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RESEARCH ARTICLE

Phase I/II study of c-MET inhibitor (DE605) combined with sorafenib in patients with advanced hepatocellular carcinoma

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Abstract

***Background*:** DE605 is a c-MET inhibitor that can be taken orally. Sorafenib is the only treatment that has been proven to increase overall survival rates in patients with advanced hepatocellular carcinoma (HCC). However, the effectiveness of sorafenib in a clinical setting is limited. By targeting multiple signaling pathways through combination therapy, patient outcomes may improve. This study aimed to establish the maximum tolerated dose (MTD) of DE605 when administered alongside sorafenib and to assess the safety and efficacy of this combination in treating patients with advanced HCC.

***Patients and methods*:** Patients with advanced HCC received treatment that combined increasing doses of DE605 and sorafenib. The first phase of the study aimed to establish the MTD of this combination. In the second phase, patients were treated with the MTD to assess the safety and effectiveness of the treatment.

***Results*:** In the first phase of the study, 27 patients were treated with sorafenib and increasing doses of DE605. In the second phase, 32 patients were enrolled. The MTD was determined to be 240 mg of DE605 once daily (QD) in combination with 400 mg of sorafenib twice daily (BID). Of the patients treated with the MTD, 9.4% had a partial response, 65.6% had stable disease, and 25% had progressive disease. The median time to progression was 2.5 months and the median overall survival was 11.6 months.

***Conclusion*:** The combination of 240 mg of DE605 QD and the standard dose of 400 mg of sorafenib BID showed significant clinical effectiveness in treating patients with advanced HCC. The early indications of antitumor activity suggest that further development of this combination therapy may be warranted.

Keywords: *c-MET inhibitor*; *DE605*; *sorafenib*; *hepatocellular carcinoma*

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Advanced hepatocellular carcinoma (HCC) is a serious and aggressive form of cancer with a poor prognosis. Without treatment, the median survival time for patients diagnosed with advanced HCC is only 6 months, which is about one-third of the survival time for patients with intermediate disease (1). HCC is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide (2). Advanced HCC that cannot be treated with loco-regional therapies has an especially poor prognosis. Sorafenib is an oral multikinase inhibitor that works by blocking tumor cell growth through the Raf/MEK/ERK signaling pathway and inhibiting angiogenesis by targeting VEGFR-2, VEGFR-3, and PDGFR-β (3). In a phase III study called SHARP, sorafenib (400 mg taken twice daily [BID]) was shown to be the first and only targeted therapy to provide a survival benefit for patients with advanced HCC who had not received prior systemic therapy. The median overall survival (OS) was 10.7 months for patients treated with sorafenib compared to 7.9 months for those given a placebo ($P < 0.001$) (4). Another phase III study conducted in the Asia-Pacific region also showed a survival benefit for sorafenib in advanced HCC, with a median OS of 6.5 months for patients treated with sorafenib compared to 4.2 months for those given a placebo ($P = 0.014$) (5). Currently, sorafenib is the only systemic therapy

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recommended by guidelines for treating advanced, unresectable HCC (6). Although sorafenib provides some benefits in treating advanced HCC, there is still a need for additional treatment options. Combination therapy that targets multiple signaling pathways may be more effective than monotherapy by potentially overcoming resistance and compensating for the activation of prosurvival pathways (7). HCC is a complex and heterogeneous tumor that involves the activation of several signaling pathways. As a result, researchers have explored the use of combination therapy that pairs sorafenib with chemotherapy or another targeted therapeutic agent to treat HCC (8). The c-Met receptor and its ligand, hepatocyte growth factor (HGF), play important roles in cancer invasion and metastasis (9, 10). c-Met is crucial for liver development and regeneration. In mice with a conditional c-Met knockout, liver repair is delayed or absent after liver injury or hepatectomy (11). On the other hand, overexpression of HGF has been shown to increase liver regeneration and cause significant liver enlargement in mice after partial hepatectomy (12). However, c-Met expression is deregulated in many human cancers, including HCC (13). In cancer, c-Met/HGF mediates cell proliferation, tumor invasion, and metastasis (14). The tumorigenicity of c-Met appears to involve the establishment of c-Met/HGF autocrine loops, overexpression of c-Met or HGF, and kinase-activating mutations in the c-Met gene (10). Overexpression of c-Met alone has been shown to be sufficient to cause HCC in Met-transgenic mice (15, 16). Additionally, high expression of c-Met has been observed in more than 80% of HCC patients and is associated with poor progression-free survival. It may also be a predictor of sensitivity to agents such as the tyrosine kinase inhibitor sorafenib (17). DE605 is a selective inhibitor of c-MET that is taken orally and does not compete with ATP. It has an inhibitory constant of 12.3 nmol/L and has been shown to be 3,000 times more selective for c-MET than 241 other kinases tested in a large kinase panel screen. Preclinical studies have demonstrated that combining DE605 with sorafenib can have additive or synergistic effects in HCC tumor xenograft models. Inhibiting HGF/c-MET signaling is a promising anticancer strategy due to the diverse effects of this signaling pathway on cancer progression (18). Several HGF- and c-MET-targeted therapeutics, including small-molecule inhibitors and monoclonal antibodies, have recently entered clinical trials and are showing promising results (19–21). In addition to being tested as a single therapeutic agent, c-Met inhibitors are also being evaluated in combination with chemotherapy agents such as sorafenib, gemcitabine, and erlotinib in clinical trials (22–24). Given the potential benefits of combining DE605 and sorafenib in treating advanced HCC, the researchers hypothesized that this combination therapy may be a viable option for patients with advanced HCC who are not responding to standard treatment. To test this hypothesis, a phase I/II study was conducted to determine the maximum tolerated dose (MTD) and to evaluate the safety and efficacy of combining DE605 and sorafenib in treating Chinese patients with advanced HCC.

Patients and methods

Patients

To be eligible for the study, patients had to meet the following criteria: diagnosed with HCC through histological examination or diagnostic imaging; no indication for surgical resection or local therapy; no prior systemic chemotherapy; measurable disease based on response evaluation criteria in solid tumours (RECIST) criteria; eastern cooperative oncology group (ECOG) performance status of 0–1; age ≥20 years; adequate blood counts and liver function; ability to take food and medication orally; and a life expectancy of ≥12 weeks. Patients were excluded from the study if they had received prior therapy for HCC within 30 days of study entry, had major surgery within 30 days of study entry, had portal vein tumor thrombus in the primary trunk, had uncontrollable hypertension or other medical conditions that could affect their participation in the study, were pregnant or lactating, or had a second primary malignancy. The study was approved by Istanbul Technical University and was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before participating in any study procedures.

Study design and treatment

The researchers conducted a prospective, open-label, non-randomized phase I/II study to determine the MTD and to evaluate the safety and efficacy of combining sorafenib and DE605 in treating patients with advanced HCC.

The study used a Bayesian sequential dose-escalation scheme based on an adaptive four-parameter Bayesian logistic regression model with overdose control. The rate of dose-limiting toxicities (DLTs) that occurred within the first treatment cycle (the first 28 days of therapy) was used to determine the MTD. DLTs were predefined as any non-hematologic grade 3/4 toxicity that required ≥7 days to resolve to grade ≤1 despite medical treatment (excluding certain specified toxicities), hepatitis B virus (HBV) reactivation or hepatitis c virus (HCV) flare, bilirubin increase ≥2 × upper limit of normal (ULN), creatinine increase ≥2 × ULN, any non-hematologic toxicity requiring ≥7 days of treatment interruption, any grade 4 hematologic toxicity, grade 3 thrombocytopenia with bleeding, grade 3 anemia requiring transfusion, grade 3 neutropenia with fever, and any persistent grade 3

hematologic toxicity requiring dose interruption for >7 days to resolve to grade ≤1.

Sorafenib was administered at a fixed dose of 400 mg BID. The first dose level of DE605 examined was 60 mg once daily (QD). At this and each subsequent dose level recommended by the model, a cohort of six evaluable patients was enrolled. Once these patients had completed their eligibility requirements (i.e., experienced a DLT or missed ≤7 doses of either agent during the first treatment cycle), the model was updated. The model recommended the next dose level for enrollment based on the probability that the DLT rate would fall within the targeted toxicity rate interval of 20–35% and corresponded to a <25% probability of the DLT rate falling within the excessive (35–60%) or unacceptable (60–100%) toxicity rate intervals. If the risk of overdose criteria for the first six-patient cohort exceeded the specified threshold, the cohort was expanded by adding three additional patients at a time (up to a maximum of 9) to increase confidence in the estimate of the toxicity probability. In all other cases, dose escalation followed the specified overdose criteria. Enrollment was halted upon completion of a cohort or expansion to allow for completion of the 28-day combined therapy treatment period and subsequent dose-escalation decision making. Within a dose level, adjustments to DE605 and sorafenib doses were permitted in case of adverse events (AEs) suspected to be related to study treatment according to an algorithm outlined in the study protocol.

Evaluations and assessments

Patients continued treatment until they experienced disease progression or unacceptable toxicity. Those who discontinued either study drug were followed up 28 days after their last dose to record any AEs. All patients were followed for survival for up to 1 year after the last study visit of the last patient enrolled. At baseline, patients underwent physical examination, vital sign measurement, height and weight measurement, ECOG performance status assessment, and laboratory assessments. During the first cycle of each dose level, vital signs, weight, ECOG performance status, and laboratory parameters were monitored weekly and physical examination was performed biweekly. Starting from day 1 of all subsequent treatment cycles at the same dose level, all assessments were conducted biweekly. Information on prior and concomitant medication use and AEs was collected throughout the study. Treatment-emergent AEs (new or worsening from baseline) and laboratory values were assessed using the Common Terminology Criteria for Adverse Events version 3.0.

Standard computed tomography or magnetic resonance imaging of the abdomen was used to assess tumor response according to RECIST criteria at baseline, approximately every 8 weeks thereafter, and at the end of treatment. Imaging of the pelvis, chest, and cranium and bone scans were performed only when clinically indicated. Efficacy was evaluated using the best overall response rate according to RECIST criteria. Other efficacy endpoints included time to progression (TTP), defined as the time from the start of study treatment to documented disease progression or death due to HCC, and OS, defined as the time from the start of study treatment to death from any cause.

Venous blood samples were collected for pharmacokinetic assessment immediately before study drug administration on day 1 of cycles 2 and 3 to measure the minimum blood concentration (Cmin) of DE605. Additional samples were collected 1 and 2 h post-dose on day 1 of cycles 2 and 3 to capture DE605 exposure near its maximum blood concentration (Cmax). Samples were also collected before dose administration at times of tumor response assessment. On all pharmacokinetic sampling days, the study drug was administered at the clinic. If samples could not be obtained as scheduled, they were collected at the next visit. All pharmacokinetic assessments were performed by Novartis Pharmaceuticals using a liquid chromatography-mass spectrometry method following liquid extraction, with a lower limit of quantitation of 0.200 ng/mL.

Statistical analysis

The safety population, which included all patients who received ≥1 dose of study medication and had a valid post-baseline assessment, was used for all analyses except for the determination of the MTD. The MTD was calculated using the dose-determining population, which included all patients who missed ≤7 daily doses at the assigned dose level or experienced a DLT during the first 28 days of treatment. At each dose level, ≥6 patients had to be enrolled to adequately assess toxicity and ≥12 patients had to be treated before the MTD could be declared. It was estimated that approximately 30 patients would be needed across all dose levels investigated to complete dose escalation and ensure a sufficient level of confidence in the posterior estimates of the DLT probability.

Results

Patient characteristics and disposition

In phase I of the study, 27 patients were enrolled and received treatment with DE605 and sorafenib at various dose levels. Cohort 1 (n = 6) received DE605 at a dose of 60 mg QD plus sorafenib at a dose of 400 mg BID. Cohort 2 (n = 8) received DE605 at a dose of 120 mg QD plus sorafenib at a dose of 400 mg BID. Cohort 3 (n = 10) received DE605 at a dose of 240 mg QD plus sorafenib at a dose of 400 mg BID. Cohort 4 (n = 3) received DE605 at a dose of 360 mg QD plus sorafenib at a dose of 400 mg BID. In phase II, 32 patients were enrolled. All patients were eligible for toxicity and efficacy evaluation. The majority of patients were HBV-positive with barcelona

clinic liver cancer (BCLC) stage C HCC and had an ECOG performance status of 0 (Table 1). The most common local therapies used prior to study enrollment were surgery and transcatheter arterial chemoembolization.

Maximum tolerated dose

In the dose escalation phase of the study, 27 patients were enrolled. No patients in cohorts 1 and 2 experienced a DLT. In cohort 3, one out of 10 patients experienced a DLT (grade 4 elevation of aspartate aminotransferase [AST]/alanine aminotransferase [ALT] levels). In cohort 4, two out of the initial three patients experienced a DLT (one with grade 3 hand-foot skin reaction [HFSR] and one with grade 3 gastrointestinal bleeding). Due to the high rate of DLTs in cohort 4, cohort 3 (DE605 at a dose of 240 mg QD plus sorafenib at a dose of 400 mg BID) was determined to be the MTD.

Treatment-related toxicity

In phase II of the study, patients were treated with the MTD to evaluate safety and efficacy. Of the 32 patients who were evaluated for toxicity data, all were eligible for toxicity and efficacy evaluation. The most common treatment-related AEs were hyperbilirubinemia (94%), AST elevation (94%), thrombocytopenia (84%), anemia (72%), ALT elevation (66%), HFSR (59%), and fatigue (53%) (Table 2). The most common grade 3/4 AEs were elevated AST (28%), thrombocytopenia (19%), neutropenia (19%), hyperbilirubinemia (13%), and ALT elevation (13%) (Table 3). Two patients discontinued treatment due to AEs.

Table 1. Patient characteristics

Variable	Phase I	Phase II
Age: year	63.6 ± 11.7	67.4 ± 10.5
Sex: no. (%)		
Male	23 (85.2)	27 (84.4)
Female	4 (14.8)	5 (15.6)
Viral infection: no. (%)		
HCV only	7 (25.9)	9 (28.1)
HBV only	15 (55.6)	20 (62.5)
Other	5 (18.5)	3 (9.4)
ECOG performance status – no. (%)		
0	21 (77.8)	23 (71.9)
1	6 (22.2)	9 (28.1)
BCLC stage: no. (%)		
B (intermediate)	7 (25.9)	11 (34.4)
C (advanced)	20 (74.1)	21 (65.6)
Macroscopic vascular invasion: no. (%)	6 (22.2)	8 (25.0)
Extrahepatic spread: no. (%)	14 (51.9)	20 (62.5)
Child-Pugh points: no. (%)		
5 points	22 (81.5)	28 (87.5)
6 points	5 (18.5)	4 (12.5)
History of prior treatment: no. (%)	26 (96.3)	30 (93.8)
Resection	18 (66.7)	22 (68.8)
Local ablation therapy	8 (29.6)	15 (46.9)
Transarterial chemoembolization	20 (74.1)	25 (78.1)

Unless otherwise noted, all data presented as *n* (%).

Efficacy

The response rate for phase II of the study is shown in Table 4. Disease stabilization was the best overall response achieved. Of the 32 patients who were evaluated for response, three (9.4%) had a partial response, 21 (65.6%) had stable disease, eight (25%) had progressive disease, and the disease control rate was 13 (40.6%). The median TTP was 2.5 months (95% confidence interval [CI], 0.3–5.6 months) and the median OS was 11.6 months (95% CI: 2.2–19.3 months).

Pharmacokinetics

Pharmacokinetic data for DE605 was evaluable for six patients in the 60-mg cohort, eight patients in the 120-mg cohort, and 10 patients in the 240-mg cohort. As shown in Fig. 1, there was minimal fluctuation in the minimum blood concentration (Cmin) of DE605 across treatment cycles. At cycle 2, the mean ± SD maximum blood concentration (Cmax) of DE605 was 95.8 ± 31.2 ng/mL in the 60-mg cohort (n = 6), 227.3 ± 68.4 ng/mL in the 120-mg cohort (n = 8), and 505.7 ± 202.5 ng/mL in the 240-mg cohort (n = 10), indicating a greater

Table 2. All adverse events in ≥10% of subjects during phase II

Parameters	*N* = 32 No. (%)
Hyperbilirubinemia	30 (93.8)
AST elevation	30 (93.8)
Thrombocytopenia	27 (84.4)
Anemia	23 (71.9)
ALT elevation	21 (65.6)
Hand-foot skin reaction (HFSR)	19 (59.4)
Fatigue	17 (53.1)
Neutropenia	15 (46.9)
Hyponatremia	14 (43.8)
Anorexia	13 (40.6)
Rash	14 (43.8)
Hypertension	13 (40.6)
Alopecia	10 (31.3)
Hypophosphatemia	8 (25.0)
Diarrhea	6 (18.8)
Fever	5 (15.6)
Bleeding	4 (12.5)
Mucositis	4 (12.5)
Hypocalcemia	4 (12.5)

Unless otherwise noted, all data presented as *n* (%).

Table 3. Summary of ≥grade 3 adverse events during phase II

Parameters	Grade 3: no. (%)	Grade 4: no. (%)	Grade 5: no. (%)
AST elevation	9 (28.1)	0 (0)	0 (0)
Thrombocytopenia	6 (18.8)	0 (0)	0 (0)
Neutropenia	6 (18.8)	0 (0)	0 (0)
Hyperbilirubinemia	4 (12.5)	0 (0)	0 (0)
ALT elevation	4 (12.5)	1 (3.1)	0 (0)
Hyponatremia	3 (9.4)	0 (0)	0 (0)
Rash	3 (9.4)	0 (0)	0 (0)
Hypophosphatemia	2 (6.3)	0 (0)	0 (0)
Anemia	1 (3.1)	0 (0)	0 (0)
HFSR	1 (3.1)	0 (0)	0 (0)
Bleeding	1 (3.1)	0 (0)	0 (0)
Sudden death	0 (0)	0 (0)	0 (0)

Unless otherwise noted, all data presented as *n* (%).

Table 4. Response rates using the response evaluation criteria in solid tumors

Response	Number of patients (%)
Complete response	0 (0)
Partial response	3 (9.4)
Stable disease	21 (65.6)
Progression disease	8 (25.0)
Disease control rate (DCR)	13 (40.6)

Unless otherwise noted, all data presented as *n* (%). The disease control rate was defined as the proportion of patients who had a best response rating of a complete response, partial response, or stable disease that was maintained for ≥4 weeks from the first manifestation of the rating.

than dose-proportional increase in Cmax. At cycle 3, the increase in Cmax appeared to be dose proportional, with a mean ± SD of 113.7 ± 33.4 ng/mL in the 60-mg cohort (n = 6), 246.5 ± 71.7 ng/mL in the 120-mg cohort (n = 8), and 511.2 ± 215.4 ng/mL in the 240-mg cohort (n = 10).

Discussion

DE605 is an oral, selective, noncompetitive ATP inhibitor of the c-MET tyrosine kinase. In this phase I/II study of patients with advanced HCC, the MTD of DE605 in combination with sorafenib at a dose of 400 mg BID was determined to be 240 mg QD. This MTD was determined based on Bayesian modeling of the observed DLTs and the overall safety profile. Treatment with sorafenib alone is generally well-tolerated, but AEs such as HFSR, rash, and liver failure occur more frequently in patients with HCC than in patients from other regions (25). In phase II of this study, the most common AEs were hyperbilirubinemia (94%), AST elevation (94%), thrombocytopenia (84%), anemia (72%), ALT elevation (66%), HFSR (59%), and fatigue (53%). Hyperbilirubinemia and thrombocytopenia are AEs associated with both DE605 and sorafenib. The frequencies of HFSR and rash were similar to those observed with sorafenib monotherapy, while the frequency of bone marrow suppression was similar to that observed with DE605 monotherapy. The frequency of elevated liver enzymes was higher than that observed with either monotherapy. The overall AE profile observed in this study was consistent with the known safety profiles of sorafenib monotherapy in patients with cancer (4, 5, 25–28). The toxicity profile of the combination of DE605 and sorafenib appeared to be similar to the combined toxicity profiles of DE605 and

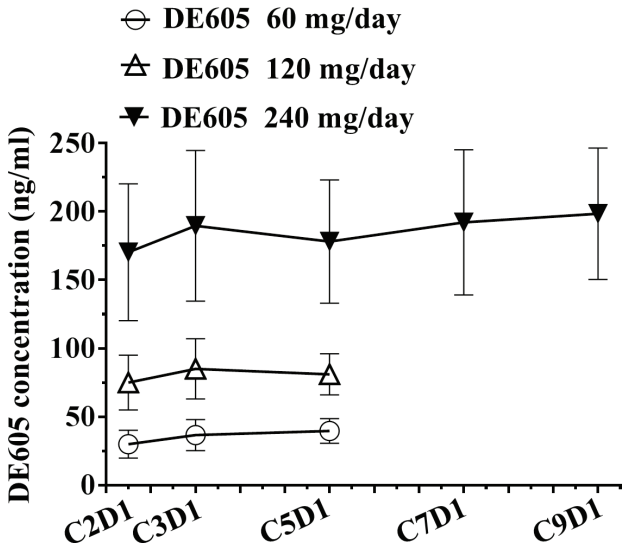

Fig. 1. DE605 Cmin by DE605 dose cohort and cycle (safety population). Mean DE605 plasma concentration versus time profiles from patients dosed with DE605 60 mg QD plus sorafenib 400 mg BID (cohort 1; n = 6), DE605 120 mg QD plus sorafenib 400 mg BID, and DE605 240 mg QD plus sorafenib 400 mg BID. Each value represents the mean ± SD.

sorafenib monotherapies. These findings suggest that the toxicity of combination therapy may be more severe than that of either DE605 or sorafenib monotherapy.

In phase II of the study, three patients had a partial response. The tumor response rate and disease control rate of the combination therapy did not appear to be higher than those reported for sorafenib monotherapy (4, 5, 25). The median TTP was only 2.5 months and was not longer than that observed with sorafenib monotherapy (4, 5). However, the median OS in this study was 11.6 months and appeared to be dissociated from the median TTP. This dissociation between TTP and OS has been reported in several studies of patients with advanced HCC (27, 28) and may be due to various treatments received after disease progression, including hepatic arterial infusion chemotherapy and palliative care.

The pharmacokinetic results for DE605 should be interpreted with caution due to the large variability associated with the estimates and the small sample sizes. However, the maximum blood concentration (Cmax) values observed for DE605 in the 240-mg cohort of this study (505.0–531.0 ng/mL) were comparable to those observed with DE605 at a dose of 240 mg/day in studies of DE605 monotherapy in patients with advanced solid tumors (516.2 ng/mL). In contrast, the minimum blood concentration (Cmin) values for DE605 in the 240-mg cohort of this study (170.2–198.4 ng/mL) were similar to those observed with DE605 at a dose of 240 mg/day in studies of DE605 monotherapy in patients with advanced solid tumors (165.7 ng/mL). The higher Cmin observed in this study may be due to the presence of mild liver cirrhosis in some patients. The pharmacokinetic analyses performed as part of this study suggested a more than dose-proportional increase in Cmin, but not Cmax, across the dose cohorts.

In conclusion, the results of this phase I/II study suggest that the MTD of DE605 in combination with sorafenib at a dose of 400 mg BID in patients with advanced HCC who have not received prior systemic therapy is 240 mg QD. Based on the safety, pharmacokinetic, and efficacy profiles observed in this study, it was concluded that the combination of DE605 at a dose of 240 mg QD and sorafenib at a dose of 400 mg BID was tolerable. Although the toxicities were slightly more severe than those observed with sorafenib monotherapy, the therapeutic effects of the combination therapy were similar. Further research is needed to identify new drugs or combination therapies with sorafenib that can improve the prognosis of patients with advanced HCC.

Conflict of interest and funding

The authors declare that they have no competing interest. This work was supported by the Provincial Funding for Clinical Studies (#v87d5).

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