Therapy in Advanced Hepatocellular Carcinoma

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Abstract

Treatment of advanced hepatocellular carcinoma (HCC) is challenging. Several randomized clinical trials are investigating the efficacy of systemic therapy, immunotherapy, and locoregional therapy as monotherapy or combined with other modalities in the treatment of HCC. Systemic therapy is the preferred treatment in advanced disease. To date, multiple first-line and second-line agents received Food and Drug Administration approval. For over a decade, sorafenib was the only first-line agent. In May 2020, combination of atezolizumab and bevacizumab has been approved as a first-line systemic regimen. Lenvatinib is another first-line agent that has multikinase activity. Second-line agents include cabozantinib, regorafenib, ramucirumab, and nivolumab. Adoptive cell transfer therapy is a highly specific immunotherapy that has shown antitumor activity against HCC. Oncolytic viruses are genetically modified viruses that infect cancer cells and induce apoptosis. Locoregional therapies such as transarterial chemoembolization and radioembolization have shown a potential benefit in selected patients with advanced HCC. In this review, we aim to summarize the treatment options available for advanced HCC.

Keywords
- hepatocellular carcinoma
- systemic therapies
- locoregional therapies

Advanced hepatocellular carcinoma (HCC) is defined as HCC with portal vein invasion or extrahepatic spread with preserved liver function and performance status ECOG 1 or 2.[1] Systemic therapy is the preferred treatment option in patients with advanced HCC. That being said, HCC is highly resistant to conventional chemotherapy agents such as doxorubicin, gemcitabine, and irinotecan due to fibrosis, p53 mutation, and efflux pumps.[2,3]

Targeted therapies are the mainstay of advanced HCC treatment as monotherapies or combined with other drugs. Locoregional therapies may play an increasing role, but further trials are needed.[3–5]

First-Line Agents: Atezolizumab + Bevacizumab, Sorafenib, and Lenvatinib

The SHARP and Asia-Pacific trials showed a survival advantage of 2.8 months with sorafenib compared with placebo in 2007 and led to its approval as first-line therapy for advanced HCC.[6–8] Sorafenib is an oral multikinase inhibitor that inhibits VEGFR, PDGFRα, EGRS, as well as RAF/MEK/ERK kinases with antiangiogenic and apoptotic activity. Sorafenib is associated with significant side effects. These include palmar-plantar erythrodysesthesia (PPE; also termed "hand–foot" syndrome; 52%), diarrhea (46%), hypertension (30%), and decreased appetite (27%).[9] Since its approval, sorafenib was the only systemic therapy for HCC until 2017. Since then, nine prospective randomized controlled trials (RCTs) have led to several other systemic agents as first- or second-line therapeutic options (►**Table 1**).[9,10]

Lenvatinib is an oral multikinase inhibitor targeting RET, KIT, PDGFR, VEGFR 1–3, and FGFR 1–4.[11] The REFLECT trial was a prospective RCT with a noninferiority design comparing lenvatinib and sorafenib, with overall survival (OS) as primary endpoint.[12,13] The trial met its primary endpoint: lenvatinib arm demonstrated median OS of 13.6 versus 12.3 months in the sorafenib arm (hazard ratio [HR]: 0.92; 95% confidence interval [CI]: 0.79–1.06). Importantly, lenvatinib improved important secondary endpoints including objective response

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Table 1 Summary of phase III clinical trials on first- and second-line agents for systemic therapy in HCC

Line	Study name	Experimental arm	Control arm	Overall survival (m)	Hazard ratio	Study identifier
First line	IMbrave 150	Bevacizumab + atezolizumab	Sorafenib	Median OS not reached	0.58	NCT03434379
	SHARP	Sorafenib	Placebo	10.7 vs. 7.9	0.69	NCT00105443
	REFLECT	Lenvatinib	Sorafenib	13.6 vs. 12.3	0.92	NCT01761266
	CheckMate 459	Nivolumab	Sorafenib	16.4 vs. 14.7	0.85, $p = 0.07$[a]	NCT02576509
Second line	RESORCE	Regorafenib	Placebo	10.7 vs. 7.8	0.63	NCT01774344
	CELESTIAL	Cabozantinib	Placebo	10.2 vs. 8.0	0.76	NCT01908426
	REACH-2	Ramucirumab	Placebo	8.5 vs. 7.3	0.71	NCT02435433
	Keynote-240	Pembrolizumab	Placebo	13.9 vs. 10.6	0.78, $p = 0.02$	NCT02702401

Abbreviation: HCC, hepatocellular carcinoma.
[a]Not significant.

rate (24% lenvatinib vs. 9% sorafenib) and progression-free survival (PFS) (7.4 vs. 3.7 months; HR: 0.66; 95% CI: 0.57–0.77; $p < 0.0001$). The most common side effects for lenvatinib included hypertension (42%), diarrhea (39%), decreased appetite (34%), and decreased weight (31%). However, lenvatinib is associated with less PPE compared with sorafenib.[12–14] Thus, the REFLECT trial was the first positive randomized phase 3 trial in 1 L HCC in over a decade.

Mounting data have shown potential synergy by combining anti-VEGF blockade with immune checkpoint inhibitors. Atezolizumab is a monoclonal antibody against PD-L1 that inhibits binding to programmed cell death 1 (PD-1) and CD80 (B7–1R) receptors on effector T-cells therapy.[15,16] Bevacizumab is an anti-VEGF monoclonal antibody which binds VEGF, thus blocking the interaction of VEGF with VEGF receptors on endothelial and other cells, leading to reduced angiogenesis and thus blocking downstream PI3-kinase/AKT, MAP kinase, and focal adhesion kinase which control survival and migration pathways.[17] The hypothesis was tested in the Phase III IMbrave 150 trial which compared the combination of atezolizumab plus bevacizumab to sorafenib. A total of 501 patients with advanced HCC who had never received systemic therapy were randomized 2:1 to atezolizumab:bevacizumab (336 patients) and sorafenib (165 patients). The primary endpoint of the study was met: the HR for death with atezolizumab–bevacizumab as compared with sorafenib was 0.58 (95% CI: 0.42–0.79; $p < 0.001$). OS at 12 months with the combination was 67.2% (95% CI: 61.3–73.1) versus 54.6% (95% CI: 45.2–64.0) with sorafenib. The PFS was also significantly improved from 4.3 to 6.8 months. Bevacizumab plus atezolizumab is the first and thus far the only regimen that showed superior results to sorafenib as first-line treatment.[16] Multiple other first-line trials with combination regimens are either actively ongoing or have finished accrual Leap-002 (NCT03713593), HIMALAYA (NCT03298451), and COSMIC 312 (NCT03755791).[18–21]

Second-Line Agents

Three agents (cabozantinib, regorafenib, and ramucirumab) have shown OS benefit over placebo in second line after progression on sorafenib. In addition, the anti-PD1 antibodies nivolumab and pembrolizumab are approved based on single-arm phase 1/2 trials in the second-line setting.[22–24]

The first agent to show an OS benefit in patients who previously tolerated sorafenib was regorafenib based on the RESORCE trial.[24] Regorafenib is a multikinase inhibitor with a broader antikinase activity than sorafenib. It is also a KIT, RET, and VEGFR kinase inhibitor.[25] Regorafenib in second line improved OS (10.6 months with regorafenib compared with 7.8 months with placebo; HR: 0.63; 95% CI: 0.50–0.79; $p < 0.0001$). Of note, to be eligible patients had to have shown progression on sorafenib and patients must have tolerated the minimum dose of the sorafenib ($\geq$400 mg/day for $\geq$20 of 28 days of treatment). The reported grade 3/4 adverse events were hypertension (15% in regorafenib group vs. 5% in placebo group), PPE (13% in regorafenib group vs. 1% in placebo group), and diarrhea (3% in regorafenib group vs. 0% in placebo group).[23,25–27]

Cabozantinib is a multitargeted tyrosine kinase inhibitor that inhibits VEGFRs, MET, and AXL.[28] Data from phase III CELESTIAL trial demonstrated an improvement of OS (10.2 months) in cabozantinib versus placebo group (8.0 months, $p = 0.0049$) in patients who had disease progression after systemic therapy (up to two previous lines, one including sorafenib).[29] The study also showed increased median PFS in cabozantinib group (5.2 months) versus placebo arm (1.9 months), $p < 0.001$. The PFS of > 5 months seen in the CELESTIAL trial is the longest PFS reported in any randomized second-line trial. Notable adverse events were PPE in the cabozantinib group (17%), hypertension (16% in cabozantinib vs. 2% in the placebo arm), elevated AST (12 vs. 2%), fatigue (10 vs. 4% in the placebo group), and diarrhea (10 vs. 2%).[22,29,30]

Ramucirumab is an anti-VEGFR2 monoclonal antibody.[31] It is the first approved drug that improved OS in biomarker-selected patients (i.e., patient selection based on serum AFP >400 ng/mL). In the REACH-2 phase III trial, patients with baseline AFP concentration $\geq$400 ng/dL were randomized to ramucirumab versus placebo.[24] The trial demonstrated was positive for the primary endpoint with ramucirumab showing an OS of 8.3 months compared with 7.3 months with placebo, $p < 0.001$. There was no significant difference in the

objective response rate. The grade 3/4 adverse events reported were hypertension (13% in the ramucirumab group vs. 5% in the placebo group) and hyponatremia (6% vs. 0). Serious adverse events of any cause happened in 35% of ramucirumab versus 29% of placebo.[24,32]

Immunotherapeutic Agents

Hepatocellular carcinoma frequently occurs in chronic liver diseases such as hepatitis C virus (HCV), hepatitis B virus (HBV), alcoholic cirrhosis, and nonalcoholic steatohepatitis (NASH). Improved survival in patients with balanced regulatory and cytotoxic T cells raised interest in therapies that can potentially reactivate exhausted T-cells. However, the liver is exposed to numerous antigens from the digestive system and is an immune-tolerant environment; therefore, leveraging immunotherapies has been more challenging than expected.[4]

There are four immunotherapy approaches in the treatment of HCC which encompasses checkpoint inhibitors, oncolytic virus (OV), adoptive T-cell transfer therapy, and HCC vaccines.[3,33]

Immune Checkpoint Inhibitors in the Second-Line Setting

Two types of checkpoint inhibitors are clinically available: PD-1/programmed cell death-ligand 1 (PD-L1) inhibitor and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor. CTLA-4 and PD-1 are negative regulators of T-cell activation system. CTLA-4 inhibits the interaction of T-cells with dendritic cells (DCs) and antigen presenting cells (APCs) consequently increase T-cell motility and dampens T-cell activation.[34] Interaction of PD-1/PD-L1 with T-cell receptors results in decreased T-cell proliferation and their cytokine production, increased T-cell tolerance, and interference with tumor recognition. Additionally, the PD-1/PD-L1 pathway plays an important role in tumor survival. Cancer cells express these receptors to avoid the immune system; hence, blocking these pathways augments the antitumor activity of T-cells.[34–36]

Nivolumab and pembrolizumab are two anti-PD-1 monoclonal antibodies that received accelerated Food and Drug Administration (FDA) approval as second-line agents in patients with advanced HCC postprogression on sorafenib. Nivolumab was tested in phase I/II CheckMate 040 clinical trial. A total of 262 patients were enrolled in this trial. The reported objective response rate was 14% by RECIST v1.1 with a median duration of response of 17 months (95% CI: 6–24) and a reported OS of 15.6 months.[10]

Based on these encouraging results, nivolumab was tested in a first-line superiority trial versus sorafenib in patients with advanced HCC. The phase III CheckMate 459 trial randomized 1,009 patients to nivolumab versus sorafenib.[37] The study failed to meet the primary endpoint OS with nivolumab (16.4 months) and was not significantly better than with sorafenib (14.7 months) (HR: 0.85 [95% CI: 0.72–1.02] $p = 0.0752$).[38] Median PFS was not different in both arms. Overall, nivolumab was better tolerated with fewer treatment-related adverse events reported in the nivolumab arm compared with sorafenib.[38–40]

In the phase II KEYNOTE-224 clinical trial, safety and efficacy of pembrolizumab were evaluated in 104 patients with advanced HCC previously treated with sorafenib.[37] The trial reported an OR of 17% based on RECIST v1.1, with a median duration of response of 12.9 months, and PFS of 4.9 months. Serious adverse events occurred in 40% of patients. In general, pembrolizumab provided durable efficacy and a safety profile similar to what was seen with other indications.[41] Based on these results, pembrolizumab was tested in the randomized phase 3 trial KEYNOTE-240 against placebo in the second-line setting. The trial had OS and PFS as coprimary endpoints with adjusted *p*-values for statistical significance. Despite an improved HR for OS (HR: 0.78; one sided, $p = 0.0238$) and PFS (HR: 0.78; one sided, $p = 0.0209$) versus placebo, the trial did not reach the predetermined threshold for statistical significance and hence was negative.[42]

Combination Systemic Therapies

Multiple ongoing trials (listed in ►**Table 2**) are examining combination systemic therapies. Another combination regimen that received accelerated FDA approval in March 2020 is nivolumab (NIVO), a PD1 inhibitor, and ipilimumab (IPI), an anti-CTLA-4 antibody, in patients who failed sorafenib. The dose approved (nivolumab 1 mg/kg + ipilimumab 3 mg/kg once every 3 weeks) showed a median OS of 23 months. However, this regimen was associated with significant toxicities and thus warrants careful patient selection.[36,43]

Adoptive Cell Transfer Therapy

Adoptive cell transfer (ACT) therapy has emerged as a form of immunotherapy in that patients' immune cells are amplified and modified in vitro, then transferred back to patients to kill tumor cells.[37] ACT improves the quality and quantity of the anticancer cells and reduces the immune system's tolerance to the cancer cells. ACT therapy is highly specific, individualized, and more durable than antibodies. ACT therapy consists of autogenous gene-modified cells with targeted activity as opposed to chemotherapy. ACT subtypes are lymphokine-activated killer cells (LAK), tumor-infiltrating lymphocytes (TILs), cytokine-induced killer (CIK) cells, and chimeric antigen receptor T-cells (CAR-T-cells) that can be used in the cancer recurrence and progress prevention.[44,45]

TILs can be rarely found in HCC, but studies have shown that there is a positive correlation between T lymphocyte infiltration and tumor recurrence and prognosis.[46] TILs isolated from tumor specimens are amplified in vitro with interleukin (IL2) and transferred to lymphocyte-deleted patients. These cells have an intense antitumor effect due to the diverse antigens and mutations in tumor cells.[47]

CIK cells consist of natural killer (NK) cells and cytotoxic T-cells that are cultured ex vivo.[45] The cytolytic effects of CIK cells are not dependent on T-cell receptors–major histocompatibility complex 1 (TCR-MHC 1). A large retrospective study by Pan et al showed that injection of CIK as postsurgery

Table 2 Ongoing clinical trials for combination immunotherapy in HCC

Anti-PD-1/ PD-L1 agent	Combining agent	Mechanism of action	Control arm	Study phase/size	Study identifier/ name
Nivolumab	Ipilimumab	Anti-CTLA4	Versus nivolumab Versus sorafenib	Phase I/II/ 1,097	NCT01658878
Durvalumab	Tremelimumab	Anti-CTLA4	Versus durvalumab Versus sorafenib	Phase III/ 1,310	NCT03298451 HIMALAYA
Durvalumab	Tremelimumab/ Bevacizumab	Anti-CTLA4/ Anti-VEGF ab	Versus durvalumab or tremelimumab monotherapy	Phase II/ 433	NCT02519348
Durvalumab	Tremelimumab/ Bevacizumab	Anti-CTLA4/ Anti-VEGF ab	Versus tremelimumab or Versus bevacizumab versus placebo	Phase III/ 888	NCT03847428 EMERALD-2
Nivolumab	Pexa-Vec	GM-CSF-armed oncolytic virus		Phase I/II/ 30	NCT03071094
Pembrolizumab	GNOS-PV02 and INO-9012	Personalized neoantigen DNA vaccine		Phase I/II 12	NCT04251117
Durvalumab	Bevacizumab	Anti-VEGF ab	Versus durvalumab monotherapy	Phase III/ 888	NCT03847428
Atezolizumab	Bevacizumab	Anti-VEGF ab	Versus sorafenib	Phase III/ 480	NCT03434379
Durvalumab	Ramucirumab	Anti-VEGFR2 ab		Phase I/ 114	NCT02572687
Pembrolizumab	Lenvatinib	TKI		Phase I/ 104	NCT03006926
Pembrolizumab	Nintedanib	TKI		Phase I/ 18	NCT02856425
SHR-1210	Apatinib	TKI	Versus sorafenib	Phase III/ 510	NCT03764293
PDR001	Sorafenib	TKI		Phase II/ 20	NCT02988440
Nivolumab	Galunisertib	TGF-β inhibitor		Phase I/II/ 75	NCT02423343
PDR001	INC280	C-met inhibitor		Phase I/II/ 90	NCT02795429
Pembrolizumab	XL888	Hsp90 inhibitor		Phase I/ 50	NCT03095781

Abbreviation: HCC, hepatocellular carcinoma.

adjuvant therapy can drastically improve OS.[48] Furthermore, there are multiple phase I and II clinical trials that indicated treatment with CIK cells can increase OS in HCC patients by 40% compare with the control group. However, a large-scale clinical trial is needed to show whether the patients can benefit from CIK immunotherapy.[48,49]

CAR-T-cells are genetically engineered T-cells that consist of monoclonal antibody to recognize specific antigens on tumor cells.[50] Unlike TCRs, these cells are independent of MHC; therefore, will not be restricted by the immune escape mechanism of tumor cells. T-cells are separated from the patient's blood and CAR-T-cells will be integrated into them. These engineered cells will be cultured in vitro and then transfused back to the patients. Although the efficacy of CAR-T-cells in the treatment of HCC has been confirmed by in vitro studies, clinical data are very limited. The very first report presented by Gao et al indicated that GPC3-targeted CAR-T-cells could lyse GPC3-positive HCC in vivo and in vitro.[50,51] There are multiple ongoing phase I/II clinical trials on the efficacy of CAR-T-cells in advanced HCC. The principal challenges in CAR-T-cell therapy are the toxicity of immune cell infusion, the liver's immunosuppressive microenvironment, and limited blood distribution in HCC tumors. The strategy to improve the infiltration of the CAR-T-cells into the tumor and reduce systemic side effects consists of local delivery into the tumor transarterially or via percutaneous arterial infusion.[52] Some major adverse events that have been reported with this therapy were cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis, and CAR-T-cell–related encephalopathy syndrome.[45,50,53]

Oncolytic Virotherapy

Preclinical studies have shown the efficacy of OVs in the treatment of cancer, especially melanoma.[54] OVs are genetically modified to infect cancer cells and induce apoptosis or necrosis. Tumor cell lysis results in DCs and antigen-presenting cells (APCs) activation with an ensuing antitumor immune response. OVs also can be engineered to express specific functional genes.[55] The virus strains that are being utilized in current clinical trials are adenovirus and vaccinia such as JX-594 (Pexa-Vec). Adenovirus failed to halt the disease progression in a clinical study, but other clinical trials showed antitumor efficacy of the vaccinia strains. Pexa-Vec is an engineered poxvirus that has an inserted human granulocyte-macrophage colony-stimulating factor (hGM-CSF) gene. Pexa-Vec is injected into the tumor directly.[56]

The Phase II trial, TRAVERSE, investigated the efficacy of Pexa-Vec and best supportive care (BSC) versus BSC alone in patients who had failed sorafenib. The trial enrolled 120 patients randomized 2:1 to experimental versus BSC. The median OS was 4.2 months for Pexa-Vec and BSC and 4.4 months for BSC ($p = 0.428$). However, the Phase 2 dose randomized trial Frontline demonstrated an increased OS with high-dose OV arm in sorafenib-naive patients with advanced HCC.[57] Therefore, a phase III RCT PHOCUS was started. Sorafenib-naive advanced HCC patients were randomized 1:1 to Pexa-Vec with sorafenib versus sorafenib alone. PHOCUS was halted due to futility analysis.[58] There is an ongoing trial evaluating the efficacy of the combination of Pexa-Vec with nivolumab (NCT03071094).

Locoregional Therapy

Image-guided locoregional therapies (LRTs) have a pivotal role in the treatment of intermediate HCC patients. Their role in advanced HCC is limited. However, there has been increasing literature examining certain LRTs for advanced HCC.[59]

Transarterial Chemoembolization

Transarterial chemoembolization (TACE) is a well-tolerated palliative intervention in the management of unresectable HCC.

Several studies showed the potential benefit of TACE in patients with advanced HCC.[60–62] A study by Chung et al compared TACE with supportive care in patients with portal vein invasion. The study demonstrated significant survival benefit of TACE over supportive care in both Child–Pugh A (median survival: 7.4 vs. 2.6 months, $p < 0.001$) and Child–Pugh B (median survival: 2.8 vs. 1.9 months, $p = 0.002$).[63] Furthermore, Kim et al reported that regardless of sorafenib, repeated TACE can be utilized to control intrahepatic HCC in advanced disease and improves survival rate. Even though TACE is contraindicated in patients with portal invasion due to the risk of hepatic insufficiency, it is feasible in the patients with preserved liver function and adequate collaterals.[60,63–65]

Transarterial Radioembolization

Transarterial radioembolization (TARE) has traditionally been utilized in the treatment of intermediate and advanced-stage HCC. Lobar portal vein thrombosis (PVT) does not interfere with TARE due to the nonembolic nature of the treatment.

The outcome of TARE depends on multiple factors, most notably baseline patient stage (Barcelona Clinic Liver Cancer [BCLC], Child–Pugh). A multicenter analysis by Sangro et al showed the median OS following radioembolization to be 24.4 months (BCLC A), 16.9 months (BCLC B), and 10.0 months (BCLC C).[66] Moreover, PVT is another prognostic factor of TARE treatment. According to Salem et al, time to progression (TTP) in patients without PVT was longer (15.5–13 months) compare with patients with PVT (5.6–5.6 months).[67]

SIRveNIB (Selective Internal Radiation Therapy v Sorafenib), was a phase III clinical trial that compared yttrium-90 (Y-90) resin microspheres TARE to sorafenib in patients with advanced HCC conducted in 11 Asia-Pacific countries. Major inclusion criteria were locally advanced HCC BCLC[68] stage B or C without extrahepatic disease with or without PVT. Patients who received more than two transarterial therapies or sorafenib or VEGF inhibitor or radiotherapy were excluded from the study. A total of 360 patients were enrolled in the study with 182 assigned to TARE and 178 assigned to sorafenib. Twenty-eight percent of TARE patients and 9.0% of the sorafenib patients did not receive allocated treatment but were analyzed with intent to treat. Median OS rates for TARE and sorafenib were 8.8 and 10 months (HR: 1.1; $p = 0.36$), respectively. Treatment-related adverse events grade ≥ 3 were significantly lower in TARE group (27.7 vs. 50.6%; $p = 0.001$). Tumor response rate and adverse events were improved in TARE group.[69]

The phase 3 SARAH trial (SorAfenib versus Radioembolization in Advanced Hepatocellular carcinoma) was conducted in 25 centers in France. A total of 467 patients (237 patients in the TARE group, 222 patients in the sorafenib group) were enrolled for the study. Median OS rates for sorafenib group were 9.9 and 8 months for TARE (HR = 1.15; $p = 0.18$). In conclusion, both trials failed to meet the primary endpoint OS. However, TARE group showed a significant better tumor response rate, quality of life, and lower side effects.[70]

SORAMIC is an RCT that randomized 424 patients to Y-90 glass beads and sorafenib (216 patients) versus sorafenib alone (208 patients). Median OS of 12.1 months with SIRT/Sorafenib was observed versus 11.4 months with sorafenib alone, respectively (HR: 1.01; $p = 0.9529$). Treatment-related adverse events were reported in 64.8% in SIRT + sorafenib arm and in 53.8% in sorafenib arm ($p = 0.04$).[71] The pitfalls of these clinical trials were study design and ITT analysis. Patients assigned to TARE group received radiotherapy 4 to 5 weeks after randomization, whereas patients in the sorafenib group received drug within 1 week. The delay may have caused liver function deterioration. Moreover, the operators were not experienced, and no learning curve was integrated in study design. Finally, several patients had previous TACE, main portal vein thrombus, and consequently the number of patients who did not receive the allocated treatment was higher in TARE group.

Finally, a meta-analysis NEMESIS was performed with a noninferiority analysis of patient level data from the three prospective RCTs—SORAMIC, SARAH, and SIRveNIB. The analysis concluded that OS with TARE is noninferior to sorafenib in the management of advanced HCC with fewer adverse events. Pooled data analysis showed higher percentage of partial response in the TARE group and higher percentage of stable disease in the sorafenib group. Subgroup analysis revealed that TARE was superior to sorafenib in patients with hepatitis B–related HCC.[72] A recent multicenter, randomized phase 2 study (DOSISPHERE-01) assigned patients with a minimum of one ≥7 cm unresectable HCC tumor to standard dosimetry (SDA) Y-90 versus personalized dosimetry arm Y-90 (PDA). The goal of the SDA group was to deliver a dose of 120 Gy to the treated volume, while the SDA's goal was to deliver at least 205 Gy to the index lesion. The primary endpoint was the response rate of the index lesion according to EASL criteria. Secondary endpoints included dose–response evaluation, safety, and OS. Of 60 patients enrolled, 56 were treated. The response rate in the PDA group was 64.5% which is significantly higher than the 31% in the SDA group ($p = 0.0095$). Median OS was significantly increased to 26.7 months (95% CI: 13.5–NR) in the PDA versus 6 months (95% CI: 3.8–14.9) in the SDA, $p = 0.0106$.[73,74]

Combination of LRT and Systemic Therapy

Multiple studies have investigated the efficacy of combining LRT and systemic therapy to minimize side effects with local delivery and improve OS and response. Indeed, TACE leads to some tumor necrosis; some cells do escape. TACE is known to cause hypoxia with the upregulation of angiogenic factors like VEGF and hypoxia-inducible factor-1α (HIF-1α). The latter results in adverse outcomes. The combined treatment of TACE with an antiangiogenic agent seems to improve the outcome.[75]

A phase II RCT TACTICS investigated the benefit of TACE combined with sorafenib in unresectable liver cancer. This trial is the only RCT that demonstrated a better PFS in TACE plus sorafenib arm, 25.5 in TACE and sorafenib, versus 13.5 months in TACE and placebo ($p = 0.006$).[76]

LRTs increase tumor immune response by inducing inflammation in the tumor. An increase in tumor-associated antigens increases the infiltration of cytotoxic T-cells. In some preclinical studies, increase in antitumor immune response occurred with the combination of LRT and an immune checkpoint inhibitor. In a recent clinical study, combined anti-CTLA-4 antibody (tremelimumab) with TACE or thermal ablation in patients with advanced HCC who had failed sorafenib demonstrated a 26.3% partial response rate. The median TTP and OS were 7.4 and 12.3 months, respectively. Moreover, the lesions treated by LRTs showed infiltration of CD3+ and CD8+ cells. The activation of the immune response by LRTs also led to a reduction in viral load in 86.7% of HCV patients.[77–81] Several ongoing trials evaluating the combination of LRTs and immune checkpoint inhibitors are listed in ►**Table 3**.

Conclusion and Future Trends

Transarterial embolization with novel systemic agents such as sunitinib has shown promising results in preclinical studies. Sunitinib is completely released as opposed to doxorubicin of which only 27% is offloaded.[82] Intraarterial sunitinib injection paused the tumor growth in an in vivo

Table 3 Ongoing trials combining LRT and immunotherapy in HCC

Study arms	Patient population	Study phase/size	Study identifier/name
Pembrolizumab +Y-90	Locally advanced, high-risk HCC	Early phase I/ 30	NCT03099564
Nivolumab + Y-90	Advanced hepatocellular carcinoma	Phase I/ 35	NCT02837029
Nivolumab + Y-90	Asians with advanced hepatocellular carcinoma	Phase II/ 40	NCT03033446
Nivolumab + SIRT Y-90	Unresectable hepatocellular carcinoma	Phase II/ 40	NCT03380130
SBRT + nivolumab or ipilimumab	Unresectable hepatocellular carcinoma	Phase I/ 50	NCT03203304
Nivolumab + TACE	Intermediate-stage hepatocellular carcinoma	Phase II/ 49	NCT03572582
Nivolumab + TACE	Intermediate-stage hepatocellular carcinoma	Phase II/III 40	NCT04268888
Durvalumab ± Bevacizumab + TACE	Locoregional hepatocellular carcinoma not amenable to curative therapy	Phase III/ 600	NCT03778957 EMERALD-1
Nivolumab + DEB-TACE	Advanced hepatocellular carcinoma—BCLC B	Early phase I/ 14	NCT03143270
Durvalumab + tremelimumab with TACE, RFA, or cryoablation	Locally advanced, advanced HCC	Phase II/ 40	NCT03380130

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; DEB-TACE, drug-eluting bead transarterial chemoembolization; HCC, hepatocellular carcinoma; LRT, locoregional therapy; RFA, radiofrequency ablation.

study while oral sunitinib showed >1000% tumor growth and bland bead embolization a 42% tumor growth. Intra-arterial sunitinib injection paused the tumor growth in an in vivo study, while oral sunitinib and bland bead embolization showed a 1,583 and 42% tumor growth.[82,83]

Considering the IMbrave 150 trial, local delivery of bevacizumab was explored after loading it on Poly (ethylene glycol) methacrylate (PEGMA) microspheres. The in vitro experiments showed 83 to 92% release after 6 hours and completely released in 24 hours.[84]

In recent years, several systemic targeted therapies and immunotherapies have become available for advanced HCC. Although some LRTs were explored, the RCT pertaining to TARE did not meet their endpoints of improved OS. However, a meta-analysis demonstrated that TARE was equivalent to sorafenib with less adverse events. In the future, combination of local delivery of immunotherapy should be explored as well as transarterial embolization with targeted therapies in combination with systemic agents.

Conflict of Interest
None declared.

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