

Phase I study of palbociclib, a cyclin-dependent kinase 4/6 inhibitor, in Japanese patients

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This phase I study in Japanese patients evaluated the safety, pharmacokinetics, and preliminary efficacy of palbociclib, a highly selective and reversible oral cyclin-dependent kinase 4/6 inhibitor, as monotherapy for solid tumors (part 1) and combined with letrozole as first-line treatment of postmenopausal patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer (part 2). Part 1 evaluated palbociclib 100 and 125 mg once daily (3 weeks on/1 week off; $n = 6$ each group) to determine the maximum tolerated dose. Part 2 evaluated palbociclib maximum tolerated dose (125 mg) plus letrozole 2.5 mg ($n = 6$). The most common treatment-related adverse event was neutropenia (all grades/grade 3/4): 100 mg, 83%/67%; 125 mg, 67%/33%; and palbociclib plus letrozole, 100%/83%. Heavier pretreatment with chemotherapy may have resulted in higher neutropenia rates observed with the 100-mg dose. Palbociclib exposure was higher with 125 vs 100 mg (mean area under the plasma concentration–time curve over dosing interval [τ]: 1322 vs 547.5 ng·h/mL [single dose], 2838 vs 1276 ng·h/mL [multiple dose]; mean maximum plasma concentration: 104.1 vs 41.4 ng/mL [single dose], 185.5 vs 77.4 ng/mL [multiple dose]). Half-life was 23–26 h. No drug–drug interactions between palbociclib and letrozole occurred. Four patients had stable disease (≥ 24 weeks in one patient with rectal cancer [100 mg] and one with esophageal cancer [125 mg]) in part 1; two patients had partial response and two had stable disease (both ≥ 24 weeks) in part 2. Palbociclib at the 125-mg dose (schedule 3/1) was tolerated and is the recommended dose for monotherapy and letrozole combination therapy in Japanese patients. The trials are registered with www.ClinicalTrials.gov: A5481010 and NCT01684215.

Palbociclib (PD-0332991) is a potent and highly selective, reversible, oral inhibitor of cyclin-dependent kinases 4 and 6 that blocks G₁- to S-phase progression of the cell cycle, thereby preventing DNA synthesis.^(1–4) Cyclin-dependent kinase 4/6 inhibition is thought to have broad applicability to the treatment of advanced cancers.⁽⁵⁾ In estrogen receptor-positive (ER+) luminal breast cancer cell lines, palbociclib was shown to arrest tumor cell growth, accompanied by an inhibition of retinoblastoma protein hyperphosphorylation, and it also showed synergistic antitumor activity when combined with tamoxifen.⁽⁶⁾

Currently, endocrine therapies such as tamoxifen, fulvestrant, and aromatase inhibitors are the standard of care for women with ER+ advanced or metastatic breast cancer; however, many patients develop resistance to these therapies.⁽⁷⁾ A randomized phase II trial (PALOMA-1/TRIO-18) evaluated palbociclib (125 mg once daily) in combination with the aromatase inhibitor letrozole (2.5 mg once daily) compared with letrozole alone as first-line therapy for postmenopausal women with ER+, human epidermal growth factor receptor 2-negative (HER2–)

advanced breast cancer.⁽⁸⁾ The combination group had significantly longer progression-free survival (PFS) compared with the letrozole monotherapy group: median PFS of 20.2 months vs 10.2 months (hazard ratio, 0.488; 95% confidence interval, 0.319–0.748; one-sided $P = 0.0004$). Palbociclib plus letrozole was generally well tolerated, with patients most commonly developing uncomplicated neutropenia.

Based on this encouraging activity and tolerability, but a lack of clinical experience with palbociclib in Japanese patients, a phase I study was designed to evaluate the safety, pharmacokinetics (PK), and preliminary efficacy of palbociclib as a single agent in Japanese patients with solid tumors and in combination with letrozole in first-line treatment of Japanese postmenopausal patients with ER+/HER2– advanced breast cancer.

Materials and Methods

Study design. This was a phase I, single-country, non-randomized, open-label, clinical study in Japanese patients

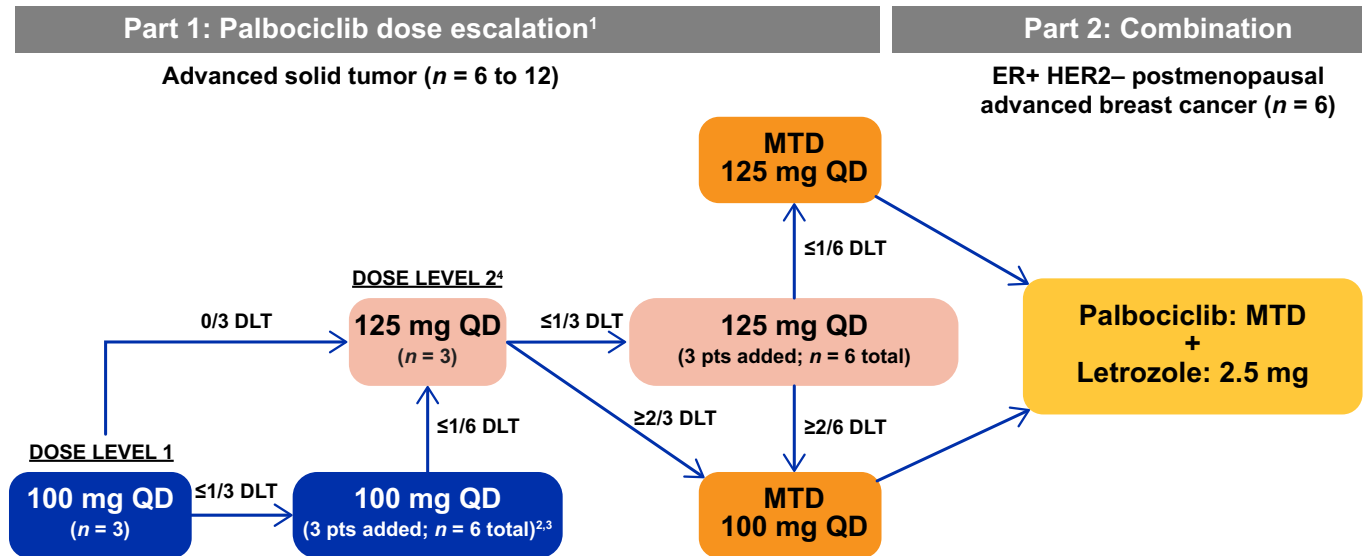


Fig. 1. Design of this phase I study of palbociclib in Japanese patients. ¹In principle, two dosages (100 mg once daily [QD] and 125 mg QD) were examined; where necessary, additional/lower dose levels (75 mg QD, dose level –1) were explored. ²If two or more patients of three to six patients at dose level 1 experienced a dose-limiting toxicity (DLT) during cycle 1, the dose was considered intolerable and a lower dose (75 mg QD, dose level –1) was used. ³If no further DLTs occurred in the three additional patients such that only one of six patients at dose level 1 experienced DLT(s) during the first cycle, then the dose was escalated to dose level 2 (125 mg QD) in a subsequent cohort of patients. ⁴If two or more patients of three to six patients at dose level 2 experienced a DLT during the first cycle, the dose was de-escalated to dose level 1 (100 mg QD) unless six patients were enrolled and evaluated at dose level 1 at that time. ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor-negative; MTD, maximum tolerated dose; pts, patients.

(NCT01684215). As shown in Figure 1, the study comprised two parts: (i) dose escalation study of palbociclib given as a single agent to identify the maximum tolerated dose (MTD) and assess the PK and preliminary efficacy of palbociclib in patients with advanced solid tumors in part 1, including the lead-in phase for PK evaluation after a single dose; and (ii) evaluation of the overall safety, PK, and preliminary efficacy of the combination of the MTD of palbociclib plus 2.5 mg letrozole in the first-line treatment of patients with ER+/HER2– advanced breast cancer in part 2. Part 1 used the 3 + 3 dose escalation scheme; target accrual for part 1 was approximately 6–12 patients, depending on the observed safety profile. For part 2, the target sample size was six patients.

The study protocol was approved by the Institutional Review Board of the National Cancer Center (Japan), and all patients gave written informed consent for participation. The study was carried out in accordance with applicable local laws and regulatory requirements, as well as the International Conference on Harmonisation’s Note for Guidance on Good Clinical Practice and the Declaration of Helsinki.

Patients. Key inclusion criteria (both study parts) included: age ≥ 20 years; Eastern Cooperative Oncology Group performance status 0–1; and adequate bone marrow, renal, and liver function. Additional inclusion criteria were as follows. For part 1, patients were required to have an advanced solid tumor, other than small-cell lung cancer or retinoblastoma, that was refractory to standard therapy or lacked an available standard therapy. For part 2, postmenopausal patients had ER+/HER2– adenocarcinoma of the breast that showed evidence of locoregionally recurrent or metastatic disease (including bone-only disease) and was not amenable to resection or radiation therapy with curative intent, and for which chemotherapy was not clinically indicated.

Key exclusion criteria (both study parts) were baseline corrected QT (QTc) interval >470 ms, history (or documented

family history) of long-QT syndrome, history of clinically significant ventricular dysrhythmias, or current treatment with antiarrhythmic medication or implanted defibrillation device for ventricular dysrhythmias. Additional exclusion criteria were as follows. For part 1, recent receipt of cytotoxic chemotherapy or radiation (within 3 weeks); hormone therapy, immunotherapy, or other biologic therapy (within 14 days), or palliative radiotherapy (within 7 days) was not allowed. For part 2, patients must not have received previous systemic anti-cancer treatment for advanced breast cancer, prior neoadjuvant or adjuvant therapy with a non-steroidal aromatase inhibitor with disease recurrence on or within 12 months of treatment, or chemotherapy, radiotherapy, investigational agents, or other anticancer therapy within 2 weeks of the study.

Study treatment. In part 1, palbociclib 100 or 125 mg once daily was taken orally without any food or drink (except for water) consumption within ± 2 h of dosing and continually in a 3-weeks-on/1-week-off treatment schedule, defining a 28-day treatment cycle; inpatient dose escalation was not permitted. For cycle 1 (in part 1 only), there was a PK lead-in phase in which a single dose was given 7 days before day 1 of cycle 1. In part 2, palbociclib was given at the MTD determined in part 1 (given once daily) plus letrozole; letrozole was to be taken continually (or alone in the event of palbociclib dosing interruption). In parts 1 and 2, palbociclib dose was interrupted or reduced if drug-related toxicity occurred according to predefined dose-modification criteria. Minimum available palbociclib dose was 75 mg once daily. Patients continued treatments until intolerable toxicity, progressive disease, or withdrawal of consent.

Assessments. *Dose-limiting toxicity criteria (part 1).* In part 1, any of the following treatment-related adverse events (AEs) during the first cycle were to be classified as dose-limiting toxicities (DLTs): (i) grade 4 neutropenia lasting >7 days, febrile neutropenia (grade ≥ 3 with body temperature $\geq 38.5^\circ\text{C}$), grade

≥3 thrombocytopenia with bleeding, or grade 4 thrombocytopenia; (ii) grade ≥3 non-hematologic toxicity with the exception of grade ≥3 nausea, vomiting, and/or diarrhea controllable with antiemetics and antidiarrheals, or grade ≥3 electrolyte abnormalities controllable with electrolyte supplementation or lacking significant clinical symptoms; and (iii) grade 3 QTc prolongation persisting after correction of any reversible cause. Additional DLT criteria included an inability to receive the next dose within 1 week of the last day of the previous cycle because of lack of hematologic recovery (platelets <50 000/μL, absolute neutrophil count [ANC] <1000/μL, or hemoglobin <8.0 g/dL) or prolonged non-hematologic toxicities attributable to palbociclib, as well as receipt of <75% of the planned dose of palbociclib in the first cycle due to toxicities attributable to palbociclib. The MTD was defined as the highest dose level studied for which the incidence of first-cycle DLT is less than 33%.

Safety. Safety assessments included AEs (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0), with the exception of febrile neutropenia and QTc DLT criteria, laboratory testing (hematology, blood chemistry, coagulation profiles, and urinalysis), 12-lead electrocardiogram monitoring, physical examination, pulse oximetry, and Eastern Cooperative Oncology Group performance status assessment. Monitoring of AEs was continuous, whereas the other parameters were assessed on days 1 and 15 of each cycle (with hematology and pulse oximetry also assessed on day 8 in cycle 1 only).

Pharmacokinetic sampling. Pharmacokinetic samples were obtained: predose and 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h postdose during the lead-in phase in part 1 (single dose); predose and 1, 2, 4, 6, 8, 12, and 24 h postdose on day 8 of cycle 1 in part 1 (multiple doses); and predose and 4 h postdose on day 15 of cycles 1 and 2, as well as predose on day 1 of cycles 2 and 3 in part 2.

Antitumor activity. Tumor measurement by computed tomography or MRI were carried out at screening, every 8 (part 1) or 12 (part 2) weeks during the study treatment period, and at the end of study treatment. Radionuclide bone scans were required at screening in part 2, every 24 weeks during study treatment, and at the end of study treatment if bone lesions were identified at screening. Assessments of tumor response and progression were carried out using computed tomography or MRI scans and categorized using Response Evaluation Criteria in Solid Tumors version 1.1. Objective responses required confirmation at least 4 weeks after the initial documented response.

Data analysis. The DLT evaluation set included all patients in whom DLTs were evaluable in cycle 1, with the PK analysis set consisting of all patients who had completed at least one day of PK blood sampling. Plasma palbociclib and letrozole concentrations were determined using a validated HPLC method with tandem mass spectrometry (lower limit of quantification, 1.00 ng/mL for palbociclib, 2.00 ng/mL for letrozole) at PPD (Richmond, VA, USA) for palbociclib and at WuXi AppTec (Shanghai, China) for letrozole. Pharmacokinetic parameters on day -7 in the lead-in phase of part 1 and day 8 of cycle 1 in part 1 were estimated using non-compartmental methods (internal software eNCA, version 2.2.4; Pfizer, Groton, CT, USA). The PK parameters assessed after single and multiple doses included maximum plasma concentration (C_{max}), terminal half-life ($t_{1/2}$), time at which C_{max} was observed (t_{max}), area under the plasma concentration–time curve from time 0 to time of last measurable plasma concen-

tration (AUC_{last}) and AUC from time 0 to infinity (AUC_{inf}) for only a single dose, AUC over dosing interval τ (AUC_{τ}) for only multiple doses. Accumulation ratio (R_{ac}) and predicted accumulation ratio to estimate linearity (R_{ss}) were also evaluated after multiple doses. The drug–drug interaction potential between palbociclib and letrozole was assessed using trough plasma concentration (C_{trough}) and plasma concentration at 4 h postdosing (C_4) of palbociclib and letrozole.

In both parts 1 and 2, the safety analysis set included all enrolled patients who receive at least one dose of study drugs. Objective response rate (complete response [CR] or partial response [PR]) and disease control rate (DCR; CR, PR, or stable disease ≥24 weeks) were calculated. Progression-free survival was also assessed; PFS data were censored on the date of the last tumor assessment during the study for patients without objective tumor progression who did not die while on the study.

Results

Each group of six patients was enrolled at two dose levels in parts 1 or 2; a total of 18 patients were enrolled. The data cut-off date was March 31, 2015. Baseline characteristics for the 18 treated patients are shown in Table 1. Overall, the study population had a good performance status and was heavily pretreated in part 1, with more than 80% of patients having received three or more prior systemic therapies.

Table 1. Baseline characteristics of Japanese patients participating in a two-part phase I trial of palbociclib

	Part 1		Part 2
	Palbociclib 100 mg, <i>n</i> = 6	Palbociclib 125 mg, <i>n</i> = 6	Palbociclib 125 mg + letrozole, <i>n</i> = 6
Median age (range), years	59 (44–65)	49 (24–69)	62 (59–76)
Female sex, <i>n</i> (%)	5 (83)	2 (33)	6 (100)
Median weight (range), kg	65 (47–94)	58 (36–81)	55 (42–62)
ECOG PS, <i>n</i> (%)			
0	5 (83)	4 (67)	3 (50)
1	1 (17)	2 (33)	3 (50)
Tumor types, <i>n</i> (%)			
Breast cancer	2 (33)	1 (17)	6 (100)
Other†	4 (67)	5 (83)	0 (0)
Prior systemic therapies,‡ <i>n</i> (%)	6 (100)	6 (100)	4 (67)‡§
Regimens			
1	0 (0)	0 (0)	0 (0)
2	0 (0)	2 (33)	2 (33)
3	1 (17)	2 (33)	1 (17)
>3	5 (83)	2 (33)	1 (17)

†Including colon cancer, medullary thyroid cancer, ovarian cancer, and rectal cancer (*n* = 1 each) in the 100-mg group; fibroma, esophageal carcinoma, rectal cancer, inflammatory myofibroblastic tumor, and pancreatic cancer (*n* = 1 each) in the 125-mg group. ‡Including adjuvant or neoadjuvant therapy. §Patients who had received adjuvant therapy (recorded as a prior systemic therapy) were eligible if therapy was not used for their locoregionally recurrent or metastatic estrogen receptor-positive breast cancer. ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety. Dose-limiting toxicity by dose level. Dose-limiting toxicity was observed in one patient per dose level in part 1 (Table 2). Both patients had breast cancer and were heavily pretreated relative to the other patients; one patient received <75% of the planned 100-mg dose because of grades 3 and 4 decreased neutrophil count, and the other patient had a decreased platelet count (grade 4) on palbociclib 125 mg. The MTD for palbociclib was determined to be 125 mg once daily and was used in part 2 in combination with letrozole.

Treatment-related adverse events. Common treatment-related AEs were hematologic toxicities, most often neutropenia and leukopenia (Table 3). All patients in part 2 developed neutropenia and leukopenia, with grade 3/4 incidences of 83% and 50%, respectively. Generally, ANC decreased with palbociclib treatment and recovered during the treatment-off period (Fig. 2).

Non-hematologic toxicities were infrequently seen, with the most commonly reported events limited to two cases per cohort. The most common all-grade non-hematologic events were increased blood creatinine with palbociclib 100 mg and fatigue and diarrhea with palbociclib 125 mg, whether given as monotherapy or with letrozole (Table 3). No grade ≥ 3 treatment-related non-hematologic AEs were observed.

Serious adverse events and deaths. Only one serious AE was reported in this study (grade 4 gastrointestinal perforation in the palbociclib plus letrozole cohort), which was not considered treatment-related. No deaths were reported in the study.

Pharmacokinetics. In the PK assessment of palbociclib 100 and 125 mg (part 1), higher than dose-proportional exposure was observed at 125 mg (Table 4, Fig. 3), whereas median t_{max} (4–5 h) and $t_{1/2}$ (23–26 h) values remained relatively constant (Table 4).

Following multiple oral doses of palbociclib plus letrozole in part 2, the geometric mean ratios of the predose (C_{trough}) and 4 h postdose (C_4) plasma palbociclib concentrations for palbociclib plus letrozole (part 2) versus palbociclib 125 mg alone (part 1) were 1.2 and 0.9, respectively (Table 5). Similarly, the geometric mean ratio of the predose plasma letrozole concentration for palbociclib plus letrozole versus letrozole alone (part 2) was 0.9 (Table 6). Therefore, there was no evidence of a drug–drug interaction between palbociclib and letrozole.

Relationship between change in absolute neutrophil count and pharmacokinetics. The maximum percentage change in ANC in cycle 1 correlated with PK parameters AUC_{τ} and C_{max} , with correlation coefficients of -0.5292 and -0.4581 , respectively (Fig. 4).

Antitumor activity. In part 1, objective responses (CR or PR) were not reported; stable disease was observed in three of six patients (Table 7) receiving palbociclib 100 mg (one with stable disease lasting ≥ 24 weeks; patient with rectal cancer) and in one of six patients receiving palbociclib 125 mg (stable disease lasted ≥ 24 weeks; patient with esophageal cancer; Table 7). Among the six patients receiving palbociclib 125 mg plus letrozole in part 2, objective response was reported in two patients (PR; Table 7), and two patients had stable disease (lasting ≥ 24 weeks in both patients; Table 7). The DCR (objective response or stable disease ≥ 24 weeks) was 17% in patients receiving palbociclib 100 or 125 mg in part 1 and 67% in patients receiving palbociclib 125 mg combined with letrozole in part 2. Maximum tumor reductions are shown in Figure 5; the greatest tumor shrinkage was observed in patients with breast cancer treated with palbociclib 125 mg plus letrozole.

Among patients receiving palbociclib 100 or 125 mg in part 1, duration of PFS ranged from 29 to 223 days and 28 to 280 days, respectively. In patients receiving palbociclib 125 mg plus letrozole in part 2, duration of PFS ranged from 31 to ≥ 592 days (Table 7).

Table 2. Dose-limiting toxicities observed in part 1 of a two-part phase I trial of palbociclib

Tumor type	Disease stage at time of study entry	Sex	Age, years	Duration from histopathologic diagnosis, years	DLT
100-mg dose group					
Ovarian cancer	III C	Female	62	3.49	None
Breast cancer	IV	Female	65	10.28	Yes†
Colon cancer	IV	Female	49	1.46	None
Medullary thyroid cancer	IV	Male	44	3.05	None
Rectal cancer	IV	Female	56	2.46	None
Breast cancer	IV	Female	65	2.36	None
125-mg dose group					
Inflammatory myofibroblastic tumor	IV B	Male	24	1.86	None
Pancreatic acinar cell carcinoma	IV	Female	24	0.52	None
Esophageal cancer	IV	Male	42	2.27	None
Fibroma	IV	Male	58	3.00	None
Breast cancer	IV	Female	69	12.08	Yes‡
Rectal cancer	IV	Male	55	2.01	None

†Less than 75% of planned dose received because of decreased neutrophil count (grades 3 and 4). ‡Decreased platelet count (grade 4). DLT, dose-limiting toxicity.

Discussion

In part 1, we evaluated two dose levels of palbociclib and confirmed that the MTD of single-agent palbociclib in Japanese patients was 125 mg, although additional higher doses were not investigated. The 125-mg dose (schedule 3/1) was tolerated and considered a recommended dose for Japanese patients and western populations as monotherapy based on the observed DLTs and overall safety profile. After identification of the recommended dose for Japanese patients, we initiated part 2 to evaluate palbociclib (125 mg) plus letrozole (2.5 mg) in Japanese women with ER+/HER2– advanced breast cancer. The observed safety profile, both with palbociclib monotherapy and the palbociclib plus letrozole combination in Japanese patients, was consistent with AE data derived from prior Western phase I and phase II studies,^(8,9) as common treatment-related AEs were hematologic toxicities, particularly uncomplicated neutropenia. Palbociclib (125 mg) plus letrozole (2.5 mg) was well tolerated in Japanese women with ER+/HER2– advanced breast cancer. Regardless of the doses and regimens of palbociclib evaluated in this study, neutrophil counts were decreased during the 3-week treatment period and quickly recovered in the 1-week-off treatment period, although an additional week of recovery was needed in some patients. In part 1, two patients who experienced DLTs were discontinued from the study; one patient because of decreased neu-

Table 3. Treatment-related adverse events (AEs) occurring in two or more patients in any palbociclib treatment cohort

AE, [†] n (%)	Part 1				Part 2	
	Palbociclib 100 mg, n = 6		Palbociclib 125 mg, n = 6		Palbociclib 125 mg + letrozole, n = 6	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Any AE	6 (100)	4 (67)	5 (83)	4 (67)	6 (100)	5 (83)
Neutrophils decreased	5 (83)	4 (67)	4 (67)	2 (33)	6 (100)	5 (83)
WBCs decreased	4 (67)	2 (33)	5 (83)	2 (33)	6 (100)	3 (50)
Blood creatinine increased	2 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Platelets decreased	1 (17)	0 (0)	2 (33)	1 (17)	3 (50)	0 (0)
Lymphocytes decreased	1 (17)	1 (17)	3 (50)	2 (33)	0 (0)	0 (0)
Fatigue	0 (0)	0 (0)	2 (33)	0 (0)	2 (33)	0 (0)
Diarrhea	0 (0)	0 (0)	2 (33)	0 (0)	1 (17)	0 (0)

[†]Graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. WBC, white blood cell.

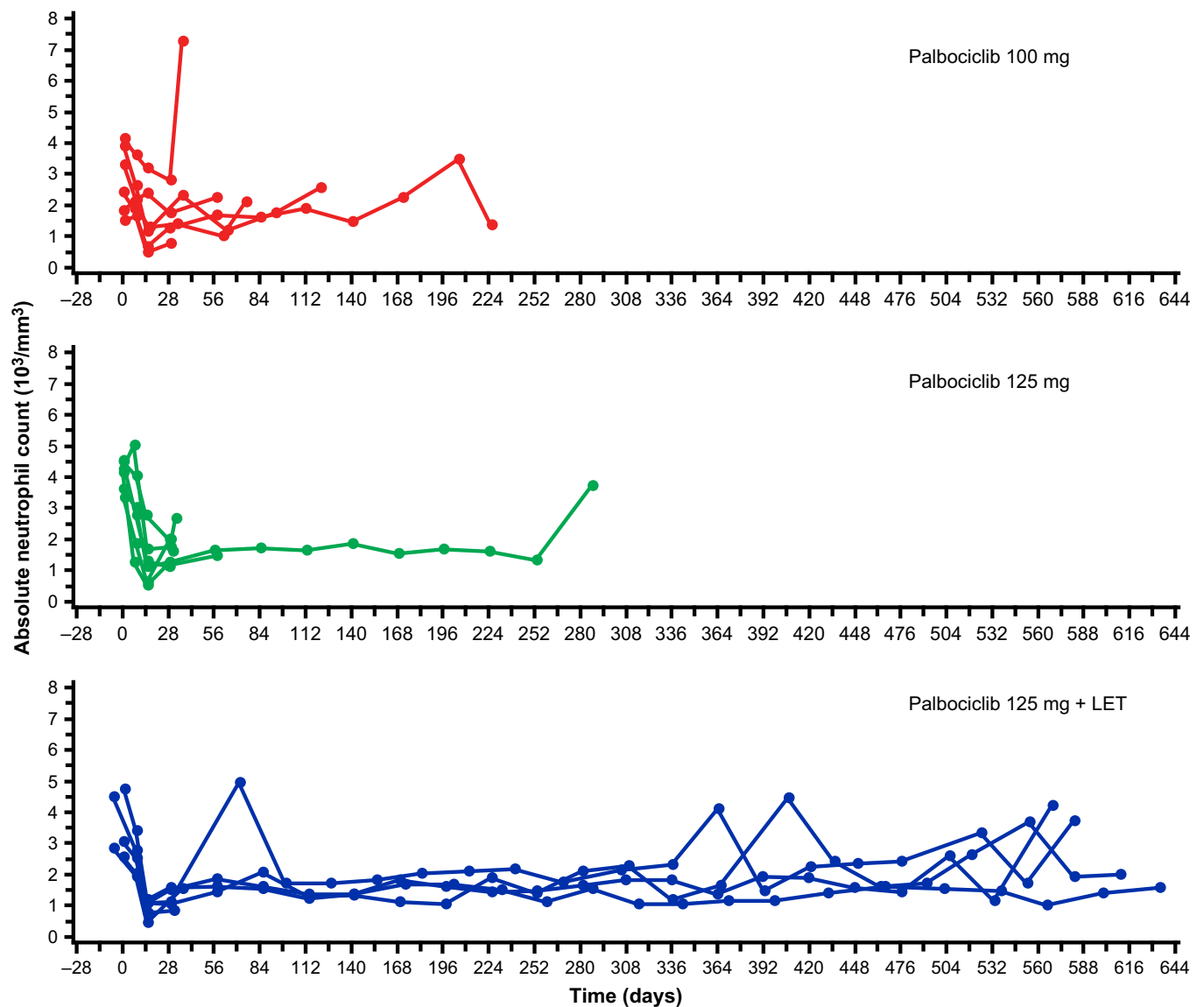


Fig. 2. Time course change in absolute neutrophil count in a phase I study of palbociclib in Japanese patients. LET, letrozole.

Table 4. Summary of plasma palbociclib pharmacokinetic parameter values (day 8 of cycle 1) following single and once-daily multiple dosing

Parameter (unit)	Summary statistics for palbociclib†			
	100 mg		125 mg	
	Single dose	Multiple doses	Single dose	Multiple doses
<i>n</i>	6	6	6	6
<i>C</i> _{max} (ng/mL)	41.4 (15)	77.4 (33)	104.1 (39)	185.5 (27)
<i>t</i> _{max} (h)	5.0 (4.0–8.0)	4.0 (4.0–6.0)	4.0 (3.9–8.0)	4.0 (4.0–6.0)
<i>t</i> _{1/2} (h)	25.7 ± 5.3	23.8 ± 6.8	23.9 ± 2.7	23.2 ± 7.7
AUC _{last} (ng·h/mL)	971.7 (31)	NA	2396 (48)	NA
AUC _{inf} (ng·h/mL)	1039 (32)	NA	2483 (49)	NA
AUC _τ ‡ (ng·h/mL)	547.5 (19)	1276 (45)	1322 (42)	2838 (43)
<i>R</i> _{ac}	NA	2.1 (1.8–3.5)	NA	1.9 (1.7–3.1)
<i>R</i> _{ss}	NA	1.1 (1.0–1.7)	NA	1.1 (0.9–1.5)

†Data are geometric mean (geometric %CV), except for *t*_{max}, *R*_{ac} and *R*_{ss} (median [range]) and *t*_{1/2} (arithmetic mean ± SD). ‡AUC_τ is the same as AUC from time 0–24 h (AUC_{0–24}) in this study. AUC_{last}, area under the plasma concentration–time curve from time zero to time of last measurable plasma concentration; AUC_τ, area under the plasma concentration–time curve over dosing interval; AUC_{inf}, area under the plasma concentration–time curve from time 0 extrapolated to infinity; *C*_{max}, maximum plasma concentration; NA, not applicable; *R*_{ac}, ratio of AUC_τ after multiple doses/AUC_τ after single dose; *R*_{ss}, ratio of AUC after multiple doses/AUC_{inf} after single dose; *t*_{1/2}, half-life; *t*_{max}, time at which *C*_{max} was observed.

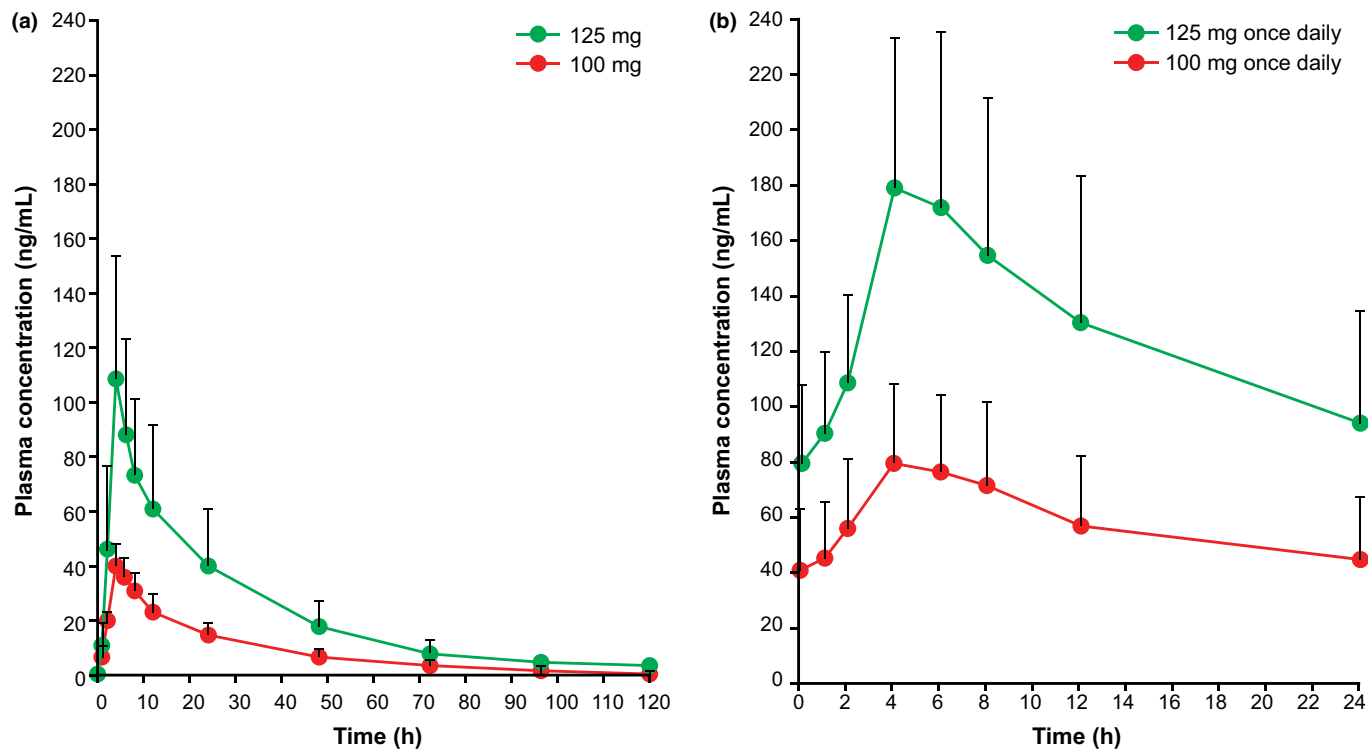


Fig. 3. Mean ± SD plasma palbociclib concentration–time profiles on pharmacokinetic lead-in phase day –7 following single oral dosing (a) and day 8 of cycle 1 following multiple oral dosing (b) in Japanese patients.

trophil count, the other because of disease progression. Although one serious AE (gastrointestinal perforation) was reported in this study, it was considered treatment-unrelated; treatment-related deaths were not reported. Overall, AEs were manageable and reversible with dose interruptions or dose reductions of palbociclib. No new safety signals were seen in either palbociclib monotherapy or palbociclib plus letrozole in Japanese patients.

In the present study, increased drug exposure, which was greater than dose proportional, was observed for palbociclib

125 mg, supporting further PK investigations for palbociclib in Japanese patients. For both single-dose and multiple-dose palbociclib, mean AUC and *C*_{max} values with the 125-mg dose were 2.2- to 2.6-fold higher than those for the 100-mg dose; however, *t*_{max} and *t*_{1/2} were similar between the 100- and 125-mg dose groups. No apparent differences in the safety profiles were noted between the 100- and 125-mg groups. Moreover, the safety profile with palbociclib monotherapy and the palbociclib plus letrozole combination in Japanese patients was similar to that observed in non-Japanese patients.^(8,9) In addition,

Table 5. Summary of palbociclib plasma concentrations following multiple oral doses of palbociclib 125 mg and letrozole 2.5 mg once daily

Parameter (unit)	Plasma palbociclib concentrations	
	Predose [C_{trough}]	4 h Postdose [C_4]
Geometric mean† (ng/mL)	88.5	155
Geometric CV (%)†	49	32
Geometric mean on day 8 of part 1 (ng/mL)	72.8	172
Geometric mean ratio (palbociclib + letrozole [part 2]/ palbociclib 125 mg alone [part 1])	1.2	0.9

†Calculated using arithmetic mean values for each patient on day 15 of cycles 1 and 2. C_4 , plasma concentration at 4 h postdose; C_{trough} , trough plasma concentration; CV, coefficient of variation.

Table 6. Summary of trough plasma letrozole concentrations following multiple oral doses of palbociclib 125 mg and letrozole 2.5 mg once daily

Parameter (unit)	Predose plasma letrozole concentrations	
	Letrozole alone	Palbociclib + letrozole
Geometric mean C_{trough} (ng/mL)	146†	131‡
Geometric CV (%)	59†	53‡
Geometric mean ratio (palbociclib + letrozole/ letrozole alone [part 2])		0.9

†Calculated by using arithmetic mean values for each patient on day 1 of cycles 2 and 3. ‡Calculated by using arithmetic mean values for each patient on day 15 of cycles 1 and 2. C_{trough} , trough plasma concentration; CV, coefficient of variation.

the results from the population PK analysis using PK data from 183 patients whose body weight ranged from 37.9 kg to 123 kg in three multinational clinical trials indicated that the effect of body weight on the PK of palbociclib was not consid-

ered to be clinically important, suggesting dose adjustment is not necessary by body weight.⁽¹⁰⁾ This result supported that the recommended dose for Japanese patients identified in part 1 was the same as that recommended for non-Japanese patients. Of note, a phase I study evaluating the PK parameters of palbociclib in healthy Japanese versus non-Asian subjects has been completed recently (NCT02059330), which should provide additional insight. Importantly, there was no evidence of a drug–drug interaction between palbociclib and letrozole in the present study. The maximum change of ANC was correlated with the PK parameters (C_{max} and AUC_{τ}) of palbociclib, although the patient who observed DLT did not show the highest C_{max} or AUC in each dose level (data not shown).

In part 1, extended stable disease (≥ 24 weeks) was observed in two patients (rectal and esophageal cancer) with palbociclib monotherapy at the 100- or 125-mg dose, who failed standard of care at the study entry, suggesting monotherapy may be effective in some tumor types. Further investigation is warranted for the evaluation of palbociclib monotherapy.

Part 2 of our study focused on the combination of palbociclib plus letrozole for the first-line treatment of postmenopausal patients with ER+/HER2– advanced breast cancer, which was preceded and supported by the encouraging PFS results reported in PALOMA-1 carried out at study sites in North America, Europe, Africa, and Asia (but not Japan).⁽⁸⁾ In the present phase I study, four of six ER+/HER2– advanced breast cancer patients still continue the treatment for over 1 year and two showed objective responses, suggesting a similar benefit is offered by the combination regimen with letrozole in postmenopausal Japanese women with ER+/HER2– advanced breast cancer as seen in PALOMA-1.⁽⁸⁾ The DCR was 67%, although two of six patients had no post-treatment tumor assessment because of discontinuation of the study in cycle 1 due to AEs or at the patient's request. To further evaluate the efficacy of the combination of palbociclib plus letrozole in Japanese patients, a phase II study is ongoing, for which enrolment is now complete. Two global randomized phase III studies (PALOMA-2 [NCT01740427] and PALOMA-3 [NCT01942135]) are also ongoing, assessing PFS as the primary endpoint in patients with advanced breast cancer.

The results from the ongoing PALOMA-3 trial showed significantly longer PFS with palbociclib plus fulvestrant com-

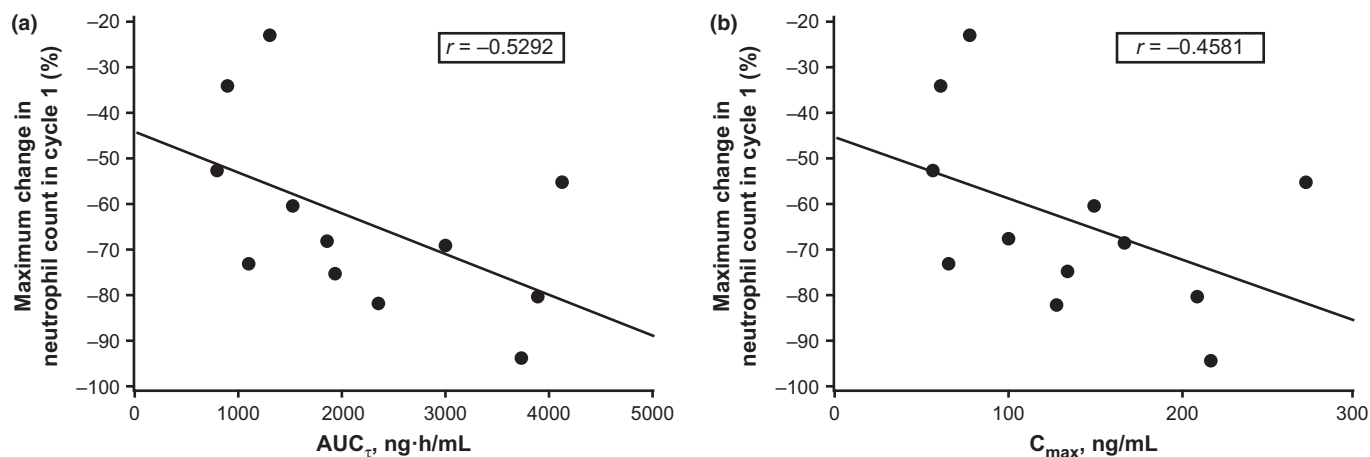


Fig. 4. Relationship between change in absolute neutrophil count and pharmacokinetic parameters area under the plasma concentration–time curve over dosing interval (AUC_{τ}) (a) and maximum plasma concentration (C_{max}) (b).

Table 7. Individual tumor response in patients treated with palbociclib as monotherapy for solid tumors (part 1) or palbociclib combined with letrozole for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer (part 2)

Primary diagnosis	Best response	Duration of objective response, days	Progression-free survival, days
Palbociclib 100 mg (part 1)			
Ovarian cancer	SD		121
Breast cancer	Indeterminate		29
Colon cancer	PD		29
Medullary thyroid cancer	PD		57
Rectal cancer	SD		223
Breast cancer	SD		75
Palbociclib 125 mg (part 1)			
Inflammatory myofibroblastic tumor	PD		28
Acinar cell carcinoma of pancreas	PD		29
Esophageal carcinoma	SD		280
Fibroma	PD		28
Breast cancer	PD		57
Rectal cancer	PD		32
Palbociclib 125 mg plus letrozole (part 2)			
Invasive ductal breast carcinoma	SD		≥582 [†]
Invasive ductal breast carcinoma	PR	≥498 [†]	≥582 [†]
Invasive ductal breast carcinoma	SD		≥592 [†]
Invasive ductal breast carcinoma	Indeterminate		36
Invasive ductal breast carcinoma	Indeterminate		31
Invasive ductal breast carcinoma	PR	≥421 [†]	≥505 [†]

[†]Ongoing at the data cut-off date. PD, progressive disease; PR, partial response; SD, stable disease.

pared with fulvestrant alone in patients with ER+/HER2– advanced breast cancer that had progressed during prior endocrine therapy.⁽¹¹⁾ Further evaluation of these therapies in Japanese patients is also warranted.

In conclusion, although a higher than dose-proportional increase in exposure was observed with palbociclib 125 mg relative to 100 mg, no interaction between palbociclib and letrozole was observed in this group of Japanese patients with advanced cancer, and one patient with esophageal cancer treated with the 125-mg dose experienced stable disease >24 weeks. The 125-mg dose (schedule 3/1) was tolerated and

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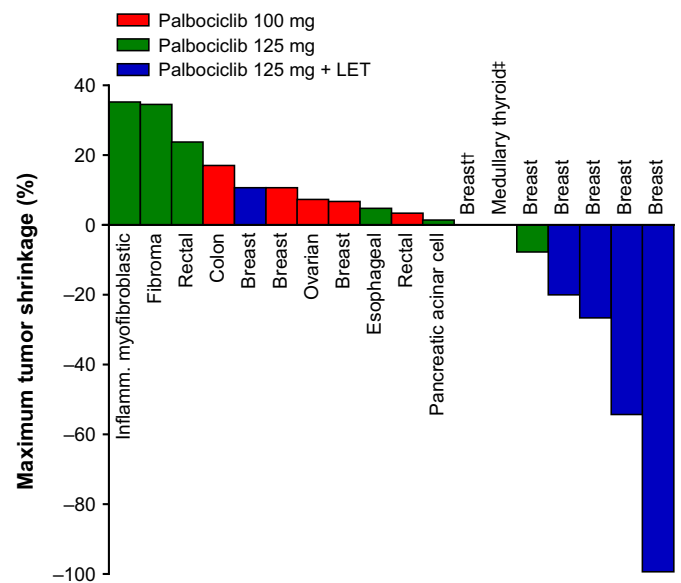


Fig. 5. Maximum shrinkage of solid tumors and estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer tumors treated with palbociclib 100 or 125 mg once daily and palbociclib 125 mg combined with letrozole (LET). Tumors were assessed using Response Evaluation Criteria in Solid Tumors version 1.1. [†]Palbociclib 125 mg + LET. [‡]Palbociclib 100 mg.

considered a recommended dose for monotherapy and letrozole combination therapy in Japanese patients. Based on these findings, the present study was expanded in Japan to phase II to further evaluate the efficacy and safety of palbociclib 125 mg once daily (3/1 schedule) in combination with letrozole for first-line treatment of postmenopausal patients with ER+/HER2– advanced breast cancer.

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