Phase I Study of Efatutazone, an Oral PPARγ Agonist, in Patients with Metastatic Solid Tumors

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Abstract. *Background: Efatutazone is a highly selective agonist of peroxisome proliferator-activated receptor gamma (PPARγ), a therapeutic target for carcinogenesis. Patients and Methods: In this phase I dose-escalation study, we assessed the safety, efficacy, and pharmacokinetics of efatutazone and the recommended dose (RD) was determined in Japanese patients with metastatic solid tumors using a 3+3 design. Results: A total of 13 patients were enrolled and received efatutazone at doses of 0.25 mg, 0.50 mg, and 0.75 mg bid for multiple 3-week cycles. No dose-limiting toxicities were observed, and the maximum tolerated dose was not reached. Partial response was confirmed in one patient and stable disease in three. Efatutazone exposure was almost dose-proportional. RD was determined to be 0.50 mg bid, corresponding to the RD in previous global phase I studies. Conclusion: Efatutazone demonstrated acceptable toxicity and gave evidence of disease control in Japanese patients with metastatic solid tumors.*

Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors and plays an important role in the regulation of inflammation, differentiation, cell cycle, apoptosis, carcinogenesis, and angiogenesis (1-5). There is extensive pre-clinical evidence for the antitumor activity of PPARγ ligands in multiple cancer models (6-9). However, exploratory efficacy results of early-phase clinical trials of PPARγ ligand monotherapy showed only a modest success rate in patients with advanced solid tumors (10-13). Recent pre-clinical studies in transplantable and chemically-induced spontaneous tumor models indicated the potential clinical efficacy of PPARγ ligands for cancer prevention and therapy when combined with other chemotherapeutic agents (2, 5, 14, 15). Several early-phase clinical trials on the safety and efficacy of PPARγ ligands combined with existing chemotherapeutic agents also demonstrated a favorable safety profile, tolerability, and clinical benefit in patients with advanced solid malignancies and no curative therapeutic options (16, 17).

Efatutazone is an oral, highly selective PPARγ agonist of the thiazolidinedione class and is more effective than second-generation thiazolidinediones such as pioglitazone and rosiglitazone (18). In pre-clinical tumor models, efatutazone inhibited proliferation of human anaplastic thyroid and pancreatic tumor cell lines *in vitro* and human colorectal and anaplastic thyroid tumor cell xenografts in nude rodents *in vivo* (19-21).

In a phase I study in patients with advanced solid tumors, efatutazone demonstrated acceptable safety, tolerability, and disease control at doses of 0.10-1.15 mg *bis in die (bid)* (22). Recently, another phase I clinical trial of efatutazone combined with paclitaxel in patients with advanced anaplastic thyroid cancer also showed a similar favorable safety profile, disease control, and disease stabilization (23).

These positive preliminary results of previous phase I studies of efatutazone and its distinct property as a highly selective PPARγ activator provide the rationale for use of efatutazone, alone or combined with other chemotherapeutic agents, as a novel intervention for the prevention and treatment of advanced malignancies, including metastatic solid tumors. This may also provide useful insight into the clinical implication of selective PPARγ activation in the control of carcinogenesis.

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This phase I dose-escalation study was designed to evaluate the safety and pharmacokinetics of efatutazone in Japanese patients with metastatic solid tumors without available standard treatment. The secondary objectives of this study were to assess the preliminary antitumor effect of efatutazone, to explore potential biomarkers of pharmacological activity, such as plasma adiponectin (24), and to determine the recommended dose (RD) for phase II studies in this patient population.

Patients and Methods

Study design. This phase I, single-center, open-label, dose-escalation study was conducted at the Shizuoka Cancer Center, Japan between February 2010 and September 2012 in accordance with the International Conference on Harmonisation, Good Clinical Practice Guidelines, the principles of the Declaration of Helsinki, and all applicable laws and regulations. The protocol was reviewed and approved by the Institutional Review Board of Shizuoka Cancer Center (approval number: 21-87). All patients provided written informed consent before enrollment.

In this dose-finding study using a 3+3 design, each patient was enrolled in only one dose group; efatutazone was administered at doses of 0.25 mg, 0.50 mg, or 0.75 mg *bid* for multiple 3-week cycles. If one of the first three patients at any dose level experienced a dose-limiting toxicity (DLT) during the first 3-week cycle (cycle 1), three more patients were enrolled. If there were no DLTs in a 3-patient cohort or if there was fever than one DLT in a 6-patient cohort, the study proceeded to the next dose level. After determining the phase II RD on the basis of the safety and tolerability data during cycle 1, an additional three patients were enrolled to evaluate the safety and pharmacokinetics of efatutazone at the RD. Efatutazone administration continued until disease progression, unacceptable toxicity, or dose delay of three weeks or more; the treatment could also be terminated if the patient or investigator requested it.

Study population. Male and female patients who met the following inclusion criteria were enrolled: Age 20 to 75 years; histologically/cytologically-confirmed metastatic solid tumor without standard treatment available; Eastern Cooperative Oncology Group (ECOG) performance status of ≤1; adequate organ and bone marrow functions documented within seven days before enrollment and no blood transfusion within one month prior to enrollment; life expectancy of at least three months; resolution of any toxicity and absence of prior therapy for grade 2 or more events as per version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (25) (excluding alopecia, grade-1 skin disorder, neuropathy, and fatigue).

Exclusion criteria included pre-existing severe fluid retention (edema, pleural, or pericardial effusion); a complication or medical history (within six months before enrollment) of heart failure (New York Heart Association functional ≥class I), myocardial infarction, stroke, severe/unstable angina pectoris, coronary/peripheral artery bypass surgery, cerebrovascular disease, pulmonary thrombosis, deep vein thrombosis, or other clinically significant thromboembolic events or pulmonary disease; clinically significant infection requiring systemic administration of antibiotics; clinically active brain metastasis; chronic diarrhea, inflammatory bowel disease, or partial bowel obstruction.

Safety assessment. Safety assessments were performed at each weekly visit and included vital signs, adverse events (AEs), ECOG performance status, and laboratory test results. Patients were evaluated for efatutazone-related DLTs during cycle 1. DLTs were defined as follows: (a) grade 3 or more neutropenia complicated by fever 38.5°C or higher, or infection, or grade 4 neutropenia lasting seven days or more; (b) grade 4 thrombocytopenia or grade 3 thrombocytopenia requiring transfusion; (c) grade 4 anemia; (d) grade 3 or more pleural or pericardial effusion, peripheral edema, or ascites unresponsive to treatment; (e) grade 3 or more uncontrollable severe fatigue, anorexia, nausea, vomiting, or diarrhea, despite maximal supportive therapy; (f) any other toxicity grade 3 or more other than those described in definitions (d) and (e). However, fever without neutropenia and transient electrolyte abnormalities were not recognized as DLTs. AEs and laboratory test results were graded according to NCI-CTCAE, version 3.0 (25).

Efficacy assessment. Efficacy assessment was performed on the basis of the change from baseline in tumor measurements evaluated using serial radiographs obtained every six weeks. The best overall response was assessed by the investigator on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.1 (26); the overall response rate [ORR: complete response (CR) + partial response (PR)], and disease control rate [DCR: CR + PR + stable disease (SD)] were calculated.

Pharmacokinetics. Blood samples were collected on day 1 (cycle 1) and day 22 (cycle 2) at the following time points: before the dose (*i.e.* 5 min before the morning dose of efatutazone) and at 0.5, 1, 2, 3, 4, 6, and 8 to 10 h after the dose. Additional samples were collected on days 8 and 15 before the dose (cycle 1). The plasma concentrations of the free form of efatutazone were measured by validated liquid chromatography–tandem mass spectrometry (22).

Biomarkers. Blood samples for the measurement of plasma adiponectin levels were collected on pre-dose day 1 (baseline), at weekly intervals during the first six weeks (cycles 1 and 2), and at the end of the treatment. Plasma adiponectin levels were determined by a validated quantitative sandwich enzyme immunoassay kit (Quantikine®; R&D systems, Inc., Minneapolis, MN, USA) method. The PPARγ assays was developed using a PPARγ-specific rabit monoclonal antibody (Cell Signaling Technology, Inc.) using the ultraVIEW Universal DAB detection kit (Roche Diagnostics). The verification of staining performance was confirmed with multiple organ cancer tissue array. Staining for each biomarker was described as strong (3+), moderate (2+), weak (1+), or absent (0), and the percentage of positively-stained tumor cells was also reported.

Results

Patients' demographics. A total of 13 patients were enrolled and efatutazone was administered *bid* at doses of 0.25 mg [number of patients studied (n)=4], 0.50 mg (n=6), and 0.75 mg (n=3). During the first 3-week cycle, rapid exacerbation of the primary disease was observed in one patient in the 0.25 mg-*bid* cohort, which led to efatutazone dose interruption and discontinuation because of confirmed disease progression before initiation of the second cycle. Therefore, an additional patient was enrolled in the 0.25-mg *bid* cohort. After RD

Table I. *Baseline characteristics (safety population).*

Characteristic	Efatutazone dose (bid)			
	0.25 mg N=4	0.50 mg N=6	0.75 mg N=3	Overall N=13
Mean (SD) age, years	67.5 (7.77)	59.5 (7.23)	64.3 (9.02)	63.1 (7.98)
Gender, n (%)				
Male	3 (75.0)	3 (50.0)	2 (66.7)	8 (61.5)
Female	1 (25.0)	3 (50.0)	1 (33.3)	5 (38.5)
Mean (SD) body weight, kg	55.68 (13.474)	61.83 (16.862)	47.87 (4.131)	56.72 (14.132)
Type of cancer, n (%)				
NSCLC	0	3 (50.0)	1 (33.3)	4 (30.8)
Esophageal cancer	1 (25.0)	1 (16.7)	1 (33.3)	3 (23.1)
Bladder cancer	0	0	1 (33.3)	1 (7.7)
GIST	1 (25.0)	0	0	1 (7.7)
Hypopharyngeal cancer	0	1 (16.7)	0	1 (7.7)
MPM	1 (25.0)	0	0	1 (7.7)
PC	1 (25.0)	0	0	1 (7.7)
Thymic cancer	0	1 (16.7)	0	1 (7.7)
ECOG PS, n (%)				
0	3 (75.0)	2 (33.3)	1 (33.3)	6 (46.2)
1	1 (25.0)	4 (66.7)	2 (66.7)	7 (53.8)
Prior therapy, n (%)				
Chemotherapy	4 (100)	6 (100)	3 (100)	13 (100)
Radiotherapy	1 (25.0)	4 (66.7)	1 (33.3)	6 (46.2)
Surgery	1 (25.0)	3 (50.0)	2 (66.7)	6 (46.2)
Other	0	0	0	0

ECOG PS, Eastern Cooperative Oncology Group performance status; GIST: gastrointestinal stromal tumor; MPM: malignant pleural mesothelioma; N, total number of patients studied; n, number of patients; NSCLC, non-small cell lung cancer; PC: pancreatic islet cell carcinoma; SD: standard deviation.

determination, three more patients were enrolled and received oral efatutazone at a dose of 0.50 mg *bid*.

The baseline patient characteristics of the overall study population are summarized in Table I. Eight males (61.5%) and five females (38.5%) were recruited, with a median age (range) of 62.0 (45-73) years. The most common types of cancer were non-small cell lung cancer (NSCLC) (n=4) and esophageal cancer (n=3). Seven out of the 13 patients had an ECOG performance status of 1, and all patients had received prior chemotherapy.

The median (range) of efatutazone treatment duration was 50.0 (21-170) days in the 0.25 mg *bid* cohort, 44.5 (42-468) days in the 0.50 mg *bid* cohort, 44.0 (41-45) days in the 0.75 mg *bid* cohort, and 44.0 (21-468) days for the overall study population.

Safety. Overall, efatutazone was well-tolerated at doses of 0.25-0.75 mg *bid*. During the DLT evaluation period (cycle 1), no DLTs were observed and the maximum tolerated dose (MTD) was not reached. On the basis of pharmacokinetics and safety profile, 0.50 mg *bid* was selected as the phase II RD for Japanese patients with metastatic solid tumors.

Table II summarizes treatment-emergent AEs that occurred throughout the study period. Most patients experienced fluid retention-related weight gain (84.6%; 11/13) and edema (84.6%; 11/13), which were manageable with diuretics and a modification of efatutazone treatment (dose interruption or reduction). Four (30.8%) patients experienced at least one serious AE (cholestatic jaundice, delirium, hemobilia, intestinal obstruction, edema, pneumonia, pneumonia aspiration, fever, and weight gain), which recovered or resolved with supportive therapy and efatutazone interruption/reduction. No AEs led to discontinuation. Grade 3 or more AEs occurred in five (38.5%) patients (pneumonia, pneumonia aspiration, abnormal hepatic function, hemobilia, cholestatic jaundice, edema, anemia, and hyponatremia) and were managed with supportive therapy or efatutazone interruption.

The most common efatutazone-related AEs were edema and weight gain (11 patients each; 84.6%); malaise (7; 53.8%); followed by anemia, hypoalbuminemia, and anorexia (6 patients each; 46.2%); increased plasma creatinine levels (5 patients; 38.5%); and neutropenia (4; 30.8%). There were no discontinuations because of drug-related AEs. One patient in the 0.25 mg-*bid* cohort experienced serious efatutazone-related AEs (grade 2 edema

Table II. *Summary of treatment-emergent adverse events (AE) throughout the study (safety population).*

	Overall n=13
Patients with at least 1 AE	13 (100)
At least 1 serious AE	4 (30.8)
At least 1 AE leading to discontinuation	0
At least 1 grade 3 or more AE	5 (38.5)
Patients with at least 1 efatutazone-related AE	13 (100)
At least 1 efatutazone-related serious AE	1 (7.7)
At least 1 efatutazone-related grade 3 or more AE	3 (23.1)
AEs occurring in 3 or more patients; MedDRA, preferred terms	
Edema	11 (84.6)
Weight gain	11 (84.6)
Anemia	7 (53.8)
Increased plasma creatinine levels	7 (53.8)
Hypoalbuminemia	7 (53.8)
Malaise	7 (53.8)
Anorexia	6 (46.2)
Neutropenia	5 (38.5)
Constipation	4 (30.8)
Nausea	4 (30.8)
Vomiting	4 (30.8)
Pleural effusion	3 (23.1)
Abnormal hepatic function	3 (23.1)
Fever	3 (23.1)
Hypercholesterolemia	3 (23.1)
Uremia	3 (23.1)
Increased low-density lipoprotein levels	3 (23.1)
Thrombocytopenia	3 (23.1)

Values represent the number (%) of patients. MedDRA, Medical dictionary for regulatory activities.

and weight gain), which resolved with supportive therapy and efatutazone interruption. Three grade 3 or more AEs related to efatutazone were observed in the 0.50 mg-*bid* cohort: grade 3 edema that occurred after the DLT evaluation period (day 27) was treated with diuretics and efatutazone dose interruption/reduction, and grade 3 hyponatremia resolved without intervention.

There were no clinically significant changes in vital signs, 12-lead electrocardiograms, or ECOG performance status during the study.

An increase in plasma creatinine levels was observed in seven (53.8%) patients, and five events were considered to be related to efatutazone. The plasma creatinine level increased in patients who had previously been treated with cisplatin, particularly when the cisplatin regimen immediately preceded the study, as shown in Figure 1.

Pharmacokinetics. Plasma concentration–time curves following oral efatutazone administration are shown in Figure 2 and Table III, respectively. Following a single-dose administration on day 1 (cycle 1), the mean plasma efatutazone concentration was lower in the 0.75 mg-*bid* cohort than in the 0.50 mg *bid* cohort. This unexpected lower plasma concentration at the higher dose would seem to be attributable to large interindividual variability among the measured values. Following repeated-dose administration on day 22 (cycle 2), increases in the plasma efatutazone concentration were almost dose-proportional. The trough plasma concentration did not increase with repeated doses.

Efficacy. All 13 patients were evaluable for efficacy analysis. A waterfall plot of the best percentage changes from baseline in the target lesion is shown in Figure 3. No patients showed CR. One patient with thymic carcinoma, received 0.50 mg *bid* and achieved confirmed PR, with 31% reduction in tumor size, and remained on treatment (duration=468 days). Three patients had SD: ore with pancreatic islet carcinoma on 0.25 mg *bid* (duration=170 days), one with malignant pleural mesothelioma on 0.25 mg *bid* (duration=84 days), and one with NSCLC on 0.50 mg *bid* (duration=123 days). For the 13 patients, the ORR was 7.7%, and the DCR was 30.8% (95% confidence interval=9.1-61.4%).

Biomarkers. On day 22 (cycle 2), the mean plasma adiponectin level increased approximately 9- to 11-fold above the baseline in the investigated dose range. The highest mean (standard deviation) change from baseline in plasma adiponectin levels was observed with 0.50 mg *bid* on day 22, compared to 0.25 mg *bid* and 0.75 mg *bid* [110.83 (63.164) μg/ml *versus* 69.55 (16.891) and 98.30 (19.173) μg/ml]. The increase in plasma adiponectin levels appeared to plateau at a dose of 0.50 mg efatutazone bid.

There were no apparent differences in the expression levels of PPARγ in the archived tumor specimens between patients with PR or SD and those with progressive disease (PD) (data not shown).

Discussion

In this phase I dose-escalation study, the safety and pharmacokinetics of efatutazone at doses of 0.25-0.75 mg *bid* were evaluated in Japanese patients with metastatic solid tumors without available standard treatment. No DLTs were observed and MTD was not reached. On the basis of population pharmacokinetic and safety analyses, 0.50 mg bid, corresponding to the global RD, was selected as the phase II RD in Japanese patients with metastatic solid tumors (22, 23).

Efatutazone at doses of 0.25-0.75 mg *bid* had an acceptable toxicity profile. Most patients experienced fluid retention-related weight gain and edema [84.6% (11/13) each], known side-effects of thiazolidinedione PPARγ agonists, and were treated with diuretics and efatutazone dose interruption/reduction. No AEs led to discontinuation.

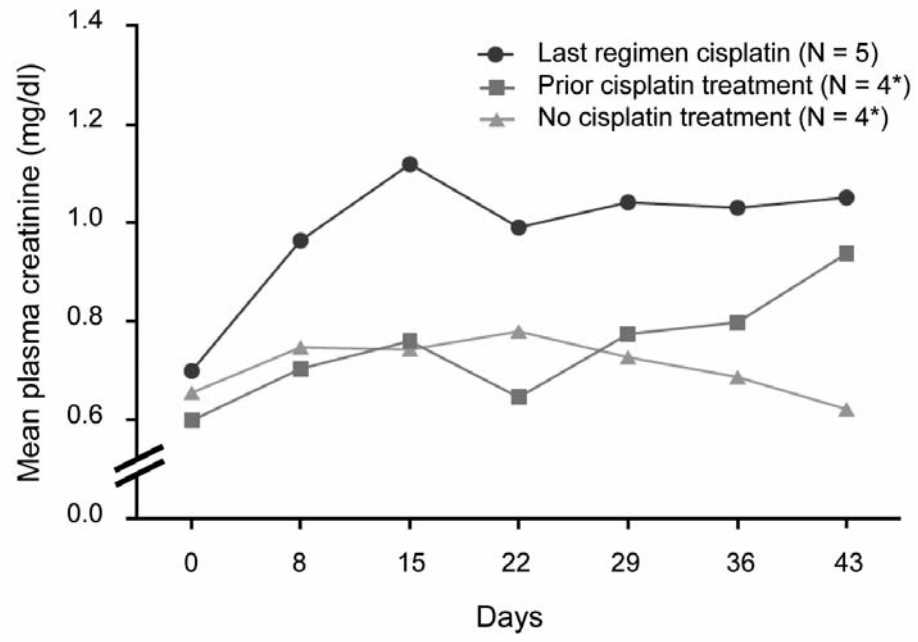

Figure 1. *On-study plasma creatinine levels by prior cisplatin treatment (safety analysis set). Number of patients studied. *N=3 in days 29, 36 and 43.*

Table III. *Summary of pharmacokinetic parameters for efatutazone.*

Parameter	Dose (bid)					
	0.25 mg		0.50 mg		0.75 mg	
	Day 1† (n=4)	Day 22‡ (n=3)	Day 1† (n=6)	Day 22‡ (n=6)	Day 1† (n=3)	Day 22‡ (n=3)
AUC_{last} (ng h/ml)	68.722 (44.428)	153.694 (57.016)	204.099 (94.164)	288.879 (128.551)	177.943 (48.121)	459.493 (122.883)
AUC_{tau}§ (ng h/ml)	96.817 (44.575)	181.943 (61.464)	262.027 (108.716)	348.230 (171.993)	217.845 (60.627)	565.425 (149.097)
C_{max} (ng/ml)	12.143 (7.088)	19.467 (6.104)	28.600 (10.494)	36.467 (15.567)	26.100 (6.322)	57.633 (11.910)
C_{trough} (ng/ml)	–	10.453 (2.409)	–	22.517 (10.739)	–	33.500 (6.180)
T_{max} (h)	3.06 (3.0–10.0)	3.02 (3.0-4.0)	3.49 (1.0-6.0)	2.98 (2.0-6.0)	3.00 (3.0-4.0)	2.87 (2.0-3.0)

†Following single-dose administration on day 1 (cycle 1). ‡Following repeated-dose administration on day 22 (cycle 2). §N=3 for day 1 in the 0.25 mg cohort; n=5 for day 1 in the 0.50 mg cohort; and n=5 for day 22 in the 0.50 mg cohort. For AUC_{last}, AUC_{tau}, C_{max}, and C_{trough}, values represent the means (standard deviation). For T_{max}, values represent the median (range) AUClast, area under the plasma concentration–time curve up to the last quantifiable time; AUC_{tau}, area under the concentration–time curve during dosing interval; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; N, number of patients studied; T_{max}, time to reach the maximum plasma concentration.

Common efatutazone-related AEs were edema and weight gain [11 (84.6%) patients each], followed by anemia, hypoalbuminemia, anorexia, malaise, and increased plasma creatinine levels. Two serious AEs related to efatutazone (grade 2 edema and weight gain) were observed in one patient in the 0.25 mg-*bid* cohort, but the symptoms resolved with diuretics and efatutazone dose interruption. Three AEs of grade 3 or more related to efatutazone occurred in three patients who received 0.50 mg *bid*, but resolved with supportive therapy and efatutazone dose interruption/reduction, or without intervention. Safety and tolerability in this study are consistent with those in previous phase I studies (22, 23). However, in this study, increased plasma creatinine levels were seen in patients with prior cisplatin treatment, particularly when the cisplatin regimen immediately preceded the study, indicating a possible association between increased plasma creatinine level and prior cisplatin treatment. In the previous phase I studies, most patients did not undergo cisplatin treatment, which is known to cause kidney failure. Therefore, the contribution of an increased plasma creatinine level to the clinical outcome in this patient population has to be further examined.

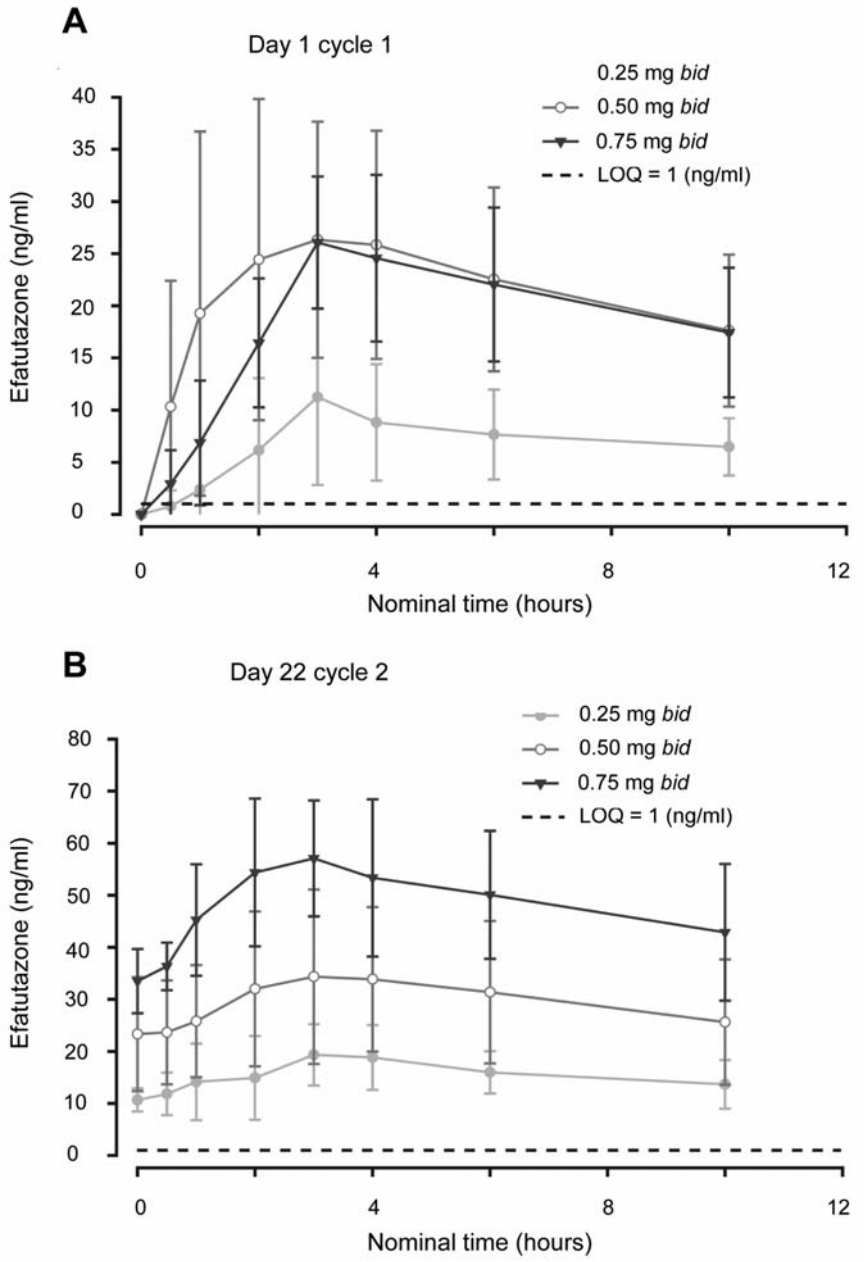

Figure 2. *Concentration–time curves of the free form of efatutazone following oral dosing on day 1 (cycle 1) (A) and day 22 (cycle 2) (B) (safety analysis set). Data are the mean±standard deviation. LOQ, Limit of quantitation.*

Pharmacokinetic analysis indicated dose-proportional exposure to efatutazone. Following single-dose administration, the plasma concentration, C_{max} and AUC_{tau} were lower in the 0.75 mg-*bid* cohort than in the 0.50 mg-*bid* cohort, apparently because of a large interindividual variability. Following repeated-dose administration, increases in the mean steady-state plasma concentrations, C_{max}, and AUC_{tau} were almost dose-proportional. Pharmacokinetic values recorded in the present study were similar to those reported in previous U.S. and Japanese phase I trials (22, 23).

Exploratory efficacy data of the 13 evaluable patients showed no CR, but one patient with thymic carcinoma who received 0.50 mg *bid* achieved PR (treatment duration: 468 days). Three patients had SD: one with pancreatic islet carcinoma on 0.25 mg *bid* (duration: 170 days), one with malignant pleural mesothelioma on 0.25 mg *bid* (duration: 84 days), and one with NSCLC on 0.50 mg *bid* (duration: 123 days).

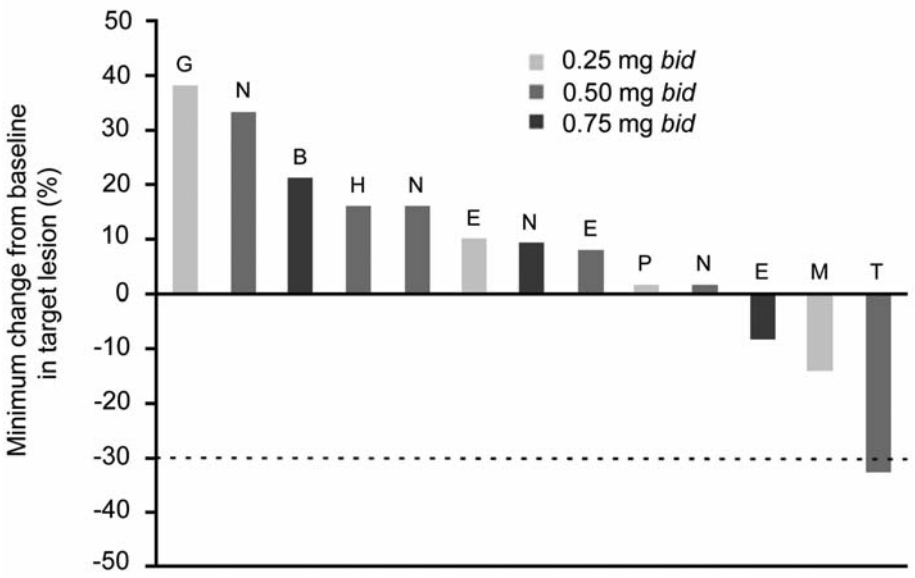

Figure 3. *Waterfall plot of the best percentage change from baseline in the target lesion (efficacy analysis set). Best percentage change from baseline in the target lesion=[(the minimum sum of the longest diameters at all measurement time points–the sum of the longest diameters at baseline)/(the sum of the longest diameters at baseline)] ×100. bid, Twice daily; PD, partial disease; PR, partial response; SD, stable disease.; G, Gastrointestinal stromal tumor; E, Esophageal cancer; N, Non-small cell lung cancer; P, Pancreatic islet cell carcinoma; B, Bladder cancer; M, Malignant pleural mesothelioma; H, Hypopharyngeal cancer; T, Thymic carcinoma.*

Among 27 patients, in a phase I trial of efatutazone for advanced malignancies, including progressive or metastatic solid tumors, one patient achieved PR, and 10 patients had SD (duration: 60 days or longer) (22). The present preliminary efficacy data are similar to those of the previous phase I studies, suggesting positive results for the clinical efficacy of efatutazone for monotherapy.

In particular, in this study, the patient achieving PR had thymic carcinoma. Advanced thymic carcinoma is a rare disease, and no standard chemotherapy has yet been established for it. Glucocorticoid receptor (GR) expression is associated with a better prognosis for thymic carcinoma (27). PPARγ is a nuclear hormone receptor, a key regulator of cellular metabolism, and a therapeutic target in carcinogenesis. PPARγ agonists are also partial agonists of GR (28, 29). This partial agonistic effect on GR may have generated tumor regression in this patient, but this option has to be further examined.

In a recent multi-national, randomized, comparative phase II study of efatutazone combined with carboplatin and paclitaxel as first-line therapy for metastatic NSCLC, efatutazone led to a significantly lower rate of and shorter progression-free survival compared to placebo, but there were no differences in overall survival (30); therefore, efatutazone does not improve the efficacy of carboplatin/paclitaxel as first-line therapy in unselected patients with NSCLC.

With regard to the clinical efficacy of other PPARγ ligands, in a phase II clinical trial investigating the efficacy of pioglitazone combined with cyclooxygenase-2 inhibitors for recurrent high-grade gliomas, SD was observed in four (29%) out of 14 patients (16). A prospective phase II study of pioglitazone combined with etoricoxib, interferon-α, and metronomic capecitabine for metastatic renal cell carcinoma also showed response in 35% of patients (CR=9%, PR=27%) (17).

Although extensive evidence suggests that PPARγ activation by ligands exerts anti-tumorigenic effects on cancer progression, PPARγ activation may also have protumorigenic effects (1, 5, 31). PPARγ activation might be found to exert opposing effects on tumor progression when PPARγ-dependent (on-target antitumorigenic) and PPARγ-independent (off-target protumorigenic) pathways occur simultaneously in the tumor and in the microenvironment (1, 5, 31). A large-scale retrospective study of the influence of thiazolidinediones on cancer risk in diabetic patients showed that thiazolidinediones seemed to reduce the risk of lung cancer, indicating a beneficial chemopreventive effect (32). The use of novel third-generation PPARγ agonists with higher selectivity, *e.g.* efatutazone, may therefore provide more selective engagement of PPARγ-dependent anti-tumorigenic pathways, while minimizing adverse PPARγ-independent cardiotoxic or protumorigenic effects.

Adiponectin is secreted by adipocytes in response to PPARγ agonist-induced gene expression both *in vivo* and *in*

vitro, and it is considered a potential biomarker of the pharmacological activity of PPARγ ligands (24). In the present study, plasma adiponectin levels increased over time and reached a plateau with efatutazone at a dose of 0.50 mg *bid*. Similar dose-dependent increases in plasma adiponectin levels have been observed in previous phase I studies (22, 23). However, the contribution of an increase in adiponectin to the clinical outcome needs further evaluation.

Although a previous phase I trial showed significantly higher expression of PPARγ and retinoid X receptor (RXR) in archived tumor specimens of patients with PR or SD than in those of patients with PD (22), the present study did not show apparent differences in the expression of PPARγ between patients with PR or SD and those with PD. Therefore, the association between clinical outcome and the expression levels of PPARγ and RXR in tumor specimens needs to be studied further.

In conclusion, efatutazone at doses of 0.25-0.75 mg *bid* showed acceptable toxicity in Japanese patients with metastatic solid tumors. DLTs were not observed, and MTD was not reached. On the basis of population pharmacokinetic and safety analyses, 0.50 mg *bid* is appropriate as the phase II RD, corresponding to the global RD determined in previous phase II studies. Common AEs of efatutazone were fluid retention-related edema and weight gain, which were treated with diuretics and efatutazone dose interruption/reduction. Pharmacokinetic analysis indicated dose-proportional exposure to efatutazone. Among the 13 evaluable patients, one with thymic carcinoma achieved PR, and three patients had SD. Therefore, efatutazone showed limited toxicity, tolerability, disease control, and disease stabilization in Japanese patients with metastatic solid tumors.

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