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REVIEW

Trial Designs for Integrating Novel Therapeutics into the Management of Intermediate-Stage Hepatocellular Carcinoma

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Abstract: Intermediate-stage hepatocellular carcinoma (HCC) consists of heterogeneous groups of patients in terms of tumor burden and organ function reserves. Although liver-directed therapy (LDT), including trans-catheter arterial chemoembolization, radio-frequency ablation or even surgical resection, is the recommended frontline treatment modality, intrahepatic and distant failures are common. The recent advances in systemic treatment, notably the introduction of immune checkpoint inhibitor (ICI)-based therapy, have significantly improved the objective tumor response rate, quality of response and overall survival in patients with recurrent and advanced HCC. Whether the combination of systemic treatment and LDT can further improve the outcome of patients with intermediate-stage HCC is currently being extensively evaluated. In this article, the recent clinical trials incorporating different ICI-based combinations with different LDT for intermediate-stage HCC were reviewed focusing on trial design issues, including patient selection, endpoint definition, and biomarker development. The strength and caveats of different combination strategies and novel biomarker development were discussed.

Keywords: immunotherapy, liver-directed therapy, biomarker

Introduction

In the past few years we have witnessed major advances in systemic therapy for hepatocellular carcinoma (HCC) in the following aspects. First, immune checkpoint inhibitor (ICI)-based combination therapy has demonstrated a survival benefit, compared with single-agent sorafenib therapy, as first-line systemic therapy for unresectable HCC, thus becoming the new standard therapy for unresectable HCC.[1–4] Anti-PD1/ anti-PDL1 ICI therapy is currently the backbone for development of new therapeutic regimens for HCC. Second, with more than a decade of struggle over failed clinical trials,[5] the platforms of clinical and translational research of drug development for HCC became more mature to accommodate new treatment options in different clinical settings.[6–9] Third, the heterogeneity of HCC biology, clinical presentation and practice patterns among different geographic regions was increasingly recognized and incorporated in clinical trials for advanced HCC as stratification factors. The difference in practice patterns was also recognized by international practice guidelines to refine treatment recommendations based on randomized controlled trials, cohort studies, as well as expert consensus[10–14]

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The advances in systemic therapy for HCC ushered in a burgeoning of clinical trials of systemic therapy in earlier stage HCC, mostly in combination with liver-directed therapy (LDT). However, initial attempts at combining the multi-kinase inhibitor (MKI) sorafenib with trans-catheter arterial chemo-embolization (TACE) did not demonstrate improved overall survival for patients who received combination therapy (Supplementary Table S1).[15–20] Design and conduct of this type of clinical trials have to tackle several challenges. TACE may not be suitable for all patients with intermediate-stage HCC, and the criteria of patient selection and determination of TACE refractoriness are still evolving.[11,21] Determination of tumor progression based on imaging criteria was subjected to evaluation bias and led to inconsistent adherence to study treatment. Furthermore, interpretation of survival benefit in these trials was confounded by heterogeneous post-progression therapy and treatment cross-over.[22,23]

To realize the therapeutic potential of the new systemic therapy in intermediate-stage HCC, the above-mentioned challenges have to be overcome, and novel approaches of biomarker development for patient enrichment and efficacy prediction have to be developed.[24] In this article, the study design of different treatment strategies for intermediate stage HCC were reviewed, in the context of the most updated practice guidelines from the Barcelona Clinic Liver Cancer (BCLC),[13] the American Association for the Study of Liver Diseases (AASLD),[25] and the European Society for Medical Oncology (ESMO).[14] Adaptation based on variations of practice patterns around the world was addressed. Novel approaches of biomarker development and future perspectives were discussed.

The Evolving Concept of Heterogeneity in Intermediate-Stage HCC

Intermediate-stage (BCLC stage B) HCC was originally defined as HCC patients with preserved liver function, good performance status, and multifocal liver tumors (>3 nodules or >3 cm in diameter) without vascular invasion or extrahepatic spread. Discussion of heterogeneity issues initially focused on the definition of tumor burden because of its direct impact on treatment choice, particularly the use of TACE. The up-to-seven criteria were the most commonly used criteria in sub-classification of BCLC stage B patients.[21,26,27] Although the criteria were developed to identify candidates for liver transplantation,[28] patients within the up-to-seven criteria were also more likely to benefit from TACE, and selected patients may even be considered for surgery or ablation therapy with curative intent.[29,30] At the other end of the spectrum, patients with diffuse, bilobar tumors or infiltrative tumors were unlikely to benefit from TACE, and systemic therapy was increasingly recommended as the first-line therapy for this subgroup of patients.[11,13,14,31] Therefore, a key issue of defining the subgroups based on liver tumor burden is to facilitate selection between liver-directed therapy and systemic therapy.[11,32]

Another key issue of sub-grouping is to stratify patients for better prognostic prediction, which is vital for clinical trial design. In previous randomized trials of TACE plus targeted therapy for intermediate-stage HCC, various criteria of tumor burden were used to stratify subjects (Supplementary Table S1). Variations of the up-to-seven criteria were also proposed, based on retrospective analysis of large patient cohorts, for predicting response to TACE and survival in intermediate-stage HCC.[33–35] These variations partly reflected the different practice patterns of liver-directed therapy in different geographic regions.[36,37] Moreover, the prognosis of HCC patients is closely related to the patients' liver function reserves, which may be impaired by the underlying liver diseases or previous liver-directed therapy. The Child–Pugh classification is at best a crude estimate of the patients' liver function status, and new scoring systems, such as the ALBI grade, the HAP score, and the ART score, may provide more detailed prognostic information.[38–40] Harmonization of the stratification criteria in international clinical trials can be a challenging task.

The multitude of liver-directed therapies added yet another aspect in the heterogeneity of management for intermediate-stage HCC. TACE was recommended as standard of care for intermediate-stage HCC primarily based on meta-analysis of early randomized trials.[41,42] However, the type and dosage of chemotherapeutic agents, the schedule and techniques of intervention, and the criteria to determine progression and re-treatment, differed from country to country and even from institution to institution.[43–45] Other liver-directed therapies, including yttrium-90 selective internal radiation therapy (Y-90 SIRT, also known as trans-arterial radioembolization, TARE), external beam radiation therapy (EBRT), and hepatic arterial infusional chemotherapy (HAIC), were recommended by regional practice guidelines, based primarily on retrospective or prospective cohort studies as well as expert opinions (Table 1).[13,46–52] Of note, HAIC was recently shown by a randomized trial from China to achieve superior overall and progression-free survival, compared

Table 1 Variations of Treatment Recommendation for Intermediate-Stage HCC by Different Practice Guidelines

	TACE	LT	Y-90 SIRT	Resection	Ablation	HAIC	EBRT
Barcelona Clinic Liver Cancer[50]	v						
European Association for the Study of the Liver[31]	v	v					
American Association for the Study of Liver Diseases[25]	v	v	v				
European Society for Medical Oncology[14]	v	v	v	v			
Pan-Asian Adapted ESMO[10]	v	v	v	v	v	v	
Hong Kong Liver Cancer staging[51]	v			v			
Asian Pacific Association for the Study of the Liver[52]	v			v	v		
China[46]	v	v		v	v		
Korean Liver Cancer Study Group[47]	v	v		v	v		v
Japan Society of Hepatology[48] †	v	v		v	v	v	
Taiwan Liver Cancer Association[49]	v	v	v	v	v		v

Note: †The detailed algorism was not provided in the 2021 update version of JSH guideline so previous version was used instead.
Abbreviations: TACE, transarterial chemoembolization; LT, liver transplantation; Y-90 SIRT, yttrium-90 selective internal radiation therapy; HAIC, hepatic arterial infusion chemotherapy; EBRT, external beam radiation therapy.

with TACE, for large unresectable HCC.[53] HAIC and EBRT may also improve survival in HCC patients with portal vein thrombosis.[54,55] These liver-directed therapies may serve as "post-progression" therapy in clinical trials for intermediate-stage HCC, and the survival analysis will be confounded by the availability and technical expertise of these treatment options.

Challenges of Designing Clinical Trials for Intermediate-Stage HCC

Although overall survival (OS) is the traditional endpoint for clinical trials pursuing regulatory approval of new treatments, using OS to evaluate the efficacy of new treatment strategies for intermediate-stage HCC has the following caveats. First, the median OS in intermediate-stage HCC usually exceeds two years but varies widely because of the different tumor characteristics mentioned earlier. Estimation of the survival outcome for the control group is thus difficult. Second, as the treatment stage migration becomes more and more common, the survival outcome of both the treatment group and the control group in new clinical trials for intermediate-stage HCC is likely to improve.[56,57] Third, the potential survival benefit of the new treatment tended to be negated by the use of post-progression therapy (liver-directed or systemic). Therefore, the value of surrogate efficacy endpoints was increasingly recognized.[6]

Using surrogate endpoints to evaluate the efficacy of new anti-cancer therapy continues to be a trade-off between efficiency of clinical trials and risk of inadequate scientific and clinical validity.[58,59] The correlation between OS and surrogate efficacy endpoints, including PFS, time to progression (TTP), and objective response rate (ORR), was explored in 21 Phase III trials of advanced HCC.[60] A moderate correlation (R = 0.83–0.84) between OS and PFS or TTP was found, and the investigators suggested that a PFS hazard ratio of ≤0.6 may predict OS benefit of new treatment for advanced HCC.[60] However, this conclusion was derived primarily from the positive trials of targeted therapy (for advanced stage HCC) in the second-line setting, in which the post-progression survival was relatively short. The confounding effect of post-progression survival will be more problematic in clinical trials for earlier stages of HCC.[61]

The most challenging issue for the design of clinical trials for intermediate-stage HCC is to overcome the confounding effects of heterogeneity of patient characteristics and treatment patterns. Stratified (block) randomization is the most commonly used method to balance important covariates among treatment groups in randomized trials. Other covariate-adaptive randomization techniques to improve the marginal balance (i.e., balance at individual covariate levels) were recommended, such as minimization or dynamic hierarchical randomization, which allowed different levels of imbalance

among the covariates.[62] However, balancing on the margins of the stratification variables will increase the variance of the treatment effect estimates more than stratified permuted blocks, thus impairing the efficiency of the primary endpoint analysis.[63] A hybrid approach to both achieving marginal balance and improving the inefficiency caused by minimization or dynamic hierarchical randomization was thus proposed.[64] In reality, although these new randomization methods may accommodate more stratification factors than conventional block randomization, some factors, such as the participating sites in international trials, are still difficult to handle, thus harmonization of practice patterns is crucial for the efficiency of clinical trials for intermediate-stage HCC.

PFS is increasingly being adopted in HCC trials as a primary endpoint. Therefore, the potential bias associated with the criteria to determine progression and re-treatment for HCC patients who received liver-directed therapy must be carefully controlled.[65] Tumor response measurement by imaging should be done at regular intervals with the same frequency among treatment arms, and the results should be centrally reviewed to avoid evaluation bias. Definition of progression and feasibility of further liver-directed therapy should be clarified to avoid variation of drop-out among treatment arms (attrition bias). In clinical trials of TACE plus targeted therapy for intermediate-stage HCC, drop-out may be due to either tumor progression or deterioration of organ function, and the drop-out patterns of different treatment arms should be analyzed in detail. Moreover, in real-world practice patients may receive repeated TACE for intra-hepatic recurrence unless major vascular invasion or extra-hepatic metastases occurred. Therefore, the criteria of "time to untreatable/unTACEable progression (TTUP)" based on response to prior TACE, occurrence of major vascular invasion or extra-hepatic metastases, and organ function reserves, were developed.[11] Three studies (BRISK-TA, ORIENTAL and TACTICS) incorporated this concept to define tumor progression, and all of the 3 studies demonstrated improved TTP for the study drug arm compared with the control arm. However, no OS benefit was observed in these studies to date.

Ongoing Trials of Immunotherapy in Intermediate Stage HCC

To obtain a comprehensive view of development of immune checkpoint inhibitors-based therapy, anti-PD1/ anti-PDL1 with and without anti-CTLA4 for intermediate stage HCC, we searched the clinical trials registered at ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), using combinations of the following keywords: (hepatocellular carcinoma) AND (intermediate stage OR locoregional OR downstage) AND (nivolumab OR pembrolizumab OR tislelizumab OR camrelizumab OR sintilimab OR cemiplimab OR toripalimab OR atezolizumab OR durvalumab OR avelumab OR ipilimumab OR tremelimumab). A total of 102 studies were screened and 42 studies, including 8 phase III and 34 phase I/II studies, were included in this review (Figure 1). The following aspects of trial design were further analyzed: types and timing of liver-directed intervention, definition of potential confounding factors, and the prospect of systemic therapy alone for intermediate stage HCC.

Type of Liver-Directed Intervention

Liver-directed therapy may induce immunogenic cell death and therefore enhance the efficacy of immunotherapy.[66] Among 42 ongoing trials as of November 21, 2021, TACE was the most commonly used local reginal therapy, followed by Y-90 SIRT. Although cell damage caused by TACE may increase exposure of tumor antigens, TACE-induced hypoxia may increase hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) production in tumor microenvironment that resulted in immune suppression.[67,68] On the other hand, Y-90 SIRT may induce more tumor infiltrating lymphocytes (TILs) than TACE or direct surgical resection.[69] In a randomized phase II study, Y-90 SIRT demonstrated significantly longer TTP and numerically better OS.[70] Non-randomized studies also suggested better tolerability, shorter hospitalization, and comparable survival compared with historical results of standard treatments.[71,72] The efficacy and safety of ICI therapy plus Y-90 SIRT was demonstrated in a phase II study by Lee et al.[73] Of 36 treated subjects, 11 subjects showed objective response as per RECIST 1.1, while ≥ grade 3 treatment-related adverse events occurred in only 5 of 36 subjects. Comparison between ICI therapy plus Y-90 SIRT and ICI therapy plus TACE is ongoing (NCT04522544).

EBRT was generally reserved for patients with localized HCC not suitable for resection or ablation,[74,75] and was only listed as a treatment option by the KLCSG and TLCA practice guideline (Table 1). A recent randomized trial

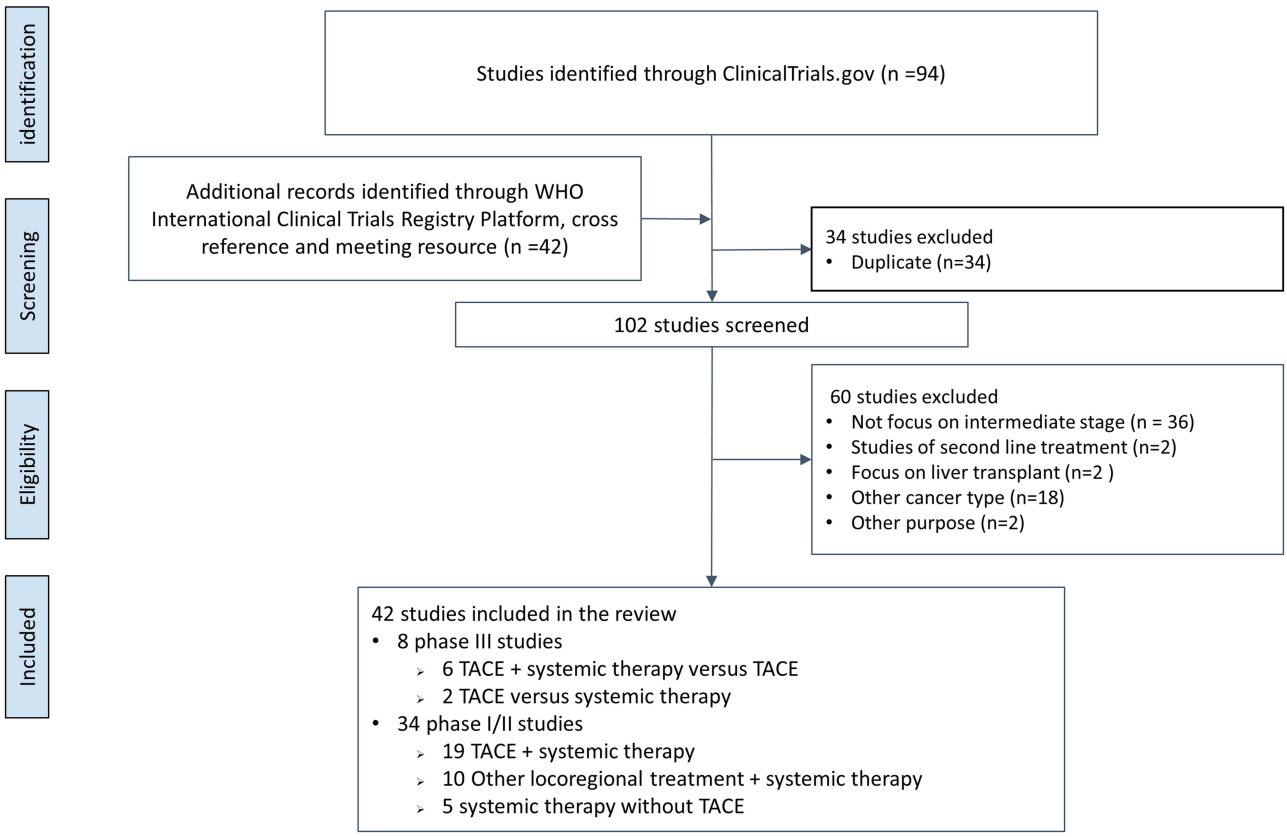

Figure 1 PRISMA flow chart for the selection of studies. Number of studies identified by search terms of (hepatocellular carcinoma) AND (intermediate stage OR locoregional OR downstage) AND (nivolumab OR pembrolizumab OR tislelizumab OR camrelizumab OR sintilimab OR cemiplimab OR toripalimab OR atezolizumab OR durvalumab OR avelumab OR ipilimumab OR tremelimumab). Last accessed on November 21, 2021.

demonstrated EBRT plus TACE was superior to sorafenib in HCC patients with vascular invasion.[54] Besides, 2 non-randomized studies using propensity score-matched analysis demonstrated comparable OS and better local control for EBRT, compared with TACE.[76,77] Induction of immunogenic cell death by EBRT has been extensively studied, which has been shown to improve antitumor efficacy of ICI therapy in other cancer types.[78–81] It is thus reasonable to explore potential synergistic antitumor immunity between EBRT and ICI therapy in HCC.

The use of HAIC was also heterogeneous in terms of types and dosage of chemotherapeutic agents and criteria of patient selection. HAIC has been widely adopted by Japanese physicians, and retrospective studies disclosed comparable efficacy between HAIC and TACE.[82–86] However, it has not been recommended by most international and regional practice guidelines.[14,31,46,47,49,52] One study group in China reported 2 positive randomized trials of HAIC using oxaliplatin, leucovorin, and fluorouracil in HCC. The first trial reported superior OS of HAIC plus sorafenib, compared with sorafenib monotherapy, in HCC patients with portal vein invasion.[55] The second trial reported superior OS, PFS, and response rate for patients with unresectable HCC, compared with sorafenib, in patients with unresectable HCC.[87] Reproducibility of these promising results should be confirmed before incorporating HAIC into clinical practice guidelines. Nevertheless, combination of HAIC and ICI therapy is reasonable because of the potential of immunogenic cell death induction by cytotoxic agents.

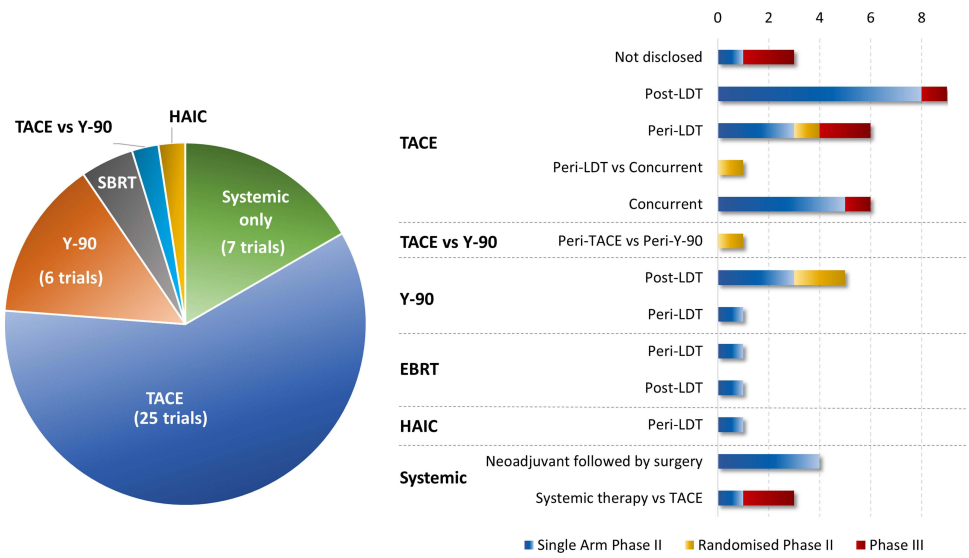

Figure 2 Ongoing trials of ICI-based therapy in intermediate stage HCC. The pie chart (left) demonstrates trial numbers of liver-directed therapy in combination with ICIs. The stacked bars (right) elucidate the composition of trial design with different liver-directed therapy. The timing of TACE are not clearly described in three trials including two randomized phase III trials.

Timing of Liver-Directed and ICI Intervention

Most of the earlier studies combining TACE and targeted therapy adopted the post-LDT approach (Figure 2). Theoretically, HIF-1α, VEGF, and other cytokines induced by TACE may promote tumor angiogenesis, recurrence and metastasis after TACE.[88–90] Therefore, immediate inhibition of angiogenesis after TACE may provide the best therapeutic effect. In the Japan-Korea Post-TACE study, central image review of response to TACE was required before randomization. This requirement resulted in delay of sorafenib treatment for subjects randomized to the sorafenib treatment arm (about 60% of subjects started treatment more than 9 weeks after TACE), and the delay of treatment start may be associated with worse clinical outcome.[15] All subsequent trials randomized the subjects before TACE and 3 studies (SPACE, TACE-2 and TACTICS) even started study drug treatment before TACE. Starting drug treatment before TACE allowed the physicians to adjust the optimal tolerated dosage of study drugs before TACE and therefore drug treatment after TACE may be less likely to be interrupted by treatment-related toxicities.

Post-LDT therapy is also the most common design of randomized trials combining TACE and ICI-based therapy (Table 2 and Figure 3).[91–94] The complexity of study design issues has been extensively reviewed elsewhere to get insight from previous trials.[22,95] Most trials incorporated more detailed definition of patient characteristics (e.g., ALBI grade,[96,97] HAP score,[6,98,99] AFP level[100]) and treatment patterns (e.g., geographic regions or study sites, drug-eluting beads versus conventional TACE) in the hope of better stratification for this very heterogeneous patient population. Several trials incorporated TACE-specific endpoints, such as time to TACE progression (TTTP), to avoid confounding by post-progression therapy. OS was not used by all trials as a primary endpoint, most likely due to concerns of confounding by post-progression therapy.

Neoadjuvant therapy became an attractive approach recently. Neoadjuvant ICI therapy may stimulate more diverse T cell responses to overcome the potential immune suppression induced by liver-directed therapy.[101] The higher response rates of ICI-based therapy may increase the opportunity of tumor downstaging, but there is a risk of delay of primary treatment and disease progression, or even hyper-progression, during neoadjuvant therapy (see below).[102–104]

Early-phase clinical trials testing ICI-based systemic therapy for intermediate-stage HCC were more flexible in endpoint selection, timing of systemic therapy, and the choice of liver-directed therapy (Tables 3–5).[73,105–112] The vast majority of these trials were single-arm studies, and PFS and ORR were commonly used as the primary endpoints. Both modified RECIST and RECIST 1.1 were used for response evaluation. Immune-related RECIST[113] was not commonly used. Systemic therapy was given before (neoadjuvant), concurrent, after (adjuvant), or both before and after liver-

Table 2 Randomized Phase III Trials of Combining TACE and ICI-Based Therapy in Intermediate Stage HCC

Study	Major Inclusion Criteria	Intervention	Primary End Points (Major Response Evaluation Criteria)[†‡]	Stratification Factors
EMERALD-1 NCT03778957 (n=600)[91]	No main portal vein thrombosis (vp3/vp4)	1:1:1 randomization to • TACE→ Durvalumab + Bevacizumab • TACE→ Durvalumab • TACE→ Placebo	PFS[†] (RECIST 1.1)	• Geographic region (Japan vs Asia [non-Japan] vs Other) • Portal vein invasion (Vp1 or Vp2 vs none) • TACE modality (DEB-TACE vs cTACE)
LEAP-012 NCT04246177 (n=950)[92]	• Localized to the liver without portal vein thrombosis • All lesion <10 cm • <10 tumor nodules • Tumor burden below 50% of liver volume	1:1 randomization to • Pembrolizumab 400mg + Lenvatinib 8 or 12 mg QD for 2–4W → TACE →Pembrolizumab 400mg Q6W + Lenvatinib 8 or 12 mg QD • Placebo + TACE	• PFS • OS (RECIST 1.1)	• Study site • ECOG PS • ALBI grade • AFP • Tumor burden
TACE-3 NCT04268888 (n=522)	• HAP score A, B or C • No hepatic artery or main portal vein occlusion	1:1 randomization to • Nivolumab x1 →TACE → Nivolumab 480mg Q4W • Placebo x1 →TACE →Placebo 480mg Q4W	OS (RECIST 1.1 for secondary endpoint PFS/ ORR)	• Study site • Baseline HAP score (A vs B vs C) • Vascular invasion (No vs Yes).
CheckMate 74W NCT04340193 (n=765)[93]	• Beyond the Milan and Up-to-7 criteria • No portal vein thrombosis • No vascular invasion	1:1:1 randomization to • Nivolumab + Ipilimumab + TACE • Nivolumab + TACE • Placebo + TACE	Time to TACE progression[†] (Newly defined criteria) [‡]	• Region (West vs Japan vs rest of Asia) • ALBI grade (1 vs 2) • AFP level (< vs ≥ 400 ng/mL)
TALENTACE NCT04712643 (n=342)[94]	• Eligible for TACE treatment • Tumor max diameter + tumor number ≥6 • No macrovascular invasion	1:1 randomization to • Atezolizumab 1200mg + Bevacizumab 15mg/kg + TACE • TACE alone	• OS • TACE PFS (Newly defined criteria)[‡]	N/A
NCT05056337 (n=220)	China Liver Cancer Staging IIb and IIIa with one of the following: ■ Portal vein thrombosis (vp3-vp4) ■ > 3 tumor nodules	1:1 randomization to • Lenvatinib 8 or 12mg QD + Toripalimab 240mg Q3W+ TACE • TACE alone	ORR [†] (mRECIST)	N/A

Notes: [†]Three randomized phase III trials (EMERALD-1, CheckMate 74W and NCT05056337) do not use OS as primary endpoint. [‡]Two trials use newly defined TACE specific primary endpoints, time to TACE progression (TTTP) in CheckMate-74W and TACE PFS in ML42612. TTTP is defined as time to progression from the first image taken after TACE. TACE PFS is defined as time from randomization to untreatable progression or TACE failure/refractoriness and any cause of death.
Abbreviations: TACE, transarterial chemoembolization; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

directed therapy (peri-LDT). In a phase I study, Harding et al reported nivolumab could be safely delivered with TACE either as adjuvant (cohort 1), as peri-LDT (cohort 2) or concurrently (cohort 3) (Table 3).[110] No new safety concern was observed; only one subject in cohort 3 experienced grade 3 transaminitis and this resolved spontaneously without recurrence after rechallenge of nivolumab. The efficacy of TACE followed by nivolumab was further demonstrated by Vogel et al in a phase II study, the IMMUTACE study.[111] Of the 49 enrolled intermediate stage subjects, the ORR

Study	Design	Medications	≤ Milan's	≤ Rule 7's	> Rule 7's	Vp 1-2	Vp 3-4
Phase III							
EMERALD-1	*Post*-TACE	Durvalumab ± Bevacizumab	●	●	●	●	
LEAP-012	*Peri*-TACE	Lenvatinib + Pembrolizumab	●	●	●		
TACE-3	+ TACE	Nivolumab	●	●	●	●	
CM-74W	*Post*-TACE	Nivolumab + Ipilimumab		●	●		
ML42612	*Post*-TACE	Atezolizumab + Bevacizumab	●	●	●		
NCT05056337	*Post*-TACE	Lenvatinib + Toripalimab	●	●	●	●	●
RENOTACE	*vs* TACE	Regorafenib + Nivolumab			●		
ABC-HCC	*vs* TACE	Atezolizumab + Bevacizumab		●	●		
Phase II							
NCT04522544	*peri*-TACE *vs* Y-90	Durvalumab + Tremelimumab	●	●	●		
NCT04541173	*Post*-Y-90	Atezolizumab + Bevacizumab	●	●	●	●	
NCT05063565	*Post*-Y-90	Durvalumab + Tremelimumab	●	●	●		
DEMAND	*Peri vs* + TACE	Atezolizumab + Bevacizumab	●	●	●		
NCT04997850	+ TACE	Lenvatinib + anti-PD-1	●	●	●		

Figure 3 Eligibility criteria of tumor burden in ongoing randomized trials. Most trials do not preclude patients with low tumor burden (within Milan's criteria) except 3 phase III trials (CheckMate-74W, RENOTACE and ABC-HCC). The RENOTACE trial, which directly compares systemic therapy with TACE, only includes patients beyond up-to-seven but without vascular invasion. Invasion of portal vein branch (Vp1-2) are acceptable in 3 phase III and 1 phase II trials. One phase III trial (NCT05056337) includes patients with main portal vein invasion (Vp3-4).

according to mRECIST was 71% and the median PFS and OS were 6.1 months and 28.3 months, respectively. The most common ≥ grade 3 adverse events were that aspartate aminotransferase increased (14%) and GGT increased (10%).

As mentioned earlier, neoadjuvant therapy is increasingly applied to intermediate stage HCC. Zhang et al reported a preliminary result of 38 subjects who underwent neoadjuvant lenvatinib plus camrelizumab/sintilimab and TACE, followed by resection if feasible.[112] The ORR based on mRECIST was 84%. Of the 19 subjects (50%) who were able to undergo conversion resection, 6 had major pathological responses. Of note, the use of systemic therapy alone for intermediate-stage HCC is now entering the stage. About 15–20% of patients enrolled into previous clinical trials of systemic therapy for unresectable HCC had intermediate-stage disease, and these patients demonstrated similar efficacy/safety outcome compared with patients with advanced-stage disease.[1,115] Retrospective studies suggested that systemic therapy may achieve better ORR and PFS compared with TACE in intermediate-stage HCC patients with high tumor burden.[116,117] Currently clinical practice guidelines suggest upfront systemic therapy for intermediate-stage HCC with huge bilobar tumors or infiltrative tumors.[11,13,14,31] Clinical trials of upfront systemic therapy, on the other hand, generally enrolled patients whose tumors exceeded the Milan criteria or the up-to-seven criteria (Table 5).[6,11]

Future Perspective: Neoadjuvant ICI-Based Therapy as "Window of Opportunity"

The increased efficacy, in terms of survival and ORR, and favorable safety profile of ICI-based combination therapy for HCC provides several "windows of opportunities" for patients with intermediate-stage disease. Surgery and other curative therapy were reasonable treatment options for selected patients with intermediate-stage HCC (Table 1),[29,118,119] and response achieved by neoadjuvant systemic therapy may increase the proportion of patients for curative therapy and improve treatment outcome.[120,121] Tumor or blood samples obtained at diagnosis may help develop predictive biomarkers of treatment efficacy, and samples obtained after treatment may help explore pharmacodynamic endpoints and mechanisms of antitumor immunity.

Table 3 Phase I/II Trials of Combining TACE and ICI-Based Therapy in Intermediate Stage HCC

Study	Major Inclusion Criteria	Intervention	Setting[†]	Primary Endpoints (Major Response Evaluation Criteria) [‡]
NCT03143270 Phase I (n=14)[110]	BCLC Stage B	Cohort 1:TACE→ Nivolumab 240 mg Q2W x 1 year Cohort 2: Nivolumab 240 mg Q2W x2→ TACE → Nivolumab 240mg Q2W x 1 year Cohort 3: Nivolumab + TACE → Nivolumab 240 mg Q2W x 1 year	Post-LDT	Safety
NCT03397654 Phase I/II (n=26)	Ineligible for surgical resection or liver transplantation.	TACE→ Pembrolizumab 200 mg Q3W	Post-LDT	Safety
IMMUTACE NCT03572582 Phase II (n=49)[111]	Tumor burden below 50% of liver volume	TACE→ Nivolumab 240 mg Q2W	Post-LDT	ORR (mRECIST)
NCT03638141 Phase II (n=30)	Intermediate stage	TACE→ Durvalumab + Tremelimumab	Post-LDT	ORR (mRECIST)
NCT03753659 Phase II (n=30)	Candidate for local ablation with one of the following: ■ Presence of ≤ 5 tumor nodules with diameters ≤ 7cm ■ Vascular infiltration	Pembrolizumab 200 mg IV Q3W x2 → ablation ± TACE→ Pembrolizumab	Peri-LDT	ORR (RECIST 1.1)
NCT03937830 Phase II (n=22)	BCLC stage B	Durvalumab 1150 mg + Tremelimumab 300 mg + Bevacizumab 7.5 mg/kg x1 → TACE → Durvalumab + Bevacizumab Q3W	Peri-LDT	6-months PFS rate (RECIST 1.1)
NCT04174781 Phase II (n=61)	Tumor burden below 50% of liver volume with one of the following: ■ BCLC stage A but beyond Milan Criteria ■ BCLC stage B	Sintilimab 200mg Q3W + TACE simultaneously	Concurrent	PFS (mRECIST)
NCT04220944 Phase I (n=45)	• BCLC stage B or C • Tumor ≥ 5 cm	Ablation + TACE→ Sintilimab 200mg Q3W	Post-LDT	PFS (mRECIST)
NCT04224636 DEMAND Randomized Phase II (n=106)[105]	• No macrovascular invasion • ≤ 7 lesions with no lesion > 7 cm	1:1 randomization to • Neoadjuvant Atezolizumab + Bevacizumab→ TACE for progressive hepatic lesion→ Atezolizumab + Bevacizumab • Concurrent Atezolizumab + Bevacizumab + TACE	Peri-LDT vs Concurrent	24-month OS rate

(*Continued*)

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Table 3 (Continued).

Study	Major Inclusion Criteria	Intervention	Setting[†]	Primary Endpoints (Major Response Evaluation Criteria) [‡]
NCT04273100 Phase II (n=56)	BCLC stage B or C	PD-1 monoclonal antibody + Lenvatinib 8 mg or 12 mg + TACE	Concurrent	ORR (N/A)
NCT04472767 Phase II (n=35)	At least one lesion amenable to TACE treatment	Nivolumab 3 mg/kg + Ipilimumab 1mg/kg x1 →TACE→ Cabozantinib 40 mg QD + Nivolumab 480 mg Q4W	Peri-LDT	• 6-month PFS rate • Complete response rate (mRECIST)
NCT04483284 Phase II (n=60)	BCLC stage B or C	Camrelizumab 200 mg Q3W + TACE	Concurrent	PFS (N/A)
NCT04517227 (n=30)	One of the following: ■ 1 nodule (5–7cm) ■ 2-3 nodules ≤ 7cm, at least 1 nodule > 3cm ■ 4-5 nodules ≤ 7cm	TACE→ Ablation→ Durvalumab 1500 mg Q4W	Post-LDT	Safety
NCT04518852 Phase II (n=60)	BCLC stage B or C	Sorafenib 400 mg QD + anti-PD-1 monoclonal antibody 200mg Q3W + TACE	Concurrent	• ORR • OS (mRECIST)
NCT04592029 Phase I (n=36)	BCLC stage B or C	TACE→ Sintilimab 200 mg Q3W + Bevacizumab 7.5/mg or 15 mg/kg Q3W	Post-LDT	• Safety • PFS (RECIST 1.1)
NCT04605185 Phase I (n=18)	Unresectable	Donafenib 100–200 mg QD + Toripalimab 240 mg Q3W + TACE	N/A	Safety (RECIST 1.1)
NCT04988945 Phase II (n=33)	Potentially resectable with one of the following: ■ Tumor size 5–25 cm and number of lesions ≤3 ■ Portal vein involvement (Vp1-3)	TACE + SBRT →Durvalumab 1500 mg Q4W + Tremelimumab 300 mg x1	Post-LDT	Downstaging for hepatectomy
NCT04842565 Phase II (n=41)	• BCLC stage B • Beyond up-to-seven criteria	Sintilimab 200 mg Q3W + TACE	Concurrent	PFS (mRECIST)
NCT04997850 Randomized Phase II (n=142)[112]	• BCLC stage B/C	Lenvatinib (8 or 12 mg QD) x 2 weeks → TACE + Lenvatinib+ Camrelizumab/ Sintilimab (200 mg Q3W)	Peri-LDT	Downstaging for hepatectomy

Notes: [†]Summary of trial design: 1 peri-LDT vs concurrent, 8 post-LDT, 5 concurrent, 3 peri-LDT, and 1 without detailed information. [‡]Summary of evaluation criteria: 7 mRECIST and 4 RECIST 1.1.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; LDT, liver-directed therapy; TACE, transarterial chemoembolization; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

Table 4 Other Liver-Directed Therapy Combined Systemic Therapy in Intermediate Stage HCC

Study	Major Inclusion Criteria	Intervention	Setting[†]	Primary Endpoints (Major Response Evaluation Criteria) [‡]
NCT03099564 Phase I (n=30)	One of the following: • Right or left portal vein involvement (excluding vp4) • 3 tumors regardless of size • Diffuse disease amenable to liver-directed therapy	Pembrolizumab 200 mg x1 → Y-90 SIRT → Pembrolizumab 200 mg Q3W	Peri-LDT	6-month PFS rate (RECIST 1.1)
NCT03203304 Phase I (n=14) Terminated	Ineligible for curative intent therapy but amenable to SBRT	SBRT→ Nivolumab 240 mg Q2W + Ipilimumab 1 mg/kg Q6W	Post-LDT	Safety
NCT03033446 Phase II (n=40)[73]	Not suitable for resection or liver transplant but amenable for Y-90 SIRT	Y-90 SIRT→ Nivolumab 240 mg Q2W	Post-LDT	ORR (RECIST 1.1)
NCT03316872 Phase II (n=30)	• Maximum 10 lesions • Total tumor diameter <20 cm • No single liver tumor >15 cm • No evidence of common or main branch bile duct invasion	Pembrolizumab 200 mg x1 → SBRT→ Pembrolizumab 200 mg Q3W	Peri-LDT	ORR (RECIST 1.1 and iRECIST)
NCT03380130 Phase II (n=42)	• Single tumors> 5 cm • Multiple tumors in the BCLC-B2 substage • Predominantly unilobar tumors with segmental or lobar portal vein invasion	Y-90 SIRT→ Nivolumab 240 mg Q2W	Post-LDT	Safety
NCT03869034 Phase II (n=40)	Tumor is confined in the hemi-hepatic, with the tumor thrombus that does not reach the main portal vein	Sintilimab + HAIC	Concurrent	PFS (RECIST 1.1)
NCT04124991 Phase I/II (n=24)	Locally advanced	Y-90 SIRT→ Durvalumab 1500 mg Q4W	Post-LDT	TTP (mRECIST)
NCT04522544 Randomized Phase II (n=84)	• Multinodular or large, solitary HCC, not eligible for resection or local ablation • No segmental portal vein or hepatic veins invasion	1:1 randomization to • Durvalumab 1500 mg + Tremelimumab 300 mg x1 → Y-90 SIRT→ Durvalumab 1500 mg Q4W • Durvalumab 1500 mg + Tremelimumab 300 mg x1 → TACE→ Durvalumab 1500 mg Q4W	Peri-LDT	ORR (RECIST 1.1)

(*Continued*)

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Table 4 (Continued).

Study	Major Inclusion Criteria	Intervention	Setting[†]	Primary Endpoints (Major Response Evaluation Criteria) [‡]
NCT04541173 Randomized phase II (n=128)	• BCLC stage B and exceed the downstaging criteria defined as one of the following: ■ Peripheral vascular involvement of any size or number (excluding vp3/vp4) ■ ≥ 6 six lesions of any size ■ one lesion 5–8 cm ■ 2–3 lesions each ≤ 5 cm ■ 4-5 lesions ≤ 3 cm with total tumor diameter ≤ 8 cm	1:1 randomization to • Y-90 SIRT→ Atezolizumab 1200 mg + Bevacizumab 15 mg/kg Q3W • Y-90 SIRT→ Placebo	Post-LDT	PFS (RECIST 1.1)
NCT05063565 Randomized phase II (n=150)	• Unilobar tumor • Tumor volume ≤25% of whole liver volume • No vascular invasion	1:1 randomization to • Y-90 SIRT→ Durvalumab 1500 mg Q4W + Tremelimumab 300 mg x1 • Y-90 SIRT→ Observation	Post-LDT	• ORR • Duration of response (mRECIST)

Notes: [†]Summary of trial design: 1 SIRT vs TACE, 6 Y-90 SIRT, 2 EBRT and 1 HAIC. [‡]Summary of evaluation criteria: 2 mRECIST and 5 RECIST 1.1. Only one study (NCT03316872) using iRECIST.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; LDT, liver-directed therapy; Y-90 SIRT, yttrium-90 selective internal radiation therapy; HAIC, hepatic arterial infusion chemotherapy; EBRT, external beam radiation therapy; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks.

Table 5 Systemic Therapy Without TACE

Study	Major Inclusion Criteria	Intervention	Primary Endpoints (Major Response Evaluation Criteria)
jRCTs071200051 Phase II (n=70)[106]	Beyond up-to-seven criteria	Atezolizumab 1200 mg + Bevacizumab 15 mg/kg	PFS (mRECIST)
RENOTACE NCT04777851 Randomized phase III (n=496)	• Multinodular HCC localized to the liver • No evidence of vascular invasion • ALBI grade 1 or 2 • Beyond up-to-seven criteria	1:1 randomization to • Regorafenib 90 mg QD + Nivolumab 480 mg Q4W • TACE alone	PFS (mRECIST)
ABC-HCC NCT04803994 Randomized phase III (n=434)[109]	• Multifocal HCC beyond Milan criteria (i.e. >3 lesions of any size OR ≥2 lesions with at least one ≥ 3 cm) • No massive multinodular pattern preventing adequate TACE • Not diffuse infiltrative HCC • Patent portal vein flow	1:1 randomization to • Atezolizumab 1200 mg + Bevacizumab 15 mg/kg • TACE alone	Time to failure of treatment strategy (judged by investigator as treatment failure)
NCT03222076 Phase II (N=30)[107]	Cohort C: Borderline resectable	Nivolumab + Ipilimumab → OP→ Nivolumab + Ipilimumab	Safety
NCT03299946 Phase I (n=15)[124]	Potentially resectable defined as one of the following: ■ Solitary tumor >5 cm ■ Unilobar multifocal disease either with >3 tumors or one tumor >3 cm ■ Bilobar disease with adequate future liver remnant, still technically resectable ■ High-risk disease features (tumor >3 cm with macrovascular invasion or AFP>400)	Cabozantinib 40 mg QD for 2 months + Nivolumab 240 mg Q2W at week 3,5,7 and 9 → OP	Safety and number of patients who complete protocol treatment
NCT03510871[108] Phase II (n=40)	Potentially resectable defined as one of the following: ■ Bilateral multiple tumors, all <5 cm ■ Tumor number >3 and all <5 cm ■ Multiple tumors all <5 cm or solitary tumor >5 cm with significant portal hypertension ■ Vascular invasion	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W, up to 4 doses→ OP	Percentage of subjects with tumor shrinkage (>10% decrease in tumor size) (RECIST1.1)
NCT04843943 Phase I/II (n=30)	Potentially resectable, China Liver Cancer Staging IIa and IIb	Sintilimab: 200 mg IV + Bevacizumab biosimilar 15 mg/kg Q3W until resectable→ OP	• Safety • Events Free Survival (RECIST1.1)

Abbreviations: TACE, transarterial chemoembolization; PFS, progression-free survival; OP, operation; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks.

Kaseb et al reported the first neoadjuvant ICI-based therapy for HCC (Table 5).[122] Patients with resectable HCC were randomized to pre-operative nivolumab monotherapy (240 mg every 2 weeks for up to 3 doses) or the same dosage of nivolumab plus ipilimumab 1 mg/kg concurrent with the first dose of nivolumab. Subjects in the nivolumab monotherapy group received adjuvant nivolumab, 480 mg every 4 weeks for up to 2 years, and subjects in the nivolumab plus ipilimumab group received adjuvant nivolumab, 480 mg every 4 weeks for up to 2 years plus ipilimumab 1 mg/kg every 6 weeks for up to 4 doses. Objective response to pre-operative therapy, according to RECIST 1.1, was achieved in 3 subjects in nivolumab group and 0 in nivolumab + ipilimumab group. Twenty of the 27 randomized subjects (13 in

nivolumab group and 14 in nivolumab + ipilimumab group) received surgery, and major pathological response was achieved in 3 subjects in nivolumab group and 3 in nivolumab + ipilimumab group. Exploratory biomarker research using CyTOF and Nanostring transcriptomic analysis suggested that (1) increased immune cell infiltration in baseline tumor samples was associated with response to nivolumab therapy but less so with nivolumab + ipilimumab therapy; (2) major pathological response was associated with increased infiltration of activated T cells in the post-treatment samples; and (3) myeloid cells expressing the V-domain Ig suppressor of T-cell activation (VISTA) in the tumor microenvironment may contribute to resistance to ICI therapy.

This study highlighted several vital design issues for neoadjuvant or peri-operative systemic therapy for HCC. The regimen approved by the US FDA for advanced HCC (nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks, with a total of 4 doses of ipilimumab)[123] was not adopted in this study, probably due to the concern of treatment-related toxicity of a higher dose of ipilimumab. Longer duration of pre-operative systemic therapy may increase the objective response rate and chance of downstaging, but again may increase the odds of treatment-related toxicity. The contribution of adjuvant therapy in long-term outcome, especially OS, is difficult to measure, considering the enormous variation of LDT and systemic therapy if the tumors recur.

Ho et al reported another pilot study of neoadjuvant cabozantinib (40 mg per day for 8 weeks) plus nivolumab (240 mg every 2 weeks at weeks 3, 5, 7 and 9) in patients with potentially resectable HCC (Table 5).[124] Objective response per RECIST 1.1 was observed in only one of 15 subjects. Of the 12 subjects who successfully underwent surgical resection, 5 had major pathological responses. NanoString and CyTOF studies of the post-treatment tissue samples showed that (1) the number of tertiary lymphoid structures (TLS), effector CD8+ T cells, CD20+ B cells and CD 138+ plasma cells were significantly higher in responders than non-responders; (2) the existence of Arg-1/PD-1 expressing myeloid-derived suppressor cells (MDSCs) near T cells and B cells was associated with resistance to ICIs combination.

Transcriptomic analysis and CyTOF were two major approaches of high-dimensional analysis of the immune microenvironment.[125] Nanostring technology pioneered using formalin-fixed, paraffin-embedded (FFPE) tumor samples to perform RNA analysis and measurement of immune cell contexture, using pre-defined gene signatures representing individual classes of immune cells. Now RNA-seq can be performed using FFPE samples, thus providing opportunities of more comprehensive exploration of immune-related gene expression patterns and regulatory mechanisms. CyTOF, on the other hand, provides phenotypic characterization of immune cells based on protein expression and may thus complement RNA-based analysis. Fresh tissue samples were required for CyTOF analysis. Newer technology, such as multiplexed ion beam imaging (MIBI), may use FFPE samples and may analyze the spatial relationship of immune cells in the tumor microenvironment. The most important opportunity provided by neoadjuvant therapy may be biomarker development. For biomarkers to predict prognosis or treatment efficacy, conventional predictive markers such as PD-L1 expression and tumor mutation burden (TMB) in HCC was limited because of the low incidence of high PD-L1 expression or high TMB in HCC. Rapid technological progress in multi-omics analysis enabled more comprehensive characterization of interaction of different immune cells in the tumor microenvironment and key signaling pathways of immune regulation.[124,126] However, a common challenge was external validation of biomarkers identified by these approaches. In addition, recent studies suggested that enrichment of particular species in the gut microbiome of HCC patients was associated with response to ICI therapy.[127,128] On the other hand, more specific pharmacodynamic assessments of drugs with different mechanisms still rely on analysis of post-treatment tumor samples, whose availability was seriously limited. Development of biomarkers using peripheral blood samples (circulating immune cells/DNA, cytokines, etc.) will greatly enhance our ability to detect direct pharmacodynamic effects of different drugs and their combinations as well as to facilitate mechanistic exploration.[129]

Conclusion

The HCC practice guidelines have evolved rapidly in the past 2–3 years to accommodate the advances in systemic therapy, to recognize the variations of practice patterns around the world, and to facilitate multi-disciplinary management, particularly in patients with intermediate-stage HCC. The advances of systemic therapy have led to a bloom of studies evaluating combination of different LDT and ICI-based systemic therapy in intermediate-stage HCC. Critical appraisal of the multiple confounding factors inherent in this patient population is vital for successful design and conduct of clinical trials as well as

interpretation of trial results, which may be available in the next few years. A neoadjuvant approach provides a chance of cure and unique opportunities to collect bio-samples for mechanistic research and biomarker development. Extensive analytic and clinical validation of the novel biomarkers must be done to realize their potential in clinical use.

Abbreviations

AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; BCLC, Barcelona Clinic Liver Cancer; EASL, European Association for the Study of the Liver; EBRT, external beam radiation therapy; ESMO, European Society for Medical Oncology; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HIF-1α, hypoxia inducible factor-1α; HKLCS, Hong Kong Liver Cancer staging; ICI, immune checkpoint inhibitor; JSH, Japan Society of Hepatology; KLCSG, Korean Liver Cancer Study Group; LDT, liver-directed therapy; LT, liver transplantation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TILs, tumor-infiltrating lymphocytes; TLCA, Taiwan Liver Cancer Association; TMB, tumor mutation burden; TTP, time to progression; TTTP, time to TACE progression; US FDA, US Food and Drug Administration; VEGF, vascular endothelial growth factor; Y-90 SIRT, yttrium-90 selective internal radiation therapy.

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