Statistical Analysis Plan
Final Analysis

A DOUBLE-BLIND PLACEBO CONTROLLED RANDOMIZED PHASE III TRIAL OF FULVESTRANT AND IPATASERTIB AS TREATMENT FOR ADVANCED HER-2 NEGATIVE AND ESTROGEN RECEPTOR POSITIVE (ER+) BREAST CANCER FOLLOWING PROGRESSION ON FIRST LINE CDK 4/6 INHIBITORAND AROMATASE INHIBITOR (FINER)

CCTG Protocol Number: MA.40

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1 Introduction:

MA.40 is an international multi-centre, double-blind, randomized phase III trial comparing ipatasertib and fulvestrant with placebo and fulvestrant in patients with advanced (metastatic or loco-regionally recurrent not amenable to curative therapy) estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 (HER-2) negative breast cancer after progression on first-line CDK 4/6 inhibitor and aromatase inhibitor (AI). This document describes the statistical analysis plan for the final analysis of MA.40.

1.1 Objectives

The Primary Objective of the trial is to compare investigator-assessed progression-free survival (PFS) using RECIST 1.1 in patients with ER+/HER2- advanced (metastatic or loco-regionally recurrent not amenable to curative therapy) breast cancer treated with ipatasertib and fulvestrant versus placebo and fulvestrant after progression on first-line CDK 4/6 inhibitor plus AI treatment. The key Secondary Objective is to compare PFS by RECIST 1.1 in the PIK3CA/AKT1/PTEN altered cohort. Other secondary objectives include comparing the following endpoints: PFS by RECIST 1.1 in the PIK3CA/AKT1/PTEN altered cohort, PFS by central radiology review, Response Rate by RECIST 1.1, Duration of response, Clinical benefit rate, Overall Survival (OS), Time to commencement of subsequent line of systemic therapy or death (TSST), adverse events, health-related quality of life and health economic.

1.2 Sample Size Determination

The statistical assumptions for the control arm are based on the median PFS of 4.8 months in the control arm of FAKTION (though no prior CDK 4/6 inhibitor exposure in this trial) and the median PFS of 5.6 months in the control arm of SOLAR-1 (6% prior CDK 4/6 inhibitor exposure). Thus we assume an H0 median PFS of 4.5 months for the placebo + fulvestrant arm. Assuming a projected hazard ratio (HR) of 0.60 of benefit and thus a projected median PFS of 7.5 months in the ipatasertib and fulvestrant arm (H1 median PFS of 7.5 months) with an $\alpha = 0.05$ (2-sided) and 92% power, a total of 250 randomized patients (ITT population) will be required. The enrollment duration will be 24 months with 30 additional months for follow-up for the secondary and overall survival endpoints. 175 events will be required to trigger the final analysis for PFS. If PFS is significant for the ITT population at 0.05 level, then the pre-specified secondary analysis for the altered subgroup will be conducted. Assuming that the incidence rate of mutations is 45% and two-sided alpha = 0.05, the power to detect a hazard ratio of 0.50 (median PFS 3.5 months versus 7.0 months) will be 87% with a total of 79 PFS events.

For the secondary endpoint of OS, it is estimated that 76 deaths will have occurred at the time of the final PFS analysis. This will provide 34% power to establish an OS benefit with an HR of 0.70 for the OS endpoint. This projection is based on an estimated median OS in the control arm of 30 months and a projected median OS of 42.86 months in the ipatasertib + fulvestrant arm.

An additional OS analysis is planned when 155 deaths are observed. This will provide 60% power to establish an OS benefit with an assumed HR of 0.70 for OS (duration of follow-up of 30 months). These projections are based on an estimated median OS in the control arm of 30 months and a projected median OS of 42.86 months in the ipatasertib + fulvestrant arm.

1.3 Timing of the Analyses

The clinical cut-off date for this final analysis was June 4th, 2024. The database will be locked for on xxxx xxth, 2025 for the analysis.

1.4 Data Collection

Data are collected, entered and managed by CCTG, Kingston, Ontario, according to the group standard data management procedure.

2 Methods and Analyses

2.1 Analyses Samples

The study populations for this analysis will include both the intention to treat (ITT) and as treated populations with data included as specified by the data cutoff date.

Analysis of pretreatment characteristics and all efficacy outcomes such as PFS and OS, will be based on the ITT population. A sensitivity analysis for efficacy outcomes will be conducted for the treated population. 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 efficacy data set consists of all patients regardless of actual treatment.

2.2 Conventions for Calculating Key Data

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

When either the day or month of a date is missing, the missing day 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. The partial date imputation will be applied to adverse event (AE) start date and concomitant medication (CM) start date only.

2.3 Analysis Conventions

When converting a number of days to other units, the following conversion factors will be used:
1 year = 365.25 days
1 month = 30.4375 days

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.

The following baseline stratification factors that will be used to adjust the analyses where appropriate are listed below:

- PIK3CA/PTEN/AKT1 alteration status: altered versus wildtype/unknown
- Prior duration of treatment with CDK 4/6 inhibitor: < 6 months versus $\geqslant$ 6 months

*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 and country (table 1). This table is for CCTG internal use only.

2.4.1.2 Randomization/Stratification

- PIK3CA/PTEN/AKT1 alteration status: altered versus wildtype/unknown
- Prior duration of treatment with CDK 4/6 inhibitor: < 6 months versus $\geqslant$ 6 months
- Centre: was used as a stratification factor in the randomization but will not be used in the stratified analysis

A minimization procedure for treatment assignment was used in this study. Stratification factors at randomization will be summarized by the treatment arm (table 2).

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

Treatment at randomization will be compared with the actual treatment received to identify any discrepancies (table 4).

2.4.1.3 Ineligibility and Major Protocol Violations

The number and percentage of ineligible patients will be presented by the treatment arm.

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

The number and percentage of major protocol violations will be presented by the treatment arm (table 5).

2.4.1.4 Summary of Follow-up

A table showing the median, min and max follow-up (defined as reverse censoring on overall survival) will be presented by treatment group and for all patients included in the analysis (table 6).

2.4.1.5 Patient Characteristics

Patient characteristics at baseline are summarized in table 7.

- Age
- Sex
- BMI
- Race
- ECOG PS
- ER status: Positive VS Negative (all patients shall be ER positive)
- PR status: Positive VS Negative
- HER2 status: 0, 1,2, 3 (all patients shall be HER 2 negative)
- Stage IV at diagnosis (Yes vs No)
- Site of disease
    - Sites of disease < 3 versus > or = 3
    - Bone only
    - Liver involvement
    - Lung involvement
    - Lung or liver involvement

2.4.1.6 Baseline Cancer Treatment

The number and percent of patients who received cancer treatment (Chemotherapy, Hormone Therapy (Neoadj vs post op), Immunotherapy, Adjuvant therapy, Neo-adjuvant therapy, Radiotherapy, Other therapy) will be summarized by treatment arm (table 7).

2.4.1.7 Baseline Hematology/Biochemistry

CTC 4.0 grades will be used to summarize the baseline hematology/biochemistry data (% with each CTC grade) for the following assessments (table 8):

- WBC,
- Granulocytes,
- Platelets,
- Hemoglobin
- Bili
- AST, ALT,
- Alk phosph
- Glucose

- HgAIc
- Albumin
- Creatinine

2.4.1.8 Baseline Non-Hematologic Adverse Events

CTC V 5.0 grades will be used to summarize the baseline non-hematologic (number for each CTC grade, total number and %) (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 the treatment arm and for all patients. Continuous variables (e.g., age) or transformed continuous variables will be presented using summary statistics (n, mean, standard deviation (SD), median, 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 (PFS)

The primary endpoint is progression-free survival (PFS) defined as time from randomization to disease progression or death from any cause, whichever occurs first. Disease progression will be investigator-assessed using the RECIST 1.1 criteria. CCTG or its designee will collect and store all tumour measurement images on all enrolled patients throughout the study to enable an independent review of imaging scans and an assessment of disease progression. If a patient has not progressed or died at the time of final analysis, PFS will be censored on the date of the last visit with adequate disease assessment. Lack of tumour assessments post-randomization or leak of baseline assessment will lead to censoring on day one after randomization. Progression documented between scheduled visits will be assigned to the date of the clinical lesion evaluation indicating progression. Death before the first PD assessment, including death between adequate assessment visits, will lead to the assignment of progression to the date of death. Death or progression after more than one missed visit will lead to the censoring of data at the date of the last visit with adequate assessment. Patients who received non-protocol anti-cancer treatment prior to a PFS event will be censored at the date of commencement of the non-protocol 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 the date of death. Otherwise, survival is censored on the last day the patient is known alive date (LKAD).

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

Where the LKAD is defined in Table 23.

2.5.1.3 Response rate

Response rate (RR) per RECIST 1.1 is defined as the number of responders (complete response and partial response, non-CR/PR for patients without measurable disease)) as a percentage of all the randomized patients.

2.5.1.4 Duration of the response

Duration of Response (DoR) will be calculated for patients with an overall best response of CR or PR as per RECIST 1.1 criteria. DoR is measured from the date of first evidence of CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. If a patient has not progressed or died at the time of the final analysis, the duration of response will be censored on the date of the last disease assessment.

2.5.1.5 Clinical Benefit Rate

Clinical Benefit Rate (CBR) will be calculated for the number of patients with an overall best response of CR, PR or SD ($\geqslant$ 6 months) as per RECIST 1.1 criteria as a percentage of all randomized patients. SD duration greater or equal to 6 months is defined as the date of randomization to the earliest of the date of objective progression, the date of death due to any cause, or the date of last disease assessment is greater or equal to 6 months.

2.5.1.6 Time to Commencement of Subsequent Line of Systemic Therapy or Death (TSST)

Time to commencement of subsequent line of systemic therapy or death (TSST) is defined as the time from randomization to the time of subsequent treatment commencement or death, whichever comes first. TSST will be censored at the date of last known alive without commencement of subsequent line of systemic therapy.

2.5.2 Analysis of Key Parameters

The comparison between treatment arms will be carried out using a two-sided test at an alpha level of 5% unless otherwise specified. All efficacy analyses will be presented by the treatment arm. The CONSORT diagram will be included.

2.5.2.1 Progression-free Survival

The primary PFS comparison between treatment arms will be performed on data derived from the ITT population. All patients will be included in the primary PFS efficacy analyses according to the arm of randomization, regardless of the actual treatment received. The PFS survival experiences of subjects in both treatment arms will be described by the Kaplan-Meier method. Stratified two-sided log-rank tests adjusting for stratification factors as defined in the protocol will be the primary method to compare PFS between the experimental and control arms. As an exploratory analysis, a Cox proportional hazards model will be used to identify and adjust for factors significantly related to progression-free survival.

A pre-specified secondary analysis for PFS in the PIK3CA/PTEN/AKT1 altered status subset will be tested using a hierarchical testing procedure [Hung, 2007]. If the result for PFS in the ITT patient population is significant at a 0.05 level, then PFS will be tested in the PIK3CA/PTEN/AKT1 altered status subset under the same 0.05 significance level. If this criterion for the PFS comparison is not met in the ITT population, no further testing for the PFS comparison will be performed in the PIK3CA/PTEN/AKT1 altered status subgroup. (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).

As a pre-specified secondary analysis, PFS analysis will be repeated by PFS events based on central radiology review.

2.5.2.2 Overall Survival, TSST

The analyses of OS and TSST will be similar to these of PFS (Table 13, 14, 15, Figure 2, 4).

2.5.2.3 Response Rate and Clinical Benefit Rate

The number and percentage of CR, PR, SD, and PD will be reported (Table 16).

The 95% confidence intervals for the response rate and clinical benefit rate will be calculated for each arm. The difference in response rate between the two arms and the corresponding 95% confidence interval will be obtained by the asymptotic normal approximation.

Median for the duration of the response will be calculated using the KM method for each arm (Table 16a).

2.6 Drug Exposure

Duration of drug exposure (fulvestrant and ipatasertib / placebo) will be reported as time from the date of the first dose of protocol therapy to the time of the last drug dose before the clinical cut-off date. The date of randomization will be used if the first dose date is unknown. If the date of discontinuation is

unknown, we use the drug injection date for fulvestrant and the drug start date + 21 days for ipatasertib / placebo.

The min, median, mean, standard deviation, and max duration of drug exposure will be reported by the treatment arm in Table 17.

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

Non-hematologic adverse events will be summarized according to CTC AE 5.0 (Table 18).

The number and percentage for Adverse Events of Special Interest (AESI) will be reported.

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.
- Grade $\geqslant$ 3 hepatotoxicity.
- Grade $\geqslant$ 3 ALT/AST elevations.
- Suspected transmission of an infectious agent by the study drug, defined as any organism, virus or infectious particle (e.g. prion protein transmitting/transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Grade $\geqslant$ 3 diarrhea.
- Grade $\geqslant$ 3 fasting hyperglycemia.
- Grade $\geqslant$ 2 pneumonitis.
- Grade $\geqslant$ 2 colitis/enterocolitis.
- Grade $\geqslant$ 3 rash.
- Erythema multiforme

2.7.1.2 Hematology/Biochemistry

Hematology/Biochemistry experience will be reported according to CTC AE 5.0 (Table 19).

2.7.1.3 Serious Adverse Event

SAE will be listed by treatment arm (Table 20).

2.8 Off-study and Death

Patients off-study (off protocol treatment): Number and % of all treated patients. Reason for going off-study (e.g. adverse event, death, progression, etc.): The number and % of all treated patients will be presented (table 21).

Deaths within 30 days from the last treatment administration. Cause of death within 30 days from the last treatment administration: The number and % of all treated patients will be presented (table 22).

2.9 Quality of Life

The EORTC QLQ-C 30 Global Score will be used for our primary assessment of 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 below:

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

Symptom Domains:

Fatigue: Questions: 10, 12, 18
Score=missing if the number of above questions not answered is greater than 1;

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

There are also six single items in EORTC QLQ-C30 about 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.

For functional domains, a higher score indicates better functioning but for symptom domains, a higher score indicates higher (worse) symptoms.

2.9.2 Analysis

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

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) Day 1 of cycle 2: If the QOL is assessed between days -2 to 27 of cycle 2
3) Day 1 of cycle 3: If the QOL is assessed between days -2 to 27 of cycle 3
4) Day 1 of cycle 4: If the QOL is assessed between days -2 to 27 of cycle 4
5) Cycle 5, 7, 9, 11: If the QoL is assessed between days - 2 to 27 of cycle 5, 7, 9, 11.
6) 4 weeks after complete of protocol treatment: If the QOL is assessed between weeks 2 and 8 after the protocol treatment

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 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 the 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 a generalized linear mixed model. The treatment arms and QOL assessment time points will be used as covariates in this analysis. The interactions between treatment arms and QOL assessment time (baseline to week 4 after treatment) will be tested using a likelihood ratio method.

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 improvement. 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 a patient's QOL response, the 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).

2.9.2.5 QOL Subscale Trend Analysis

Plots of QoL scores over time by treatment arms over time (From baseline to week 4 after treatment) will be reported for global QOL, each subscale and symptom item.

Note: Patient-reported outcomes version of the adverse events (PRO-CTCAE), health economic and correlative sciences will be analyzed separately.

3 Tables

Table 1 Accrual by Centre

Centre	Number of accrual (%)		
	Ipatasertib N = ***	Placebo 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 (%)		
	Ipatasertib N = ***	Placebo N = ***	Total N = ***
PIK3CA/PTEN/AKT1			
Altered	** (**)	** (**)	** (**)
Wildtype/Unknown	** (**)	** (**)	** (**)
Prior duration of treatment with CDK 4/6 inhibitor			
<6months			
>/=6months	** (**)	** (**)	** (**)
	** (**)	** (**)	** (**)
Source: Centralized Randomization File			

Table 3: Treatment Received

	Number of accrual (%)		
Actual treatment received	Ipatasertib N = ***	Placebo N = ***	Total N = ***
Ipatasertib	XX (XX)	XX (XX)	XX (XX)
Placebo			
No treatment			

Table 4: Stratification Factor at Randomization vs. at Baseline

Data set: All Randomized Patients			
	Number of patients (%)		
At randomization	At baseline	Ipatasertib N = ***	Placebo N = ***
PIK3CA/PTEN/AKT1			
Altered	Altered	** (**)	** (**)
Wildtype/Unknown	Altered	** (**)	** (**)
Altered	Wildtype/Unknown		
Wildtype/Unknown	Wildtype/Unknown		
Prior duration of treatment with CDK 4/6 inhibitor		** (**)	** (**)
<6months	<6months	** (**)	** (**)
>/=6months	<6months		
<6months	>/=6months		
>/=6months	>/=6months		

Table 5: Eligibility Status

Total patients allocated	Ipatasertib N = ***	Placebo 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 6: Summary of Follow-up

Data set: All Randomized Patients			
	Number of patients		
	Placebo N = ***	Ipatasertib N = ***	Total N = ***
Median*	***	***	***
Min	**	**	**
Max	**	**	**

Median Follow-up based on inverse OS

Table 7: Patient Characteristics

All randomized patients	Ipatasertib N = ***	Placebo N = ***	Total N = ***
AGE			
<=39	XX (XX)		
40-49	XX (XX)		
50-59			
60-69			
>=70	XX (XX)		
Median (Range)	XX (XX)		
Sex			
M			
F			
Race			
Ethnicity			
ECOG PS			
0			
1			
2			
Prior Chemotherapy in advanced disease setting (Y versus N)			
Sites of metastases <3 Or =3			
Bone only			
Lung involvement			
Liver involvement			
Lung or Liver involvement			
ER status			
Positive			
Negative			
PR status			
Positive			
Negative			
HER2 status			
0			

1			
2			
3			

Table 8. Baseline Hematology / Biochemistry

CTC AE 5.0 Hematology / Biochemistry table

Table 9. Baseline Non-Hematologic Adverse Events

CTC AE 5.0 Non-Hematologic Adverse Event table

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

Data set: All Randomized Patients				
	Univariate HR (95% CI)	Log-rank p-value	Multivariate HR(95% CI) (1)	Multivariate p-value
Treatment (Ipatasertib vs. Placebo) (stratified at randomiation)	***	***	--	--
Treatment (Ipatasertib vs. Placebo) (un-stratified)				

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

Table 11: PFS by Subsets

Data set: All Randomized Patients			
	Number of patients (%)		
	Ipatasertib N (# of event)	Placebo N (# of event)	HR (95% C.I)
PIK3CA/PTEN/AKT1			
Altered	** (**)	** (**)	(** , **)
Wildtype/Unknown	** (**)	** (**)	(** , **)
Prior duration of treatment with CDK 4/6 inhibitor			
<6months	** (**)	** (**)	(** , **)
>/=6months	** (**)	** (**)	(** , **)

Table 12: PFS Event Summary

Data set: All randomized Patients		
	Number of Patients (%)	
	Ipatasertib N = ***	Placebo N = ***
Patients with PFS event	*** (**)	*** (**)
Progression	**	**
	**	**
…		
	**	**
	**	**
	**	**
	**	**
	**	**
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
Treatment (Ipatasertib vs. Placebo) (stratified)	*** (*, *)	***	*** (*, *)	***
Treatment (Ipatasertib vs. Placebo) (un-stratified)	*** (*, *)	***	*** (*, *)	***
	*** (*, *)	***	*** (*, *)	***
	*** (*, *)	***	*** (*, *)	***
	*** (*, *)	***	*** (*, *)	***
Other factors…				

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

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Table 14: OS by Subsets

Data set: All Randomized Patients			
	Number of patients (%)		
	Ipatasertib N (# of event)	Placebo N (# of event)	HR (95% C.I)
PIK3CA/PTEN/AKT1			
Altered	** (**)	** (**)	(** , **)
Wildtype/Unknown	** (**)	** (**)	(** , **)
Prior duration of treatment with CDK 4/6 inhibitor			
<6months	** (**)	** (**)	(** , **)
>/=6months	** (**)	** (**)	(** , **)

Table 15: Death Summary

	Number of Patients (%) Data set: All randomized Patients		
	Ipatasertib N =	Placebo N =	Total N =
Patients who died			
Cause of Death			
Breast Cancer only			
Other primary malignancy			
Other conditions or circumstances			
Patients who were censored			
Reason Censored			
Still Alive			
Withdrawal of Consent			

Table 16. Best Response

Data set: All Randomized Patients			
	Number of patients		
	Placebo N = ***	Ipatasertib N = ***	Total N = ***
CR	XX (%)	XX (%)	XX (%)
PR	**	**	**
SD	**	**	**
PD			
In-evaluable			

Table 16a. Response Duration

Data set: All Randomized Patients			
	Number of patients		
	Placebo N = ***	Ipatasertib N = ***	Total N = ***
Median*	***	***	***
Min	**	**	**
Max	**	**	**

* Based on the KM method

Table 17. Drug Exposure

Data set: All treated Patients			
	Number of patients		
	Placebo N = ***	Ipatasertib N = ***	Total N = ***
Median*	***	***	***
Min	**	**	**
Max	**	**	**

Table 18. Non-Hematologic Adverse Events

CTC AE 5.0 non-hematology adverse events table

Table 19. Hematology / Biochemistry (Follow-up)

CTC AE 5.0 Hematology / Biochemistry table

Table 20. Serious Adverse Events

As in the meeting book table.

Table 21. Off Protocol Treatment

Data set: All treated Patients			
Off treatment	Number of patients		
	Ipatasertib N = ***	Placebo N = ***	Total N = ***
Cause1	***	***	***
2	**	**	**
3			
4			

Note: One table for each type of treatment (oral and iv)

Table 22. Death on Trial within 30 days of last Treatment

Data set: All treated Patients			
Cause of Death	Number of patients		
	Ipatasertib N = ***	Placebo N = ***	Total N = ***
Cause1	***	***	***
2	**	**	**
3			
4			

Table 23. Dates Used to Derive the Last Known Alive date (LKAD)

CDASH data	**CRF Section Name**	**Date Variable as the source of LKAD**	**Description**	**Note**
MA40_WC	Withdraw of consent	DS_DSSTDAT_ WITHDRAWAL	Date of consent withdrawal	
MA40_LTFU	Lost to follow-up	DS_DSSTDAT_LOST	Date of lost to follow-up	
MA40_F5 MA40_F5P MA40_F5S	Form 5/ Form 5s/ Form 5p	VISDAT	End date of visit	
MA40_F9	F9	RS_RSDAT	Date of Relapse / Progression	
MA40_PE	Physical Exam	VISDAT	Date of Exam	Post baseline
MA40_TRT_IV	Drug Administration	EC_ECSTDAT	Dose administrate date where the EC_ECDSTXT_PERFORMED (actual dose given) not equal to 0.	IM protocol therapy
MA40_LES_TAR MA40_LES_NTAR MA40_LES_NEW	Lesion evaluation	TU_TUDAT	Date of Test for Target, non-target and new lesion	Post baseline
MA40_RADIO	Other Radiology Investigations	TU_TUDAT_OTHERRAD	Assessment Date	Post baseline
MA40_LAB	Hematology and Biochemistry	TEST_DT	Date of blood collection	Test done
MA40_ECG	Cardiac Function (ECG)	EG_EGDAT	Date of ECG	Post baseline
MA40_HOSP	Hospitalization	HO_HOSTDAT, HO_HOENDAT	Admission Date and Discharge Date	
MA40_AE	Adverse Event (Post baseline SAE only)	AE_AESTDAT_PA, AE_AEENDAT_PA	Date of onset and Date of Resolution of SAE only	complete dates
MA40_LAB	Tests (Numeric) (SAE)	TEST_DT	CollectionDate of Worst Value, Collection Date of recovery	Post baseline
MA40_SAE_NONNUM	Tests (Nonnumeric) (SAE)	STDAT_TESTS_SAE	Date of Test	
MA40_CANCERTX_1 Treatment Folders only	Cancer Treatment (Surgery)	PR_PRSTDAT_NEWTX_PA	date of surgery	complete dates
MA40_CANCERTX_2 Treatment Folders only	Cancer Treatment (RT)	PR_PRSTDAT_NEWTX_PA PR_PRENDAT_NEWTX_PA	First Fraction Date, Last Fraction Date	complete dates
MA40_CANCERTX_3 Treatment Folders only	Cancer Treatment Systemic Therapy	CM_CMSTDAT_NEWTX_PA, CM_CMENDAT_PA	Start Date End Date	complete dates
MA40_PREG	Pregnancy Test	LB_LBDAT_PREG	Date of pregnancy test	

Figure 1. KM plot for PFS

Figure 2. KM plot for OS

Figure 3. KM plot for Duration of Response

Figure 4. KM plot for TSST