

Overview



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Title: Phase I/II Study of Weekly Oraxol for the Second-Line Treatment of Patients With Metastatic or Recurrent Gastric Cancer

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Disclosures

Seock-Ah Im: Roche, Novartis, AstraZeneca (C/A), AstraZeneca (RF); **Jin-A Jung:** Hanmi Pharmaceutical Co., Ltd. (E); **Yung-Jue Bang:** Hanmi Pharmaceutical Co., Ltd. (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Lessons Learned

- Oraxol, a novel oral formulation of paclitaxel, displayed modest efficacy as second-line chemotherapy for gastric cancer.
- Considering its favorable toxicity profiles, further studies are warranted in various solid tumors including gastric cancer.

Author Summary: Abstract and Brief Discussion

Background

Oraxol consists of paclitaxel and HM30181A, a P-glycoprotein inhibitor, to increase the oral bioavailability of paclitaxel. This phase I/II study (HM-OXL-201) was conducted to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of Oraxol. In addition, we investigated the efficacy and safety of Oraxol as second-line chemotherapy for metastatic or recurrent gastric cancer (GC).

Methods

In the phase I component, paclitaxel was orally administered at escalating doses (90, 120, or 150 mg/m² per day) with a fixed dose (15 mg/day) of HM30181A. Oraxol was administered 6 times per cycle (days 1, 2, 8, 9, 15, and 16) every 4 weeks. In the phase II component, the efficacy and safety of Oraxol were evaluated.

Results

In the phase I component, the MTD could not be determined. Based on toxicity and pharmacokinetic data, the RP2D of oral paclitaxel was determined to be 150 mg/m². In the phase II component, 4 of 43 patients (9.3%) achieved partial responses. Median progression-free survival and overall survival were 2.6 and 10.7 months, respectively. Toxicity profiles were favorable, and the most common drug-related adverse events (grade ≥3) were neutropenia and diarrhea.

Conclusion

Oraxol exhibited modest efficacy and favorable toxicity profiles as second-line chemotherapy for GC.

Discussion

Paclitaxel has been administered intravenously because of its poor oral bioavailability. Because paclitaxel is insoluble in water, the original formulation of paclitaxel contains the vehicle Cremophor EL (CrEL); however, the addition of CrEL causes hypersensitivity reactions and exerts an additive effect on paclitaxel-induced neuropathy. The original formulation of paclitaxel inconveniences patients and increases the risk of toxicities. Consequently, there have been many efforts to develop a new formulation of paclitaxel.

Oraxol is composed of a paclitaxel capsule and an HM30181A tablet (Hanmi Pharmaceutical Co., Ltd., Seoul, Republic of Korea, <http://www.hanmipharm.com>). HM30181A, [2-(2-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenyl}-2*H*-tetrazol-5-yl)-4,5-dimethoxyphenyl]amide, is a novel inhibitor of P-glycoprotein in the gastrointestinal mucosa. In this phase I/II study (HM-OXL-201), both paclitaxel and HM30181A were administered simultaneously on an empty stomach.

In the phase I component of this study ($n = 10$), no dose-limiting toxicity was observed, and thus the MTD could not be determined. In gastric cancer cell lines, paclitaxel exhibited cytotoxicity at concentrations $>0.01 \mu\text{M}$. In the pharmacokinetic analysis, the means of $T_{>0.01}$ (time of plasma concentration of paclitaxel $>0.01 \mu\text{M}$) at three paclitaxel dose levels were 17.7, 43.2, and 47.5 hours, respectively. The area under the plasma concentration-time curves also increased according to the paclitaxel dose. Based on these toxicity and pharmacokinetic data, dose level 3 (oral paclitaxel 150 mg/m² per day and HM30181A 15 mg/day, both on days 1, 2, 8, 9, 15, and 16 every 4 weeks) was determined as the RP2D.

In the phase II component ($n = 46$), this weekly Oraxol regimen displayed favorable toxicity profiles. The incidence of severe neutropenia (grade ≥3) was 30.4%, which was similar to that reported in previous phase III trials of conventional weekly paclitaxel (second line) in metastatic or recurrent GC. Severe nonhematologic toxicities were rare. Particularly, Oraxol appears to cause less peripheral neuropathy than conventional weekly paclitaxel. In our study, weekly Oraxol was associated with a response rate (RR) of 9.3% and progression-free survival (PFS), and overall survival (OS) of 2.6 and 10.7 months, respectively (Table 1). Statistically, our study did not meet the primary endpoint (RR); however, clinically, Oraxol appears to have efficacy similar to other cytotoxic agents commonly used as second-line chemotherapy in metastatic or recurrent GC. Regarding conventional weekly paclitaxel, RRs of 9%–20.9% and PFS and OS of 2.9–4.4 and 7.4–9.5 months, respectively, were reported. Although weekly Oraxol treatment did not meet the primary endpoint in this study, we demonstrated that Oraxol has its own advantages (favorable safety profiles, including less neuropathy and no hypersensitivity reactions, and the convenience of oral administration) over conventional paclitaxel. Consequently, we believe that Oraxol is worthy of further investigation. In particular, the combination of Oraxol with various chemotherapeutic agents is expected to be very promising because Oraxol displayed favorable toxicity profiles.

Trial Information

Disease	Gastric cancer
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	1 prior regimen
Type of study - 1	Phase II
Type of study - 2	Single Arm

Primary Endpoint	To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of a 2-consecutive-day dosing schedule of weekly Oraxol (the phase I component)
Primary Endpoint	Response rate (RR; the phase 2 component)
Secondary Endpoint	To assess the pharmacokinetic profiles and overall safety of the therapy (the phase I component)
Secondary Endpoint	Overall survival (OS), progression-free survival (PFS), response duration, and safety profile (the phase II component)

Additional Details of Endpoints or Study Design

The phase I component of this study enrolled patients with histologically confirmed advanced solid tumors for which no more effective chemotherapy or standard treatment was available. Patients were required to have at least one measurable and/or evaluable lesion that could be assessed by imaging. The phase II component enrolled patients with histologically confirmed metastatic or recurrent gastric cancer (GC) that had progressed following first-line palliative chemotherapy or that had recurred within 6 months after the completion of adjuvant chemotherapy. Patients were required to have at least one measurable tumor lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients who previously received taxane chemotherapy were excluded. For both phase I and II components, other inclusion criteria were same, as follows: aged ≥ 19 years; Eastern Cooperative Oncology Group performance status grade 0–2; life expectancy ≥ 3 months; adequate function of bone marrow (absolute neutrophil count [ANC] $\geq 1,500/\text{mm}^3$, hemoglobin ≥ 9.0 g/dL, and platelet count $\geq 100,000/\text{mm}^3$) and other organs; and no prior surgery, radiation therapy, chemotherapy, or immunotherapy in the previous 4 weeks. The exclusion criteria in the phase I and II components were same, as follows: metastasis to the central nervous system, significant gastrointestinal bleeding, massive ascites requiring therapeutic paracentesis, and uncontrolled infection or other serious comorbidity. Patients taking the following medications were excluded: cyclosporin A, verapamil, ritonavir, saquinavir, indinavir, nelfinavir, vitamin A,azole antibiotics, macrolide antibiotics, steroid hormones, dihydropyridine calcium channel blockers, terfenadine, quinidine, midazolam, and phenacetin. If the patient stopped the medication and completed a washout period of ≥ 1 week, then the patient could be enrolled in this study.

The phase I component was performed at two institutions (Seoul National University Hospital and National Cancer Center), and four additional institutions joined the phase II component. In the phase I component of this study, the MTD was defined as the highest dose at which $< 30\%$ of patients experienced a dose-limiting toxicity (DLT) during the first cycle of therapy. DLT was defined as follows: (a) grade 3/4 nausea, vomiting, or diarrhea despite adequate preventive medications (antiemetics or antidiarrheals); (b) grade 3 nonhematologic toxicity that lasted ≥ 7 days (except alopecia); (c) grade 4 nonhematologic toxicity regardless of duration; (d) grade 3/4 febrile neutropenia; (e) grade 4 neutropenia that lasted ≥ 7 days; and (f) grade 4 thrombocytopenia, grade 3 thrombocytopenia accompanying bleeding or requiring platelet transfusion, or grade 3 thrombocytopenia lasting ≥ 7 days. Dose escalation followed the standard 3 + 3 design. Dose escalation above level 3 (oral paclitaxel 300 mg/m² per week) was not planned in this study. If the MTD could not be determined after level 3, it was planned that the RP2D would be determined considering the overall toxicity profiles and the plasma concentration of paclitaxel during the phase I component. For pharmacokinetic analyses of the phase I component, at least two patients at each dose level underwent blood sampling during the first cycle. The sampling times were immediately before drug administration; 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 10, and 24 hours after treatment on days 1 and 2 and 0.5 hour after administration on day 8. The levels of both paclitaxel and HM30181A were analyzed. The methods used for measuring drug concentrations were previously described in detail [1].

In the phase II component of this study, patients were treated with the RP2D, and treatment was repeated every 4 weeks. PFS was defined as the time between the first date of chemotherapy and the date of progressive disease (PD) or death by any cause. OS was estimated from the date of initiating chemotherapy to death. The response duration was measured from the time when the criteria for response (complete response [CR] or partial response [PR]) were first met until the date of PD confirmation or death. This study was designed to detect a response rate (RR) of 17% (H1: alternative hypothesis) compared with a minimal, clinically meaningful RR of 5% (H0: null hypothesis). Simon's minimax two-step design was used [2], with a type I error of 5% (two-sided) and power of 80%. Twenty-four patients were initially enrolled. When two or more responses were observed, the second stage was implemented to enroll an additional 15 patients for a total of 39 evaluable patients. To reject the null hypothesis, 5 responses were required among 39 patients. Assuming a 10% dropout rate, a total sample size of 44 patients was required. PFS and OS analyses were conducted using the Kaplan-Meier method (IBM SPSS Statistics, IBM Corp, Armonk, NY, <http://www.ibm.com>). Tumor assessments using computed tomography were performed every two cycles or if PD was suspected. RECIST was used for the tumor-response assessment.

Investigator's Analysis

Inactive because results did not meet the primary endpoint

Drug Information

Drug 1

Generic/Working name

Oraxol (oral paclitaxel [capsules] and HM30181A [tablets])

Trade name

Oraxol

Company name

Hanmi Pharmaceutical Co., Ltd., Seoul, Korea

Drug class

Microtubule-targeting agent

Dose

per

Route

oral (po)

Schedule of Administration

The study drug (Oraxol) consisted of two components: oral paclitaxel (capsule) and HM30181A (tablet). The dosing regimens are shown in Figure 1. Oral paclitaxel was administered at three dose levels: level 1, 180 mg/m² per week (90 mg/m² per day for 2 consecutive days); level 2, 240 mg/m² per week (120 mg/m² per day for 2 consecutive days); and level 3, 300 mg/m² per week (150 mg/m² per day for 2 consecutive days). Oral paclitaxel was administered using a 2-consecutive-day dosing schedule every week for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by 1 week off treatment. HM30181A was administered at a fixed dose (15 mg/day) on an empty stomach simultaneously with oral paclitaxel. Treatment was repeated every 4 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. In the phase II component of this study, patients were treated with the RP2D, and treatment was repeated every 4 weeks. To initiate the next cycle of chemotherapy (day 1 of each cycle), the criteria of ANC \geq 1,500/mm³ and platelet count \geq 100,000/mm³ were required to be met. To administer the study drugs on days 8 and 15, the ANC and platelet count were required to be \geq 1,000/mm³ and \geq 75,000/mm³, respectively. If a hematologic toxicity that met the criteria of DLTs, a grade 2 hepatic toxicity, a grade 2 peripheral neuropathy, or other grade 3 nonhematologic toxicity (except nausea, vomiting, anorexia, and alopecia) developed, then the paclitaxel dose was reduced to 135 mg/m² per day. If the aforementioned toxicities occurred again, then the dose was reduced to 120 mg/m² per day. If these toxicities developed again at a paclitaxel dose of 120 mg/m² per day; if they persisted for \geq 2 weeks; or if a grade 3 hepatic toxicity, a grade 3 peripheral neuropathy, or other grade 4 nonhematologic toxicity (except nausea, vomiting, anorexia, and alopecia) developed, then the study drugs were permanently withdrawn.

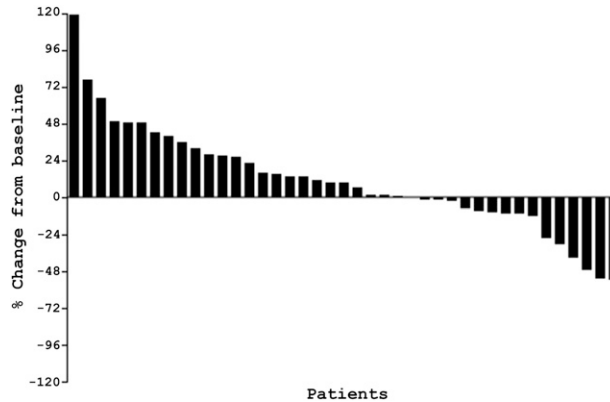
Patient Characteristics

Number of patients, male	35
Number of patients, female	11
Stage	Metastatic or recurrent gastric cancer
Age	Median (range): 63.5 (39.0–82.0)
Number of prior systemic therapies	Median (range): 1
Performance Status: ECOG	0 — 13 1 — 32 2 — 1 3 — 0 Unknown — 0
Other	In the phase I and II components, 10 and 46 patients were enrolled, respectively.
Cancer Types or Histologic Subtypes	Stomach cancer (adenocarcinoma) 46

Primary Assessment Method

Control Arm: Total Patient Population

Number of patients screened	46
Number of patients enrolled	46
Number of patients evaluable for toxicity	46
Number of patients evaluated for efficacy	43
Evaluation method	RECIST 1.1
Response assessment CR	<i>n</i> = 0 (0)
Response assessment PR	<i>n</i> = 4 (9.3)
Response assessment SD	<i>n</i> = 17 (39.5)
Response assessment PD	<i>n</i> = 20 (46.5)
Response assessment OTHER	<i>n</i> = 2 (4.7)
(Median) duration assessments PFS	2.6 months, CI: 1.7–3.5
(Median) duration assessments OS	10.7 months, CI: 7.2–14.2
(Median) duration assessments response duration	5.4 months
(Median) duration assessments duration of treatment	51.5 days



Waterfall plot of tumor response in the phase II component ($n = 41$). Among 43 patients who were evaluated for efficacy, 2 patients did not undergo the planned computed tomography evaluation at 8 weeks (2 cycles after the initiation of Oraxol treatment). These two patients were excluded in this waterfall plot.

Adverse Events

Adverse Events At All Dose Levels, Cycle 1

Name	*NC/NA	1	2	3	4	5	All Grades
Fatigue (asthenia, lethargy, malaise)	78%	9%	11%	2%	0%	0%	22%
Anorexia	72%	24%	4%	0%	0%	0%	28%
Nausea	89%	9%	0%	2%	0%	0%	11%
Vomiting	98%	0%	0%	2%	0%	0%	2%
Mucositis/stomatitis (functional/symptomatic)	93%	0%	7%	0%	0%	0%	7%
Diarrhea	70%	20%	4%	7%	0%	0%	30%
Pain - Abdomen	96%	4%	0%	0%	0%	0%	4%
Pruritus/itching	91%	4%	4%	0%	0%	0%	9%
Hair loss/alopecia (scalp or body)	74%	26%	0%	0%	0%	0%	26%
Neuropathy: sensory	98%	0%	2%	0%	0%	0%	2%
Neuropathy: motor	98%	0%	2%	0%	0%	0%	2%
Neurology - Neuropathy that was not specified as either motor or sensory	93%	4%	2%	0%	0%	0%	7%
Neutrophils/granulocytes (ANC/AGC)	67%	0%	2%	17%	13%	0%	33%
Hemoglobin	93%	0%	4%	2%	0%	0%	7%
Leukocytes (total WBC)	96%	0%	2%	0%	2%	0%	4%
Platelets	98%	0%	2%	0%	0%	0%	2%

Adverse Events Legend

*No Change from Baseline/No Adverse Event

Treatment-emergent adverse events related to the study drug in the phase II component ($n = 46$). In both phase I and II components, physical examination, blood tests (complete blood count [CBC], chemistry, and electrolytes), and urine analyses were performed before each cycle of chemotherapy. On days 8 and 15 of each cycle, a CBC was performed before the administration of study drugs. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Assessment, Analysis, and Discussion

Completion

Study completed

Pharmacokinetics / Pharmacodynamics

Not collected

Investigator's Assessment

Inactive because results did not meet the primary endpoint

Discussion

In patients with metastatic or recurrent gastric cancer (GC), a doublet of fluoropyrimidine and platinum with or without a third drug is considered the standard first-line palliative chemotherapy. Recently, three phase III clinical trials demonstrated a survival benefit from second-line cytotoxic chemotherapy using a taxane or irinotecan [3–6]. In addition, ramucirumab, an antibody against vascular endothelial growth factor receptor 2, also exhibited a survival benefit compared with supportive care alone in a phase III trial [7]. Consequently, second-line palliative chemotherapy has become widely used in clinical practice. For second-line chemotherapy, weekly paclitaxel is one of the most widely used regimens [8–10], and it has been used as the reference regimen in several multinational randomized clinical trials [11, 12].

Paclitaxel is active against a wide variety of solid tumors including GC [8–15]. Because of the poor oral bioavailability of paclitaxel, which originates mainly from its high affinity for P-glycoprotein in the gastrointestinal mucosa [16], it must be administered intravenously. The original formulation of paclitaxel (Taxol; Bristol-Myers Squibb, New York, NY, <http://www.bms.com>) also contains the vehicle Cremophor EL (CrEL). This formulation of paclitaxel containing CrEL inconveniences patients and increases the risk of toxicities. Therefore, there have been many efforts to overcome the drawbacks of this paclitaxel formulation and develop a new oral formulation [1, 17, 18].

Recently, Hanmi Pharmaceutical (<http://www.hanmipharm.com>) developed Oraxol, an oral drug composed of paclitaxel and HM30181A [1, 19]. HM30181A, [2-(2-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenyl}-2*H*-tetrazol-5-yl)-4,5-dimethoxyphenyl]amide, inhibits P-glycoprotein in the gastrointestinal mucosa [19]. A previous study demonstrated that the coadministration of HM30181A (10 mg/kg) greatly increased the oral bioavailability of paclitaxel from 3.4% to 41.3% in rats [19]. In addition, the safety and pharmacokinetics of HM30181A were evaluated in healthy Korean volunteers [20]. In the previous first-in-human phase I study (HM-OXL-101), a solution formulation of Oraxol was administered once a week (on days 1, 8, and 15 every 4 weeks). Among the 24 patients enrolled, toxicities were generally mild, and the maximum tolerated dose (MTD) could not be defined. The effective plasma concentration was achieved at 120 mg/m² per week, and the absorption of paclitaxel tended to be limited at doses >300 mg/m² per week [1]. In the present phase I/II study (HM-OXL-201), a new formulation of Oraxol (paclitaxel capsule and HM30181A tablet) was used. A new schedule of weekly Oraxol (a 2-consecutive-day dosing schedule) was designed to maintain the plasma concentration of paclitaxel at therapeutic levels for a longer time.

In the phase I component of the present study, 10 patients were enrolled (Table 2). At dose level 3, one patient had an infection with Gram-positive bacteremia with a normal ANC on day 2 of the first cycle, but that was not considered to be caused by the study medication; therefore, this patient was replaced by another patient. The remaining patients completed the planned doses of Oraxol during the first cycle. The overall toxicities were mild, and no dose-limiting toxicity (DLT) was observed. Consequently, the MTD could not be determined. In GC cell lines, paclitaxel exhibited cytotoxicity at concentrations >0.01 μM [1, 21]. In the pharmacokinetic study of the phase I component of this study, the plasma concentration of paclitaxel over time reached the previously known effective range (0.01–0.1 μM) [1, 22] at all three paclitaxel dose levels (Fig. 2; Tables 3 and 4). The means of T_{>0.01} (time of plasma concentration of paclitaxel >0.01 μM) at three paclitaxel dose levels were 17.7, 43.2, and 47.5 hours, respectively (Table 4). The area under the plasma concentration-time curves (AUCs) also increased according to the paclitaxel dose. Based on these toxicity and pharmacokinetic data, dose level 3 was determined to be the recommended phase II dose (RP2D). Compared with the AUCs of paclitaxel in the HM-OXL-101 study [1], the AUCs of paclitaxel in this study were smaller; however, T_{>0.01} was longer at the PR2D (300 mg/m² per week; 47.5 hours [HM-OXL-201] vs. 39.7 hours [HM-OXL-101]) (Table 4). The median number of chemotherapy cycles in the phase I component of the present study was 2 (range: 1–3 cycles), and the median duration of Oraxol treatment was 40 days (range: 2–60 days). Compliance with Oraxol was excellent: all patients achieved 100% compliance (Table 6). Treatment-emergent adverse events (TEAEs) that developed during the phase I treatment period are presented in Table 5. Among the TEAEs related to Oraxol, only 1 patient (10%) experienced a severe TEAE (grade 3 anemia). Regarding the tumor response to study drugs (Table 2), two patients achieved stable disease (SD), and seven patients had progressive disease (PD).

In the phase II component of this study, between April 2011 and April 2012, 46 patients were enrolled (Table 7). As of September 2013, the median follow-up duration was 8.2 months (range: 0.6–22.8 months). The median number of chemotherapy cycles was 2 (range: 1–18 cycles), and the median duration of chemotherapy was 51.5 days (range: 2–502 days). The mean value of compliance for oral paclitaxel during the whole treatment period was 99.3% (range: 83.3%–100%) (Table 5). In the phase II component, three patients withdrew their consent to this study before any tumor response evaluation: one patient withdrew because of fever and delirium on day 13 of cycle 1 (not related to the study drug), a second patient withdrew because of grade 3 diarrhea on day 15 of the second cycle (possibly related to the study drug), and a third patient withdrew because of tumor bleeding and mesenteric artery occlusion/small bowel infarction. The third patient had

taken Oraxol for 2 days of the first cycle. The serious adverse event developed on day 8, and the patient died of the event on day 20 of the first cycle. These three patients were excluded from the efficacy evaluation, but they were included in the safety evaluation. Regarding adverse events, all TEAEs (regardless of a causal relationship with Oraxol) and TEAEs related to Oraxol are presented in Table 8. The overall toxicity profiles were extremely favorable. Treatment-related mortality was not observed during the whole study period. No hypersensitivity reactions developed. Among severe TEAEs related to Oraxol (grade ≥ 3), neutropenia was the most common (30.4%); however, no febrile neutropenia developed. Severe non-hematologic toxicities (grade ≥ 3) were rare, and diarrhea was the most common event (6.5%). Among 43 patients who were evaluated for efficacy, two patients underwent an unplanned tumor response evaluation using computed tomography (CT). These two patients did not undergo the planned CT evaluation at 8 weeks (2 cycles after the initiation of Oraxol treatment), but they were included in the efficacy evaluation. The efficacy results are presented in Table 1 and Figure 3. Among the 4 patients with PR, 3 patients experienced tumor progression, and 1 patient withdrew consent in the PR status (13.4 months after the initiation of Oraxol). The median response duration of these 4 patients was 5.4 months (95% confidence interval: 3.1–7.6 months).

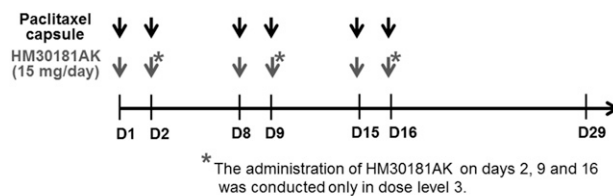
In the phase II component, this weekly Oraxol regimen displayed favorable toxicity profiles (Table 8). The incidence of severe neutropenia was 30.4%, which was similar to that reported in previous phase III trials of second-line weekly paclitaxel in GC (18.8%–30.2%) [10–12]. In particular, Oraxol appears to cause less peripheral neuropathy (all grades: $< 10\%$ of patients; grade ≥ 3 : no patients), which is one of the most frequent nonhematologic toxicities that patients receiving paclitaxel encounter, compared with conventional weekly paclitaxel (all grades: 21.7%–57.4% of patients; grade ≥ 3 : 0%–7.4% of patients) [10–12]. In our study, weekly Oraxol was associated with a response rate (RR) of 9.3% and progress-free survival (PFS) and overall survival (OS) of 2.6 and 10.7 months, respectively. From a statistical perspective, because the RR of weekly Oraxol was 9.3%, our study did not meet the primary endpoint. Considering that conventional weekly paclitaxel showed the RR in the range of 9%–20.9% in previous phase III trials [10–12], the assumption (H1) of RR of 17% in this study using weekly Oraxol might have been too high to achieve. In contrast, from a clinical perspective concerning the second-line treatment of metastatic or recurrent GC, weekly Oraxol does not appear to be inferior to other cytotoxic agents commonly used as second-line chemotherapy in GC [3–5, 10–12]. Regarding weekly paclitaxel, RRs of 9%–20.9% and PFS, and OS of 2.9–4.4 and 7.4–9.5 months, respectively, were reported in previous phase III trials [10–12]. Although the primary endpoint was not met, we demonstrated that Oraxol has its own advantages (favorable safety profiles, including less neuropathy and no hypersensitivity reactions, and the convenience of oral administration) over conventional paclitaxel. Consequently, we believe that Oraxol is worthy of further investigation. In particular, the combination of Oraxol with various chemotherapeutic agents is expected to be very promising because Oraxol displayed favorable toxicity profiles. Further studies of Oraxol as monotherapy or in combination with other chemotherapeutic drugs are warranted in various solid tumors including GC.

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Figures and Tables



Level	Paclitaxel capsule	HM30181AK
1	90 mg/m ² /day (day 1, 2, 8, 9, 15 and 16; every 4 weeks)	15 mg/day (day 1, 8 and 15; every 4 weeks)
2	120 mg/m ² /day (day 1, 2, 8, 9, 15 and 16; every 4 weeks)	15 mg/day (day 1, 8 and 15; every 4 weeks)
3	150 mg/m ² /day (day 1, 2, 8, 9, 15 and 16; every 4 weeks)	15 mg/day (day 1, 2, 8, 9, 15 and 16; every 4 weeks)

Figure 1. Treatment schema in the phase I component.

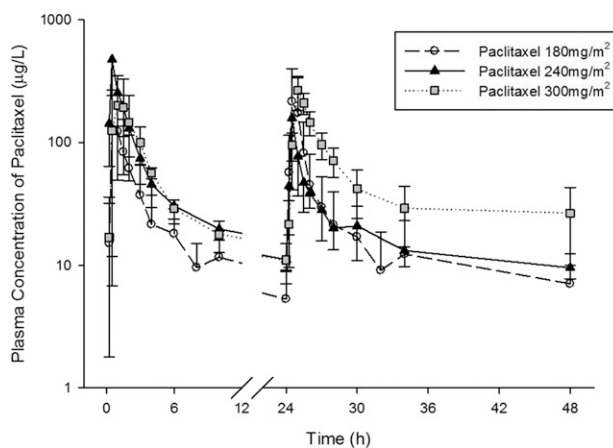


Figure 2. Mean concentration profile of paclitaxel after the administration of oral paclitaxel and HM30181A by paclitaxel dose group.

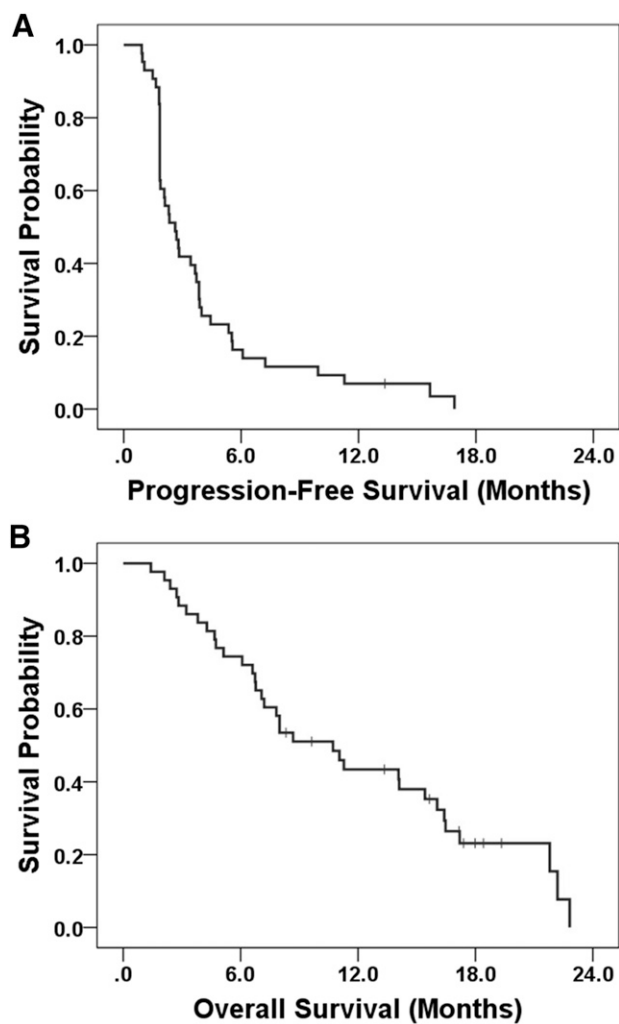


Figure 3. Survival probability. **(A):** Progression-free survival. **(B):** Overall survival.

Table 1. Efficacy results of the phase II component

Efficacy parameters (<i>n</i> = 43^a)	Results
Tumor response to Oraxol, <i>n</i> (%)	
Complete response	0 (0.0)
Partial response	4 (9.3)
Stable disease	17 (39.5)
Progressive disease	20 (46.5)
Not evaluable	2 (4.7)
Overall response rate, % (95% CI)	9.3 (2.6–22.1)
Disease control rate, % (95% CI)	48.8 (33.3–64.5)
Progression-free survival, months, median (95% CI)	2.6 (1.7–3.5)
Overall survival, months, median (95% CI)	10.7 (7.2–14.2)

^aAmong 43 patients who were evaluated for efficacy, 2 patients underwent an unplanned tumor response evaluation using CT. These 2 patients did not undergo the planned CT evaluation at 8 weeks (2 cycles after the initiation of Oraxol treatment), but they were included in the efficacy evaluation. Abbreviations: CI, confidence interval; CT, computed tomography.

Table 2. Patient characteristics and response to Oraxol in the phase I component

Phase I	Level 1 (<i>n</i> = 3) ^a	Level 2 (<i>n</i> = 3) ^b	Level 3 (<i>n</i> = 4) ^c	Total (<i>n</i> = 10)
Age (years)				
Median	66.0	58.0	54.5	56.5
Minimum, maximum	46.0, 71.0	44.0, 63.0	51.0, 76.0	44.0, 76.0
Sex, <i>n</i>				
Male	2	2	4	8
Female	1	1	0	2
Tumor type, <i>n</i>				
Stomach cancer (adenocarcinoma)	3	3	2	8
Colon cancer (adenocarcinoma)	0	0	1	1
Carcinoma of unknown primary site	0	0	1	1
Prior surgery, <i>n</i>				
Subtotal gastrectomy	1	1	2	4
Total gastrectomy	2	2	0	4
Left hemicolectomy	0	0	1	1
None	0	0	1	1
Prior palliative chemotherapy, <i>n</i>				
0–1 regimen	0	0	0	0
2 regimens	1	0	0	1
3 regimens	1	2	1	4
4 regimens	0	1	1	2
≥5 regimens	1	0	2	3
Prior radiation therapy, <i>n</i>				
No	2	2	2	6
Yes	1	1	2	4
ECOG PS, <i>n</i>				
0	3	3	2	8
1	0	0	2	2
2	0	0	0	0
Best overall response to Oraxol, <i>n</i>				
Complete response	0	0	0	0
Partial response	0	0	0	0
Stable disease	0	2	0	2
Progressive disease	3	1	3	7
Not applicable	0	0	1 ^d	1 ^d

^aLevel 1: HM30181A tablet 15 mg plus paclitaxel capsule 180 mg/m²/week,

^bLevel 2: HM30181A tablet 15 mg plus paclitaxel capsule 240 mg/m²/week

^cLevel 3: HM30181A tablet 15 mg plus paclitaxel capsule 300 mg/m²/week

^dIn one patient who developed Gram-positive bacteremia, which was not considered to be caused by the study medication, the tumor-response evaluation could not be done because of early dropout from this study.

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 3. Pharmacokinetic results of paclitaxel after administration of Oraxol (oral paclitaxel and 15 mg of HM30181A)

Pharmacokinetic parameters	Day 1	Day 2
Paclitaxel 180 mg/m ² , <i>n</i>	3	3
<i>C</i> _{max}		
μg/L	137.3 ± 137.3	215.5 ± 182.0
μM	0.16 ± 0.16	0.25 ± 0.21
<i>C</i> _{max} /dose, μg/L/mg	0.98 ± 0.99	1.53 ± 1.31
<i>T</i> _{max} , h	1.00 [0.50, ~6.00]	0.5 [0.5, ~0.5]
<i>t</i> _{1/2} , h	11.68 ± 4.56	17.28 ± 3.43
MRT, h	7.23 ± 2.29	6.37 ± 0.64
CL/F, L/h	777.5 ± 1,039.7	640.3 ± 858.0
<i>V</i> _z /F, L	9,902 ± 11,364	16,062 ± 21,383
AUC _{last}		
μg × h/L	462.8 ± 343.9	527.2 ± 431.1
μM × h	0.54 ± 0.40	0.62 ± 0.50
AUC _{inf}		
μg × h/L	563.0 ± 424.5	697.7 ± 542.2
μM × h	0.66 ± 0.50	0.82 ± 0.63
AUC _{last} /dose, h × μg/L/mg	3.28 ± 2.51	3.73 ± 3.13
AUC _{%extra} , %	15.66 [15.35, ~19.68]	29.38 [20.18, ~29.86]
AUC _{inf} /dose, h × μg/L/mg	3.98 ± 3.09	4.94 ± 3.94
Paclitaxel 240 mg/m ² , <i>n</i>	3	3
<i>C</i> _{max}		
μg/L	504.6 ± 439.9	159.4 ± 114.3
μM	0.59 ± 0.52	0.19 ± 0.13
<i>C</i> _{max} /dose, μg/L/mg	2.65 ± 2.31	0.89 ± 0.65
<i>T</i> _{max} , h	0.52 [0.50, ~1.48]	0.52 [0.50, ~2.00]
<i>t</i> _{1/2} , h	14.59 ± 1.44	14.96 ± 4.85
MRT, h	5.57 ± 1.23	8.16 ± 1.84
CL/F, L/h	154.2 ± 12.7	303.0 ± 107.7
<i>V</i> _z /F, L	3,259 ± 534	6,325 ± 2,057
AUC _{last}		
μg × h/L	993.7 ± 76.9	456.3 ± 120.4
μM × h	1.16 ± 0.09	0.53 ± 0.14
AUC _{inf}		
μg × h/L	1,227 ± 93.8	655.5 ± 119.9
μM × h	1.44 ± 0.11	0.77 ± 0.14
AUC _{%extra} , %	20.08 [16.46, ~20.46]	33.87 [23.38, ~35.82]
AUC _{last} /dose, h × μg/L/mg	5.28 ± 0.45	2.51 ± 1.04
AUC _{inf} /dose, h × μg/L/mg	6.51 ± 0.54	3.57 ± 1.16
Paclitaxel 300 mg/m ² , <i>n</i>	3	3
<i>C</i> _{max}		
μg/L	250.6 ± 100.4	276.2 ± 73.3
μM	0.29 ± 0.12	0.32 ± 0.09
<i>C</i> _{max} /dose, μg/L/mg	0.92 ± 0.43	1.02 ± 0.42
<i>T</i> _{max} , h	1.50 [1.00, ~3.00]	1.00 [0.98, ~1.50]
<i>t</i> _{1/2} , h	16.44 ± 2.66	18.45 ± 10.89
MRT, h	6.48 ± 1.45	7.63 ± 1.31

CL/F, L/h	278.9 ± 125.8	181.1 ± 91.0
V _z /F, L	6,444 ± 2,691	5,006 ± 3,529
AUC _{last}		
μg × h/L	846.3 ± 283.1	1,157.1 ± 409.7
μM × h	0.99 ± 0.33	1.36 ± 0.48
AUC _{inf}		
μg × h/L	1,119 ± 382.3	1,744 ± 611.4
μM × h	1.31 ± 0.45	2.04 ± 0.72
AUC _{%extra} , %	28.13 [15.43, ~29.27]	30.88 [22.22, ~45.23]
AUC _{last} /dose, h × μg/L/mg	3.11 ± 1.33	4.28 ± 2.01
AUC _{inf} /dose, h × μg/L/mg	4.14 ± 1.92	6.36 ± 2.52

All values except T_{max} and AUC_{%extra} are presented as mean ± SD. T_{max} and AUC_{%extra} are presented as median [minimum, maximum]. Abbreviations: AUC_{%extra}, [(AUC_{inf}-AUC_{last}) / AUC_{inf}] × 100; AUC_{inf}, area under the plasma concentration-time curve from 0 to infinite time; AUC_{last}, area under the plasma concentration-time curve from 0 to last time to measure plasma concentration; CL/F, oral clearance; C_{max}, maximum plasma concentration; h, hours; MRT, mean residence time; SD, standard deviation; t_{1/2}, elimination half-life; T_{max}, time required to reach C_{max}; V_z/F, apparent volume of distribution following oral administration.

Table 4. Comparison of paclitaxel pharmacokinetic results between HM-OXL-101 [1] and HM-OXL-201

Pharmacokinetics	HM-OXL-101 (Oraxol solution)	HM-OXL-201 (Oraxol capsule)
Dosage level 1	180 mg/m ^{2a}	180 mg/m ² (90 × 2 mg/m ²) ^b
AUC _{last} (μg × h/L)	1,673.9	990.10 ± 739.37
AUC _{inf} (μg × h/L)	1,985.0	1,160.6 ± 858.63
T _{>0.01} (h)	40.75 ± 9.90	17.72 ± 15.84
T _{>0.05} (h)	4.63 ± 0.18	4.63 ^a ± 0.88
T _{>0.1} (h)	2.5 ± 0	2.38 ^a ± 0.18
Dosage level 2	240 mg/m ^{2b}	240 mg/m ² (120 × 2 mg/m ²) ^b
AUC _{last} (μg × h/L)	2,547.4 ± 1,000.3	1,450.0 ± 55.92
AUC _{inf} (μg × h/L)	2,971.2 ± 941.1	1,649.1 ± 73.66
T _{>0.01} (h)	47.77 ± 0.04	43.16 ± 8.12
T _{>0.05} (h)	7.33 ± 2.65	3.98 ± 1.20
T _{>0.1} (h)	4.92 ± 3.00	2.56 ± 0.81
Dosage level 3	300 mg/m ^{2b}	300 mg/m ² (150 × 2 mg/m ²) ^b
AUC _{last} (μg × h/L)	3,135.0 ± 1,450.1	2,003.5 ± 514.55
AUC _{inf} (μg × h/L)	3,481.1 ± 1,580.0	2,590.1 ± 528.17
T _{>0.01} (h)	39.7 ± 13.94	47.46 ± 0.41
T _{>0.05} (h)	7.98 ± 3.06	12.91 ± 12.28
T _{>0.1} (h)	5.67 ± 3.70	3.34 ± 0.77

All values are presented as mean ± SD. In the HM-OXL-101 study, Oraxol was administered once a week, and the blood-sampling times for paclitaxel were 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 24, 34, and 48 hours. In the present study (HM-OXL-201), Oraxol was administered twice a week (days 1 and 2), and the blood-sampling times were 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 10, and 24 hours on days 1 and 2. In the present study (HM-OXL-201), total AUC_{last} [= AUC_{last}(day 1) + AUC_{last}(day 2)] and total AUC_{inf} [= AUC_{inf}(day 1) + AUC_{inf}(day 2)] are presented. In this table, AUC_{last} of the HM-OXL-201 study was calculated as follows; AUC_{last}, AUC_{last} (day 1) + AUC_{last} (day 2).

^an = 2.

^bn = 3.

Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from 0 to infinite time; AUC_{last}, area under the plasma concentration-time curve from 0 to last time to measure plasma concentration; h, hours; T_{>0.01}, time of plasma concentration of paclitaxel >0.01 μM; T_{>0.05}, time of plasma concentration of paclitaxel >0.05 μM; T_{>0.1}, time of plasma concentration of paclitaxel >0.1 μM.

Table 5. Treatment-emergent adverse events that developed in the phase I component (*n* = 10)

System organ class preferred term	TEAEs					TEAEs related to the study drug				
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total
Gastrointestinal disorders										
Abdominal pain	2 (20)	3 (30)	1 (10)	0	6 (60)	0	0	0	0	0
Nausea	3 (30)	2 (20)	0	0	5 (50)	2 (20)	0	0	0	2 (20)
Diarrhea	3 (30)	0	0	0	3 (30)	2 (20)	0	0	0	2 (20)
Rectal tenesmus	0	1 (10)	0	0	1 (10)	0	0	0	0	0
General disorders and administration site conditions										
Pyrexia	2 (20)	1 (10)	0	0	3 (30)	0	0	0	0	0
Fatigue	0	1 (10)	0	0	1 (10)	0	1 (10)	0	0	1 (10)
Mucosal inflammation	1 (10)	0	0	0	1 (10)	1 (10)	0	0	0	1 (10)
Blood and lymphatic system disorders										
Neutropenia	0	2 (20)	0	0	2 (20)	0	2 (20)	0	0	2 (20)
Anemia	0	0	1 (10)	0	1 (10)	0	0	1 (10)	0	1 (10)
Leukocytosis	1 (10)	0	0	0	1 (10)	0	0	0	0	0
Thrombocytopenia	0	1 (10)	0	0	1 (10)	0	1 (10)	0	0	1 (10)
Musculoskeletal and connective tissue disorders										
Flank pain	0	1 (10)	0	0	1 (10)	0	0	0	0	0
Muscular weakness	1 (10)	0	0	0	1 (10)	0	0	0	0	0
Musculoskeletal discomfort	1 (10)	0	0	0	1 (10)	0	0	0	0	0
Myalgia	0	1 (10)	0	0	1 (10)	0	0	0	0	0
Metabolism and nutrition disorders										
Anorexia	2 (20)	0	0	0	2 (20)	1 (10)	0	0	0	1 (10)
Hypokalemia	0	0	1 (10)	0	1 (10)	0	0	0	0	0
Investigations										
Alanine aminotransferase increased	0	1 (10)	0	0	1 (10)	0	0	0	0	0
Aspartate aminotransferase increased	0	1 (10)	0	0	1 (10)	0	0	0	0	0
γ-glutamyltransferase increased	0	1 (10)	0	0	1 (10)	0	0	0	0	0
Nervous system disorders										
Dizziness	0	1 (10)	0	0	1 (10)	0	0	0	0	0
Neuropathy	1 (10)	0	0	0	1 (10)	1 (10)	0	0	0	1 (10)
Eye disorders										
Eye hemorrhage	1 (10)	0	0	0	1 (10)	0	0	0	0	0
Infections and infestations										
Bacteremia	0	0	1 (10)	0	1 (10)	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders										
Hemoptysis	1 (10)	0	0	0	1 (10)	0	0	0	0	0

Data are shown as number (percentage). MedDRA version 10.0 (<http://www.meddra.org>). If TEAEs repeatedly occurred in a patient, it was regarded as one case with the most severe event recorded.

Abbreviation: TEAEs, treatment-emergent adverse events.

Table 6. Summary of compliance (safety population)

Compliance	Phase I				Phase II RD (n = 46)
	Level 1 (n = 3)	Level 2 (n = 3)	Level 3 (n = 4)	Total (n = 10)	
Oral paclitaxel					
Cycle 1					
n	3	3	4	10	46
Mean (SD)	100 (0)	100 (0)	100 (0)	100 (0)	99.6 (2.46)
Median	100	100	100	100	100
Minimum, maximum	100, 100	100, 100	100, 100	100, 100	83.3, 100
Cycle 2					
n	2	2	3	7	38
Mean (SD)	100 (0)	100 (0)	100 (0)	100 (0)	99.1 (3.77)
Median	100	100	100	100	100
Minimum, maximum	100, 100	100, 100	100, 100	100, 100	83.3, 100
Whole treatment period					
n	3	3	4	10	46
Mean (SD)	100 (0)	100 (0)	100 (0)	100 (0)	99.3 (2.95)
Median	100	100	100	100	100
Minimum, maximum	100, 100	100, 100	100, 100	100, 100	83.3, 100
HM30181A					
Cycle 1					
n	3	3	4	10	46
Mean (SD)	100 (0)	100 (0)	100 (0)	100 (0)	99.6 (2.46)
Median	100	100	100	100	100
Minimum, maximum	100, 100	100, 100	100, 100	100, 100	83.3, 100
Cycle 2					
n	2	2	3	7	38
Mean (SD)	100 (0)	100 (0)	100 (0)	100 (0)	99.1 (3.77)
Median	100	100	100	100	100
Minimum, maximum	100, 100	100, 100	100, 100	100, 100	83.3, 100
Whole treatment period					
n	3	3	4	10	46
Mean (SD)	100 (0)	100 (0)	100 (0)	100 (0)	99.2 (2.95)
Median	100	100	100	100	100
Minimum, maximum	100, 100	100, 100	100, 100	100, 100	83.3, 100

Compliance (%) = (number of tablets actually administered / number of tablets to be administered) × 100. Level 1: HM30181A tablet 15 mg plus paclitaxel capsule 180 mg/m²/week. Level 2: HM30181A tablet 15 mg plus paclitaxel capsule 240 mg/m²/week. Level 3: HM30181A tablet 15 mg plus paclitaxel capsule 300 mg/m²/week. RD: HM30181A tablet 15 mg plus Hanmi paclitaxel capsule 300 mg/m²/week. Abbreviations: RD, recommended dose; SD, standard deviation.

Table 7. Patient characteristics in the phase II component

Characteristics (n = 46)	Results
Age (years)	
Median (range)	63.5 (39.0–82.0)
Sex, n (%)	
Male	35 (76.1)
Female	11 (23.9)
ECOG PS, n (%)	
0	13 (28.3)
1	32 (69.6)
2	1 (2.2)
Disease status (first-line chemotherapy), n (%)	
Recurrent after curative surgery	17 (37.0)
Unresectable (distant metastasis)	26 (56.5)
Unresectable (locally advanced)	3 (6.5)
Prior gastrectomy, n (%)	
None	18 (39.1)
Subtotal gastrectomy	15 (32.6)
Total gastrectomy	13 (28.3)
Prior adjuvant chemotherapy, n (%)	
No	33 (71.7)
Yes	13 (28.3)
First-line chemotherapy, n (%)	
S-1/cisplatin	11 (23.9)
Capecitabine/oxaliplatin ^a	8 (17.4)
Capecitabine/cisplatin ^b	7 (15.2)
5-FU/oxaliplatin	4 (8.7)
5-FU/cisplatin	3 (6.5)
S-1/oxaliplatin	3 (6.5)
5-FU/irinotecan	3 (6.5)
Doxifluridine/cisplatin	1 (2.2)
S-1	3 (6.5)
Capecitabine ^c	3 (6.5)
Metastatic sites, n (%)	
Lymph node	23 (50.0)
Liver	19 (41.3)
Peritoneum	14 (30.4)
Lung	4 (8.7)
Ovary	3 (27.3) ^d
Adrenal gland	2 (4.3)

^aOne patient received capecitabine/oxaliplatin plus sunitinib.

^bTwo patients received capecitabine/cisplatin plus sorafenib.

^cOne patient received capecitabine plus trastuzumab.

^dAmong female patients (n = 11).

Abbreviations: 5-FU, 5-fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 8. Treatment-emergent adverse events that developed in the phase II component (*n* = 46)

System organ class preferred term	TEAEs						TEAEs related to the study drug					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Gastrointestinal disorders												
Abdominal pain	4 (8.7)	8 (17.4)	4 (8.7)	0	0	16 (34.8)	2 (4.3)	0	0	0	0	2 (4.3)
Diarrhea	10 (21.7)	2 (4.3)	3 (6.5)	0	0	15 (32.6)	9 (19.6)	2 (4.3)	3 (6.5)	0	0	14 (30.4)
Nausea	7 (15.2)	4 (8.7)	2 (4.3)	0	0	13 (28.3)	4 (8.7)	0	1 (2.2)	0	0	5 (10.9)
Dyspepsia	5 (10.9)	1 (2.2)	0	0	0	6 (13.0)	1 (2.2)	0	0	0	0	1 (2.2)
Vomiting	1 (2.2)	2 (4.3)	2 (4.3)	0	0	5 (10.9)	0	0	1 (2.2)	0	0	1 (2.2)
Constipation	1 (2.2)	4 (8.7)	0	0	0	5 (10.9)	0	0	0	0	0	0
General disorders and administration site conditions												
Fatigue	5 (10.9)	7 (15.2)	1 (2.2)	0	0	13 (28.3)	4 (8.7)	5 (10.9)	1 (2.2)	0	0	10 (21.7)
Mucosal inflammation	0	3 (6.5)	0	0	0	3 (6.5)	0	3 (6.5)	0	0	0	3 (6.5)
Metabolism and nutrition disorders												
Anorexia	10 (21.7)	3 (6.5)	3 (6.5)	0	0	16 (34.8)	11 (23.9)	2 (4.3)	0	0	0	13 (28.3)
Skin and subcutaneous tissue disorders												
Alopecia	12 (26.1)	0	0	0	0	12 (26.1)	12 (26.1)	0	0	0	0	12 (26.1)
Pruritus	3 (6.5)	3 (6.5)	0	0	0	6 (13.0)	2 (4.3)	2 (4.3)	0	0	0	4 (8.7)
Blood and lymphatic system disorders												
Neutropenia	0	1 (2.2)	9 (19.6)	6 (13.0)	0	16 (34.8)	0	1 (2.2)	8 (17.4)	6 (13.0)	0	15 (32.6)
Anemia	0	2 (4.3)	2 (4.3)	1 (2.2)	0	5 (10.9)	0	2 (4.3)	1 (2.2)	0	0	3 (6.5)
Leukopenia	0	1 (2.2)	0	1 (2.2)	0	2 (4.3)	0	1 (2.2)	0	1 (2.2)	0	2 (4.3)
Thrombocytopenia	0	1 (2.2)	0	0	0	1 (2.2)	0	1 (2.2)	0	0	0	1 (2.2)
Respiratory, thoracic and mediastinal disorders												
Dyspnea	2 (4.3)	2 (4.3)	1 (2.2)	0	0	5 (10.9)	0	0	0	0	0	0
Nervous system disorders												
Neuropathy ^a	2 (4.3)	1 (2.2)	0	0	0	3 (6.5)	2 (4.3)	1 (2.2)	0	0	0	3 (6.5)
Peripheral sensory neuropathy	2 (4.3)	1 (2.2)	0	0	0	3 (6.5)	0	1 (2.2)	0	0	0	1 (2.2)
Peripheral motor neuropathy	0	1 (2.2)	1 (2.2)	0	0	2 (4.3)	0	1 (2.2)	0	0	0	1 (2.2)
Musculoskeletal and connective tissue disorders												
Back pain	2 (4.3)	4 (8.7)	0	0	0	6 (13.0)	1 (2.2)	0	0	0	0	1 (2.2)
Investigations												
Alanine aminotransferase increased	0	1 (2.2)	0	0	0	1 (2.2)	0	0	0	0	0	0
Aspartate aminotransferase increased	0	1 (2.2)	0	0	0	1 (2.2)	0	0	0	0	0	0
Blood alkaline phosphatase increased	0	0	1 (2.2)	0	0	1 (2.2)	0	0	0	0	0	0
Hepatobiliary disorders												
Hyperbilirubinemia	0	2 (4.3)	0	0	0	2 (4.3)	0	0	0	0	0	0

Data are shown as number (percentage). This table shows all TEAEs that developed in $\geq 10\%$ of patients (during all treatment periods) regardless of the causal relationship to the study drug, TEAEs related to the study drug that developed in $\geq 5\%$ of patients, and adverse events of interest (all hematologic toxicities, all hepatic toxicities, and peripheral neuropathy) regardless of frequency.

^aNeuropathy that was not specified as either motor or sensory was included.

Abbreviation: TEAEs, treatment-emergent adverse events.

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