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The Treatment Path in Hepatocellular Carcinoma

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Abstract: The treatment approach for hepatocellular carcinoma (HCC) depends on the stage and extent of disease, the severity of the underlying liver disease, and the overall performance status of the patient. Treatment consists of 4 main strategies: surgery (eg, resection and liver transplant), locoregional procedures (eg, ablation and transarterial embolization), systemic therapies, and best supportive care. For patients with early-stage tumors, surgical treatment or ablation can be curative. Patients with intermediate-stage disease can be candidates for embolization, administered as either transarterial chemoembolization (TACE) or transarterial radioembolization (TARE). Systemic therapy is reserved for patients with advanced or unresectable disease. For the past decade, the multitargeted kinase inhibitor sorafenib has been the only agent approved for unresectable HCC. This approval was followed by several clinical trials investigating other multitargeted kinase inhibitors, but none showed any benefit over single-agent sorafenib. Most patients progress after treatment with first-line sorafenib. In April 2017, the US Food and Drug Administration approved regorafenib for patients with HCC who have been previously treated with sorafenib. In a phase 3 trial, regorafenib significantly improved overall survival vs placebo. A consideration with systemic treatments is the proactive management of adverse events, including toxicities associated with the drugs and progression of liver disease.

Advances in the Management of Hepatocellular Carcinoma

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There are several primary liver cancers, each arising from a different liver cell type. Most liver cancers arise in the hepatocytes, and are therefore referred to as hepatocellular carcinoma (HCC).

Epidemiology of HCC

HCC, the most common primary cancer of the liver, is a significant public health issue. It is the second-leading cause of cancer-related deaths worldwide. In the United States, approximately 40,710 new cases of hepatobiliary cancers (liver and intrahepatic bile duct cancers) are estimated for 2017, accounting for approximately 2.4% of all cancer diagnoses.¹ HCC incidence has more than tripled since 1980.

In the United States, hepatobiliary cancers are almost 3 times more common in men than women (age-adjusted incidence across races is 13.3 vs 4.6 new cases per 100,000 persons).¹ HCC incidence rates are highest among the Asian/Pacific Islander, Hispanic, and American Indian/Alaska Native populations (age-adjusted incidence in men of 20.2, 19.7, and 18.7 new cases per 100,000 persons, respectively). However, these rates have been rising rapidly in the Hispanic population and declining among people of Asian descent.^{2,3}

Hepatobiliary cancers occur only rarely in younger patients. The median age at diagnosis is 63 years. Patients ages 54 years or younger account for 16.6% of all cases.¹ The percentage of newly diagnosed cases of hepatobiliary cancers in the United States peaks in patients ages 55 to

64 years (37.0%), and then decreases in the subsequent decades of life (24.3% in patients ages 65 to 74 years; 16.2% in patients ages 75 to 84 years; and 5.8% in patients older than 84 years).

HCC has 2 characteristic presentations at diagnosis: it can be a single tumor that grows in size or, more commonly, it can consist of many small nodules that arise throughout the liver. Patients diagnosed with localized disease have the best prognosis, with a 5-year relative survival rate of 31.1%. Approximately one-quarter of patients (27%) are diagnosed when their cancer has spread to regional lymph nodes. The 5-year relative survival rate at this stage of diagnosis decreases to 10.7%. A small but significant proportion of patients (18%) are diagnosed with metastatic liver cancer, referring to distant spread of the primary liver tumor (as opposed to secondary liver metastasis from a primary tumor arising at a distinct site). The 5-year relative survival rate for these patients is poor, at just 2.8%. When considering all degrees of tumor spread at diagnosis, the overall 5-year relative survival rate for all patients diagnosed with hepatobiliary cancers is 17.6%, reflecting the poor prognosis of this disease. In a small subgroup of patients with small tumors and compensated liver disease, however, long-term survival is possible with the use of potentially curative therapies, including liver transplant, resection, or ablation.

Etiology and Risk Factors

Risk factors for the development of HCC include

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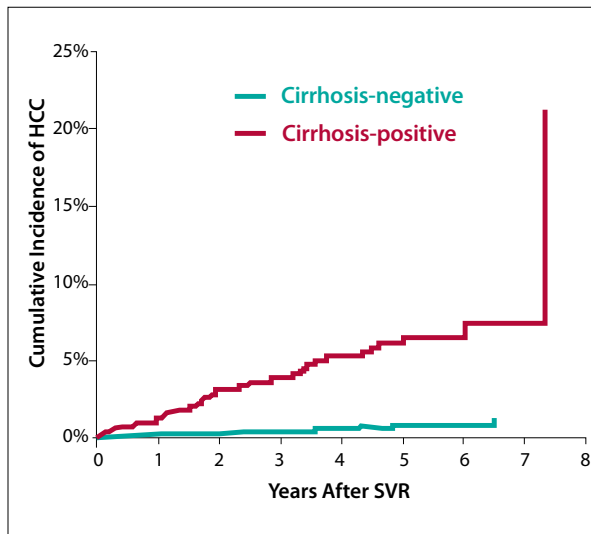


Figure 1. Cumulative incidence of hepatocellular carcinoma among patients with hepatitis C virus who achieved an SVR. Data are stratified by the presence or absence of cirrhosis at the time of the SVR. SVR, sustained virologic response. Gray's log-rank test, $P < .0001$. Adapted from El-Serag HB et al. *Hepatology*. 2016;64(1):130-137.¹²

hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infections.⁴ The impact of these risk factors, and thus the underlying etiology of HCC, varies in different regions. For example, chronic HBV is the primary cause of HCC in Southeast Asia and sub-Saharan Africa, where HBV is endemic. In contrast, HCV is the leading cause of HCC throughout most of Europe, Japan, and North America.^{5,6}

In most patients, HCC arises in the setting of a histologically abnormal liver.⁷ All of the risk factors for HCC increase the risk for liver cirrhosis. Globally, cirrhosis is an underlying factor in 60% to 80% of HCC cases; in the United States, cirrhosis is found in approximately 90% of patients with HCC.⁸

In the United States, approximately half of the increase in HCC cases observed over the past few decades is attributable to an aging subset of patients with chronic HCV. In a study of veterans with chronic HCV, the prevalence of HCC increased 10-fold (from 0.07% to 1.3%) between 1996 and 2006.⁹ Retrospective studies have suggested that in the United States, nearly 50% of patients at liver transplant centers have HCV, approximately 15% have HBV, and approximately 5% are coinfecting.¹⁰ The widespread virologic cure achieved with direct-acting antiviral agents (ie, sustained virologic response) has been associated with a significant reduction—though not elimination—of HCC risk (Figure 1).^{3,11,12}

Among patients with chronic HBV, those with seropositivity for the hepatitis B e antigen and the hepatitis

B surface antigen have a higher risk for developing HCC, as do those patients with a high serum HBV DNA viral load.¹³⁻¹⁶

Nonalcoholic fatty liver disease (NAFLD), another important risk factor for HCC, likely explains part of the link between HCC and metabolic syndrome.¹⁷ Most of the increased HCC risk in NAFLD is limited to those who develop cirrhosis. A study of 195 patients with cirrhosis caused by nonalcoholic steatohepatitis (NASH) found that 12.8% of patients developed HCC, at an annual incidence of 2.6%.¹⁸ Recent reports suggest that, in rare instances, NASH can progress directly to HCC without the development of cirrhosis. Between 3% and 13% of all patients with HCC in the United States do not have cirrhosis, and most of these cases are likely caused by NAFLD/NASH.^{3,19} If these reports are confirmed, this finding represents a major threat to the current understanding and implementation of HCC surveillance and prevention.

Excessive alcohol consumption and the resulting cirrhosis are also risk factors for the development of HCC.²⁰ However, the degree to which alcohol serves as an independent risk factor is unknown, with studies confounded by the presence of other HCC risk factors (such as chronic hepatitis infection).

Less common risk factors for the development of HCC include autoimmune hepatitis,²¹ environmental exposure to the *Aspergillus* fungus aflatoxin (which may contaminate grains, particularly in the developing world and in the presence of HBV), genetic hemochromatosis (leading to excessive iron absorption), porphyria cutanea tarda, α -1 antitrypsin deficiency, and Wilson disease.^{4,6,22,23}

Screening and Diagnosis

Most patients with HCC have symptoms of chronic liver disease and cirrhosis. Onset of HCC among patients with underlying cirrhosis is typically heralded by added decompensation of liver disease, abdominal pain, worsening ascites, or encephalopathy. Among the small group of patients who develop HCC in the absence of cirrhosis, the onset of disease is relatively acute, with few preceding symptoms. With the increasing use of HCC surveillance, including both imaging and α -fetoprotein (AFP), in at-risk individuals, it is becoming more frequent to detect patients at an asymptomatic stage. This has important prognostic implications, as these patients are more likely to be candidates for potentially curative therapies.

Current guidelines from both the American Association for the Study of Liver Diseases (AASLD) and the National Comprehensive Cancer Network (NCCN)

Table 1. BCLC Classification of Hepatocellular Carcinoma

Stage	Description
Very early	PS 0, Child-Pugh A, single HCC <2 cm
Early	PS 0, Child-Pugh A-B, single HCC or 3 nodules <3 cm
Intermediate	PS 0, Child-Pugh A-B, multinodular HCC
Advanced	PS 1-2, Child-Pugh A-B, portal neoplastic invasion, nodal metastases, distant metastases
Terminal	PS >2, Child-Pugh C

BCLC, Barcelona Clinic Liver Cancer; PS, performance status.

Data from Llovet JM et al. *Semin Liver Dis.* 1999;19(3):329-338.³⁴

recommend screening for at-risk patients.^{6,7} The purpose of screening and surveillance of high-risk groups (primarily patients with cirrhosis) is to detect tumors less than 2 cm in diameter. AASLD guidelines recommend ultrasound screening every 6 months, owing to the limited sensitivity and specificity associated with serum AFP testing. In contrast, the NCCN guidelines recommend periodic screening with both ultrasound and AFP testing every 6 to 12 months, with the idea that the utility of AFP is strengthened when it is used in combination with imaging.

Abnormal surveillance tests should be followed by more detailed cross-sectional imaging studies using contrast, such as computed tomography (CT) or magnetic resonance imaging (MRI). Advancements in cross-sectional imaging have greatly improved the ability to diagnose HCC without the use of biopsy to confirm the diagnosis. The Liver Imaging Reporting and Data System (LI-RADS) has standardized the reporting of

cross-sectional imaging in the presence of liver masses. The LI-RADS system is used to interpret and report CT and MRI screening for HCC.²⁴ In cases where doubt remains or the radiologic features are atypical, follow-up with either additional cross-sectional imaging or liver mass biopsy is indicated.

Staging HCC

Several staging systems for HCC have been validated. One of the most widely used tools is the Barcelona Clinic Liver Cancer (BCLC) staging system, which is often considered a standard for evaluating prognosis and assigning appropriate treatment (Table 1).²⁵ The BCLC staging system incorporates the patient's performance status, number and size of nodules, cancer symptoms, and liver function (as determined by the Child-Pugh classification system). The Child-Pugh scoring system incorporates 5 clinical measures of liver disease, and each is assigned a score of 1 to 3 points (with 3 points indicating the most severe impact; Table 2). These measures are: encephalopathy, ascites, and levels of bilirubin, albumin, and prothrombin. Scores from each of these 5 measures are summed together to determine the overall severity of disease. A sum of 5 or 6 points is referred to as class A disease, a sum of 7 to 9 points is considered class B disease, and a sum of 10 to 15 points is considered class C disease (the most severe).²⁶

Strategies for Treating Patients With HCC

One treatment approach for HCC is to classify patients according to the presence or absence of underlying cirrhosis. As previously mentioned, it is possible for patients to develop HCC even if they do not have cirrhosis, particularly in the settings of chronic HBV infection or NAFLD. When HCC is detected in these

Table 2. Child-Pugh Classification^a

Finding	1 Point	2 Points	3 Points
Encephalopathy grade	None	Mild	Severe
Ascites	Absent	Mild to moderate	Severe, refractory
Serum bilirubin (mg/dL)	<2	2-3	>3
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.71-2.20	>2.20

^aChild-Pugh class is assessed according to the following criteria: A, 5-6 points; B, 7-9 points; C, 10-15 points. When there are several test results for 1 test item, the lower point result is used to determine the Child-Pugh class.

INR, international normalized ratio.

Data from Lencioni R, Crocetti L. *Radiology.* 2012;262(1):43-58.³⁵

patients, resection for tumors up to 10 cm is possible with a curative intent.

Most patients diagnosed with HCC will have underlying cirrhosis. In this cohort, patients can be categorized according to the presence or absence of 4 characteristics: (1) limited number of lesions (1 or 2 small tumors); (2) adequate liver function (intact synthetic function of the liver with no decompensation); (3) absence of portal vein thrombosis or invasion; and (4) an overall good physical status. Patients possessing all 4 of these characteristics are the best candidates for the application of potentially curative therapy, which may take the form of surgical resection of the tumor, localized ablation of the tumor (eg, radiofrequency ablation or microwave ablation), or liver transplant. All of these options offer the potential for a long-term cure. These patients are typically detected through screening and surveillance programs.

A second and expanding group of patients are those in whom one of these 4 characteristics is not present. For example, the patient may have a large tumor or multiple tumors, liver decompensation or portal vein thrombosis, or several comorbidities that negatively affect his or her overall physical status. For these patients, the application of potentially curative treatments may not be possible.

Summary of Treatment Approaches

Surgical resection is recommended only for patients with preserved hepatic function.^{7,20} For patients without cirrhosis and very early-stage HCC, surgery is the treatment of choice. Surgery may also be an option for patients with cirrhosis. The best results occur in those patients with a small tumor (<3 cm in diameter), no portal hypertension, and a normal bilirubin level.^{27,28} Unfortunately, fewer than 5% of patients in the United States are considered candidates for hepatic resection. Surgical resection is more common in Asian countries, where patients with HCC tend to be younger, have no or minimal cirrhosis, and have underlying HBV as the cause of their HCC. Surgical resection is curative in only a minority of patients because the underlying chronic liver disease continues to increase the risk for developing a new liver lesion. The 5-year risk for recurrence following resection reaches 70%.²⁰

In contrast, liver transplant is associated with a very low risk for recurrence in selected patients who meet the Milan criteria (1 mass \leq 5 cm, or \leq 3 masses each with a diameter \leq 3 cm). However, few patients qualify or are eligible for liver transplant owing to the strict criteria in place to ensure that the available organs are distributed to those most likely to have excellent outcomes. Among patients with HCC who meet the Milan criteria for orthotopic liver transplant, the 4-year overall survival rate following liver transplant is 85%.²⁹

The most common type of localized ablation therapy is radiofrequency ablation, which is considered the optimal treatment for patients with early-stage HCC who are not eligible for surgical resection or transplant.²⁰ In randomized clinical studies, radiofrequency ablation has been more effective than the previous standard of ethanol injection for patients with small tumors (2 to 3 cm in diameter).³⁰ The short-term outcomes with radiofrequency ablation are excellent, with a 2-year overall survival rate of 98%. However, long-term outcomes reflect the noncurative nature of radiofrequency ablation; 5-year recurrence rates approach 70%. Microwave ablation is a newer method of ablation that offers the additional advantage of ablating larger tumors in fewer sessions.

Transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) both entail localized delivery to the HCC nodules of either chemotherapy (in the case of TACE) or radiotherapy using radioactive yttrium-90 (in the case of TARE). Patients who are good candidates for these procedures include those with multiple nodules that are located within a single lobe (as opposed to multiple lobes), no portal vein thrombosis, and no liver decompensation. Both TACE and TARE can be delivered in multiple treatments. The optimal chemotherapeutic agent or TACE schedule is not well-established, but the use of a drug-eluting, controlled-release bead has been associated with reductions in both hepatic and systemic side effects together with an increase in local tumor response.^{31,32} Radioembolization with yttrium-90 microspheres has demonstrated success as a palliative therapy for patients with intermediate-stage HCC.³³ Although no randomized controlled trials have compared these 2 interventions, observational studies suggest equivalent efficacy in well-chosen patients.

Systemic therapies are reserved for patients with unresectable disease. Sorafenib is an established standard of care for unresectable HCC, and it is indicated as first-line treatment. Sorafenib was the only treatment option for these patients until regorafenib was approved in April 2017. The clinical trials supporting the use of these agents in HCC are summarized in the next section.

Unmet Needs in the Treatment of HCC

The increase in the incidence, prevalence, and mortality of HCC coupled with its high mortality make it an area of intense investigation and study. There are several unmet needs, of which the most impactful would be primary prevention, focusing on the treatment and prevention of viral hepatitis. Despite the advent of efficacious HBV and HCV antiviral treatments, the proportion of patients with these chronic viral infections who are detected and linked to care remains small. Therefore, interventions to

increase screening, diagnosis, linkage, and treatment of patients with viral hepatitis should have a beneficial effect on the burden of HCC. Despite the availability of a relatively inexpensive vaccination for HBV, it remains poorly utilized in many parts of the world that are endemic for this infection.

The magnitude, determinants, and pathways of HCC development in the setting of metabolic syndrome and NAFLD remain unclear, and therefore constitute an area of urgent unmet need, especially given the high prevalence of the underlying risk factors (eg, obesity, diabetes).

Secondary prevention for HCC will also play a role, through the detection, staging, and enrollment of patients with cirrhosis into an HCC surveillance program. There is a need to devise and implement methods for efficient detection of patients with cirrhosis.

A last unmet need pertains to therapy. Most patients diagnosed with HCC are ineligible for liver transplant or surgical resection. It is therefore necessary to expand the pool of curative options. In addition, it will be important to develop personalized strategies for systemic therapies that target different pathways, with the aim of improving survival.

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Recent Developments in Systemic Therapy for Hepatocellular Carcinoma

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Systemic therapy is typically reserved for patients with advanced disease who are not eligible for transplant, resection, or locoregional therapy. Clinical studies conducted over the years have offered little evidence to support a benefit in overall survival with the use of cytotoxic chemotherapies, and the responses to these agents are modest at best.¹⁻³ As such, the systemic agents currently in use and under investigation for unresectable HCC focus on the targeted treatment of this disease. After its FDA approval in 2007, sorafenib was the lone targeted agent indicated for unresectable HCC. This changed with the approval of regorafenib in 2017. Treatment continues to evolve in response to the recently presented phase 3 results on lenvatinib and the emerging data on checkpoint inhibitors.

Sorafenib in the First-Line Treatment Setting

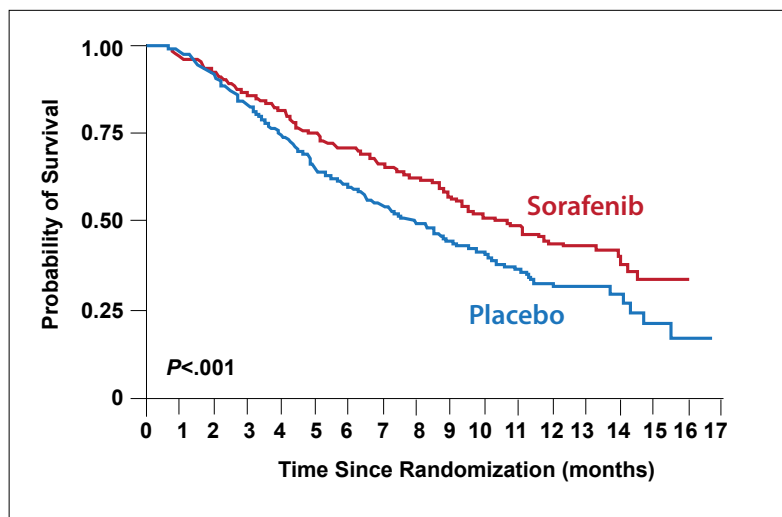
Sorafenib, an oral multikinase inhibitor, is the established standard of care for the first-line treatment of unresectable HCC.⁴⁻⁶ Sorafenib affects several intracellular signaling pathways, including those mediated by the RAF kinases, KIT, FLT-3, RET, and RET/PTC; the vascular endothelial growth factor receptors (VEGFRs); and the platelet-derived growth factor receptor (PDGFR) β . Importantly, several of these kinases are thought to play important roles in cell processes, such as tumor cell signaling, angiogenesis, and apoptosis. The efficacy and safety of sorafenib for the treatment of unresectable HCC has been demonstrated in 2 randomized phase 3 trials: SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) and Sorafenib-AP (Sorafenib Asia-Pacific).^{5,6}

SHARP was a multicenter, international, double-blind, randomized, placebo-controlled phase 3 clinical trial that enrolled patients with unresectable HCC and measurable disease who had not received prior systemic therapy.⁵ Enrollment criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and well-preserved liver function, as indicated

by Child-Pugh class A. Patients had adequate hematologic, renal, and hepatic function. A total of 602 patients were randomly assigned to treatment with continuous sorafenib (400 mg twice daily) or placebo. Treatment continued until the patient developed unacceptable toxicity or progression (radiologic or symptomatic). Baseline characteristics were well-balanced between the 2 treatment arms, with 38% of patients showing macroscopic vascular invasion and 51% with extrahepatic spread (most commonly to the lymph nodes and lungs). Most patients (>90% in each treatment arm) had an ECOG performance status of 0 or 1. The etiology of HCC was varied within each treatment arm, and included HCV, alcohol, and HBV.

At the second planned interim analysis, sorafenib proved superior to placebo in the primary endpoint of median overall survival (10.7 months vs 7.9 months; hazard ratio [HR], 0.69; 95% CI, 0.55-0.87; $P<.001$; Figure 2), which translates to a 31% reduction in the risk for death.⁵ In an exploratory analysis, the survival benefit with sorafenib remained significant even after consideration of baseline characteristics such as ECOG performance status, presence or absence of macroscopic vascular invasion, extent of tumor burden, Child-Pugh status, and levels of AFP, albumin, alkaline phosphatase, and total bilirubin. The corresponding 1-year survival rate was 44% with sorafenib and 33% with placebo ($P=.009$). The co-primary endpoint, time to symptomatic progression, showed no significant difference between the sorafenib and placebo arms (4.1 months vs 4.9 months, respectively; $P=.77$). In contrast, the median time to independently reviewed radiologic progression (a secondary endpoint) was significantly prolonged with sorafenib compared with placebo (5.5 months vs 2.8 months; HR, 0.58; 95% CI, 0.45-0.74; $P<.001$). There were no complete responses in either treatment group. Sorafenib was associated with a higher disease control rate, with 43% of patients achieving stable disease or better vs 32% of patients treated with placebo ($P=.002$).

Figure 2. Overall survival in the SHARP trial. SHARP, Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol. Adapted from Llovet JM et al. *N Engl J Med.* 2008;359(4):378-390.⁵



Sorafenib was relatively well-tolerated in the SHARP trial. The majority of drug-related adverse events were grade 1 or 2 in severity and gastrointestinal, dermatologic, or constitutional in nature.⁵ All-grade adverse events occurring at a significantly greater incidence in the sorafenib arm relative to the placebo arm included diarrhea (39% vs 11%), hand-foot skin reaction (21% vs 3%), anorexia (14% vs 3%), alopecia (14% vs 2%), weight loss (9% vs 1%), and voice changes (6% vs 1%). Grade 3/4 toxicities that were significantly higher with sorafenib included diarrhea (8% vs 2%), hand-foot skin reaction (8% vs <1%), and weight loss (2% vs 0%). The rate of drug discontinuation owing to an adverse event was similar between the 2 treatment arms (38% vs 37%). However, the rate of dose reductions owing to adverse events was much higher with sorafenib (26%) than placebo (7%).

The SHARP trial was designed and conducted with the goal of obtaining regulatory approval for sorafenib in the United States, Europe, and other countries that participated in the study. The results of a parallel study, the Sorafenib-AP trial, were subsequently published to support its regulatory approval in China and other Asian-Pacific countries.⁶ Sorafenib-AP was a similarly designed, multinational, double-blind, placebo-controlled, randomized phase 3 trial. Patients had measurable unresectable HCC with no prior systemic therapy, an ECOG performance status of 0, 1, or 2, and Child-Pugh liver function class A, with adequate renal, hepatic, and hematologic function. Baseline characteristics were similar between the 2 arms, with the majority of patients having an ECOG performance status of 0 or 1, 35% showing macroscopic vascular invasion, and 69% with extrahepatic spread (primarily to the lungs and lymph nodes). Nearly three-quarters of patients in each arm had HBV infection at baseline.

A total of 271 patients were randomly assigned in a 2:1 fashion to treatment with either continuous sorafenib (400 mg twice daily) or placebo.⁶ Because the Sorafenib-AP trial was designed in parallel with the SHARP trial, no primary efficacy endpoint was designated in the study protocol. However, many of the same endpoints reported for the SHARP trial were also reported for this study.

In the Sorafenib-AP trial, the median overall survival was superior for those patients treated with sorafenib vs placebo (6.5 months vs 4.2 months; HR, 0.68; 95% CI, 0.50-0.93; $P=.014$).⁶ The corresponding 6-month rate of overall survival was higher in the sorafenib group (53.3%) than in the placebo group (36.7%). The median time to radiologic progression was significantly prolonged with sorafenib vs placebo (2.8 months vs 1.4 months; HR, 0.57; 95% CI, 0.42-0.79; $P=.0005$). In contrast, there was no difference in the median time to symptomatic progression between the 2 arms (3.5 months vs 3.4 months, respectively; $P=.50$), a trend that was also seen in the SHARP trial. No patient achieved a complete response. The disease control rate (stable disease or better) was more than doubled in the sorafenib arm (35.3% vs 15.8%; $P=.0019$).

The overall frequency of drug-related adverse events was higher with sorafenib (81.9%) compared with placebo (38.7%).⁶ All-grade adverse events that were more common with sorafenib included hand-foot skin reaction (45.0% vs 2.7%), diarrhea (25.5% vs 5.3%), alopecia (24.8% vs 1.3%), fatigue (20.1% vs 8.0%), rash or desquamation (20.1% vs 6.7%), hypertension (18.8% vs 1.3%), and anorexia (12.8% vs 2.7%). Adverse reactions of grade 3 or 4 in severity that were more common with sorafenib than placebo included hand-foot skin reaction (10.7% vs 0%), diarrhea (6.0% vs 0%), fatigue (3.4% vs 1.3%), hypertension (2.0% vs 0%), and rash or desquamation (0.7% vs 0%). Overall,

a similar proportion of patients in each arm discontinued treatment owing to adverse events (19.5% vs 13.3%, respectively), whereas a greater number of patients in the sorafenib arm required a dose reduction (30.9% vs 2.7%), most frequently for hand-foot skin reaction and diarrhea.

Other Multitargeted Kinase Inhibitors for First-Line Treatment

It is important to realize that both of these studies—SHARP and the Sorafenib-AP trial—were conducted in patients with a good performance status and Child-Pugh A cirrhosis. Both of these factors have been shown to be significantly associated with patient prognosis.⁷ Another important point is that while both studies reached statistical significance, the clinical benefit was relatively modest; sorafenib extended overall survival by 2.8 months in the SHARP trial and 2.3 months in the Sorafenib-AP trial. This benefit, however, represented the first real advancement in the treatment of unresectable HCC, and led to the investigation of alternative oral multitargeted kinase inhibitors for the treatment of this disease.⁸ None have demonstrated superiority compared with single-agent sorafenib, and therefore sorafenib continues to be the standard of care in first-line therapy for unresectable HCC. The remainder of this section describes some of these studies, all of which were conducted in patients with unresectable HCC with Child-Pugh class A disease and an ECOG performance status of 0 or 1, who had not received prior systemic therapy.

The oral multitargeted agent sunitinib is a potent antiangiogenic agent that inhibits VEGFR and PDGFR. Promising phase 2 data⁹⁻¹¹ led to an open-label phase 3 trial comparing sunitinib with sorafenib.¹² The study randomly assigned 1074 patients to sunitinib (37.5 mg once daily) or the standard dose of sorafenib (400 mg twice daily). The study was terminated early for both futility and safety reasons. The median overall survival was 7.9 months with sunitinib and 10.2 months with sorafenib (HR, 1.30). The median progression-free survival was 3.6 months vs 3.0 months, respectively (HR, 1.13), and the median time to progression was 4.1 months vs 3.8 months (HR, 1.13). Patients who were treated with sunitinib experienced more frequent and severe adverse events (including grade 3/4 thrombocytopenia [29.7%] and neutropenia [25.7%]).

Like sunitinib, linifanib is an oral multitargeted agent that preferentially targets the VEGFR and PDGFR. Linifanib demonstrated initial activity against HCC in a phase 2 study.¹³ Linifanib was evaluated in an open-label, randomized phase 3 study of 1035 patients with unresectable HCC.¹⁴ Patients were randomly assigned to treatment with either linifanib (17.5 mg daily) or sorafenib

(400 mg twice daily). Linifanib was associated with an improved objective response rate (13.0% vs 6.9%) and a longer median time to progression (5.4 months vs 4.0 months) compared with sorafenib. However, there was no significant difference between the treatment arms in the primary endpoint of median overall survival (9.1 months with linifanib vs 9.8 months with sorafenib; HR, 1.046; 95% CI, 0.896-1.221). Therefore, the study did not meet its predefined criteria for superiority or noninferiority. Furthermore, linifanib appeared to be associated with a worse toxicity profile, with a higher rate of grade 3/4 adverse events, discontinuations, and dose interruptions and reductions.

The multitargeted kinase inhibitor brivanib preferentially targets the VEGFR and fibroblast growth factor receptor (FGFR). After demonstrating activity in a phase 2 study,^{15,16} brivanib was then tested in the double-blind, multinational, phase 3 BRISK-FL study (First Line Hepato Cellular Carcinoma), which randomly assigned 1155 patients with unresectable HCC to treatment with either brivanib (800 mg once daily) or sorafenib (400 mg twice daily).¹⁷ The primary endpoint of noninferiority in overall survival was not met; the median overall survival was 9.5 months with brivanib vs 9.9 months with sorafenib (HR, 1.06; 95% CI, 0.93-1.22). Brivanib was also associated with a higher incidence of grade 3/4 hypertension, fatigue, and hyponatremia, as well as higher rates of discontinuation owing to adverse events.

Given that no other oral small-molecule multitargeted kinase inhibitor was able to demonstrate superior efficacy when directly compared with sorafenib in the first-line setting, another strategy sought to improve upon single-agent sorafenib with the combination of sorafenib and the epidermal growth factor receptor inhibitor erlotinib. The phase 3 SEARCH trial (Sorafenib and Erlotinib, a Randomized Trial Protocol for the Treatment of Patients With Hepatocellular Carcinoma) randomly assigned 720 patients to treatment with sorafenib (400 mg twice daily) plus either erlotinib (150 mg once daily) or placebo.¹⁸ The addition of erlotinib did not significantly improve median overall survival (9.5 months for the combination vs 8.5 months for sorafenib alone; HR, 0.929; $P=.408$). The median time to progression was also similar between the treatment arms (3.2 months vs 4.0 months; HR, 1.135; $P=.18$). The objective response rate was higher with the combination compared with single-agent sorafenib (6.6% vs 3.9%, respectively), but the disease control rate (stable disease or better) was significantly reduced with the combination (43.9% vs 52.5%; $P=.021$). The frequencies of rash or desquamation, anorexia, and diarrhea were higher in the sorafenib plus erlotinib arm. Alopecia and hand-foot skin reaction were more frequent in the single-agent sorafenib arm.

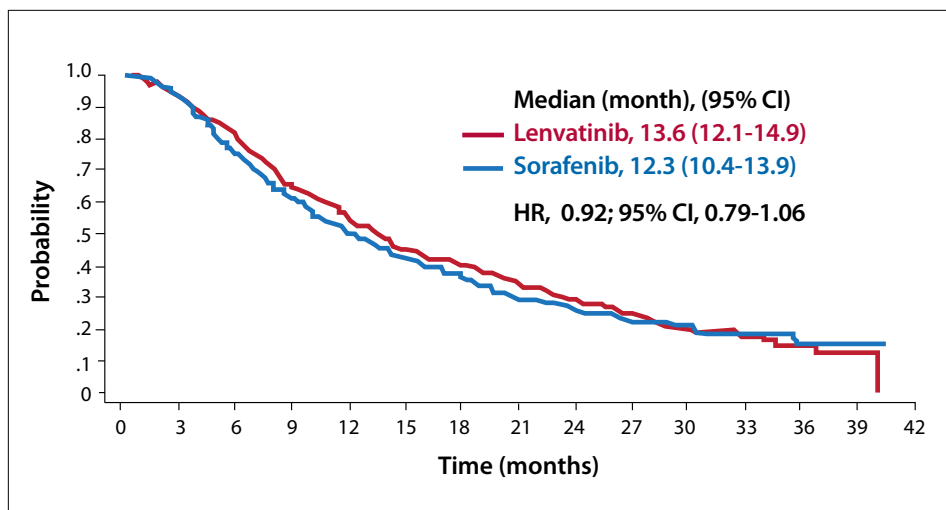


Figure 3. Overall survival in a phase 3 trial of lenvatinib. Adapted from Cheng A-L et al. ASCO abstract 4001. *J Clin Oncol.* 2017;35(suppl 15).²¹

New Data With Lenvatinib in the First-Line Setting

Lenvatinib is an inhibitor of multiple receptor tyrosine kinases, including VEGFR 1-3, FGFR 1-4, PDGFR α , receptor tyrosine-protein, and KIT. Currently, lenvatinib is approved as a single agent for the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, as well as in combination with everolimus for the treatment of recurrent advanced renal cell carcinoma.¹⁹ It is also being explored as a treatment for unresectable HCC.

In a phase 2, single-arm, open-label study of 46 Asian patients with unresectable HCC who had not received prior systemic therapy, lenvatinib (12 mg once daily) showed promising antitumor activity.²⁰ The median time to progression was 7.4 months, and the disease control rate was 78%. In this population, the median overall survival was 18.7 months. The most frequent adverse events of any grade were hypertension (76%), palmar-plantar erythrodysesthesia syndrome (65%), decreased appetite (61%), and proteinuria (61%). Most patients required either a dose reduction (74%) or a drug discontinuation (22%) owing to an adverse event.

This activity prompted the REFLECT study (A Multicenter, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib [E7080] Vs Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma), an international, open-label, noninferiority phase 3 trial to compare lenvatinib vs sorafenib for the first-line treatment of unresectable HCC. Results from this study were presented at the 2017 American Society of Clinical Oncology Annual Meeting.²¹ Data presented were from 954 patients randomly assigned to lenvatinib (either 8 mg or 12 mg once daily, based on

body weight) or sorafenib (400 mg twice daily). At baseline, most patients (64%) had an ECOG performance status of 0, and two-thirds of patients had macroscopic vascular invasion, extrahepatic spread, or both. Nearly all patients had Child-Pugh class A disease. HBV infection was present in approximately half of patients at baseline.

Single-agent lenvatinib significantly improved median progression-free survival vs sorafenib (7.4 months vs 3.7 months; HR, 0.66; 95% CI, 0.57-0.77; $P < .00001$).²¹ Other endpoints also demonstrated improvement with lenvatinib vs sorafenib, including median time to progression (8.9 months vs 3.7 months; HR, 0.63; 95% CI, 0.53-0.73; $P < .00001$) and objective response rate (24.1% vs 9.2%; OR, 3.13; 95% CI, 2.15-4.56; $P < .00001$) per modified Response Evaluation Criteria In Solid Tumors (mRECIST).²² Although a benefit in improved median overall survival was not observed with lenvatinib, the criteria for noninferiority (with the noninferiority margin set at 1.08 based on previous phase 3 trials of sorafenib) was met. Median overall survival was 13.6 months for lenvatinib vs 12.3 months for sorafenib (HR, 0.92; 95% CI, 0.79-1.06; Figure 3).

A similar proportion of patients in each arm had either a dose reduction (37% and 38% for the lenvatinib and sorafenib arms, respectively) or dose discontinuation (9% and 7%, respectively), owing to adverse events.²¹ The most frequent grade 3/4 treatment-related adverse events reported with lenvatinib and sorafenib were hypertension (23% vs 14%), decreased weight (8% vs 3%), decreased platelet count (6% vs 3%), elevated aspartate aminotransferase (5% vs 8%), decreased appetite (5% vs 1%), diarrhea (4% vs 4%), and palmar-plantar erythrodysesthesia (3% vs 11%).

Based on these data, it is anticipated that lenvatinib will be submitted for FDA approval as an alternative to

sorafenib in the first-line setting for unresectable HCC. There is currently no evidence-based guidance to suggest which treatment would be optimal for a particular patient population. Selection will be based on the safety profile of each agent, as well as any underlying differences in the patient characteristics between the SHARP trial and the REFLECT trial.

When to Initiate Second-Line Treatment

Despite the positive results associated with sorafenib as first-line treatment for unresectable HCC, all patients eventually experience disease progression. Approximately half of these patients are eligible to proceed to second-line treatment. Candidates for second-line therapy should have good functional status as well as adequate hepatic function.

Until recently, these considerations were of limited importance because there was no FDA-approved treatment option for the second-line setting, where the overall survival is approximately 8 months.²³ For several years, phase 3 trials of second-line therapies failed to show improvement. Therapies with negative results included brivanib, everolimus, and ramucirumab.²⁴⁻²⁶ This changed in April 2017 with the approval of regorafenib for the treatment of patients with HCC who have been previously treated with sorafenib.²⁷

Regorafenib in the Second-Line Setting

Regorafenib is a multitargeted kinase inhibitor with a broad target profile, including RET, VEGFR, KIT, PDGFR α/β , and FGFR, among several other tyrosine kinases. These targets play critical roles in angiogenesis, oncogenesis, metastasis, and tumor immunity. In preclinical studies, regorafenib was found to be more potent than sorafenib.^{28,29} Subsequently, an open-label phase 2 trial demonstrated that regorafenib had anti-tumor activity in 36 patients with unresectable HCC that had progressed following first-line treatment with sorafenib.³⁰ In this single-arm study, 72.2% achieved disease control (stable disease or better), with a median time to progression of 4.3 months. In this study, the median overall survival was 13.8 months following second-line treatment with regorafenib. Several patients required discontinuation (n=20) and dose reductions (n=15) owing to adverse events. The most common all-grade treatment-related adverse events were hand-foot skin reaction, diarrhea, fatigue, hypothyroidism, anorexia, hypertension, nausea, and voice changes.

Based on the initial efficacy results of this phase 2 trial, regorafenib was then evaluated in the randomized, double-blind, placebo-controlled, international phase 3 RESORCE trial (Regorafenib After Sorafenib in Patients

With Hepatocellular Carcinoma).²³ Patients in this trial had unresectable and measurable HCC, with documented radiologic progression during first-line sorafenib treatment. The trial randomly assigned 573 patients in a 2:1 fashion to treatment with regorafenib (160 mg once daily) or placebo, both administered for the first 3 weeks of a 4-week cycle. Treatment was continued until either progression (symptomatic or radiologic) or unacceptable toxicity. All patients had Child-Pugh class A disease. The proportion of patients recruited from Asian countries was limited to 40% of the overall study population. Baseline characteristics of patients were evenly distributed between treatment groups. Most patients (66%) had an ECOG performance status of 0 and either extrahepatic disease (72%) or macroscopic vascular invasion (29%). The etiology of HCC was varied in both arms, and was caused by HBV, alcohol, HCV, or nonalcoholic steatohepatitis.

The RESORCE trial met its primary endpoint. The median overall survival was 10.6 months with regorafenib vs 7.8 months with placebo (HR, 0.63; 95% CI, 0.50-0.79; $P<.0001$; Figure 4).²³ The benefit in overall survival was maintained across all preplanned subgroup analyses, including age, sex, ECOG performance status, AFP level, presence of extrahepatic disease or macroscopic vascular invasion, and disease etiology. Improvements were also shown in several secondary endpoints. Median progression-free survival (by mRECIST) was 3.1 months with regorafenib vs 1.5 months with placebo. The median time to progression was also extended with regorafenib, at 3.2 months, vs 1.5 months with placebo. The objective response rate was 11% with regorafenib vs 4% with placebo. The disease control rate (stable disease or better) was significantly higher with regorafenib vs placebo (65% vs 36%, respectively; $P<.0001$).

The most frequently reported and clinically relevant grade 3 or 4 adverse events for regorafenib vs placebo were hypertension (15% vs 5%), hand-foot skin reaction (13% vs 1%), fatigue (9% vs 5%), and diarrhea (3% vs 0%).²³ Drug-related adverse events resulted in treatment interruptions or dose reductions in 54% of patients treated with regorafenib and 10% of patients in the placebo group. Discontinuations owing to adverse events occurred in 10% of the regorafenib arm and 4% of the placebo arm.

The efficacy and safety results from the RESORCE trial led to the FDA approval of regorafenib in the second-line setting for unresectable HCC. The treatment plan now includes use of regorafenib for patients who require therapy after sorafenib. It is important to realize that the patient population enrolled in the study had good liver function (Child-Pugh A). Although all patients had progressed on sorafenib, they had been able to tolerate treatment.

Figure 4. Median OS in the RESORCE trial. HR, hazard ratio; RESORCE, Regorafenib After Sorafenib in Patients With Hepatocellular Carcinoma. Adapted from Bruix J et al. *Lancet*. 2017;389(10064):56-66.²³

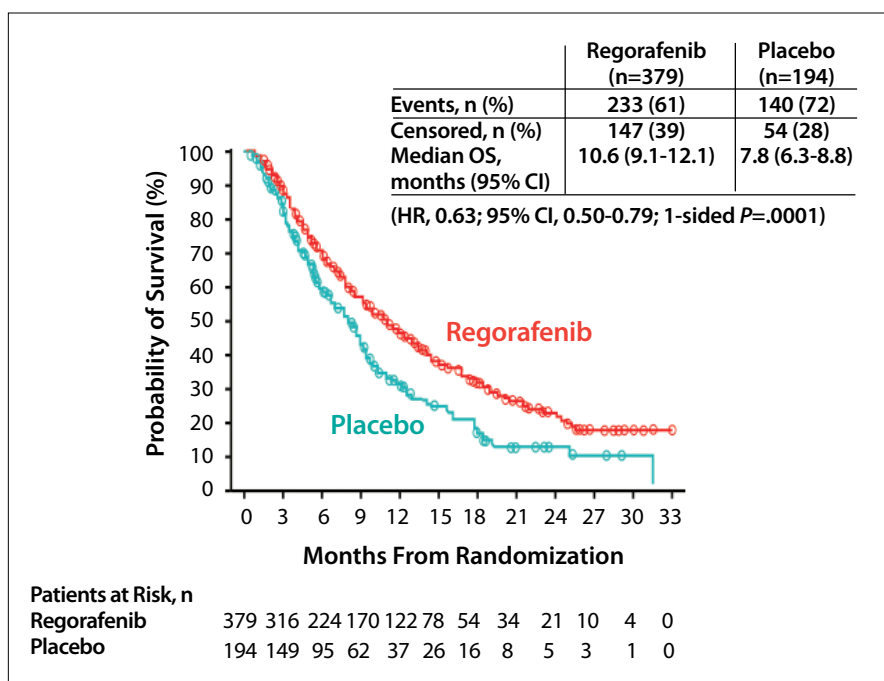


Table 3. Responses With Nivolumab in the Dose-Expansion Phase of the CheckMate 040 Trial

	Uninfected Untreated/Intolerant (n=56; 95% CI)	Uninfected Progressor (n=57; 95% CI)	HCV Infected (n=50; 95% CI)	HBV Infected (n=51; 95% CI)	All Patients (n=214; 95% CI)
Objective response	13 (23%; 13-36)	12 (21%, 11-34)	10 (20%; 10-34)	7 (14%; 6-26)	42 (20%; 15-26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable disease	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Progressive disease	13 (23%)	18 (23%)	14 (28%)	23 (45%)	68 (32%)
Not evaluable	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)
Overall survival					
6 months	89% (77-95)	75% (62-85)	85% (72-93)	84% (71-92)	83% (78-88)
9 months	82% (68-90)	63% (49-74)	81% (66-90)	70% (55-81)	74% (67-79)
KM median	NR	13.2 (8.6-NE)	NR	NR	NR
PFS (months), KM median	5.4 (3.9-8.5)	4.0 (2.6-6.7)	4.0 (2.6-5.7)	4.0 (1.3-4.1)	4.0 (2.9-5.4)

KM, Kaplan-Meier estimate; NE, not estimable; NR, not reported; PFS, progression-free survival. Data from El-Khoueiry AB et al. *Lancet*. 2017;389(10088):2492-2502.³¹

Checkpoint Inhibition as an Emerging Strategy in HCC

In recent years, inhibitors of the programmed death receptor 1 (PD-1) and PD-1 ligand (PD-L1) checkpoints have become an important therapy for many advanced solid tumors, including melanoma, non-small cell lung cancer, and renal cell carcinoma. This class of antibody agents has also been evaluated in unresectable HCC, with some promising early results. The anti-PD-1 anti-

body nivolumab was investigated in a phase 1/2, open-label, noncomparative, dose-escalation study in patients with advanced HCC.³¹ In the dose-expansion phase of this study, nivolumab (3 mg/kg every 2 weeks) was associated with an objective response rate of 20% (Table 3). The safety profile observed in this trial was manageable, with no new safety signals reported. A phase 3 study that will compare first-line treatment with nivolumab vs sorafenib in a head-to-head fashion is now recruiting patients.³² Another anti-PD-1 antibody, pembrolizumab,

is being evaluated in second-line HCC treatment settings.³³ In a phase 2 study, the checkpoint inhibitor durvalumab is being investigated with tremelimumab (targeting another checkpoint molecule, CTLA-4), as a monotherapy or in combination.³⁴ Other strategies are focused on combinations with these checkpoint inhibitors, for example, pembrolizumab plus lenvatinib.

Conclusion

The recent approval of regorafenib for patients who require treatment after sorafenib and the newly presented phase 3 trial data comparing sorafenib and lenvatinib in the first-line setting have reinvigorated the field of targeted therapy development in advanced HCC. Early data with nivolumab and other checkpoint inhibitors are evolving, and phase 3 trials are ongoing to determine the overall survival benefits in advanced HCC. Future studies should define the optimal sequence and combination of targeted therapies and checkpoint inhibitors in advanced HCC, identify additional novel targets, and apply molecular classification to future trial design.

Disclosure

Dr Zhu has served as an advisor or consultant to Bayer, Eisai, BMS, Merck, and Novartis.

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The Evolving Role of Radioembolization in Hepatocellular Carcinoma

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Interventional radiologists have a variety of methods, including both needle-based and catheter-based therapies, to treat patients with HCC. The needle-based interventions, which include radiofrequency ablation and microwave ablation, are generally limited to smaller tumors. In patients with more extensive disease (eg, bilobar disease), catheter-based techniques are more commonly applied. These techniques involve the delivery of a particular substance into the tumor via the arteries directed toward that tumor. Most frequently, a chemotherapeutic agent (often in the form of a drug-eluting bead or microsphere) is delivered in this fashion, in a process termed transarterial chemoembolization (TACE). TACE has been used for several decades. Transarterial radioembolization (TARE) has gained widespread use in the past 5 to 10 years.

TARE in Clinical Practice

Most interventional radiologists who perform oncologic procedures perform chemoembolization of some type. In the United States, approximately half of these procedures are performed using doxorubicin-eluting microspheres (a process termed DEB-TACE). However, radioembolization is being performed with increasing frequency, particularly in academic centers. In TARE, microspheres containing either yttrium-90 (Y-90) or ethiodized oil labeled with iodine¹³¹ or rhenium¹⁸⁸ are administered into the artery via a percutaneous route.¹ Because TARE does not exert any macro-embolic activity, all of the treatment-related effects from this strategy are caused by the radiation carried by the microspheres. Two devices to administer these microspheres via catheter are available. They deliver radioactive microspheres averaging either 25 μ m or 33 μ m in diameter.

No randomized controlled trials have directly compared TARE with TACE. Abundant cohort data, however,

demonstrate that TARE is associated with better patient outcomes, including a longer time to disease progression. For example, in a meta-analysis of published studies (N=1499) comparing TARE with TACE for unresectable HCC, TARE resulted in better median overall survival (HR, 0.74; 95% CI, 0.61-0.90), 3-year overall survival rate (relative risk, 1.75; 95% CI, 1.01-3.03; *P*=.05), and time to progression (HR, 0.61; 95% CI, 0.41-0.89).² TARE also seems to be better tolerated by patients, as it can be performed as an outpatient procedure and results in fewer symptoms. TARE was associated with fewer days of hospitalization (mean difference, -2.66; 95% CI, -4.08 to -1.24) and fewer complications, such as abdominal pain (relative risk, 0.30; 95% CI, 0.11-0.83; *P*=.02).² Given these and other reports in the literature, TARE is gaining in popularity.

Types of TARE Devices

There are 2 types of radioembolization devices available: resin microspheres and glass microspheres. Those 2 types of devices differ in terms of how dosimetry is calculated and how they behave once delivered. It is important to understand that just as the different TACE procedures cannot be treated as one, these TARE devices should also not be considered the same. Each has its own particular delivery method and treatment program. These factors are important to consider when evaluating the efficacy and safety data supporting their use. It should also be understood that the quality of the data in evaluation of almost every treatment modality for HCC is limited to some degree by factors such as patient population, definition, size, stratification, and randomization. As a result, much of the work of interventional oncologists for HCC must be performed using empirical evidence, based on cohort or retrospective data, and without the benefit of comparative groups.

Impact of Patient Selection

The characteristics of a patient under evaluation for TARE also lends important information to how TARE can best be applied. These characteristics include clinical status and serologic status, as well as medical history. The population of patients with HCC tends to be extremely variable, and patient-related and disease-related characteristics can help determine outcome to TARE. For example, patients who do not have portal vein invasion or metastatic disease would be likely to have a longer life expectancy following TARE than patients who have either or both of these characteristics.

Staging systems are an important way to assess many of these characteristics at once. In HCC, several staging systems have been suggested, and many have been validated.³ One of the most widely used systems, the BCLC classification, provides a simultaneous assessment of 4 disease elements: tumor extension, liver functional reserve, physical status, and cancer-related symptoms.⁴ Tumor extension includes the total number of tumors, tumor size, and the presence or absence of portal vein invasion or extrahepatic metastasis. The second element, liver functional reserve, is used in place of a Child-Pugh grade. Physical status is determined based on the patient's ECOG performance status, and the cancer-related symptoms reflect the degree of disease severity.

Based on how they score within each element, patients are then assigned to 1 of 5 BCLC categories: 0, A, B, C, and D.⁴ BCLC stage 0 (defined as very early-stage disease) describes patients with well-preserved liver function (Child-Pugh A) who are diagnosed with 1 small asymptomatic liver nodule measuring under 2 cm, and who are without vascular invasion or satellites. BCLC stage A (defined as early-stage disease) corresponds to patients with a Child-Pugh A or B status, who have been diagnosed with either a single nodule of any size or a maximum of 3 nodules, all measuring less than 3 cm. A BCLC stage of B (defined as intermediate-stage disease) includes patients with a Child-Pugh A or B status who have multiple nodules, but are without vascular invasion or extrahepatic metastasis. In contrast, BCLC stage C (defined as advanced-stage disease) is used to describe patients with Child-Pugh A or B status, but have vascular invasion or extrahepatic metastasis, as well as cancer-related symptoms (ECOG performance status of 0, 1, or 2). Patients with a Child-Pugh grade of C, in any tumor stage, and with any degree of cancer-related symptoms (ECOG performance status >2) are classified as having BCLC stage D disease (defined as terminal-stage disease).

Patients with a BCLC stage of 0 or A qualify for potentially curative treatment options, such as surgical resection, liver transplant, and ablation.³ BCLC stage B

disease is most often treated with TARE or TACE, whereas systemic therapy (with sorafenib in the first-line setting and regorafenib in the second-line setting) is reserved for patients with BCLC stage C disease. Among patients with BCLC stage D disease, their advanced liver dysfunction precludes treatment, and best supportive care is therefore recommended.

Evaluation of Y-90 Resin Microspheres

Several studies have evaluated Y-90 resin microspheres for HCC. A retrospective analysis of Y-90 resin microspheres in the first-line setting for unresectable HCC showed that administration of these spheres improved median overall survival as compared with active treatment or supportive care (16.0 vs 8.0 months; $P < .05$).⁵ In a larger analysis of 325 patients with unresectable BCLC stage A or B disease, enrolled in the multicenter ENRY study (European Network on Radioembolization With Yttrium-90 Resin Microspheres), survival outcomes were shown to be comparable with TACE and transarterial embolization.⁶

Y-90 resin microspheres are currently under evaluation in HCC. Results from the recently completed SARAH study (Sorafenib vs Radioembolisation in Advanced Hepatocellular Carcinoma) were reported at the 2017 European Association for the Study of the Liver International Liver Congress.⁷ The randomized, controlled, open-label, multicenter phase 3 SARAH trial enrolled patients with locally advanced or inoperable HCC who did not respond to other treatments or had failed 2 rounds of TACE. The trial randomly assigned 459 patients to TARE administered using Y-90 resin microspheres or sorafenib (400 mg twice daily).

The SARAH study failed to meet its primary endpoint, improvement in overall survival. Median overall survival was 8.0 months with Y-90 resin microspheres vs 9.9 months with sorafenib (HR, 1.15; $P = .18$; Figure 6).⁷ The difference in median progression-free survival was also not significantly different between the Y-90 resin microsphere and sorafenib groups (4.1 months vs 3.7 months; HR, 1.03; 95% CI, 0.85-1.25; $P = .76$). The difference in the objective response rate between the 2 treatment arms did reach statistical significance, at 19.0% with Y-90 resin microspheres vs 11.6% with sorafenib ($P = .042$). There was a statistically significant reduction in the risk for cancer progression in the liver with Y-90 resin microspheres vs sorafenib ($P = .014$).

The incidence of all-grade treatment-related adverse events was significantly lower in patients treated with Y-90 resin microspheres vs sorafenib (76.5% vs 94.0%, respectively; $P < .001$).⁷ The incidence of grade 3 or higher adverse events was also lower with Y-90 resin microspheres vs sorafenib (40.7% vs 63.0%). Quality of life, assessed

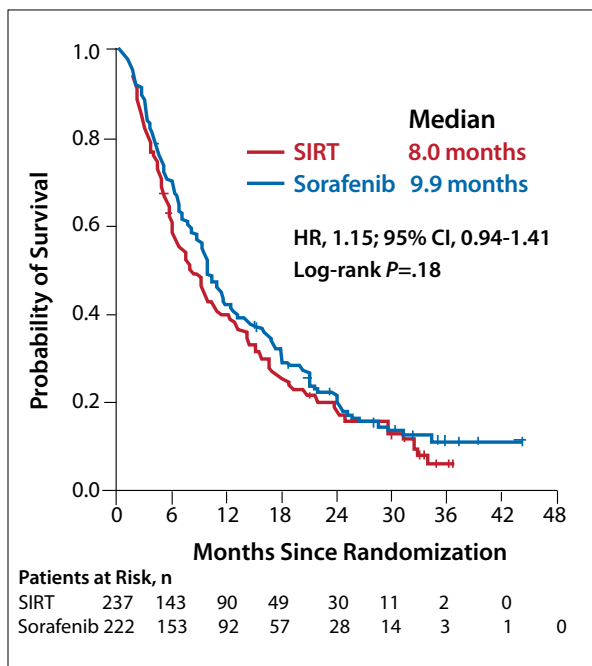


Figure 6. The SARAH study did not meet its primary endpoint, improvement in overall survival. HR, hazard ratio; SARAH, Sorafenib vs Radioembolisation in Advanced Hepatocellular Carcinoma; SIRT, selective internal radiation therapy. Adapted from Vilgrain V et al. Abstract GS-012. Presented at: the 2017 International Liver Congress.⁷

using the Global Health Status scale of the EORTC QLQ-C30 questionnaire, was significantly improved in patients in the Y-90 resin microsphere arm compared with the sorafenib arm ($P=.005$). This advantage tended to increase with time ($P=.045$).⁷

It is important to note that the enrollment criteria for the SARAH study required that patients had not

responded to other treatments or had failed 2 rounds of TACE. Therefore, the study essentially selected for a patient population who had previously not responded well to locoregional therapies.

The SIRveNIB trial (Phase III Multi-Centre Open-Label Randomized Controlled Trial of Selective Internal Radiation Therapy [SIRT] Versus Sorafenib in Locally Advanced Hepatocellular [AHCC Protocol 06]) compared Y-90 resin microspheres vs sorafenib, but in an Asian-Pacific population.⁸ The trial enrolled 360 patients. Like the SARAH trial, SIRveNIB did not meet its primary endpoint of improvement in overall survival. Among the intent-to-treat population, overall survival was 8.84 in the Y-90 arm and 10.02 months in the sorafenib arm, a difference that was not statistically significant (HR, 1.12; $P=.360$; Figure 7). The tumor response rate was 16.5% with Y-90 vs 1.7% with sorafenib ($P<.001$).

The ongoing SORAMIC trial (Sorafenib and Microtherapy Guided by Primovist Enhanced MRI in Patients With Inoperable Liver Cancer) is comparing single-agent sorafenib vs the sequential use of Y-90 resin microspheres followed by sorafenib.⁹

Evaluation of Y-90 Glass Microspheres

Two ongoing clinical trials aim to investigate Y-90 glass microspheres in HCC. The STOP-HCC (TS-103) trial (Efficacy Evaluation of TheraSphere in Patients With Inoperable Liver Cancer) is an open-label, prospective, multicenter, randomized, phase 3 trial designed to evaluate Y-90 glass microspheres in patients with unresectable HCC in whom sorafenib treatment is planned.¹⁰ Patients will be randomly assigned to receive Y-90 glass microspheres followed by sorafenib, or to go straight to sorafenib treatment. The primary endpoint is overall survival. Secondary endpoints include time to progression,

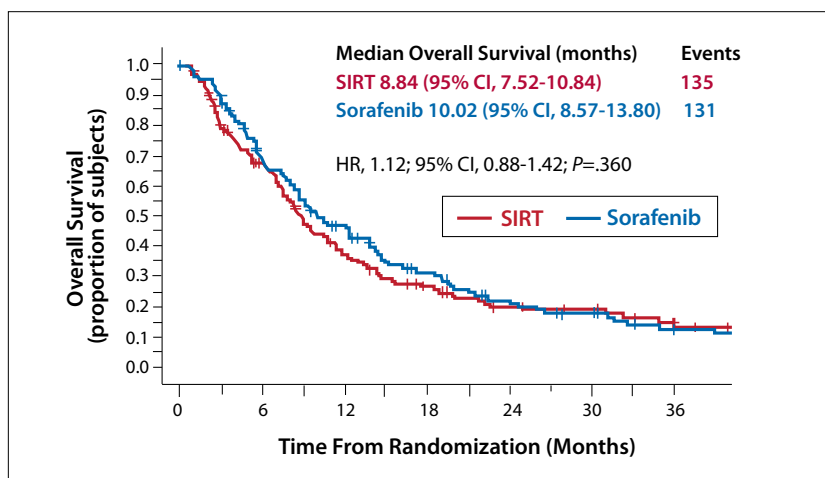


Figure 7. The SIRveNIB study did not meet its primary endpoint, improvement in overall survival. HR, hazard ratio; SIRT, selective internal radiation therapy; SIRveNIB, Phase III Multi-Centre Open-Label Randomized Controlled Trial of Selective Internal Radiation Therapy [SIRT] Versus Sorafenib in Locally Advanced Hepatocellular [AHCC Protocol 06]. Adapted from Pierce HW, Gandhi M. Abstract 4002. Presented at: the 2017 American Society of Clinical Oncology Annual Meeting.⁸

time to untreatable progression, time to symptomatic progression, tumor response, quality of life, and safety.

The YES-P (TS-104) trial (Efficacy Evaluation of TheraSphere to Treat Inoperable Liver Cancer With Blockage of the Portal Vein) is an open-label, prospective, multicenter, randomized, phase 3 trial that will compare Y-90 glass microspheres vs sorafenib in patients with unresectable HCC and portal vein thrombosis.¹¹ The primary endpoint for the YES-P trial is overall survival, and secondary endpoints include time to progression, time to worsening of portal vein thrombosis, time to symptomatic progression, tumor response, quality of life, and safety.

Impact of Recent Data on Patient Care

Because of the complicated treatment landscape, patients with HCC must be managed by a multidisciplinary team. This strategy will permit all of the potential interventions—systemic, surgical, transplant, and interventional radiology—to be at the ready. In this way, the team of physicians can approach the patient in an unbiased way to provide the best possible care. By looking at patients closely and keeping track of the data to determine which patients do the best with which therapies, it is possible to establish a series of interventions that will be more beneficial than just a single one. This approach will help to ensure that patients achieve the outcomes they need and deserve.

Disclosure

Dr Johnson is a consultant for BTG International Ltd, Bayer, Boston Scientific, Cook, Scientia, and Surefire. He is

a shareholder of EndoShape and has received research grants from BTG International Ltd and Novate.

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The Treatment Path in Hepatocellular Carcinoma: Further Observations

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H&O How is the management of patients with HCC evolving?

Matthew S. Johnson, MD The management of these patients is evolving as we gain a better understanding of patient populations and how to define them. As we look at the concomitant diseases (cirrhosis, hepatitis, alcoholism, NAFLD), we need to gain a better understanding of which disease etiologies respond best to which therapies.

H&O What are the most interesting new treatment options?

Matthew S. Johnson, MD Checkpoint inhibitors will likely usher in a new era of treatment for HCC, if the promising results demonstrated with nivolumab continue to evolve. The recent approval of regorafenib now provides a second-line treatment for patients who before had no other options after progression on sorafenib. For treatment to continue to move forward, we will need to improve our understanding of the molecular basis of this disease.

H&O What areas of future research should be emphasized in HCC?

Matthew S. Johnson, MD For the future, in addition to identifying new agents for HCC, another important goal will be to understand the synergies between current and new interventions, and to understand which patients will benefit most from what combination of therapies. To do this, we will need to understand the disease better than we do right now. For those of us who perform locoregional therapy, it is becoming increasingly important to look at the blood flow, the relative position of the tumors in the liver, and the position of the tumors in relation to other vital or nonvital structures, and to put all of these things together. A better understanding of this complicated milieu will allow us to provide the best care we can for patients.

Disclosure

Dr Johnson is a consultant for BTG International Ltd, Bayer, Boston Scientific, Cook, Scientia, and Surefire. He is a shareholder of EndoShape and has received research grants from BTG International Ltd and Novate.

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Epidemiology of HCC

- Second-leading cause of cancer-related deaths worldwide
- Incidence has more than tripled since 1980
- The median age at diagnosis is 63 years
- Incidence rates are highest among the Asian/Pacific Islander, Hispanic, and American Indian/Alaska Native populations

HCC, hepatocellular carcinoma.
Data from the National Cancer Institute, Surveillance, Epidemiology, and End Results Program. Cancer stat facts: liver and intrahepatic bile duct cancer, 2017. <http://seer.cancer.gov/statfacts/html/livb18.html>. Accessed July 1, 2017.

Diagnosis of HCC

- Most patients with HCC have symptoms of chronic liver disease and cirrhosis
- Onset of HCC among patients with underlying cirrhosis is typically heralded by added decompensation of liver disease, abdominal pain, worsening ascites, or encephalopathy
- Among the small group of patients who develop HCC in the absence of cirrhosis, the onset of disease is relatively acute, with few preceding symptoms
- With the increasing use of HCC surveillance in at-risk individuals, it is becoming more frequent to detect patients at an asymptomatic stage

Systemic Treatment of HCC

- Systemic therapy is typically reserved for patients with advanced disease who are not eligible for transplant, resection, or locoregional therapy
- Clinical studies show little benefit in overall survival with the use of chemotherapy, and the responses to these agents are modest at best¹⁻³
- The targeted agent sorafenib was FDA-approved in 2007
- The next approval was for regorafenib in 2017

FDA, US Food and Drug Administration.
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Regorafenib in the Second-Line Setting

- Regorafenib is a multitargeted kinase inhibitor with a broad target profile
- In the phase 3 RESORCE trial, regorafenib improved overall survival as compared with placebo (10.6 months vs 7.8 months; $P < .0001$)
- The benefit in overall survival was maintained across all preplanned subgroup analyses
- Improvements were also shown in several secondary endpoints, such as PFS and time to progression
- The objective response rate was 11% with regorafenib vs 4% with placebo
- The disease control rate was 65% with regorafenib vs 38% with placebo

PFS, progression-free survival; RESORCE, Regorafenib After Sorafenib in Patients With Hepatocellular Carcinoma. Data from Bruix J et al. *Lancet*. 2017;389(10094):56-65.

Emerging Systemic Treatment Options

- Lenvatinib
- Nivolumab
- Pembrolizumab
- Durvalumab

Radioembolization in HCC

- Interventional radiologists have a variety of methods, including both needle-based and catheter-based therapies, to treat patients with HCC
- The needle-based interventions, which include radiofrequency ablation and microwave ablation, are generally limited to smaller tumors
- Catheter-based techniques are more common in patients with extensive disease. These techniques involve the delivery of a particular substance into the tumor via the arteries directed toward that tumor

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