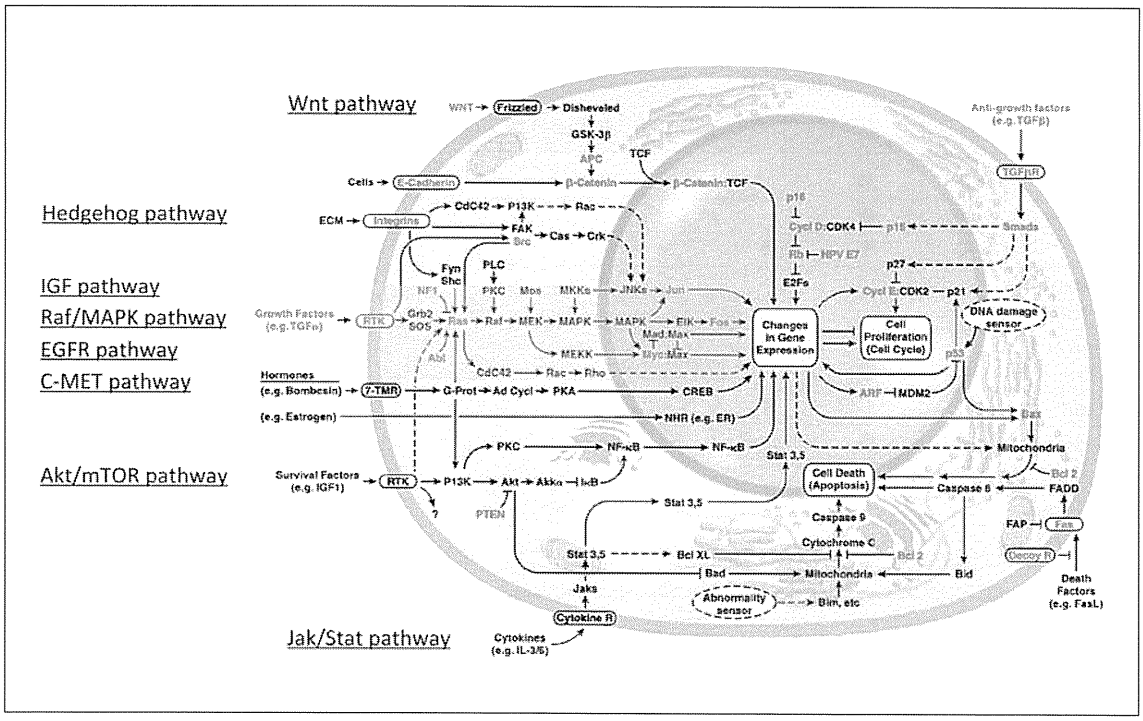

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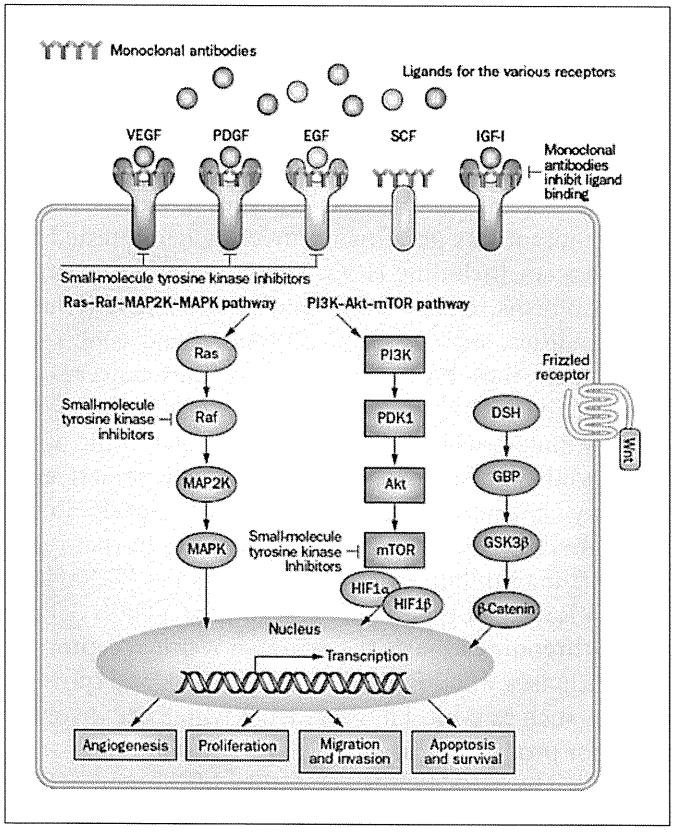

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Fig. 1. Signal transduction in solid cancer cells including HCC. Some of the genes known to be functionally altered are highlighted in red. These signaling pathways including growth factor pathway, Wnt pathway, Hedgehog pathway, Akt/mTOR pathway, and Jak/Stat pathway can be a molecular target for treatment of HCC [cited and modified from 10, with permission].

Fig. 2. Signaling pathways and molecular-targeted agents. Monoclonal antibodies (VEGFR: bevacizumab, EGFR: cetuximab), tyrosine kinase inhibitors (VEGFR: sorafenib, brivanib, linifanib, axitinib, EGFR: erlotinib, lapatinib), serine/threonine kinase inhibitors (Raf: sorafenib, mTOR: rapamycin and everolimus, PIK: KL-755) [cited and modified from 11, with permission].

Table 1. Molecular-targeted agents for HCC: targets and development status in Japan as of March 2011

Agents	Targets (angiogenesis)			Targets (proliferation)				Positioning	Development status
	VEGFR	PDGFR	FGF	EGFR	Raf	mTOR	TRAIL-R2 DR5		
Sorafenib	●	●			●			1st line	Approved
Sunitinib	●	●						1st line	PIII terminated
E7080	●	●	●					1st/2nd line	PII ongoing
Tigatuzumab (CS1008)							●	1st line	PI/II ongoing
Linifanib (ABT-869)	●	●						(Sorafenib combination) 1st line	PIII ongoing
Brivanib	●		●					1st line, 2nd line, TACE adjuvant	PIII ongoing
TSU-68	●	●						TACE combination	PIII ongoing
Ramucirumab	●							2nd line	PIII ongoing
Everolimus (RAD001)						●		2nd line	PIII ongoing
Axitinib	●	●						2nd line	PIII ongoing

tal cancers. One study reported that 30% of HCCs have Ras mutations [16]. To our knowledge, no agents targeting Ras are planned to enter clinical trials at the present. 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, such as point mutations and gene rearrangements, have been reported in various cancers [17]; however, in HCC, *ras/raf* mutations are rare, and no *k-ras* or *b-raf* mutations have been detected [18]. On the other hand, wild-type Raf-1 was reported to be hyperactivated in many cancers, including HCC [19–21]. Sorafenib inhibits Raf, and has multiple characteristics in that it exhibits 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 [22].

MEK. The MEK family consists of MEK1 and MEK2 proteins, which specifically phosphorylate tyrosine and threonine residues, and phosphorylates downstream Erk1 and Erk2 [23]. 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 [14]. The MEK inhibitors CI-1040, PD0325901, AZD6244 and RDEA119/BAY869766 have been tested in several cancers including solid tumors such as HCC. Recently, results of phase I of AS703026 and E6201 studies against solid tumors were reported in ASCO2010. 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.

PI3K/Akt/mTOR Pathway

The PI3K/Akt/mTOR pathway also plays an important role in cell growth, survival regulation, metabolism and antiapoptosis. 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, while mTORC1 (mTOR-raptor) is activated downstream of Akt; thus, both molecules regulate protein synthesis [24].

A study of 528 HCC samples showed that the expression of pAkt, PTEN, p27 and S6 ribosomal protein (pS6) was a poor prognostic factor for survival [25]. 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 -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 [26]. In an extensive analysis of 314 HCC samples in terms of mutation analysis, DNA copy number changes, mRNA levels and immunostaining, Villanueva et al. [27] 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.

The PI3K inhibitor RG7321 and the Akt inhibitor perifosine target the PI3K/Akt/mTOR pathway and are in early stages of clinical development, while 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 EverOlimus for LiVer cancer Evaluation) 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. Since mTOR inhibitors exhibit 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, since the mTOR pathway is stimulated by factors such as EGFR, PDGFR and TGF-α, 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 [28].

VEGF/VEGFR, PDGFR, FGFR

Angiogenesis is an important event not only for HCC but also for cancer growth and metastasis, and occurs due to complex alterations involving promoting factors such as VEGF, angiopoietin and FGF, and inhibitory factors including thrombospondin (TSP) and angiostatin, as well as 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 -2 and is involved in angiogenesis and the maintenance of mature blood vessels, while VEGF-C and -D mainly bind to VEGFR-3, and are involved in lymphangiogenesis [29, 30]. VEGF isoforms such as $VFGF_{121}$ and $VEGF_{165}$ have been identified, and isoform subtypes also exist, such as $EGF_{166}b$. Thus, it is clear that these growth factors do not exhibit angiogenesis-promoting effects alone, and they have attracted attention as new therapeutic targets [31].

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 [32]. In addition, a meta-analysis has demonstrated that VEGF expression is a prognostic factor in HCC [33].

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 multikinase 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% [34]. Since sunitinib has a lower IC_{50} for each target than sorafenib, it is expected to exhibit 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 [35]. In that study, sunitinib was administered at 50 mg/day for 4 weeks followed by 2 weeks of rest per cycle [34], whereas Zhu et al. [35] 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 the above trial results, Forner et al. [36] casted doubt on whether the drugs at this dose could maintain tolerance and ensure efficacy. Consequently, the trial was terminated in March 2010 because of the recommendation by data monitoring committee (DMC) based on interim analysis, showing relatively high toxicity and no superior efficacy to sorafenib.

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. Since brivanib targets FGF and VEGF, and is associated with relatively mild adverse effects, a second-line study of brivanib in sorafenib-ineffective and -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 [37]. The median time to progression (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%) in total. 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% [38]. The global phase III trial of TACE in combination with TSU-68 has just started in January 2011.

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, a phase III global study of axitinib, which is currently being tested in renal cell carcinoma, has also been started as a second-line agent in 2011.

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 [39]. EGFR overexpression has been reported in many cancers, and in HCC. For example, Buckley et al. [40] 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.

EGFR-targeting drugs include anti-EGFR antibodies, such as cetuximab and panitumumab, and small-molecule inhibitors of EGFR tyrosine kinases such as gefitinib, etc., and have been used widely for the treatment of several cancers other than HCC. Unfortunately, except for phase II trial data, there are little 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. [41] and Thomas et al. [42] have reported the results of phase II studies of erlotinib in HCC; the median OSs in their studies were 13 and 10.7 months, respectively. A phase III clinical study (SEARCH study: Sorafenib and Erlotinib, A Randomized Trial Protocol for the Treatment of Pa-

tients with Hepatocellular Carcinoma) for sorafenib in combination with erlotinib versus sorafenib plus placebo is ongoing. Since erlotinib is associated with a high incidence of skin rash, dry skin, and gastrointestinal toxicity, such as 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. [43] 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%), which necessitates further evaluation for 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 [44, 45].

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 the treatment of colorectal cancer [46]. Similarly, the results of sorafenib in combination with bevacizumab (vertical inhibition) have been reported [47]. Although some therapeutic responses were obtained, the combination therapy resulted in greater toxicity [47], 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 [48]. In Japan, lapatinib is indicated for the 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%) [49].

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, such as EGF and TGF-α, 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 [50].

The EGFR offers a very interesting therapeutic target. As described above, the use of erlotinib in combination with sorafenib is still in the research stage. However, based on the results of phase II studies, the efficacy of cetuximab or lapatinib as a 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

Since 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 a therapeutic target. 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 [51]. These abnormalities activate the downstream signaling cascade, leading to epithelial-mesenchymal transition and increased proliferative, migratory, invasive and metastatic potentials of cancer cells [51].

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 as 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. In addition, the results of a phase I study of ARQ-197 in combination with sorafenib were reported in ASCO 2010 (abstr. No. 3024).

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 [52] and

the functions of IGF and IGFR in HCC [53] have been reported.

IGF-targeting drugs are currently being developed, and mainly including anti-IGF-1R antibodies, such as BIIB022, AVE1642 and cixutumumab (IMC-A12). A phase II study of cixutumumab, a phase Ib/II study of sorafenib versus sorafenib plus BIIB022, and phase I/II studies of AVE1642 as monotherapy or in combination with sorafenib or erlotinib are ongoing.

Sorafenib: Trial Results and Clinical Experience

Clinical Results for Sorafenib in HCC

As described above, sorafenib is a multikinase inhibitor of tumor growth and angiogenesis, and exhibits a strong inhibitory effect on C- and B-Raf serine/threonine kinases (comprising the Raf/MEK/ERK pathway), VEGFR and PDGFR tyrosine kinases, and Flt-3 and c-kit [22]. To date, sorafenib is the only molecular-targeted agent approved for the treatment of HCC based on the results of two large-scale clinical trials, namely the SHARP (Sorafenib HCC Assessment Randomized Protocol) study [54] and the Asia-Pacific study [55]. The median OSs for the sorafenib group in the SHARP and Asia-Pacific studies were 10.7 months (vs. 7.9 months for the placebo group, $p < 0.001$; HR 0.69) and 6.5 months (vs. 4.2 months for the placebo group, $p = 0.014$; HR 0.68), respectively, indicating that sorafenib prolongs survival by approximately 30%. These data should compel HCC specialists to challenge their preconception that systemic anticancer drug therapy is not effective for HCC.

Current Status regarding the Use of Sorafenib in Japan

Sorafenib was approved in Japan in May 2009. A survey has confirmed that, at the time of writing (May 2011), over 10,000 patients have been prescribed sorafenib. Across several centers, 100 Japanese patients have achieved CR or near CR (superresponded PR), which was not observed in the SHARP or Asia-Pacific trials. This suggests that some Japanese patients may be very sensitive to sorafenib [56]. The reason for this or predictive biomarkers is now actively under investigation.

On the other hand, it has been reported that hand-foot syndrome occurs early after sorafenib administration [57] more often than was noted in the SHARP and Asia-Pacific studies, and the drug is often discontinued because of the adverse effects in many patients [57]. As demonstrated in the SHARP and Asia-Pacific studies, sorafenib is only used to achieve stable disease; therefore, it is important to improve drug efficacy by extending the period of administration for as long as possible. Therefore, it is no exaggeration to say that, in the case of sorafenib, the 'successful management of side effects' is equal to 'successful treatment'. According to the 'post-TACE phase III clinical study' [57] performed in Japan and Korea, it is strongly speculated that physicians who are unaccustomed to prescribing molecular-targeted agents and who fail to see marked efficacy, as induced by conventional chemotherapeutic agents, often do not understand the properties of this drug, and they (as well as the patients) do not fully comprehend therapeutic efficacy. Moreover, they feel too anxious about side effects

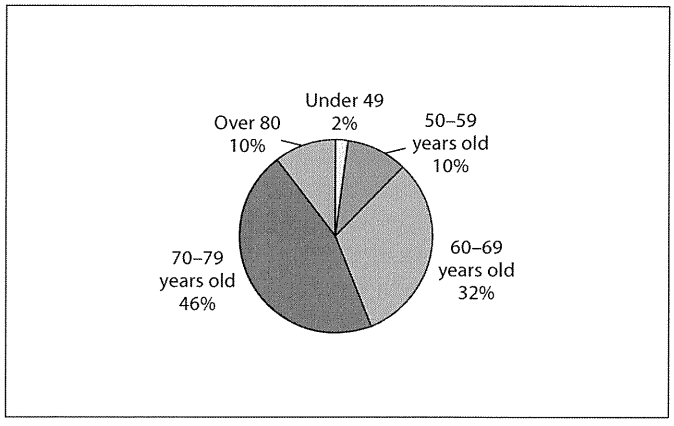

Fig. 3. Age distribution of patients treated with sorafenib.

Table 2. Patients' background treated with sorafenib (n = 113; data from Kinki University Hospital)

Age	70.1 (31–90)	
Gender	M	80 (70.8%)
	F	33 (29.2%)
Etiology	HBV	23 (20.4%)
	HCV	60 (53.1%)
	NBNC	30 (26.5%)
Child-Pugh score	5	64 (56.6%)
	6	33 (29.2%)
	7	16 (14.2%)
Child-Pugh grade	A	97 (85.8%)
	B	16 (14.2%)
Stage	III	51 (45.1%)
	IVA	28 (24.8%)
	IVB	34 (30.1%)

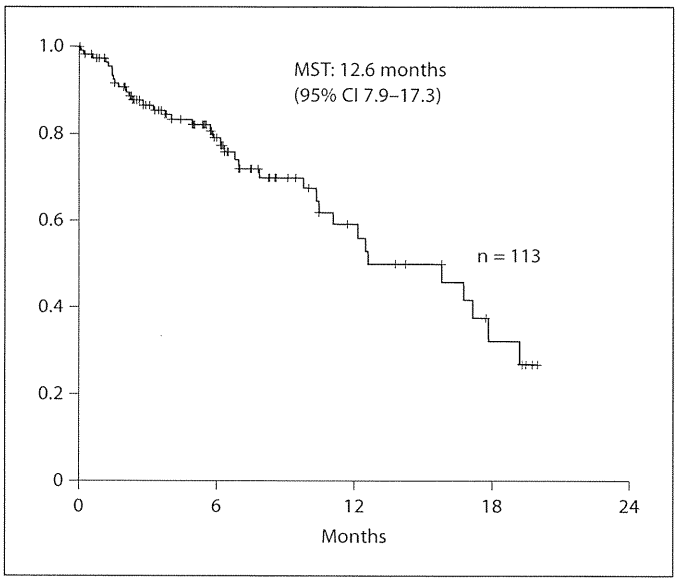

Fig. 4. Overall survival in patients treated with sorafenib.

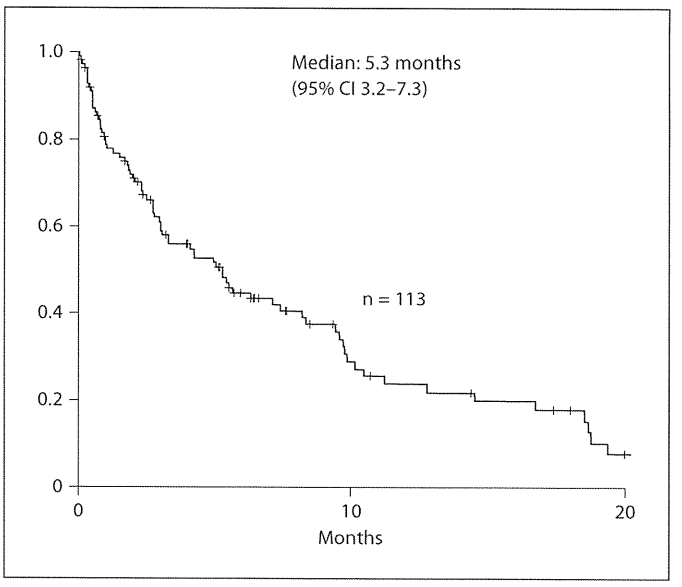

Fig. 5. Treatment duration in patients treated with sorafenib.

that have not been encountered before. These circumstances may result in treatment discontinuation in many patients. Clearly, greater awareness among physicians for therapeutic efficacy and approaches to manage adverse effects is needed to improve treatment outcomes.

Experience of Sorafenib Use at Our Institute

Since the approval of sorafenib on May 20, 2009, we have treated approximately 150 patients with sorafenib during 20 months, but few have discontinued therapy due to adverse effects or patient refusal to continue. Of these 113 patients, 2 achieved CR [56]. These 2 CR patients, in whom pulmonary, adrenal metastases and intrahepatic lesions all disappeared, survived free of recurrence for more than 3 and 2 years, respectively at the time of writing (May 2011), i.e., they are still alive at the present. In other patients who apparently achieved SD, the tumor marker levels reached a plateau after sorafenib administration, when their levels were rising rapidly before sorafenib administration. Even if hepatic lesions do not show a clear tendency to undergo necrosis or regression on CT images, three tumor markers (AFP, PIVKA-II and AFP-L3) are widely considered to serve as surrogate markers. In fact, there is very little data on serum tumor markers, except for AFP, outside Japan. Nevertheless, Japanese researchers have demonstrated the value of changes in these markers and the antitumor efficacy of sorafenib [56].

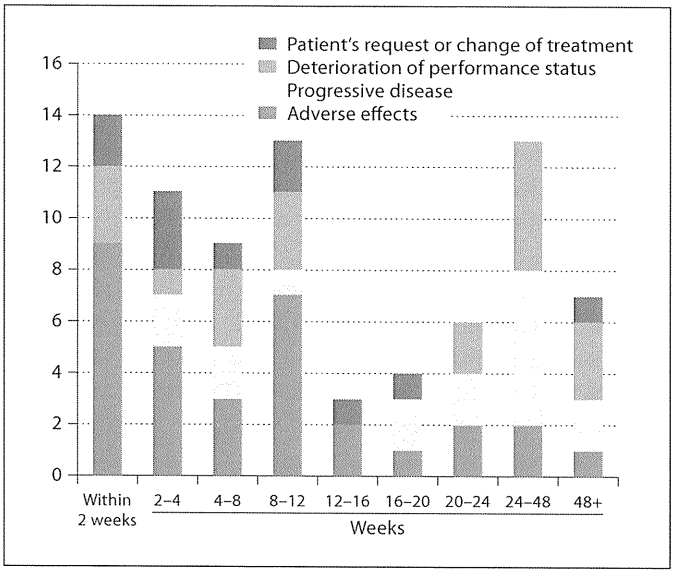

Fig. 6. Causes of discontinuation of sorafenib. Only 17 of 113 (15%) cases were terminated due to PD. Most of discontinuation of sorafenib due to adverse effects was within 12 weeks.

Interestingly, it was previously demonstrated that the levels of PIVKA-II or DCP tend to be increased by inducing hypoxia [58]. Therefore, PIVKA-II or DCP may be a good predictive marker for evaluating the hypoxic response to antiangiogenic therapy for HCC [59].

Of 113 patients, 85.8% was Child-Pugh A stage and 53.1% of patients were HCV-related HCC (table 2). A total of 56% of patients were over 70 years of age (fig. 3). The initial status of patients treated with sorafenib is listed in table 3. Median survival time (MST) was 12.6 months (fig. 4) and median treatment duration was 5.3 months (fig. 5). The causes of discontinuation are listed in figure 6. Only 10% of the 113 patients showed PD by RECIST. However, since the speed with which the patient develops progressive disease may slow down due to tumor growth inhibition, it is very difficult to determine when to discontinue treatment because of tumor refraction. Important issues for future studies include: (1) to identify biomarkers that can predict therapeutic responses, including CR or PR, in patient groups; (2) to evaluate the role of tumor markers in the determination of therapeutic responses; (3) to establish response evaluation criteria that can determine the therapeutic responses to molecular-targeted agents, and (4) to develop effective second-line therapies after sorafenib failure (fig. 2, 7) [11, 60].

According to the consensus-based treatment algorithm by the Japan Society of Hepatology (fig. 7) [60], updated in 2010 [61], sorafenib is indicated for the treatment of patients with Child-Pugh A HCC with extrahepatic metastasis, vascular invasion or refractoriness to TACE or arterial infusion chemotherapy.

In addition to the pharmaceutical-sponsored clinical trials of linifanib and brivanib as first- and second-line therapy in sorafenib-refractory patients, investigator-initiated trials (IIT) of sorafenib in combination with hepatic arterial infusion chemotherapy (SILIUS trial: trial No. NCT01214343), pharmaceutical and IIT trials of sorafenib in combination with TACE (SPACE, TACICS (trial No. NCT 01217034) and BRISK-TA trials), and a trial to test the inhibitory effect of sorafenib on tumor recurrence after curative treatment (STORM trial) are ongoing, and the results of these trials are eagerly awaited (fig. 7) [60].

The working hypotheses in these studies can be deduced by extrapolating the MST and hazard ratios in OS calculated in a subanalysis of the SHARP study (table 4). The results obtained suggest that starting treatment with molecular-targeted drugs at an earlier tumor stage in combination with standard treatment options such as resection, ablation, TACE or hepatic arterial infusion chemotherapy can improve the prognosis of HCC. Thus, sorafenib has the potential to induce a paradigm shift in the treatment of HCC. For example, in a subanalysis of the SHARP trial, the hazard ratios for OS and MST ratio in intermediate-stage HCC without vascular invasion or extrahepatic spread were 0.52 and 1.50, respectively (table 4). This suggests that survival of early-stage HCC and intermediate-stage HCC may be prolonged from 5 to 7.5–10 years by using sorafenib in an adjuvant setting after curative treatment, and from 3 to 4.5–6 years by using sorafenib in combination with TACE (fig. 8) [60].

Table 3. Initial status of patients treated with sorafenib

Refractory to TACE	36
Impossible of TACE due to:	
AP shunt	2
Stenosis of artery	5
Macrovascular invasion	4
Multiple nodules at first diagnosis	3
Portal vein invasion at first diagnosis	8
Hepatic vein invasion at first diagnosis	1
Extrahepatic spread	28
Refractory to HAIC	4
Refractory to standard treatment	2
Candidate of clinical trials: SILIUS (phase I)	12
Patient's request	6
Bile duct invasion	1
Others	1

Table 4. Subanalysis data of the SHARP study (data from M. Sherman et al., ASCO 2008)

	Advanced HCC	
	with vascular invasion and extrahepatic spread	without vascular invasion or extrahepatic spread
Hazard ratio	0.77	0.52
95% CI	0.60–0.99	0.32–0.85
Median OS (MST)		
Sorafenib	8.9 months (n = 209)	14.5 months (n = 90)
95% CI	7.6–10.3 months	14.0 months (N/E)
Placebo	6.7 months (n = 212)	10.2 months (n = 91)
95% CI	5.2–8.0 months	8.6–15.5 months

Summary and Future Prospects

Several clinical trials [34, 35, 37, 41, 42, 50, 62–66] of the molecular-targeted agents are ongoing. Angiogenesis-inhibiting drugs, particularly sorafenib, have been evaluated for HCC, and drugs targeting EGFR and mTOR are being developed. The results (numerical values) of phase II clinical trials show no marked differences in the

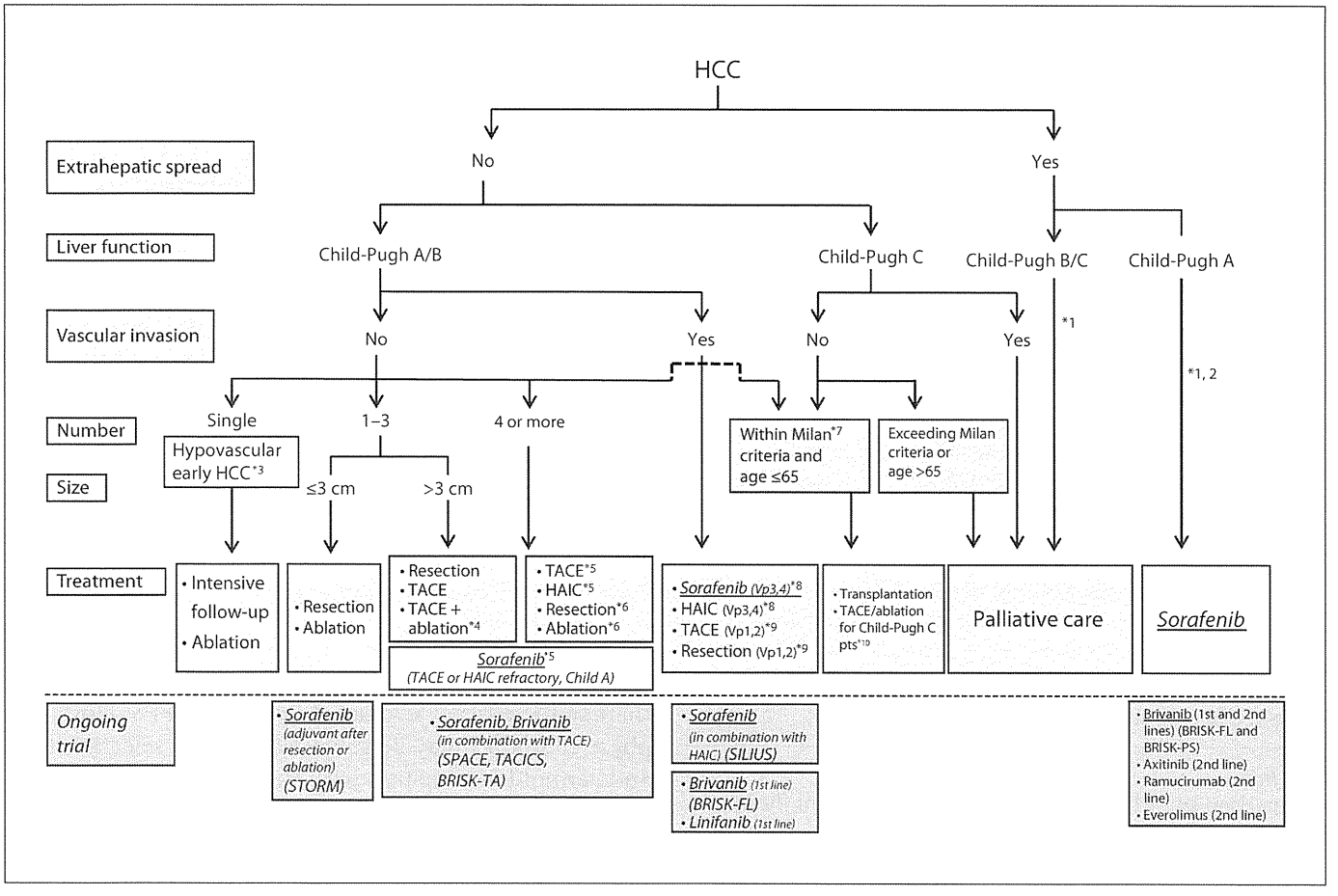

Fig. 7. Consensus-based Treatment Algorithm for Hepatocellular Carcinoma proposed by Japan Society of Hepatology (JSH) revised in 2010 [cited and modified from 60, with permission]. Footnotes: *1 = Treatment should be performed as if extrahepatic spread is negative, when extrahepatic spread is not considered as a prognostic factor in Child-Pugh class A/B patients. *2 = Sorafenib is the first choice of treatment in this setting as a standard of care. *3 = Intensive follow-up observation is recommended for hypovascular nodules by the Japanese Evidence-Based Clinical Practice Guidelines. However, local ablation therapy is frequently performed in the following cases: (1) when the nodule is diagnosed pathologically as early HCC, (2) when the nodules show decreased uptake on Gd-EOB-MRI, or (3) when the nodules show decreased portal flow by CTAP, since these nodules frequently progress to advanced HCC. *4 = Even for HCC nodules exceeding 3 cm in diameter, TACE in combination with ablation is frequently performed when resection is not indicated. *5 = Transcatheter arterial chemoembolization (TACE) is the first choice of treatment in this setting. Hepatic arterial infusion chemotherapy (HAIC) using an implanted port is also recommended for TACE-refractory patients. The regimen for this treatment is usually low-dose FP (5FU + CDDP) or intra-arterial 5FU infusion combined with systemic interferon therapy. Sorafenib is also recommended for TACE- or HAIC-refractory patients with Child-Pugh class A liver function. *6 = Resection is sometimes performed when more than 4 nodules are detected. Ablation is sometimes performed in combination with TACE. *7 = Milan criteria: tumor size ≤3 cm and tumor number ≤3, or solitary tumor ≤5 cm. Even when liver function is good (Child-Pugh A/B), transplantation is sometimes considered for frequently recurring HCC patients. *8 = Sorafenib and HAIC are recommended for HCC patients with major portal invasion such as Vp3 (portal invasion in the 1st portal branch) or Vp4 (portal invasion in the main portal trunk). *9 = Resection and TACE are frequently performed when portal invasion is minor, such as Vp1 (portal invasion in the 3rd or more peripheral portal branch) or Vp2 (portal invasion in the 2nd portal branch). *10 = Local ablation therapy or subsegmental TACE is performed even for Child-Pugh C patients when transplantation is not indicated when there is no hepatic encephalopathy, no uncontrollable ascites, and a low bilirubin level (<3.0 mg/dl). However, it is regarded as an experimental treatment because there is no evidence of a survival benefit in Child-Pugh C patients. A prospective study is necessary to clarify this issue.

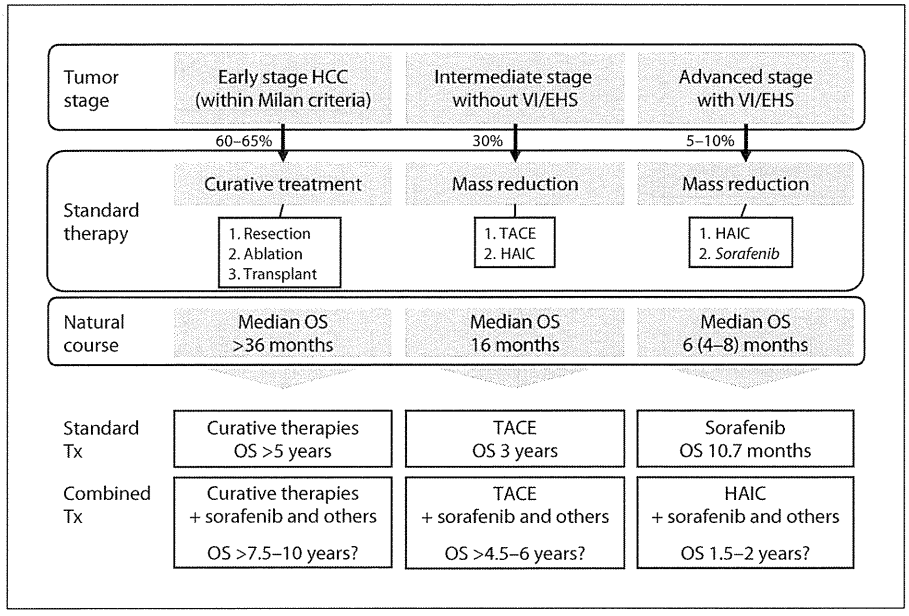

Fig. 8. Outcomes of standard treatment modalities and expected future outcomes of combination therapy with molecular-targeted agents. By combining molecular-targeted agents with resection or ablation, life expectancy is expected to be prolonged to 7.5–10 years. In addition, for intermediate-stage HCC, the prognosis is expected to be improved to 4.5–6 years by combination with TACE. OS = Overall survival.

Table 5. Ongoing clinical trials (PIII)

First line
Comparison study between sorafenib and single agent (head to head):
Sunitinib → endpoint did not meet!
Brivanib
Linifanib
Combination with sorafenib and another agent:
DXR, erlotinib (SEARCH), everolimus, CS-1008, etc.
Second line
Sorafenib failure: brivanib, everolimus (RAD001), ramucirumab, axitinib, S-1, etc.
Combination with standard therapy
Adjuvant setting after surgery or RFA: *STORM*
Combination with TACE: *SPACE, BRISK-TA, TACTICS, ECOG1208*
Combination with HAIC: *SILIUS*

TACTICS Phase II study = Transcatheter Arterial Chemoembolization Therapy In Combination with Sorafenib (ClinicalTrials.gov ID: NCT01217034); SILIUS = Randomized Controlled Trial Comparing Efficacy of Sorafenib versus Sorafenib In combination with Low-dose cisplatin/fluorouracil hepatic arterial InfUSion chemotherapy in Patients with Advanced Hepatocellular Carcinoma And Exploratory Study of Biomarker Predicting Its Efficacy (ClinicalTrials.gov ID: NCT01214343); HAIC = hepatic arterial infusion chemotherapy.

therapeutic efficacy evaluated by TTP or PFS. However, phase II studies may be subject to patient selection bias and cannot be compared with the results of other trials. Thus, when determining the therapeutic efficacy of drugs, we should review the efficacy of the respective drugs, and consider where the theoretical target molecules are present and what combinations of drugs have a theoretical rationale, and thus evaluate options for monotherapy and combination therapy based on the efficacy and safety data obtained from phase III clinical trials.

Molecular-targeted agents that have been introduced into clinical use in recent years are approved for the treatment of specific cancer and are then frequently used to treat other cancers. Although not discussed here, studies to identify predictors of efficacy (i.e., biomarkers) for angiogenesis inhibitors and EGFR tyrosine kinase inhibitors, and factors involved in drug resistance, are making steady progress, and the associated therapeutic strategies are undergoing major changes. Therefore, even in the treatment of HCC, it is necessary for HCC specialists to expand their knowledge of and techniques for applying existing treatment modalities (resection, ablation, TACE, arterial infusion chemotherapy) to physically remove, destroy or necrotize the tumor, and to better understand clinical oncology, particularly the role and mechanisms of action of molecular-targeted agents. We are entering an era in which physicians treating HCC should pay close attention to the development of therapeutic agents not only for HCC but also for other cancers, and be aware of

the use of molecular-targeted agents for treating cancers in clinical and basic research settings, and understand approaches to limit or control adverse effects associated with these drugs.

Although sorafenib was recently approved, many issues remain to be addressed, including (1) how to determine and define refractoriness, and (2) whether to continue TACE or hepatic arterial infusion chemotherapy (a de facto standard in Japan) in patients with TACE-refractory tumors or portal tumor thrombi before starting sorafenib therapy. For oncology, in particular, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has approved several drugs based on results from global clinical trials and from Japanese phase I study data alone. We strongly recommend that, based on the molecular-targeted agents currently under development, clinical studies (including IITs) should be conducted aggressively, and therapeutic strategies should be devised to resolve the limitations of currently used therapeutic approaches and to improve the therapeutic outcomes (table 5).

The introduction of sorafenib to treat HCC in 2007 in Western countries and in 2009 in Japan was undoubtedly the *real* beginning of a paradigm shift of HCC treatment, representing a significant breakthrough for HCC treatment not previously experienced for this unique tumor.

Disclosure Statement

The author has no conflict of interest to declare.

References

1 Farazi PA, DePinho RA: Hepatocellular carcinoma pathogenesis: from genes to environment. Nat Rev Cancer 2006;6:674–687.
2 Minguez B, Tovar V, Chiang D, et al: Pathogenesis of hepatocellular carcinoma and molecular therapies. Curr Opin Gastroenterol 2009;25:186–194.
3 Villanueva A, Newell P, Chiang DY, et al: Genomics and signaling pathways in hepatocellular carcinoma, Semin Liver Dis 2007;27: 55–76.
4 Laurent-Puig P, Zucman-Rossi J: Genetics of hepatocellular tumors. Oncogene 2006;25: 3778–3786.
5 Llovet JM, Bruix J: Molecular-targeted therapies in hepatocellular carcinoma. Hepatology 2008;48:1312–1327.
6 Hopfner M, Shuppan D, Scherubl H: Growth factor receptors and related signaling pathways as target for novel treatment strategies of hepatocellular cancer. World J Gastroenterol 2008;14:1–14.
7 Campbell JS, Hughes SD, Gilbertson DG, et al: Platelet-derived growth factor C induces liver fibrosis, steatosis, and hepatocellular carcinoma. Proc Natl Acad Sci USA 2005; 102:3389–3394.
8 Ogasawara S, Yano H, Iemura A, et al: Expression of basic fibroblast growth factor and its receptors and their relationship to proliferation of human hepatocellular carcinoma cell lines. Hepatology 1996;24:198–205.
9 Kudo M: Hepatocellular carcinoma 2009 and beyond: from the surveillance to molecular-targeted therapy. Oncology 2008;75:S1–S12.
10 Hanahan D, Weinberg RA: The hallmarks of cancer. Cell 2000;100:57–70.
11 Spangenberg HC, Thimme R, Blum HE: Targeted therapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2009;6:423–432.
12 Roberts PJ, Der CJ: Targeting the Ras-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 2007;26:3291–3310.
13 Schmidt CM, McKillop IH, Cahill PA, et al: Increased MAPK expression and activity in primary human hepatocellular carcinoma. Biochem Biophys Res Commun 1997;236: 54–58.
14 Huynh H, Nguen TT, Chow KH, et al: Overexpression of the mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK in hepatocellular carcinoma: Its role in tumor progression and apoptosis. BMC Gastroenterol 2003;3:19.
15 Calvisi DF, Ladu S, Gorden A, et al: Ubiquitous activation of Ras and Jak/Stat pathways in human HCC. Gastroenterology 2006;130: 1117–1128.
16 Bos JL: Ras oncogenes in human cancer: review. Cancer Res 1989;49:4682–4689.
17 Beeram M, Patnaik A, Rowinsky EK: Ras: a strategic target for therapeutic development against cancer. J Clin Oncol 2005;23:6771–6790.
18 Tannapfel A, Sommerer F, Benicke M, et al: Mutations of the BRAF gene in cholangiocarcinoma but not in hepatocellular carcinoma. Gut 2003;52:706–712.
19 Jenke HS, Deml E, Oesterle D: C-raf expression in early rat liver tumorigenesis after promotion with polychlorinated biphenyls or phenobarbital. Xenobiotica 1994;24:569–580.
20 Beer DG, Neveu MJ, Paul DL, et al: Expression of the c-raf protooncogene, γ-glutamyltranspeptidase, and gap junction protein in rat liver neoplasms. Cancer Res 1998;48: 1610–1617.
21 Hwang YH, Choi JY, Kim S, et al: Over-expression c-raf-1 proto-oncogene in liver cirrhosis and hepatocellular carcinoma. Hepatol Res 2004;29:113–121.
22 Wilhelm SM, Adnane L, Newell P, et al: Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther 2008;7:3129–3140.
23 Ohren JF, Chen H, Pavlovsky A, et al: Structures of human MAP kinase kinase 1(MEK1) and MEK2 describe novel non-competitive kinase inhibition. Nat Struct Mol Biol 2004; 11:1192–1197.
24 Engelma J: Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer 2009;9:550–562.
25 Zhou L, Huang Y, Li J, et al: The mTOR pathway is associated with the poor prognosis of human hepatocellular carcinoma. Med Oncol 2010;27:255–261.
26 Chen J, Wang Q, Fu X, et al: Involvement of PI3K/PTEN/AKT/mTOR pathway in invasion and metastasis in hepatocellular carcinoma: association with MMP-9. Hepatol Res 2009;39:177–186.
27 Villanueva A, Chiang DY, Newell P, et al: Pivotal role of mTOR signaling in hepatocellular carcinoma. Gastroenterology 2008;135: 1972–1983.
28 Treiber G: mTOR inhibitors for hepatocellular carcinoma: a forward-moving target. Expert Rev Anticancer Ther 2009;9:247–261.

29 Ferrara N, Davis-Smyth T: The biology of vascular endothelial growth factor. Endocr Rev 1997;18:4–25.
30 Griffioen AW, Molema G: Angiogenesis: potentials for pharmacologic intervention in the treatment of cancer, cardiovascular diseases, and chronic inflammation. Pharmacol Rev 2000;52:237–68.
31 Harper SJ, Bates DO: VEGF-A splicing: the key to anti-angiogenic therapeutics? Nat Rev Cancer 2008;8:880–887.
32 Fernandez M, Semela D, Bruix J, et al: Angiogenesis in liver disease. J Hepatol 2009;50: 604–620.
33 Schoenleber SJ, Kurtz DM, Talwalkar JA, et al: Prognostic role of vascular endothelial growth factor in hepatocellular carcinoma: systematic review and meta-analysis. Br J Cancer 2009;100:1385–1392.
34 Faivre S, Raymond E, Boucher E, et al: Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: an open-label, multicenter, phase II study. Lancet Oncol 2009;10:794–800.
35 Zhu AX, Sahani DV, Duda DG, et al: Efficacy, safety, and potential biomarker of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. J Clin Oncol 2009;27:3027–3035.
36 Forner A, Llovet JM, Bruix J: Sunitinib and the benefits of a negative study. Lancet Oncol 2009;10:743–744.
37 Raoul JL, Flinn RS, Kang YK, et al: An open-label phase II study of first- and second-line treatment with brivanib in patients with hepatocellular carcinoma. J Clin Oncol 2009; 27(suppl):A4577.
38 Kanai F, Yoshida H, Tateishi R, et al: Final results of a phase I/II trial of the oral anti-angiogenesis inhibitor TSU-68 in patients with advanced hepatocellular carcinoma. J Clin Oncol 2008;26:A4589.
39 Ciardiello F, Tortora G: EGFR antagonists in cancer treatment. N Engl J Med 2008;358: 1160–1174.
40 Buckley AF, Burgart LJ, Sahai V, et al: Epidermal growth factor receptor expression and gene copy number in conventional hepatocellular carcinoma. Am J Clin Pathol 2008; 129:245–251.
41 Philip PA, Mahoney MR, Allmer C, et al: Phase II study of erlotinib (OSI-774) in patients with advanced hepatocellular cancer. J Clin Oncol 2005;23:6657–6663.
42 Thomas MB, Chadhal R, Glover K, et al: Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. Cancer 2007;110:1059–1066.
43 Thomas MB, Morris JS, Chadha R, et al: Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. J Clin Oncol 2009;27:843–850.
44 Modified Folfox7/bevacizumab or modified Xelox/bevacizumab with or without erlotinib in first-line metastatic colorectal cancer (MCRC): results of the feasibility phase of the DREAM-OPTIMOX3 study (GERCOR). J Clin Oncol. ASCO Annual Meeting Proceedings, 2007, part I, vol 25, No 18S, 4097.
45 Tournigand B, Samson W, Scheithauer C, et al: mFolfox-bevacizumab or Xelox-bevacizumab then bevacizumab alone or with erlotinib in first-line treatment of patients with metastatic colorectal cancer (mCRC): interim safety analysis of DREAM study. J Clin Oncol 2009;27:15S, ASCO Annual Meeting, abstr No 4077C.
46 Hecht JR, Mitchell E, Chidiac T, et al: A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2008;27:672–680.
47 Azad NS, Posadas EM, Kwitkowski VE, et al: Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and antitumor activity. J Clin Oncol 2008;26:3709–3714.
48 Burris HA III, Hurwitz HI, Dees EC, et al: Phase I safety, pharmacokinetics, and clinical activity of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. J Clin Oncol 2005;23:5305–5313.
49 Bekaii-Saab T, Markowitz J, Prescott N, et al: A multi-institutional phase II study of the efficacy and tolerability of lapatinib in patients with advanced hepatocellular carcinomas. Clin Cancer Res 2009;15:5895–5901.
50 Zhu AX, Stuart K, Blaszkowsky LS, et al: Phase 2 study of cetuximab in patients with advanced hepatocellular carcinoma. Cancer 2007;110:581–589.
51 Comoglio PM, Giordano S, Trusolino L: Drug development of MET inhibitors: targeting oncogene addiction and expedience. Nat Rev Drug Disc 2008;7:501–516.
52 Scharf JG, Braulke T: The role of the IGF axis in hepatocarcinogenesis. Horm Metab Res 2003;35:685–693.
53 Chen YW, Boyartchuk V, Lewis BC: Differential roles of insulin-like growth factor receptor- and insulin receptor-mediated signaling in the phenotypes of hepatocellular carcinoma cells. Neoplasia 2009;11:835–845.
54 Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.
55 Cheng AL, Kang YK, Chen Z, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.
56 Kudo M: Positioning of a molecular-targeted agent, sorafenib, in the treatment algorithm for hepatocellular carcinoma in Japan, including its impact on complete remission. Oncology 2010;78(suppl 1):154–166.
57 Kudo M, Imanaka K, Chida N, et al: Phase III study of sorafenib after transarterial chemoembolization in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011, in press.
58 Murata K, Suzuki H, Okano H, et al: Hypoxia-induced des-γ-carboxyprothrombin production in hepatocellular carcinoma. Int J Clin Oncol 2010;36:161–170.
59 Ueshima K, Kudo M, Takita M, Nagai T, Tatsumi C, Ueda T, Kitai S, Ishikawa E, Yada N, Inoue T, Hagiwara S, Minami Y, Chung H, Sakurai T: Des-γ-carboxyprothrombin may be a promising biomarker to determine the therapeutic efficacy of sorafenib for hepatocellular carcinoma. Dig Dis 2011;29:321–325.
60 Kudo M: The 2008 Okuda Lecture. Management of hepatocellular carcinoma: from surveillance to molecular-targeted therapy. J Gastroenterol Hepatol 2010;25:439–452.
61 Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojiro M, Makuuchi M; for the HCC Panel of Japan Society of Hepatology: Management of hepatocellular carcinoma in Japan: Consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 2011;29:339–364.
62 Abou-Alfa GK, Schwartz L, Ricci S, et al: Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006;24:4293–4300.
63 Toh H, Chen PJ, Carr BI, et al: A phase II study of ABT-869 in hepatocellular carcinoma: Interim analysis. J Clin Oncol 2009;27: 15S, suppl, A4581.
64 Siegel AB, Cohen EI, Ocean A, et al: Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. J Clin Oncol 2008;26: 2992–2998.
65 O'Dwyer PJ, Giantonio BJ, Levy DE, et al: Gefitinib in advanced unresectable hepatocellular carcinoma: results from the Eastern Cooperative Oncology Group's Study E1203. J Clin Oncol 2006;24:18S, suppl, A4143.
66 Ramanathan RK, Belani CP, Singh DA, et al: A phase II study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. Cancer Chemother Pharmacol 2009; 64:777–783.

Digestive Diseases

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mTOR Inhibitor for the Treatment of Hepatocellular Carcinoma

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Key Words
Hepatocellular carcinoma · mTOR inhibitor · RAD001 · Evelorimus

Abstract
Mammalian target of rapamycin (mTOR) plays a central role in the regulation of cellular growth, proliferation, and survival via a cytoplasmic serine/threonine kinase. mTOR also works as a nutrition sensor to monitor cellular metabolism. mTOR is located downstream in the PI3K/Akt pathway, in which Akt and the tuberous sclerosis complex (TSC) 1/2 are involved, to form a signal transduction pathway. New anticancer agents that target mTOR in the PI3K/Akt pathway of the signal transduction pathways involved in cell proliferation control have recently been developed and are already commercially available. A phase III clinical trial of mTOR inhibitor for hepatocellular carcinoma (HCC) is now ongoing worldwide to expand indications. RAD001 is a signal-transduction inhibitor (STI) that targets mTOR (more specifically, mTORC1). mTORC1 signaling is intricately regulated by mitogens, growth factors, energy, and nutrients. mTORC1 is a regulator essential for general protein synthesis, located downstream of the PI3K/AKT/mTOR pathway, which is dysregulated in most human cancers. Inhibiting mTOR with molecules, such as RAD001, generates additive effects that accompany upstream and downstream target inhibition; alternatively, upstream receptor inhibition is compensated for by inhibiting the downstream pathway, even if some resistance develops against receptor inhibition regardless of initial or acquired resistance. In conclusion, RAD001 is a potential targeted agent for HCC and therefore final results of a phase III study are awaited.

Introduction

With advances in the molecular biology of tumors, new anticancer agents, such as molecular targeted agents, have been developed. Traditional anticancer agents exhibit nonselective cytotoxic activity, while molecular targeted agents target molecules associated with the proliferation, angiogenesis, apoptosis, metastasis, etc., of cancer cells. Also, new anticancer agents that target mammalian target of rapamycin (mTOR) in the PI3K/Akt pathway of the signal transduction pathways involved in cell proliferation control have recently been developed and are already commercially available. A phase III clinical study of mTOR inhibitor for hepatocellular carcinoma (HCC) is ongoing to expand indications.

PI3K/Akt Pathway and mTOR

mTOR plays a central role in the regulation of cellular growth, proliferation, and survival via a cytoplasmic serine/threonine kinase. mTOR also works as a nutrition sensor to monitor cellular metabolism. mTOR is located downstream in the PI3K/Akt pathway, in which Akt and

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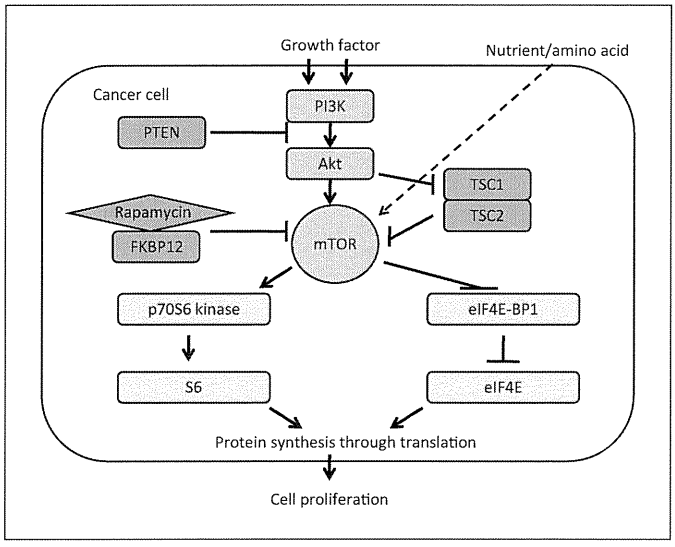


Fig. 1. PI3K/Akt/mTOR signaling pathway.

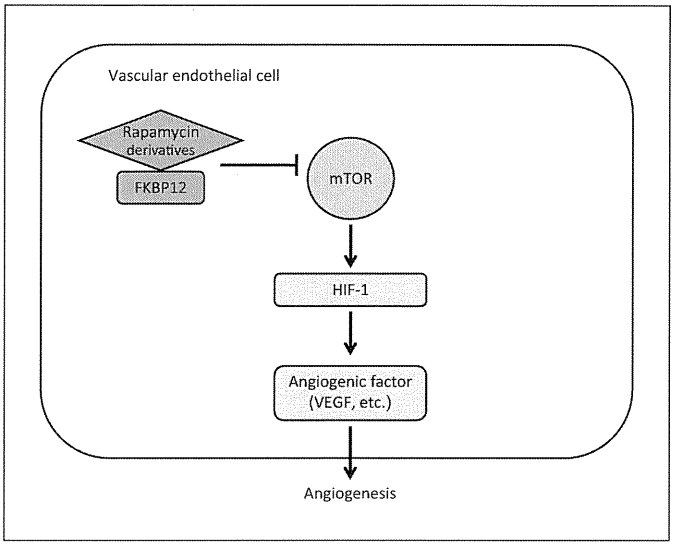


Fig. 2. mTOR/HIF-1/VEGF signaling pathway.

the tuberous sclerosis complex (TSC) 1/2 are involved, to form a signal transduction pathway [1, 2]. The PI3K/Akt pathway is involved in protein synthesis and translation via mTOR, while acting on cell-cycle progression and antiapoptosis via signal transduction to play an important role in cell proliferation. mTOR is a serine/threonine kinase (289 kDa) activated by Akt or Rheb. Activated Akt suppresses TSC, a tumor suppressor gene. Then, TSC suppresses Rheb [3, 4]. Reportedly, this pathway depends on various growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF), as well as the nutritional and oxygen state, etc., and is activated in various cancers [5, 6]. mTOR causes cell proliferation through the following steps (fig. 1): mTOR activates p70S6 kinase that efficiently translates mRNA into a protein by phosphorylating the S6 of 40S ribosomal protein [7], and mTOR phosphorylates eukaryotic initiation factor (eIF)-4 E-binding protein (eIF4E-BP) 1 that binds to eIF4E, a translation initiation factor, to release eIF4E bound to 4E-BP1 and initiate the translation of proteins required for shifting from G_1 to S phases of the cell cycle [8]. p70S6k is a serine/threonine kinase that phosphorylates S6 protein, a component of the ribosomal 40S subunit, and has cell proliferation and antiapoptotic effects when activated [9] (fig. 1).

p70S6k is also considered to be a positive regulator of hypoxia-inducible factor (HIF)-1, a potential master switch for the gene expression of factors that play an important role in angiogenesis (e.g. VEGF) [10] (fig. 2).

mTOR as a Molecular Target of Cancer

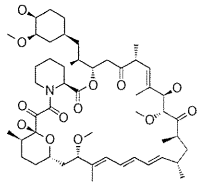
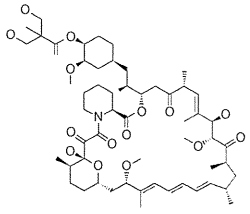
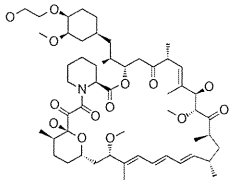
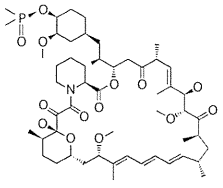
Sirolimus (rapamycin), an mTOR inhibitor, is an agent clinically developed as an antifungal or immunosuppressive drug. Recently, its anticancer effects have attracted attention. Basic and clinical research on rapamycin derivatives, temsirolimus (Torisel™), RAD001 (Afinitor®), and deforolimus (AP23573, MK8669), has been conducted. In addition, an inhibitor (PI-103) for both PI3K and mTOR factors has been clinically developed.

The mTOR signaling pathway is enhanced in various cancers. Increased eIF4E in colorectal cancer and activated Akt and p70S6 kinases in neuroblastoma and thyroid cancer have been reported. Reportedly, cells showing the deletion or mutation of tumor suppressor genes (e.g. PTEN and p53) are highly susceptible to mTOR inhibitors.

The macrolide antibiotic rapamycin, an mTOR inhibitor, binds to FKBP12 (FK-506 binding protein) to form a rapamycin/FKBP12 complex. This complex binds to mTOR to arrest the cell cycle at the G_1 phase and exert antitumor effects through apoptosis induction [7, 11, 12].

Furthermore, inhibitory effects of rapamycin on tumor angiogenesis have recently been demonstrated. Such inhibitory effects on tumor angiogenesis include decreased VEGF production and apoptosis induction in neovascular endothelial cells that are stimulated by VEGF induced in the PI3K/Akt pathway [13–16].

Table 1. mTOR inhibitor

Drug	Chemical structure	Development phase	Administration route
Rapamycin (sirolimus)		phase I	oral
CCI-779 (temsirolimus)		phase III	oral, injection
RAD001 (everolimus)		phase III	oral
AP23573		phase I/II	oral, injection

At present, a clinical study is ongoing on a new mTOR-targeting anticancer agent, a rapamycin derivative that acts as an mTOR inhibitor, to develop a second-line agent against HCC (tables 1, 2).

Mechanism of Action and Characteristics as an Anticancer Agent

Inhibition of Tumor Cell Proliferation

The PI3K/Akt/mTOR signaling pathway is enhanced in various cancers, suggesting mTOR dependence of tumor cell proliferation caused by increased protein synthesis [10]. mTOR targeting is expected to be applied to therapy. Rapamycin and its derivative bind to FKBP12 to form a complex, and further bind to mTOR to inhibit the pathway downstream of mTOR to exert cytostatic antitumor effects by arresting the cell cycle at the G_1 phase [11] (fig. 1).

Inhibition of Tumor Angiogenesis

Inhibitory effects on angiogenesis have attracted attention as additional anticancer effects of mTOR inhibitor. Rapamycin inhibits the activation of HIF-1, a factor involved in angiogenesis, as previously described [17]. In addition, rapamycin strongly inhibits VEGF production and the proliferation of vascular endothelial cells caused by VEGF [13].

Preclinical and Clinical Studies of RAD001 in the Various Cancers

RAD001 (everolimus), a rapamycin derivative, is an mTOR inhibitor that can be administered orally. Reportedly, RAD001 dose-dependently inhibits cell proliferation and angiogenesis both in vivo and in vitro. Currently, clinical studies of various phases are ongoing employing monotherapy or combined therapy with cytocidal

Table 2. Results of mTOR inhibitor in clinical trials

mTOR inhibitor	Subject	Trial phase	Treatment line	Dose-associated drug	Dose/ schedule	Results
Temsirolimus	advanced HCC	randomized phase II	1st, 2nd	25 vs. 75 vs. 250 mg	i.v./weekly	RR 7% (CR 1 case), PFS 5.8 months
	advanced RCC	phase III	1st	25 vs. IFN-α vs. IFN-α + T 25 mg	i.v./weekly	median OS: IFN-α 7.3 months, T 10.9 months, IFN-α + T 8.4 months
	recurrent glioblastoma	phase II	1st, 2nd	250 mg	i.v./weekly	PFS, 6 months, 7.9%
	advanced breast cancer	randomized phase II	2nd line	75 vs. 250 mg	i.v./weekly	RR 9.2%, TTP 12 weeks
	malignant lymphoma	phase II	2nd	250 mg	i.v./weekly	RR 38%, TTP 6.5 months
RAD001	metastatic RCC	phase II	2nd, 3rd	10 mg	oral/daily	RR 29%
	advanced RCC	phase III	2nd, 3rd	placebo vs. 10 mg	oral/daily	placebo 1.9 months, E 4 months
	metastatic gastric cancer	phase II	2nd, 3rd	10 mg	oral/daily	DCR (CR+PR+SD 8 weeks) 59.4%
	advanced HCC	phase I/II		10 mg	oral/daily	RR 30%, RFS 3.8 months, OS 8.4 months
Deforolimus	advanced sarcoma	phase II	1st	12.5 mg	i.v./5 days/2 weeks	CBR (CR+PR+SD 16 weeks) 28%
	relapsed hematologic malignancy	phase II	2nd	12.5 mg	i.v./5 days/2 weeks	RR 10%, SD 40%

CBR = Clinical benefit response; CR = complete response; DCR = disease control rate; E = everolimus; IFN = interferon; OS = overall survival; PFS = progression-free survival; PR = partial response; RCC = renal cell cancer; RR = response rate; SD = stable disease; T = temsirolimus.

antineoplastic and molecular targeted agents in various cancers, such as neuroendocrine tumor, breast cancer [18], stomach cancer [19], lung cancer, malignant lymphoma, and advanced gastrointestinal stromal tumor, and mainly in renal cell cancer [20, 21] (table 2).

In a phase II study of first- and second-line therapies for metastatic renal cancer (10 mg, daily administration), RAD001 was effective in 12 of 41 patients (29%) [20]. Based on these results, a randomized double-blind phase III clinical study of RAD001 (10 mg, daily administration) and placebo was conducted on an international scale, including Japan, in patients with advanced renal cell cancer, in whom the standard therapy with sorafenib tosilate or sunitinib alone or both was ineffective. RAD001 significantly prolonged progression-free survival, a primary endpoint, from 1.9 to 4 months, and reduced the risk of cancer progression by 70% [21]. The rate of adverse drug reactions that led to withdrawal was as low as 6%.

A randomized phase II clinical study was conducted in postmenopausal patients with ER-positive breast cancer using response rates to letrozole and RAD001 (10 mg, daily administration) and letrozole and placebo as primary endpoints; the response rate was significantly higher in the letrozole and RAD001 group than in the letrozole and placebo group (47 vs. 58%, respectively, p = 0.035) [18].

In a phase I clinical study conducted in Japan, responses were noted in patients with advanced/recurrent stomach cancer, in whom all other chemotherapies were ineffective. Thus, a phase II clinical study was conducted employing monotherapy with RAD001 (10 mg, daily administration) in patients with metastatic stomach cancer, in whom pretreatment was ineffective. This therapy was desirable because DCR, a primary endpoint, was favorable (59.4%) and progression-free survival was as long as 84 days, although as many as half of the patients underwent a third therapy [19].

Major adverse events of RAD001, reported in the phase I study involving once-weekly and daily single administration for advanced cancer, include rash, stomatitis, fatigue, nausea, anorexia, diarrhea, vomiting, hyperlipemia, hyperglycemia, and thrombocytopenia. Noninfective pneumonitis as a characteristic toxicity requires caution on using RAD001.

In the phase I study involving the once-weekly administration of RAD001, PK/PD is also examined using p70S6 kinase as a biomarker. The major toxicities include anorexia, general malaise, eruption, stomatitis, headache, hyperlipemia, and gastrointestinal disorder. PR was noted in patients with non-small cell lung cancer. RAD001 inhibited the p70S6 kinase activity of peripheral blood mononuclear cells for 3–5 days in doses of 5 and 10 mg, and inhibited the activity for at least 7 days in 7 of 8 patients at a dose of 20 mg. The phase II study (10 mg, daily administration) was conducted in 25 patients with metastatic renal cancer, with PR being 33%.

RAD001 is a selective inhibitor of mTOR, which specifically targets the mTOR-raptor signal transduction complex (mTORC1). RAD001 interacts with FKBP12, an intracellular receptor protein, with high affinity to exert its activity. The FKBP12/RAD001 complex binds to mTORC1 to inhibit signal transduction. The effects on mTORC1 signal transduction are generated by regulating the phosphorylation of downstream effectors. The most characteristic downstream effectors include S6 ribosomal protein kinase (S6K1), a translational regulator, and 4E-binding protein (4E-BP), a eukaryotic growth factor. Inhibiting mTORC1 suppresses the functions of S6K1 and 4E-BP1, and has effects on the translation of mRNAs that encode major proteins involved in cell cycle regulation, glycolysis, and adaptation to low-oxygen conditions. Consequently, tumor proliferation and HIFs (e.g. HIF-1 transcription factor) are inhibited. Furthermore, the expression of factors (e.g. VEGF), involved in the promotion of tumor angiogenesis, is suppressed by the inhibition of HIFs. RAD001 strongly inhibits the growth and proliferation of tumor cells, endothelial cells, fibroblasts, and vascular smooth muscle cells. RAD001 was demonstrated to control tumor proliferation, glycolysis, and angiogenesis in solid tumors in vivo, thereby inhibiting tumor proliferation through two independent mechanisms, i.e. direct antitumor activity and inhibition of the tumor stroma. This is consistent with the finding that mTORC1 plays a central role in the control system.

RAD001 is a signal-transduction inhibitor (STI) that targets mTOR (more specifically, mTORC1). mTORC1 signaling is intricately regulated by mitogens, growth factors, energy, and nutrients. mTORC1 is a regulator essential for general protein synthesis, located downstream of the PI3K/AKT/mTOR pathway. The PI3K/AKT/mTOR pathway is dysregulated in most human cancers [22]. Inhibiting mTORC1 with RAD001 in vivo was demonstrated to suppress the proliferation of solid tumors, glycolysis, and angiogenesis through both direct antitumor effects and inhibition of the tumor stroma. This is consistent with the known function of mTORC1. RAD001 inhibits the proliferation of human umbilical vein endothelial cells (HUVEC), induced by VEGF, in vitro, and inhibited the angiogenesis caused by VEGF in a chamber-implanted mouse model and in orthotopic melanoma-transplanted and xenograft mouse models [23–26].

Many nonclinical studies have demonstrated that this pathway plays a role in tumor proliferation. In a gain-of-function model, kinases, such as AKT, were constitutively activated, and the same malignant tumors as those that arise in patients with highly activated kinases almost certainly developed. RAD001 markedly inhibits the growth of various human tumor cell lines in vitro and suppress tumor growth in vivo in xenograft, allograft, or orthotopic graft animal models. RAD001 has inhibitory effects on cell proliferation in nanomolar quantities, and, thus, is therapeutically applicable in the doses used in clinical studies. In addition, the inhibitory effects of RAD001 on vascular endothelium proliferation and angiogenesis have been demonstrated.

The following can be considered: inhibiting mTOR with molecules, such as RAD001, generates additive effects that accompany upstream and downstream target inhibition; alternatively, upstream receptor inhibition is compensated for by inhibiting the downstream pathway, even if some resistance develops against receptor inhibition (regardless of initial or acquired resistance). The results demonstrate that RAD001 can be used with other anticancer agents (e.g. paclitaxel, doxorubicin, cisplatin, carboplatin, gemcitabine, imatinib, EGFR/VEGF STI, and letrozole) and radiotherapy. Furthermore, a combination of RAD001 and a cytolytic drug is also effective. The beneficial interaction observed with these combinations was facilitated by inhibiting the involvement of mTOR in the cell survival-associated mechanism (anti-apoptotic mechanism that protects cells from the effects of the cytolytic drug).

mTOR as a Target in the Treatment of HCC

Besides the finding that mTOR plays a key role in cell biology, it was also demonstrated that mTOR and S6K are overexpressed in 15–41% of HCCs, and mTOR inhibitors have antitumor effects in various HCC cell lines and animal models [27–30]. Activation of mTOR is correlated with the development of HCC and recurrence after the excision of early HCC. Regulating this specific intracellular pathway (Ras-Raf pathway) with RAD001 is potentially more effective in suppressing sorafenib-resistant tumors.

A phase I/II trial conducted by Zhu et al. [31] revealed a median RFS of 3.8 months, median TTP of 3.9 months, and median OS of 8.4 months in 25 patients without a few severe adverse effects. RAD001 responded well to the sorafenib failure patients too (median RFS 3.4 months, median OS 7.9 months).

Currently, a phase III clinical trial as a second line to sorafenib is in progress globally in patients who are unresponsive and intolerant to sorafenib. The results of this trial are eagerly awaited to give patients with advanced HCC, who failed to respond sorafenib, additional hope for prolonged survival.

Conclusions

mTOR inhibitor RAD001 is expected to be a potential targeted agent for HCC in patients where sorafenib treatment failed as well as in sorafenib-naive patients.

Disclosure Statement

The author has no conflict of interest to declare.

References

1 Wullschleger S, Loewith R, Hall MN: TOR signaling in growth and metabolism. Cell 2006;124:471–484.
2 Bjornsti MA, Houghton PJ: The TOR pathway: a target for cancer therapy. Nat Rev Cancer 2004;4:335–348.
3 Sabatini DM, Erdjument-Bromage H, Lui M, Tempst P, Snyder SH: RAFT1: a mammalian protein that binds to FKBP12 in a rapamycin-dependent fashion and is homologous to yeast TORs. Cell 1994;78:35–43.
4 Schmelzle T, Hall MN: TOR, a central controller of cell growth. Cell 2000;103:253–262.
5 Shaw RJ, Cantley LC: Ras, PI3K and mTOR signalling controls tumour cell growth. Nature 2006;441:424–430.
6 Pouyssegur J, Dayan F, Mazure NM: Hypoxia signalling in cancer and approaches to enforce tumour regression. Nature 2006;441:437–443.
7 Seufferlein T, Rozengurt E: Rapamycin inhibits constitutive p70S6k phosphorylation, cell proliferation, and colony formation in small cell lung cancer cells. Cancer Res 1996;56:3895–3897.
8 Rosenwald IB, Kaspar R, Rousseau D, Gehrke L, Leboulch P, Chen JJ, et al: Eukaryotic translation initiation factor 4E regulates expression of cyclin D1 at transcriptional and post-transcriptional levels. J Biol Chem 1995;270:21176–1180.
9 Hu L, Zaloudek C, Mills GB, Gray J, Jaffe RB: In vivo and in vitro ovarian carcinoma growth inhibition by a phosphatidylinositol 3-kinase inhibitor (LY294002). Clin Cancer Res 2000;6:880–886.
10 Hudson CC, Liu M, Chiang GG, Otterness DM, Loomis DC, Kaper F, et al: Regulation of hypoxia-inducible factor 1α expression and function by the mammalian target of rapamycin. Mol Cell Biol 2002;22:7004–7014.
11 Grewe M, Gansauge F, Schmid RM, Adler G, Seufferlein T: Regulation of cell growth and cyclin D1 expression by the constitutively active FRAP-p70S6K pathway in human pancreatic cancer cells. Cancer Res 1999;59:3581–3587.
12 Abraham RT, Gibbons JJ: The mammalian target of rapamycin signaling pathway: twists and turns in the road to cancer therapy. Clin Cancer Res 2007;13:3109–3114.
13 Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, et al: Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med 2002;8:128–135.
14 Yu Y, Sato JD: MAP kinases, phosphatidylinositol 3-kinase, and p70S6 kinase mediate the mitogenic response of human endothelial cells to vascular endothelial growth factor. J Cell Physiol 1999;178:235–246.
15 Suhara T, Mano T, Oliveira BE, Walsh K: Phosphatidylinositol 3-kinase/Akt signaling controls endothelial cell sensitivity to Fas-mediated apoptosis via regulation of FLICE-inhibitory protein (FLIP). Circ Res 2001;89:13–19.
16 Bruns CJ, Koehl GE, Guba M, Yezhelyev M, Steinbauer M, Seeliger H, et al: Rapamycin-induced endothelial cell death and tumor vessel thrombosis potentiate cytotoxic therapy against pancreatic cancer. Clin Cancer Res 2004;10:2109–2119.
17 Huang S, Houghton PJ: Targeting mTOR signaling for cancer therapy. Curr Opin Pharmacol 2003;3:371–377.
18 Baselga J, van Dam PA, Greil R, et al: Improved clinical and cell cycle response with an mTOR inhibitor, daily oral RAD001 (everolimus) plus letrozole versus placebo plus letrozole in a randomized phase II neoadjuvant trial in ER + breast cancer. J Clin Oncol 2008;26 (ASCO 2008, abstr 530).
19 Muro K, Boku N, Yamada Y, et al: Multicenter phase II study of RAD001 for previously treated metastatic gastric cancer; preliminary results. J Clin Oncol 2008;26 (ASCO 2008, abstr 4541).
20 Jac J, Giessinger S, Khan M, et al: A phase II trial of RAD001 in patients with metastatic renal cell carcinoma. J Clin Oncol 2007;25(suppl 18):5107.
21 Motzer RJ, Escudier B, Oudard S, et al: RAD001 vs. placebo in patients with metastatic renal cell carcinoma after progression on VEGFr-TKI therapy; results from a randomized, double-blind, multicenter phase-III study. J Clin Oncol 2008;26 (ASCO 2008, abstr LBA5026).
22 Boulay A, Lane HA: The mammalian target of rapamycin kinase and tumor growth inhibition. Recent Results Cancer Res 2007;172:99–124.
23 Shinohara ET, Cao C, Niermann K, Mu Y, Zeng F, Hallahan DE, et al: Enhanced radiation damage of tumor vasculature by mTOR inhibitors. Oncogene 2005;24:5414–5422.
24 Mabuchi S, Altomare DA, Cheung M, Zhang L, Poulikakos PI, Hensley HH, et al: RAD001 inhibits human ovarian cancer cell proliferation, enhances cisplatin-induced apoptosis, and prolongs survival in an ovarian cancer model. Clin Cancer Res 2007;13:4261–4270.
25 Mabuchi S, Altomare DA, Connolly DC, Klein-Szanto A, Litwin S, Hoelzle MK, et al: RAD001 (everolimus) delays tumor onset and progression in a transgenic mouse model of ovarian cancer. Cancer Res 2007;67:2408–2413.
26 Manegold PC, Paringer C, Kulka U, Krimmel K, Eichhorn ME, Wilkowski R, et al: Antiangiogenic therapy with mammalian target of rapamycin inhibitor RAD001 (everolimus) increases radiosensitivity in solid cancer. Clin Cancer Res 2008;14:892–900.
27 Sahin F, Kannangai R, Adegbola O, Wang J, Su G, Torbenson M: mTOR and p70S6 kinase expression in primary liver neoplasms. Clin Cancer Res 2004;10:8421–8425.
28 Schumacher G, Oidtmann M, Rueggeberg A, Jacob D, Jonas S, Langrehr JM, et al: Sirolimus inhibits growth of human hepatoma cells alone or combined with tacrolimus, while tacrolimus promotes cell growth. World J Gastroenterol 2005;11:1420–1425.
29 Semela D, Piguet AC, Kolev M, Schmitter K, Hlushchuk R, Djonov V, et al: Vascular remodeling and antitumoral effects of mTOR inhibition in a rat model of hepatocellular carcinoma. J Hepatol 2007;46:840–848.
30 Sieghart W, Fuereder T, Schmid K, Cejka D, Werzowa J, Wrba F, et al: Mammalian target of rapamycin pathway activity in hepatocellular carcinomas of patients undergoing liver transplantation. Transplantation 2007;83:425–432.
31 Zhu AX, Abrams TA, Miksad R, Blaszkowsky LS, Meyerhardt JA, et al: Phase 1/2 study of everolimus in advanced hepatocellular carcinoma. Cancer DOI: 10.1002/cncr.26165.

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Future Treatment Option for Hepatocellular Carcinoma: A Focus on Brivanib

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Key Words
Hepatocellular carcinoma · Molecular targeted therapy · Brivanib · Sorafenib

Abstract
Hepatocellular carcinoma (HCC), one of the most common cancers worldwide, is particularly prevalent in the Asia-Pacific region. Guidelines on the treatment of HCC in Japan come from both consensus-based and evidence-based treatment algorithms. However, patients with extensive liver damage and/or more advanced disease (major vascular invasion and/or extrahepatic spread) are currently ineligible for any treatment. Recent knowledge of hepatocarcinogenesis has led to the targeting of new pathways, particularly the angiogenic pathway, with a specific focus on the vascular endothelial growth factor receptor (VEGFR). Apparently the most studied systemic antiangiogenic agent for HCC is sorafenib. An updated version of the aforementioned treatment algorithms recommends sorafenib therapy for advanced HCC patients with Child-Pugh A liver function and extrahepatic spread or major vascular invasion. Moreover, sorafenib is recommended for use in HCC patients who are refractory or intolerant to transarterial chemoembolization (TACE) with well-preserved liver function (Child-Pugh A). However, one of the unresolved issues is anti-VEGF resistance. It is speculated that novel antiangiogenic agents that combine inhibition of other pathways such as fibroblast growth factor receptor signaling in addition to VEGFR signaling might provide a potential mechanism to overcome anti-VEGF resistance in HCC. Brivanib inhibits both VEGF and fibroblast growth factor receptor signaling. To further investigate the benefits of brivanib for advanced HCC, a broad-spectrum, global, phase III development plan, the Brivanib studies in HCC patients at RISK (BRISK) clinical program, has been initiated. Clinical benefits seen with brivanib in the first-line setting, and following the failure of sorafenib therapy, highlight the potential to improve the clinical course of patients with advanced HCC, and this agent may provide a novel therapeutic option for the growing population of patients for whom no other treatment choice exists.

Introduction

Hepatocellular carcinoma (HCC), one of the most common cancers worldwide, is particularly prevalent in the Asia-Pacific region, with more than two thirds of global cases occurring in Asia-Pacific countries [1, 2]. In Japan, HCC is now the third leading cause of cancer death among males and females, and is responsible for the death of more than 33,000 Japanese citizens every year [3]. Throughout the Asia-Pacific region, the most important etiologic factors related to HCC are hepatitis B virus (HBV) and hepatitis C virus (HCV). Among Japanese

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HCC patients, the primary etiology is HCV, with approximately 70–80% chronically infected with HCV and only a small proportion with HBV (<16%) [4, 5].

Treatment Algorithm and Unmet Medical Needs

Guidance on the treatment of HCC in Japan comes from both consensus-based and evidence-based treatment algorithms [6, 7]. As nationwide HCC screening programs are common in Japan, most patients present in the early stages of the disease and are eligible for potentially 'curative' treatments, such as surgical resection or local ablation (radiofrequency ablation or percutaneous ethanol injection) [6, 7]. If resection or ablation is contraindicated, or if the disease has progressed, then transarterial chemoembolization (TACE) or hepatic infusion chemotherapy may be recommended [6, 7]; however, patients with extensive liver damage and/or more advanced disease (major vascular invasion and/or extrahepatic spread) are currently ineligible for these treatments [6]. As such, there remains a significant unmet medical need for patients with advanced HCC in Japan.

Present Status of Molecular Targeted Therapy

Recent knowledge of hepatocarcinogenesis has led to the targeting of new pathways, particularly the angiogenic pathway, with a specific focus on the vascular endothelial growth factor receptor (VEGFR). Indeed, agents that inhibit angiogenesis via blockade of the VEGFR have seen some success in the treatment of HCC. Moreover, recent research data suggest the potential for an additional synergistic role for antiangiogenic agents whereby they might be used following TACE therapy to increase response rates [8]. Apparently the most studied systemic antiangiogenic agent for HCC is sorafenib. This is an oral multikinase inhibitor that targets the tyrosine kinase activity of VEGFRs 1, 2, and 3, as well as platelet-derived growth factor receptor-β, and has recently demonstrated some efficacy over placebo in Child-Pugh A patients with advanced HCC [9]. Similar results have been observed in a study of sorafenib for patients with advanced HCC conducted in the Asia-Pacific region [10], and a recent phase 1 study has indicated favorable safety/tolerability and promising antitumor activity in a Japanese population [11]. On the basis of these results, sorafenib has been approved in Japan for the treatment of advanced HCC since May 2009.

Indication of Sorafenib in Treatment Algorithm

There are, however, unresolved issues regarding the optimal use of sorafenib for HCC. To date, survival benefits in clinical trials have been modest, and a relatively high incidence of hand-foot syndrome (all-grade events reported in ~20–45% of patients) [9, 10] and an increased risk of bleeding events have been reported in the international literature [12]. In Japan, primarily due to the design of the pivotal trials and the available data in HCC patients, sorafenib use has been strictly regulated and limited to patients with Child-Pugh A cirrhosis who are not candidates for resection, ablation, or TACE. Moreover, post-marketing surveillance of sorafenib in Japan has raised safety concerns regarding interstitial pneumonia, hepatic coma, and hepatic failure, which has led to revision of the Japanese package insert. Updated version of the aforementioned treatment algorithms recommend sorafenib therapy for advanced HCC patients with Child-Pugh A liver function and extrahepatic spread or major vascular invasion. Moreover, sorafenib is recommended for use in HCC patients who are refractory or intolerant to TACE with well-preserved liver function (Child-Pugh A) (for details, see Kudo, fig. 7, p. 299) [13–15].

Anti-VEGF Resistance

Recent studies suggest that tumor progression following treatment with antiangiogenic agents that target the VEGF signaling pathway alone may result from either evasive or intrinsic resistance [16]. Furthermore, there is strong evidence to support the hypothesis that evasive resistance to anti-VEGF blockade is associated with reactivation of tumor angiogenesis by alternative signaling pathways, one such mechanism of resistance being activation of the fibroblast growth factor (FGF) signaling pathway [17, 18]. Basic FGF (FGF2) is a potent angiogenic factor. Indeed, expression of FGF2 enhances growth, invasion, and angiogenesis of many tumor types [19, 20]. Moreover, recent evidence has shown that FGF is overexpressed and activated in HCC and that high FGF2 levels may predict for a poor clinical outcome among patients with HCC [20].

Importance of FGF Signaling

Considering the proposed importance of FGF signaling in HCC angiogenesis, it is clear that novel antiangiogenic agents that combine inhibition of FGF receptor sig-