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The Trend of the Treatment of Advanced Hepatocellular Carcinoma: Combination of Immunotherapy and Targeted Therapy

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Opinion Statement

Hepatocellular carcinoma (HCC) is a common type of tumor worldwide. The development of systemic treatment of advanced HCC has remained stagnant for a considerable period. During the last years, a series of new treatment regimens based on the combination of immunotherapeutic drugs and targeted drugs have been gradually developed, increased the objective response rate (ORR), overall survival (OS), and progression free survival (PFS) of HCC patients. Among the different combination therapy groups, atezolizumab plus bevacizumab and sintilimab plus IBI-305 seem to have unique advantages, while head-to-head comparisons are still needed. A comprehensive understanding of the developments, the ongoing clinical trials and the mechanisms of combination of immunotherapy and targeted therapy might lead to the development of new combination strategies and solving current challenges such as the molecular biomarkers, the clinical administration order of drugs and the second-line treatments after combination therapy.

Keywords Hepatocellular carcinoma · Immunotherapy · Targeted drugs · Combination therapy

Introduction: The Development of Anti-Tumor Drugs in HCC

Hepatocellular carcinoma (HCC) is one of the common malignant tumors worldwide. In 2020, there were 905,677 new cases and 830,180 deaths of HCC globally, ranking sixth and third in morbidity and mortality, respectively, and imposing a substantial disease burden [1]. Due to the subtle early symptoms, HCC has often been in the middle or advanced stage when diagnosed, precluding curative treatments such as surgery and resulting in low 5-year survival rates and poor prognosis. Consequently, systemic therapy constitutes a primary treatment strategy for advanced HCC [2].

The heterogeneity of HCC poses a significant challenge, delaying the development of anti-HCC drugs. In 1997, rituximab, as the first anti-tumor targeted drug, was approved for non-Hodgkin lymphoma. It wasn't until a decade later, in 2007, that sorafenib became the first targeted drug approved by the U.S. Food and Drug Administration (FDA) for HCC and was recommended as the first-line treatment for HCC by National Comprehensive Cancer Network (NCCN) Guidelines in 2008 (Fig. 1). Despite a low objective response rate (ORR) and less-than-ideal therapeutic effects, sorafenib had remained the only first-line targeted drug for HCC for over a decade [3]. This picture changed in 2018 with the approval of lenvatinib as the first-line treatment for HCC, despite the remained challenges such as a low ORR, severe secondary resistance, and limited choices of therapeutic agents without fundamental improvement [4].

Meanwhile, significant strides have been made in the immune checkpoint inhibitor (ICI)-centered immunotherapy

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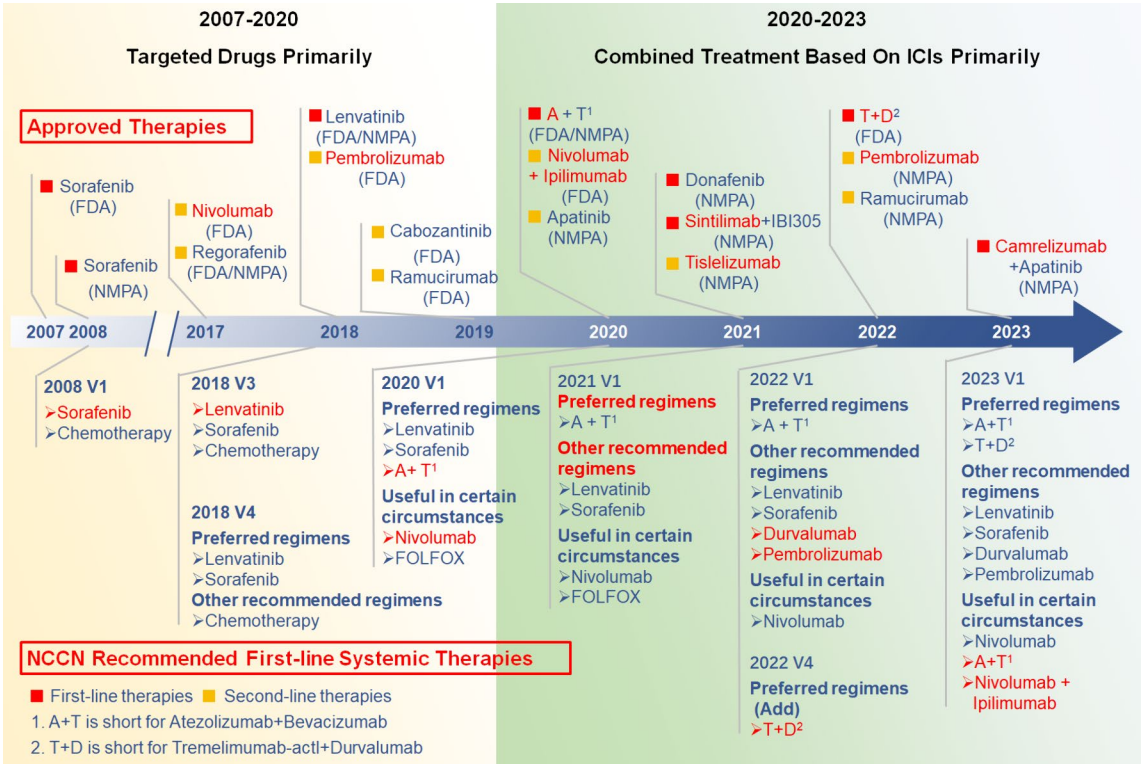

Fig. 1 Timeline of systemic treatments for advanced HCC. Positioned above the time axis are the first and second-line drugs approval by the U.S. FDA and the China NMPA, and the drugs in red are immune checkpoint inhibitors; positioned below the time axis are the first line treatments recommended by the NCCN guidelines, and the red marks the differences between versions

over the past decade. By targeting and blocking the immune checkpoints such as PD-1, PD-L1 and CTLA-4, immunotherapy activates cytotoxic $CD8^+$ T lymphocytes, obstructing immune escape of tumor cells and thus exerting anti-tumor effects [5, 6]. ICIs have significantly prolonged the overall survival (OS) in melanoma, non-small cell lung cancer (NSCLC), colorectal cancer (CRC) [7–9] and other tumors, representing the "third revolution" in cancer treatment following chemotherapy and targeted therapy. In 2017, nivolumab was recommended by the NCCN Guidelines as the second-line treatment for HCC, marking the beginning of an era of immunotherapy for advanced HCC. Despite the effectiveness of nivolumab and pembrolizumab in various solid tumors, their efficacy on HCC is limited, making them the second-line treatment options [10, 11]. However, with the initiation of clinical trials such as IMbrave150, ORIENT32 and HIMALAYA since 2020, immunotherapy-based combination therapy has been gradually developed for advanced HCC [12–14]. In comparison to previous strategies of targeted drugs or immunotherapy alone, combination therapy effectively prolongs progression-free survival (PFS) and OS, and achieves a synergistic effect (1 + 1 > 2) [15]. Here, we provide a comprehensive review of relevant ongoing and completed clinical trials and the mechanisms of ICIs combined with targeted therapy.

Combination Therapy Based on Atezolizumab

Atezolizumab is a PD-L1 monoclonal antibody that has been approved by the FDA for various tumors, including SCLC, NSCLC, and metastatic castration-resistant prostate cancer [16–18].

Combination Therapy of Atezolizumab and Bevacizumab

Bevacizumab is a VEGF-A monoclonal antibody that exerts anti-tumor effects by inhibiting the binding of VEGF-A to VEGFR-2 [19]. It has been approved for the treatment of CRC, NSCLC, and renal cell carcinoma [20–22]. In 2020, based on the results of IMbrave150, atezolizumab in combination with bevacizumab was approved by the FDA as the first-line treatment for unresectable advanced HCC (Fig. 1). Moreover, it was also recommended by the NCCN Guidelines version 1.2020 as a preferred first-line systemic therapy for HCC.

IMbrave150 is a global, open-label, randomized phase III clinical trial involving 501 patients from 17 countries [13]. The results showed that compared with sorafenib,

atezolizumab plus bevacizumab significantly extended median PFS (mPFS, 6.8 vs. 4.3 months, $p < 0.001$) and mOS (19.2 vs. 13.4 months, $p < 0.001$), and increased ORR (33.2% vs. 13.3%, $p < 0.0001$) and disease control rate (DCR) (72.3% vs. 55.1%). Moreover, 10.2% of patients in the combination therapy group achieved complete response (CR), while no patients in the sorafenib group achieved CR. In terms of safety, the combination therapy group did not exhibit new adverse events (AEs), with 61.1% experiencing AEs of grade 3 or higher, and 15.5% discontinuing the trial due to AEs. In contrast, 60.9% of patients in the sorafenib group experienced AEs of grade 3 or higher, with 10.3% discontinuing the trial due to AEs, indicating an overall manageable safety profile.

Moreover, the subgroup data of IMbrave150 for the Chinese population, presented at the 2021 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO-GI), demonstrated an mOS of 24 months in the atezolizumab plus bevacizumab group, significantly longer than that in the sorafenib group (11.4 months) and superior to the global data. Safety data in the Chinese population were consistent with the global population, and no new AEs were observed.

However, conflicting results have been presented in different studies. A retrospective, multicenter, real-world study, which involved 2205 advanced HCC patients, showed an mOS of 16.4 months in the atezolizumab plus bevacizumab group, with no significant difference from the lenvatinib group ($p = 0.739$) [23]. Furthermore, subgroup analysis revealed a significantly longer mOS in patients with hepatitis B/C viral infections in the atezolizumab plus bevacizumab group than the lenvatinib group ($p = 0.024$), whereas in patients with non-alcoholic fatty liver disease (NAFLD)/non-alcoholic fatty liver (NAFL), the lenvatinib group showed significantly longer mOS than the atezolizumab plus bevacizumab group ($p = 0.014$) [23]. In contrast to this study, another study involved 161 patients detected no significant differences among patients of different etiologies in ORR, mPFS and OS (viral vs. non-viral: ORR 22.1% vs. 23.1%, mPFS 4.4 vs. 4.4 months and OS 14.0 vs. 13.1 months; NAFLD vs. others: 21.1% vs. 23.9%, mPFS 3.1 vs. 4.1 months and OS 14.2 vs. 14 months) under the treatment of atezolizumab plus bevacizumab [24].

The effectiveness and safety of standard-dose and low-dose bevacizumab in combination with atezolizumab in the treatment of HCC were also evaluated among 151 patients [25]. The results showed no significant differences between standard-dose group and low-dose group in mOS (14.9 vs. 11.2 months, $p = 0.13$), mPFS (8.4 vs. 5.7 months, $p = 0.59$) and bleeding event rate (20.0% vs. 25.0%, $p = 0.23$). These results suggest that low-dose bevacizumab in combination with atezolizumab may be as effective as standard-dose one, potentially avoiding resource wastage and alleviating financial burdens on patients, which provides a theoretical basis for future clinical standards and precision medicine [26].

In summary, although atezolizumab plus bevacizumab is currently recommended as the first-line treatment option by the FDA and NCCN Guidelines, further understanding of its applicable population and drug dosage is needed to achieve precise medicine as early as possible.

Combination Therapy of Atezolizumab and Cabozantinib

Cabozantinib is a multi-targeted small molecular tyrosine kinase inhibitor (TKI) that inhibits various targets including VEGFR1, VEGFR2, VEGFR3, MET and ALX [27, 28]. Moreover, cabozantinib can modulate immune activity, strengthen tumor suppression, and enhance immune response [29]. It has been approved by the FDA for the treatment of medullary thyroid cancer and advanced renal cell carcinoma. In 2019, based on the CELESTIAL trial results, it was also approved for the treatment of HCC patients previously treated with sorafenib.

COSMIC-312 is a global, multicenter, randomized, open-label phase III trial that included 837 patients, aiming to evaluate the efficacy of the combination therapy of atezolizumab and cabozantinib compared with sorafenib in the first-line treatment for advanced HCC (Table 1) [30]. The results showed that mPFS in the combination therapy group was superior to that in the sorafenib group (6.8 vs. 4.2 months, $p = 0.0012$), so did the ORR (11% vs. 4%) and DCR (78% vs. 65%), but not mOS (15.4 vs. 15.5 months, $p = 0.44$). In terms of safety, a total of 324 patients (76%) experienced AEs of grade 3 or higher, dominated by hypertension, in the combination therapy group, and the overall tolerability was good. In contrast, 118 patients (57%) had AEs of grade 3 or higher in the sorafenib group. In conclusion, atezolizumab in combination with cabozantinib improves PFS and increases the ORR in patients with advanced HCC, but there is a lack of robust evidence regarding OS benefits.

Ongoing Clinical Trials of Combination Therapy Based on Atezolizumab

Irpagratinib (ABSK-011) is a highly selective FGFR4 inhibitor [43]. The results of a phase II clinical trial presented at the ESMO Congress 2023 revealed an impressive ORR of 43.5% among FGF19-positive patients with HCC, much higher than that among patients treated with the second-line drugs such as regorafenib and rivoceranib (11%) [44]. Currently, a phase II clinical trial (NCT05441475) is underway, investigating the safety and tolerability of atezolizumab in combination with ABSK-011 in the treatment of advanced or unresectable HCC (Table 2).

Table 1 The clinical trial outcomes of the combination of immunotherapy and targeted therapy for advanced HCC

Trials	Line	Phase	Treatment arms	Number of patients	mOS (mouths)	mPFS (mouths)	ORR (%)	DCR (%)	CR (%)	PR (%)	SD (%)	PD (%)	AEs (grade > = 3)	References
IMbrave 150	First	III	Atezolizumab + Bevacizumab	336	19.2	6.8	33.2	72.3	10.2	23.1	39.1	20.3	61.1%	[12]
			Sorafenib	165	13.4	4.3	13.3	55.1	1.9	11.4	41.8	25.3	60.9%	
COSMIC-312	First	III	Atezolizumab + Cabozantinib	432	15.4	6.8	13.0	82.0	< 1	12.0	69.0	13.0	83.0%	[30]
			Sorafenib	217	15.5	4.2	5.0	63.0	0.0	5.0	58.0	21.0	62.0%	
ORIENT-32	First	III	Sintilimab + IBI-305	380	NR	4.6	25.0	72.0	1.0	24.0	49.0	26.0	56.0%	[13]
			Sorafenib	191	10.4	2.8	8.0	64.0	0.0	8.0	56.0	34.0	48.0%	
NCT04401813	First	II	Sintilimab + Ilenvatinib	97	NR	14.3	66.7	94.4	22.2	44.4	27.8	5.6	25.0%	[31]
KEYNOTE-524	First	Ib	Pembrolizumab + Lenvatinib	104	22	9.3	46.0	88.0	11.0	35.0	42.0	7.0	67.0%	[32]
LEAP-002	First	III	Pembrolizumab + Lenvatinib	395	21.2	8.4	40.8	84.3	9.0	31.0	44.0	9.0	63.5%	[33]
			Lenvatinib	399	19	8.1	34.1	83.2	10.0	25.0	49.0	10.0	58.3%	
NCT03347292	First	Ib	Pembrolizumab + Regorafenib	35	/	/	32.0	88.0	1.0	31.0	56.0	/	86.0%	[34]
			Regorafenib	22	/	/	18.0	91.0	0.0	18.0	73.0	/	50.0%	
Study 117	First	Ib	Nivolumab + Lenvatinib	30	/	/	76.7	96.7	13.3	63.3	20.0	3.3	/	[35]
IMMUNIB	First	II	Nivolumab + Lenvatinib	50	27.1	9	28.0	74.0	6.0	22.0	46.0	12.0	59.1%	[36]
VEGF Liver 100	Second	Ib	Avelumab + Axitinib	22	14.1	3.8	31.8	72.7	/	/	/	/	0.0%	[37]
CARES-310	First	III	Camrelizumab + Rivoceranib	272	22.1	5.6	25.0	78.0	/	/	/	/	88.0%	[38]
			Sorafenib	271	15.2	3.7	19.0	54.0	/	/	/	/	68.0%	
COMPASSION-08	First	Ib/II	Cadonilimab + Lenvatinib	31	0.271	8.6	35.5	90.3	0.0	35.5	54.8	9.7	25.8%	[39]
			High-dose cadonilimab + Lenvatinib	28	NR	9.8	35.7	92.9	0.0	35.7	57.1	3.6		
ChiCTR2100050076	First	II	Tislelizumab + Sorafenib	32	/	/	17.0	65.0	/	/	/	/	35.0%	[40]
/	Second	II	Tislelizumab + Regorafenib	28	NR	6.4	28.6	71.0	11.0	18.0	42.4	/	/	[41]
NCT05148195	Second	II	Envafolimab + Suvemcitug	20	/	/	11.1	72.2	0.0	11.1	61.1	27.8	45.0%	[42]

mPFS, median progression-free survival; mOS, median overall survival; ORR, overall response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; AE, adverse event

Combination Therapy Based on Sintilimab

Sintilimab is a humanized IgG4 monoclonal antibody that can bind to PD-1, blocking the interaction of PD-1 with PD-L1 and PD-L2 [45]. It has been approved for the treatment of classical Hodgkin lymphoma, NSCLC, and esophageal cancer by the China National Medical Products Administration (NMPA) [46–48].

Combination Therapy of Sintilimab and Bevacizumab Biosimilar (IBI-305)

IBI-305 is a biosimilar of bevacizumab, which is an anti-VEGF antibody with a high binding affinity for VEGF [49]. It has been approved for the treatment of malignant tumors such as NSCLC [47] and CRC [50]. In 2021, based on the results of the ORIENT-32 trial, sintilimab in combination with IBI-305 was approved as the first-line treatment for HCC by the NMPA.

ORIENT-32 is a phase III clinical trial including a total of 571 untreated, unresectable HBV-related liver cancer patients (Table 1, Fig. 1) [12]. The results showed that the OS in the combination therapy group was significantly longer than that in the sorafenib group. With a median follow-up period of 10 months, mOS was not reached in the combination therapy group, while it was 10.4 months in the sorafenib group ($p < 0.0001$), mPFS in the combination therapy group (4.6 months) was significantly longer than in the sorafenib group (2.8 months), with a 43.1% reduction in the risk of death ($p < 0.0001$). The combination therapy group had a significantly higher ORR than the sorafenib group (20.3% vs. 4.1%), and a superior DCR to the sorafenib group (72% vs. 64%). In addition, 209 individuals (56%) experienced AEs of grade 3 or higher in the combination therapy group, while there were 89 individuals (48%) experiencing AEs of grade 3 or higher in the sorafenib group. No new AEs were detected in the combination therapy group.

Table 2 The ongoing clinical trials of immunotherapy combined with targeted therapy in HCC

Clinical trial ID	Immune checkpoint inhibitors	Targeted drugs	Line	Phase	Estimated enrollment patients	Recruitment status	Location countries
NCT04444167	AK104	Lenvatinib	First line	Phase 1/2	30	Recruiting	China
NCT04344158	AK105	Anlotinib	First line	Phase 3	648	Not yet recruiting	China
NCT04418401	anti-PD-1 antibody	Donafenib	Postoperative adjuvant therapy	Phase 1	30	Recruiting	China
NCT05441475	Atezolizumab	ABSK-011	First line	Phase 2	62	Recruiting	China
NCT04829383	Atezolizumab	Bevacizumab	First line	Phase 2	50	Active, not recruiting	United States
NCT06096779	Atezolizumab	Bevacizumab	First line	Phase 2	120	Recruiting	United States
NCT05856864	Cadonilimab	Ramucirumab	Second line	Phase 1	30	Recruiting	China
NCT05644379	Cadonilimab	Regorafenib	Second line	Phase 1	30	Recruiting	China
NCT04443309	Camrelizumab	Lenvatinib	First line	Phase 1/2	53	Recruiting	China
NCT05048017	Camrelizumab	Regorafenib	Second line	Phase 2	20	Recruiting	China
NCT05760599	Candonilimab	Bevacizumab	Second line	Phase 2	30	Recruiting	China
NCT05312216	Durvalumab	Lenvatinib	First line	Phase 2	25	Not yet recruiting	China
NCT05557838	Durvalumab	Tremelimumab	First line	Phase 3	300	Recruiting	China
NCT04720716	IBI310	Sintilimab	First line	Phase 3	490	Recruiting	China
NCT04542837	KN046	Lenvatinib	First line	Phase 2	55	Recruiting	China
NCT04828486	Pembrolizumab	Futibatinib	First line	Phase 2	25	Recruiting	United States
NCT05408221	Rulonilimab	Lenvatinib	First line	Phase 2/3	576	Recruiting	China
NCT04560894	SCT-I10A	SCT510	First line	Phase 2/3	621	Recruiting	China
NCT04042805	Sintilimab	Lenvatinib	First line	Phase 2	36	Recruiting	China
NCT05162352	Sitilimab	Donafenib	First line	Phase 2	30	Unknown status	China
NCT04183088	Tislelizumab	Regorafenib	First line	Phase 2	125	Recruiting	China
NCT05453383	Toripalimab	Anlotinib	Second line	Phase 2	30	Recruiting	China
NCT04368078	Toripalimab	Lenvatinib	Second line	Phase 2	76	Recruiting	China
NCT06031480	TQB2450	Anlotinib	First line	Phase 2	55	Not yet recruiting	China
NCT04503902	Treprizolizumab	Donafenib	First line	Phase 1/2	46	Recruiting	China

Combination Therapy of Sintilimab and Lenvatinib

In a phase II clinical trial (NCT04042805) with 26 newly diagnosed unresectable advanced HCC patients, the efficacy of sintilimab in combination with lenvatinib was evaluated [31]. The results showed that the ORR was 35%, and the DCR was 92%. Among these patients, 7 cases (27%) successfully achieved downstaging and underwent liver resection, and 1 case (4%) underwent curative ablation and stereotactic radiotherapy. With a median follow-up period of 9 months, neither mPFS nor mOS was reached. In addition, 5 patients (19%) experienced AEs of grade 3 or higher, indicating an overall manageable safety profile. The above results suggest that the combination of sintilimab and lenvatinib is a feasible neoadjuvant treatment option. However, further validation with a larger sample size is still needed.

Ongoing Clinical Trials of Combination Therapy Based on Sintilimab

Donafenib is a multi-receptor TKI that can inhibit the activity of various tyrosine kinases, including VEGFR and RAF, thereby restraining tumor growth and angiogenesis [51]. Based on the results of the ZGDH3 trial, donafenib was approved by the NMPA as the first-line treatment for HCC in 2021 [52]. Currently, a phase II clinical trial (NCT05162352) evaluating the combination of sintilimab and donafenib as the first-line treatment for advanced HCC is underway, with 30 patients to be recruited (Table 2).

Combination Therapy Based on Pembrolizumab

Pembrolizumab is an anti-PD-1 monoclonal antibody that has been approved by the FDA for the treatment of 18 different cancers, such as melanoma, NSCLC, and squamous cell carcinoma [53–55]. In 2018, FDA approved the use of pembrolizumab in the second-line treatment for HCC based on the results of cohort 1 of the KEYNOTE-224 trial (Fig. 1) [10]. In the same year, the NCCN Guidelines version 4.2018 recommended pembrolizumab as the second-line treatment option for HCC patients in Child–Pugh class A. In 2022, based on data from cohort 2 of the KEYNOTE-224 trial, pembrolizumab was incorporated in the other recommended regimens for the first-line treatment for HCC by the NCCN Guidelines version 1.2022 (Fig. 1).

Combination Therapy of Pembrolizumab and Lenvatinib

KEYNOTE-524 (NCT03006926) is a single-arm phase Ib clinical trial evaluating the efficacy of pembrolizumab in combination with lenvatinib on advanced HCC patients, with a total of 106 patients enrolled (Table 1). The results showed an mOS of 22.0 months, an mPFS of 9.3 months, and an ORR of 46% in the combination therapy group, with 11% of patients achieving complete tumor disappearance and CR [32]. Therefore, the combination of pembrolizumab and lenvatinib received "Breakthrough Therapy Designation" from the FDA in 2019 as the first-line treatment for HCC patients.

However, the results of a global phase III large-scale clinical trial LEAP-002 subsequently demonstrated that the combination therapy and lenvatinib monotherapy displayed a 24-month OS of 21 vs. 19 months, an mPFS of 8.2 vs. 8 months, and an ORR of 40.8% vs. 34.1%, showing no statistically significant differences [33]. It was worth noting that, different from IMbrave and HIMALAYA, LEAP-002 used lenvatinib rather than sorafenib as a control for the first time. Moreover, in LEAP-002, the OS of the control group was much longer than that reported in the REFLECT trial (13.6 months) and other historical data, which may be related to the population selected [56]. According to further subgroup analysis, HBV-related HCC patients rather than non-HBV-related HCC ones obtained survival benefits from pembrolizumab plus lenvatinib. In the LEAP-002 trial, a relatively small proportion of HBV-related HCC patients and Asian populations was enrolled, and there were also fewer patients with microvascular invasion (MVI) in the lenvatinib group than the REFLECT trial (15.5% vs. 23%) [33]. These factors may affect the efficacy of the combination therapy, so more refined population segmentation may be necessary.

Ongoing Clinical Trials of Combination Therapy Based on Pembrolizumab

Regorafenib is an oral TKI that selectively targets VEGFR1, TIE-2, RET, RAF-1, BRAF, PDGFR, FGFR, and CSF1R [57]. It exhibits stronger anti-angiogenic and anti-tumor growth effects than sorafenib, and can also inhibit tumor metastasis and the production of immune-related proteins. Regorafenib has been approved for the second-line treatment for CRC [58], gastrointestinal stromal tumors [59], and HCC [60].

In an open-label phase Ib clinical trial (NCT03347292), which has completed patient recruitment, the safety and

efficacy of pembrolizumab in combination with regorafenib as the first-line treatment for advanced HCC were assessed (Table 1) [34]. The preliminary results showed that among the 23 evaluable patients, 7 (30%) achieved partial response (PR), and 14 (61%) had stable disease (SD), resulting in an overall DCR of 91%. The overall safety profile was manageable, and no new AEs were identified.

Futibatinib is an irreversible FGFR inhibitor approved as the second-line treatment for intrahepatic cholangiocarcinoma [61]. Currently, a phase II clinical trial is ongoing to assess the safety and efficacy of futibatinib in combination with pembrolizumab in the second-line treatment for FGF19-positive HCC (NCT04828486) (Table 2).

Combination Therapy of Nivolumab and Lenvatinib

Nivolumab is the first FDA-approved anti-PD-1 monoclonal antibody and has been approved for the treatment of several cancers, including esophageal squamous cell carcinoma, CRC and head and neck cancer [62–64]. In 2017, it was approved by the FDA as the second-line treatment for HCC patients resistant to sorafenib (Fig. 1). It was also recommended by the NCCN Guidelines version 4.2017 as the second-line treatment and incorporated in the first-line treatment for patients in Child–Pugh class A/B who were not applicable for TKIs and other anti-angiogenic agents in version 1.2021.

Study 117 (NCT03418922) is a phase Ib clinical trial investigating the tolerability and safety of nivolumab in combination with lenvatinib as the first-line treatment for advanced HCC (Table 1). The results manifested that out of the 30 patients, 4 (13%) achieved CR, and 19 (63%) achieved PR, DCR was 96.7%. Hand-foot syndrome (56.7%) and dysphonia (53.3%) were the most common adverse reactions [35]. Through dose adjustment and supportive care, these adverse reactions were effectively controlled. To sum up, nivolumab plus lenvatinib demonstrates good tolerability and safety in the treatment of HCC.

Another phase II clinical trial, the IMMUNIB trial (AIO-HEP-0218/ass), focused on the safety and efficacy of nivolumab in combination with lenvatinib as the first-line treatment for advanced HCC [36]. It was found that among the 50 patients, the ORR was 28%, with a CR rate of 6.0% and a PR rate of 22.0%. mPFS was 9.0 months, median time to progression (mTTP) was 11.5 months, and mOS was 27.1 months. In terms of safety, 29 patients (59.1%) experienced at least one AE of grade 3 or higher. Although the expected ORR of 40% was not reached, nivolumab in combination with lenvatinib is pending further investigation in larger cohorts as supported by mOS (27.1 months).

Combination Therapy of Avelumab and Axitinib

Avelumab is an anti-PD-L1 drug approved by the FDA for urothelial tumors [65] and renal cell carcinoma [66]. As a potent TKI targeting VEGFR1/2/3, axitinib has been approved for the second-line treatment for advanced renal cell carcinoma patients [67]. In 2019, an ASCO-reported phase Ib clinical study demonstrated the anti-tumor activity of avelumab in combination with axitinib in HCC.

VEGF Liver 100 (NCT03289533) is a phase Ib clinical trial evaluating the tolerability and safety of avelumab in combination with axitinib as the first-line treatment for advanced HCC, with a total of 22 patients enrolled [37]. According to mRECIST, the DCR in the avelumab plus axitinib group was 72.7%, with an mPFS of 3.8 months and an ORR as high as 31.8%. In terms of safety, the most common grade 3 AEs were hypertension (50.0%) and hand-foot-skin reaction (22.7%), with no grade 4/5 AEs reported, and no patients discontinued treatment due to AEs.

In conclusion, the combination of avelumab and axitinib exhibits a favorable safety profile, substantial anti-tumor activity, and a higher ORR than any monotherapy in the treatment of HCC. These promising findings warrant further investigation in phase II and III clinical trials.

Combination Therapy of Camrelizumab and Rivoceranib

Camrelizumab is a humanized anti-PD-1 monoclonal antibody approved by the NMPA for various cancers, including Hodgkin lymphoma, NSCLC, esophageal squamous cell carcinoma and nasopharyngeal carcinoma, and also as the second-line treatment for HCC [68–71]. Rivoceranib, a VEGFR2 inhibitor, inhibits tumor angiogenesis by competitively binding to the ATP-binding site of intracellular VEGFR-2 [72]. It is approved by the NMPA for the treatment of metastatic/advanced gastric cancer and the second-line treatment for HCC. In 2023, based on the results of the CARES-310 trial, the combination of camrelizumab and rivoceranib was approved by the NMPA as the first-line treatment for HCC (Fig. 1).

CARES-310 is a global, randomized, open-label clinical trial evaluating the efficacy and safety of camrelizumab in combination with rivoceranib compared to sorafenib in the first-line treatment for advanced HCC, with 543 patients enrolled (Table 1). The results indicated a significant extension of mPFS (5.6 vs. 3.7 months, $p < 0.0001$) and mOS (22.1 vs. 15.2 months, $p < 0.0001$) in the combination therapy group as compared to the sorafenib group [38, 73]. CARES-310 is the only clinical trial to date that has

obtained positive results for both PFS and OS from ICIs in combination with small molecule TKIs in the first-line treatment for advanced HCC.

Currently, several clinical trials based on camrelizumab in combination with targeted therapies are ongoing (Table 2). For example, NCT04443309 is a single-arm, open-label, non-randomized, single-center phase I/II clinical trial designed to evaluate the safety, tolerability, and efficacy of camrelizumab in combination with lenvatinib in the first-line treatment for advanced liver cancer. NCT05760599 is a phase II clinical trial aiming to assess the effectiveness and safety of camrelizumab in combination with bevacizumab as the second-line treatment for patients resistant to atezolizumab plus bevacizumab. NCT05048017 is a phase II trial evaluating the safety and efficacy of regorafenib in combination with PD-1 inhibitors (camrelizumab, toripalimab, and pembrolizumab) in the second-line treatment for HCC.

Combination Therapy Based on Cadonilimab

Cadonilimab is a bispecific antibody that targets both PD-1 and CTLA-4. By completely eliminating ADCC, ADCP, and CDC effects by the modification of the Fc segment, it effectively avoids the loss of effector T cells and immune-related adverse reactions caused by Fc-mediated immune cell activation [74, 75]. It has been approved by the NMPA for the treatment of recurrent or metastatic cervical cancer [76].

COMPASSION-08 is a multicenter, open-label, single-arm, phase Ib/II clinical trial evaluating the safety and efficacy of cadonilimab in combination with lenvatinib in the first-line treatment for advanced HCC [39]. 59 patients were enrolled and received either 6 mg/kg cadonilimab every 2 weeks plus lenvatinib (cohort A) or 15 mg/kg cadonilimab every 3 weeks plus lenvatinib (cohort B). The results showed that the ORR in the cohort A and cohort B was 35.5% and 35.7%, respectively, with an mPFS of 8.6 months and 9.8 months. mOS in the cohort A was 27.1 months, while mOS was not reached in the cohort B. In terms of safety, grade $\geq$ 3 AEs occurred in 66.1% of patients with the most common being hypertension (20.3%), decreased platelet count (8.5%), increased alanine aminotransferase (6.8%), rash (6.8%), and decreased appetite (6.8%) [39]. These results suggest that cadonilimab in combination with lenvatinib demonstrates certain efficacy and manageable safety in a small sample size, providing a basis for subsequent large-sample phase III clinical trials [77].

Additionally, clinical trials exploring the combination of cadonilimab and other targeted drugs in the treatment of HCC are ongoing (Table 2). For example, NCT05856864 is an open-label, single-arm, single-center phase I/II clinical trial aiming to assess the safety and efficacy of cadonilimab in combination with ramucirumab in the treatment of HCC following a failed systemic therapy. NCT05644379 is an open-label, single-arm, single-center clinical trial designed to assess the safety and efficacy of cadonilimab in combination with regorafenib in the second-line treatment for HCC.

Combination Therapy Based on Tislelizumab

Tislelizumab is a humanized IgG4 anti-PD-1 monoclonal antibody that has been approved by the NMPA for the first-line treatment of various cancers, including esophageal squamous cell carcinoma, NSCLC, classical Hodgkin lymphoma, urothelial carcinoma, and nasopharyngeal carcinoma [78–82]. Based on the results of the RATIONALE-208 trial [83], NMPA approved tislelizumab monotherapy as the second-line treatment for HCC in 2021 (Fig. 1).

Combination Therapy of Tislelizumab and Sorafenib

In an ongoing phase II clinical trial (ChiCTR2100050076), the effectiveness and safety of tislelizumab in combination with sorafenib in the treatment of advanced HCC were evaluated, with 32 patients enrolled [40]. According to preliminary data, the ORR assessed by RECIST v1.1 was 17%, and the DCR was 65%. As assessed by mRECIST, the ORR and DCR increased to 24.2% and 75%, respectively. In terms of safety, 75% of patients experienced AEs, and 35% of patients had AEs of grade 3 or higher [40]. The combination of tislelizumab and sorafenib demonstrates promising anti-tumor effects, showing a relatively high ORR and a manageable safety profile in the first-line treatment for HCC [41]. These findings lay the groundwork for subsequent large-scale phase III clinical trials.

Combination Therapy of Regorafenib and Tislelizumab

In a single-arm phase II clinical trial, regorafenib or tislelizumab alone demonstrated clinical benefits in the second-line treatment for advanced HCC. In an ongoing study, the safety and efficacy of the combination of regorafenib and tislelizumab as the second-line treatment for unresectable HCC were evaluated. The primary endpoints include the safety and tolerability of the combination therapy, while the secondary endpoints are the ORR assessed by mRECIST, PFS, and DCR [84].

A total of 28 patients who have undergone at least one prior first-line treatment were included, with 67.9% receiving treatment with TKIs and 21.4% receiving

treatment with TKIs plus PD-1 antibodies. The results showed an ORR of 28.6% and a DCR of 71%, including 3 cases of CR, 5 cases of PR, and 12 cases of SD. mPFS was 6.4 months, and mOS was not reached. In terms of safety, AEs of grade 1 and 2 were most common, dominated by rash (6/28; 21%), hypertension (9/28; 32%), hand-foot syndrome (18/28; 64%), and fatigue (7/28; 25%) [84]. Therefore, the combination of regorafenib and tislelizumab appears to be an effective and well-tolerated second-line treatment for HCC, warranting further validation in larger cohorts.

Furthermore, in an ongoing randomized phase II clinical trial (NCT04183088), the safety and efficacy of tislelizumab in combination with regorafenib in the first-line treatment for advanced HCC were evaluated (Table 2).

Combination Therapy of Envafolimab and Suvemcitug

Suvemcitug is a novel human-rabbit chimeric IgG1 monoclonal antibody that selectively binds to and blocks the interaction of VEGFA with VEGFR1 and VEGFR2, thereby suppressing tumor angiogenesis and ultimately inhibiting tumor growth and metastasis [85]. Envafolimab is a PD-L1 antibody that can be administered subcutaneously and it has been approved by the NMPA for the treatment of adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) advanced solid tumors and chronic hepatitis B [86, 87].

In an open-label, multi-cohort, multicenter phase II clinical trial (NCT05148195), 20 HCC patients who had previously undergone at least one first-line treatment were enrolled in cohort B and treated with envafolimab in combination with suvemcitug until disease progression or unacceptable toxicity (Table 1) [42]. The primary endpoint was ORR evaluated by RECIST v1.1, and the secondary endpoints included DCR, PFS, and safety. The primary results showed that the ORR was 11.1%, the DCR was 72.2%, and mPFS was 4.3 months. The most common AEs of grade 3 or higher were proteinuria (20.0%), hypertension (5%), decreased platelets (5%), elevated bilirubin (5%), elevated gamma-glutamyl transferase, esophagitis (5%), and oral ulcer (5%), with no treatment-related deaths reported [42].

It can be seen that the combination of envafolimab and suvemcitug does not present new safety issues and demonstrates certain anti-tumor activity in patients who have previously undergone the first-line treatment. Further large-scale clinical studies are anticipated for validation.

Other Ongoing Clinical Trials on Immunotherapy Combined with Targeted Therapy

Based on ICIs, combination therapy has shown promising clinical benefits in advanced HCC. In addition to the above-mentioned therapies, an increasing number of drug combinations are undergoing clinical trials (Table 2). For instance, pascolizumab (AK105), an anti-PD-1 inhibitor, was approved by the NMPA in 2021 as the second- and third-line treatment for Hodgkin lymphoma, nasopharyngeal carcinoma, NSCLC, gastric cancer, and HCC [88]. Currently, a phase III clinical trial (NCT04344158) on pascolizumab in combination with a multi-target TKI anlotinib for the first-line treatment for advanced HCC is ongoing.

KN046, a PD-L1/CTLA-4 bispecific antibody, received FDA Orphan Drug Designation in 2020 in the treatment of thymic epithelial tumors [89]. A phase II clinical trial (NCT04542837) is underway to evaluate the combination of KN046 and lenvatinib as the first-line treatment for advanced, unresectable and metastatic HCC.

JS001sc, an anti-PD-1 inhibitor, was approved by the FDA in 2023 as the first-line treatment for nasopharyngeal carcinoma. In the treatment of HCC, JS001sc is being investigated in combination with various TKIs (regorafenib, cabozantinib, and anlotinib) in ongoing clinical trials (NCT04503902).

Camrelizumab, a human PD-L1 monoclonal antibody, demonstrates excellent clinical benefits in the treatment of advanced HCC [90]. Based on the results of HIMALAYA, the FDA approved camrelizumab for the treatment of HCC in 2022. An ongoing open-label phase II clinical trial (NCT05312216) aims to assess the efficacy and safety of camrelizumab in combination with lenvatinib as the first-line treatment for unresectable HCC.

SCT-I10A, a recombinant humanized anti-PD-1 IgG4 monoclonal antibody [91], is currently being investigated in combination with SCT510 [92], a candidate biosimilar to bevacizumab, in the treatment of advanced HCC in a phase II/III clinical trial (NCT04560894).

TQB2450, a PD-L1 monoclonal antibody, has not yet been approved for any indication [93], but it has shown excellent performance in clinical trials. In the treatment of advanced HCC, a phase II clinical trial (NCT06031480) is ongoing to evaluate the combination of TQB2450 and anlotinib.

Rulonilimab, an anti-PD-1 IgG1 monoclonal antibody, in combination with lenvatinib for advanced HCC is currently undergoing phase II and III clinical trials (NCT05408221).

Currently, it cannot be concluded whether the above therapies in clinical trials have significant clinical benefits. However, it is clear that ICI-based targeted immunotherapy will change the landscape of advanced HCC treatment in the future, offering a growing number of drug options for different patients.

The Applications of Combination Therapy Beyond Advanced HCC

Combination therapy of ICIs and targeted drugs is primarily employed for patients with advanced, unresectable HCC. Nowadays, some studies have explored the clinical benefits of combination therapies in the early, intermediate, or perioperative stage of HCC [94–96]. IMbrave050 is the first successful phase III clinical trial of adjuvant therapy for HCC. This trial included 668 patients who underwent curative resection or ablation, and they were randomly assigned at a 1:1 ratio to the combination group (atezolizumab plus bevacizumab) and the control group. The results revealed that the recurrence-free survival (RFS) rate in the combination group was significantly higher than in the control group (78% vs. 65%) [13]. Additionally, the 12-month recurrence rate was significantly lower in the combination group than in the control group (20% vs. 34%). Moreover, the combination therapy reduced the risk of disease recurrence, distant metastasis, or death in HCC patients by 28%.

Local treatment and transarterial chemoembolization (TACE) is the standard treatment protocol for mid-stage HCC. Ongoing phase III clinical trials, including ABC-HCC (NCT04803994) and RENOTACE, aim to evaluate the effectiveness and safety of combination regimens such as atezolizumab plus bevacizumab or regorafenib plus nivolumab in comparison to TACE. Some trials such as EMERALD-1, EMERALD-3, LEAP-012 and ML-42612 are even attempting to compare the efficacy of triple or quadruple therapies based on immunotherapy with TACE alone [97, 98]. It remains unclear whether immunotherapy-based regimens are more effective than TACE, but it can be asserted that if these clinical trials are successful, they will change the current treatment paradigm for HCC [96].

Despite significant progress in targeted immunotherapy in the perioperative period of HCC, there are still debates regarding its prospects. One reason is that no guidelines and high-quality clinical trials are available in favor of targeted immunotherapy in the perioperative period of HCC globally [99]. And due to frequent hepatitis or cirrhosis in HCC patients, excessive drug therapy may have more drawbacks than benefits [100].

Mechanisms of Combination Therapy

Inhibition of Angiogenesis

There is a significant abnormal proliferation of blood vessels in tumor tissues [101–103], which restricted the delivery of anti-tumor drugs and hindered immune cell infiltration, including cytotoxic T cells. The aberrant vascular proliferation is often caused by the abnormal activation of VEGF [104]. Therefore, the combination of anti-angiogenic targeted drugs and ICIs not only promotes vascular normalization in tumors, making it easier for drugs to reach tumor tissues, but also encourages the aggregation of immune cells and enhances immune function (Fig. 2) [104, 105]. The activation of immune cells, in turn, promotes vascular normalization, creating a positive feedback regulatory mechanism [101]. This explains why the combination of targeted drugs and immunotherapy can achieve a synergistic effect ($1+1>2$). The dual effects of these therapies not only target the tumor cells directly but also modulate the tumor microenvironment, improving drug delivery and enhancing the overall anti-tumor immune response [106].

Modulation of PD-L1 Expression

Aberrant upregulation of PD-L1 expression and the absence of PD-L1 can both result in the ineffectiveness of ICIs [102, 106].

Studies indicate that lenvatinib, when used in combination with ICIs, can inhibit FGFR4 in tumor cells, phosphorylate GSK3β at serine 9, and subsequently activate the protein degradation pathway of PD-L1, leading to a decrease of PD-L1 expression (Fig. 2) [106–108]. Study on melanoma also suggests that regorafenib can block the downstream JAK1/2-STAT1 and MAPK signaling pathways through the RET-Src signaling axis [109], thereby inhibiting the IFN-γ-induced PD-L1 expression, promoting the activation of $CD8^+$ T cells, and sensitizing the effect of ICI [110]. In addition, VEGF can also regulate the PD-L1 expression as found by studies. Therefore, the anti-VEGF effect of bevacizumab can directly impact the PD-L1 expression in DCs, Tregs, MDSCs and TAMs, enhancing the immune response [111, 112].

Enhancement of Immune Cell Infiltration and Modulation of Immune Cell Differentiation

Targeted drugs can sensitize ICIs by regulating the differentiation and infiltration of various immune cells at multiple levels (Fig. 2). The infiltration of Tregs is considered one of the main causes of immunosuppression [113]. Following anti-PD-1 treatment, the increased levels of IL-2 produced by effector T cells can induce FOXP3 transcription through CD25 activation, promoting the differentiation of naïve T lymphocytes into Tregs [114]. When combined with ICIs, lenvatinib is believed to block FGFR4 in naïve T cells, inhibit downstream STAT5 phosphorylation, reduce the IL-2/CD25 axis activity, and suppress the differentiation of naïve T lymphocytes into Tregs [115]. Similarly, another study on the combination of

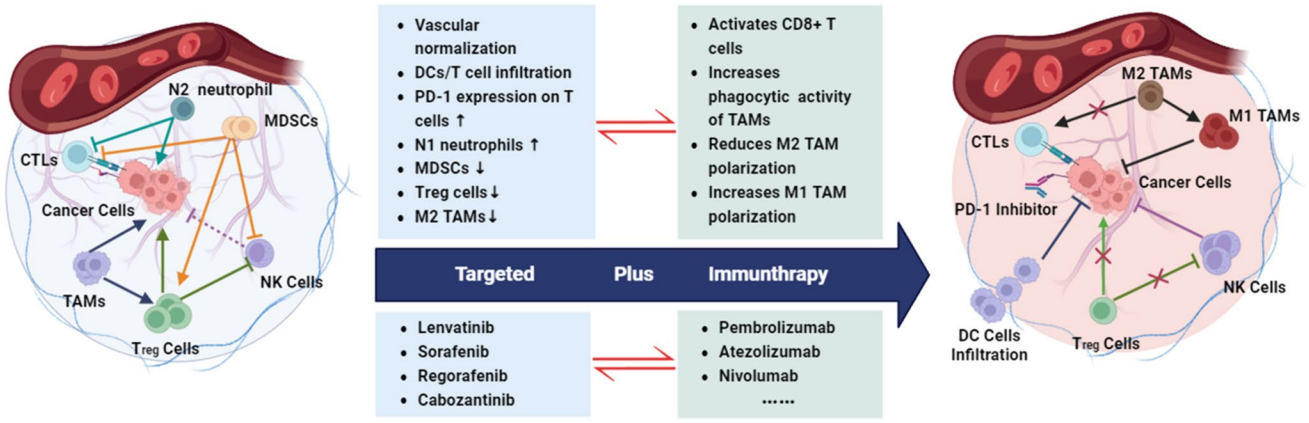

Fig. 2 Mechanisms of combination immune checkpoint inhibitors and targeted drugs. This involves the concerted suppression of abnormal vascular proliferation, modulation of PD-1 expression, and restructuring of the tumor microenvironment, collectively fostering a synergistic sensitization effect

lenvatinib and ICIs showed that lenvatinib can not only inhibit Tregs but also suppress immune inhibitory signals such as TGF-β [108]. Xie et al. found that regorafenib, when used in combination with ICIs, could enhance T cell cytotoxicity, inhibit Treg infiltration, and reverse immunosuppression by inhibiting the IFN-γ/NSDHL/SREBP1/TGF-β1 signaling axis [112]. Similar results have been obtained in studies on bevacizumab and cabozantinib [110, 111].

In addition to Tregs, immune cells such as macrophages and NK cells are also considered to be regulated in the combination therapy [116]. Studies in animal models of HCC revealed that regorafenib with an anti-angiogenic effect can inhibit the polarization of M2 macrophages by blocking the phosphorylation of p38 in bone marrow-derived macrophages (BMDMs) and suppressing the downstream CREB1/KIF4 activity [109, 115]. Simultaneously, it promotes IFN-γ secretion, facilitates M1 macrophage polarization, increases the M1/M2 ratio, and enhances $CD8^+$ T cell proliferation and activation, thereby independently regulating the immune microenvironment and sensitizing immunotherapy [117].

When combined with atezolizumab, bevacizumab is believed to block VEGF, accelerate the proliferation and maturation of DCs in lymphoid organs, enhance the antigen-presenting ability of DCs, activate more cytotoxic T lymphocytes, and reverse immunosuppression by inhibiting the proliferation of MDSCs and M2-like TAMs [102, 103, 118].

Discussion

The development of systemic treatment of advanced HCC has remained stagnant for a considerable period. It was not until 2018, 11 years after the approval of sorafenib in 2007, based on a non-inferiority trial that lenvatinib changed the situation that only one first-line drug was available for advanced HCC [119]. ICI has been approved to be used in HCC since 2017, and it is noteworthy that, when used alone, ICIs produce a slightly better OS than lenvatinib, but they fall short in the ORR compared with lenvatinib [11]. Instead, the focus has shifted directly to combination therapies, represented by atezolizumab plus bevacizumab, and the treatment of HCC has entered a phase of accelerated development. Recently clinical trials suggest that ICI-based combination therapies will likely dominate the future of systemic treatment for advanced HCC [120]. Despite significant clinical efficacy of targeted immunotherapy, several issues are still worth exploring to achieve more precise drug use.

Firstly, primary and acquired resistance caused by the high heterogeneity of tumors is an inevitable issue in the use of anti-tumor drugs [121, 122]. Therefore, finding suitable biomarkers to predict the response, standardize patient enrollment, and promote the development of precision medicine is of great significance.

Nowadays, the molecular biomarkers for the separate use of some targeted and immune drugs have been investigated. According to the NCCN Guidelines, ramucirumab is suitable for patients with AFP > 400 ng/ml [123], while nivolumab plus ipilimumab should be used for tumor mutational burden-high (TMB-H) patients [124, 125]. Recently studies focus on molecular biomarkers in liquid biopsy, such as ctDNAs, CTCs and miRNAs, for predicting drug efficacy and survival [126–128]. However, combination therapy is more complex than a single drug, so these molecular biomarkers applicable to a single drug may be not useful for the combination therapy.

Currently, only two studies show that the expression levels of TGF-β in serum, as well as the expression levels of FGFR4 and Tregs infiltration in tumors, may serve as molecular biomarkers for regorafenib in combination with

sintilimab and lenvatinib plus anti-PD-1, respectively [112, 123]. But these studies all had a small sample size, and more clinical validation is required. The molecular biomarkers for predicting the efficacy of combination therapy are extremely scarce, which require more investigation.

Secondly, among all these treatments, which should be used precedence? Mohamad et al. conducted a high-quality network meta-analysis to evaluate OS, PFS, ORR, and safety of the first-line systemic treatment regimens for HCC from 2007 to 2022 in randomized controlled trials [129]. All treatment regimens showed significant survival advantages in OS compared with the placebo, and ICIs combined with TKIs demonstrated comparable efficacy to dual immunotherapy. Among these regimens, camrelizumab plus rivoceranib and sintilimab plus IBI-305 showed significant advantages in PFS and ORR over other first-line treatments. Regarding safety, the combination of atezolizumab and bevacizumab had the best safety profile, with no increase in the risk of AEs causing treatment discontinuation [130]. Similarly, another study also indicated that sintilimab plus IBI-305 and camrelizumab plus rivoceranib significantly extended both OS and PFS, while tislelizumab was identified as the most cost-effective first-line treatment for unresectable HCC in China [131]. And considering the effectiveness and safety, atezolizumab plus bevacizumab and sintilimab plus IBI-305 have unique advantages. Nevertheless, head-to-head comparisons have not been conducted among different combination therapy groups in completed studies, posing challenges to clinicians and patients in making treatment choices [132].

Thirdly, the clinical administration order of drugs is still controversial, which may impact patient survival and safety [133]. In a systematic review and meta-analysis on 13 studies involving 2414 patients, the impact of different administration orders on the prognosis of NSCLC patients treated with targeted immunotherapies was evaluated. The results showed that compared with ICI monotherapy, targeted drugs followed by ICI monotherapy did not display PFS and OS benefits [134]. However, when targeted drugs and ICIs were administered simultaneously or when ICIs were used first followed by targeted drugs, clinical benefits were observed in both PFS and OS.

Appropriate administration orders can also reduce the toxicity of drugs. For example, in the treatment of ovarian cancer, the simultaneous use of PARP and WEE1 inhibitors can effectively inhibit tumor growth [135]. However, concurrent treatment may lead to severe AEs and poor patient tolerance. In contrast, sequential treatment preserves the synergistic therapeutic effects of drugs while significantly reducing toxicity, improving patient tolerance. Currently, there is a lack of relevant studies on the administration orders in the targeted immunotherapy for HCC. Therefore, further clinical trials are needed to support the clinical benefits of sequential treatment for HCC patients.

Fourthly, debate is ongoing over the second-line treatment strategies for patients resistant to combination therapy. Some scholars argue that targeted drugs, such as sorafenib, lenvatinib, regorafenib, cabozantinib, or ramucirumab, have similar efficacy in the second-line treatment, while others recommend sorafenib and lenvatinib as the second-line treatment, with previously used second-line drugs (regorafenib, cabozantinib, or ramucirumab) as the third-line or later treatment [34, 136]. Among the currently approved drugs for systemic therapy, only a few have been directly compared, and there is limited research on treatment for patients resistant to targeted immunotherapy.

A retrospective study involving 36 patients found that lenvatinib still demonstrated significant efficacy on patients with HCC following failed PD-1/PD-L1 inhibitor treatment, with an ORR of 55.6% [137]. These preliminary findings offer a theoretical basis for the use of lenvatinib or sorafenib after the failure of atezolizumab plus bevacizumab treatment [138]. However, some studies suggest that the combination of TKIs and ICIs yields better clinical outcomes than sorafenib and lenvatinib among patients resistant to atezolizumab plus bevacizumab [23, 24]. In a multicenter retrospective real-world study, a total of 673 advanced HCC patients were enrolled from 22 centers in 5 Asia–Pacific countries and regions (Korea, Singapore, Hong Kong, Thailand, and Taiwan), and they had disease progression after the first-line treatment with atezolizumab plus bevacizumab and underwent different second-line treatments, including sorafenib, lenvatinib, and TKIs combined ICIs. The results showed that TKIs combined with ICIs yielded longer PFS and OS (6.4 and 18.9 months, respectively) than sorafenib and lenvatinib (2.1 months and 7.2 months for sorafenib; 3.7 months and 8 months for lenvatinib) [23]. More head-to-head comparisons and large-sample clinical trials are required for the selection of subsequent treatment after resistance to targeted immunotherapy.

Fifthly, the use of ICIs may lead to autoimmune-related AEs (irAEs), and combination therapy often results in more widespread adverse reactions. For instance, in COSMIC-312 [30] and ORIENT-32 [12] trials, the combination therapy exhibited a higher incidence of AEs of grade 3 or higher than the monotherapy [139, 140]. Furthermore, the combination therapy may unveil specific adverse reactions not observed in the monotherapy. For example, grade 3 stomatitis was observed in melanoma patients treated with vemurafenib plus cobimetinib, while it was not identified in the monotherapy group. It is worth noting that most immunotherapeutic drugs receive accelerated approval (3–4 years earlier) by the FDA [141]. This has raised concerns about the safety of immunotherapy, as irAEs typically emerge several months later, well beyond the assessment period (1–2 months) of early clinical safety studies [142, 143]. Additionally, due to the limited number of patients in early clinical studies, it

is challenging to detect rare and fatal AEs. Thus, the use of immunotherapeutic drugs and vigilance and management of irAEs have become subjects of extensive discussion.

Moreover, the use of immunotherapy inevitably increases patients' medical expenses. Taking the first-line drugs as an example, the annual medical expense of lenvatinib is $100,156, while that of atezolizumab plus bevacizumab goes up to $296,691 for a patient weighing 60 kg. In China, considering the coverage of medical insurance, the annual medical expense of lenvatinib monotherapy is only one-seventh of the combination therapy. Price will also be a consideration for the widespread acceptance and application of targeted immunotherapy in the real world.

In conclusion, the landscape for the treatment of advanced liver cancer has undergone significant changes since the last decade, with an increasing number of relevant clinical studies on targeted and immune drugs. In the future, more drugs will be applied in clinical practice, necessitating careful attention to the approval, monitoring, and management of systemic therapeutic drugs for HCC.

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Data Availability All data generated during this study are included in this published article and the corresponding references.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Written informed consent for publication was obtained from all participants.

Competing Interests The authors declare no competing interests.

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