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ORIGINAL PAPER

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Design and rationale for the non-interventional Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) study

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SUMMARY

Background: Hepatocellular carcinoma (HCC) is a complicated condition influenced by multiple confounding factors, making optimum patient management extremely challenging. Ethnicity, stage at diagnosis, comorbidities and tumour morphology affect outcomes and vary from region to region, and there is no common language to assess patient prognosis and make treatment recommendations. Despite recent efforts to reduce the incidence of HCC, most patients present with unresectable disease. Non-surgical treatments include ablation, transarterial chemoembolisation and the multikinase inhibitor, sorafenib, but their effects in all patient subgroups are not known and further information is needed to optimise the use of these treatments. **Aims:** The Global Investigation of Therapeutic DEcisions in Hepatocellular Carcinoma and Of its Treatment with SorafeNib (GIDEON) study (ClinicalTrials.gov identifier NCT00812175; http://clinicaltrials.gov/) is an ongoing global, prospective, non-interventional study of patients with unresectable HCC who are eligible for systemic therapy and for whom the decision has been taken to treat with sorafenib under real-life practice conditions. The aim of this study is to evaluate the safety and efficacy of sorafenib in different subgroups, especially Child-Pugh B where data are limited. **Discussion:** This study will recruit 3000 patients from > 40 countries and follow them for approximately 5 years to compile a large and robust database of information that will be used to analyse local, regional and global differences in baseline characteristics, disease aetiology, treatment practice patterns and treatment outcomes, with a view to improve the knowledge base used to guide physician treatment decisions and to improve patient outcomes.

What's known
- HCC is a complex disease influenced by multiple confounding factors that vary from region to region, making optimum patient management extremely complex.
- Sorafenib is an oral multikinase inhibitor with proven efficacy in patients with unresectable HCC, but data in Child-Pugh B are limited.
- There is a need to fully evaluate existing treatments in all patient subgroups to optimise their use.

What's new
- GIDEON will generate data from 3000 patients to evaluate the effects of sorafenib in different patient subgroups, and the resulting large database will be used to analyse local, regional and global differences that influence patient prognosis and management, with a view to refine HCC staging and evaluation and better inform treatment decisions

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, but because of the poor prognosis associated with this disease, it is the third most common cause of cancer-related death (1). Over 80% of patients with HCC are in developing countries, with particularly high incidence rates in sub-Saharan Africa and Southeast Asia (1). There is a low incidence of HCC in developed countries such as the USA, Australia and the UK, but these rates are rising (2).

Risk factors for the development of HCC have been well documented and include the presence of cirrhosis, infection with hepatitis B and C viruses, heavy alcohol intake, diabetes and obesity (1,2). Although surveillance and vaccination programmes have reduced the incidence of HCC in certain populations (3,4), the majority of patients still present with unresectable disease and are unsuitable for surgery. Current treatments for unresectable disease include loco-regional interventions and systemic therapies, although further data on all treatments are required to fully understand their potential, e.g. in patient groups not included in clinical trials.

Non-surgical loco-regional treatment options include ablation therapy and transarterial chemoembolisation (TACE). Ablation therapy is associated with a 5-year survival rate of 40–70%, with best responses seen among patients with single tumours

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and preserved liver function (5). However, TACE is recommended for patients with large/multifocal tumours with no vascular invasion or extra-hepatic spread and is associated with objective response rates of 16–60% (3). Although survival benefits have been reported in only two randomised controlled trials (RCTs) (6,7), a robust meta analysis showed that the treatment with TACE was associated with significant improvements in 2-year survival vs. control (8). However, TACE treatment has a number of important limitations. Residual tumour growth following treatment means that treatment repetition is necessary. Additionally, many of the clinical studies investigating TACE have used a wide range of treatment strategies, including different types of embolic particle, chemotherapy, emulsifying agent and numbers of treatment sessions. For this reason, there is no clear evidence to support an optimum treatment strategy (9). Also, TACE therapy is only possible in patients where the arterial blood supply to the tumour can be isolated, and is not recommended in patients with portal vein thrombosis, those with Child-Pugh C liver function or those with a total serum bilirubin level > 3 mg/ml, as all of these factors have been identified as predictors of poor prognosis in patients treated with TACE (9). Finally, treatment with TACE is associated with considerable side effects; the most commonly reported being postembolisation syndrome that occurs in > 50% of treated patients (3). Other less frequent but more serious complications include hepatic abscess and cholecystitis. Further research is therefore needed to optimise TACE treatment strategy and ensure treatment efforts are directed at patients who will most likely benefit.

Systemic therapies investigated for unresectable HCC have included single-agent and combination chemotherapy regimens, but their efficacy has been disappointing and their use is no longer recommended (9). More recently, the Sorafenib HCC Assessment Randomized Protocol trial, a multicentre, Phase III, double-blind, placebo-controlled trial of 602 Western patients with unresectable HCC, showed that treatment with the oral multikinase inhibitor, sorafenib (Nexavar®; Onyx Pharmaceuticals, Inc., Emeryville, CA, USA; Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ, USA; Bayer Schering Pharma AG, Berlin, Germany), was associated with a significant improvement in survival compared with placebo [median overall survival (OS) of 10.7 months vs. 7.9 months for sorafenib and placebo respectively, $p < 0.001$] (10). As a result, sorafenib is the first systemic anticancer therapy indicated for treating these patients (9). Similar benefits (median OS of 6.5 months vs. 4.2 months for sorafenib and placebo respectively, $p = 0.014$) were reported in a Phase III, randomised, double-blind, placebo-controlled trial of 226 patients with unresectable HCC from the Asia-Pacific region, thus confirming the efficacy of sorafenib in a broad geographic patient population (11). However, all patients included in these two large RCTs had preserved liver function (Child-Pugh A), and our knowledge regarding the efficacy of sorafenib in patients with hepatic impairment is limited to small subgroups of patients from Phase I and II studies (12,13). Further studies to evaluate the efficacy of sorafenib among all patient groups are therefore needed.

Current treatment guidelines for unresectable disease are therefore based on the best available evidence, including non-randomised trials, case studies and expert opinion; however, significant data gaps exist. Further evidence is needed to fully evaluate current treatment options and optimise their use to improve patient outcomes.

Against this background, the Global Investigation of Therapeutic DEcisions in Hepatocellular Carcinoma and Of its Treatment with SorafeNib (GIDEON) study is an ongoing global, non-interventional study (NIS) of patients with unresectable HCC who are to receive sorafenib as part of their standard clinical care. The study should produce the largest, most robust database of information on factors influencing treatment and outcome of patients with HCC. This manuscript will include details of the GIDEON aims and objectives, study design, target recruitment and timeline. It will also describe the planned analyses and discuss how it is hoped that findings from this study will allow us to gain a detailed understanding of the factors that influence the prognosis and management of these patients, and how this in turn will help us to refine HCC staging and evaluation, better inform treatment choices and ultimately improve outcomes for patients with HCC.

The GIDEON study

Aims, objectives and rationale for GIDEON

Non-interventional studies, or observational studies, are postauthorisation safety studies (PASS) that are usually conducted to gain further information about a licensed product. Observational studies are characterised by the fact that assignment to a particular therapy strategy is not mandated by a study protocol but reflects the participating physician's current practice. The physician alone decides which treatment, if any, is appropriate. In NIS, the decision to include a patient in a study is separate from the treatment decision. Furthermore, no additional diagnostic or monitoring interventions are mandated for the patient as a result of inclusion in an NIS. NIS serve a wide range of purposes but are of particular value

in providing information in wider populations or subgroups not covered in RCTs (14). NIS also enable information to be gathered on other parameters not usually assessed in the clinical trial setting, such as patient acceptance and compliance, physician adherence to information and directions for use and prescription behaviour. The importance of NIS in the literature is increasingly recognised, and guidelines were developed to improve the analysis and reporting of observational studies (15). NIS provide opportunities to enhance the evidence base for established drugs and therapies and increase understanding of the impact of treatments in real-world practice (14).

GIDEON is a global, prospective NIS of patients with unresectable HCC who are candidates for systemic therapy and for whom the decision has been taken to treat with sorafenib. It was initiated to fulfil the postapproval commitment to organisations such as the European Medicines Agency to gather data on the safety and efficacy of sorafenib in patients with Child-Pugh B liver function. Additional goals are to compile a large and robust database of HCC treatment patterns and outcomes among patients with unresectable disease who are candidates for systemic therapy, to answer clinically relevant questions and gain a better understanding of the safety of sorafenib with loco-regional therapies, given either concomitantly or sequentially. Data will also be gathered in the USA and possibly other regions on the characteristics, disease course and treatment outcomes of patients with newly diagnosed HCC or recurring disease after curative treatments, who are not candidates for systemic therapy with sorafenib.

Based on these goals, the primary objective of GIDEON is to evaluate the safety of sorafenib in patients with unresectable HCC in real-life practice conditions. Secondary objectives are to: evaluate the efficacy [OS, progression-free survival (PFS), time to progression (TTP), response rate and stable disease rate] of sorafenib in these patients; determine the duration of therapy according to various patient characteristics; evaluate methods of patient evaluation, diagnosis and follow-up; assess comorbidities and their influence on treatment and outcome in real-life practice rather than a controlled clinical trial setting and evaluate the practice patterns of the physicians involved in the care of these patients.

This study was conducted according to established regulations and recommendations relating to the conduct of NIS; volume 9A of the Rules Governing Medicinal Products in the European Union (16). When required, documented approval from the appropriate ethics committee(s)/institutional review board was obtained for all participating centres prior to the study, according to Good Clinical Practice and local laws, regulations and organisations.

Establishing a global NIS

GIDEON is a Phase IV, international, prospective, open-label, multicentre, non-interventional PASS of patients with unresectable HCC receiving sorafenib under real-life conditions. Approximately, 3000 eligible patients will be recruited by participating physicians from > 40 countries across Europe, Latin America and the Asia-Pacific region and from the USA (Figure 1) and will be observed from the start

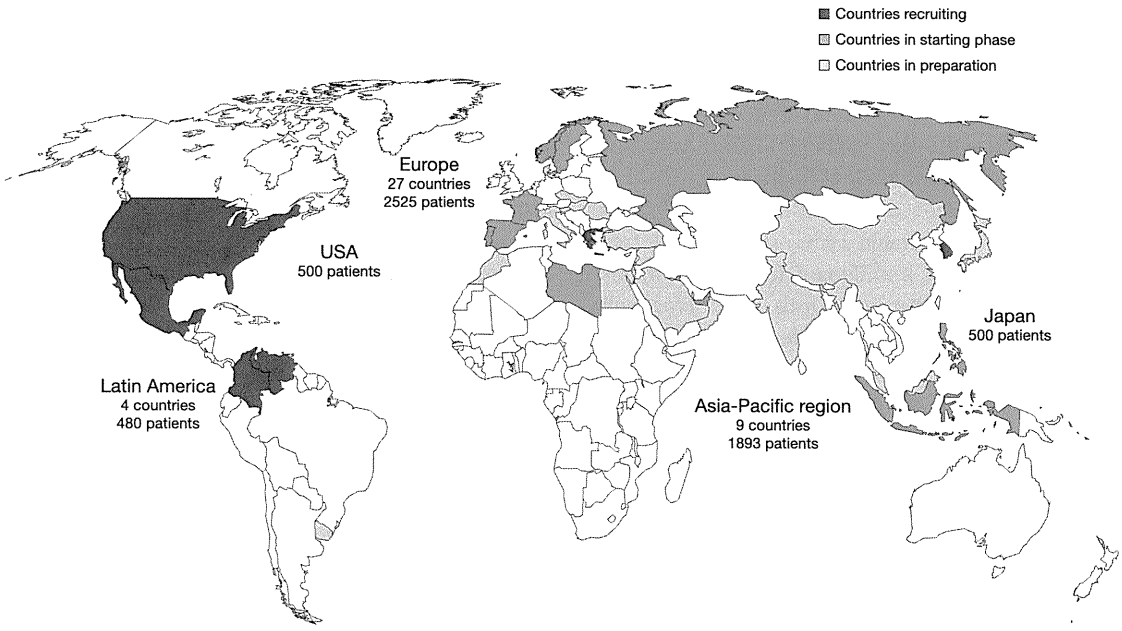


Figure 1 The global reach of GIDEON

of sorafenib therapy to patient withdrawal, loss to follow-up, death or final visit.

An overview of the GIDEON timeline and planned analyses is shown in Figure 2. The first patient's first visit was recorded in January 2009 and the last patient's first visit is anticipated to occur in quarter four of 2012. Interim analyses for safety will be conducted after 500 and 1500 patients have been recruited and followed for 4 months, with the final analysis anticipated in quarter two or three of 2014. The study will end 12 months after enrolment of the 3000th eligible patient, irrespective of whether the final patient dies or not, is lost to follow-up or survives.

Patients to be included in GIDEON

Patients with histologically or cytologically documented or radiographically diagnosed unresectable HCC who are candidates for systemic therapy, and for whom a decision has been made to treat with sorafenib, are eligible for inclusion in GIDEON if they have a life expectancy of > 8 weeks and have provided signed informed consent. Patient exclusion criteria are based on the approved local product information for sorafenib.

Data collection

All data will be collected using case report forms (CRFs). These will be available as paper and electronic versions, with participating countries and their sites able to choose the format of preference. Data will be collected from all enrolled patients at study entry and start of sorafenib, then at intervals normally used by the prescribing physician (estimation: ≥ 6 to ≤ 12 weeks), or until patient death, withdrawal or loss to follow-up, or if significant changes in a patient's disease are observed. All data will be verified through spot site monitoring, which will take place at up to 10% of all sites involved in the study. An overview of the visit schedule and data collected at each visit is shown in Figure 3. Study end-points are summarised in Figure 4. All adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria version 3.0 (National Cancer Institute, Bethesda, MD, USA), and their likely relationship to sorafenib therapy will be documented. Tumour assessments will be made by computed tomography or other equivalent radiographical method and will be evaluated using the Response Evaluation Criteria in Solid Tumors.

The population of patients who entered this study and received at least one dose of sorafenib will be valid for intent-to-treat safety and efficacy analysis. However, patients who received sorafenib in the past will be excluded from efficacy analysis. All baseline demographic data will be summarised for the intent-to-treat population. AEs and other safety parameters, including blood pressure, Child-Pugh grade and Eastern Cooperative Oncology Group performance status (ECOG PS), will be summarised using the safety population.

Planned subgroup analyses conducted globally, regionally and by country will include: the impact of baseline characteristics on safety, particularly Child-Pugh B; the relationship between baseline characteristics and efficacy; the duration of sorafenib therapy and reasons for discontinuation; the effect of other treatments for HCC on outcome and the impact of different practice patterns on outcome. In addition, subgroup analyses for specific regions may be conducted, such as: an evaluation of common treatments for HCC in Asia; referral and diagnostic patterns in Europe; duration of treatment, tolerability and compliance in Latin America and patient selection for loco-regional therapy in Japan. However, all subgroup analyses performed will depend on the actual data collected.

Statistical considerations for GIDEON

An overall sample size of 3000 patients with unresectable HCC treated with sorafenib is expected to be

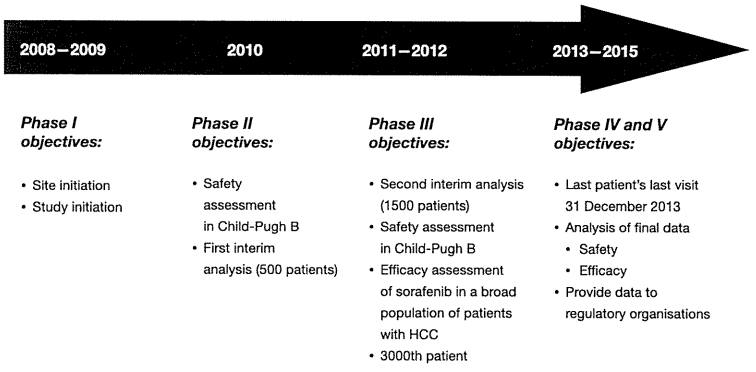
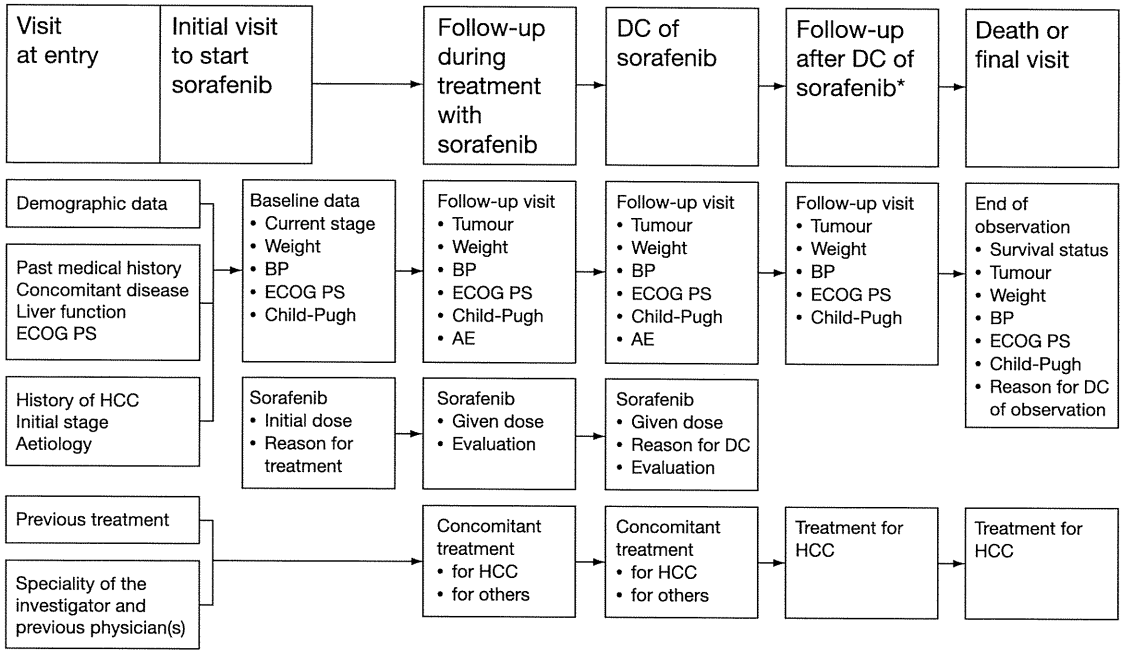
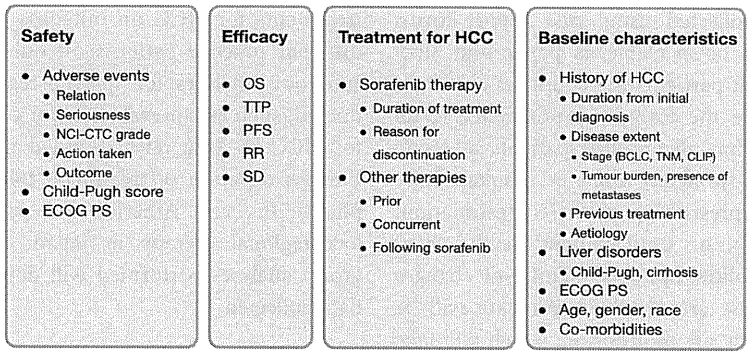


Figure 2 An overview of the GIDEON timeline and planned analyses



*Applicable if patient discontinues therapy, is alive and not lost to follow-up
AE, adverse event; BP, blood pressure; DC, discontinuation;
ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma

Figure 3 GIDEON patient assessment schedule



BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; NCI-CTC, National Cancer Institute-Common Toxicity Criteria; OS, overall survival; PFS, progression-free survival; RR, response rate; SD, stable disease; TNM, tumour node metastases; TTP, time to progression

Figure 4 Overview of the GIDEON safety, efficacy, treatment and baseline patient assessments and end-points

sufficient to allow for evaluation of safety of the overall population as well as specific subgroups. With this sample size, there would be an 84% chance of observing an AE with a true incidence of 1% in at least 25 patients.

All baseline, safety and efficacy data were analysed using descriptive statistics. Kaplan–Meier estimates were calculated for the OS, PFS and TTP efficacy end-points. At the time of the analyses, any patient alive or lost to follow-up, without disease progression or death or without documented radiological progression will be censored at the last date of evaluation for OS, PFS and TTP analyses, respectively. Exploratory subgroup analyses of efficacy and safety data may also be performed, stratified by prognostic/predictive baseline factors such as stage, Child-Pugh score, ECOG PS, region and age, as appropriate. Data regarding administration of sorafenib such as duration, given dose, continuation or discontinuation of therapy and dose modification of sorafenib therapy, including reason(s) for discontinuation, will be summarised in a descriptive manner. Treatments for HCC other than sorafenib before, during and after therapy with sorafenib will be summarised descriptively as per available data. The sample size was calculated to collect data to allow for sufficient

evaluation of safety monitoring of all treated patients. Interim analyses are planned during the study primarily for summarising and monitoring safety data, and will be conducted after 500 patients and 1500 patients are enrolled and have been treated on study for at least 4 months.

Discussion

What will GIDEON achieve?

GIDEON is a global PASS initiated to collect more information on the safety and efficacy of sorafenib in patients with unresectable HCC. This is the largest prospective HCC NIS in the world, which will enrol 3000 patients from > 40 countries globally. The compilation of a database of this size in HCC has not previously been undertaken; as no other global registries exist in this area, it is anticipated that the data collected here will be an important contribution to our knowledge and will help to answer important and clinically relevant questions relating to the natural disease course of HCC and liver dysfunction, long-term efficacy and safety of sorafenib therapy, physicians' practice patterns and patients' perspectives.

The number of factors influencing HCC and its disease course make it extremely difficult to accurately assess patient prognosis and make optimum treatment recommendations. The geographical variation of these factors has also prevented the establishment of a universal system to assess all patients. Findings from GIDEON could help to establish a globally applicable staging classification, which could facilitate the accurate and consistent assessment of all patients and help to provide a common language for the broad HCC multidisciplinary team on which to base treatment recommendations. In addition, as GIDEON will collect data regarding the differences in physician treatment practice patterns and outcomes, it may be possible to analyse these data with a view to optimise the role of all members of this large multidisciplinary team and streamline patient care.

Although potentially curative therapy via surgical resection or transplant is possible for some patients with HCC, there is a lack of cadaveric transplants available, and the majority of patients are unsuitable for surgery at presentation. In addition, the recurrence rate of HCC after curative treatment is high and the long-term curable rate is low (17). Thus, non-surgical treatments play a central role in the management of these patients. However, there is still a relative shortage of RCTs to fully evaluate these treatments in all patient subgroups, and more work is needed to fully understand the benefits of each of these treatments and to establish their place in the HCC treatment armamentarium. One of the main focuses of GIDEON is to gain further information on the optimum duration of sorafenib therapy as well as the safety and efficacy of sorafenib in different subgroups of patients, especially patients who are generally excluded from RCTs to minimise errors or confounding factors in the study, i.e. patients who have moderate liver dysfunction (Child-Pugh B) where data are currently limited. However, information is also being gathered regarding the safety and outcomes following other treatments before, during and after sorafenib therapy; thus, it is anticipated that the information gathered in this study will help to improve our understanding of the risks and benefits associated with each of these treatment approaches, which could help us to establish an optimum treatment algorithm for these patients.

In addition to GIDEON, a large clinical trial programme for sorafenib is ongoing that should help us to fully establish its optimum place in therapy. One area of interest is the role of sorafenib as adjuvant therapy to improve survival of patients with HCC. To date, treatments such as radiotherapy and chemotherapy and their combination have been used to reduce tumour size and improve patients' quality of life (18). TACE has recently been shown to be the only palliative treatment that can benefit HCC patients ineligible for curative treatments because of advanced tumour stage or poor hepatic functional reserve; however, the survival gain appears marginal (19) and other effective treatments are urgently needed. Against this background, a large Phase III, randomised, double-blind, placebo-controlled trial of adjuvant sorafenib following either surgical resection or local ablation is currently in progress (STORM study) (20). The primary end-point is recurrence-free survival, with secondary end-points including time to recurrence and OS. Estimated accrual to this trial is 1100 patients and data are due to be reported in 2014.

Another area of interest is the efficacy of sorafenib in combination with, and subsequent to, TACE therapy. A large randomised Phase II trial has been initiated to evaluate the role of sorafenib in combination with TACE in the treatment of patients with intermediate disease (SPACE study) (21). Estimated enrolment to this trial is 350 patients, and final results are expected in late 2010. In addition to this, a Phase III, double-blind, randomised, placebo-controlled trial of sorafenib following TACE in Japanese patients with unresectable, advanced disease is ongoing (Japan post-TACE study) (22). The target recruitment of 414 patients has already been reached and final results are anticipated in early 2010.

Finally, the effects of sorafenib in combination with other targeted agents in HCC are also of

interest, and a large Phase III, randomised, double-blind trial evaluating the efficacy, safety and health-related quality of life of sorafenib plus erlotinib vs. sorafenib plus placebo for the first-line treatment of advanced HCC is in progress (SEARCH study) (23). The target recruitment for this study is 700 patients and the estimated final data collection date is July 2011.

These ongoing studies form a comprehensive and well-integrated clinical trial programme, which will provide data from several points in the treatment pathway. GIDEON is also a key component of this programme, as it will provide data from the entire unresectable patient population treated under real-life conditions, not in a non-restrictive setting and within the approved indication, and will enable the collection of data from populations not commonly included in RCTs, such as those with Child-Pugh B liver function. Thus, in addition to the ongoing interventional studies, the information collected in GIDEON will significantly contribute to the current body of evidence, which helps inform treatment decisions.

What are the limitations of GIDEON?

The information gathered in GIDEON will form a large and robust database that will be analysed to improve our understanding of the global, regional and local differences in patient demographics, disease course and treatment outcomes, with a view to improve our knowledge base and improve patient outcomes. However, as this is an observational NIS, it is associated with a number of limitations. The lack of randomisation to specific treatment arms and the lack of a placebo-control arm will limit any robust evaluation of the efficacy of any of the treatments received by these patients during the course of the study. Comparisons between sorafenib-treated and untreated patients in the USA will be limited because of the small sample size of patients in the USA who will not receive sorafenib. The value of some subgroup analyses may also be limited by small patient numbers, although these analyses may still be hypothesis-generating and could help direct future research. However, given these limitations, it will be important to consider findings from GIDEON together with emerging data from large RCTs, to fully evaluate the safety and efficacy of these treatments and draw any definitive conclusions.

Another possible limitation in GIDEON is that all data will be collected via the completion and submission of CRFs, which could delay data collection and evaluation. However, electronic versions of the CRF have been compiled with a view to facilitate this process and to reduce any lengthy delays in completing and analysing the data collected.

As with any observational study, a number of biases may also exist. The lack of blinding of either the treating physician or the patient to study treatment may introduce a bias in reporting treatment outcomes. It is also possible that physicians engaged in GIDEON may be more likely to choose sorafenib therapy for a larger proportion of their patients than would be representative of normal treatment practice patterns in that area, although all patients receiving sorafenib therapy must be eligible according to the locally approved product information for sorafenib. Finally, while study procedures regarding data collection and verification are in place for GIDEON, it should be noted that in an NIS, potential exists for less robust data than might be expected from an RCT.

Conclusions

GIDEON is the largest global, prospective, open-label NIS ever conducted among patients with unresectable HCC. The study was initiated to further evaluate the safety and efficacy of sorafenib in different patient subgroups, including Child-Pugh B. The collection of information regarding patient baseline demographics, disease aetiology, treatments and outcomes from approximately 3000 patients worldwide, over a period of approximately 5 years, will also enable the compilation of a large and robust database that will be used to analyse local, regional and global differences, with a view to answer some important questions and fill significant data gaps. It is therefore anticipated that findings from GIDEON, together with data from large RCTs, will help improve the knowledge base used to guide physician treatment decisions and may enable physicians to make better informed treatment choices and ultimately improve patient outcomes.

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Author contributions

All authors are members of the Global Steering Committee for the GIDEON study and have been involved in the discussion and modification of the GIDEON protocol. All authors provided critical review of the manuscript and approved the final version for publication.

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REVIEW ARTICLE

Current status of molecularly targeted therapy for hepatocellular carcinoma: clinical practice

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Abstract In recent years, molecular-targeted agents have been used clinically to treat various malignant tumors. In May 2009, sorafenib (Nexavar®) was approved in Japan for "unresectable hepatocellular carcinoma (HCC)", and was the first molecular-targeted agent for use in liver cancer. To date, sorafenib is the only molecular-targeted agent whose survival benefit has been demonstrated in two global phase III randomized controlled trials, and it has now been approved worldwide. Phase III clinical trials are now underway to compare other molecular-targeted agents with sorafenib as first-line treatment agents, and to evaluate other multi-kinase inhibitors of the vascular endothelial growth factor and platelet-derived growth factor receptors, as well as drugs targeting the epidermal growth factor receptor, insulin-like growth factor receptor, and mammalian target of rapamycin, in addition to other molecules targeting other components of the signal transduction pathways. This review outlines the main pathways involved in the development and progression of HCC and the agents that target these pathways.

Keywords Hepatocellular carcinoma · Molecular-targeted agent · Sorafenib · Sunitinib · Brivanib · Complete remission

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Introduction

Advances in molecular cell biology over the last decade have clarified the mechanisms involved in cancer growth, invasion, and metastasis, and enabled the development of molecular-targeted agents, best represented by trastuzumab for breast cancer, imatinib and rituximab for hematopoietic tumors, and gefitinib and erlotinib for lung cancer. These molecular-targeted agents are broadly classified into two categories: drugs targeting cancer cell-specific molecules and nonspecific molecular-targeted drugs for molecular biological abnormalities induced in the host stroma or blood vessels by the presence of cancer. Examples of the former approach include: trastuzumab, which targets HER2, the expression of which is a poor prognostic factor for breast cancer; rituximab, which is used to treat B cell lymphoma, and targets CD20 expressed on normal and neoplastic mature B cells; and imatinib, which binds to the ATP-binding site of Bcr-abl, a protein that causes chronic myelogenous leukemia. However, no critical target molecules responsible for treatment response have been identified in hepatocellular carcinoma (HCC).

In recent years, clinical trials have been conducted for many agents that act on growth factor receptors (for example epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR)) and intracellular signaling pathways. In addition, multi-kinase inhibitors, including sorafenib, have emerged and have been evaluated. Clinical trials are now ongoing to compare drugs with the same mechanism of action and to test the combined efficacy and relative merits of these drugs with existing drugs for many cancers. Because the main treatment option for metastatic, advanced stage cancers, for example breast and colorectal cancer, is systemic chemotherapy, clinical trials are ongoing to investigate how to

combine molecular-targeted agents with standard therapies based on the results of long-term, large-scale clinical trials, and to identify which molecular-targeted agents should be used as initial or second-line therapy. However, for HCC, background liver damage limits the indication for systemic chemotherapy and no anti-cancer drugs were found to be effective in a large-scale randomized controlled trial (RCT). However, now that the usefulness of sorafenib has been demonstrated in clinical trials, the development of drugs that are effective for poor-prognosis advanced HCC with distant metastasis and vascular invasion is eagerly awaited.

Signaling pathways and molecular-targeted agents in HCC

As in other cancers, the molecular mechanisms involved in the development and progression of HCC are complex. It has been shown that, after HBV/HCV infection and alcohol or aflatoxin B1 exposure, genetic and epigenetic changes occur, including oncogene activation and tumor-suppressor gene inactivation, because of an inflammation-induced increase in hepatocyte turnover and oxidative stress-induced DNA damage. Through apoptosis and cell proliferation, these changes lead to the multistep development and progression of a hyperplastic to dysplastic nodule, early HCC, and advanced HCC. A number of studies have reported changes in gene expression, chromosomal amplification, mutations, deletions and copy number alterations (gain/loss), somatic mutations, CpG hypermethylation, DNA hypomethylation, and molecular abnormalities, which can constitute therapeutic targets [1–5].

The binding of growth factors to their receptor proteins activates protein-phosphorylating enzymes, thus activating a cascade of proliferative signaling pathways to transmit proliferative signals into the nucleus. Growth factors, for example epidermal growth factor (EGF), transforming growth factor (TGF)-α/β, insulin-like growth factor (IGF), and vascular endothelial growth factor (VEGF), also function in liver regeneration after injury, whereas fibroblast growth factor (FGF) and the platelet-derived growth factor (PDGF) family are involved in liver fibrosis and HCC growth [6–8]. The receptors for these growth factors are broadly classified into G-protein-coupled receptors and protein kinases. On ligand binding, these receptors activate their downstream intracellular molecules in a cascade fashion. Many of the growth factor receptors and oncogenes have tyrosine kinase activity, and the tyrosine kinases are classified into transmembrane receptor tyrosine kinases such as the EGFR and VEGFR, and cytoplasmic non-receptor tyrosine kinases such as Abl and Src. On the other hand, Raf, MAP kinase/ERK kinase (MEK), and mammalian target of rapamycin (mTOR) are serine/threonine kinases.

In general, the mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/Akt/mTOR, c-MET, IGF, Wnt-β-catenin, and hedgehog signaling pathways, and the VEGFR and PDGFR signaling cascades show altered activity in HCC, and agents targeting these pathways are under development (Fig. 1, Table 1) [9]. Many molecular-targeted agents are now under development; the target signaling pathways and growth factors are outlined below.

MAPK pathway (RAS/RAF/MEK/ERK)

The MAPK intracellular signaling pathway, which is mainly involved in cell growth and survival, and regulates cell differentiation, is upregulated in cancer cells. Therefore, this pathway has been extensively studied as a therapeutic target. The MAPK pathway is a common downstream pathway for the EGFR, PDGFR, and VEGFR, and is universally used for signal transduction downstream of cytokine receptors, integrin complexes, and G-protein receptors to Ras. The MAPK pathway also plays an important role in HCC in that its activation is reportedly involved in HCC growth and survival [5]. The downstream extracellular signaling-regulated kinase (ERK) is activated by two upstream protein kinases, which are coupled to growth factor receptors by Ras proteins. Ras, which is activated by ligand binding, activates Raf serine/threonine kinases and MEK (MAP kinase/ERK kinase), whereas MEK phosphorylates and activates ERK, which phosphorylates proteins involved in cell growth, apoptosis resistance, extracellular matrix production, and angiogenesis [10–13].

Raf and Ras inhibitors

Raf and Ras are proto-oncogenes. In particular, K-Ras mutations are commonly observed in many cancers, including pancreatic and colorectal cancers. One study reported that 30% of HCCs have Ras mutations [14]. To our knowledge, no agents targeting Ras are planned to enter clinical trials in the near future. However, because the binding of Ras protein to the cell membrane and its functional activation require farnesylation, several farnesyltransferase inhibitors are being tested for Ras-related tumors. In addition, vaccine therapy for mutant Ras proteins is currently being tested for solid cancers, including HCC.

The Raf family consists of three isoforms, A-Raf, B-Raf, and C-Raf/Raf-1. Genetic abnormalities, for example point mutations and gene rearrangements, have been reported in various cancers [15]; however, in HCC, *ras/raf* mutations

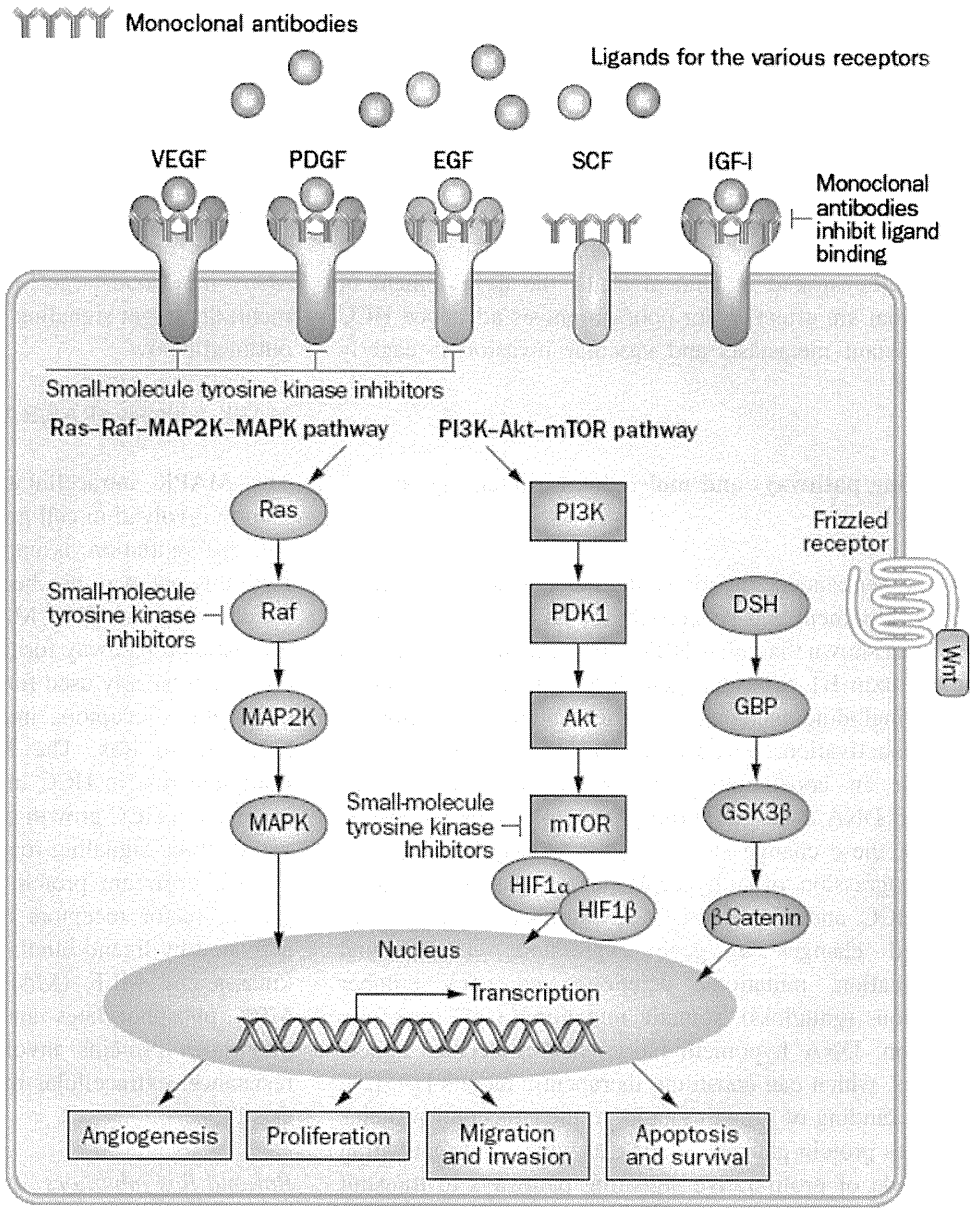

Fig. 1 Signaling pathways and the site of action of molecular-targeted agents (modified from Villanueva A et al. [3] and Llovet and Bruix [5])

are rare, and no *k-ras* or *b-raf* mutations have been detected [16]. On the other hand, wild-type Raf-1 was reported to be hyperactivated in many cancers, including HCC [17–19]. Sorafenib inhibits Raf, and has multiple characteristics in that it has strong inhibitory activity against Raf-1 (C-Raf) kinase, B-Raf (wild-type B-Raf and mutant V600E B-Raf) serine/threonine kinase, the pro-angiogenic receptor tyrosine kinases VEGFR, PDGFR, and FGFR1, and tyrosine kinases such as c-kit, Flt-3, and RET, which are involved in tumor progression and overall prognosis [20].

MEK

The MEK family consists of MEK1 and MEK2 proteins, which specifically phosphorylate tyrosine and threonine residues, and phosphorylates downstream Erk1 and Erk2 [21].

In an immunohistochemical study, MEK1/2 overexpression, ERK1/2 overexpression, and ERK1/2 phosphorylation were observed in 100% (46/46), 91% (42/46), and 69% (32/46) of HCCs, respectively, and the in-vitro treatment of HepG2 and Hep3B cells with MEK1/2 inhibitors inhibited cell growth and upregulated apoptosis [22].

The MEK inhibitors CI-1040, PD0325901, AZD6244, and RDEA119/BAY869766 have been tested in several cancers including solid tumors such as HCC. A phase II study of AZD6244 (selumetinib, ARRY-142866) and a phase I/II study of RDEA119/BAY869766 in combination with sorafenib are being conducted.

Table 1 Molecular-targeted agents being tested in HCC

Agent	Antiangiogenic targets					Antiproliferative targets				Antiepigenetic targets				Developmental status	Company
	VEGF	FGF	VEGFR	PDGFR	FGFR	EGFR	Raf	MEK	mTOR	RAR	RXR	HDAC	Heparanase		
Sorafenib[a] (Nexavar)			●	●			●							Approved	Bayer
Sunitinib[a] (Sutent)			●	●										Phase III stopped	Pfizer
NIK-333 (Acyclic Retinoid)										●	●			Phase II/III complete	Kowa
Brivanib			●		●									Phase III ongoing	Bristol-Myers Squibb
TSU-68			●	●	●									Phase II complete	Taiho
TAC-101										●				Phase II stopped	Taiho
Erlotinib (Tarceva)						●								Phase II complete	Roche
Bevacizumab (Avastin)	●													Phase II ongoing	GenentechA
AZD2171 (Cediranib)			●											Phase II recruiting	AstraZeneca
Gefitinib (Iressa)						●								Phase II complete	AstraZeneca
Lapatinib						●								Phase II ongoing	GlaxoSmithKline
Thalidomide	●													Phase II ongoing	TTY BioPharm
Linifanib			●	●										Phase III initiated Abott	
AZD6244								●						Phase II ongoing	AstraZeneca
PI-88	●	●											●	Phase II complete	Progen
Cecuximab						●								Phase II complete	Merck
RAD001									●					Phase III initiated	Novartis
PXD101 (Belinostat)												●		Phase I/II ongoing	Curagen

Sources: Trial Trove, ClinicalTrials.Gov (NCI), Evaluate Pharma, IMS Knowledge Link, Esplcom, IDdB3, BioPharm Insight, MedTrack

[a] Sorafenib and sunitinib also have antiproliferative affects through multi-tyrosine kinase inhibition

PI3K/Akt/mTOR pathway

The PI3K/Akt/mTOR pathway also plays an important role in cell growth, survival regulation, metabolism, and anti-apoptosis. The membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP_2) is phosphorylated by phosphatidylinositol 3-kinase (PI3K) into phosphatidylinositol 3,4,5-triphosphate (PIP_3), which binds to and activates the serine/threonine kinase Akt. The tumor-suppressor gene product PTEN (phosphatase and tensin homolog deleted on chromosome) is antagonistic to PI3K activity. PTEN is a lipid phosphatase that dephosphorylates inositol phosphates such as PIP_3. The inactivation of PTEN through gene deletion increases PIP_3 levels, and activates Akt, which inhibits apoptosis, leading to the development of tumors. The serine/threonine kinase mTOR is an important mediator in the PI3K/Akt pathway that binds intracellularly to a protein called raptor or rictor, and exists as two different complexes, complex 1 and 2 (mTORC1 and mTORC2). mTORC2 (mTOR-rictor) activates Akt whereas mTORC1 (mTOR-raptor) is activated downstream of Akt; thus, both molecules regulate protein synthesis [23].

A study of 528 HCC samples showed that expression of pAkt, PTEN, p27, and S6 ribosomal protein (pS6) was a poor prognostic factor for survival [24]. A tissue microarray analysis of HCC samples revealed that the loss of PTEN and overexpression of pAkt and p-mTOR were correlated with tumor grade, intrahepatic metastasis, vascular invasion, TNM stage, Ki-67 labeling index, and matrix metalloproteinase (MMP)-2 and (MMP)-9 upregulation, Meanwhile, PTEN mRNA expression in the cancerous tissue was downregulated, compared with that in the non-cancerous tissue. The levels of PTEN, MMP-2, and MMP-9 mRNA expression were correlated with tumor stage and metastasis, and the levels of PTEN and MMP-9 mRNA expression were inversely correlated [25]. In an extensive analysis of 314 HCC samples in terms of mutation analysis, DNA copy number changes, mRNA levels, and immunostaining, Villanueva et al. found that activation of the IGF pathway, upregulation of EGF, dysregulation of PTEN, and aberrant mTOR signaling were present in half of the samples, and that inhibiting mTOR activity with everolimus was effective in improved survival and suppression of recurrence [26].

The PI3K inhibitor RG7321 and the Akt inhibitor perifosine target the PI3K/Akt/mTOR pathway and are in early stages of clinical development, whereas the mTOR inhibitors everolimus (RAD001), sirolimus (Rapamune), and temsirolimus (CCI-779) are at more advanced stages of development. Everolimus is used to treat sorafenib-intolerant patients or for patients showing disease progression after sorafenib administration. A phase III study to compare everolimus and a placebo (EVOLVE-1: Advanced Hepatocellular Carcinoma after Disease Progression or Intolerance to Sorafenib *Ever*O*limus* for *LiV*er cancer *E*valuation) and a phase I/randomized phase II study (sorafenib + everolimus vs. sorafenib alone) to test the efficacy and tolerance of sorafenib in combination with everolimus are underway. Because mTOR inhibitors have cytostatic and antiangiogenic effects, they are expected to be effective in combination with other angiogenesis inhibitors such as bevacizumab, and may be appropriate for administration after transarterial chemoembolization (TACE). Furthermore, because the mTOR pathway is stimulated by factors such as EGFR, PDGFR, and TGFα, and is closely related to other signaling pathways including the Ras/Raf/MEK/ERK pathway, they are likely to show promising efficacy when used in combination with other growth factor inhibitors [27].

VEGF/VEGFR, PDGFR, FGFR

Angiogenesis is an important event not only for HCC but also for cancer growth and metastasis, and occurs because of complex alterations involving promoting factors such as VEGF, angiopoietin, and FGF, inhibitory factors including thrombospondin (TSP) and angiostatin and the surrounding tissue. The VEGF family consists of VEGF-A, B, C, D, and E, and placental growth factor (PIGF). The VEGFR family comprises VEGFR-1 (flt-1), VEGFR-2 (flk-1/KDR), and VEGFR-3 (flt-4). VEGF-A binds to VEGFR-1 and VEGFR-2 and is involved in angiogenesis and the maintenance of mature blood vessels, whereas VEGF-C and VEGF-D mainly bind to VEGFR-3, are involved in lymphangiogenesis [28, 29]. VEGF isoforms such as $VFGF_{121}$ and $VEGF_{165}$ have been identified, and isoform subtypes also exist, for example $EGF_{166}b$. Thus, it is clear that these growth factors do not exhibit angiogenesis-promoting effects alone, and they have attracted attention as new therapeutic targets [30].

HCC typically exhibits active angiogenesis. During the progression from early to well, and to moderately differentiated HCC, angiogenesis increases and cancer cells acquire the ability to invade vessels and metastasize. Scientific and clinical studies have revealed that, during the progression from hepatitis to cirrhosis, angiogenesis and disruption of the vascular architecture are linked to the progression of HCC, and contribute to increased hepatic vascular resistance and portal hypertension, and decreased hepatocyte perfusion [31]. In addition, a meta-analysis has demonstrated that VEGF expression is a prognostic factor in HCC [32].

Phase II studies have been started to test the usefulness of bevacizumab (Avastin®), which directly targets VEGF, in TACE-treated HCC, and the use of bevacizumab in

combination with erlotinib (Tarceva®), an EGFR tyrosine kinase inhibitor.

Sunitinib (Sutent®) is a multi-kinase inhibitor that inhibits tyrosine kinases such as VEGFR-1, 2, 3, PDGFR-α, β, and c-Kit. A phase II study of sunitinib in 37 advanced HCC patients showed that the median progression-free survival (PFS) and median overall survival (OS) were 3.7 and 8 months, respectively. In that study, adverse events included grade 3/4 thrombocytopenia in 37.8% of patients, neutropenia in 24.3%, asthenia in 13.5%, and hand–foot syndrome in 10.8% [33]. Because sunitinib has a lower IC_{50} for each target than sorafenib, it is expected to have greater antitumor activity. However, this factor may be responsible for the higher incidence of adverse events with sunitinib. The main evaluation item in the above phase II trial was the response rate, which did not reach the expected value, leading to the conclusion that it was a negative study [34]. In that study sunitinib was administered at 50 mg/day for 4 weeks followed by 2 weeks of rest per cycle [33], whereas Zhu et al. [34] used a dosing schedule of 37.5 mg/day for 4 weeks followed by 2 weeks of rest per cycle, and reported that the median PFS and OS were 3.9 and 9.8 months, respectively. An ongoing global cooperative phase III controlled clinical trial to compare sorafenib and sunitinib head-to-head and to seek approval for first-line indications for advanced HCC adopted a sunitinib dosing schedule of 37.5 mg/day. However, in a "Reflection and Reaction" regarding these trial results, Forner et al. cast doubt on whether the drugs at this dose could maintain tolerance and ensure efficacy [35]. Because recruitment is progressing well, the results are expected to be available soon.

Brivanib is a kinase inhibitor that selectively inhibits VEGFR-1, 2, and 3, and FGFR-1, 2, and 3. As for sunitinib, an international global phase III clinical trial to compare brivanib and sorafenib head-to-head and to seek approval for first-line therapy for advanced HCC has already been started, and the results are eagerly awaited. Japanese centers are participating in this clinical trial. Because brivanib targets FGF and VEGF, and is associated with relatively mild adverse effects, a second-line study of brivanib in sorafenib-ineffective and sorafenib-intolerant patients and a trial to evaluate the use of brivanib in combination with TACE are underway. Depending on the results of these trials, indications for use in HCC may be obtained; therefore, positive results are eagerly anticipated. The results have been reported for a phase II study of brivanib in 55 patients (cohort A) who had not received systemic therapy for curatively unresectable HCC and 46 patients (cohort B) previously treated with angiogenesis inhibitors such as sorafenib or thalidomide [36]. The median TTP and OS were 2.8 and 10 months, respectively, in cohort A versus 1.4 and 9.8 months, respectively, in cohort B. Adverse events included fatigue (51.5%), diarrhea (41.6%), hypertension (42.6%), anorexia (41.6%), and nausea/vomiting (40.6/30.7%). Thus, these results demonstrated the efficacy of brivanib as a second-line treatment. The results of three phase III clinical trials, BRISK-PS (sorafenib failure or sorafenib-intolerant patients; brivanib + best supportive care (BSC) vs. placebo + BSC), BRISK-FL (advanced HCC; brivanib vs. sorafenib), and BRISK-TA (patients with unresectable HCC, brivanib vs. placebo as post-TACE adjuvant therapy) are awaited. Japanese centers participated in all three trials.

In a Japanese phase I/II trial of TSU-68, an oral molecular inhibitor of VEGFR, PDGFR, and FGFR, to test its safety and efficacy in 35 HCC patients, the response rate was 5.6% (CR, PR, SD, PD, and NE in 1, 2, 15, 16, and 1 patients, respectively), and the disease control rate was 51.4% [37].

In addition, several phase I/II trials are being conducted to assess kinase inhibitors such as linifanib (ABT-869) and cediranib (AZD2171), which inhibit VEGFR, PDGFR, CSF-1R (cFms), Kit, and Flt3. Furthermore, axitinib, which is currently being tested in renal cell carcinoma, has also attracted attention as a promising agent for treatment of HCC because of its efficacy and mild side effects.

EGF/EGFR

EGFR is a member of the human epidermal growth factor receptor (HER) family that includes EGFR (erbB1), HER2/neu (erbB3), and HER4 (erb4). All members of this family, except HER3, have an intracellular tyrosine kinase domain, and the binding of a ligand to its extracellular domain triggers signal transduction through the above-described MAPK and PI3K/Akt/mTOR pathways. Thus, these receptors are involved in cell growth, differentiation, survival and adhesion [38]. EGFR overexpression has been reported in many cancers, and in HCC. For example, Buckley et al. reported that EGFR, detected by immunohistochemical analysis, was overexpressed in 50 (66%) of 76 HCCs, and that fluorescence in-situ hybridization (FISH) showed extra EGFR gene copies in 17 (45%) of 38 HCCs [39].

EGFR-targeting drugs, which include anti-EGFR antibodies, such as cetuximab and panitumumab, and small-molecule inhibitors of EGFR tyrosine kinases such as gefitinib, etc., have been used widely for treatment of several cancers other than HCC. Unfortunately, except for phase II trial data, there are few clinical data on the efficacy of these drugs for the treatment of HCC.

Similar to gefitinib (Iressa®), erlotinib (Tarceva®) is an oral EGFR tyrosine kinase inhibitor. Philip et al. and Thomas et al. have reported the results of phase II studies of erlotinib in HCC [40, 41]; the median OSs in their

studies were 13 and 10.7 months, respectively. A phase III clinical study (SEARCH study: *S*orafenib and *E*rlotinib, a R*a*ndomized T*r*ial Protocol for the Treatment of Patients with *H*epatocellular Carcinoma) of sorafenib in combination with erlotinib versus sorafenib plus placebo is ongoing. Because erlotinib is associated with a high incidence of skin rash, dry skin, and gastrointestinal toxicity, for example diarrhea, the results of the SEARCH study should be evaluated to assess whether this combination therapy can be used in clinical settings. Thomas et al. conducted a phase II clinical study of erlotinib in combination with bevacizumab in 40 advanced HCC patients, and reported promising results; the median PFS and OS were 9 and 15.7 months, respectively. However, they noted frequent treatment-related grade 3/4 toxicities, including fatigue (20%), hypertension (15%), gastrointestinal bleeding (12.5%), wound infection (5%), diarrhea (10%), elevated transaminase levels (10%), and thrombocytopenia (10%) [42], which necessitates further evaluation of drug tolerance. Although a clinical study of erlotinib in combination with bevacizumab (OPTIMOX-3 study) was also conducted in colorectal cancer patients, no tolerance was observed, which led to a change in the protocol [43, 44].

After the introduction of a number of molecular-targeted drugs, strategies for the inhibition of similar or different signaling pathways (vertical or horizontal inhibition) with several drugs have been proposed. However, the combined use of molecular-targeted agents has remained largely unsuccessful, including panitumumab in combination with bevacizumab for treatment of colorectal cancer [45]. Similarly, results for sorafenib in combination with bevacizumab (vertical inhibition) have been reported [46]. Although some therapeutic response was obtained, the combination therapy resulted in greater toxicity [46], suggesting the need for detailed evaluation of the dosing regimen.

Lapatinib (Tykerb®) is a dual inhibitor of EGFR and HER-2/neu, and inhibits tumor growth by downregulating MAPK, AKT, and p70S6 kinase [47]. In Japan, lapatinib is indicated for treatment of breast cancer. In a phase II clinical trial of lapatinib in 26 patients with unresectable advanced HCC, the median PFS and OS were 1.9 and 12.6 months, respectively, and adverse events included diarrhea (73%), nausea (54%), and skin rash (42%) [48].

Cetuximab (Erbitux®) is a human/mouse chimeric monoclonal antibody consisting of the variable region of a mouse anti-human EGFR monoclonal antibody and the human IgG1 constant region. Cetuximab inhibits the binding of endogenous EGFR ligands, for example EGF and TGFα, to EGFR. In a phase II clinical trial of cetuximab in 30 patients with unresectable or metastatic HCC, the median PFS and OS were 1.4 and 9.6 months, respectively, and treatment-related toxicities included grade 3 hypomagnesemia (3.3%) and grade 1/2 acne-like rash (83.3%), which was observed for the duration of anti-EGFR therapy in that study [49].

The EGFR is a very interesting therapeutic target. As described above, use of erlotinib in combination with sorafenib is still in the research stage. However, on the basis of results from phase II studies, the efficacy of cetuximab or lapatinib as monotherapy seems to be limited, and the results of further studies evaluating their efficacy in sorafenib-refractory or intolerant patients are awaited with interest.

HGF/c-Met pathway

Because the hepatocyte growth factor (HGF)/Met pathway is involved in tumor growth, invasion, and angiogenesis in a wide range of neoplasms, HGF and Met have recently attracted attention as therapeutic targets. HGF is a heterodimer consisting of α and β chains bound together by a disulfate bond. The α chain contains four kringle domains, and the β chain contains a serine protease-like domain. Met is a receptor tyrosine kinase for the HGF ligand, and contains a semaphorin-like domain. HGF or Met overexpression and Met gene mutations and duplications have been reported in various cancers, and abnormalities due to HGF/Met pathway activation have also been noted [50]. These abnormalities activate the downstream signaling cascade, leading to epithelial-mesenchymal transition and increased proliferative, migratory, invasive and metastatic potentials of cancer cells [50].

HGF/c-MET-targeted drugs, including kinase inhibitors, HGF inhibitors, and decoy c-Met receptor molecules, are being developed. Of particular interest is ARQ-197, a c-Met receptor tyrosine kinase inhibitor which is a non-ATP-competitive molecule that binds near the ATP-binding site. A randomized phase II study of ARQ-197 versus placebo is ongoing in patients with unresectable HCC after systemic therapy failure.

IGF/IGFR

The IGF/IGFR system is involved in cell growth and the chemotherapeutic response. The ligands IGF-I and II bind to their receptors IGF-1R and IGF-2R, and are involved in DNA synthesis and cell growth. Abnormalities in IGF and IGF-1R or their overexpression have been reported in various cancers, including HCC. Their associations with disease stage, metastasis, and survival [51] and the functions of IGF and IGFR in HCC [52] have been reported.

IGF-targeting drugs are currently being developed, and mainly include anti-IGF-1R antibodies, for example BIIB022, AVE1642, and cixutumumab (IMC-A12). A phase II study of cixutumumab, a phase Ib/II study of