CANCER RESEARCH UK & UCL CANCER TRIALS CENTRE
UCL Cancer Institute

CONCEPT

STATISTICAL ANALYSIS PLAN

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Contents

1. Summary description of the trial

Trial objectives	**Primary:** To compare the progression-free survival between the two groups (defined as the time from randomisation to the first of one of the following: development of disease progression (RECIST 1.1) or death from any cause). **Secondary:** • To assess Clinical Benefit Rate (CBR) defined as stable disease rate + partial response rate + complete response rate according to RECIST 1.1 criteria with a confirmation no less than 4 weeks after the criteria for response are first met recorded from the start of treatment to completion of 6 cycles of treatment. • To assess Objective Response Rate (ORR) in each group; defined as CR and PR with a confirmation no less than 4 weeks after the criteria for response are first met recorded from the start of treatment to completion of 6 cycles of treatment. ○ In the Bristol sub-pilot study, blood samples for CTC count will be correlated to radiological response. • To assess the time to response in each group – time from randomisation to the CT scan showing response as per RECIST 1.1. • To assess the overall survival (time from randomisation to the date of death due to any cause) in each treatment group. • To assess the time to next cytotoxic chemotherapy treatment from the date of completion of trial chemotherapy (for both ER+ve and ER-ve patients – it is assumed that some ER+ve patients will be commenced on endocrine treatment after finishing trial chemotherapy even in the absence of disease progression). • To evaluate safety and tolerability. • To assess quality of life using EQ-5D and FACT-B assessment tools (measured at baseline, prior to cycles 3 and 5 and at the end of treatment visit).
Sample size	A total of 127 PFS events are required to detect a 35.3% hazard rate reduction in PFS (HR=0.647) with 85% power using the log-rank test at a one-sided 10% significance level. A total of approximately 160 patients (80 in each arm) are required to achieve the targeted number of PFS events.

Group A	6 cycles of chemotherapy using cabazitaxel 25mg/m^2
Group B	6 cycles of chemotherapy using paclitaxel 80mg/m^2
Primary outcome measure	Progression-free survival
Secondary outcome measures	• Clinical Benefit Rate (CBR) • Objective Response Rate (ORR) • Overall survival • Time to next cytotoxic chemotherapy treatment • Time to response • Quality of life • Safety: frequency, severity, seriousness and relatedness of study treatment-emergent adverse events

2. Recruitment, follow-up, and baseline characteristics

The following should be obtained:

- The month and year between which patients were recruited (eg between January 2000 and June 2006)
- The age range of patients recruited (eg 25 to 87 years)
- The number of centres that recruited patients
- The country (or countries) from which patients were recruited
- The length of follow up (patients who have died should be censored). This is obtained for all patients, and in each trial arm (to check that they are similar)
- A table of baseline characteristics, in each trial arm. This should contain age, gender, and any stratification factors used in the randomisation. Other variables could be disease stage, performance status/ECOG score, body weight, and other key biological and physiological measurements.
    - For categorical variables, each column will contain N (%)
    - For continuous variables, each column will contain the mean or median value, and in brackets, the standard deviation or 25-75th centile values
    - P-values for comparing the trial arms should not be reported (see Senn SJ (1994) Testing for baseline balance in clinical trials, Statistics in Medicine 13: 1715-1726)
- The number of patients who were ineligible in each trial arm, and the reasons why they were ineligible
- The number of patients who were recruited to the trial but withdrew later on, and the reasons (if available)
- List any possible major protocol violations or ineligibility criteria that would lead to the patient not being included in the analysis, eg patient later found not to have the cancer of interest

Ineligible patients

The following patients were found to be ineligible and have been excluded from all analyses.

ID	Reason ineligible
…	
…	
…	
…	

Baseline characteristics (eligible patients)

	Cabazitaxel N=??	Paclitaxel N=??
		Median (range)
Age, years		
BMI, kg/m^2		
Systolic BP, mmHg		
Diastolic BP, mmHg		
Haemoglobin, g/L		
Neutrophils, x 10^9/L		
Platelets, x 10^9/L		
ALT, IU/L		
		Number of patients (%)
ECOG		
0		
1		
ER status		
Negative		
Positive		
Previous docetaxel		
No		
Yes		

3. Efficacy

3.1. Primary endpoint analyses

The primary efficacy endpoint is PFS, defined as the time from date of randomisation to whichever comes first of date of tumour progression (RECIST 1.1) or date of death from any cause. Patients who do not progress or die will be censored at the earlier between the date of last valid tumour assessment without evidence of tumour progression and the cut-off date. Patients who have no tumour assessments after baseline and do not die will be censored on the day of randomisation.

The PFS analyses will be repeated where patients who have not progressed are censored at the date they were last known to be alive.

PFS will be compared between the two treatments by the log-rank test, stratified by previous chemotherapy in neo-adjuvant/adjuvant setting (docetaxel or no docetaxel) and subtype tumour (ER positive or ER negative) as specified at the time of randomisation.

Estimates of the hazard ratio and corresponding 80% and 95% confidence intervals will be provided using a stratified Cox proportional hazards model, stratified by the same baseline stratification factors as those used for the log-rank test, with treatment arm as a single covariate.

The PFS curves will be estimated using Kaplan-Meier estimates as well as PFS rates and associated 80% CI at 1, 3, 6, 9 & 12 months. The median PFS and associated 80% and 95% CI will also be provided.

		Cabazitaxel (N=??)	**Paclitaxel (N=??)**
Number of PFS events			
Number of progressions			
Number of deaths			
Median PFS, months	(80% CI)		
	(95% CI)		
Hazard ratio	(80% CI)		
	(95% CI)		
P-value			
1-month PFS rate (80% CI)			
3-month PFS rate (80% CI)			
6-month PFS rate (80% CI)			
9-month PFS rate (80% CI)			
12-month PFS rate (80% CI)			

3.2. Secondary endpoint analyses

3.2.1. Response rates

Best tumour response from start of treatment to the completion of 6 cycles

	Cabazitaxel (N=??)	**Paclitaxel (N=??)**
	N(%)	N(%)
Complete Response		
Partial Response		
Stable Disease		
Progressive Disease		
Not evaluated		
Did not receive treatment[1]		
CBR[2] (95% CI) P-value		
ORR[3] (95% CI) P-value		

[1]Excluded from denominator
[2]Clinical Benefit Rate (CR + PR + SD)
[3]Objective Response Rate (CR + PR)

3.2.2. Time to response

Time to response curves will be estimated using the Kaplan-Meier method and the corresponding median survival times and 95% CI will be estimated. A hazard ratio comparing treatment arms with corresponding 95% CI and p-value will be estimated using a Cox proportional hazards model.

3.2.2.1. Time to first response

Time to first response will be measured from date of randomisation to date of CT scan showing first response as per RECIST 1.1 (PR or CR). Patients who do not respond will be censored at the date last seen.

	Cabazitaxel (N=??)	**Paclitaxel (N=??)**
Number of responses		
Median time to first response, months (95% CI)		
Hazard ratio (95% CI)		
P-value		

3.2.2.2. Time to best response

Time to best response will be measured from date of randomisation to date of CT scan showing best response as per RECIST 1.1 (PR or CR). Patients who do not respond will be censored at the date last seen.

	Cabazitaxel (N=??)	**Paclitaxel (N=??)**
Best response		
CR		
PR		
Median time to best response, months (95% CI)		
Hazard ratio (95% CI)		
P-value		

3.2.3. Overall survival

OS curves for each treatment arm will be estimated using the Kaplan-Meier method and presented separately for all randomised patients and only patients who started treatment (at least 1 cycle of trial chemotherapy). The median survival times and 95% CIs will be estimated. Univariate and multivariate Cox proportional hazards models will be used to adjust hazard ratios for stratification factors.

Median survival times

	Cabazitaxel	**Paclitaxel**
	Median OS (95% CI)	
All patients (N=??)		
Patients who received treatment (N=??)		

Results of univariate and multivariate Cox proportional hazards models of overall survival

Variable	**Univariate**		**Multivariate**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
All patients N=??				
Treatment (Cabzitaxel vs Paclitaxel)				
Previous chemotherapy (docetaxel vs no docetaxel)				
Subtype tumour (ER+ve vs ER-ve)				
Patients who received treatment N=??				
Treatment (Cabzitaxel vs Paclitaxel)				
Previous chemotherapy (docetaxel vs no docetaxel)				
Subtype tumour (ER+ve vs ER-ve)				

Cause of death

Cause of death	Cabazitaxel (N=??)	Paclitaxel (N=??)
Progressive disease		
Treatment-related		
Combination of cancer related & treatment related		
Other		
Not known		

3.2.4. Subgroup analyses

Hazard ratios comparing treatment arms for PFS and OS will be reported for the following subgroup factors:

- Age (<65 vs ≥65)
- ECOG
- ER status
- Neoadjuvant/adjuvant docetaxel
- Previous CDK inhibitor treatment (among ER +ve patients only)

All PFS analyses will be repeated twice, once censoring patients who do not progress or die at the date of last valid tumour assessment without evidence of tumour progression, and once censoring patients who do not progress or die at the date they were last known to be alive.

3.2.5. Time to next cytotoxic chemotherapy or death

Time to next cytotoxic chemotherapy will be measured from the date of completion of trial therapy to the date of next cytotoxic chemotherapy or death. Patients who do not start another line of cytotoxic chemotherapy will be censored at the date last seen.

Time to next cytotoxic chemotherapy curves will be estimated using the Kaplan-Meier method and the corresponding median survival times and 95% CI will be estimated. A hazard ratio comparing treatment arms with corresponding 95% CI and p-value will be estimated using a Cox proportional hazards model.

	Cabazitaxel (N=??)	**Paclitaxel (N=??)**
Number of patients starting 2nd line cytotoxic chemotherapy		
Number of patients who died before starting 2nd line cytotoxic chemotherapy		
Median time to 2nd line start, months (95% CI)		
Hazard ratio (95% CI)		
P-value		

Additional treatments

Additional treatments will be listed by treatment arm. Not all patients who progress will go on to receive further treatment and not all patients will progress before receiving additional treatment.

	Cabazitaxel	**Paclitaxel**
Additional treatment before progression		
…		
…		
First recorded treatment after progression		
…		
…		
Second recorded treatment after progression		
…		
…		

3.2.6. Treatment compliance

Compliance to Chemotherapy

		Cabazitaxel (N=??)	**Paclitaxel (N=??)**
		N (%)	N (%)
Number of cycles received			
	6		
	5		
	4		
	3		
	2		
	1		
	0		
Missing data (number of cycles unknown)			
Dose delay	Cycle		
	1		
	2		
	3		
	4		
	5		
	6		
Any delay			
Dose reduction	Cycle		
	1		
	2		
	3		
	4		
	5		
	6		
Any reduction			
Dose interruption	Cycle		
	1		
	2		
	3		
	4		
	5		
	6		
Any dose interruption			

Reasons for stopping treatment

Reason for stopping treatment	Cabazitaxel (N=??)	Paclitaxel (N=??)
Completion of 6 cycles		
Adverse Event		
Disease progression		
Death		
Patient's decision		
Physician's decision		
Other		

Reasons for non-compliance

	Cabazitaxel (N=??)	Paclitaxel (N=??)
	N (%)	N (%)
Any dose delays		
Reason 1		
Reason 2		
…		
Any dose reductions		
Reason 1		
Reason 2		
…		
Any dose interruptions		
Reason 1		
Reason 2		
…		

3.2.7. Efficacy by treatment compliance

The difference in progression-free survival and overall survival depending on number of completed chemotherapy cycles will be compared between treatment arms using Cox proportional hazards models. If there is any imbalance in baseline factors between the treatment arms then hazard ratios from models which adjust for the baseline factors may be reported alongside the unadjusted values. In cases where the proportional hazards assumption is violated, analyses will be performed instead using the Restricted Mean Survival Time (RMST).

	No. patients	No. events	PFS HR (Cab vs Pac), 95% CI, p-value
All patients			
Completed 3-6 cycles			
Completed 4-6 cycles			

All PFS analyses will be repeated twice, once censoring patients who do not progress or die at the date of last valid tumour assessment without evidence of tumour progression, and once censoring patients who do not progress or die at the date they were last known to be alive.

	No. patients	No. events	OS HR (Cab vs Pac), 95% CI, p-value
All patients			
Completed 3-6 cycles			
Completed 4-6 cycles			

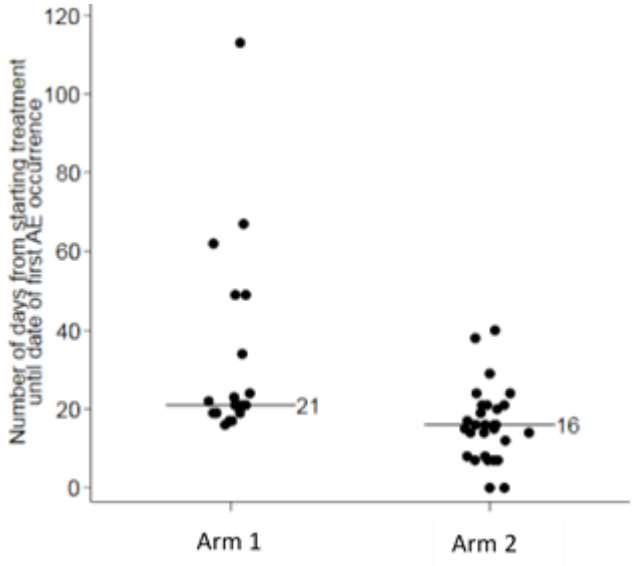
3.2.8. Toxicity

All adverse events that occur after the subject has started treatment until the end of treatment visit, which is not due to progression of disease (advanced breast cancer), will be reported. Only the worst grade seen is reported (patients with any grade 3+ AE would not be counted within the worst grade 1-2).

System Organ Class	Adverse Event	Cabazitaxel N=??		Paclitaxel N=??	
		G 1-2	G 3+	G 1-2	G 3+
		N(%)		N(%)	
Blood and lymphatic system disorders	Any				
	Anaemia				
	…				
Cardiac disorders	Any				
	Chest pain				
	…				
…	…				
Any AE					

Scatter plots will be produced to display the time to first event for the most common adverse events as well as any of particular interest.
Pre-specified events of interest are: Alopecia, Neuropathy & Neutropaenic sepsis

Example of scatter plot:



- There will be a separate scatter plot for each adverse event of interest
- Horizontal lines represent the median time to first event for that particular AE.

3.2.9. Quality of Life

As well as through the methods described below, quality of life measures may also be presented graphically to aid in interpretation.

EQ-5D

For EQ-5D, descriptive summary statistics (size, mean, standard deviation, median, range) will be provided for the single index utility score and the VAS by treatment group as well as for the difference in means at baseline, prior to cycles 3 and 5 and at the end of treatment. Change from baseline will also be described.

		Baseline		**Prior to cycle 3**		**Prior to cycle 5**		**End of treatment**	
		Cab N=??	**Pac N=??**	**Cab N=??**	**Pac N=??**	**Cab N=??**	**Pac N=??**	**Cab N=??**	**Pac N=??**
Single index utility	Mean (SD) Median (range)								
VAS	Mean (SD) Median (range)								
Difference in means	Difference 95% CI P-value								
Change from baseline	Change 95% CI P-value	- - -	- - -						

Note: P-values are from t-tests

For each EQ-5D item, information on the frequency and proportion of the population reporting level 1 (no problems), level 2 (some problems) and level 3 (extreme problems) per item will be reported by treatment group.

EQ-5D Dimension		Baseline		Prior to cycle 3		Prior to cycle 4		End of treatment	
		Cab N=?? N (%)	Pac N=?? N (%)	Cab N=?? N (%)	Pac N=?? N (%)	Cab N=?? N (%)	Pac N=?? N (%)	Cab N=?? N (%)	Pac N=?? N (%)
Mobility	Level 1								
	Level 2								
	Level 3								
Self-care	Level 1								
	Level 2								
	Level 3								
Usual activities	Level 1								
	Level 2								
	Level 3								
Pain/ Discomfort	Level 1								
	Level 2								
	Level 3								
Anxiety/ Depression	Level 1								
	Level 2								
	Level 3								

Note: Level 1 = “No problems”, Level 2 = “Some problems”, Level 3 = “Extreme problems”

FACT-B

For FACT-B, descriptive summary statistics will be provided for the overall score and subscales of the FACT-B, by treatment group, at baseline, prior to cycles 3 and 5 and at the end of treatment.

		Baseline		Prior to cycle 3		Prior to cycle 5		End of treatment	
		Cab N=??	Pac N=??	Cab N=??	Pac N=??	Cab N=??	Pac N=??	Cab N=??	Pac N=??
Total score	Mean (SD) Median (range)								
Physical well-being	Mean (SD) Median (range)								
Social well-being	Mean (SD) Median (range)								
Emotional well-being	Mean (SD) Median (range)								
Functional well-being	Mean (SD) Median (range)								
Breast cancer subscale	Mean (SD) Median (range)								

4. Incidents and Serious breaches (if applicable)

Details of incidents occurring during the trial that were identified as potentially affecting data integrity must be included in the final clinical study report. Such incidents should be added to the SAP using the table below:

Description or summary of incidents during the trial assessed as having an impact on the trial data	Possible effect on trial data	Analyses to be carried out	Patients affected*

Details of any serious breach occurring during the trial for which a possible impact on data has been identified in the final clinical study report. Details of relevant information included in the serious breach report to the MHRA regarding the impact on data should be included in the report, this may include specific analyses carried out at the time of the serious breach report. If the trial has had a serious breach (requiring reporting or further analyses), this should be added to the SAP using the table below:

Description of the incident/ serious breach	Possible effect on trial data	Analyses to be carried out	Patients affected*

*This could be a list of ID numbers or a description i.e. all patients randomised between XX and YY or a file path to an excel file containing a list of patients.

Revision Chronology:			
Version Number	**Effective date**	**Reason for change and Summary of changes**	**Author**
01	**3/12/2019**	**Creation of document**	**Will Wilson**
02	**17/06/2020**	**Implementation of comments from CI and trials team**	**Will Wilson**