Integration of Systemic and Liver-Directed Therapies for Locally Advanced Hepatocellular Cancer: Harnessing Potential Synergy for New Therapeutic Horizons

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ABSTRACT

Treatment options in locally advanced hepatocellular carcinoma (HCC) have evolved considerably over the past few years with the recent approval of multiple systemic therapies and significant advances in locoregional therapy. Given the poor prognosis for patients with unresectable HCC, there is significant interest in rationally designed combination therapies. This article reviews the treatment options available to patients with locally advanced HCC and discusses the rationale, ongoing trials, and future prospects for combining locoregional and systemic therapy in both the definitive and neoadjuvant settings.

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Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer death and the sixth most common cancer type worldwide.¹ In 2020, there were an estimated 42,810 new patients with liver cancers and 30,160 deaths from liver cancers in the United States, of which HCC makes up the vast majority.² Unfortunately, the prognosis for HCC remains poor, with 5-year survival of only 18%,^{1,2} among the worst of any malignancy worldwide.

HCC is a heterogeneous disease, with variable outcomes depending on tumor stage. Curative-intent surgical resection, transplantation, or ablation are recommended for patients with early-stage tumors, defined by the Barcelona Clinic Liver Cancer (BCLC) system as stage 0 or A. For locally advanced, multifocal, or unresectable HCC disease (BCLC stage B), locoregional therapies (LRTs) including transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and external-beam radiation therapy (EBRT) are commonly considered. For patients with BCLC stage C HCC, defined by macrovascular invasion and/or distant metastases, systemic therapy is the historical standard of care. However, for liver-confined BCLC stage C disease or limited extrahepatic spread, LRT can be effective as well, with the potential to mitigate the toxicities of systemic therapy.

Systemic therapy options for unresectable or metastatic HCC have evolved considerably since 2007, when sorafenib was the only FDA-approved therapy, to the current day, wherein 9 systemic therapy regimens have full or accelerated FDA approval. Atezolizumab combined with bevacizumab is now a standard first-line treatment for unresectable or metastatic HCC based on the landmark IMbrave150 study showing the superiority of this regimen over sorafenib.^{3,4} Sorafenib and lenvatinib each remain standard first-line options, and multiple other vascular endothelial growth factor (VEGF)-directed

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therapies and immunotherapies represent options in subsequent lines. Liver function and comorbidities are important considerations for patients with more advanced disease, and most of the above agents have been evaluated primarily in patients with Child-Pugh A liver function. Therapeutic options are limited for patients with significant hepatic dysfunction, including those with Child-Pugh B or C liver disease.

Multidisciplinary evaluation for patients with HCC has become essential as systemic and LRT options have expanded and evolved. In the treatment of patients with BCLC stage B and C disease, both local and systemic therapies are used depending on a variety of factors, including disease distribution, underlying liver function, comorbidities, and the expertise of the treating center.⁵⁻⁷ Despite recent progress, however, prognosis remains poor. The combination of systemic therapy and LRT in this patient group represents a promising approach to improve outcomes.

In this review, we discuss the preclinical rationale and emerging clinical evidence for combining locoregional and systemic therapies in BCLC stage B and C HCC, including the potential of neoadjuvant combination therapy to improve the downstaging of tumors for surgical resection.

Locoregional Therapies

LRTs are frequently used in patients with BCLC stage B or C HCC. TACE has historically been the standard of care for most patients with BCLC stage B disease,⁸ but TARE and ablative EBRT, also known as stereotactic body RT (SBRT), are emerging treatment options in patients with unresectable disease. Both TACE and TARE are more frequently used in multifocal disease, whereas SBRT is more often used for large solitary tumors with or without vascular invasion.

Conventional TACE has been the standard of care for intermediate-stage BCLC stage B HCC for many years based on 2 randomized controlled trials showing a survival benefit over best supportive care.⁸⁻¹⁰ Drug-eluting bead TACE has more recently been adopted by many centers based on the results of the PRECISION V trial, which showed fewer adverse events compared with conventional TACE although no significant improvement in overall survival (OS).¹¹

TARE is an emerging treatment approach in these patients, and retrospective data and a small phase II prospective randomized trial have shown that TARE yields improved local control with less toxicity than TACE, although without significant improvement in OS.^{5,12} Improved modeling and targeting of the radiation dose delivered to the tumor by TARE may further enhance disease control.¹³ TARE with resin beads has been compared with sorafenib in 2 phase III trials in BCLC stage B and C

HCC without distant metastases. Both of these trials included some patients with portal vein thrombus. The SARAH study, conducted in France, and the SIRveNIB study, conducted in the Asia-Pacific region, both showed a significantly higher overall response rate for TARE but similar disease control and similar OS, their primary endpoint.^{14,15}

SBRT has also shown promising efficacy in the management of locally advanced HCC, with local control rates ranging from 87% to 100% at 1 year and OS in the range of 60% to 69% at 2 years in phase II studies.^{16,17} One recent phase II study of SBRT that included patients with tumors up to 12 cm and those with macrovascular invasion showed a 2-year local control rate of 94.8%.¹⁸ Indicative of these emerging data, recent NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Hepatobiliary Cancers¹⁹ and the American Association for the Study of Liver Diseases (AASLD) guidelines⁷ both list radiation as a liver-directed therapy option for the management of locally advanced HCC, but neither recommend one form of LRT over another. We recommend that treatment decisions for patients with BCLC stage B or C HCC be made after multidisciplinary evaluation and discussion.

Portal vein tumor thrombus (PVTT) is a relative contraindication for TACE, and systemic therapy has historically been the mainstay of treatment of BCLC stage C HCC with PVTT.²⁰ However, both TARE and EBRT can be safely used in these patients, and emerging data indicate that the combination of RT and TACE may be superior to systemic therapy in this setting.^{6,21} Indeed, a recently published phase II randomized controlled trial showed a time to progression of 31.0 versus 11.7 weeks and an OS of 55.0 versus 43.0 weeks in patients with HCC and PVTT receiving TACE + EBRT versus sorafenib, respectively.²¹ In addition, several trials suggest that combinations of RT and TACE may offer better outcomes than either alone for appropriately selected patients. For example, a meta-analysis of 11 randomized controlled trials comparing TACE + RT versus TACE alone showed improved local control but with potentially greater toxicity, which may limit such use in patients with compromised hepatic function.²² Combinations of TACE and RT, along with TACE and other locally ablative treatments such as radiofrequency ablation and microwave ablation, continue to be the subject of numerous ongoing clinical trials.

Systemic Therapy

Sorafenib, a multikinase inhibitor with activity against the VEGF, platelet-derived growth factor, and Raf signaling pathways, became the first systemic therapy to gain FDA approval for the management of unresectable or metastatic HCC in 2007. This approval was based on the SHARP trial, which showed that sorafenib yielded an

improvement in median OS of 10.7 vs 7.9 months for placebo (hazard ratio [HR], 0.69; 95% CI, 0.55–0.87).²³ More recently, lenvatinib, a multityrosine kinase inhibitor with activity against VEGF, platelet-derived growth factor, fibroblast growth factor, Ret, and KIT and with a similar toxicity profile to sorafenib, was shown to be noninferior to sorafenib, with a median OS of 13.6 versus 12.3 months (HR, 0.92; 95% CI, 0.79–1.06)²⁴ and an objective response rate (ORR) of 19% versus 7%, respectively. Lenvatinib received FDA approval for unresectable HCC in the first-line setting in 2018. Multiple additional single-agent targeted therapies, including regorafenib, ramucirumab, and cabozantinib, have been approved in the post-sorafenib setting, as have the PD-1 inhibitors pembrolizumab and nivolumab.²⁵ Nivolumab and pembrolizumab showed promising response rates of 14% and

17%, respectively, in the post-sorafenib setting in the CheckMate 040 and KEYNOTE-240 trials, giving immunotherapy its first major foothold in HCC.²⁵ Combinations of immune checkpoint inhibitors (ICIs) have demonstrated higher response rates than single agents, with nivolumab in combination with the CTLA-4 inhibitor ipilimumab showing an ORR of 32% in the second-line setting, suggesting a promising route forward in treating this disease.²⁶

In May 2020, a combination of the PD-L1 inhibitor atezolizumab and the anti-VEGF-A antibody bevacizumab was approved for the first-line treatment of unresectable or metastatic HCC based on the results of the IMbrave150 study.^{3,4} This combination showed an ORR of 29.8% versus 11.3% and a median OS of 19.2 versus 13.4 months compared with sorafenib, respectively.^{25,26}

Table 1. Ongoing Prospective Trials Combining RT and Systemic Therapies

Trial	Study Type	N (Anticipated)	ClinicalTrials.gov Identifier	Agent Class
RTOG1112: sorafenib ± SBRT	Randomized phase III	368	NCT01730937	Anti-VEGF TKI
Sorafenib ± TACE + SBRT	Randomized phase III	54	NCT04387695	Anti-VEGF TKI
Sorafenib ± proton RT	Randomized outcomes trial	220	NCT01141478	Anti-VEGF TKI
Sorafenib + RT + HAIC (5-FU)	Single-arm phase II	47	NCT02425605	Anti-VEGF TKI
Sorafenib + RT	Single-arm phase II	86	NCT03535259	Anti-VEGF TKI
Sorafenib + RT	Single-arm phase II	45	NCT01328223	Anti-VEGF TKI
Axitinib vs RT vs RT + axitinib	Randomized phase II 2 × 2	160	NCT03732105	Anti-VEGF TKI
Apatinib ± RT	Randomized phase II	50	NCT03520257	Anti-VEGF TKI
Axitinib + RT	Phase I	9	NCT02814461	Anti-VEGF TKI
SBRT ± sintilimab	Randomized phase II/III	116	NCT04167293	Anti-PD-1/PD-L1
Sintilimab ± SBRT	Randomized phase II	84	NCT04547452	Anti-PD-1/PD-L1
Durvalumab + tremelimumab + SBRT	Single-arm phase II	70	NCT03482102	Anti-PD-1/PD-L1
Carrelizumab + SBRT	Single-arm phase II	39	NCT04193696	Anti-PD-1/PD-L1
START-FIT: avelumab + TACE + SBRT	Single-arm phase II	33	NCT03817736	Anti-PD-1/PD-L1
PEMRAD: pembrolizumab + SBRT	Single-arm phase II	30	NCT03316872	Anti-PD-1/PD-L1
IBI308 (anti-PD-1) + SBRT	Single-arm phase II	30	NCT03857815	Anti-PD-1/PD-L1
Toripalimab + SBRT	Single-arm phase II	30	NCT04169399	Anti-PD-1/PD-L1
Durvalumab + SBRT ± tremelimumab	Single-arm phase II	30	NCT04430452	Anti-PD-1/PD-L1
Nivolumab + SBRT ± ipilimumab	Phase I	50	NCT03203304	Anti-PD-1/PD-L1
Sintilimab (anti-PD-1) + SBRT	Phase I	20	NCT04104074	Anti-PD-1/PD-L1
Carrelizumab + apatinib + SBRT	Single-arm phase II	27	NCT04523662	Anti-PD-1/PD-L1
Neoantigen T-cell infusion + RT	Single-arm phase I/II	40	NCT03199807	Cell therapy
Dendritic cell infusion + PCV13 + RT	Phase I	26	NCT03942328	Cell therapy
CAPOX + RT	Phase I	30	NCT02403544	Chemotherapy
Endostatin + RT	Single-arm phase II	61	NCT03208335	Anti-VEGF
Galunisertib + RT	Phase I	15	NCT02906397	Anti-TGF-β

Abbreviations: CAPOX, capecitabine/oxaliplatin; HAIC, hepatic arterial infusion chemotherapy; PCV13, pneumococcal 13-valent conjugate vaccine; RT, radiation therapy; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TGF-β, transforming growth factor β; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Notably, the safety and tolerability of the combination therapy were better than those of sorafenib. These results have ushered in a new era of immunotherapy and anti-VEGF combinations in HCC and establish a new standard of care. Despite these recent advances in systemic therapy, most patients with advanced HCC still experience disease progression within a year of starting therapy. Given this finding, the NCCN Guidelines emphasize that patients first be considered for enrollment on a clinical trial because the optimal immunotherapy combinations remain uncertain. There is also increasing interest in the potential of combinations of systemic therapy and LRT to enhance disease control in patients with BCLC stage B and C HCC.¹⁹

Combinations of LRT With Angiogenesis Inhibitors

Since sorafenib was approved for the treatment of unresectable HCC in 2007, there has been considerable investigation into the combination of LRTs and angiogenesis inhibitors. LRTs provide increased local disease control, whereas systemic angiogenic inhibitors can better treat microscopic disease outside the LRT treatment field. Numerous trials combining sorafenib and other VEGF targeting agents with a variety of LRTs are ongoing or completed (Tables 1–3). Sorafenib has a dual effect on HCC growth. It inhibits neoangiogenesis and tumor oxygen and nutrient supply through its activities on VEGF signaling while also blocking cancer mitogenic signaling, slowing growth, and lowering the tumor apoptotic threshold.²⁷ This latter effect may enable enhanced tumor killing by LRT, whereas the anti-VEGF activity of sorafenib may prevent revascularization and HCC relapse after TACE by inhibiting neoangiogenesis. Sorafenib has been shown to increase radiation sensitivity both in vitro and in vivo in human HCC xenograft models, at least in part through the inhibition of VEGF-mediated ERK signaling.²⁸ In addition, sorafenib and other VEGF inhibitors

can promote the transient “normalization” of dysfunctional intratumoral blood vessels, paradoxically increasing blood flow and oxygen delivery to poorly perfused regions of the tumor while simultaneously inhibiting new blood vessel formation in the longer term.²⁷ Vascular normalization can increase drug delivery to poorly perfused tumor regions, enhancing the efficacy of TACE and TARE, and reduce tumor hypoxia, enabling increased free-radical generation by radiation.

Although there is a promising preclinical rationale for combining LRTs with angiogenesis inhibitors, clinical results thus far have been mixed. The combination of TACE with sorafenib in unresectable HCC has shown improvement in median progression-free survival compared with TACE alone,²⁹ and sorafenib combined with a hepatic arterial infusion of FOLFOX (fluorouracil/leucovorin/oxaliplatin) showed improved median OS compared with sorafenib alone in patients with HCC and PVTT,³⁰ but most studies have failed to show an OS benefit with the combination.^{31,32} In the case of TARE, a phase II study of glass-bead TARE with or without sorafenib in patients with unresectable HCC actually showed a significant survival benefit for TARE alone over the combination of TARE and sorafenib.³³ In addition, the recent phase III SORAMIC trial comparing the combination of resin-bead TARE and sorafenib versus sorafenib alone showed that the combination did not improve median OS.³⁴ The large phase III RTOG 1112 study evaluating the combination of sorafenib and SBRT in patients with locally advanced HCC has recently closed to accrual, but results are not yet available (ClinicalTrials.gov identifier: NCT01730937).

Biological Rationale for Combining LRT and ICIs (±Angiogenesis Inhibitors)

The recent approval of multiple ICIs in HCC has raised significant interest in exploring combinations of these agents with LRTs in locally advanced HCC. Emerging preclinical and clinical data suggest that these

Table 2. Ongoing Prospective Trials Combining TARE and Systemic Therapies

Trial	Study Type	N	ClinicalTrials.gov Identifier	Agent Class
Sorafenib + TARE	Single-arm phase II	40	NCT01900002	Anti-VEGF TKI
Nivolumab + TARE	Single-arm phase II	40	NCT03380130	Anti-PD-1/PD-L1
Nivolumab + TARE	Single-arm phase II	40	NCT03033446	Anti-PD-1/PD-L1
Durvalumab + tremelimumab + TARE	Phase Ib	32	NCT04605731	Anti-PD-1/PD-L1
Pembrolizumab + TARE	Early phase I	30	NCT03099564	Anti-PD-1/PD-L1
Nivolumab + TARE	Phase I/Ib	27	NCT02837029	Anti-PD-1/PD-L1
Durvalumab + TARE	Single-arm phase I/II	24	NCT04124991	Anti-PD-1/PD-L1
Nivolumab + TARE	Early phase I	2	NCT03812562	Anti-PD-1/PD-L1

Abbreviations: TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Table 3. Selected Prospective Trials Combining TACE and Systemic Therapies

Trial	Study Type	N	ClinicalTrials.gov Identifier	Agent Class
EMERALD-1: durvalumab ± bevacizumab ± TACE	Randomized phase III	600	NCT03778957	Anti-PD-1/PD-L1
CheckMate 74W: TACE ± nivolumab ± ipilimumab	Randomized phase III	765	NCT04340193	Anti-PD-1/PD-L1
LEAP-012: TACE ± pembrolizumab + lenvatinib	Randomized phase III	950	NCT04246177	Anti-PD-1/PD-L1
TACE-3: TACE ± nivolumab	Randomized phase II/III	522	NCT04268888	Anti-PD-1/PD-L1
IMMUTACE: nivolumab + TACE	Phase II	49	NCT03572582	Anti-PD-1/PD-L1
Pembrolizumab + TACE	Single-arm phase I/II	26	NCT03397654	Anti-PD-1/PD-L1
Nivolumab + TACE	Phase I	14	NCT03143270	Anti-PD-1/PD-L1
rAd-p53 vs TACE	Randomized phase II	120	NCT02418988	Gene therapy
TACE ± iNKT cell infusion	Randomized phase II/III	144	NCT04011033	Cell therapy
IVY02: TACE ± autologous immune killer cells	Randomized phase II/III	60	NCT03592706	Cell therapy
TACE ± arginine hydrochloride ± trimetazidine hydrochloride	Randomized phase III	300	NCT03274427	Metabolic agent
TACE + sorafenib or lenvatinib or anti-PD-1	Randomized phase III	90	NCT04229355	Anti-VEGF TKI/PD-1
Lenvatinib ± TACE	Randomized phase III	336	NCT03905967	Anti-VEGF TKI
ECOG-E1208: sorafenib ± TACE	Randomized phase III	400	NCT01004978	Anti-VEGF TKI
TACE ± sorafenib	Randomized phase III	458	NCT00494299	Anti-VEGF TKI
Sorafenib ± TACE	Randomized phase II/III	246	NCT01906216	Anti-VEGF TKI
TACE ± sorafenib	Randomized phase III	162	NCT04103398	Anti-VEGF TKI
Sorafenib ± TACE	Randomized phase III	158	NCT04143191	Anti-VEGF TKI
Sorafenib ± TACE	Randomized phase III	120	NCT01833299	Anti-VEGF TKI
Apatinib + TACE	Single-arm phase II	22	NCT03510416	Anti-VEGF TKI
TACE-2: TACE ± sorafenib	Randomized phase III	412	NCT01324076	Anti-VEGF TKI
PRODIGE16: TACE ± sunitinib	Randomized phase III	78	NCT01164202	Anti-VEGF TKI
STAH: sorafenib ± TACE	Randomized phase III	339	NCT01829035	Anti-VEGF TKI
ORIENTAL: TACE ± orantinib	Randomized phase III	888	NCT01465464	Anti-VEGF TKI

Abbreviations: iNKT, invariant natural killer T cell; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

combinations can enhance response compared with either approach alone. LRTs may help promote systemic antitumor immunity through the induction of immunogenic cell death, resulting in the release of tumor antigens and inflammatory intracellular contents, the latter of which can increase innate immune recognition of tumor cells and promote activation of the adaptive immune system (Figure 1). Increased immune recognition of the tumor synergizes with checkpoint inhibition, which helps maintain the anticancer immune response. There may be further synergy with the addition of antiangiogenic therapy to these combinations, which has been found to promote the antitumor immune response through multiple mechanisms.^{25,35}

The potential of LRTs to enhance anticancer immune responses has long been hypothesized based on the observation of abscopal responses after EBRT, in which tumors outside the radiation field shrink after irradiation of a distant site.³⁶ Abscopal responses with local therapy are seen in HCC, although they are rare and

mainly limited to case reports in the literature.³⁷ The mechanism behind this phenomenon is thought to be immune-mediated,^{38,39} and radiation has been shown to activate systemic anticancer immune responses in both patients and preclinical models.^{38–42}

TARE has also been shown to induce systemic immune activation, with increased tumor necrosis factor- α on circulating CD8⁺ and CD4⁺ T cells and a CD8⁺ T-cell signature correlated with response.⁴³ Cell death induced by embolization and/or the cytotoxic chemotherapy used in TACE is also immunogenic. Indeed, serum levels of immunogenic cell death biomarkers can predict TACE response,⁴⁴ and TACE has been shown to increase cytotoxic CD8⁺ T-cell and T-helper 17 cell activity and to decrease T-regulatory cell activity in the tumor microenvironment.^{45,46} Although thermal ablation is not often used in the BCLC stage B or C disease setting, it has also been shown to be highly immunogenic.^{47,48}

RT and other LRTs activate anticancer immunity by inducing immunogenic tumor cell death, which involves

Figure 1. Schematic of LRT/immunotherapy combination rationale. Left: Anti-VEGF therapy in combination with immune checkpoint blockade (such as with the combination of atezolizumab + bevacizumab). VEGF inhibition leads to vascular normalization and increased DC and T-cell activity, enhancing the efficacy of immune checkpoint blocking antibodies. Right: Radiation and TACE lead to cGAS-STING pathway activation and immunogenic cell death with the subsequent release of a variety of cytokines and damage-associated molecular patterns, stimulating immune cell recruitment and activity. The combination of these agents may further enhance anticancer activity of each individual agent.

Abbreviations: ANXA1, annexin A1; APC, antigen-presenting cell; CALR, calreticulin; cGAS, cyclic GMP-AMP synthase; CTL, cytotoxic T-lymphocyte; DC, dendritic cell; EBRT, external-beam radiation therapy; HCC, hepatocellular carcinoma; HMGB1, high-mobility group box 1; IFN, interferon; LRT, locoregional therapy; STING, stimulator of interferon genes; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; Th1, T helper type 1 cell; VEGF, vascular endothelial growth factor.

the release of HMGB1, adenosine triphosphate, and ANXA1, among other factors, and increased surface expression of “eat-me” signals, such as calreticulin, on dying cancer cells. These signals stimulate antigen-presenting cell recruitment, activation, and tumor cell uptake, promoting the initial generation of an anticancer immune response.³⁵ Both RT and cytotoxic chemotherapy also cause the release of DNA and RNA into the cytoplasm of damaged tumor cells, triggering cGAS-STING and Toll-like receptor signaling and subsequent inflammatory cytokine and chemokine release into the tumor microenvironment.⁴⁹ In preclinical mouse models, cytosolic DNA and cGAS-STING activation promotes type I interferon production and the recruitment and activation of Batf3-dependent dendritic cells and cytotoxic CD8⁺ T lymphocytes in the tumor and draining lymph nodes, stimulating anticancer immunity.^{39,49–51}

It is thought that the addition of ICIs will help maintain this LRT-mediated antitumoral immune response, which may synergize with checkpoint inhibition. A preclinical combination of LRT with ICIs has shown impressive antitumor immunity in a number of tumor types. In HCC, the combination of radiation with CTLA-4 and PD-1 blockade can markedly reduce tumor growth in preclinical models.^{52–54} Similarly, the addition of cryoablation to CTLA-4 therapy has been shown to slow growth and induces immune rejection of subsequent tumors.⁵⁵

Early clinical data in other malignancies combining RT with checkpoint inhibition do, in some contexts, support the rationale for combining LRT with systemic immunotherapies in HCC. An analysis of 2 recent randomized phase II clinical trials in metastatic non-small cell lung cancer showed that the addition of RT to

pembrolizumab increased response duration, even at nonirradiated lesions, with an improvement in OS from 8.7 months with pembrolizumab alone to 19.2 months with pembrolizumab + RT.⁵⁶ In contrast, in metastatic head and neck cancer, a recent phase II study of nivolumab ± SBRT to a single metastatic lesion failed to show improved OS or response rates at nonirradiated lesions.⁵⁷ The tumor type, clinical setting, and proper sequencing of these LRT/immunotherapy combinations remains the subject of significant study.

The approval of atezolizumab and bevacizumab for HCC and the promising efficacy of other immunotherapy/VEGF inhibitor combinations, including the combination of pembrolizumab and lenvatinib and of nivolumab, ipilimumab, and cabozantinib,^{58,59} suggest the potential of these systemic combinations to be paired with LRT and indicate the potential immunomodulatory effects of VEGF blockade. VEGF blockade can enhance anticancer immunity through a variety of mechanisms, including normalizing dysfunctional blood vessels, increasing immune cell migration into tumors, and reducing hypoxia-mediated immune suppression, and through the prevention of direct VEGF-mediated dendritic cell dysfunction and inhibition of cytotoxic T-cell function.^{25,60} In turn, resistance to antiangiogenic therapies may be mediated in part by an immune-suppressive microenvironment characterized by higher T-regulatory cell infiltration and stronger PD-L1 expression,^{61,62} arguing for the benefit of PD-1/L1 axis inhibition. Indeed, in preclinical models of HCC, lenvatinib increased tumor infiltration by CD8⁺ T cells and enhanced the antitumor effect of PD-1 inhibition.⁶³ This preclinical evidence supports further clinical investigation into LRT/immunotherapy combinations in HCC.

Clinical Combinations of LRT and ICIs (±Angiogenesis Inhibitors)

To date, case series and single-arm studies combining LRT with ICIs in HCC have continued to suggest possible synergistic effects. A case series of 5 patients with locally advanced HCC who received SBRT and the PD-1 inhibitor nivolumab showed both safety and durable (100%) disease control at 1 year.⁶⁴ A phase I study of 14 patients with advanced HCC who received SBRT followed by nivolumab with or without the CTLA-4 inhibitor ipilimumab showed fair tolerability in both arms and preliminary efficacy. At a median follow-up of 8.3 months, the authors observed 72% disease control (50% in the nivolumab-alone arm and 87.5% in the ipilimumab/nivolumab arm). The ORR in the SBRT/ipilimumab/nivolumab arm was 50%, with all of the responding patients showing durable responses lasting >18 months (range, 18.2–27.3 months).⁶⁵ Many trials of RT and immunotherapy are ongoing, including a phase II/III trial of

SBRT and sintilimab (ClinicalTrials.gov identifier: NCT04167293) and phase II trials combining SBRT with durvalumab and tremelimumab (NCT03482102), carelizumab (NCT04193696), toripalimab (NCT04169399), and pembrolizumab (NCT03316872), among other agents (Table 1). A study in 21 patients with BCLC stage C HCC combined the CTLA-4 inhibitor tremelimumab with local ablative therapy (10 treated with radiofrequency ablation and 11 with chemoembolization). Of patients with lesions outside the treatment zone, 26% achieved a partial response, with a median time-to-progression of 7.4 months and significant increases in CD8⁺ T cells seen in responders at 6 weeks posttreatment.⁶⁶ Although these combinations have shown promise, caution must be exercised whenever novel agents are combined before prospective safety data are available. For example, increased luminal gastrointestinal toxicity has been reported when anti-VEGF agents were combined with RT.^{67–69} However, increased gastrointestinal toxicity has not been seen consistently in other contexts,^{70,71} suggesting the need for well-designed, prospective studies to establish the toxicity of novel combination therapies.

A number of ongoing studies are investigating the combination of intra-arterial therapies and ICIs, including the phase III CheckMate 74W study of TACE with nivolumab and ipilimumab (ClinicalTrials.gov identifier: NCT04340193) and phase II studies investigating TARE with nivolumab (NCT03033446, NCT03380130), TARE with pembrolizumab (NCT03099564), and TARE with durvalumab (NCT04124991), with additional studies planned (Tables 2 and 3).

Because of the positive results of the IMbrave150 study,^{3,4} significant clinical interest has been raised in exploring the addition of LRT to ICI and angiogenesis inhibitor combinations. To this end, 2 large randomized phase III trials of TACE in combination with dual VEGF and PD-1 inhibition are ongoing, including EMERALD-1 (durvalumab/bevacizumab; ClinicalTrials.gov identifier: NCT03778957) and LEAP-012 (pembrolizumab/lenvatinib; NCT04246177) (Table 3).

Ongoing LRT and systemic therapy trials are listed in Tables 1–3.

Neoadjuvant Combination Therapy

When feasible, surgery offers the best outcomes of any available treatment modality for HCC, with 5-year survival rates of 60% to 80%.⁵ However, many patients with BCLC stage B or C disease are not surgical candidates because of comorbid cirrhosis or high tumor burden. Furthermore, those with large, multifocal tumors or with PVTT who undergo resection have a worse prognosis.^{5,72} Unfortunately, tumor recurrence from either intrahepatic metastases or de novo tumor development complicates

as many as 75% of resections at 5 years,⁷³ and several neoadjuvant and adjuvant approaches have been tested in this setting with the hope of reducing these recurrence rates. Cytotoxic chemotherapy, TACE, and sorafenib have individually been evaluated in the neoadjuvant and adjuvant settings with mixed results.^{74–77} At this time, the guidelines of the AASLD and the European Association for the Study of the Liver do not recommend neoadjuvant or adjuvant therapy in most patients with resectable HCC outside of a clinical trial, but significant interest remains in these strategies. A number of large trials of immunotherapy in the adjuvant setting postresection are ongoing, including CheckMate 9DX (nivolumab; ClinicalTrials.gov identifier: NCT03383458), EMERALD-2 (durvalumab/bevacizumab; NCT03847428), JUPITER-04 (toripalimab; NCT03859128), and KEYNOTE-937 (pembrolizumab; NCT03867084).

Of particular and emerging interest in the treatment of borderline or unresectable BCLC stage B or C HCC is the potential of neoadjuvant therapies to downstage patients. Early data from a phase II trial of neoadjuvant nivolumab versus nivolumab combined with ipilimumab showed pathologic complete response rates of 25%, suggesting that this approach may enable some patients with locally advanced disease to successfully proceed to surgery.⁷⁸ These data, and the results of the IMbrave150 study, which showed an ORR of 29.8% with 7.7% complete response in patients receiving atezolizumab and bevacizumab,^{3,4} raise the prospect that both LRT and immunotherapy, either alone or in combination, may be useful in downstaging unresectable HCC to enable curative-intent resection. Although clinical outcomes from most studies investigating immunotherapy and LRT in the neoadjuvant setting are pending, case reports provide a proof of concept that immunotherapy combinations can downstage patients with unresectable HCC.⁷⁹ Of particular promise are studies that combine ICIs and LRT in the neoadjuvant setting. A recent case series of 5 patients with locally advanced HCC treated using SBRT and checkpoint inhibition reported 40% complete response, with 39% median tumor shrinkage and 1 patient proceeding to curative-intent radiofrequency ablation.⁶⁴ Based on these findings, the START-FIT trial (ClinicalTrials.gov identifier: NCT03817736) has been launched to evaluate the sequential combination of TACE, hypofractionated SBRT, and the ICI avelumab to downstage locally advanced HCC before hepatectomy.

Although the role of surgery is controversial in the setting of HCC with PVTT, data support the role of neoadjuvant RT before resection in this population. In a recent randomized multicenter study of patients with resectable HCC and PVTT, neoadjuvant RT provided significantly increased disease-free survival and OS

compared with surgery alone, with an HR for HCC-related mortality of 0.35 (95% CI, 0.23–0.54) on multivariate analysis, and OS of 27.4% versus 9.4% at 24 months, respectively, despite the use of very low radiation doses well below the ablative range. The regimen was tolerable, with minimal grade ≥ 3 toxicity and the vast majority of patients proceeding to surgery.⁸⁰ The addition of immunotherapy to neoadjuvant regimens like this may further improve these promising initial results. As improved systemic therapy and LRT combinations are identified in more advanced disease, the potential for these agents to successfully downstage patients with borderline resectable HCC, enabling curative therapy, should continue to be explored. We await the results of ongoing studies investigating a variety of neoadjuvant approaches (supplemental eTable 1, available with this article at JNCCN.org).

Conclusions

The treatment landscape in HCC continues to evolve rapidly, with the combination of liver-directed therapy and systemic therapy holding real promise for patients with HCC. Preliminary correlative studies and preclinical data suggest a biological rationale for the combination of LRTs with immunotherapy and VEGF inhibitors, and emerging clinical data in patients with BCLC stage B and C disease reinforce the promise of this approach. Multidisciplinary evaluation of patients with HCC is increasingly critical as traditional options for treatments by stage begin to expand. Systemic therapy is now being evaluated in early-stage disease, and liver-directed therapy is being evaluated in late-stage disease; the optimal approach and setting to combine these approaches will be guided by the highly anticipated results of several ongoing studies.

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Integration of Systemic and Liver-Directed Therapies for Locally Advanced Hepatocellular Cancer: Harnessing Potential Synergy for New Therapeutic Horizons

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eTable 1: Ongoing Prospective Trials of Neoadjuvant Systemic and Local Therapy

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Trial	Study Type	N	ClinicalTrials.gov Identifier	Agent Class
Carrelizumab + apatinib	Randomized phase II/III	514	NCT04521153	Anti-PD-1/PD-L1 + anti-VEGF TKI
Pembrolizumab + lenvatinib	Randomized outcomes trial	192	NCT04425226	Anti-PD-1/PD-L1 + anti-VEGF TKI
Cemiplimab	Randomized phase II	94	NCT03916627	Anti-PD-1/PD-L1
Sintilimab + TACE	Single-arm phase II	61	NCT04174781	Anti-PD-1/PD-L1 + TACE
Nivolumab ± BMS-813160 or BMS-986253	Randomized phase II	50	NCT04123379	Anti-PD-1 + anti-CCR2/5 or anti-IL-8
Pembrolizumab	Single-arm phase II	50	NCT03337841	Anti-PD-1/PD-L1
Nivolumab + ipilimumab	Single-arm phase II	40	NCT03510871	Anti-PD-1/PD-L1 + anti-CTLA-4
Nivolumab + ipilimumab	Single-arm phase II	40	NCT03510871	Anti-PD-1/PD-L1 + anti-CTLA-4
START-FIT: SBRT + TACE + avelumab	Single-arm phase II	33	NCT03817736	Anti-PD-1/PD-L1 + RT + TACE
Durvalumab + lenvatinib	Single-arm	20	NCT04443322	Anti-PD-1/PD-L1 + anti-VEGF TKI
Nivolumab + cabozantinib	Phase I	15	NCT03299946	Anti-PD-1/PD-L1 + anti-VEGF TKI
Nivolumab ± ipilimumab	Randomized phase II	30	NCT03222076	Anti-PD-1/PD-L1 + anti-CTLA-4
Nivolumab ± ipilimumab	Randomized phase II	30	NCT03222076	Anti-PD-1/PD-L1 + anti-CTLA-4
Tislelizumab	Single-arm phase II	27	NCT04615143	Anti-PD-1/PD-L1
Toripalimab	Single-arm phase Ib/II	20	NCT03867370	Anti-PD-1/PD-L1
SHR-210 (PD-1) + apatinib	Single-arm phase II	20	NCT04297202	Anti-PD-1/PD-L1 + anti-VEGF TKI
SBRT	Randomized phase II/III	214	NCT04025437	RT
RT	Randomized phase II	50	NCT02580929	RT
SBRT	Phase I	30	NCT04587739	RT
SBRT	N/A	35	NCT04186234	RT
HAIC (mFOLFOX)	Randomized phase III	344	NCT03851913	HAIC (mFOLFOX)
HAIC (mFOLFOX)	Randomized phase III	230	NCT03368651	HAIC (mFOLFOX)
HAIC (mFOLFOX)	Randomized phase III	40	NCT04595864	HAIC (mFOLFOX)
HAIC (FOLFOX)	Randomized phase III	252	NCT03469479	HAIC (FOLFOX)

Abbreviations: FOLFOX, fluorouracil/leucovorin/oxaliplatin; HAIC, hepatic arterial infusion chemotherapy; IL, interleukin; mFOLFOX, modified FOLFOX; N/A, not available; RT, radiation therapy; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.