Received: 23 August 2018 | Revised: 17 December 2018 | Accepted: 24 December 2018

DOI: 10.1111/cas.13923

ORIGINAL ARTICLE

WILEY Cancer Science

Phase I study of alpelisib (BYL719), an α-specific PI3K inhibitor, in Japanese patients with advanced solid tumors

Yuichi Ando[1] | Satoru Iwasa[2] | Shunji Takahashi[3] | Hideo Saka[4] | Tomoyuki Kakizume[5] | Kazuto Natsume[5] | Naoko Suenaga[5] | Cornelia Quadt[6] | Yasuhide Yamada[2]

[1]Nagoya University Hospital, Nagoya, Japan

[2]National Cancer Center Hospital, Tokyo, Japan

[3]The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

[4]Nagoya Medical Center, Nagoya, Japan

[5]Novartis Pharma K.K., Tokyo, Japan

[6]Novartis Pharmaceuticals AG, Basel, Switzerland

Correspondence
Yuichi Ando, Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Japan.
Email: yando@med.nagoya-u.ac.jp

Present addresses
Yasuhide Yamada, National Center for Global Health and Medicine, Tokyo, Japan

Yasuhide Yamada, Hamamatsu University School of Medicine, Shizuoka, Japan

Funding information
Novartis Pharmaceuticals Corporation

This phase I study aimed to determine tolerability and preliminary efficacy of single-agent alpelisib (BYL719) in Japanese patients with advanced solid malignancies. The primary objective of the study was to estimate the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of oral alpelisib in patients with advanced solid tumors who had progressed despite standard therapy. The expansion part included patients with *PIK3CA* mutation/amplification; safety, preliminary efficacy, pharmacokinetic (PK)/pharmacodynamic profile, and food effect on the PK profile of alpelisib at the MTD/RP2D were determined. Oral alpelisib was given as a single agent on a continuous 28-day treatment cycle once daily. Overall, 33 patients received alpelisib. Dose-limiting toxicities were observed in 2 patients in the escalation part (at 400 mg/day) and 1 patient in the expansion part (at 350 mg/day). The RP2D of alpelisib was determined as 350 mg/day based on overall safety profile in the dose escalation part and previous data from a Western population; the MTD was not determined. The most common all-grade treatment-suspected adverse events were hyperglycemia and maculopapular rash (48.5% each) and diarrhea (45.5%). The PK of alpelisib in the Japanese population was similar to that reported in the Western population. The overall response rate, disease control rate, and median progression-free survival at 350 mg/day were 3%, 57.6%, and 3.4 months, respectively. Alpelisib as single agent showed a favorable safety profile and encouraging preliminary efficacy in Japanese patients with advanced solid tumors.

KEYWORDS
alpelisib, BYL719, Japanese, *PIK3CA*, solid tumor

1 | INTRODUCTION

The phosphatidylinositol 3-kinase (PI3K)/AKT and mTOR pathways regulate several processes involved in cell survival, protein synthesis, cell proliferation and differentiation, metabolism, senescence, motility, and angiogenesis.[1] Several studies indicate that molecular alterations can occur at multiple levels in the PI3K/AKT/mTOR pathway, which include activating mutations and/or overexpression of receptor tyrosine kinases, activating mutations and/or amplifications of PI3Ks, and inactivating mutations or deletion of phosphatase and tensin homolog (PTEN).[2-4] Dysregulation of the PI3K signaling pathway has been implicated in tumorigenesis as well as resistance to anticancer therapies.[1] Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α

ClinicalTrials.gov number: CBYL719X1101/NCT01387321.

(*PIK3CA*) mutation and PTEN loss have been frequently reported in several solid tumors such as breast cancer (BC), non-small-cell lung cancer, glioblastoma multiforme, head and neck squamous cell carcinoma, and ovarian cancer.[5] Preclinical and emerging clinical data suggest that targeting the PI3K/AKT/mTOR pathway could improve outcomes by enhancing the treatment benefits of endocrine therapy (ET).[6]

Several PI3K inhibitors are currently being evaluated in clinical trials. Pan-Class I-PI3K inhibitors, which act by targeting all 4 class I PI3K isoforms, have shown modest clinical efficacy in clinical trials.[1,7] The toxicities associated with pan-PI3K inhibitors, such as buparlisib (BELLE-2 and BELLE-3 trials) and pictilisib (FERGI trial), limit the clinical utility of these agents. Hence, there is a need to explore more tolerable treatment options, such as isoform-selective PI3K inhibitors that target a specific PI3K isoform.[8] Phosphatidylinositol 3-kinase α (PI3Kα), which is the most frequently altered PI3K isoform in solid tumors, plays a prominent role in PI3K signaling. Thus, inhibitors that selectively target the PI3Kα isoform could provide an improved therapeutic window and minimize toxicities compared to pan-PI3K inhibitors.[1] However, the pharmacodynamics (PD) and pharmacokinetics (PK) of anticancer agents can vary based on the patient's ethnicity, possibly leading to varied safety and efficacy outcomes.[9] This necessitates evaluation of anticancer agents in specific ethnic populations.

Alpelisib is an oral selective inhibitor of the α-isoform of class I PI3K. Results from preclinical studies show that alpelisib inhibits PI3K signaling and prevents AKT phosphorylation in cell lines harboring *PIK3CA* mutations, and blocks tumor growth in xenograft models.[10] In a first-in-human (FIH) phase I study (CBYL719X2101/NCT01219699) in Western patients with advanced solid malignancies with *PIK3CA* alterations, alpelisib showed a tolerable safety profile and encouraging preliminary activity, supporting the rationale for selective PI3Kα inhibition in combination with other agents for the treatment of *PIK3CA*-mutant tumors.[11]

Preclinical and clinical studies among Japanese patients indicate that *PIK3CA* mutations is common in Japanese patients with advanced BC that is refractory to ET. The frequency of *PIK3CA* mutation in Japanese patients is similar to that of Caucasian patients. Thus, there is a need to evaluate the safety and efficacy of *PIK3CA* inhibitors in Japanese patients with advanced BC.[12]

Despite the encouraging clinical activity, especially in patients with estrogen receptor-positive (ER+) BC, the safety and tolerability of alpelisib in Japanese patients are unknown.[13] Here, we present the findings of a phase I trial to investigate the safety and tolerability and to determine the maximum tolerated dose (MTD) (and/or recommended phase II dose [RP2D]) of alpelisib in Japanese patients with advanced solid malignancies (CBYL719X1101/NCT01387321).

2 | MATERIALS AND METHODS

2.1 | Study design and treatment

This was a phase I, multicenter, open-label, dose-escalation study of single-agent alpelisib in Japanese patients, with an expansion part at the MTD/RP2D. The expansion part was designed to further evaluate the safety, preliminary efficacy, PK/PD profile, and food effect on the PK profile of alpelisib at the MTD/RP2D.

The dose-escalation part included patients with advanced solid tumors who had progressed despite standard therapy. The expansion part enrolled patients with documented genetic alterations of the PI3K pathway (*PIK3CA* mutation or amplification). Oral alpelisib was given as a single agent on a continuous 28-day treatment cycle once daily (qd) until unacceptable toxicity, disease progression, investigator's decision, or patient's withdrawal of consent.

The starting dose of alpelisib in Japanese patients was chosen based on the experience in the Western FIH study; the dose was half of the highest dose that had been investigated in Western patients at the time of study start, and at which no dose-limiting toxicities (DLTs) were observed. Five dose levels of alpelisib (90, 180, 270, 350, and 400 mg/day) were investigated in the current study. A maximum of 2 dose reductions or reduction to 60 mg/day alpelisib, whichever was higher, was allowed for each patient in case of toxicity. If a patient required a dose delay of more than 21 days from the intended day of the next scheduled dose, the patient was to be discontinued from the study treatment.

2.2 | Patient population

This study enrolled Japanese patients (more than or 18 years) with histologically confirmed, advanced, unresectable solid tumors whose disease had progressed on (or who had not been able to tolerate) standard therapy, or for whom no standard therapy existed. In order to evaluate the sensitivity of *PIK3CA*-mutant tumors to alpelisib, the expansion part of the study enrolled patients with *PIK3CA* mutation and/or amplification confirmed by molecular prescreening using an archival or fresh tumor biopsy sample. Patients with measurable or nonmeasurable disease as per RECIST version 1.1, ECOG performance status ≤2, and adequate organ function at screening (including fasting plasma glucose <140 mg/dL/7.8 mmol/L) were eligible. Key exclusion criteria included prior treatment with a PI3K inhibitor, brain metastasis, impaired cardiac function or clinically significant cardiac disease, peripheral neuropathy NCI-CTC grade ≥2, or diarrhea NCI-CTC grade ≥2. Patients were excluded if they had clinically manifested diabetes mellitus (DM), a history of gestational DM, or documented steroid-induced DM.

2.3 | Study objectives and endpoints

The primary objective was to estimate the MTD and/or RP2D of oral alpelisib given as a single agent in Japanese patients. The MTD was defined as the highest drug dosage not causing medically unacceptable DLT in more than 33% of the treated patients in the first cycle of treatment. The determination of the MTD was based on the incidence of DLTs during cycle 1. In brief, the DLT was defined an adverse event (AE) or abnormal laboratory value assessed as clinically relevant, occurring 28 days or less following the administration of alpelisib in the first cycle of treatment, which was at least possibly

related to alpelisib, unrelated to underlying (tumor) disease, disease progression, intercurrent illness, or concomitant medications, and met any of the criteria defined in the study protocol.

Secondary objectives included overall safety and tolerability, full PK profile of alpelisib after single (cycle 1 day 1) and multiple (cycle 1 day 8 and cycle 2 day 1) treatments, and preliminary efficacy of alpelisib (overall response rate [ORR], disease control rate [DCR], and progression-free survival [PFS]).

Exploratory objectives included assessment of food effect on the full PK profile of alpelisib under fed and fasted conditions after multiple treatments (on cycle 1 day 22 and cycle 2 day 1 in the dose-expansion part) of alpelisib, evaluation of PI3K pathway inhibition in glucose metabolism markers such as fasting glucose and fasting C-peptide in blood, evaluation of PI3K pathway inhibition in skin and tumor tissue using immunochemistry, assessment of relationship between baseline target gene/molecular alteration status and clinical outcome, and assessment of molecular mechanisms of AEs.

2.4 | Safety and efficacy assessments

Safety was monitored by physical examination (including neurologic examination), vital signs, weight, ophthalmologic examination, fasting glucose monitoring, and repeat cardiac assessments (including electrocardiogram, cardiac imaging, and cardiac enzymes) as well as monitoring and recording of all AEs and serious AEs (SAEs) and monitoring of laboratory evaluations. Adverse events were assessed according to Common Terminology Criteria for Adverse Events version 4.0, except for hyperglycemia. Hyperglycemia was graded as: grade 0, fasting plasma glucose <140 mg/dL; grade 1, 140-199 mg/dL; grade 2, 200-249 mg/dL; grade 3, 250-399 mg/dL; and grade 4, ≥400 mg/dL. Tumor response was assessed by computed tomography or MRI (according to RECIST version 1.1) at baseline, every 8 weeks thereafter, and at the end of treatment. Overall response rate was defined as the rate of complete response (CR) and partial response (PR) of target and nontarget lesions according to RECIST; DCR was defined as the proportion of patients with a best overall response of CR, PR, or stable disease (SD). Progression-free survival was defined as the time from the first date of exposure to study drug to the date of first radiologically documented disease progression or death due to any cause.

2.5 | Pharmacokinetic assessments and biomarkers

Blood samples for PK analyses were obtained on days 1 and 8 of cycle 1 and day 1 of cycle 2, at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours postdose, and on day 1 of cycles 3-6 at predose in the escalation part. Patients in the expansion part were randomized into 2 treatment groups (group A and group B). Patients in group A received alpelisib under fasted conditions on cycle 2 day 1 and under fed conditions on all other study days. Patients in group B received alpelisib under fasted conditions on cycle 1 day 22 and under fed conditions on all other study days. Blood samples were obtained on days 1 and 22 of cycle 1 and day 1 of cycle 2, at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours postdose, and on day 1 of cycles 3-6 at predose in the expansion part. Plasma concentrations of alpelisib were determined using a validated liquid chromatography-mass spectrometry/mass spectrometry method with a lower limit of quantification of approximately 1 ng/mL. The PK parameters were estimated using a noncompartmental method with Phoenix WinNonlin (Princeton, NJ, USA). The dose proportionality of alpelisib was assessed using a power model on log-transformed parameters, ie log (parameter) = log (α) + β*log (dose) + error.

Tumor biopsy samples were collected at screening (pretreatment), on cycle 3 day 1 (4-6 hours postdose), and tumor progression (within 3 days from the last dose) for patients in the escalation as well as expansion parts. Archival formalin-fixed paraffin-embedded tumor samples, representing original diagnostic material and/or a prior tissue-proven recurrence, were collected and assessed for *PIK3CA* mutation and/or amplification prior to treatment initiation for molecular prescreening. If archival tumor tissue was not available, a fresh tumor biopsy was provided instead. The tumor (archival and/or fresh) material was also analyzed using next-generation sequencing to identify potential biomarkers predictive of efficacy and to assess potential PD biomarkers. Pre- and posttreatment skin biopsies were analyzed at screening, on cycle 3 day 1, and at progressive disease for baseline status and posttreatment changes in p-S6, p-4EBP1, and p-Akt expression. Pre- and posttreatment fresh tumor biopsies were collected at the same time and were paired with blood samples to allow analysis of nonfasting glucose and nonfasting C-peptide levels. In addition, glucose metabolism markers were analyzed on cycle 1 day 2, cycle 1 day 9, and cycle 2 day 2 at pre-dose and 2 and 4 hours postdose.

2.6 | Statistical analysis

A Bayesian logistic regression model for dose escalation with overdose control was applied to guide dose escalation and to estimate the MTD in the dose-escalation part. The MTD was defined as the highest drug dosage not causing medically unacceptable DLT in more than 33% of the treated patients in the first cycle of the treatment. For continuous data, descriptive statistics (n, mean, SD, median, minimum and maximum) are used. For categorical data, the number and percentage of patients or events are presented. No statistical hypothesis testing was carried out. To assess the effect of food on the PK of alpelisib, patients received alpelisib in a fasted or fed condition on cycle 1 day 22 and cycle 2 day 1 in a cross-over fashion during the expansion part at the R2PD (350 mg/day).

The full analysis set (FAS) consisted of all patients who received at least 1 dose of alpelisib. The dose-determining set consisted of all patients eligible for the safety set and enrolled in the dose-escalation part who had either experienced DLT at any time during cycle 1 or met the minimum safety evaluation requirements without experiencing DLT in cycle 1. The safety set consisted of all patients who received at least 1 dose of alpelisib and had at least 1 post-baseline safety assessment (where the statement that a patient had no AEs constitutes a safety assessment). In the escalation part, FAS was considered for the PK analysis. The PK analysis set (PAS) for the expansion part consisted of all patients enrolled in the dose-expansion

TABLE 1 Demographics of Japanese patients with advanced solid tumors (n = 33)

	90 mg (n = 3)	180 mg (n = 4)	270 mg (n = 5)	350 mg (n = 6)	400 mg (n = 7)	350 mg Expansion (n = 8)	All (n = 33)
Age, years; median (range)	52.0 (34-61)	60.5 (39-70)	63.0 (40-76)	55.5 (52-67)	48.0 (24-72)	54.5 (31-72)	55.5 (24-76)
Sex, female/male	1 (33.3)/2 (66.7)	1 (25.0)/3 (75.0)	4 (80.0)/1 (20.0)	2 (33.3)/4 (66.7)	2 (28.6)/5 (71.4)	7 (87.5)/1 (12.5)	17 (51.5)/16 (48.5)
ECOG-PS							
0	2 (66.7)	4 (100)	2 (40.0)	4 (66.7)	4 (57.1)	6 (75.0)	22 (66.7)
1	1 (33.3)	0 (0.0)	3 (60.0)	2 (33.3)	3 (42.9)	1 (12.5)	10 (30.3)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (3.0)
Primary site of cancer							
Breast	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (50.0)	4 (12.1)
Stomach	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	1 (14.3)	1 (12.5)	4 (12.1)
Lung	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)	3 (9.1)
Bile duct	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.1)
Pancreas	0 (0.0)	1 (25.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.1)
Uterus	0 (0.0)	1 (25.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	2 (6.1)
Other	3 (100)	1 (25.0)	2 (40.0)	3 (50.0)	4 (57.1)	3 (37.5)	16 (48.4)
No. of prior antineoplastic medication regimens							
1	2 (66.7)	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1 (12.5)	5 (15.2)
2	0 (0.0)	1 (25.0)	1 (20.0)	1 (16.7)	2 (28.6)	0 (0.0)	5 (15.2)
3	0 (0.0)	0 (0.0)	1 (20.0)	3 (50.0)	3 (42.9)	0 (0.0)	7 (21.2)
4	1 (33.3)	1 (25.0)	2 (40.0)	0 (0.0)	0 (0.0)	3 (37.5)	7 (21.2)
5	0 (0.0)	1 (25.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (12.5)	3 (9.1)

Data are shown as n (%) unless otherwise indicated.
PS, performance status.

TABLE 2 Reasons for discontinuation of treatment with alpelisib in Japanese patients with advanced solid tumors (n = 33)

Reason	90 mg (n = 3)	180 mg (n = 4)	270 mg (n = 5)	350 mg (n = 6)	400 mg (n = 7)	350 mg expansion (n = 8)	All (n = 33)
AE	0 (0.0)	0 (0.0)	2 (40.0)	2 (33.3)	3 (42.9)	2 (25.0)	9 (27.3)
Progressive disease	3 (100.0)	2 (50.0)	3 (60.0)	4 (66.7)	3 (42.9)	6 (75.0)	21 (63.6)
Patient/guardian decision	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.1)
Death[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	1 (3.0)

[a]Not related to study drug.
AE, adverse event.

part in the FAS who received identical doses of alpelisib on cycle 1 day 22 and cycle 2 day 1.

2.7 | Study oversight

This study was approved by the institutional review board or ethics committee at each participating center and was undertaken in accordance with the Good Clinical Practice principles and applicable local regulations. All patients provided written informed consent.

3 | RESULTS

3.1 | Patients and treatment

Overall, 33 patients (median age, 55 years) were treated with alpelisib tablets on a qd schedule (Table 1). Most of the patients (97.0%) had an ECOG performance status of either 0 or 1 at baseline. The most frequently reported cancer sites were breast and stomach, reported in 4 patients each (12.1%, respectively).

Out of 33 patients, 25 received alpelisib in the dose-escalation part at 5 dose levels (90 mg/day, 3 patients; 180 mg/day, 4 patients; 270 mg/day, 5 patients; 350 mg/day, 6 patients; and 400 mg/day, 7 patients). In the expansion part, 8 patients received alpelisib at the RP2D of 350 mg/day under fasted or fed condition.

All patients discontinued study treatment, with disease progression being the most common reason for discontinuation (63.6%). Treatment discontinuation due to AEs was reported in 9 patients (27.3%) (Table 2). Maculopapular rash (3 patients, 9.1%) was the most common suspected AE leading to study drug discontinuation. Maculopapular rash and hyperglycemia were the most common AEs leading to study drug interruption and/or dose adjustment of alpelisib (7 and 6 out of 33 patients, respectively).

In the dose-escalation part, the median duration of exposure to alpelisib was 71.0 days (range, 6-462 days). At the 350 mg (all) dose level, the median duration of exposure was 92.0 days (range, 6-462 days). The median relative dose intensity was 92.3% overall and 93.9% across all patients at the 350 mg/day dose level. The relative dose intensity was lowest (73.7%) for the 400 mg/day dose level, which exceeded the RP2D. Overall, 17 patients (51.5%) had relative dose intensity between 90% and 100%.

3.2 | Safety

In the dose-escalation part, 3 DLTs were observed in 2 of the 5 patients who were eligible for the dose-determining set and received 400 mg/day. One patient had grade 3 maculopapular rash and another patient had grade 3 maculopapular rash and grade 2 conjunctivitis. Neither of them met the DLT criteria. However, the investigators judged these events as DLTs based on the total clinical observations. The RP2D of alpelisib as a single agent in Japanese patients was determined as 350 mg/day. The MTD was not determined based on the observed safety and PK data from the CBYL719X1101 study and

TABLE 3 Dose-limiting toxicities (DLT) in Japanese patients with advanced solid tumors treated with alpelisib: Escalation and expansion part

Dose level	Dose, mg	Patients enrolled, n	DLT, n	DLT
1	90	3	0	–
2	180	4	0	–
3	270	5	0	–
4	350	6	0	–
5	400	7	1	Maculopapular rash (Gr 3)
			1	Maculopapular rash/conjunctivitis (Gr 2)
Expansion	350	8	1	Infection of the tumor (Gr 4)

–, not applicable; Gr, grade.

TABLE 4 Adverse events (AE; any grade [≥10%] in all patients and grade 3/4), suspected to be alpelisib-related, in Japanese patients with advanced solid tumors

AE (preferred term), n (%)	90 mg (n = 3)	180 mg (n = 4)	270 mg (n = 5)	350 mg (n = 6)	400 mg (n = 7)	350 mg Expansion (n = 8)	350 mg All (n = 14)	All (n = 33)
Hyperglycemia								
Any grade	0 (0.0)	1 (25.0)	1 (20.0)	6 (100.0)	2 (28.6)	6 (75.0)	12 (85.7)	16 (48.5)
Grade 3/4	0 (0.0)	0 (0.0)	1 (20.0)	3 (50.0)	0 (0.0)	3 (37.5)	6 (42.9)	7 (21.2)
Maculopapular rash								
Any grade	0 (0.0)	1 (25.0)	2 (40.0)	6 (100)	5 (71.4)	2 (25.0)	8 (57.1)	16 (48.5)
Grade 3/4	0 (0.0)	0 (0.0)	2 (40.0)	1 (16.7)	4 (57.1)	1 (12.5)	2 (14.3)	8 (24.2)
Diarrhea								
Any grade	1 (33.3)	0 (0.0)	4 (80.0)	3 (50.0)	3 (42.9)	4 (50.0)	7 (50.0)	15 (45.5)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite								
Any grade	1 (33.3)	1 (25.0)	1 (20.0)	2 (33.3)	3 (42.9)	3 (37.5)	5 (35.7)	11 (33.3)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis								
Any grade	0 (0.0)	0 (0.0)	2 (40.0)	2 (33.3)	2 (28.6)	2 (25.0)	4 (28.6)	8 (24.2)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia								
Any grade	0 (0.0)	1 (25.0)	1 (20.0)	2 (33.3)	2 (28.6)	2 (25.0)	4 (28.6)	8 (24.2)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus								
Any grade	1 (33.3)	2 (50.0)	0 (0.0)	1 (16.7)	3 (42.9)	0 (0.0)	1 (7.1)	7 (21.2)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis acneiform								
Any grade	2 (66.7)	0 (0.0)	1 (20.0)	1 (16.7)	2 (28.6)	0 (0.0)	1 (7.1)	6 (18.2)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash								
Any grade	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (14.3)	4 (50.0)	4 (28.6)	6 (18.2)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	3 (37.5)	3 (21.4)	4 (12.1)
Anemia								
Any grade	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)	3 (37.5)	3 (21.4)	5 (15.2)
Grade 3/4	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Nausea								
Any grade	0 (0.0)	1 (25.0)	0 (0.0)	1 (16.7)	2 (28.6)	0 (0.0)	1 (7.1)	4 (12.1)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

(Continues)

TABLE 4 (Continued)

AE (preferred term), n (%)	90 mg (n = 3)	180 mg (n = 4)	270 mg (n = 5)	350 mg (n = 6)	400 mg (n = 7)	350 mg Expansion (n = 8)	350 mg All (n = 14)	All (n = 33)
Vomiting								
Any grade	0 (0.0)	1 (25.0)	0 (0.0)	1 (16.7)	1 (14.3)	1 (12.5)	2 (14.3)	4 (12.1)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood creatinine increased								
Any grade	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	2 (25.0)	2 (14.3)	4 (12.1)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood insulin increased								
Any grade	0 (0.0)	1 (25.0)	0 (0.0)	1 (16.7)	2 (28.6)	0 (0.0)	1 (7.1)	4 (12.1)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight decreased								
Any grade	0 (0.0)	1 (25.0)	0 (0.0)	1 (16.7)	1 (14.3)	1 (12.5)	2 (14.3)	4 (12.1)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (3.0)

considering the data from the CBYL719X2101 study, in which antitumor efficacy was observed from 270 mg/day. In the expansion part, 1 out of 8 patients had a DLT (grade 4 infected neoplasm) at 350 mg/day, whereas no DLT occurred at doses ≤350 mg/day in the dose-escalation part (Table 3). Among 33 patients, the most common AEs (>30%) of any grade, suspected to be related to alpelisib, were hyperglycemia and maculopapular rash (n = 16, 48.5% each), diarrhea (n = 15, 45.5%), and decreased appetite (n = 11, 33.3%) (Table 4). Treatment-related grade 3/4 AEs were reported in 20 patients (60.6%). The most frequently reported (≥10%) grade 3/4 suspected AEs were maculopapular rash (8 patients, 24.2%), hyperglycemia (7 patients, 21.2%), and rash (4 patients, 12.1%). Dose reductions due to AEs were reported in 72.7% (n = 24) (mainly due to maculopapular rash [n = 7, 21.2%], hyperglycemia [n = 6, 18.2%], diarrhea [n = 5, 15.2%], and rash [n = 5, 15.2%]). Maculopapular rash was managed with dose interruptions and/or oral antihistaminics and topical, oral (0.5-0.75 mg/kg qd), and i.v. steroids. Hyperglycemia was managed with dose interruption and/or antidiabetic medications, such as insulin, metformin, glimepiride, miglitol, and voglibose. Serious AEs were reported in 19 patients (57.6%), with 9 patients (27.3%) having SAEs suspected to be treatment-related. Thirteen patients (39.4%) had an increase of QT >60 ms and 1 patient had an increase of QTcB >60 ms. None of these changes in electrocardiogram intervals were considered clinically meaningful by the investigators.

3.3 | Efficacy

Among the 33 patients, 1 patient (3.0%) had PR and 18 patients (54.5%) had SD. The waterfall plot indicates that several patients experienced tumor shrinkage; 3 of them had a reduction of more than 30% in the sum of longest diameters. In the dose-escalation part, 1 patient with uterine cancer (350 mg/day) had a confirmed PR and 1 patient with gastrointestinal stromal tumor (400 mg/day) had an unconfirmed PR (Figure 1). In the dose-expansion part, 1 patient with hormone receptor-positive, Human epidermal growth factor receptor 2 (HER2)-negative BC harboring a *PIK3CA* mutation achieved an unconfirmed PR. The overall response rate (CR or PR) was 3.0% (1/33 patients) (95% confidence interval [CI], 0.1-15.8). The overall DCR (CR or PR or SD) was 57.6% (19/33 patients). The DCRs at RP2D in the expansion part and in all patients were 75.0% (6/8 patients) and 78.6% (11/14 patients), respectively. The median PFS at 350 mg/day was 3.4 months (95% CI, 2.8-5.6).

3.4 | Pharmacokinetics

3.4.1 | Escalation part

Alpelisib plasma exposure (maximum plasma concentration [Cmax] and area under the curve from time 0 to 24 hours [AUC0-24]) increased dose-dependently over the dose range from 90 to 400 mg/day. The median accumulation ratio on cycle 1 day 8 and cycle 2 day 1 ranged from 1.1 to 1.3 and 0.7 to 1.4, respectively.

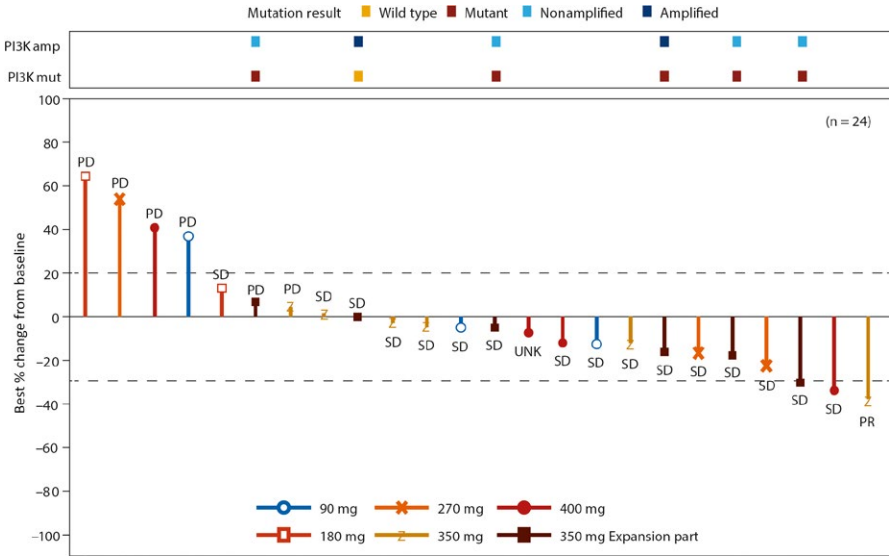

FIGURE 1 Best percent change from baseline in sum of longest diameters. amp, amplified; mut, mutated, PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown

TABLE 5 Pharmacokinetic analyses in escalation part of phase I trial of alpelisib in Japanese patients with advanced solid tumors

Dose, mg (enrolled #)	Median Tmax (min-max), h	Median Cmax (min-max), ng/mL	Median AUC0-24 (min-max), h*ng/mL	Median T1/2 (min-max), h	Median Racc (min-max)
C1D1					
90 (n=3)	2.00 (1.50-3.00)	1070 (1070-1390)	7600 (5650-8620)	5.36 (5.05-5.91)	–
180 (n=4)	2.46 (1.50-3.00)	1820 (1370-2990)	15500 (14000-21900)	5.35 (4.67-6.40)	–
270 (n=5)	2.02 (2.00-23.3)	2660 (2000-3530)	25300 (16100-34000)	5.12 (4.54-5.24)	–
350 (n=6)	1.77 (1.00-3.00)	3490 (2000-6810)	27600 (18000-40300)	5.65 (4.73-7.46)	–
400 (n=7)	2.00 (1.50-3.00)	4850 (2070-7050)	40700 (21500-76600)	5.76 (3.39-6.80)	–
C1D8					
90 (n=3)	2.00 (1.00-3.00)	1290 (1260-1320)	8410 (6500-8640)	5.82 (5.07-6.28)	1.11 (1.00-1.15)
180 (n=4)	3.00 (1.50-4.03)	2350 (1590-3680)	17600 (16900-24600)	5.56 (5.55-6.21)	1.11 (1.11-1.12)
270 (n=5)	3.55 (3.00-8.00)	3260 (1000-4140)	32900 (22300-41900)	5.38 (5.12-6.82)	1.23 (0.895-1.28)
350 (n=6)	2.50 (1.50-3.00)	3800 (2570-5330)	33500 (25600-41000)	5.35 (4.61-7.06)	1.30 (1.05-2.21)
400 (n=7)	3.00 (2.00-4.02)	4920 (2130-7340)	49100 (18300-75300)	6.03 (4.92-8.90)	1.22 (0.453-1.91)
C2D1					
90 (n=3)	3.00 (1.50-4.00)	999 (921-1250)	8720 (6950-11600)	6.25 (5.42-6.91)	1.23 (1.15-1.34)
180 (n=4)	1.50 (0.50-3.00)	1820 (1800-2970)	21300 (15400-22100)	6.26 (5.73-6.45)	1.10 (0.973-1.39)
270 (n=5)	3.50 (3.00-4.00)	3120 (1890-4340)	29100 (23900-34300)	5.52 (5.34-5.71)	1.41 (1.33-1.49)
350 (n=6)	2.25 (1.50-4.00)	5020 (2530-6620)	43400 (21300-50200)	5.15 (4.85-8.14)	1.25 (1.12-2.10)
400 (n=7)	2.00 (2.00-2.00)	4390 (4390-4390)	26500 (26500-26500)	-	0.695 (0.695-0.695)

AUC0-24, area under the curve from zero to 24 h; C, cycle; D, day; Cmax, maximal drug concentration; Racc, accumulation ratio; Tmax, time to maximum concentration.

Steady-state was achieved by day 8 (Table 5). Dosing at 350 mg/day resulted in a low mean clearance (CL/F) of 11.0 L/h on cycle 1 day 8. On cycle 1 day 8, the estimated β (derived from power model analysis) for Cmax, AUC0-24, and area under the plasma concentration-time curve from time zero to time of last measurable concentration (AUClast) were 0.82 (90% CI, 0.499-1.142), 1.06 (90% CI, 0.791-1.327), and 1.05 (90% CI, 0.772-1.337), respectively, indicating that alpelisib exposure is generally dose proportional.

3.4.2 | Expansion part

The safety and PK profile were similar to that of the escalation part. Six out of 8 patients were eligible for the PAS of the expansion part. Only 1 patient received 350 mg/day by cycle 2, while for 3 and 2 patients the dose was reduced to 270 mg/day or 180 mg/day before cycle 1 day 22, respectively. A positive food effect was observed on the steady-state PK of alpelisib compared to a fasted state. The

TABLE 6 Summary of statistical analysis of dose-normalized area under the curve from 0 to 24 hours (AUC0-24) and maximal drug concentration (Cmax) by condition (pharmacokinetics analysis set) for the expansion part of a phase I trial of alpelisib in Japanese patients with advanced solid tumors (n = 33)

					Food comparison	
PK parameter (unit)	Treatment	n[a]	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	90% CI
AUC0-24 ([h*ng/mL]/[mg dose])	Fasted	5	72.10	Fed:fasted		
	Fed	5	113.00		1.56	1.02-2.39
Cmax ([ng/mL]/[mg dose])	Fasted	6	5.40			
	Fed	6	9.62	Fed:fasted	1.78	1.13-2.79

[a]Number of subjects with nonmissing values.
CI, confidence interval; Geo, geometric.

TABLE 7 Summary of somatic mutational status (full analysis set) among 33 Japanese patients treated with alpelisib for advanced solid tumors

	Dose escalation part					Expansion part	
	90 mg (n = 3)	180 mg (n = 4)	270 mg (n = 5)	350 mg (n = 6)	400 mg (n = 7)	350 mg expansion (n = 8)	All (n = 33)
BRAF	1	0	0	0	2	0	3
KRAS	0	2	2	0	1	2	7
PIK3CA	0	0	0	0	1	6	7
TP53	0	2	2	2	2	3	11
PTEN	1	0	0	0	0	0	1

geometric mean values of dose-normalized Cmax and AUC0-24 in the fed state were 78% and 56% higher than those in the fasted state, respectively (Table 6). These data indicate that food intake had a positive effect on the exposure of alpelisib.

3.5 | Biomarker assessments

In the dose-escalation part, an increase in C-peptide levels was observed in most patients, whereas the changes in glucose levels were not consistent. Phosphorylation of AKT, S6, and 4EBP1 in skin biopsy samples tended to decrease after alpelisib treatment. *PIK3CA* mutation or amplification was detected in tumor tissue (archival samples or fresh biopsy) of 7 out of 33 patients (Figure 1, Table 7). Somatic mutations in the *TP53* gene were identified in 11 patients. *KRAS*, *BRAF*, and *PTEN* mutations were identified in tumor samples of 7, 3, and 1 patients, respectively (Table 7). Three patients had a molecular alteration in *BRCA2*, and one of these 3 patients, a patient with uterine cancer, was reported to have a PR.

4 | DISCUSSION

This was a first trial of alpelisib in Japanese patients evaluating the safety, tolerability, MTD, and preliminary efficacy of single-agent alpelisib in patients with advanced solid tumors who had progressed despite standard therapy. The expansion part of the study enrolled patients with documented genetic alterations of the PI3K pathway (*PIK3CA* mutation or amplification). The RP2D of alpelisib was determined as 350 mg/day without further dose escalation to determine the MTD, taking into account the observed safety and PK data in this study and the efficacy data of the FIH study, in which antitumor efficacy was observed from 270 mg/day.[11] Alpelisib 400 mg/day was the highest dose tested, whereas a dose of 350 mg/day was well tolerated. No intermediate dose levels were tested in this study. Overall, patients were able to receive >90% of the planned dose at the RP2D. Seventeen patients (51.5%) had relative dose intensity between 90% and 100%. The RP2D and the safety profile determined in Japanese patients are in line with findings from the FIH study evaluating the safety, MTD, and preliminary efficacy of single-agent alpelisib in Western patients with advanced solid tumors with *PIK3CA* alterations. In the previous study (NCT01219699), the MTDs of alpelisib as a single agent were determined as 400 mg/day and 150 mg twice daily.[11] In Japanese patients, the most common (more than 30% incidence) all-grade treatment-suspected AEs were hyperglycemia and maculopapular rash (48.5% each), diarrhea (45.5%), and decreased appetite (33.3%). Hyperglycemia is an on-target effect of alpelisib.[11] Hyperglycemia was generally managed by study drug interruption and/or antidiabetic medication. Maculopapular rash was managed by study drug interruption and/or oral antihistamines and topical, oral, and i.v. steroids. The AE profile of alpelisib observed here was also similar to that reported in a randomized phase Ib/II study (NCT01872260), which enrolled patients with ER+, HER2– advanced BC to evaluate the efficacy and safety of alpelisib in combination with letrozole. In this study, the most common (more than

40% incidence) all-grade AEs included hyperglycemia (62.3%), diarrhea (60.9%), and nausea (44.9%).[13]

The safety profile of alpelisib in Japanese patients was also consistent with other isoform-selective PI3K inhibitors, such as the beta-sparing PI3K inhibitor taselisib, in patients with locally advanced or metastatic solid malignancies. Grade 3 or higher AEs that were suspected to be taselisib-related were observed in 41% of patients. Hyperglycemia (15%), rash (12%), fatigue (6%), diarrhea (6%), and pruritus (6%) were the most common grade 3 or higher AEs (>5%) suspected to be related to taselisib.[14] Compared to taselisib (6%), the incidence of alpelisib-related diarrhea of grade 3 or higher was lower in the Western population treated with alpelisib (2.2%) and not reported (0%) in the Japanese patients in the current trial.[11]

In Japanese patients, alpelisib showed encouraging preliminary efficacy. Overall, the ORR was 3% and the DCR was 57.6% (19 of 33 patients). At the RP2D of 350 mg/day, the DCR across all patients was 78.6% (11 of 14 patients), including 1 patient achieving PR and 10 patients achieving SD. The median PFS at 350 mg/day for all patients (n = 14) was 3.4 months (95% CI, 2.8-5.6). These results are in line with the findings from the Western population (NCT01219699), where ORR of 6.0% and DCR of 58.2% were reported in patients with advanced solid malignancies. The median PFS in patients with ER+/HER2− advanced breast cancer was 5.5 months (95% CI, 3-7) at ≥270 mg/day alpelisib as single-agent treatment.[11]

Alpelisib in combination with letrozole has shown encouraging clinical outcomes in patients with advanced ER+ BC who were not eligible for curative surgery or radiotherapy (NCT01872260). The ORR, DCR, and clinical benefit rate were 22.4%, 83.6%, and 58.5%, respectively. The median PFS was reported to be 14.3 months.[13]

Pharmacokinetic exposures (AUC and Cmax) for alpelisib in Japanese patients were similar to those previously reported (CBYL719X2101). A positive food effect was observed on the steady-state PK of alpelisib. Compared to a fasted state, the geometric mean of dose-normalized Cmax and AUC0-24 were 78% and 56% higher in a fed state, respectively. Thus food intake has a positive effect on the exposure of alpelisib, suggesting that the drug is effective in a fed condition as compared to a fasted condition in Japanese patients. Alpelisib as single agent showed a favorable safety profile and encouraging preliminary efficacy in Japanese patients with advanced solid tumors. However, as the current trial is an early-phase study with a small number of patients, further research is necessary to discuss the potential differences in safety profile between patients of different ethnicities. Ongoing trials such as SOLAR-1 and BYLieve are now evaluating the efficacy and safety of alpelisib 300 mg/day in combination with ET in hormone receptor-positive, HER2− advanced BC patients with/without *PIK3CA* mutational status.

ACKNOWLEDGMENTS

We thank the patients who took part in this study and their families, as well as the investigators, research coordinators, and staff at each study site. We also thank Susmita Bhattacharjee (Novartis Healthcare) for medical editorial assistance with this manuscript.

CONFLICT OF INTEREST

YA reports grants and personal fees from Chugai, Takeda, Kyowa Hakko Kirin, Eisai, Taiho, Nippon Kayaku, Yakult Honsha, Mochida, Merck Serono, Ono, Eli Lilly, Novartis, Hisamitsu, personal fees from Janssen, GlaxoSmithKline, Terumo, Bayer, Meiji Seika, Benesse, Boehringer Ingelheim, Bristol-Myers Squibb, Sawai, Otsuka, and Shionogi, outside the submitted work. ST reports grants from Novartis, Chugai, Astrazeneka, Daiichisankyo, Bayer, and Parexel, outside the submitted work. SI and HS have nothing to disclose. NK, TK, and NS report personal fees from Novartis during the conduct of the study; CQ reports personal fees from Novartis during the conduct of the study.

ORCID

Yuichi Ando https://orcid.org/0000-0002-6849-2297

REFERENCES

1. Akinleye A, Avvaru P, Furqan M, Song Y, Liu D. Phosphatidylinositol 3-kinase (PI3K) inhibitors as cancer therapeutics. *J Hematol Oncol*. 2013;6:88.
2. Li J, Yen C, Liaw D, et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. *Science*. 1997;275:1943-1947.
3. Liu P, Cheng H, Roberts TM, Zhao JJ. Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat Rev Drug Discovery*. 2009;8:627-644.
4. Turner N, Pearson A, Sharpe R, et al. FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer. *Can Res*. 2010;70:2085-2094.
5. LoRusso PM. Inhibition of the PI3K/AKT/mTOR Pathway in Solid Tumors. *J Clin Oncol*. 2016;34:3803-3815.
6. Ciruelos Gil EM. Targeting the PI3K/AKT/mTOR pathway in estrogen receptor-positive breast cancer. *Cancer Treat Rev*. 2014;40:862-871.
7. Pirali T, Ciraolo E, Aprile S, et al. Identification of a Potent Phosphoinositide 3-Kinase Pan Inhibitor Displaying a Strategic Carboxylic Acid Group and Development of Its Prodrugs. *ChemMedChem*. 2017;12:1542-1554.
8. Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. *Nat Rev Drug Discovery*. 2014;13:140-156.
9. Noguchi S, Masuda N, Iwata H, et al. Efficacy of everolimus with exemestane versus exemestane alone in Asian patients with HER2-negative, hormone-receptor-positive breast cancer in BOLERO-2. *Breast Cancer*. 2014;21:703-714.
10. Fritsch C, Huang A, Chatenay-Rivauday C, et al. Characterization of the novel and specific PI3Kalpha inhibitor NVP-BYL719 and development of the patient stratification strategy for clinical trials. *Mol Cancer Ther*. 2014;13:1117-1129.
11. Juric D, Rodon J, Tabernero J, Janku F, et al. Phosphatidylinositol 3-Kinase alpha-Selective Inhibition With Alpelisib (BYL719) in PIK3CA-Altered Solid Tumors: Results From the First-in-Human Study. *J Clin Oncol*. 2018;36:1291-1299.
12. Maruyama N, Miyoshi Y, Taguchi T, Tamaki Y, Monden M, Noguchi S. Clinicopathologic analysis of breast cancers with PIK3CA mutations in Japanese women. *Clin Cancer Res*. 2007;13:408-414.
13. Juric DGA, Hamilton E, Boni V, et al. Alpelisib plus letrozole in estrogen receptor-Positive (ER+), human epidermal growth

factor receptor 2-negative (HER2–) advanced breast cancer (aBC): Safety and preliminary efficacy analysis from a phase 1b trial. SABCS 2017: American Association for Cancer Research, 2017.

14. Juric D, Krop I, Ramanathan RK, et al. Phase I dose-escalation study of taselisib, an oral PI3K inhibitor, in patients with advanced solid tumors. *Cancer Discov*. 2017;7:704-715.

How to cite this article: Ando Y, Iwasa S, Takahashi S, et al. Phase I study of alpelisib (BYL719), an α-specific PI3K inhibitor, in Japanese patients with advanced solid tumors. *Cancer Sci*. 2019;110:1021–1031. https://doi.org/10.1111/cas.13923