Novel Combination Approaches to Locoregional and Systemic Therapy in the Management of Primary and Metastatic Liver Tumors

Michelle Dai[1,2]; Bryan-Clement Y. Tiu, MPH[3*]; Millennie Chen[4*]; Caitlyn Sing[3]; Vinay Sharma[3]; Juan Pablo Hoyos[3]; Riley Scherr[3]; Wei Ju Lin, MS[2]; Joseph A. Breuer, MD, MSc[3]; Farshid Dayyani, MD, PhD[5]; David Imagawa, MD, PhD[6]; and Nadine Abi-Jaoudeh, MD[7]

[1]Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania

[2]College of Osteopathic Medicine, Touro University Nevada, Henderson, Nevada

[3]University of California, Irvine School of Medicine, Irvine, California

[4]University of California, Riverside School of Medicine, Riverside, California

[5]Division of Hematology/Oncology, Department of Medicine, University of California Irvine, Orange, California

[6]Department of Surgery, University of California Irvine, Orange, California

[7]Department of Radiological Sciences, University of California Irvine, Orange, California

Mr Tiu and Ms Chen contributed equally to this work.

Corresponding author:
Michelle Dai
Email: mmdai@sas.upenn.edu
Tel: (831) 586-0080

Abstract: Several pathways and mutations must develop or be in place for the onset of cancer. Therefore, therapies should ideally target as many of these pathways as possible to improve outcomes. Combining several agents has proven to be more effective than the use of monotherapy in the treatment of renal cell carcinoma, hepatocellular carcinoma, and other cancers. Combination therapy can also include locoregional therapies such as ablation and embolization with systemic agents for synergistic effects. This review article discusses the current literature and clinical trials covering these multifactorial combination therapies in primary and metastatic liver tumors.

Keywords
Ablation, hepatocellular carcinoma, immune checkpoint inhibitor, radioembolization, transarterial chemoembolization, tyrosine kinase inhibitor

Introduction

Primary liver cancer is the sixth most diagnosed cancer and the third leading cause of cancer death globally.[1] The incidence of hepatocellular carcinoma (HCC) is on the rise. Surgery (resection or transplant) and ablation are the only curative treatments for primary liver cancer,

but most patients are not suitable candidates. Additionally, the liver is the most common site of metastasis, particularly for colorectal carcinoma (CRC). When CRC is localized or regional, the 5-year survival rates are 89.9% and 71.7%, respectively. When CRC is distant or of unknown metastatic status, the 5-year survival rates drop to 13.8% and 35%, respectively.[2] More than 700,000 patients in the United States are affected by either primary or metastatic liver tumors every year.[3] The patient prognosis worsens and the response to systemic therapies is reduced in those with liver involvement. Immunotherapy has demonstrated improved overall survival (OS) in several cancer types, but has been disappointing in solid organ tumors, especially those with liver involvement. Image-guided locoregional therapies are effective in controlling liver disease. Moreover, percutaneous ablations and embolizations have an immunomodulatory effect but fail to elicit a significant antitumor response on their own. Combination locoregional and systemic therapies can theoretically have synergistic effects. This review article focuses on combination locoregional and systemic therapies in primary liver tumors and in metastatic liver disease with gastrointestinal cancer (see Table and see eTable at www.hematologyandoncology.net).

Novel Combination Approaches in the Management of Primary Liver Tumors

Until 2017, the tyrosine kinase inhibitor (TKI) sorafenib, which has activity against RAF kinase, platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR), was the only approved systemic agent for advanced HCC. Approval was based on a 2.7-month improvement in OS.[4] In the past 5 years, several regimens have demonstrated significant improvement in OS of advanced HCC. In the global IMbrave150 phase 3 trial, 501 patients with unresectable HCC who were not previously treated with systemic therapies were randomized in a 2:1 ratio to receive either a combination of the anti–programmed death ligand 1 (anti–PD-L1) agent atezolizumab (Tecentriq, Genentech) and the anti–vascular endothelial growth factor (anti-VEGF) antibody bevacizumab, or standard-of-care treatment with sorafenib alone. Combination therapy with atezolizumab and bevacizumab vs sorafenib at primary analysis showed improved OS (stratified hazard ratio [HR] for death, 0.58; 95% CI, 0.42-0.79; P<.001), median progression-free survival (PFS; 6.8 vs 4.3 months; stratified HR for progression or death, 0.59; 95% CI, 0.47-0.76; P<.001), and overall response rate (ORR; 27.3% vs 11.9%, P<.001).[5] Updated data 12 months following primary analysis showed similar results, with median OS and PFS significantly higher in the combination arm than with sorafenib (19.2 vs 13.4 months; HR, 0.66; P<.001 and 6.9 vs 4.3 months; HR, 0.65; P<.001).[6] Results of the IMbrave150 trial led to a paradigm shift in the treatment of advanced HCC, and combination therapy with atezolizumab and bevacizumab replaced sorafenib as the preferred first-line treatment for advanced HCC.[7]

In the global phase 3 HIMALAYA trial, a combination of single-dose tremelimumab plus regular-interval durvalumab (Imfinzi, AstraZeneca), known as STRIDE, was evaluated against sorafenib as a first-line therapy in patients with unresectable HCC who were not previously treated with systemic therapies.[8] Combination therapy with STRIDE led to significant improvement in median OS and OS rate at 36 months when compared with sorafenib (16.43 vs 13.77 months and 30.7% vs 20.2%, respectively). More recently, survival data at 48 months were presented for the STRIDE regimen.[9] This was the first study in advanced HCC to show long-term survival with systemic therapy alone. There was no significant difference in median PFS between treatment groups. However, it is well established that PFS is not an appropriate surrogate outcome for immunotherapy regimens because the benefits of immunotherapy are most evident in the 'tail' of long-term survivors. Thus, the STRIDE regimen might provide an alternative first-line treatment option with a wider range of eligibility compared with IMbrave150 (additionally including patients who are not bevacizumab-eligible). Both the IMbrave150 and HIMALAYA trials led to a paradigm shift in the first-line treatment approach for advanced HCC from sorafenib to immunotherapy-based combinations.

Other immunotherapy-based combinations were also explored. The phase 3 COSMIC-312 trial evaluated atezolizumab and cabozantinib (Cabometyx, Exelixis), a TKI targeting VEGFR and mesenchymal-epithelial transition factor (MET), vs sorafenib. This combination did not demonstrate an improvement in OS (15.4 vs 15.5 months),[10] despite a significant improvement in PFS. The phase 1/2 randomized clinical trial CheckMate 040 aimed to assess the efficacy and safety of the combination of nivolumab (Opdivo, Bristol Myers Squibb) and ipilimumab (Yervoy, Bristol Myers Squibb) in patients with treatment-naive advanced HCC and those who were previously treated with sorafenib.[11] The treatment arm consisting of nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg demonstrated an ORR of 32% (95% CI, 20%-47%) and a median OS of 22.8 months. The adverse events identified were consistent with those of previous studies investigating nivolumab and ipilimumab in other tumor types. Most adverse events resolved by following established treatment algorithms. Based on these results, the combination received accelerated

Table. Therapeutics and Mechanisms Used in Treatment of Primary Liver Tumors and Metastatic Colorectal Cancer

Therapeutic class	Mechanism	Agents or techniques
Immune checkpoint inhibitors	Inhibition of cancer-induced immune checkpoint activation (immunological escape)	Atezolizumab (anti–PD-L1) Axatilimab/SNDX-6352 (CSF-1R blocker) Durvalumab (anti–PD-L1) Ipilimumab (anti–CTLA-4) Nivolumab (anti–PD-1) Pembrolizumab (anti–PD-1) Sintilimab (anti–PD-1) Tremelimumab (anti–CTLA-4)
Tyrosine kinase inhibitors	Inhibition of signal transduction of growth factors via blocking of tyrosine kinases	Brivanib (VEGFR/FGFR) Cabozantinib (VEGFR/MET) Lenvatinib (VEGF/FGF) Orantinib (multikinase) Sorafenib (VEGFR)
Other monoclonal antibodies	Monoclonal antibodies targeting growth factors or markers associated with tumor growth	Bevacizumab (anti-VEGF) Cetuximab (anti-EGFR) Codrituzumab (anti-GPC3) Ramucirumab (anti-VEGFR2)
Other chemotherapeutics	Inhibition of uncontrolled growth and proliferation of tumors	Doxorubicin (anthracycline) FUdR Irinotecan (TopI inhibitor) M9241/NHS-IL12 (IL-12 heterodimer immunocytokine) SD-101 (TLR9 agonist) Tirapazamine (hypoxia-activated chemotherapeutic)
Adoptive cell therapy	Immunotherapy using T cells with genetically engineered TCRs or CARs to enhance cancer cell cytotoxicity	CART-133 (chimeric CD133-directed T cells) CT0180 (chimeric anti-GPC3 T cell) ET140202 (AFP- and GPC3-guided TCR T cell)
Radiation therapy	Delivery of local internal radiation to tumors	Brachytherapy Y90 (radioembolization)
Ablation techniques	Tissue necrosis by localized temperature-induced cytotoxicity	Cryoablation MWA RFA
Embolization techniques	Tumor ischemia induced by selective angiographic occlusion of arterial blood supply	cTACE DEB-TACE TACE TAE TATE

AFP, alpha-fetoprotein; CAR, chimeric antigen receptor T cell; CSF-1R, colony-stimulating factor 1 receptor; cTACE, conventional transarterial chemoembolization; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; DEB-TACE, drug-eluting bead transarterial chemoembolization; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FUdR, fluorodeoxyuridine; GPC3, glypican 3; IL-12, interleukin 12; MET, mesenchymal-epithelial transition factor; MWA, microwave ablation; PD-1, programmed death 1; PD-L1, programmed death ligand 1; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TAE, transarterial embolization; TATE, transarterial tirapazamine embolization; TCR, T-cell receptor; TLR9, Toll-like receptor 9; TopI, DNA topoisomerase I; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; Y90, yttrium-90.

approval for second-line therapy for HCC. Long-term follow-up of at least 44 months showed that the median OS remained at 22.2 months for this treatment arm, with durable responses and no new safety signals since primary analysis.[12]

CheckMate 9DW is a phase 3 trial evaluating

nivolumab and ipilimumab as first-line treatment compared with standard-of-care sorafenib or lenvatinib (Lenvima, Eisai) in patients with advanced HCC.[13]

The developments of systemic therapies and improvements in locoregional therapies enable the exploration of novel combinations with potential synergistic effects to improve OS.

Combination Therapy in Early-Stage HCC

Surgery and locoregional therapies are staples in the care of patients with early and intermediate HCC, but both approaches have shortfalls. Recurrence following surgery and ablation remains unacceptably high. An ongoing phase 2 clinical trial (N=30) is investigating the peri-interventional administration of pembrolizumab (Keytruda, Merck) with local ablation through radiofrequency ablation (RFA), microwave ablation (MWA), brachytherapy, or a combination of transarterial chemoembolization (TACE) plus RFA, MWA, or brachytherapy.[14,15] Combination with the anti–PD-1 antibody pembrolizumab aims to inhibit the tumor's ability to overcome adaptive immune responses to increased antigen release following tumor ablation. Early clinical data have suggested that the treatment regimen displays an acceptable safety profile. Another ongoing study is investigating the supplementation of local ablation with another anti–PD-1 antibody, sintilimab, in patients with unresectable HCC.[16] The 45-patient phase 1 clinical study aims to evaluate the efficacy and safety of MWA combined with TACE followed by an intravenous sintilimab infusion beginning 3 to 7 days after the first locoregional therapy.

The IMbrave050 and EMERALD-2 trials examined systemic adjuvant therapies after ablation or surgery in early HCC.[17,18] Preliminary results of IMbrave050 were reported in 2023.[17] This phase 3 trial enrolled patients who were at high risk for recurrence following ablation or surgery for HCC. They were randomized in a 1:1 ratio to receive atezolizumab and bevacizumab every 3 weeks for 1 year vs surveillance. The trial met its endpoint of prolonged recurrence-free survival for the experimental group, although the OS results are still pending. Based on the preliminary data, it is possible that the OS endpoint will not be met. Some claim that this is because of crossover; but if an eventual transition to systemic therapies down the line confers similar advantages, is that not an argument to stagger therapies? Locoregional therapies are very effective where curative options fail. Moreover, recurrence after treatment with atezolizumab and bevacizumab may select for more aggressive tumors, with a paucity of effective systemic therapeutic options after atezolizumab and bevacizumab regimen failure.

Combination Therapies in Intermediate-Stage HCC

Multiple trials have attempted to compare the effects of combination therapies with TACE in patients with unresectable HCC. Initially, TACE was studied in combination with VEGFR inhibitors, such as sorafenib. The combination was theoretically very appealing. One major pitfall of TACE is the lack of ischemia and ensuing hypoxia, with an increase in levels of VEGF and hypoxia-inducible factor 1 alpha (HIF1A) noted after TACE.[19-21] Moreover, the increase in VEGF and HIF1A is correlated with prognosis and response. Therefore, combining TACE with an anti-VEGF agent was hypothesized to counteract the negative effects of hypoxia. Several trials attempted the combination of an anti-VEGF agent with TACE, but the initial trials all failed to meet their endpoints.

The SPACE trial, a phase 2 randomized, double-blind, placebo-controlled study evaluating TACE plus sorafenib, showed no survival benefit vs the use of TACE alone.[22] Failure of this study may have been attributed to the short course of sorafenib, resulting in an inability to produce a meaningful effect.

TACE-2 was a phase 3 trial comparing continuous sorafenib plus drug-eluting bead TACE (DEB-TACE) vs placebo plus DEB-TACE. Results showed no difference in PFS or OS between the combination therapy of sorafenib and placebo.[23] The reason for the trial was attributed to the evaluation of response and progression per modified Response Evaluation Criteria in Solid Tumors (RECIST) and RECIST 1.1. Another study evaluating the combination of TACE plus sorafenib was stopped prematurely owing to safety concerns. These concerns were reported based on the greater number and severity of adverse events, possibly related to an aggressive and continuous sorafenib schedule with higher doses during DEB-TACE.[24] One study evaluating the tolerability and efficacy of TACE plus sorafenib in Asian patients achieved a median PFS of 384 days (95% CI, 322-469) and a time to progression of 415 days (95% CI, 338-491); however, a significant median OS was not achieved.[25] The post-TACE trial evaluated the administration of sorafenib vs placebo in patients who had a tumor reduction of more than 25% within 1 to 3 months after treatment with TACE, and showed no difference in median time to progression between the sorafenib arm (5.4 months) and the control arm (3.7 months).[26]

One explanation for the trial's failure was the prolonged time between TACE and the initiation of the TKI. Other TKIs were studied with TACE, including adjunct brivanib plus TACE vs TACE alone in patients with intermediate-stage HCC.[27] This was a multinational, randomized, double-blind, placebo-controlled, phase 3 study

that included 502 patients (brivanib, 249; placebo, 253) and did not meet its OS objectives (26.4 vs 26.1 months; *P*=.528). Additionally, this study was terminated 2 years earlier than originally planned, when 2 other similar phase 3 studies (BRISK-FL and BRISK-PS) failed to meet OS objectives.[28,29] A trial of orantinib produced similar results. The ORIENTAL trial, a randomized, double-blind, placebo-controlled phase 3 study, included 888 patients, with 444 receiving orantinib and 444 receiving a placebo following conventional TACE. No improvement in OS was shown with the combination therapy vs placebo.[30]

The TACTICS trial, a multicenter, phase 2, randomized controlled trial, included 156 patients, with 80 receiving TACE plus sorafenib and 76 receiving TACE alone. This trial provided TACE on demand (if a lesion was present) with sorafenib initiated before TACE, and maintenance therapy after TACE with a dose reduction option in case of side effects. The primary endpoint of PFS was defined as the time to TACE failure and not per modified RECIST/RECIST 1.1. The TACTICS trial met its endpoint and showed a significantly prolonged median PFS for patients treated with TACE plus sorafenib vs TACE alone (25.3 vs 13.5 months; *P*<.01).[31]

IMMUTACE, a single-arm, phase 2, open-label study, evaluated TACE combined with nivolumab in patients with intermediate-stage HCC. This study reported an ORR of 71.4% (95% CI, 56.7%-83.4%), supporting the initiation of the ongoing phase 3 TACE-3 and CheckMate 74W trials.[32,33] CheckMate 74W is an ongoing phase 3 study evaluating the safety and tolerability of nivolumab with and without ipilimumab in combination with TACE vs TACE alone in patients with intermediate liver cancer. This randomized 26-patient study will be assessing time to TACE progression (TTTP) via blinded independent central review (BICR), and will also evaluate OS, PFS, and event-free survival, with an anticipated primary completion date of December 2023.[34] Another similar study that is currently being performed, under the name TACE-3, is looking at OS and TTTP in 522 patients with intermediate-stage HCC who are being randomly assigned to receive TACE or transarterial embolization (TAE) vs TACE/TAE and nivolumab at 480 mg intravenously.[35] The addition of TKIs and immunotherapies with TACE are being explored. In fact, a 40-patient, single-arm study is comparing the addition of cabozantinib to ipilimumab/nivolumab plus TACE for patients with unresectable HCC.[36] Another ongoing multicenter randomized controlled trial of 342 patients is comparing TACE combined with atezolizumab and bevacizumab vs TACE alone in patients with untreated HCC, and will assess TACE PFS and OS as primary outcomes. This actively recruiting study has an estimated primary completion date in February 2029.[37] The LEAP-012 trial consists of a 450-patient randomized trial with the primary outcome being PFS per RECIST 1.1 and OS when comparing pembrolizumab plus lenvatinib in combination with TACE vs the placebo plus TACE.[38] Results from all these previously mentioned promising approaches are highly anticipated.

Two ongoing phase 3 clinical trials are evaluating durvalumab in combination with other systemic and locoregional therapies.[39,40] The 724-patient, randomized EMERALD-1 trial is evaluating the efficacy of a durvalumab and bevacizumab combination with TACE in patients with locoregional HCC.[40] The primary objective of this study is to compare the PFS of the combination vs TACE alone. The global EMERALD-3 study, which is actively recruiting patients, is evaluating the STRIDE regimen (used in the HIMALAYA trial)[8] with the first-line therapy lenvatinib administered concurrently with TACE.[39,41] It aims to determine the PFS and OS of TACE plus STRIDE with and without lenvatinib compared with TACE alone in patients with locoregional HCC not amenable to curative therapy.

The addition of a greater number of systemic therapies and locoregional therapies is accompanied by greater adverse events, decreased tolerability, and lower patient adherence. Local delivery of systemic agents is being actively studied. Doxorubicin is the most widely used in TACE. It is one of the agents in conventional TACE and the most common agent in DEB-TACE.[42,43] It is not effective against HCC.[44] Local delivery of the anti-VEGF TKI inhibitor sorafenib was explored to maximize local effects while preventing the known adverse events, which occur in 20% of patients. Local delivery of lyophilized form of sorafenib with ethiodized oil (Lipiodol) demonstrated that most of the drug still circulated systemically.[45-47] Novel beads have been developed to load sorafenib. More interestingly, another group developed a new liposomal formulation that enables loading of any drug including lipophilic neutral drugs on commercially available beads. They tested the formulation in the VX2 rabbit model and demonstrated that loading of sorafenib and regorafenib (Stivarga, Bayer HealthCare) was feasible because the drugs eluted locally without systemic escape.[48] As these discoveries progress into clinical studies, combinations of TACE with a locally delivered TKI plus systemic agents will become commonplace.

Several new agents are also being explored. For example, the hypoxia-activated agent tirapazamine has been studied during transarterial embolization with very promising results in a phase 1 dose escalation trial.[49] Transarterial tirapazamine embolization (TATE) showed encouraging results, with a complete response rate of 60% and an ORR of 84% per modified RECIST, warranting future studies. Moreover, another phase 1

study conducted in Asia reproduced these results, with an improved response rate even in patients whose disease failed to respond to TACE.[50]

Combination Therapies in the Advanced Setting

In the past, locoregional therapies did not play a significant role in advanced HCC. Because disease was usually more widespread, locoregional therapies were deemed unnecessary. However, radioembolization for diffuse liver-dominant disease was still utilized, with disappointing results from combination trials. The SORAMIC trial randomized patients with unresectable advanced HCC to sorafenib plus selective internal radiation therapy (SIRT) with yttrium-90 (Y90)-loaded resin microspheres (n=216) vs sorafenib alone (n=208).[51] The trial identified no significant difference in median OS between the arms (12.1 vs 11.4 months; *P*=.9529).

With the advent of immunotherapies and improved systemic therapies, the addition of locoregional therapies in the advanced or even metastatic setting is being reexamined. The randomized, phase 3 LAUNCH trial showed that combination therapy with TACE plus lenvatinib in 170 patients showed improved ORR (54.1% vs 25.0%; *P*<.001) and prolonged OS (median OS, 17.8 vs 11.5 months) when compared with 168 patients treated with lenvatinib alone.[52]

Immunotherapies, although very effective against some tumors, demonstrate disappointing results in cold or excluded tumors. Locoregional therapies are known to induce an immunomodulatory response that is too small by itself to have an effect; however, when combined with immunotherapy, there is potential for a synergistic response.

Percutaneous ablation has been shown to possess immunomodulatory effects even in immunosuppressive cancers such as HCC,[53-56] colorectal carcinoma,[57,58] and pancreatic adenocarcinoma, which is generally considered a very cold tumor.[59] Thermal ablation results in necrosis and induces local inflammation with T-cell infiltration.[53,54,59-63] Moreover, tumor antigens become available, leading to the initiation of a systemic immune response.[53,64,65] A 2016 study in patients with advanced HCC who received tremelimumab with subtotal ablation (defined as complete ablation of 1 lesion while others were not treated) found an increase in peritumoral infiltration of CD8+ cells in postablation biopsy specimens compared with preablation, postimmunotherapy specimens.[54]

TACE also has demonstrated an immunomodulatory response. TACE has clinically been associated with an increase in circulating GPC3-specific cytotoxic T lymphocytes, interleukin 6 (IL-6), CD4+ cells, the CD4+/CD8+ ratio, and natural killer cells. It also has been shown to decrease regulatory T cells, which are known to have an inhibitory effect on the immune response. These effects do not result in an immune reaction on their own but may result in a widespread immune response to the tumor when combined with immunotherapy. In an ongoing phase 2a clinical trial, the PD-1 inhibitor nivolumab is being administered in combination with TATE in patients with metastatic HCC with disease progression while on a prior immune checkpoint inhibitor.[66] The primary aim of the study is to evaluate whether TATE-induced tumor necrosis can activate host immune responses and synergistically enhance the effects of immune checkpoint inhibition. Results of these studies are forthcoming.

The REACH-2 trial was the first positive phase 3 study using the anti-VEGFR2 agent ramucirumab (Cyramza, Lilly) in a biomarker-selected population with advanced HCC.[67] Subgroup analysis showed significant OS in groups with baseline alpha-fetoprotein (AFP) levels greater than 400 ng/mL (HR, 0.697; 95% CI, 0.520-0.934; *P*=.0156). Biomarkers such as glypican-3 (GPC3) can also serve as a target in novel molecular therapeutics. The anti–glypican-3 monoclonal antibody codrituzumab was used in combination with atezolizumab in a phase 1 study involving patients with advanced HCC that was refractory to prior treatments.[68] This combination was well-tolerated and showed antitumor activity in patients with high GPC3 expression.

Gene engineering technology in adoptive cell therapies (ACT) has allowed for synthetic receptor expression on T cells, such as chimeric antigen receptor (CAR) T cells and novel T-cell receptors (TCRs). Many clinical trials are in the early phase exploring the safety of potential targets for CAR T-cell therapy.[69] In a phase 2 study, researchers examined the use of CD133-directed CAR T cells in patients with refractory advanced HCC.[70] Among 21 patients, 1 showed a partial response, 14 maintained stable disease, and 6 experienced disease progression. The median OS was 12 months and the median PFS was 6.8 months. Another early-phase study over intermediate HCC patients failing first- or second-line therapy is using a modified TCR targeting the AFP/MHC complex with GPC3-guided costimulation (ET140202), either in combination with sorafenib or TAE, or alone.[71] Currently, cell therapies for HCC are very early in development, and none have yet to be approved.

Moreover, local delivery of systemic agents is another area of active research. Loading TKIs such as sorafenib, regorafenib, lenvatinib, or an anti-VEGF agent such as bevacizumab on embolic agents would enable therapeutic activity while minimizing the side effects caused by systemic administration. This has been successfully performed in rabbits and is being studied in

large animals before transitioning to the clinic. Moreover, preclinical studies are examining immune-mediated drugs loaded on to drug-eluting microspheres for transarterial embolization.

Recent endeavors in genomics found that novel locus rs2242652(A) in telomerase reverse transcriptase (TERT) is associated with a decreased risk of HCC at genome-wide significance.[72] It is possible that future therapeutics could enhance the expression of this gene. However, the treatment implications of this require further study at this time.

Metabolic dysfunction–associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH), can be accelerated into HCC (MASH-HCC) through chronic inflammation and hepatocellular injury, mediated by an increased subset of CD8+, PD-1+ T cells.[73,74] It differs from other etiologies of HCC because of lower surveillance rates, thus favoring the development of HCC and reducing the efficacy of immune checkpoint inhibitors.[75,76] Resection and liver transplant have shown increased survival rates in MASH-HCC,[77,78] whereas ablation, TACE, and TARE have shown no differences in OS.[79-81]

Novel Combination Therapies for Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) is less common than HCC. Its prognosis is poor, especially in more advanced settings. Radioembolization with systemic chemotherapies has been shown to be efficacious for intrahepatic cholangiocarcinoma. Other trials have attempted to study locoregional therapies with systemic agents in ICC. Unfortunately, several trials have been terminated or suspended without results.[82-85] However, a few trials are underway, and their results are highly anticipated.

The phase 1 PERIO trial is exploring pressure enabled delivery of SD-101 with checkpoint blockade for primary liver tumors.[86] SD-101 is a Toll-like receptor 9 (TLR9) agonist. It binds to the TLR9 found on immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs). TLR9 activation is hypothesized to promote antitumor T-cell function by priming the immune cells.[87-89] In this trial, 2 cycles of SD-101 will be administered locally alone, combined with pembrolizumab in a second cohort, or combined with ipilimumab/nivolumab in another cohort. Each cycle of SD-101 consists of intrahepatic arterial infusion of SD-101 once a week for 3 consecutive weeks, with 1 month between cycles.

Axatilimab (SDX-6352) is a CSF-1R blocker. CSF-1R is believed to activate donor-derived pro-inflammatory macrophages, which have a role in graft-versus-host disease. In a planned single-arm phase 2 trial, axatilimab and durvalumab will be combined with TACE or radioembolization in patients with unresectable intrahepatic cholangiocarcinoma confined to the liver.[90] The study will examine safety and tolerability as well as ORR.

Selective biomarkers have also shown potential in ICC. A recent discovery found that YC-1, a small molecule specifically active in HCC and ICC, could be targeted through the sulfotransferase enzyme SULT1A1.[91] Sulfonation of YC-1 opens new potential for selective targeting of SULT1A1, which represents a novel therapeutic class.

Novel Combination Approaches in the Management of Liver Tumors in Metastatic Colorectal Cancer

Colorectal adenocarcinoma is the most common metastatic lesion found in the liver. The current gold standard for colorectal liver metastases is chemotherapy. For patients with oligometastatic disease, the gold standard is surgery for surgical candidates and ablation for nonsurgical candidates.[92] Transarterial infusion and embolotherapy are also part of the guidelines.

TARE for Liver Metastases in Colorectal Cancer

Y90 radioembolization is considered an optional locoregional therapy for colorectal liver metastases that are inoperable and/or refractory to systemic therapy alone. One of the first prospective studies to describe the use of Y90 embolization for colorectal liver metastases refractory to systemic therapy alone was by Hendlisz and colleagues, in which 44 patients who were randomly assigned to receive 5-fluorouracil (5-FU) alone or in combination with Y90 radioembolization were assessed for time to local progression (TTLP) and OS. It was demonstrated that the average TTLP was 5.5 months for the Y90/5-FU arm compared with 2.5 months for the 5-FU–alone arm. The median OS was 10.0 vs 7.3 months, respectively.[93]

Several trials showed that Y90 radioembolization improved OS and PFS in salvage therapy. However, 3 large prospective randomized trials (FOXFIRE, SIRFLOX, and FOXFIRE-Global) failed to demonstrate an improvement of OS in patients treated with Y90 radioembolization as first-line therapy. Several criticisms were leveled at the trials, including the inclusion of a significant portion of patients with extrahepatic disease whose primary tumors were in place. Nonetheless, Y90 radioembolization is not recommended in the first line as a result of these trials. In the prospective open-label phase 3 EPOCH trial, Mulcahy and colleagues affirmed the impact of Y90 radioembolization in combination with second-line systemic chemotherapy.[94] The HR for PFS was 0.69 (95% CI, 0.54-0.88; 1-sided P=.0013), with

a median PFS of 8.0 months (95% CI, 7.2-9.2) for the combination group and 7.2 months (95% CI, 5.7-7.6) for the chemotherapy-only group. The HR for hepatic PFS was 0.59 (95% CI, 0.46-0.77; 1-sided *P*<.0001), with a median hepatic PFS of 9.1 months (95% CI, 7.8-9.7) and 7.2 months (95% CI, 5.7-7.6), respectively. TARE with chemotherapy also showed an increased response, with rates of 34.0% (95% CI, 28.0-40.5) and 21.1% (95% CI, 16.2-27.1; 1-sided *P*=.0019) for the TARE and chemotherapy groups, respectively. Unfortunately, TARE with chemotherapy failed to increase OS, with a median OS of 14.0 months (95% CI, 11.8-15.5), compared with 14.4 months (95% CI, 12.8-16.4; 1-sided *P*=.7229) for the chemotherapy-only group.

TACE for Liver Metastases in Colorectal Cancer

DEB-TACE has been used in the treatment of unresectable colorectal liver metastases following the failure of standard systemic chemotherapy. In a prospective, multi-institutional, single-arm study by Martin and colleagues, 55 patients underwent DEB-TACE with irinotecan-loaded beads after the failure of standard therapies.[95] The median disease-free survival (DFS) and OS were 247 and 343 days, respectively. The presence of extrahepatic disease (*P*=.001) and the extent of prior chemotherapy (*P*=.007) were significant predictors of OS. Tumor response (defined as complete response, partial response, or stable disease by the European Association for the Study of the Liver criteria) was seen in 89% of patients at 3 months and 54% of patients at 12 months, suggesting that DEB-TACE alone is effective for the treatment of unresectable, refractory colorectal liver metastases.

As an EGFR antagonist, the monoclonal antibody cetuximab induces increased tumor cell apoptosis and is used in combination with irinotecan chemotherapy owing to its differing toxicity profile as compared with chemotherapy. In a study conducted by Fiorentini and colleagues, it was concluded that cetuximab in association with irinotecan-loaded drug-eluting beads (DEBIRITUX) is an efficacious and promising second-line treatment of unresectable colorectal liver metastases.[96] After 3 months of therapy, the ORR was 50%, the median PFS was 9.8 months, and the OS was 20.4 months, with 75.0% and 39.1% of patients alive at 1 and 2 years, respectively.

In a prospective study, Fiorentini and colleagues compared the tumor response, OS, and PFS of patients with colorectal liver metastases treated with either TACE alone or a combination of bevacizumab and TACE.[97] It was found that treatment with TACE plus bevacizumab may improve tumor responses and delay disease progression in unresectable colorectal liver metastases, as TACE plus bevacizumab resulted in a better disease control rate at 1 month (100% vs 84%; *P*<.05) and 3 months (96% vs 76%; *P*<.001). However, there was no statistically significant difference in OS observed between the 2 treatment groups (18 months [range, 7-16 months] for TACE/bevacizumab; 15.8 months [range, 5-52 months] for TACE), and neither did PFS differ significantly between the 2 arms at 13 months (range, 3-24) vs 11.15 months (range, 4-51).

Certain combination trials are exploring transarterial locoregional therapies with systemic therapies in patients with metastatic colorectal cancer that has failed to respond to multiple lines of chemotherapy. Existing first-line chemotherapies produce a median OS of 30 months from a diagnosis of metastasis. However, as therapy inevitably fails and the disease progresses, the number of responders and the duration of response shortens. Patients with colorectal liver metastases whose disease has failed to respond to at least 2 lines of therapy have a median PFS of 2 months and an OS of 6 to 7 months, with a response rate of less than 2%.[98,99] In the trial, patients whose disease has failed to respond to more than 2 lines of chemotherapy are randomized to either TATE and pembrolizumab or standard-of-care systemic therapy.[100] The rationale of the trial is to use locoregional therapies as a vaccine to boost immunotherapy.

Another trial is exploring the local delivery of chemotherapies, specifically a mixture of floxuridine and dexamethasone, through a hepatic artery infusion pump with systemic therapy and M9241 for colorectal carcinoma and intrahepatic cholangiocarcinoma.[101] M9241 is an investigational immunocytokine composed of two IL-12 heterodimers fused to a monoclonal antibody targeting DNA in necrotic tumor regions. M9241 enables the targeted delivery of IL-12 into tumor tissue. IL-12 is a proinflammatory cytokine that regulates adaptive immunity. It has been shown to be safe in prostate cancer and some other solid cancers.[102] The trial's primary endpoint is ORR.

Conclusion

In recent years, exciting developments in novel combination approaches have emerged in the management of both primary liver cancers (including both HCC and ICC) and colorectal liver metastases. Combinations of locoregional and systemic treatment modalities have focused on enhancing immune response and tumor control. Optimizing synergistic actions from systemic therapies combined with both well-established locoregional therapies such as TACE and Y90 as well as novel approaches to locoregional therapy (ie, arterially-directed immunotherapy) has demonstrated improved outcomes over monotherapies and shows promise for the treatment of liver cancer. It has been shown that dual and triplet

therapy is more effective than monotherapy in primary and metastatic liver cancer. However, we know from the cardiology literature that polypharmacy is correlated with lower adherence, and the side effects of targeted therapy are known to be more severe and numerous than those of blood pressure medications. In light of this, local delivery of immunotherapy and targeted therapy can maximize treatment benefits without the cumulative or additive side effects associated with systemic delivery. Therefore, combination therapies involving numerous strategies are the most likely avenue for the best outcomes.

Disclosures

Dr Dayyani has received research grants (to institution) from AstraZeneca, Bristol Myers Squibb, Merck, Genentech/Roche, Taiho, Exelixis, Trishula, Leap Therapeutics; has served on the speakers bureau of Amgen, Eisai, Ipsen, Exelixis, Sirtex, Deciphera, Ipsen, and Natera; and has consulted for Natera, QED, Eisai, Exelixis, and Genentech/Roche. Dr Imagawa has shares in and is part owner of Bruin Biosciences; is a consultant for Incyte; is a principal investigator on sponsored research by BeiGene and Eisai; and is on the speakers bureau of Eisai. Dr Abi-Jaoudeh has received research grants (to institution) from Philips Medical Systems, Teclison, Guerbet SA, Varian, Instylla HES, BlackSwan Vascular, Sirtex Medical, and AngioDynamics; has served on advisory boards with Genentech/F. Hoffmann-La Roche Ltd, QED, Eisai, The Lynx Group, AstraZeneca, and Pfizer; and has served as a consultant for Johnson & Johnson, Innova Vascular, Medtronic, and HistoSonics. The other authors have no conflicts of interest.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. SEER*Explorer: an interactive website for SEER cancer statistics. Surveillance Research Program, National Cancer Institute; April 19, 2023. https://seer.cancer.gov/statistics-network/explorer/. Updated June 8, 2023. Accessed July 10, 2023.
3. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17-48.
4. Xie B, Wang DH, Spechler SJ. Sorafenib for treatment of hepatocellular carcinoma: a systematic review. *Dig Dis Sci*. 2012;57(5):1122-1129.
5. Finn RS, Qin S, Ikeda M, et al; IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894-1905.
6. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76(4):862-873.
7. Chiang CL, Chan SK, Lee SF, Choi HC. First-line atezolizumab plus bevacizumab versus sorafenib in hepatocellular carcinoma: a cost-effectiveness analysis. *Cancers (Basel)*. 2021;13(5):931.
8. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid*. 2022;1(8).
9. Sangro B, Chan S, Kelley R, et al. Four-year overall survival update from the phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma [ESMO abstract SO-15]. *Ann Oncol*. 2023;34(1)(suppl).
10. Kelley RK, Rimassa L, Cheng AL, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(8):995-1008.
11. Yau T, Kang YK, Kim TY, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. *JAMA Oncol*. 2020;6(11):e204564.
12. El-Khoueiry AB, Yau T, Kang YK, et al. Nivolumab (NIVO) plus ipilimumab (IPI) combination therapy in patients (Pts) with advanced hepatocellular carcinoma (aHCC): long-term results from CheckMate 040 [ASCO abstract 269]. *J Clin Oncol*. 2021;39(3)(suppl).
13. ClinicalTrials.gov. A study of nivolumab in combination with ipilimumab in participants with advanced hepatocellular carcinoma (CheckMate 9DW). https://clinicaltrials.gov/ct2/show/NCT04039607. Identified: NCT04039607. Updated October 30, 2023. Accessed November 2, 2023.
14. ClinicalTrials.gov. IMMULAB - immunotherapy with pembrolizumab in combination with local ablation in hepatocellular carcinoma (HCC). https://clinicaltrials.gov/ct2/show/NCT03753659. Identifier: NCT03753659. Updated November 14, 2022. Accessed June 28, 2023.
15. Vogel A, Goetze TO, Hausner G, et al. The IMMULAB trial: a phase II trial of immunotherapy with pembrolizumab in combination with local ablation for patients with early stage hepatocellular carcinoma (HCC) [ASCO abstract TPS4159]. *J Clin Oncol*. 2021;39(15)(suppl).
16. ClinicalTrials.gov. Combined locoregional treatment with immunotherapy for unresectable HCC. https://clinicaltrials.gov/ct2/show/NCT04220944. Identifier: NCT04220944. Updated September 24, 2021. Accessed June 28, 2023.
17. Chow P, Chen M, Cheng AL, et al. IMbrave050: phase 3 study of adjuvant atezolizumab + bevacizumab versus active surveillance in patients with hepatocellular carcinoma (HCC) at high risk of disease recurrence following resection or ablation [AACR abstract CT003]. *Cancer Res*. 2023;83(8)(suppl).
18. ClinicalTrials.gov. Assess efficacy and safety of durvalumab alone or combined with bevacizumab in high risk of recurrence HCC patients after curative treatment (EMERALD-2). https://clinicaltrials.gov/ct2/show/NCT03847428. Identifier: NCT03847428. Updated September 13, 2023. Accessed November 2, 2023.
19. Baek JH, Jang JE, Kang CM, Chung HY, Kim ND, Kim KW. Hypoxia-induced VEGF enhances tumor survivability via suppression of serum deprivation-induced apoptosis. *Oncogene*. 2000;19(40):4621-4631.
20. Li X, Feng GS, Zheng CS, Zhuo CK, Liu X. Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level. *World J Gastroenterol*. 2004;10(19):2878-2882.
21. Wang B, Xu H, Gao ZQ, Ning HF, Sun YQ, Cao GW. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization. *Acta Radiol*. 2008;49(5):523-529.
22. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. *J Hepatol*. 2016;64(5):1090-1098.
23. Meyer T, Fox R, Ma YT, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2017;2(8):565-575.
24. Sieghart W, Pinter M, Reisegger M, et al. Conventional transarterial chemoembolisation in combination with sorafenib for patients with hepatocellular carcinoma: a pilot study. *Eur Radiol*. 2012;22(6):1214-1223.
25. Chao Y, Chung YH, Han G, et al. The combination of transcatheter arterial chemoembolization and sorafenib is well tolerated and effective in Asian patients with hepatocellular carcinoma: final results of the START trial. *Int J Cancer*. 2015;136(6):1458-1467.
26. Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer*. 2011;47(14):2117-2127.
27. Kudo M, Han G, Finn RS, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. *Hepatology*. 2014;60(5):1697-1707.
28. Johnson PJ, Qin S, Park JW, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol*. 2013;31(28):3517-3524.
29. Llovet JM, Decaens T, Raoul JL, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol*. 2013;31(28):3509-3516.
30. Kudo M, Cheng AL, Park JW, et al. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocel-

lular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. *Lancet Gastroenterol Hepatol*. 2018;3(1):37-46.
31. Kudo M, Ueshima K, Ikeda M, et al; TACTICS study group. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *Gut*. 2020;69(8):1492-1501.
32. IMMUTACE. IMMUTACE: a phase 2 single-arm, open-label study of transarterial chemoembolization in combination with nivolumab performed for intermediate-stage hepatocellular carcinoma. *Gastroenterol Hepatol (N Y)*. 2021;17(11)(suppl 6):16-17.
33. Saborowski A, Waldschmidt D, Hinrichs J, et al. IMMUTACE: A biomarker-orientated phase II, single-arm, open-label AIO study of transarterial chemoembolization (TACE) in combination with nivolumab performed for intermediate-stage hepatocellular carcinoma (HCC; AIO-HEP-0217)—updated efficacy results [ASCO abstract 4116]. *J Clin Oncol*. 2022;40(16)(suppl).
34. ClinicalTrials.gov. A study of nivolumab and ipilimumab and nivolumab alone in combination with trans-arterial chemoembolization (TACE) in participants with intermediate stage liver cancer (CheckMate 74W). https://clinicaltrials.gov/ct2/show/NCT04340193. Identifier: NCT04340193. Updated October 12, 2023. Accessed November 2, 2023.
35. ClinicalTrials.gov. Nivolumab in combination with TACE/TAE for patients with intermediate stage HCC (TACE-3). https://clinicaltrials.gov/ct2/show/NCT04268888. Identifier: NCT04268888. Updated July 16, 2020. Accessed June 29, 2023.
36. ClinicalTrials.gov. Cabozantinib combined with ipilimumab/nivolumab and TACE in patients with hepatocellular carcinoma. https://clinicaltrials.gov/ct2/show/NCT04472767. Identifier: NCT04472767. Updated April 11, 2023. Accessed July 11, 2023.
37. ClinicalTrials.gov. A study of TACE combined with atezolizumab plus bevacizumab or TACE alone in patients with untreated hepatocellular carcinoma. https://clinicaltrials.gov/ct2/show/NCT04712643. Identifier: NCT04712643. Updated September 1, 2023. Accessed November 2, 2023.
38. ClinicalTrials.gov. Safety and efficacy of lenvatinib (E7080/MK-7902) with pembrolizumab (MK-3475) in combination with transarterial chemoembolization (TACE) in participants with incurable/non-metastatic hepatocellular carcinoma (MK-7902-012/E7080-G000-318/LEAP-012). Accessed June 29, 2023. https://clinicaltrials.gov/ct2/show/record/NCT04246177. Identifier: NCT04246177. Updated September 13, 2023. Accessed November 2, 2023.
39. ClinicalTrials.gov. Evaluate durvalumab and tremelimumab +/- lenvatinib in combination with TACE in patients with locoregional HCC (EMERALD-3). https://clinicaltrials.gov/ct2/show/NCT05301842. Identifier: NCT05301842. Updated October 2, 2023. Accessed November 2, 2023.
40. ClinicalTrials.gov. A global study to evaluate transarterial chemoembolization (TACE) in combination with durvalumab and bevacizumab therapy in patients with locoregional hepatocellular carcinoma (EMERALD-1). https://clinicaltrials.gov/ct2/show/NCT03778957. Identifier: NCT03778957. Updated October 11, 2023. Accessed November 2, 2023.
41. Abou-Alfa GK, Fan J, Heo J, et al. A randomised phase III study of tremelimumab (T) plus durvalumab (D) with or without lenvatinib combined with concurrent transarterial chemoembolisation (TACE) versus TACE alone in patients (pts) with locoregional hepatocellular carcinoma (HCC): EMERALD-3 [ESMO abstract 727TiP]. *Ann Oncol*. 2022;33(7)(suppl).
42. Lencioni R, Petruzzi P, Crocetti L. Chemoembolization of hepatocellular carcinoma. *Semin Intervent Radiol*. 2013;30(1):3-11.
43. Young S, Craig P, Golzarian J. Current trends in the treatment of hepatocellular carcinoma with transarterial embolization: a cross-sectional survey of techniques. *Eur Radiol*. 2019;29(6):3287-3295.
44. Abou-Alfa GK, Shi Q, Knox JJ, et al. Assessment of treatment with sorafenib plus doxorubicin vs sorafenib alone in patients with advanced hepatocellular carcinoma: phase 3 CALGB 80802 randomized clinical trial. *JAMA Oncol*. 2019;5(11):1582-1588.
45. Higashihara H, Ono Y, Tanaka K, Tomotake K, Tomiyama N. Recent technical advances in conventional transarterial chemoembolization for hepatocellular carcinoma in Japan. *Int J Gastrointest Interv*. 2021;10(4):152-160.
46. Takayasu K, Arii S, Ikai I, et al; Liver Cancer Study Group of Japan. Overall survival after transarterial lipiodol infusion chemotherapy with or without embolization for unresectable hepatocellular carcinoma: propensity score analysis. *AJR Am J Roentgenol*. 2010;194(3):830-837.
47. de Baere T, Arai Y, Lencioni R, et al. Treatment of liver tumors with lipiodol TACE: technical recommendations from experts opinion. *Cardiovasc Intervent Radiol*. 2016;39(3):334-343.
48. Abi-Jaoudeh N, Sadeghi B, Javan H, et al. Drug-eluting embolic loaded with tyrosine kinase inhibitor targeted therapies for transarterial chemoembolization in a VX2 model. *Cancers (Basel)*. 2023;15(12):3236.
49. Abi-Jaoudeh N, Dayyani F, Chen PJ, et al. Phase I trial on arterial embolization with hypoxia activated tirapazamine for unresectable hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2021;8:421-434.
50. Liu CH, Peng CM, Hwang JI, et al. Phase I dose-escalation study of tirapazamine chemoembolization for unresectable early- and intermediate-stage hepatocellular carcinoma. *J Vasc Interv Radiol*. 2022;33(8):926-933.e1.
51. Ricke J, Klümpen HJ, Amthauer H, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. *J Hepatol*. 2019;71(6):1164-1174.
52. Peng Z, Fan W, Zhu B, et al. Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: a phase III, randomized clinical trial (LAUNCH). *J Clin Oncol*. 2023;41(1):117-127.
53. Dromi SA, Walsh MP, Herby S, et al. Radiofrequency ablation induces antigen-presenting cell infiltration and amplification of weak tumor-induced immunity. *Radiology*. 2009;251(1):58-66.
54. Duffy AG, Ulahannan SV, Makorova-Rusher O, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol*. 2017;66(3):545-551.
55. Mizukoshi E, Yamashita T, Arai K, et al. Enhancement of tumor-associated antigen-specific T cell responses by radiofrequency ablation of hepatocellular carcinoma. *Hepatology*. 2013;57(4):1448-1457.
56. Dumolard L, Ghelfi J, Roth G, Decaens T, Macek Jilkova Z. Percutaneous ablation-induced immunomodulation in hepatocellular carcinoma. *Int J Mol Sci*. 2020;21(12):4398.
57. Ito F, Ku AW, Bucsek MJ, et al. Immune adjuvant activity of pre-resectional radiofrequency ablation protects against local and systemic recurrence in aggressive murine colorectal cancer. *PLoS One*. 2015;10(11):e0143370.
58. Lemdani K, Mignet N, Boudy V, et al. Local immunomodulation combined to radiofrequency ablation results in a complete cure of local and distant colorectal carcinoma. *OncoImmunology*. 2019;8(3):1550342.
59. Giardino A, Innamorati G, Ugel S, et al. Immunomodulation after radiofrequency ablation of locally advanced pancreatic cancer by monitoring the immune response in 10 patients. *Pancreatology*. 2017;17(6):962-966.
60. Zerbini A, Pilli M, Penna A, et al. Radiofrequency thermal ablation of hepatocellular carcinoma liver nodules can activate and enhance tumor-specific T-cell responses. *Cancer Res*. 2006;66(2):1139-1146.
61. Zhang H, Hou X, Cai H, Zhuang X. Effects of microwave ablation on T-cell subsets and cytokines of patients with hepatocellular carcinoma. *Minim Invasive Ther Allied Technol*. 2017;26(4):207-211.
62. Ravindranath MH, Wood TF, Soh D, et al. Cryosurgical ablation of liver tumors in colon cancer patients increases the serum total ganglioside level and then selectively augments antiganglioside IgM. *Cryobiology*. 2002;45(1):10-21.
63. Osada S, Imai H, Tomita H, et al. Serum cytokine levels in response to hepatic cryoablation. *J Surg Oncol*. 2007;95(6):491-498.
64. Slovak R, Ludwig JM, Gettinger SN, Herbst RS, Kim HS. Immuno-thermal ablations - boosting the anticancer immune response. *J Immunother Cancer*. 2017;5(1):78.
65. Waitz R, Solomon SB. Can local radiofrequency ablation of tumors generate systemic immunity against metastatic disease? *Radiology*. 2009;251(1):1-2.
66. ClinicalTrials.gov. Combination of TATE and PD-1 inhibitor in liver cancer (TATE-PD1). Accessed June 28, 2023. https://clinicaltrials.gov/ct2/show/NCT03259867. Identifier: NCT03259867. Updated September 21, 2023. Accessed November 2, 2023.
67. Zhu AX, Kang YK, Yen CJ, et al; REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(2):282-296.
68. Cheng AL, Yen CJ, Okusaka T, et al. A phase I, open-label, multi-center, dose-escalation study of codrituzumab, an anti-glypican-3 monoclonal antibody, in combination with atezolizumab in patients with locally advanced or metastatic hepatocellular carcinoma [ESMO abstract 697P]. *Ann Oncol*. 2018;29(8)(suppl).
69. Zheng Y, Fu Q, Zhao Q, et al. Phase I trial of chimeric anti-GPC3 scFv-CD3ε engineered T cells (CT0180) in patients with advanced hepatocellular carcinoma [ASCO abstract 4095]. *J Clin Oncol*. 2023;41(16)(suppl).
70. Dai H, Tong C, Shi D, et al. Efficacy and biomarker analysis of CD133-directed CAR T cells in advanced hepatocellular carcinoma: a single-arm, open-label, phase II trial. *OncoImmunology*. 2020;9(1):1846926.
71. ClinicalTrials.gov. ET 140202 -T cell combined with TAE or sorafenib in the

treatment of liver cancer. https://clinicaltrials.gov/study/NCT03965546. Identifier: NCT03965546. Updated August 8, 2019. Accessed December 31, 2022.
72. Buch S, Innes H, Lutz PL, et al. Genetic variation in *TERT* modifies the risk of hepatocellular carcinoma in alcohol-related cirrhosis: results from a genome-wide case-control study. *Gut*. 2023;72(2):381-391.
73. Wolf MJ, Adili A, Piotrowitz K, et al. Metabolic activation of intrahepatic CD8+ T cells and NKT cells causes nonalcoholic steatohepatitis and liver cancer via cross-talk with hepatocytes. *Cancer Cell*. 2014;26(4):549-564.
74. Huby T, Gautier EL. Immune cell-mediated features of non-alcoholic steatohepatitis. *Nat Rev Immunol*. 2022;22(7):429-443.
75. Pfister D, Núñez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. *Nature*. 2021;592(7854):450-456.
76. Tan DJH, Ng CH, Lin SY, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. *Lancet Oncol*. 2022;23(4):521-530.
77. Molinari M, Kaltenmeier C, Samra PB, et al. Hepatic resection for hepatocellular carcinoma in nonalcoholic fatty liver disease: a systematic review and meta-analysis of 7226 patients. *Ann Surg Open*. 2021;2(2):e065.
78. Wong RJ, Chou C, Bonham CA, Concepcion W, Esquivel CO, Ahmed A. Improved survival outcomes in patients with non-alcoholic steatohepatitis and alcoholic liver disease following liver transplantation: an analysis of 2002-2012 United Network for Organ Sharing data. *Clin Transplant*. 2014;28(6):713-721.
79. Wong CR, Njei B, Nguyen MH, Nguyen A, Lim JK. Survival after treatment with curative intent for hepatocellular carcinoma among patients with vs without non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2017;46(11-12):1061-1069.
80. Young S, Sanghvi T, Rubin N, et al. Transarterial chemoembolization of hepatocellular carcinoma: propensity score matching study comparing survival and complications in patients with nonalcoholic steatohepatitis versus other causes cirrhosis. *Cardiovasc Intervent Radiol*. 2020;43(1):65-75.
81. Schotten C, Bechmann LP, Manka P, et al. NAFLD-associated comorbidities in advanced stage HCC do not alter the safety and efficacy of Yttrium-90 radioembolization. *Liver Cancer*. 2019;8(6):491-504.
82. ClinicalTrials.gov. DEB-TACE combined with apatinib and PD-1 for the treatment of intrahepatic cholangiocarcinoma. https://clinicaltrials.gov/study/NCT04834674. Identifier: NCT04834674. Updated April 8, 2021. Accessed July 19, 2023.
83. ClinicalTrials.gov. A trial of systemic chemotherapy in combination with conventional transarterial chemoembolization in patients with advanced intra-hepatic cholangiocarcinoma. https://clinicaltrials.gov/study/NCT02994251. Identifier: NCT02994251. Updated December 30, 2019. Accessed July 19, 2023.
84. ClinicalTrials.gov. TACE plus tegafur versus TACE for intrahepatic cholangiocarcinoma after curative resection. https://clinicaltrials.gov/study/NCT02588755. Identifier: NCT02588755. Updated March 31, 2016. Accessed July 19, 2023.
85. ClinicalTrials.gov. 90Y transarterial radioembolization (TARE) plus gemcitabine and cisplatin in unresectable intrahepatic cholangiocarcinoma. https://clinicaltrials.gov/study/NCT02512692. Identifier: NCT02512692. Updated November 19, 2021. Accessed July 19, 2023.
86. ClinicalTrials.gov. Pressure enabled delivery of SD-101 with checkpoint blockade for primary liver tumors. https://clinicaltrials.gov/study/NCT05220722. Identifier: NCT05220722. Updated September 28, 2023. Accessed November 2, 2023.
87. Melisi D, Frizziero M, Tamburrino A, et al. Toll-like receptor 9 agonists for cancer therapy. *Biomedicines*. 2014;2(3):211-228.
88. Humbert M, Guery L, Brighouse D, Lemeille S, Hugues S. Intratumoral CpG-B promotes antitumoral neutrophil, cDC, and T-cell cooperation without reprograming tolerogenic pDC. *Cancer Res*. 2018;78(12):3280-3292.
89. Cohen EEW, Nabell L, Wong DJ, et al. Intralesional SD-101 in combination with pembrolizumab in anti-PD-1 treatment-naïve head and neck squamous cell carcinoma: results from a multicenter, phase II trial. *Clin Cancer Res*. 2022;28(6):1157-1166.
90. ClinicalTrials.gov. Durvalumab and SNDX-6532 following chemo or radio-embolization for patients with intrahepatic cholangiocarcinoma. https://clinicaltrials.gov/study/NCT04301778. Identifier: NCT04301778. Updated September 6, 2023. Accessed November 2, 2023.
91. Shi L, Shen W, Davis MI, et al. SULT1A1-dependent sulfonation of alkylators is a lineage-dependent vulnerability of liver cancers. *Nat Cancer*. 2023;4(3):365-381. doi:10.1038/s43018-023-00523-0
92. NCCN Guidelines®. NCCN clinical practice guidelines in oncology: colon cancer. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed July 10, 2023.
93. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol*. 2010;28(23):3687-3694.
94. Mulcahy MF, Mahvash A, Pracht M, et al; EPOCH Investigators. Radioembolization with chemotherapy for colorectal liver metastases: a randomized, open-label, international, multicenter, phase III trial. *J Clin Oncol*. 2021;39(35):3897-3907.
95. Martin RC, Robbins K, Tomalty D, et al. Transarterial chemoembolisation (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: an interim report. *World J Surg Oncol*. 2009;7:80.
96. Fiorentini G, Aliberti C, Sarti D, et al. Locoregional therapy and systemic cetuximab to treat colorectal liver metastases. *World J Gastrointest Oncol*. 2015;7(6):47-54.
97. Fiorentini G, Sarti D, Nardella M, et al. Transarterial chemoembolization alone or followed by bevacizumab for treatment of colorectal liver metastases. *Hepat Oncol*. 2021;9(1).
98. Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.
99. Mayer RJ, Van Cutsem E, Falcone A, et al; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909-1919.
100. ClinicalTrials.gov. An open label phase II study for the treatment of liver metastatic colorectal cancer and non-small cell lung cancer with a combination of TATE (trans-arterial tirapazamine embolization) and pembrolizumab. https://clinicaltrials.gov/study/NCT04701476. Identifier: NCT04701476. Updated September 21, 2023. Accessed November 2, 2023.
101. ClinicalTrials.gov. M9241 in combination with hepatic artery infusion pump (HAIP) and systemic therapy for subjects with metastatic colorectal cancer or intrahepatic cholangiocarcinoma. https://clinicaltrials.gov/study/NCT05286814. Identifier: NCT05286814. Updated October 18, 2023. Accessed November 2, 2023.
102. Strauss J, Deville JL, Sznol M, et al. First-in-human phase Ib trial of M9241 (NHS-IL12) plus avelumab in patients with advanced solid tumors, including dose expansion in patients with advanced urothelial carcinoma. *J Immunother Cancer*. 2023;11(5):e005813.

Supporting Online Material

eTable. Studies and Clinical Trials Involving Combination Approaches in the Treatment of Primary Liver Tumors and mCRC

		Trial	Clinical trial registration	Year	Study phase	Primary endpoint	Outcome	Therapy
Primary liver tumors	Early HCC	IMMULAB[14]	NCT03753659	Ongoing	2	ORR	Ongoing	pembrolizumab + RFA/MWA/ brachytherapy ± TACE
		Sintilimab + LRT[16]	NCT04220944	Ongoing	1	PFS	Ongoing	MWA + TACE + sintilimab
		IMbrave 050[17]	NCT04102098	2023	3	RFS	RFS HR 0.72 (95% CI 0.56-0.93); *P*=.0120	atezolizumab + bevacizumab
		EMERALD-2[18]	NCT03847428	Ongoing	3	RFS	Ongoing	resection/ablation ± durvalumab ± bevacizumab
	Intermediate HCC	SPACE[22]	NCT00855218	2016	2	TTP	Median TTP 169 d (95% CI 166-219) vs 166 d (95% CI 113-168) HR 0.797 (95% CI 0.588-1.080); *P*=.072	DEB-TACE (doxorubicin) + sorafenib vs DEB-TACE (doxorubicin)
		TACE-2[23]	ISRCTN93375053[a]	2017	2	PFS	Median PFS 238.0 d (95% CI 221.0-281.0) vs 235.0 d (95% CI 209.0-322.0) HR 0.99 (95% CI 0.77-1.27); *P*=.94	DEB-TACE (doxorubicin) + sorafenib vs DEB-TACE (doxorubicin)
		START[25]	NCT00990860	2015	2	AEs	Cumulative grade 3 AE incidence 40% Only 4 severe AEs related to sorafenib	cTACE + sorafenib
		Sorafenib + TACE[26]	N/A	2011	3	TTP	Median TTP 5.4 mo (95% CI 3.8-7.2) vs 3.7 mo (95% CI 3.5-4.0) HR 0.87 (95% CI 0.70-1.09); *P*=.252	cTACE + sorafenib vs cTACE
		Brivanib + TACE[27]	N/A	2014	3	OS	Median OS 26.4 mo (95% CI 19.1-NR) vs 26.1 mo (95% CI 19.0-30.9) HR 0.90 (95% CI 0.66-1.23); *P*=.5280	TACE + brivanib vs TACE
		BRISK-FL[28]	NCT00858871	2013	3	OS	Median OS 9.5 mo (95.8% CI 8.4-10.7) vs 9.9 mo (95.8% CI 8.5-11.5) HR 1.06 (95.8% CI 0.93-1.22); *P*=.3730	brivanib vs sorafenib
		BRISK-PS[29]	NCT00825955	2013	3	OS	Median OS 9.4 mo vs 8.5 mo HR 0.89 (95.8% CI 0.69-1.15); *P*=.3307	brivanib + BSC vs BSC

eTable. (*Continued*) Studies and Clinical Trials Involving Combination Approaches in the Treatment of Primary Liver Tumors and mCRC

		Trial	Clinical trial registration	Year	Study phase	Primary endpoint	Outcome	Therapy
Primary liver tumors	Intermediate HCC	ORIENTAL[30]	NCT01465464	2018	3	OS	Median OS 31.1 mo (95% CI 26.5-34.5) vs 32.3 mo (95% CI 28.4-NR) HR 1.090 (95% CI 0.878-1.352); *P*=.435	cTACE + orantinib vs cTACE
		TACTICS[31]	NCT01217034	2020	2	OS/PFS	Median PFS 25.2 mo vs 13.5 mo HR 0.59 (95% CI 0.41-0.87); *P*=.006 OS: not analyzed	cTACE + sorafenib vs cTACE
		IMMUTACE[32]	NCT03572582	2021	2	ORR	ORR 71.4% (CR: 16.3%, PR: 55.1%, SD 4.1%, PD: 14.3%)	DEB-TACE + nivolumab
		TACE-3[35]	NCT04268888	Ongoing	2/3	OS/ TTTP	Ongoing	TACE/TAE + nivolumab vs TACE/TAE
		CheckMate 74W[34]	NCT04340193	Ongoing	3	AEs	Ongoing	TACE + nivolumab ± ipilimumab vs TACE
		LEAP-012[38]	NCT04246177	Ongoing	3	OS/PFS	Ongoing	TACE + lenvatinib + pembrolizumab vs TACE
		EMERALD-1[40]	NCT03778957	Ongoing	3	PFS	Ongoing	TACE + durvalumab ± bevacizumab vs TACE
		EMERALD-3[39]	NCT05301842	Ongoing	3	PFS	Ongoing	TACE + durvalumab + tremelimumab ± lenvatinib vs TACE
		TATE[49]	NCT02174549	2021	1	Dose determination	Max TPZ dose: 10 mg/m^2 IV and 20 mg/m^2 IA CR 60% (95% CI 38.7-78.9)	tirapazamine + TAE
		TATE[50]	104CONS10288-tirapazamine[b]	2022	1	Dose determination	Selected phase 2 dose: 35 mg IA fixed dose CR 47.1% (95% CI 23.0-72.2)	tirapazamine + TAE
		ET140202[71]	NCT03965546	Ongoing	1	AEs	Ongoing	ET140202 (AFP and GPC3 guided TCR-T cell) + sorafenib vs ET140202 + TAE vs ET140202

eTable. (*Continued*) Studies and Clinical Trials Involving Combination Approaches in the Treatment of Primary Liver Tumors and mCRC

		Trial	Clinical trial registration	Year	Study phase	Primary endpoint	Outcome	Therapy
Primary liver tumors	Advanced HCC	IMbrave 150[5]	NCT03434379	2020	3	OS/PFS	OS at 12 mo: 67.2% (95% CI 61.3-73.1) vs 54.6% (95% CI 45.2-64.0) HR 0.58 (95% CI 0.42-0.79); *P*<.001 Median PFS 6.8 mo (95% CI 5.7-8.3) vs 4.3 mo (95% CI 4.0-5.6) HR 0.59 (95% CI 0.47-0.76); *P*<.001	atezolizumab + bevacizumab vs sorafenib
		COS-MIC-312[10]	NCT03755791	2022	3	OS/PFS	Median PFS 6.8 mo (99% CI 5.6-8.3) vs 4.2 mo (99% CI 2.8-7.0) HR 0.63 (99% CI 0.44-0.91); *P*=.0012 Median OS 15.4 mo (96% CI 13.7-17.7) vs 15.5 mo (12.1-NE) HR 0.90 (96% CI 0.69-1.18); *P*=.44	cabozantinib ± atezolizumab vs sorafenib
		HIMALAYA[9]	NCT03298451	2022	3	OS	Median OS 16.43 mo (STRIDE) (95% CI 14.16-19.58) vs 16.56 mo (durvalumab) (95% CI 14.06-19.12) vs 13.77 mo (sorafenib) (95% CI 12.25-16.13) HR (STRIDE vs sorafenib) 0.78 (96.02% CI 0.65-0.93); *P*=.0035	STRIDE vs durvalumab vs sorafenib
		CheckMate 040[11]	NCT01658878	2021	1/2	AEs/ORR	ORR arm A 32% (95% CI 20-47) ORR arm B 27% (95% CI 15-41) ORR arm C 29% (95% CI 17-43)	nivolumab + ipilimumab
		CheckMate 9DW[13]	NCT04039607	Ongoing	3	OS	Ongoing	nivolumab + ipilimumab vs sorafenib vs lenvatinib
		SORAMIC[51]	NCT01126645	2019	2	OS/TTR	Median OS 12.1 mo (95% CI 10.7-14.9) vs 11.4 mo (95% CI 9.9-14.0) HR 1.01 (95% CI 0.81-1.25); *P*=.9529	sorafenib + Y90 vs sorafenib
		LAUNCH[52]	NCT03905967	2023	3	OS	Median OS 17.8 mo (95% CI 16.1-19.5) vs 11.5 mo (95% CI 10.3-12.7) HR 0.45 (95% CI 0.33-0.61); *P*<.001	lenvatinib + TACE vs lenvatinib
		Tremelimumab + LRT[54]	NCT01853618	2017	1/2	AEs	No DLTs	tremelimumab + RFA/TACE/cryoablation
		TATE-PD1[66]	NCT03259867	Ongoing	2a	ORR	Ongoing	TATE + nivolumab

eTable. (*Continued*) Studies and Clinical Trials Involving Combination Approaches in the Treatment of Primary Liver Tumors and mCRC

		Trial	Clinical trial registration	Year	Study phase	Primary endpoint	Outcome	Therapy
Primary liver tumors	Advanced HCC	REACH-2[67]	NCT02435433	2019	3	OS	Median OS 8.5 mo (95% CI 7.0-10.6) vs 7.3 mo (95% CI 5.4-9.1) HR 0.710 (95% CI 0.531-0.949); *P*=.0199	ramucirumab + BSC vs BSC
		Codrituzumab + atezolizumab[68]	JapicCTI-163325[c]	2020	1	AEs	No DLTs in dose escalation	codrituzumab + atezolizumab
		CT0180[69]	NCT04756648	Ongoing	1	DLTs/AEs	Ongoing	CT0180 (chimeric anti-GPC3 T cells)
		CART-133[70]	NCT02541370	2020	1/2	AEs	Median OS 12 mo (95% CI 9.3-15.3) Median PFS 6.8 mo (95% CI 4.3-8.4)	CART-133 (chimeric CD133-directed T cells)
	ICC	PERIO-02[86]	NCT05220722	Ongoing	1	AEs	Ongoing	SD-101 vs SD-101 + pembrolizumab vs SD-101 + ipilimumab + nivolumab
		Durvalumab + SNDX-6352[90]	NCT04301778	Ongoing	2	ORR/AEs	Ongoing	durvalumab + SNDX-6352 (axatilimab) + TACE/Y90
mCRC		DEBIRI[95]	N/A	2009	N/A	DFS/OS/TRR	Median DFS 247 d Median OS 343 d TRR (EASL criteria) 89% at 3 mo, 54% at 12 mo TRR (RECIST criteria) 71% at 3 mo, 40% at 12 mo	DEB-TACE w/irinotecan-loaded beads
		DEBIRITUX[96]	N/A	2015	N/A	ORR/AEs/OS/PFS	ORR 50% (CR 10%, PR 40%) Grade ≥2 TRAEs 25% Median OS 20.4 mo Median PFS 9.8 mo	DEB-TACE (irinotecan) + cetuximab
		EMBOBEVA[97]	NCT03732235	2021	Observational	TTP	Median TTP 8 mo (range 3-15) vs 2.08 mo (range 1.03-11), *P*<.001	DEB-TACE (irinotecan) + bevacizumab vs DEB-TACE (irinotecan)
		TATE + pembrolizumab[100]	NCT04701476	Ongoing	2	OS/ORR	Ongoing	TATE + pembrolizumab vs standard of care (TAS-102 or regorafenib)

eTable. (*Continued*) Studies and Clinical Trials Involving Combination Approaches in the Treatment of Primary Liver Tumors and mCRC

	Trial	Clinical trial registration	Year	Study phase	Primary endpoint	Outcome	Therapy
mCRC	M9241 + HAIP[101]	NCT05286814	Ongoing	2	ORR	Ongoing	M9241 (NHS-IL12) + HAIP FUdR and dexamethasone + FOLFOX/FOLFIRI OR GemOX

[a]Registered in ISRCTN Registry.

[b]Registered in Taiwan Clinical Trial Registry.

[c]Registered in Japan Registry for Clinical Trials.

AE, adverse event; AFP, alpha-fetoprotein; BSC, best supportive care; CR, complete response; cTACE, conventional transarterial chemoembolization; d, days; DEB-TACE, drug-eluting bead transarterial chemoembolization; DFS, disease-free survival; DLT, dose-limiting toxicities; STRIDE, durvalumab plus tremelimumab; EASL, European Association for the Study of the Liver; FOLFIRI, leucovorin, 5-fluorouracil, and irinotecan; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; FUdR, floxuridine; GemOX, gemcitabine and oxaliplatin; HAIP, hepatic artery infusion pump; HCC, hepatocellular carcinoma; HR, hazard ratio; IA, intraarterial; ICC, intrahepatic cholangiocarcinoma; IV, intravenous; LRT, locoregional therapy; mCRC, metastatic colorectal cancer; MWA, microwave ablation; NR, not reached; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RFA, radiofrequency ablation; RFS, recurrence-free survival; SD, stable disease; TACE, transarterial chemoembolization; TAE, transarterial embolization; TATE, transarterial tirapazamine embolization; TPZ, tirapazamine; TRAE, treatment-related adverse event; TRR, tumor response rate; TTLP, time to liver progression; TTP, time to progression; TTR, time to recurrence; TTTP, time to TACE progression; Y90, yttrium 90 radioembolization.