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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Ibrance® / Palbociclib

PROTOCOL NO.: A5481010

PROTOCOL TITLE:

A Phase 1/2 Study of the Efficacy, Safety, and Pharmacokinetics of Oral PD-0332991 (Palbociclib), a Cyclin-Dependent Kinase 4 and 6 (CDK4/6) Inhibitor, as Single Agent in Japanese Patients With Advanced Solid Tumors or in Combination With Letrozole for the First-Line Treatment of Postmenopausal Japanese Patients With ER(+) HER2(−) Advanced Breast Cancer

Study Centers:

A total of 16 centers in Japan took part in the study and enrolled patients; 2 in Phase 1 and 16 in Phase 2. Two (2) centers of Phase 1 of study also participated in Phase 2 of study.

Study Initiation, Primary Completion and Final Completion Dates:

Phase 1:
Study Initiation Date: 19 October 2012
Primary Completion Date: 31 March 2015 (Data cutoff)
Study Completion Date: 07 February 2018

Phase 2:
Study Initiation Date: 24 June 2014
Primary Completion Date: 04 March 2016 (Data cutoff)
Final Completion Date: 25 October 2018

Phase of Development:

Phase 1/2

Study Objectives:

Phase 1 Part 1:

Primary Objective:

- To assess safety and tolerability at increasing dose levels of single-agent palbociclib in Japanese patients with advanced solid tumor, in order to estimate the maximum tolerated dose (MTD).

Secondary Objectives:

- To evaluate the overall safety profile of single-agent palbociclib in Japanese cancer patients;
- To characterize the single and multiple dose pharmacokinetics (PK) of palbociclib when given as a single agent to Japanese cancer patients;
- To document any anti-tumor activity of single-agent palbociclib in Japanese cancer patients.

Phase 1 Part 2:

Primary Objective:

- To assess the overall safety and tolerability of palbociclib and letrozole when administered in combination in Japanese patients with estrogen receptor (ER)-positive human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC).

Secondary Objectives:

- To characterize PK of palbociclib and letrozole when administered in combination in Japanese patients with ER-positive HER2-negative ABC;
- To explore the efficacy of palbociclib and letrozole when administered in combination in Japanese patients with ER-positive HER2-negative ABC.

Phase 2:

Primary Objective:

- To evaluate the efficacy of palbociclib in combination with letrozole as measured by progression-free survival (PFS) probability at 12 months (1-year PFS probability) in postmenopausal Japanese patients with ER-positive HER2-negative ABC.

Secondary Objectives:

- To evaluate the efficacy of palbociclib in combination with letrozole as measured by objective response rate (ORR), disease control rate (DCR) (complete response [CR] + partial response [PR] + stable disease [SD] ≥24 weeks), duration of response (DOR), PFS, 1-year survival probability and overall survival (OS);
- To assess the safety and tolerability of palbociclib in combination with letrozole;
- To evaluate measure of health-related quality of life of palbociclib in combination with letrozole;

- To evaluate the full-profile PK of palbociclib in combination with letrozole in a subset of patients (n=6);

- To determine plasma trough concentrations of palbociclib in combination with letrozole in all patients;

- To characterize alterations in genes, proteins, and ribonucleic acids (RNAs) relevant to the cell cycle (eg, Cyclin D1 [CCND1] amplification, cyclin-dependent kinase inhibitor [CDK] N2A deletion), drug targets (eg, CDK 4/6), and tumor sensitivity and/or resistance (eg, Ki67, retinoblastoma protein [Rb]) in tumor tissue samples.

METHODS

Study Design:

This study was comprised of a Phase 1 portion and a Phase 2 portion.

Phase 1:

The Phase 1 portion was a single-country, non-randomized, open-label, clinical study, comprised of 2 parts: 1) a dose escalation part for palbociclib as a single agent in patients with advanced solid tumors (Part 1); 2) a cohort to study palbociclib (at the MTD identified in Part 1) in combination with letrozole in the first-line treatment of patients with ER-positive HER2-negative ABC (Part 2). Safety, tolerability, preliminary efficacy, and PK profile of palbociclib were evaluated as a single agent in Japanese patients with advanced solid tumors (Part 1) and palbociclib in combination with letrozole in the first-line treatment of Japanese patients with ER-positive HER2-negative ABC (Part 2).

The original data for the Phase 1 portion of this study was collected till a data cutoff date of 31 March 2015. At the time of the data cutoff date, all patients from Part 1 of Phase 1 portion discontinued the study treatments, and 4 patients from Part 2 of Phase 1 portion remained on treatment. The Part 2 of Phase 1 portion was continued to further follow patients for safety and efficacy. After palbociclib was approved by the Ministry of Health, Labour and Welfare (MHLW) in Japan on 27 September 2017, this study continued as a post-marketing clinical study and, the Phase 1 portion of this study was closed when the 4 patients on treatment could access commercial palbociclib.

The data of the original analysis cutoff date for Phase 1 Part 1 and Part 2 have been presented, also the updated safety data from Part 2 of the Phase 1 portion; and brief update regarding efficacy analysis from Part 2 of the Phase 1 portion that was conducted at the time of study completion (Last Subject Last Visit: 07 February 2018) have been presented.

The schedules of study activities for Phase 1 Part 1 are summarized in Table 1 and Table 2 and for Phase 1 Part 2 are summarized in Table 3 and Table 4.

Table 1. Schedule of Activities (Phase 1 Part 1)

Protocol Activity	Screening[a] ≤28 Days Prior to PK Lead-In Dose	PK Lead-In -7 (±1)[b]	Treatment Cycles (1 Cycle=28 Days)								End of Treatment[c]	Follow-Up[d]
			Day 1		Day 8		Day 15		Day 22			
			-1[b]	±2	±1[b]	±2	±1[b]	±2	±1[b]	±2		
Baseline documentation												
Informed consent[e]	X											
Medical/tumor history	X											
Baseline signs and symptoms[f]	X											
Physical examination[g]	X	X	X				X[b]				X	
ECOG performance status	X	X	X				X[b]				X	
Laboratory												
Hematology[h]	X	X	X		X[b]		X[b]				X	
Blood chemistry[i]	X	X	X				X[b]				X	
Coagulation[j]	X	X	X[b]									
Urinalysis[k]	X										X	
Urine/serum pregnancy test[l]	X	X	Day 1 every cycle								X	
12-lead ECG[m]	X	X	X[b]				X[b]				X	
Pulse oximetry[n]	X	X	X		X[b]		X[b]				X	
Tumor/lung assessments												
Tumor/lung assessment (CT/MRI)[o]	X	Every 8 weeks									X	
Other clinical assessments												
Drug compliance[p]		X	X----------X								X	
AE[q]	X----------X										X	X
Concomitant medications/treatments[r]	X----------X										X	X
Study treatment												
Palbociclib		X	X----------Day 1-21----------X									
PK												
Plasma PK[s]		X[s]			X[s]							

Abbreviations: AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; Ca=calcium; Cl=chloride; CR=complete response; Cr=creatinine; CT=computed tomography; ECG=electrocardiogram; ECOG=eastern cooperative oncology group; EOT=End of Treatment; Hb=hemoglobin; Mg=magnesium; MRI=magnetic resonance imaging; Na=sodium; P=phosphorous; PK=pharmacokinetic; PR=partial response; PT=prothrombin time; PTT=partial thromboplastin time; SAE=serious adverse event; TB=total bilirubin; TP=total protein; WBC=white blood cell.

a. Screening: All assessments were performed prior to PK lead-in dose with palbociclib unless otherwise indicated. Acceptable time windows for performing each assessment were described in the column headings.

Table 1. Schedule of Activities (Phase 1 Part 1)

b. Cycle 1 only. PK lead-in occurred prior to Cycle 1 Day 1. Hematology, blood chemistry, coagulation, pulse oximetry and 12-lead ECG were not required if screening assessment was performed within 7 days prior to PK lead-in dose and if clinically significant findings were not observed.
c. End of Treatment: Performed within 1 week following last dose of palbociclib or study withdrawal.
d. Follow-Up: Follow-up visit was completed approximately 28 days after last dose of palbociclib or study withdrawal wherever possible.
e. Informed Consent: Signed and dated Institutional Review Board approved informed consent was required before any protocol-specific screening procedures were performed. Procedures performed as standard of care prior to signed and dated informed consent document, and within the 28-day screening window could be used for study eligibility. Patients also had to be asked to sign an additional consent document after Cycle 1 for confirmation of their willingness to continue participation in the study beyond Cycle 1.
f. Baseline Signs and Symptoms: Patients were asked about any signs and symptoms experienced within the past 14 days prior to PK lead-in dose. Clinically significant baseline signs and symptoms were recorded on the AE case report form page.
g. Physical Examination: Included an examination of major body systems, weight, blood pressure (seated position), pulse rate (all at Screening, on Day -7 [PK lead-in dose], Day 1 and Day 15 of Cycle 1 and Day 1 of each subsequent cycle) and height (at Screening only).
h. Hematology: WBC count, platelet count, Hb, and WBC differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes). Additional hematology could be performed as clinically indicated. Frequency was to be increased as clinically indicated to monitor neutropenia, thrombocytopenia, and anemia.
i. Blood Chemistry: BUN, Cr, albumin, AST, ALT, TB, ALP, Na, K, Cl, Ca, Mg, P, glucose, TP and uric acid. Additional chemistries performed as clinically indicated.
j. Coagulation: PT or international normalized ratio, PTT or activated PTT. Additional coagulation studies performed as clinically indicated.
k. Urinalysis: Screening and EOT only. Urine protein and blood. Dipstick was acceptable. If positive, microscopic analysis was performed and 24-hour urine was collected (only for protein excretion).
l. Urine/serum pregnancy test (for women of childbearing potential only): Pregnancy tests were performed on 2 occasions prior to starting study therapy - once at the start of Screening and once at the Baseline visit, immediately before study drug administration (within 72 hours of PK lead-in dose). Following a negative pregnancy result at Screening, appropriate contraception had to be commenced and a further negative pregnancy result was then required at the Baseline visit before the patients could receive the study drug. Pregnancy tests were also routinely repeated at every cycle during the active treatment period, at the EOT. It could also be repeated as per request of Institutional Review Board/Independent Ethics Committees or if required by local regulations.
m. 12-lead ECG: At each time point, 3 consecutive 12-lead ECGs were performed approximately 2 minutes apart.
n. Pulse oximetry: Pulse oximetry was performed at each time point as described, and then as clinically indicated (upon occurrence of dyspnea [shortness of breath, fever, cough etc]).
o. Tumor/lung assessment (CT/MRI): Tumor assessments included all known or suspected disease sites. Imaging could include chest, abdomen and pelvis CT or MRI scans. Brain scans and bone scans were performed at Baseline if disease was suspected and on-study as appropriate to follow disease. Baseline central nervous system imaging was only required in symptomatic patients to rule out central nervous system metastases. During the treatment period, repeat CT or MRI imaging was performed every 8 weeks ±1 week window after Cycle 1 Day 1. Confirmation of CR or PR was to be completed no <1 month after the initial response. The next scheduled tumor measurement could be used as the confirmatory scan. If a patient discontinued treatment for a reason other than CT or MRI scan evidence of tumor progression, an attempt was made to obtain CT/MRI at discontinuation if the prior CT or MRI scans were performed >4 weeks earlier. After completion of Cycle 12 (after the 48th week), tumor assessment was done only if clinically indicated. As clinically indicated, chest CT/MRI was also used for examination of lung symptoms/disease. Upon occurrence of dyspnea (shortness of breath, fever, cough etc) during treatment, chest CT/MRI was repeated if indicated.

Table 1. Schedule of Activities (Phase 1 Part 1)

p. Drug Compliance: All bottle(s) including any unused capsules were returned to the clinic for drug accountability.
q. Adverse Events: AEs were documented and recorded at each visit using National Cancer Institute Common Terminology Criteria for AEs Version 4.0. Patients had to be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities had resolved, whichever was later; or earlier than 28 days should the patient have commenced another anticancer therapy in the meantime. For SAEs, the active reporting period to the Sponsor or its designated representative began from the time that the patient provided informed consent, which was obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study drug, through and including 28 calendar days after the last administration of the study drug. SAEs occurring to a patient after the active reporting period had ended were to be reported to the Sponsor if the Investigator became aware of them; at a minimum, all SAEs that the Investigator believed had at least a reasonable possibility of being related to study drug were to be reported to the Sponsor.
r. Concomitant medications/treatments: Concomitant medications and treatments were recorded from 28 days prior to the start of palbociclib and up to 28 days after the last dose of palbociclib.
s. Plasma PK: Blood sampling for palbociclib concentration determination was required in PK lead-in phase and Cycle 1 Day 8 for all patients. Additional PK sampling could be indicated in conjunction with QT prolongation or collection of other biological specimens suitable for PK testing (eg, pleural fluid, ascites, etc).

Table 2. Blood Sampling Time Points for Pharmacokinetic Analysis (Phase 1 Part 1)

Study Days	**Day -7 (±1)**												**Cycle 1 Day 8 (±1)**							
Hour[a]	0[b]	1	2	4	6	8	12	24	48	72	96	120	0[b]	1	2	4	6	8	12	24
PK blood collection[c]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

The patient was admitted to hospital for at least 2 days for full PK sampling on Day -7 and Day 8 of Cycle 1.
Abbreviations: K_2EDTA=dipotassium ethylenediaminetetraacetic acid; PK=pharmacokinetic.
a. For PK blood collection, variation of up to 10% or 10 minutes, whichever was later, of the nominal time from dosing was not captured as a protocol deviation.
b. Taken immediately prior to any palbociclib dosing.
c. At least 4 mL of whole blood was drawn into a tube containing K_2EDTA for each time point.

Table 3. Schedule of Activities (Phase 1 Part 2)

Protocol Activity	Screening[a] ≤28 Days Prior to Cycle 1 Day 1	Treatment Cycles[b] (1 Cycle=28 Days)								End of Treatment[c, b]	Follow-Up[d]
		Day 1		Day 8		Day 15		Day 22			
		-1[e]	±2	±1[e]	±2	±1[e]	±2	±1[e]	±2		
Baseline documentation											
Informed consent[f]	X										
Medical/tumor history	X										
Baseline signs and symptoms[g]	X										
Physical examination[h]	X	X				X[e]				X	
ECOG performance status	X	X				X[e]				X	
Laboratory											
Hematology[i]	X	X		X[e]		X[e]				X	
Blood chemistry[j]	X	X				X[e]				X	
Coagulation[k]	X	X[e]									
Urinalysis[l]	X									X	
12-lead ECG[m]	X	X[e]				X[e]				X	
Pulse oximetry[n]	X	X		X[e]		X[e]				X	
Tumor/lung assessments											
Tumor/lung assessment (CT/MRI)[o]	X	Every 12 weeks								X	X[o]
Radionuclide bone scan, whole body[p]	X	Every 24 weeks								X	X[p]
Other clinical assessments											
Drug compliance[q]		X----------X								X	
AEs[r]	X----------X									X	X
Concomitant medications/treatments[s]	X----------X									X	X
Study treatment											
Palbociclib		X----------Days 1-21----------X									
Letrozole		X----------X									
Sparse PK											
Plasma PK[t]		X[t]				X[t]					

Table 3. Schedule of Activities (Phase 1 Part 2)

Abbreviations: AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; Ca=calcium; Cl=chloride; Cr=creatinine; CT=computed tomography; ECG=electrocardiogram; ECOG=eastern cooperative oncology group; EOT=End of Treatment; Hb=hemoglobin; Mg=magnesium; PK=pharmacokinetic; MRI=magnetic resonance imaging; Na=sodium; P=phosphorous; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PT=prothrombin time; PTT=partial thromboplastin time; SAE=serious adverse event; TB=total bilirubin; TP=total protein; WBC=white blood cell.

a. Screening: All assessments were performed prior to Cycle 1 Day 1 dose with palbociclib and letrozole unless otherwise indicated. Acceptable time windows for performing each assessment were described in the column headings.
b. All assessments were performed prior to dosing with study medications on the visit day unless otherwise indicated.
c. End of Treatment: Performed within 1 week following last dose of palbociclib and letrozole or study withdrawal.
d. Follow-Up: Follow-up visit was completed approximately 28 days after last dose of palbociclib and letrozole or study withdrawal.
e. Cycle 1 only. Hematology, blood chemistry, coagulation, pulse oximetry and 12-lead ECG were not required on Cycle 1 Day 1 if screening assessment was performed within 7 days prior to Cycle 1 Day 1 and if clinically significant findings were not observed.
f. Informed Consent: Signed and dated Institutional Review Board-approved informed consent was required before any protocol-specific screening procedures were performed. Procedures performed as standard of care prior to signed and dated informed consent document, and within the 28 day screening window could be used for study eligibility.
g. Baseline signs and symptoms: Patients were asked about any signs and symptoms experienced within the past 14 days prior to Cycle 1 Day 1. Clinically significant Baseline signs and symptoms were recorded on the AE case report form page.
h. Physical examination: Included an examination of major body systems, weight, blood pressure (seated position), pulse rate (at Screening, Day 1 and Day 15 of Cycle 1 and Day 1 of each subsequent cycle), and height (at Screening only).
i. Hematology: WBC, platelet count, Hb, and WBC differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes). Additional hematology performed as clinically indicated. Frequency was increased as clinically indicated to monitor neutropenia, thrombocytopenia, and anemia.
j. Blood chemistry: BUN, Cr, albumin, AST, ALT, TB, ALP, Na, K, Cl, Ca, Mg, P, glucose, TP and uric acid. Additional chemistries performed as clinically indicated. Additionally, HbA1c was measured during the active treatment phase in all patients every 3 months from Cycle 1 Day 1 (ie, Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1, etc), and at the EOT visit.
k. Coagulation: PT or international normalized ratio, PTT or activated PTT. Additional coagulation studies performed as clinically indicated.
l. Urinalysis: Screening and EOT only. Urine protein and blood. Dipstick was acceptable. If positive, microscopic analysis was performed and 24-hour urine was collected (only for protein excretion).
m. 12-lead ECG: At each time point, 3 consecutive 12-lead ECGs were performed approximately 2 minutes apart.
n. Pulse oximetry: Pulse oximetry was performed at each time point as described, and then as clinically indicated (upon occurrence of dyspnea [shortness of breath, fever, cough etc]).
o. Tumor/lung assessment (CT/MRI): CT/MRI scans of chest, abdomen, pelvis, any clinically indicated sites of disease, and of bone lesions; clinical evaluation of superficial disease.
p. Radionuclide bone scan, whole body required at specified time points.
q. Drug compliance: All bottle(s) including any unused capsules and tablets were returned to the clinic for drug accountability. Drug accountability was to be performed on Day 1 of every cycle prior to dispense of drug supply for the next cycle.
r. Adverse events: AEs were to be documented and recorded at each visit using NCI CTCAE Version 4.0. Patients had to be followed for AEs for 28 days

Table 3. Schedule of Activities (Phase 1 Part 2)

after the last treatment administration or until all drug related toxicities had resolved, whichever was later; or earlier than 28 days should the patient have commenced another anticancer therapy in the meantime. For SAEs, the active reporting period to the Sponsor or its designated representative began from the time that the patient provided informed consent, which was obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study drug, through and including 28 calendar days after the last administration of the study drug. SAEs occurring to a patient after the active reporting period had ended were to be reported to the Sponsor if the Investigator became aware of them; at a minimum, all serious events that the Investigator believed had at least a reasonable possibility of being related to study drug were to be reported to the Sponsor.

s. Concomitant medications/treatments: Concomitant medications and treatments were recorded from 28 days prior to the start of palbociclib or letrozole and up to 28 days after the last dose of palbociclib or letrozole.

t. Plasma PK: Blood sampling taken at specific time points (see Table 4).

Table 4. Blood Sampling Time Points for Pharmacokinetic Analysis (Phase 1 Part 2)

	Cycle 1 (1 Cycle=28 Days)		Cycle 2 (1 Cycle=28 Days)			Cycle 3 (1 Cycle=28 Days)
Study Days	**Day 15 (±1)**		**Day 1 (±2)**	**Day 15 (±2)**		**Day 1 (±2)**
Hour[a]	**0 (Predose)[b]**	**4**	**0 (Predose)[b]**	**0 (Predose)[b]**	4	**0 (Predose)[b]**
Palbociclib[c]	√	√	-	√	√	-
Letrozole[c]	√	√	√	√	√	√

Abbreviations: AE=adverse event; K_2EDTA=dipotassium ethylenediaminetetraacetic acid; K_3EDTA=tripotassium ethylenediaminetetraacetic acid; PK=pharmacokinetic; SAE=serious adverse event.

a. For PK blood collection, variation of up to 10% or 10 minutes, whichever was later, of the nominal time from dosing was not captured as a protocol deviation.

b. Taken immediately prior to any palbociclib dosing.

c. Plasma PK: Blood sampling for palbociclib and letrozole was collected predose, and 4 hours after dosing on Day 15 of Cycle 1 and Cycle 2, and blood sampling for letrozole was collected predose on Day 1 of Cycle 2 and Cycle 3. At each sampling time point, 3 mL of blood (total 6 mL) was drawn into a tube for each analyte, containing K_2EDTA for palbociclib and K_3EDTA for letrozole. Blood collection for palbociclib and letrozole was repeated during a later cycle, if the sample collection was missed for any reason, or if the PK data collected were deemed invaluable by the Sponsor. Additional blood samples could be requested from patients experiencing unexpected AEs or SAEs, or AEs that led to permanent discontinuation.

Phase 2:

The Phase 2 portion was a single-country, non-randomized, open-label, single-cohort, multi-center clinical study to evaluate the efficacy and safety of palbociclib in combination with letrozole for the first-line treatment of postmenopausal Japanese patients with ER-positive HER2-negative ABC.

The original data for Phase 2 portion of this study was collected till a data cutoff date of 04 March 2016. At the time of the data cutoff date, 43 patients were assigned to palbociclib 125 mg in combination with letrozole, 42 patients were treated, 27 patients remained on treatment, and 38 patients remained both on treatment and on the study follow-up. The Phase 2 portion was continued to further follow patients for efficacy and safety. After palbociclib was approved by the MHLW in Japan on 27 September 2017, the study was continued as a post-marketing clinical study until sufficient number of PFS events were obtained.

The data of the original analysis cutoff date for Phase 2 have been presented, also the updated data of efficacy, including median PFS, and safety from the Phase 2 portion after the last subject last visit (25 October 2018) have been presented.

The schedules of study activities for Phase 2 is summarized in Table 5 and Table 6.

Table 5. Schedule of Activities (Phase 2)

Protocol Activity	Screening	Active Treatment Phase[a] - 1 Cycle=28 Days			End of Treatment/ Withdrawal[d]	Post Treatment Follow-Up[e]
		Cycles 1 and 2		Cycles ≥3		
Study Day	**Within 28 Days Prior to C1D1 Unless Specified Otherwise**	**Day 1[b,c]**	**Day 15**	**Day 1[c]**		
Time Window		**±2d**	**±2d**	**±2d**		**±7d**
Baseline documentation						
Informed consent process[f]	X					
Medical/tumor history[g]	X					
Baseline signs/symptoms		X[h]				
Tumor tissue for biomarker[i]	X				X[i]	
Physical examination/vital signs[j]	X	X[b]		X	X	
ECOG performance status	X	X		X	X	
Laboratory studies						
Hematology[k]	X	X[b]	X	X	X	
Blood chemistry[k]	X	X[b]	X	X	X	
12-Lead ECG	X	X[b]		X[l]	X	
Disease assessment						
CT/MRI scans of chest, abdomen, pelvis, any clinically indicated sites of disease, and of bone lesions; clinical evaluation of superficial disease[m]	X	◀--▶[n,m] Performed every 12 weeks (±7 days) from the date of C1D1			X	X[m]
Radionuclide bone scan, whole body[m]	X	◀--▶[o] Performed every 24 weeks (±7 days) from the date of C1D1			X	X[m]
Other clinical assessments						
Drug compliance[p]		◀--▶				
AE reporting[q]	X	X	X	X	X	X
Review concomitant medications/treatments[r]	X	X	X	X	X	X
FACT - breast questionnaire[s]		X[s]		X	X	
Survival follow-up						X
Study treatment						
Letrozole		Once Daily ◀--▶[t]				

Table 5. Schedule of Activities (Phase 2)

Palbociclib		◀--▶[u] Once daily on Day 1 to Day 21 of each cycle followed by 7 days off				
Special laboratory studies						
Pharmacokinetics[v]			X			

Abbreviations: AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=Blood urea nitrogen; C=cycle; Ca=calcium; Cr=Creatinine; CT=computed tomography; D=day; ECG=electrocardiogram; ECOG=eastern cooperative oncology group; EOT=End of Treatment; ER=estrogen receptor; FACT-B=functional assessment of cancer therapy-breast; FFPE=formalin-fixed paraffin-embedded; Hb=Hemoglobin; HER=human epidermal growth factor receptor; Mg=magnesium; MRI=magnetic resonance imaging; Na=sodium; SAE=serious adverse event; TB=total bilirubin; WBC=White blood cell.

a. Active Treatment Phase: All assessments performed prior to dosing with study medications on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment were described in the column headers. For the purposes of this study 1 cycle was 28 days. A cycle could be longer than 28 days if persistent toxicity delayed the initiation of the subsequent cycle.
b. CI/D1: Blood chemistry, hematology, 12-lead ECG and physical examination were not required if acceptable screening assessment was performed within 7 days prior to C1D1.
c. Cycle X, Day 1: In the event that the start of a new cycle was delayed due to treatment-related toxicity, procedures required on Day 1 of the given cycle were performed when palbociclib was resumed. New cycle Day 1 procedures (ie, physical examination, ECOG performance status, ECG, quality of life questionnaires, blood chemistry, hematology) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether study drug resumed and (2) if performed within 7 days prior to study drug resumption.
d. EOT/withdrawal: EOT/withdrawal visit was performed and the assessment was completed as soon as possible but no later than 4 weeks (ie, 28 days) + 7 days from last dose of study treatment and prior to the initiation of any new anticancer therapy. Tumor assessments could be skipped if completed within the previous 8 weeks on study.
e. Post-treatment follow-up: After discontinuation of study treatment, post-treatment follow-up (including survival status and post-study anticancer therapy evaluation) collected every 6 months (±7 days) from the last dose of study treatment. Telephone contact was acceptable.
f. Informed consent was accepted >28 days from C1D1 but must have been obtained prior to any protocol-required assessments being performed (with the exception of certain imaging assessments).
g. Medical/oncological history: included information on prior anticancer treatments.
h. Baseline signs/symptoms: Baseline tumor-related signs and symptoms recorded as medical history at the C1D1 visit prior to initiating treatment and then reported as AEs during the study if they worsened in severity or increased in frequency.
i. Mandatory tumor tissue for confirmatory testing and for biomarker assessments: Tumor tissue was required for patient participation. Submission of FFPE tumor samples (blocks) of adequate size to allow for three 0.6 mm diameter × 5 mm deep core punches that used to generate a tissue microarray were needed. If FFPE tissue block could not be submitted, at least 12 glass slides, each containing an unstained 5-micron FFPE tissue section, required for patient participation. Tissue sample from a metastatic or recurrent tumor lesion must be provided whenever possible. If such tissue sample was unavailable, a de novo fresh biopsy was recommended when, in the Investigator's judgment, such biopsy was feasible and could be safely performed. In a case of metastatic tissue being collected, a sample of the original diagnostic tissue (ie, archival) was collected when available and sent to the Sponsor-designated central laboratories for assessment of biomarkers associated with sensitivity and/or resistance to palbociclib (eg, Ki67 [nuclear protein],

Table 5. Schedule of Activities (Phase 2)

cyclin-dependent kinase inhibitor 2A (p16), retinoblastoma protein). Retrospective confirmation of ER status and HER2 status when required to be repeated for eligibility purpose was performed using the most recent tumor sample. Original diagnostic tumor tissue used for confirmation of ER and HER2 status in the event that a recurrent/metastatic tissue sample was not available and a fresh biopsy of the recurrent/metastatic lesion was not feasible. An optional fresh tumor biopsy was collected at the EOT visit, only for patients who discontinued study treatment due to disease progression. The tumor tissue was used to determine possible mechanisms of resistance. Tissue samples from all patients were used for additional biomarker analyses.

j. Physical examination/vital signs: A full physical examination including an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at Screening only), weight, blood pressure and pulse rate, which performed by a physician, registered nurse or other qualified health care provider, were required at Screening and, Day 1 of Cycles 1 and 2. Symptom-directed physical examinations, blood pressure, weight and pulse rate were performed at subsequent visits.
k. Hematology and blood chemistry panel: Hematology included Hb, WBC, absolute neutrophils (or WBC differential), platelet count. Blood chemistry included AST/ALT, ALP, Na, K, Mg, total Ca, TB, BUN (or urea), serum Cr, albumin and Hb A1c. Hb A1c was measured every 3 months (ie, C1D1, C4D1, C7D1, C10D1, etc), and at the EOT visit. Additional hematology/chemistries panels were performed as clinically indicated.
l. 12-lead ECG: At each time point, 3 consecutive 12-lead ECGs were performed approximately 2 minutes apart (triplicate ECG needs to be completed in 10 minutes). 12-lead ECGs performed on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 were performed as clinically indicated.
m. Disease assessments.
n. CT/MRI scans of chest, abdomen, pelvis, any clinically indicated sites of disease, and of bone lesions; clinical evaluation of superficial disease.
o. Radionuclide Bone scan, whole body.
p. Drug compliance: All bottle(s) including any unused capsules/tablets returned to the clinic for drug accountability. Drug accountability was performed on Day 1 of every cycle prior to dispense of drug supply for the next cycle.
q. Adverse events: For SAEs, the active reporting period began from the time that the patient provided informed consent through and including 28 calendar days after the last administration of the study drug. Following the active safety reporting period, other SAEs of which the Investigator became aware reported to the Sponsor, unless the SAE was attributed by the Investigator to complications of either the underlying malignancy or any subsequent anticancer therapy or to the patients' participation in a subsequent clinical study. AEs (serious and non serious) recorded on the CRF from the time the patient had taken at least 1 dose of study treatment through last patient visit.
r. Concomitant medications/treatments: Concomitant medications and treatments were recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment.
s. FACT-B assessments: Patients completed questionnaires prior to any study or medical procedure on Day 1 of Cycles 1, 2 and 3 and then Day 1 of every other cycle thereafter starting with Cycle 5 (ie, Cycle 5, 7, 9, etc), and at the EOT visit. All self-assessment questionnaires were completed by patients while in the clinic and were not taken home. Interviewer administration in clinic used under special circumstances.
t. Letrozole: Administered orally, daily, and continuously.
u. Palbociclib: Administered orally, daily from Day 1 to Day 21 (21 days) of every 28-day cycle followed by 7 days off treatment.
v. Pharmacokinetic: Blood sampling taken at specific time points (see Table 6).

Table 6. Blood Sampling Time Points for Pharmacokinetic Analysis (Phase 2)

Study Days	**Cycle 1 Day 15**								**Cycle 2 Day 15**
Hours[a]	**0 (Predose)[b]**	**1**	**2**	**4**	**6**	**8**	**10**	**24**	**0 (Predose)[b]**
Full-profile PK subset (n=6) at the selected sites									
Blood collection for full-profile PK[a,c]	√	√	√	√	√	√	√	√	√
All other patients									
Blood collection for trough concentrations[a,c]	√	-	-	-	-	-	-	-	√

Abbreviations: AE=adverse event; K_2EDTA=dipotassium ethylenediaminetetraaceticacid; PK=pharmacokinetic; n=number of patients, SAE=serious adverse event.

a. All efforts made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% or 10 minutes, whichever was longer, of the nominal time from dosing were not captured as a protocol deviation, as long as the exact time of the sample collection and the most recent dosing time was noted.

b. Taken immediately prior to any palbociclib dosing.

c. At each sampling time-point, 3 mL of blood was drawn into a tube containing K_2EDTA. Blood collection for palbociclib repeated during a later cycle, if the sample collection was missed for any reason, or if the PK data collected were deemed invaluable by the Sponsor. Additional blood samples were requested from patients experiencing unexpected AEs or SAEs, or AEs that led to permanent discontinuation.

Number of Subjects (Planned and Analyzed):

For Phase 1 Part 1 a total of 6-12 patients were planned and 12 patients were enrolled. For Phase 1 Part 2, 6 patients were planned and 6 patients were enrolled. All 18 patients in Phase 1 (Part 1 and Part 2) were analyzed for safety, PK and efficacy.

For Phase 2, a total of 40 patients were planned, 43 patients were enrolled, and 42 patients were treated and analyzed.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Phase 1:

Phase 1 Part 1: Japanese patients ≥20 years of age with advanced solid tumor, that was refractory to standard therapy or for which no standard of care therapy was available, were included in the study.

Phase 1 Part 2: Postmenopausal Japanese patients ≥20 years of age with ER-positive HER2-negative ABC who have had no prior systemic anticancer therapy for their locoregionally recurrent or metastatic ER-positive breast cancer disease, were included in the study.

- Patients having active uncontrolled or symptomatic central nervous system (CNS) metastases, as indicated by clinical symptoms, cerebral edema, spinal cord compression, carcinomatous meningitis, leptomeningeal disease and/or progressive growth were excluded. Patients with a history of CNS metastases or cord compression were eligible if they had been definitively treated and were clinically stable off anticonvulsants and steroids for 4 weeks before the first dose of study treatment in Part 1 and the study registration in Part 2.

- Patients were also excluded from the study who had major surgery within the following predefined period.

  Part 1: Within 3 weeks prior to the first dose of study treatment.

  Part 2: Within 2 weeks prior to the study registration.

Phase 2:

Postmenopausal Japanese patients with ER-positive HER2-negative ABC with ≥20 years of age, previously untreated with any systemic anticancer therapy, were included in the study.

- Patients having HER2-positive tumor as defined by documentation of erbB-2 gene amplification by fluorescence in situ hybridization (FISH) (as defined by a HER2/CEP17 ratio ≥2) or chromogenic in situ hybridization (CISH) or INFORM HER2 dual ISH or documentation of HER2-overexpression by IHC (defined as IHC3+, or IHC2+ with FISH or CISH confirmation) based on local laboratory results utilizing 1 of the sponsor-approved assays were excluded from the study.

- Patients with advanced, symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and >50% liver involvement) were also excluded from the study.

Study Treatment:

Phase 1:

Two (2) dose levels (100 mg once daily [QD] and 125 mg QD) of palbociclib were examined in Phase 1 Part 1 and 1 dose level (MTD of palbociclib as single agent + 2.5 mg of letrozole) was examined in Phase 1 Part 2. Palbociclib was orally administered QD continuously for 3 weeks followed by 1 week off treatment (Schedule 3/1), defining a treatment period that was 28 days in duration.

Palbociclib was originally formulated as capsules containing 25 mg or 100 mg of palbociclib isethionate salt. Afterwards, palbociclib was supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base.

Phase 2:

One (1) combination regimen (MTD of palbociclib single agent: 125 mg administered orally QD continuously for 3 weeks followed by 1 week off treatment over a 28-day cycle [Schedule 3/1] + 2.5 mg of letrozole on continuous schedule) was examined in Phase 2.

For Phase 1 and Phase 2 portion of study, Letrozole (Femara) was commercially available as film-coated tablets and was supplied by the study sites. Each tablet contained 2.5 mg letrozole as active ingredient.

Efficacy, Safety and Pharmacokinetic Endpoints:

Phase 1 Part 1:

Primary Endpoint:

- First-Cycle Dose-Limiting Toxicities (DLTs).

Secondary Endpoints:

- Adverse events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for AEs Version 4.0 [NCI CTCAE Version 4.0]), timing, seriousness and relationship to study therapy (for palbociclib as single agent);

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE Version 4.0) and timing (for palbociclib as single agent);

- Plasma PK parameters of palbociclib after single and multiple dosing when given as single agent;

- Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (for palbociclib as single agent);

- Time-to-event endpoint: DOR (for palbociclib as single agent).

Phase 1 Part 2:

Primary Endpoint:

- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE Version 4.0), timing, seriousness and relationship to study therapy (palbociclib in combination with letrozole).

Secondary Endpoints:

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE Version 4.0) and timing (palbociclib in combination with letrozole);

- Plasma concentrations of palbociclib and letrozole to provide limited PK data when palbociclib and letrozole were combined;

- Objective tumor response, as assessed using the RECIST Version 1.1 (palbociclib in combination with letrozole);

- Time-to-event endpoint: DOR and PFS (palbociclib in combination with letrozole).

Phase 2:

Primary Endpoint:

- Investigator-assessed 1-year PFS.

Secondary Endpoints:

- Investigator-assessed overall response (OR) and disease control (DC) (CR + PR + SD ≥24 weeks);

- DOR, PFS, 1-year survival and OS;

- Type, incidence, severity (as graded by NCI CTCAE Version 4.0), seriousness and relationship to study medications of AEs and laboratory abnormalities;

- Functional Assessment of Cancer Therapy-Breast (FACT-B);

- Plasma concentrations and PK parameters of palbociclib in a subset of patients (n=6) and trough concentrations for all patients when combined with letrozole;

- Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1, CDKN2A), proteins (eg, Ki67, pRb, p16), and RNA expression (eg, cdk4, cdk6).

Safety Evaluations:

In Phase 1 Part 1, first-cycle DLTs were evaluated as the primary endpoint. Other safety endpoints included AEs, laboratory abnormalities, and electrocardiogram (ECG), physical examination, pulse oximetry, and Eastern Cooperative Oncology Group (ECOG) performance status.

In Phase 2 of study, safety endpoints included AEs, laboratory abnormalities, ECG, physical examination, and ECOG performance status.

Severity of AEs was graded according to CTCAE Version 4.0.

Statistical Methods:

Analysis Sets:

Full Analysis Set (FAS): The FAS included all enrolled patients who received at least 1 dose of study drug (palbociclib).

Pharmacokinetic Analysis Set: The PK concentration set was defined as all patients treated who had at least 1 concentration in at least 1 treatment period. The PK parameter analysis set was defined as all patients treated who had at least 1 of the PK parameters of primary interest in at least 1 PK sampling period.

Response Evaluable Set: The response evaluable analysis set was defined as all patients in the FAS who had at least 1 measurable disease and an adequate baseline tumor assessment.

DLT Evaluation Set: The DLT evaluation set included all patients whom DLTs were evaluable in Cycle 1 in Phase 1 Part 1 including PK lead-in phase. The replaced patients were excluded from the DLT evaluation set.

Patient Reported Outcome (PRO) Analysis Set: The PRO analysis set was defined as a subset of the FAS, who had both baseline and at least 1 complete post-baseline PRO assessment.

Safety Analysis Set: The safety analysis set included all enrolled patients who received at least 1 dose of study drug (palbociclib).

Phase 1:

Efficacy:

Phase 1: Tumor response was presented in the form of patient data listings that included, but were not limited to, Part 1/Part 2, tumor type, starting dose, tumor response at each visit, and best OR. For Part 2, ORR and DCR were estimated and PFS was listed.

Pharmacokinetics:

Plasma concentration/time data of palbociclib were summarized descriptively and presented graphically. Individual values and descriptive statistics for PK parameters were provided.

Safety:

AEs constituting DLTs were listed per dose level. The number and percentage of patients who experienced any AE, serious adverse event (SAE), treatment-related AEs, and treatment-related SAEs were summarized according to worst toxicity grades. The number and percentage of patients who experienced laboratory test abnormalities were summarized according to worst toxicity grade observed for each laboratory assay.

Phase 2:

Efficacy:

The FAS was used for efficacy analysis.

All primary and secondary endpoints based on radiological (and photographical where applicable) assessments of tumor burden (ie, PFS, objective response, DOR, disease control) were derived using the Investigator's assessment (OR according to RECIST criteria). One (1)-year PFS was estimated using the Kaplan-Meier method and a 90% confidence interval (CI) for the logarithm (log) (−log [1-year PFS probability]) was calculated using a normal approximation and then back transformed to give a CI for the 1-year PFS itself. The 25^{th}, 50^{th}, and 75^{th} percentiles of the event-free time and the corresponding 95% CIs were also estimated using the Kaplan-Meier method and Brookmeyer and Crowley method. PFS analyses were based on the FAS.

The ORR was estimated by dividing the number of patients with confirmed objective response (CR or PR) by the number of patients in the analysis set. A 95% CI for the response rates was provided. In addition, the best OR was summarized. Objective response analyses were based on the FAS and response evaluable set.

The DCR was estimated by dividing the number of patients with CR, PR, or SD ≥24 weeks by patients in the analysis set. A 95% CI for the DCR was provided. Disease control analyses were based on the FAS and response evaluable set.

DOR was summarized using the Kaplan-Meier method and displayed graphically, where appropriate. The median event time and 95% CI for the median were provided. DOR analysis was based on the subgroup of patients with objective response in the FAS.

OS was summarized using the Kaplan-Meier method and displayed graphically, where appropriate. The median event time and 95% CI were estimated. OS analyses set were based on the FAS.

Breast cancer-specific quality of life scores for PRO and change from Baseline scores were summarized using means (with 95% CIs) and medians at each assessment point. In addition,

analyses were performed to determine if the change from Baseline scores achieved the appropriate minimally important difference cutoffs for the scale being examined. In addition to the above analyses, an examination of the time to deterioration was also carried out using the Kaplan-Meier method.

As biomarker analysis, for baseline measurements of ER status, Rb, CCND1, p16, Ki67, descriptive statistics were provided. For baseline ER status, Rb, CCND1 and p16, the number and percentage of patients in each category were provided.

Pharmacokinetics:

Individual values and descriptive statistics for PK parameters were provided. The full-profile PK subset is defined as 6 patients who were planned the intensive PK sampling on Cycle 1 Day 15. For the full-profile PK subset, plasma concentration-time data for palbociclib obtained after administration on Cycle 1 Day 15 were summarized descriptively and presented graphically. For all patients, individual values and descriptive statistics of C_{trough} (steady state) of palbociclib on Day 15 of both Cycle 1 and Cycle 2 were provided.

Safety:

The number and percentage of patients who experienced any AE, SAE, treatment-related AE, and treatment-related SAE were summarized according to worst toxicity grades. The number and percentage of patients who experienced laboratory test abnormalities were summarized according to worst toxicity grade observed for each laboratory assay.

RESULTS

Subject Disposition and Demography:

Results from the final analysis of both the Phase 1 Part 1 portion and the Phase 2 portion of the study at the original cutoff date are presented. For the analyses other than PK, original data cutoff date was set on 31 March 2015 for the Phase 1 portion and 04 March 2016 for the Phase 2 portion. For the PK analyses, cutoff dates of 29 November 2013 for the Phase 1 portion and 28 October 2015 for the Phase 2 portion were used.

The patients ongoing at the time of original data cutoff dates were also evaluated and supplemental data of those patients were collected till 07 February 2018 for Phase 1 Part 2 portion (end of Phase 1 Part 2 portion) and 25 October 2018 for Phase 2 portion. This supplemental data is also presented in this public disclosure synopsis.

Phase 1:

At the data cutoff date of 31 March 2015, the patient disposition was as follows:

Part 1 (Single Agent Dose Escalation):

A total of 6 patients were assigned to each palbociclib dose 100 mg and 125 mg respectively and treated. All patients discontinued the study by the data cutoff date. In all patients, the

reason for discontinuation was "objective progression or relapse" with the exception of 1 patient in the palbociclib 100 mg group who discontinued due to an AE.

In the palbociclib 100 mg group, 1 patient was male and 5 patients were female, with the median age of 59.0 years (range: 44 to 65 years). In the palbociclib 125 mg group, 4 patients were male and 2 patients were female, with the median age of 48.5 years (range: 24 to 69 years). Primary diagnosis was varied among patients in Part 1 of the study. In the palbociclib 100 mg and 125 mg groups, the current disease stage was Stage IV in most patients. All patients had measurable disease at Baseline with an ECOG performance status of 0 or 1. All patients were analyzed for efficacy, PK, and safety.

Part 2 (Combination Therapy With Letrozole):

Six (6) patients were assigned to palbociclib 125 mg that was determined as MTD in Part 1, in combination with letrozole. All were treated and at the data cutoff date, 4 patients out of 6 patients were ongoing in the study. Two (2) patients discontinued for reasons other than disease progression; "AE" and "other" (request of the patient).

All 6 patients were female with Stage IV invasive ductal breast carcinoma, with a median age of 62.0 years (range: 59 to 76 years). All patients had measurable disease at Baseline with an ECOG performance status of 0 or 1. All patients were analyzed for efficacy, PK, and safety.

The details of patient disposition at the end of the study is shown in Table 7.

Table 7. Patient Disposition at the End of Study

Number (%) of Patients	**Part 1**		**Part 2**
	Palbociclib 100 mg	**Palbociclib 125 mg**	**Palbociclib 125 mg/ Letrozole**
Assigned to study treatment	6 (100)	6 (100)	6 (100)
Treated	6	6	6
Completed	0	0	0
Ongoing at date of cutoff	0	0	4 (66.7)
Discontinued	6 (100)	6 (100)	2 (33.3)
Adverse event	1 (16.7)	0	1 (16.7)
Objective progression or relapse	5 (83.3)	6 (100)	0
Other	0	0	1 (16.7)[a]

a. Request of the patient.

The patient disposition and patients analyzed at the end of Phase 1 Part 2 Portion is provided in Table 8.

Table 8. Patient Disposition and Patients Analyzed at the End of Phase 1 Part 2 Portion

Number (%) of Patients	Part 2
	Palbociclib 125 mg/Letrozole
Assigned to study treatment	6 (100.0)
Treated	6
Completed	0
Discontinued	6 (100.0)
Adverse event	1 (16.7)
Other	5 (83.3)
Study completion	4 (66.7)
Request of the patient	1 (16.7)
Analyzed for efficacy	6
Analyzed for safety	
Adverse events	6
Laboratory data	6

Discontinuations had been attributed to the last study treatment received.

Phase 2:

A total of 43 patients were assigned to palbociclib 125 mg in combination with letrozole and 42 patients were treated. A total of 4 patients out of 43 patients discontinued the study (till cutoff date: 04 March 2016). The reasons for discontinuation of study were "patient died" for 3 patients and "patient refused further follow-up" for 1 patient.

At the final study completion date: 25 October 2018, all the patients discontinued the study including 30 patients terminated by the sponsor due to close of the study. All the treated patients in the study were analyzed for efficacy and safety.

Patient evaluation groups and disposition at the end of the study is summarized in Table 9.

Table 9. Patient Evaluation Groups and Disposition at End of Study

Number (%) of Patients	Palbociclib Plus Letrozole
Assigned to study treatment	43
Treated	42
Completed	0
Discontinued study	42 (97.7)
Study terminated by sponsor	30 (71.4)
Patient died	8 (19.0)
Patient refused further follow-up	4 (9.5)
Analyzed for efficacy	
Full analysis set	42 (97.7)
Response evaluable set	36 (83.7)
Patient-reported outcome analysis set	42 (97.7)
Analyzed for safety	
Adverse events	42 (97.7)
Laboratory data	42 (97.7)

Discontinuations had been attributed to the last study treatment received.
The number of patients for completed, discontinued and ongoing was as per the patient summary at the end of study.

Demographic characteristics are provided in Table 10. All 42 patients were female, whose median age was 62.5 years (range: 43 to 84 years). Patients had a median weight of 50.4 kg (range: 38.6 to 74.5). Most patients had breast cancer (38 patients); 3 patients had invasive ductal breast carcinoma and 1 patient had tubular breast carcinoma. Twelve (12) patients (28.6%) had Stage IV disease at study entry. All patients had ECOG performance status of 0 or 1.

Table 10. Demographic and Baseline Characteristics – Phase 2 (Full Analysis Set)

	Palbociclib Plus Letrozole (N=42)
Gender, n	
Male	0
Female	42
Age (years), n (%)	
<18	0
18-44	2 (4.8)
45-64	24 (57.1)
≥65	16 (38.1)
Median (range)	62.5 (43-84)
Mean (standard deviation)	60.9 (8.7)
Race, n (%)	
Asian	42 (100)
ECOG performance status, n (%)	
0	39 (92.9)
1	3 (7.1)
Disease site (visceral/non-visceral), n (%)[a]	
Visceral	20 (47.6)
Non-visceral	22 (52.4)
Disease site (bone only/other), n (%)[b]	
Bone only	6 (14.3)
Other	36 (85.7)
Disease free interval, n (%)[c]	
≤12 months	8 (19.0)
>12 months	20 (47.6)
De novo metastatic	14 (33.3)
Stage at initial diagnosis, n (%)	
Stage I	5 (11.9)
Stage IA	1 (2.4)
Stage IIA	8 (19.0)
Stage IIB	9 (21.4)
Stage IIIA	2 (4.8)
Stage IIIB	1 (2.4)
Stage IIIC	1 (2.4)
Stage IV	12 (28.6)
Unknown	3 (7.1)

Abbreviations: ECOG=Eastern Cooperative Oncology Group; N=total number of patients; n=number of patients affected.

a. Visceral refers to lung (including pleura) and/or liver involvement.
b. As per baseline disease site and baseline/screening tumor assessment information combined. Involved sites include both target and non-target sites. Sites with multiple lesions were counted once. Patients might have contributed to ≥1 category.
c. Disease free interval was calculated as the time between end of adjuvant or neoadjuvant treatment and onset of metastatic disease or disease recurrence.

Efficacy and Pharmacokinetic Results:

Efficacy Results:

Phase 1:

The efficacy results at the time of original data cutoff date (31 March 2015) are summarized in Table 11. In Part 1, no objective response (CR/PR) was reported. The best overall tumor response was SD in 3 patients in the palbociclib 100 mg group and 1 patient in the palbociclib 125 mg group. Among them, SD ≥24 weeks was observed in 1 patient with rectal cancer in the palbociclib 100 mg group and 1 patient with oesophageal carcinoma in the palbociclib 125 mg group. The best overall tumor response was indeterminate (discontinued the study for the reasons other than disease progression) in 1 patient in the palbociclib 100 mg group.

In Part 2, objective response was reported in 2 (33.3%) patients; both were PR.
Two (2) patients had a best overall tumor response of SD ≥24 weeks and 2 patients had a best response of indeterminate, who discontinued the study for the reasons other than disease progression. At the data cutoff date, PFS was 505 days and duration of response was 421 days in one of the patients with PR, PFS was 582 days and duration of response was 498 days in the other patient with PR. PFS was 582 days and 592 days, respectively in the 2 patients with SD.

Table 11. Summary of Best Overall Tumor Response

Number (%) of Patients	Part 1		Part 2
	Palbociclib 100 mg N=6	Palbociclib 125 mg N=6	Palbociclib 125 mg/ Letrozole N=6
CR	0	0	0
PR	0	0	2 (33.3)
Stable/no response	3 (50.0)	1 (16.7)	2 (33.3)
Objective progression	2 (33.3)	5 (83.3)	0
Symptomatic deterioration	0	0	0
Early death	0	0	0
Indeterminate	1 (16.7) [a]	0	2 (33.3)[a]
Objective response and rate (CR + PR)	0	0	2 (33.3)
95% exact confidence interval for objective response rate[b]	[0.0, 45.9]	[0.0, 45.9]	[4.3, 77.7]

Abbreviations: CR=complete response; N=number of patients; PR=partial response.
a. Discontinued the study for the reasons other than disease progression.
b. Using exact method based on binomial distribution.

The results of the best overall tumor response at the end of Phase 1 Part 2 Portion were identical to the data obtained till the original cutoff date (31 March 2015), but the duration of response and PFS for 4 patients on treatment at the time of original data cutoff have been updated.

The PFS was 1593 days and duration of response was 1509 days for 1 of the patient with PR, PFS was 1512 days and duration of response was 1428 days for another patient with PR. PFS was 1590 days and 1602 days, respectively, for the 2 patients with SD.

Phase 2:

Progression-Free Survival:

The Investigator-assessed 1-year PFS probability was 75.0% (90% CI: 61.3%, 84.4%) till the data cutoff date: 04 March 2016. Out of 42 patients in the FAS, 12 patients (28.6%) had PFS events. Most events (11/12 events) were associated with objective progression. The median PFS was not reached (95% CI: 16.7 months, not estimable [NE]). Twenty-seven (27) patients (64.3%) were still in follow-up for PFS.

At the final study completion date: 25 October 2018, the Investigator-assessed 1-year PFS probability was 75.6% (90% CI: 62.4%, 84.7%). Out of 42 patients in the FAS, 24 (57.1%) patients had PFS events. Most events (23/24 events) were associated with objective progression. The median PFS was approximately 3 years (35.7 months) (95% CI: 21.7, 46.7 months).

PFS details at the final study completion are summarized in Table 12.

Table 12. Progression-Free Survival (Full Analysis Set)

Number (%) of Patients	**Palbociclib Plus Letrozole (N=42) n (%)**
Number with event	24 (57.1)
Type of event	
Objective progression	23 (54.8)
Death without objective progression	1 (2.4)
Number censored	18 (42.9)
Reason for censorship	
Given new anti-cancer treatment prior to tumor progression	13 (31.0)
Off treatment prior to progression	5 (11.9)
Probability (%) of being event free at Month 12[a] (90% CI[b])	75.6 (62.4, 84.7)
Probability (%) of being event free at Month 12[a] (95% CI[b])	75.6 (59.4, 86.1)
Kaplan-Meier estimates of time to event (month)	
Quartiles (95% CI)[c]	
25%	13.8 (5.3, 27.9)
50%	35.7 (21.7, 46.7)
75%	NR (44.1, NE)

Abbreviations: CI=confidence interval; N=number of patients; n=number of patients in specific category; NE=not estimable; NR=not reached.

a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley method.

Objective Response:

At the data cutoff date: 04 March 2016, out of 42 patients in the FAS, 17 (40.5%) patients had OR (all were PR), and 24 (57.1%) patients had SD as their best response. The ORR was 40.5% (95% CI: 25.6%, 56.7%).
In the response evaluable set (36 patients), 17 (47.2%) patients had objective response (all were PR), and (50.0%) patients had SD as their best response. The ORR was 47.2% (95% CI: 30.4%, 64.5%).

At the final study completion date: 25 October 2018, in the FAS (42 patients), 20 (47.6%) patients had confirmed objective response (19 were PR and 1 was CR), and 21 (50.0%) patients had SD as their best response. The ORR was 47.6% (95% CI: 32.0%, 63.6%) where as, it was 40.5% till the previous cutoff date (04 March 2016). One (1) patient improved from PR to CR, and 3 patients improved from SD to PR.

In the response evaluable set (36 patients), 20 (55.6%) patients had objective response (19 were PR and 1 was CR), and 15 (41.7%) patients had SD as their best response. The ORR was 55.6% (95% CI: 38.1%, 72.1%) where as, it was 47.2% till the previous cutoff date (04 March 2016).

Best overall tumor response after the final study completion is summarized in Table 13.

Table 13. Best Overall Tumor Response (Full Analysis Set)

Number (%) of Patients	**Palbociclib Plus Letrozole**	
	Full Analysis Set (N=42) n (%)	**Response Evaluable Set (N=36) n (%)**
Best overall response		
CR	1 (2.4)	1 (2.8)
PR	19 (45.2)	19 (52.8)
Stable/no response	21 (50.0)	15 (41.7)
Objective progression	1 (2.4)	1 (2.8)
Objective response and rate (CR + PR)	20 (47.6)	20 (55.6)
95% exact confidence interval for objective response rate[a]	32.0, 63.6	38.1, 72.1

Abbreviations: CR=complete response; N=number of patients; n=number of patients in specific category; PR=partial response.
a. Using exact method based on binomial distribution.

Disease Control Rate:

In the FAS (42 patients), the DCR was 85.7% (95% CI: 71.5%, 94.6%) at the data cutoff date: 04 March 2016. In the response evaluable set (36 patients), the DCR was 83.3% (95% CI: 67.2%, 93.6%).

At the final study completion date: 25 October 2018, the DCR was 85.7% (95% CI: 71.5%, 94.6%) in the FAS (42 patients). In the RE (36 patients), the DCR was 83.3% (95% CI: 67.2%, 93.6%). Disease control is summarized in Table 14.

Table 14. Disease Control (Full Analysis Set)

Number (%) of Patients	Palbociclib Plus Letrozole	
	Full Analysis Set (N=42) n (%)	Response Evaluable Set (N=36) n (%)
Best overall response		
CR	1 (2.4)	1 (2.8)
PR	19 (45.2)	19 (52.8)
Stable disease ≥24 weeks	16 (38.1)	10 (27.8)
Stable disease <24 weeks	5 (11.9)	5 (13.9)
Objective progression	1 (2.4)	1 (2.8)
Disease control and rate	36 (85.7)	30 (83.3)
95% exact confidence interval for disease control rate[a]	71.5, 94.6	67.2, 93.6

Abbreviations: CR=complete response; N=number of patients; n=number of patients in specific category; PR=partial response.
a. Using exact method based on binomial distribution.

Duration of Response:

At the data cutoff date: 04 March 2016, the majority of patients (14 out of 17 patients) who had an OR did not have subsequent disease progression or death after the response. The median DOR by the Kaplan-Meier method was not reached (95% CI: 6.5 months, NE).

At the final study completion date: 25 October 2018, 11 out of 20 patients who had an OR did not have subsequent disease progression or death after the response. The median DOR by the Kaplan-Meier method was 41.4 months (95% CI: 19.0 months, NE). The DOR is summarized in Table 15.

Table 15. Duration of Response (Full Analysis Set)

Number (%) of Patients	**Palbociclib Plus Letrozole (N=42) n (%)**
Number of patients with objective response	20 (100)
Number with event	9 (45.0)
Type of event	
Objective progression	9 (45.0)
Death without objective progression	0
Number censored	11 (55.0)
Reason for censorship	
Given new anti-cancer treatment prior to tumor progression	8 (40.0)
Withdrew consent for follow-up	1 (5.0)
In follow-up for progression	2 (10.0)
Probability (%) of being event free at Month 12[a] (95% CI[b])	80.0 (55.1, 92.0)
Kaplan-Meier estimates of time to event (month)	
Quartiles (95% CI[c])	
25%	21.9 (5.7, 41.4)
50%	41.4 (19.0, NE)
75%	NR (41.4, NE)

Abbreviations: CI=confidence interval; N=number of patients; n=number of patients in specific category; NE=not estimable; NR=not reached.

a. Estimated from the Kaplan-Meier curve.
b. Calculated from the Product-limit method.
c. Based on the Brookmeyer and Crowley method.

Overall Survival:

At the cutoff date: 04 March 2016, only 3 deaths were reported. Most (90.5%) of patients were still in follow-up for OS. The median OS was not reached. The survival probability at 12 months was 92.9% (95% CI: 79.5%, 97.6%).

At the final study completion date: 25 October 2018, only 8 deaths were reported. Most of the patients (30 [71.4%]) were still in follow-up for OS. The median OS was not reached. The survival probability at 12 months was 92.9% (95% CI: 79.5%, 97.6%) and this had not changed from the earlier cutoff date. The OS is summarized in Table 16.

Table 16. Overall Survival (Full Analysis Set)

Number (%) of Patients	Palbociclib Plus Letrozole (N=42) n (%)
Number of deaths	8 (19.0)
Cause of death	
Disease under study	7 (16.7)
Study treatment toxicity	1 (2.4)
Unknown	0
Other	0
Number censored	34 (81.0)
Reason for censorship	
Patient remains in follow-up	30 (71.4)
Patient no longer being followed for survival	4 (9.5)
Number of patients with last contact date >1 year prior to data cutoff date	3 (7.1)
Survival probability (%) at 12 months[a] (95% CI[b])	92.9 (79.5, 97.6)
Kaplan-Meier estimates of time to event (month)	
Quartiles (95% CI[c])	
25%	47.5 (29.1, NE)
50%	NR (47.5, NE)
75%	NR

Abbreviations: CI=confidence interval; N=number of patients; n=number of patients in specific category; NE=not estimable; NR=not reached.

a. Estimated from the Kaplan-Meier curve.
b. Calculated from the Product-limit method.
c. Based on the Brookmeyer and Crowley method.

Patient-Reported Outcomes:

PROs were evaluated using FACT-B, functional assessment of cancer therapy-general (FACT-G), and trial outcome index (TOI) scores. Higher scores represented better quality of life.

At the data cutoff date: 04 March 2016, up to Cycle 11 where majority of patients participated in this study, the mean FACT-B, FACT-G, and TOI scores showed numerical deterioration but the changes were not statistically significant based on the 95% CI values up to and including Cycle 5. It was observed to be statistically significant based on 95% CI in Cycle 7 (FACT-B, FACT-G and TOI scores), Cycle 9 (FACT-B and TOI scores), and Cycle 11 (FACT-B and FACT-G scores). However, those mean scores did not cross the minimal important difference (MID) threshold and hence were not considered clinically meaningful.

The proportion of patients who achieved improvement of MID from Baseline in FACT-B, FACT-G, and TOI scores during the treatment period ranged 11.43% to 31.71%, 15.15% to 28.95%, and 11.43% to 26.83% up to Cycle 11, respectively.

The median times (95% CI) to deterioration in FACT-B, FACT-G, and TOI scores were 3.0 (1.9, 6.2) months, 3.0 (1.9, 5.5) months, and 3.8 (2.3, 7.9) months, respectively.

After the final study completion date: 25 October 2018, up to Cycle 41, the mean FACT-B, FACT-G, and TOI scores showed numerical deterioration, though those mean scores did not change beyond MID. The mean (standard deviation) change from Baseline in FACT-B, FACT-G, and TOI scores till Cycle 41 were -5.70 (8.505), -5.06 (7.229) and -2.27 (7.964), respectively.

No big differences were observed for changes of each score.

Biomarker:

CCND1 was positive in 42 patients (100%) and ER, Rb, and p16 were positive in 41 patients (97.6%). There were 23 patients (54.8%) with Ki67 positive cells >20%.

The median PFS by Ki67 positive cells >20% was 16.7 months (95% CI: 9.3 months, NE). The median PFSs by Ki67 positive cells ≤20% were not reached.

Pharmacokinetic Results:

Phase 1 (Data cutoff date: 29 November 2013):

After a single oral dose of 100 mg or 125 mg palbociclib in Japanese patients with advanced solid tumor, the median maximum plasma concentration (C_{max}) generally achieved by 4-5 hours post-dosing in both groups. Following attainment of C_{max}, the plasma palbociclib concentrations declined over time with mean terminal elimination half-life ($t_{½}$) of 25.7 hours and 23.9 hours in 100 mg and 125 mg groups, respectively. In 100 mg and 125 mg groups, geometric mean apparent clearance (CL/F) were 96.4 L/h and 50.3 L/h, and geometric mean apparent volume of distribution (V_z/F) were 3514 L and 1730 L, respectively.

After multiple oral doses of palbociclib at doses of 100 mg and 125 mg QD in Japanese patients with advanced solid tumor, the median C_{max} was generally achieved by 4 hours post-dosing in both groups, similar to that observed after single dose. Following attainment of C_{max}, the plasma palbociclib concentrations declined over time with mean $t_{½}$ of 23.8 hours and 23.2 hours in 100 mg and 125 mg groups, respectively. The median accumulation ratio (R_{ac}) values were 2.1 and 1.9 for 100 mg and 125 mg groups, respectively, consistent with the predicted values from $t_{½}$. The median predicted accumulation ratio to estimate linearity (R_{ss}) was 1.1 at both dose levels, indicating CL/F did not change with time.

For both single-dose and multiple-dose palbociclib, geometric mean AUC and C_{max} values with the 125 mg dose were 2.2- to 2.5-fold higher than those for the 100 mg dose although time for C_{max} (T_{max}) and $t_{½}$ were similar between the 100 mg and 125 mg groups.

When palbociclib and letrozole were administered in combination in Japanese patients with ER-positive HER2-negative ABC, no drug-drug interaction between palbociclib and letrozole was observed.

Phase 2 (Data cutoff date: 28 October 2015):

Following 15 daily 125 mg oral doses of palbociclib with letrozole (Cycle 1 Day 15) palbociclib steady-state geometric mean area under the plasma concentration-time curve over dosing interval τ (AUC_{tau}) and C_{max} were 1979 ng•h/mL and 124.7 ng/mL, respectively. The palbociclib geometric mean CL/F was 63.2 L/h. The median time to C_{max} (T_{max}) was 4.90 hours.

The inter-patient variability (geometric % coefficient of variation) of palbociclib steady-state AUC_{tau} and C_{max} was 16% and 26%, respectively.

Predose concentrations on Day 15 of Cycles 1 and 2 were similar, and geometric mean of within-patient mean C_{trough} obtained from Day 15 of Cycles 1 and 2 was 90.1 ng/mL.

Safety Results:

Dose-Limiting Toxicity (Phase 1 Only):

DLT was evaluated during Cycle 1 in Part 1. DLTs were reported in 1 of 6 patients in the palbociclib 100 mg group (<75% of the planned dose of study drug received due to neutrophil count decreased) and 1 of 6 patients in the palbociclib 125 mg group (Grade 4 platelet count decreased). As a consequence, the MTD of single agent palbociclib in this Japanese population and the recommended dose for Part 2 was determined as 125 mg QD administered with the Schedule 3/1.

Non Serious Adverse Events:

At the data cutoff: 31 March 2015, in Part 1, commonly reported all-causality AEs (occurring in ≥3 patients) in the palbociclib 100 mg group were neutrophil count decreased (5 patients) and white blood cell count decreased (4 patients). Commonly reported all-causality AEs (occurring in ≥3 patients) in the palbociclib 125 mg group were white blood cell count decreased (5 patients), diarrhea (4 patients), neutrophil count decreased (4 patients), and lymphocyte count decreased (3 patients). Commonly reported Grade 3 or 4 all-causality AEs (occurring in ≥2 patients) in the palbociclib 100 mg group were neutrophil count decreased (4 patients) and white blood cell count decreased (2 patients); all of these were considered treatment related. Commonly reported Grade 3 or 4 all-causality AEs (occurring in ≥2 patients) in the palbociclib 125 mg group were anemia, lymphocyte count decreased, neutrophil count decreased, and white blood cell count decreased (2 patients each); lymphocyte count decreased, neutrophil count decreased, and white blood cell count decreased (2 patients each) were considered treatment related.

In Part 2, commonly reported all-causality AEs (occurring in ≥3 patients) were neutrophil count decreased (6 patients), white blood cell count decreased (6 patients), and platelet count decreased (4 patients). Commonly reported Grade 3 or 4 all-causality AEs (occurring in ≥2 patients) were neutrophil count decreased (5 patients) and white blood cell count decreased (3 patients); all of these were considered treatment related.

Treatment-emergent AEs reported >1 patient in any of treatment group (all-causalities) for Phase 1 Part 1 and Part 2 are summarized in Table 17. Commonly reported treatment-related AEs across the treatment groups were neutropenia and leukopenia (the MedDRA preferred terms were neutrophil count decreased and white blood cell count decreased, respectively).

Table 17. Treatment-Emergent Adverse Events Reported >1 Patient in Any of Treatment Group (All-Causalities)

Number (%) of Patients	Part 1				Part 2	
	Palbociclib 100 mg N=6		Palbociclib 125 mg N=6		Palbociclib 125 mg/ Letrozole N=6	
	Total	Grade 3-4[a]	Total	Grade 3-4[a]	Total	Grade 3-4[a]
Any adverse events	6 (100)	6 (100)	6 (100)	4 (66.7)	6 (100)	6 (100)
Blood and lymphatic system disorders						
Anaemia	0	0	2 (33.3)	2 (33.3)	0	0
Gastrointestinal disorders						
Constipation	1 (16.7)	0	2 (33.3)	0	1 (16.7)	0
Diarrhoea	1 (16.7)	0	4 (66.7)	0	1 (16.7)	0
Stomatitis	0	0	2 (33.3)	0	1 (16.7)	0
General disorders and administration site conditions						
Fatigue	0	0	2 (33.3)	0	2 (33.3)	0
Malaise	2 (33.3)	0	0	0	0	0
Pyrexia	0	0	1 (16.7)	0	2 (33.3)	1 (16.7)
Infections and infestations						
Upper respiratory tract infection	0	0	0	0	2 (33.3)	0
Investigations						
Aspartate aminotransferase increased	2 (33.3)	0	1 (16.7)	0	1 (16.7)	0
Blood alkaline phosphatase increased	2 (33.3)	1 (16.7)	2 (33.3)	0	0	0
Blood creatinine increased	2 (33.3)	0	0	0	1 (16.7)	0
Lymphocyte count decreased	1 (16.7)	1 (16.7)	3 (50.0)	2 (33.3)	0	0
Neutrophil count decreased	5 (83.3)	4 (66.7)	4 (66.7)	2 (33.3)	6 (100)	5 (83.3)
Platelet count decreased	1 (16.7)	0	2 (33.3)	1 (16.7)	4 (66.7)	0
White blood cell count decreased	4 (66.7)	2 (33.3)	5 (83.3)	2 (33.3)	6 (100)	3 (50.0)
Skin and subcutaneous tissue disorders						
Dry skin	2 (33.3)	0	0	0	0	0

The SAE/non SAE results were not separated out.
Medical Dictionary for Regulatory Activities Version 17.1 coding dictionary applied.
Adverse events occurred during pharmacokinetic lead-in phase were not included.
Abbreviations: N=number of patients; SAE=serious adverse event.
a. No Grade 5 events were reported.

At the end of Phase 1 Part 2 portion, commonly reported all-causality AEs (occurring in ≥3 patients) were neutrophil count decreased (6 patients), white blood cell count decreased (6 patients), platelet count decreased (4 patients), diarrhea (4 patients) and fall (4 patients). Among the all-causality AEs (occurring in >1 patient), nausea and peripheral sensory neuropathy were newly reported and number of patients with the other all-causality AEs (occurring in >1 patient) were either slightly increased or remained the same since the original data cutoff date. No Grade 5 events were reported. Grade 4 all-causality AEs were neutrophil count decreased (2 patients) and gastrointestinal perforation (1 patient). Grade 3 all-causality AEs were neutrophil count decreased (4 patients), white blood cell count decreased (3 patients), supraventricular tachycardia (1 patient), urinary tract infection (1 patient) and pyrexia (1 patient).

Commonly reported treatment-related AEs (occurring in ≥3 patients) were neutrophil count decreased (6 patients), white blood cell count decreased (6 patients), and platelet count decreased (3 patients). No Grade 5 events were reported. Grade 4 treatment-related AE was neutrophil count decreased (2 patients). Grade 3 treatment-related AEs were neutrophil count decreased (4 patients), white blood cell count decreased (3 patients) and supraventricular tachycardia (1 patient).

All-causality and treatment-related AEs reported in >1 patient at the end of Phase 1 Part 2 are summarized in Table 18.

Table 18. Treatment-Emergent Adverse Events in Any of Treatment Group (All-Causalities and Treatment-Related, Reported in >1 Patient)

Number (%) of Patients	Part 2			
	Palbociclib 125 mg/Letrozole N=6			
	All-Causalities		Treatment-Related	
	Total	Grade 3 or 4[a]	Total	Grade 3 or 4[a]
Any adverse events[b]	6 (100)	6 (100)	6 (100)	6 (100)
Eye disorders				
Conjunctival haemorrhage	2 (33.3)	0	0	0
Gastrointestinal disorders				
Abdominal pain upper	2 (33.3)	0	1 (16.7)	0
Constipation	2 (33.3)	0	1 (16.7)	0
Diarrhoea	4 (66.7)	0	1 (16.7)	0
Nausea	2 (33.3)	0	0	0
General disorders and administration site conditions				
Fatigue	2 (33.3)	0	2 (33.3)	0
Mucosal inflammation	2 (33.3)	0	2 (33.3)	0
Pyrexia	2 (33.3)	1 (16.7)	0	0
Infections and infestations				
Nasopharyngitis	2 (33.3)	0	0	0
Upper respiratory tract infection	2 (33.3)	0	0	0
Injury, poisoning and procedural complications				
Fall	4 (66.7)	0	0	0
Investigations				
Alanine aminotransferase increased	2 (33.3)	0	2 (33.3)	0
Aspartate aminotransferase increased	2 (33.3)	0	2 (33.3)	0
Neutrophil count decreased	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Platelet count decreased	4 (66.7)	0	3 (50.0)	0
White blood cell count decreased	6 (100.0)	3 (50.0)	6 (100.0)	3 (50.0)
Nervous system disorders				
Headache	2 (33.3)	0	0	0
Peripheral sensory neuropathy	2 (33.3)	0	2 (33.3)	0
Respiratory, thoracic and mediastinal disorders				
Upper respiratory tract inflammation	2 (33.3)	0	0	0

The SAE/non SAE results were not separated out.
Medical Dictionary for Regulatory Activities, Version 20.1 coding dictionary applied.
Adverse events were graded according to the NCI CTCAE Version 4.0.
Adverse events occurred during pharmacokinetic lead-in phase were not included.
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; NCI=National Cancer Institute; SAE=serious adverse event.

a. No Grade 5 adverse events were reported.
b. Any adverse event without consideration of the minimum >1 patient cutoff used in this table.

Deaths and Serious Adverse Events:

At the original data cutoff date (31 March 2015), in Phase 1 Part 1, no deaths were reported within 28 days after the last dose of study drug, no SAEs were reported. In Part 2, 1 patient had an SAE of gastrointestinal perforation, which was considered not related to palbociclib treatment.

At the end of Phase 1 Part 2 portion, no on-treatment deaths were reported and apart from gastrointestinal perforation, 1 additional SAE of supraventricular tachycardia was reported which was considered related to palbociclib.

Permanent Discontinuations due to Adverse Events:

At the original data cutoff date (31 March 2015), permanent discontinuations due to an AE (neutrophil count decreased) were reported in 1 patient each in Part 1 and Part 2.

No new permanent treatment discontinuations were reported after the original data cutoff date (31 March 2015).

Laboratory Test Abnormalities and Vital Signs Data:

Commonly reported Grade 3 or 4 laboratory test abnormalities were neutrophils and white blood cells. No apparent trends of vital signs were observed during the study. No patients had a QTc value of >500 msec or increase of ≥30 msec from Baseline.

At the end of Phase 1 Part 2 portion, no new clinically relevant findings were observed in laboratory safety parameters and vital signs data.

Phase 2:

Non-Serious Adverse Events:

At the data cutoff date: 04 March 2016, the most common (≥20% of patients) all-causality AEs in decreasing frequency were neutrophil count decreased (81.0%), stomatitis (73.8%), white blood cell count decreased (61.9%), nasopharyngitis (38.1%), alanine aminotransferase increased (23.8%), constipation (23.8%), anemia (21.4%), malaise (21.4%), and platelet count decreased (21.4%).

All-causality AEs with maximum Grade 3 or 4 were reported in 38 (90.5%) patients. The most common (≥10% of patients) Grade 3 or 4 all-causality AEs were neutrophil count decreased (73.8%), white blood cell count decreased (42.9%), and neutropenia (16.7%). Grade 5 all-causality AE (subarachnoid hemorrhage) was reported in 1 (2.4%) patient.

At the final study completion date: 25 October 2018, the most common (≥20% of patients) all-causality AEs in decreasing frequency were neutrophil count decreased (81.0%), stomatitis (76.2%), white blood cell count decreased (71.4%), nasopharyngitis (45.2%), alanine aminotransferase increased (28.6%), constipation (28.6%), aspartate

aminotransferase increased (26.2%), anemia (23.8%), malaise (23.8%), platelet count decreased (21.4%), neutropenia (21.4%), nausea (21.4%) and fall (21.4%).

All-causality AEs with maximum Grade 3 or 4 were reported in 39 (92.9%) patients. The most common (≥10% of patients) Grade 3 or 4 all-causality AEs were neutrophil count decreased (76.2%), white blood cell count decreased (52.4%), and neutropenia (19.0%).

The most common (≥20% of patients) treatment-related AEs in decreasing frequency were neutrophil count decreased (81.0%), stomatitis (73.8%), white blood cell count decreased (71.4%), constipation (23.8%), alanine aminotransferase increased (23.8%), aspartate aminotransferase increased (23.8%), platelet count decreased (21.4%), anemia (21.4%) and neutropenia (21.4%).

Treatment-related AEs with maximum Grade 3 or 4 were reported in 39 (92.9%) patients. The most common (≥10% of patients) maximum Grade 3 or 4 treatment-related AEs were neutrophil count decreased (76.2%), white blood cell count decreased (52.4%), and neutropenia (19.0%). Only 1, Grade 5 treatment-related AE (subarachnoid hemorrhage) was reported in 1 (2.4%) patient at the original data cutoff date: 04 March 2016 and no other Grade 5 AE was reported till the final completion date.

All-causality and treatment-related AEs at the cutoff date of 25 October 2018 with an incidence of ≥5% of patients are summarized in Table 19 and Table 20, respectively.

Table 19. Treatment-Emergent Adverse Events Reported in ≥5% of Patients (All-Causality) by Preferred Term, All Cycles (Safety Analysis Set)

Number (%) of Patients System Organ Class Preferred Term	Palbociclib Plus Letrozole (N=42)	
	Total n (%)	Grade 3 or 4 n (%)
Any AEs	42 (100.0)	39 (92.9)
Blood and lymphatic system disorders		
Anaemia	10 (23.8)	3 (7.1)
Leukopenia	5 (11.9)	3 (7.1)
Neutropenia	9 (21.4)	8 (19.0)
Cardiac disorders		
Palpitations	4 (9.5)	0
Gastrointestinal disorders		
Cheilitis	5 (11.9)	0
Constipation	12 (28.6)	0
Dental carries	4 (9.5)	0
Diarrhoea	5 (11.9)	0
Gastritis	3 (7.1)	0
Nausea	9 (21.4)	0
Stomatitis	32 (76.2)	0
Vomiting	6 (14.3)	0
General disorders and administration site conditions		
Influenza like illness	5 (11.9)	0
Malaise	10 (23.8)	0
Pain	3 (7.1)	0
Pyrexia	3 (7.1)	0
Infections and infestations		
Angular cheilitis	4 (9.5)	0
Cellulitis	4 (9.5)	0
Conjunctivitis	4 (9.5)	0
Nasopharyngitis	19 (45.2)	0
Oral herpes	3 (7.1)	0
Pharyngitis	8 (19.0)	0
Upper respiratory tract infection	6 (14.3)	0
Injury, poisoning and procedural complications		
Contusion	3 (7.1)	0
Fall	9 (21.4)	0
Investigations		
Alanine aminotransferase increased	12 (28.6)	4 (9.5)
Aspartate aminotransferase increased	11 (26.2)	1 (2.4)
Neutrophil count decreased	34 (81.0)	32 (76.2)
Platelet count decreased	9 (21.4)	0
Weight decreased	5 (11.9)	0
White blood cell count decreased	30 (71.4)	22 (52.4)
Metabolism and nutrition disorders		
Decreased appetite	6 (14.3)	1 (2.4)
Musculoskeletal and connective tissue disorders		
Arthralgia	5 (11.9)	0
Musculoskeletal stiffness	4 (9.5)	0
Myalgia	4 (9.5)	0
Osteoporosis	3 (7.1)	0
Pain in extremity	4 (9.5)	0
Nervous system disorders		
Dizziness	4 (9.5)	0
Dysgeusia	4 (9.5)	0
Headache	7 (16.7)	0

Table 19. Treatment-Emergent Adverse Events Reported in ≥5% of Patients (All-Causality) by Preferred Term, All Cycles (Safety Analysis Set)

Number (%) of Patients System Organ Class Preferred Term	Palbociclib Plus Letrozole (N=42)	
	Total n (%)	Grade 3 or 4 n (%)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	6 (14.3)	0
Oropharyngeal pain	4 (9.5)	0
Skin and subcutaneous tissue disorders		
Alopecia	8 (19.0)	0
Dermatitis acneiform	3 (7.1)	0
Dry skin	4 (9.5)	0
Eczema	3 (7.1)	0
Nail disorder	3 (7.1)	0
Pruritus	4 (9.5)	0
Rash	8 (19.0)	0
Rash maculo-papular	3 (7.1)	0
Vascular disorders		
Hot flush	3 (7.1)	0
Hypertension	5 (11.9)	2 (4.8)

The SAE/non SAE results were not separated out.
MedDRA Version 21.1 coding dictionary applied.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in specific category; SAE=serious adverse event.

Table 20. Treatment-Emergent Adverse Events Reported in ≥5% of Patients (Treatment-Related) by Preferred Term, All Cycles

Number (%) of Patients System Organ Class Preferred Term	Palbociclib Plus Letrozole (N=42)	
	Total n (%)	Grade 3 or 4 n (%)
Any AEs	42 (100.0)	39 (92.9)
Blood and lymphatic system disorders		
Anaemia	9 (21.4)	2 (4.8)
Leukopenia	5 (11.9)	3 (7.1)
Neutropenia	9 (21.4)	8 (19.0)
Cardiac disorders		
Palpitations	3 (7.1)	0
Gastrointestinal disorders		
Cheilitis	5 (11.9)	0
Constipation	10 (23.8)	0
Diarrhoea	5 (11.9)	0
Nausea	5 (11.9)	0
Stomatitis	31 (73.8)	0
General disorders and administration site conditions		
Malaise	7 (16.7)	0
Infections and infestations		
Angular cheilitis	4 (9.5)	0
Oral herpes	3 (7.1)	0
Investigations		
Alanine aminotransferase increased	10 (23.8)	4 (9.5)
Aspartate aminotransferase increased	10 (23.8)	1 (2.4)
Neutrophil count decreased	34 (81.0)	32 (76.2)
Platelet count decreased	9 (21.4)	0
Weight decreased	3 (7.1)	0
White blood cell count decreased	30 (71.4)	22 (52.4)
Metabolism and nutrition disorders		
Decreased appetite	3 (7.1)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	3 (7.1)	0
Myalgia	4 (9.5)	0
Osteoporosis	3 (7.1)	0
Nervous system disorders		
Dysgeusia	4 (9.5)	0
Headache	6 (14.3)	0
Respiratory, thoracic and mediastinal disorders		
Epistaxis	5 (11.9)	0
Oropharyngeal pain	3 (7.1)	0
Skin and subcutaneous tissue disorders		
Alopecia	8 (19.0)	0
Dry skin	4 (9.5)	0
Nail disorder	3 (7.1)	0
Pruritus	3 (7.1)	0
Rash	5 (11.9)	0
Rash maculo-papular	3 (7.1)	0
Vascular disorders		
Hot flush	3 (7.1)	0
Hypertension	4 (9.5)	2 (4.8)

The SAE/non SAE results were not separated out.
MedDRA Version 21.1 coding dictionary applied.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in specific category; SAE=serious adverse event.

Permanent Discontinuations due to Adverse Events:

At the data cutoff date of 04 March 2016, AEs associated with permanent discontinuations of palbociclib were reported in 7 (16.7%) patients. These events included neutrophil count decreased (2 patients) and alanine aminotransferase increased, aspartate aminotransferase increased, malaise, subarachnoid hemorrhage, cerebral hemorrhage and neutropenia (1 patient each). Except for cerebral hemorrhage in 1 patient, these events were considered treatment related. Three (3) patients discontinued palbociclib but continued letrozole only.

At the data cutoff date of 25 October 2018, 1 additional patient who had neutropenia, permanently discontinued palbociclib only.

Death and Serious Adverse Events:

At the cutoff date of 04 March 2016, SAEs were reported in 3 (7.1%) patients. These events included vomiting, malaise, dizziness, and subarachnoid hemorrhage in 1 patient, febrile neutropenia in 1 patient, and cerebral hemorrhage in 1 patient. Of these, subarachnoid hemorrhage and febrile neutropenia were considered treatment related.

Since the start of the study, 1 death was reported from start of treatment to last dose including 28 days after last dose due to study treatment toxicity (subarachnoid hemorrhage) (till data cutoff date: 04 March 2016). Seven (7) death cases were reported during the follow-up period and the cause of death was disease under study, for all 7 cases.

At the data cutoff date of 25 October 2018, the SAEs were reported in 4 (9.5%) patients. One (1) additional patient since the original cutoff date reported an SAE of osteoarthritis.

Laboratory Test Abnormalities and Vital Signs Data:

At the cutoff date of 04 March 2016, hematology values with a maximum Grade 4 were neutrophils (21.4% of patients) and white blood cells (4.8%). Hematology values with a maximum Grade 3 were neutrophils (69.0% of patients), white blood cells (50.0%), anemia (7.1%), and platelets (2.4%). No clinical chemistry values with maximum Grade 4 were reported. Chemistry values with a maximum Grade 3 were alanine aminotransferase (9.5%), aspartate aminotransferase (2.4%), and hypermagnesemia (2.4%).

At the final study completion date: 25 October 2018, hematology values with a maximum Grade 4 were neutrophils (23.8%) and white blood cells (4.8%). Hematology values with a maximum Grade 3 were neutrophils (69.0%), white blood cells (57.1%), anemia (7.1%), and platelets (2.4%). No clinical chemistry values with maximum Grade 4 were reported. Chemistry values with a maximum Grade 3 were alanine aminotransferase (9.5%), aspartate aminotransferase (2.4%), and hypermagnesemia (2.4%).

At the cutoff date of 04 March 2016, no apparent increasing or decreasing trends of vital signs were observed during the study. No patients had a QT interval corrected for heart rate (QTc) value of ≥500 msec or an increase of ≥60 msec from Baseline. Same results were seen at the data cutoff date of 25 October 2018.

CONCLUSIONS:

Phase 1:

Two (2) dose levels of single-agent palbociclib 100 mg and 125 mg were studied in the Part 1 of this Phase 1 study in a total of 12 patients with solid tumors, and palbociclib 125 mg QD in combination with letrozole in 6 patients with ER-positive HER2-negative ABC was studied in the Part 2. Following findings were noted.

- DLTs were reported in 1 patient (<75% of planned dose of study drug received due to neutrophil count decreased) among 6 patients in the palbociclib 100 mg and 1 patient (Grade 4 platelet count decreased) among 6 patients in the 125 mg group. The MTD of single agent palbociclib in Japanese population was determined as 125 mg QD for Schedule 3/1.

- The single agent palbociclib at 100 mg and 125 mg QD (Schedule 3/1), and the combination therapy of palbociclib 125 mg QD (Schedule 3/1) plus letrozole 2.5 mg QD were tolerable and manageable in Japanese patients. No apparent differences in the safety profiles noted among the 3 treatment groups investigated in this study. Commonly reported treatment-related AEs across the treatment groups were neutropenia and leukopenia which were commonly reported as Grade 3 or 4. Most of these AEs were manageable and reversible without any medication. No death or treatment-related SAEs were reported at the original data cutoff date of 31 March 2015.

- For both single-dose and multiple-dose palbociclib, geometric mean AUC and C_{max} values with the 125 mg dose were 2.2- to 2.5-fold higher than those for the 100 mg dose although T_{max} and $t_{½}$ were similar between the 100 mg and 125 mg groups.

- No drug-drug interaction between palbociclib and letrozole was observed when palbociclib and letrozole were administered in combination in Japanese patients.

- Among 12 patients treated in Part 1 (palbociclib single agent), the best overall tumor response of SD was reported in 4 patients including 2 patients with an SD ≥24 weeks. Of 6 patients with ER-positive HER2-negative ABC treated in combination therapy with letrozole in Part 2, 2 patients had an objective response (2 PR) and 2 patients had an SD ≥24 weeks, and these 4 patients were still ongoing in the study and all were with PFS >500 days at the original data cutoff date of 31 March 2015.

- Overall, palbociclib 125 mg QD (Schedule 3/1) was considered as a recommended dose for single agent and in combination with standard of care letrozole regimen in Japanese patients.

- In the Phase 1 Part 2 portion of study, palbociclib in combination with letrozole remained tolerable and manageable in Japanese patients with ER-positive, HER2-negative ABC with a longer treatment duration, while maintaining tumor response and disease control. Overall, the safety profile of palbociclib was consistent with that reported in the original data collected till cutoff date of 31 March 2015), and no new safety signals were observed in Part 2 of the Phase 1 portion of the study.

Phase 2 (Data Cutoff: 04 March 2016):

- The combination of palbociclib and letrozole resulted in an Investigator-assessed 1-year PFS probability of 75.0% (90% CI: 61.3%, 84.4%) which far exceeded the protocol-defined lower limit of the 90% CI of 40%. The median PFS was not reached.

- The ORR was 40.5% (95% CI: 25.6%, 56.7%) with 17 PRs. DCR was 85.7%. Although the median DOR was not reached, the responses were durable as the lower limit of the 95% CI was 6.5 months at the time of data cutoff.

- The median OS was not reached. The survival probability at Month 12 was 92.9% (95% CI: 79.5%, 97.6%).

- Up to Cycle 11, the mean FACT-B, FACT-G, and TOI scores showed numerical deterioration, though those mean scores did not change beyond MID. No clinically meaningful deterioration of quality of life was observed when treated with palbociclib plus letrozole.

- When palbociclib was administered in combination with letrozole in Japanese patients with ER-positive HER2-negative ABC in Phase 2, palbociclib steady-state mean AUC_{tau} and C_{max} were 1979 ng•h/mL and 124.7 ng/mL, respectively.

- Predose concentrations on Day 15 of Cycles 1 and 2 were similar, and geometric mean of within-patient mean C_{trough} obtained from Day 15 of Cycles 1 and 2 was 90.1 ng/mL.

- The combination therapy of palbociclib 125 mg QD (Schedule 3/1) plus letrozole 2.5 mg QD was generally tolerated and manageable by dosing interruption, dose reduction, and/or standard medical therapy. The most commonly reported treatment-related AEs were neutropenia, stomatitis, and leukopenia by clustered preferred term.

In conclusion, these results suggested efficacy of palbociclib in combination with letrozole, and the combination was generally tolerable with a manageable safety profile in the first-line treatment of Japanese postmenopausal patients with ER-positive HER2-negative ABC.

The results obtain in the Phase 2 portion of study (data cutoff: 25 October 2018) were as follows:

- The updated analysis with longer follow-up showed the median PFS approximately 3 years for palbociclib in combination with letrozole (35.7 months [95% CI: 21.7, 46.7]).

- The ORR was 47.6% (95% CI: 32.0%, 63.6%) with 1 CR and 19 PRs. The DCR was 85.7% with 1 CR, 19 PRs and 16 SDs ≥24 weeks. The median DOR was 41.4 months (95% CI: 19.0, NE).

- The median OS was not reached. The survival probability at 12 months was 92.9% (95% CI: 79.5%, 97.6%).

- Up to Cycle 41, the mean FACT-B, FACT-G, and TOI scores showed numerical deterioration, though those mean scores did not change beyond MID. No clinically meaningful deterioration of quality of life was observed when patients were treated with palbociclib plus letrozole;

- Palbociclib in combination with letrozole remained tolerated and generally manageable with a longer treatment duration by dosing interruption, dose reduction, and/or standard medical therapy. Overall, the safety profile of palbociclib was consistent with that reported in the original data collected till cutoff date of 04 March 2016, and no new safety signals were observed at the end of Phase 2.