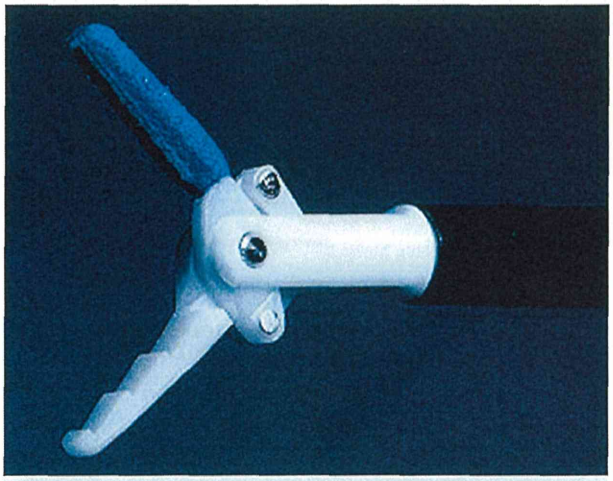

Fig. 1 The tip of the prototype scissors-type electrosurgical knife (single use electrosurgical incision forceps FD-Y0005; Olympus Medical Systems, Tokyo, Japan).

and colon. The ESG-100 was used as the electrocautery system, with various settings between 15 and 80 W in the pulse-cut fast mode.

Following ESD, the pigs were euthanized using potassium chloride and somnopentyl. The organs of interest were then extracted and observed macroscopically. The animal experiments were approved by the ethics committee of the Olympic Medical Systems.

Human feasibility study

This was a prospective feasibility study of ESD using the new scissors-type electrosurgical knife for patients with early esophageal or gastric cancer. The study protocol was approved by the ethics committee and institutional review board of the National Cancer Center Hospital East (number 2010–045). The study was conducted in accordance with the Ethical Guideline for Clinical Research by the Ministry of Health, Labour and Welfare, and the Declaration of Helsinki. The study was also registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (number UMIN000004941).

The inclusion criteria were: 1) a primary and solitary lesion of intramucosal esophageal or gastric cancer; 2) histologically confirmed intestinal type gastric cancer without ulceration, with diameter ≤2 cm, or histologically confirmed esophageal squamous cell or basaloid carcinoma, with diameter ≤3 cm; 3) age ≥20–≤75 years; 4) performance status ≤1; 5) no history of surgery or radiation for prior esophageal or gastric cancer; 6) adequate organ function; 7) provision of written informed consent.

ESD procedure

Two operators (T.Y., H.O.), who were experienced in ESD (>500 cases) using the insulated-tip (IT)-knife performed all procedures. The ESG-100 was used as the electrocautery system, and the setting was pulse-cut fast mode with a power range of 15–40 W, as determined during the preliminary animal studies. The procedure was performed as follows. 1) Marking spots were made surrounding the lesion. 2) A solution that contained normal saline and hyaluronic acid was injected into the submucosal layer to elevate the lesion. 3) An initial circumferential incision was performed using the scissors-type electrosurgical knife. 5) An additional injection was performed after the circumferential incision, and the dissection of the expanding submucosal layer was performed using the same device.

Following ESD, resected specimens were fixed in formalin, and 2-mm sections were cut for histological evaluation by an experienced pathologist, according to the Japanese Classification of each cancer type [6, 7]. Patients were observed during hospitalization for 1 week to evaluate adverse events, and endoscopic observation was performed once to identify any perforation or bleeding.

Study end points

The primary end point was serious adverse events (SAE) related to ESD. SAE were defined as perforation during or after ESD that required surgical intervention, and bleeding was defined as that which required endoscopic intervention or a transfusion within 7 days after ESD. Secondary end points were the en bloc resection rate and the number of adverse events. Mechanical or electrical problems and errors encountered while using the new device were also evaluated.

Results

Live porcine model

The sharpness of the scissors was maintained during 200 repeated cuts in each tissue material, and the tip of the device did not deteriorate. Damage to the surrounding tissue was minimal (**Fig. 2**). ESD was completed in six areas in the esophagus, five areas in the stomach, and one area in the colon in three live pigs. The median procedure time was 17.5 minutes in the esophagus, 20 minutes in the stomach, and 25 minutes in the colon. Specimens were approximately 20 mm in diameter. The scissors opened and closed smoothly during the procedures, and no bleeding or perforation occurred. The surrounding tissue burn damage was minor, and no transmural thermal injury was observed macroscopically at the resection sites of each organ.

ESD in patients

Between February and May 2011, four patients were enrolled into the feasibility study. Patient and lesion characteristics are presented in **Table 1**, and the outcomes of the ESD procedures and histological findings are summarized in **Table 2**. All ESD procedures were completed. The mean procedure time was 31 minutes, and en bloc resection was achieved in all cases. There were no serious adverse events. All lesion specimens were determined to have a tumor depth limited to within the mucosal layer, with margins free of invasion. The procedure for a patient with esophageal squamous cell carcinoma is presented in **Video 1**. The scissors opened and closed smoothly, and no electrical problems, such as electrical shock or burn injury to patients, operators, or assistants, or electrical power failure, were experienced.

Video 1

Endoscopic submucosal dissection using the new scissors-type knife in a patient with esophageal squamous cell carcinoma.

Online content including video sequences viewable at: www.thieme-connect.de

Table 1 Patient and lesion characteristics.

	Case 1	Case 2	Case 3	Case 4
Age, years	58	70	63	59
Sex	Male	Female	Male	Male
Performance status*	0	0	0	0
Organ	Stomach	Stomach	Esophagus	Stomach
Location	Lower anterior	Lower anterior	Middle thoracic	Lower greater curvature
Size, mm	5	5	20	20

* According to the Eastern Cooperative Oncology Group.

Discussion

This study is significant because it evaluates a new electrosurgical knife for ESD across a wide range of conditions, from ex vivo animal experiments to the first human feasibility study. Patients did not experience any serious adverse events during or after ESD, and electrical stability, and the durability and sharpness of the device were confirmed.

Most devices developed to improve safety during ESD are derived from a needle knife. Operators press the tip of these devices perpendicularly to the mucosa, and pull the device upward. During dissection of the submucosal layer, the device is pressed into the swelling submucosal layer and cutting is achieved by moving the device parallel to the muscle layer. These complicated techniques themselves exacerbate the risk of perforation during ESD. Perforations occurred in approximately 5% of gastric lesions undergoing ESD using the IT-knife, despite the procedure being carried out by skilled operators [8]. The scissors-type device cuts only the grasped materials; therefore, in theory, accidental perforation should rarely occur.

Other scissors-type devices such as the Clutch Cutter (Fujifilm, Tokyo, Japan) or SB knife (Sumitomo Bakelite, Tokyo, Japan) are already commercially available [9–11]. However, the novel device described here has two important features that distinguish it from other devices: a ceramic covered tip and a single stainless steel blade. In contrast, previously released scissors-type devices have a fluoroplastic-coated tip and stainless steel blade electrodes on both sides of the scissors. Ceramic materials can tolerate high temperatures, and are more durable compared with fluoroplastic; this results in high quality insulation even after frequent use. Furthermore, the single-side electrode of the scissors results in a narrow area of contact space and a subsequently higher current density. This high-quality of insulation and increased current density allows more rapid movement of the incision electrode, leading to an increase in the incision speed and a decrease in surrounding tissue damage. Indeed, the mean procedure time in the current study was 31 minutes for lesions with a mean diameter of 31 mm, whereas in a previous report using a different scissors-type device, a mean of 103 minutes was needed for gastric lesions with a mean diameter of 30 mm [10].

Despite the very interesting preliminary data presented in this study, the study limitations include the small number of patients with small lesions in locations that were easy to access. Further-

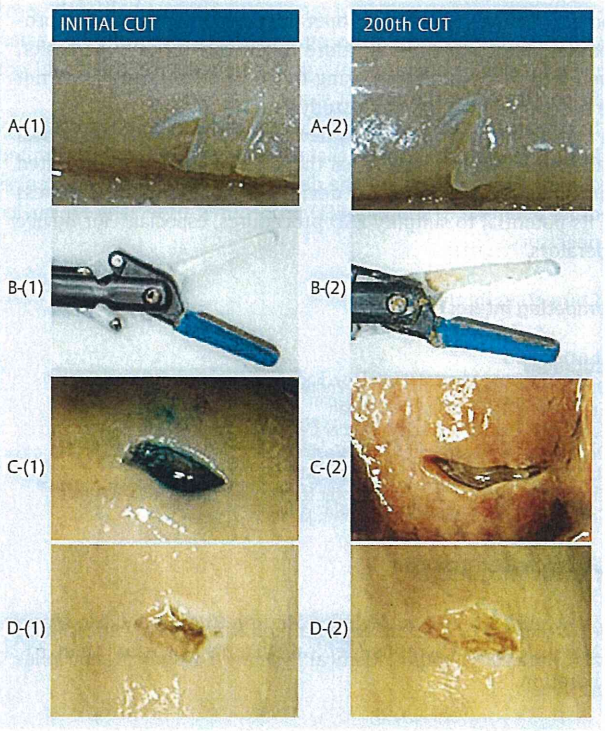

Fig. 2 Results of preliminary experiments in ex vivo animal material. Images of initial (1) and 200th (2) cut for each material (chicken tenderloin [A], porcine stomach [C] and esophagus [D]). In all samples, the sharpness of the scissors was maintained after 200 cuts (B-1 and B-2), and the surrounding tissue damage was minor. Material adhering to the tip of the device was minimal.

Table 2 Outcome of endoscopic submucosal dissection, and histological findings.

	Case 1	Case 2	Case 3	Case 4
Completion	Complete	Complete	Complete	Complete
Procedure time, minutes	32	18	42	32
En bloc or piecemeal	En block	En block	En block	En block
Collection of specimen	Yes	Yes	Yes	Yes
Adverse events				
Bleeding	No	No	No	No
Perforation	No	No	No	No
Major axis of specimen, mm	35	35	25	29
Histological type	tub1	tub1	SCC	tub1
Tumor depth	T1a	T1a	T1a	T1a
Ulceration	Absent	Absent	Absent	Absent
Horizontal margin	Negative	Negative	Negative	Negative
Vertical margin	Negative	Negative	Negative	Negative

tub1, well-differentiated tubular adenocarcinoma; SCC, squamous cell carcinoma.

more, only two experienced operators performed all of the procedures. Although the procedure might theoretically be easier, even for novice operators, using this new device, this could not be confirmed by the current study.

In conclusion, ESD using this new scissors-type electrosurgical knife is feasible. It is hoped that this study will extend the limited clinical data available for the device and increase the awareness of its potential to simplify ESD procedures, especially for novice operators.

Competing interests: None

Institutions

[1] Department of Gastroenterology, Endoscopy Division, National Cancer Center Hospital East, Kashiwa, Japan
[2] Endoscopy Division, Shizuoka Cancer Center, Shizuoka, Japan
[3] Department of Gastroenterology, Gastrointestinal Oncology Division, National Cancer Center Hospital East, Kashiwa, Japan
[4] Clinical Trial Section, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Acknowledgments

We would like to acknowledge Mr. Koh Kimura and Mr. Masumi Matsushita, of Olympus Medical Systems Corp., for their collaboration.

References

1 *Ono H, Kondo H, Gotoda T* et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225–229
2 *Oyama T, Tomori A, Hotta K* et al. Endoscopic submucosal dissection of early esophageal cancer. Clin Gastroenterol Hepatol 2005; 3: 67–70
3 *Oka S, Tanaka S, Kaneko I* et al. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. Gastrointest Endosc 2006; 64: 877–883
4 *Oda I, Saito D, Tada M* et al. A multicenter retrospective study of endoscopic resection for early gastric cancer. Gastric Cancer 2006; 9: 262–270
5 *Gotoda T, Yamamoto H, Soetikno RM.* Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006; 41: 929–942
6 The Japan Esophageal Society. Guideline for the clinical and pathologic studies on carcinoma of the esophagus. 10th: edn. Tokyo: Kanehara Syuppan; 2007
7 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. 13th: edn. Tokyo: Kanehara & Co; 1999
8 *Ono H, Hasuike N, Inui T* et al. Usefulness of a novel electrosurgical knife, the insulation-tipped diathermic knife-2, for endoscopic submucosal dissection of early gastric cancer. Gastric Cancer 2008; 11: 47–52
9 *Akahoshi K, Akahane H, Murata A* et al. Endoscopic submucosal dissection using a novel grasping type scissors forceps. Endoscopy 2007; 39: 1103–1105
10 *Akahoshi K, Honda K, Akahane H* et al. Endoscopic submucosal dissection by using a grasping-type scissors forceps: a preliminary clinical study (with video). Gastrointest Endosc 2008; 67: 1128–1133
11 *Homma K, Otaki Y, Sugawara M* et al. Efficacy of novel SB knife Jr examined in a multicenter study on colorectal endoscopic submucosal dissection. Dig Endosc 2012; 24: 01117–120

Cancer Science
Japanese Cancer Association JCA
Open Access

Phase I study of olaratumab in Japanese patients with advanced solid tumors

Toshihiko Doi,[1] Yan Ma,[2,5] Aruna Dontabhaktuni,[2] Cornelia Nippgen,[3] Johannes Nippgen[4,6] and Atsushi Ohtsu[1]

[1]National Cancer Center Hospital East, Kashiwa, Chiba, Japan; [2]ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, Bridgewater, New Jersey, USA; [3]Lilly Deutschland GmbH, Bad Homburg, Germany; [4]ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, Heidelberg, Germany

Key words

IMC-3G3, monoclonal antibody, olaratumab, phase 1, platelet-derived growth factor receptor

Correspondence

Toshihiko Doi, National Cancer Center Hospital East, 5-1, Kashiwanoha 6-chome, Kashiwa-shi, Chiba 277-8577, Japan.

Tel: +81-7133-1111, Ext. 2256; Fax: +81-4-7134-6928; E-mail: tdoi@east.ncc.go.jp

[5]Present address: Allergan, Irvine, California, USA.

[6]Present address: Glycotope GmbH, Berlin, Germany.

Funding Information

This study was designed and funded by ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company. Olaratumab was provided by ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company. ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, collected and analyzed the data and contributed to data interpretation. All authors had full access to the study data, participated in the writing of the manuscript, and had final responsibility for the decision to submit the manuscript. Medical writing assistance was funded by Eli Lilly and Company and ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company.

Clinical Trials.gov identifier: NCT01199822

Received January 21, 2014; Revised May 7, 2014; Accepted May 8, 2014

Cancer Sci **105** (2014) 862–869

doi: 10.1111/cas.12444

Olaratumab (IMC-3G3) is a fully human IgG1 monoclonal antibody that selectively binds the external domain of human platelet-derived growth factor receptor-α with high affinity and blocks ligand binding. This was a single-center, dose-escalation, phase I trial of olaratumab in Japanese patients with advanced/refractory solid malignancies. Three to six patients were enrolled into each of three cohorts: Patients received i.v. olaratumab: 10 mg/kg on days 1 and 8 every 3 weeks (cohort 1); 20 mg/kg every 2 weeks (cohort 2); and 15 mg/kg on days 1 and 8 every 3 weeks (cohort 3). Doses were escalated from cohort 1 through cohort 3. The primary objective was to establish the safety and pharmacokinetic profile of olaratumab. Sixteen patients were treated across three cohorts. There were no dose-limiting toxicities, so the maximum tolerated dose was not reached. The most common olaratumab-related treatment-emergent adverse events (TEAEs) were proteinuria (25.0%) and elevated aspartate transaminase (12.5%). One patient (cohort 2) had two olaratumab-related Grade 3 TEAEs (increased aspartate aminotransferase and tumor hemorrhage); otherwise, olaratumab-related TEAEs were Grade 1/2. Seven patients (43.8%) had a best response of stable disease. Based on the pharmacokinetic concentration profile of olaratumab, the trough concentrations following single and multiple doses at 15 mg/kg on days 1 and 8 every 3 weeks (cohort 3) and multiple doses at 20 mg/kg every 2 weeks (cohort 2) were above the 155 μg/mL target. Thus, these two doses could represent an acceptable schedule for future trials in Japanese patients. Olaratumab had an acceptable safety profile and was well tolerated.

The platelet-derived growth factor receptor family (PDGFR) consists of PDGFRα and PDGFRβ.[1] These receptors and their ligands are involved in normal organ development and function, wound-healing, and the pathogenesis of malignant and non-malignant diseases.[1] The PDGFRα/platelet-derived growth factor (PDGF) axis is required for vascular endothelial growth factor production by tumor stroma and the regulation of tumoral angiogenesis.[2]

Platelet-derived growth factor receptor-α is expressed in several types of cancer on transformed cells and in tumor stroma.[3–6] PDGFRα expression is associated with disease progression, diminished patient survival, and metastases to lymph nodes and bone.[7–10] Due to the effects of the PDGFRα/PDGF axis on tumor growth and tumor-associated vasculature, there is interest in developing therapeutic inhibitors of this pathway.[11,12] Most of these inhibitors are small molecule tyrosine kinase inhibitors (TKIs) that typically inhibit multiple kinases.[11,12]

Olaratumab (IMC-3G3) is a fully human IgG1 monoclonal antibody that selectively binds human PDGFRα with high affinity (approximately 40 pM) and blocks ligand-binding.[13] This antibody inhibits the proliferation and growth of a variety of human tumor cell lines both *in vitro* and *in vivo*.[5,6,13] Based on its activity in preclinical models involving human cells,[5,6,13] olaratumab entered clinical development. One phase I trial in patients with advanced tumors is complete (CP15-0601; I5B-IE-JGDC)[14] and several phase II trials are ongoing. Here, we report the results of a phase I trial of olaratumab in a cohort of Japanese patients (CP15-0907; I5B-IE-JGDF) with advanced solid tumors.

Materials and Methods

Patients. Patients (≥20 years old) with advanced primary or recurrent solid tumors not responding to standard therapy, or for whom no standard therapy was available, were eligible. Other enrollment criteria included Eastern Cooperative Oncology Group Performance Status of 0–1; estimated life expectancy >3 months; and adequate hematologic, hepatic, renal, and coagulation function.

Patients with known brain metastases were excluded due to risk of bleeding. Other exclusion criteria included chemotherapy or radiotherapy within 28 days (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or presence of ongoing side effects ≥Grade 2 due to agents administered >28 days prior to study entry; uncontrolled intercurrent illness; participation in clinical trials of unapproved agents within 4 weeks of study entry for small molecules or within 8 weeks for monoclonal antibodies; and hepatitis B virus antigen, hepatitis C virus antibody, or human immunodeficiency virus antibody positivity.

This study was conducted in accordance with the Good Clinical Practices, Japanese Good Clinical Practices, the Declaration of Helsinki, and approval by the medical institution's Ethical Review Board. Patients provided written informed consent prior to inclusion. The ClinicalTrials.gov identifier is NCT01199822.

Study design. This was a single-center, open-label, dose-escalation, phase I trial. The primary objective was to establish the safety and pharmacokinetic (PK) profile of olaratumab administered on day 1 every 2 weeks (q2w) or on days 1 and 8 every

Table 1. Baseline demographics and disease characteristics

	Number of patients, *n* (%) (unless otherwise indicated)			
	Cohort 1 (10 mg/kg) *n* = 3	Cohort 2 (20 mg/kg) *n* = 7	Cohort 3 (15 mg/kg) *n* = 6	All cohorts *N* = 16
Age, years				
Median (range)	69.6 (59.6–71.4)	60.9 (35.6–70.3)	59.1 (50.5–69.7)	60.7 (35.6–71.4)
Sex				
Male	3 (100.0)	5 (71.4)	2 (33.3)	10 (62.5)
Female	0	2 (28.6)	4 (66.7)	6 (37.5)
Race				
Asian (Japanese)	3 (100.0)	7 (100.0)	6 (100.0)	16 (100.0)
Type of cancer†				
Colorectal	1 (33.3)	5 (71.4)	1 (16.7)	7 (43.8)
Gastric	1 (33.3)	0	1 (16.7)	2 (12.6)
Gastrointestinal stroma	0	2 (28.6)	2 (33.3)	4 (25.0)
Head and neck	1 (33.3)	0	1 (16.7)	2 (12.5)
Sarcoma	0	0	1 (16.7)	1 (6.3)
Duration of disease, months‡				
Median (range)	45.6 (2.4–61.4)	66.3 (32.5–90.4)	48.5 (25.5–102.5)	49.6 (2.4–102.5)
ECOG performance status				
0	3 (100.0)	7 (100.0)	5 (83.3)	15 (93.8)
1	0	0	1 (16.7)	1 (6.3)
Metastatic site				
Lung	2 (66.7)	2 (28.6)	3 (50.0)	7 (43.8)
Liver	1 (33.3)	6 (85.7)	3 (50.0)	10 (62.5)
Lymph nodes	1 (33.3)	2 (28.6)	3 (50.0)	6 (37.5)
Peritoneal	1 (33.3)	1 (14.3)	2 (33.3)	4 (25.0)
Pleural	1 (33.3)	0	0	1 (6.3)
Other	0	3 (42.9)	3 (50.0)	6 (37.5)
Prior disease-related therapy				
Chemotherapy§	2 (66.7)	7 (100.0)	6 (100.0)	15 (93.8)
Other¶	0	2 (28.6)	1 (16.7)	3 (18.8)
Missing	1 (33.3)	0	0	1 (6.3)
Prior disease-related radiotherapy				
Yes	0	0	1 (16.7)	1 (6.3)
No	3 (100.0)	7 (100.0)	4 (66.7)	14 (87.5)
Missing	0	0	1 (16.7)	1 (6.3)
Prior disease-related surgery				
Yes	2 (66.7)	6 (85.7)	6 (100.0)	14 (87.5)
No	0	1 (14.3)	0	1 (6.3)
Missing	1 (33.3)	0	0	1 (6.3)

†Not coded and was presented as reported. ‡Duration of disease is time (in months) from date of histologic/cytologic confirmation of advanced solid tumor to date of first dose. If the day of first confirmation of cancer is unknown, it was replaced by 15MMMYYYY. §Includes agents such as cetuximab, sunitinib, imatinib, aflibercept, and bevacizumab. ¶Other than chemotherapy, hormonal therapy, immunotherapy, and biologic therapy. ECOG, Eastern Cooperative Oncology Group.

Table 2. Olaratumab-related treatment-emergent adverse events across all cycles†,‡

Preferred term	Number of patients, *n* (%)		
	Cohort 1 (10 mg/kg) *n* = 3	Cohort 2 (20 mg/kg) *n* = 7	Cohort 3 (15 mg/kg) *n* = 6
Patients with any AE	1 (33.3)	6 (85.7)	1 (16.7)
Hematologic			
Anemia	0	1 (14.3)	0
Leukopenia	0	1 (14.3)	0
Non-hematologic			
Aspartate aminotransferase increased	0	2 (28.6)	0
Cough	1 (33.3)	0	0
Dermatitis	0	0	1 (16.7)
Diarrhea	0	1 (14.3)	0
Fatigue	0	1 (14.3)	0
Fibrin D-dimer increased	0	1 (14.3)	0
Hyperglycemia	0	1 (14.3)	0
Hypertension	0	1 (14.3)	0
Proteinuria	0	3 (42.9)	1 (16.7)
Rash	0	1 (14.3)	0
Tumor hemorrhage	0	1 (14.3)	0

†For each preferred term, each patient is counted only once per preferred term. ‡AEs with missing relationship to study drug were considered as related. AE, adverse event.

Table 3. Efficacy of olaratumab

	Cohort 1 (10 mg/kg) *n* = 3	Cohort 2 (20 mg/kg) *n* = 7	Cohort 3 (15 mg/kg) *n* = 6
Best overall tumor response, *n* (%)			
CR	0	0	0
PR	0	0	0
SD	2 (66.7)†	3 (42.9)‡	2 (33.3)§
PD	1 (33.3)	3 (42.9)	4 (66.7)
NE	0	1 (14.3)	0
Objective response rate (CR+PR), %	0.0	0.0	0.0
Disease control rate (CR+PR+SD), %	66.7	42.9	33.3
95% CI¶	9.4–99.2	9.9–81.6	4.3–77.7
Duration of SD, *n* (%)			
Median, months	2.8	2.8	4.9
95% CI	–	2.8–N/A	4.2–5.6

†Carcinoid tumor of rectum; parotid tumor. ‡Colon cancer; gastrointestinal stromal tumor; rectal. §Hypopharyngeal cancer; leiomyosarcoma of inferior vena cava origin. ¶Binomial exact confidence interval. CI, confidence interval; CR, complete response; N/A, not attainable; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

3 weeks (q3w) in this patient population. Exploratory analyses included preliminary assessment of antitumor activity and assessment of the pharmacodynamic effect of olaratumab.

Patients received i.v. olaratumab (infusion rate not exceeding 25 mg/min) q2w or on days 1 and 8 q3w. One cycle was defined as 6 weeks. Tumor response was evaluated radiographically every 6 weeks, starting from the first drug administration and independently from the treatment cycle. After cycle 1, patients experiencing a complete response (CR), partial response (PR), or stable disease (SD) received olaratumab at their cohort dose and schedule until there was evidence of progressive disease (PD) or until other withdrawal criteria were met.

Treatment cohorts. Olaratumab dosing was based on baseline body weight; the dose was recalculated if there was a ≥10% weight change from baseline. A minimum of three patients were enrolled in each cohort. The cohort 1 dose was 10 mg/kg administered on days 1 and 8 q3w. Dose escalation from cohort 1 to cohort 2 (20 mg/kg q2w) occurred after all cohort 1 patients completed the first cycle of therapy or discontinued due to a dose-limiting toxicity (DLT). Enrollment into cohort 3 (15 mg/kg q3w) occurred after all cohort 2 patients completed the first cycle of therapy or discontinued due to a DLT. Intrapatient dose escalations were not permitted. Patients who did not complete the first 6 weeks (one cycle) of treatment for reasons other than a DLT were replaced.

If one DLT was observed in any cohort during cycle 1, 3 additional patients were enrolled into that cohort. If no additional DLTs were observed, dose escalation continued. If a patient did not recover from the DLT to ≤ Grade 1 within 2 weeks, the patient was discontinued from the study.

A DLT was defined as one of the following conditions: if considered by the investigator to be definitely, probably, or possibly related to olaratumab; grade 4 neutropenia lasting >7 days; grade ≥3 thrombocytopenia with bleeding or requiring platelet transfusions; grade ≥3 neutropenia associated with fever; grade 3 or 4 non-hematologic toxicity; grade ≥3 skin toxicity (despite pre-emptive and supportive care); and/or grade ≥3 diarrhea, nausea, or vomiting (despite pre-emptive and supportive care).

Dose adjustments. Dose reductions were not permitted. Dose delays were permitted after cycle 1 for patients with non-life-threatening, reversible grade 3–4 adverse events (AEs) that resolved to grade ≤1 within 2 weeks. For these AEs, treatment could resume within 2 weeks and could continue until PD or other withdrawal criteria were met.

Determination of maximum tolerated dose. This trial used a conventional 3 + 3 design. If ≥2 patients in cohort 1 experienced a DLT, the study was to be discontinued. If ≥2 patients in cohort 2 or 3 experienced a DLT, then the cohort 1 dose was to be the maximum tolerated dose (MTD). If no MTD was determined, both cohorts 2 and 3 were to be expanded to six patients, with the goal of obtaining enough data for a PK analysis.

Pharmacokinetic assessments. Serum olaratumab was quantitated by using a validated ELISA. For the 10 mg/kg (cohort 1) and 15 mg/kg (cohort 3) (dosed on day 1 and day 8 every 3 weeks) q3w groups, PK samples were collected up to 168 h post end of day 1 infusion and 336 h post end of day 8 infusion. For the 20 mg/kg q2w group (cohort 2), PK samples were collected up to 336 h post end of infusion following the first (cycle 1, day 1) and fifth (cycle 2, day 1) infusions. Beginning cycle 3, samples were collected prior to and 1 h after completion of the first infusion in every subsequent cycle. The PK parameters were calculated from individual serum concentrations versus time profiles by noncompartmental analysis method by using WINNONLIN (Version 5.3; Certara, St. Louis, MO, USA).

Pharmacodynamic assessments. Human PDGF-AA and PDGF-BB in sodium heparin plasma collected at pre-specified

time points was quantitatively determined by using an ELISA at Intertek Laboratories (Houston, TX, USA).

For cohorts 1 and 3, PD markers were analyzed using plasma samples (from approximately 7 mL of blood) obtained prior to the first infusion; immediately after the first infusion; and 1, 4, 8, 24, and 168 h following the completion of the first infusion, prior to and 1 h following the completion of the fifth infusion and ninth infusion, and prior to and 1 h following the completion of the infusion every 6 weeks thereafter. A blood sample for PD assessment was also taken at the end of study visit.

For cohort 2, PD markers were analyzed using plasma samples obtained prior to the first infusion; immediately after the end of the first infusion; 1, 4, 8, 24, 168, and 336 h following the completion of the first infusion; prior to and 1 h following the completion of the fourth infusion and seventh infusion; and prior to and 1 h following the completion of the infusion every 6 weeks thereafter. A blood sample for PD assessment was also taken at the end of study visit.

Safety assessments. Adverse events were coded by the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.02.[15]

Disease assessment. Baseline tumor burden was assessed within 28 days prior to study registration. Patients were evaluated for response according to the Response Evaluation Criteria in Solid Tumors (v 1.0) after every cycle.[16] Confirmatory scans were obtained ≥4 weeks following initial documentation objective response.

Data and statistical analysis. The anticipated sample size was 18 patients. This sample size was based on cohort size. Data were analyzed using SAS® software (Cary, NC, USA), version 9.2.

Analysis populations. The safety population included all enrolled patients who received any olaratumab, regardless of study eligibility, and was based on the actual initial therapy that a patient received, regardless of any other cohort to which the patient was assigned. The safety population was used for the analysis of baseline characteristics, safety data, and efficacy data. The MTD population included all enrolled patients who completed cycle 1 or discontinued during cycle 1 due to a DLT.

Results

Patient characteristics and treatment. Sixteen patients at one Japanese center received olaratumab. One additional patient signed an informed consent form and was enrolled in the study, but was considered a screen failure and was not treated due to pneumonia at the time of study entry. Across all cohorts, the median age was 60.7 years (range 35.6–71.4). The majority of patients were male (62.5%) and had colorectal or gastric type cancers (81.3%); all patients were Asian (Japanese). Table 1 shows the baseline demographics and disease characteristics.

Dose. The median duration of treatment was 13.1 (range 7.0–13.6), 6.0 (range 3.0–13.4), and 7.0 (range 7.0–25.1) weeks in cohort 1 (n = 3), cohort 2 (n = 7), and cohort 3 (n = 6), respectively. The median number of infusions was 8.0 (range 4.0–8.0), 3.0 (range 2.0–6.0), and 4.0 (range 4.0–16.0) in cohort 1, cohort 2, and cohort 3, respectively. The median relative dose intensity was >85% in all three cohorts.

Safety. There were no DLTs in this trial; therefore, the MTD was not reached, consistent with the previous phase I trial.[14] One patient experienced an AE that met DLT definitions (grade 3 olaratumab-related tumor hemorrhage), but this event occurred outside the DLT assessment period (patient discontinued treatment prior to the completion of cycle 1 because, in the investigator's opinion, continued treatment was inappropriate); thus, the event was not considered a DLT.

There were four dose delays; two occurring in cohort 2 and 1 each occurring in cohorts 1 and 3. Two dose delays were caused by AEs in cohort 2 (grade 1 olaratumab-related proteinuria) and

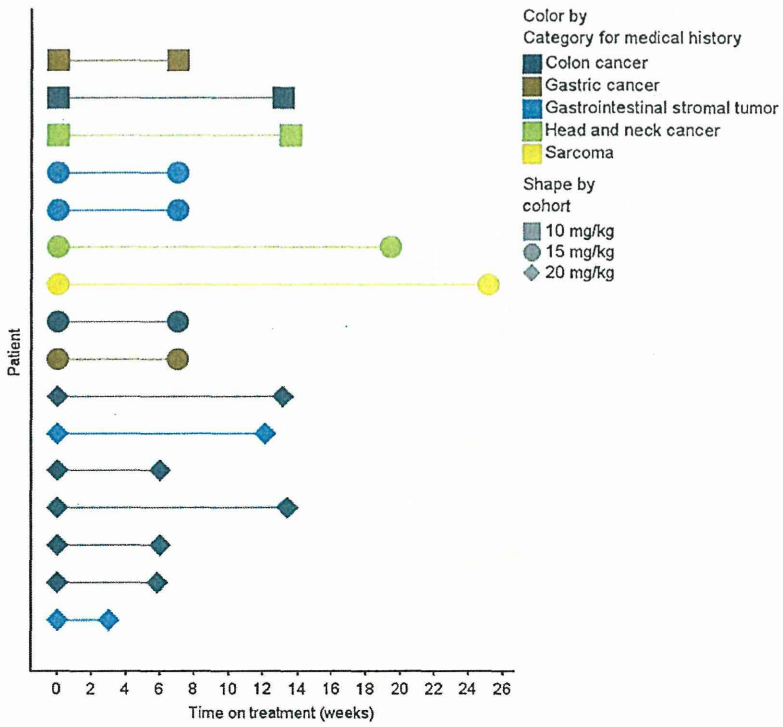

Fig. 1. Time on treatment. The duration of treatment for each patient is shown.

cohort 3 (fatigue/anorexia/weight loss). There were no infusion interruptions. No AE led to treatment discontinuation.

All patients experienced at least one AE of any grade. Across all cohorts and cycles, the most frequently reported treatment-emergent adverse events (TEAEs) regardless of causality were pyrexia (4 [25.0%]), proteinuria (4 [25.0%]), constipation (3 [18.8%]), and anorexia (3 [18.8%]). During cycle 1, the most frequently reported TEAEs regardless of causality were pyrexia (4 [25.0%]), constipation (3 [18.8%]), and proteinuria (3 [18.8%]).

Table 2 shows TEAEs that were assessed as olaratumab-related occurring through all cycles. The most common olaratumab-related TEAEs were proteinuria (4 [25.0%]) and elevated aspartate aminotransaminase (2 [12.5%]). One patient (cohort 2) had two grade 3 olaratumab-related AEs (i.e., increased aspartate aminotransferase and tumor hemorrhage); both AEs occurred in cycle 1.

Two serious AEs, both occurring in cycle 1, were reported during the trial (malignant neoplasm and tumor hemorrhage). The tumor hemorrhage was considered by the investigator to be olaratumab-related. There were no patient deaths due to AEs on study or within 30 days of the last olaratumab dose. One patient (cohort 3) died due to PD, approximately 2 months after the patient's last olaratumab dose.

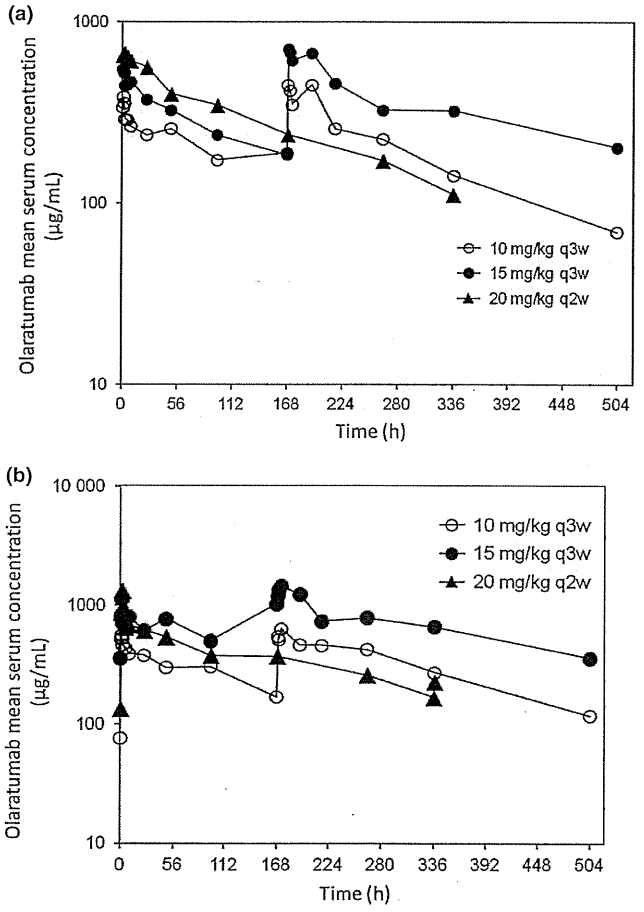

Fig. 2. Arithmetic mean olaratumab serum concentration versus time profiles following the first dose (a) and multiple (b) doses of olaratumab. Semi-log scales are shown in each plot. h, hour; q2w, every 2 weeks; q3w, every 3 weeks.

Efficacy. The best overall response was SD (Table 3). The disease control rate (CR+PR+SD) was 66.7% in cohort 1, 42.9% in cohort 2, and 33.3% in cohort 3. The median duration of SD was 2.8 months in cohort 1 and cohort 2, and 4.9 months in cohort 3.

Of the seven patients with a best response of SD, two patients in cohort 3 experienced disease stabilization >4 months; these patients had hypopharyngeal cancer (4.2 months) and leiomyosarcoma of inferior vena cava origin (5.6 months). The others experienced disease stabilization that lasted approximately 2.8 months each. Figure 1 shows time on treatment for each patient.

Pharmacokinetics. Non-compartmental PK analysis was conducted for three patients from cohort 1, six patients from cohort 2, and six patients from cohort 3; one patient was excluded from PK analysis due to a dosing error (protocol deviation). The mean serum concentration versus time profiles following the first and multiple doses of olaratumab infusion are shown in Figure 2(a,b) respectively. The second peak, occurring at approximately 169 h for the 10 mg/kg (cohort 1) and 15 mg/kg (cohort 3) dose groups, is associated with the second infusion of olaratumab given on day 8 (168 h).

The PK parameters following the first infusion and multiple infusions of olaratumab at 10 mg/kg q3w (cohort 1), 15 mg/kg q3w (cohort 3), and 20 mg/kg q2w (cohort 2) are summarized in Table 4. After a single infusion, PK parameters, including area under the serum concentration versus time curve from zero to infinity ($AUC_{(0-\infty)}$), total body clearance of drug calculated after intravenous administration (CL), and terminal phase volume (V_z), were not calculated for the 10 mg/kg (cohort 1) and 15 mg/kg (cohort 3) dose groups; the terminal elimination $t_{1/2}$ was calculated following day 8 infusion because of the unique dosing schedules of these cohorts (patients received first infusion on day 1 and second infusion on day 8 q3w). The individual terminal elimination $t_{1/2}$ following the first and multiple doses ranged from 4.42 to 9.38 days and 4.06 to 8.83 days, respectively, across all dose groups and dosing schedules. Due to the relatively short PK sampling time (336 h) post end of infusion, the true terminal elimination phase may not have been completely captured and accurately estimated. Therefore, $t_{1/2}$ and its associated parameters, including $AUC_{(0-\infty)}$ and CL, should be interpreted with caution. The olaratumab maximum observed serum drug concentration (C_{max}) following the first infusion appeared to increase with dose.

Individual serum concentration-time profiles exhibited a multi-phasic decline (data not shown). Following the multiple doses (fifth dose for the 10 mg/kg [cohort 1] and 15 mg/kg [cohort 3] dose groups and fourth dose for the 20 mg/kg [cohort 2] dose group), individual serum concentrations were higher than the first dose, reflecting some accumulation of olaratumab following multiple infusions (individual patient accumulation ratio, calculated using AUC [R_A, AUC] ranged from 1.30 to 1.72) (data not shown).

Following multiple infusions of olaratumab at 10 mg/kg q3w and 20 mg/kg q2w, the geometric mean trough concentrations (C_{last}) were close to or above the target trough concentration (155 μg/mL) associated with antitumor activity in preclinical xenograft studies.[14] However, olaratumab infusion at 15 mg/kg q3w generated geometric mean pre-dose serum concentrations above 155 μg/mL (target trough concentration) throughout the study (Table 4).

Comparative analyses of clearance (steady state clearance; CLss) and exposure (area under the concentration versus time curve during one dosing interval; AUCτ), following multiple

Table 4. *Summary of olaratumab pharmacokinetic parameters*

Regimen	Geometric mean (CV%)†		
	10 mg/kg (*N* = 3)‡,§ q3w	15 mg/kg (*N* = 6)§ q3w	20 mg/kg (*N* = 6) q2w
After the first dose			
C_{max} (μg/mL)	362.322; 436.172	587 (40)	735 (29)¶
t_{max} (h)††	1.20; 1.73	1.45 (1.18–9.14)	2.22 (1.27–3.28)¶
C_{last} (μg/mL)	203.320; 176.762	173 (46)	110 (19)
$AUC_{(0-168)}$ (μg/h/mL)	NC	48 000 (47)§§	63 400 (21)
$AUC_{(0-tlast)}$ (μg/h/mL)	35 500; 35 600	43 600 (45)	92 500 (20)‡‡
$AUC_{(0-\infty)}$ (μg/h/mL)	NC	NC	126 000 (12)¶
$t_{1/2}$ (days)‡‡	5.33; 6.38	7.29 (6.04–9.38)¶¶	6.42 (4.42–8.00)¶
CL (mL/h/kg)	NC	NC	0.159 (12)¶

Regimen	Geometric mean (CV%)†		
	10 mg/kg (*N* = 3)††† q3w	15 mg/kg (*N* = 6)†††‡‡‡ q3w	20 mg/kg (*N* = 6)¶¶ q2w
After multiple doses			
C_{max} (μg/mL)	658.391; 546.854§§§	920.832§§§	1160 (91)
t_{max} (h)‡‡	1.74; 2.21§§§	2.18§§§	2.21 (1.70–3.30)
C_{last} (μg/mL)	151.101; 121.188	360.948	181 (37)
$AUC_{(0-168)}$ (μg/h/mL)	53 500; 44200	82 800	77 400 (30)
AUC_{τ} (μg/h/mL)	NC	NC	123 000 (29)¶¶¶
$t_{1/2}$ (days)‡‡‡	4.06; 7.33††††	8.25††††	7.33 (5.42–8.83)
CL_{ss} (mL/h/kg)	NC	NC	0.163 (29)
R_A (AUC)‡‡‡‡	1.55	1.38	1.46 (15)

†The single value is reported when $n = 1$; values are separated by semicolon when $n = 2$. ‡$n = 2$ for all parameters. One patient, whose samples were not collected for the initial 168 h, was excluded from PK analysis. §C_{max}, C_{last}, AUC_{0-168}, and $AUC_{0-tlast}$ are calculated following the first infusion (day 1) and $t_{1/2}$ is calculated following the second infusion (day 8) in day-1 and day-8 dosing in 21-day cycles (q3w). ¶$n = 5$. ††Median (range). ‡‡Geometric mean (range). §§$n = 4$. ¶¶$n = 3$. †††Patient received first infusion on day 1 and second infusion on day 8 in 21-day cycles (q3w). ‡‡‡$n = 1$ for all parameters. §§§C_{max}, t_{max}, and $AUC_{(0-168)}$ are calculated following the first infusion (day 1) in day 1 and day 8 dosing in 21-day cycles (q3w). ¶¶¶Dosing interval (τ) is 336 h. ††††$t_{1/2}$ is calculated following the second infusion (day 8) in day 1 and day 8 dosing in 21-day cycles (q3w). ‡‡‡‡Intercycle accumulation of olaratumab calculated as $AUC_{(0-504)}$ (Cycle 2)/$AUC_{(0-504)}$ (Cycle 1) for 10 and 15 mg/kg (q3w) and $AUC_{(0-336)}$ (Cycle 2)/$AUC_{(0-336)}$ (Cycle 1) for 20 mg/kg (q2w). $AUC_{(0-168)}$, area under the concentration versus time curve from zero to 168 h; $AUC_{(0-336)}$, area under the concentration versus time curve from zero to 336 h; $AUC_{(0-504)}$, area under the concentration versus time curve from zero to 504 h; $AUC_{(0-\infty)}$, area under the serum concentration versus time curve from zero to infinity; $AUC_{(0-tlast)}$, area under the concentration versus time curve from zero to time *t*, where t is the last scheduled sampling time point with a measurable drug concentration; AUC_{τ}, area under the concentration versus time curve during one dosing interval; C_{last}, last quantifiable serum drug concentration; C_{max}, maximum observed serum drug concentration; CL, total body clearance of drug calculated after intravenous administration; CL_{ss}, total body clearance of drug calculated after intravenous administration at steady state; CV, coefficient of variation; *N*, number of patients with assessable PK; NC, not calculated; PK, pharmacokinetic; q2w, every 2 weeks; q3w, every 3 weeks; R_A, accumulation ratio; $t_{1/2}$, terminal elimination half-life; t_{max}, time of maximal concentration.

infusions of olaratumab 20 mg/kg q2w, were conducted between this study of Asian patients and the US phase 1 study of non-Asian patients.[14] The results of this analysis are presented in Figure 3. As shown in the figure, the PK parameters CLss and AUCτ appear to be comparable between Asian and non-Asian patients. However, due to the small sample size, a statistical analysis was not conducted.

Circulating biomarkers. For PDGF-BB, all samples were below the limit of quantitation, so no further analysis was performed.

Prior to the initial olaratumab dose, the median PDGF-AA expression was 11.30 ng/mL for cohort 1, 11.00 ng/mL for cohort 2, and 17.35 ng/mL for cohort 3. Until 24 h following the first infusion, the median PDGF-AA expression increased to 42.15, 62.35, and 48.18 ng/mL for cohort 1, cohort 2, and cohort 3, respectively. However, no trend was identified for the biomarker level change over time for any cohort at later time points. When analyzed by patient, the best overall responses did not seem to be related to the largest change from baseline in PDGF-AA (data not shown).

Discussion

Inhibitors of the PDGF/PDGFR axis are being sought as anticancer agents.[11,12] Most of these agents are small molecule TKIs that inhibit multiple kinases and have complex toxicities.[11,12,17,18] Monoclonal antibodies specifically targeting PDGFR are expected to offer an advantage in terms of specificity and minimizing AEs.

This is the first report of the use of olaratumab, a fully human IgG1 monoclonal antibody that selectively binds human PDGFRα,[13] in Japanese cancer patients. As an IgG1 antibody, olaratumab has the potential to induce antibody-dependent cellular cytotoxicity;[19] however, this has not been experimentally tested. This report follows an earlier report of a phase I trial conducted in the United States.[14] In the current report, 16 Japanese patients with advanced solid tumors, who had not responded to standard therapy or for whom no standard therapy was available, were treated with olaratumab in an open-label, dose-escalation, phase 1 trial. This study met

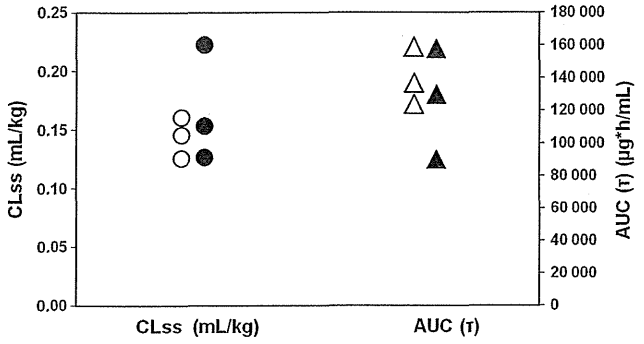

Fig. 3. Comparison of PK parameters clearance and exposure between non-Asian and Asian patients following multiple infusions of olaratumab. Shown are CLss (circles) and AUC_τ (triangles) for the 20 mg/kg-every-2-weeks groups. White circles (○) = CLss, non-Asian patients; black circles (●) = CLss, Asian patients; white triangles (△) = AUC_τ, non-Asian patients; black triangles (▲) = AUC_τ Asian patients. AUC_τ, area under the concentration versus time curve during one dosing interval; CLss, total body clearance of drug calculated after intravenous administration at steady state.

its objectives to establish the safety and PK profile of olaratumab.

In this trial, most AEs were mild to moderate in severity. The most frequently reported olaratumab-related AEs were proteinuria (25.0%) and increased aspartate aminotransferase (12.5%). These AEs were distributed across the three cohorts, and thus did not appear to be dose-related. There were only two grade 3 olaratumab-related non-laboratory AEs (elevated aspartate transaminase and tumor hemorrhage) during the trial, both occurring in cycle 1 and in the same patient. No infusion reactions or interruptions were reported and the majority of patients in the safety population received a relative dose intensity of at least 80%.

In this trial, no fluid retention, ascites, or edemas were reported. The PDGFR may be involved in the control of interstitial fluid pressure through PDGF-BB.[20] The use of small molecule multi-kinase TKIs that inhibit PDGFR is sometimes associated with fluid retention,[17,18] and blockade of PDGFRβ in cancer patients by a humanized, pegylated di-Fab was associated with ascites and fluid retention.[21] Fluid retention was not observed in our trial with selective PDGFRα blockade, even in patients with prolonged exposure (up to 25 weeks). This observation supports the hypothesis that PDGFRα is less likely to be involved in the fluid retention observed with nonspecific PDGFR blockade by small molecules or with a selective PDGFRβ blockade.

In this trial, there were no DLTs and the MTD was not reached, which is consistent with the previous US trial.[14] Over the three dose ranges, olaratumab had an acceptable safety profile and was well tolerated in this patient population.

Based on the PK concentration profile of olaratumab, the trough concentrations following single and multiple doses of olaratumab at 15 mg/kg on days 1 and 8 every 3 weeks (cohort 3), and multiple doses at 20 mg/kg every 2 weeks (cohort 2), were above 155 μg/mL, the concentration that was efficacious in preclinical xenograft studies.[14] Thus, olaratumab dosed at 15 mg/kg on days 1 and 8 every 3 weeks and at 20 mg/kg every 2 weeks could represent an acceptable schedule for future trials in Japanese patients. Based on the comparative analysis of both the clearance (CLss) and exposure (AUCτ), the observed PK in the Asian patient population appears to be similar to the non-Asian patient population observed in the previous US phase I trial.[14]

The best overall response in this trial was SD, achieved by 7 of 16 patients (43.8%). Of these seven patients, four had tumors that were located in the gastrointestinal tract; the remaining three patients had tumors of diverse origins. Two patients, both in cohort 3, experienced disease stabilization >4 months (hypopharyngeal cancer [SD = 4.2 months]) and leiomyosarcoma of inferior vena cava origin [SD = 5.6 months]), which indicates some preliminary antitumor activity.

In nude mice, treatment with olaratumab inhibited the growth of human glioblastoma (U118) and leiomyosarcoma (SKLMS-1) xenografts and decreased the amount of tumor-associated phosphotyrosyl-PDGFRα in the glioblastoma model.[13] In cultured cells, olaratumab inhibited PDGF-induced mitogenesis, PDGFRα autophosphorylation, and the phosphorylation of downstream signaling molecules. At this time, it is not known if the same changes occur in patient tumors or whether pharmacologically active concentrations can be achieved in human tumor tissue. Our trial showed that the median plasma PDGF-AA expression increased for 24 h after the first infusion in all three cohorts, but no trend was noted at later time points and best overall responses seemed unrelated to the largest change in PDGF-AA from baseline. Because biomarker studies were not performed in the US trial, comparisons cannot be made with this trial; nonetheless, an increase in PDGF-AA may be a compensatory mechanism that results from PDGFRα inhibition and/or sequestration.

Based on its safety and preliminary efficacy in this trial and the previous phase 1 trial,[14] olaratumab has advanced to phase II trials. Olaratumab is being tested as monotherapy and in combination with other agents in several tumor types.

Acknowledgments

This trial was supported by ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company. The authors wish to acknowledge the patients, their families, and the study personnel who participated in this clinical trial. The authors thank Lori Kornberg (inVentiv Health Clinical) and Susan Johnson (ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company) for medical writing assistance, and Joseph Durrant (inVentiv Health Clinical) for editorial support.

Disclosure Statement

Aruna Dontabhaktuni is an employee of ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company and owns stock in Eli Lilly and Company. Cornelia Nippgen is an employee of Eli Lilly and Company. Johannes Nippgen and Yan Ma were employed by ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, during the conduct of this trial. Toshihiko Doi and Atsushi Ohtsu report no conflicts of interest.

References

1 Heldin CH, Westermark B. Mechanism of action and in vivo role of platelet-derived growth factor. *Physiol Rev* 1999; **79**: 1283–316.

2 Dong J, Grunstein J, Tejada M *et al.* VEGF-null cells require PDGFR alpha signaling-mediated stromal fibroblast recruitment for tumorigenesis. *EMBO J* 2004; **23**: 2800–10.

3 Adams SF, Hickson JA, Hutto JY, Montag AG, Lengyel E, Yamada SD. PDGFR-alpha as a potential therapeutic target in uterine sarcomas. *Gynecol Oncol* 2007; **104**: 524–8.
4 Fleming TP, Saxena A, Clark WC *et al.* Amplification and/or overexpression of platelet-derived growth factor receptors and epidermal growth factor receptor in human glial tumors. *Cancer Res* 1992; **52**: 4550–3.
5 Matei D, Emerson RE, Lai YC *et al.* Autocrine activation of PDGFRalpha promotes the progression of ovarian cancer. *Oncogene* 2006; **25**: 2060–9.
6 Stock P, Monga D, Tan X, Micsenyi A, Loizos N, Monga SP. Platelet-derived growth factor receptor-alpha: a novel therapeutic target in human hepatocellular cancer. *Mol Cancer Ther* 2007; **6**: 1932–41.
7 Carvalho I, Milanezi F, Martins A, Reis RM, Schmitt F. Overexpression of platelet-derived growth factor receptor alpha in breast cancer is associated with tumour progression. *Breast Cancer Res* 2005; **7**: R788–95.
8 Chott A, Sun Z, Morganstern D *et al.* Tyrosine kinases expressed *in vivo* by human prostate cancer bone marrow metastases and loss of the type 1 insulin-like growth factor receptor. *Am J Pathol* 1999; **155**: 1271–9.
9 Henriksen R, Funa K, Wilander E, Backstrom T, Ridderheim M, Oberg K. Expression and prognostic significance of platelet-derived growth factor and its receptors in epithelial ovarian neoplasms. *Cancer Res* 1993; **53**: 4550–4.
10 Sulzbacher I, Birner P, Traxler M, Marberger M, Haitel A. Expression of platelet-derived growth factor-alpha alpha receptor is associated with tumor progression in clear cell renal cell carcinoma. *Am J Clin Pathol* 2003; **120**: 107–12.
11 Dai Y. Platelet-derived growth factor receptor tyrosine kinase inhibitors: a review of the recent patent literature. *Expert Opin Ther Pat* 2010; **20**: 885–97.
12 Levitzki A. PDGF receptor kinase inhibitors for the treatment of PDGF driven diseases. *Cytokine Growth Factor Rev* 2004; **15**: 229–35.
13 Loizos N, Xu Y, Huber J *et al.* Targeting the platelet-derived growth factor receptor alpha with a neutralizing human monoclonal antibody inhibits the growth of tumor xenografts: implications as a potential therapeutic target. *Mol Cancer Ther* 2005; **4**: 369–79.
14 Chiorean EG, Sweeney C, Youssoufian H *et al.* A phase I study of olaratumab, an anti-platelet–derived growth factor receptor alpha (PDGFRα) monoclonal antibody, in patients with advanced solid tumors. *Cancer Chemother Pharmacol* 2014; **73**: 595–604.
15 National Cancer Institute. Cancer therapy evaluation program common terminology criteria for adverse events, version 4.0. Available from URL: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
16 Therasse P, Arbuck SG, Eisenhauer EA *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16.
17 Demetri GD, von Mehren M, Blanke CD *et al.* Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; **347**: 472–80.
18 Faivre S, Delbaldo C, Vera K *et al.* Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006; **24**: 25–35.
19 Adams GP, Weiner LM. Monoclonal antibody therapy of cancer. *Nat Biotechnol* 2005; **23**: 1147–57.
20 Rodt SA, Ahlen K, Berg A, Rubin K, Reed RK. A novel physiological function for platelet-derived growth factor-BB in rat dermis. *J Physiol* 1996; **495**: 193–200.
21 Jayson GC, Parker GJ, Mullamitha S *et al.* Blockade of platelet-derived growth factor receptor-beta by CDP860, a humanized, PEGylated di-Fab', leads to fluid accumulation and is associated with increased tumor vascularized volume. *J Clin Oncol* 2005; **23**: 973–81.

Cancer Science
Japanese Cancer Association JCA
Open Access

Phase I dose-escalation study of buparlisib (BKM120), an oral pan-class I PI3K inhibitor, in Japanese patients with advanced solid tumors

Yuichi Ando,[1] Megumi Inada-Inoue,[1] Ayako Mitsuma,[1] Takayuki Yoshino,[2] Atsushi Ohtsu,[2] Naoko Suenaga,[3] Masahiko Sato,[3] Tomoyuki Kakizume,[3] Matthew Robson,[3] Cornelia Quadt[4] and Toshihiko Doi[2]

[1]Nagoya University Hospital, Nagoya; [2]National Cancer Center Hospital East, Kashiwa; [3]Novartis Pharma K.K., Tokyo, Japan; [4]Novartis Pharmaceuticals, East Hanover, New Jersey, USA

Key words
BKM120, buparlisib, Japanese patients

Correspondence
Yuichi Ando, Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8560, Japan.
Tel: +81-52-744-1903; Fax: +81-52-744-1903;
E-mail: yando@med.nagoya-u.ac.jp

Funding information
Novartis Pharma (CBKM120X1101).

Received September 15, 2013; Revised December 19, 2013; Accepted December 28, 2013

Cancer Sci **105** (2014) 347–353

doi: 10.1111/cas.12350

Buparlisib (BKM120) is an oral pan-phosphatidylinositol 3-kinase inhibitor, targeting all four isoforms of class I PI3K (α, β, γ and δ). This open-label Phase I dose-escalation study was conducted to determine the maximum tolerated dose of continuous daily buparlisib in Japanese patients with advanced solid tumors. Secondary objectives included safety and tolerability, pharmacokinetics, antitumor activity and pharmacodynamic marker changes. Fifteen patients were treated at 25 mg/day (n = 3), 50 mg/day (n = 3) and 100 mg/day (n = 9) dose levels. One dose-limiting toxicity of Grade 4 abnormal liver function occurred at 100 mg/day. Considering the safety profile and the maximum tolerated dose in the first-in-man study of buparlisib in non-Japanese patients, further dose escalation was stopped and 100 mg/day was declared the recommended dose. The most common treatment-related adverse events were rash, abnormal hepatic function (including increased transaminase levels), increased blood insulin levels and increased eosinophil count. Hyperglycemia was experienced by two patients, one Grade 1 and one Grade 4, and mood alterations were experienced by three patients, two Grade 1 and one Grade 2. Pharmacokinetic results showed that buparlisib was rapidly absorbed in a dose-proportional manner. Best overall response was stable disease for six patients, including one unconfirmed partial response. In these Japanese patients with advanced solid tumors, buparlisib had a manageable safety profile, with similar pharmacokinetics to non-Japanese patients. The recommended dose of 100 mg/day will be used in future studies of buparlisib in Japanese patients.

The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is frequently activated in cancer,[1] and is implicated in the maintenance of a tumorigenic phenotype, tumor progression and resistance to anticancer therapy.[2–5] Oncogenic pathway activation can occur through multiple mechanisms, including overexpression or activation of upstream receptor tyrosine kinases, or genetic alteration of individual pathway components. For example, activating mutations in the *PIK3CA* gene, which encodes the p110α isoform of the PI3K class IA catalytic subunit, are commonly found in cancer.[2] Given its pivotal role in cancer development and progression, pharmacologic inhibition of PI3K is currently being investigated as a potential therapeutic strategy for a range of tumors.

Buparlisib (BKM120 [Novartis Pharma AG, Basel, Switzerland]) is an oral pan-PI3K inhibitor that targets all four isoforms of class I PI3K (α, β, γ and δ).[6] Buparlisib has demonstrated antiproliferative, pro-apoptotic and antitumor activity in cancer cell lines and tumor xenograft models, as a single agent[6] and in combination with other anticancer therapies.[7–9] In a first-in-man Phase I study in predominantly European and US patients with advanced solid tumors (NCT01068483), the maximum tolerated dose (MTD) of single-agent buparlisib given on a continuous daily schedule was 100 mg.[10] Dose-limiting toxicities (DLT) occurred in seven of 30 evaluable patients, including epigastralgia, skin rash, mood alteration and hyperglycemia.[10] In the safety expansion portion of the trial (n = 66), buparlisib was well tolerated with a minority of patients experiencing Grade 3/4 adverse events (AE).[11]

The primary objective of this open-label Phase I dose-escalation study was to determine the MTD of oral buparlisib on a continuous daily schedule in adult Japanese patients with advanced solid tumors. Secondary objectives included assessments of safety and tolerability, characterization of the pharmacokinetic profile, evaluation of preliminary antitumor activity and changes in pharmacodynamic markers (as a measure of PI3K inhibition) of buparlisib.

Materials and Methods

Patient eligibility. Japanese patients ≥20 years of age with histologically confirmed, advanced, unresectable solid tumors whose disease had progressed, or who were unable to tolerate standard therapy, or for whom no standard therapy existed were eligible. Other key inclusion criteria include: one

measurable or non-measurable lesion according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.0; an Eastern Cooperative Oncology Group performance status ≤2; life expectancy ≥12 weeks; adequate bone marrow, hepatic and renal functions; fasting plasma glucose levels ≤140 mg/dL (7.8 mmol/L); a negative pregnancy test ≤7 days of starting treatment for pre-menopausal and peri-menopausal women; and availability of a representative archival or fresh tissue specimen. Key exclusion criteria were: prior treatment with a PI3K inhibitor; clinically significant chronic liver disease; medically documented history of, or active, major mood or psychiatric disorder, or Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 anxiety; and clinically manifest diabetes mellitus or a history of gestational diabetes mellitus.

The study protocol was reviewed by regulatory authorities and approved by the ethics committees of all participating institutions. All patients provided written informed consent prior to any study assessments being performed. The study was conducted in accordance with the Declaration of Helsinki, guidelines for Good Clinical Practice as defined by the International Conference on Harmonization, and the Japanese Ministry of Health, Labour and Welfare.

Study design and treatment. In this Phase I open-label dose-escalation study (CBKM120X1101; NCT01283503), oral buparlisib was administered once daily, on a continuous schedule in 28-day cycles, starting at 25 mg/day. Patients received buparlisib until disease progression, unacceptable toxicity, investigator's decision or patient's withdrawal of consent.

An adaptive Bayesian logistic regression model (BLRM) with overdose control (EWOC) was used to guide dose escalation.[12,13] The MTD was defined as the highest drug dosage not causing medically unacceptable DLT in more than 33% of treated patients during Cycle 1, which also satisfied the BLRM EWOC criteria. The population for MTD determination (the dose-determining set) consisted of patients treated for ≥21 days in Cycle 1, or who discontinued earlier due to a DLT. Patients who did not experience a DLT in Cycle 1 were observed for ≥28 days after the first dose, and completed all safety evaluations required for dose-determining decisions. To ensure the MTD recommendation was accurate, before a drug dosage could be declared, at least 15 patients eligible for the dose-determining set had to be enrolled, including at least six eligible patients receiving the estimated MTD. Intra-patient dose escalation was not permitted within the first four treatment cycles. The MTD was planned to be determined using the BLRM recommendation, plus a medical review of available clinical, pharmacokinetic and laboratory data.

Definition of dose-limiting toxicity. Dose-limiting toxicities were assessed using the National Cancer Institute's CTCAE v3.0, and defined as AE or abnormal laboratory values that occurred within Cycle 1 and were suspected to be related to buparlisib. In addition, a DLT had to meet any of the criteria described in Table S1.

Safety and antitumor activity assessments. All patients who received at least one dose of the study drug and had at least one post-baseline safety assessment were eligible for safety evaluation. Routine clinical and laboratory assessments were conducted at baseline, and throughout the study. Other safety assessments included electrocardiogram and regular administration of a patient self-rating mood questionnaire (nine-item patient health questionnaire; PHQ-9).

Adverse events were collected continuously from the first dose to 4 weeks following the last dose of buparlisib, and graded using CTCAE v3.0 unless otherwise stated (Table S2). Mood alterations were defined as all AE belonging to one of the following MedDRA high-level group terms: mood disorders and disturbances, not elsewhere classified, and psychiatric and behavioral symptoms, not elsewhere classified.

Assessments of preliminary antitumor activity were performed in all patients who had received at least one dose of buparlisib. Radiologic response was measured by computed tomography (CT) or MRI according to RECIST v1.0 at baseline, at the end of Cycle 2 and every 8 weeks thereafter.

Pharmacokinetic and pharmacodynamic assessments. Blood was sampled for pharmacokinetic assessments after overnight fasting pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 h post-dose on Days 1, 8 and 28 of Cycle 1, and pre-dose and 2–4 h post-dose on Day 1 of every other cycle from Cycle 3. Plasma samples were assayed using a validated liquid chromatography-tandem mass spectrometry assay (limit of quantitation was 0.25 ng/mL using 0.1 mL of plasma). Pharmacokinetic parameters, including the time of maximum buparlisib plasma concentration (T_{max}), maximum plasma concentration of buparlisib (C_{max}), area under the concentration–time curve over 24 h (AUC_{0-24}), buparlisib half-life ($T_{1/2}$) and the accumulation ratio (Racc), were determined using a non-compartmental method.

Time-dependent changes in glucose metabolism markers (fasting plasma glucose, insulin and C-peptide levels) were collected pre-dose, and 0.5, 1, 2, 4 and 24 h post-dose at baseline (Cycle 1 Day 1), and then at Cycle 1 Days 8 and 28.

Follow up. Patients whose treatment was interrupted or permanently discontinued due to a DLT, a study-related AE or an abnormal laboratory value were assessed at least once per week for 4 weeks and subsequently at 4-week intervals until resolution or stabilization of the event. Patients who required a dose delay ≥21 days from the last dose were discontinued from the study, and were followed for toxicities. Patients who discontinued study treatment were followed for AE and serious adverse events (SAE) for 28 days following the last dose of buparlisib.

Results

Patient characteristics. Fifteen patients were enrolled at two centers in Japan between October 2009 and October 2011 (Table 1). All 15 patients received at least one dose of buparlisib and so were evaluable for safety and preliminary efficacy.

Dose escalation and maximum tolerated dose. All 15 patients were evaluable for MTD determination. Of these, three patients were each allocated to the 25 and 50 mg/day dose cohorts, and nine patients to the 100 mg/day cohort. One DLT was reported in the study; this was Grade 4 abnormal liver function, which showed elevated liver function tests on Day 28 of Cycle 1, in a patient treated at 100 mg/day. Buparlisib was temporarily interrupted, but the patient did not resume study drug due to progressive disease and discontinued from the study. Recovery occurred approximately 1 month after onset. This DLT was the only incidence of Grade 3/4 abnormal liver function reported in Cycle 1, regardless of duration. The BLRM permitted a further dose increase to 150 mg/day, but considering safety information other than DLT, and the non-Japanese recommended Phase II dose, 100 mg/day was declared as the recommended dose (RD), instead of the MTD, for use in future buparlisib studies in Japanese patients.

Safety and tolerability. The median duration of exposure to buparlisib was 56 (range: 28–167) days in all patients and 37 (range: 28–129) days in patients receiving 100 mg/day. One

Table 1. Baseline patient characteristics

Characteristic	Buparlisib			
	25 mg/day *n* = 3	50 mg/day *n* = 3	100 mg/day *n* = 9	All *n* = 15
Median age, years (range)	66 (44–67)	47 (22–66)	58 (35–71)	58 (22–71)
Sex, *n*				
Male	2	3	7	12
Female	1	0	2	3
ECOG performance status, *n*				
0	3	2	5	10
1	0	1	4	5
Prior antineoplastic regimens, *n*				
Number of prior antineoplastic medication regimens, median (range)	0 (0–3)	5 (3–5)	4 (0–9)	3 (0–9)
Number of patients with >3 prior antineoplastic medication regimens	0	1	5	6
Primary site of tumor, *n*				
Rectum	0	0	3	3
Salivary gland	2	0	1	3
Head and neck	0	1	1	2
Colon	0	1	1	2
Breast	0	0	1	1
Esophagus	0	0	1	1
Skin melanoma	1	0	0	1
Peripheral nerve sheath	0	1	0	1
Unknown	0	0	1	1

ECOG, Eastern Cooperative Oncology Group.

patient had their dose reduced from 100 to 50 mg/day due to abnormal hepatic function, which occurred in Cycle 3. A total of 11 patients required dose interruptions due to AE.

All 15 patients experienced at least one AE suspected to be related to buparlisib (Table 2). Drug-related Grade 3/4 AE were abnormal hepatic function (including increased ALT /AST, $n = 6$) and anemia ($n = 2$). Mood alteration was experienced by 3 patients treated at 100 mg/day (all Grade 1 or 2); one patient was treated with tranquillizers; treatment was not required in the other two patients. No dose reductions or trial withdrawals resulting from mood alterations occurred.

Six patients treated at 100 mg/day experienced at least one SAE: abnormal hepatic function (Grade 3/4; including increased ALT/AST levels, $n = 3$), pneumonitis (Grade 3; $n = 1$), dyspnea (Grade 2; $n = 1$) and hyperglycemia (Grade 4; $n = 1$), infectious pneumonia (Grade 2; $n = 1$), delirium (Grade 2; $n = 1$) and hemorrhage (Grade 4; $n = 1$). With the exceptions of delirium and hemorrhage, these SAEs were all considered related to buparlisib. Two patients, both in the

Table 2. Study drug-related adverse events by treatment cohort and Grade

Adverse events, *n*†	Buparlisib							
	25 mg /day *n* = 3		50 mg /day *n* = 3		100 mg /day *n* = 9		All *n* = 15	
	All	G3/4	All	G3/4	All	G3/4	All	G3/4
Rash	0	0	0	0	7	0	7	0
Abnormal hepatic function/increased transaminase levels	2	2	0	0	4	4	6	6
Increased blood insulin levels	0	0	1	0	5	0	6	0
Increased eosinophil count	3	0	0	0	3	0	6	0
Increased blood C-peptide levels	0	0	1	0	3	0	4	0
Pruritus	0	0	1	0	3	0	4	0
Decreased appetite	0	0	0	0	4	0	4	0
Fatigue	0	0	0	0	4	0	4	0
Prolonged activated partial thromboplastin time	0	0	1	0	2	0	3	0
Anemia	0	0	0	0	3	2	3	2
Mood alteration	0	0	0	0	3	0	3	0

†Adverse events (any Grade) reported in ≥3 patients; and all Grade 3/4 events considered related to the study drug. G, Grade.

100 mg/day cohort, died during the study period (i.e. including the time on treatment and the safety follow-up period) as a result of SAEs (hemorrhage and pneumonitis). The patient with hemorrhage died 5 days after discontinuation of buparlisib due to a fistula in one of the cancer lesions resulting from tumor necrosis (Fig. 1): this was considered unrelated to buparlisib. A 71-year-old male patient died from aggravation of pneumonitis (Grade 5) 11 days after discontinuing buparlisib, for which a relationship to the study drug could not be ruled out. This patient was a non-smoker, with a diagnosis of adenocarcinoma of the rectum, multiple metastases, including the lung, pleura and lymph nodes, and a left pleural effusion, which was detected by a CT scan prior to study enrollment. A CT scan taken 32 days after the first dose of buparlisib administration showed pneumonitis and worsening disease with increased left pleural effusion. At the time of onset, infectious pneumonitis was suspected rather than interstitial pneumonia. Despite antibiotic treatment, the patient's condition remained unchanged. When a follow-up CT examination was performed 10 days after the last dose of buparlisib, ground glass opacities were found. The patient's respiratory function deteriorated abruptly, and the patient died the following day.

Five patients discontinued the study due to AE. In four patients, AE leading to discontinuation were considered related to the study treatment: abnormal hepatic function (including increased ALT/AST; two patients receiving 25 mg/day and 1 receiving 100 mg/day), and increased lipase levels (one patient receiving 100 mg/day). The remaining 10 patients discontinued due to disease progression.

Antitumor activity. The best overall response was stable disease for six patients and progressive disease for seven patients (Table 3; Fig. 2). The best percentage change from baseline in

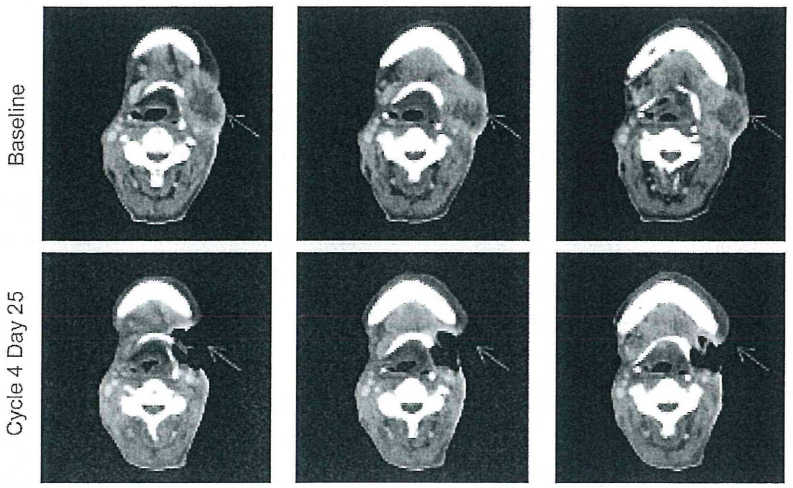

Fig. 1. Antitumor activity with buparlisib (100 mg /day) in a patient with head and neck squamous cell carcinoma and metastasis to the neck lymph node. A 58-year-old male patient experienced a 76% reduction in neck lesion size (from 59 mm at baseline to 14 mm in Cycle 4). As the second confirmation according to Response Evaluation Criteria In Solid Tumors was not obtained, this unconfirmed partial response was recorded as stable disease. The left internal carotid artery was compressed and narrowed by the tumor. During study treatment, fistulae developed in the skin of the neck region followed by arterial hemorrhage from the rapidly degraded tumor lesion. Although the patient recovered and restarted buparlisib at 50 mg/day in Cycle 5, they eventually died from hemorrhage 5 days after buparlisib discontinuation, which was considered unrelated to the study drug. Sequential images of computed tomography scans taken at baseline and on Cycle 4 Day 25 are shown. The arrow marks the region of interest.

Table 3. Activity of oral buparlisib in Japanese patients with advanced solid tumors according to response evaluation criteria in solid tumors v1.0

Clinical activity, *n* (%)	Buparlisib			
	25 mg/day *n* = 3	50 mg/day *n* = 3	100 mg/day *n* = 9	All *n* = 15
Complete response	0	0	0	0
Partial response	0	0	0	0
Stable disease	2 (66.7)	1 (33.3)	3 (33.3)†	6 (40.0)
Disease progression	1 (33.3)	2 (66.7)	4 (44.4)	7 (46.7)
Unknown	0	0	2 (22.2)	2 (13.3)

†Includes one patient with unconfirmed partial response.

target lesions for all patients is also shown in Fig. S1. The duration of stable disease ranged from 55 to 116 days. The disease control rate, defined as rates of complete response plus partial response plus stable disease, was 40%.

Pharmacokinetic and pharmacodynamics analyses. Pharmacokinetic data were obtained from all 15 patients, apart from at Cycle 1 Day 8 in two of the nine patients receiving buparlisib 100 mg/day (Table 4). Buparlisib was rapidly absorbed, achieving C_{max} 1.0–1.5 h post-dose, as demonstrated by the T_{max} values obtained on Days 1, 8 and 28 of Cycle 1 (Table 4; Fig. S2). At the MTD, buparlisib accumulated 2.8-fold on Cycle 1 Day 8 and 2.9-fold on Cycle 1 Day 28 compared with Cycle 1 Day 1, which was consistent with a half-life of approximately 40 h. Doses of buparlisib ≥50 mg/day led to steady-state exposure levels ≥10 000 ng*h/mL, which are estimated to be efficacious based on preclinical studies. C_{max} and AUC_{0-24} of buparlisib increased dose proportionately by 25–100 mg/day.

Modest time-dependent increases in glucose metabolism markers were observed with buparlisib treatment (see supporting information).

Discussion

This Phase I dose-escalation study evaluated the MTD of continuous once-daily buparlisib in Japanese patients with advanced solid tumors. Instead of the MTD, the RD of single-agent buparlisib was declared as 100 mg/day. Although the BLRM allowed higher doses to be evaluated, the decision to

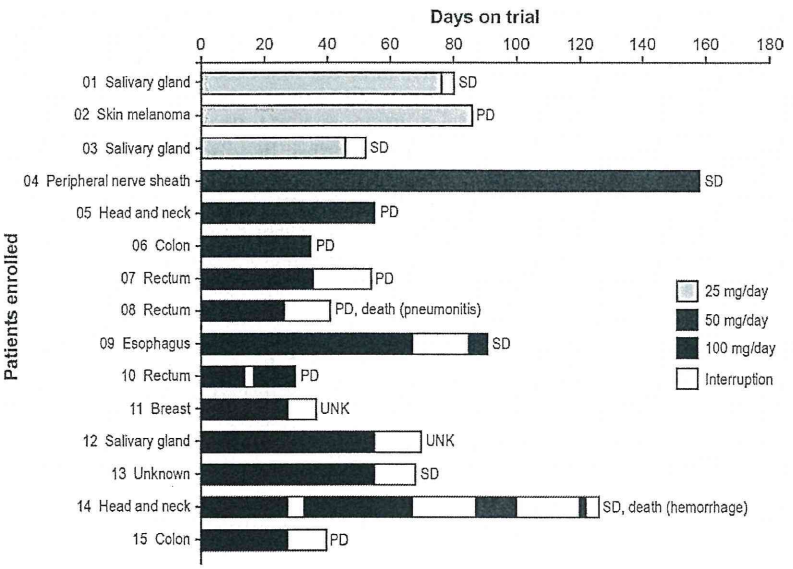

Fig. 2. Duration of buparlisib treatment according to dose and radiologic response. Study participants are shown according to primary tumor site, buparlisib dose, days on trial and tumor response according to Response Evaluation Criteria In Solid Tumors v1.0. PD, progressive disease; SD, stable disease; UNK, unknown.

Table 4. Pharmacokinetic profile of oral buparlisib in adult Japanese patients with advanced solid tumors in Cycle 1

Dose (mg/day)	Day	*n*	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)	$T_{1/2}$ (h)†	Racc
25	1	3	1.00	289 (45)	2060 (474)	36.8 (9.2)	—
	8	3	1.00	549 (275)	4640 (1230)	43.8 (NR)	2.25 (0.15)
	28	3	1.00	530 (131)	6800 (3040)	NR	3.20 (0.67)
50	1	3	1.02	595 (212)	3830 (834)	NR	—
	8	3	1.10	738 (221)	9550 (3200)	NR	2.58 (1.16)
	28	3	1.50	767 (121)	11400 (3320)	NR	3.09 (1.29)
100	1	9	1.50	1080 (331)	8800 (1530)	30.6 (9.6)	—
	8	7	1.02	1930 (560)	24300 (6190)	39.5 (25.2)	2.78 (0.66)
	28	9	2.98	1790 (503)	25000 (7950)	41.8 (16.9)	2.87 (0.83)

AUC_{0-24}, area under the curve from 0 to 24 h; C_{max}, maximum plasma concentration; NR, not reported; Racc, accumulation rate (AUC [Day 8]/AUC [Day 1] or AUC [Day 28]/AUC [Day 1]); $T_{1/2}$, half-life; T_{max}, time at which maximum plasma concentration is achieved. Values are presented as median for T_{max} and mean (standard deviation) for other parameters. †For $T_{1/2}$ analysis, for the 25-mg/day dose, $n = 2$ on Day 1 and $n = 1$ on Day 8; for the 100 mg/dose $n = 4$ on Day 1, $n = 3$ on Day 8, and $n = 2$ on Day 28.

halt dose escalation and declare the RD was made on the basis of comparable pharmacokinetics with non-Japanese patients enrolled in the first-in-man study,[10] and the safety profile of buparlisib in Japanese patients in this study. Therefore, the RD of once-daily buparlisib in Japanese patients with advanced solid tumors is the same as the MTD for buparlisib in the first-in-man study.[10]

Buparlisib was generally well tolerated, with an AE profile reflective of on-target inhibition of the PI3K/Akt/mTOR pathway. The most common treatment-related AE were rash, abnormal hepatic function (including increased ALT/AST levels), increased blood insulin levels and increased eosinophil count, which are consistent with those AE reported in the first-in-man study,[10] and for other pan-PI3K inhibitors.[14–16] One DLT of abnormal liver function was reported in a patient in Cycle 1, and five further cases of Grade 3/4 abnormal hepatic function (including increased ALT/AST levels) were reported in Cycle 2 and thereafter. The hepatic toxicity was managed based on the Manual for Drug-Induced Liver Injury by the Ministry of Health, Labour and Welfare (Japanese Health Authority) guidelines[17] and the Guidance for Industry, Drug-Induced Liver Injury of the FDA.[18] Liver toxicity is considered to be a class effect of PI3K/Akt/mTOR pathway inhibitors.[16,19,20] In clinical trials of PI3K inhibitors, liver enzyme abnormalities have been observed with varying frequencies. In a Phase I study investigating the PI3K inhibitor PX866, Grade 3 AST elevations were observed in two of 84 patients.[16] In another Phase I study of the PI3K/mTOR inhibitor BGT226 in 57 patients with advanced solid tumors and lymphoma, AST elevations were the most frequently observed Grade 2 or higher biochemical abnormality ($n = 9$ Grade 2; $n = 3$ Grade 3).[20] In the first-in-man study of buparlisib, Grade 3/4 liver toxicities (including transaminase increase and hyperbilirubinemia) were observed in nine patients (11%; mostly at 100 mg/day), and did not result in DLT.[11] It is unknown whether differences in the occurrence of severe liver toxicity are significant between Japanese and non-Japanese patients because of the small sample size of this study, and potential differences in tumor types and treatment history. It is also unclear whether abnormal hepatic function is related to pharmacokinetic exposure to buparlisib. Incidences of abnormal hepatic function will be monitored in Phase II/III trials.

Hyperglycemia is another class effect of PI3K inhibitors due to the central role of PI3K/Akt/mTOR pathway in glucose homeostasis regulation.[1] Inhibition of PI3K can lead to increased blood glucose levels by disrupting insulin signaling, inhibiting glycogen synthesis and reducing peripheral glucose uptake.[21–23] Grade 4 hyperglycemia was observed in one patient receiving 100 mg/day in Cycle 2. In the first-in-man study, Grade 3/4 hyperglycemia occurred in three patients (9%), including two DLT at 150 mg/day.[11] Clinical experience of buparlisib has shown that hyperglycemia can be managed with standard antidiabetes drugs, including metformin, and subcutaneous insulin where necessary.[10] An *in vivo* study has suggested that fasting prior to drug administration and a low carbohydrate diet may reduce the extent of hyperglycemia caused by PI3K/Akt/mTOR pathway inhibition.[21]

Glucose metabolism markers have been proposed as pharmacodynamic markers of PI3K inhibition. In this small study, there was a non-significant trend towards increased plasma glucose, C-peptide, and insulin levels with increasing concentrations of buparlisib. As no patient with diabetes participated in the study, the change in insulin levels reflected C-peptide levels as expected. Some patients in the 100 mg/day cohort showed increased glucose levels, but this was not thought to be associated with buparlisib exposure or clinical outcomes. In the first-in-man study, glucose metabolism markers indicated dose-dependent inhibition of PI3K signaling by buparlisib.[10] Increases in C-peptide levels were observed at lower doses of buparlisib than those associated with hyperglycemia, indicating that increased pancreatic insulin/C-peptide release can effectively compensate for decreased glucose transport and metabolism due to PI3K inhibition at buparlisib doses less than 100 mg/day.[10] Fasting blood glucose increases were also more evident at higher buparlisib doses,[10] which is similar to the results observed here.

One patient in the 100 mg/day cohort died from drug-induced pneumonitis 11 days after discontinuing buparlisib due to progressive disease with a new lung lesion. As the patient's respiratory function abruptly deteriorated just prior to his death, the investigator reasoned that the main cause of death was aggravation of pneumonitis rather than progression of cancer. This patient had lung pathology prior to entering the study, and was pretreated with multiple therapies previously associated with pneumonitis, possibly due to drug-induced lung injury. These include bevacizumab,[24] oxaliplatin,[25–27] levofolinate,[27] 5-FU,[26,28] irinotecan[29,30] and cetuximab.[31,32] It has been speculated that inhibition of the PI3K/mTOR pathway may affect the immune system. However, unlike mTOR inhibitors that cause pneumonitis with varying frequencies,[33–38] the PI3K inhibitor buparlisib has rarely been associated with pneumonitis in studies involving more than 500 patients (unpublished data). As a basic precaution for

patient safety, studies of buparlisib have required lung imaging as part of the study protocol at baseline and throughout the study if clinically indicated.

Mood alterations were observed in the first-in-man study of buparlisib: one DLT at 80 mg/day and two DLT at 100 mg /day.[10] In Japanese patients, no Grade 3/4 mood alterations or DLT were observed. This difference between the two studies may be reflective of a protocol amendment excluding patients predisposed to mood alteration from the Japanese study, and the introduction of careful monitoring using PHQ-9. The incidence of all-grade mood alterations was similar between studies (3/15 [20%] in Japanese patients and 7/35 [20%] in non-Japanese patients).[10] No dose reductions or trial withdrawals resulting from mood alterations occurred. In the first-in-man study, buparlisib-induced mood disorders were reversible, and resolved quickly upon treatment discontinuation.[10] The incidence of mood alterations with buparlisib has been attributed to its ability to cross the blood–brain barrier[39] and to inhibit PI3K signaling in the brain parenchyma.[40] The precise mechanism of buparlisib-induced mood disorders is still under investigation, but the PI3K/Akt/mTOR pathway is thought to play a role in neurotransmitter signaling.[41–44] The ability of buparlisib to cross the blood–brain barrier may also have a beneficial effect on brain lesions.[40]

Conclusions about the clinical activity of buparlisib cannot be made from the present study due to the small sample size and the heterogeneity of the patients enrolled. However, preliminary signs of clinical activity were observed, including stable disease and an unconfirmed partial response, indicating therapeutic potential in advanced solid tumors. Based on preclinical data, genetic alterations of the PI3K/Akt/mTOR pathway, such as somatic *PIK3CA* mutations or PTEN loss, have been proposed to predict the response to PI3K pathway inhibitors, but early clinical results are inconclusive.[45–50] Unfortunately, molecular profiling data were not available for the patient who experienced an unconfirmed partial response to determine whether the tumor harbored an alteration in the PI3K pathway.

In conclusion, the results of this Phase I dose-escalation study demonstrate that the pan-class I inhibitor buparlisib has a manageable safety profile, has favorable pharmacokinetics, and has shown preliminary signs of antitumor activity in this small population of Japanese patients. Importantly, the safety and pharmacokinetic profiles of buparlisib were similar to those reported in the first-in-man trial in non-Japanese patients.[10] The buparlisib dose of 100 mg/day has been determined as the RD for future studies of this schedule in Japanese patients. Phase III trials of buparlisib in patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer are ongoing (BELLE-2 and BELLE-3).

Acknowledgments

We thank Dr Michio Imawari (Showa University School of Medicine) for consultation on hepatic toxicity, and Dr Masahiro Endo (Shizuoka Cancer Center), Dr Akifumi Kato (Kanagawa Cardiovascular and Respiratory Center) and Dr Masashi Takahashi (Shiga University of Medical Science) for external review of the interstitial lung disease case. We would also like to thank the patients who participated in this study and their families. Kate Gaffey PhD and Alison Lovibond PhD provided medical editorial assistance, funded by Novartis.

Disclosure statement

This study was supported by research funding from Novartis Pharma (CBKM120X1101). Yuichi Ando has received research funding from Novartis. Takayuki Yoshino has received honoraria from Takeda, Chugai and Merck Serono, and has received research funding from Yakult, Taiho, Daiichi-Sankyo and Lilly. Toshihiko Doi has received honoraria as lecture fees and research funding from Novartis. Naoko Suenaga, Masahiko Sato, Tomoyuki Kakizume, Matthew Robson and Cornelia Quadt are employees of Novartis Pharma, and Matthew Robson owns stocks in Novartis Pharma. The other authors have no conflict of interest to declare.

References

1 Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat Rev Genet* 2006; **7**: 606–19.
2 Liu P, Cheng H, Roberts TM, Zhao JJ. Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat Rev Drug Discov* 2009; **8**: 627–44.
3 Saal LH, Johansson P, Holm K *et al.* Poor prognosis in carcinoma is associated with a gene expression signature of aberrant PTEN tumor suppressor pathway activity. *Proc Natl Acad Sci USA* 2007; **104**: 7564–9.
4 Huang WC, Hung MC. Induction of Akt activity by chemotherapy confers acquired resistance. *J Formos Med Assoc* 2009; **108**: 180–94.
5 Miller TW, Balko JM, Arteaga CL. Phosphatidylinositol 3-kinase and anti-estrogen resistance in breast cancer. *J Clin Oncol* 2011; **29**: 4452–61.
6 Maira SM, Pecchi S, Huang A *et al.* Identification and characterization of NVP-BKM120, an orally available pan-class I PI3-Kinase inhibitor. *Mol Cancer Ther* 2012; **11**: 317–28.
7 Ren H, Chen M, Yue P *et al.* The combination of RAD001 and NVP-BKM120 synergistically inhibits the growth of lung cancer in vitro and in vivo. *Cancer Lett* 2012; **325**: 139–46.
8 Mueller A, Bachmann E, Linnig M *et al.* Selective PI3K inhibition by BKM120 and BEZ235 alone or in combination with chemotherapy in wild-type and mutated human gastrointestinal cancer cell lines. *Cancer Chemother Pharmacol* 2012; **69**: 1601–15.
9 Park E, Park J, Han SW *et al.* NVP-BKM120, a novel PI3K inhibitor, shows synergism with a STAT3 inhibitor in human gastric cancer cells harboring KRAS mutations. *Int J Oncol* 2012; **40**: 1259–66.
10 Bendell JC, Rodon J, Burris HA *et al.* Phase I, dose-escalation study of BKM120, an oral pan-Class I PI3K inhibitor, in patients with advanced solid tumors. *J Clin Oncol* 2012; **30**: 282–90.
11 Grana B, Burris H, Rodon J *et al.* Oral PI3 kinase inhibitor BKM120 monotherapy in patients (pts) with advanced solid tumors: an update on safety and efficacy. *J Clin Oncol* 2011; **29** (suppl; abstr 3043).
12 Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med* 2008; **27**: 2420–39.
13 Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: Efficient dose escalation with overdose control. *Stat Med* 1998; **17**: 1103–20.
14 Von Hoff DD, LoRusso P, Tibes R *et al.* A first-in-human phase I study to evaluate the pan-PI3K inhibitor GDC-0941 administered QD or BID in patients with advanced solid tumors. *J Clin Oncol* 2010; **28** (suppl; abstr 2541).
15 Munster PN, van der Noll R, Voest EE *et al.* Phase I first-in-human study of the PI3 kinase inhibitor GSK2126458 (GSK458) in patients with advanced solid tumors (study P3K112826). *J Clin Oncol* 2011; **29** (suppl; abstr 3018).
16 Hong DS, Bowles DW, Falchook GS *et al.* A multicenter phase I trial of PX-866, an oral irreversible phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors. *Clin Cancer Res* 2012; **18**: 4173–82.
17 Japanese Health Authority, 2008. Manual for drug-induced liver injury by the Ministry of Health, Labour and Welfare (in Japanese). Available from URL: http://www.info.pmda.go.jp/juutoku/juutoku_index.html
18 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), 2009. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. Available from URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.
19 Shimizu T, Tolcher AW, Papadopoulos KP *et al.* The clinical effect of the dual-targeting strategy involving PI3K/AKT/mTOR and RAS/MEK/ERK pathways in patients with advanced cancer. *Clin Cancer Res* 2012; **18**: 2316–25.

20 Markman B, Tabernero J, Krop I *et al.* Phase I safety, pharmacokinetic, and pharmacodynamic study of the oral phosphatidylinositol-3-kinase and mTOR inhibitor BGT226 in patients with advanced solid tumors. *Ann Oncol* 2012; **23**: 2399–408.
21 Crouthamel MC, Kahana JA, Korenchuk S *et al.* Mechanism and management of AKT inhibitor-induced hyperglycemia. *Clin Cancer Res* 2009; **15**: 217–25.
22 Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: Insights into insulin action. *Nat Rev Mol Cell Biol* 2006; **7**: 85–96.
23 Knight ZA, Gonzalez B, Feldman ME *et al.* A pharmacological map of the PI3K family defines a role for p110alpha in insulin signaling. *Cell* 2006; **125**: 733–47.
24 Ready NE, Dudek AZ, Pang HH *et al.* Cisplatin, irinotecan, and bevacizumab for untreated extensive-stage small-cell lung cancer: CALGB 30306, a phase II study. *J Clin Oncol* 2011; **29**: 4436–41.
25 Pontes LB, Armentano DP, Soares A, Gansl RC. Fatal pneumonitis induced by oxaliplatin: description of three cases. *Case Rep Oncol* 2012; **5**: 104–9.
26 Fuse N, Doi , Ohtsu A, T, Ohtsu A *et al.* Feasibility of oxaliplatin and infusional fluorouracil/leucovorin (FOLFOX4) for Japanese patients with unresectable metastatic colorectal cancer. *Jpn J Clin Oncol* 2007; **37**: 434–9.
27 Nakagawa M, Hamada A, Yoshihara Y *et al.* A case of interstitial lung diseases in patient treated with oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX). *Gan To Kagaku Ryoho* 2011; **38**: 317–20.
28 Hardy R, Cummings C, Faulkner M, Obianyo I. Pneumocystis carinii pneumonia following 5-fluorouracil administration. *J Natl Med Assoc* 1987; **79**: 1205–9.
29 Fukuda M, Soda H, Fukuda M *et al.* Irinotecan and cisplatin with concurrent split-course radiotherapy in locally advanced non-small-cell lung cancer: a multi-institutional phase 2 study. *Cancer* 2007; **110**: 606–13.
30 Takeda K, Negoro S, Kudoh S *et al.* Phase I/II study of weekly irinotecan and concurrent radiation therapy for locally advanced non-small cell lung cancer. *Br J Cancer* 1999; **79**: 1462–7.
31 Chakravarthy AB, Tsai CJ, O'Brien N *et al.* A phase I study of cetuximab in combination with gemcitabine and radiation for locally advanced pancreatic cancer. *Gastrointest Cancer Res* 2012; **5**: 112–18.
32 Blumenschein GR Jr, Paulus R, Curran WJ *et al.* Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. *J Clin Oncol* 2011; **29**: 2312–18.
33 Duran I, Siu LL, Oza AM *et al.* Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *Eur J Cancer* 2006; **42**: 1875–80.
34 Maroto JP, Hudes G, Dutcher JP *et al.* Drug-related pneumonitis in patients with advanced renal cell carcinoma treated with temsirolimus. *J Clin Oncol* 2011; **29**: 1750–6.
35 Motzer RJ, Escudier B, Oudard S *et al.* Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. *Cancer* 2010; **116**: 4256–65.
36 White DA, Camus P, Endo M *et al.* Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. *Am J Respir Crit Care Med* 2010; **182**: 396–403.
37 Soria JC, Shepherd FA, Douillard JY *et al.* Efficacy of everolimus (RAD001) in patients with advanced NSCLC previously treated with chemotherapy alone or with chemotherapy and EGFR inhibitors. *Ann Oncol* 2009; **20**: 1674–81.
38 Iacovelli R, Palazzo A, Mezi S, Morano F, Naso G, Cortesi E. Incidence and risk of pulmonary toxicity in patients treated with mTOR inhibitors for malignancy. A meta-analysis of published trials. *Acta Oncol* 2012; **51**: 873–9.
39 Nanni P, Nicoletti G, Palladini A *et al.* Multiorgan metastasis of human HER-2(+) breast cancer in Rag2(−/−);Il2rg(−/−) mice and treatment with PI3K inhibitor. *PLoS ONE* 2012; **7**: e39626.
40 Maira M, Schnell C, Lollini P *et al.* Preclinical and preliminary clinical activity of NVP-BKM120, an oral pan-class I PI3K inhibitor, in the brain. *Ann Oncol* 2012; **23** (suppl; abstr 1675).
41 Beaulieu JM, Sotnikova TD, Marion S, Lefkowitz RJ, Gainetdinov RR, Caron MG. An Akt/beta-arrestin 2/PP2A signaling complex mediates dopaminergic neurotransmission and behavior. *Cell* 2005; **122**: 261–73.
42 Beaulieu JM, Sotnikova TD, Yao WD *et al.* Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade. *Proc Natl Acad Sci USA* 2004; **101**: 5099–104.
43 Chen L, Han L, Shi Z *et al.* LY294002 enhances cytotoxicity of temozolomide in glioma by down-regulation of the PI3K/Akt pathway. *Mol Med Rep* 2012; **5**: 575–9.
44 Bychkov E, Ahmed MR, Dalby KN, Gurevich EV. Dopamine depletion and subsequent treatment with L-DOPA, but not the long-lived dopamine agonist pergolide, enhances activity of the Akt pathway in the rat striatum. *J Neurochem* 2007; **102**: 699–711.
45 Janku F, Tsimberidou AM, Garrido-Laguna I *et al.* PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. *Mol Cancer Ther* 2011; **10**: 558–65.
46 Janku F, Wheler JJ, Westin SN *et al.* PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. *J Clin Oncol* 2012; **30**: 777–82.
47 Juric D, Baselga J. Tumor genetic testing for patient selection in phase I clinical trials: The case of PI3K inhibitors. *J Clin Oncol* 2012; **30**: 765–6.
48 Ihle NT, Lemos R Jr, Wipf P *et al.* Mutations in the phosphatidylinositol-3-kinase pathway predict for antitumor activity of the inhibitor PX-866 whereas oncogenic Ras is a dominant predictor for resistance. *Cancer Res* 2009; **69**: 143–50.
49 O'Brien C, Wallin JJ, Sampath D *et al.* Predictive biomarkers of sensitivity to the phosphatidylinositol 3' kinase inhibitor GDC-0941 in breast cancer preclinical models. *Clin Cancer Res* 2010; **16**: 3670–83.
50 Gonzalez-Angulo AM, Blumenschein GR Jr. Defining biomarkers to predict sensitivity to PI3K/Akt/mTOR pathway inhibitors in breast cancer. *Cancer Treat Rev* 2012; **39**: 313–20.

Supporting Information

Additional supporting information may be found in the online version of this article:

Fig. S1. Best percentage change from baseline in target lesions according to dose of buparlisib and radiologic response.

Fig. S2. Mean buparlisib plasma concentration profile on (A) Cycle 1 Day 1; (B) Cycle 1 Day 8; and (C) Cycle 1 Day 28 (pharmacokinetics analysis set).

Table S1. Criteria for dose-limiting toxicities.

Table S2. Criteria for grading non-CTCAE adverse events.

Data S1. Information on pharmacodynamic analyses.

Invest New Drugs (2014) 32:261–270
DOI 10.1007/s10637-013-9948-5

PHASE I STUDIES

Phase I study of sunitinib plus S-1 and cisplatin in Japanese patients with advanced or metastatic gastric cancer

Narikazu Boku · Kei Muro · Nozomu Machida · Satoshi Hashigaki · Nobuyuki Kimura · Mie Suzuki · Mariajose Lechuga · Yoshinori Miyata

Received: 28 November 2012 / Accepted: 1 March 2013 / Published online: 12 May 2013

Summary *Background* This phase I, dose-finding study evaluated the maximum tolerated dose (MTD), safety, pharmacokinetics, and antitumor activity of sunitinib plus S-1/cisplatin in Japanese patients with advanced/metastatic gastric cancer. *Patients and methods* Patients received oral sunitinib on a continuous daily dosing (CDD) or 2-weeks-on/2-weeks-off schedule (Schedule 2/2; 25 mg/day or 37.5 mg/day), plus S-1 (80–120 mg/day)/cisplatin 60 mg/m^2. *Results* Twenty-seven patients received treatment, including 26 patients treated per protocol (sunitinib 25 mg/day CDD schedule, $n=4$; sunitinib 25 mg/day Schedule 2/2, $n=16$ [dose-limiting toxicity (DLT) cohort, $n=6$ plus expansion cohort, $n=10$]; sunitinib 37.5 mg/day Schedule 2/2, $n=6$). One patient erroneously self-administered sunitinib 12.5 mg/day and was excluded from the analyses. The MTD was sunitinib 25 mg/day on Schedule 2/2. DLTs were reported for: 2/4 patients given sunitinib 25 mg/day on the CDD schedule; 1/6 patients administered sunitinib 25 mg/day on Schedule 2/2 (grade [G] 3 neutropenic infection, G4 thrombocytopenia, and S-1 dose interruption ≥5 days), and 3/6 patients given sunitinib 37.5 mg/day on Schedule 2/2. Results below are for the overall MTD cohort ($n=16$). The most frequently reported G3/4 adverse events were neutropenia (93.8 %) and leukopenia (75.0 %). The objective response rate was 37.5 %; six additional patients experienced no disease progression for ≥24 weeks. Median progression-free survival was 12.5 months. No pharmacokinetic drug–drug interactions were observed between sunitinib/S-1/cisplatin and S-1/cisplatin. *Conclusions* The MTD of sunitinib was 25 mg/day on Schedule 2/2 combined with cisplatin/S-1 in patients with advanced/metastatic gastric cancer. This regimen had a manageable safety profile and preliminary antitumor activity.

Keywords Sunitinib · Gastric cancer · Phase I · Dose-finding

Presented in part on the clinical trial registry located at ClinicalTrials.gov (identification No. NCT00553696) and at:

N. Boku (✉)
Department of Clinical Oncology, St. Marianna University School of Medicine, 2-16-1, Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan
e-mail: n.boku@marianna-u.ac.jp

K. Muro
Department of Clinical Oncology, Aichi Cancer Center, Nagoya, Japan

N. Machida
Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan

S. Hashigaki
Clinical Statistics, Pfizer Japan, Tokyo, Japan

N. Kimura
Clinical Pharmacology, Pfizer Japan, Tokyo, Japan

M. Suzuki
Clinical Research, Pfizer Japan, Tokyo, Japan

M. Lechuga
Pfizer Oncology, Pfizer Italia Srl, Latina, Italy

Y. Miyata
Department of Oncology, Saku Central Hospital, Saku, Japan

Introduction

Gastric cancer is the second most common cause of cancer-related death worldwide, with more than 730,000 deaths estimated to have occurred in 2008 [1]. Globally, the

5-year survival rate for gastric cancer is approximately 20 % [2], and most patients present with advanced, non-resectable disease [3–5].

Despite recent advances in the treatment for gastric cancer [6], a standard chemotherapy regimen has not been established for recurrent or unresectable advanced gastric cancer; combination chemotherapy is associated with significant survival and quality of life advantages, compared with best supportive care [7, 8]. The use of a 5-fluorouracil (5-FU)-based regimen in combination with a platinum analog is the most widely accepted first-line treatment regimen, although combination therapy does have a higher associated toxicity burden compared with single-agent chemotherapy [8].

Blockade of receptors such as vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) has been shown to inhibit tumor-related angiogenesis and tumor growth [9, 10]. Not only are these receptors expressed in gastric cancers but they are known to have direct effects on the growth and metastasis of this disease [9–14].

Sunitinib malate (SUTENT®; Pfizer Inc., New York, NY, USA) is an oral, multitargeted, tyrosine kinase inhibitor of VEGFRs 1–3, PDGFR-α and -β, and other receptors [15–17]. Sunitinib is approved multinationally for the treatment of unresectable and/or metastatic imatinib-resistant/-intolerant gastrointestinal stromal tumor, advanced/metastatic renal cell carcinoma, and unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors. Phase II study results in advanced gastric cancer have shown that sunitinib had activity as a single-agent; progression-free survival (PFS) was 2.3 months and overall survival was 6.8 months in the second-line setting [18].

In preclinical tumor models, sunitinib has been shown to enhance the antitumor activity of 5-FU and cisplatin, suggesting that sunitinib might enhance the effect of chemotherapy in cancer patients [19, 20]. In the First-Line Advanced Gastric Cancer Study (FLAGS), the combination of S-1, an oral derivative of 5-FU, and cisplatin was found to be effective when administered as a 3-week on/1-week off regimen (Schedule 3/1) [21]. Therefore, this phase I, dose-finding study was conducted to determine the maximum tolerated dose (MTD) and overall safety profile of sunitinib plus S-1 and cisplatin in Japanese patients with advanced/metastatic gastric cancer. Tolerability, pharmacokinetics (PK), and antitumor activity were also evaluated.

Materials and methods

Study population

Patients (male or female) eligible for inclusion in this study were aged ≥20 years, had an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ function, and histologically or cytologically confirmed Stage IV gastric adenocarcinoma or gastroesophageal junction adenocarcinoma not amenable to surgery or radiation. Prior adjuvant therapy was permitted with a recurrence-free interval of >3 months after the completion of adjuvant therapy. Prior chemotherapy in the advanced/metastatic setting was not permitted; one regimen of chemotherapy, such as S-1 monotherapy, without progressive disease was allowed if the duration of treatment was less than 4 weeks.

Exclusion criteria included central nervous system (CNS) metastases, carcinomatous meningitis, or uncontrolled hypertension (blood pressure >150/100 mmHg). Patients with severe/unstable angina, myocardial infarction, coronary artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, including transient ischemic attack, or pulmonary embolism within 12 months prior to starting study treatment were also excluded.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the declaration of Helsinki, and applicable local regulatory requirements and laws. Approval from the institutional review board or independent ethics committee with the appropriate jurisdiction was required for each participating investigator/center. Written informed consent was obtained from all patients.

Study design

This was a phase I, open-label, dose-finding study of sunitinib in combination with S-1 and cisplatin in patients with advanced/metastatic gastric cancer (NCT00553696). Patients received open-label, oral S-1 at a starting dose of 80–120 mg/day (based on body surface area) on Schedule 3/1 and a cisplatin 60 mg/m^2 infusion on day 1 that was repeated every 28 days. Patients were allocated to different doses of oral sunitinib based on a 3+3 design. Initially, sunitinib was planned to be administered on a continuous daily dosing (CDD) schedule or on Schedule 3/1. After four patients received treatment in the CDD arm, the protocol was revised to use a 2-week-on/2-week-off schedule (Schedule 2/2), instead of Schedule 3/1, due to the pattern of adverse events (AEs). Patients received sunitinib 25 mg/day on a CDD schedule, or 25 mg/day or 37.5 mg/day on Schedule 2/2 in 4-week cycles (Fig. 1).

Initially, three patients were enrolled to receive sunitinib 25 mg/day on the CDD schedule in combination with S-1 and cisplatin 60 mg/m^2. If no patients experienced a dose-limiting toxicity (DLT) in cycle 1 then patients would be enrolled to the next highest dose level. If no more than one of the initial three patients experienced a DLT within cycle 1, then the cohort was expanded to a total of six patients. If no more than one of these six patients experienced a DLT,