

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

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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 p110 α 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 <i>n</i> = 3	50 mg/day <i>n</i> = 3	100 mg/day <i>n</i> = 9	All <i>n</i> = 15
Median age, years (range)	66 (44–67)	47 (22–66)	58 (35–71)	58 (22–71)
Sex, <i>n</i>				
Male	2	3	7	12
Female	1	0	2	3
ECOG performance status, <i>n</i>				
0	3	2	5	10
1	0	1	4	5
Prior antineoplastic regimens, <i>n</i>				
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, <i>n</i>				
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 tranquilizers; 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, <i>n</i> †	Buparlisib							
	25 mg /day <i>n</i> = 3		50 mg /day <i>n</i> = 3		100 mg /day <i>n</i> = 9		All <i>n</i> = 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

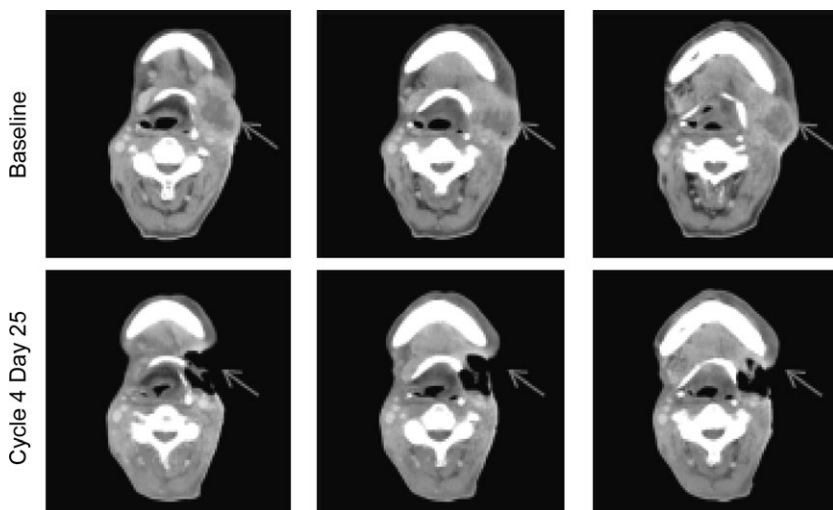


Fig. 1. Antitumor activity with buparlisib (100 mg/day) in a patient with head and neck squamous cell carcinoma and metastasis to the neck lymph node. A 58-year-old male patient experienced a 76% reduction in neck lesion size (from 59 mm at baseline to 14 mm in Cycle 4). As the second confirmation according 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 $\geq 10\ 000$ 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

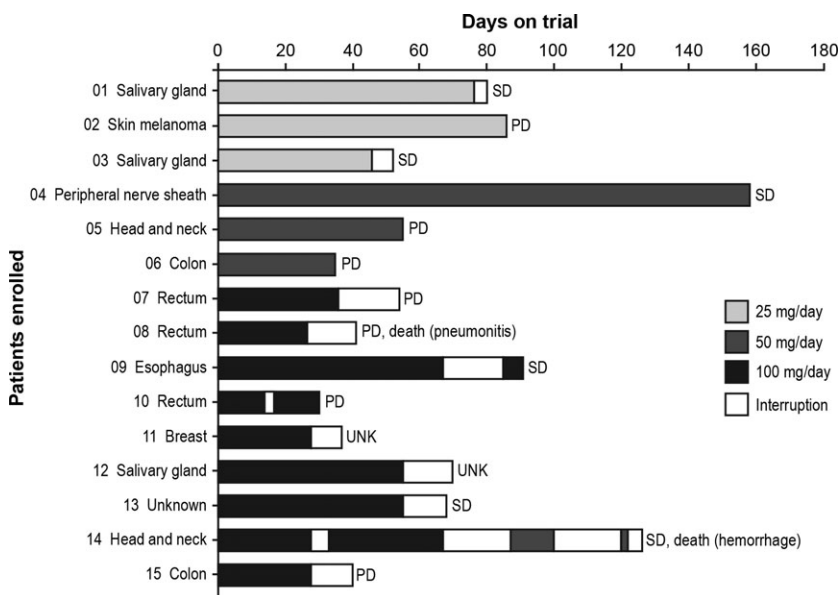


Fig. 2. Duration of buparlisib treatment according to dose and radiologic response. Study participants are shown according to primary tumor site, buparlisib dose, days on trial and tumor response according to Response Evaluation Criteria In Solid Tumors v1.0. PD, progressive disease; SD, stable disease;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

AUC₀₋₂₄, 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⁾ levo-folinate,⁽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 pre-clinical 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).

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Disclosure statement

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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.