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Adjuvant and Neoadjuvant Therapies for Hepatocellular Carcinoma

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Conflicts of Interest:

Arndt Vogel consults for AstraZeneca, Bayer, Bristol Myers Squibb, BTG, Eisai, Eli Lilly, Imaging Equipment, Ipsen, MSD, Roche, Servier, Sirtex, and Terumo. Robert C. Grant consults and advises AstraZeneca. He consults for Ipsen and Knight Therapeutics. He advises Eisai. He received grants from Pfizer. He is employed by Guardant Health, Incyte, and Tempus. Tim Meyer consults for Geneos Therapeutics, Ipsen, Roche, and Signant Health. He is on the speakers' bureau for Guerbet. He received grants from MSD. He is employed by Adaptimmune, AstraZeneca, Bristol Myers Squibb, Boston Scientific, and Eisai. Gonzalo Sapisochin consults and received grants from Roche. He consults for AstraZeneca, Chiesi, HepaRegeniX, Integra, and Novartis. He received grants from Bayer. Grainne M. O'Kane consults and advises AstraZeneca. He consults and received grants from Roche. He consults for Incyte and Servier. He is employed by Eisai and MSD. Anna Saborowski is employed by AstraZeneca, Eisai, Eli Lilly, Ipsen, MSD, Pierre-Fabre, Roche, and Servier.

Search strategy and selection criteria

We searched MEDLINE and PubMed databases, using the terms "hepatocellular carcinoma", or "liver cancer", "adjuvant therapy", "neoadjuvant therapy" focusing on randomized trials and other high-quality studies published in English up to September 2023. Publications within the past 5 years were prioritized, although older, relevant, high-quality studies were also selected. Meeting abstracts (from peer-reviewed congresses) were also included if deemed to be of high quality and could potentially change practice.

Author contributions

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Abstract

Immune-oncology based regimens have shown efficacy in advanced hepatocellular carcinoma and have been implemented as standard of care as first line therapy. Their efficacy, including high response rates, and safety justifies their evaluation in earlier disease stages. Following negative results for adjuvant sorafenib in the global STORM trial in 2015, four global phase 3 trials, featuring different immune checkpoint inhibitor combinations, entered in parallel the race in the adjuvant setting. The IMbrave050 trial, comparing adjuvant atezolizumab in combination with bevacizumab to active surveillance following curative-intent resection or ablation, was the first to report, fast-tracking the results of the first interim analysis and demonstrating an improvement in recurrence free survival. The trial has provoked a discussion on the horizon of expectations from adjuvant treatment and the clinical relevance of efficacy endpoints. Moreover, major pathological responses reported from early phase 2 data in the neoadjuvant setting provide a strong rational for the evaluation of these concepts in phase 3 trials. In this review, we summarize current evidence and outline future directions for systemic therapies in early-stage hepatocellular carcinoma.

Introduction

The treatment paradigm for HCC has been transformed over the past 6 years. With an expanding armamentarium of effective systemic therapies for advanced disease, there is now an opportunity to integrate systemic treatment into earlier stages of disease. This shift is already reflected in recent guidelines where the use of systemic treatment is an option for patients in intermediate stage with more extensive disease where benefit of local therapy is uncertain (1-3). In some cases, systemic treatment and/or locoregional therapies (LRT) may result in downstaging rendering curative approaches or drug free status possible.

Surgery, in the form of liver resection (LR) or liver transplantation (LT) represents the mainstay curative therapy for HCC (2, 4). The 5-year overall survival after LR and LT can be up to 70-80% and therefore should be offered to all eligible patients. Liver resection is generally reserved for patients with single HCC, with no limitation in the size of the tumor, in patients with no extrahepatic disease, no vascular invasion and no or mild portal hypertension. Even though many Western centers follow the BCLC guidelines for eligibility for LR there is no worldwide consensus on what the definition of resectability is. **Table 1** summarizes what we consider to be resectable, borderline resectable and not resectable disease. Some centers, mainly in Asia, have demonstrated reasonable outcomes when resection is offered for patients with unilobar multifocal disease or peripheral portal vein tumor thrombus. Which HCC patient qualifies for LT is subject to local jurisdiction and multidisciplinary discussion, and different limitations in terms of tumor burden and alpha fetoprotein (AFP) level apply. LT can also be considered for patients with non-resectable, multifocal disease, specifically for those with liver limited disease and exceptional response to local or systemic therapies.

Recurrence rates however remain unacceptably high after curative-intent treatment and over half of all patients experience recurrence within five years (5, 6). Consequently, there is a great interest in combining local therapies with systemic therapies to improve cure rates. Inhibition of immune checkpoints (ICI), particularly the programmed cell death protein 1 (PD-1) and programmed-death ligand (PD-L1) interaction, have revolutionized the medical treatment of HCC. IMbrave150, an international phase 3 trial, demonstrated a significantly prolonged survival for the combination of atezolizumab (a monoclonal antibody targeting PD-L1) and bevacizumab (a monoclonal antibody targeting vascular endothelial growth factor [VEGF]) over sorafenib (7). Based on these results, atezolizumab and bevacizumab was established as an FDA- and EMA

approved standard of care for first-line treatment of HCC. Subsequent phase 3 trials confirmed the efficacy of VEGF/ICI combinations (e.g. ORIENT-32 and CARES-310 (8, 9)). In addition, the concept of dual checkpoint inhibition has been demonstrated in CheckMate040 with nivolumab and ipilimumab and validated in the HIMALAYA study with durvalumab and tremelimumab in a Phase 3 first-line setting (10, 11). The evidence for ICI in advanced disease provides a context for understanding their role in the adjuvant setting.

Neoadjuvant treatment for HCC

The delivery of treatment prior to surgery has several important goals (**Table 2**). Firstly, non-visible or micro metastatic disease may be eradicated, reducing the early recurrences seen within two years of resection in HCC (6). Secondly, treatment prior to surgery may reduce the extent of required surgical resection, which may conserve liver function thus improving outcomes. Downstaging to resectability can further expand the number of patients who can benefit from curative approaches. Thirdly, neoadjuvant approaches can provide prognostic information with an increasing recognition of major pathologic response (MPR) as a surrogate for overall survival in other tumour types (12, 13). Noteworthy is the heterogeneity in definitions of this endpoint with non-small cell lung cancer and melanoma studies defining this as <10% viable tumour cells remaining. In HCC, both <10% and < 30% viable cells have been used to define MPR or 'significant necrosis rates' (**Table 3**). Future strategies may seek to personalise adjuvant approaches based on MPR. In this regard, neoadjuvant trials provide a unique opportunity to demonstrate drug sensitivity and develop predictive biomarkers. Surgeons may be concerned that neo-adjuvant therapy may delay curative surgery and risk disease progression that renders the patient inoperable. Based on the available evidence we propose that neoadjuvant therapies should be explored in resectable patients with HCC. These trials need to implement well-defined eligibility and selection criteria to demonstrate the full benefits of neoadjuvant (immune-) therapies.

Neoadjuvant approaches with locoregional therapies (LRT)

With emerging evidence correlating pathologic response and OS, locoregional therapies may have been considered an optimal approach in the neoadjuvant setting. There have however been several retrospective analyses evaluating pre-operative TACE with very mixed results and some

studies suggesting inferior outcomes (14-17). A systematic review and meta-analyses overall found no benefit of pre-operative TACE (18), whereas a randomized clinical trial suggested improved outcomes with pre-operative TACE compared to up front surgery. This study, however, was conducted in a higher risk population with disease burden beyond Milan criteria and the superior outcome may be more related to effective downstaging than improvement of truly resectable patients (19). Indeed, heterogeneity in study populations and inconsistent definitions of resectability mean that neoadjuvant studies can be difficult to translate globally. In this regard, a randomized trial compared neoadjuvant radiation and surgery versus surgery alone in patients with HCC and Cheng type II/III portal vein thrombus (PVT) (20), a population considered unresectable by BCLC guidelines (1). Neoadjuvant radiation improved disease-free survival rates, and corresponding OS rates at 24 months were 9.4% in surgery alone arm versus 27.4% in the neoadjuvant group. Most would consider this approach downstaging therapy with select patients only likely to benefit. Nevertheless, this study highlights a potential role for radiation in patients particularly with PVT and future trials will seek to explore this further (**Table 4**). Indeed, multiple studies have documented downstaging to resectability with the use of LRT including TARE and HAIC (21, 22); however randomized data are lacking. TARE may overcome limitations of the liver remnant by providing volumetric changes equivalent to PVE (23). Notably yttrium 90 (^{90}Y)- labelled microspheres delivered as selective internal radiation therapy (SIRT) has been evaluated prospectively in cirrhotic patients in the neoadjuvant setting, but only with limited feasibility documented, suggesting that strict selection criteria need to be applied (24). Prospective studies are ongoing evaluating the role of LRT alone or in combination with systemic treatment as downstaging strategies (**Table 5**).

Neoadjuvant treatment with tyrosine kinase inhibitors

Multi-receptor tyrosine kinases sorafenib and lenvatinib are considered first line treatment options in advanced HCC (25, 26), however are now more often used in later lines. While sorafenib mainly results in disease stabilisation in patients with advanced HCC, responses by RECIST 1.1 have been observed in up to 20% in patients treated with lenvatinib (25).

In a neoadjuvant phase 2 study of 19 evaluable patients, sorafenib induced unexpected high responses of 32% by mRECIST and 24% of patient had necrosis rates ≥50% in the surgical specimen (27). A 4-week course of dovitinib was evaluated in a phase II study of patients with

stage 0, A and B HCC, prior to locoregional therapy including RFA. Response rates were 45% by modified RECIST. Seven patients proceeded to transplant (28). Given the superior efficacy of ICIs, neoadjuvant approaches with TKIs are likely to be in combination with ICIs rather than as single agents (**Table 4**).

Advantages of neoadjuvant immunotherapy in resectable HCC

The administration of immune checkpoint inhibitors prior to surgery either alone or in combination has distinct advantages. Early pre-clinical studies demonstrated improved efficacy of neoadjuvant immunotherapy versus adjuvant in breast cancer mouse models supported by sustained levels of peripheral CD8+ T cells (29). Additionally, it has been shown that with the primary tumour in situ and therefore endogenous antigens, a neoadjuvant approach will generate more diverse T cell responses with an expansion in tumour resident T cell clones compared to adjuvant treatment (30). Indeed, a critical output from ICI use is to achieve peripheral clonal expansion of primed and activated effector T cells that can infiltrate tumour and adjacent tissue (31). In this regard interrogating biomarkers of response to the combination of atezolizumab and bevacizumab has highlighted the importance of pre-existing tumour immunity (32). Notably resectable disease with generally a smaller tumour burden or volume may in itself be a predictor of response (33). A number of studies in HCC have equated a larger tumour volume with a more immunosuppressive TME. The early Hoshida subclass S2 correlated larger tumours with decreased interferon target genes (34). Smaller tumours often show less intratumoural heterogeneity (ITH) with more progressive disease or new lesions acquiring somatic mutations with evident tumour clonality promoting an immune evasive TME (35, 36). Critical to ICI response is also effective antigen presentation. A recent study leveraging HCC samples treated in the neoadjuvant setting, documented the importance of dendritic cell subsets in ensuring differentiation of progenitor exhausted T cells to an effector activated state (37). HLA-LOH has been found in up to 17% of multifocal HCC (38).

Nivolumab and pembrolizumab have both been approved in combination with chemotherapy in NSCLC and triple negative breast cancer respectively in the neoadjuvant setting. Both pivotal studies evaluated both event-free survival and pathologic complete response as primary endpoints (13, 39). Perhaps more notably in resectable stage III-IV melanoma neoadjuvant plus adjuvant pembrolizumab demonstrated a 23% increase in event free survival over adjuvant

pembrolizumab alone without compromising safety (40). Completed and ongoing neoadjuvant studies in HCC are mixed with regard to the use of continuing systemic treatment post-operatively (**Table 2 and Table 4).**

Pre-operative immune checkpoint inhibitor studies in HCC

There have been four published phase I/II pre-operative ICI studies in HCC. An additional two completed studies have been presented in abstract form (**Table 2**). Endpoints in these early trials focused on safety, feasibility and responses including pathologic responses with several studies exploring translational endpoints. Importantly, these early studies have documented safety of the approach with very few surgical delays. Consistently, MPR, regardless of the definition, appears to correlate with recurrence free survival. Like the aforementioned studies, pre-existing inflamed tumours appear to represent biomarkers of ICI response and MPR. Studies incorporating cell free ctDNA analyses also demonstrate the utility in the peri-operative setting (41)

Kaseb et al explored 6 weeks of nivolumab vs nivolumab plus ipilimumab in resectable HCC pre-operatively (42). In the nivolumab arm (n=13), patients continued therapy in the adjuvant setting for up to years. In the nivolumab plus ipilimumab arm (n=14), post-operatively, ipilimumab was administered up to 4 times every 6 weeks and nivolumab continued similarly up to 2 years. The primary endpoint was safety and tolerability as measured by the number of grade 3 or higher adverse events (AEs) and secondary endpoints included overall response rates. Although the combination resulted in higher grade 3-4 AEs (43% vs 23%) there were no surgical delays in either arm. Twenty of 27 patients underwent surgery; of the seven that did not have surgery, four patients had disease progression. The high rate of unresected patients (26%) is concerning in a population considered resectable and underscores the need for appropriate patient selection in neoadjuvant trials (in this study, 8 had tumors > 10 cm, 9 were multifocal and 4 had fibrosis score >2). MPR was defined as ≥ 70% necrosis and was achieved in 3 patients in each arm. Five patients had a pCR. Notably despite the MPR in the nivolumab and ipilimumab arm, no responses by RECIST 1.1 were documented, highlighting the potential discordance between imaging and pathologic responses in 'window of opportunity' studies. After a median follow-up of 24.6 months none of the 6 patients who achieve a MPR had evidence of recurrence. In matched specimens where MPR was evident there was a clear increase in tumour infiltrating leukocytes (TILs) and increased expression of effector T cell gene signatures. Non responders

tended to have a myeloid-rich TME. In this study pathologic responses in the combination arm were evident regardless of baseline tumour specimen immune status, highlighting the impact of T cell priming peripherally with additional CTLA-4 inhibitor use. This compared to nivolumab monotherapy where baseline tumour specimens showed a high burden of TILs.

The PRIME-HCC phase 1b trial also included patients with resectable HCC who received the combination of nivolumab and ipilimumab neo-adjuvantly. D'Alessio and colleagues provided updated outcomes on 23 patient patients evaluable for radiological response and 19 available for pathological outcomes (43). Eight patients (42%) achieved a MPR (≥70%) including 6 patients (32%) achieving a pCR. At a median follow-up of 14.5 months (95% CI, 7.4-21.6), no patients who achieved a MPR experienced disease recurrence. Grade 3 AEs were reported in 23% with no grade 3/4 AEs and one patient experienced a surgical delay due to grade 2 hypothyroidism. Baseline density of CD8+ and CD4+ T cells by mIHC associated with MPR. Additionally, dynamic changes in ctDNA levels correlated with responses.

Marron and colleagues evaluated cemiplimab (PD-1 inhibitor) in a single arm phase 2 trial in which 21 patients were enrolled and 20 underwent surgical resection (44). Two cycles (6 weeks) of cemiplimab were administered pre-operatively and for up to 24 weeks post-surgery. The primary endpoint was significant tumour necrosis rates defined as >70% necrosis and was achieved in 4/20 (20%) of patients. Necrosis rates correlated with MRI reports of necrosis, however, similarly RECIST responses and pathologic responses did not necessarily correlate. One patient who developed pneumonitis had a 2-week delay in surgery. In total 7 patients (33%) experienced grade 3 AEs with no grade 4/5 AEs in this study. Baseline tissue analysed by both mIHC and RNAseq confirmed a correlation with pre-existing immune cell populations and pathologic responses. For these TME analyses responders and non-responders were considered with a cut-off of 50% necrosis rates. In reporting the overall outcome from these small single centre trials, it is important to define outcomes according to intention to treat and fully understand the reasons that patients did not proceed to resection. This will enable the study population to be refined accordingly in future trials.

The use of TKI/ICI combinations have also been evaluated predominantly in more advanced HCC beyond what would be considered upfront resectable. Ho and colleagues employed the strategy of combining nivolumab with cabozantanib in patients with 'borderline (BR)' or 'locally

advanced' HCC with the aim of converting disease to resectable (45). An 8-week period of cabozantinib and nivolumab was delivered in 15 patients, including four with PVT. There was a 2-week run in of cabozantinib monotherapy. Of 12 patients who underwent successful surgical resection 5 (42%) had an MPR (< 10% viable tumour cells) including one patient with a pCR. Grade 3 or higher TRAEs were evident in 13.3% (n=2). Integrated -omic approaches evaluated the impact peripherally and in tumour tissue post cabozantinib monotherapy and at resection. PBMC analyses (n=6) and tissue (n=4) demonstrated an increase in peripheral effector and memory T cells post cabozantinib monotherapy. Core biopsies also supported a shift toward a less immunosuppressive TME on transcriptional analyses. Tumoral regions of responders at resection again revealed enrichment of CD3+ and CD8+ T cells, together with a higher density of CD20+ B cells. Tertiary lymphoid structures (TLS) were also more abundant. Constructed tissue micro arrays further supported immune cell infiltration using image mass cytometry; notably the spatial distribution of B cells in responders was quite distinct. CyTOF subtyping in tissue further clarified an activated T cell phenotype in responders, while PBMC analyses highlighted lymphoid and myeloid infiltrates which paralleled higher levels of chemokines responsible for this influx in plasma.

Xia et al enrolled 18 patients into their phase 2 study of peri-operative camrelizumab (PD-1 inhibitor) and rivoceranib (also known as apatinib), of which 13 (72.2%) had BCLC C HCC (41). Patients received 6 weeks of combination treatment pre-operatively and for an additional 6 months post-surgery. 17 patients received surgery, and 13 eligible patients proceeded to adjuvant treatment. The denominator for MPR was 13 as 4 patients were excluded due to mixed CCA/HCC at resection and protocol violations. Three of 18 (16.7%) of patients had ≥ grade 3 treatment related AEs, two of whom required steroids. Post-operatively biliary leakage occurred in 17.6%. MPR was achieved in 4 patients. This study documented the utility of ctDNA post operatively with the ability to clear ctDNA associating with improved RFS, and tissue analyses highlighted the importance of enriched dendritic cell infiltration at baseline as a possible biomarker of MPR. Additional studies are shown in **Table 4.**

Implications of neo-adjuvant/downstaging treatments in liver transplantation

Given the response rates of immunotherapy in the advanced setting and the high drop-out from the waiting list due to HCC progression, there is growing interest on the use of single or

combination ICI regimens in the pre-transplant setting. The main goals in this setting are: 1) bridging therapy; maintain the patient within transplant criteria while waiting for a suitable organ (in many centers this wait can be up to a year), avoiding the development of local and distant tumor progression 2) downstaging; in this case, patients with tumors that are initially beyond each jurisdiction transplant criteria could benefit of a combination of locoregional and systemic therapy to become transplantable (i.e. when tumor burden is beyond transplant criteria or in patients with portal vein tumor thrombus and no extrahepatic disease).
Notably, due to the inherent risk of rejection, the use of ICI prior to (as well as after) organ transplantation remains controversial and warrants investigation in prospective trials such as NCT05879328 (ImmunoXXL), NCT05185505 and NCT05027425.

Outcomes after curative-intent therapies

The absolute benefit of adjuvant therapy relates directly to the risk of recurrence, which for HCC can be broadly grouped into features that reflect the tumor aggressive and the underlying liver disease. Various nomograms predict recurrence risk after ablation (46, 47), surgical resection (48, 49), and liver transplantation (50). Tumor features that increase the risk of recurrence include male gender, tumor size, tumor number, differentiation, microvascular invasion, extracapsular extension, and alpha-fetoprotein levels. Liver function predicts survival after RFA and surgery, and the Albumin-Bilirubin (ALBI) grade provides a reliable measurement (51, 52). Importantly, anti-cancer therapies would not be expected to improve liver function in the adjuvant setting.
Recurrent HCC follows a distinct pattern, broadly characterized by early recurrences stemming from the primary tumor and late recurrences assumed to be stemming from the field defect of a diseased liver. Most recurrences occur within the liver, but not at the surgical margin (53). Clinically, recurrences can be divided into early or late, depending on whether they occur before or after two years (54). Early recurrences are more often multifocal or extrahepatic and tend to occur in the presence of tumor-related risk factors. In contrast, late recurrences are more strongly associated with underlying cirrhosis and liver dysfunction (53-55). Genomic profiling confirmed late recurrences are more likely to have a distinct clonal original; however, a third of early recurrences also stemmed from a distinct clonal ancestor (56).

Treatment of Comorbidities

Antiviral Therapy

Among patients with HCC in the setting of viral hepatitis, suppression or eradication of the virus can improve liver function and may improve oncological outcomes. Antiviral therapy for HBV reduces the risk of reactivation after surgery, reduces the risk of recurrence, and improves overall survival, even with low levels of HBV DNA (57-59). An ongoing randomized phase 3 trial will compare outcomes between antiviral therapies entecavir and tenofovir after surgery for HBV-associated HCC (NCT02650271).

Direct-acting antiviral therapy for HCV is highly effective at achieving a sustained virologic response and improving liver function, particularly for patients with preserved liver function at presentation (60, 61). Whether direct-acting antiviral therapy improves outcomes after curative-intent therapy for HCC remains controversial. No randomized trials have been published to date. An individual patient data meta-analysis of observational studies provides inconclusive results comparing HCC recurrence between patients who were and were not treated with direct-acting antivirals (62).

Immunosuppression

After liver transplantation, recurrent HCC can be more aggressive in the setting of immunosuppression (63, 64). After transplantation, patients are ineligible for palliative-intent immune checkpoint inhibition because of the high risk of graft failure (65). The role of specific immunosuppressive protocols on HCC recurrence remains controversial, given the established association between calcineurin inhibitors and the development of cancers (66). In the open-label randomized phase 3 SILVER trial, patients who received liver transplantation for HCC were randomized to mTOR-based immunosuppression with sirolimus versus mTOR-inhibitor free immunosuppression (67). The two arms showed no significant difference in the primary endpoint of recurrence-free survival (P=0.28), although a pre-planned secondary analysis showed recurrence-free was improved with sirolimus out to three years and overall survival out to five years.

Local Treatment Modalities

Transarterial Chemoembolization

Transarterial chemoembolization (TACE) is a standard treatment for intermediate (Stage B) Barcelona Clinic Liver Cancer (BCLC) HCC without diffuse, infiltrative, or extensive bilobar involvement (1, 2, 68). Meta-analyses of small randomized and observational studies show a potential benefit of adjuvant TACE, particularly where high-risk features are present (69, 70). How these results generalize is unclear, considering that nine of the ten randomized studies were conducted in China, the proportion of intrahepatic recurrences did not differ after TACE, and the TACE regimens were heterogeneous. Adjuvant TACE is therefore not recommended in Western countries.

Radiotherapy

Radiotherapy can achieve high rates of local control in HCC and stereotactic body radiotherapy improves outcomes when added to sorafenib in advanced disease (71). A meta-analysis of observational and three randomized trials recently showed benefits to adjuvant radiotherapy when added to hepatectomy (72). Like with TACE, the studies were relatively small, exclusively performed in China, and used heterogeneous protocols, so how these findings generalize remains unknown.

Selective Internal Radiotherapy

Several small, randomized trials demonstrate a signal of benefit for selective internal radiotherapy as adjuvant therapy; however, these trials use various protocols and radioactive compounds (73-75). Transarterial radioembolization with yttrium-90 (TARE) provides high objective response rates for localized unresectable HCC thus may provide a rationale as local treatment for downstaging (21, 76).

Hepatic Arterial Infusion Pump Chemotherapy

Hepatic arterial infusion pump chemotherapy (HAIC) delivers chemotherapy directly to the arterial bed surrounding tumors and minimizes toxicity through first-pass metabolism (77). HAIC in the adjuvant setting has been evaluated in two randomized trials and a meta-analysis, showing recurrence-free and overall survival benefits, particularly among patients with microvascular invasion. Prophylactic hepatic artery infusion chemotherapy improved survival after curative resection in patients (22, 78, 79).

Systemic Therapies

Cytotoxic Chemotherapies

Cytotoxic chemotherapy has limited activity in advanced HCC (80, 81) (80, 82). Nonetheless, several randomized trials evaluated chemotherapy in the adjuvant setting, with conflicting results. While one small trial showed benefits to capecitabine over supportive care (83), other trials of chemotherapy showed no benefit (84-86) or worse outcomes (87, 88).

Tyrosine Kinase Inhibitors

After the SHARP trial showed a survival benefit with the tyrosine multikinase inhibitor (TKI) sorafenib in advanced disease, the STORM trial evaluated sorafenib after curative-intent therapies (47)(89). STORM was a phase 3 double-blind placebo-controlled international randomized trial compared up to four years of sorafenib to placebo. All patients received curative-intent treatment with surgical resection or local ablation. Key eligibility criteria included any size lesion for resection, less than 5 cm solitary tumor or two to three tumors smaller than 3 cm for ablation, Child-Pugh score 5-7 (7 in the absence of ascites), Eastern Cooperative Oncology Group (ECOG) score 0, and alpha-fetoprotein lower than 400 ng/mL. Overall, 1,114 patients were randomized. Over 90% of HCCs were solitary, with the median tumor size being 3.5 mm in both arms and over 30% had microvascular invasion. Approximately 60% of patients had cirrhosis, but over 95% had Child-Pugh scores of 5-6. About half had underlying HBV. The primary outcome of recurrence-free survival (RFS) was equivalent for sorafenib and placebo (hazard ratio [HR] 0.94, P=0.26), with median RFS of 35.9 and 33.7 months in the sorafenib and placebo arms, respectively. No differences were observed among subgroups or for overall survival (OS). A subsequent analysis revealed no *a priori* biomarker predicted a benefit from sorafenib in follow-up analyses (90). No phase 3 trials to date have evaluated the adjuvant effects of other TKIs used in advanced HCC, such as lenvatinib, regorafenib, cabozantinib.

Immune therapies before immune checkpoint inhibition

Immunity plays a central role in the pathogenesis of HCC (91). The liver is an immunotolerant organ to guard against autoimmunity developing from exposure to gastrointestinal antigens (92). Chronic inflammatory conditions like HBV lead to further immune suppression (91). Together,

these immunosuppressive pressures enable the growth of HCC through complex pathways which are yet to be fully characterized. As a result, randomized trials tested various immunostimulatory strategies in HCC. Two randomized phase 3 trials compared adjuvant interferon, with no benefit in RFS observed over control or observation (93, 94). Another phase 3 randomized trial compared infusions of autologous cytokine-induced killer cells, showing improved RFS and OS (95, 96). Overall, this was one of the first positive studies in the adjuvant setting in HCC albeit it must be acknowledged that there were some imbalances in baseline characteristics, the study included mainly HBC-related HCC and the majority of patients were treated with local ablation and not surgery.

Post-operative immune checkpoint inhibitor studies in HCC

IMbrave 050 was the first phase 3 randomized trial to report results evaluating adjuvant ICI for HCC (97). Key eligibility criteria were treatment with curative-intent ablation or resection, Child-Pugh A, ECOG 0-1, no extrahepatic disease or macrovascular invasion except Vp1/Vp2, and high risk of recurrence (**table 6).** Four to twelve weeks following surgical resection, patients were randomized to atezolizumab 1200 mg and bevacizumab 15 mg/kg IV every three weeks for twelve months or 17 cycles. The primary endpoint was RFS assessed by an independent review. The 668 patients who were randomized were balanced across age (median approximately ~ 60 years), sex (~80% male), and ethnicity (~80% Asian). HCC characteristics among the 87% of patients treated with resection showed median tumor sizes 5.3 and 5.9 cm in the atezolizumab and bevacizumab versus active surveillance arms, with the largest tumors measuring 18 and 25 cm. Approximately 10% of patients had multiple tumors, with fewer than 3% having three or more. HCC characteristics after ablation included a median tumor diameter of 2.5 and 2.6 cm. Approximately 25-30% of patients had two or three tumors. For the primary endpoint after the first interim analysis and 243 events, the HR for RFS was 0.72 (95%CI 0.56-0.93, *P*=0.01), with median RFS not reached. RFS at one year was 78 *versus* 65% in the atezolizumab and bevacizumab *versus* active surveillance arms, respectively. The RFS Kaplan-Meier curves showed an early separation apparent at three months before merging towards two years. OS was immature, with only a 7% event-patient ratio and 47 deaths. There were numerically more deaths in the experimental arm (27 *versus* 20), including 3 due to COVID-19. Safety was comparable to IMbrave150, with numerically fewer serious and treatment-related adverse events, although

2/332 (0.6%) versus 0/330 (0%) patients experienced grade 5 treatment-related adverse events on the investigational arm.

Critical discussion of IMbrave050 and potential implications for future adjuvant trials

Although IMbrave050 can be regarded as a milestone in the treatment of HCC, adjuvant therapy with atezolizumab and bevacizumab cannot yet be unequivocally recommended. The early report of IMbrave050 raises some interesting points for discussion, that may also have some more general implications for clinical trials in the (neo-)adjuvant setting.

1. IMbrave050 met the threshold for statistical significance to improve RFS at the (early) timepoint of the first interim analysis, and accordingly all subsequent analyses will be descriptive. As a consequence, the follow-up was relatively short, and the median RFS has not been reached in either arm. Of note, it appears that the RFS curves come together at around 18 months and further follow-up is needed to establish whether the benefit is durable. An unexpectedly low number of events at the time of the first interim analysis, prevents any conclusion for the secondary endpoint of OS, and it will require several years until meaningful OS data will be available. So, whilst the trial met the threshold of statistical significance, clinical significance remains to be established.

This scenario raises two important questions for clinical trials in the adjuvant setting. First, what defines clinical benefit? Second, what is the value of an early read-out in the adjuvant setting and what justifies immediate implementation in clinical practice? As a general concept, one would assume that adding systemic therapies to resection or ablation will not only delay recurrence but will also increase the number of patients that will be eventually cured. The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) has been developed as one of the first validated and reproducible tools to assess the magnitude of clinical benefit from new cancer therapies (98). Different forms that match defined clinical scenarios are available: Form 1 of the ESMO-MCBS can be applied for adjuvant and neoadjuvant therapies with curative intent. The MCB-scale is graded A, B or C, and features improvement of survival as the most important criterium. Grades A (>5% improvement of survival at ≥3 years follow-up) and B (≥3% but ≤5% improvement at ≥3 years follow-up) indicate a high level of clinical benefit. Beyond overall survival data, the scale makes allowance for early data demonstrating high RFS also in the absence of mature survival data. If RFS is the primary endpoint, a HR of <0.65 is required for grade A and a HR of

0.65 to 0.8 for grade B. Of note, ESMO clearly states that studies initially evaluated based on RFS criteria alone will need to be revaluated when mature survival data are available. According to ESMO-MCBS, the benefit of IMbrave050 would be considered as high (grade B) at this early read-out. However, as discussed above and in line with the ESMO recommendation - more mature data are required to truly ascertain the clinical benefit of Atezolizumab/Bevacizumab in the adjuvant setting.

2. Although a global trial, 82% recruitment was from Asia and 62% had a history of hepatitis B virus (HBV) infection. In the advanced setting, according to IMbrave150 and other ICI-based trials, (8, 10, 99-101) these sub-populations performed better although interestingly in IMbrave050, the subgroup analysis is not consistent with the former observation. Nevertheless, it is not completely clear, whether the benefit extends to a western population where alcohol- and steatosis-related liver diseases dominate. In light of the geographical variation in the size of patient populations and recruitment rates, additional measures might need to be implemented to capture the whole "picture" of a global disease such as liver cancer. This implies that not only a more granular distinction of the underlying liver disease may be required (such as MASLD, MetALD and ALD), but also that recruitment is capped for defined baseline characteristics such as region, ethnicity, underlying liver disease, and disease stage.

3. Toxicity is an important consideration especially in the adjuvant setting where there is a proportion of patients that would have been cured without adjuvant therapy and another proportion which will relapse despite therapy, and only a minority that derive a substantial survival benefit. In other cancers, it is clear that as the relative risk of relapse reduces, so does the absolute benefit of adjuvant therapy, and this scenario is recapitulated in the IMbrave050 by a HR of 1.06 in tumors with a diameter of ≤ 5 cm. Given that the treatment associated mortality was at about 6%, the extrapolation of these results to those with lower risk of relapse requires further evidence. In addition, it needs to be considered that 41% of patients in the experimental arm experienced ≥ grade 3 adverse events compared to 13% in the surveillance arm, mostly hypertension (18% vs 1%) and proteinuria (9% vs 0%). In general, treatment-related toxicity is accepted to a certain threshold, but specifically in the adjuvant setting this threshold needs to be very low, specifically in the context of studies in which the long-term survival benefit is not assured.

4. The implementation of systemic therapy in the adjuvant setting raises additional questions: First, the impact of adjuvant therapy on tumor biology including pattern of recurrence and post-recurrence survival is not defined in HCC. Along this line, adjuvant treatment with FOLFOX after resection of liver metastasis from colorectal cancer significantly improved RFS in the JCOG0603 trial but failed to improve overall survival. Of note, adjuvant therapy also changed the pattern of recurrent metastasis after hepatectomy, with a relative increase in lung and other distant metastases (102). Thus, improvement in RFS does not guarantee an overall survival benefit and in new indications for adjuvant therapies such as HCC the long-term impact on survival needs to be ascertained.

Second, the consequences of adjuvant therapy on response to subsequent therapy needs to be evaluated. In this regard, anti-drug antibodies (ADAs) may be of specific concern in the context of HCC. A recent meta-analysis reported the development of ADAs against atezolizumab in up to 31% of patients and the presence of high-level ADAs (17.4% of cases) was associated with a worse outcome in advanced HCC (103, 104). Hence, adjuvant treatment may have an impact on the efficacy of subsequent systemic therapies in the palliative setting.

5. Despite being only hypothesis-generating, subgroup analyses already suggest that the benefit of the adjuvant therapy is limited to a portion of patients. To improve patient stratification, and to align clinical observations with molecular correlates, investing in the translational program would be highly valuable.

Ongoing Trials

A search of clinicaltrials.gov and clinicaltrialsregister.eu on September 18, 2023, revealed six ongoing phase 3 trials evaluating ICI after curative-intent therapy for HCC (**Table 6**). All trials had RFS as the primary endpoint, except for KEYNOTE-937, which has a dual primary endpoint of RFS and OS. In addition to IMbrave050, NCT04639180, and NCT05862337 assess ICI and anti-VEGF agents. Two trials, CheckMate9DX and KEYNOTE-937, assess ICI monotherapy. EMERALD-2 is a three-arm study with ICI/VEGF and ICI monotherapy arms. Together, the results of these studies may determine whether VEGF is required in the adjuvant setting. They may also reveal whether there are differences between specific agents and whether differences in eligibility criteria are important.

Summary of the Current Guidelines

Among current guidelines, only the American Association for the Study of Liver Diseases (AASLD) guidelines have been updated since the presentation of IMbrave050 (105). The AASLD guidelines state that "AASLD recommends use of adjuvant immune checkpoint inhibitor-based systemic therapy in patients at high risk of recurrence after liver resection or local ablation (Level 2, Strong Recommendation)". Other guidelines were all published prior to the presentation of IMbrave050, and none recommend specific adjuvant therapies (2, 3, 106-111), except for the Chinese Guidelines which recommend adjuvant TACE, interferon, or Huaier granule (112)

Conclusion

Current evidence points to several promising approaches to offer curative strategies to an increasing number of patients with HCC. First, treatments that benefit advanced disease are being evaluated for potential benefit in the (neo)adjuvant setting, as discussed above. Second, the availability of resected tissue presents opportunities to develop predictive biomarkers which may identify patients that derive a particular benefit from ICIs. Third, downstaging protocols, that rely on the high responses observed with sequential or parallel applications of systemic and local therapies are gaining increasing attention. Finally, ongoing research into treating liver fibrosis may reduce the risk of late recurrences due to de-novo HCCs (113).

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Table 1. Proposed Definition of Resectability in HCC

Resectable	"Borderline" resectable	Not resectable
Single Tumor and No limitation in tumor size and No need for vascular resection and Child-Pugh A and AFP < 1000 ng/mL and No vascular invasion and No Extrahepatic Disease and Portal gradient <10mmgH	No Extrahepatic Disease and Multifocal unilobar disease or Need for vascular resection and reconstruction or Child-Pugh ≤B7 or Portal hypertension ≤15 mgH or AFP > 1000 ng/mL or Portal Tumor Thrombus Vp1-4	Multifocal bilobar disease or Child Pugh ≥B8 or Portal hypertension ≥15 mgH or Presence of Extrahepatic Disease

Table 2 : Advantages and disadvantages of approaches to peri-operative treatment in HCC

	Adjuvant (resectable)	**Neoadjuvant (resectable)**	**Downstaging/ conversion**	**Transplant Neoadjuvant/ downstaging**
Rationale	Reduce recurrences and improve overall survival (OS)	Reduce recurrences and improve OS Improve surgical outcomes	Improve chances curative tx Limit extent of surgery	Improve chances getting to transplant/cure
Advantages	RFA and surgery may augment immune response Doesn't delay resection May select high risk features	Tumour in situ Generate diverse immune response Faster endpoints eg MPR Translational research	Downstage to resectability treats micrometastatic disease	May improve outcomes in those high risk pts/ drop off patients
Disadvantages	Surgery immunosuppressive	Toxicity Delay of surgery	Few	Toxicity Graft rejection

Table 3: Published or present neoadjuvant trials of ICI/ICI-combinations in resectable or potentially resctable HCC

Trial/NCT	Phase	Treatment arms	N	1°EP	Adjuvant	MPR definition	MPR n (%)	pCR* n (%)	ORR	Drop out rate*	Surgical delays (n/%)
Marron et al NCT03916627	2	Cemiplimab	21	MPR	6 mths	>70%	4/20 (20%)	3/20 (15%)	3/20 (15%)	1/21 (5%)	1 (5.8%)
Kaseb et al NCT03222076	2	Nivolumab vs Nivolumab+ ipilimumab	27	Safety + tolerability	2 yrs	>70%	3/9 (33%) 3/11 (27%)	2/9 (22%) 3/11 (27%)	3/13 (23%) 0/11(0%)	7/27 (26%)	0
Xia et al NCT04297202	2	Camrelizumab/ apatinib	18	ORR MPR	6 mths	>90%	3/17 18%	1/17 (6%)	3/18 (17%)	1/18 (6%)	0
Ho et al NCT03299946	1	Cabozanatinib/ nivolumab	15	Safety + tolerability	No	>90%	5/12 (42%)	1/12 (8%)	1/14 (7%)	3/15 (20%)	0
PRIME-HCC NCT03682276	1b/2	Ipilimumab/ Nivolumab	26	Delay to surgery/ safety	No	>70%	8/19 (42%)	6/19 (32%)	6/23 (26%)	1/20 (0.5)	1 (4%)
Shi et al NCT03867370	1b/2	Toripalimab vs Toripalimab/ Lenvatinib	16	MPR	48 wks	>50%	2/8 (25%) 1/8 (13%)	1/16 (6%)	n.a.	0/16 (0%)	0

* Included with MPR group also

BR = borderline; MPR= major pathologic response; ORR = overall response rate by RECIST1.1; yrs = years; mths= months; wks=, * cancellation of surgery not related to TRAE

Table 4: Ongoing neoadjuvant trials of ICI/ICI-combinations and LRT/LRT-combinations in resectable or potentially resctable HCC

	Sponsor	Phase	Treatment arms	Pop. included	N =	1ºEndpoint	Adjuvant
Immune checkpoint inhibitor/ combination trials							
NEOTOMA NCT05440864	University Health Network	2	STRIDE	Resectable	28	Safety and feasibility	Yes
PRIMER-1 NCT05185739	University College, London	2	Pembrolizumab+Lenvatinib Pembrolizumab Lenvatinib	Resectable	60	MPR	Yes
NCT04721132	M.D. Anderson Cancer Center	2	Atezolizumab + Bevacizumab	Resectable	30	Safety & Tolerability pCR	No
AURORA NCT03337841	Kindai University	2	Pembrolizumab	Resectable Suitable RFA	50	1 year RFS	Yes
NCT04123379	Icahn School of Medicine	2	Nivolumab Nivolumab+BMS-813160 Nivolumab + BMS-986253	Resectable	50 *	Significant necrosis rates	Yes
DYNAMIC NCT04954339	Tae Won Kim, Asan Medical Center	2	Atezolizumab +Bevacizumab	Potentially resectable or high risk rectable	45	pCR rate	No
NCT05194293	Academic and Community Cancer Research United	2	Durvalumab + Regorafenib	Clinical T1b/T2 or T3	30	ORR	No
NCT04658147	Sidney Kimmel Comprehensive Cancer	1	Relatlimab + Nivolumab Nivolumab	Resectable as per AASLD or OPTN	20	Feasibility/ safety	Yes

	Center at Johns Hopkins						
NCT04888546	Chinese Academy of Medical Sciences	1/2	Anlotinib + TQB2450	Resectable with high risk recurrence	20	pCR ORR	Yes
NCT04701060	Tianjin Medical University Cancer Institute& Hospital	2	Camrelizumab + Apatinib	Resectable	30	ORR	Yes
CAPT NCT04930315	Zhejiang University	2	Camrelizumab+Apatinib Adjuvant alone	BCLC B/C	78	1-year RFS	Yes
NCT04224480	National Cancer Centre, Singapore	1	Pemnbrolizumab	Resectable <5 lesions No VP2/3	45	RFS	Yes
AB-LATE02 NCT04727307	University Hospital, Montpellier	2 randomized	Atezolizumab-RFA-Atezolizumab+Bevacizumab vs.RFA	Eligible RFA	202	RFS	Yes
LRT+/- combination trials							
NCT04521153	Shanghai Zhongshan Hospital	2 randomized	Camrelizumab+apatinib –Surgery-Tace - Camrelizumab + aptatinib Surgery + TACE	CNLC stage Ib/IIa/IIb/IIIa Excludes main PVTT	290	3yr EFS MPR	Yes
NCT04857684	Massachusetts General Hospital	1	SBRT +Atezolizumab/Bevacizumab	Resectable	20	Safety	No
NCT04174781	Zhejiang University	2	TACE + Sintilimab	BCLC A/B beyond Milan	61	PFS	No

NeoconceptA NCT04777942	Sun Yat-sen University	UK	TACE-HAIC (FOLFOX)-surgery Surgery	High risk BCLC A	320	PFS	No
NeoconceptB NCT04424043	Sun Yat-sen University	UK	TACE-HAIC (FOLFOX)-surgery Surgery	BCLC B Resectable tumour no. ≤4	280	PFS	No
KARCHER-1 NCT04587739	University Hospital, Lille	1	SBRT	Single nodule 3-8cm	30	Feasibility	No
NCT03851913	Sun Yat-sen University	3 randomized	Transarterial chemoinfusion-surgery Surgery	Resectable HCC Beyond Milan Criteria	344	OS	No

ICI= Immune checkpoint inhibitor; LRT= Lorcoregional therapy; MPR= major pathologic response; ORR = overall response rate; RFS = recurrence free survival; PFS= progression free survival; EFS= event-free survival; OS = overall survival; SBRT = stereotactic body radiotherapy; UK = unknown; PVTT = portal vein tumour thrombus; pCR = pathologic complete response; RFA = radiofrequency ablation

Table 5: Trials specifically evaluating downstaging/conversion treatment or surgery with PVTT

Trial/NCT	Sponsor	Phase	Treatment arms	Pop. included	N =	1°Endpoint
NCT04974281	Fudan University	1	PD-1 antibody+Lenvatinib+TACE	BCLC B/C	50	Resection rate
NCT04988945	The University of Hong Kong	2	TACE+SBRT+Durvalumab+ Tremelimumab	Unresectable HCC	33	% Downstaged
ADVANCE-HCC NCT05137899	OCOG	2	SBRT+ Atezolizumab/Bevacizumab	PVTT	70	Hepatectomy rate
PLATIC NCT04814043	Sun Yat-sen University	2	Sintilimab + Lenvatinib+ TACE-HAIC	Potentially resectable	52	Conversion rate
NCT03368651	Sun Yat-sen University	3	Transarterial chemoinfusion – surgery Surgery	Resectable with PVTT	230	OS
Neoconcept C NCT04181931	Sun Yat-sen University	UK	TACE+HAIC (FOLFOX)-Surgery Surgery	PVTT (exc VP4)	320	PFS
NCT03591705	Sun Yat-sen University	UK	TACE-HAIC TACE	Potentially resectable	240	PFS
NCT04967482	Second Affiliated Hospital of Guangzhou Medical University	UK	TACE Deb-TACE	Unresectable large HCC	216	Success rate of conversion to surgery
CCGLC-001 NCT05713994	Tongji Hospital	observational	HAIC+ Atezolizumab/Bevacizumab	Unresectable	300	% resection

			HAIC + IBI305 + Sintilimab HAIC + apatinib + camrelizumab HAIC + TKI +anti-PD-1			
TACE-TKI-ICI NCT05717738	Tongji Hospital	observational	TACE + Atezolizumab/Bevacizumab TACE + IBI305 + Sintilimab TACE + apatinib + camrelizumab TACE + TKI +anti-PD-1	Unresectable	300	% resection

PFS= progression free survival; OS = overall survival; SBRT = stereotactic body radiotherapy; UK = unknown; PVTT = portal vein tumour thrombus

Table 6: Ongoing or completed phase 3 trials evaluating immune checkpoint inhibition in the adjuvant setting in hepatocellular carcinoma

Trial Name, NCT ID	High-Risk HCC Criteria after Surgery	High-Risk HCC Criteria after Ablation	Comparison
IMbrave 050, NCT04102098	- ≤3 tumors, with largest tumor >5 cm regardless of vascular invasion, or poor tumor - ≥4 tumors, with largest tumor ≤5 cm regardless of vascular invasion, or poor tumor - ≤3 tumors, with largest tumor ≤5 cm with vascular invasion, and/or poor tumor differentiation	- 1 tumor >2 cm but ≤5 cm - Multiple tumors (≤4 tumors), all ≤5 cm	Atezolizumab 1200 mg and bevacizumab 15 mg/kg IV q3weeks x 1 year *versus* active surveillance
Checkmate 9DX(76), NCT03383458	- Up to three tumors, at least one with a diameter > 5 cm None with a diameter - 5 cm but with confirmation of microvascular invasion or poorly /undifferentiated HCC - More than three tumors, none with a diameter > 5 cm	- Solitary tumor > 3cm but <=5 cm - Multiple tumors (up to 4), none with a diameter > 5 cm	Nivolumab 480 mg q4weeks x 1 year versus placebo
EMERALD-2(77), NCT03847428	Excludes Vp1-Vp4. Otherwise N/A	N/A	Durvalumab + bevacizumab *versus* durvalumab + placebo versus placebo
KEYNOTE-937(78), NCT03867084	- Intermediate risk of recurrence: solitary tumor ≥2 cm and ≤3 cm without microvascular invasion and not histologic grade 3 or 4 - High risk of recurrence: solitary tumor ≥2 and <10 cm with microvascular invasion or same size and histologic grade 3 or 4, or multiple tumors, none >10 cm, regardless of microvascular invasion or histologic grade - Very high risk of recurrence: single tumor or multiple tumors of any size involving a major branch of the portal or hepatic	- Intermediate risk of recurrence: Solitary tumor ≥2 cm and ≤3 cm - High risk of recurrence: 2-4 tumors, all ≥2 cm and ≤3 cm or one solitary tumor >3 cm	Pembrolizumab 200 mg IV q3week x 1 year *versus* placebo

	vein, regardless of microvascular invasion or histologic grade. - Stage IIIB tumor(s) with direct invasion of adjacent organs or with perforation of visceral peritoneum will not be eligible	and ≤5 cm	
NCT04639180	N/A	N/A	Camrelizumab + apatinib (specific dosing N/A) *versus* active surveillance
NCT05862337	N/A	N/A	Anlotinib + Penpulimab *versus* placebos