Curr Oncol Rep (2016) 18: 9
DOI 10.1007/s11912-015-0494-5



# Advances in Local and Systemic Therapies for Hepatocellular Cancer

**Ali A. Mokdad**[1] · **Amit G. Singal**[2] · **Adam C. Yopp**[1]

Published online: 15 January 2016


**Abstract** Global incidence and mortality of hepatocellular carcinoma (HCC) has increased over the past two decades. Although transplantation and surgical resection offer a chance for cure and long-term survival, most patients present with more advanced tumor stage when these therapies are not possible. Although rarely curative, locoregional therapy with transarterial chemoembolization or radioembolization offers a survival benefit for those with liver-isolated HCC who are not amenable to curative therapies. Patients with metastatic disease or macrovascular invasion are treated with systemic therapy; however, median survival remains below 1 year. Patients with severe liver dysfunction or poor performance status should be treated with best supportive care given poor prognosis and no survival benefit for treatment. Lack of predictive and prognostic biomarkers in intermediate and advanced HCC tumors has hampered integration of clinical and molecular data to aid tailoring treatment decisions. However, with increasingly complex treatment decisions, optimal outcomes are achieved through multidisciplinary care.

This article is part of the Topical Collection on *Gastrointestinal Cancers*

✉ Adam C. Yopp
adam.yopp@utsouthwestern.edu

[1] Division of Surgical Oncology, Department of Surgery, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA

[2] Division of Digestive and Liver Diseases, Department of Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA

**Keywords** Hepatocellular carcinoma · Liver cancer · Systemic therapy · Staging · Locoregional therapy · Liver disease

## Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide and is the fastest growing cause of cancer-related death in the USA. The incidence and mortality of HCC increased twofold over the past two decades accounting for over 800,000 deaths worldwide in 2013 [1].

Patients diagnosed with HCC are a heterogeneous group with a combination of underlying chronic liver dysfunction and a concomitant malignancy. Complete hepatic resection, liver transplantation, or ablative therapies remain the most effective therapies for early-stage HCC with 5-year survival rates exceeding 60 % in most centers [2, 3]. However, the majority of HCC patients present with advanced disease not amenable to curative therapies due to multifocality, tumor vascular invasion, presence of metastatic disease, and/or poor functional hepatic reserve. In fact, less than 40 % of HCC patients are candidates for curative therapy, and therefore, most are treated with locoregional or systemic therapy [4••, 5].

The Barcelona Clinic Liver Cancer (BCLC) classification is a validated staging system for HCC that incorporates tumor stage, degree of liver dysfunction, and performance status. The BCLC staging system defines four subgroups with differential prognosis and is unique in that it is linked to a recommended treatment algorithm [6] (Fig. 1). Although widely accepted by the European Association for Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD), the BCLC staging system was originally designed as a tool to separate early-stage HCC tumors with

curative therapy options from later-stage HCC tumors with a paucity of viable treatment options. However, between these two extremes, is a very large and heterogeneous group of patients with different tumor characteristics and underlying liver function. For this large subset of patients classified as "non-curative," treatment options include locoregional and systemic therapies. Heterogeneity of these patients oftentimes precludes distinct treatment options leading to a lack of consensus among treatment providers. Furthermore, there is a lack of prognostic or predictive biomarkers for treatment response to individualize therapy decisions, further impairing the treatment decision-making process.

The aim of this review is to discuss current locoregional and systemic therapies in the treatment of intermediate and advanced HCC and to highlight potential prognostic and predictive tissue and blood biomarkers as stratification tools for non-curative-staged HCC.

## Non-curative HCC

Non-curative HCC account for over 80 % of patients newly diagnosed with HCC in the Western world and including a heterogeneous group of patients, including those with intermediate- (BCLC B), advanced- (BCLC C), and end-stage (BCLC D) disease [7] (Fig. 1). BCLC stage B patients have preserved liver function and performance status but have tumor burden that exceeds curative treatment options; these patients can be treated with locoregional therapy and achieve median survival exceeding 2 years. Patients with metastatic disease or vascular tumor invasion (BCLC C) can be treated with systemic therapy but typically have median survival of less than 1 year even with treatment. Patients with BCLC stage D HCC have either poor performance status or Child Pugh C liver dysfunction, with median survival typically less than 6 months [4••]; these patients derive no benefit from HCC-directed therapy and are only eligible for best supportive care. Although the BCLC staging system makes treatment recommendations appear clean and distinct, recent data suggest treatment decisions are becoming increasingly complex and there is a benefit for a multidisciplinary treatment approach [8, 9, 10••].

## Locoregional Therapy: Intra-arterial Approaches

### Transarterial Chemoembolization

HCC is a unique solid liver tumor relying on preferential hepatic arterial vascular supply [11]. Intra-arterial catheter-based transarterial chemoembolization (TACE) treatment relies on the injection of chemotherapeutic agents, typically cisplatin or doxorubicin in a Lipiodol emulsion, directly into arterial tumoral feeding branches followed by selective embolization of the branches with embolic agents including polyvinyl alcohol, starch microspheres, metallic coils, or gelatin particles inducing tumor necrosis [11–14].

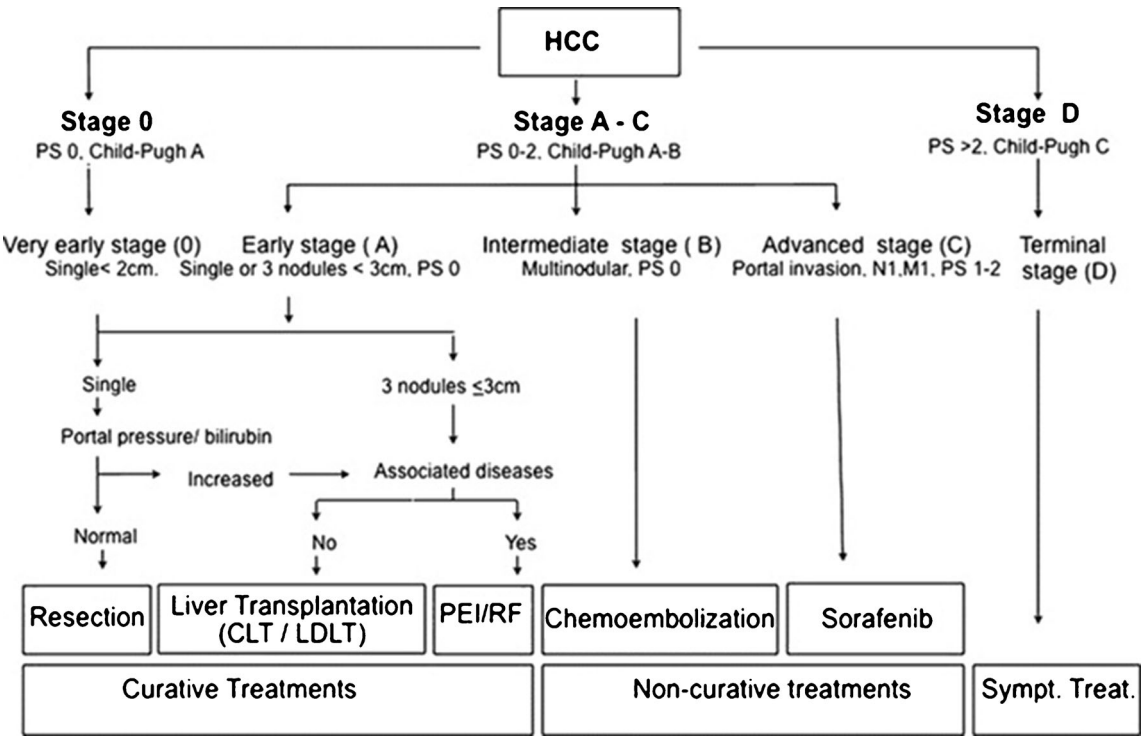


**Fig. 1** Barcelona Clinic Liver Cancer (BCLC) classification for hepatocellular carcinoma [83] (from www.thieme.com (reprinted with permission))

The use of TACE as a treatment modality for unresectable HCC was first described in 1980 by Yamada et al., who detailed a single institution experience with hepatic artery embolization in 32 patients with unresectable HCC [15]. Subsequently, the efficacy of TACE in treating non-curative HCC tumors has been examined in several randomized controlled trials over the last 30 years. The first large-scale randomized trial was conducted by the Group d'Etude et de Traitement du Carcinoma Hepatocullaire [16]; there was no difference in overall survival between best supportive care and cisplatin-Lipiodol emulsion plus gelatin sponge chemoembolization, but a significant reduction in tumor growth was evident. Until the publication of two landmark randomized controlled trials by Lo et al. and Llovet et al. in 2002, a lack of efficacy with TACE, measured by increased overall survival, was seen in a multitude of prospective clinical trials [17••, 18••].

Lo et al. reported both improved tumor response and survival in patients undergoing chemoembolization using an emulsion of cisplatin in Lipiodol and gelatin sponge embolic particles compared to best supportive care (hazard ratio (HR), 0.50 (95 % confidence interval (CI), 0.31–0.81); $p = 0.005$) [17••]. In contrast to previous studies, the investigators used a varying dose of cisplatin-Lipiodol emulsion based on tumor size and there was not a predetermined limit on the number of chemoembolization procedures performed; instead, treatments were repeated until complete tumor necrosis.

Llovet et al., in a similar study, also demonstrated a survival benefit in patients undergoing chemoembolization using a doxorubicin-Lipiodol emulsion and gelatin sponge embolic particles compared with best supportive care (HR, 0.47 (95 % CI, 0.25–0.91); $p = 0.025$) [18••]. Due to superiority within the chemoembolization group, the study was stopped early despite less than 40 patients accrued to either arm. Interestingly, the trial also included a third cohort of patients undergoing embolization alone without chemotherapy. Although bland embolization was more efficacious than best supportive care alone, a final analysis comparing bland embolization to chemoembolization was not performed. Thus, it is unclear whether the addition of chemotherapy to ischemia-producing embolization of tumoral feeding arteries provides any additive effect or whether embolization alone is sufficient [18••]. A clinical trial comparing bland embolization and TACE has never been completed, and likely never will, due to excessive trial cost of accruing a large sample size and provider bias.

The two studies by Lo et al. and Llovet et al. form the backbone of two meta-analyses demonstrating the benefit of TACE compared with best supportive care or other palliative care treatments [19, 20]. However, a recent Cochrane review challenged the conclusions of these meta-analyses by concluding that there is a lack of evidence to support TACE or TAE in the treatment of unresectable HCC [21]. The discrepancy in findings between the Cochrane review and the two meta-analyses highlights the difficulty in evaluating the efficacy of TACE. A lack of institutional procedural standardization of associated chemotherapy emulsions, number of treatments, and timing of follow-up imaging has hampered efforts to directly correlate TACE with improved survival outcome measures. As TACE is considered standard of care in the treatment of intermediate-stage HCC by most institutions and specialty societies, it is unlikely that a large randomized trial powered appropriately for outcome with standardization of procedure will ever be undertaken.

Evaluating the response to TACE is critical to measuring the effects of treatment and correlating response to prognosis. The most commonly used assessment tools to measure the effect of treatment in solid tumors include the World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST), both evaluating unidimensional and bidimensional tumor measurements in response to treatment [22, 23]. The use of WHO and/or RECIST criteria in measuring TACE efficacy has the potential for overtreatment of tumors, as treatment induced necrosis is oftentimes not associated with reduction in tumor size. As a result, guidelines advocating the use of residual viable tumor diameter instead of overall tumor size are more appropriate in evaluating TACE efficacy. EASL guidelines, published in 2001, recommend two-dimensional measurements of viable HCC tumors without taking into consideration overall size or number of tumors to assess TACE efficacy [24]. Viable tumor refers to lesions with characteristic arterial enhancement and delayed washout on contrast enhanced imaging. More recently, the shortcomings of the EASL guidelines were addressed by the modified RECIST (mRECIST) criteria [25••]. These criteria include residual viable tumor, number of tumors, and overall tumor size to measure treatment response. Both the EASL and mRECIST criteria have demonstrated intra- and inter-observer agreement, yet it is unclear what percentage of tumor necrosis correlates with an objective response and subsequent survival outcome measures [26–28]. Moreover, it is also unclear on the timing of post-procedural follow-up imaging and whether the initial or the best response, regardless of number of TACE treatments, correlates to overall survival [29, 30]. Furthermore, there is a lack of data to suggest whether TACE should be administered in an on-demand or scheduled fashion based on initial tumor location and initial response to the treatment [30].

The decision to continue with additional TACE treatments after the initial treatment fails to achieve a meaningful tumor necrosis is complex and oftentimes determined not only by tumor characteristics but also tolerance of the procedure in terms of underlying liver function and patient performance status. The Assessment for Re-treatment with TACE (ART) scoring system developed by Hucke et al. attempts to identify patients who after an initial procedure may not have further benefit from additional procedures [31••]. Using radiologic tumor response, aspartate transaminase (AST) level, and Child Pugh

score, the investigators were able to identify patients with a dismal prognosis following first and subsequent TACE procedures who were unlikely to benefit from additional procedures. Although externally validated, the ART score has yet to be universally accepted, likely due to questions of whether the scoring system identifies patients who fail to benefit from additional procedures or if the patient should not have undergone TACE in the first place [29]. The lack of a consensus regarding patient benefit from further locoregional therapies and consideration of alternative treatment regimens is a striking gap in knowledge of the intermediate-staged HCC patient.

Although conventional TACE (cTACE) with a chemotherapy emulsion has been evaluated in clinical trials, the advent of drug-eluting beads (DEB) as an embolic agent is a potential solution to the heterogeneity of chemotherapy emulsion solutions and Lipiodol induced imaging artifacts [32]. DEB-TACE utilizes embolic microspheres impregnated with doxorubicin to deliver chemotherapy in a controlled fashion with little to no systemic exposure [32]. Several recent studies have compared the efficacy of DEB-TACE with cTACE. The PRECISION V study, a phase II randomized controlled trial comparing doxorubicin cTACE with doxorubicin DEB-TACE, demonstrated that although DEB-TACE was associated with less doxorubicin associated adverse events there was no difference in either tumor response rates or tumor necrosis [33]. Unfortunately, this study was likely underpowered to detect a difference in local response due to an unexpectedly large number of responses in the cTACE cohort. Additionally, there was a lack of evaluation of overall outcome measures including overall and progression-free survival, again calling into question the correlation between local response and outcome. More recently, Golferi et al and Burrel et al demonstrated DEB-TACE and cTACE appear to be equally efficacious in overall survival, but DEB-TACE is associated with less periprocedural abdominal pain and better overall patient tolerability [34, 35]. Although there appears to be no survival benefit of DEB-TACE compared to cTACE in current studies, improved patient tolerability and a more homogenous treatment approach in the DEB-TACE regimen will likely lead to preferential use in the treatment of intermediate staged HCC.

## Radioembolization

Although HCC is a radiosensitive tumor, external beam radiation has not gained widespread acceptance in the treatment of HCC, in part due to concerns about toxicity. Intra-arterial radiation or transarterial radioembolization (TARE), using small microspheres loaded with the radionuclide yttrium-90 ($^{90}$Y), a β-emitter with a short half-life and shallow depth of penetrance, has been used in the treatment of patients with HCC and preserved liver function [36••]. Currently, two commercially available $^{90}$Y microsphere systems are commonly available, glass based (TheraSphere) and resin based (SirSphere), each with different size of sphere, radioactivity per sphere, and embolic characteristics. Both systems are injected into the hepatic arterial tumor supply and emit a higher dose of radiation to tumor tissue with less exposure to normal liver parenchyma than external beam radiation [36••].

Currently, there are no randomized controlled trials comparing TARE with either locoregional (cTACE or DEB-TACE) or systemic therapy in the treatment of HCC. However, multiple studies demonstrating encouraging outcome measures following TARE compared to historical controls or cTACE/DEB-TACE have been published [37–40] (Table 1).

## Single Arm or Historical Studies

Salem et al detailed their longitudinal, single institution experience in 291 patients undergoing a total of 526 $^{90}$Y TheraSphere treatments over the course of five years [38]. Overall response rates were 42 % by WHO criteria and

**Table 1** Summary of clinical trials of transarterial radioembolization in HCC

| Reference | Year | BCLC stage | Number of patients | Median TTP (months, 95 % CI) | Median OS (months, 95 % CI) |
|---|---|---|---|---|---|
| Hilgard | 2010 | B | 51 | 11.8 (6.1–17.2) | 16.4 (12.1–NR) |
| | | C | 55 | 8.0 (5.9–NR) | 10.0 (6.0–NR) |
| Salem | 2010 | A | 48 | 25.1 (8–27) | 26.9 (17–30.2) |
| | | B | 83 | 13.3 (4.4–18.1) | 17.2 (13.5–29.6) |
| | | C | 107 | 6.0 (4.6–8.8) | 7.3 (6.5–10.1) |
| Sangro | 2011 | A | 52 | NR | 24.4 (18.6–38.1) |
| | | B | 87 | NR | 16.9 (12.8–22.8) |
| | | C | 183 | NR | 10.0 (7.7–10.9) |
| Mazzaferro | 2013 | B | 17 | 13.0 (6–NR) | 18.0 (12–38) |
| | | C | 35 | 7.0 (6–12) | 13 (9–17) |

*NR* not reached

57 % by EASL criteria with an overall time to progression (TTP) of 7.9 months (95 % CI, 6-10.3). Surprisingly, 52 % of treated patients had advanced stage HCC (BCLC C), a stage usually treated with systemic therapy. Overall survival correlated to extent of extrahepatic disease, underlying liver function, and malignant portal venous thrombus (PVT). Median overall survival (OS) of patients with metastatic disease was only 5.4 months (95 % CI, 2.7-7.5). Patients with an absence of PVT and metastatic disease and Child Pugh score A liver function had the longest overall survival post-treatment with median OS of 22.1 months (17.2-32.5). This is in comparison to a presence of PVT and Child Pugh score A (10.4 months), presence of PVT and Child Pugh score B (5.6 months), and absent PVT and Child Pugh Score B (7.7 months).

In a similar single institution study, Hilgard et al documented their experience with $^{90}$Y TheraSpheres in a retrospective analysis of 108 patients with HCC and no evidence of extrahepatic metastases [37]. Overall response rates were 15 % by WHO and 40 % by EASL criteria with an overall TTP of 10.0 months (95 % CI, 6.1-16.4). Similar to other studies over 50 % of treated patients had BCLC C or advanced HCC tumors. Although median survival was 16.4 months in the entire cohort, presence of a malignant PVT was associated with worse survival than its absence (10.0 vs. 16.4 months, p=n.s.). Similar findings were seen in studies by Sangro et al and Mazzaferro et al where presence of malignant PVT was associated with worse overall outcome measures despite high response rates, up 40 %, by WHO or EASL criteria [39, 40].

### Comparison to TACE or Systemic Therapy

A multitude of single institution, retrospective studies have compared outcome measures between TACE and TARE with varying results. Unfortunately, most studies are limited by low patient numbers in either treatment arm and/or inequality of baseline patient tumor characteristics. The studies by Salem et al and Carr et al represent the only studies comparing TACE and TARE with at least 90 patients in each cohort [41, 42]. Salem et al document their single institution experience with cisplatin-Lipiodol TACE (123 patient) versus $^{90}$Y TheraSpheres (122 patients) in a group of HCC patients with no evidence of malignant PVT or extrahepatic metastases treated over a period of 9 years. Both TACE and TARE treatment had similar response rates by both EASL (69 % vs. 72 %) and WHO (36 vs. 49 %) criteria. Despite prolonged TTP in the TARE group (13.3 vs. 8.4 months, $p = 0.02$), there was no difference in overall survival (20.5 vs. 17.4 months, p=n.s.). Although the authors point to a significant decrease in reduced toxicity in the TARE cohort as measured by reductions in abdominal pain it is difficult to ascertain the clinical significance as pain was not stratified by grade of event.

In a similar single institution retrospective study by Carr et al, HCC patients treated with either cTACE (691 patients) or $^{90}$Y TheraSpheres (99 patients) over a 14-year period were examined. In this study although there was a significant benefit in overall survival with TARE compared to TACE (11.5 vs. 8.5 months, $p < 0.05$), there was a preponderance of patients in the TACE cohort with malignant PVT (42 % vs. 28 %) that undoubtedly biased the outcome result.

There are at least 3 clinical trials currently accruing patients comparing TACE vs. TARE in patients with advanced HCC [43]. Unfortunately, none of the trials use overall survival as a primary endpoint, instead utilizing either TTP or progression-free survival as an endpoint. It is unclear whether time to progression outcomes are surrogates for overall survival in the treatment of HCC with locoregional therapies. Furthermore, to perform an efficacy trial comparing TACE and TARE powered to demonstrate a difference in overall survival, accrual would require 1000 patients, a number that is likely cost-prohibitive [41]. An additional concern regarding TARE treatment is overall cost of the procedure compared to TACE. Based on Medicare reimbursements costs for TACE approached $17,000 compared to $31,000 (unilobar radioembolization) and $48,000 (bilobar radioembolization) for TARE, costs which for relative equivalence in efficacy must be accounted for in the decision-making process [44].

Currently there is only one published study comparing systemic therapy with locoregional therapy for the treatment of intermediate or advanced HCC [45]. This study, using a propensity score-matching model, demonstrated no difference in overall outcome between patients treated with systemic therapy (sorafenib) and TARE. Unfortunately, this study has many limitations including small sample size and the inclusion of patients with BCLC B (intermediate) tumor stage, who are not routinely treated with systemic therapy. Preliminary data by Salem et al demonstrating median overall survival following TARE in the BCLC C cohort (without extrahepatic metastases) approaching historical data from the randomized, phase III Sorafenib Hepatocellular Assessment Randomized Protocol (SHARP) trial with systemic sorafenib provided the impetus to the Sorafenib versus Radioembolization in Advanced Hepatocellular Carcinoma (SARAH) trial comparing TARE with systemic therapy in this patient cohort [36••, 46••]. The SARAH trial has recently completed accrual, and the results of the trial with a primary endpoint of overall survival are expected in 2016. A positive signal from the SARAH trial might significantly alter the landscape in the treatment of advanced HCC, a subgroup previously only treated with systemic therapy.

## Locoregional Therapy: Radiation Approaches

Traditionally the role of external beam radiation therapy (EBRT) has been limited to the palliative treatment of symptomatic HCC metastases [47, 48]. Historically, due to the relative radiosensitivity of HCC, tumoricidal radiation doses

delivered by conventional EBRT could oftentimes not be achieved due to potential complications of radiation induced liver disease (RILD). With the technological advances in radiation therapy including precision targeting of tumors and sparing of normal liver parenchyma the use of radiation therapy is a viable alternative to traditional locoregional approaches.

Specifically the use of stereotactic body radiotherapy (SBRT) has raised interest in the use of radiation therapy to treat HCC. SBRT is a highly conformal technique of non-coplanar radiation therapy delivered in a small number of large fractions. Although large, randomized clinical trials demonstrating clinical efficacy of SBRT in HCC are currently lacking, a number of phase I/II clinical trials have demonstrated promising results that SBRT can be administered safely with acceptable efficacy [49, 50]. Currently, a randomized phase III study of sorafenib versus SBRT followed by sorafenib is currently underway and will provide further insight into the appropriate use of SBRT in both intermediate and advanced HCC.

## Systemic Therapy

Prior to 2008, the treatment of advanced (BCLC C) HCC with systemic therapy offered no survival benefit compared to best supportive care. The use of single agent systemic cytotoxic chemotherapy regimens including irinotecan, gemcitabine or doxorubicin historically demonstrated low response rates with little to no clinical efficacy [51, 52]. Combination chemotherapy regimens using cytotoxic chemotherapeutic agents have fared no better with response rates ranging from 0 % to 40 % and limited clinical efficacy [53]. A recent study compared single agent doxorubicin to a combination of cisplatin, interferon, doxorubicin and 5-fluorouracil (PIAF) [54]. Despite an improvement in response (10 % for doxorubicin vs. 21 % for PIAF) the study failed to show an improvement in overall survival (6.8 vs. 8.6 months, respectively; P = 0.83).

The lack of appropriate traditional chemotherapeutic agents led to the investigation of molecular targeted agents, which have been shown to be efficacious in other tumor models. Sorafenib, an oral multikinase inhibitor that blocks tumor cell proliferation by targeting the Raf/MEK/ERK signaling pathway and exerting an anti-angiogenic effect by targeting the tyrosine kinase receptors, VEGFR-2, VEGFR-3 and PDGF-β, is the first biologically targeted agent to show efficacy in the treatment of advanced stage HCC [51, 52]. In a phase III randomized controlled trial (SHARP trial), patients with advanced hepatocellular carcinoma (not eligible for surgical resection or transplantation) and preserved liver function (Child-Pugh A score) were randomly assigned to either systemic sorafenib or placebo treatment [46••]. There was a significantly longer survival and radiologic time to progression (TTP) outcome in the cohort of patients that received sorafenib with little or no toxicity. Grade 3 drug-related events included diarrhea (8 % in the sorafenib group vs. 2 % in the placebo group), hand-foot skin reaction (8 % vs. 1 %), hypertension (2 % vs. 1 %) and abdominal pain (2 % vs. 1 %); there were no grade 4 drug-related adverse events in any of these categories in either study group. Although sorafenib is the current standard of care for patients with advanced HCC, prolongation of radiologic TTP was less than 3 months when compared to best supportive care: 5.5 months versus 2.8 months, respectively. Overall survival was prolonged less than 3 months compared to best supportive care, 10.7 months versus 7.9 months, respectively.

In a parallel clinical trial (Pan-Asian) with similar eligibility criteria to the SHARP trial completed in an Asia-Pacific population, sorafenib improved both median overall survival (6.5 vs. 4.2 months, p = 0.014) and median TTP (2.8 vs. 1.4 months, p = 0.0005) compared to placebo alone [55••]. The difference in absolute overall survival and TTP between the SHARP and Pan-Asian trials were likely secondary to higher degrees of advanced tumor stage in the Pan-Asian trial, although the difference between the treatment and placebo groups remained similar in both trials.

Although sorafenib is currently the standard of care for the treatment of advanced HCC, the modest improvement in outcome measures have led to the testing of a wide array of other molecular targeted agents. Seven randomized phase III clinical trials have evaluated molecular targeted agents either in the first-line setting versus sorafenib or in the second-line setting versus placebo with no evidence of superiority [56–62] (Table 2).

The reasons for the lack of positive results of the trials are multifactorial and include a lack of knowledge about underlying tumor biology, poor trial design, drug toxicity, and non-potent systemic agents [63••]. The seven failed trials not only had similar inclusion criteria as the SHARP trial but also failed to enrich for patients that were more likely to response to therapy. Although there is a glaring lack of biomarkers to predict response to sorafenib therapy, most molecular targeted agents utilized in other cancers, including breast, colon, and lung, rely on predictive biomarkers to avoid treating patients with little to no expected benefit.

### First-Line Setting Clinical Trials

Brivanib, a tyrosine kinase inhibitor, with dual inhibition of fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) demonstrated activity against advanced HCC in a single arm phase II clinical trial (OS, 10 months, 95 % CI 6.8-15.2) [64]. Using a non-inferiority trial design with OS as the primary endpoint, brivanib failed to achieve its endpoint in the subsequent randomized phase III clinical trial (brivanib, 9.5 months, vs. sorafenib, 9.9 months; HR = 1.07 (95 % CI, 0.94–1.2)) [56]. The use of a non-inferiority trial methodology likely doomed the trial from the onset as the margin to demonstrate non-inferiority was quite slim, and

**Table 2** First and second-line setting randomized phase III clinical trials in HCC

| Reference | Year | Cohort | Number of patients | Median TTP (months) | Median OS (months) |
|---|---|---|---|---|---|
| First-line clinical setting | | | | | |
| Llovet | 2008 | Placebo | 303 | 2.8 | 7.9 |
| | | Sorafenib | 299 | 5.5 | 10.7 |
| Cheng | 2009 | Placebo | 76 | 1.4 | 4.2 |
| | | Sorafenib | 150 | 2.8 | 6.5 |
| Johnson | 2013 | Brivanib | 577 | 4.1 | 9.5 |
| | | Sorafenib | 578 | 4.2 | 9.9 |
| Cheng | 2013 | Sunitinib | 530 | 3.8 | 7.2 |
| | | Sorafenib | 544 | 4.1 | 10.2 |
| Cainap | 2015 | Linifanib | 514 | 5.4 | 9.1 |
| | | Sorafenib | 519 | 4 | 9.8 |
| Zhu | 2015 | Sorafenib and Erlotinib | 362 | 4 | 8.5 |
| | | Sorafenib | 358 | 3.2 | 9.2 |
| Second-line setting | | | | | |
| Llovet | 2013 | Placebo | 108 | 2.7 | 8.2 |
| | | Brivanib | 226 | 4.2 | 9.4 |
| Zhu | 2014 | Placebo | 184 | 2.6 | 7.3 |
| | | Everolimus | 362 | 3.0 | 7.6 |
| Zhu | 2015 | Placebo | 282 | 2.1 | 7.6 |
| | | Ramucirumab | 283 | 2.8 | 9.2 |

*NR* not reached

the investigators were instead relying on trial success to be determined by fewer adverse events and lower drug cost in the brivanib arm.

Sunitinib, a multikinase inhibitor, with targets (other than β-raf) similar to sorafenib, demonstrated modest efficacy and significant adverse events in two separate single arm phase II trials in patients with advanced HCC [65, 66]. Based on the phase II data, a dose of 37.5 mg of sunitinib was used in randomized phase III clinical trial comparing sunitinib to sorafenib in 1074 patients with advanced HCC [57]. The trial was terminated early due to both futility and a high number of adverse events in the sunitinib arm. Results at the termination point demonstrated a median OS for sunitinib of 7.9 months vs. 10.2 months in the sorafenib cohort (HR = 1.30 (95 % CI, 1.13–1.5)). Grade 3 or 4 adverse events occurred in 82 % of sunitinib vs. 74 % of sorafenib patients with treatment-related deaths increased by a factor of 10 in the sunitinib cohort (3.2 % vs. 0.3 %). Given the findings of modest efficacy with high rates of toxicity from the phase II trials, outcomes from the phase III trial were not unexpected and calls into question whether the phase III trial should have ever been initiated in the first place.

Linifanib, a inhibitor of VEGF and platelet derived growth factor receptors, demonstrated marginal efficacy in a single arm phase II clinical trial in advanced HCC (median OS, 9.7 months; median TTP, 5.4 months) [67]. Using a non-inferiority trial design randomizing 1030 patients, linifanib failed to meet the primary endpoint of median OS when compared to sorafenib alone (9.1 months vs. 9.8 months, HR = 1.04) [68]. The study was terminated early due to futility. In addition to concerns about limited efficacy, linifanib was associated with increased grade 3 or 4 adverse events compared to sorafenib (85 % vs. 75 %, $p < 0.001$).

Erlotinib, an inhibitor of epidermal growth factor receptor (EGFR), demonstrated marginal efficacy in two single arm phase II trials with median OS of 10 and 13 months [69, 70]. Despite a lack of preclinical evidence, investigators hypothesized that the addition of erlotinib to sorafenib would act in a synergistic way to improve outcomes through dampening EGFR activation seen in sorafenib exposure [71]. Seven hundred and twenty patients were randomized in a phase III clinical trial to sorafenib alone or sorafenib plus erlotinib [59]. Median OS was not statistically different between the two groups (9.5 vs. 8.5 months, $p = 0.408$). Although combination therapy had a similar adverse event profile as sorafenib alone, withdrawal rates for adverse events were higher in the combination group highlighting a possible cumulative effect.

## Second-Line Setting Clinical Trials

Brivanib was also tested in the second-line setting in patients who either progressed on sorafenib or were intolerant to therapy. Compared to placebo the primary endpoint of the phase III trial, median OS, was not met (9.4 months, brivanib, vs. 8.2 months, placebo, HR 0.89 (95 % CI, 0.7–1.2)) [60]. Failure of this trial

was likely due to the unexpected length of survival in the placebo arm, secondary to a positive selection bias. In the placebo arm only 12 % of patients had evidence of a malignant portal venous thrombus compared to 25 % in the brivanib arm.

Everolimus, an inhibitor of the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (mTOR) pathway was also investigated in the second-line setting in advanced HCC patients. A total of 546 patients with HCC who had disease progression or were intolerant of sorafenib were randomized in a 2:1 fashion to everolimus or placebo, respectively [61]. Median OS, the primary endpoint, was similar in both groups, (7.6 months, everolimus, vs. 7.3 months, placebo, HR 1.05 (95 % CI, 0.86–1.3)).

Ramucirumab, a VEGF receptor 2 inhibitor, also failed to meet its primary endpoint in the second-line setting. In a phase III clinical trial 585 patients were randomized to either ramucirumab or placebo [62]. Median OS for the ramucirumab group was 9.2 months compared to 7.6 months in the placebo group (HR, 0.87 (95 % CI, 0.7–1.1)). Interestingly, patients with an a-fetoprotein (AFP) above 400 ng/ml had a prolonged OS and TTP with ramucirumab treatment compared to placebo. This finding is currently being evaluated in a phase III second-line trial stratifying patients by AFP level [43].

Similar to first-line setting clinical trials, all failed second-line regimens failed to include prospective biomarkers to select patients that may have a response to the selected therapy.

## Adjuvant Setting Clinical Trial

After curative surgical resection for early-stage HCC, the recurrence rate approaches 70 % in most series [2, 3]. Recurrence of HCC within the first year following resection is thought to be generally secondary to the underlying tumor biology of the resected tumor, unlike late recurrence which is generally de novo tumors related to underlying cirrhosis [3, 72]. It is, at this early recurrence time point, where administration of adjuvant therapy offers the most benefit. However, to date, there has been a lack of clinical trials demonstrating efficacy for systemic therapy to either improve rates of recurrence or overall survival following surgical resection. In the largest trial to date (STORM), 1114 patients were randomized to either sorafenib or placebo following curative resection or ablation of early-stage HCC [73]. The trial failed to meet the primary endpoint, recurrence free survival, 33.4 months, sorafenib, and 33.8 months, placebo. The failure of the trial highlights the difficulty in extrapolating a positive, albeit modest, signal from a cohort of patients with advanced HCC to a cohort with early-stage disease with likely different disease biology of hepatocarcinogenesis.

## Combination Locoregional and Systemic Therapy

Following locoregional therapy with cTACE or DEB-TACE, preclinical and clinical models have demonstrated upregulation of VEGF mediated angiogenesis leading to transient tumor proliferation. In a phase II clinical trial 307 patients with intermediate stage HCC (BCLC B) were randomized to placebo or sorafenib following DEB-TACE [74]. Although the trial met its primary endpoint of TTP, the overall improvement was only 3 days in the sorafenib group compared to placebo. Although other smaller trials have demonstrated a modest improvement in outcomes following combination systemic and locoregional therapy there is no proven benefit for combination therapy at this time [75–78].

## Future Directions of Systemic Therapy

Despite the abject failure of phase III clinical trials in the treatment of advanced HCC following the modest success of sorafenib, at least 5 large clinical trials are currently accruing patients in the second-line setting. The obvious difference between these trials and previously completed trials is the use of tissue or blood based biomarkers as eligibility criteria for trial entry. The use of predictive biomarkers hopefully will improve the selection of patients most likely to benefit from the treatment [63••].

## Lack of Predictive Tissue and Blood Biomarkers to Tailor Therapy in Non-curative HCC

The treatment of non-curative HCC is heterogeneous and oftentimes based on a lack of convincing clinical trial data to support current treatment trends. Despite increasing incidence and mortality rates for HCC worldwide and the majority of patients presenting with tumors outside of curative therapies, only three clinical trials investigating two modalities have demonstrated efficacy [17••, 46••, 55••]. Moreover, it is clear from single institution, retrospective data that there appears to be a lack of consensus in the treatment of intermediate and advanced HCC patients despite guidelines advocated by national and international organizations [79–81]. Without any evidence of prospective clinical data, patients with intermediate and advanced HCC are oftentimes treated with locoregional and/or systemic therapy depending on provider and institutional bias or preference.

The lack of clear consensus in the treatment of intermediate and advanced HCC is likely secondary to the knowledge gap about the tumor biology of patients who present with non-curative tumors. Currently, the diagnosis of HCC routinely relies on characteristic radiologic imaging without a tissue biopsy. Although this decreased the risks of unnecessary tissue biopsies, this practice has hampered the integration of tumor biology into clinical management decisions [5, 63••, 82].

To date, more than 20 gene signatures derived from either tumoral or non-tumoral adjacent tissue have been correlated with survival and recurrence outcome measures [82]. Unfortunately, there are no published or gene bank accessible signatures of tumors from intermediate or advanced stage HCC. Every currently available gene signature is from surgically resected specimens from early-stage HCC. From a genomic perspective it is

clear that HCC is a highly heterogenic and drivers of hepatocarcinogenesis responsible for early-stage disease may not be transferrable to patients with more aggressive tumor biology [82]. Hopefully, with the increasing number of open clinical trials requiring pre-treatment tissue biopsy, further genomic profiling of intermediate and advanced tumors will help fill this significant knowledge gap and provide molecular information needed to tailor treatment decisions.

## Conclusions

HCC is the fastest growing cause of cancer-related death in the western world with the majority of patients presenting with tumors only eligible for non-curative therapies. Currently, patients with multifocal tumors – without evidence of metastatic disease or macrovascular invasion – are typically treated with locoregional therapies including TACE and TARE, with no known significant difference in outcomes between different locoregional options. Patients with metastatic disease or macrovascular invasion are typically treated with systemic therapy, with sorafenib being the only systemic agent with demonstrated proven, albeit modest, efficacy. The lack of tissue biopsy to diagnosis HCC has undoubtedly led to a poor understanding of the tumor biology for intermediate and advanced HCC and a lack of predictive/prognostic biomarkers. This knowledge gap will hopefully be filled with the advent of future clinical trials mandating a tissue diagnosis.

### Compliance with Ethical Standards

**Conflict of Interest** Ali A. Mokdad declares that he has no conflict of interest.

Amit G. Singal has compensation from Bayer for service on an advisory board.

Adam C. Yopp declares that he has no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:

•• Of importance


1. Global Burden of Disease Cancer Collaboration. The global burden of cancer 2013. JAMA Oncol. 2015;1:505–27. doi:10.1001/jamaoncol.2015.0735.
2. Seshadri RM, Besur S, Niemeyer DJ, et al. Survival analysis of patients with stage I and II hepatocellular carcinoma after a liver transplantation or liver resection. HPB (Oxford). 2014;16:1102–9. doi:10.1111/hpb.12300.
3. Mazzaferro V, Lencioni R, Majno P. Early hepatocellular carcinoma on the procrustean bed of ablation, resection, and transplantation. Semin Liver Dis. 2014;34:415–26. doi:10.1055/s-0034-1394365.
4.•• Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329–38. doi:10.1055/s-2007-1007122. **Standard staging algorithm for HCC that accounts for both liver tumor staging and underlying liver function. Endorsed by AASLD, EASL, and NCCN**.
5. European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL–EORTC Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56:908–43. doi:10.1016/j.jhep.2011.12.001.
6. Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology. 1999;29:62–7. doi:10.1002/hep.510290145.
7. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379:1245–55. doi:10.1016/S0140-6736(11)61347-0.
8. Poon RT-P, Cheung TT-T, Kwok PC-H, et al. Hong Kong consensus recommendations on the management of hepatocellular carcinoma. Liver Cancer. 2015;4:51–69. doi:10.1159/000367728.
9. Torzilli G, Belghiti J, Kokudo N, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. Ann Surg. 2013;257:929–37. doi:10.1097/SLA.0b013e31828329b8.
10.•• Yopp AC, Mansour JC, Beg MS, et al. Establishment of a multidisciplinary hepatocellular carcinoma clinic is associated with improved clinical outcome. Ann Surg Oncol. 2014;21:1287–95. doi:10.1245/s10434-013-3413-8. **First published report detailing the benefits of a multidisciplinary HCC clinic in terms of survival outcome**.
11. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. Gastroenterology. 2004;127:S179–88.
12. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. J Hepatol. 2015;62:1187–95. doi:10.1016/j.jhep.2015.02.010.
13. de Baere T, Arai Y, Lencioni R, et al. Treatment of liver tumors with lipiodol TACE: technical recommendations from experts opinion. Cardiovasc Intervent Radiol. 2015. doi:10.1007/s00270-015-1208-y.
14. Idée J-M, Guiu B. Use of Lipiodol as a drug-delivery system for transcatheter arterial chemoembolization of hepatocellular carcinoma: a review. Crit Rev Oncol Hematol. 2013;88:530–49. doi:10.1016/j.critrevonc.2013.07.003.
15. Yamada R, Nakatsuka H, Nakamura K, et al. Hepatic artery embolization in 32 patients with unresectable hepatoma. Osaka City Med J. 1980;26:81–96.
16. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. N Engl J Med. 1995;332:1256–61. doi: 10.1056/NEJM199505113321903
17.•• Lo C-M, Ngan H, Tso W-K, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35:1164–71. doi:10.1053/jhep.2002.33156. **Landmark trial demonstrating a benefit of transarterial chemoembolization in locally advanced HCC. This trial along with the trial by Llovet et al have changed the management of intermediate stage HCC**.
18.•• Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with

unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359:1734–9. doi:10.1016/S0140-6736(02)08649-X. **Landmark trial demonstrating a benefit of transarterial chemoembolization in locally advanced HCC. This trial along with the trial by Lo et al have changed the management of intermediate stage HCC**.

19. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37:429–42. doi:10.1053/jhep.2003.50047.
20. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology. 2002;224:47–54. doi:10.1148/radiol.2241011262.
21. Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev. 2011.
22. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–16.
23. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981;47:207–14.
24. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421–30.
25.•• Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30:52–60. doi:10.1055/s-0030-1247132. **A report illustrating the benefits of using tumor viability in addition to tumor size as a measure of response to HCC treatment. Although proposed as an endpoint for prospective clinical trials mRECIST still has not become preferred over RECIST for measurement of response**.
26. Jung ES, Kim JH, Yoon EL, et al. Comparison of the methods for tumor response assessment in patients with hepatocellular carcinoma undergoing transarterial chemoembolization. J Hepatol. 2013;58:1181–7. doi:10.1016/j.jhep.2013.01.039.
27. Shim JH, Lee HC, Kim S-O, et al. Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology. 2012;262:708–18. doi:10.1148/radiol.11110282.
28. Gillmore R, Stuart S, Kirkwood A, et al. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. J Hepatol. 2011;55:1309–16. doi:10.1016/j.jhep.2011.03.007.
29. Forner A, Gilabert M, Bruix J, Raoul J-L. Treatment of intermediate-stage hepatocellular carcinoma. Nat Rev Clin Oncol. 2014;11:525–35. doi:10.1038/nrclinonc.2014.122.
30. Raoul J-L, Sangro B, Forner A, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev. 2011;37:212–20. doi:10.1016/j.ctrv.2010.07.006.
31.•• Hucke F, Sieghart W, Pinter M, et al. The ART-strategy: sequential assessment of the ART score predicts outcome of patients with hepatocellular carcinoma re-treated with TACE. J Hepatol. 2014;60:118–26. doi:10.1016/j.jhep.2013.08.022. **The first publication attempting to predict the benefits of TACE in patients with HCC. The ART guidelines are not widely used in HCC likely due to poor correlation between outcome and initial TACE**.
32. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol. 2007;46:474–81. doi:10.1016/j.jhep.2006.10.020.
33. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33:41–52. doi:10.1007/s00270-009-9711-7.
34. Golfieri R, Giampalma E, Renzulli M, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer. 2014;111:255–64. doi:10.1038/bjc.2014.199.
35. Burrel M, Reig M, Forner A, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol. 2012;56:1330–5. doi:10.1016/j.jhep.2012.01.008.
36.•• Salem R, Mazzaferro V, Sangro B. Yttrium 90 radioembolization for the treatment of hepatocellular carcinoma: biological lessons, current challenges, and clinical perspectives. Hepatology. 2013;58:2188–97. doi:10.1002/hep.26382. **Retrospective review of a single institution practice of treating intermediate and advanced HCC with radioembolization. Illustrates the main concerns with the utilization of radioembolization and the need for further randomized trials**.
37. Hilgard P, Hamami M, Fouly AE, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology. 2010;52:1741–9. doi:10.1002/hep.23944.
38. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010;138:52–64. doi:10.1053/j.gastro.2009.09.006.
39. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011;54:868–78. doi:10.1002/hep.24451.
40. Mazzaferro V, Sposito C, Bhoori S, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology. 2013;57:1826–37. doi:10.1002/hep.26014.
41. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2011;140:497.e2–507. doi:10.1053/j.gastro.2010.10.049.
42. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer. 2010;116:1305–14. doi:10.1002/cncr.24884.
43. US National Library of Medicine ClinicalTrials.gov. https://clinicaltrials.gov/ct2/home. Accessed 29 Sep 2015.
44. Rostambeigi N, Dekarske AS, Austin EE, et al. Cost effectiveness of radioembolization compared with conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Vasc Interv Radiol. 2014;25:1075–84. doi:10.1016/j.jvir.2014.04.014.
45. Gramenzi A, Golfieri R, Mosconi C, et al. Yttrium-90 radioembolization vs sorafenib for intermediate-locally advanced hepatocellular carcinoma: a cohort study with propensity score analysis. Liver Int. 2015;35:1036–47. doi:10.1111/liv.12574.
46.•• Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378–90. doi:10.1056/NEJMoa0708857. **First and only phase III clinical trial demonstrating a benefit of systemic therapy (sorafenib) in the treatment of advanced HCC. Six subsequent phase III**

**trials have failed to demonstrate improved efficacy compared to sorafenib**.

47. Zeng ZC, Tang ZY, Fan J, et al. Consideration of role of radiotherapy for lymph node metastases in patients with HCC: retrospective analysis for prognostic factors from 125 patients. Int J Radiat Oncol Biol Phys. 2005;63:1067–76.
48. Kaizu T, Karasawa K, Tanaka Y, et al. Radiotherapy for osseous metastases from hepatocellular carcinoma: a retrospective study of 57 patients. Am J Gastroenterol. 1998;93:2167–71.
49. Lasley FD, Mannina EM, Johnson CS, et al. Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child Pugh class A and B enrolled in a phase I-II trial of stereotactic body radiation therapy. Pract Radiat Oncol. 2015;5:e443–9.
50. Bujold A, Massey CA, Kimm JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol. 2013;13:1631–9.
51. Mathurin P, Rixe O, Carbonell N, et al. Review article: overview of medical treatments in unresectable hepatocellular carcinoma—an impossible meta-analysis? Aliment Pharmacol Ther. 1998;12:111–26.
52. Leung TW, Johnson PJ. Systemic therapy for hepatocellular carcinoma. Semin Oncol. 2001;28:514–20.
53. Yeo W, Mok TS, Zee B, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst. 2005;97:1532–8. doi:10.1093/jnci/dji315.
54. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004;64:7099–109. doi:10.1158/0008-5472.CAN-04-1443.
55.•• Cheng A-L, Kang Y-K, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25–34. doi:10.1016/S1470-2045(08)70285-7. **The companion trial to SHARP in an Asian population. This trial also demonstrated a benefit using sorafenib to treat advanced HCC. Like the SHARP trial the benefit in survival was less than 3 monts**.
56. Johnson PJ, Qin S, Park J-W, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol. 2013;31:3517–24. doi:10.1200/JCO.2012.48.4410.
57. Cheng A-L, Kang Y-K, Lin D-Y, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol. 2013;31:4067–75. doi:10.1200/JCO.2012.45.8372.
58. Cainap C, Qin S, Huang W-T, et al. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol. 2015;33:172–9. doi:10.1200/JCO.2013.54.3298.
59. Zhu AX, Rosmorduc O, Evans TRJ, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2015;33:559–66. doi:10.1200/JCO.2013.53.7746.
60. Llovet JM, Decaens T, Raoul J-L, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol. 2013;31:3509–16. doi:10.1200/JCO.2012.47.3009.
61. Zhu AX, Kudo M, Assenat E, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA. 2014;312:57–67. doi:10.1001/jama.2014.7189.
62. Zhu AX, Park JO, Ryoo B-Y, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015;16:859–70. doi:10.1016/S1470-2045(15)00050-9.
63.•• Llovet JM, Hernandez-Gea V. Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design. Clin Cancer Res. 2014;20:2072–9. doi:10.1158/1078-0432.CCR-13-0547. **Outstanding overview of the reasons for the multitude of failed trials for systemic therapy in HCC**.
64. Finn RS, Kang Y-K, Mulcahy M, et al. Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res. 2012;18:2090–8. doi:10.1158/1078-0432.CCR-11-1991.
65. Zhu AX, Sahani DV, Duda DG, et al. Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. J Clin Oncol. 2009;27:3027–35. doi:10.1200/JCO.2008.20.9908.
66. Koeberle D, Montemurro M, Samaras P, et al. Continuous Sunitinib treatment in patients with advanced hepatocellular carcinoma: a Swiss Group for Clinical Cancer Research (SAKK) and Swiss Association for the Study of the Liver (SASL) multicenter phase II trial (SAKK 77/06). Oncologist. 2010;15:285–92. doi:10.1634/theoncologist.2009-0316.
67. Toh HC, Chen P-J, Carr BI, et al. Phase 2 trial of linifanib (ABT-869) in patients with unresectable or metastatic hepatocellular carcinoma. Cancer. 2013;119:380–7. doi:10.1002/cncr.27758.
68. Chang YS, Adnane J, Trail PA, et al. Sorafenib (BAY 43-9006) inhibits tumor growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models. Cancer Chemother Pharmacol. 2007;59:561–74. doi:10.1007/s00280-006-0393-4.
69. Philip PA, Mahoney MR, Allmer C, et al. Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular cancer. J Clin Oncol. 2005;23:6657–63. doi:10.1200/JCO.2005.14.696.
70. Thomas MB, Chadha R, Glover K, et al. Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. Cancer. 2007;110:1059–67. doi:10.1002/cncr.22886.
71. Duran I, Hotté SJ, Hirte H, et al. Phase I targeted combination trial of sorafenib and erlotinib in patients with advanced solid tumors. Clin Cancer Res. 2007;13:4849–57. doi:10.1158/1078-0432.CCR-07-0382.
72. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis. 2005;25:181–200. doi:10.1055/s-2005-871198.
73. Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2015. doi:10.1016/S1470-2045(15)00198-9.
74. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): phase II, randomized, double-blind SPACE trial. ASCO Meet Abstr. 2012;30, LBA154.
75. Pawlik TM, Reyes DK, Cosgrove D, et al. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol. 2011;29:3960–7. doi:10.1200/JCO.2011.37.1021.
76. Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer. 2011;47:2117–27. doi:10.1016/j.ejca.2011.05.007.
77. Sansonno D, Lauletta G, Russi S, et al. Transarterial chemoembolization plus sorafenib: a sequential therapeutic scheme for HCV-related intermediate-stage hepatocellular carcinoma: a randomized clinical trial. Oncologist. 2012;17:359–66. doi:10.1634/theoncologist.2011-0313.

78. Chao Y, Chung Y-H, Han G, et al. The combination of transcatheter arterial chemoembolization and sorafenib is well tolerated and effective in Asian patients with hepatocellular carcinoma: final results of the START trial. Int J Cancer. 2015;136:1458–67. doi:10.1002/ijc.29126.
79. Borzio M, Fornari F, De Sio I, et al. Adherence to American Association for the Study of Liver Diseases guidelines for the management of hepatocellular carcinoma: results of an Italian field practice multicenter study. Future Oncol. 2013;9:283–94. doi:10.2217/fon.12.183.
80. Leoni S, Piscaglia F, Serio I, et al. Adherence to AASLD guidelines for the treatment of hepatocellular carcinoma in clinical practice: experience of the Bologna Liver Oncology Group. Dig Liver Dis. 2014;46:549–55. doi:10.1016/j.dld.2014.02.012.
81. Kim BK, Kim SU, Park JY, et al. Applicability of BCLC stage for prognostic stratification in comparison with other staging systems: single centre experience from long-term clinical outcomes of 1717 treatment-naïve patients with hepatocellular carcinoma. Liver Int. 2012;32:1120–7. doi:10.1111/j.1478-3231.2012.02811.x.
82. Llovet JM, Villanueva A, Lachenmayer A, Finn RS. Advances in targeted therapies for hepatocellular carcinoma in the genomic era. Nat Rev Clin Oncol. 2015;12:408–24. doi:10.1038/nrclinonc.2015.103.
83. Forner A A et al. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis. 2010;30(1):61–74.