An Update on Randomized Clinical Trials in Hepatocellular Carcinoma

Hao-Wen Sim, BMedSci, FRACP, Jennifer Knox, MD, MSC, FRCPC, Laura A. Dawson, MD, FRCPC*

INTRODUCTION

The management of hepatocellular carcinoma (HCC) remains challenging on several accounts. First, most patients harbor background liver cirrhosis, which complicates treatment choice due to risk of liver failure. Second, HCC is driven by a variety of causes, including viral hepatitis, alcohol, and fatty liver disease, which may explain variation in the underlying biological mechanisms and treatment responses in different populations. Third, there are numerous treatment options to choose from. The Barcelona Clinic Liver Cancer classification provides a framework for treatment selection.

Early-stage disease is usually amenable to curative approaches, such as liver transplantation, surgical resection, and local ablation. There has been no definitive comparison of transplantation, surgical resection, and local ablation.

Radiofrequency ablation is currently the preferred technique for local ablation. Tranarterial chemoembolization is currently the preferred technique for regional therapy, and confers survival benefit compared with best supportive care.

For advanced disease, the standard of care in the first-line setting is sorafenib. Regorafenib has recently shown survival benefit in the second-line setting.

Disclosure Statement: The authors have nothing to disclose.

* Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, 610 University Avenue, Toronto, Ontario M5G 2M9, Canada; Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, 610 University Avenue, Toronto, Ontario M5G 2M9, Canada

* Corresponding author.

E-mail address: Laura.Dawson@rmp.uhn.on.ca

http://dx.doi.org/10.1016/j.soc.2017.05.006
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transplantation, surgical resection, and local ablation. Noncurative approaches include regional, radiation, and systemic therapy. Ultimately, treatment choice requires careful consideration of tumor extent, performance status, and underlying liver function, and is commonly determined by multidisciplinary team consensus.

This article reviews the evidence from randomized clinical trials that lay the foundation for contemporary HCC management. A discussion of prevention and screening trials, followed by the supporting data for the aforementioned treatment modalities are presented. Much of the literature remains controversial because many randomized trials are small and underpowered, with varying selection criteria, and are often single-institution studies based on specific populations. The emphasis is on those randomized clinical trials that have defined the current treatment algorithm.

**PREVENTION AND SCREENING**

Screening for HCC has become standard practice for high-risk patients, such as those with established cirrhosis or viral hepatitis. The key evidence supporting this comes from a large randomized trial conducted in China in the early 1990s. A total of 18,816 subjects with known hepatitis B infection were randomly assigned to either screening with 6-monthly alpha-fetoprotein testing and ultrasonography, or no screening. Despite low compliance with screening, there was a significant reduction in mortality from HCC in the screened group (83.2 per 100,000) compared with controls (131.5 per 100,000), corresponding to a statistically significant mortality ratio of 0.63. This mortality reduction was attributed to the detection of HCC at an earlier stage in the screened group, in which tumors were still amenable to a curative approach.

Beyond screening of infected hepatitis B patients, it has been demonstrated that antiviral suppression significantly reduces the incidence of HCC. In the seminal trial evaluating the efficacy of lamivudine for chronic hepatitis B, 651 subjects were randomly assigned to either lamivudine or placebo for a maximum of 5 years. HCC occurred in 4% of the lamivudine group versus 7% of the placebo group (hazard ratio [HR] 0.49, \( P = .047 \)). There was a similar reduction in hepatic decompensation events. Previous prevention studies in hepatitis B were inconclusive but were based on less effective interferon therapy. Based on these data, antiviral therapy is used to delay progression of liver disease and reduce complications such as HCC.

For patients with hepatitis C, treatment has historically consisted of pegylated interferon and ribavirin. Multiple studies have assessed treatment effect on HCC risk. Meta-analysis of pooled data from 20 studies, including 4 randomized controlled trials, revealed a favorable and statistically significant risk ratio of 0.43 in treated hepatitis C subjects. Notably, this benefit was driven by the subjects who achieved sustained virologic response and there was no benefit of ongoing therapy for nonresponders. The new generation of potent direct-acting antivirals, such as ledipasvir or sofosbuvir, is expected to yield further benefits, although data are still emerging.

**TREATMENT**

**Transplantation**

With rare exceptions, HCC is the only solid organ malignancy in which curative transplantation is a treatment option. This is made possible by the propensity of early HCC to spread locally instead of distantly, and the technical capabilities of liver transplantation surgery. Transplantation affords the unique benefit of simultaneously addressing both the tumor and the underlying tumorigenic liver. Eligibility for orthotopic liver transplantation is traditionally based on Milan criteria (solitary lesion 5 cm or less, or
3 lesions each 3 cm or less). Critically, availability is limited by the shortage of donor organs.

Despite transplantation, recurrence occurs in approximately 20% of cases. A large contemporary randomized trial, the Sirolimus in Liver Transplant Recipients with HCC (SiLVER) study, investigated whether recurrence risk could be reduced by using sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, instead of conventional immunosuppression with a calcineurin inhibitor following transplantation. This was based on the success of mTOR inhibitors in treating other cancers such as renal cell carcinoma. A total of 525 subjects were randomized 4 to 6 weeks after transplantation and followed for at least 5 years. Those treated with sirolimus had significantly longer recurrence-free survival (RFS) (3-year HR 0.70, 95% CI 0.48–1.00, \( P = .050 \)) and overall survival (OS) (5-year HR 0.70, 95% CI 0.49–1.00, \( P = .048 \)) during the initial period. Although this difference was not statistically significant at study end at 8 years, there was a consistent trend to improved outcomes. Toxicity and rejection episodes were comparable. Accordingly, the SiLVER study supports preferential use of mTOR-based immunosuppression pending further data in this setting.

**Surgical Resection**

Surgical resection has been a standard curative treatment of early HCC, particularly given the shortage of donor organs for transplantation. Even so, many patients are not suitable candidates due to the extent of underlying liver disease and medical comorbidities. Careful patient selection is necessary to minimize the risk of liver failure and ensure an adequate future functional liver remnant, incorporating Child-Pugh classification, model of end-stage liver disease score, and assessment of portal hypertension.

Regarding surgical technique, a noteworthy randomized trial investigated the optimal margin of resection. A total of 169 subjects with solitary HCC were randomized to resection with the intention of either 1 cm or 2 cm resection margins. OS and RFS were significantly longer in the 2 cm group (5-year OS 75% vs 49%, \( P = .008 \); 5-year RFS 53% vs 41%, \( P = .046 \)). It is conceivable that the poor outcomes in the 1 cm group were due to a high rate of inadvertent incomplete resection. There was no significant difference in operative morbidity or mortality. This suggests that the 2 cm margin of resection does not unduly compromise residual liver function, yet produces superior outcomes.

There have been no large, robust randomized trials to definitively address the comparison of surgical resection with the other curative treatment modalities (transplantation and local ablation). However, the following trials have been frequently cited. Chen and colleagues randomized 180 subjects with solitary HCC less than 5 cm to either surgical resection or radiofrequency ablation (RFA). It is notable that more than 20% of the subjects assigned to RFA withdrew their consent and proceeded with surgery. Over a 4-year period, there was no significant difference in OS or RFS. Feng and colleagues randomized 168 subjects with up to 2 lesions less than 4 cm to either surgical resection or RFA. Over a 3-year period, there was no significant difference in OS or RFS. Huang and colleagues randomized 230 subjects with HCC within Milan criteria to either surgical resection or RFA. Over a 5-year period, OS and RFS favored surgical resection (5-year OS 76% vs 55%, \( P = .001 \); 5-year RFS 51% vs 29%, \( P = .017 \)). Huang and colleagues randomized 76 subjects with up to 2 lesions less than 3 cm to either surgical resection or percutaneous ethanol injection (PEI). After a mean follow-up of 3 years, there was a nonsignificant trend to improved survival with surgery, particularly for lesions larger than 2 cm. These results are conflicting, and their interpretation is hampered by small sample size and short follow-up. There
are concerns regarding adherence to treatment allocation and the generalizability of results from these single-institution trials. Based on the available data, the consensus is that surgical resection and local ablation are comparable for carefully selected subjects, such as solitary lesions less than 2 cm.\textsuperscript{12} For tumors of increasing size and number, there is uncertainty, and the standard approach of surgical resection is preferred.

**Perioperative therapy**

There is no standard neoadjuvant or adjuvant treatment with global acceptance for resected HCC. The most widely studied adjuvant treatment has been interferon. Two meta-analyses evaluated the same 7 randomized trials of adjuvant interferon versus placebo, with 620 subjects enrolled in total.\textsuperscript{13,14} Both meta-analyses concluded that interferon was beneficial (2-year mortality ratio 0.65; OS HR 0.52, 95% CI 0.38–0.71, \(P < .001\)). However, there was significant heterogeneity in subject populations and treatment regimens, with 6 trials investigating interferon-alpha and 1 investigating interferon-beta, and treatment durations varying from 1 to 3 years. Moreover, the benefits of interferon need to be carefully weighed against the severe adverse effects, which were substantial even in these highly selected noncirrhotic patients. The benefits may also be partly explained by the effect of interferon on suppression of viral hepatitis. Interferon has yet to be evaluated in the current era of improved direct-acting antivirals. Due to these concerns, interferon has not been widely adopted in clinical practice.

Other potential adjuvant options have been examined, including systemic and transhepatic arterial chemotherapy with fluoropyrimidines, anthracyclines and platinum compounds, vitamin A and K2 analogues, and the heparanase inhibitor PI-88. Meta-analysis of 8 randomized trials of chemotherapy and 5 randomized trials of vitamin analogues did not reveal any efficacy.\textsuperscript{14} The heparanase inhibitor PI-88 showed preliminary activity in a phase II trial,\textsuperscript{15} but the subsequent phase III PI-88 in the Adjuvant Treatment of Patients with Hepatitis Virus-Related HCC After Surgical Resection (PATRON) trial did not meet the primary endpoint of disease-free survival at interim analysis.

More recently, the multikinase inhibitor sorafenib was investigated as a potential adjuvant treatment, based on its established efficacy in the advanced setting. In the Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of HCC (STORM) trial, an international phase III randomized double-blind placebo-controlled trial, there were 1114 subjects with early HCC who had successfully undergone surgical resection or local ablation.\textsuperscript{16} They were randomized to receive either sorafenib 400 mg orally twice a day or placebo for a maximum of 4 years. No significant difference was noted in RFS (HR 0.94, 95% CI 0.78–1.13, \(P = .26\)) or OS (HR 1.00, 95% CI 0.76–1.30, \(P = .48\)). A possible contributing factor was the relatively low-dose intensity in the sorafenib group (mean duration of treatment and daily dose were 12.5 months and 577 mg, respectively), reportedly due to a reduced acceptance of adverse events in an adjuvant compared with advanced setting, and over a protracted treatment duration. Despite these numerous studies, there is no standard adjuvant treatment of HCC.

**Local Ablation**

Local ablation encompasses a range of techniques, including PEI, percutaneous acetic acid injection (PAI), RFA, microwave ablation, laser ablation, and cryoablation, which are commonly used to treat small HCC with curative intent. As previously described, randomized data comparing surgical resection and local ablation have been conflicting but with a trend to greater benefit from surgery for tumors of
increasing size and number. Consequently, local ablation is usually reserved for patients who are not surgical candidates.

RFA has emerged as the preferred local ablation technique. This is based on evidence from multiple small randomized trials in which RFA was compared with the historical practice of PEI or PAI. There were 3 key trials from Asia. Lin and colleagues\textsuperscript{17} randomized 157 subjects with HCC less than 4 cm to either RFA, PEI, or high-dose PEI, defined as injection of twice the conventional dose of ethanol per session. OS was longest with RFA, relative to PEI ($P = .014$) and high-PEI ($P = .023$). In a separate study, Lin and colleagues\textsuperscript{18} randomized 187 subjects to either RFA, PEI, or PAI. RFA was superior with respect to overall, recurrence-free and local recurrence rates (3-year OS RFA 74% vs PEI 51% vs PAI 53%, $P = .038$). Shiina and colleagues\textsuperscript{19} randomized 232 subjects with up to 3 lesions, each less than 3 cm, with predominantly hepatitis C cirrhosis. RFA resulted in improved survival compared with PEI (4-year OS 74% vs 84%, $P = .01$), with a similar incidence of adverse events.

In Italy, Lencioni and colleagues\textsuperscript{20} studied 102 subjects with HCC within Milan criteria, randomized to undergo either RFA or PEI. Data revealed longer RFS and a nonsignificant numerical improvement in OS with RFA (2-year RFS 64% vs 43%, $P = .012$; 2-year OS 98% vs 88%, $P = .138$). In a similar study, Brunello and colleagues\textsuperscript{21} studied 139 subjects. After a median follow-up of 2 years, there was a small nonsignificant difference in OS favoring RFA (HR 0.88, 95% CI 0.50–1.53, $P = .640$). Giorgio and colleagues\textsuperscript{22} studied 285 subjects with HCC less than 3 cm. Unlike previous studies, there was no suggestion of difference between RFA and PEI (5-year OS 70% vs 68%; 5-year local recurrence rate 11.7% vs 12.8%).

Meta-analyses of these collective studies concluded that RFA was the superior local ablation technique.\textsuperscript{23–25} In particular, the effectiveness of PEI seemed to diminish when used to ablate larger tumors. Utility of RFA is limited in tumors with proximity to major biliary or vascular structures, due to respective risks of biliary injury and heat-sink effect.

There is emerging experience with newer techniques such as laser and microwave ablation. Ferrari and colleagues\textsuperscript{26} randomized 81 subjects with HCC less than 4 cm to either laser ablation or RFA. In this small study, the difference in OS between laser ablation (5-year OS rate 23%) and RFA (41%) did not reach statistical significance ($P = .330$). For both groups, survival outcomes were improved for subjects with Child-Pugh A liver function ($P<.001$), lesions under 25 mm ($P<.001$), and solitary lesions ($P = .048$). Di Costanzo and colleagues\textsuperscript{27} conducted a noninferiority study of laser ablation versus RFA. For 140 subjects with HCC within Milan criteria, laser ablation was statistically noninferior for all study endpoints. Shibata and colleagues\textsuperscript{28} randomized 72 subjects to either microwave ablation or RFA, and found that local progression was not statistically significantly different. Survival endpoints were not reported in this study. Based on these limited data, laser and microwave ablation may be comparable techniques, but larger studies are needed before they can be widely adopted.

Finally, there has been interest in the combination of RFA and transarterial chemoembolization (TACE), with the intent of extending the effective ablation zone to deal with larger tumors. A recent meta-analysis included 6 randomized trials between 2005 and 2013 enrolling 534 subjects in total.\textsuperscript{29} Combination therapy resulted in longer OS (HR 0.62, 95% CI 0.49–0.78, $P<.001$) and RFS (HR 0.55, 95% CI 0.40–0.76, $P<.001$) compared with RFA alone. It was notable that tumor size was a significant prognostic factor and that subjects with HCC up to 7 cm were included, which is beyond the usual criteria for local ablation. Seemingly, the benefit of combination therapy was greatest in subjects with intermediate-sized HCC. The utility of this approach relative to other modalities such as surgical resection and transplantation remains unclear.
Regional Therapy

Even though HCC has a reduced propensity for extrahepatic spread, patients with bulky multifocal or bilobar liver involvement may no longer be amenable to the local curative treatments previously described. However, there is a good rationale for regional hepatic-directed therapies for disease control, in which there is selective intravascular delivery of embolizing agents, chemotherapy, or radioactive particles into the hepatic arterial branches supplying the tumor.

Phase III studies have shown that TACE is associated with a survival benefit compared with best supportive care. Llovet and colleagues\(^3\) carefully selected a group of subjects with HCC not suitable for curative treatment because of multifocality, with Child-Pugh A liver function and good performance status. Only 112 of 903 HCC subjects fulfilled these inclusion criteria. They were randomized to bland embolization, doxorubicin chemoembolization, or supportive care. The trial was stopped early due to an interim analysis showing a substantial OS benefit of chemoembolization over supportive care (HR 0.47, 95% CI 0.25–0.91, \(P = .025\)). Direct comparison between the 2 embolization arms was not possible because of the early study termination. In a similar manner, Lo and colleagues\(^3\) selected 80 out of 279 Asian subjects with newly diagnosed HCC. Subjects were randomized to either cisplatin chemoembolization or supportive care. OS was significantly longer in the chemoembolization group (3-year OS 26% vs 3%, \(P = .002\)).

A meta-analysis of multiple small randomized trials of chemoembolization corroborated these findings.\(^3\) Relative to supportive care, there was a significant OS benefit in 4 trials of 323 subjects treated with doxorubicin-based or cisplatin-based chemoembolization (OR 0.42, 95% CI 0.20–0.88). A Cochrane systematic review of 9 trials with 645 subjects showed a nonsignificant numerical benefit only (HR 0.88, 95% CI 0.71–1.10).\(^\) However, the results from chemoembolization and bland embolization trials were pooled together, and several favorable trials were excluded due to methodological limitations. On the whole, TACE is recommended for patients with intermediate-stage HCC, that is, tumors that are no longer amenable to curative treatment, but lacking major vascular invasion or extrahepatic spread. An important caveat is that subjects were carefully selected for these trials, which precludes the extrapolation of findings to those with a higher degree of liver dysfunction or more advanced disease.

The optimal regimen of embolic materials and chemotherapy for transarterial therapy has not been defined. A systematic review of multiple small randomized and non-randomized studies found that no chemotherapeutic agent was superior.\(^3\) Studies included disparate patient populations, with varying tumor burdens and degrees of cirrhosis, and used a diverse repertoire of treatment regimens. The most common chemotherapeutic agents were doxorubicin, cisplatin, and epirubicin.

Regarding the comparison of chemoembolization with bland embolization, 2 recent randomized trials suggested similar outcomes. Meyer and colleagues\(^3\) randomized 86 subjects to either cisplatin chemoembolization or bland embolization. Over a median follow-up of 2 years, median OS and progression-free survival (PFS) were 17.3 and 16.3 months (\(P = .74\)), and 7.2 and 7.5 months (\(P = .59\)), respectively. Brown and colleagues\(^3\) randomized 101 subjects to either doxorubicin drug-eluting bead chemoembolization or bland embolization. Over a median follow-up of 3 years, median OS and PFS were 19.6 and 20.8 months (\(P = .64\)), and 6.2 and 2.8 months (\(P = .11\)), respectively. Regrettably, because these studies were underpowered and it is conceivable that a relevant difference in efficacy could be overlooked, chemoembolization remains the usual practice.
A drug-eluting bead delivery system has been developed with the intention of enhancing chemotherapy delivery to the tumor while minimizing systemic absorption. When comparing drug-eluting beads with conventional TACE, small studies suggested similar efficacy, with a possible improvement in toxicity profile. Lammer and colleagues randomized 212 subjects to either doxorubicin drug-eluting beads or conventional doxorubicin-based TACE. There was no significant difference in the primary endpoint of tumor response. However, reductions in liver toxicity \((P<.001)\) and systemic side-effects \((P<.001)\) were noted. Sacco and colleagues made the same comparison in a randomized trial of 67 subjects, with no observed difference in efficacy but a decreased rate of transaminitis \((P = .007)\). Golfieri and colleagues randomized 177 subjects to either doxorubicin drug-eluting beads or conventional epirubicin-based TACE. One-year and 2-year survival rates were 86% versus 57%, and 84% versus 55%, respectively \((P = .949)\). The only apparent advantage of drug-eluting bead therapy was reduced postprocedural abdominal pain.

Several trials have examined the combination of TACE followed by systemic therapy. The Sorafenib or Placebo in Combination with TACE for Intermediate-Stage HCC (SPACE) study was a randomized, double-blind, placebo-controlled Italian trial enrolling 307 subjects with intermediate-stage HCC, Child-Pugh A liver function, and Eastern Cooperative Oncology Group (ECOG) 0 performance status. Subjects underwent TACE with doxorubicin drug-eluting beads, followed by either sorafenib 400 mg orally twice a day or placebo, continued indefinitely until progression, toxicity, or subject withdrawal. The primary endpoint of time to progression was not meaningfully different for sorafenib versus placebo \((median 169 vs 166 days, HR 0.80, P = .072)\). Similar phase III trials have been conducted in Japan and Europe with negative findings. It is possible that the low sorafenib dose intensity in the treatment groups contributed to the negative findings in these trials, in a manner analogous to the adjuvant STORM study. The multikinase inhibitor brivanib was also evaluated in combination with TACE in the Brivanib Studies in HCC Patients at Risk (BRISK)- TACE study, but this study was terminated early due to disappointing findings in related trials of brivanib in the advanced setting.

An emerging alternative to TACE is transarterial radioembolization (TARE). Yttrium-90 \((^{90}Y)\) beads are incorporated into glass (TheraSphere, Nordion Inc, Ottawa) or resin microspheres (SIRTex, Sirtex Medical Limited, Sydney) and delivered as transarterial brachytherapy. A meta-analysis of retrospective studies showed no significant difference between TARE and TACE in terms of complication profile and survival rates \((OS HR 1.06, 95% CI 0.81–1.46, P = .567)\). In terms of the only available randomized data, there was recent publication of a phase II trial of \(^{90}Y\) TARE versus conventional TACE. A total of 179 subjects were identified as suitable candidates for transarterial therapy. Of these, 24 were randomized to \(^{90}Y\) TARE and 21 to conventional TACE. Although the trial was underpowered for efficacy assessment, there was a promising improvement in median time to progression with TARE \((>26 vs 6.8 months, P = .001)\) and comparable median OS \((17.7 vs 18.6 months, P = .99)\). These findings are preliminary and, at present, TACE remains the evidence-based preference for regional therapy.

Radiation Therapy

Radiotherapy was traditionally limited to the palliation of extrahepatic metastases. However, technological advances in treatment planning and delivery now permit the administration of therapeutic doses to the primary tumor, while sufficiently sparing surrounding liver parenchyma to mitigate radiation-induced liver disease. Radiotherapy also potentially overcomes some of the technical limitations of RFA because there is no heat sink effect and no tumor size limitation. As such, stereotactic body
radiation therapy (SBRT) has become a viable option for patients with localized HCC who do not meet criteria for the aforementioned treatments.

To date, the results of several randomized phase III trials are still awaited. The RTOG (Radiation Therapy Oncology Group) 1112 trial (NCT01730937) is accruing subjects with intermediate-stage or advanced-stage HCC, Child-Pugh A liver function, and good performance status, yet who are unsuitable for transplantation, surgical resection, local ablation or regional therapy. Subjects are randomized to either SBRT followed by sorafenib or sorafenib alone for a maximum duration of 5 years. The primary endpoint is OS, with expected study completion in 2020. Other upcoming randomized trials include TACE followed by SBRT versus TACE alone (NCT02470533; NCT02794337), SBRT versus TACE as bridging therapy for transplantation (NCT02182687), and SBRT versus repeat TACE after incomplete response to TACE (NCT02323360). Owing to the lack of supporting phase III data, SBRT has yet to become an accepted standard of care in most international guidelines.

**Systemic Therapy**

**First-line treatment**

Despite advances in chemotherapeutics, HCC has remained notoriously resistant to systemic therapy. Numerous clinical trials have evaluated cytotoxic, hormonal, targeted and immunotherapy agents (Table 1), yet few have resulted in meaningful improvements.

Historically, doxorubicin was considered to be the agent of choice. Lai and colleagues conducted a prospective randomized trial in the 1980s, in which 106 subjects with advanced HCC received either doxorubicin 60 to 75 mg/m\(^2\) every 3 weeks or no treatment. OS was dismal in both groups but improved from a median of 7.5 to 10.6 weeks with use of doxorubicin ($P = .036$), suggesting antitumor activity. This benefit was offset by unacceptable rates of sepsis and cardiotoxicity, which conferred high mortality at that time.

In subsequent decades, doxorubicin was used as the comparator in trials of cytotoxic chemotherapy. Yeo and colleagues compared PIAF (cisplatin 20 mg/m\(^2\) Days D1-4, interferon-alpha 5 MU/m\(^2\) D1-4, doxorubicin 40 mg/m\(^2\) D1, 5-fluorouracil 400 mg/m\(^2\) D1-4 every 3 weeks) versus doxorubicin 60 mg/m\(^2\) every 3 weeks. Of the 94 subjects in each treatment arm, median OS was 8.7 and 6.8 months, respectively ($P = .83$). This improvement was not statistically significant and PIAF (cisPlatin, Interferon-alpha, doxorubicin (Adriamycin), 5-Fluorouracil) was associated with severe myelosuppression. Gish and colleagues evaluated nolatrexed, a novel thymidylate synthase inhibitor, in a multicenter randomized phase III trial of 445 subjects. Subjects received either nolatrexed 800 mg/m\(^2\) D1-5 as a continuous infusion every 3 weeks or doxorubicin 60 mg/m\(^2\) every 3 weeks. Median OS was 22.3 and 32.3 weeks, respectively ($P = .007$), in favor of doxorubicin. Due to these findings, development of nolatrexed was discontinued. In the FOLFOX4 versus doxorubicin as palliative chemotherapy in advanced hepatocellular carcinoma patients (EACH) study, 371 Asian subjects were randomized to either 5-fluoruracil 400 mg/m\(^2\) bolus followed by 600 mg/m\(^2\) as a continuous infusion D1-2, leucovorin 200 mg/m\(^2\) D1-2, oxaliplatin 85 mg/m\(^2\) D1 (FOLFOX4) every 2 weeks or doxorubicin 50 mg/m\(^2\) every 3 weeks. There was a trend to OS improvement with FOLFOX4 (median 6.4 vs 5.0 months, respectively; $P = .07$), which reached statistical significance in a post hoc subgroup analysis of the 279 of 371 subjects from China ($P = .03$).

Hormonal agents were studied on the basis that HCC occasionally expressed sex hormone and/or somatostatin receptors. Unfortunately, several well-conducted randomized phase III trials of tamoxifen versus placebo, megestrol acetate versus
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<th>Study, Year</th>
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<td>Lai et al, 1988</td>
<td>Prospective randomized trial Single institution</td>
<td>106</td>
<td>Doxorubicin 60–75 mg/m² q3wk</td>
<td>No treatment</td>
<td>mOS: 2.4 m vs 1.7 m, ( P = .036 )</td>
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<td>Yeo et al, 2005</td>
<td>Phase III Single institution</td>
<td>188</td>
<td>PIAF (cisplatin 20 mg/m² D1-4, interferon α-2b 5 MU/m² D1-4, doxorubicin 40 mg/m² D1, 5-fluorouracil 400 mg/m² D1-4 q3wk)</td>
<td>Doxorubicin 60 mg/m² q3wk</td>
<td>mOS: 8.7 m vs 6.8 m, HR 0.97 (95% CI 0.71–1.32), ( P = .83 )</td>
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<td>Gish et al, 2007</td>
<td>Phase III Multicenter (North America, Europe, South Africa)</td>
<td>445</td>
<td>Nolatrexed 800 mg/m² D1-5 q3wk</td>
<td>Doxorubicin 60 mg/m² q3wk</td>
<td>mOS: 5.1 m vs 7.4 m, HR 1.33, ( P = .007 )</td>
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<td>5-fluorouracil 400 mg/m² bolus, then 600 mg/m² infusion D1-2, leucovorin 200 mg/m² D1-2, oxaliplatin 85 mg/m² D1 (FOLFOX4) q2wk</td>
<td>Doxorubicin 50 mg/m² q3wk</td>
<td>mOS: 6.4 m vs 5.0 m, HR 0.80 (95% CI 0.63–1.02), ( P = .07 )</td>
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<td><strong>Hormonal agents</strong></td>
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<td>CLIP-01 study, CLIP group, 1998</td>
<td>Prospective randomized trial Multicenter (Italy)</td>
<td>477</td>
<td>Tamoxifen 40 mg daily</td>
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<td>Tamoxifen 20 mg daily</td>
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<td>mOS: 4.8 m vs 4.0 m, ( P = .25 )</td>
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<td>1. Tamoxifen 120 mg daily 2. Tamoxifen 60 mg daily</td>
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<td>mOS: 2.2 m vs 2.1 m vs 2.7 m, ( P = .011 )</td>
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<td>mOS: 1.9 m vs 2.1 m, HR 1.25 (95% CI 0.92–1.71), ( P = .16 )</td>
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<td>mOS: 6.5 m vs 7.0 m, HR 1.14 (95% CI 0.88–1.45), <em>P</em> = .34</td>
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<td>Phase III Multicenter (France)</td>
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<td>Long-acting octreotide 30 mg q4wk</td>
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<td>HECTOR study, Becker et al, 2007</td>
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<td>Long-acting octreotide 30 mg q4wk</td>
<td>Placebo</td>
<td>mOS: 4.7 m vs 5.3 m, HR 1.11 (95% CI 0.76–1.63), <em>P</em> = .59</td>
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<tr>
<td>Dimitroulopoulos et al, 2007</td>
<td>Prospective randomized trial Single institution Only eligible if somatostatin receptor positive</td>
<td>61</td>
<td>Long-acting octreotide 30 mg q4wk</td>
<td>Placebo</td>
<td>Mean survival: 11.3 m vs 6.4 m, <em>P</em> &lt; .01&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>SHARP study, Llovet et al, 2008</td>
<td>Phase III Multicenter (Europe, Americas, Australasia)</td>
<td>602</td>
<td>Sorafenib 400 mg bid</td>
<td>Placebo</td>
<td>mOS: 10.7 m vs 7.9 m, HR 0.69 (95% CI 0.55–0.87), <em>P</em> &lt; .001&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Asia-Pacific study, Cheng et al, 2009</td>
<td>Phase III Multicenter (Asia)</td>
<td>271</td>
<td>Sorafenib 400 mg bid</td>
<td>Placebo</td>
<td>mOS: 6.5 m vs 4.2 m, HR 0.68 (95% CI 0.50–0.93), <em>P</em> = .014&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>SUN 1170 study, Cheng et al, 2013</td>
<td>Phase III Multicenter (Asia, Europe, North America)</td>
<td>1074</td>
<td>Sunitinib 37.5 mg daily</td>
<td>Sorafenib 400 mg bid</td>
<td>mOS: 7.9 m vs 10.2 m, HR 1.30 (95% CI 1.13–1.50), <em>P</em> = .001&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>BRISK-FL study, Johnson et al, 2013</td>
<td>Phase III Multicenter (Asia, Europe, Americas, Australia, Africa)</td>
<td>1155</td>
<td>Brivanib 800 mg daily</td>
<td>Sorafenib 400 mg bid</td>
<td>Noninferiority study (boundary HR 1.08) mOS: 9.5 m vs 9.9 m, HR 1.06 (95.8% CI 0.93–1.22), NS</td>
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<tr>
<td>LIGHT study, Cainap et al, 2015</td>
<td>Phase III Multicenter (Asia, Europe, North America, Africa)</td>
<td>1035</td>
<td>Linifanib 17.5 mg daily</td>
<td>Sorafenib 400 mg bid</td>
<td>Noninferiority study (boundary HR 1.05) mOS: 9.1 m vs 9.8 m, HR 1.05 (95% CI 0.90–1.22), NS</td>
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<tr>
<td>Study</td>
<td>Phase</td>
<td>Multicenter (Location)</td>
<td>n</td>
<td>Intervention 1</td>
<td>Intervention 2</td>
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<tr>
<td>Hsu et al, 2012</td>
<td>II</td>
<td>Taiwan</td>
<td>67</td>
<td>Vandetanib 300 mg daily</td>
<td>Placebo</td>
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<tr>
<td>Palmer et al, 2015</td>
<td>Combined analysis of 2 phase II studies (white and Asian populations)</td>
<td>188</td>
<td>Nintedanib 200 mg bid</td>
<td>Sorafenib 400 mg bid</td>
<td>mOS: 11.4 m vs 11.0 m, HR 0.91 (95% CI 0.65–1.29), NS</td>
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<td>Cheng et al, 2016</td>
<td>II</td>
<td>Asia</td>
<td>165</td>
<td>Dovitinib 500 mg D1-5 weekly</td>
<td>Sorafenib 400 mg bid</td>
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<tr>
<td>SEARCH study, Zhu et al, 2015</td>
<td>III</td>
<td>Asia, Europe, Americas</td>
<td>720</td>
<td>Sorafenib 400 mg bid + erlotinib 150 mg daily</td>
<td>Sorafenib 400 mg bid + Placebo</td>
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<td>CALGB 80802 study, Abou-Alfa et al, 2016</td>
<td>III</td>
<td>North America</td>
<td>356</td>
<td>Sorafenib 400 mg bid + doxorubicin 60 mg/m² q3wk</td>
<td>Sorafenib 400 mg bid</td>
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<tr>
<td>Ciuleanu et al, 2016</td>
<td>II</td>
<td>Europe, North America</td>
<td>101</td>
<td>Sorafenib 400 mg bid + mapatumumab 30 mg/kg q3wk</td>
<td>Sorafenib 400 mg bid + Placebo</td>
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<tr>
<td>Cheng et al, 2015</td>
<td>II</td>
<td>Asia, North America</td>
<td>163</td>
<td>Sorafenib 400 mg bid + tigatuzumab 6 mg/kg weekly</td>
<td>Sorafenib 400 mg bid</td>
</tr>
</tbody>
</table>

Abbreviations: CALGB, Cancer and Leukemia Group B; CLIP, cancer of the liver Italian program; D, days; HECTOR, hepatocellular carcinoma treatment with octreotide; mOS, median overall survival; NS, not statistically significant; SHARP, sorafenib HCC assessment randomized protocol; SUN 1170, Sunitinib 1170 study.

Statistically significant in favor of intervention.

Statistically significant in favor of control.
placebo,\textsuperscript{55} and octreotide versus placebo\textsuperscript{56,57} consistently demonstrated lack of efficacy in unselected subjects with advanced HCC. Dimitroulopoulos and colleagues\textsuperscript{58} screened 127 subjects with advanced HCC, and identified 61 with positive uptake on octreotide scintigraphy. They were randomized to either octreotide or placebo. In this small study, mean survival time was longer in the octreotide group (49 vs 28 weeks, \(P<.01\)), suggesting a possible benefit in selected subjects.

On the whole, cytotoxic and hormonal agents have been disappointing, with limited efficacy and often significant toxicity concerns. In the new era of molecular targeted therapies, sorafenib became the first agent to show consistent survival benefit in advanced HCC. Sorafenib is a small molecule multikinase inhibitor which blocks Raf, vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) signaling, thereby disrupting tumor growth and angiogenesis. Two major trials were pivotal to the adoption of sorafenib as the standard first-line treatment of advanced HCC. The Sorafenib HCC Assessment Randomized Protocol (SHARP) study was a randomized, double-blind, placebo-controlled phase III trial of 602 advanced HCC subjects with Child-Pugh A liver function.\textsuperscript{59} Subjects were accrued between March 2005 and April 2006 from multiple centers throughout Europe, America, and Australasia. The main causes of underlying liver disease were hepatitis C and alcoholic cirrhosis. Subjects received either sorafenib 400 mg orally twice a day or placebo. Median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group (HR 0.69, 95\% CI 0.55–0.87, \(P<.001\)). A second randomized trial was conducted in the Asia-Pacific region of predominantly hepatitis B subjects with advanced HCC and Child-Pugh A liver function.\textsuperscript{60} A total of 271 subjects were randomized between September 2005 and January 2007 in a 2:1 ratio to either sorafenib or placebo. Median OS was 6.5 months in the sorafenib group and 4.2 months in the placebo group (HR 0.68, 95\% CI 0.50–0.93, \(P=.014\)), thus corroborating the positive findings of the SHARP study.

There were several noteworthy points from these trials. First, both trials enrolled a highly select group of subjects with Child-Pugh A liver function and excellent performance status (92\% and 95\% of subjects were ECOG 0 or 1 in the SHARP and Asia-Pacific studies, respectively). Results cannot be readily extrapolated to subjects commonly encountered in clinical practice, who may have compromised liver function or poor performance status. Second, despite being a significant advancement, the efficacy of sorafenib is modest, with median OS still less than 1 year. Third, although the relative benefit of sorafenib was similar in both trials, subjects in the Asia-Pacific study had worse prognosis overall. This may reflect differences in the underlying biology of HCC due to hepatitis B versus other causes. Finally, survival was improved in the absence of radiologic response, with no complete responses, and 2\% and 5\% partial response rates in the SHARP and Asia-Pacific studies, respectively. The implication is that sorafenib may be predominantly tumoristatic, making radiologic assessment a less reliable determinant of efficacy.

Newer molecular targeted therapies have been compared against or in combination with sorafenib in randomized trials. Common targets included VEGF, PDGF, fibroblast growth factor (FGF) and epidermal growth factor (EGF) signaling pathways. Sunitinib, a broad-spectrum inhibitor of VEGF, PDGF, c-KIT, and RET signaling, was compared against sorafenib in a large randomized trial involving 1074 subjects.\textsuperscript{61} The trial was terminated early for futility and safety reasons (median OS: sunitinib 7.9 vs sorafenib 10.2 months). The BRISK–First-Line (BRISK-FL) study evaluated brivanib, an inhibitor of VEGF and FGF signaling, in a noninferiority design involving 1155 subjects.\textsuperscript{62} The Linifanib versus Sorafenib in Subjects with Advanced HCC (LIGHT) study evaluated linifanib, an inhibitor of VEGF and PDGF signaling, in a noninferiority design involving 1035
In both BRISK-FL and LIGHT, the predefined noninferiority margins were not met (median OS: brivanib 9.5 vs sorafenib 9.9 months; linifanib 9.1 vs sorafenib 9.8 months). Furthermore, brivanib and linifanib were associated with greater adverse effects and high rates of discontinuation. Randomized trials evaluating sorafenib versus vandetanib (VEGF and EGF inhibitor), nintedanib (VEGF, PDGF, and FGF inhibitor), and dovitinib (VEGF, PDGF, and FGF inhibitor) have also been negative.

Combination trials have been negative as well. Based on 2 promising single-arm phase II trials that showed activity of erlotinib, an EGF pathway inhibitor, the Sorafenib Plus Erlotinib in Patients with Advanced HCC (SEARCH) trial randomized 720 subjects with advanced HCC to either sorafenib plus erlotinib, or erlotinib alone. In this adequately powered study, OS was similar in both groups (median 9.5 vs 8.5 months, HR 0.93, \( P = .408 \)). Abou-Alfa and colleagues conducted a randomized phase II trial of 96 subjects who received either sorafenib plus doxorubicin, or sorafenib alone. Median OS was 13.7 months in the combination group and 6.5 months in the sorafenib-only group (\( P = .006 \)). However, the subsequent phase III Cancer and Leukemia Group B (CALGB) 80802 trial failed to confirm these findings. Of 356 subjects, OS was 8.9 months in the combination group and 10.5 months in the sorafenib-only group. The discordant findings may be related to improved statistical power in the phase III trial yielding more robust results. There were also differences in the study populations, with the phase III trial including a greater proportion of Asian subjects with underlying hepatitis B infection, and consisting of a more representative real-world, but less fit, subject cohort who tolerated the combination therapy poorly. Notably, throughout all these comparative studies, sorafenib demonstrated consistent efficacy across diverse populations and remains the first-line standard of care.

Going forward, novel targeted therapies and immunotherapy agents are being investigated. Mapatumumab and tigatuzumab, agonists of the proapoptotic TRAIL (TNF-related apoptosis-inducing ligand) pathway, showed insufficient activity in randomized phase II trials. Randomized trials are currently underway for a range of immunotherapy agents, including checkpoint inhibitors such as ipilimumab, tremelimumab, nivolumab, pembrolizumab, and durvalumab (NCT01658878; NCT02576509; NCT02702401; NCT02519348); cytokine modulators, such as galunisertib (NCT02178358); and oncolytic virus therapy (NCT02562755). The particular allure of immunotherapy is that HCC is mediated by viral hepatitis in many cases and, historically, has been amenable to immune-based approaches such as interferon. Already, encouraging response rates with manageable toxicity have been reported in phase II checkpoint inhibitor trials (NCT01658878) and the results of randomized phase III trials are eagerly awaited.

For the present, sorafenib remains the only agent with demonstrable albeit modest survival benefit in treatment-naïve advanced HCC. Accordingly, in patients with suitable liver function and performance status, sorafenib is the global standard of care for first-line treatment.

**Second-line treatment**

There is an unmet need for effective treatments in the second-line setting. Analogous to the trials conducted in the first-line setting, many molecular targeted therapies have been evaluated without success (Table 2). Randomized placebo-controlled trials of brivanib (VEGF and FGF inhibitor), axitinib (VEGF inhibitor), everolimus (mTOR inhibitor), codirituzumab (inhibitor of cell surface molecule GPC3), and ADI-PEG20 (arginine depletion) have failed to demonstrate OS improvement.

Recently, the potent multikinase inhibitor regorafenib was evaluated in the second-line Regorafenib for Patients with HCC Who Progressed on Sorafenib Treatment
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Design</th>
<th>Number of Subjects</th>
<th>Intervention</th>
<th>Control</th>
<th>Results</th>
</tr>
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<tr>
<td>BRISK-PS study, Llovet et al, 2013</td>
<td>Phase III Multicenter (Europe, Asia, Americas)</td>
<td>395</td>
<td>Brivanib 800 mg daily</td>
<td>Placebo</td>
<td>mOS: 9.4 m vs 8.2 m, HR 0.89 (95.8% CI 0.69–1.15), ( P = .331 )</td>
</tr>
<tr>
<td>Kang et al, 2015</td>
<td>Phase II Multicenter (Asia, Europe, North America)</td>
<td>202</td>
<td>Axitinib 5 mg bid</td>
<td>Placebo</td>
<td>mOS: 12.7 m vs 9.7 m, HR 0.91 (95% CI 0.65–1.27), ( P = .287 )</td>
</tr>
<tr>
<td>EVOLVE-1 study, Zhu et al, 2014</td>
<td>Phase III Multicenter (Asia, Europe, North America, Australia)</td>
<td>546</td>
<td>Everolimus 7.5 mg daily</td>
<td>Placebo</td>
<td>mOS: 7.6 m vs 7.3 m, HR 1.05 (95% CI 0.86–1.27), ( P = .68 )</td>
</tr>
<tr>
<td>Abou-Alfa et al, 2016</td>
<td>Phase II Multicenter (North America, Asia, Europe)</td>
<td>185</td>
<td>Codrituzumab 1600 mg q2wk</td>
<td>Placebo</td>
<td>mOS: 8.7 m vs 10m, HR 0.96 (95% CI 0.65–1.41), ( P = .82 )</td>
</tr>
<tr>
<td>Abou-Alfa et al, 2016</td>
<td>Phase III Multicenter (North America, Asia, Europe)</td>
<td>635</td>
<td>ADI-PEG20 18 mg/m² weekly</td>
<td>Placebo</td>
<td>mOS: 7.8 m vs 7.4 m, HR 1.02 (95% CI 0.85–1.23), ( P = .884 )</td>
</tr>
<tr>
<td>RESORCE study, Bruix et al, 2017</td>
<td>Phase III Multicenter (Europe, Asia, Americas)</td>
<td>573</td>
<td>Regorafenib 160 mg daily D1-21 q4wk</td>
<td>Placebo</td>
<td>mOS: 10.6 m vs 7.8 m, HR 0.63 (95% CI 0.50–0.79), ( P &lt; .001^a )</td>
</tr>
<tr>
<td>Santoro et al, 2013</td>
<td>Phase II Multicenter (Europe, North America)</td>
<td>107</td>
<td>Tivantinib 360 mg bid (later amended to 240 mg bid due to high neutropenia rate)</td>
<td>Placebo</td>
<td>mOS: 6.6 m vs 6.2 m, HR 0.90 (95% CI 0.57–1.40), ( P = .63 ) For MET-high subgroup: 7.2 m vs 3.8 m, HR 0.38 (95% CI 0.18–0.81), ( P = .01^a )</td>
</tr>
<tr>
<td>REACH study, Zhu et al, 2015</td>
<td>Phase III Multicenter (North America, Asia)</td>
<td>565</td>
<td>Ramucirumab 8 mg/kg q2wk</td>
<td>Placebo</td>
<td>mOS: 9.2 m vs 7.6 m, HR 0.87 (95% CI 0.72–1.05), ( P = .14 ) For high AFP subgroup: 7.8 m vs 4.2 m, HR 0.67 (95% CI 0.51–0.90), ( P = .006 )</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADI-PEG, pegylated arginine deiminase; REACH, Ramucirumab versus Placebo in Participants with Advanced HCC; RESORCE, Regorafenib for Patients with HCC Who Progressed on Sorafenib Treatment.

\(^a\) Statistically significant in favor of intervention.
This was a randomized, double-blind, placebo-controlled phase III trial enrolling 843 subjects between May 2013 and December 2015 from multiple centers (38% Asia, 62% rest of world). Eligible subjects had Child-Pugh A liver function, ECOG 0 or 1 performance status, and tolerated sorafenib well previously. This represented a highly select cohort of second-line subjects who likely had favorable tumor biology. Subjects were randomized to either regorafenib 160 mg orally daily or placebo in a 2:1 ratio, with crossover permitted following the final analysis. Remarkably, the trial demonstrated a significant survival benefit in favor of regorafenib, with median survival of 10.6 months for regorafenib versus 7.8 months for placebo (HR 0.63, 95% CI 0.50–0.79, P<.001). There was comparable benefit across prespecified subgroups, including geographic region, cause, and tumor extent. Regorafenib seemed to be tolerable in this subject cohort, with almost half of the regorafenib group receiving full protocol dose without reductions, and with no significant decrement in health-related quality of life. Accordingly, this trial represents an important advance in the treatment of HCC, with regorafenib likely to become a standard second-line treatment.

In terms of upcoming randomized trials, the METIV-HCC trial (NCT01755767) is comparing tivantinib (MET inhibitor) against placebo in subjects selected for high tumor MET expression, based on promising phase II data. The Ramucirumab versus Placebo in Participants with Advanced HCC (REACH)-2 trial (NCT02435433) is comparing ramucirumab (VEGF inhibitor) against placebo in subjects selected for elevated baseline alpha-fetoprotein, due to findings from the REACH trial. The Cabozantinib versus Placebo in Subjects with HCC Who Have Received Prior Sorafenib (CELESTIAL) trial (NCT01908426) is evaluating cabozantinib (VEGF and MET inhibitor) and has progressed beyond the first interim analysis. Checkpoint inhibitors durvalumab and tremelimumab are under investigation in NCT02519348.

SUMMARY

HCC has become a major area for research. Many clinical uncertainties remain, due to reliance on evidence from small, single-institution studies. Future randomized studies must be multicenter, adequately powered, and incorporate appropriate subject stratification. There will need to be an acceptance of tumor evaluation and tissue banking to advance understanding of the disease. In particular, it is acknowledged that the mechanisms behind liver carcinogenesis and progression of disease are complex, with heterogeneous behavior related to differences in underlying biology and etiologic factors. Advancement is required in molecular characterization of HCC to identify novel oncogenes and tumor suppressors, and to better identify subsets of patients who will most likely respond to the various treatment modalities and systemic options. Reassuringly, there are promising clinical trials encompassing the breadth of HCC management, from prevention to locoregional therapy to systemic therapy, which offer hope in ameliorating this disease.

REFERENCES


