Hepatocellular carcinoma (HCC)
Scientific overview and clinical trials management

Giovanni Piazzi, Biol. Sc., PMP, Therapeutic Strategy Lead, Therapeutic Strategy and Medical Delivery, Oncology, Quintiles
Alma Panganiban MD, FPCP, FPSMO, Medical Director, Asia Medical Sciences Group, Quintiles
Swati Ranade, MBBS, DA, DNB, Associate Medical Director, Asia Medical Sciences, Quintiles
Brad Smith, Ph.D., Vice President Translational Medicine, Quintiles
Zorica Spadaccini, PhD, Associate Clinical Project Manager Director, Oncology, Asia Pacific Delivery Unit, Quintiles
Souhil Zaim, MD, Chief Medical Officer, Median Technologies

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, and the burden of this devastating cancer is expected to increase further in coming years given the current unmet medical needs.

This white paper presents a comprehensive scientific overview of HCC integrated by operational aspects on how to manage clinical trials in this indication.
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Executive summary

Liver cancer is a leading cause of cancer-related death worldwide. It is the fifth most common cancer in men (554,000 cases, 7.5% of the total) and the ninth in women (228,000 cases, 3.4%). In men, the regions of high incidence are Eastern and South-Eastern Asia (ASRs 31.9 and 22.2 respectively). In women, the rates are generally much lower. Liver cancer is the second most common cause of death from cancer worldwide, estimated to be responsible for nearly 746,000 deaths in 2012 (9.1% of the total) and prognosis is very poor.

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. The incidence of HCC is expected to rise in the United States and across the world, given the increasing prevalence of hepatitis C and B infections, alcohol consumption, diabetes, toxin exposure, and obesity. Various interventions, such as resection, chemoembolisation, radiofrequency ablation, cryotherapy, or liver transplantation are often not feasible.

Sorafenib remains the only approved systemic treatment for advanced tumors and the need for safer and more effective treatment remains. Considering that no biomarkers are able to predict response to sorafenib and recent trials in first and second line have not provided treatment alternatives, the development of novel and innovative therapies is crucial.

This white paper provided a detailed analysis of HCC from the scientific and clinical trial management point of view.

Section 1 provides a comprehensive scientific overview, including the medical aspects, the imaging methodology specific for HCC and the current biomarker approach.

Section 2 is focused on the operational aspects of conducting HCC trials, with a particular emphasis on the specifics of the Asia Pacific Region, a key area for the clinical trials in this indication given the high disease incidence.

Section 1 – Scientific overview

Epidemiology

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, and the burden of this devastating cancer is expected to increase further in coming years. Previous epidemiologic studies have highlighted striking global variations in the incidence of HCC, which is particularly high in much of East Asia and sub-Saharan Africa, and lower, but on the increase, in North America and most of Europe. This variation appears to be related to the complex etiology of HCC with different risk factors, primarily infection with hepatitis B or hepatitis C virus, responsible for driving HCC incidence rates in different regions.

Liver cancer is largely a problem of the less developed regions where 83% (50% in China alone) of the estimated 782,000 new cancer cases worldwide occurred in 2012. It is the fifth most common cancer in men (554,000 cases, 7.5% of the total) and the ninth in women (228,000 cases, 3.4%). In men, the regions of high incidence are Eastern and South-Eastern Asia (ASRs 31.9 and 22.2 respectively). In women, the rates are generally much lower. According to the GLOBOCAN estimates, the overall male: female incidence ratio is 2.4, and this ratio is even higher in areas of greater HCC risk.

Liver cancer is the second most common cause of death from cancer worldwide, estimated to be responsible for nearly 746,000 deaths in 2012 (9.1% of the total). The prognosis for liver cancer is very poor (overall ratio of mortality to incidence of 0.95), and as such the geographical patterns in incidence and mortality are similar.
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Risk factors
HCC is a complex disease associated with many risk factors and cofactors. In most patients, HCC is preceded by cirrhosis of the liver and, unsurprisingly, common causes of cirrhosis have been identified as key risk factors for HCC. Of particular importance is chronic infection with HBV or hepatitis C virus (HCV). Indeed, it has been estimated that HBV is responsible for 50%–80% of HCC cases worldwide, whereas 10%–25% of cases are thought to be a result of HCV infection. To date, eight HBV genotypes (A to H) have been classified. Patients with HBV genotype C have a higher risk for developing HCC, and a genetic mutation has been identified in some of these patients that may contribute to this greater risk.

Other environmental and genetic risk factors include excessive alcohol consumption, dietary exposure to aflatoxin, diabetes, obesity, or hereditary hemochromatosis. The growing burden of diabetes and obesity worldwide may drive future increases in HCC incidence, particularly in developed countries where, to date, the impact of the obesity epidemic has been most marked.

Diagnosis
Diagnosis of HCC should be based on imaging techniques and/or biopsy. The diagnostic algorithm has been validated and it is shown in Figure 2.²
**Treatment strategies**

There are multiple therapeutic modalities available for HCC, and the selection of a particular therapy depends on the stage of HCC, the degree of underlying liver synthetic function, other medical co-morbidities, and the availability of the treatment modality and local clinical expertise. Treatment choices are guided by staging classification systems and treatment guidelines.

The Barcelona Clinic Liver Cancer (BCLC) staging system, which was devised from the results of cohort studies and RCTs (Randomized Clinical Trials), is widely recognized, it has been externally validated and is endorsed by both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL). It includes variables linked to tumor stage and function, physical status and cancer-related symptoms to stage patients, and it combines each stage with a treatment algorithm as shown in Figure 3.³
Figure 3 Updated BCLC staging system and treatment strategy; 2011

Surgical resection
Surgical resection represents potentially curative treatment option for carefully selected patients. Surgery is the mainstay of HCC treatment. Resection and transplantation achieve the best outcomes in well-selected candidates (5-year survival of 60–80%), and compete as the first option in patients with early tumors on an intention-to-treat perspective. Tumor recurrence complicates 70% of cases at 5 years, reflecting either intrahepatic metastases (true recurrences) or the development of de novo tumors. Presently, there is a lack of effective adjuvant therapies to prevent recurrence after resection. Several strategies to prevent and treat recurrence have been tested in the setting of randomized studies. Interferon is the most frequently evaluated drug so far. Further studies in the adjuvant settings are required.

Liver transplantation
Liver transplantation is the first treatment choice for patients with small multinodular tumors (≤3 nodules ≤3 cm) or those with single tumors ≤5 cm (Milan Criteria) and advanced liver dysfunction including decompensated cirrhosis (Child–Pugh B and C cirrhosis). Selected “optimal candidates” reported 70% 5-year survival with a recurrence rate below 15%.

The major drawback of liver transplantation as a treatment of HCC is the scarcity of donors. Increases in waiting time have led to 20% of transplant candidates dropping out of the lists before receiving the procedure. Since HCC can progress while patients are on the transplant list, loco regional bridging therapies such as chemoembolization and radiofrequency ablation (RFA) are routinely employed to maintain the tumor burden within Milan criteria and prevent dropout on the waiting list.

Loco regional therapy
In patients with early stage HCC who are not eligible for resection or transplantation, several forms of loco regional therapies, such as radiofrequency ablation (RFA), percutaneous alcohol injection (PEI), cryoablation and transarterial therapies, can be used.

The major drawback of liver transplantation as a treatment of HCC is the scarcity of donors. Increases in waiting time have led to 20% of transplant candidates dropping out of the lists before receiving the procedure.
Local ablation is considered the first line treatment option for patients at early stages not suitable for surgical therapies. PEI causes coagulation necrosis of tumors by cellular dehydration. Thermal ablative therapies are classified as either hyperthermic treatments (heating of tissue at 60°C) including radiofrequency ablation (RFA), microwave ablation and laser ablation or cryoablation (freezing of tissue at -20°C and -60°C). Most procedures are performed using a percutaneous approach, although in some instances ablation with laparoscopy is recommended.

RFA causes thermal necrosis to tumors by delivering electromagnetic energy through single or multiple needle electrodes inducing a wider region of complete tumor necrosis, and because of this has largely replaced PEI. The decision regarding which technique to employ is usually based on tumor size, tumor location, presence of portal vein thrombus, and local expertise. RFA is the preferred ablative technique for patients with small tumors located away from major vessels and diaphragm and is currently the first-line therapy employed in this patient group. However, RFA can be associated with pain, intraperitoneal bleeding, tumor seeding, hepatic abscess formation, bile duct injury and hepatic decompensation. Further, RFA also has limitations in terms of tumor location where it may be contraindicated in certain areas of the liver due to the potential damage to adjacent tissues and loss of efficacy due to large blood vessels causing the heat-sink phenomena.

Microwave ablation, laser ablation and cryoablation have been proposed for local ablation in HCC. Microwave ablation has an important advantage compared to RFA, which is that treatment efficacy is less affected by vessels located in the proximity of the tumor.

Non-chemical non-thermal ablation techniques are currently undergoing clinical investigation. Irreversible electroporation is currently in clinical evaluation, after pre-clinical positive approach.

**Trans-arterial therapies – transarterial chemoembolization (TACE)**

For patients presenting with intermediate stage HCC, transarterial chemoembolization (TACE) is the standard clinical treatment. The dual blood supply of the liver and arterializations of HCC allows the administration of chemotherapeutic and embolizing agents selectively into the artery supplying the tumor.

Randomized studies have established TACE as the standard of care for asymptomatic patients with multinodular HCC with no vascular invasion and with Child–Pugh class cirrhosis. The most common complication in patients treated with TACE is a postembolization syndrome occurring in more than 50% of patients.

More centers are now using the recently developed doxorubicin-loaded drug-eluting beads TACE (DEB-TACE-DC Bead®; Biocompatibles UK Ltd, Farnham, UK) since delivery with this strategy increases the intratumoral delivery of cytotoxic drugs in a predictable manner that limits systemic adverse events. DEB-TACE minimizes a number of variables inherent with conventional, lipiodol-based TACE technique by using a uniform size of beads with predefined doses of chemotherapy.

Transarterial brachytherapy or radioembolization is another palliative treatment for intermediate stage HCC. Radioembolization involves hepatic arterial injection of yttrium-90 microspheres (Y-90) as glass (TheraSphere®; Nordion, ON, Canada) or resin (SIR-Spheres®; Sirtex Medical, Sydney, Australia). The Y-90 particles are smaller in size than the drug-eluding beads used for TACE. Their smaller size allows them to be preferentially trapped at the capillary bed leading to less tumor ischemia and angioeneogenesis.

**Combination TACE and sorafenib**

Since angioeneogenesis plays a major role in the pathogenesis of HCC, the combination of TACE and angiogenesis inhibitors like sorafenib for intermediate stage HCC has strong rationale. A number of combination strategies are under investigation. Currently, the combination of TACE and sorafenib is undergoing evaluation as part of a multinational, randomized, placebo-controlled trial.
**Systemic therapy**

Sorafenib, an oral multi-tyrosine kinase inhibitor, was the first and remains the only drug that has demonstrated survival benefits in patients with advanced HCC. Following an initial Phase II study showing a signal of efficacy, the large double-blinded placebo controlled Phase III SHARP trial was conducted, leading to positive survival results. In this trial, the benefit of sorafenib was to increase the median overall survival from 7.9 months in the placebo group to 10.7 months in the sorafenib group (HR = 0.69; 95% CI, 0.55–0.87; p = 0.00058), which represents a 31% decrease in the relative risk of death. In addition, sorafenib showed a significant benefit in terms of time to progression (TTP) assessed by independent radiological review with a median TTP of 5.5 months for sorafenib and 2.8 months for placebo.

The magnitude of survival benefit was similar to that demonstrated in a parallel Phase III trial conducted in the Asian-Pacific population, in which hepatitis B was the main cause of HCC. In this later trial, the median overall survival was 6.5 months in the sorafenib group versus 4.2 months in the placebo group (HR = 0.68; 95% CI, 0.50–0.93; p = 0.014). The worse outcome of patients included in this trial, regardless of treatment allocation, compared with the SHARP investigation, is due to the fact that the patients had more advanced diseases (ECOG 1–2 or metastatic disease). From these trials, sorafenib emerged as well tolerated; the most common grade 3 drug-related adverse events observed in these studies included diarrhea and hand-foot skin reaction, which occurred in 8–9%, and 8–16% of patients, respectively. Drug discontinuation due to adverse events was 15% in the sorafenib arm and 7% in the placebo arm. Drug-related adverse events were considered manageable, and no death related with toxicity was described. As a result, sorafenib received the European Medicines Agency (EMEA) authorization in October 2007 and was approved by the U.S. Food and Drug Administration (FDA) in November 2007.

The panel of experts recommends using sorafenib as the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child–Pugh A class) and with advanced tumors – BCLC C – or those tumors progressing on loco-regional therapies (concept of treatment migration). No clear recommendation can be made in Child–Pugh B patients, although cohort studies have reported a similar safety profile in patients of this class with no decompensation. It is recommended to maintain sorafenib at least until progression, and beyond that point second-line studies can be considered. Sorafenib is currently being tested in the adjuvant setting after resection or complete local ablation for early stages, in combination with chemoembolization for intermediate stages, in combination with erlotinib or systemic doxorubicin in advanced stages and as first-line treatment in Child–Pugh B patients.

Sorafenib remains the only approved systemic treatment for advanced tumors. Considering that no biomarkers are able to predict response to sorafenib and recent trials have not provided treatment alternatives, the development of novel and innovative therapies is crucial.

**Drugs under clinical development**

**mTOR inhibitors.** Rapamycin (sirolimus) and its analogs (temsirolimus and everolimus) are agents blocking the mTOR signaling cascade and have been tested in preclinical and early clinical investigations. Everolimus, an mTOR blocker approved for kidney cancer therapy, is being tested in Phase III for a second line indication.

**EGFR inhibitors.** Five EGFR inhibitors have been tested: erlotinib, gefitinib, cetuximab, lapatinib and vandetanib. Erlotinib showed activity in a Phase II study with mixed HCC populations with median survival of 13 months, and is currently being tested in combination with sorafenib in Phase III. The other drugs either have not shown meaningful signals of efficacy in Phase II, such as gefitinib and lapatinib, or are still in early stages of investigation.

**Anti-angiogenic agents.** Sunitinib is an oral multi-tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma, gastrointestinal stromal tumors and pancreatic neuroendocrine tumors. A recent multicenter, open-label sorafenib-controlled randomized Phase III trial was prematurely discontinued for safety issues and futility reasons. This drug is presently not recommended for treatment of HCC.
**Brivanib alaninate.** Brivanib, an oral VEGFR and FGFR tyrosine kinase inhibitor, was evaluated in two Phase II studies in first and second-line patients with an advanced tumor. The median overall survival was 10 months in the first-line treated group and 9.8 months in the second-line treated group, with manageable adverse events. However, Brivanib in two randomized Phase III clinical trials in the first-line (BRISKFL) and second-line (BRISK-PS) settings has not shown promising results.

**Bevacizumab.** Bevacizumab, a recombinant, humanized monoclonal antibody directed against VEGF, has been evaluated as single agent or in combination with erlotinib or chemotherapy. Data from Phase II clinical trials suggests that bevacizumab may be a relatively effective and tolerable treatment for advanced HCC. Despite the initial encouraging results, there is no Phase III development plan for bevacizumab. Large-scale randomized controlled trials are needed to further characterize the efficacy and safety profile and determine which patients are most likely to benefit from treatment.

**Linifanib,** an oral tyrosine kinase inhibitor targeting VEGF and PDGF, and ramucirumab, a monoclonal antibody against VEGFR2 are currently being tested in Phase III studies in first-line and second-line indication, respectively. As per preliminary results of Phase III multicentre study comparing linifanib to sorafenib, linifanib failed to demonstrate superiority or non-inferiority in terms of OS when compared with sorafenib (linifanib: 9.1 mo; sorafenib: 9.8 mo; P = NS). Other new anti-angiogenic agents, such as vatalanib, axitinib, cediranib, and Pazopanib are at very early stages of investigation.

**Combinations of antiangiogenics with chemotherapy** are being evaluated. Based on encouraging data from a Phase II trial of sorafenib plus doxorubicin, a Phase III randomized study of sorafenib plus doxorubicin compared with sorafenib alone (CALGB 80802) is underway in patients with advanced HCC. Examples of ongoing Phase II trials include the combination of sorafenib with gemcitabine/oxaliplatin (GEMOX), modified FOLFOX, or capecitabine/oxaliplatin. Antiangiogenics are also being combined with targeted therapies.

**C-mesenchymal-epithelial transition factor-1 inhibitor (c-MET).** C-MET is a membrane receptor that is essential for hepatocyte and tissue remodeling of liver after hepatic injury. The activation of c-MET is implicated in the proliferation, invasion and metastases of cancer cell. Tivantinib is an oral tyrosine kinase inhibitor of c-MET. A randomized Phase II trial comparing the use of tivantinib vs. placebo as the second line treatment, showed that the TTP was slightly improved in the tivantinib arm (tivantinib 1.6 mo; placebo 1.4 mo; P = 0.04). In particular, a more obvious improvement of TTP was noted in patients with tumors over expressing c-MET (tivantinib arm: 2.7 mo; placebo arm: 1.4 mo; HR = 0.38, 95%CI: 0.18-0.81, P = 0.01). Currently, a Phase III study is underway to compare tivantinib vs. placebo in subjects with c-MET over expressing HCC who have failed one prior systemic therapy.

Carbozantinib is an oral TKI with activity against both c-MET and VEGFR-2. Phase III clinical trial testing the efficacy of carbozantinib in the second-line setting is currently underway.

**Histone deactylase inhibitor.** A Phase I/II clinical trial assessed HDAC inhibitor, belinostat, for treatment of advanced HCC. Amongst the 42 patients treated in the Phase II portion, reasonable efficacy was demonstrated in a heavily pretreated population, with disease stabilization rate of 47.6% and PFS of 2.64 months. In the aforementioned Phase II trial on HCC, it was shown that tumors with high HR23B histoscores is associated with a higher rate of disease stabilization (P = 0.036). Further studies are required to study the clinical role of HR23B as predictive biomarker in HCC.

**Pexastimogene devacirepvec (Pexa-Vec) or JX594.** Oncolytic viruses (OVs) are tumor-selective, multi-mechanistic antitumor agents. With genetic engineering of OVs and rational combinations further potentiate OVs as cancer vaccines. JX-594 (Pexa-Vec) is an oncolytic and immunotherapeutic vaccinia virus. It is also engineered to express GM-CSF, which activates a systemic immune response to kill tumor cells throughout the body.
In a randomized dose-finding Phase II trial in patients with advanced liver cancer, high dose Pexa-Vec was associated with significantly improved survival (P=0.02; median survival duration 14.1 mo vs. 6.7 mo). Pexa-Vec was well-tolerated at both high and low doses with the most frequent adverse events consisting of flu-like symptoms lasting less than 24 hours. Phase III trial to assess Pexa-Vec followed by sorafenib in the first-line treatment of patients with advanced HCC is planned. In summary, OVs properly armed or in rational combinations are potent therapeutic cancer vaccines.

Medical review summary
Despite concerted efforts, molecular targeted therapy has demonstrated only modest benefit to date in the treatment of advanced HCC. Since sorafenib’s approval, multiple multikinase inhibitors as single agents and in combination have been compared with sorafenib in large randomized Phase III trials. Unfortunately, these regimens failed to improve survival rates or show better tolerability with equal efficacy.

A better understanding of the molecular hepatocarcinogenesis is critical for identifying novel targets. Alternatively, it might require moving beyond the antiangiogenesis approach and targeting cell autonomous pathways, such as the hepatocyte growth factor (HGF)/c-MET, PI3K/AKT/mTOR, or Wnt/β-Catenin or FGF/FGFR pathways. Additional pathways and their role in targeted therapy such as the extrinsic/intrinsic apoptotic pathway, Hedgehog signaling, JAK/STAT signaling, TGF-β signaling, Notch pathway, ubiquitin–proteasome pathway, nuclear factor-jB signaling, cell cycle control, and the role of the tumor microenvironment have to be further defined. Similarly, the potential role of recently described oncoMIRs relevant to hepatocarcinogenesis should be confirmed by clinical investigations. Drugs targeting the immune system or cancer stem cells have also gained interest in HCC.

Imaging
Imaging plays a pivotal role in the management of patients with HCC or with chronic liver disease at risk of developing HCC.

Many staging systems are available to select and stratify patients for treatment: these staging systems rely on the tumor stage (size and number of lesions, vascular invasion, extra-hepatic extent), liver functional status, patient physical status and cancer-related symptoms. Treatment options are available for the management of patients with HCC and guidelines issued by EASL3 and AASLD2 provide a frame for the clinical management of patients and for clinical trials.

Imaging is used as part of surveillance of patients at risk of developing HCC, is used for local and extra-hepatic staging, to guide biopsy and to deliver local therapy such as percutaneous ethanol injection or TACE and to monitor response to therapy, recurrence or treatment complications.

Imaging HCC is unique in that it follows specific patterns related to the nature of tumor genesis and development and the associated comorbidity: HCC rarely occurs on a healthy liver and develops typically in and as a consequence of an underlying chronic liver disease, cirrhosis. The pattern of development of HCC is believed to follow a multi-step process of carcinogenesis with development of nodules and cellular transformations within nodules leading to HCC (Figure 4).

Each of these nodular transformations has an imaging pattern that can be identified with MRI and is characterized by signal changes within nodules seen by ultrasonography and MRI and vascular patterns seen with dynamic CT and MRI.
Detection of liver nodules can be part of surveillance programs for HCC of particular at-risk populations (patients with cirrhosis of any cause or chronic hepatitis B). Typically, active surveillance includes serology of the alpha-fetoprotein (AFP) and imaging with ultrasonography; CT and/or MRI are used to further characterize lesions, especially for the evaluation of the vascular profile on dynamic post-contrast series and for the extent of disease.

Regenerative or dysplastic nodules are typically small lesions that do not exceed 2 cm. Imaging characteristics of such lesions on ultrasound and CT or MRI allow for their characterization: smaller size, homogeneity and absence of a hypervascular profile represent usual features of benign pre-cancerous lesions (Figure 5).

Using the Barcelona Clinic Liver Cancer (BCLC) criteria, management of liver lesions based on size and imaging characteristics can be summarized as follows.
**Early Stage**  
*Lesions of 1 cm or more:*
Early stage HCC is typically silent and detection is usually made at a later stage when disease is more advanced.

Detection of a liver lesion of 1 cm or more within a cirrhotic liver is highly suspicious of HCC. If such a lesion displays a characteristic arterial hypervascular pattern on dynamic CT or MRI, biopsy is not needed to confirm the diagnosis of HCC. A second negative imaging dynamic study with CT or MRI is needed before referring to biopsy for confirmation of HCC.

The characteristic hypervascular pattern includes rapid uptake of contrast at the arterial phase followed by a rapid washout at the delayed portal/venous phase (Figure 6).

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**Figure 6 Typical MRI features of HCC.**
Low signal on T1-w imaging (a) and high signal on T2-w imaging (b), with arterial enhancement after Gd injection (c) and rapid washout with delayed peripheral enhancement of a pseudo-capsule (d).

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**Lesions less than 1 cm:**
These lesions are unlikely HCC and serial follow-up with ultrasonography is recommended to detect size changes that may correspond to HCC transformation. Dynamic imaging studies with CT or MRI are to be performed according to size.

Intent of treatment at early stage is curative, options include surgical resection, transplantation or local ablation (chemical: percutaneous ethanol injection, thermal: radio-frequency).

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**Intermediate to advanced stage**
The role of imaging in intermediate and advanced stages is to evaluate vascular invasion, typically the portal vein or its branches and the extent of disease to the regional porta hepatitis lymph node station and/or to other organs.

Large, infiltrative and/or multifocal HCC without nodal or extra-hepatic spread represents the intermediate stage HCC. Therapy of choice for this stage is delivered through arterial catheterization. Various protocols for pharmaceutical infusion and/or arterial embolization are employed as standard of care, these protocols are typically performed as a radiology interventional procedure with or without CT guidance.
Advanced stage HCC presents with extension to the portal vessels that is characteristic to HCC and/or a nodal or extra-hepatic extension. These patients are usually treated with sorafenib or enrolled in clinical trials with a systemic targeted therapy.

The role of imaging in this setting is to establish a baseline of tumor load and to monitor treatment effects over time for response and radiological progression.

**Monitoring therapy**

With the advent of the first positive trial in advanced HCC with sorafenib, the need for standardized monitoring tools for the evaluation of efficacy of systemic targeted therapies became apparent, in particular for phase II trials where time to progression is recommended as an endpoint.

Monitoring of therapy effects using the established RECIST criteria was the basis for the approval of sorafenib. The integration of the EASL and AASLD criteria that amend RECIST provides a frame for a standardized approach in the objective evaluation of HCC patients in clinical trials as an increasing number of novel targeted therapies are being tested. The amendments to RECIST were summarized in a new set of criteria, modified RECIST (mRECIST) that are specific to HCC.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RECIST</th>
<th>mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurability and response definition</td>
<td>Longest diameter of all target lesions</td>
<td>Longest vascular (viable) component of hepatic lesions</td>
</tr>
<tr>
<td></td>
<td>Same as RECIST for non-hepatic lesions</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>15 mm in short axis</td>
<td>20 mm in short axis for porta hepatitis lymph nodes</td>
</tr>
<tr>
<td>Ascites</td>
<td>Non-target lesion</td>
<td>Only if confirmed by cytology</td>
</tr>
<tr>
<td>New liver lesion</td>
<td>No size criterion</td>
<td>10 mm minimum and typical hypervascular pattern or subsequent 10mm interval growth at follow-up scan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Advantages</th>
<th>RECIST</th>
<th>mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonly used</td>
<td>Require “more” expert reviewers</td>
<td></td>
</tr>
<tr>
<td>“Validated” for sorafenib</td>
<td>Yet to be “validated”</td>
<td></td>
</tr>
<tr>
<td>Accepted by regulators for registration trials</td>
<td>To be discussed with regulators for registration trials</td>
<td></td>
</tr>
</tbody>
</table>

Median Technologies, a central imaging review service provider, provides technology and service solutions that enable lesion detection, quantification and tracking for longitudinal assessment of HCC patients (Figure 7). Image processing software allows semi-automated comparison of tumor burden in the liver, lymph nodes and other organs for a standardized endpoint evaluation of patients in clinical trials using the RECIST or the mRECIST criteria.
Lesions are segmented semi-automatically; size, volume and density of lesions are extracted for a longitudinal objective evaluation with RECIST and mRECIST.

**Figure 7 Snapshot of Median’s Lesion Management Solution displaying serial CTs of a patient with multifocal HCC.**

**Biomarker review**

The progression of hepatocellular carcinoma (HCC) is characterized by a lack of clinical symptoms until the disease has advanced, leading to greater lethality. Less than 50% of patients are diagnosed at the localized disease stage or have potentially curative treatments available at diagnosis. As a result, a great deal of effort has been put into the identification of markers for early detection and prognosis. However, HCC biomarkers and diagnostics often reflect not only the presence of liver tumors but also viral hepatitis, liver cirrhosis and inflammation. Therefore, the need to identify new markers and approaches for early detection, as well as prognosis, continues in the clinic. Targeted therapies in HCC are also being pursued, driving the development of markers predictive of response based upon the targets and mechanisms of action of the drugs. HCC oncogenic drivers and molecular classification are yet to be defined especially in comparison to more well-understood indications such as colon, breast or lung cancer. While Sorafenib remains the only targeted therapy approved in HCC, there are development programs targeting EGFR, IGF-IR, c-MET, PI3K and other pathways. Interestingly, some of the proposed prognostic markers are the same markers that may be predictive of response to targeted therapies approved or in development in this indication. The knowledge gained from the extensive diagnostic research may help guide the field towards a better understanding of HCC biology and the development of novel targeted agents.

**Detection and prognosis**

Alpha-fetoprotein (AFP) has been the primary HCC diagnostic tumor marker since it was first introduced over forty years ago. However, AFP’s involvement in liver regeneration means the marker is associated with not only HCC but also various other liver diseases. Serum AFP may be detected in up to 50% of patients with cirrhosis and chronic hepatitis.\(^\text{13}\) The poor specificity of the AFP test has led to further development of new cut-offs and use of modified AFP tests such as fucosylated AFP (AFP-L3) and Des-gamma-carboxy prothrombin (DCP; 2). Many additional serum protein markers for early detection have been identified, including DKK1, GP73 and PIVKA-II.\(^\text{14}\) The superiority of these tests versus AFP is not established although they may be combined with AFP to improve the specificity and sensitivity of the diagnostic test.
Recent studies linking changes in microRNA expression profiles and epigenetic changes of specific gene promoters to early detection of HCC have generated excitement in the field. These tests will require the same level of technical and clinical validation as other markers. In addition, adoption of miRNA and epigenetic tests has not occurred in the diagnostic market and it is not clear if a small number of miRNA will provide sufficient unique information to support a diagnosis.

A large number of potential prognostic biomarkers and tests have been explored to inform treatment decisions in HCC related to standards of care. For example, CD151 and CXCL5 levels have been linked to surgical approaches, AFP and LDH for transarterial chemoembolization (TACE) and PIVKA-II and VEGF for radiofrequency ablation (RFA). More generally, serum markers such as AFP, Ang2, VEGF, HGF, TGF-β and MIF and tissue markers, including CXCL5, Capn4, M-CSF and various immune cells have been reported to be predictive of outcome in HCC. Future prognostic tests may follow expression of stem cell markers such as CD90, CD133, CD13 and EpCAM. Enumeration of circulating tumor cells (CTC) has also been explored as a novel prognostic approach. Clinical evidence has been obtained to support the utility of this method following curative resection. The development of more sensitive CTC isolation platforms in order to make the approach useful in a larger percentage of patients may make this method more feasible in the clinic.

### Biomarkers for targeted therapies

Sorafenib has been a primary focus for targeted therapy research in HCC and continues to influence our understanding of the disease. The proposed mechanism of action of Sorafenib in HCC is thought to be via cell proliferation and death as well as angiogenesis. No predictive biomarkers have been clinically validated for Sorafenib in HCC despite suboptimal patient response to the drug. VEGF-A has been a focus for biomarker research for Sorafenib, similar to other angiogenesis inhibitors. While VEGF is over-expressed in HCC, other growth factors such as PDGF, FGF and other more novel proteins are also expressed and may also influence response to targeted therapies. Tests for VEGF-A are technically challenging, due to multiple forms and binding proteins, and continue to hinder researchers in the field. The finding that Bevatumab, another VEGF pathway and angiogenesis inhibitor, was ineffective in HCC also challenges use of this marker. A recent report indicated that VEGF-A amplification may be predictive of response to Sorafenib in HCC through a cell proliferation mechanism rather than angiogenesis. This result may reflect the complexity of targeted therapies and predictive biomarkers in HCC. Predictive biomarkers for other targeted therapies may be similar to other indications including c-MET and IGF-IR over-expression or over-expression of the receptor ligands. However, genetic alterations such as amplification or mutation have not been found or successfully utilized in this indication to support drug approval and use. Emerging drug targets in HCC include notch, TGF-β, hedgehog and beta-catenin although those targets may present more limited biomarker options due to the lack of assays and reagents for research and test development.

### Summary

Future development of biomarkers in HCC may follow a more systems biology, global approach as has been suggested by recent genomic and proteomic studies. The current classification systems including the Cancer of the Liver Italian Program, the Barcelona Clinic Liver Cancer system, the Chinese University Prognostic Index, and the Japanese Integrated Staging schema may also not reflect the molecular complexity of the disease. The development and use of new classification systems and further exploration of sensitivity and resistance mechanisms to current therapies will identify new drug targets as well as new diagnostic markers.
Section 2 – Quintiles’ experience

Operational aspects
Choosing the right countries and sites is critical to the success of an HCC cancer program. Careful country/site identification represents the major mechanism by which patient recruitment can be facilitated. Initial country/site recommendations for a given trial should be based on a data-driven process which includes a country algorithm and site tiering based on weighted variables tailored to the success of the specific studies. Using a variety of data sources, Quintiles has developed a preliminary country ranking algorithm for HCC studies that includes the characteristics and key success factors summarized in Table 3.

Table 3 Country ranking algorithm data points and source

<table>
<thead>
<tr>
<th>Data points</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintiles historical start-up timeline</td>
<td>Quintiles regulatory database</td>
</tr>
<tr>
<td>Estimated patient population</td>
<td>GLOBOCAN 2008</td>
</tr>
<tr>
<td>Past enrolment rates in similar studies</td>
<td>Quintiles investigator database</td>
</tr>
<tr>
<td>Number of experienced investigators</td>
<td>Quintiles investigator database</td>
</tr>
<tr>
<td>Quintiles indication experience (overall studies)</td>
<td>Quintiles investigator database</td>
</tr>
<tr>
<td>Global indication experience</td>
<td>Biopharm clinical</td>
</tr>
<tr>
<td>Number of competing studies</td>
<td>Biopharm clinical</td>
</tr>
<tr>
<td>Number of patients targeted by studies recruiting</td>
<td>Biopharm clinical</td>
</tr>
<tr>
<td>Impact of competing trials</td>
<td>Biopharm clinical</td>
</tr>
</tbody>
</table>

Table 4 indicates the result of this country ranking methodology in HCC as of May 2014. This ranking is updated on an ongoing basis, depending on available data. Also, the ranking is tailored to the needs of each specific study, taking into account the key challenges and success factors. The resulting tiering is specific and tailored to the needs of each protocol.

Table 4 Country tiering for HCC

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium, Canada, China, Italy, France,</td>
<td>Australia, Austria, Czech Republic,</td>
<td>Argentina, Bosnia, Brazil, Bulgaria,</td>
</tr>
<tr>
<td>Germany, Malaysia, Poland, Philippines,</td>
<td>Egypt, Finland, Latvia, Greece, Hong</td>
<td>Chile, Colombia, Croatia, Estonia,</td>
</tr>
<tr>
<td>Russia, Singapore, Spain, South Korea,</td>
<td>Kong, India, Japan, Mexico, Serbia,</td>
<td>Denmark, Hungary, Indonesia, Ireland,</td>
</tr>
<tr>
<td>Taiwan, Thailand, Ukraine, UK and U.S.</td>
<td>South Africa, Vietnam</td>
<td>Israel, Jordan, Lebanon, Lithuania,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Netherlands, New Zealand, Norway, Peru,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Portugal, Romania, Saudi Arabia, Slovakia,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sweden, Switzerland, Turkey, United Arab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emirates</td>
</tr>
</tbody>
</table>

Quintiles has an extensive database of investigators with HCC cancer experience, including a total of 1713 sites across 56 countries. Having access to this large network of sites allows Quintiles to efficiently run HCC cancer trials in all the regions of the globe.

Quintiles can implement the most efficient strategy specifically tailored for each protocol or program based on customer needs and preferred marketing and regulatory tactics.
At Quintiles, our site relationships are a top priority. We have constructed a worldwide network of elite Partner and Prime sites, which typically recruit at a rate above that of non partner sites. As shown in Table 5 and Figure 8, considering our network of site we do have 76 classified as Prime Sites and 287 classified as Partner sites. In addition to recruiting at a rate above those of non-partner sites, these sites offer time savings during the start-up process.

Quintiles’ knowledge of patient-referral patterns on a global basis enables quick identification of key investigators and maximization of referrals.

### Table 5 Total HCC cancer sites per region in Quintiles network

<table>
<thead>
<tr>
<th>Region</th>
<th>Non-partner</th>
<th>Partner</th>
<th>Prime</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific</td>
<td>246</td>
<td>39</td>
<td>7</td>
<td>292</td>
</tr>
<tr>
<td>Europe/Middle East/Africa</td>
<td>540</td>
<td>164</td>
<td>24</td>
<td>728</td>
</tr>
<tr>
<td>Japan</td>
<td>37</td>
<td></td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>Latin America</td>
<td>101</td>
<td>22</td>
<td></td>
<td>123</td>
</tr>
<tr>
<td>North America</td>
<td>426</td>
<td>62</td>
<td>45</td>
<td>533</td>
</tr>
<tr>
<td>Total</td>
<td>1350</td>
<td>287</td>
<td>76</td>
<td>1713</td>
</tr>
</tbody>
</table>

### Figure 8 Summary of HCC cancer sites in Quintiles’ database

- **Tier 1: Optimal**
  - 130 partner/prime sites and 320 non-partner sites
  - Actual metrics in liver cancer and HCC trials with Quintiles: High performing sites

- **Tier 2: Good**
  - 233 partner and 70 non partner sites
  - These sites have also enrolled well in liver cancer and HCC trials but have not had an enrollment rate that would consider them a high performing site. These sites are still considered valuable and have performed at or slightly below the country median average for these trials. All partner sites, regardless of performance in liver cancer and HCC trials have also been placed in this tier.

- **Tier 3: Viable**
  - 960 non partner sites
  - Sites that have experience in liver cancer and HCC trials with Quintiles but do not have actual metrics to measure for tier 1 or 2, or the metrics are below the country median. This tier also includes sites that were no enrollers in liver cancer and HCC trials and sites that have self stated capability but have no metrics in liver cancer and HCC trials.

In the past 10 years Quintiles has provided services for close to 30 hepatocellular carcinoma studies (30% Phase I, 37% Phase II and 33% Phase III) involving approximately 5900 patients, in 2115 project sites in 38 countries worldwide.
The average enrollment rate globally across all the studies within the Quintiles Investigator Performance database since 2005 (12 studies with enrollment data) is 0.28 patients/site/month. This rate is included as a general indicator for planning purposes. Enrollment performance by study and country is highly variable based on protocol design and the indication landscape at the time of study startup, and therefore this rate needs to be confirmed through a feasibility exercise for each protocol based on design, the regions countries involved and the level of the investigator's interest.

The presence of competing trials can affect the availability of both patients and sites for clinical trial participation. An examination of the trial landscape was conducted using www.biopharmclinical.com, which includes data retrieved from www.clinicaltrials.gov and other public sources globally. A search on 14 May 2014 found over 633 trials globally with 313 trials open for enrollment (256 interventional, 56 observational and 1 expanded access), of which 283 were recruiting.

For each new protocol being started, it is extremely important to conduct a specific assessment of the competitive landscape, taking into account the patient population being targeted. However, it is also important to have a full knowledge of the competitive environment at a given site, so that the site can ensure that it has enough staff and resources to manage all clinical and administrative tasks.
Quintiles recommends that the following recruitment strategies (to be included in a global Recruitment Strategy Plan – RSP) are considered for HCC cancer trials:

1. Engage and motivate the investigators to actively recruit appropriate HCC patients from their site and
2. Support investigators in driving referrals from their existing referral network.

**Figure 10 Suggested recruitment strategies for HCC trials**

**HCC recruitment strategies**

- **Leverage data from previous study with the same compound to keep study at the top of the PI’s mind**
- **Patients pre-identification prior to Site Initiation Visit**
- **Study Branding and Investigator tools (I/E cards, protocol reference booklets, posters) and patient-facing materials**
- **Recruitment milestones delivery**
- **Site Recruitment Action Plan (SRAP) agreed by the sites with the CRA**
- **Investigator Portal to serve as a communication “hub”**
- **Referral partners – “bridging tools” study brochures, lunch-and-learn slide presentations, and posters**

**Figure 11 Support investigators in driving referrals**

**Outreach to referral network**

Identify qualified HCC patients across multidisciplinary teams

- Raise study awareness
- Educate staff about HCC study and eligibility criteria
- Facilitate patient identification via pre-ID website

To reach out to referring physicians, which types of tools have been most effective?

- 2012 Quintiles survey (N=731)

- **Letter**: 47%
- **Email**: 47%
- **Brochure**: 32%
- **PowerPoint slides**: 37%
- **Website**: 23%
- **Tools not needed**: 14%
- **Referrals not common**: 14%

**HCC trials in Asia – challenges and opportunities**

Asia is a very attractive solution for HCC clinical trials, both early and later phase studies, as HCC is largely concentrated in countries with developing economies such as Asia.
### Table 7 Challenges, solutions and opportunities in conducting HCC trials in Asia

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of patient awareness about clinical trials</td>
<td>Patient education</td>
<td>Large HCC patient population</td>
</tr>
<tr>
<td>Asian patients traditionally rely on local herbal remedies</td>
<td>Physician-patient relationship</td>
<td>Cost effective patient recruitment</td>
</tr>
<tr>
<td>Smaller hospitals in smaller cities</td>
<td>Support physician engagement and influence</td>
<td>Large hospital infrastructures in larger cities</td>
</tr>
<tr>
<td>Patient advocacy groups are not prevalent</td>
<td>Targeting physicians/investigators who are a part of specific consortiums</td>
<td>Increasing pool of trained and motivated clinical researchers</td>
</tr>
<tr>
<td></td>
<td>Robust training and oversight critical for success and quality data outputs</td>
<td>Untapped source of physicians/investigators and potentially treatment naïve patients</td>
</tr>
</tbody>
</table>

One important contributing factor to the appeal of HCC trials in Asia is the cost of research in Asian countries which in general is significantly less than the cost in Western countries such as USA and Europe. Considering a typical large Phase III trial conducted on a global basis, the cost per patient for a patient randomized in Asia Pacific region could be in the range of 40 to 60% lower than the cost for the same patient in U.S. and Western Europe. With well informed strategies and clinical study designs to accommodate the nuances of Asia, along with limited treatment options, and a large population base with high HCC incidence, conducting HCC studies in Asia provides an opportunity to cost effectively recruit more patients across a smaller pool of sites than otherwise would be possible in more developed countries.

The health care system also supports clinical research in Asia, with large hospital infrastructures and an increasing pool of trained and motivated clinical researchers especially in larger cities. Conversely, smaller hospitals with inadequate research set-up are prevalent in smaller locales and are not optimal. However, they do represent an untapped source of physicians/investigators and potentially treatment naïve patients. Robust training and oversight would be critical for success and quality data outputs.

For almost all South East Asian countries, patients are seen and treated by both hepatologists and medical oncologists. Both specialists are equally suitable and acceptable as investigators for HCC studies. However, if mRECIST for HCC is utilized, appropriate training of relevant personnel (optimally radiologist) is required.

There are several factors that must be considered in managing HCC clinical trials in Asia. Lack of patient awareness about clinical trials, including patient participation and compliance are several such factors. Patient advocacy groups are not prevalent in Asia. Furthermore, Asian patients traditionally rely on local herbal remedies. Patient education regarding treatment options is important in managing compliance and minimizing confounding factors. Physicians are critical in this process based on physician-patient relationship and can help overcome apprehension and scepticism of non-traditional treatments, thereby allowing patients to tap into clinical trials as an option for treatment. In Asia specifically, it is the physician-patient relationship which is important in fostering patient interest in the study. Consequently, physician engagement and influence are key factors in managing patient recruitment.

Targeting physicians / investigators who are a part of specific consortiums, such as the Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group or the Korean Liver Cancer Study Group (KLCSG), assures investigator interest, engagement and more focused recruitment.
<table>
<thead>
<tr>
<th>Country</th>
<th>Sorafenib reimbursement status</th>
<th>Country considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>N</td>
<td>Clinical benefit of sorafenib is not seen as relevant in China; consequently no reimbursement is provided for sorafenib. In addition, many Chinese patients cannot afford drugs not covered by insurance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on the World Cancer Report 2014 issued by The International Agency for Research of Cancer, approximately 50% of total new cases of HCC in the world are from China. It is important to involve the Chinese Society for Clinical Oncology (CSCO), the largest oncologist association in China. Given the long duration expected to obtain regulatory approval, it is necessary to upfront carefully plan China involvement taking into consideration the number of patients required from China and the overall study duration. Export of biological samples requires an export permit per shipment; the application process of which is complicated and lengthy.</td>
</tr>
<tr>
<td>India</td>
<td>Y</td>
<td>Generic sorafenib is available at specific institutions (CGHS, Railway Hospital, ESI, etc.) and is reimbursed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCC cases are prevalent in India but under diagnosed and under reported. There are few specific institutes which specialize in treating them. Advanced cases are treated by Medical Oncologists at local centers. There are specific regulatory processes to be followed which can be challenging, vis-a-vis the consenting process and patient compensation requirements.</td>
</tr>
<tr>
<td>Indonesia</td>
<td>N</td>
<td>Require Material Transfer Agreement (MTA) approval from National Institute of Health Research and Development (NIHRD) to export specimens out of Indonesia.</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>N</td>
<td>No additional considerations.</td>
</tr>
<tr>
<td>Japan</td>
<td>Y</td>
<td>HCC is not as prevalent in Japan compared to some other Asian countries, so recruitment would be challenging if there are competing trials.</td>
</tr>
<tr>
<td>Malaysia</td>
<td>N</td>
<td>If the source of any ingredient of the Study Drug (Investigational Product/placebo/comparators) contains porcine and/or bovine, it may be culturally unacceptable.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>However, Bayer HealthCare provides a Patient Assistance Programme (NexPAP). Bayer and the Malaysian Liver Foundation offer sorafenib to eligible patients diagnosed with inoperable liver cancer after they have completed two months’ treatment with the drug.</td>
</tr>
<tr>
<td>Philippines</td>
<td>N</td>
<td>Same regulatory requirements as other clinical trials. Some institutions do not approve pharmacogenomics testing.</td>
</tr>
<tr>
<td>Singapore</td>
<td>N</td>
<td>Same regulatory requirements as other clinical trials. Applicant to obtain RA’s Clinical Trial Certificate and is required to assume responsibilities as local importer for medical devices used in clinical trials (e.g., needles, tubes, ECGs – anything not sourced locally and/or not registered locally).</td>
</tr>
<tr>
<td>South Korea</td>
<td>Y</td>
<td>30% co-payment system covered by national health insurance. Sorafenib is reimbursed for patients with unresectable advanced or metastatic HCC who fulfil the criteria: (1) Stage III; (2) Child-Pugh A; (3) ECOG Performance 0-2.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Private insurance is not a significant factor. However, Patient Compensation Rule is required for RA/IRB submission. A Korean Pharmaceutical Traders Association (KPTA) letter must accompany each shipment (import) of investigational drug.</td>
</tr>
<tr>
<td>Taiwan</td>
<td>Y</td>
<td>Sorafenib is reimbursed for patients with metastatic or inoperable advanced HCC with Child-Pugh A.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The ICF must specify any genetic testing and specific gene(s) to be tested, including how long the sample will be stored for. The central lab address to manage the sample has to be listed on ICF. Furthermore, the Sponsor must provide a warranty letter to state the sample will be used per Taiwan law and regulations.</td>
</tr>
<tr>
<td>Thailand</td>
<td>Y</td>
<td>Civil Services Medical Benefit Scheme, CSMBS, for government officers and their family which covers 10% of population.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No additional considerations.</td>
</tr>
<tr>
<td>Vietnam</td>
<td>Y</td>
<td>Very limited reimbursement. Sorafenib only reimbursed 50% for patients with progressed liver cancer only.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No challenge in conducting HCC trials in Vietnam based on patient need – there are few who can afford treatment.</td>
</tr>
</tbody>
</table>
Competition for HCC trials is particularly strong in Asia Pacific. Quintiles adds value based on our longstanding presence in the region (since 1995) and well established/proven oncology relationships. Asia-based service lines include clinical operations, clinical project management, data management, regulatory affairs, pharmacovigilance, medical and scientific services, quality assurance and central laboratory. Operations have grown organically and Quintiles is now well-established in five sub-regions including: South East Asia and Korea, Australia and New Zealand, India, Greater China and Japan.

Quintiles’ established connections with key opinion leaders and HCC consortiums include but are not limited to Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group, Chinese Society for Clinical Oncology (CSCO), Taiwan LiverNet Consortium and Japan Clinical Oncology Group (JCOG).

**Conclusion**

Despite concerted efforts, molecular targeted therapy has demonstrated only modest benefit to date in the treatment of advanced hepatocellular carcinoma (HCC).

Since sorafenib’s approval, other regimens failed to improve survival rates or show better tolerability with equal efficacy.

A better understanding of the molecular hepatocarcinogenesis is critical for identifying novel targets. Future development of biomarkers in HCC may follow a more systems biology, global approach as has been suggested by recent genomic and proteomic studies that performed broad, unbiased biomarker discovery. The current classification systems may also not reflect the molecular complexity of the disease. The development and use of new classification systems and further exploration of sensitivity and resistance mechanisms to current therapies will identify new drug targets as well as new diagnostic markers.

Given the unmet need, an expansion of the clinical development plans for new drugs in this indication is predicted.

Quintiles is the ideal partner for clinical development of new drugs for HCC. Quintiles combines medical expertise with global/regional operational experience and presence which particularly includes Asia Pacific, a key focus area for HCC trials.

Quintiles’ team of medics within the Oncology Therapeutic Area and Asia Pacific Region can support the sponsor team to make sure the final study design is feasible and in line with desired objectives. In addition, Quintiles’ Translational Medicine team within Center for Integrated Drug Development can provide recommendations and support for the clinical, laboratory and biomarker strategies for drug development as well as the development of innovative tools for targeted drugs and companion diagnostics.

As an integral part of our HCC study management, Median Technologies, a central imaging review service provider, provides technology and service solutions that enable lesion detection, quantification and tracking for longitudinal assessment of HCC patients.

**Acknowledgment**

The authors would like to thank Rick Turner for medical writing assistance.
References


About the authors

**Giovanni Piazzi, Biol. Sc., PMP**
Therapeutic Strategy Lead, Therapeutic Strategy and Medical Delivery, Oncology, Quintiles
Giovanni Piazzi has 21 years’ clinical trials experience, including 13 years in the Quintiles Oncology Therapeutic Area focusing exclusively on the execution and project management of large global oncology trials. His experience as Clinical Project Manager encompasses a wide variety of different cancers type and project phases. In his current role as Therapeutic Strategy Lead, combines strategic and operational expertise to help customers with delivery strategies for projects and programs. Prior to joining Quintiles he worked at Synthélabo and SmithKline Beecham.

**Alma Panganiban**
Medical Director, Asia Medical Sciences Group, Quintiles
Dr. Panganiban has more than 8 years experience in Oncology and academia and is Board Certified in Medical Oncology. She has served as Medical and Scientific Advisor in different clinical trials in Asia in several oncology indications including HCC. She has led clinical protocol development and implementation for compounds in clinical trials across indications in oncology and Hematology. Prior to joining Quintiles, she was the Medical Director in Eli Lilly Philippines and the Regional Oncology Medical Advisor for South East Asia and Pakistan. She provided strategic guidance and medical support to the clinical trials conducted in these regions. In her current role at Quintiles, she has been the medical advisor for Phase I, II and III trials with oversight and responsibilities for managing various aspects of clinical trials.

**Swati Ranade, MBBS, DA, DNB**
Associate Medical Director, Asia Medical Sciences, Quintiles
Dr. Swati Ranade has more than 13 years of total experience, with extensive experience in Clinical trials; having worked in both pharmaceuticals and CRO over a period of 10 yrs. She has served as Medical and Scientific Advisor in different therapeutic areas including oncology, diabetes, cardiovascular / metabolic. She has led early clinical development of NCEs and Biosimilars in several of these therapeutic areas including clinical implementation for compounds in clinical trials for breast cancer, hematologic malignancies, head and neck cancer and lung cancer. In her current role at Quintiles, she has been the medical advisor for Phase I, II and III trials with medical oversight and responsibilities for execution of large global trials. Prior to joining Quintiles, she worked at Wockhardt India Ltd and Daiichi Sankyo India.
About the authors

Brad Smith, PhD
Vice President Translational Medicine, Quintiles
Brad supports laboratory, clinical and diagnostic strategies for drug development as well as the development of innovative tools for targeted drugs and companion diagnostics. Previously, Dr. Smith led Corporate Development at Cell Signaling Technology, an innovative biotechnology company in the life sciences field. In this position, Dr. Smith focused on new diagnostic and clinical partnerships and markets. His previous positions at Cell Signaling Technology include management of research and clinical technology development departments and laboratories. Previous to Cell Signaling Technology, Dr. Smith directed product development and production at Santa Cruz Biotechnology, helping to build that company into one of the largest supplier of research tools for basic research. Dr. Smith's scientific background includes research positions at Stanford University and University of California, San Francisco focused on cellular signaling mechanisms of disease. Dr. Smith holds a Doctoral degree from Stanford University and Master's and Bachelor's degrees from University of California, Santa Cruz.

Zorica Spadaccini, PhD
Associate Clinical Project Manager Director, Oncology, Asia Pacific Delivery Unit, Quintiles
Zorica Spadaccini, PhD has over 20 years experience in the pharmaceutical industry and CRO setting, encompassing regulatory, project management and clinical functional areas. Dr. Spadaccini has been with Quintiles for the past 6 years and prior to joining Quintiles worked in Australia and the US in both CRO and pharma roles, including Pfizer and Shire. Dr. Spadaccini has experience in devising strategy for global drug development and in FDA interactions, having designed, implemented and interpreted trials in a number of therapeutic areas, including oncology. Her experience encompasses execution and project management of Phase Ib dose escalation and PK studies through to pivotal large Phase III global trials.

Souhil Zaim, MD
Chief Medical Officer, Median Technologies
Dr. Zaim is a board-certified radiologist with over 20 years of experience in imaging for clinical trials. Dr. Zaim trained and practiced as a clinical radiologist at the University hospital in Paris VI, France and spent 4 years at the University of California, San Francisco as an Assistant Professor of Radiology. Prior to joining Median, he spent 12 years at Synarc Inc., a central core lab exclusively dedicated to clinical trials. Dr. Zaim has authored over thirty publications in imaging in oncology and arthritis, most of which have data from clinical trials or observational epidemiological studies.