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PHASE II STUDIES

A phase II trial of a selective c-Met inhibitor tivantinib (ARQ 197) monotherapy as a second- or third-line therapy in the patients with metastatic gastric cancer

Yoon-Koo Kang · Kei Muro · Min-Hee Ryu · Hirofumi Yasui · Tomohiro Nishina · Baek-Yeol Ryoo · Yukimasa Kamiya · Shiro Akinaga · Narikazu Boku

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Summary *Background* Tivantinib is a selective, non-ATP competitive, small-molecule inhibitor of c-Met and is under development in several cancers including non-small cell lung and hepatocellular carcinoma. Activation of c-Met has been frequently found in metastatic gastric cancer (MGC) and is associated with poor prognosis. In this single-arm study, we evaluated the efficacy of tivantinib monotherapy in Asian patients with previously treated MGC. This is the first clinical report from the trials evaluating the efficacy of a selective c-Met inhibitor for MGC. *Patients and methods* Eligibility criteria included: MGC with at least one measurable lesion; 1 or 2 prior chemotherapy regimens; and ECOG PS 0 or 1. Tivantinib was daily administered orally. The primary endpoint was the disease control rate (DCR). Pre-treatment tumor tissue was collected to evaluate the biomarkers related to efficacy. *Results* Thirty patients, including 12 patients with prior gastrectomy, received tivantinib: median age 62.5 years; ECOG PS 0/1 (8/22); 1/2 prior regimen (16/14). No objective response was observed, and DCR was 36.7 %. Median progression-free survival was 43 days (95 % CI: 29.0-92.0). Grade 3 or 4 adverse events occurred in 13 patients (43.3 %), in whom neutropenia (N=4) and anemia (N=4) were recognized as drug-related. c-Met gene amplification was observed in 2 patients (6.9 %). No obvious relationship was identified between efficacy and biomarkers including gene amplification of c-Met, expression of c-Met, p-Met and HGF. *Conclusion* Tivantinib as a monotherapy showed a modest efficacy in previously treated MGC, and further studies taking account of predictive biomarkers and/or combination with other chemotherapy may be needed in MGC.

Keywords c-Met inhibitor · Tivantinib · ARQ 197 · Gastric cancer · Phase II study

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Y.-K. Kang (✉) · M.-H. Ryu · B.-Y. Ryoo
Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, South Korea
e-mail: ykkang@amc.seoul.kr

K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, 1-1, Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

H. Yasui · N. Boku
Division of Gastrointestinal Oncology, Shizuoka Cancer Center, 1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan

T. Nishina
Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, 160 Kou Minamiumemoto-cho, Matsuyama 791-0280, Japan

Y. Kamiya · S. Akinaga
Development Division, Kyowa Hakko Kirin Co., Ltd., 1-6-1, Ohtemachi, Chiyoda-ku, Tokyo 100-8186, Japan

Introduction

Gastric cancer is the fourth most common malignancy and the second leading cause of cancer death in the world where 988,000 of new cases and 736,000 deaths are estimated to have occurred annually, with one half of the patients found in Eastern Asia in 2008 [1]. In the first-line setting of metastatic gastric cancer (MGC), combination chemotherapy based on

fluoropyrimidine (fluorouracil or its derivatives) and platinum is currently regarded as the standard treatment. Recently, as the first molecular-targeted therapy for MGC, an anti-HER2 antibody trastuzumab demonstrated a survival benefit in HER2 positive patients, but HER2 positive patients are limited to around 20 % of MGC [2]. In the second-line setting, although irinotecan and taxanes (paclitaxel, docetaxel) are currently used for the palliative chemotherapy, clinical benefit of these agents had not been provided by a large clinical trial at the time of designing this trial [3]. Therefore, a standard second-line or third-line chemotherapy is needed for MGC.

c-Met and its ligand, hepatocyte growth factor (HGF), play important roles in oncogenesis. Aberrant activation of the HGF/c-Met signaling pathway may lead to increased tumor cell proliferation, resistance to apoptosis, invasive growth, and tumor angiogenesis [4]. Gene amplification of c-Met, overexpression of c-Met, or elevation of serum HGF are known to correlate with poor prognosis in MGC [5–9]. In view of the critical role of the HGF/c-Met signaling pathway in gastric cancer progression, several biologics and low-molecular-weight compounds, which interfere with HGF/c-Met axis, are currently under clinical investigation. However, the clinical impact of HGF/c-Met axis inhibition is still unknown [10]. In addition, relevant biomarkers have not been defined to select a MGC patient population potentially responding to HGF/c-Met inhibitors.

Tivantinib (also known as ARQ 197) is a low-molecular-weight compound, and is the first in class, orally available selective inhibitor of c-Met [11]. Tivantinib disrupts c-Met phosphorylation in a non-ATP competitive manner, distinguishing it from other c-Met inhibitors in clinical trials [12]. Growth inhibition in c-Met expressing gastric cancer cell lines was induced by exposure to tivantinib in vitro and in vivo [11]. Tivantinib has been studied in several clinical trials across various tumor types and demonstrated efficacy in two placebo-controlled randomized phase 2 studies in non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC) [13, 14]. The previous phase 1 study in the Japanese patients with solid tumors showed that cytochrome P450 2C19 (CYP2C19) genotype affect the pharmacokinetics and the tolerability of tivantinib. CYP2C19 is known to have genetic polymorphisms leading to enzymatic dysfunction. Thus the recommended phase 2 dose of tivantinib in Asian population was determined by a pretreatment test for CYP2C19 polymorphism; a 360 mg twice daily dose for consecutive days was recommended for patients with at least one wild-type allele of CYP2C19, who are the majority (approximately 80 %) of the Asian population [15].

This is the first clinical trial evaluating the efficacy of a selective c-Met inhibitor in MGC patients. The primary endpoint was to assess the disease control rate (DCR) of tivantinib in the patients with MGC.

Patients and methods

Study design

This was a phase 2, open-label, single-arm, multicenter trial among Korean and Japanese patients with MGC. The primary objective was to assess the DCR, defined as the proportion of patients demonstrating complete response (CR), partial response (PR), or stable disease (SD). Secondary objectives included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), safety profiles, and predictive biomarkers. In addition, the pharmacokinetic (PK) differences between Korean and Japanese or between patients with and without prior gastrectomy were also evaluated. All results were analyzed in the full analysis set (FAS), which included all eligible patients who received at least one dose of tivantinib.

For the PK analysis, 18 patients (9 Korean and 9 Japanese) without any history of gastrectomy were divided into three groups, and the patients received a single dose of 120, 240 or 360 mg tivantinib on the first day of administration (day 1). The remaining 12 patients (6 Korean and 6 Japanese) with gastrectomy were treated with 360 mg on day 1. On day 2 and thereafter, all patients started daily continuous tivantinib at the dose of 360 mg bid between meals until disease progression, symptomatic deterioration, unacceptable toxicity, treatment interruption for any reason more than 14 days, or withdrawal of informed consent. Dose adjustments were gradually allowed from 360 mg bid to 240 mg bid and then 120 mg bid, if grade ≥3 toxicity was observed and patients were able to recover within 14 days of drug interruption.

This study was sponsored by Kyowa Hakko Kirin Co., Ltd. and conducted in accordance with institutional guidelines, Good Clinical Practice guidelines and the Declaration of Helsinki. Documented approvals from the Institutional Review Boards were obtained. All patients provided written informed consent. This trial was registered in ClinicalTrials.gov as NCT01152645.

Patient population

The participating centers included Asan Medical Center (Korea), Shizuoka Cancer Center (Japan), Aichi Cancer Center Hospital (Japan) and Shikoku Cancer Center (Japan).

Patients were eligible if they had a histologically or cytologically confirmed MGC; ≥ 20 years of age with informed consent; previously treated with 1 or 2 prior chemotherapies; CYP2C19 genotype with at least one wild-type allele; at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [16]; ECOG performance status 0 or 1; adequate organ functions; and consent to tumor sample submission for biomarker analysis. Key exclusion criteria were any prior treatment with c-Met inhibitors; surgery for cancer within 4 weeks prior to the first dose of

tivantinib; any concomitant anticancer treatment including chemotherapy, hormone therapy, radiotherapy, immunotherapy, or another investigational drug used within 2 weeks; multiple primary neoplasm within 5 years; inability to take oral tivantinib twice daily; central nervous system metastasis; gastrointestinal disorders that might interfere with the absorption of tivantinib and underlying uncontrolled complication.

Efficacy evaluation

The primary efficacy objective was to assess the DCR, which was defined as the proportion of patients with CR, PR, or SD as the best overall response according to the following criteria based on the RECIST version 1.1. PR or CR was confirmed 4 weeks after first detection of response. Patients were assigned a best overall response of SD if they achieved SD after the 8 weeks treatment with tivantinib. The investigators measured tumor size at baseline, 4 and 8 weeks after the beginning of treatment, and every 6 weeks thereafter. The response and progression was determined by the central radiology review committee for the primary objective evaluation. The DCR was summarized in terms of percentage, with a 95 % confidence interval (CI), and was calculated primarily based on the assessment of the central radiology review. A sample size of 30 patients will provide ≥99 % power to indicate that the lower limit of the 95 % CI of the DCR will exceed the threshold of 20 % (futility rate), if the DCR with tivantinib is expected to be 60 % (targeted rate).

Pharmacokinetics analysis

Blood samples were obtained on day 1 (pre, 1, 2, 4, 6, 10, 12, and 24 h after the first dose of 120 mg, 240 mg or 360 mg), and before dosing on day 15 and day 29. Plasma samples were stored at -20 °C until analysis, and concentration of tivantinib in the plasma was measured by liquid chromatography/tandem mass spectrometry. PK parameters were calculated by noncompartmental analysis using WinNonlin (Pharsight, Mountain View, CA).

Biomarker analysis

Biomarkers tested herein were c-Met expression, phosphorylated c-Met (p-Met) expression, HGF expression and c-Met gene copy number in tumor samples and HGF concentration in serum samples.

Paraffin-embedded tumor samples from fresh or archived tumor specimens were collected from all the patients. Optional re-biopsy after 3 weeks treatment with tivantinib was done in the patients with an additional consent. The immunohistochemistry (IHC) for c-Met, p-Met and HGF, and fluorescence in situ hybridization (FISH) for c-Met and centromere 7 (CEP7, as an assay control) were conducted by a commercial laboratory (SRL Inc., Tokyo, Japan). The following antibodies were used for IHC: anti-c-Met (clone C12, Santa Cruz Biotechnology, Inc., TX, USA), anti-phospho-c-Met (Tyr1349) rabbit mAb (clone 130H2, Cell Signaling Technology, Inc., MA, USA), and anti-human HGFα rabbit IgG (Immuno-Biological Laboratories Co., Ltd., Fukuoka, Japan). The results of the IHC staining were quantified using the H-score which ranges from 0 to 300 on the basis of both the percentage of positive tumor area (0-100) and the staining intensity (0, no staining; 1, weak staining; 2, moderate staining; or 3, intense staining). High c-Met expression was defined if H-score on tumor cell membrane or in tumor cell cytoplasm exceeded 100, which approximates the median score among the tested samples. c-Met copy number per cell was determined by FISH with the use of Vysis D7S522/CEP 7 FISH Probe Kit (Abbott Molecular Inc., IL, USA). c-Met gene amplification was defined as previously reported; a ratio of c-Met/CEP7 of higher than 2.2 [8].

Blood samples for serum HGF were also collected on day 1 (pre-treatment and 12 h after the first dose) and on day 29. The concentration of serum HGF was measured by a commercial laboratory, SRL Inc.

Results

Patient characteristics and treatment

A total of 31 patients were enrolled from July 2010 to June 2011. The FAS population, which is defined as the patients who received at least one dose of tivantinib, included 30 patients; the remaining patient did not receive study medication due to the determination of ineligibility after the registration. Table 1 shows the patient characteristics of the FAS population. Of 30 patients, 80 % of patients were male and the median age was 62.5 years. There were no notable differences in patient characteristics between Korean and Japanese except the distribution of ECOG PS. On the data cut-off date for this report, all patients had discontinued the study treatment.

The median duration of treatment was 56.5 days and the median relative dose intensity was 94.4 %. Ninety-seven percent of the patients discontinued this study due to disease progression.

Efficacy and biomarkers

Of 30 patients in the FAS, 11 achieved disease control (0 CR; 0 PR; 11 SD), resulting in the DCR of 36.7 % (95 % CI: 19.9–56.1 %). The lower limit of its 95 % CI did not exceed the target threshold of 20 % (Table 2). The median PFS was 43.0 days (95 % CI: 29.0–92.0 days), and the median survival time was 344.5 days (95 % CI: 227.0–380.0 days) (Fig. 1). The median duration of stable disease was 98.0 days (95 % CI: 92.0–347.0 days) among the 11 subjects who achieved a best overall response of SD.

Table 1 Patients characteristics

		Overall	Ethnicity	
		n = 30	Japanese *n* = 15	Korean *n* = 15
Sex	Female	6 (20.0 %)	3(20.0 %)	3 (20.0 %)
	Male	24 (80.0 %)	12(80.0 %)	12 (80.0 %)
Age	Median (range)	62.5 (41-70)	63.0(41-70)	59.0 (43-70)
Tumor histology	Well differentiated	3 (10.0 %)	2(13.3 %)	1 (6.7 %)
	Moderately differentiated	10 (33.3 %)	3(20.0 %)	7 (46.7 %)
	Poorly differentiated	14 (46.7 %)	8(53.3 %)	6 (40.0 %)
	Other	2 (6.7 %)	1(6.7 %)	1 (6.7 %)
	Unknown	1 (3.3 %)	1(6.7 %)	0 (0.0 %)
ECOG PS	0	8 (26.7 %)	8(53.3 %)	0 (0.0 %)
	1	22 (73.3 %)	7(46.7 %)	15 (100.0 %)
Prior chemotherapies	1	16 (53.3 %)	9(60.0 %)	7 (46.7 %)
	2	14 (46.7 %)	6(40.0 %)	8 (53.3 %)
Gastrectomy	Yes	12 (40.0 %)	6(40.0 %)	6 (40.0 %)
	No	18 (60.0 %)	9(60.0 %)	9 (60.0 %)
Current cancer diagnosis	Advanced	23 (76.7 %)	11(73.3 %)	12 (80.0 %)
	Recurrent	7 (23.3 %)	4(26.7 %)	3 (20.0 %)
CYP2C19 genotype [a]	*1/*1	12 (40.0 %)	6(40.0 %)	6 (40.0 %)
	*1/*2	13 (43.3 %)	6(40.0 %)	7 (46.7 %)
	*1/*3	5 (16.7 %)	3(20.0 %)	2 (13.3 %)

*1 is the wild type genotype, whereas *2 and *3 are the major polymorphism leading to functional deficiency

[a] CYP2C19 genotype

Archival or fresh biopsy tumor samples and blood samples were collected from all patients for the exploration of the predictive biomarker of tivantinib. One tumor specimen did not contain tumor cells, thus a total of 29 tumor samples was analyzed for IHC and FISH assessment. Regarding the IHC analysis, 11 patients (37.9 %) had high c-Met expression (H-score >100) in tumor cell cytoplasm and only 1 patient (3.4 %) had high c-Met expression on tumor cell membrane. For the FISH analysis, only 2 patients (6.9 %) harbored c-Met gene amplification. As a result, none of these pretreatment biomarkers were found to demonstrate any correlation with best overall response (disease control) or treatment duration in this study (Fig. 2, Supplemental tables).

We conducted post-treatment biopsy in 4 patients, and no apparent change of biomarkers including c-Met, p-Met and HGF expression was observed in the post-treatment samples. Serum HGF concentration was also not changed dramatically from baseline to 12 h or 29 days after treatment (data not shown).

Table 2 Tumor responses

Best overall responses (*n* = 30)					DCR (%) [95 % CI]	ORR (%) [95 % CI]
CR	PR	SD	PD	NE		
0	0	11	19	0	36.7 [19.9-56.1]	0 [0.0-11.6]

Safety and pharmacokinetics

Of the 30 patients, AEs occurred in 29 (96.7 %), and AEs with grade ≥3 according to CTCAE v4.0 occurred in 13 patients (43.3 %). The most common drug-related AEs included nausea in 7 patients (23.3 %) and anemia and decreased appetite

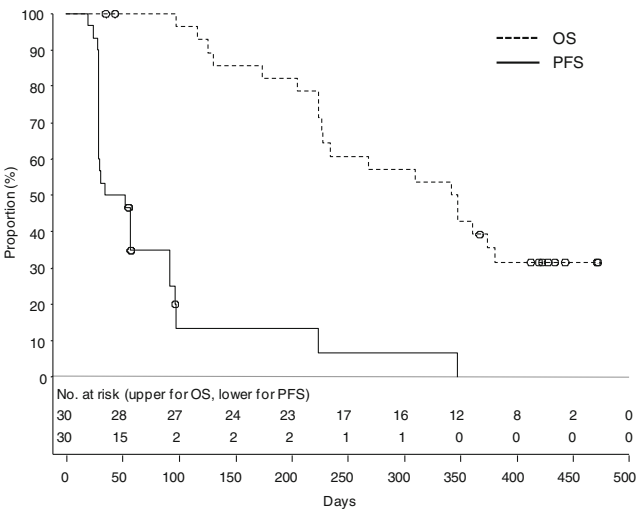

Fig. 1 Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) in the MGC patients treated with tivantinib. The *solid* and *dot curves* indicate PFS and OS, respectively. PFS was determined according to RECIST criteria, based on the assessment by the central radiology review committee

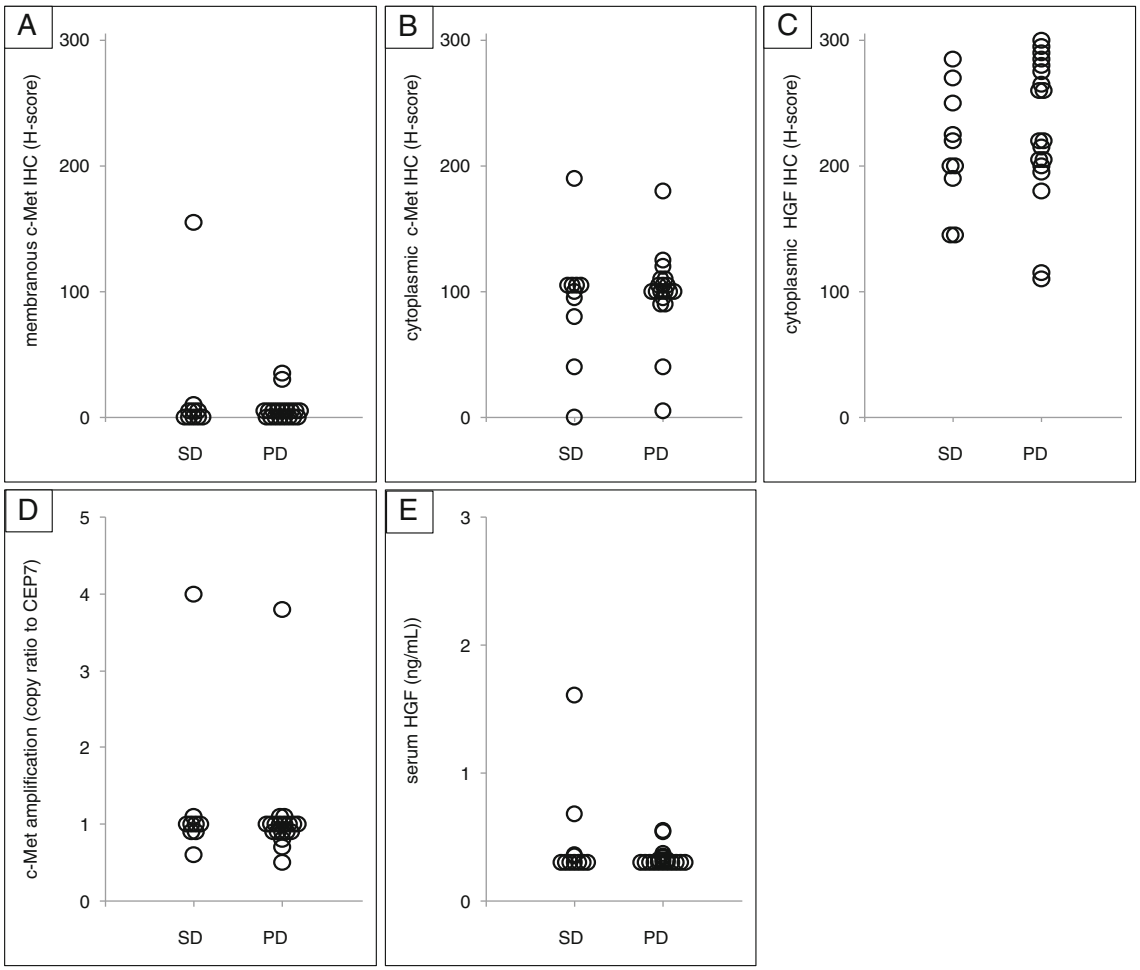

Fig. 2 Relationship between tumor responses and predictive biomarkers. The H-score for membranous c-Met (**A**), cytoplasmic c-Met (**B**) and HGF (**C**) as well as c-Met gene copy number ration per CEP7 (**D**) and the concentration of serum HGF (**E**) are dotted for each individual with his/her tumor response

in 6 patients (20.0 %) respectively. The drug-related adverse events of grade ≥3 were mainly hematological toxicities including neutropenia, febrile neutropenia, leukopenia and anaemia (Table 3). In the four patients who experienced neutropenia of grade ≥3, plasma trough concentrations on day 15 were 3680, 3680, 4180 and 4600 ng/mL, respectively. Although two patients missed several doses by day 15, their plasma concentrations of tivantinib were relatively high compared to other patients without severe neutropenia (N=19, 1513±1121 ng/mL, mean±SD), being consistent with the preceding report [17]. There was one AE (gastric stenosis) who needed treatment-discontinuation, and no treatment-related death was observed.

No clear difference was seen in the plasma concentration-time profile between Korean and Japanese patients after the first dose of tivantinib at any tested dose (120 mg, 240 mg or 360 mg). There was also no clear difference in pharmacokinetics between patients with and without prior gastrectomy (Fig. 3).

No clear relationship between efficacy and pharmacokinetics parameters of tivantinib was observed (Supplemental figure).

Discussion

This is the first clinical trial evaluating the efficacy of a selective c-Met inhibitor in second- or third-line MGC. The efficacy of tivantinib resulted in a DCR of 36.7 % with 95 % CI: 19.9–56.1 %, in which the lower limit of its 95 % CI did not exceed the target threshold of 20 %. Recently, Korean investigators reported the results of a phase III study demonstrating that the DCR after 6 weeks of treatment with docetaxel and with irinotecan were 59.5 % and 52.0 %, respectively, in patients with MGC with one or two prior chemotherapy regimens [18]. Compared with the Korean phase III trial in similar patients, we concluded that tivantinib has modest efficacy in non-selected MGC patients.

To select patients who may respond to the tivantinib, we assessed c-Met overexpression (IHC) and c-Met amplification (i.e. c-Met copy number), as candidates for predictive biomarkers. IHC analysis showed a broad level of c-Met expression among the tested patients, and 11 of 29 patients (37.9 %) with H-score >100 in either cytoplasm or membrane were

Table 3 Drug-related adverse events occurring in ≥2 patients

Drug-related adverse events (n=30)	All grades		≥Grade 3	
	n	(%)	n	(%)
Any drug-related adverse event	28	(93)	10	(33)
Nausea	7	(23)	0	
Anemia	6	(20)	4	(13)
Anorexia	6	(20)	0	
Fatigue	5	(17)	0	
Lymphocyte count decreased	5	(17)	0	
Neutrophil count decreased	5	(17)	4	(13)
White blood cell decreased	5	(17)	1	(3)
Malaise	4	(17)	0	
Aspartate aminotransferase increased	3	(10)	1	(3)
Diarrhea	3	(10)	0	
Alanine aminotransferase increased	2	(7)	1	(3)
Alkaline phosphatase increased	2	(7)	0	
Blood and lymphatic system disorders	2	(7)	0	
Fever	2	(7)	0	
Hyperuricemia	2	(7)	1	(3)
Mucositis oral	2	(7)	0	
Pain	2	(7)	0	
Pruritus	2	(7)	0	
Vomiting	2	(7)	0	

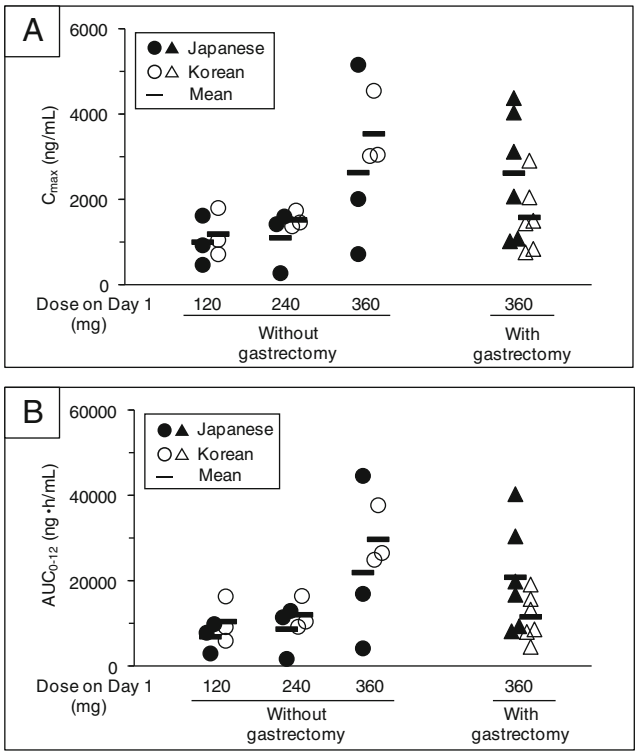

Fig. 3 The plasma exposures to tivantinib on day 1. C_{max} (**A**) or $AUC_{0\text{-}12}$ (**B**) are dotted for each individual treated with the indicated doses. The *closed* and *open dots* represent exposures of Japasese and Korean patients, respectively. The history of gastrectomy for each patient was indicated at the bottom of the figure

recognized as c-Met high expressers. The c-Met high expression ratio was consistent with previous reports where 40-65 % of gastric cancer was recognized as c-Met high expression [6, 19]. However, our study did not find a particularly favorable efficacy in c-Met high expression population, suggesting that c-Met high expression in our setting may not be suitable for a predictive biomarker of tivantinib. This might be unexpected because two precedent placebo-controlled phase II studies for NSCLC [13, 20] and HCC [14, 21] demonstrated a favorable efficacy in selected population with c-Met high expression using IHC method. We think that one of the reasons for the unexpected results would be due to the immature IHC method using invalidated anti-c-Met antibody clones. Our IHC assay showed that c-Met was predominantly expressed on cytoplasm in the majority of tumor tissue samples, whereas only one patient showed a membranous high expression, although c-Met protein is known as transmembraneous receptor tyrosine kinase. On the other hand, our result showed that two patients (6.9 %) harboring c-Met amplification, and the frequency was consistent with literature showing that c-Met gene amplification was observed in very small population in gastric cancer [8, 22]. Catenacci and colleagues reported a durable complete response with an anti-c-Met antibody onartuzumab in a patient with MGC harboring the c-Met gene polysomy associated with high expression [23]. In this study, the c-Met-amplified patient did not show a notable efficacy, and this small-size phase II could not clearly show the potential of c-Met amplification as a useful predictive biomarker for tivantinib responder.

Our results demonstrated that tivantinib was also well tolerated at the daily dose of 360 mg bid in MGC patients with at least one allele of wild type CYP2C19. It is consistent with the previous phase I studies which demonstrated the tolerability of a daily continuous dose of 360 mg bid in Western countries [24, 25] and Japan [17]. Of note, tivantinib was tolerated even in the patients with a history of gastrectomy, and this fact was supported by PK analysis showing that tivantinib exposure was mostly constant regardless of prior gastrectomy. This would be a favorable feature of tivantinib as a possible treatment for the gastric cancer, where gastrectomy is the standard care for the early stage. As was the case for previous phase I study [17], this study showed that hematological toxicities including neutropenia, leukopenia and anemia were the most frequent drug-related adverse events to tivantinib, and novel toxicities specific for MGC were not suggested in this study. In addition, this study demonstrated that the incidence of severe neutropenia is related to the high exposure to tivantinib, as shown in the previous Japanese phase I study [17]. It could be concluded that there was no major safety

issue in the use of tivantinib of 360 mg bid for Asian patients with previously treated MGC who had at least one allele of wild type CYP2C19.

As a conclusion, although c-Met is an attractive molecular target for the treatment of MGC, tivantinib monotherapy showed a marginal efficacy for unselected MGC as a single agent. Further studies for the validation of predictive biomarkers and/or combination with chemotherapy or other molecular targeted agents might be warranted.

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Conflict of interest Y. K. Kang received honoraria from Kyowa Hakko Kirin Co., Ltd. Y. Kamiya and S. Akinaga are employees of Kyowa Hakko Kirin Co., Ltd. All remaining have declared no conflict of interest.

Ethical standards This study was conducted in accordance with institutional guidelines, Good Clinical Practice guidelines and the Declaration of Helsinki. Documented approvals from the Institutional Review Boards were obtained. All patients provided written informed consent before study participation.

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