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ORIGINAL ARTICLE

Phase 1 study of abemaciclib, an inhibitor of CDK 4 and 6, as a single agent for Japanese patients with advanced cancer

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Abstract
Purpose To confirm the safety and tolerability, evaluate the pharmacokinetics (PK), and investigate the antitumor activity of abemaciclib in Japanese patients with advanced cancer.
Methods We conducted a non-randomized, single-arm, open-label, dose-escalation phase 1 study of abemaciclib administered orally every 12 h (Q12H) on a 28-day cycle at doses of 100 mg (Cohort 1, $n = 3$), 150 mg (Cohort 2, $n = 3$), or 200 mg [Cohort 3, $n = 6$, maximum tolerated dose (MTD)]. Dose escalation was based on the frequency of dose-limiting toxicity (DLT). MTD, as established in the previous phase 1 study in non-Japanese patients, was the highest dose level at which <33 % of patients experienced DLT.
Results Eleven of the 12 patients who received treatment with abemaciclib discontinued: 10 patients due to progressive disease, and 1 due to a DLT (Cohort 3, grade 2 nausea). Diarrhea, the most common treatment-emergent adverse event (AE), was managed supportively and did not require study treatment discontinuation. There were no drug-related serious AEs and no patients with corrected QT (QTc) > 480 ms or QTc change of >60 ms from baseline. The abemaciclib PK profile was characterized by slow absorption and high PK variability after single or repeated doses. Two patients, one with breast cancer and one with neuroendocrine tumor, experienced >30 % decrease in tumor size from baseline.
Conclusions In Japanese patients with advanced cancer, single-agent abemaciclib has an acceptable safety profile and demonstrates antitumor activity at a dose of 200 mg Q12H. These findings support ongoing development of abemaciclib for diverse populations with advanced cancer.

Keywords Abemaciclib · Advanced cancer · CDK 4/6 inhibitor · Japanese · Pharmacokinetics · Phase 1 study · Safety profile

Introduction

The cyclin-dependent kinases, CDK4 and CDK6, play an integral role in regulating the cell cycle by initiating the transition of cells through the G1 restriction point [1]. Aberrant activation of these kinases promotes cell cycle progression, which is a common mechanistic feature in human cancers [2, 3]. Therefore, pharmacologic inhibition of CDK4 and CDK6 may arrest tumor growth by preventing progression of tumor cells through the G1 restriction point. Various preclinical and clinical studies support CDK4 and CDK6 as potential tumor targets [4, 5]. Inhibitors of CDK4 and CDK6 have been investigated in clinical studies for the treatment of various cancers with evidence of anticancer effects in multiple tumor types, including hormone receptor-positive (HR^+) breast cancer [6].

In clinical studies of breast cancer, several CDK4/6 inhibitors have been evaluated for efficacy, including palbociclib, ribociclib, and abemaciclib. PALOMA-3 is a randomized phase 3 study of palbociclib plus fulvestrant

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compared with placebo plus fulvestrant as second-line therapy for metastatic estrogen receptor positive (ER^+), human epidermal growth factor receptor-2 negative ($HER2^-$) breast cancer which demonstrated that progression-free survival was significantly longer in the experimental arm [7]. MONALEESA-2 is an ongoing phase 3 study that randomizes patients with metastatic $HR^+/HER2^-$ disease to letrozole with or without ribociclib in the first-line setting [8]. MONARCH-2 is a randomized phase 3 study of abemaciclib plus fulvestrant compared to placebo plus fulvestrant as a second-line therapy for women with HR^+, $HER2^-$ advanced breast cancer [9]. MONARCH-3 is a randomized phase 3 study of abemaciclib plus nonsteroidal aromatase inhibitor (NSAI; anastrazole or letrozole) compared to placebo plus NSAI in the first-line setting for women with HR^+, $HER2^-$ advanced breast cancer [10].

Abemaciclib (LY2835219) is an oral, small molecule inhibitor with selectivity for CDK4 and CDK6 [11], which is distinguished from other drugs in its class by a clinical safety profile that enables dosing on a continuous schedule to achieve sustained target inhibition. A multicenter phase 1 study for patients with advanced cancer established the maximum tolerated dose (MTD) for abemaciclib as a single agent at 200 mg every 12 h (Q12H) (NCT01394016) [12]. Collectively, phase 1 and 2 studies for patients with advanced solid tumors and hematologic malignancies have shown evidence that single-agent abemaciclib has acceptable safety and clinical activity against multiple human tumors, including breast cancer, lung cancer, melanoma, and mantle cell lymphoma [12–15].

The aim of this phase 1 study in Japanese patients with advanced cancer was to evaluate abemaciclib at doses up to the MTD established in the previous phase 1 study in non-Japanese patients. The primary objective was to confirm the safety and tolerability of abemaciclib in Japanese patients with advanced cancer. Secondary objectives were to evaluate the pharmacokinetic (PK) parameters and antitumor activity of abemaciclib in this population.

Materials and methods

Study design

This clinical study was a non-randomized, single-arm, open-label, dose-escalation phase 1 study of oral abemaciclib (LY2835219), Eli Lilly and Company (Indianapolis, USA) in Japanese patients with advanced cancer up to the MTD of 200 mg Q12H. The study was conducted at a single clinical site in Japan from 21 December 2013 (first patient enrolled) to data cutoff on April 1, 2015; one patient is still on study treatment. Written approval was provided by the institutional review board, and the study was conducted in accordance with international ethics guidelines, including the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practices Guideline [E6]. Informed consent was obtained from each patient before any protocol procedures or administration of study drug. This study was registered at ClinicalTrials.gov (NCT02014129).

Study population

To be eligible, patients had histologically or cytologically confirmed advanced and/or metastatic cancer (solid tumor or lymphoma) with measurable or non-measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) or the Revised Response Criteria for Malignant Lymphoma [16, 17]. Patients were required to be appropriate candidates for experimental therapy in the judgment of the investigator after prior standard therapies had failed, to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score ≤ 1 [18], to have adequate hepatic, hematologic, and renal function, and to have discontinued all previous therapies (including chemotherapy, radiotherapy, immunotherapy, and investigations therapy) ≥ 21 days prior to first dose of abemaciclib and recovered from acute toxicities.

Patients were specifically excluded if they met any of the following exclusion criteria: medical history of presyncope or syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia, or sudden cardiac arrest; evidence at baseline of ventricular tachycardia, ventricular fibrillation, abnormally prolonged corrected QT by Bazett's formula (QTcB) interval, or acute myocardial ischemia determined by electrocardiogram (ECG); presence of serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study; or symptomatic central nervous system malignancy or metastasis.

Treatment plan

Abemaciclib was administered Q12H without food for 1 h before or after the dose on a 28-day cycle. In Cycle 1, the initial dose of abemaciclib was taken on day 3 to enable PK sampling over 72 h following a single dose; the remaining doses were taken every 12 h on days 1–28. Abemaciclib was administered at one of 3 dose levels (100, 150, and 200 mg). Dose escalation proceeded, in cohorts of 3–6 patients, based on the frequency of dose-limiting toxicities (DLTs) observed in Cycle 1 until either ≥ 33 % of patients in one cohort experienced a DLT or the MTD was reached.

Adherence with study drug was assessed at each visit by direct questioning, reviewing the patient diary, and counting returned capsules. Patients were required to take

≥75 % of the intended dose to be deemed adherent with study drug administration.

Baseline and treatment assessments

Safety

In this study, adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03). A DLT was defined as an AE between day 3 and day 29 of Cycle 1 that was possibly related to abemaciclib and fulfilled any of the following criteria: grade 3 non-hematological toxicity, except for nausea, vomiting, diarrhea, electrolyte disturbance, or tumor lysis syndrome that could be controlled with treatment; grade 3 nausea, vomiting, diarrhea, or electrolyte disturbance that persisted >2 days despite maximal supportive intervention; grade 4 hematological toxicity that persisted >5 days; grade 3 thrombocytopenia with bleeding; febrile neutropenia; toxicity that required >25 % omissions of planned dose during Cycle 1 and considered a DLT by the investigator. Laboratory tests, including chemistry, hematology, and urinalysis panels, as well as observation of vital signs (including systolic and diastolic blood pressure, pulse rate, weight), were conducted at regular, prespecified time points. Time-matched ECGs were performed in triplicate at the same time as PK sampling ('PK-matched ECGs'). QT values were corrected using QTcB and Fridericia's (QTcF) formulae.

Pharmacokinetic evaluation

The following PK parameter estimates were included for abemaciclib: maximum observed plasma concentration (C_{max}); area under the plasma concentration versus time curve (AUC) from time zero to last time point with a measurable plasma concentration [$AUC_{(0–tlast)}$]; AUC from time zero to infinity [$AUC_{(0–\infty)}$]; AUC during 1 dosing interval at steady state ($AUC_{\tau,ss}$); time to reach maximal observed plasma concentration (t_{max}); elimination half-life ($t_{½}$); apparent volume of distribution at steady state (V_{ss}/F); and apparent total body clearance (CL/*F*). PK parameter estimates were calculated by standard non-compartmental methods (Phoenix® WinNonlin version 6.3, Certara, New Jersey, USA).

Efficacy

Efficacy was primarily assessed by determining the extent of antitumor activity, including the best overall response and time to event variables according to tumor measurement by RECIST 1.1 for patients with solid tumors or Revised Response Criteria for Malignant Lymphoma for patients with malignant lymphoma [16, 17]. Best overall response for solid tumors was defined as complete response, partial response, stable disease, progression/relapsed disease, or no evaluable response according to the evaluation criteria. Efficacy was also assessed by evaluation of tumor markers, when possible, and PS using the ECOG scale [18].

Statistical analysis

Sample size was based on the requirement for 3 or 6 patients at each dose level to assess the incidence of DLTs. MTD was defined as the highest dose level at which <33 % of patients experienced DLT. This study included at least three patients in each cohort with six patients enrolled at the MTD (200 mg Q12H) to collect additional data on safety, PK, and efficacy.

Details of patient disposition, demographics, and baseline disease characteristics were summarized for each cohort. Safety data (including vital signs, AEs, and PK-matched ECGs) were summarized by cohort in frequency tables or by summary statistics. A linear regression model was used to investigate the relationship between QTc changes from baseline and plasma abemaciclib concentration. PK parameters were summarized using descriptive statistics by dose. Efficacy data were listed and summarized by cohort using frequency tables or summary statistics. All efficacy analyses were performed on the full analysis set of patients, which was defined as patients who received at least 1 dose of any study drug. A waterfall plot of the maximal percent change in tumor size from baseline was determined for patients with solid tumors.

Results

Patient disposition and baseline characteristics

A total of 12 patients were enrolled in the 3 study cohorts as follows: Cohort 1, abemaciclib 100 mg Q12H ($n = 3$); Cohort 2, abemaciclib 150 mg Q12H ($n = 3$); and Cohort 3, abemaciclib 200 mg Q12H ($n = 6$). All enrolled patients received at least 1 dose of study drug (full analysis set) and were evaluable for DLTs. Of the 12 patients enrolled in the study, 11 patients (91.7 %) discontinued from treatment because of physician decision related to progressive disease ($n = 10$, 83.3 %) or an AE ($n = 1$, 8.3 %). One patient in Cohort 3 had reached Cycle 10 and was receiving ongoing treatment as of April 1, 2015 (day 297).

Overall, patients had a mean age of 59.1 years (range 37–73 years), a mean weight of 55.6 kg (range 37.2 to 74.7 kg) and a mean duration of cancer of 2.6 years (Table 1). All patients had metastatic solid tumors and had

Table 1 Patient demographics and disease characteristics

Characteristic	100 mg Q12H ($n = 3$)	150 mg Q12H ($n = 3$)	200 mg Q12H ($n = 6$)	Total ($n = 12$)
Male [*n* (%)]	2 (66.7)	2 (66.7)	1 (16.7)	5 (41.7)
Mean age (years)	61.3	63.0	56.0	59.1
Mean weight (kg)	67.7	49.2	52.7	55.6
Mean height (cm)	161.5	158.9	153.9	157.1
Mean disease duration since diagnosis (years)	1.6	1.5	3.7	2.6
Primary tumor type				
Pancreatic	1	0	2	3
Esophageal	1	1	0	2
Colorectal	1	0	0	1
Bile duct	0	1	0	1
Sarcoma	0	1	1	2
Neuroendocrine carcinoma	0	0	1	1
Cervix	0	0	1	1
Breast	0	0	1	1
ECOG performance status score				
0	3 (100.0)	2 (66.7)	6 (100.0)	11 (91.7)
1	0	1 (33.3)	0	1 (8.3)
Prior curative surgery [*n* (%)]	1 (33.3)	3 (100.0)	4 (66.7)	8 (66.7)
Prior curative radiotherapy [*n* (%)]	0	1 (33.3)	1 (16.7)	2 (16.7)
Number of prior systemic therapies [*n* (%)]				
1 Regimen	1 (33.3)	1 (33.3)	1 (16.7)	3 (25.0)
2 Regimens	0	1 (33.3)	1 (16.7)	2 (16.7)
≥3 Regimens	2 (66.7)	1 (33.3)	4 (66.7)	7 (58.3)

cm centimeter, *ECOG* Eastern Cooperative Oncology Group, *kg* kilogram, *Q12H* dose every 12 h

received at least 1 prior systemic therapy at study entry (Table 1). At baseline, 11 patients (91.7 %) had ECOG PS = 0 and 1 patient (8.3 %) had ECOG PS = 1. Finally, all patients received ≥75 % of planned doses during Cycle 1 except for 1 patient who experienced DLT.

Safety

Eight patients (66.7 %) completed 1 cycle and 1 patient (8.3 %) each completed <1 cycle, 2 cycles, 3 cycles, and 10 cycles, respectively. Overall, relative dose intensity (mean) was greater in Cohort 2 (98.2 %) than Cohort 1 (88.3 %) or Cohort 3 (74.7 %).

Diarrhea was the most common treatment-emergent AE (TEAE) possibly related to study drug and was experienced by 1 patient in Cohort 1, 2 patients in Cohort 2, and 6 patients in Cohort 3 (Table 2). However, these events were manageable and no patients discontinued study treatment because of diarrhea. TEAEs (regardless of causality) that were at least Grade 3 occurred in no patients in Cohort 1, 2 patients in Cohort 2, and 3 patients in Cohort 3. One AE leading to discontinuation on day 15 of treatment, which was considered possibly related to study drug, occurred in the patient in Cohort 3 who experienced DLT (Grade 2 nausea). Although serious AEs were reported by 2 patients in Cohort 2 (biliary tract infection in 1 patient; gastric fistula and lung infection in 1 patient) and 2 patients in Cohort 3 (cancer pain and decreased appetite in 1 patient; deep vein thrombosis in 1 patient), none of these events were considered related to abemaciclib.

Grade 3–4 toxicities related to study drug were seen among patients in Cohort 2 and Cohort 3, but not among patients in Cohort 1 (Table 2). Hematological toxicities seen in Cohort 2 and Cohort 3 were asymptomatic and manageable.

There were no clinically relevant changes in vital signs; moreover, laboratory abnormalities were predominantly CTCAE grade 1 or 2. Consistent with the observation that abemaciclib inhibits renal efflux transporters [multidrug and toxin extrusion (MATE) 1 and 2-K] that mediate active secretion of creatinine from the proximal tubule, grade 1 and 2 increases in serum creatinine were seen in 50.0 and 25.0 % of patients, respectively. Importantly, these increases in creatinine occurred during treatment but generally returned to within normal range following cessation of treatment. There were no patients with QTcB or QTcF of >480 ms or QTcB/QTcF change of >60 ms from baseline. One patient in Cohort

Table 2 Treatment-emergent adverse events (events were graded using the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03)) related to study drug with at least one occurrence of grade ≥3 toxicity in at least one cohort

Preferred term[a]	100 mg Q12H ($n = 3$)		150 mg Q12H ($n = 3$)		200 mg Q12H ($n = 6$)		Total ($n = 12$)	
	All grades	Grades 3–4	All grades	Grades 3–4	All grades	Grades 3–4	All grades	Grades 3–4
Leukopenia	2 (66.7 %)	0	1 (33.3 %)	1 (33.3 %)	5 (83.3 %)	3 (50.0 %)	8 (66.7 %)	4 (33.3 %)
Neutropenia	2 (66.7 %)	0	1 (33.3 %)	1 (33.3 %)	4 (66.7 %)	1 (16.7 %)	7 (58.3 %)	2 (16.7 %)
Thrombocytopenia	2 (66.7 %)	0	1 (33.3 %)	1 (33.3 %)	2 (33.3 %)	0	5 (41.7 %)	1 (8.3 %)
Anemia	0	0	1 (33.3 %)	0	2 (33.3 %)	1 (16.7 %)	3 (25.0 %)	1 (8.3 %)
Lymphopenia	0	0	1 (33.3 %)	1 (33.3 %)	0	0	1 (8.3 %)	1 (8.3 %)
Diarrhea	1 (33.3 %)	0	2 (66.7 %)	0	6 (100.0 %)	1 (16.7 %)	9 (75.0 %)	1 (8.3 %)

Q12H dose every 12 h, *mg* milligram

[a] Consolidated terms for neutropenia include neutropenia and neutrophil count decreased; leukopenia includes leukopenia and white blood cell count decreased; lymphopenia includes lymphopenia and lymphocyte count decreased; anemia includes anemia, hemoglobin decreased, and red blood cell count decreased; thrombocytopenia includes thrombocytopenia and platelet count decreased

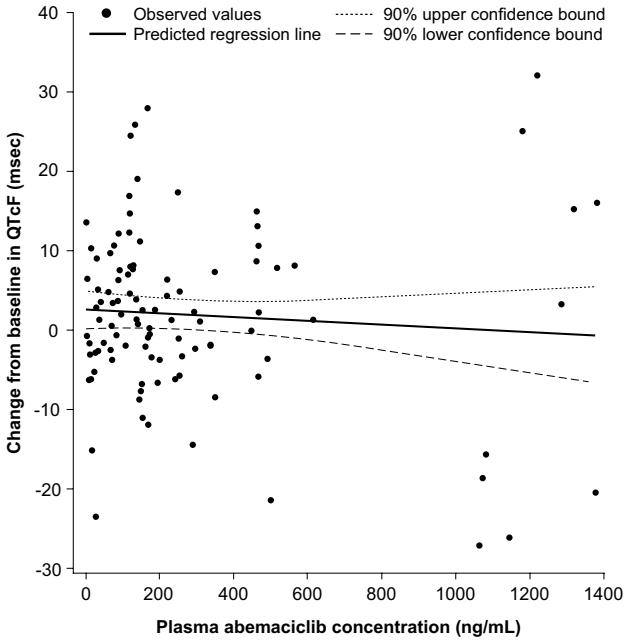

Fig. 1 Change in QTcF from baseline versus time-matched abemaciclib plasma concentration. $n = 102$, $R^2 = 0.005$, change = 2.5105 − 0.0023 * concentration. *QTcF* corrected QT interval using Fridericia's formula

2 was observed with a change in QTcB/QTcF of >30 ms from baseline, and 1 patient in Cohort 3 had a change in QTcB of >30 ms from baseline. However, no relationships were detected between change in QTcF and plasma concentrations of abemaciclib in the Japanese population (Fig. 1).

Pharmacokinetic evaluation

PK data for abemaciclib after a single oral administration from pre-dose (day 3 of Cycle 1) through 72 h post-dose (day 1 of Cycle 1) were available from all 12 patients. The PK profile of abemaciclib after a single oral administration was characterized by slow absorption (median t_{max} range approximately 5–6 h post-dose) with $t_{½}$ 14.2–27.5 h (Table 3; Fig. 2a). High PK variability was observed with coefficients of variation (CVs) reaching maximum values of 87 and 94 % for C_{max} and $AUC_{(0-tlast)}$, respectively. The PK of abemaciclib at steady state after repeated oral administration was studied using data available from a total of nine patients (two patients each in Cohort 1 and 2, and 5 patients in Cohort 3) on day 28 of Cycle 1 (from pre-dose through 24 h post-dose). The PK profile of abemaciclib at steady state after repeated oral administration was also characterized by slow absorption (with a median $t_{max,ss}$ of approximately 4 h post-dose) (Table 3). High PK variability at steady state was observed with CVs of 64 and 73 % for $C_{max,ss}$ and $AUC_{\tau,ss}$, respectively.

The mean concentrations in Cohort 3 were lower than those in Cohort 1 or Cohort 2 (Fig. 2b), most likely because 1 patient each in Cohort 1 and Cohort 2 had relatively high exposures to abemaciclib.

Efficacy

Maximal percent change in tumor size from baseline for all patients with measurable disease ranged approximately from 35 % decrease in tumor size to 25 % increase in tumor size (Fig. 3). In Cohort 3, decreases in tumor size from baseline greater than 30 % were noted in 2 patients: One patient had breast adenocarcinoma that was estrogen receptor negative (ER^-), progesterone receptor negative (PR^-), and human epidermal growth factor receptor-2 positive ($HER2^+$) and one patient (who completed Cycle 10 as of the reporting cutoff) had neuroendocrine carcinoma of the small intestine. Although no radiologically confirmed

Table 3 Summary of abemaciclib pharmacokinetic parameters (expressed as geometric mean unless otherwise stated) following a single oral dose on day 3 and at steady state on day 28 following twice-daily oral dosing

Variable	100 mg Q12H ($n = 3$)	150 mg Q12H ($n = 3$)	200 mg Q12H ($n = 6$)
Single dose			
n	3	3	6
Dose (mg)	100	150	200
t_{max} [h, median (range)]	5.93 (5.92–7.98)	5.95 (3.95–6.05)	4.97 (3.95–5.95)
C_{max} [ng/mL (%CV)]	127 (51)	167 (40)	214 (87)
$AUC_{(0–tlast)}$ [ng h/mL (% CV)]	3880 (71)	3960 (39)	5170 (94)
$AUC^{b}_{(0–\infty)}$ [ng h/mL (% CV)]	6970, 6450[a]	4450 (39)	5480 (95)
CL/*F* [L/h (% CV)]	14.3, 15.5[a]	33.7 (39)	36.5 (95)
V_{ss}/F [*L* (% CV)]	633, 577[a]	1120 (41)	947 (90)
$t_{1/2}$ [h (range)]	27.5, 24.1[a]	21.9 (19.3–24.6)	16.3 (14.2–22.6)
Steady state			
n	2	2	5
Daily dose (mg)	200	300	400
$t_{max,ss}$ [h, median (range)]	3.95, 6.03[a]	3.98, 3.98[a]	4.02 (2.05–6.00)
$C_{min,ss}$ [ng/mL (% CV)]	132.56, 1044.12[a]	1176.16, 102.65[a]	210 (89)
$C_{max,\ ss}$ [ng/mL (% CV)]	231.58, 1379.20[a]	1381.46, 148.86[a]	298 (64)
$AUC_{\tau,ss}$ [ng h/mL (% CV)]	2070, 14,100[a]	15,500, 1460[a]	3020 (73)

AUC area under the plasma concentration versus time curve, $AUC_{(0–tlast)}$ AUC from time zero to last time point with a measurable plasma concentration, $AUC_{(0–\infty)}$ AUC from time zero to infinity, $AUC_{\tau,ss}$ AUC during one dosing interval at steady state, *CL/F* apparent total body clearance, $C_{max,ss}$ maximum observed plasma concentration at steady state, $C_{min,ss}$ minimum observed plasma concentration at steady state, *% CV* percent coefficient of variation, $t_{1/2}$ elimination half-life, $t_{max,ss}$ time to reach maximum observed plasma concentration at steady state, V_{ss}/F apparent volume of distribution at steady state

[a]

[b] Individual values are reported when $n < 3$

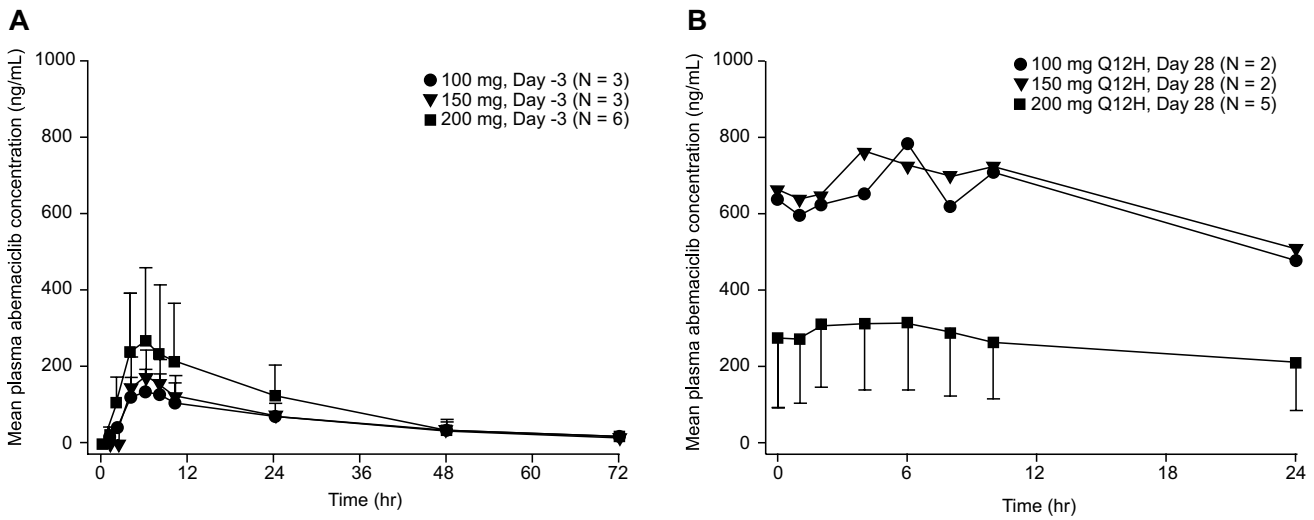

Fig. 2 Abemaciclib plasma concentration (arithmetic mean ± SD*) versus time following a single oral dose on day 3 (**a**) and at steady state on day 28 following twice-daily oral dosing (**b**). *Q12H* dosing every 12 h, *SD* standard deviation. *SD is presented only for samples with $n \geq 3$

responses were observed in the study, durable disease control (>10 cycles) was achieved for 1 patient in Cohort 3. ECOG PS worsened from baseline to follow-up or final cycle in six patients.

Discussion

In this phase 1 study in Japanese patients with advanced cancer, abemaciclib demonstrated a safety profile that was

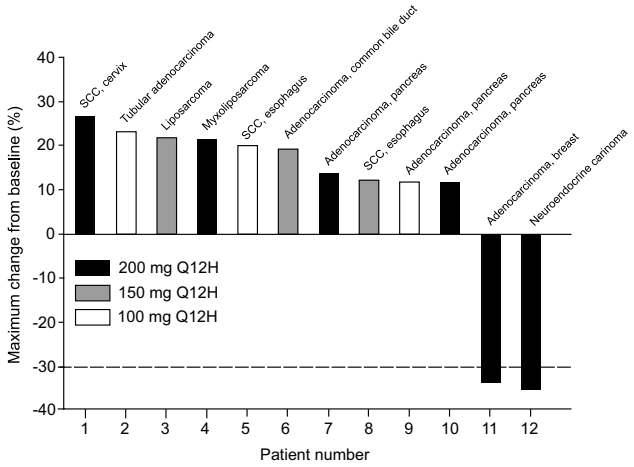

Fig. 3 Waterfall plot of maximal percent change in tumor size from baseline. *SCC* squamous cell carcinoma

manageable up to the previously established MTD (200 mg Q12H). Only 1 patient experienced DLT (Grade 2 nausea), which required dose omission. Diarrhea was manageable with supportive measures and hematological toxicity was acceptable. The PK profile was characterized by slow absorption and high PK variability. The elimination half-life of abemaciclib showed lower variability compared with other PK parameters, which suggests underlying variability in absorption rather than clearance. Regarding efficacy, 1 of 6 patients at the 200 mg Q12H dose achieved durable disease control for >10 cycles and continued to receive ongoing abemaciclib treatment at the reporting cutoff and at Cycle 22 as of February 26, 2016.

The overall safety and PK results of this phase 1 study in Japanese patients were similar to those observed in non-Japanese patients [12]. The most common DLT noted among non-Japanese patients was grade 3 fatigue, whereas one case of grade 2 nausea was noted among Japanese patients in this study. In both Japanese and non-Japanese patients, TEAEs were most commonly related to the gastrointestinal, renal, and hematopoietic systems. PK profiles of abemaciclib were similar in Japanese and non-Japanese patients. No remarkable differences in the PK of abemaciclib were observed between non-Japanese patients and the Japanese patients enrolled in this study. Although responses were not observed in this study, antitumor activity was evident in the Japanese population, with 2 patients experiencing decreases in tumor size greater than 30 %.

Abemaciclib inhibits renal efflux transporters [MATE 1 and 2-K] that mediate active secretion of creatinine from the proximal tubule. As such, increases in serum creatinine during abemaciclib therapy may not accurately reflect renal function. Instead, measures of glomerular filtration rate that are independent of renal efflux transporters (such as cystatin C) may yield a more accurate estimate of renal function than serum creatinine for patients receiving abemaciclib. In this study, mild increases in serum creatinine occurred during treatment but generally returned to within normal range following cessation of treatment. Based on these results, alternative methods to serum creatinine should be used if needed to evaluate renal function for patients receiving abemaciclib.

Two patients in Cohort 3 had significant decrease in tumor size, suggesting that 200 mg Q12H is the dose recommended by efficacy. Interestingly, one patient with hormone receptor-negative and $HER2^+$ breast cancer experienced an antitumor effect, indicating potential activity in $HER2^+$ disease.

Because the current study focused specifically on Japanese patients, these results must be considered in the context of previously reported studies [12–15]. Importantly, the overall design of this study is consistent with recommendations for phase 1 clinical studies, which principally aim to establish the recommended dose and schedule of an investigational drug for further efficacy testing in phase 2 and 3 studies [19].

In conclusion, this phase 1 study for Japanese patients with advanced solid tumors demonstrated that single-agent abemaciclib has an acceptable safety profile with evidence of antitumor activity. The safety profile observed at doses up to the MTD establishes 200 mg Q12H as the recommended dose for abemaciclib as a single agent in this population. These findings support ongoing development of abemaciclib for diverse populations with advanced cancer.

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Compliance with ethical standards

Conflict of interest Kitano, Tanabe, Tamura, and Shimomura have no conflicts of interest to declare. Kondo has received research funding from AstraZeneca, Eli Lilly Japan K.K., and Bayer Yakuhin, Ltd. Yamamoto has received research funding for clinical trials from Chugai Pharmaceutical Co., Ltd, Taiho Pharma, Eisai Co., Ltd, Quintiles, Astellas, Bristol-Myers Squibb, Kyowa-Hakko Kirin, Novartis Pharmaceuticals Japan, Daiichi-Sankyo, Pfizer, and Boehringer Ingelheim. Iwasa has received research funding for clinical trials from Eli Lilly Japan K.K. Fujiwara has served on advisory boards for Novartis Pharmaceuticals Japan and ONO Pharmaceuticals Japan, and received research funding for clinical trials from AstraZeneca, Eli Lilly Japan K.K, Chugai, Eisai Co., Daiichi-Sankyo, and MerckSerono. Ogasawara, Mori, and Asou are current employees of Eli Lilly Japan K.K.

Turner and Chan are current employees of and own stock in Eli Lilly and Company.

Role of the sponsor Eli Lilly Japan K.K. was involved in the study design, data collection, data analysis, and preparation of the manuscript.

Role of contributors All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. KO, PKT, HA, and EMC were involved in the study design and data analyses. S Kitano, S Kondo, NY, KT, YT, SI, AS, and YF were investigators in the study and were involved in data collection. KO and JM conducted the statistical analysis.

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