Breakthroughs in hepatocellular carcinoma therapies

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Hepatocellular carcinoma (HCC) is one of the few cancers with a 5-year survival below 20% and an incidence-to-mortality ratio near 1. However, we have witnessed several recent breakthroughs in therapy that have the potential to reverse this dismal prognosis (Table 1). These breakthroughs can be readily identified by examining changes in current treatment options as well as emerging novel therapies[1]. However, perhaps the most important turning point has been that HCC is no longer seen with a nihilistic perspective as a neoplasm for which few treatments can be efficacious. Better knowledge of the disease's natural history and evolutionary stages has provided a clinically oriented stratification of patients and a treatment allocation paradigm to guide therapeutic decisions and optimize survival benefit. The Barcelona Clinic Liver Cancer (BCLC) model represents the most widely validated and endorsed staging and treatment allocation system. It has been updated to incorporate recent evidence, guiding evaluation of tumor stage and prognosis of patients at baseline, followed by an evidence-based treatment allocation proposal that accounts for individual patient's clinical characteristics and preferences to recommend the optimal treatment strategy[2] (Figure 1).

Herein, we describe major developments in the therapeutic realm using a stage-oriented sequence, although the traditional stage-specific treatment approach is likely outdated. There are increasing data about potential expansion of surgical therapies, including liver transplantation, to select patients with minimally impaired liver function and/or limited intermediate-stage HCC and increased use of systemic therapies for some patients with extensive, bilobar liver-localized disease. Instead, our presentation is meant to parallel

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clinical prioritization, first describing options with curative intent that provide longer disease-free survival, and then detailing non-curative locoregional and systemic therapy options.

Curative Surgical or Ablative Therapies

Liver transplantation, surgical resection, and local ablative therapies comprise the curative-intent treatment options for HCC, each providing a 5-year survival of approximately 70%. Although techniques for these therapies are mature, with minor advances in recent years compared to other treatments, there have been breakthroughs in our understanding of tumor biology and patient eligibility, increasing the proportion of patients who can benefit from each of these therapies.

Surgical Resection

Eligibility for surgical resection depends on several factors including tumor burden, the degree of liver dysfunction, portal hypertension, and planned extent of the hepatectomy including future liver remnant (FLR)[2–4]. Resection remains the treatment of choice for patients with localized HCC in the absence of cirrhosis, although non-cirrhotic HCC accounts for a minority of cases in the Western world despite higher proportions being reported in those with nonalcoholic steatohepatitis (NASH)[5]. In patients with underlying cirrhosis, resection had historically been largely limited to those with a unifocal tumor in the setting of compensated cirrhosis, lack of clinically significant portal hypertension, and an adequate FLR. Clinically significant portal hypertension [hepatic vein pressure gradient (HVPG)   10mmHg] is associated with risk of liver failure and is optimally measured by HVPG measurement[6]; however, lack of ascites, portosystemic varices, and a platelet count >100,000 are often used as non-invasive surrogates for lack of portal hypertension in routine clinical practice[7]. Introduction of minimally invasive surgical (MIS) approaches, in parallel with advances in intra-and peri-operative management, have expanded patient eligibility for surgical resection. MIS approaches, including laparoscopic and robotic-assisted hepatectomy, are widely used for limited minor resections in anatomically favorable locations, although use of these techniques for major hepatectomies is typically limited to high-volume centers. Meta-analyses of comparative studies, with or without propensity score matching, have reported MIS approaches are associated with decreased operative blood loss, shorter length of stay, and decreased 30-day morbidity compared to open resection; however, recurrence-free survival (RFS) or overall survival (OS) appear similar between the two techniques[8,9]. Given these differences, MIS approaches may extend resection criteria, allowing some patients with mild portal hypertension to safely undergo minor liver resection. Future studies are needed to define which patients with mild portal hypertension are best treated with MIS resection +/− salvage liver transplant versus up-front transplantation.

Although surgical resection is primarily reserved for patients with BCLC stage 0/A HCC, increasing data highlight that it may also play a role in select patients with BCLC stage B HCC. A meta-analysis of 18 studies comparing surgical resection to TACE reported a significant survival advantage for surgical resection in patients with limited multifocal

disease (HR 0.56, 95%CI 0.35–0.90), although available data are limited by channeling bias[10]. There are also data, primarily from Asia, suggesting resection can also be effective in select patients with PVTT[11,12], although data from Western centers using this approach are more limited and less encouraging. Studies to better identify which patients beyond BCLC stage A who could benefit from resection instead of locoregional or systemic therapies is an area of need.

Although resection affords long-term survival, the risk of post-operative recurrence remains high, highlighting a need for (neo)adjuvant therapy. Factors associated with recurrence include older age, male sex, degree of liver dysfunction, and tumor size, number, grade/ differentiation, micro- and macrovascular invasion, presence of satellite lesions, and AFP levels[13–15]. In hepatitis C-associated HCC, sustained virological response (SVR) after direct acting antiviral (DAA) therapy does not increase HCC recurrence risk and improves survival[16–18]. However, there are no proven (neo)adjuvant therapies for patients. Studies evaluating (neo)adjuvant tyrosine kinase inhibitors (TKIs) have failed to demonstrate improved RFS and OS[19]. Recent phase I-II studies have suggested neoadjuvant immune checkpoint inhibitors, such as cabozantinib plus nivolumab and nivolumab +/– ipilimumab, can induce major pathologic responses in 30–40% of patients, although we are awaiting phase III data to determine if these therapies can improve RFS and OS[20,21].

Liver Transplantation

Liver transplantation (LT) is regarded as the optimal treatment for patients with early-stage HCC who are ineligible for resection due to liver dysfunction or tumor multifocality, as it provides a cure for both the HCC and the underlying liver disease. In a seminal article published in 1996, Mazzaferro and colleagues defined the Milan Criteria as providing optimal post-transplant outcomes, with 5-year survival exceeding 70% and ~10% five-year recurrence[22]. Since that time, several criteria with larger tumor burden including the UCSF criteria, up-to-seven criteria, extended Toronto criteria, and Kyoto criteria have also been shown to achieve acceptable post-transplant outcomes (Table 2)[23–26]. Beyond tumor burden at presentation, response to locoregional therapy and changes in tumor burden are increasingly used to identify those with favorable tumor biology. In patients exceeding Milan criteria but within defined limits of HCC tumor size and number, post-transplant outcome in those successfully downstaged to Milan criteria do not significantly differ from those who present within Milan criteria[27–29]. A randomized controlled trial (RCT) of 74 patients who presented beyond Milan criteria, were downstaged, and then subsequently randomized to LT versus non-transplant therapies, reported 5-year survival of 77% in the LT group versus 31% for others (HR 0.32, 95%CI 0.11–0.92)[30]. Based on these data, patients whose initial tumor burden exceeds Milan criteria can be considered for LT following successful downstaging to within Milan criteria. However, the downstaging strategy must pay attention to practicalities including accurate assessment of initial tumor staging and treatment response during follow-up, including a requirement for durable responses 6 months to ensure optimal outcomes[31]. In the United States, UNOS-DS criteria define the upper limits of downstaging to receive priority for deceased donor liver transplantation. Although patients beyond these criteria can still undergo living donor liver transplant, liberalizing criteria results in a higher risk of waitlist dropout, higher post-

transplant recurrence, and lower post-transplant survival[32]. In addition to tumor burden, serum biomarkers including alpha fetoprotein (AFP) have prognostic value, with even low-level AFP elevations associated with increased post-LT recurrence[33]. Patients with marked elevations, such as AFP >1000 ng/mL, must achieve lower post-treatment levels for acceptable post-transplant outcomes, although the magnitude of required decrease needs validation[34,35]. Studies are ongoing to define the optimal LT criteria that achieve acceptable post-LT outcomes and maximize transplant benefit for the greatest number of patients with HCC.

Neoadjuvant LRT such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), local ablation, and external beam radiation therapy (EBRT) is often used as a bridge to reduce the risk of waitlist dropout[36,37]. A single-center case series and selected case reports suggest that immune checkpoint inhibitors may also be safe as bridging therapy, although larger studies evaluating longer post-transplant outcomes and defining the optimal washout period are still needed[38].

One of the limitations of transplantation is a shortage of available organs compared to those in need of LT[39]. To address this issue, living donor liver transplantation (LDLT) is an option for patients with HCC – including those beyond typical selection criteria. Initial concerns of increased HCC recurrence with LDLT for HCC were primarily related to patient selection, and recent reports have demonstrated improved survival for patients within Milan Criteria using LDLT compared to deceased donor LT when analyzed on an intention-to-treat basis, primarily due to reduced risk of wait-list dropout[40,41].

Local ablative therapy

Local ablative therapy (LAT) offers a curative treatment option in patients with solitary HCC who are ineligible for surgery. Specifically, LAT may be considered for patients with centrally located tumors requiring major hepatectomy or those with very early-stage HCC, as RCTs demonstrate LAT affords similar survival and is cost-effective compared to resection in patients with BCLC stage 0 HCC[42]. LAT yields 3-year RFS and OS of ~46% and 76%, respectively, for unifocal HCC ≤ 3 cm[43,44]. Patients with HCC >3 cm experience lower objective response rates (ORR), higher recurrence rates, and worse OS compared to those with smaller tumors. Although initial radiologic objective response may be improved by combining ablation with TACE, survival benefit of this strategy is not proven. Contrast-enhanced ultrasound immediately after ablation can also assess for viable disease and enable retreatment as needed to optimize ORR.

The first LAT modality was percutaneous ethanol injection, although this has since been replaced in most centers by radiofrequency ablation, microwave ablation, and cryoablation– all of which induce superior ORR with fewer sessions. Although there are no randomized data showing superiority of one ablative modality over another, microwave ablation may be less susceptible to heat sink effects near large vessels and is now used as the primary LAT in many centers[45–47]. Irreversible electroporation (IRE), which uses high-current electrical pulses to induce cell death, has also been proposed as another form of LAT to avoid heat sink effects, although this approach is time consuming and has not been widely adopted. Early data suggest histotripsy, a sonic beam approach for LAT, may not only be another

approach to induce ORR but also induce immunomodulatory effects to also induce abscopal effects in other untreated lesions, as also suggested for other LATs. Similarly, there are data that external beam radiation therapy, including stereotactic approaches, can induce high rates of local tumor control although larger cohorts evaluating clinically important outcomes including overall survival are still needed[48–51].

Locoregional Therapies and Management of Intermediate Stage HCC

We are currently at the cusp of a paradigm shift in the treatment strategy for intermediate-stage HCC, i.e., liver-localized multifocal HCC beyond the Milan Criteria. Traditionally, AASLD and EASL had both recommended transarterial chemoembolization (TACE) as the only recommended treatment for patients with intermediate-stage HCC[52,53], whereas guidelines from the Japan Society of Hepatology included a broader portfolio of treatment options including surgical resection, TACE, hepatic arterial infusion chemotherapy, and systemic therapy[54]. In recent years, recommendations regarding initial therapy for patients with intermediate stage disease have dramatically changed. Systemic therapy is now recommended for patients with large intrahepatic tumor burden by the latest AASLD guidance[55], the European Society for Medical Oncology guideline[56], and the updated version of the BCLC system[2]. The 2022 BCLC Update stratifies the BCLC-B stage into 3 groups of patients according to tumor burden and liver function: 1) the "Extended Liver Transplant" group can be candidates for liver transplantation because of expanded criteria and/or downstaging, 2) those with "well-defined nodules, preserved portal flow and selective access" can be candidates for selective TACE, and 3) patients with diffuse, infiltrative, extensive bilobular liver involvement who are recommended for systemic therapy[2]. Additionally, there is increasing recognition that post-TACE management can differ by response to therapy, with liver transplantation considered for those with sufficiently robust objective response and systemic therapy considered for those with inadequate response (Figure 2). This development is related to increasing adoption of two important concepts that push the management of these patients beyond a traditional TACE-only approach: "TACE refractory" and "TACE unsuitable"[57–59].

Transarterial chemoembolization

TACE remains the primary recommended strategy with patients with limited tumor burden, without vascular invasion or extrahepatic spread, compensated liver disease, and no cancer-related symptoms[44,60]. In well selected patients, TACE induces objective responses in >50% of patients and significantly prolongs survival compared to no treatment. With optimal selection criteria, median survival of patient cohorts should be around 30 months[61]. While the potential benefits of TACE were long recognized and previously overemphasized in the absence of effective systemic therapies, the potential adverse effects of TACE are increasingly recognized in light of effective systemic therapies. The OPTIMIS is a global non-interventional study evaluating 1650 patients with HCC undergoing TACE in clinical practice highlighted that repeated TACE sessions not only had decreasing objective responses but also associated with risks of hepatic injury, manifested as increases in AST, ALT, bilirubin, and INR[62]. Therefore, repeated TACE is increasingly reserved for patients

who tolerated the TACE with minimal adverse events and with evidence of objective tumor response (Figure 2).

TACE Refractory

Considering this risk-to-benefit ratio, the concept of TACE refractoriness was initially proposed in 2011[63], updated in 2014 [64], and has now subsequently been adopted worldwide[65–68]. Whereas TACE failure was historically defined by stage migration from BCLC stage B to stage C, TACE refractoriness expands treatment failure to include patients without objective response after two TACE sessions. Therefore, these patients should then be considered for subsequent lines of therapy, with the idea to preserve liver function and allow patients to benefit from effective systemic therapy options. Retrospective clinical studies have supported this approach, with longer survival observed in patients who were promptly switched to systemic therapy after meeting TACE refractory criteria compared to those who were continued on repeated TACE[69,70].

TACE Unsuitable

Another central concept for the management of patients with intermediate-stage HCC has been the concept of TACE unsuitability, i.e., patients who are not ideal candidates for TACE as initial therapy despite having liver localized disease and falling within the BCLC B stage. Similar to TACE refractory, the concept of TACE unsuitable is based on the risk of treatment-related hepatic dysfunction exceeding the incremental benefit of TACE over systemic therapy. Although there is widespread acceptance of TACE unsuitability as a concept, including by many expert interventional radiologists, there are multiple proposed criteria for TACE unsuitable. An Asia-Pacific Expert Consensus statement defined TACE unsuitable as HCC beyond up-to-seven criteria, ALBI grade 2 liver function, and tumors that are likely to be TACE resistant (e.g., extranodular growth pattern, confluent multinodular HCC, massive HCC, poorly differentiated)[58]; whereas the BCLC system uses terms such as diffuse, infiltrative, extensive bilobar involvement[2]. Similarly, patients beyond up-to-seven criteria but who are within downstaging criteria would often be treated with upfront locoregional therapy to maximize chance of objective response.

For TACE unsuitable HCC, recently approved systemic therapy options provide an alternative strategy to induce responses in a large proportion of patients. Objective responses using RECIST criteria can be observed in 30% of patients using Atezolizumab plus Bevacizumab[71] and ~20% using Durvalumab plus Tremelimumab[72] or using Lenvatinib alone[73]. Subgroup analyses of clinical trial data[74] and available retrospective cohort studies suggest even higher response rates may be observed in patients with intermediate-stage HCC; however, it should be noted that patients with >50% liver involvement were excluded from some clinical trials, including REFLECT [73]. These therapies may be particularly beneficial in patients with larger intrahepatic tumor burden, for whom selective TACE is not possible. This concept was supported by a retrospective propensity-score matched analysis, in which upfront TACE versus Lenvatinib was compared in a group of patients with tumors exceeding up-to-seven criteria[75]. Those patients who received up-front Lenvatinib had significantly better overall survival (median 37.9 vs. 21.3 months; HR 0.48, 95%CI 0.16 – 0.79). In part, this differential survival was believed to be mediated by better preservation

of liver function, with ALBI scores significantly degrading in the patients undergoing TACE but not those on lenvatinib. This proof-of-concept is now being evaluated in large phase II and phase III studies, including the ABC Trial (NCT04803994) randomizing patients with multifocal HCC beyond Milan Criteria to TACE or Atezolizumb plus Bevacizumab.

In the retrospective proof-of-concept study by Kudo and colleagues, there were some patients who had objective responses with lenvatinib which facilitated subsequent TACE (in a more selective fashion than initially possible), raising the concept of systemic-locoregional sequential therapy[76]. This practice is also possible in patients treated with immune checkpoint inhibitor combinations, such as atezolizumab plus bevacizumab, including in patients with positron emission tomography (PET)-positive HCC or those with large tumor burden[77]. In a multi-center retrospective cohort study including 110 patients with intermediate-stage HCC who were treated with atezolizumab plus bevacizumab, 38 (35%) achieved curative conversion and 24 (22%) achieved cancer-free, drug-free status. Among those who achieved curative conversion, seven underwent resection, 13 underwent radiofrequency ablation, 15 underwent curative TACE, and three received systemic therapy only[78]. These data highlight the potential for currently available systemic therapy options to achieve a high response rate[79] (and "downstaging", facilitating conversion to locoregional or surgical therapies. Notably, this concept is contrarian to traditional practice patterns in oncology, wherein once systemic therapy is initiated and achieves a response, it is continued as long as the regimen remains effective. However, for HCC, especially for patients with intermediate-stage HCC, extremely effective treatments (e.g., resection or ablation) could be available if objective responses are achieved. There are limited data at this time to guide these decisions and analysis of studies will need to be detailed to avoid flaws[31]. Thus, it seems reasonable that an option of curative conversion should always be considered, particularly given pathological CR can be rarely achieved by systemic therapy or locoregional therapy alone. Although clearly an extrapolation of data, this practice could also be potentially supported by the XXL Trial[30], which demonstrated the benefit of conversion to potentially curative surgical therapy in those who achieved a response to locoregional therapy.

Combination Therapies

In addition to sequential therapies, there has also been interest in combining systemic and locoregional therapies to increase objective responses, PFS, and overall survival. Systemic therapy with tyrosine kinase inhibitors (TKIs) has several theoretical benefits: (i) inducing tumor necrosis, thereby potentially achieving "downstaging"; (ii) reducing hypoxic stress caused by TACE thus aiming to suppress the hypoxia-induced release of cytokines [e.g., vascular endothelial growth factor (VEGF)], that could prime progression and metastasis; and (iii) normalizing tumor vasculature that could enhance the effect of TACE[80]. These theoretical benefits prompted several trials evaluating the combination of sorafenib and TACE, with all failing to show any benefit in the primary outcomes of time-to-progression (TTP) or progression-free survival (PFS). Recently, the TACTICS trial demonstrated the combination of sorafenib plus TACE improved PFS (HR 0.59, 95% CI, 0.41–0.78) compared to TACE alone[81], although this failed to translate into an OS benefit (36.2 vs. 30.8 months, respectively; HR 0.86, 95% CI 0.61–1.22)[82]. At this time, existing phase II

and phase III studies have failed to demonstrate a benefit in proposed primary outcomes. However, there have been questions if overall survival is the optimal primary endpoint of locoregional therapies, particularly considering continued improvements in post-progression therapies, highlighting a need for validated, accurate surrogate measures that can be used in clinical trials[83,84]. Although a moderate correlation between PFS and overall survival has been suggested in systemic therapy trials, it is unclear if this is true for locoregional therapies as prior trials evaluating combination studies failed to show any correlation (r = 0.56).

With the introduction of immune checkpoint inhibitors in the advanced stage setting, there has been renewed interest in evaluating the combination of systemic and locoregional therapies. It is theorized that TACE may induce release of neoantigens which could then augment responses with systemic therapy, induced synergistic effects by using the two in combination. Accordingly, there are several ongoing phase III studies evaluating TACE in combination with immune checkpoint inhibitors.

Transarterial Radioembolization

Transarterial radioembolization (TARE) is an alternative intra-arterial therapy for early- and intermediate-stage HCC. Early studies with TARE failed to show a benefit compared to systemic therapy for patients with advanced-stage disease[85–87]; however, recent data have demonstrated efficacy in patients with BCLC stage A or B disease using a radiation segmentectomy approach[88,89]. In 2021, TARE using Y90 was granted FDA-approval based on results of the LEGACY Study, which reported objective responses in 88.3% of patients with solitary HCC up to 8 cm (median size 2.7 cm)[90]. The DOSISPHERE-01 trial also demonstrated the benefit of personalized dosimetry when performing TARE with a goal of >205Gy to the targeted area, with significantly improved objective responses and survival compared to standard dosimetry[91]. The choice between TACE and TARE is often determined by center expertise and availability given limited direct comparative data. A recent meta-analysis of comparative studies found TARE was associated with improved TTP but without significant difference in overall survival[92]. However, comparison of TTP between the two modalities can be difficult given post-radiation changes complicating interpretation of response.

Systemic therapy

While surgery and locoregional options were present for decades and have undergone progressive refinements and developments to increase effectiveness, the area of systemic therapy for HCC was lacking an effective intervention until 2007[93]. Conventional chemotherapy was applied by default with more hope than evidence and adverse events due to toxicity often precluded any significant benefit. Neither intravenous administration, nor selective intraarterial administration, emulsified in lipiodol or not, were proven to offer survival benefit in large and robust trials with adequate sample size. Finally, a better understanding of the molecular mechanisms responsible for cancer progression and dissemination allowed generation of agents that would selectively act on specific targets driving HCC progression. Tyrosine-kinase inhibitors and antibodies aimed at angiogenesis

and proliferation targets were tested in early phase development trials following successes in other neoplasms such as breast, lung, colorectal or renal cell cancer. Delay in these agents entering the field of HCC was related in part to the nihilist view about the likelihood of treatment efficacy versus safety concerns in the presence of underlying liver disease.

Tyrosine kinase inhibitors

Sorafenib was the sole agent that was tested in such manner after an initial phase 2 confirmed its safety[94]. Although the marginal rate of tumor response initially classified the study as negative, subsequent analysis of the data suggested a delay in tumor progression and improved survival as compared with natural history data. This experience paints a tail of caution for overreliance on non-validated surrogate outcomes[83,84,95], i.e., objective responses in this case, as this nearly led to the discard of the first efficacious systemic therapy for advanced HCC. The pivotal phase 3 SHARP Trial had several important aspects that were applied to subsequent trials: 1) acceptance of a placebo-controlled trial with avoidance of any conventional chemotherapy in the control arm, 2) careful patient selection with avoidance of patients with decompensated liver disease, 3) introduction of stratification factors to secure a balance between arms, and 4) its use of overall survival as the primary endpoint given lack of validation for PFS as a valid surrogate outcome in patients with HCC[96]. SHARP also allowed treatment beyond progression as it was already envisioned that some progression would not have a major impact. Later studies confirmed that pattern of progression is a key aspect in prognosis prediction and trials analysis[97]. As now known, sorafenib significantly improved survival (median 10.7 vs. 7.9 months, HR 0.69, 95%CI 0.55 – 0.87) with a tolerable safety profile including low risk of liver dysfunction[96]. Adverse events, including hand-food skin reaction, were shown to suggest drug activity and predict a better outcome[98,99].

The success of sorafenib represented a revolution in the field and opened the era where several agents would be tested in the first-line and second-line settings. However, in all instances for the following 10 years, studies turned negative, and the HCC field was classified as a graveyard[100–104]. We had to wait 10 years to see another agent come to market, with the landscape changing in a positive manner in 2017. Data from positive phase 3 trials in the first- and second-line setting are detailed in Table 3. In the first-line setting, Lenvatinib showed non-inferiority to sorafenib in terms of overall survival but demonstrated significant improvements in secondary outcomes including PFS and objective response rates[74]. Second-line therapies demonstrated as superior to placebo in phase 3 RCTs included regorafenib[105] and cabozantinib[106]. Although ramucirumab initially failed to demonstrate a benefit in all-comers in the second-line setting, a subsequent RCT (REACH-2) showed a survival benefit in patients with AFP >400ng/mL[107].

Immune Checkpoint Inhibitors

Unexpectedly, single agent immune checkpoint inhibitors failed to improve overall survival in the first-line setting (nivolumab vs sorafenib)[102] or second-line setting (pembrolizumab vs. placebo)[103] despite durable response rates of ~15–20%. Subsequent RCTs from China have demonstrated non-inferiority of tislelizumab vs. sorafenib in the first-line setting

[RATIONALE-301 (NCT03412773) study] and superiority of pembrolizumab vs placebo in the second-line setting[108].

The prominent position of targeted therapy was finally lost in 2020 when the combination of Atezolizumab (a checkpoint inhibitor of the programmed cell death receptor) and the antibody bevacizumab (a powerful inhibitor of the vascular endothelial growth factor receptor) was proven superior to sorafenib in the 1st line setting in the IMBRAVE150 phase 3 trial[109]. VEGF inhibition is not only cytotoxic but also has immunomodulatory effects including increased cytotoxic T lymphocytes and dendritic cells as well as decreased regulators T cells, tumor associated macrophages and myeloid derived suppressor cells[110]. The combination of Atezolizumab plus Bevacizumab provided a median survival of 19.2 months, compared to 13.4 months for sorafenib, and was well tolerated with minimal grade 3–4 adverse events[71]. The risks of bleeding due to bevacizumab were minimized by restricting to patients with well-preserved liver function and confirming absence of high-risk varices or other stigmata on an upper endoscopy within 6 months prior to randomization. The improvement in survival was statistically significant and clinically relevant, and the safety of the treatment was evident. Therefore, Atezolizumab-bevacizumab was immediately established as the preferred treatment option in patients considered for systemic therapy[2,111,112]. Patients with high risk of bleeding, severe vascular disorders, or autoimmune conditions (including post-transplant patients) would not be optimal candidates for the combination, thus leaving some patient subgroups to still be considered for sorafenib or Lenvatinib, although these agents also have some risk of GI bleeding. More success was around the corner with positive data obtained by the combination of Tremelimumab (CTLA-4 inhibitor) and Durvalumab (a PD-L1 inhibitor) in the 1st line vs sorafenib[72]. CTLA-4 inhibition is an independent mechanism to block negative inhibition enhance priming of T lymphocytes in lymphoid organs[113]. Interesting, this combination was the first successful treatment that did not act upon the VEGF pathway. It offered a significant survival benefit vs sorafenib, providing a median overall survival of 16.4 months and 3-year survival of 30.7%, compared to 13.8 months and 20.2%, respectively for sorafenib. The HIMALYA Trial also showed non-inferiority of durvalumab as single agent compared to sorafenib[72].

While we have not discussed negative trials in depth, it is worth noting recent failure in 1st line of Lenvatinib plus pembrolizumab (LEAP-002[114]), cabozantinib plus atezolizumab (COSMIC-312)[115], and TARE vs. sorafenib in the first-line setting[85–87]. These trials failed to improve overall survival despite promising signals for high objective responses or PFS, highlighting that these are imperfect surrogates for overall survival. Further, these agents may significantly improve outcomes for a subgroup of patients (i.e., improving the tail of the survival curve), whereas many others do not benefit, providing similar median survival estimates. These negative trials highlight the continued need for surrogate outcomes for overall survival as well as a need for treatment response biomarkers that can help maximize likelihood of objective response and improved survival.

Systemic Therapy Options in Child Pugh B

Although there have been notable advances in systemic therapy options, it is notable that all were evaluated in patients with preserved liver function. There remains a need for safe and effective therapies for patients with Child Pugh B cirrhosis, which comprise a sizable portion of patients seen in clinical practice. There are real world data demonstrating safety of TKIs, primarily sorafenib, as well as data for single-agent immune checkpoint inhibition in select patients with Child Pugh B cirrhosis[116]. The CheckMate 040 phase II study included a subset of 49 patients with Child Pugh B7 disease who were safely treated with Nivolumab, with no unexpected safety signals. A recent metanalysis shows that the heterogeneity of published data excessive and prevents a valid recommendation[117]. Although these therapies may be safe, it is important to consider that the competing risk of liver-related mortality likely mitigates any survival benefit of HCC-directed therapy. The competing risk of liver-related mortality varies among patients with Child Pugh B cirrhosis, with higher risk in patients with CTP score 9 compared to those with CTP score 7, so the former patient would likely derive less benefit than the latter patient. Other factors including patient performance status and goals of care should also be taken into account when considering treatment in these patients.

Future Developments

With recent breakthroughs, there has been a breakdown of previously existing treatment silos, with patients transitioning across the BCLC system from left to right and vice versa. As above, we are becoming increasing cognizant of treatment failure or ineligibility, most evident with TACE in the intermediate stage space. We are also observing high response rates with locoregional and systemic treatments, allowing downstaging of some patients to liver transplantation or surgical resection despite being ineligible at first presentation. This complexity highlights the importance of multidisciplinary care when managing HCC patients in the contemporary landscape[118,119].

In this vein, combination studies using TKIs with TACE failed to improve PFS or OS, although combinations are now being revisited with immune checkpoint inhibitors. Several phase 3 trials examining combinations of immune checkpoint inhibitors +/− TKIs are currently underway for both early-stage and intermediate-stage HCC (Figure 3). Based on the favorable outcomes in advanced HCC, there is a fair chance that these trials will be successful, which would transform our approach for early- and intermediate-stage HCC.

Despite these breakthroughs, there continues to be work that needs to be performed (Table 4). First, there remains a stark difference in survival between patients with early-stage HCC and those with larger tumor burden, highlighting a need for efforts to promote surveillance and early tumor detection. In parallel with continued research evaluating novel therapeutics, we must continue to promote surveillance effort to maximize the proportion of patients detected at an early stage[120,121]. Second, as discussed above, most therapies were evaluated in patients with preserved liver function and there remains a need for therapies that are safe and ideally prolong survival in patients with Child Pugh B cirrhosis[116,117]. Third, despite major advancements in the stratification of patients according to molecular profile, we still lack the data to link a specific profile with a clinical decision about the best

treatment option to propose or the treatment that should be avoided[1,122]. There is a strong need for treatment response biomarkers to better select patients[123]. In parallel, the potential role of clinical factors including underlying liver disease etiology as potential moderators of treatment response should be properly investigated[124–126]. This critical knowledge gap remains an area of immense need, leaving room for continued breakthroughs over the next couple decades. Ongoing trials using novel designs such as umbrella trials not only have the potential to identify new treatment combinations but also to potentially identify treatment response biomarkers that could be used to tailor therapy decisions.

Summary

As exposed, the field of HCC has experienced a major improvement in management, and we have witnessed the dawn of a new area in all areas of treatment. Earlier diagnosis, better tumor staging, and improved evaluation of liver function have primed a better selection of patients to be proposed for any intervention, as well as development of novel approaches. This has been especially intense in the field of systemic therapy that has evolved from an absence of effective options to a plethora of agents that improve survival. Further improvements will take place with novel agents or combinations, but to bring HCC to precision oncology, there is need to further investigate the oncogenic mechanisms that govern tumor progression and dissemination in order to ultimately, treat patients according to such mechanisms and abandon the era of one size fits all.

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Amit Singal has served as a consultant or on advisory boards for Genentech, AstraZeneca, Bayer, Eisai, Exelixis, FujiFilm Medical Sciences, Exact Sciences, Roche, Glycotest, Freenome, and GRAIL.

Masatoshi Kudo has served as a consultant or on advisory boards for Eli Lilly, Bayer, Eisai, Chugai, Roche, AstraZeneca, Takeda, MSD, Gilead Sciences, Taiho, Sumitomo Dainippon Pharma, Takeda, Otsuka, EA Pharma, AbbVie and GE Healthcare.

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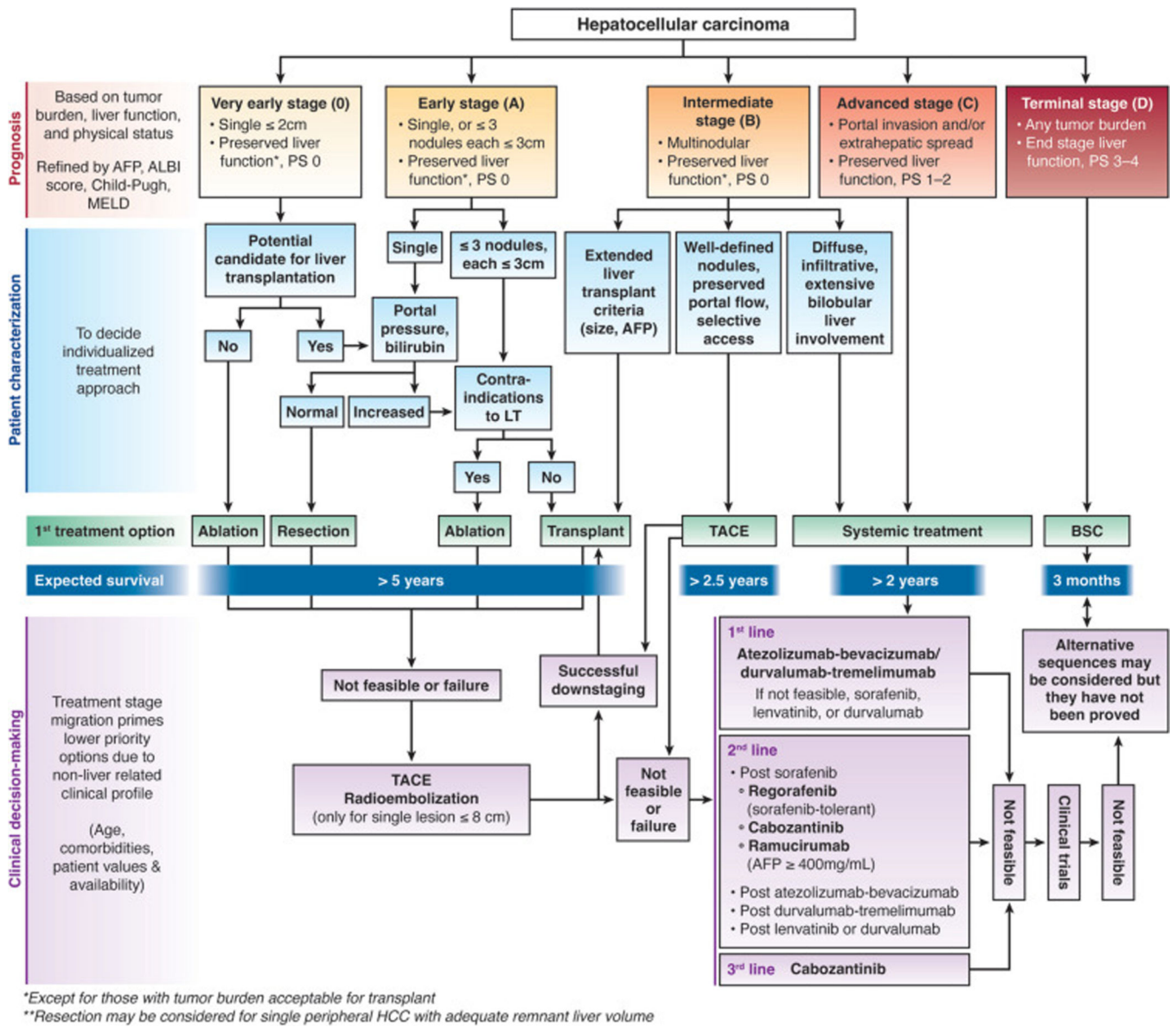
Figure 1.
Updated BCLC Staging and Treatment Algorithm. AFP, α-fetoprotein; ALBI, albumin-bilirubin; BSC, best supportive care; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; PS, performance status; TACE, transarterial chemoembolization.
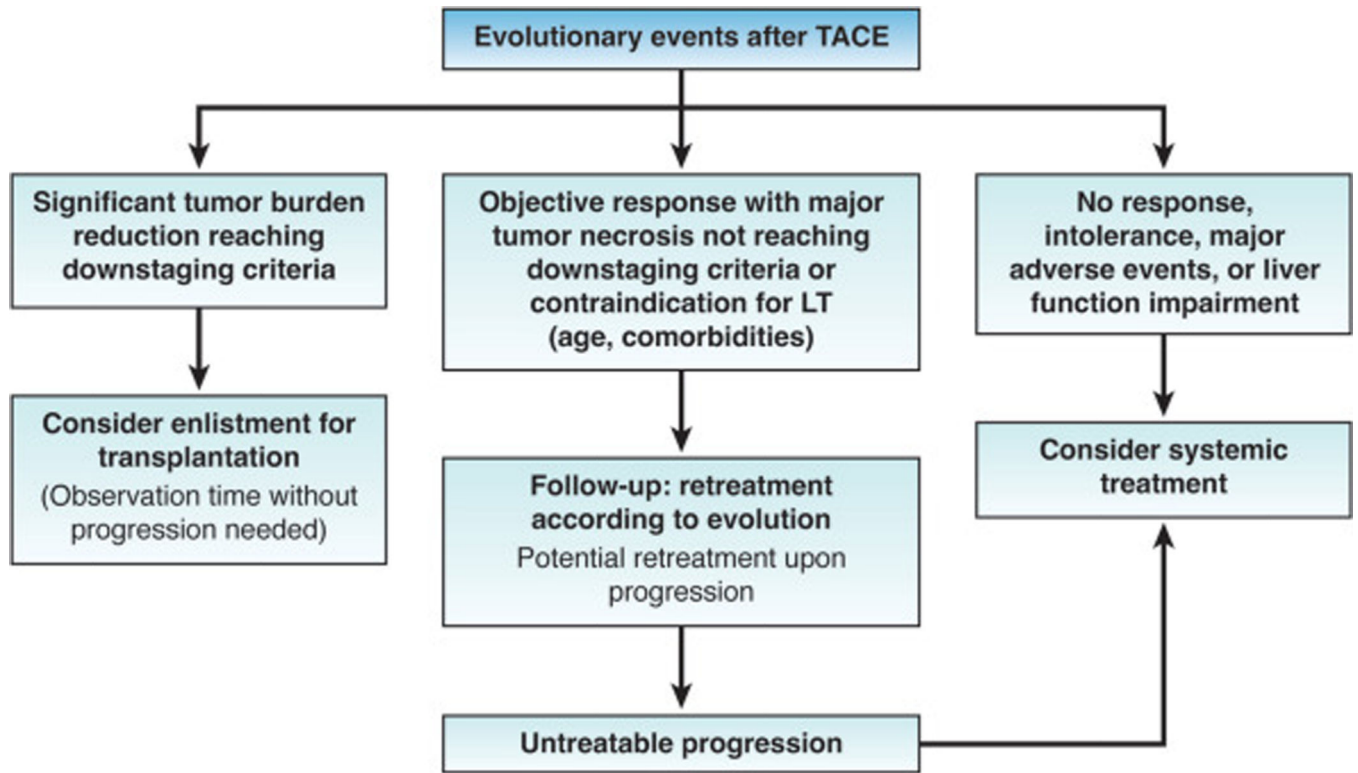
Figure 2.
Response-guided treatment strategy after TACE.[2] LT, liver transplantation; TACE, transarterial chemoem bolization.
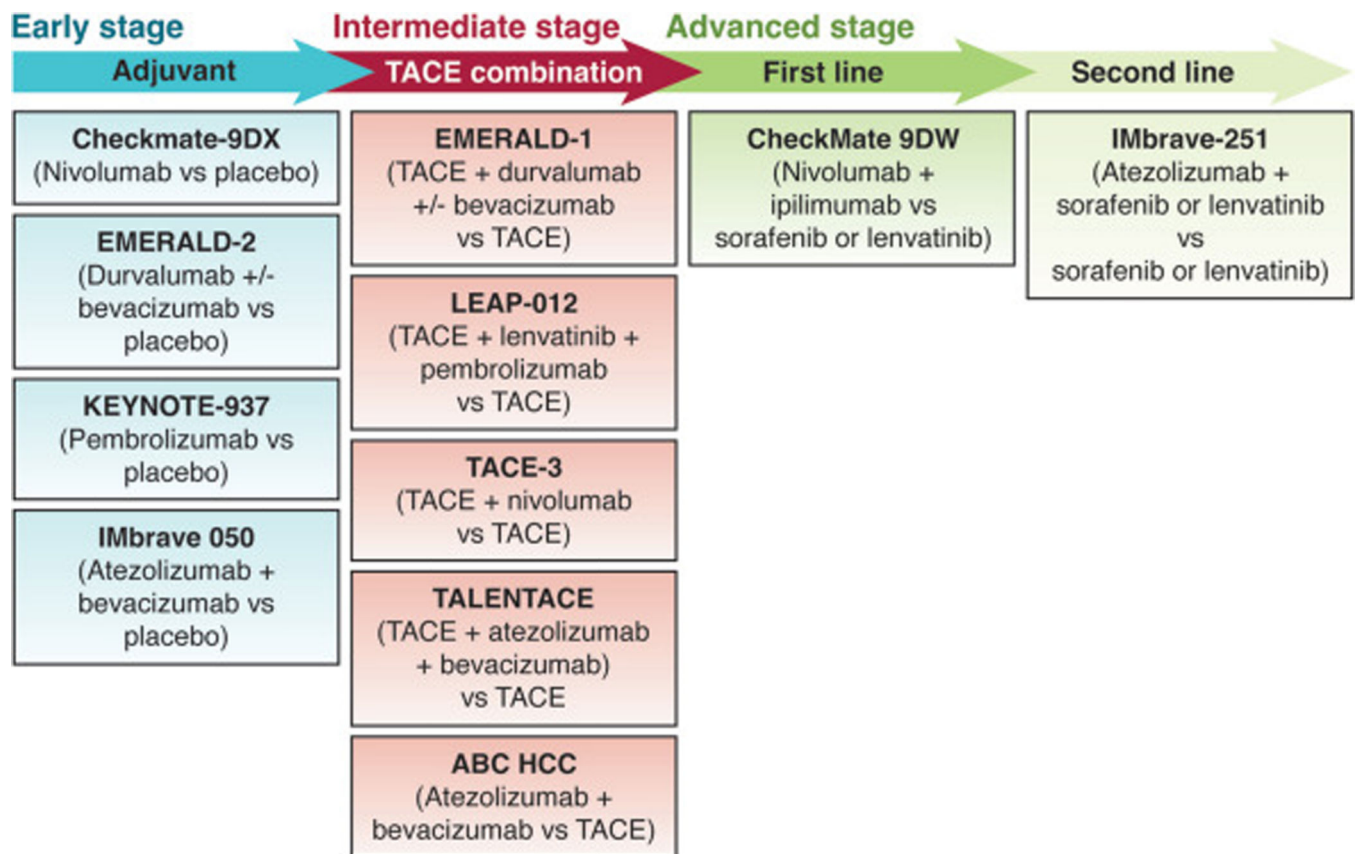
Figure 3.
Ongoing phase III trials. ABC, Atezolizumab plus Bevacizumab versus transarterial Chemoembolization; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; TALENTACE, **T**ecentriq plus **A**vastin **L**iver **E**nvision Tomorrow-**T**ACE (A phase III, open-label, randomized study of on-demand TACE combined with atezolizumab plus bevacizumab [atezo/bev] or on-demand TACE alone in patients with untreated hepatocellular cacinoma).

Table 1.

Breakthroughs in the field of Hepatocellular Carcinoma

- Incorporation of HCC screening in clinical practice
- Development and validation of non-invasive diagnostic criteria
- Stratification of patients into relevant evolutionary stages linked to treatment
- Establishment of liver transplantation as curative treatment for HCC, including concept of downstaging
- Improved selection criteria and introduction of minimally invasive techniques for surgical resection
- Incorporation of ablation as an effective therapy competing with surgery for very-early-stage HCC
- Proof of survival benefit of chemoembolization
- Recognition and incorporation of concepts of TACE unsuitable and TACE refractory in clinical practice
- Demonstration of objective responses with radioembolization, particularly with radiation segmentectomy technique for early-stage HCC
- Availability of effective systemic therapy, including immunotherapy combinations, in sequential lines
- Refined trial design to evaluate new interventions at any stage

Table 2.

Examples of Expanded Criteria for Liver Transplantation

Expanded Criteria	
UCSF Criteria	One tumor 6.5 cm OR 2–3 tumors, each 4.5 cm, with total tumor volume 8 cm
Up-to-Seven Criteria	Diameter or largest tumor (cm) + number of tumors 7
Extended Toronto Criteria	Biopsy demonstrating well to moderate differentiation for patients beyond Milan Criteria and ECOG performance status 0–1
Total tumor volume <115 cm	Sum of volume for each tumor 115 cm³
Kyoto Criteria	Number or tumors 10, maximum diameter of each tumor 5 cm, and serum DCP 400 mAU/mL
5–5-500 Rule	Numbers of nodules 5, nodule size 5 cm, and AFP 500 ng/mL

Table 3.

Outcomes reported in systemic treatment positive phase III trials

LINE	Study	Systemic Therapy	n	FU m, median (IQR)	ORR RECIST 1.1, %(95CI)	CR RECIST 1.1, n(%)	TTP (m), median (95CI)	PFS (m), median (95CI)	OS (m), median (95CI)
1L	Llovet JM, et al. NEJM 2008	Sorafenib	299		n=7 (2%) PR	0	5.5 (4.1–6.9)		10.7 (9.4–13.3)
	Kudo M, et al. Lancet 2018	Lenvatinib	478	27.7 (23.3–32.8)	n=90 18.8 % (15.3–22.3)	2 (<1)	8.9 (7.4–9.2)	7.4 (6.9–8.8)	13.6 (12.1–14.9)
		Sorafenib	476	27.2 (22.6–31.3)	n=31 6.5 % (4.3–8.7)	1 (<1)	3.7 (3.6–5.4)	3.7 (3.6–4.6)	12.3 (10.4–13.9)
	Finn RS, et al. NEJM 2020 Cheng, et al. J Hepatol 2022	Atezolizumab-bevacizumab	336	17.6 (0.1–28.6)	30% (22.5–32.5)	25 (8.0)	-	6.9 (5.7 – 8.6)	19.2 (17.0–23.7)
		Sorafenib	165	10.4 (0–27.9)	11 % (7–17)	1 (<1.0)	-	4.3 (4.0–5.6)	13.4 (11.4–16.9)
	Ren Z, et al. Lancet Oncol 2021	Sintilimab + IBI305 (Bevacizumab biosimilar)	380	10.0 (8.5–11.7)	21% (17–25) PR	0	5.2 (4.2–5.8)	4.6 (4.1–5.7)	Not reached
		Sorafenib	191	10.0 (8.4–11.7)	4 % (2–8) PR	0	2.8 (2.7–3.2)	2.8 (2.7–3.2)	10.4 (8.5-Not reached)
	Abou-Alfa, et al. NEJM evidence 2022	Tremelimumab + Durvalumab (STRIDE)	393	33.18	20.1%	12 (3.1)	5.4 (3.8–5.6)	3.78 (3.75.3)	16.43 (14.2–19.6)
		Durvalumab	389	32.56	17.0%	6 (1.5)	3.8 (3.7–5.4)	3.65 (3.2–3.7)	16.56 (14.1–19.1)
		Sorafenib	389	32.23	5.1% PR	0	5.6 (5.1–5.8)	4.07 (3.8–5.5)	13.77 (12.3–16.1)
	Qin S. et al ESMO 2022	Camrelizumab + Rivoceranib	272	14.5 (for OS)	25.4 (20.3–31.0)	3 (1.1)	7.2 (5.6–8.2)	5.6 (5.5–6.3)	22.1 (19.1–27.2)
		Sorafenib	271		5.9 (3.4–9.4)	1 (0.4)	3.7 (3.6–3.7)	3.7 (2.8–3.7)	15.2 (13.0–18.5)
2L	Bruix J, et al. Lancet 2017	Regorafenib	379	7.0 (3.7–12.6)	n=25 (7%) PR	0	3.2 (2.9–4.2)§	3.1 (2.8–4.2)§	10.6 (3.1–12.1)
	Abou-Alfa, et al. NEJM 2018	Cabozantinib*	470		n=18 (4%) PR	0	-	5.2 (4.0–5.5)	10.2 (9.1–12.0)
	X Zhu et al. Lancet Oncol 2019	Ramucirumab	197	7.6 (4.0–12.5)	n=9 4.6 % (1.7–7.5) PR	0	-	2.8 (2.8–4.1)	8.5 (7.0–10.6)
	Qin S, et al. Journal of Oncology (Presented at ASCO feb 2022)	Pembrolizumab	300	33.8 (18.7–49.0)	12.7%	Not specified	2.7	2.6 (1.5–2.8)	14.6 (12.6–18.0)

Abbreviations: FU: Follow-up; ORR: Overall response rate; CR: Complete response; PR: Partial response; TTP: Time-to-progression; PFS: Progression-free survival; m: Months; OS: Overall survival; 95CI: 95% Confidence Interval.

§ by mRECIST.

* includes data as 3L option.

Table 4.

Unmet needs in the field of Hepatocellular Carcinoma

- Validation of blood-based biomarkers for HCC surveillance and diagnosis
- Validation of biomarkers and molecular profiles to predict prognosis and treatment response
- Increase the application of surgery through liver function preservation/improvement
- Increase the access to liver transplantation
- Develop tools to predict treatment failure prior to clinic-radiologic progression
- Effective adjuvant therapy and co-interventions to improve recurrence-free and progression-free survival for early- and intermediate stage HCC, respectively
- Increased efficacy of locoregional and systemic treatments to achieve complete response
- Efficacious and safe treatments for patients with Child Pugh B cirrhosis
- Further data to support inclusion of external beam radiation therapy into guidelines
- Valid surrogate endpoints of survival that can be used for clinical trials