Systemic treatment and targeted therapy in patients with advanced hepatocellular carcinoma

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Abstract
Background: Advanced hepatocellular carcinoma (HCC) is a malignancy of global importance: it is the sixth most common cancer and the third most common cause of cancer-related mortality worldwide. Despite decades of efforts by many investigators, systemic chemotherapy or hormone therapy has failed to demonstrate improved survival in patients with HCC. Ongoing studies are evaluating the efficacy and tolerability of combining Sorafenib with erlotinib and other targeted agents or chemotherapy. Aims: On the basis of placebo-controlled, randomized phase III trials, Sorafenib has shown improved survival benefits in advanced HCC and has set a new standard for future clinical trials. The successful clinical development of Sorafenib in HCC has ushered in the era of molecularly targeted agents in this disease, which is discussed in this educational review. Material and Methods: Many molecularly targeted agents that inhibit angiogenesis, epidermal growth factor receptor, and mammalian target of rapamycin are at different stages of clinical development in advanced HCC. Future research should continue to unravel the mechanism of hepatocarcinogenesis and to identify key relevant molecular targets for therapeutic intervention. Identification and validation of potential surrogate and predictive biomarkers hold promise to individualize patients’ treatment to maximize clinical benefit and minimize the toxicity and cost of targeted agents. Results: Systemic therapy with various classes of agents, including hormone and cytotoxic agents, has provided no or marginal benefits. Improved understanding of the mechanism of hepatocarcinogenesis, coupled with the arrival of many newly developed molecularly targeted agents, has provided the unique opportunity to study some of these novel agents in advanced HCC. Conclusions: The demonstration of improved survival benefits by Sorafenib in advanced HCC has ushered in the era of molecular-targeted therapy in this disease, with many agents undergoing active clinical development.

Keywords: Systemic treatment, Targeted therapy, Hepatocellular carcinoma, Sorafenib, Bevacizumab, Sunitinib, Erlotinib; Brivanib, ABT 869, Pazopanib.

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Systemic therapy in hepatocellular carcinoma: Historical perspectives
Despite extensive efforts by many investigators, systemic therapy with many classes of agents for HCC has been ineffective, as evidenced by low response rates and no demonstrated survival benefit (Table 1) [1, 2]. The finding that various hormone receptors are present in HCC has led many investigators to examine the role of hormone manipulation in this disease. Several lines of evidence have suggested an association between estrogen and HCC [3, 4]. Estrogen receptors are expressed in normal human liver, in chronic hepatitis, in benign hepatic tumour tissues, and rarely in HCC at a low concentration [6]. In preclinical models, estrogens are involved in stimulating hepatocyte proliferation in vitro and may promote liver
tumour growth in vivo [7]. The persistent administration of estrogens, particularly in the form of oral contraceptives, has been associated with an increased incidence of hepatic adenomas and a small increased risk of HCC [6]. Tamoxifen, an antiestrogenic compound, has been shown to reduce the level of estrogen receptors in the liver [8]. Tamoxifen has been extensively studied in HCC. Six large randomized studies (four of which were double-blind trials) have failed to demonstrate improved survival with tamoxifen in advanced HCC [8-13]. Antiandrogen therapies have also failed to improve survival in randomized studies in patients with advanced HCC [12, 14]. Although a large number of controlled and uncontrolled studies have been performed with most classes of chemotherapeutic agents, no single or combination chemotherapy regimen is particularly effective in HCC [5]. The response rate tends to be low, and the response duration is short. The response criteria used in some of the earlier studies were poorly defined. Most of the earlier studies did not stratify patients on the basis of the severity of underlying cirrhosis or other factors, making comparison of study results difficult. More importantly, any survival benefit of systemic chemotherapy for HCC remains to be determined. Doxorubicin is perhaps the most widely used agent in HCC. Despite the initial encouraging reports from Uganda for single-agent Doxorubicin, subsequent studies have failed to confirm these data. In a large study of Doxorubicin in advanced HCC, no responses were noted among 109 patients [15]. Among 475 patients who received Doxorubicin in various studies, a 16% response rate was documented, with a median survival of 3 to 4 months [16].

A variety of combination chemotherapy regimens has been studied in HCC. Although a few of them have shown improved response rates, most of these have not been studied in large randomized phase III studies. The most impressive results from phase II studies are from the chemotherapeutic regimen that uses the combination of cisplatin, interferon Alfa, Doxorubicin, and 5-fluorouracil (PIAF) [17]. This regimen produced a partial response (PR) rate of 26%. In 9 of the 50 patients, the initially unresectable tumours became resectable after chemotherapy. In four of these patients, the resected specimens had a pathologic complete response and the Alfa-fetoprotein (AFP) levels fell to within the reference range. Unfortunately, this regimen was also associated with marked hematoletic and gastrointestinal toxicity. Yeo and colleagues subsequently examined the efficacy of this regimen in a randomized phase III study comparing PIAF with single-agent Doxorubicin [18]. A total of 188 patients with unresectable HCC were enrolled. The median survival of the Doxorubicin and PIAF groups was 6.83 months (95% confidence interval [95% CI], 4.80–9.56) and 8.67 months (95% CI, 6.36–12.00), respectively (P = 0.83), which failed to reach statistical significance for the study primary end point.

The difficulty of developing effective chemotherapy in HCC may in part be due to the inherent resistance in the tumour conferred by the multidrug-resistant gene MDR-1 [19, 21]. In addition, the underlying cirrhosis present in most patients may lead to portal hypertension with hypersplenism, platelet sequestration, varices and gastrointestinal bleeding, hepatic encephalopathy, hypoalbuminemia, differential drug binding and distribution, and altered pharmacokinetics, limiting the selection and adequate dosing of most cytotoxic agents.

### Table 1 Systemic therapies that have not demonstrated improved overall survival benefits in advanced hepatocellular carcinoma.

| Therapy Type | Description |
|--------------|-------------|
| Hormones agents | tamoxifen, antiandrogen |
| Chemotherapy (single agent or combination) | Octreotide, Interferon, Thalidomide, Arginine deiminase |

### Sorafenib Improves Survival In Advanced HCC

Sorafenib is an oral multikinase inhibitor that blocks tumour cell proliferation by targeting the Raf/MEK/ERK signalling pathway and exerts an antiangiogenic effect by targeting the tyrosine kinases of vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, and platelet-derived growth factor receptor (PDGFR)-beta [22]. In preclinical models, Sorafenib exhibited antitumor activity in HCC cells and xenograft models [22, 23]. In a phase II study of 137 patients with advanced HCC, Sorafenib provided orally at 400 mg twice daily induced a PR in 2.2% of patients, a minor response in 5.8%, and stable disease lasting C4 months in 34% [24]. Median time to progression (TTP) was 4.2 months, and median overall survival (OS) was 9.2 months. The international, phase III, placebo-controlled Sorafenib HCC Assessment Randomized Protocol (SHARP) trial evaluated 602 patients with advanced HCC who had not undergone prior systemic therapy to receive either Sorafenib at 400 mg twice daily (299 patients) or placebo (303 patients) [25]. The primary end point of the study was OS. Patients with underlying Child-Pugh A cirrhosis accounted for 95% and 98% in the Sorafenib and placebo groups, respectively. Median OS was 10.7 months in the Sorafenib group and 7.9 months in the placebo group (hazard ratio of death in the Sorafenib group, 0.69; P = 0.001). The median TTP was 5.5 months in the Sorafenib group and 2.8 months in the placebo group (P = 0.001). In another Asian-Pacific randomized phase III study, Sorafenib also demonstrated improved OS in patients with advanced HCC, mostly in patients with hepatitis B virus infection [26]. OS was 6.5 months in the Sorafenib group versus 4.2 months in the placebo group (hazard ratio in the Sorafenib group, 0.68; P = 0.014). The safety profiles of Sorafenib seem favorable; however, grade III diarrheal, hand-and-foot skin reaction, and fatigue were observed. The successful development of Sorafenib has validated the use of molecularly targeted agents in HCC. This is the first agent ever to have shown improved survival benefits in this disease. It highlights the importance of selecting the right patient population (good
performance status and preserved hepatic function) for clinical trial design. The major benefits of Sorafenib are mainly manifested as disease stabilization rather than radiologic response. However, many questions remained unanswered: what is the mechanism of action mediating the clinical benefits of Sorafenib? Who are at risk for developing toxicities? What is the escape and resistance mechanism of Sorafenib failure? Will Sorafenib benefit patients with worsening underlying cirrhosis? Will Sorafenib prove to be beneficial in patients in earlier stages of disease that is, after surgical resection, high-risk transplantation, or radiofrequency ablation, as well as transarterial chemoembolization? Some of these questions are addressed in ongoing and planned clinical trials.

**Sorafenib-Based Regimens Under Development**

Abou-Alfa and colleagues reported their experience from a randomized, double-blinded, phase II study comparing Doxorubicin in combination with Sorafenib versus Doxorubicin with placebo in patients with advanced HCC [27]. Patients had Eastern Cooperative Oncology Group performance status of 0–2, Child-Pugh A cirrhosis, and no prior systemic therapy. They received Doxorubicin at 60 mg/m² intravenously every 21 days (cycle) plus either Sorafenib at 400 mg orally twice daily or placebo, for a maximum of six cycles of Doxorubicin. Patients could continue with single-agent Sorafenib or placebo afterward. The primary end point was TTP by independent review. Ninety-six patients were randomized in this study. The median OS and TTP were 13.7 and 8.6 months for the Doxorubicin? Sorafenib arm and 6.5 and 4.8 months for the Doxorubicin ? Placebo arm, respectively. Of note, the response rate was only 4% in the Doxorubicin? Sorafenib arm and 2% for the Doxorubicin? Placebo arm. Despite the encouraging results, the control arm was Sorafenib making the relative contribution of Doxorubicin, if any, difficult to assess in the Sorafenib/Doxorubicin arm. The safety profiles seemed to be comparable, including approximately 50% grade 3-4 neutropenia events in both arms. Because of the lack of consensus on the best chemotherapeutic agents/regimens in HCC and the safety concerns including cardiac toxicity for Doxorubicin, other investigators are investigating the efficacy and tolerability of combining Sorafenib with Capecitabine and Oxaliplatin or Gemcitabine and Cisplatin in advanced HCC. Given the complexity of hepatocarcinogenesis and heterogeneity of HCC, targeting HCC by means of a combination of Sorafenib and another agent inhibiting a distinct pathway represents an appealing strategy. On the basis of this rationale, preclinical data, phase I experience, and single-agent activity and tolerability in HCC, a randomized international phase III study comparing Sorafenib plus erlotinib versus Sorafenib plus placebo as first-line treatment in advanced HCC is ongoing. The primary end point of the study is OS. Other Sorafenib-based combinations, including mTOR inhibitors and insulin growth factor receptor (IGF-R) inhibitors, are at an early stage of development.

**Antiangiogenic Agents**

HCCs are vascular tumours, and increased levels of vascular endothelial growth factor (VEGF) and microvessel density have been observed [28-31]. High VEGF expression has been associated with worse survival [32-34]. Therefore, inhibition of angiogenesis represents a potential therapeutic target in HCC, and several antiangiogenic agents have entered clinical studies in HCC.

**Bevacizumab**

Bevacizumab is a recombinant humanized monoclonal antibody that targets VEGF. In addition to its direct antiangiogenic effects, Bevacizumab may enhance chemotherapy administration by “normalizing” tumour vasculature and lowering the increased interstitial pressure in tumours [35, 36]. Several studies have explored the use of Bevacizumab either as a single agent or in combination with cytotoxic or molecularly targeted agents in patients with advanced HCC (Table 2). Siegel et al. reported their experience using single-agent bevacizumab in HCC in a phase II study [37]. Two dosages of Bevacizumab, 5 mg/kg and 10 mg/kg administered intravenously once every 2 weeks, were tested in patients with HCC with no overt extrahepatic metastases or invasion of major blood vessels. Of the 46 patients with data available for efficacy, 6 had objective responses (13%; 95% CI, 3–23), and 65% were progression free at 6 months. Median progression-free survival (PFS) time was 6.9 months (95% CI, 6.5–9.1), and median survival was 12.4 months (95% CI, 9.4–19.9). Malka and colleagues also reported their early experience using Bevacizumab as a single agent in HCC in a phase II study [38]. The combination of Bevacizumab with cytotoxic agents was also evaluated in three phase II studies. Zhu and colleagues completed a phase II study that used Bevacizumab in combination with Gemcitabine and Oxaliplatin (GEMOX-B) in advanced HCC [39]. This regimen had moderate antitumor activity in HCC with an overall response rate of 20% in evaluable patients. An additional 27% of patients had stable disease with a median duration of 9 months (range, 4.5 to 13.7 months). The median OS was 9.6 months and the median PFS was 5.3 months. The combination of Bevacizumab with Capecitabine and Oxaliplatin or with Capecitabine alone in patients with advanced HCC was also reported (Table 3) [40, 41]. Thomas and colleagues reported their single-center phase II experience using the combination of Bevacizumab and Erlotinib in patients with advanced HCC [42]. Bevacizumab was provided at 10 mg/kg intravenously once every 14 days and Erlotinib at 150 mg orally daily. Of the 40 patients with efficacy data available, a 25% response rate was observed. The median PFS was 9 months and OS was 15 months. The above studies demonstrated early evidence of antitumor activity of Bevacizumab in HCC. Despite the overall good tolerability profiles, the risk of bleeding, hypertension, and thromboembolic events remain to be further characterized. Moreover, as a result of the nonrandomized nature, small sample size, and patient selection bias inherent in single-arm studies, the relative contributions, if any, from
any chemotherapy regimens or erlotinib remain unknown and warrant further investigations.

Table 2 Phase II studies of bevacizumab-based regimens in hepatocellular carcinoma.

| Study         | Regimen            | patient No. | RR (%) | Median PFS/TTP (months) | Median survival (months) |
|---------------|--------------------|-------------|--------|-------------------------|--------------------------|
| Siegel [37]   | B                  | 46          | 13     | 6.9                     | 12.4                     |
| Malka [38]    | B                  | 24          | 12.5   | NR                      | NR                       |
| Zhu [39]      | Gemox-B            | 33          | 20     | 5.3                     | 9.6                      |
| Sun [40]      | Capox-B            | 30          | 10     | 5.4                     | NR                       |
| Hsu [41]      | Cap-B              | 25          | 16     | 4.1                     | 10.7                     |
| Thomas [42]   | Erlotinib-B        | 40          | 25     | 9.0                     | 15.6                     |

RR: Response rate, PFS: Progression free survival, TTP: Time to progression, B: Bevacizumab, Gemox-B: Gemcitabine-oxaliplatin-bevacizumab, Capox-B: Capcitabine-oxaliplatin-bevacizumab, NR: Not reported.

Table 3 Phase II trials of epidermal growth factor receptor inhibitors in hepatocellular carcinoma.

| Drug           | Year | Patient No. | RR (%) | Median PFS (months) | Median OS (months) |
|----------------|------|-------------|--------|---------------------|-------------------|
| Erlotinib      | 2005 | 38          | 9      | 3.2                 | 13                |
| Erlotinib      | 2007 | 40          | 0      | 3.1                 | 6.3               |
| Lapatinib      | 2009 | 40          | 5      | 2.3                 | 6.2               |
| Cetuximab      | 2007 | 32          | 0      | 2                   | _                 |
| Cetuximab      | 2007 | 30          | 0      | 1.4                 | 9.6               |
| GEMOX + Cetuximab | 2008 | 45          | 20     | 4.7                 | 9.5               |
| CAPOX + Cetuximab | 2008 | 25          | 10     | 4.3                 | _                 |

RR: Response rate, PFS: Progression free survival, OS: Overall survival, GEMOX: Gemcitabine-oxaliplatin, CAPOX: Capcitabine-oxaliplatin.

**Sunitinib**

Sunitinib is an oral multikinase inhibitor that targets receptor tyrosine kinases (RTKs) including VEGFR-1, VEGFR-2, PDGFR-a/b, c-KIT, FLT3, and RET kinases [43-45]. Zhu and colleagues performed a study in patients with advanced HCC that used sunitinib at 37.5 mg orally once daily on a standard 4-weeks-on, 2-weeks-off regimen (6 weeks per cycle) [46]. The primary end point of the study was PFS. Of the 34 patients enrolled, one patient had a PR of 20 months duration, and an additional 10 patients (38.5%) had stable disease of at least 12 weeks duration. The median PFS was 3.9 months and OS was 9.8 months. In another European/Asian phase II study, sunitinib was administered at 50 mg daily for 4 weeks every 6 weeks to patients with unresectable HCC [47]. The primary end point of the study was overall response rate according to Response Evaluation Criteria in Solid Tumours criteria. Of the 37 patients enrolled, one patient (2.7%) experienced PR, and 13 patients (35%) had stable disease as their best response. The median OS was 8.0 months and PFS was 3.7 months. Preliminary results from two other phase II studies were also presented, one that used 37.5 mg for a 4-weeks-on, 2-weeks-off schedule, and the other with 37.5 mg continuous daily dosing.

In terms of toxicity, the studies that used the lower dose (37.5 mg) reported acceptable safety profiles. The most common adverse events included hematologic toxicities, fatigue, and an increase in transaminase [46, 47]. Grade 3 or 4 adverse events occurred in no more than 20% of the patients in any category. At the higher dose of 50 mg daily, sunitinib treatment led to more pronounced grade 3-4 toxicities and a higher death rate of 10% in this patient population [47].

Although the lower dose at 37.5 mg seems to be more tolerable, it remains uncertain whether the continuous or intermittent schedule is better. A randomized phase III study comparing sunitinib at 37.5 mg continuous daily dosing versus Sorafenib at 400 mg twice daily in advanced HCC (clinical trial identifier: NCT00699374) is ongoing.

**Brivanib**

Brivanib alinate is a dual inhibitor of VEGFR and fibroblast growth factor receptor (FGFR)-signaling pathways that can induce tumour growth inhibition in mouse HCC xenograft model [48]. A phase II study was conducted to assess the efficacy and safety of brivanib in patients with unresectable locally advanced or metastatic HCC who had received either no prior systemic therapy (cohort A) or one prior regimen of angiogenesis inhibitor (cohort B) [49]. The treatment schedule consisted of continuous daily dosing of brivanib at 800 mg. Of the 96 patients enrolled, 55 patients were in cohort A and 41 in cohort B, including 38 whose disease failed to respond to Sorafenib. In cohort A, median OS was 10 months and TTP was 2.8 months (95% CI, 1.4–3.9). PR was seen in 5% of patients, and disease control rate was 47%. Interestingly, a 50% decrease in serum AFP from baseline was seen in 40% of patients in both cohorts A and B. Most frequently observed grade 3-4 adverse events included fatigue (16%), high levels of AST (7.3%), diarrhea (4.9%), and headache (4.9%) in cohort B. Brivanib is undergoing additional evaluation in phase III studies in both the first-line setting in comparison with Sorafenib and in the Sorafenib-refractory setting in comparison with best supportive care in advanced HCC.

**ABT-869**

ABT-869 is an orally active, potent, and selective inhibitor of VEGFR and PDGFR. Preliminary results from an open-label, multicenter phase II study of ABT-869 in advanced HCC were reported [50]. ABT-869 was provided at 0.25 mg/kg daily in Child-Pugh A or once every other day in Child-Pugh B patients until disease progressed or toxicity became intolerable. The primary end point was the progression-free rate at 16 weeks. Of the 44 patients enrolled, 34 had data available for analysis (28 with Child A and 6 with Child B cirrhosis). The estimated response rate was 8.7% (95% CI, 1.1–28) for the 23 patients with Child A cirrhosis. For all 34 patients, median TTP was 112 days (95% CI, 110–not estimable), median PFS was 112 days (95% CI, 61–168), and median OS was 295 days (95% CI, 182–333). The most common adverse events for
all patients were hypertension (41%), fatigue (47%), diarrhea (38%), rash (35%), proteinuria (24%), vomiting (24%), cough (24%), and oedema peripheral (24%). The most common grade 3-4 adverse events were hypertension (20.6%) and fatigue (11.8%). The early evidence of efficacy and tolerable safety profiles has encouraged further development of ABT-869 in HCC.

**Pazopanib**

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit. Reports from a phase I study to determine the maximum tolerated dose (MTD), safety, pharmacokinetics, pharmacodynamics, and efficacy of pazopanib in patients with locally unresectable and/or advanced HCC were presented [51]. Eligibility criteria included unresectable and/or metastatic HCC with at least one target lesion, recovery from prior systemic regimens, Eastern Cooperative Oncology Group performance status of 0 or 1, Child Pugh A, and adequate organ function. Doses of pazopanib were escalated from 200 mg once daily to 800 mg daily in a 3 + 3 design. In the 27 Asian patients enrolled, MTD was determined to be 600 mg once daily. PR was observed in two patients (7%; one at 800 mg, one at 600 mg) and stable disease of 4 months in 11 patients (41%). Median TTP at the MTD was 137.5 days (range, 4–280 days). Changes in tumour dynamic contrast-enhanced magnetic resonance imaging parameters were seen after repeated dose pazopanib administration.

**AZD2171**

AZD2171 (cediranib) is a potent oral pan-VEGFR tyrosine kinase inhibitor with activity against platelet-derived growth factor receptors and c-Kit. AZD2171 is a potent inhibitor of both KDR (IC50=0.002 IM) and Flt-1 (IC50=0.005 IM), and shows activity against c-kit, platelet-derived growth factor receptor beta (PDGFRb) and Flt-4 at nanomolar concentrations [52]. Alberts and colleagues reported their early experiences of toxicity and efficacy of AZD2171 from a phase II study in patients with advanced HCC [53]. AZD2171 was provided at 45 mg orally once daily on a 28-day treatment cycle. Twenty-eight patients have been accrued, and 19 patients had toxicity data available for assessment. Of these, 16 patients (84%) developed grade 3 toxicity. Fatigue, hypertension, and anorexia accounted for most adverse events. Despite a lack of grade 4 events, a high rate of refusal of further treatment was encountered and seemed to be related to the high rate of grade 3 fatigue. Patients received a median of one cycle of treatment (range, 1–8 cycles) while on the study. We are currently conducting a single-arm phase II study that uses AZD2171 at 30 mg daily to assess the tolerability and safety in advanced HCC.

**PTK787**

PTK787/ZK 222584 (Vatalanib) is an oral angiogenesis inhibitor targeting all known VEGFR tyrosine kinases, including VEGFR-1/flt-1, VEGFR-2/KDR, and VEGFR-3/ Flt-4, PDGFR, and the c-kit with a higher selectivity for VEGFR-2 [54, 55]. Koch and colleagues reported the early experience of an open-label, multicenter phase I study to characterize the safety, tolerability, and pharmacokinetic profile of PTK787 administered once daily at a dose of 750 mg to 1250 mg in patients with unresectable HCC [56]. Patients were stratified into three groups with mild, moderate, and severe hepatic dysfunction, respectively, on the basis of total bilirubin and AST (aspartate aminotransferase)/alanine aminotransferase levels. The maximal tolerated dose of PTK787 was defined as 750 mg daily. Of patients in all groups, 18 had efficacy data available. No complete response or PR was observed. Nine patients had a best response of stable disease, and nine had progressive disease. There are no studies planned to develop this agent in the treatment of HCC at this time.

### Epidermal Growth Factor Receptor (EGFR) Inhibitors

The expression of several EGF family members, specifically EGF, TGF-α, and heparinbinding epidermal growth factor, as well as EGFR, has been described in several HCC cell lines and tissues [57-62]. Multiple strategies to target EGFR signaling pathways have been developed, and two classes of anti-EGFR agents have established clinical activity in cancer: monoclonal antibodies that competitively inhibit extracellular endogenous ligand binding, and small molecules that inhibit the intracellular tyrosine kinase domain. (Table 3) summarizes phase II studies with EGFR inhibitors. Other than the modest activity with erlotinib, the rest of the EGFR inhibitors failed to show any activity as single agents in advanced HCC.

#### EGFR Tyrosine Kinase Inhibitors

Two phase II clinical studies have evaluated the safety and efficacy of Erlotinib (Tarceva) provided at 150 mg daily in patients with advanced HCC [63, 64]. In the study by Philip and colleagues, 3 (9%) of 38 patients experienced PR, and 12 patients (32%) were free of progression of disease at 6 months [63]. Median OS time for this cohort was 13 months. In another report by Thomas et al. 17 (43%) of 40 patients achieved PFS at 16 weeks, and the PFS rate at 24 weeks was 28% (64). No PR or complete response was observed in this study. The median time to failure, defined as either disease progression or death, was 13.3 weeks. The median time of OS was 25.0 weeks (95% CI, 17.9–42.3) from the date of Erlotinib therapy initiation. In the Eastern Cooperative Oncology Group’s E1203 study, Gefitinib provided at 250 mg daily was examined in a single-arm phase II study [65]. A two-stage design was used, and 31 patients were accrued to the first stage. One patient had PR and seven patients had stable disease. The median PFS was 2.8 months (95% CI 1.5–3.9) and median OS was 6.5 months (95% CI, 4.4–8.9). The criterion for secondstage accrual was not met, and the authors concluded that gefitinib as a single agent was not active in advanced HCC. Lapatinib, a selective dual inhibitor of both EGFR and HER-2/NEU tyrosine kinases, also demonstrated modest activity in HCC [66]. Among the
40 patients with advanced HCC, the response rate was 5%, PFS 2.3 (95% CI, 1.7–5.6) months, and OS of 6.2 (95% CI, 5.1–infinity) months.

**Monoclonal Antibodies Against EGFR**

Cetuximab, a chimeric monoclonal antibody against EGFR, was tested in two phase II studies in patients with advanced HCC. In our study, 30 patients with advanced HCC were enrolled [67]. The initial dose of cetuximab was 400 mg/m^2^ provided intravenously, followed by weekly intravenous infusions at 250 mg/m^2^. No responses were seen. Five patients had stable disease (median time, 4.2 months; range, 2.8–4.2 months). The median OS was 9.6 months (95% CI, 4.3–12.1) and the median PFS was 1.4 months (95% CI, 1.2–2.6). Cetuximab trough concentrations were not notably altered in patients with Child-Pugh A and B cirrhosis. Gruenwald and colleagues reported their preliminary experience of cetuximab in a similarly designed study in HCC [68]. Of the 32 patients enrolled, 27 patients had efficacy data available. No responses were seen, and the median TTP for all patients was 8.0 weeks. The combination of cetuximab with gemcitabine and oxaliplatin (GEMOX) was evaluated in a phase II study [69]. All patients received cetuximab at an initial dose of 400 mg/m^2^ followed by 250 mg/m^2^ weekly, gemcitabine 1000 mg/m^2^ on day 1, and oxaliplatin at 100 mg/m^2^ on day 2, repeated every 14 days until disease progression or limiting toxicity. Of the 45 patients enrolled, the confirmed response rate was 20% and disease stabilization rate was 40%. The median PFS and OS were 4.7 months and 9.5 months, respectively. The 1-year survival rate was 40%. Given the reported antitumor activity of GEMOX in prior phase II studies and the lack of activity of cetuximab as single agents, the relative contribution of cetuximab to this regimen remains to be defined. The combination of cetuximab with capecitabine and oxaliplatin was evaluated in a single-arm phase II study [70]. Patients received capecitabine at 850 mg/m^2^ twice daily for 14 days, oxaliplatin on day 1 at 130 mg/m^2^ intravenously, and cetuximab at 400 mg/m^2^ on day 1 followed by 250 mg/m^2^ weekly in a 21-day cycle. Of the 25 patients enrolled, data for efficacy were available for 20 patients. Response rate was 10% (95% CI, 1–33), and TTP was 4.3 months (95% CI, 2.3–5.0). Although most patients tolerated the treatment well, diarrheal and electrolyte abnormalities including hypoglycemia and hypocalcemia were more pronounced in this population.

**mTOR Inhibitors**

mTOR functions to regulate protein translation, angiogenesis, and cell-cycle progression in many cancers, including HCC. Preclinical data have demonstrated that mTOR inhibitors were effective in inhibiting cell growth and tumour vascularization in HCC cell lines and HCC tumour models. The importance of the mTOR pathway in HCC was examined in a comprehensive study with 314 HCC and 37 nontumoral tissues that used a series of molecular techniques to assess mutation, DNA copy number changes, messenger RNA and gene expression, and protein activation [71]. Aberrant mTOR signalling (p-RPS6) was present in half of the cases and chromosomal gains in rapamycin-insensitive companion of mTOR (RICTOR) (25% of patients), and positive p-RPS6 staining correlated with HCC recurrence after resection.

A number of mTOR inhibitors (sirolimus, temsirolimus, and everolimus) are available clinically. Retrospective studies in patients who underwent liver transplantation for HCC have shown that patients who received sirolimus for immunosuppression had a much lower rate of tumour recurrence than those who received calcineurin inhibitors. Clinical studies with mTOR inhibitors alone and in combination with either targeted agents or chemotherapeutic agents in advanced HCC are at an early stage of clinical development. Chen and colleagues recently reported their early experience of a randomized phase I pharmacokinetic study of everolimus in advanced HCC [72]. Two different schedules were tested: continuous daily dosing and once-weekly dosing. A total of 36 patients were enrolled. Dose-limiting toxicities observed included hyperbilirubinemia, high levels of alanine aminotransferase, thrombocytopenia, infection, diarrheal, and cardiac ischemia. The MTD for weekly and daily dosing schedules was determined to be 70 and 7.5 mg, respectively. Interestingly, reactivation of hepatitis B and C virus was observed in four and one patients, respectively. The disease control rate of 31 evaluable patients was 61% (10 of 16) and 46.7% (7 of 15, including one case of PR) of patients receiving daily and weekly treatment, respectively. Another phase I/II study that evaluated everolimus with a continuous daily dosing schedule in advanced HCC is ongoing.

**MEK Inhibitor**

HCC is characterized by frequent MEK/ERK activation in the absence of RAS or RAF mutation. A multicenter, singlearm phase II study with a two-stage design was conducted with AZD6244, a specific inhibitor of MEK, in advanced HCC [73]. The primary end point was response rate. AZD6244 was administered orally at a dose of 100 mg twice a day. Of the 19 patients enrolled, 16 had response data available. Despite the good tolerability of AZD6244, it showed minimal activity in advanced HCC. No response was observed, and stable disease was observed in 37.5% of the patients. The median TTP was only 8 weeks (95% CI, 6.6–11.1).

**Other Molecularly Targeted Agents Under Development In HCC**

Many genetic and epigenetic changes occur during hepatocarcinogenesis. These pathways include the PI3 K/Akt/mTOR pathway, hepatocyte growth factor/c-Met pathway, and IGF and IGF-R, as well as the Wnt-b-catenin pathway. Multiple agents targeting these key pathways are under early-stage evaluation in HCC.
Conclusions
Despite decades of efforts by many investigators, no studies with systemic chemotherapy or hormone therapy have demonstrated improved survival in patients with advanced HCC. Sorafenib has emerged as the new standard treatment for advanced HCC. Ongoing studies are evaluating the efficacy and tolerability of combining Sorafenib with Erlotinib and other targeted agents or chemotherapy. Many molecularly targeted agents are at different stages of clinical development in HCC, and several agents, including Sunitinib and Brivanib, are being tested in phase III studies. Combining targeted agents that inhibit different pathways in hepatocarcinogenesis is an area of active investigation. Future research should continue to unravel the mechanism of hepatocarcinogenesis and to identify key relevant molecular targets for therapeutic intervention. While we are developing other antiangiogenic and targeted agents in HCC, it is imperative that we continue our efforts to identify and validate surrogate and predictive biomarkers that would be helpful to predict clinical efficacy, toxicity, and resistance to these agents. We hope that we will continue to improve the efficacy of systemic therapy in advanced HCC in the coming years.

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