

Role of immunotherapy in the management of hepatocellular carcinoma: current standards and future directions

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ABSTRACT

The multikinase inhibitor sorafenib was the only approved systemic therapy in advanced hepatocellular carcinoma (HCC) for about a decade. In recent years, the number of approved agents has increased significantly as a result of a number of positive phase III clinical trials. Lenvatinib as a first-line treatment, and regorafenib, cabozantinib, and ramucirumab in the second-line setting are now approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency.

In phase II studies, immunotherapy with nivolumab and monotherapy using pembrolizumab yielded impressive results for overall survival in therapy-naïve and pretreated patients, leading to the accelerated approval by the FDA of nivolumab and pembrolizumab for second-line treatment. However, phase III trials of nivolumab in the first line and pembrolizumab in the second line as single agents failed to reach statistical significance, although clinical benefit for a subset of patients with long durations of response could be demonstrated. Despite that setback, immunotherapy for HCC is a promising therapeutic approach, and the combination of immunotherapy with other treatment modalities such as monoclonal antibodies, tyrosine kinase inhibitors, or local therapies has the potential to increase the overall response rate and survival.

Recently, the results of a phase III trial of combination atezolizumab–bevacizumab compared with sorafenib showed a highly significant survival benefit and median overall survival that was not reached in the immunotherapy arm, making the combination the preferred standard of care in first-line therapy.

Despite the impressive results and generally good toxicity profile of immunotherapy, patients who respond to therapy constitute only a subset of the overall population, and response rates are still limited.

This review focuses on the currently reported results and ongoing clinical trials of checkpoint inhibitor–based immunotherapy in HCC.

Key Words Hepatocellular carcinoma, immunotherapy, checkpoint inhibitors, nivolumab, pembrolizumab, durvalumab, tremelimumab, ipilimumab

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INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive tumour, usually arising in the context of liver cirrhosis. The incidence of HCC has been rising worldwide during the last 20 years because of the increased number of patients with known risk factors such as chronic viral hepatitis B (HBV) or hepatitis C (HCV) and non-alcoholic steatohepatitis¹. With approximately 840,000 cases worldwide and 781,000 deaths in the year 2018, HCC was the 5th most common cancer and 2nd most frequent cause of cancer mortality².

Curative treatment options in HCC are liver resection, liver transplantation, and local ablation. Unfortunately, most cases are diagnosed at an intermediate or advanced stage, not amenable to potentially curative treatments³, making systemic therapy an important part of the therapeutic armamentarium.

For about a decade, the only systemic therapy with a proven survival benefit (10.7 months vs. 7.9 months in the phase III SHARP trial) was the multikinase inhibitor sorafenib⁴, which was approved for the first-line treatment of HCC in the United States and the European Union. After

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a number of failed phase III trials evaluating other kinase inhibitors, the noninferiority of lenvatinib compared with sorafenib was demonstrated in the phase III REFLECT trial, and lenvatinib was added to the treatment guidelines of the European Association for the Study of the Liver and the European Society for Medical Oncology⁵.

In the second line, after progression on or intolerance to sorafenib, the multikinase inhibitor regorafenib, tested in the RESORCE trial, was the first agent to show a survival benefit (10.6 months vs. 7.8 months for placebo)⁶. Other approved second-line options are cabozantinib, an inhibitor of vascular endothelial growth factor (VEGF) receptors and the MET and TAM kinases (10.2 months vs. 8.0 months for placebo, CELESTIAL trial)⁷, and ramucirumab, a monoclonal antibody that targets VEGF receptor 2 in patients with elevated alpha-fetoprotein at 400 ng/mL or greater (8.5 months vs. 7.3 months, REACH-2 trial)⁸.

Despite the increased number of systemic therapeutic options, prognosis is still limited: about 12–14 months in first-line therapy and 8–11 months in second-line therapy with the currently approved kinase inhibitors. The survival benefit with tyrosine kinase inhibitor (TKI) therapy is further limited in patients with impaired liver function; because of the risk of further deterioration of liver function, treatment should be limited to patients with compensated cirrhosis⁹. The common side effects of TKI therapy—such as diarrhea, asthenia, weight loss, and hand–foot skin reaction—can severely limit patient compliance, the tolerated dose, and quality of life. Those limitations of the available therapeutic approaches demonstrate a medical need for more effective systemic therapy in HCC that will further improve on overall survival (OS) while preserving quality of life.

After an impressive clinical benefit was demonstrated and checkpoint inhibitors were approved in melanoma, the use of those drugs in other tumour entities, including HCC, was extensively investigated¹⁰. Here, we review the currently available evidence for immunotherapy in HCC.

DISCUSSION

PD-1, PD-L1, and CTLA-4 Inhibitors

Clinical trials of immune checkpoint inhibitors (ICIs) have used mainly monoclonal antibodies inhibiting PD-1, PD-L1, or CTLA-4 (Figure 1). Currently PD-1/-L1 and CTLA-4 blockade are successfully used in routine clinical practice, and immunotherapy has become a new promising method for inhibiting HCC tumour progression, recurrence, and metastasis. Table 1 presents a list of currently approved ICIs in HCC.

The subsections that follow discuss the checkpoint inhibitors that are currently approved or in clinical development. The reported results of clinical trials with ICIs are presented in Table II, and ongoing trials are presented in Table III.

Nivolumab

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that blocks PD-1. It was first tested in a noncomparative prospective phase I/II study (CheckMate 040, NCT01658878 at <https://ClinicalTrials.gov/>)

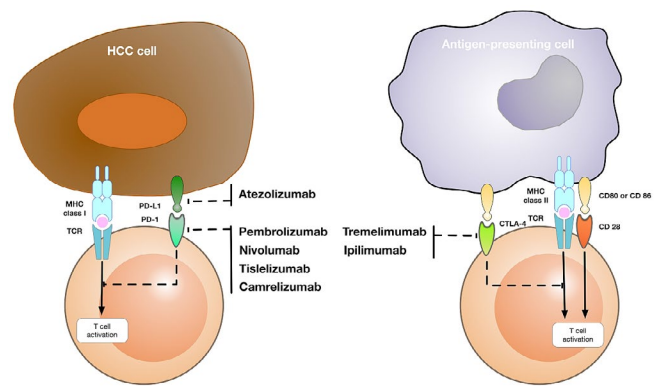


FIGURE 1 Targets and available checkpoint inhibitors in hepatocellular carcinoma (HCC). MHC = major histocompatibility complex; TCR = T cell receptor.

TABLE 1 Current approval status of immunotherapy in hepatocellular carcinoma

Agent	Type	Line	U.S. FDA	EMA
Nivolumab	Anti-PD-1	2	Yes (Sep 2017)	No
Pembrolizumab	Anti-PD-1	2	Yes (Nov 2018)	No
Atezolizumab	Anti-PD-L1	1	Yes (May 2020) ^a	Yes (Nov 2020)
Ipilimumab	Anti-CTLA-4	2	Yes (Mar 2020) ^b	No

^a In combination with bevacizumab.

^b In combination with nivolumab.

FDA = Food and Drug Administration; EMA = European Medicines Agency.

in patients who were either treatment-naïve ($n = 80$) or pretreated with sorafenib ($n = 182$). The study had two phases: a dose-escalation phase (groups of participants received nivolumab 0.1–10 mg/kg every 2 weeks) and a dose-expansion phase (all participants received nivolumab 3 mg/kg every 2 weeks)¹⁴. Inclusion criteria were well-preserved liver function (Child–Pugh score: ≤ 7), antiviral therapy in case of HBV infection, and histologically confirmed HCC. Primary endpoints were safety, tolerability, and the objective response rate (ORR). The ORR and the disease control rate (DCR) were 20% and 64% respectively, with 2 patients experiencing a complete response (CR). At 9 months, the OS was 94%, and the median OS duration was 28.6 months in patients naïve to sorafenib and 15 months in patients already treated with sorafenib. The trial reported an acceptable safety profile and durable responses of 9.9 months in patients who achieved disease control¹⁴. Based on those data, nivolumab was approved by the U.S. Food and Drug Administration (FDA) in September 2017 for use in HCC after sorafenib treatment²⁸.

Based on the CheckMate 040 trial, the CheckMate 459 phase III study (see NCT02576509 at <https://ClinicalTrials.gov/>) compared first-line treatment with nivolumab or with sorafenib in 743 patients with advanced HCC, using OS as the primary endpoint. Additional endpoints were the ORR and progression-free survival (PFS). Patients were randomized 1:1 to receive intravenous (IV) nivolumab 240 mg every

TABLE II Clinical trials with reported results for immunotherapy in hepatocellular carcinoma

Reference (trial name, ClinicalTrials.gov ID)	Phase	Target	Treatment line	Primary endpoint	Sample Size	Note	ORR (%)	DCR (%)	PFS (months)	TTP (months)	OS (months)	DOR (months)	Prior sorafenib (%)	Grade 3/4 AEs (%)	Result
<i>Single agents</i>															
<i>Atezolizumab</i>															
Lee et al., 2020 ¹¹ (GO30140, NCT02715531)	IB	PD-1	2	PFS	59	Group F: atezolizumab monotherapy	17.0	49	3.4	Not reported	Not reached	Not reached	0	14	No comparator arm
<i>Camrelizumab (SHR-1210)</i>															
Qin et al., 2020 ¹² (NCT02989922)	II	PD-1	2	ORR, OS at 6 months	217		32.0	44.2	2.1	Not reported	13.8	Not reached	100	22	No comparator arm
<i>Durvalumab</i>															
Wainberg et al., 2017 ¹³ (NCT01693562)	I/II	PD-1	1/2	Safety	40		10.0	32.5	2.7	Not reported	13.2	Not reported	93	20	No comparator arm
<i>Nivolumab</i>															
El-Khoueiry et al., 2017 ¹⁴ (CheckMate 040, NCT01658878)	I/II	PD-1	1/2	Safety and tolerability	48	Dose-escalation arm	15.0	58	4.1	3.4	28.6	17	77	25	No comparator arm
El-Khoueiry et al., 2017 ¹⁴ (CheckMate 040, NCT01658878)	I/II	PD-1	1/2	ORR	214	Dose-expansion arm	20.0	64	4		15	9.90	68		No comparator arm
Yau et al., 2019 ¹⁵ (CheckMate 459, NCT02576509)	III	PD-1	1/2	OS	743		17.6	76.4	Not reported	7.4	12.3	Not reported	0	22.3	Negative
<i>Pembrolizumab</i>															
Zhu et al., 2018 ¹⁶ (KEYNOTE-224, NCT02702414)	II	PD-1	2	ORR	104		18.0	61	Not reported	Not reported	12.9	Not reported	100	24	No comparator arm
Finn et al., 2020 ¹⁷ (KEYNOTE-240, NCT02702401)	III	PD-1	2	PFS, OS	413		18.3	62.2	3	Not reported	13.9	13.8	100	52.7	Negative
<i>Tislelizumab</i>															
Desai et al., 2020 ¹⁸ (NCT02407990)	IA/IB	PD-1	1	Safety	50		12.2	51	2.1	Not reported	13.6 (IA) 9.3 (IB)	Not reported	Pre-treated	47.5	No comparator arm
<i>Tremelimumab</i>															
Wolchok et al., 2008 ¹⁹ (NCT01008358)	II	CTA-4	1/2	Tumour response (RECIST)	21		17.6	76.4	Not reported	6.5	8.2	Not reported	24	Not reported	No comparator arm
<i>Combination with immunotherapy</i>															
<i>Durvalumab-tremelimumab</i>															
AstraZeneca, 2020 ²⁰ (Study 22, NCT02519348)	II	PD-1, CTA-4	1/2	Safety	326	Results from the T300 plus durvalumab arm	24.0	Not reported	Not reported	Not reported	18.7	Not reached	Not reported	35.1	No comparator arm

TABLE II Continued

Reference (trial name, ClinicalTrials.gov ID)	Phase	Target	Treatment line	Primary endpoint	Sample Size	Note	ORR (%)	DCR (%)	PFS (months)	TTP (months)	OS (months)	DOR (months)	Prior sorafenib (%)	Grade 3/4 AEs (%)	Result
Nivolumab–ipilimumab Yau <i>et al.</i> , 2019 ²¹ (CheckMate 040, NCT01658878)	I/II	PD-1, CTA-4	2	Safety, ORR	148	OS results from the nivoli/ipi3 arm	31.0	49	Not reported	Not reported	23	17	100	37	No comparator arm
<i>Combination with TKI or anti-VEGF</i>															
Atezolizumab–bevacizumab Finn <i>et al.</i> , 2020 ²² (IMbrave 150, NCT03434379)	III	PD-1 VEGF	1	OS, PFS	336		27.3	73.6	6.8	Not reported	Not reached	Not reported	0	56.5	Positive
Lee <i>et al.</i> , 2020 ¹¹ (GO30140, NCT02715531)	IB	PD-1, VEGF	1	ORR	104	Group A	36.0	71	7.3	Not reported	17.1	Not reached	0	53	No comparator arm
Lee <i>et al.</i> , 2020 ¹¹ (GO30140, NCT02715531)	IB	PD-1 VEGF	1	PFS	60	Group F	20.0	67	5.6	Not reported	Not reached	Not reported	0	37	No comparator arm
Avelumab–axitinib Kudo <i>et al.</i> , 2019 ²³ (VEGF Liver 100, NCT03289533)	I	PD-1 VEGF	1	Safety	22		13.6	68.2	5.5	Not reported	Not reported	Not reported	0	Not reported	No comparator arm
Camrelizumab (SHR-1210)–apatinib Xu <i>et al.</i> , 2019 ²⁴ (NCT02942329)	IA/IB	PD-1, tyrosine kinases	1/2	OS rate	18		50.0	93.8	5.8	Not reported	Not reached	Not reached	83	60.6	No comparator arm
Durvalumab–ramucirumab Bang <i>et al.</i> , 2019 ²⁵ (NCT02572687)	IB	PD-1, VEGF	2	Safety	28		11.0	61	4.4	Not reported	Not reported	Not reported	Pre-treated	Not reported	No comparator arm
Pembrolizumab–lenvatinib Finn <i>et al.</i> , 2020 ²⁶ (NCT03006926)	IB	PD-1, tyrosine kinases	1	DLT, ORR, and DOR	104		46.0	86	9.3	Not reported	22	8.6	4	67	No comparator arm
<i>Combination with local therapy</i>															
Tremelimumab and subtotal ablation Duffy <i>et al.</i> , 2017 ²⁷ (NCT01853618)	I/II	CTA-4	1	Safety	32		26.3	Not reported		7.4	12.3	Not reported	66	Not reported	No comparator arm

ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival; TTP = time to progression; OS = overall survival; DOR = duration of response; AEs = adverse events; RECIST = Response Evaluation Criteria in Solid Tumors; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; DLT = dose-limiting toxicity.

TABLE III Selection of ongoing clinical trials of immunotherapy in hepatocellular carcinoma

Immunotherapy drug (combination therapies)	Comparator	Trial name (ClinicalTrial.gov ID)	Phase	Target	Setting	Primary completion date ^a	Status
Anti-PD-1 (lenvatinib and TACE)		PLTHCC (NCT04273100)	II	PD-1, tyrosine kinases	Local control	Q4 2020	Recruiting
Atezolizumab (cabozantinib)		COSMIC-312 (NCT03755791)	III	PD-L1, tyrosine kinases	First-line	Q2 2021	Recruiting
Atezolizumab (bevacizumab)		IMbrave050 (NCT04102098)	III	PD-L1, VEGF	Adjuvant	Q3 2023	Recruiting
Avelumab	Placebo	(NCT03389126)	II	PD-L1	Second-line	Q1 2020	Active, not recruiting
Camrelizumab	Placebo	RESCUE (NCT03463876)	II	PD-1, tyrosine kinases	Second-line	Q3 2019	Active, not recruiting
Camrelizumab	Placebo	(NCT03463876)	I/II	PD-1, tyrosine kinases	Neoadjuvant or bridging	Q3 2019	Active, not recruiting
Camrelizumab	Placebo	(NCT04483284)	II	PD-1, local therapy	Local control	Q4 2020	Recruiting
Durvalumab (tremelimumab and local therapy)		(NCT02821754)	II	PD-L1, CTLA-4, local therapy	Adjuvant	Q4 2020	Recruiting
Durvalumab (bevacizumab)		EMERALD-1 (NCT03778957)	III	PD-1, VEGF, local therapy	Local control	Q3 2021	Recruiting
Durvalumab (bevacizumab)		EMERALD-2 (NCT03847428)	III	PD-1, VEGF	Adjuvant	Q3 2022	Recruiting
Durvalumab (tremelimumab, TACE)	Placebo	(NCT03482102)	II	PD-L1, CTLA-4, local therapy	Local control	Q4 2020	Active, not recruiting
Durvalumab (tremelimumab or bevacizumab)	Sorafenib	Study 22 (NCT02519348)	II	PD-L1, CTLA-4 or VEGF	First-line	Q4 2020	Active, not recruiting
Durvalumab (tremelimumab)	Sorafenib	HIMALAYA (NCT03298451)	III	PD-L1, CTLA-4	First-line	Q4 2020	Active, not recruiting
Nivolumab	Placebo	CheckMate 9DX (NCT03383458)	III	PD-1	Adjuvant	Q1 2023	Recruiting
Nivolumab (DEB-TACE)	Placebo	(NCT03143270)	Pilot	PD-1, local therapy	Local control	Q2 2022	Recruiting
Nivolumab (TACE)	Placebo	IMMUTACE (NCT03572582)	II	PD-1, local therapy	Local control	Q4 2022	Active, not recruiting
Nivolumab (⁹⁰ Y radioembolization)	Placebo	(NCT03033446)	II	PD-1, local therapy	Local control	Q4 2019	Recruiting
Nivolumab (sorafenib)	Placebo	(NCT03439891)	Pilot	PD-1, tyrosine kinases	First-line	Q2 2022	Recruiting
Nivolumab (ipilimumab)	Placebo	PRIME-HCC (NCT03682276)	I/II	PD-1, CTLA-4	Neoadjuvant	Q4 2020	Recruiting
Nivolumab (ipilimumab)	Placebo	CheckMate 9DW (NCT04039607)	III	PD-1, CTLA-4	First-line	Q4 2023	Recruiting
Nivolumab (cabozantinib)	Placebo	(NCT03299946)	I	PD-1, tyrosine kinases	Neoadjuvant	Q4 2019	Active, not recruiting
Nivolumab (lenvatinib)	Placebo	IMMUNIB (NCT03841201)	II	PD-1, tyrosine kinases	First-line	Q3 2021	Recruiting
Nivolumab (ipilimumab)	Placebo	(NCT03222076)	II	PD-1, CTLA-4	Neoadjuvant or adjuvant	Q4 2022	Active, not recruiting
Pembrolizumab	Placebo	KEYNOTE-394 (NCT03062358)	III	PD-1	Second-line	Q2 2021	Active, not recruiting
Pembrolizumab	Placebo	KEYNOTE-937 (NCT03867084)	III	PD-1	Adjuvant	Q3 2025	Recruiting

TABLE III Continued

Immunotherapy drug (combination therapies)	Comparator	Trial name (ClinicalTrials.gov ID)	Phase	Target	Setting	Primary completion date ^a	Status
Pembrolizumab (lenvatinib)	Placebo	LEAP-002 (NCT03713593)	III	PD-1, tyrosine kinases	First-line	Q2 2022	Active, not recruiting
Pembrolizumab (TACE)	Placebo	PETAL (NCT03397654)	IB	PD-1	Local control	Q2 2020	Recruiting
Pembrolizumab	Placebo	(NCT03419481)	II	PD-1	First-line	Q3 2020	Recruiting
Pembrolizumab (elbasvir/grazoprevir)	Placebo	(NCT02940496)	I/II	PD-1, HCV therapy	Second-line	Q4 2021	Recruiting
Pembrolizumab (local therapy)	Placebo	IMMULAB (NCT03753659)	II	PD-1, local therapy	Local control	Q3 2022	Recruiting
Tislelizumab	Placebo	RATIONALE-208 (NCT03419897)	II	PD-1	Second-line	Q2 2021	Active, not recruiting
Tislelizumab	Sorafenib	RATIONALE-301 (NCT03412773)	III	PD-1	Second-line	Q2 2021	Active, not recruiting

^a Actual or estimated.

TACE = transarterial chemoembolization; VEGF = vascular endothelial growth factor; DEB-TACE = drug-eluting bead TACE.

2 weeks ($n = 371$) or oral sorafenib 400 mg twice daily ($n = 372$). Initial results were presented at the congress of the European Society for Medical Oncology in June 2019²⁹. The difference in OS (16.4 months for nivolumab and 14.7 months for sorafenib) failed to meet statistical significance [hazard ratio (HR): 0.85; 95% confidence interval (CI): 0.72 to 1.02; $p = 0.0752$]. The ORR was 15% for nivolumab and 7% for sorafenib, with 14 (4%) and 5 (1%) patients respectively achieving a CR. Grade 3 or 4 adverse events (AEs) were observed in 22% and 49% of the patients respectively¹⁵. Although the difference was not statistically significant per the pre-specified protocol, the improvements in OS, ORR, and the CR rate were deemed clinically meaningful. Long-term survival data at a minimum follow-up of 33.6 months were presented at the 2020 virtual World Congress on Gastrointestinal Cancer of the European Society for Medical Oncology³⁰. The 33-month OS rates for nivolumab and sorafenib were 29% (95% CI: 25% to 34%) and 21% (95% CI: 17% to 25%) respectively. The OS benefit was more pronounced in patients with chronic HBV and HCV, at 16.1 months compared with 10.4 months (HR: 0.79; 95% CI: 0.59 to 1.07) for HBV and 17.5 months compared with 12.7 months (HR: 0.72; 95% CI: 0.51 to 1.02) for HCV. An important finding was the slower deterioration of liver function with nivolumab therapy as evidenced by albumin–bilirubin levels and Child–Pugh scores.

Nivolumab monotherapy is currently being evaluated in the adjuvant phase III trial CheckMate 9DX (see NCT03383458 at <https://ClinicalTrials.gov/>) in patients with HCC who are at high risk of recurrence after curative hepatic resection or ablation. Patients are being randomized 1:1 to receive either IV nivolumab 480 mg every 4 weeks for up to a year, or placebo. The primary endpoint is recurrence-free survival³¹.

Pembrolizumab

Pembrolizumab is another humanized anti-PD-1 antibody. It was investigated in the phase II KEYNOTE-224 trial (see NCT02702414 at <https://ClinicalTrials.com/>) as second-line treatment after failure of or intolerance to an initial TKI¹⁶.

The study recruited 104 patients for a dose-limiting toxicity phase and an expansion phase. Inclusion criteria were an Eastern Cooperative Oncology Group 1–2 performance status, previous sorafenib treatment, and well-preserved liver function classed Child–Pugh A. Patients received a fixed dose of pembrolizumab 240 mg every 3 weeks for 2 years or until disease progression. An ORR of 18%, with 1 complete response, and a DCR of 61% were recorded. The OS was 12.9 months, and treatment-related adverse events occurred in 24% (grade 3) and 1% (grade 4) of patients. Immune-mediated hepatitis was reported in 3 patients, but no viral flares occurred. Most AEs were changes in laboratory results. The trial led to the accelerated approval by the FDA, in November 2018, of pembrolizumab for patients pretreated with sorafenib³².

Building on the results of the KEYNOTE-224 study, the phase III KEYNOTE-240 trial (see NCT02702401 at <https://ClinicalTrials.gov/>) was initiated¹⁷. Altogether, 413 patients were randomized in a 2:1 ratio to pembrolizumab (a 200 mg fixed dose every 3 weeks for up to 35 cycles) or to placebo in this double-blind trial conducted in 27 countries. Median OS was 13.9 months for pembrolizumab compared with 10.6 months for placebo (HR: 0.781; 95% CI: 0.611 to 0.998; $p = 0.0238$), and the PFS was 3.0 months (95% CI: 2.8 months to 4.1 months) compared with 2.8 months (95% CI: 2.5 months to 4.1 months). The ORR was 18.3% for pembrolizumab compared with 4.4% in the placebo arm. The CR, progressive disease, and DCR rates were 2.2%, 16.2%, and 62.2% in the treatment arm and 0%, 4.4%, and 53.3% in the placebo arm. Again, no hepatitis flares were recorded. Although pembrolizumab reduced the risk of death by 22%, the trial again failed to meet the pre-specified OS endpoint of $p = 0.0174$, despite demonstrating the same benefit as in the phase II trial and a clinical benefit of durable responses for patients who achieved a response to treatment. The increasing availability of other approved agents for second-line therapy (resulting in post-study treatment) and an imbalance of macrovascular invasion in the treatment arm might have contributed to a better-than-anticipated OS in the placebo arm.

Despite this negative trial, the clinical evaluation of pembrolizumab for the treatment of HCC is ongoing. Recently, early data relating to combined pembrolizumab–lenvatinib were reported. Those results are discussed later in this article, in the Combination Strategies for Immune Therapy section.

An ongoing trial of pembrolizumab monotherapy in the palliative setting is the phase III KEYNOTE-394 trial (see NCT03062358 at <https://ClinicalTrials.gov/>) using the regimen and inclusion criteria of KEYNOTE-240 in Asian patients³³.

The KEYNOTE-937 trial (NCT03867084) investigates a different oncologic setting, comparing placebo with pembrolizumab (a fixed dose of 200 mg on day 1 of each 21-day cycle for up to 17 cycles) as adjuvant therapy after a complete radiologic response following surgical resection or local ablation³⁴.

A phase II trial comparing pembrolizumab with placebo in HBV-related HCC (NCT03419481) will focus on changes in the immune environment by comparing serial changes in cytokine profiles and tumour-infiltrating lymphocytes in tumour samples.

In another small trial in HCV-associated HCC, pembrolizumab is being combined with antiviral therapy (elbasvir/grazoprevir, NCT02940496).

Tislelizumab

Tislelizumab (BGB-A317) is a humanized immunoglobulin G4 monoclonal antibody with high affinity and binding specificity for PD-1. It is differentiated from the currently approved PD-1 antibodies by an engineered Fc region, which is believed to minimize potentially negative interactions with other immune cells¹⁸.

In a dose-finding phase IA/IB study (see NCT02407990 at <https://ClinicalTrials.gov/>), tislelizumab was evaluated in range of doses, with a 200 mg fixed dose every 3 weeks being chosen for further evaluation. In pretreated patients, the ORR and DCR were 12.2% (95% CI: 4.6% to 24.8%) and 51.0% (95% CI: 36.3% to 65.6%) respectively, with the most common treatment-emergent AEs being decreased appetite, rash, decreased weight, and cough. In 1 patient, a grade 5 AE of acute hepatitis occurred¹⁸.

A global randomized phase III trial (RATIONALE-301, NCT03412773) comparing tislelizumab with sorafenib in patients with HCC who have no received prior systemic therapy is currently recruiting. The primary endpoint is OS³⁵.

Camrelizumab

Camrelizumab (SHR-1210) is a humanized monoclonal anti-PD-1 antibody. A phase II trial in Chinese patients with HCC given camrelizumab 3 mg/kg every 2 weeks ($n = 109$) or every 3 weeks ($n = 108$) reported an ORR of 14.7%, an OS probability of 74.4% at 6 months, and a median OS duration of 13.8 months¹².

Further results are discussed in the Combination Strategies for Immune Therapy section.

Atezolizumab

Atezolizumab is a fully humanized immunoglobulin G1 isotype monoclonal antibody against PD-L1.

Within the GO30140 trial (see NCT02715531 at <https://ClinicalTrials.gov/>), 59 patients who had not previously

received systemic therapy were treated with atezolizumab 1200 mg monotherapy every 3 weeks. Median PFS was 3.4 months (95% CI: 1.9 months to 5.2 months), significantly shorter than in the comparator arm of combined atezolizumab–bevacizumab. No grade 3 or 4 treatment-related AEs were observed in the monotherapy arm¹¹. Combined atezolizumab–bevacizumab is discussed in the ICI and Anti-VEGF subsection.

Durvalumab

Durvalumab is a fully human immunoglobulin G1κ monoclonal antibody that blocks the interaction of PD-L1 with PD-1.

A phase I/II trial of durvalumab monotherapy (see NCT01693562 at <https://ClinicalTrials.gov/>) in 40 patients with HCC mostly pretreated with sorafenib gave IV durvalumab 10 mg/kg every 2 weeks for 12 months or until disease progression. The resulting ORR was 10.3%, and median survival was 13.2 months, with grade 3 and 4 events (mostly elevated aspartate aminotransferase and alanine aminotransferase)¹³.

Tremelimumab

Tremelimumab is a fully human immunoglobulin G2 monoclonal antibody directed against CTLA-4. Anti-CTLA-4 antibodies outcompete the binding of the CD28 co-stimulatory receptor to CD80 and CD86 with higher avidity, thus releasing a natural “brake” signal for T cell activation³⁶.

Tremelimumab is the first checkpoint inhibitor that was tested in patients with HCC. In a phase II trial (see NCT01008358 at <https://ClinicalTrials.gov/>), 21 patients with HCC and HCV were treated with tremelimumab 5 mg/kg on day 1 of every 90-day cycle for up to 4 cycles. Of the 17 assessable patients, 18% experienced a partial response, and the DCR was 76%. Although 45% of patients experienced a grade 3 or higher rise in transaminases after the first dose, that rise was transient and not associated with a decline in liver function. Interestingly, a significant drop in viral load was observed³⁷.

Ipilimumab

Ipilimumab is another fully human monoclonal antibody targeting CTLA-4¹⁹.

Ipilimumab was evaluated in combination with nivolumab for the treatment of HCC. Results are discussed in the Combination Strategies for Immune Therapy section that follows.

Combination Strategies for Immune Therapy

ICIs and TKIs

The combination of ICIs with targeted agents is expected to exert synergistic effects. In addition to a direct effect of TKIs on tumour cells, an indirect contribution affecting immune cells is posited³⁸. Given that several antiangiogenic agents have already demonstrated efficacy in treating HCC, those agents are being evaluated in combination with ICIs in clinical trials³⁹.

Sorafenib is a multikinase inhibitor of Raf-1 and B-Raf; the vascular endothelial growth factor receptors 1, 2, and 3; and platelet-derived growth factor receptor β ⁴⁰. Since

the demonstration of a significant survival benefit in the practice-changing SHARP trial (see NCT00105443 at <https://ClinicalTrials.gov/>), sorafenib is the first approved systemic therapy for advanced HCC⁴.

Combined nivolumab–sorafenib is currently being tested in a small pilot trial (NCT03439891)⁴¹.

Lenvatinib is multikinase inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α , RET, and KIT. In the phase III REFLECT study (NCT01761266), lenvatinib was proved to be noninferior to sorafenib in the first-line treatment of unresectable HCC, being associated with a median survival of 13.6 months (95% CI: 12.1 months to 14.9 months) compared with 12.3 months for sorafenib (95% CI: 10.4 months to 13.9 months; HR: 0.92; 95% CI: 0.79 to 1.06). The ORR was statistically significantly improved with lenvatinib treatment (24.1% vs. 9.2% with sorafenib), as was the DCR (75.5% vs. 60.5%)⁴².

Lenvatinib and pembrolizumab were tested in a phase IB trial (KEYNOTE-524/Study 116, NCT03006926) in patients with unresectable HCC who received oral lenvatinib daily (12 mg if ≥ 60 kg, 8 mg if < 60 kg) and IV pembrolizumab (200 mg on day 1 of a 21-day cycle)²⁶. In the 104 patients who were enrolled, median OS was 22 months, with an ORR of 46.0% (95% CI: 36.0% to 56.3%) and a DCR of 86%. Grade 3 or 4 treatment-related AEs occurred in 67% of the patients. On trial, 3 deaths occurred (1 acute respiratory failure, 1 liver insufficiency, and 1 intestinal perforation) that could be attributed to the drugs; bleeding complications were not reported²⁶.

Based on those promising efficacy data, a double-blind randomized phase III trial of lenvatinib–pembrolizumab compared with lenvatinib alone is ongoing (LEAP-002, NCT03713593), and the FDA has granted breakthrough therapy designation to that combination, although it is not yet approved⁴³.

The anti-PD-1-antibody camrelizumab was tested in combination with apatinib (a selective vascular endothelial growth factor receptor 2 TKI). In that small phase IA/IB trial in 18 Chinese patients with advanced HCC and chronic HBV who did or did not have prior sorafenib exposure, an ORR of 44% was observed, and median OS was not reached (NCT02942329). The treatment was well tolerated, and toxicity was manageable²⁴. A phase II single-arm open-label trial for patients with advanced HCC for whom sorafenib failed or was intolerable has been initiated (RESCUE, NCT03463876). The primary endpoint is ORR, with secondary endpoints duration of response (DOR), DCR, and time to objective response.

The COSMIC-312 trial (NCT03755791) is an ongoing phase III trial of combined atezolizumab–cabozantinib for patients who are therapy-naïve. In 3 arms, the combination is being compared with single-agent sorafenib and single-agent cabozantinib. Primary endpoints are PFS and OS.

ICIs and Anti-VEGF Therapy

Hepatocellular carcinoma regularly displays increased vascularity and overexpresses VEGF, leading to disease development and progression. In addition, VEGF mediates immunosuppression within the tumour and its micro-environment⁴⁴. Both factors make HCC targetable with anti-VEGF therapy⁴⁵.

Ramucirumab is a fully human monoclonal immunoglobulin G1 antibody against VEGF receptor 2. In a small phase IB study (see NCT02572687 at <https://ClinicalTrials.gov/>) in patients pretreated with sorafenib, ramucirumab in combination with durvalumab was associated with an ORR of 11% and a DCR of 61%²⁵.

Bevacizumab is a humanized monoclonal antibody that inhibits the interaction of VEGF A with the VEGF receptors on the surface of endothelial cells. In a phase II trial, bevacizumab was evaluated as a single agent in advanced HCC, with 43 patients being treated with bevacizumab 5 mg/kg or 10 mg/kg every 2 weeks⁴⁶. Treatment toxicity was generally low: 37% patients experienced grades 3–4 toxicities, with 3 cases of hemorrhage. Because of the approval of sorafenib, the study was stopped, and bevacizumab was not evaluated in a phase III study.

The open-label phase IB study GO30140 (NCT02715531) examined combined IV atezolizumab 1200 mg and IV bevacizumab 15 mg/kg every 3 weeks in patients with unresectable carcinoma not amenable to curative treatment who had received no previous systemic treatment. Because liver cirrhosis is present in most patients with HCC, leading to compromised coagulation, bleeding is of special concern with an anti-VEGF therapy. Patients with untreated or incompletely treated high-risk varices were excluded from participating.

Patients were treated in two groups:

- Group A: all patients received IV atezolizumab 1200 mg and IV bevacizumab 15 mg/kg every 3 weeks
- Group F: patients were randomly assigned (1:1) to receive IV atezolizumab 1200 mg plus IV bevacizumab 15 mg/kg every 3 weeks or atezolizumab alone

The ORR in group A was 36% (95% CI: 26% to 46%), and the PFS in group F (combination treatment) was 5.6 months (95% CI: 3.6 months to 7.4 months).

The most common grade 3 or 4 treatment-related AEs were hypertension (13% group A, 5% group F) and proteinuria (7% and 3%). In group A, 3 treatment-related deaths occurred (1 abnormal hepatic function, 1 hepatic cirrhosis, and 1 pneumonitis). Bleeding complications were not increased compared with those observed in previous anti-VEGF therapy trials¹¹.

Combined atezolizumab–bevacizumab compared with sorafenib was further evaluated in a 2:1 ratio ($n = 336$ atezolizumab–bevacizumab, $n = 165$ sorafenib) in the global phase III IMbrave150 trial (NCT03434379) in a first-line setting of unresectable HCC. Inclusion criteria were an Eastern Cooperative Oncology Group 0–1 performance status, well-preserved liver function (Child–Pugh score: ≤ 6), no history of autoimmune disease, and untreated or incompletely treated esophageal or gastric varices. Disease causes were predominantly HBV and HCV, with non-viral causes constituting 30% of the atezolizumab–bevacizumab arm and 32% of the sorafenib arm. Macrovascular invasion was frequent at 38% and 43%, and 82% and 81% were staged as Barcelona Clinic Liver Cancer C²². Median PFS was 6.8 months (95% CI: 5.7 months to 8.3 months) in the combination group and 4.3 months (95% CI: 4.0 months to 5.6 months) in the sorafenib group. The HR for disease

progression or death was 0.59 (95% CI: 0.47 to 0.76; $p < 0.001$). Median OS was not reached in the combination arm. Of patients in the atezolizumab–bevacizumab group, 56.5% experienced grade 3 or 4 adverse events, but high-grade toxic effects apart from hypertension were infrequent²². Bleeding complications were observed in 7% of the atezolizumab–bevacizumab group and in 4.5% of the sorafenib group; such events were not a limiting toxicity risk. Combined atezolizumab–bevacizumab is already approved by the FDA, and approval by the European Medicines Agency is expected. With that approval, atezolizumab–bevacizumab is expected to become the most widely used first-line therapy in advanced HCC.

ICI and ICI

A couple of trials have explored combination therapy using two ICIs.

Nivolumab–Ipilimumab: Initial results for combined nivolumab–ipilimumab were reported from the single-arm phase I/II CheckMate 040 trial (see NCT01658878 at <https://ClinicalTrials.gov/>)²¹. Patients previously treated with sorafenib in advanced HCC were randomized to 3 treatment arms:

- Arm 1: nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks (4 doses), followed by nivolumab 240 mg every 2 weeks
- Arm 2: nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks (4 doses), followed by nivolumab 240 mg every 2 weeks
- Arm 3: nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks

The primary endpoints were safety and tolerability, and secondary endpoints included ORR, DOR, DCR, and OS.

In arm 1, the ORR was 31%, with 7 patients reaching a CR; OS was 23 months. The combination was well tolerated, with 37% grade 3 or 4 treatment-related AEs (mostly pruritus and rash). In 5% of patients, the AEs led to treatment discontinuation. The ORR was more than double the rate seen with nivolumab monotherapy (31% vs. 14%).

Based on the results of that phase I/II trial, which demonstrated a median OS of 22.8 months in arm 1, combined nivolumab–ipilimumab received accelerated approval by the U.S. FDA.

Currently, a phase III trial of nivolumab (1 mg/kg every 3 weeks) plus ipilimumab (3 mg/kg for 4 doses) compared with the current standard TKI agents (sorafenib or lenvatinib) in the first-line setting is recruiting participants (CheckMate 9DW, NCT04039607). The primary endpoint is OS, and secondary endpoints are ORR, DOR, and time to symptom deterioration.

In the United Kingdom, nivolumab–ipilimumab is currently being evaluated in a 2-phase design in patients ineligible for liver transplantation and planned for resection (PRIME-HCC, NCT03682276). The primary endpoints are delay to surgery, safety, and tolerability; secondary outcomes are ORR and pathologic response rate⁴⁷.

Durvalumab–Tremelimumab: In the phase II Study 22 trial (NCT02519348), durvalumab and tremelimumab

were tested each as monotherapy, and durvalumab was tested in combination with tremelimumab or bevacizumab. Primary outcomes were safety and evaluation of dose-limiting toxicities.

Results were presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program. All arms had an acceptable safety profile. The best OS, at 18.7 months, was associated with the combination of a single priming dose of tremelimumab 300 mg combined with durvalumab 1500 mg and continuation of durvalumab 1500 mg every 4 weeks. Grade 3 or 4 AEs were seen in 35.1% of patients, and the ORR was 24.0%²⁰.

Combination durvalumab–tremelimumab is currently being evaluated in a phase III trial (HIMALAYA, NCT03298451) as a first-line treatment in patients with advanced HCC. In a 4-arm design, durvalumab monotherapy and combination durvalumab–tremelimumab are being compared with sorafenib treatment. The primary endpoint is OS, and secondary endpoints are time to progression, PFS, ORR, DCR, and DOR⁴⁸.

ICIs and Local Therapy

The combination of ablative therapies (with their potential to result in shedding of tumour-associated antigens) with immunotherapy (capable of augmenting the immune response) might act synergistically²⁷.

In a phase I/II trial (NCT01853618), the combination of IV tremelimumab (at 2 dose levels—3.5 mg/kg and 10 mg/kg—every 4 weeks for 6 doses, followed by 3-monthly infusions) with an ablation procedure was explored. On day 35, patients underwent subtotal radiofrequency ablation or chemoablation. For the 19 patients who could be evaluated, median OS was 12.3 months (95% CI: 9.3 months to 15.4 months), and an abscopal partial response effect outside the area of local treatment was achieved in 25%²⁷.

The currently running phase IB PETAL trial (NCT03397654) is testing the use of pembrolizumab after transarterial chemoembolization (TACE) in a small single-arm multicentre study, with primary outcomes of safety and tolerability.

The phase II PLTHCC trial (NCT04273100) evaluated TACE in combination with the anti–PD-1 antibody lenvatinib, with a primary endpoint of ORR. An even broader range of local ablation modalities (radiofrequency ablation, microwave ablation, brachytherapy, or TACE) is being tested in the phase II IMMULAB study (NCT03753659), again with ORR as the primary outcome measure.

Combined checkpoint inhibition using durvalumab–tremelimumab combined with TACE, cryotherapy, or radiofrequency ablation with respect to PFS is being tested in the NCT02821754 phase II trial. Preliminary results showed a 20% ORR and a DCR of 60%⁴⁹.

The phase III EMERALD-1 trial (NCT03778957) is examining TACE in combination with durvalumab–bevacizumab. The primary endpoint is PFS.

Adjuvant and Neoadjuvant Therapy with ICI

Given the high recurrence rate and lack of therapeutic options with proven benefit in the adjuvant setting after the negative results of a phase III trial evaluating sorafenib (STORM, NCT00692770), adjuvant therapy remains an unmet medical need, and immunotherapy is under active evaluation^{50,51}.

Combination nivolumab–cabozantinib is being evaluated in a phase I trial (NCT03299946) with the primary endpoints being number of AEs and number of patients who proceed to surgery⁵².

In addition, the efficacy and safety of durvalumab alone or in combination with bevacizumab after curative resection or ablation with a high risk of recurrence is being evaluated in the phase III double-blind placebo-controlled EMERALD-2 trial (NCT03847428). The primary endpoint is recurrence-free survival.

Another phase III trial is the IMbrav050 study (NCT04102098) which is testing combination atezolizumab–bevacizumab, with a primary endpoint of PFS.

A perioperative concept using neoadjuvant and adjuvant administration of nivolumab–ipilimumab or placebo in patients with resectable HCC is in phase II evaluation (NCT03222076). The trial is no longer recruiting; results are awaited.

SUMMARY

Despite an increasing number of approved drugs, systemic therapy of HCC is still a challenge. Because of underlying liver cirrhosis in most cases, treatment has to be adapted to a patient's liver functional reserve and performance status.

Therapy with the TKIs sorafenib, lenvatinib, regorafenib, and cabozantinib has been associated with improved survival in patients with well-preserved liver function, OS being more than 24 months with sequential treatment in some cases⁵³. Ramucirumab is a therapeutic option for patients with serum alpha-fetoprotein 400 ng/mL or more, representing a subset of cases with a limited prognosis.

The impressive results of the phase II trials for nivolumab in the first line¹⁴ and pembrolizumab in the second line led to accelerated approval of those drugs by the FDA and to high expectations for the results of the phase III studies. Unfortunately, CheckMate 459¹⁵ and the KEYNOTE-240 trial¹⁷ both failed to reach statistical significance. Each trial demonstrated longer OS with ICI therapy and durable responses in a number of patients. There could be a couple of reasons for the failure of those trials.

Patients in CheckMate 459 experienced longer OS (16.4 months vs. 14.7 months; HR: 0.85). The excellent survival in both arms is probably attributable to the subsequent therapy that patients received (49% for nivolumab and 53% for sorafenib, with 20% of patients treated with sorafenib receiving subsequent immunotherapy), which contributed to the negative result. The effect of improved survival in the comparison arm of clinical trials as more options of subsequent therapies become available is depicted in Figure 2 for first-line trials and Figure 3 for second-line trials.

The statistical design of the KEYNOTE-240 trial, with its dual endpoint and 2 interim analyses, required high stringency for a positive outcome. With a 22% decrease in death, a clinically meaningful result was achieved, and the median DOR was 13.8 months. Survival in the sorafenib control arm was again very long, at 10.6 months, attributable to the exclusion of macrovascular invasion, better management of patients, and the availability, after the study, of second-line treatments, including immunotherapy, that

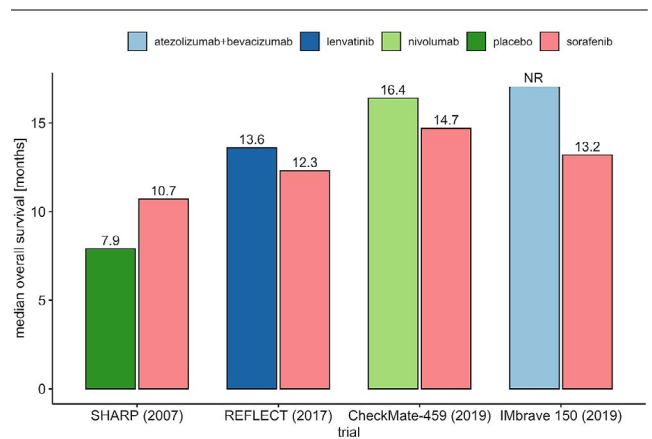


FIGURE 2 Positive phase III first-line trials evaluating tyrosine kinase inhibitor therapy and phase III trials evaluating checkpoint immunotherapy. NR = not reached.

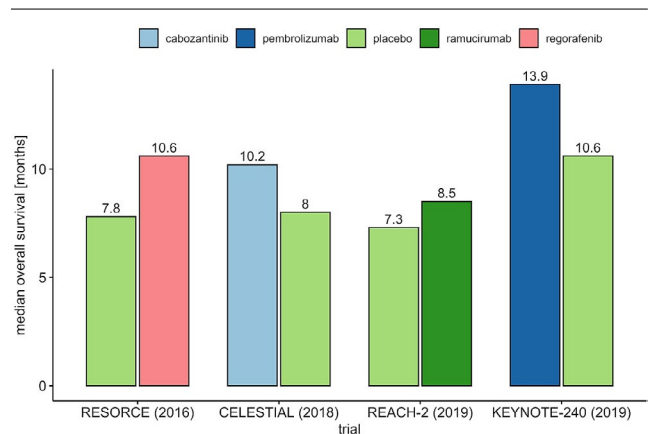


FIGURE 3 Positive phase III second-line trials evaluating tyrosine kinase inhibitor therapy and phase III trials evaluating checkpoint immunotherapy

were not available at study start⁵⁴. While failing statistical significance, both trials demonstrated clinical benefit.

Although single-agent immunotherapy could not demonstrate superiority to the standard of care, combination atezolizumab–bevacizumab in the IMbrave150 trial was associated with an unprecedented survival benefit, the median OS not being reached in the verum arm²². The atezolizumab–bevacizumab combination is expected to become the new standard of care in first-line therapy of HCC. The selection of patients remains crucial to address safety and efficacy concerns: alternative therapies should be preferred in the presence of prior organ transplantation or uncontrolled autoimmune disease, given the risk of organ rejection and high-grade flares. In inflammatory bowel disease (even in a clinically stable clinical situation), the risk for gastrointestinal AEs such as high-grade diarrhea and perforations is increased⁵⁵. And although no excessive bleeding risk was reported in the study, long-term experience will demonstrate the necessary management (such as ligation therapy for esophageal varices and patients at risk for bleeding events).

An important aspect of TKI therapy is the management of AEs. Diarrhea, hand-foot skin reaction, worsening of liver function, weight loss, and fatigue can severely impair patient quality of life and could lead to a need for dose interruption or modification.

Immunotherapy with ICIs challenges patients and physicians with a novel spectrum of side effects. Although AEs with immunotherapy can be life-threatening, they are usually mild and do not affect quality of life in a serious way. An analysis of health-related quality of life in the CheckMate 459 trial (comparing nivolumab with sorafenib) demonstrated a longer time to first deterioration and time to definitive deterioration. A greater proportion of patients receiving nivolumab did not experience an increased burden of side effects (50%–67.7% vs. 26.8%–45% with sorafenib)⁵⁶. Immunotherapy has the potential to stabilize or even improve quality of life for patients with HCC and might be beneficial in a sequence with TKIs to counteract loss of appetite, weight loss, and fatigue.

The ORRs for TKI therapies are generally limited, reaching 24.1% with lenvatinib in the REFLECT trial⁴². Because of those low response rates, TKIs are rarely used in a neoadjuvant setting. The ORR was 33% in the IMbrave150 trial and 46% if evaluated by the modified Response Evaluation Criteria in Solid Tumors in the early trial of pembrolizumab with lenvatinib²⁶. An increasingly better tumour response will open new options for patients achieving tumour size reductions, leading to secondary resectability and possibly liver transplantation.

Another important medical need is an effective adjuvant therapy after resection and ablation to reduce the high number of recurrences. The STORM trial (NCT00692770) was not able to demonstrate a benefit of adjuvant sorafenib treatment⁵⁰, but immunotherapy might be effective in that setting while having a limited impact on quality of life during treatment. That concept is currently being evaluated in a number of trials that are using single-agent immunotherapy or combinations with anti-VEGF receptor therapy.

The positive results of IMbrave150 for systemic therapy in HCC has added another important weapon in the fight for longer and better survival. But despite the enthusiasm, questions remain. A significant percentage of tumours are not responsive to immunotherapy, and so far, no biomarkers to predict response have been uncovered. An immunologic classification of patients applicable in a real-world setting would help to guide treatment decisions. And to reach optimal survival results, cohort studies and clinical trials will be needed to identify the best therapeutic sequence of the available agents. Despite those challenges, immunotherapy has already become and will continue to be a mainstay of systemic therapy in HCC.

CONFLICT OF INTEREST DISCLOSURES

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