AstraZeneca

Statistical Analysis Plan

Study Code	D8664C09827
Edition Number	Version 1.0
Date	13-01-2021

A Multi-centre, Single-arm, Prospective, Interventional Study to Assess Efficacy and Safety of Neoadjuvant Hormone Therapy using Zoladex (Goserelin) and Casodex (Bicalutamide) in Patients with Advanced Prostate Cancer Undergoing Radical Prostatectomy (NARNIA)

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Study Statistician

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Global Product Statistician

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A Multi-centre, Single-arm, Prospective, Interventional Study to Assess Efficacy and Safety of Neoadjuvant Hormone Therapy using Zoladex (Goserelin) and Casodex (Bicalutamide) in Patients with Advanced Prostate Cancer Undergoing Radical Prostatectomy (NARNIA)

Study Medical Advisor

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this study Statistical Analysis Plan.

Abbreviation or special term	Explanation
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AR	Androgen Receptor
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CAB	Complete Androgen Blockage
CI	Confidence Interval
CK	Creatine Kinase
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic Acid
DRE	Digital Rectal Examination
ECG	Electrocardiogram
EDC	Electronic Data Capture
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eLND	extended Lymph Node Dissection
FAS	Full Analysis Set
GCP	Good Clinical Practice
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HL	Hy's Law
ICH	International Conference on Harmonisation
LHRH	Luteinizing Hormone-releasing Hormone
IMP	Investigational Medicinal Product
IP	Investigational Product
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NHT	Neoadjuvant Hormone Therapy
OS	Overall Survival
PCWG3	Prostate Cancer Working Group 3

PFS	Progression Free Survival
PHL	Potential Hy's Law
PI	Principal Investigator
PSA	Prostate Specific Antigen
RALP	Robot-assisted Laparoscopic Prostatectomy
RECIST	Response Evaluation Criteria in Solid Tumours
RP	Radical Prostatectomy
RPAS	RP Analysis Set
RRP	Radical Retropubic Prostatectomy
SAE	Serious Adverse Event
SD	Standard Deviation
TBL	Total Bilirubin
ULN	Upper Limit of Normal

AMENDMENT HISTORY

Date	Brief description of change
NA	NA

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

To evaluate the efficacy of neoadjuvant hormonal therapy in the subjects with locally advanced prostate cancer through the rate of radical resection following neoadjuvant hormonal therapy (NHT).

1.1.2 Secondary objectives

- To investigate the efficacy of NHT before radical prostatectomy (RP) in subjects with locally advanced prostate cancer by assessment of PSA, percentage of positive surgical margin for primary tumor, incidence of seminal vesicle invasion and involvement of bilateral pelvic lymph nodes.
- To observe surgical-related variables and complications.
- To evaluate the safety of NHT using goserelin and bicalutamide.

1.1.3 Exploratory objectives

- Occurrence of homologous recombination repair gene mutation (HRRm) in the patients with locally advanced prostate cancer.

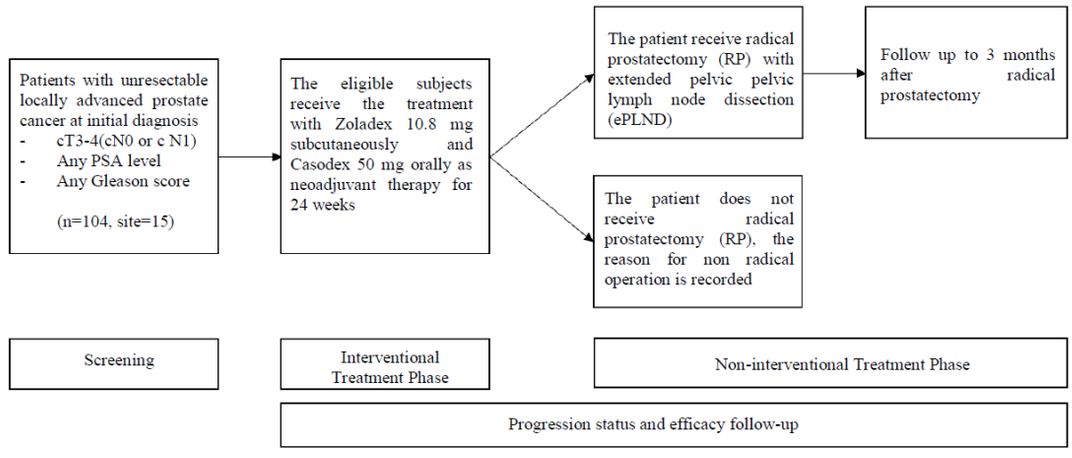
1.2 Study design

This is a multi-centre, single-arm and prospective study to explore the efficacy and safety of neoadjuvant hormone therapy (NHT) for advanced prostate cancer patients undergoing radical prostatectomy (RP). A total of 104 subjects with locally advanced prostate cancer and oligometastatic prostate cancer at clinical stage of T3 and T4 (N0 or N1) will be enrolled at almost 15 centres in China.

The eligible subjects will receive Casodex 50 mg orally per day in combination with Zoladex 10.8 implant subcutaneously per 12 weeks as neoadjuvant therapy for 24 weeks, and then will be assessed for resectability of the primary tumour. The subjects will undergo a RP [RALP (robot-assisted laparoscopic prostatectomy), laparoscopic RP or RRP (radical retropubic prostatectomy)] plus ePLND thereafter if the primary tumour is assessed as resectable. Surgical margin status and involvement of pelvic lymph nodes will be evaluated. Subjects will be prescribed post-surgical treatment such as continuous ADT and metastasis-directed therapy upon investigator's discretion and be followed-up for up to 3 months. The reason for failure to operate will be collected for the patients who actually can not receive radical prostatectomy following NHT.

The subjects will return for all regular clinical visits and perform all scheduled assessments until the end of study.

Figure 1 Study flow chart



Definition of resectability: clear lateral border of prostate in digital rectal examination, and clear bladder neck with no invasion in radiological examination or cystoscopy, no invasion of urethra or external sphincter at the apex of prostate

1.3 Number of subjects

This is a single-arm, prospective study and the primary endpoint is the actual radical prostatectomy rate. An approximate sample size of 104 subjects provides a precision of 6.1% based on the bilateral 95% confidence interval (CI) for the resectability rate of 90% assuming a dropout rate of 10% (half width of 95% CI).

2. ANALYSIS SETS

2.1 Definition of analysis sets

Full analysis set (FAS)

The FAS will include all subjects who received at least one dose of study drug, irrespective of whether some of these subjects may have discontinued treatment prior to the trial's end.

RP analysis set (RPAS)

The RPAS will be a subset of FAS, which included FAS subjects who actually received RP surgery.

The analysis of assessments related to RP or post RP will be conducted based on RPAS, except for analysis for primary endpoint. Where denominator of actual rate of radical resection following neoadjuvant hormonal therapy (NHT) will be based on number of subjects in FAS.

2.2 Protocol deviations

All protocol deviations (major and minor) will be reviewed and listed. The list of protocol deviations will be finalized and documented before the database lock. The number and percentage of subjects with protocol deviations (major/minor) will be summarized by protocol deviation category based on FAS. Major deviations will be those which are considered to potentially impact upon the interpretation of the primary endpoint in the study. Major deviations will be listed separately.

3. PRIMARY AND SECONDARY VARIABLES

3.1 PRIMARY ENDPOINT

- **Actual radical prostatectomy rate**
  Actual radical prostatectomy rate is defined as the percentage of the subjects who actually received radical prostatectomy after receiving NHT, including those who early discontinued from treatment. Denominator will be based on number of subjects in FAS.

3.2 SECONDARY ENDPOINT

- **The mean PSA by the end of NHT and PSA change from baseline**
  The mean PSA by the end of NHT is defined as the average PSA level by the end of NHT where all non-missing PSA level records at each visit (up to end of treatment visit) will be summarized. PSA change from baseline is defined as the change of PSA level at each visit from baseline (at enrollment) value, and this value will only be derived if both baseline and post-baseline records are non-missing values. Post-surgical visits will only be summarized for RP analysis set.
- **Percentage of positive surgical margins for primary tumor**
  Percentage of positive surgical margin of primary tumor is defined as the percentage of subjects with tumor at the margin positively resected in the postoperative pathological RP specimen. The denominator will be based on the RP analysis set.
- **Incidence rate of seminal vesicle invasion and involvement rate of bilateral pelvic lymph nodes**
  Incidence of seminal vesicle invasion and involvement of pelvic lymph node is defined as the percentage of subjects with seminal vesicle invasion and those with unilateral or bilateral pelvic lymph node metastasis in the postoperative pathology of RP specimen. Denominator will be based on RP analysis set.
- **Pathological downstaging rate**
  Pathological downstaging is defined as the tumor stage assessment has decreased from baseline pathology diagnosis records to post RP surgery assessment. Pathological downstaging rate will be derived as the percentage of pathological downstaging subjects out of all RP analysis set subjects.
- **Rate of Post-surgical PSA decreased to the less than 0.1ng/ml**
  Rate of post-surgical PSA decreased to less than 0.1ng/ml referred to the percentage of subjects with any post-surgical follow-up records of serum PSA level < 0.1 ng/mL, including the termination visit, out of all RP analysis set subjects.
- **Surgical-related variables and complications**
  - Reason for not conducting the RP surgery will be summarized for those in FAS but not in RPAS, where percentage for each category of reasons will be derived with number of subjects in FAS as denominator. Missingness will be summarized as a separate category if applicable.
  - Operative Duration is defined as the time (mins) from incision to finishing suturing, and will be derived based on the time difference from stop date/time to start date/time as recorded for the RP surgery.
  - Intraoperative Estimated Blood Loss will be estimated using haematocrit parameters collected during the RP surgery where results will be recorded in mL.
  - Duration of Indwelling Catheterization (Days) is defined as days from the start of surgery to removal of catheter

- Complications will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 23.0 or later). Where results will be summarized as the percentage of subjects who experience complications and percentage of subjects with complications needing intervention, based on RP analysis set.
- Urine function will be measured by dichotomous outcomes (continence or incontinence), which incontinence is primarily defined as the use of pads or absence of leakage. Time to Continence (Days) and urinary continence rate at 12 weeks after surgery will be reported. Time to Continence (Days) is defined as days from surgery to the earliest recorded date of continence during post-surgical follow-up period. Subjects who remained incontinence or with missing urine function records at the time of analysis will be censored at his latest visit day with non-missing urine function record. Subjects with no post-surgery records will be censored at day 1. While for continence rate at 12 weeks, missingness will summarized as a separate category.
- Erectile function will be measured by dichotomous outcomes (potent or impotent). Potent or not will be primarily determined by a single question raised by investigator at week 12 visit after RP surgery on whether the patient has experienced erections sufficiently firm for sexual intercourse. Potent rate is defined as the proportion of the subjects who are assessed as potent out of all RP analysis set subjects**.**
- AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA V23.0 or above). Summary for AEs will be presented by System Organ Class (SOC) and Preferred Term (PT), where details of analysis will be described in next section.

3.3 EXPLORATORY ENDPOINTS

- Incidence of homologous recombination repair mutation in tumor tissue
  Below 15 homologous recombination repair related genes will be tested for all subjects in RP analysis set:BRCA1, BRCA2, ATM, PALB2, CDK12, RAD54L, RAD51B, RAD51C, RAD51D, FANCL, CHEK1, CHEK2, PPP2R2A, BRIP1 and BARD1.
  Among which percentage of subjects with harmful germline and tumor tissue mutation will be summarized based on RP analysis set, and specific percentage for each specific mutation will be summarized as well.

3.4 OTHER ENDPOINTS

- **Laboratory safety assessments (Hematology, Chemistry, Urinalysis)**

  Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the timepoints as indicated in the Study Plan.

  The clinical chemistry, haematology and urinalysis assessments will be performed at a local laboratory at the Investigate site. Sample tubes and volume may vary depending on laboratory method used and routine practice at each site.

  The following laboratory variables will be assessed:

Table 1 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatase (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Creatine kinase (CK)

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

- **Eastern Cooperative Oncology Group (ECOG)**

Eastern Cooperative Oncology Group (ECOG) performance status scale will be used to evaluate the subject's general well-being and activities of daily life at visit as specified in the schedule, and the scale will be assessed by the investigator following below criteria:.
Grade 0: Fully active, able to carry on all pre-disease performance without restriction.
Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
Grade 3: Capable of only limited self-care, confined to a bed or chair >50% of waking hours
Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Grade 5: Dead

- **Study Medication Compliance Rate**

Compliance with study medication—based on the drug accountability data—will be calculated as the number of implants or tablets taken (dispensed counts – returned counts) divided by the prescribed number of implants or tablets expressed as a percentage.
Compliance to study medication (Zoladex or Casodex) will be calculated as follows:

$$\frac{\text{actual implants or tablets taken}}{\text{expected implants or tablets taken}} \text{x } 100\%$$

For subjects who permanently stop the study medication, the number of expected implants or tablets taken will be counted by the date of study withdrawal.
Above analyses will be performed based on FAS..

4. ANALYSIS METHODS

4.1 General principles

Statistical analysis will be performed by Wuxi CDS using SAS® Enterprise Guide version 7.1.
The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will include number of non-missing subjects (n), number of missing subjects (missing), arithmetic mean (or geometric mean if appropriate), standard deviation (SD), median, quartiles (Q1 and Q3), minimum, and maximum values for continuous variable, and frequency counts and percentages for categorical variables. The 95% CI will be provided when appropriate. Missingness might be summarized as a separate category as applicable. Data will be examined for skewness, outliers, and systematic missing data when appropriate. Transformations will be undertaken as needed.
- For continuous data, arithmetic mean (or geometric mean if appropriate), quartiles (Q1 and Q3) will be rounded to 1 additional decimal place compared to the original data and standard deviation (SD) to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages as well as the upper limit and lower limit of 95% CI will be rounded to 1 decimal place.
- Partial date conventions are provided in Appendix 1. Other missing data will not be imputed.
- Target Study day: The initial value of target study day (First Day) is defined as Day 1 of study treatment. The following target study days will be calculated as week x-previous week x.

The end of the treatment is defined as end of NHT, and specifically, the end of treatment effects for Zoladex (12 weeks after last injection, in terms of V4 at 180±10 day). The end of the study is defined as 'the last visit of the subject undergoing the study'. Specifically, for subjects did not undergo RP surgery, the end of study visit will be same as the end of treatment visit. For subjects conducted RP surgery, If one has requested or was requested by the investigator, to quit the study prior to his 90±5 days visit, then an end of study visit should be conducted unless the end of study visit is within 7 days from last scheduled visit. Otherwise his end of study visit will be the 90 day post-surgery visit.

4.1.1 Visit window definition

For treatment period, all post-baseline visits before RP surgery must occur within ± 5 days from the scheduled date, all regarding assessments should be performed within the specified time window.

Visit post radical operation should be conducted at 180±10. And if a subject chose not to conduct the RP surgery, the reason should be recorded at the same visit.

For post-surgical follow-up period, all visits must occur within ± 5 days from the scheduled date. All assessments will be performed within the specified time window.

If multiple readings are recorded within a single visit window, please refer to the rules below.

- If there are 2 or more observations within the same visit window, then the non-missing 1 closest to the visit will be used in the analysis.

- If 2 observations are equidistant from the visit, then the non-missing observation with the earlier collection date will be used in the analysis. If 2 observations are collected on the same day, then the non-missing 1 with the earlier collection time will be included in the analysis.

- If 2 observations are collected on the same day with missing time, the more conservative record will be included in the analysis

4.2 Missing Data Handling Rules

No imputation for missing data will be applied other than those as specified in Appendix 1. All statistical analyses will be primarily carried out on non-missing data.. In presentation of categorical variables, unknown and missing data will be presented as a separate category.

4.3 Analysis methods

4.3.1 Subject disposition

All screened and enrolled subjects will be accounted for in the subject disposition table.
The number and percentage of subjects will be summarized based on following classification:

- Screened
- Screen Failure
- FAS
- Completed Treatment Period
- RPAS
- Completed Study
- Early discontinue from study:
- Reason for early discontinuation:
    - Adverse Event
    - Death
    - Lost to Follow-up
    - Physician Decision
    - Withdrawal by Subject
    - Other

Only reasons with more than 0 subjects recorded will be presented. Specific disposition information will be listed including subject number and completion or discontinuation date

4.3.2 Demographic and baseline characteristics

Demographic and baseline characteristics will be analysed primarily based on FAS.
Demographic variables include following: age, sex, race.
Baseline characteristics including following variables:

- Physical examination variables include following: General appearance, Respiratory, Cardiovascular, Abdomen, Other. Results of each category will be recorded as normal or abnormal, where those did not undergo physical examination will be summarized as “not done”.
- The overall evaluation of ECG (in categories as listed: Normal, Non-clinical significant, clinical significant, not done).

Above demographic and baseline characteristics will be analyzed using descriptive statistics as

specified in general considerations section, and listed individually for each subject.

4.3.3 Medical and Surgical history

The Medical and Surgical history will be summarized by per SOC and PT using MedDRA Version 23.0 or above . The number and percentage of subjects with any medical and surgical history as well as each specific term will be summarized by SOC and PT and sorted by descending order of frequencies. Un-coded terms will be summarized as a separate category. All Medical and Surgical history will also be listed individually for each subject.
Above analyses will be performed based on FAS.

4.3.4 Medications and Procedures

The Medications will be presented and coded using WHODrug Global March 1, 2020 or higher version.
See Appendix 1 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the most conersativez case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.
- 'Concomitant' medications are medications which:
  - started prior to, on or after the first dose of study medication but no later than the end of study medication,
  - AND ended on or after the date of first dose of study medication or were ongoing at the end of the treatment.
- 'Post' medications are medications which started after the end of study medication.

Prior, Concomitant and Post Medications will be listed individually for each subject. The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication within each therapeutic class (ATC-Level 2) and generic term.
Prior and concomitant Procedures will also be listed individually for each subject. The number and percentage of subjects using each procedure will be displayed together with the number and percentage of subjects using at least one procedures.

Previous/current cancer therapy and previous/current radiotherapy will be summarized using same method as described above.

Above analyses will be performed based on FAS.

4.3.5 Exposure

4.3.5.1 Study Medication Exposure

Exposure to investigational product (Zoladex or Casodex) i.e., dosage of study drug and duration of exposure (days) will be summarized and listed individually for each subject by Zoladex and Casodex separately.
For Zoladex, the number of injection will be summarized as continuous variable. While for Casodex, total dosage, daily dose and duration will be summarized. Number and percentage of subjects with at least one dose interruption/delay record and with at least one dose reduction record will be

summarized as well.

For Casodex:

Duration of exposure (days) = date of last dose of Casodex taken – date of first dose of Casodex taken – days of Casodex not taken+ 1.

Above analyses will be based on FAS.

4.3.5.2 Study Medication Compliance Rate

Study medication compliance rate will be summarized by Zoladex and Casodex, where both compliance rate will be summarized as continuous variables by Casodex and Zoladex. Each subject's expected tablets/implants and actual tablets/implants as well as the ratio between them (in form of percentage) will be listed.

4.3.6 Analysis of the primary variable (s)

The number and percentage of subjects received radical prostatectomy after NHT will be summarised with 95% confidence interval provided.

4.3.7 Analysis of the secondary variable(s)

4.3.7.1 PSA level, mean PSA level by the end of NHT, resection margin status, seminal vesicle invasion, involvement of bilateral pelvic lymph nodes ,pathological downstaging and rate of post-surgical PSA decreased to less than 0.1ng/ml

PSA level will be summarized by visit, and change from baseline value will be summarized for post-baseline visits. PSA level and average PSA level by the end of NHT will be analysed based on FAS. While other variables will be summarized using descriptive statics based on RP analysis set. Shift table for pathological stage between baseline and post-surgery assessment might be provided as applicable.

4.3.7.2 Surgical variables and complications

- Operative Duration and Intraoperative Estimated Blood Loss will be summarized as continuous variables. Reasons for not performing RP will be summarized by category. For duration of Indwelling Catheterization (Days), summary statistics will be calculated based on those who had non-missing indwelling catheter end date, as count and percentage of missingness will be summarized separately.
- Complications
  The number and percentage of subjects with any complications and any complications needing intervention will be summarized by SOC and Preferred Term (PT) for RP analysis set.
  All information of radical prostatectomy related complications including start/stop date and outcome will be listed individually for each subject.

4.3.7.3 Urine Function and Erectile function

- Urinary rate and erectile rate at 12 weeks after surgery will be calculated with 95% confidence interval provided. Denominator will be based on RPAS where percentage of subjects with missing records will be reported as a separate category.
- Time to continence (in Days) will be summarized as continuous variable. Median time to continence will be estimated using Kaplan-Meier method and a Kaplan-Meier plot might be

provided as applicable. Subjects who remained incontinence or with missing urine function records will be censored at his latest visit day with non-missing urine function record. Subjects with no post-surgery records will be censored at day 1.

4.3.7.4 Adverse events(AEs)

Treatment-emergent AEs (TEAEs) are defined as the AEs occurring on or after the first dosing of study drug and up to 4 weeks after discontinuation of study drug. All AEs will be listed and summarized. See Appendix 1 for handling of partial dates for AEs, in the case where it is not possible to define TEAEs, the AEs will be identified as TEAEs.

AEs will be categorized into one or more of the following categories depending on the type of events reported:

- AEs
- SAEs
- Treatment-emergent AEs,
- Drug-related AEs (Zoladex related, Casodex related)
- Drug-related SAEs
- AEs leading to study drug discontinuation
- AEs with an outcome of death
- AEs of CTCAE Grade 3 or higher

An overall summary of the number and percentage of subjects in each category will be presented, as will an overall summary of the number of events in each category.

The number and percentage of subjects with TEAEs in each category above will be summarized and events in each category will be further summarized by MedDRA SOC and PT.

All related information (such as SOC/PT, CTCAE Grade, outcome, etc.) about adverse event will be listed for each subject and each term, based on following category: Deaths, SAEs and AEs.

Above analyses will be performed based on FAS.

4.4 Safety assessments

All safety assessments analyses will be performed based on FAS.

- **Laboratory assessments (Hematology, Chemistry, Urinalysis)**
  Value and change from baseline on continuous data (test results) will be summarized using descriptive statistics at each scheduled time point. Shift tables for evaluation of laboratory parameters from baseline to each scheduled time point will be provided. All laboratory assessments will be listed. Clinically significant laboratory results will be flagged, listed and summarized separately.
- **Physical Examination、ECG and Vital Signs**
  Vital Sign test value at each visit and change from baseline values will be summarized using descriptive statistics. Shift tables for evaluation from baseline to each scheduled time point will be provided by each parameter. All physical examination, ECG and vital signs results will be listed. Clinically significant results will be flagged, and listed separately.
- **Eastern Cooperative Oncology Group (ECOG)**

  The ECOG performance status scale (Grade 0-5) will be summarised by the frequency counts and percentage for each grade at each time point. The Shift tables will be performed based on Baseline (Visit 1) and other time points. All information about ECOG will be listed for each subject.

Above analyses will be performed based on FAS.

4.5 Exploratory endpoints

All the subjects receiving surgical treatment will receive germline and tumor tissue gene test after surgery. The frequency counts and percentage of subjects with harmful t-HRRm detected in tumor tissue gene test or germline homologous recombination repair mutation will be summarized respectively.

Above analyses will be performed based on RPAS.

5. INTERIM ANALYSES

No interim analyses are planned.

6. CHANGES OF ANALYSIS FROM PROTOCOL

NA

7. APPENDIX 1: PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment-emergent Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/Missing	If start date < study treatment start date, then not TEAE If start date >= study treatment start date, then TEAE
Partial, but known components show that it cannot be on or after study treatment start date	Known/Partial/Missing	Not TEAE
Partial, could be on or after study treatment start date	Known/ Partial/Missing	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), if partial or missing date exist. If stop date < study treatment start date, then not TEAE If stop date >= study treatment start date, then TEAE
Missing	Known/ Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), if partial or missing date exist. If stop date < study treatment start date, then not TEAE If stop date >= study treatment start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study treatment start date, assign as prior If stop date >= study treatment start date and start date <= end of treatment+3 months, assign as concomitant If start date > end of treatment+3 months, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study treatment start date, assign as prior If stop date >= study treatment start date and start date <= end of treatment+3 months, assign as concomitant If start date > end of treatment+3 months, assign as post treatment
	Missing	If start date <= end of treatment+3 months, assign as concomitant If start date > end of treatment+3 months, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study treatment start date, assign as prior If stop date >= study treatment start date and start date <= end of treatment+3 months, assign as concomitant If start date > end of treatment+3 months, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study treatment start date, assign as prior If stop date >= study treatment start date and start date <= end of treatment+3 months, assign as concomitant If start date > end of treatment+3 months, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If start date <= end of treatment+3 months, assign as concomitant If start date > end of treatment+3 months, assign as post treatment
Missing	Known	If stop date < study treatment start date, assign as prior If stop date >= study treatment start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study treatment start date, assign as prior If stop date >= study treatment start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant