Finn et al. After an additional 12 months of follow-up, the combination of atezolizumab + bevacizumab maintained a sustained clinical efficacy benefit over sorafenib. The median OS was 19.2 months in the combination group versus 13.4 months with sorafenib (HR=0.66 [95% CI, 0.52–0.85], P=0.0009). The updated data also showed an ORR of 29.8% by RECIST v1.1 in the combination group compared to 11.3% in the sorafenib group. More patients in the combination group achieved a complete response (CR=7.7%), making this combination regimen the longest OS ever seen in first-line phase III studies and confirming its status as a standard of care for patients with advanced HCC who have not received any systemic therapy before.

Combination therapies in clinical trials

Regorafenib enhances T cell efficacy by modulating various immunoreactive molecules, facilitating antigen presentation, and triggering T cell differentiation and accumulation [122]. Tumor-associated macrophages, linked to angiogenesis in the tumor microenvironment (TME), exhibit TIE2 expression strongly associated with cancer cell intravasation into the circulatory system [123]. This evidence supports the rationale for combining regorafenib and pembrolizumab as a first-line treatment for advanced hepatocellular carcinoma (HCC), a combination under investigation in a multicenter dose-escalation phase IIb trial (NCT03347292, Table 3).

Simultaneously, the combination of lenvatinib with pembrolizumab has demonstrated promising antitumor activity and manageable toxicity in unresectable HCC through a phase Ib clinical trial (KEYNOTE-524/NCT03006926, Table 3). This combination received Breakthrough Therapy designation from the FDA in July 2019 [124]. Efficacy data from KEYNOTE-524 revealed an objective response rate (ORR) of 46% (95% CI, 36–56.3%) per modified Response Evaluation Criteria in Solid Tumors (mRECIST), with a median progression-free survival (mPFS) of 9.3 months (95% CI, 5.6–9.7) and a median overall survival (mOS) of 22 months (95% CI, 20.4–NE) [125]. As a single-arm study, lenvatinib + pembrolizumab from KEYNOTE-524 did not show significant improvement over approved therapies. Therefore, a phase III trial is currently evaluating the efficacy and safety of this combination compared to lenvatinib + placebo as a first-line option (LEAP-002/NCT03713593, Table 3).

Cabozantinib not only modulates peripheral and intratumor immune landscapes but also induces changes in the phenotype of MC38-CEA tumor cells, thereby increasing their vulnerability to cytotoxic effects mediated by T cells [126]. The immunogenic and immune subset modulations of cabozantinib support its clinical investigation in combination with immunotherapy. Multiple active trials are assessing the efficacy of cabozantinib in combination with nivolumab/atezolizumab, including the COSMIC-312 phase III trial (NCT03755791, Table 3).

To enhance the ORR beyond single-use nivolumab, various combinations are being explored in clinical trials (Table 3), including sorafenib (NCT03439891), lenvatinib (NCT03418922), BMS-986253 (IL-8 inhibitor, NCT04050462), mogamulizumab (CCR4 inhibitor,

NCT02705105), galunisertib (TGFβ inhibitor, NCT02423343), and Pexa-Vec (antitumor vaccine, NCT03071094).

Avelumab (a PD-L1 inhibitor) is under investigation in combination with axitinib/regorafenib through phase 1/2 trials (NCT03289533, NCT03475953, Table 3). The VEGF Liver 100 trial (NCT03289533) is a phase Ib trial assessing the safety and efficacy of avelumab + axitinib (VEGFR inhibitor) as a first-line treatment in advanced HCC patients. Interim results presented at the 2019 ASCO GI Cancer conference by Kudo et al. reported an ORR per mRECIST of 31.8% (95% CI, 13.9–54.9%) and mPFS of 3.8 months (95% CI, 1.9–7.3) [127].

Camrelizumab was evaluated in combination with apatinib (VEGFR-2, RET, c-kit inhibitor) for treating advanced HCC patients in NCT02942329 [128]. As of the data cutoff on June 15, 2018, 8 of 16 evaluable HCC patients achieved a partial response, with an ORR of 50% (95% CI, 24.7–75.4%). This combination is being investigated in a phase III trial as a first-line treatment (NCT03764293) versus sorafenib and a phase II trial as a second-line treatment (NCT03463876) (Table 3).

A study examining tivozanib (selective VEGFR 1–3 tyrosine kinase inhibitor) in combination with durvalumab for untreated advanced HCC updated its phase Ib data at the 2021 ASCO GI Conference. NCT03970616 (Table 3), which enrolled 7 patients, reported that untreated advanced HCC patients tolerated this combination well, with two achieving a partial response [129]. The phase II portion of the study is ongoing.

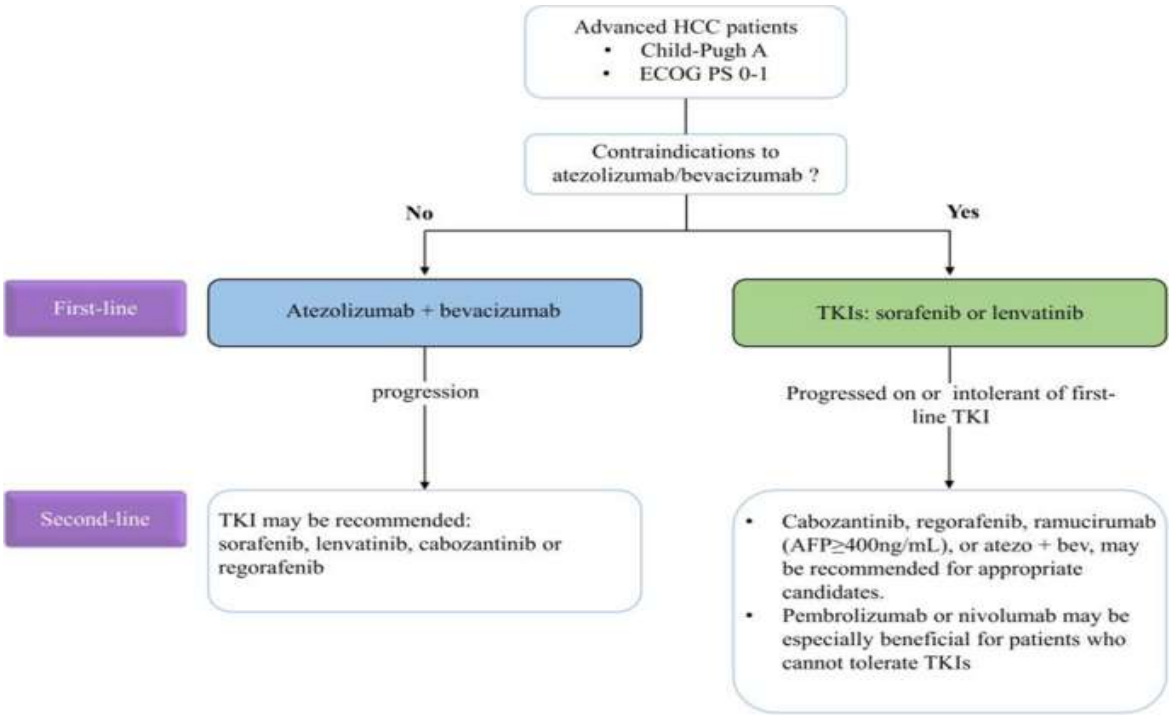
Results from NCT02519348 (Table 3), evaluating durvalumab (D) combined with tremelimumab (T) in advanced HCC patients, were reported at the 2020 ASCO Virtual Scientific Program. T300+D (T 300 mg + D 1500 mg 1 dose followed by D Q4 weekly) provided the best benefit-risk profiles. The confirmed ORR by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in T300 + D was 24% (95% CI, 14.9–35.3%), mOS was 18.7 months (95% CI, 10.8–NR), and grade 3/4 treatment-related adverse events were observed in 26 patients (35.1%) in T300 +D [130]. T300 + D and durvalumab monotherapy are being investigated in the HIMALAYA trial (NCT03298451) as a first-line treatment for advanced HCC patients. Additionally, a phase III trial evaluating the efficacy and safety of IBI310 (CTLA-4 inhibitor) plus sintilimab (PD-1 inhibitor) versus sorafenib as a first-line treatment for advanced HCC is currently recruiting (NCT04720716, Table 3).

Suggested systemic treatment strategies

Recently approved systemic agents provide additional treatment options for patients with advanced hepatocellular carcinoma (HCC); however, the absence of head-to-head comparative studies between first- and second-line systemic treatment regimens has resulted in uncertainty in clinical decision-making. Therefore, systematic reviews and network meta-analyses are of particular significance at this stage. A meta-analysis involving 14 clinical trials by Sonbol et al. indicated that in the first-line setting, atezolizumab + bevacizumab demonstrated superiority over sorafenib (HR=0.58), lenvatinib (HR=0.63), and nivolumab (HR=0.68). In the second-line setting, all drugs exhibited a progression-free survival (PFS) benefit compared to placebo, with regorafenib and cabozantinib showing an additional overall survival (OS) benefit. Notably, cabozantinib and regorafenib exhibited a PFS advantage over ramucirumab and pembrolizumab, and only regorafenib demonstrated a statistically significant OS benefit compared to ramucirumab (HR=0.71). For patients with advanced HCC and alpha-fetoprotein (AFP) levels at or above 400 ng/mL, there was no significant difference in PFS or OS among regorafenib, cabozantinib, and ramucirumab [164]. Park et al.,

incorporating 13 first-line studies and 11 second-line studies, reached similar conclusions. In first-line therapies, atezolizumab + bevacizumab conferred the greatest OS benefit, while lenvatinib showed the highest objective response rate (ORR). In second-line therapies, cabozantinib demonstrated the most significant PFS and ORR benefits compared to placebo [165]. In 2020, the American Society of Clinical Oncology (ASCO) convened an expert panel to conduct a systematic review of published phase III trials and develop evidence-based clinical practice guidelines for systemic therapy in advanced HCC [166]. According to these guidelines, atezolizumab + bevacizumab is considered the standard treatment for most patients with advanced HCC in Child-Pugh grade A and Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–1, as detailed in Fig. 5. For patients with contraindications to immunotherapy, sorafenib or lenvatinib is preferred as the first-line treatment.

Fig 5.



Suggested systemic treatment strategies for advanced HCC. This algorithm is derived from recommendations of "Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline"

Conclusions.

Undoubtedly, advanced hepatocellular carcinoma (HCC) has entered a pivotal phase with the advent of systemic treatments (see Fig. 4). Common characteristics of cancers include angiogenesis and immune evasion [167]. A notable breakthrough in the era of immune combination therapy is the atezolizumab + bevacizumab regimen, proven to be more effective than sorafenib in the first-line treatment of advanced HCC. This achievement is considered a milestone, ushering in a new era for advanced HCC treatment. Notably, atezolizumab + bevacizumab is now advocated as a preferred first-line treatment [164, 165, 166]. This prompts questions about the validity of existing second-line treatment options and the potential for existing first-line tyrosine kinase inhibitors (TKIs) to serve as second-line

treatments after immunotherapy. These questions await clarification in future studies. Concurrently, several phase III trials in the first-line setting are underway, including CheckMate-9DW, LEAP2, COSMIC-312, and HIMALAYA (refer to Table 3), contributing to an expanding array of potential first-line treatment choices and adding complexity to clinical decision-making.

Our review not only provides a comprehensive list of FDA-approved drugs for HCC treatment but also synthesizes information on novel drug candidates currently under investigation. Phase I/II or phase III studies have shown promising results for selective inhibitors targeting VEGFR, c-MET, TGFβ, endoglin, and FGFR4, positioning these compounds as promising prospects for future treatments. In the realm of immunotherapy, alongside the well-established PD-1/PD-L1 and CTLA-4 targets, a growing number of immune checkpoint inhibitors (ICIs) like LAG-3, TIM-3, and GITR are progressively proving their efficacy. Simultaneously, the identification of more hepatocellular carcinoma-specific tumor-associated antigens (TAAs) is driving the development of additional immunotherapeutic approaches, including antibody-drug conjugates (ADCs), CAR-T cell therapy, and bispecific T-cell engagers (BiTEs).

While the development of new drugs for HCC may not be as remarkable as in some other tumor types, predictive biomarkers remain scarce, with exceptions such as AFP for ramucirumab and potentially FGF19 for FGFR4 inhibitors. Recent clinical trials suggest that a singular drug may not suffice for HCC treatment [168], underscoring the significance of combination therapy as a focal point in current research for the systemic treatment of advanced HCC. Additionally, the quest for biomarkers predicting treatment responses is crucial for guiding systemic therapy strategies. As new therapeutic strategies continue to unfold, there is optimism that treatment outcomes for HCC will experience significant improvement in the future.

Abbreviations

ADCs:
Antibody-drug conjugates

AEs:
Adverse events

ASCO:
American society of clinical oncology

BiTE:
Bispecific T cell engager

CAR-T:
Chimeric antigen receptor T Cells

CI:
Confidence interval

CTL:
Cytotoxic T lymphocyte

CTLA-4:
Cytotoxic T lymphocyte associated antigen 4

DCR:
Disease control rate
FGF:
Fibroblast growth factor
FGFR:
Fibroblast growth factor receptor
HCC:
Hepatocellular carcinoma
HR:
Hazard ratio
ICIs:
Immune checkpoint inhibitors
MDSCs:
Myeloid-derived suppressor cells
ORR:
Objective response rate
OS:
Overall survival
PDGFR:
Platelet-derived growth factor receptor
PFS:
Progression-free survival
RECIST:
Response evaluation criteria in solid tumors
TAMs:
Tumor-associated macrophages
TKIs:
Tyrosine kinase inhibitors
TME:
Tumor microenvironment
TRAEs:
Treatment-related adverse events
Tregs:
T-regulatory cells
TTP:
Time to progression
VEGFR:
Vascular endothelial growth factor receptor

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