Statistical Analysis Plan
Final Analysis

RANDOMIZED PHASE II STUDY COMPARING TWO DIFFERENT SCHEDULES OF PALBOCICLIB PLUS SECOND LINE ENDOCRINE THERAPY IN WOMEN WITH ESTROGEN RECEPTOR POSITIVE, HER2 NEGATIVE ADVANCED/METASTATIC BREAST CANCER (PALESTRA)

Canadian Cancer Trials Group (CCTG) Protocol Number: MA.38

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1 Introduction:

Canadian Cancer Trials Group (CCTG) MA.38 is a randomized phase II trial to estimate the hazards ratio of the progression-free survival of two different dose regimens of palbociclib in combination with endocrine therapy (fulvestrant or tamoxifen or Aromatase Inhibitor) as second line therapy in women with ER positive, HER2 negative, advanced/metastatic breast cancer. This document is to describe the statistical analysis plan for the final analysis of MA.38.

1.1 Objectives

The **primary objective** of this trial is to **estimate** the hazard ratio of the progression-free survival (PFS) of two different dose regimens of palbociclib in combination with endocrine therapy (fulvestrant or tamoxifen or Aromatase Inhibitor). The **Secondary Objectives** include evaluating the following endpoints: Safety and Tolerability, Response Rate Duration of Response, Clinical Benefit Rate, Overall Survival (OS) and Quality of Life (QoL).

1.2 Sample Size Determination

The objective of this trial was neither to test superiority nor to test noninferiority between two arms. The sample size is based on estimating the hazard ratio (HR) of two arms (experimental vs. control) within a 90% confidence interval (CI). For a 1:1 randomization with 1 year accrual and one-year additional follow-up. If we observe approximately 58 progression events in each arm, the upper bound of the 90% CI will be 1.36 times the estimated HR and the lower bound will be 0.74 times the estimated HR. Assuming a median PFS of approximately 10 months for both treatment arms, duration of accrual and follow-up both at 1 year, and a dropout rate of 10%, the study would need to enroll approximately 90 subjects in each arm.

1.3 Timing of the Analyses

There will be no interim analysis for efficacy. An interim safety analysis was conducted in August, 2016, when 24 patients were enrolled and evaluable for toxicity. The final analysis will be conducted with a total of 116 PFS events observed. This is expected to happen two years after the trial activation.

1.4 Data Collection

Data are collected, entered and managed by CCTG, Kingston, Ontario, according to the group standard data management procedures. The clinical cut-off date will beApril 16, 2018.

2 Methods and Analyses

2.1 Analyses Samples

Patients were randomized to the following two treatment arms:

- Arm 1: Palbociclib 100 mg po daily.
- Arm 2: Palbociclib 125 mg po daily 3 out of 4 weeks

The study populations for this analysis will include both the intention to treat (ITT) population and the as treated population.

Analysis of pretreatment characteristics and all efficacy outcomes such as PFS and OS, will be based on the ITT population. The efficacy data set consists of all patients regardless of actual treatment.
Those who received at least one dose of protocol therapy (i.e. the as treated population) will form the basis of the safety analyses. The response analyses will include patients with measurable disease or those with non measurable disease who experience a CR. QOL analyses will include all patients who completed at least one QOL assessment (either baseline or follow-up).

2.2 Conventions for Calculating Key Data

In general, baseline evaluations are those collected closest, but prior to or on the day of randomization. If pre-randomization assessment was not done, a pre-treatment assessment will be used as baseline assessment.

When either day or month of a date is missing, the missing day and/or month will be imputed by the midpoints within the smallest known interval. For example, if the day of the month is missing for any date used in a calculation, the 15th of the month will be used to replace the missing day. If the month and day of the year are missing for any date used in a calculation, the first of July of the year will be used to replace the missing data.

2.3 Analysis Conventions

All comparisons between treatment arms will be carried out using a two-sided test at an alpha level of 5% unless otherwise specified. No formal adjustments will be made for the multiplicity of inferences for the other clinical endpoints.

Baseline stratification factors (excluding centre) that will be used to adjust the analyses where appropriate are listed below:

- Visceral metastases (yes versus no)
- duration of exposure to most recent endocrine therapy prior to randomization (4 groups)
  - duration $\geqslant$ 6 months versus < 6 months in the advanced/metastatic setting
  - duration $\geqslant$ 24 months versus < 24 months in the adjuvant setting
- Planned use of Fulvestrant versus Tamoxifen versus Aromatase Inhibitor (AI)

*Add missing/unknown category whenever appropriate.

2.4 Randomization and Pre-treatment Characteristics

2.4.1 Definitions and Variables

2.4.1.1 Accrual

- Number (%) of randomized patients per study center (table 1).

2.4.1.2 Randomization/Stratification

A minimization procedure for treatment assignment was used in this study.

- Centre
- Visceral metastases (yes versus no)
- duration of exposure to most recent endocrine therapy prior to randomization (4 groups)
  - duration $\geqslant$ 6 months versus < 6 months in the advanced/metastatic setting
  - duration $\geqslant$ 24 months versus < 24 months in the adjuvant setting
- Planned use of Fulvestrant versus Tamoxifen versus Aromatase Inhibitor (AI)

Stratification factor at randomization (excluding centre) will be summarized by treatment arm (table 2).

Number and percentage of actual treatment received will be summarized by treatment arm (table 3).

2.4.1.4 Ineligibility and Major Protocol Violations

Number and percentage of ineligible patients will be presented by treatment arm.

Reasons for ineligibility: percentage for each reason and combination of reasons of ineligibility will be presented by treatment arm.

The number and percentage of major protocol violations will be presented by treatment arm. (table 4)

2.4.1.4 Summary of Follow-up

A table showing the median (calculated by KM method with inverse OS), min and max follow-up (defined as reverse censoring on survival) will be presented by treatment group and for all patients included in analysis. (table 5)

2.4.1.5 Patient Characteristics

Patient characteristics at baseline are summarized in table 6.

- Age (Median, Q1 Q3, range)
- Age (40-49, 50-59, 60-69, 70+)
- Race
- ECOG PS
- Menopausal Status
- Visceral metastasis (at baseline)
- Duration of exposure to most recent endocrine therapy prior to randomization (at baseline)
- Planned use of endocrine therapy: Fulvestrant versus Tamoxifen versus Aromatase Inhibitor (at baseline)

- Histology
- ER status
- PR status
- Grade

*An unknown category will be added when appropriate.

2.4.1.6 Baseline Hematology/Biochemistry

CTC 4.0 grades will be used to summarize the baseline hematology/biochemistry data (% with each CTC grades) for the following assessments (table 7)

2.4.1.7 Baseline Non-Hematologic Adverse Events

CTC 4.0 grades will be used to summarize the baseline Non-Hematologic (number for each CTC grades, total number and %) (table 8).

2.4.1.8 Baseline Concomitant Medication

Number and percent of patients received concomitant mediation will be summarized by treatment arm (table 9).

2.4.2 Analysis of pre-treatment Characteristics

No formal statistical tests will be performed to assess the homogeneity of baseline characteristics between the arms. Categorical variables will be tabulated by treatment arm and for all patients. Continuous variables (e.g., age) will be presented using summary statistics (n, median, Q1, Q3, min and max) or specified cutoff categories by treatment arm and for all patients. Analyses will be based on all randomized patients by arm based on the ITT population.

2.5 Efficacy

2.5.1 Definitions and Variables

2.5.1.1 Progression-free Survival (PSF)

The primary endpoint is progression free survival (PFS) defined as time from randomization to progression or death from any cause. Disease progression will be investigator assessed using the RECIST 1.1 criteria. If a patient has not progressed or died at the time of final analysis, PFS will be censored on the date of the last disease assessment. If a patient received anti-cancer RT treatment, PFS will be censored at the date of anti-cancer treatment.

PFS Time (months) =

((date of PFS event or last disease assessment date - date of randomization) + 1) / 30.4375

2.5.1.2 Overall Survival (OS)

For patients who have died, overall survival is calculated in months from the day of randomization to date of death. Otherwise, survival is censored at the last day the patient is known alive (LKA).

OS Time (months) =
((date of death or LKA - date of randomization) + 1) / 30.4375

2.5.1.3 Response Rate

Response will be evaluated in this study using the revised international RECIST Criteria (1.1)
All patients who have received at least one dose of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified as CR, PR, SD and PD. Patients with non measurable disease will only have a best response of either CR or 'Non CR/Non PD'.

2.5.1.4 Response Duration

For patients with documented CR or PR, duration of response is calculated from the time of CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented or death occurs. If a patient has not progressed or died at the time of the final analysis, duration of response will be censored on the date of the last disease assessment.

2.5.1.5: Clinical Benefit Rate

Clinical benefit includes patients with documented CR, RP or SD for those with measurable disease and CR for with non measurable disease.

2.5.2 Analysis of Key Parameters

All efficacy analyses will be presented by treatment arm. The CONSORT diagram will be included.

2.5.2.1 Progression-free Survival

No formal statistical tests will be performed for PFS. A Kaplan-Meier curve for PFS in each treatment arm will be displayed.

The difference between the two treatment arms will be estimated using the **hazard ratio** stratified by the stratification factors at randomization (exclude centre).

The analysis of PFS will also be presented for each level of each stratification factor and hazard ratio with corresponding 90% CI will be reported. An un-stratified Cox regression model with stratification factors as

covariates will be fitted. In all regression analyses, all patients with missing value in any covariate will be deleted from the analysis. (Table 10, 11, Figure 1)

For patients who developed PFS events, the type of progression events and summary of progression will be tabulated (Table 12).

2.5.2.2 Overall Survival

The analyses of OS will be similar to these of PFS (table 13, 14, 15, Figure 2).

KM plots for survival curves and estimations of HRs with (90% CI) will be reported.

2.5.2.3 Response Rate and Clinical Benefit Rate

Response rates (percentages of CR/PR as best response) will be reported by treated arms for patients evaluable for response.

Clinical benefit rates (percentages of CR/PR/SD as best response) will be reported by treated arms for patients evaluable for response.

Response rates and clinical benefit rates will be compared between two arms using the Cochran-Mantel-Haenszel test adjusting for stratification factors at randomization (Table 16).

2.5.2.4 Duration of Response

Duration of response (median, Q1, Q3, min, max) will be reported by treated arms for patients with CR/ PR. The difference in duration of response between the two treatment arms will be tested using the log-rank test adjusting for stratification factors at randomization (Table 17).

2.6 Drug Exposure

Drug exposure will be measured up to the date of PD.

Cumulative dose (mg) is the sum of all study medication doses received.

Mean, SD, Median, Q1, Q3, minimum and maximum of total amount will be reported for the treated population by treatment arm.

Daily dose
Mean, SD, Median, Q1, Q3, minimum and maximum of daily dose amount will be reported for the treated population by treatment arm.

Planned Dose intensity (mg/ week) Planned Dose Intensity: Planned total dose per cycle divided by number of planned weeks in the cycle

Actual Dose intensity (mg/ week)
Mean, SD, Median, Q1, Q3, minimum and maximum of actual dose intensity for the treated population by treatment arm

Actual Dose Intensity: Actual total dose per cycle divided by number of actual weeks in the cycle.

Relative Dose Intensity (%)
Mean, SD, Median, Q1, Q3, minimum and maximum of relative dose intensity will be reported for the treated population by treatment arm.

Relative Dose Intensity: Actual total dose intensity / planned dose intensity x 100%

90% or more relative dose intensity

Number and % of patients with 90% or more relative dose intensity will be reported.

Dose intensity (mg/ week), relative dose intensity (%) and number (%) of patients will 90% or more relative dose intensity for cycle 1 and 2 will also be reported.

Dose information will be reported in table 18.

Dose modification for palbociclib
- Any modification: Yes / No
- If yes, reason of dose modification.

Number and percentage of dose modification will be reported for treated population by treatment arm.

Dose reduction for palbociclib
- Any reduction: Yes / No
- If yes, reason of dose reduction

Number and percentage of dose reduction for treated population by treatment arm

Dose discontinuation for palbociclib
- Any discontinuation: Yes / No
- If yes, reason of dose discontinuation

Number and percentage of dose discontinuation will be reported for treated population by treatment arm

Number and percentage of drug modification/reduction/discontinuous will be reported for treated population by treatment arms (table 19).

2.7 Safety

2.7.1 Definitions and variables

All toxicity/side effects data collected post randomization will be included in the analyses of toxicities.

2.7.1.1 Non-hematologic adverse events (CTCAE 4.0)

Non-hematologic adverse events will be summarized according to CTC AE 4.0 (table 20).

Number and % of grade 3 or 4 neutropenia, febrile neutropenia, infection and fatigue

2.7.1.2 Hematology/Biochemistry (CTCAE 4.0)

Hematology/Biochemistry experienced will be reported according to CTC AE 4.0 (table 21).

Incidence of grade 3 or 4 neutropenia, anemia and thrombocytopenia by arm

Cumulative incidence curve for time to first episode of grade 3 or 4 neutrophils (in Hematology/Biochemistry from) by arm for all treated patients using the Kaplan-Meier method (cumulative incidence = 1 – KM). Patients without any grade 3 or 4 neutrophils will be censored at last time of assessment. (Figure 3).

Median time to neutrophil nadir count on study (range)

Median time to first episode of grade 3 or 4 neutropenia (range).

2.7.1.3 Serious adverse event (SAE)

SAE will be listed by treatment arm (table 22). SAE that met the protocol requirements for expedited reporting (serious, unexected and related) will be identified.

2.8 Off study and death

Patients off-study (off protocol treatment): Number and % of all treated patients. Reason for going off-study: Number and % of all treated patients will be presented (table 23).

Deaths within 30 days from last treatment administration will be reported. Cause of death within 30 days from last treatment administration: Number and % of all treated patients will be presented (table 24).

2.9 Quality of Life

2.9.1 Definitions and Variables

2.9.1.1. EORTC QLQ-C30

There are five functional domains and three symptom domains that can be derived from EORTC QLQ-C30 (see below for definitions). If the number of unanswered questions in each domain is within a limit specified with the definition for each domain, the score is calculated as for function domains of Physical, Emotional, Cognitive and Social:

Score=100-(((Total score for the answered questions/(Total questions answered))-1)*100/3).

For symptom domains:

Score=(((Total for the answered questions/(Total questions answered))-1)*100/3)

Otherwise, the score will be recorded as "missing". For each single item, the score will be recorded as "missing" if the answer to this item is missing.

Functional Domains:

Physical: Questions: 1, 2, 3, 4, 5, 6, 7
Score=missing if number of above questions not answered is greater than 3;
Emotional: Questions: 21, 22, 23, 24
Score=missing if number of above questions not answered is greater than 2;
Cognitive: Questions: 20, 25
Score=missing if number of above questions not answered is greater than 0;
Social: Questions: 26, 27
Score=missing if number of above questions not answered is greater than 0;

Symptom Domains:

Fatigue: Questions: 10, 12, 18
Score=missing if number of above questions not answered is greater than 1;
Nausea and vomiting: Questions: 14, 15
Score=missing if number of above questions not answered is greater than 0;
Pain: Questions: 9, 19
Score=missing if number of above questions not answered is greater than 0.

There are also six single items in EORTC QLQ-C30 pertaining to common symptoms and one global assessment that can be derived from EORTC QLQ-C30. The single items are:

Single Items:

Dyspnea: Question 8;
Sleep/Insomnia: Question 11;
Appetite: Question 13;
Constipation: Question 16;
Diarrhea: Question 17;
Financial: Question 28.

They are all scored using the following formula:

Score= (Answer to the question-1)*100/3.

The Global Assessment includes Questions 29 and 30. If number of the questions not answered is greater than 0, its score will be "missing"; Otherwise,

Score= ((Total for the answered questions/(Total questions answered))-1)*100/6.

Axillary

Axillary module (Question 31 to 33):

Score=100-(((Total score for the answered questions/(Total questions answered))-1)*100/6).
Score=missing if number of above questions not answered is greater than 2;

2.9.2 Analysis

All analyses on quality of life scores will be exploratory and will include all randomized patients.

2.9.2.1 Determination of Assessment Times

The following will be the scheme to determining the time frame of a QOL assessment:

1) Baseline: Baseline evaluation is the QOL questionnaire collected closest, but prior to, the first day of starting study treatment/randomization;
2) Week 4 evaluation: If the QOL is assessed between week 1 and week 5
3) Week 8 evaluation: If the QOL is assessed between week 6 and week 10
4) Week 12 evaluation: If the QOL is assessed between week 11 and week 18
5) Week 24 evaluation: If the QOL is assessed between week 19 and week 30
6) Week 36 evaluation: If the QOL is assessed between week 31 and week 42

2.9.2.2 Calculation of Compliance Rates

The following method will be used to calculate the compliance rates of QOL assessment. The compliance rate is calculated as the number of forms received out of the number of forms expected at each assessment point defined based on the following principles:

1) At baseline: the number of forms expected is the total number of patients who are eligible for the study and required to fill out QOL questionnaires.
2) FU period: the number expected at each assessment is the number of patients with baseline data minus the number of patients who have died or progressed during that and previous follow up period (with assessment window defined by 2.9.2.1).

2.9.2.3 Cross-sectional analysis

The mean and standard deviation of QOL scores at baseline and mean and standard deviation of QOL change scores from baseline at each assessment time will be calculated. Then Wilcoxon Rank-Sum test is

used to compare two treatment arms in terms of change in QOL score at each assessment time from baseline.

Mean change in scores over time will be analyzed using generalized linear mixed model.

2.9.2.4 QOL response analysis

QOL response is calculated as follows for a functional domain: A change score of 10 points from baseline was defined as clinically relevant. Patients will be assessed as improved if they have reported a score of 10-points or better than baseline at any time of the QOL assessment. Conversely, patients will be assessed as worsened if there is a reported score that is at least 10 points worse than baseline at any time of the QOL assessments without meeting the criteria for improved. Patients whose scores are intermediate between these values at every QOL assessment will be considered as stable. In contrast to functional domains, for the determination of patient's QOL response, classification of patients into improved and worsened categories is reversed for symptom domains and single items. A Chi-square test will be performed to compare the distributions of these three categories between two arms (improved, stable or worse).

3 Tables

Table 1 Accrual by centre

Centre	Number of accrual (%)		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
xxxx	XX (XX)	XX (XX)	XX (XX)

Table 2: Accrual by Stratification Factors at Randomization

Data set: All Randomized Patients			
	Number of patients (%)		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Visceral metastases			
Yes	** (**)	** (**)	** (**)
No	** (**)	** (**)	** (**)
Duration of exposure to most recent endocrine therapy prior to randomization			
$\geqslant$ 6 months (advance)			
< 6 months (advance)			
$\geqslant$ 24 months (adjuvant)			
< 24 months (adjuvant)			
Planned use endocrine			
Fulvestrant			
Tamoxifen			
Armastase Inhibitor			
Source: Centralized Randomization File			

Table 3: Treatment received

	Number of accrual (%)		
Actual treatment received	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Pal 100mg	XX (XX)	XX (XX)	XX (XX)
Pal 125mg			
No treatment			

Table 4: Eligibility status

Total patients allocated	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Ineligible	XX (XX)		
Total eligible patients	XX (XX)		
REASONS FOR INELIGIBILITY			
Reason 1	XX (XX)		
Reason 2	XX (XX)		
Major Protocol Violations			
XXX			
XXX			

Table 5: Summary of Follow-up

Data set: All Randomized Patients			
	Number of patients		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Median*	***	***	***
Min	**	**	**
Max	**	**	**

Median Follow-up based on inverse OS

Table 6: Patient characteristics

All randomized patients	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
AGE			
<=39	XX (XX)		
40-49	XX (XX)		
50-59			
60-69			
>=70	XX (XX)		
Median (Range)	XX (XX)		
Q1, Q3			
Gender			
F			
Race			
Asian			
Black or African American			
etc			
ECOG PS			
0			
1			
2			
MENOPAUSAL STATUS			
As in meeting book			
Visceral metastasis (at baseline)			
Yes			
No			
Duration of exposure to most recent endocrine therapy prior to randomization (at baseline)			
$\geqslant$ 6 months (advance)			
< 6 months (advance)			
$\geqslant$ 24 months (adjuvant)			
< 24 months (adjuvant)			
Planned use of endocrine therapy (at baseline)			

Fulvestrant			
Tamoxifen			
Aromatase Inhibitor			
Histology			
Ductal			
Lobular			
ER status			
Negative			
Positive			
PR status			
Negative			
Positive			
Grade			
1			
2			
3			
Unknown			

Table 7. Baseline Hematology / Biochemistry

CTC AE 4.0 Hematology / Biochemistry table

Table 8. Baseline Non-Hematologic Adverse Event

CTC AE 4.0 Non-Hematologic Adverse Event table

Table 9. Baseline Concomitant Medication

All randomized patients	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Any baseline Concomitant Medication			
Yes	XX (XX)		
No	XX (XX)		

Table 10. Log Rank and Cox Regression Model for PFS Survival

Data set: All Randomized Patients				
	Univariate HR (95% CI)		Multivariate HR(95% CI) [1]	
Treatment (Arm 1 vs. Arm 2) (stratified)	***		--	
Treatment (Arm 1 vs. Arm 2) (un-stratified)				
ECOG PS (0 vs 1 or 2)				
Age (continuous)				
Histology (Ductal vs Labural)				
Grade				

(1) Based on Cox Model with all factors included.

Table 11: PFS by Subsets

Data set: All Randomized Patients			
	Number of patients (%)		
	Palbociclib 100mg N (# of events)	Palbociclib 125mg N (# of events)	HR (95% C.I)
Visceral metastasis (at baseline)			
Yes	** (**)	** (**)	** (**)
No	** (**)	** (**)	** (**)
Duration of exposure to most recent endocrine therapy prior to randomization (at baseline)			
$\geqslant$ 6 months (advance)	** (**)	** (**)	** (**)
< 6 months (advance)	** (**)	** (**)	** (**)
$\geqslant$ 24 months (adjuvant)	** (**)	** (**)	** (**)
< 24 months (adjuvant)	** (**)	** (**)	** (**)
Planned use of endocrine therapy (at baseline)			
Fulvestrant	** (**)	** (**)	** (**)
Tamoxifen	** (**)	** (**)	** (**)
Aromatase Inhibitor	** (**)	** (**)	** (**)

Table 12: PFS event Summary

Data set: All randomized Patients		
	Number of Patients (%)	
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***
Patients with PFS event	*** (**)	*** (**)
Progression event	**	**
Death	**	**
Patients who were censored	*** (**)	*** (**)
Reason Censored		
No PFS event	**	**
Withdrawal of Consent	**	**

Table 13. Log Rank and Cox Regression Model for Overall Survival

Data set: All Randomized Patients				
	Univariate HR (95% CI)	Log-rank p-value	Multivariate HR(95% CI) (1)	Multivariate p-value
Same as PFS (table 10)	*** (*, *)	***	*** (*, *)	***
	*** (*, *)	***	*** (*, *)	***
	*** (*, *)	***	*** (*, *)	***
	*** (*, *)	***	*** (*, *)	***
	*** (*, *)	***	*** (*, *)	***
	*** (*, *)	***	*** (*, *)	***

(1) Based on Cox Model with all factors included.

Table 14: OS by Subsets

Data set: All Randomized Patients			
	Number of patients (%)		
	Palbociclib 100mg N (# of events)	Palbociclib 125mg N (# of events)	HR (95% C.I)
Same as table 11			
	** (**)	** (**)	** (*, *)
	** (**)	** (**)	** (*, *)
	** (**)	** (**)	** (**)
	** (**)	** (**)	** (**)

Table 15: Death Summary

	Number of Patients (%) Data set: All randomized Patients		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N =
Patients who died			
Cause of Death			
Breast Cancer only			
Other primary malignancy			
Other condition or circumstance			
Patients who were censored			
Reason Censored			
Still Alive			
Withdrawal of Consent			

Table 16: Response to Treatment

	Number of Patients (%) **Data set: All treated patients with measurable disease**		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	
Response to treatment			
CR	XX (%)	XX (%)	XX (%)
PR			
SD			
PD			

*Stratification CMH test p-value for response rate: (CR+PR)/(CR+PR+SD+PD)

**Stratification CMH test p-value for clinical benefit rate: (CR+PR+SD)/(CR+PR+SD+PD)

Table 17: Duration of Response

	Number of Patients (%) **Data set: All patients with CR/PR**		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Stratified p-value from log rank test
Duration of response			
Median	XX	XX	p-value =
Min	XX	XX	-
Max	XX	XX	-
Q1	XX	XX	-
Q3	XX	XX	-

Table 18: Dose information

Data set: All treated Patients: Cumulative dose (mg)			
	Number of patients		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Median	***	***	***
Min	**	**	**
Max	**	**	**
Q1			
Q3			

Cumulative dose (mg)

n
Mean
Std
Median
Min
Max
Q1
Q3

Similar tables for
Daily dose(mg),
Dose intensity (mg/week)
Relative dose intensity (percent)
Cycle 1 and 2 dose intensity (mg/week)
Cycle 1 and 2 relative dose intensity (percent)

90% or more dose intensity: N and percent

Data set: All treated Patients			
90% or more dose intensity: N and percent	Number of patients		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
No	***	***	***
Yes	**	**	**

Cycle 1 and 2 90% or more dose intensity: N and percent

Data set: All treated Patients			
Cycle 1 and 2 90% or more dose intensity: N and percent	Number of patients		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
No	***	***	***
Yes	**	**	**

Table 19: Dose modifications

Data set: All treated Patients			
Al least one dose modification	Number of patients		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Yes	**	**	**
Reason of dose modifications Reason 1 Reason 2 …			

Data set: All treated Patients			
Al least done dose Reduction	Number of patients		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Yes	**	**	**
Reason of dose reduction Reason 1 Reason 2 …			

Data set: All treated Patients			
Patients with dose discontinuation	Number of patients		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Yes	**	**	**
Reason of dose discontinuation Reason 1 Reason 2 …			

Table 20.Non-Hematology adverse events

CTC AE 4.0 Non-Hematology adverse events table

Table 21. Hematology / Biochemistry (Follow-up)

Hematology / Biochemistry table

Table 22. Serious Adverse Events

As in meeting book table.

Table 23. Off protocol treatment

Data set: All treated Patients			
Off treatment	Number of patients		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Cause1	***	***	***
2	**	**	**
3			
4			

Table 24. Death on Trial

Data set: All Randomized Patients			
Cause of Death	Number of patients		
	Palbociclib 100mg N = ***	Palbociclib 125mg N = ***	Total N = ***
Cause1	***	***	***
2	**	**	**
3			
4			

Figure 1. KM plot for PFS

Figure 2. KM plot for OS

Figure 3. Cumulative incidence plot for grade 3 or 4 neutrophils