



# Combined locoregional and systemic therapy for advanced hepatocellular carcinoma: finally, the future is obscure

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Hepatocellular carcinoma (HCC) remains a devastating disease worldwide with a growing incidence and high mortality rate (1). Very few patients present with early stage disease that can be treated with curative intent with transplant, surgical resection, or in some cases, ablation. Intermediate stage patients are treated primarily with transarterial liver-directed therapies, including transarterial chemoembolization (TACE), chemoembolization with drug-eluting beads (DEB-TACE) or radioembolization with yttrium-90 (Y90), and advanced stage patients are primarily treated with systemic therapy or palliative care (2). Recently, growing experience and outcomes for external beam radiation therapy (XRT), particularly with the advent of 3D conformal techniques that reduce non-target hepatotoxicity, have gained interest and have become recognized as a locoregional therapy for HCC (3-6). As the available armamentarium of agents has increased for use in HCC, there has been growing interest in combination therapies to maximally leverage the relative strengths of each therapy, and potentially to produce synergistic effects. How best to use the available treatments remains a topic of active research.

## Therapies for advanced HCC

The landscape for HCC therapy has been evolving most

rapidly for advanced disease. Particularly in the setting of central venous invasion, the somber outcomes for this disease have historically been minimally impacted by any therapy, if at all (7,8). For over a decade, sorafenib has remained the sole agent showing benefit over placebo in advanced HCC, and that, just a modest increase in overall survival at best (7-9). In conjunction with the challenging side effect profile which reduces adherence in many patients, the limits of this therapy for advanced disease have opened extensive research for alternative agents. Newer therapies for advanced HCC have shown efficacy in the first or second line, and some with arguably improved patient tolerability compared with sorafenib. These include other multikinase inhibitors such as lenvatinib, regorafenib, and cabozantinib, as well as the vascular endothelial growth factor (VEGF) inhibitor, ramucirumab (10-13).

## Combination therapy and immunotherapy for HCC

Given the inflammatory milieu of cirrhosis as a common background for HCC, research has increasingly examined whether immunotherapy may hold promise for therapeutic efficacy. Immunotherapy for HCC has focused on monoclonal antibodies blocking immune checkpoint inhibition pathways, primarily the programmed

cell death pathway via the PD-1 receptor on T cells or its cognate ligand, PD-L1, on tumor cells and cells of the tumor microenvironment (14). Additionally, the immune checkpoint pathway mediated by the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) receptor on T cells and its cognate ligand on antigen presenting cells has also been explored as a therapeutic target (14). A putative role for two PD-1 inhibitors, nivolumab and pembrolizumab, has been examined for efficacy in advanced HCC in the first or second line with encouraging early results (15,16). Despite this, larger phase III trials using these agents as monotherapy failed to reach predefined statistically significant study endpoint targets, although some signals were noted showing putative improved differential responses in those getting immunotherapy (17,18). Combination therapy with lenvatinib and pembrolizumab (Keynote-524) in the first line for Barcelona Clinic Liver Cancer (BCLC) stages B and C disease in patients ineligible for locoregional therapy showed promising early anti-tumor activity with good tolerance (19), and a phase 3 trial looking at this combination is currently underway (LEAP-002) (20). A recent phase 3 randomized controlled trial (IMBRAVE 150) using the anti-PD-L1 antibody, atezolizumab, plus the VEGF inhibitor, bevacizumab, compared to sorafenib has arguably been the most exciting representation of the relevance of immunotherapy for advanced HCC (21). Results from this trial showed that the median overall survival for the experimental arm was not yet reached at a median follow up interval of 8.6 months, with a 27.3% objective response rate (ORR) and moderately improved progression-free survival (PFS) (21). Importantly, the combination treatment was relatively well tolerated, with a similar incidence of adverse events compared to sorafenib, but with improvement in quality of life deterioration (21). The results from the IMBRAVE 150 trial have been so promising, there is new expectation this therapy may finally make a true dent in the lack of effective systemic therapy outcomes for advanced HCC seen thus far with so many prior agents. Furthermore, these experiences are showing efficacy for agents beyond multikinase inhibitors for demonstrable response rates in HCC.

All this is good, but it does serve to complicate matters. We have so many more therapeutic combinations at our disposal, and still so many ongoing trials promising newer results. The challenge will be how best to sift through the available data to arrive at a rational treatment algorithm that can benefit the most patients. Several trials are currently underway examining the role of combination therapies in

HCC (Table 1). Moreover, the positive outcomes from these newer agents have spurred several clinical trials pushing the use of combination and systemic therapies as first line in early and intermediate stage disease.

### Role of XRT for HCC

So, where does XRT fall in this melee? External beam radiotherapy has been studied in every phase of HCC, with early stage therapy being explored as an alternative ablative modality, and its use in intermediate and advanced stages offered for palliative disease control (3,4). More recently, XRT has been increasingly explored in combination therapy regimens. Combination XRT and TACE was shown in a phase 2 prospective study including 90 patients to improve outcomes for advanced HCC with portal venous invasion compared to sorafenib monotherapy (5). In addition, RTOG 1112 is further examining the role of combination therapy using stereotactic body radiotherapy (SBRT) and sorafenib.

More recently, Kim *et al.* presented a small-scale phase 2 clinical trial with 47 patients examining the role of upfront chemoradiation using XRT in combination with hepatic arterial chemoinfusion with 5-fluorouracil (5-FU) and leucovorin via an implanted arterial pump, followed by systemic therapy with sorafenib (22). Nearly half (44.1%) of the cohort presented with a solitary mass, potential rationale for a targeted approach upfront, and one third of the cohort (34%) underwent synchronous TACE for lesions outside of the radiation treatment field. Radiation was provided over 20–25 fractions for a median dose of 60 Gy in the treatment bed. Median OS was 24.6 months for the cohort, and 13.0 months for the subgroup with main or first-branch portal vein invasion. By imaging, an ORR of 53.2% was achieved, with 44.7% ORR 4 weeks after completion of chemoradiation. Median PFS was 6.8 months, with the majority of disease progression occurring either in the liver outside the XRT treatment zone, or in distant metastases. The authors concluded that chemoradiation with maintenance sorafenib therapy provided favorable responses for advanced HCC (22).

The study by Kim *et al.*, while provocative, leaves more questions than answers, presenting yet another twist on combination therapies for advanced HCC, this time using chemoradiation in combination with systemic therapy. This, of course, should not be surprising in the present HCC treatment landscape. As often the case when comparing results from Asia and Western regions,

**Table 1** Current trials for first-line combination therapy in HCC

Trial	NCT Identifier	Study phase	HCC Stage	Primary outcome	Therapy
<b>Systemic therapies</b>					
COSMIC-021	NCT03170960	Phase 1/2	BCLC B/C	ORR	Cabozantinib + IO (atezolizumab)
COSMIC-312	NCT03755791	Phase 3	BCLC C	OS/PFS	Cabozantinib +IO (atezolizumab) vs. sorafenib
HIMALAYA	NCT03298451	Phase 3	BCLC C	OS	IO (durvalumab anti PD-L1 ± tremelimumab anti-CTLA-4) vs. sorafenib
RATIONALE-301	NCT03412773	Phase 3	BCLC B/C	OS	IO (tislelizumab) vs. sorafenib
LEAP-002	NCT03713593	Phase 3	BCLC C	OS/PFS	Lenvatinib ± IO (pembrolizumab)
CS1003	NCT04194775	Phase 3	BCLC B/C	OS/PFS	Lenvatinib ± IO (CS1003 anti-PD1)
CheckMate 9DW	NCT04039607	Phase 3	BCLC C	OS	IO (nivolumab + ipilimumab) vs. sorafenib/lenvatinib
SHR1210	NCT03605706	Phase 3	BCLC C	OS	IO (SHR1210 anti-PD-1) + FOLFOX4 vs. sorafenib/FOLFOX4 alone
ORIENT 32	NCT03794440	Phase 2/3	BCLC B/C	OS/ORR	IO (sintilimab anti-PD-1) + IBI305 (anti-VEGF) vs. sorafenib
IO/antiphosphatidylserine	NCT03519997	Phase 2	BCLC C	ORR	IO (pembrolizumab) + bavituximab (anti-PS)
IO pre-transplant	NCT04035876	Phase 2	Pre-transplant	DCR	IO (camrelizumab anti-PD-1) + apatinib
<b>Ablation/resection + systemic</b>					
EMERALD-2	NCT03847428	Phase 3	BCLC A	RFS	Resection/ablation ± IO (durvalumab) ± bevacizumab
IMBRAVE-050	NCT04102098	Phase 3	BCLC A	RFS	Resection/ablation ± IO (atezolizumab) + bevacizumab
IMMULAB	NCT03753659	Phase 2/1-arm	BCLC A	ORR	Neoadjuvant/adjuvant IO (pembrolizumab) + ablation
CheckMate 9DX	NCT03383458	Phase 3	BCLC A	RFS	Resection/ablation ± IO (nivolumab)
KEYNOTE-937	NCT03867084	Phase 3	BCLC A	RFS/OS	Resection/ablation ± IO (pembrolizumab)
SOURCE	NCT04143191	Phase 3	BCLC A	RFS	Resection + sorafenib ± TACE
FOLFOX HAI	NCT03851913	Phase 3	BCLC A/B	OS	Resection ± neoadjuvant mFOLFOX6 HAI
FOLFOX HAI	NCT03368651	Phase 3	BCLC C	OS	Resection ± neoadjuvant mFOLFOX6 HAI
JUPITER 04	NCT03859128	Phase 2/3	BCLC A	RFS	Resection ± IO (toripalimab anti-PD-1)
CA209-956	NCT03222076	Phase 2	Pre-resection	AE	Resection + neoadjuvant IO (nivolumab ± ipilimumab anti-CTLA-4)
<b>Transarterial + systemic</b>					
EMERALD-1	NCT03778957	Phase 3	BCLC B/C	PFS	TACE ± IO (durvalumab) ± bevacizumab
LEAP-012	NCT04246177	Phase 3	BCLC B/C	OS/PFS	TACE ± IO (pembrolizumab) + lenvatinib
FOLFOX HAI	NCT03164382	Phase 3	BCLC C	OS	FOLFOX HAI vs. sorafenib
FOLFOX HAI	NCT03775395	Phase 3	BCLC C	OS	FOLFOX HAI + sorafenib vs. +lenvatinib
FOLFOX HAI	NCT02856126	Phase 3	BCLC C	OS	FOLFOX HAI + sorafenib vs. TACE + sorafenib
TACE-3	NCT04268888	Phase 2/3	BCLC B	OS/TTTP	TACE ± IO (nivolumab)

Table 1 (continued)

Table 1 (continued)

Trial	NCT Identifier	Study phase	HCC Stage	Primary outcome	Therapy
CheckMate 74W	NCT04340193	Phase 3	BCLC B	OS/TTP	TACE + IO (nivolumab + ipilimumab) vs. +nivolumab
TAIPD1-HCC	NCT03869034	Phase 2	BCLC B/C	PFS	FOLFOX HAI + IO (sintilimab)
NASIR-HCC	NCT03380130	Phase 1	BCLC B/C	AE	Y90 SIRT + IO (nivolumab)
PETAL	NCT03397654	Phase 1/2	BCLC B	AE	TACE + IO (pembrolizumab)
IMMUTACE	NCT03572582	Phase 2	BCLC B	ORR	TACE + IO (nivolumab)
TACE + IO	NCT03638141	Phase 2	BCLC B	ORR	TACE + IO (durvalumab + tremelimumab)
TRIPLET	NCT04191889	Phase 2	BCLC C	ORR	FOLFOX HAI + IO (camrelizumab) + apatinib
HCRN: GI15-225	NCT03099564	Phase 1	BCLC B/C	PFS	Y90 SIRT + IO (pembrolizumab)
XRT + systemic					
RTOG-1112	NCT01730937	Phase 3	BCLC B/C	OS	Sorafenib ± SBRT
ISBRT01	NCT04167293	Phase 2	BCLC C	PFS	TACE/HAI + SBRT + IO (sintilimab) vs. + SBRT alone
XRT + transarterial					
SBRT + TACE	NCT03895359	Phase 3	BCLC A/B	OS/TTP	TACE ± SBRT
TACE-EBRT	NCT03116984	Phase 3	BCLC B/C	OS	TACE ± XRT
TACE-EBRT	NCT03939845	Phase 3	BCLC C	OS	TACE ± XRT
TACE-SBRT	NCT02794337	Phase 2/3	BCLC B	TTP	TACE + XRT vs. TACE + sorafenib

HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer stage; IO, immunotherapy; ORR, objective response rate; PFS, progression-free survival; RFS, recurrence-free survival; DCR, disease control rate (proportion of patients with complete response, partial response, and stable disease); OS, overall survival; AE, adverse events; TTP, time to progression; XRT, external beam radiation therapy; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; HAI, hepatic arterial infusion.

the underlying etiology of hepatitis B virus (HBV) as the driver of liver disease, and HCC, makes it difficult to generalize outcomes. As a dramatic example, nearly 20% of the patients in this cohort achieved definitive transplant or resection, even some with main portal vein tumor invasion (22). This phenomenon is effectively never seen in Western cohorts with primarily hepatitis C virus (HCV), alcohol or non-alcoholic steatohepatitis (NASH) related liver disease with the greater proportion of patients with HCC and concomitant cirrhosis. Furthermore, it is unclear whether outcomes were censored for transplant or resection, an effect which would artificially inflate the effect of the studied therapy. In addition, based on the treatment history of the patients on the trial, the combined outcomes are really reflective of multi-part therapy combining chemoinfusion, XRT, TACE, and systemic therapy with sorafenib. The heterogeneity of this experience, along with the heterogeneity of patient cohort, is relevant and may

have significantly impacted the results, particularly when a control cohort treated with sorafenib alone was not studied. In many ways, this was a missed opportunity, although arguably not the goal of a phase II trial. That said, 27.7% of the cohort ultimately did not receive sequential sorafenib therapy, and 10.6% were rendered ineligible due to toxicity from XRT, further impacting a clear understanding of outcomes (22). In regard to the choice of treatments on trial, experience with chemoradiation and chemoinfusion via an implantable pump for HCC has been limited outside of Asia, has had conflicting results, and may not be routinely available. Furthermore, chemoradiation with hypofractionation has not been rigorously compared to other radiation delivery techniques such as SBRT, which has gained favor for HCC in North America (6). Additionally, sorafenib has been shown less effective against HBV-related HCC (7), leaving open the question of whether even better outcomes on trial may have been observed with different

maintenance systemic therapy regimens. Nevertheless, this study contributes to the mounting interest in combining XRT and systemic therapy, both with existing molecular targeted agents and with immunotherapy. It is therefore important to carefully interpret the results of this study within the larger context of current trials underway for advanced HCC.

### **Combination locoregional and systemic therapy for HCC**

Combination therapies for HCC are increasingly being seen to provide superior treatment responses compared to monotherapies. This has been observed with TACE and ablation in early stage disease and is now being considered more fervently in intermediate and advanced stage disease. Although in the adjuvant setting, addition of sorafenib historically has not shown superiority over monotherapy with TACE or resection/ablation (23,24), current phase III trials are underway examining the role of newer systemic therapies with resection or ablation in early stage HCC, and with TACE for intermediate stage disease (*Table 1*). Both strategies include immune checkpoint inhibition as part of the treatment paradigm, with the idea that tumor antigens may be released as part of locoregional therapy to augment the efficacy of immunotherapy. More aggressive combination therapies for advanced HCC have also been explored, with several including combination systemic therapies, but also combination locoregional and systemic therapies (*Table 1*). In this realm, locoregional radiotherapies are intriguing, as the potential immunogenicity of radiotherapy has been proposed as a rationale for combination therapies with immune checkpoint inhibition (25). From the perspective of transarterial therapy, the small (30–60 micron) particles used in radioembolization are less likely to pose ischemic risks in the setting of portal venous invasion with advanced HCC (26). With external beam radiotherapy, the concept of treatment tolerability and ability to target suitable radiation fields with portal venous invasion is of interest (6,27). Considering the majority of patients presenting with advanced HCC nevertheless have liver-only or liver-dominant disease, there is appeal in a combination approach that not only delivers maximum potential therapy to the site of greatest tumor burden, but also provides additional putative durability of treatment response by way of systemic therapy given the high-risk profile for rapid disease progression.

### **Concluding remarks**

Despite the four decades during which locoregional therapies have been used for HCC, primarily by way of TACE, it is notable that it has only been in the last twenty years that we have shown through rigorous trials that this therapy is superior to best supportive care. Over the last decade, treatment of HCC has arguably been without much controversy: transplantation or resection for those few who were candidates, ablation for the majority with early stage disease who were not surgical candidates, TACE or radioembolization for intermediate stage disease, and sorafenib or palliative care for those with advanced disease. It has really been in the last few years where we have seen the emergence of newer therapeutics, and more aggressive combination therapies, that we have increased the potential for actually changing outcomes for this grave disease. As such, for patients other than those with early stage disease where transplantation or resection remain the best chance for a durable outcome, it has become very challenging now to know what the optimum therapies are. This obfuscation, while potentially frustrating, could be welcomed because now we truly have more options on the table. In many ways, the increasing heterogeneity of treatments for HCC mimics the high degree of molecular heterogeneity in HCC itself. Improved molecular diagnostics of patient tumors by way of increasing biopsy banks will therefore be crucial to better identify those most likely to benefit from the increasing availability of therapeutic options. Furthermore, big data analytical tools, including omics-based approaches, will undoubtedly be needed to help sift through the heterogeneity of patient treatments and outcomes. To invoke the infamous quote by Mark Twain, “*If you don’t like the weather in New England now, just wait a minute.*” Such is the current climate of HCC therapies, and it will be incumbent on all of us to keep our eyes on the horizon.

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