PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: A5481004

PROTOCOL TITLE: Phase 1/2 Open-Label Study of the Safety and Efficacy of PD 0332991 in Combination With Bortezomib and Dexamethasone in Patients With Refractory Multiple Myeloma

Study Centers: Fourteen (14) centers took part in study and enrolled subjects: 11 in the United States, 2 in Germany and 1 in the Czech Republic.

Study Initiation, Primary Completion and Final Completion Dates:
Study Initiation Date: 13 February 2008
Primary Completion Date: 05 August 2012 (date of data cut-off for analysis)
Final Completion Date: 16 March 2013 (last subject last visit)

Phase of Development: Phase 1/2

Study Objectives:

Phase 1:

Primary Objective:

- To determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of palbociclib in combination with bortezomib and dexamethasone in subjects with relapsed/refractory multiple myeloma (MM).

Secondary Objectives:

- To determine the pharmacodynamic (PD) effects of palbociclib in combination with bortezomib and dexamethasone in pre- and post-treatment serum and myeloma specimens;
- To evaluate the plasma pharmacokinetics (PK) of palbociclib when administered in combination with bortezomib and dexamethasone to subjects with refractory MM;
- To document any clinical evidence of anti-tumor activity.

Phase 2:

Primary Objective:

- To evaluate the anti-tumor activity of palbociclib in combination with bortezomib and dexamethasone based on objective response rate (ORR) as defined by International Myeloma Working Group Uniform Response Criteria (IMWGURC).

Secondary Objectives:

- To assess the safety of palbociclib in combination with bortezomib and dexamethasone;
- To assess additional evidence of anti-tumor activity as measured by duration of (objective) response (DR), progression-free survival (PFS), time to progression (TTP) and overall survival (OS);
- To explore correlation of potential biomarkers with treatment-related outcomes;
- To explore patient reported outcomes (PROs).

METHODS

Study Design: This was a multicenter, open-label, Phase 1 dose escalation, safety and PK/PD study of palbociclib in combination with bortezomib and dexamethasone followed by a Phase 2 efficacy study of the same combination in subjects with relapsed or refractory MM. Both Phase 1 and Phase 2 consisted of a screening period of up to 28 days, a treatment period that continued until discontinuation criteria were met, and a follow-up visit completed approximately 28 days after the last dose of study treatment. Long-term follow-up was conducted by telephone contact every 3 months until death or until 1 year after the last dose of palbociclib.

Phase 1:

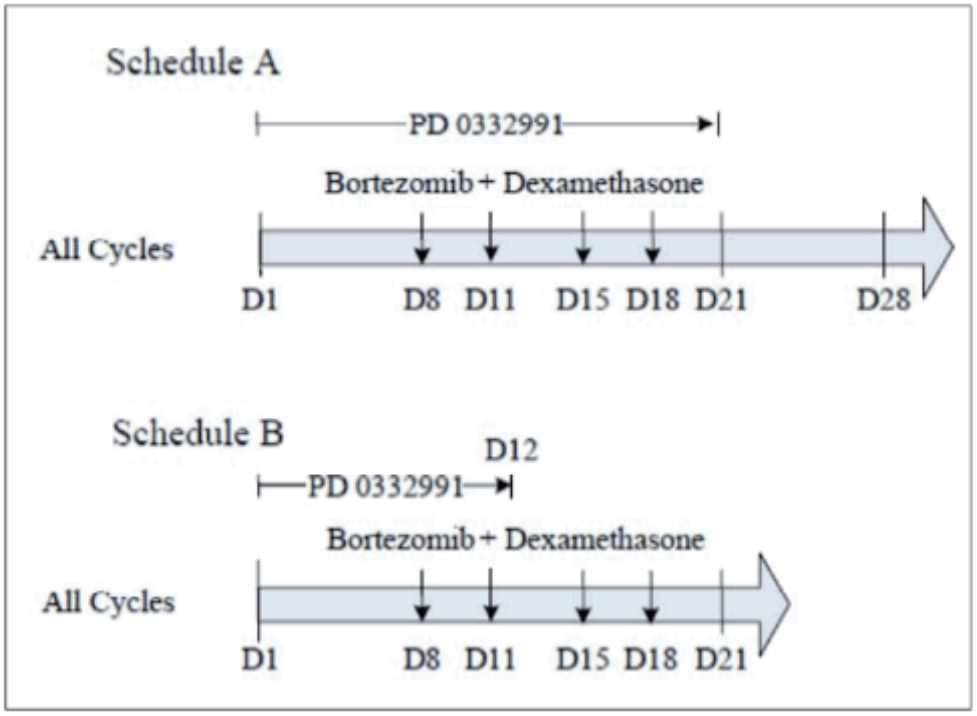
Two (2) schedules (Schedules A and B) for palbociclib administration (Figure 1) were sequentially evaluated. The study design of each schedule followed a 3+3 dose escalation scheme, with planned doses of palbociclib and bortezomib starting from 100 mg/1.0 mg/m^2 and escalating up to a maximum dose of 125 mg/1.3 mg/m^2, respectively. In both schedules, the MTD was defined as the dose level at which 0 of 6 or 1 of 6 subjects experienced a dose-limiting toxicity (DLT) during the first treatment cycle with the next higher dose having at least 2 of 3 to 6 subjects who experienced DLTs. The RP2D was determined based upon the MTD and the overall safety and tolerability profile of the study treatment.

Phase 2:

Subjects received palbociclib in combination with bortezomib and dexamethasone at the RP2D and schedule (Schedule A or B) as determined in the Phase 1 part of the study. Subjects continued with the assigned study treatment until withdrawal criteria were met.

A Simon Two-Stage Minimax design was used to determine the sample size for Phase 2 and to test the effectiveness of the treatment. The treatment was not considered of further interest if the ORR (stringent complete response [sCR], complete response [CR], very good partial response [VGPR] or partial response [PR]) was ≤28% in the first 25 response evaluable subjects (Stage 1). If this Stage 1 criterion was not met, then approximately 17 additional response evaluable subjects were to be enrolled into the subsequent Stage 2 portion of the Phase 2 study giving a total enrolment of approximately 42 response evaluable subjects. At the End of the Study, an observed ORR of at least 38.1% (or ≥16 responses out of 42 subjects) was to be attained in order to recommend further studies in this subject population.

Figure 1. Study Design and Plan



D = day.

Number of Subjects (Planned and Analyzed): It was planned to enroll 15 to 20 subjects in the Phase 1 study. A total of 21 subjects were enrolled and treated in Phase 1, 9 in Schedule A, and 12 in Schedule B. There were 25 response evaluable subjects planned to be enrolled in Stage 1 and 17 response evaluable subjects planned to be enrolled in Stage 2 of the Phase 2 study, giving a total enrollment of 42 response evaluable subjects. Thirty-two (32) subjects were enrolled and 30 were treated in Stage 1 of Phase 2. Stage 2 of the Phase 2 study did not proceed.

Diagnosis and Main Criteria for Inclusion: Male and female subject's ≥18 years old who met the following criteria were included in the study:

- Diagnosis of symptomatic MM as defined by International Myeloma Working Group (IMWG);

- Phase 1: Relapsed or relapsed/refractory myeloma after at least 1 previous treatment and with a life expectancy >3 months;

- Phase 2: Measurable (as defined by IMWGURC) progressive disease after at least 1 previous treatment.

Main Exclusion Criteria:

- History of allogeneic stem cell transplant;

- Phase 2 only: Prior palbociclib therapy or prior history of other advanced/metastatic malignancy other than MM. Prior bortezomib therapy was allowed only if there was a demonstrated positive response and disease progression occurred off therapy;

- Significant blood level changes, eg, very low platelets, while on previous bortezomib therapy;

- Prior radiation therapy to >25% of the bone marrow (whole pelvis is 25%).

Study Treatment:

Phase 1 – Schedules A and B:

Doses of palbociclib in combination with bortezomib and dexamethasone were studied sequentially, beginning with 100 mg once daily (QD) of palbociclib for each schedule with at least 3 subjects in each dose level. Palbociclib capsules were administered per oral (PO), QD for 3 weeks (21 days) with 1 week (7 days) off treatment for Schedule A and QD for 12 days with 9 days off treatment for Schedule B.

Bortezomib and dexamethasone were administered on Days 8, 11, 15 and 18 of each cycle. Bortezomib was given by intravenous bolus (taking 3 to 5 seconds to administer) in the dose range of 0.7 to 1.3 mg/m^2. Dexamethasone tablets were administered at a dose of 20 mg PO for all cohorts and schedules, administered approximately 30 minutes prior to each bortezomib injection. The possible dose escalation and de-escalation levels for palbociclib and bortezomib are presented in Table 1.

Intrasubject dose escalation was allowed in this study. Subjects continued treatment at their initially assigned dose level for at least 2 cycles, after which they could receive the next higher dose level provided it was shown to be safe.

Phase 2:

Eligible subjects received palbociclib in combination with bortezomib and dexamethasone administered at the RP2D as per dosing schedule (Schedule A or B) determined in the Phase 1 part of the study.

Table 1. Dose Escalation or De-Escalation Levels for Schedules A and B

Dose Level	Palbociclib (PO)	Bortezomib (IV)	Dexamethasone (PO)
-3a[a]	50 mg	1.0 mg/m^2	20 mg
-3	50 mg	0.7 mg/m^2	20 mg
-2	75 mg	0.7 mg/m^2	20 mg
-1	75 mg	1.0 mg/m^2	20 mg
1	100 mg	1.0 mg/m^2	20 mg
2	125 mg	1.0 mg/m^2	20 mg
3	125 mg	1.3 mg/m^2	20 mg
3a[b]	100 mg	1.3 mg/m^2	20 mg

This table was also used for dose de-escalation levels.
IV = intravenous; MTD = maximum tolerated dose; PO = per oral.
a. Dose level -3a was only evaluated if dose level -3 was tolerated.
b. Dose level 3a was tested only if MTD was exceeded at dose level 3.

Efficacy and Safety Endpoints:

Phase 1

Primary Endpoint:

- First cycle DLTs to determine the MTD and RP2D of palbociclib in combination with bortezomib and dexamethasone.

Secondary Endpoints:

- Changes in the phosphorylation status of the Rb protein in the myeloma cells, and changes in the tumor and soluble biomarkers (markers predictive of inhibition of tumor proliferation and/or induction of apoptosis) from samples collected pre- and post-treatment;
- Tumor response.

Phase 2

Primary Endpoint:

- ORR of palbociclib in combination with bortezomib and dexamethasone as defined by IMWGURC.

Secondary Endpoints:

- TTP, PFS and DR as defined by the IMWGURC;
- OS;
- Overall safety profile characterized by type, incidence, severity, timing, seriousness and relationship to study medications of adverse events (AEs) and any laboratory abnormalities.

- PRO as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the Quality of Life Questionnaire Multiple Myeloma Module (QLQ-MY20), and the Modified Version of the Brief Pain Inventory - Short Form (m-BPI-sf).

Safety Evaluations: Safety was assessed by summaries of all AEs, physical examination, weight assessments, vital signs, Eastern Cooperative Oncology Group performance status, 12-lead electrocardiogram (ECGs), and the results of laboratory tests.

Statistical Methods: Analysis sets were defined by phase of the study.

Phase 1:

The DLT analysis set included all enrolled subjects who received at least 1 dose of study treatment and did not have a major deviation in the first cycle.

Phase 1 and Phase 2:

The full analysis set included all enrolled subjects.

The response analysis set (RAS) included all enrolled subjects who received study treatment, had an adequate baseline tumor assessment and measurable disease (only Phase 2 required measurable disease).

The safety analysis set (SAS) included all enrolled subjects who received at least 1 dose of study treatment.

The PRO analysis set included all enrolled subjects that received study treatment, had a baseline PRO assessment, and completed at least 1 on-study PRO assessment.

The exploratory biomarker analysis set included all enrolled subjects who started treatment and had baseline and on-study biomarker samples successfully analyzed for any of the exploratory biomarkers except for cytogenetics, which had a baseline value only.

Phase 2:

Primary response analysis set (PRAS) was defined as the consecutive (by first treatment day) subjects in RAS that were response-evaluable (up to 25 subjects for Stage 1 and up to 42 subjects for Stage 2).

Efficacy Analysis: Data were reported separately for Phases 1 and 2. Phase 1 was reported by dose/schedule and overall, as appropriate. Phase 2 was reported overall.

The Phase 1 primary analysis was based on the DLT analysis set.

The Phase 2 primary analysis of ORR was based on the PRAS and included the number of response-evaluable subjects, number of subjects with objective response, and the ORR (%) with its associated exact 95% confidence interval (CI).

Phase 1 and Phase 2: Best tumor response was based on the PRAS and included the number and percentage of subjects with sCR, CR, VGPR, PR, stable/no response, progressive disease (objective), symptomatic (ie, global deterioration), early death, and indeterminate. An estimate of probability of ORR and the exact CI for the probability of ORR were provided.

Phase 2: DR was based on the RAS and included the median duration (based on Kaplan-Meier estimates), 95% CI for the median duration, and range (minimum, maximum).

The following secondary analyses were based on the SAS and included the range and 95% CIs on the estimates:

- PFS: the median and the probability of remaining alive and progression-free at 1 year (based on Kaplan-Meier estimates).
- TTP: the median and the probability of remaining progression-free at 1 year (based on Kaplan-Meier estimates).
- OS: the median and the probability of being alive at 1 year (based on Kaplan-Meier estimates).

Median event time was estimated using method of Kaplan-Meier and 95% 2-sided CIs were calculated.

Exploratory biomarker, PRO and safety data were summarized descriptively.

RESULTS

Subject Disposition and Demography:

Subject Disposition:

Phase 1: Disposition of subjects in Phase 1, treated according to Schedules A and B are shown in Table 2 and Table 3, respectively.

Table 2. Subject Evaluation Groups for Phase 1 – Schedule A

Number of Subjects	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2/ Dexamethasone 20 mg	Palbociclib 75 mg / Bortezomib 1.0 mg/m^2/ Dexamethasone 20 mg	Total
Treated	3	6	9
Completed	0	0	0
Discontinued	3	6	9
Objective progression or relapse, n (%)	3 (100)	5 (83.3)	
Global deterioration of health status, n (%)	0	1 (16.7)	

Discontinuations occurring outside the lag period have been attributed to the last study treatment received.
n = number of subjects.

Table 3. Subject Evaluation Groups for Phase 1 – Schedule B

Number of Subjects	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2/ Dexamethasone 20 mg	Palbociclib 125 mg / Bortezomib 1.0 mg/m^2/ Dexamethasone 20 mg	Total
Treated	7	5	12
Completed	0	0	0
Discontinued	7	5	12
Subject refused continued treatment for reason other than adverse event, n (%)	0	1 (20.0)	
Objective progression or relapse, n (%)	3 (42.9)	1 (20.0)	
Adverse event, n (%)	3 (42.9)	2 (40.0)	
Global deterioration of health status, n (%)	1 (14.3)	1 (20.0)	

Discontinuations occurring outside the lag period have been attributed to the last study treatment received.
n = number of subjects.

Phase 2: Thirty-two (32) subjects were enrolled and 30 were treated. At the time of data cut-off for analysis (05 August 2012), 1 subject (3.3%) was still on treatment and ongoing in the study, with the other 29 subjects (96.7%) having discontinued treatment (Table 4); 13 of these 29 subjects were still in long-term follow-up.

Post the data cut-off, the ongoing subject was discontinued due to the Investigator's assessment that it was not in the subject's best interest to continue the study treatment. The subject subsequently died post study. Of the 13 subjects who were in long-term follow-up, 10 subjects completed their follow-up, 2 subjects died, and 1 subject refused further follow-up.

Table 4. Subject Disposition at End of Treatment with Palbociclib: Phase 2 – Schedule B

Number of Subjects	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg
Ongoing, n (%)	1 (3.3)
Reason for discontinuation, n (%)	
AE	4 (13.3)
Global deterioration of health status	2 (6.7)
Objective progression or relapse	16 (53.3)
Subject no longer willing to continue treatment for reason other than AE	2 (6.7)
Other	5 (16.7)
Total	29 (96.7)

AE = adverse event; n = number of subjects.

Analysis Populations:

Phase 1: Analysis populations for subjects in Schedule A and B are presented in Table 5 and Table 6, respectively.

Table 5. Analysis Populations for Subjects in Phase 1 – Schedule A

Number of Subjects	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg	Palbociclib 75 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg	Total
Analyzed for safety:			
Adverse events	3	6	9
Laboratory data	3	6	9
Evaluable for:			
Dose-limiting toxicity	3	5	8
Efficacy	1	5	6

Table 6. Analysis Populations for Subjects in Phase 1 – Schedule B

Number of Subjects	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg	Palbociclib 125 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg	Total
Analyzed for safety:			
Adverse events	7	5	12
Laboratory data	7	5	12
Evaluable for:			
Dose-limiting toxicity	6	4	10
Efficacy	7	5	12

Phase 2: Analysis populations for subjects in Phase 2 are presented in Table 7.

Table 7. Analysis Populations for Subjects in Phase 2 – Schedule B

Number of Subjects	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg
Analyzed for safety:	
Adverse events	30
Laboratory data	30
Evaluable for:	
Time to event	30
Response	25

Demography:

Phase 1: Demographic characteristics for subjects in Phase 1 are presented in Table 8.

Table 8. Demographic Characteristics – Phase 1

	Schedule A			Schedule B			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects	**4**	**5**	**9**	**11**	**1**	**12**	**15**	**6**	**21**
Age (years):									
<18	0	0	0	0	0	0	0	0	0
18-44	1	1	2	1	0	1	2	1	3
45-64	2	2	4	6	1	7	8	3	11
≥65	1	2	3	4	0	4	5	2	7
Median	59.5	60.0	60.0	63.0	57.0	61.0	60.0	58.5	60.0
Mean	55.3	57.8	56.7	60.4	57.0	60.1	59.0	57.7	58.6
SD	12.4	12.6	11.8	10.2	0.0	9.8	10.6	11.2	10.5
Range	37-65	38-71	37-71	38-72	57-57	38-72	37-72	38-71	37-72

SD = standard deviation.

Phase 2: Demographic characteristics for all enrolled subjects in Phase 2 are presented in Table 9.

Table 9. Demographic Characteristics – Phase 2

	Schedule B		
	Male	Female	Total
Number of Subjects Assigned to Treatment	**15**	**17**	**32**
Age (years):			
<18	0	0	0
18-44	0	0	0
45-64	7	6	13
≥65	8	11	19
Median	68.0	67.0	67.0
Mean	66.8	65.3	66.0
SD	10.4	5.4	8.1
Range	53-85	54-75	53-85

SD = standard deviation.

Efficacy Results:

Efficacy results presented are those at the time of data cut-off (05 August 2012). At the time of data cut-off, 1 subject was ongoing in the Phase 2 part of study, and OS is also presented at the time of database lock (15 November 2013).

Biomarkers: At Cycle 1/Day 8, in both schedules and at both dose levels within a schedule, there were falls from predose values in phosphorylated Rb to either very low values or 0 in all cases, except for 1 subject (Schedule B, palbociclib 125 mg / bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose group) where the values were 37%, falling to 32%.

For the 2 subjects in Schedule A with Cycle 1/Day 21 data, phosphorylated Rb values remained at 0% at that time point. For the 7 subjects in Schedule B with Cycle 1/Day 18 data, phosphorylated Rb values had returned to levels similar to predose values at that time point.

In all 4 cases where end of treatment data or data acquired after time off study treatment (2 subjects in Schedule A, 2 subjects in Schedule B), phosphorylated Rb values had returned to levels similar to predose values, at times ranging from 7 to 59 days off treatment.

Of the 3 subjects in Schedule A at the palbociclib 100 mg / bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose level with interleukin-6 (IL-6) data predose and at Cycle 1/Day 8, all showed an increase in IL-6 from the predose value. None of these subjects had IL-6 data at Cycle 1/Day 21 or later. Of the 5 subjects in Schedule A at the palbociclib 75 mg / bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose level with IL-6 data predose and at Cycle 1/Day 8, all showed a decrease in IL-6 from the predose value. Of the 3 subjects with IL-6 data predose and at Cycle 1/Day 21, 2 showed a decrease from the predose value, and 1 showed an increase from the predose value.

Of the 5 subjects in Schedule B at the palbociclib 100 mg / bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose level with IL-6 data predose and at Cycle 1/Day 8, 2 showed a decrease from the predose value, 2 showed an increase from the predose value and 1 had both values <1.2 pg/mL. Of the 5 subjects in Schedule B at the palbociclib 100 mg / bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose level with IL-6 data predose and at Cycle 1/Day 18, 2 showed a decrease from the predose value, 2 showed an increase from the predose value and 1 had both values <1.2 pg/mL. Of the 4 subjects in Schedule B at the palbociclib 125 mg / bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose level with IL-6 data predose and at Cycle 1/Day 8, 3 showed a decrease from the predose value and 1 showed an increase from the predose value. Of the 2 subjects in Schedule B at the palbociclib 125 mg / bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose level with IL-6 data predose and at Cycle 1/Day 18, 1 showed a decrease from the predose value and 1 showed an increase from the predose value.

Best Overall Response:

Phase 1: Best overall response data for subjects in Schedule A who were evaluable for efficacy are presented in Table 10.

Table 10. Best Overall Response – Phase 1: Schedule A

	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg n (%)	**Palbociclib 75 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg n (%)**	**Total n (%)**
Number of subjects	1 (100)	5 (100)	6 (100)
Stringent complete response (sCR)	0	0	0
Complete response (CR)	0	0	0
Very good partial response (VGPR)	0	1 (20.0)	1 (16.7)
Partial response (PR)	0	0	0
Stable disease	0	1 (20.0)	1 (16.7)
Progressive disease	1 (100)	3 (60.0)	4 (66.7)
Indeterminate	0	0	0
Objective response rate (sCR, CR, VGPR or PR)	0	1 (20.0)	1 (16.7)
95% exact confidence interval[a]	0.0, 97.5	0.5, 71.6	0.4, 64.1

n = number of subjects.
a. Using exact method based on binomial distribution.

Best overall response data for subjects in Schedule B who were evaluable for efficacy are presented in Table 11.

Table 11. Best Overall Response – Phase 1: Schedule B

	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg n (%)	Palbociclib 125 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg n (%)	Total n (%)
Number of subjects	7 (100)	5 (100)	12 (100)
Stringent complete response (sCR)	0	0	0
Complete response (CR)	0	0	0
Very good partial response (VGPR)	0	1 (20.0)	1 (8.3)
Partial response (PR)	0	0	0
Stable disease	4 (57.1)	2 (40.0)	6 (50.0)
Progressive disease	3 (42.9)	1 (20.0)	4 (33.3)
Indeterminate	0	1 (20.0)	1 (8.3)
Objective response rate (sCR, CR, VGPR or PR)	0	1 (20.0)	1 (8.3)
95% exact confidence interval[a]	0.0, 41.0	0.5, 71.6	0.2, 38.5

n = number of subjects.
a. Using exact method based on binomial distribution.

Phase 2: Best overall response data for subjects in Phase 2 are presented in Table 12. Since the ORR was <28%, the Stage 1 criteria were not met and the study did not continue into Stage 2.

Table 12. Best Overall Response – Phase 2 (Primary Response Analysis Set)

	Schedule B (N=25) n (%)
Stringent complete response (sCR)	0
Complete response (CR)	1 (4.0)
Very good partial response (VGPR)	1 (4.0)
Partial response (PR)	3 (12.0)
Stable disease	11 (44.0)
Progressive disease	9 (36.0)
Indeterminate	0
Objective response rate (sCR, CR, VGPR or PR)	5 (20.0)
95% exact confidence interval[a]	6.8, 40.7

n = number of subjects; N = number of subjects treated in group evaluable for response.
a. Using exact method based on binomial distribution.

Overall Survival: OS data at the time of data cut-off for the primary analysis (05 August 2012) are presented in Table 13. A median Kaplan-Meier estimate was not reached, although subjects were only followed-up for survival for 1 year post last dose.

Table 13. Overall Survival - Phase 2 (Data Cut-Off 05 August 2012)

	Schedule B (N=30) n (%)
Number of deaths	10 (33.3)
Cause of death	
Disease under study	6 (20.0)
Study treatment toxicity	0
Unknown	1 (3.3)
Other	3 (10.0)
Number censored	20 (66.7)
Reason for censorship	
Alive[a]	18 (60.0)
Subject no longer willing to participate	2 (6.7)
Lost to follow-up	0
Number of subjects with last contact date >1 year prior to data cutoff date	5 (16.7)
Survival probability at month 12[b] (95% confidence interval)[c]	68.1 (47.6, 82.0)
Kaplan-Meier estimates of time to event (months)	
Quartiles (95% confidence interval)[d]	
25%	11.1 (6.7, -)
50%	- (11.8, -)
75%	- (-,-)

"-" = could not be calculated.
n = number of subjects; N = number of subjects treated in group evaluable for time to event.
a. Data updated post data cut-off (05 August 2012).
b. Estimated from the Kaplan-Meier curve.
c. Calculated from the product-limit method.
d. Based on the Brookmeyer and Crowley method.

Overall survival data at database lock (15 November 2013) are presented in Table 14. There were an additional 2 subjects who died since data cut-off (05 August 2012), both due to the disease under study.

Table 14. Overall Survival - Phase 2 (Database Lock 15 November 2013)

	Schedule B (N = 30) n (%)
Number of deaths	12 (40.0)
Cause of death	
Disease under study	8 (26.7)
Study treatment toxicity	0
Unknown	1 (3.3)
Other	3 (10.0)
Number censored	18 (60.0)
Reason for censorship	
Alive	15 (50.0)
Subject no longer willing to participate	3 (10.0)
Survival probability at Month 12[a] (95% confidence interval)[b]	68.1 (47.6, 82.0)
Kaplan-Meier estimates of time to event (months)	
Quartiles (95% confidence interval)[c]	
25%	11.1 (6.7, 17.5)
50%	21.1 (11.8, -)
75%	- (-)

"-" = could not be calculated.
n = number of subjects; N = number of subjects treated in group evaluable for time to event.
a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley method.

Time to Progression: TTP data are presented in Table 15.

Table 15. Time to Progression - Phase 2

	Schedule B (N=30) n (%)
Number with event	17 (56.7)
Number censored	13 (43.3)
Reason for censorship	
No adequate baseline assessments	4 (13.3)
No on-study disease assessments	0
Given new anti-cancer treatment prior to tumor progression	2 (6.7)
Death on treatment without progression	0
Off treatment prior to progression	6 (20.0)
Withdrew consent for follow-up	1 (3.3)
Lost to follow-up	0
Unacceptable gap (>8 weeks) between palbociclib to the most recent prior adequate assessment	0
In follow-up for progression	0
Probability of being event free at Month 12[a] (95% confidence interval)[b]	26.1 (7.7, 49.6)
Kaplan-Meier estimates of time to event (months)	
Quartiles (95% confidence interval)[c]	
25%	1.4 (0.7, 2.8)
50%	3.9 (1.4, 7.4)
75%	12.5 (4.4, -)

"-" = could not be calculated.
n = number of subjects; N = number of subjects treated in group evaluable for time to event.
a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley method.

The number of subjects with progression and the probability of being progression free at Month 12 was unchanged at the time of database lock (15 November 2013).

Progression-Free Survival: PFS data are presented in Table 16.

Table 16. Progression-Free Survival - Phase 2

	Schedule B (N=30) n (%)
Number with event	17 (56.7)
Type of event	
Objective progression	17 (56.7)
Death without objective progression	0
Number censored	13 (43.3)
Reason for censorship	
No adequate baseline assessments	4 (13.3)
No on-study disease assessments	0
Given new anti-cancer treatment prior to tumor progression	2 (6.7)
Off treatment prior to progression	6 (20.0)
Withdrew consent for follow-up	1 (3.3)
Lost to follow-up	0
Unacceptable gap (>8 weeks) between palbociclib or death to the most recent prior adequate assessment	0
In follow-up for progression	0
Probability of being event free at Month 12[a] (95% confidence interval)[b]	26.1 (7.7, 49.6)
Kaplan-Meier estimates of time to event (months)	
Quartiles (95% confidence interval)[c]	
25%	1.4 (0.7, 2.8)
50%	3.9 (1.4, 7.4)
75%	12.5 (4.4, -)

"-" = could not be calculated.
n = number of subjects; N = number of subjects treated in group evaluable for time to event.
a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley method.

The number of subjects with objective progression and the probability of PFS at Month 12 was unchanged at the time of database lock (15 November 2013).

Duration of Objective Response: DR data are presented in Table 17.

Table 17. Duration of Objective Response - Phase 2

	Schedule B (N=25) n (%)
Number of subjects with events	2 (8.0)
Number of subjects censored	3 (12.0)
Kaplan-Meier estimates of duration of response (sCR, CR, VGPR or PR) in months:	
Quartiles (95% confidence interval)[a]	
25%	1.6 (1.6, -)
50%	4.6 (1.6, -)
75%	- (1.6, -)

"-" = could not be calculated.
CR = complete response; n = number of subjects; N = number of subjects treated in group evaluable for time to event; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.
a. Based on the Brookmeyer and Crowley method.

DR results at the time of database lock (15 November 2013) were consistent with those from the time of data cut-off (05 August 2012).

Patient Reported Outcomes:

For the disease symptoms scale within the EORTC QLQ-MY20, there appeared to be a possible trend towards an improvement in symptomology/problems. For the remaining items on the EORTC QLQMY20 and each item on the EORTC QLQ-C30 and m-BPI-sf, results and their changes from Baseline were stable over time until later cycles, when the number of subjects had decreased to a few in number.

Safety Results:

Dose-Limiting Toxicity: In Schedule A, 2 of 3 subjects in the palbociclib 100 mg/ bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose group experienced DLTs (inability to deliver at least 80% of the planned palbociclib or bortezomib doses during Cycle 1 due to toxicity; Grade 3 neutropenia/Grade 4 thrombocytopenia and Grade 3 neutropenia and fever, respectively, during Cycle 1). In the next dose level, palbociclib 75 mg/ bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose group, 2 of 6 subjects experienced DLTs (inability to deliver at least 80% of the planned palbociclib or bortezomib doses during Cycle 1 due to toxicity; Grade 3 thrombocytopenia and Grade 4 thrombocytopenia, respectively, during Cycle 1).

Review of these DLTs resulted in cancellation of Schedule A dosing and moving to a 12/21-day dosing regimen, Schedule B. At the palbociclib 100 mg/ bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose level in Schedule B, 1 subject out of 7 experienced a DLT (inability to deliver at least 80% of the planned palbociclib or bortezomib doses during Cycle 1 due to toxicity [unspecified]).

At the palbociclib 125 mg/ bortezomib 1.0 mg/m^2 / dexamethasone 20 mg dose level, 2 out of 5 subjects experienced DLTs (inability to deliver at least 80% of the planned palbociclib or bortezomib doses during Cycle 1 due to toxicity; Grade 4 thrombocytopenia and Grade 3 neutropenia for 1 subject, and Grade ≥3 nonhematologic treatment-related toxicity of metabolic acidosis for 1 subject).

Thus Phase 2 of the study proceeded using the MTD and RP2D, palbociclib 100 mg/ bortezomib 1.0 mg/m^2 / dexamethasone 20 mg over a 12/21-day dosing cycle (Schedule B).

Adverse Events: All AEs and serious AEs up to the time of database lock (15 November 2013) are presented in this section.

Treatment-emergent non-serious AEs (all causalities and treatment-related) for Phase 1 are presented in Table 18.

Table 18. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term – Phase 1

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)			Palbociclib 75 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 125 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:												
Evaluable for adverse events	3			7			6			5		
With adverse events	3 (100.0)			7 (100.0)			6 (100)			5 (100)		
Blood and lymphatic system disorders	3 (100.0)	17	17	6 (85.7)	90	89	6 (100.0)	68	61	5 (100.0)	57	51
Anaemia	0	0	0	2 (28.6)	5	5	2 (33.3)	3	3	1 (20.0)	1	0
Febrile neutropenia	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Hyperviscosity syndrome	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Leukopenia	0	0	0	2 (28.6)	10	9	0	0	0	1 (20.0)	6	6
Lymphopenia	0	0		3 (42.9)	23	23	0	0	0	2 (40.0)	14	14
Neutropenia	2 (66.7)	9	9	3 (42.9)	9	9	6 (100.0)	23	20	4 (80.0)	13	10
Thrombocytopenia	3 (100.0	8	8	5 (71.4)	43	43	5 (83.3)	40	38	4 (80.0)	23	21
Ear and labyrinth disorders	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Ear pain	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Eye disorders	1 (33.3)	1	0	0	0	0	1 (16.7)	1	0	2 (40.0)	2	0
Blepharitis	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Chalazion	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Dry eye	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Eyelid ptosis	1 (33.3)	1	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders	3 (100.0)	7	2	2 (28.6)	9	7	5 (83.3)	17	7	2 (40.0)	2	1
Abdominal distension	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Abdominal pain	0	0	0	0	0	0	2 (33.3)	2	0	0	0	0
Constipation	2 (66.7)	3	0	1 (14.3)	1	1	3 (50.0)	4	2	0	0	0
Diarrhoea	0	0	0	1 (14.3)	6	6	0	0	0	1 (20.0)	1	1
Dyspepsia	1 (33.3)	1	0	0	0	0	0	0	0	0	0	0
Flatulence	0	0	0	0	0	0	1 (16.7)	1	1	0	0	0
Gastritis	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Gastroesophageal reflux disease	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Melaena	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Nausea	2 (66.7)	2	1	0	0	0	3 (50.0)	3	2	0	0	0
Oesophagitis	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Oral pain	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0
Stomatitis	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0
Tongue coated	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Vomiting	1 (33.3)	1	1	0	0	0	2 (33.3)	2	2	0	0	0
General disorders and administration site conditions	2 (66.7)	3	1	3 (42.9)	3	3	4 (66.7)	7	1	4 (80.0)	10	6

Table 18. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term – Phase 1

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)			Palbociclib 75 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 125 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Asthenia	0	0	0	1 (14.3)	1	1	0	0	0	0	0	0
Chest discomfort	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Chest pain	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Chills	0	0	0	0	0	0	2 (33.3)	2	0	0	0	0
Fatigue	1 (33.3)	1	0	2 (28.6)	2	2	1 (16.7)	1	0	2 (40.0)	5	5
Gait disturbance	1 (33.3)	1	0	0	0	0	0	0	0	0	0	0
Oedema peripheral	0	0	0	0	0	0	0	0	0	2 (40.0)	2	1
Pain	0	0	0	0	0	0	3 (50.0)	3	1	0	0	0
Peripheral swelling	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Pyrexia	1 (33.3)	1	1	0	0	0	1 (16.7)	1	0	0	0	0
Infections and infestations	0	0	0	2 (28.6)	2	0	3 (50.0)	7	0	4 (80.0)	6	2
Cellulitis	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Conjunctivitis	0	0	0	0	0	0	1 (16.7)	1	0	1 (20.0)	1	0
Eye infection	0	0	0	0	0	0	0	0	0	1 (20.0)	1	1
Fungal infection	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Herpes zoster	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Hordeolum	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Klebsiella bacteraemia	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Nasopharyngitis	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0
Pneumonia	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Respiratory tract infection	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Upper respiratory tract infection	0	0	0	1 (14.3)	1	0	0	0	0	2 (40.0)	2	1
Urinary tract infection	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	1 (14.3)	2	0	1 (16.7)	1	0	1 (20.0)	1	1
Contusion	0	0	0	1 (14.3)	2	0	0	0	0	0	0	0
Fall	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Overdose	0	0	0	0	0	0	0	0	0	1 (20.0)	1	1
Investigations	0	0	0	5 (71.4)	72	57	2 (33.3)	4	2	2 (40.0)	49	21
Alanine aminotransferase decreased	0	0	0	0	0	0	0	0	0	1 (20.0)	2	0
Blood albumin decreased	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Blood bicarbonate decreased	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0
Blood bicarbonate increased	0	0	0	1 (14.3)	3	0	0	0	0	2 (40.0)	3	0
Blood bilirubin decreased	0	0	0	0	0	0	0	0	0	1 (20.0)	3	0
Blood chloride increased	0	0	0	0	0	0	0	0	0	1 (20.0)	3	0
Blood creatinine decreased	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0

Table 18. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term – Phase 1

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)			Palbociclib 75 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 125 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Blood creatinine increased	0	0	0	3 (42.9)	4	2	0	0	0	0	0	0
Blood glucose increased	0	0	0	0	0	0	0	0	0	2 (40.0)	2	2
Blood lactate dehydrogenase increased	0	0	0	0	0	0	0	0	0	2 (40.0)	3	0
Blood phosphorus decreased	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0
Blood phosphorus increased	0	0	0	1 (14.3)	1	0	0	0	0	2 (40.0)	6	0
Blood potassium decreased	0	0	0	1 (14.3)	1	0	1 (16.7)	1	1	1 (20.0)	3	0
Blood sodium decreased	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0
Blood sodium increased	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Blood uric acid increased	0	0	0	0	0	0	0	0	0	1 (20.0)	3	0
Body height decreased	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
General physical condition abnormal	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Haemoglobin decreased	0	0	0	2 (28.6)	12	8	0	0	0	1 (20.0)	1	1
Neutrophil count decreased	0	0	0	3 (42.9)	13	13	0	0	0	2 (40.0)	9	9
Platelet count decreased	0	0	0	1 (14.3)	21	21	0	0	0	0	0	0
Weight increased	0	0	0	0	0	0	1 (16.7)	1	1	0	0	0
White blood cell count decreased	0	0	0	1 (14.3)	13	13	0	0	0	2 (40.0)	9	9
Metabolism and nutrition disorders	1 (33.3)	1	0	4 (57.1)	11	2	3 (50.0)	8	0	3 (60.0)	8	6
Decreased appetite	1 (33.3)	1	0	0	0	0	1 (16.7)	1	0	1 (20.0)	1	0
Dehydration	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Hypercalcaemia	0	0	0	2 (28.6)	3	0	1 (16.7)	1	0	0	0	0
Hyperglycaemia	0	0	0	1 (14.3)	1	1	0	0	0	2 (40.0)	5	5
Hyperphosphataemia	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Hypoalbuminaemia	0	0	0	1 (14.3)	2	0	0	0	0	0	0	0
Hypocalcaemia	0	0	0	1 (14.3)	3	0	0	0	0	0	0	0
Hypokalaemia	0	0	0	1 (14.3)	1	1	2 (33.3)	2	0	0	0	0
Hypomagnesaemia	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Hyponatraemia	0	0	0	1 (14.3)	1	0	1 (16.7)	1	0	0	0	0
Metabolic acidosis	0	0	0	0	0	0	0	0	0	1 (20.0)	1	1
Overweight	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Musculoskeletal and connective tissue disorders	2 (66.7)	5	0	4 (57.1)	5	1	4 (66.7)	10	5	2 (40.0)	4	0
Arthralgia	0	0	0	2 (28.6)	2	1	1 (16.7)	1	0	0	0	0
Arthritis	0	0	0	0	0	0	0	0	0	1 (20.0)	2	0
Back pain	1 (33.3)	2	0	1 (14.3)	1	0	1 (16.7)	1	1	2 (40.0)	2	0
Joint stiffness	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Muscle spasms	0	0	0	0	0	0	1 (16.7)	2	2	0	0	0

Table 18. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term – Phase 1

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)			Palbociclib 75 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 125 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Muscular weakness	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Musculoskeletal chest pain	0	0	0	0	0	0	1 (16.7)	1	1	0	0	0
Musculoskeletal pain	1 (33.3)	1	0	1 (14.3)	1	0	0	0	0	0	0	0
Musculoskeletal stiffness	1 (33.3)	1	0	0	0	0	0	0	0	0	0	0
Pain in extremity	0	0	0	0	0	0	2 (33.3)	3	1	0	0	0
Pain in jaw	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0
Spinal disorder	1 (33.3)	1	0	0	0	0	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (33.3)	3	0	1 (14.3)	1	0	0	0	0	0	0	0
Neoplasm	1 (33.3)	2	0	0	0	0	0	0	0	0	0	0
Neoplasm skin	1 (33.3)	1	0	0	0	0	0	0	0	0	0	0
Plasmacytoma	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0
Nervous system disorders	3 (100.0)	6	5	1 (14.3)	1	1	3 (50.0)	3	0	2 (40.0)	2	1
Coordination abnormal	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Dizziness	1 (33.3)	1	1	0	0	0	0	0	0	0	0	0
Headache	1 (33.3)	1	1	0	0	0	1 (16.7)	1	0	1 (20.0)	1	0
Hypoaesthesia	2 (66.7)	2	1	0	0	0	0	0	0	0	0	0
Hypogeusia	1 (33.3)	1	1	0	0	0	0	0	0	0	0	0
Neuropathy peripheral	1 (33.3)	1	1	1 (14.3)	1	1	1 (16.7)	1	0	1 (20.0)	1	1
Psychiatric disorders	2 (66.7)	3	2	1 (14.3)	1	0	4 (66.7)	8	0	0	0	0
Anxiety	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Depression	0	0	0	0	0	0	1 (16.7)	2	0	0	0	0
Hallucination	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Insomnia	2 (66.7)	3	2	0	0	0	1 (16.7)	1	0	0	0	0
Mental status changes	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Mood altered	0	0	0	0	0	0	1 (16.7)	2	0	0	0	0
Stress	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Acute kidney injury	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Reproductive system and breast disorders	1 (50.0)	1	0	0	0	0	0	0	0	0	0	0
Vaginal discharge	1 (50.0)	1	0	0	0	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (33.3)	3	3	2 (28.6)	6	2	4 (66.7)	6	1	3 (60.0)	7	0
Cough	1 (33.3)	1	1	1 (14.3)	1	0	2 (33.3)	2	0	1 (20.0)	1	0
Dysphonia	0	0	0	1 (14.3)	1	0	0	0	0	0	0	0
Dyspnoea	0	0	0	1 (14.3)	2	0	1 (16.7)	1	0	2 (40.0)	2	0

Table 18. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term – Phase 1

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)			Palbociclib 75 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 125 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Epistaxis	0	0	0	0	0	0	1 (16.7)	1	1	0	0	0
Haemoptysis	0	0	0	1 (14.3)	1	1	0	0	0	0	0	0
Hypoxia	0	0	0	1 (14.3)	1	1	1 (16.7)	1	0	0	0	0
Nasal congestion	1 (33.3)	1	1	0	0	0	0	0	0	1 (20.0)	1	0
Nasal dryness	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Pleural effusion	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Rhinitis allergic	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Rhinorrhoea	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Sneezing	1 (33.3)	1	1	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	2 (28.6)	2	2	1 (16.7)	2	0	1 (20.0)	1	0
Drug eruption	0	0	0	0	0	0	1 (16.7)	2	0	0	0	0
Rash	0	0	0	2 (28.6)	2	2	0	0	0	0	0	0
Rash erythematous	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Social circumstances	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Walking aid user	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Vascular disorders	0	0	0	0	0	0	2 (33.3)	3	0	1 (20.0)	1	0
Hot flush	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Hypertension	0	0	0	0	0	0	1 (16.7)	1	0	1 (20.0)	1	0
Orthostatic hypotension	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (v18.0) coding dictionary applied.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1: The number of occurrences of treatment emergent all causalities adverse events.
n2: The number of occurrences of treatment emergent causally related to treatment adverse events.
MedDRA = Medical Dictionary for Regulatory Activities.

Treatment-emergent serious AEs (all causalities and treatment-related) for Phase 1 are presented in Table 19.

Table 19. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 1

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 100 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)			Palbociclib 75 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule A)			Palbociclib 125 mg / Bortezomib 1.0 mg/m^2 / Dexamethasone 20 mg (Schedule B)		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:												
Evaluable for adverse events	3			7			6			5		
With adverse events	0			0			3 (50.0)			5 (100)		
Blood and lymphatic system disorders	0	0	0	0	0	0	0	0	0	2 (40.0)	3	1
Febrile neutropenia	0	0	0	0	0	0	0	0	0	1 (20.0)	1	1
Thrombocytopenia	0	0	0	0	0	0	0	0	0	1 (20.0)	2	0
Cardiac disorders	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Atrial fibrillation	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Gastrointestinal disorders	0	0	0	0	0	0	0	0	0	1 (20.0)	1	1
Dysphagia	0	0	0	0	0	0	0	0	0	1 (20.0)	1	1
General disorders and administration site conditions	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Pyrexia	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Infections and infestations	0	0	0	0	0	0	1 (16.7)	1	0	1 (20.0)	4	0
Bacteraemia	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Sepsis	0	0	0	0	0	0	0	0	0	1 (20.0)	4	0
Investigations	0	0	0	0	0	0	0	0	0	2 (40.0)	3	0
Blood creatinine increased	0	0	0	0	0	0	0	0	0	2 (40.0)	3	0
Metabolism and nutrition disorders	0	0	0	0	0	0	0	0	0	1 (20.0)	2	2
Metabolic acidosis	0	0	0	0	0	0	0	0	0	1 (20.0)	2	2
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Back pain	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Nervous system disorders	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Central nervous system haemorrhage	0	0	0	0	0	0	0	0	0	1 (20.0)	1	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Respiratory failure	0	0	0	0	0	0	1 (16.7)	1	0	0	0	0
Vascular disorders	0	0	0	0	0	0	0	0	0	1 (20.0)	1	1
Deep vein thrombosis	0	0	0	0	0	0	0	0	0	1 (20.0)	1	1

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (v18.0) coding dictionary applied.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1: The number of occurrences of treatment emergent all causalities adverse events.
n2: The number of occurrences of treatment emergent causally related to treatment adverse events.
MedDRA = Medical Dictionary for Regulatory Activities.

Treatment-emergent non-serious AEs (all causalities and treatment-related) for Phase 2 are presented in Table 20.

Table 20. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term – Phase 2

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Schedule B		
	n (%)	n1	n2
Number (%) of subjects:			
Evaluable for adverse events	30	-	-
With adverse events	30 (100)	-	-
Blood and lymphatic system disorders	27 (90.0)	303	294
Anaemia	17 (56.7)	35	31
Haemoglobinaemia	1 (3.3)	1	1
Leukopenia	5 (16.7)	45	45
Lymphopenia	2 (6.7)	4	4
Neutropenia	11 (36.7)	62	59
Pancytopenia	1 (3.3)	5	5
Thrombocytopenia	23 (76.7)	151	149
Cardiac disorders	5 (16.7)	9	9
Angina pectoris	1 (3.3)	5	5
Bundle branch block left	1 (3.3)	1	1
Cyanosis	1 (3.3)	1	1
Palpitations	2 (6.7)	2	2
Endocrine disorders	1 (3.3)	1	0
Hypothyroidism	1 (3.3)	1	0
Eye disorders	9 (30.0)	14	11
Cataract	1 (3.3)	1	0
Conjunctival haemorrhage	2 (6.7)	2	2
Eye disorder	1 (3.3)	1	0
Eye irritation	1 (3.3)	1	1
Eye swelling	1 (3.3)	1	1
Vision blurred	4 (13.3)	5	4
Visual impairment	2 (6.7)	3	3
Gastrointestinal disorders	20 (66.7)	65	49
Abdominal distension	1 (3.3)	2	0
Abdominal pain	2 (6.7)	3	1
Constipation	9 (30.0)	11	9
Diarrhoea	12 (40.0)	13	11
Dry mouth	1 (3.3)	1	1
Dyspepsia	1 (3.3)	1	1
Flatulence	1 (3.3)	1	0
Nausea	11 (36.7)	19	18
Non-infective gingivitis	1(3.3)	1	0
Palatal oedema	1 (3.3)	1	0
Stomatitis	4 (13.3)	5	3
Tongue coated	1 (3.3)	1	1
Tongue disorder	1 (3.3)	1	0
Toothache	2 (6.7)	2	1
Vomiting	3 (10.0)	3	3
General disorders and administration site conditions	25 (83.3)	86	58
Asthenia	1 (3.3)	1	1
Catheter site erythema	1 (3.3)	3	2
Catheter site pruritus	1 (3.3)	1	0
Chest pain	6 (20.0)	7	2
Chills	3 (10.0)	3	2
Fatigue	22 (73.3)	40	30
Influenza like illness	1 (3.3)	3	3

Table 20. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term – Phase 2

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Schedule B		
	n (%)	n1	n2
Injection site pain	1 (3.3)	1	0
Injection site reaction	1 (3.3)	1	0
Oedema	1 (3.3)	1	1
Oedema peripheral	7 (23.3)	11	8
Pain	3 (10.0)	3	1
Peripheral swelling	1 (3.3)	1	1
Pyrexia	9 (30.0)	10	7
Infections and infestations	19 (63.3)	42	15
Atypical pneumonia	1 (3.3)	1	1
Bronchitis	4 (13.3)	4	1
Bronchopneumonia	1 (3.3)	1	0
Conjunctivitis	2 (6.7)	2	1
Herpes zoster	1 (3.3)	1	1
Infection	1 (3.3)	1	0
Influenza	2 (6.7)	2	0
Meningitis pneumococcal	1 (3.3)	1	0
Nasopharyngitis	4 (13.3)	5	4
Oral candidiasis	1 (3.3)	2	1
Oral herpes	1 (3.3)	1	1
Pneumonia	1 (3.3)	1	1
Respiratory tract infection	1 (3.3)	1	0
Rhinitis	1 (3.3)	1	1
Sinusitis	2 (6.7)	2	1
Staphylococcal infection	1 (3.3)	1	0
Streptococcal endocarditis	1 (3.3)	1	0
Tooth infection	1 (3.3)	1	0
Upper respiratory tract infection	3 (10.0)	6	1
Urinary tract infection	1 (3.3)	1	0
Viral infection	3 (10.0)	6	1
Injury, poisoning and procedural complication	8 (26.7)	12	1
Bone contusion	1 (3.3)	1	0
Contusion	2 (6.7)	2	0
Fall	1 (3.3)	1	0
Muscle strain	1 (3.3)	1	0
Periorbital haemorrhage	1 (3.3)	2	1
Post procedural haemorrhage	1 (3.3)	1	0
Postoperative wound complication	1 (3.3)	1	0
Tendon rupture	1 (3.3)	1	0
Wound	2 (6.7)	2	0
Investigations	12 (40.0)	37	19
Blood creatinine increased	1 (3.3)	1	0
Blood creatinine increased	6 (20.0)	6	2
Blood sodium decreased	1 (3.3)	1	0
Blood uric acid increased	1 (3.3)	1	0
C-reactive protein increased	1 (3.3)	2	2
Cardiac murmur	1 (3.3)	1	0
Clostridium test positive	1 (3.3)	1	0
Granulocyte count decreased	1 (3.3)	1	1
Haemoglobin decreased	2 (6.7)	4	4
Platelet count decreased	1 (3.3)	2	2
Prothrombin time prolonged	1 (3.3)	1	0
Troponin increased	1 (3.3)	1	0
Weight decreased	3 (10.0)	3	1
Weight increased	2 (6.7)	5	1

Table 20. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term – Phase 2

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Schedule B		
	n (%)	n1	n2
White blood cell count decreased	2 (6.7)	6	6
pH urine increased	1 (3.3)	1	0
Metabolism and nutrition disorders	11 (36.7)	29	5
Decreased appetite	4 (13.3)	4	2
Hyperglycaemia	3 (10.0)	9	2
Hyperphosphataemia	1 (3.3)	1	0
Hyperuricaemia	1 (3.3)	1	0
Hypocalcaemia	1 (3.3)	1	0
Hypokalaemia	5 (16.7)	8	1
Hypomagnesaemia	1 (3.3)	2	0
Hyponatraemia	2 (6.7)	2	0
Hypophosphataemia	1 (3.3)	1	0
Musculoskeletal and connective tissue disorders	21 (70.0)	61	15
Arthralgia	6 (20.0)	9	1
Back pain	9 (30.0)	17	1
Bone pain	1 (3.3)	1	1
Fasciitis	1 (3.3)	1	0
Fistula	1 (3.3)	1	0
Flank pain	1 (3.3)	1	0
Joint swelling	1 (3.3)	1	0
Muscle spasms	5 (16.7)	8	6
Muscle twitching	1 (3.3)	1	1
Muscular weakness	1 (3.3)	1	1
Musculoskeletal chest pain	4 (13.3)	4	1
Musculoskeletal pain	3 (10.0)	3	0
Neck pain	1 (3.3)	1	0
Pain in extremity	8 (26.7)	9	2
Spinal pain	1 (3.3)	1	1
Synovial cyst	1 (3.3)	1	0
Synovitis	1 (3.3)	1	0
Nervous system disorders	20 (66.7)	39	29
Anosmia	1 (3.3)	1	0
Disturbance in attention	2 (6.7)	2	2
Dizziness	6 (20.0)	7	6
Dizziness postural	1 (3.3)	1	1
Headache	8 (26.7)	9	3
Hypoaesthesia	1 (3.3)	1	1
Monoplegia	1 (3.3)	1	0
Neuropathy peripheral	9 (30.0)	13	12
Paraesthesia	1 (3.3)	1	1
Peripheral sensory neuropathy	2 (6.7)	2	2
Sciatica	1 (3.3)	1	1
Psychiatric disorders	7 (23.3)	15	10
Affective disorder	1 (3.3)	1	1
Anxiety	2 (6.7)	2	2
Confusional state	1 (3.3)	2	0
Depression	2 (6.7)	3	2
Hallucination	1 (3.3)	1	0
Insomnia	2 (6.7)	3	3
Irritability	1 (3.3)	1	1
Listless	1 (3.3)	1	1
Mental status changes	1 (3.3)	1	0

Table 20. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term – Phase 2

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Schedule B		
	n (%)	n1	n2
Renal and urinary disorders	2 (6.7)	2	0
Nocturia	1 (3.3)	1	0
Renal failure	1 (3.3)	1	0
Respiratory, thoracic and mediastinal disorders	22 (73.3)	42	18
Chronic obstructive pulmonary disease	2 (6.7)	2	0
Cough	8 (26.7)	8	3
Dry throat	1 (3.3)	1	0
Dysphonia	1 (3.3)	1	1
Dyspnoea	8 (26.7)	10	6
Dyspnoea exertional	3 (10.0)	3	2
Epistaxis	1 (3.3)	1	0
Haemoptysis	1 (3.3)	1	1
Hiccups	1 (3.3)	1	1
Nasal dryness	1 (3.3)	1	0
Oropharyngeal pain	3 (10.0)	3	2
Pleurisy	1 (3.3)	1	1
Productive cough	4 (13.3)	4	0
Rales	1 (3.3)	1	0
Rhinorrhoea	2 (6.7)	2	1
Sinus congestion	2 (6.7)	2	0
Skin and subcutaneous tissue disorders	7 (23.3)	10	6
Dry skin	2 (6.7)	2	0
Ecchymosis	2 (6.7)	2	1
Erythema	1 (3.3)	1	1
Hyperhidrosis	1 (3.3)	1	1
Night sweats	1 (3.3)	1	0
Rash	2 (6.7)	3	3
Vascular disorders	7 (23.3)	12	8
Circulatory collapse	1 (3.3)	1	1
Haematoma	2 (6.7)	3	3
Hot flush	1 (3.3)	2	2
Hypertension	4 (13.3)	5	2
Pallor	1 (3.3)	1	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (v18.0) coding dictionary applied.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1: The number of occurrences of treatment emergent all causalities adverse events.
n2: The number of occurrences of treatment emergent causally related to treatment adverse events.
MedDRA = Medical Dictionary for Regulatory Activities.

Treatment-emergent serious AEs (all causalities and treatment-related) for Phase 2 are presented in Table 21.

Table 21. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 2

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v18.0) Preferred Term	Schedule B		
	n (%)	n1	n2
Number (%) of subjects:			
Evaluable for adverse events	30	-	-
With adverse events	11 (36.7)	-	-
Blood and lymphatic system disorders	3 (10.0)	3	2
Febrile neutropenia	3 (10.0)	3	2
Cardiac disorders	2 (6.7)	2	1
Angina unstable	2 (6.7)	2	1
Gastrointestinal disorders	1 (3.3)	1	1
Vomiting	1 (3.3)	1	1
General disorders and administration site conditions	3 (10.0)	7	2
Asthenia	1 (3.3)	1	0
Disease progression	1 (3.3)	2	0
Fatigue	1 (3.3)	1	0
Pyrexia	2 (6.7)	3	2
Immune system disorders	1 (3.3)	1	0
Hypersensitivity	1 (3.3)	1	0
Infections and infestations	5 (16.7)	8	3
Bacteraemia	1 (3.3)	1	0
Bronchopneumonia	1 (3.3)	3	1
Pneumonia	4 (13.3)	4	2
Metabolism and nutrition disorders	1 (3.3)	1	1
Hyperglycaemia	1 (3.3)	1	1
Musculoskeletal and connective tissue disorders	1 (3.3)	1	0
Bone pain	1 (3.3)	1	0
Psychiatric disorders	2 (6.7)	2	1
Confusional state	1 (3.3)	1	0
Suicide attempt	1 (3.3)	1	1
Respiratory, thoracic and mediastinal disorders	3 (10.0)	3	0
Chronic obstructive pulmonary disease	1 (3.3)	1	0
Pneumonia aspiration	1 (3.3)	1	0
Pneumothorax	1 (3.3)	1	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (v18.0) coding dictionary applied.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1: The number of occurrences of treatment emergent all causalities adverse events.
n2: The number of occurrences of treatment emergent causally related to treatment adverse events.
MedDRA = Medical Dictionary for Regulatory Activities.

Discontinuations due to AEs in Phase 1: Discontinuations due to AEs are presented in Table 22. Five (5) subjects discontinued due to AEs, all of them in Schedule B.

Table 22. Discontinuations due to Adverse Events in Phase 1

Serial Number	Treatment at Onset	Event Onset Day (Cycle)	Event Stop Day	Preferred Term	Causality	Grade	SAE	Outcome
1	Bortezomib (1.0 mg/m^2) Dexamethasone (20 mg) Palbociclib (125 mg)	17 (1)	19	Febrile neutropenia	Related Unrelated Related	4	Yes	Resolved
2	Bortezomib (1.0 mg/m^2) Dexamethasone (20 mg) Palbociclib (125 mg)	159 (7)	183	Dysphagia	Unrelated Related Unrelated	2	Yes	Resolved
3	Bortezomib (1.0 mg/m^2) Dexamethasone (20 mg) Palbociclib (100 mg)	106 (5)	110	Neutropenia	Related Unrelated Related	4	No	Resolved
4	Bortezomib (1.0 mg/m^2) Dexamethasone (20 mg) Palbociclib (100 mg)	50 (3)	60	Thrombocytopenia	Related Unrelated Related	4	No	Resolved
5	Bortezomib (1.0 mg/m^2) Dexamethasone (20 mg) Palbociclib (100 mg)	73 (4)	Ongoing	Neuropathy peripheral	Related Unrelated Related	1	No	Still present

Medical Dictionary for Regulatory Activities (v16.0) coding dictionary applied.
SAE = serious adverse event.

Discontinuations due to AEs in Phase 2: Discontinuations due to AEs are presented in Table 23. Five (5) subjects discontinued due to AEs.

Table 23. Discontinuations due to Adverse Events in Phase 2

Serial Number	Treatment at Onset	Event Onset Day (Cycle)	Event Stop Day	Preferred Term	Causality	Grade	SAE	Outcome
1	Bortezomib (last dose on Day 403) Dexamethasone (last dose on Day 403) Palbociclib (last dose on Day 398)	411 (FUP)	487	Neuropathy peripheral	Related Unrelated Unrelated	3	No	Resolved
2	Bortezomib (last dose on Day 61) Dexamethasone (last dose on Day 61) Palbociclib (last dose on Day 55)	82 (FUP)	114	Neuropathy peripheral	Related Unrelated Unrelated	2	No	Resolved
3	Bortezomib (2.2 mg/m2) Dexamethasone (20 mg) Palbociclib (75 mg)	179 (8)	204	Fatigue	Unrelated Unrelated Related	2	No	Resolved
4	Bortezomib (1.9 mg) Dexamethasone (20 mg) Palbociclib (100 mg)	19 (1)	22	Hyperglycaemia	Unrelated Related Unrelated	4	Yes	Resolved
5	Bortezomib (1.95 mg) Dexamethasone (20 mg) Palbociclib (100 mg)	154 (7)	243	Suicide attempt	Related Related Related	3	Yes	Resolved

Medical Dictionary for Regulatory Activities (v16.0) coding dictionary applied.
FUP = follow-up; SAE = serious adverse event.

Deaths in Phase 1: There was 1 on-study death (deaths from start of treatment up to and including 28 days following last dose) and 6 during the follow-up period. The cause of death for the on-study death was sepsis which was considered unrelated to any of the study medications. Causes of death that occurred during the follow-up period included unknown (4 subjects [44.4%]), disease under study (2 subjects [22.2%]) and other (multifocal leukoencephalopathy) in 1 subject (11.1%).

Deaths in Phase 2: One (1) subject (3.3%) in Schedule B died while on-study (including within 28 days of last dose) due to disease progression and 9 subjects (30.0%) died during follow-up. Causes of death that occurred during follow-up included disease under study (6 subjects [20.0%]), other (4 subjects [13.3%]) and unknown in 1 subject (3.3%). The 4 causes of death given as other included hypoxemic respiratory failure, multisystem organ failure, coronary artery disease, and pneumonia and septic shock. There were no deaths that were considered treatment-related.

Deaths After Data Cut-Off: Two (2) additional subjects died between 05 August 2012 (data cut-off) and 15 November 2013 (database lock), both due to disease under study.

Laboratory Evaluations, Vital Signs and Physical Findings in Phase 1: Grade 3 chemistry toxicities were few and generally single instances within a dose group. Hematology laboratory findings were consistent with the AE findings of thrombocytopenia, neutropenia and anemia for both treatment schedules and at both dose levels within schedules. In Schedule A and Schedule B, shifts in hemoglobin were generally a worsening of 1 grade but there were notable worsenings of Common Toxicity Criteria (CTC) Grade for the other hematological parameters (platelets, white blood cells [WBCs], absolute neutrophils and absolute lymphocytes) in both schedules, with several instances of 2- and 3-grade shifts and shifts to Grade 4 toxicity evident. Shifts in chemistry parameters were uncommon and were generally a worsening of 1 grade in 1 subject to Grade 1 or 2.

No notable vital sign or ECG effects were observed.

Laboratory Evaluations, Vital Signs and Physical Findings in Phase 2: Instances of Grade 4 laboratory toxicities were all hematological in nature: platelets - 8 (26.7%) subjects, absolute lymphocytes - 4 (13.3%) subjects and absolute neutrophils and WBC - 2 (6.7%) subjects each. Grade 3 hematological laboratory toxicities were prevalent, occurring in between 25% and 50% of subjects. Grade 3 chemistry toxicities were few and generally single instances. Shifts in hemoglobin were generally a worsening of 1 grade (21 subjects) but there were notable worsenings of CTC Grade for the other hematological parameters (platelets, WBCs, absolute neutrophils and absolute lymphocytes). Shifts in chemistry parameters were uncommon and were generally a worsening of 1 grade in 1 subject to Grade 1 or 2. There were no shifts to Grade 4 toxicities.

No notable vital sign or ECG effects were observed.

CONCLUSIONS:

The MTD/RP2D for Phase 2 was determined to be palbociclib 100 mg / bortezomib 1.0 mg/m^2 / dexamethasone 20 mg on Schedule B based on the DLTs observed and overall safety data from the Phase 1 part of the study.

In Phase 2, the ORR was 20.0% (5 subjects, 1 with CR, 1 with VGPR and 3 with PR); however, this ORR (20.0%) did not meet defined criteria to proceed to Stage 2 of the study.

Based on the data from the Phase 1 and Phase 2 portions of the study, the safety profile of the 21/28-day Schedule A was similar to that of the 12/21-day Schedule B.

The most common treatment-emergent AEs reported were neutropenia and thrombocytopenia in Phase 1, and thrombocytopenia and fatigue in Phase 2. The hematologic events were consistent with the safety profile of palbociclib and bortezomib.

Hematologic AEs were common and accounted for the majority of treatment-related AEs as well as all causality AEs that were Grade 3 or above in severity on both Schedule A and B.

No notable ECG effects were observed.

No notable effects on vital signs were observed.

No notable effects on clinical chemistry parameters were observed.

Modulation of baseline phosphorylated Rb levels to either very low values or 0, postdose, is consistent with the known mechanism of action of palbociclib.

There was no correlation between IL-6 values and best overall response.

PRO results were stable over time, until subject numbers dropped.