Statistical Analysis Plan

for

A Phase I Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of AC699 in Patients with Estrogen Receptor Positive/Human Epidermal Growth Factor Receptor 2 Negative (ER+/HER2-) Locally Advanced or Metastatic Breast Cancer

Sponsor:	**Accutar Biotechnology, Inc.**
Study Drug:	**AC699**
Development Innovations Protocol Number:	**BRE401**
Accutar Biotechnology, Inc. Protocol Number:	**AC699-001**
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History of Changes

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
0.1	08AUG2023	Initial internal draft submitted to Accutar
0.2	01SEP2023	Application of first round updates from Accutar

Statistical Analysis Plan Review and Approval

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Glossary

ADI	Actual Dose Intensity
AE	Adverse Event
BOR	Best Overall Response
CBR	Clinical Benefit Rate
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFF	Efficacy Evaluable Set
ER	Estrogen receptor
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NE	Not Evaluable
ORR	Objective Response Rate
PD	Progressive Disease
PDI	Planned Dose Intensity
PK	Pharmacokinetics
PFS	Progression-Free Survival
PR	Partial Response
PT	Preferred Term
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Stable Disease
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event

WHO	World Health Organization

1 Introduction

This document describes the Statistical Analysis Plan for the Accutar Biotechnology, Inc. AC699-001 (BRE401) study, "A Phase I Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Anti-Tumor Activity of AC699 in Patients with Estrogen Receptor Positive/Human Epidermal Growth Factor Receptor 2 Negative (ER+/HER2-) Locally Advanced or Metastatic Breast Cancer."

1.1 Background and Rationale

Nearly 80% of breast cancers express estrogen receptors (ER), hormone-regulated transcription factors (DeSantis et al. 2019) and both preclinical and clinical studies highlight an important oncogenic role for estrogen and ERs mediated through proliferation and survival pathways (Spicer and Pike 1993). Several therapies have been developed to antagonize the oncogenic ER function.

A newly emerging technology, E3 ligase-engaged chimeric degraders, has been used to induce more potent and deeper ER degradation. Chimeric degraders degrade a protein of interest by connecting an ER ligand to an E3-recruiting ligand with an optimal linker. This subsequently brings ER within close proximity of E3 ligase and induces subsequent robust ubiquitination and degradation of ER. This is a first-in-human study of the chimeric ER degrader, AC699.

The dose-escalation portion of this study will begin with 100 mg once daily.

1.2 Objectives

Table 1 Study Objectives and Corresponding Endpoints

Primary Objective:	**Endpoints/Variables:**
Evaluate the safety and tolerability of AC699	Incidence and severity of dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), and clinically significant Grade 3 or higher laboratory abnormalities
Secondary Objectives:	**Endpoints/Variables:**
Evaluate the preliminary anti-tumor activity of AC699	Objective response rate (ORR [CR+PR]) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, clinical benefit rate (CBR) (complete response [CR]+partial response [PR]+stable disease [SD] ≥6 months), duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS)

Characterize the pharmacokinetics (PK) profile of a single dose and after multiple doses of AC699	PK parameters
Exploratory Objectives:	**Endpoints/Variables:**
Evaluate the pharmacodynamic effect of AC699 in ERα degradation	Change of ERα expression in tumors from baseline to post-treatment if tumor tissue is available from paired biopsies
Evaluate the relationship between ERα degradation on circulating tumor cells and administration of AC699	Correlation between circulating tumor cell count at baseline and post-treatment, and anti-tumor activity (ORR, CBR, DOR, DCR, and PFS)
Evaluate the relationship between estrogen receptor gene 1 mutation status and anti-tumor activity of AC699	Correlation between estrogen receptor gene 1 mutational status and anti-tumor activity (ORR, CBR, DOR, DCR, and PFS)
Evaluate the relationship between circulating tumor DNA levels and anti-tumor activity of AC699	Correlation between circulating tumor DNA levels at baseline & post-treatment and anti-tumor activity (ORR, CBR, DOR, DCR, and PFS)

1.3 Responsibility

The final statistical analysis of AC699-001 study will be performed by Development Innovations.

2 Study Methods

2.1 Trial Design

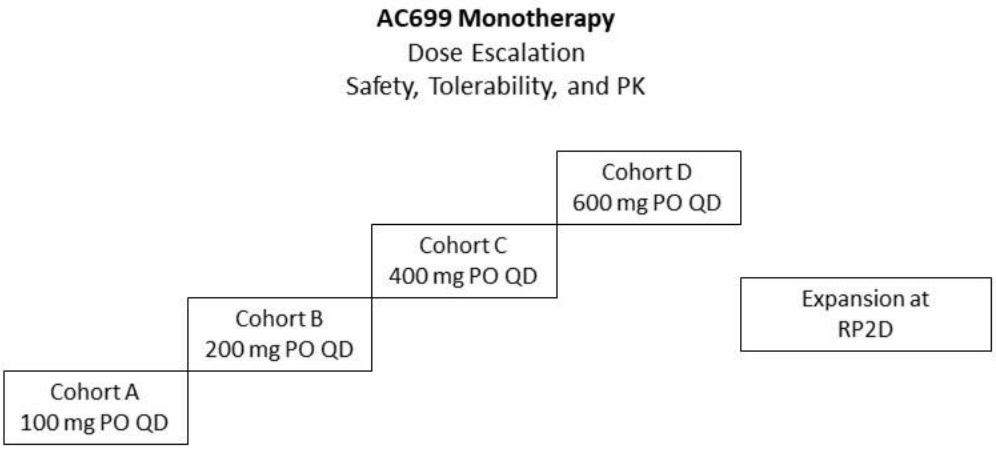
This study is a Phase I, first-in-human, open-label dose-escalation study of AC699 given as a single agent. Pending the totality of data, including but not limited to safety and pharmacokinetics, selected dose level(s) may be expanded to approximately 15 patients (per dose level) to further support the evaluation of the objectives set hereabove. Approximately 60 patients may be enrolled in this study.

AC699 will be administered orally once daily. The starting dose will be 100 mg once daily on a 28-day per cycle schedule. The dose will be increased a maximum of 2-fold per a 3+3 dose escalation design only following approval from the Safety Review Committee (SRC). If suggested by emerging safety or PK findings, or as appropriate based on other data from previous cohorts, alternative dosing levels and/or dosing schedule may be considered. The

study will identify a maximum tolerated dose (MTD) if possible, assessed with safety and tolerability data. The totality of data collected on AC699 treatment may be used to suggest a recommended Phase II dose.

The planned dose escalation study schema is presented in Figure 1. However, dose levels may be adjusted, and additional dose levels may be tested if suggested by the acquired clinical data and is deemed safe by the SRC.

Figure 1 Study Schema



2.2 Randomization

Not applicable.

2.3 Sample Size Justification

The actual number of dose levels to be explored in this study will depend on determination of the non-tolerable dose based on DLTs. The MTD will be defined based on DLTs. Other safety data, as well as PK profiles observed during the conduct of the study and any trends for anti-tumor activity will also be collected. Treatment cycles will occur consecutively as per the Schedule of Assessments. If one patient experiences a DLT at a given dose level, then that dose level will be expanded to 6 patients. Evaluation of a cohort of at least 3 patients completing 1 cycle of treatment (28 days) is required prior to proceeding to the next dose level. In addition, selected dose levels may be expanded to approximately 15 patients (per dose level).

The study will enroll approximately 60 patients, but the actual number will depend on the actual data.

2.4 Hypothesis Testing Framework

Not applicable due to no hypothesis testing being done.

2.5 Statistical Interim Analysis and Stopping Guidance

No formal interim analyses are planned.

2.6 Timing of Final Analysis

The final analysis will take place after the last patient last visit and the database has been locked.

2.7 Timing of Outcome Assessments

Refer to the Schedule of Assessments in the Protocol.

3 Statistical Principles

3.1 *P*-values and Confidence Intervals (CIs)

There are no formal hypotheses for this study. Instead, CIs will be presented.

3.1.1 Confidence Intervals

All CIs will be two-sided 95% exact CIs by Clopper-Pearson unless stated otherwise.

3.2 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol or as mandated by applicable regulations. Protocol deviations will be classified as major/important or minor. Major/important protocol deviations are those that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

The specific protocol deviation criteria will be listed in the Protocol Deviation Management Plan, which is developed by Development Innovations in consultation with the Sponsor. The protocol deviations will be separate from the database and provided by Development Innovations in an Excel file.

Major/important protocol deviations will be listed.

3.3 Analysis Sets

The following analysis sets (populations) will be used in this study:

- Full/Safety Analysis Set (SAF) is defined as all patients who have received at least one dose of study treatment. Patients will be included in the cohort in which they have been treated.
- Efficacy Evaluable Set (EFF) is defined as all patients who have received any dose of study treatment and have at least one adequate post-baseline response assessment.
- PK Analysis Set is defined as all patients who have received at least one dose of study treatment and have at least one sample collection of blood with a measurable concentration of study drug in plasma.

For safety analyses, participants will be summarized under the actual dose level and the analyses will be performed using the Safety Analysis Set.

For efficacy analyses, participants will be summarized under the initial planned dose level and the primary analysis population will be the Efficacy Evaluable Set.

For all other analyses (e.g., demographics and baseline characteristics), participants will be summarized under the actual dose level and the analyses will be performed using the Safety Analysis Set, unless otherwise specified.

3.4 General Analysis Considerations

3.4.1 Deriving Study Day

The following definitions are used for study day:

- *Day* 1 = *Date of first dose of AC699 received*
- *Study Day = Study date – Date of first dose of AC699 received* + 1
  if study date is on or after date of Date of first dose of *AC699* or
  Study Day = Study date – Date of first dose of AC699 received
  if study date is before date of Date of first dose of *AC699*.

3.4.2 Baseline Definition

Baseline value is defined as the last non-missing value prior to the first dose of *AC699*. For assessments without time collected such as physical examination, vital signs, labs, and Eastern Cooperative Oncology Group (ECOG), those that occur on Study Day 1 are considered as pre-dose.

3.4.3 Missing Data

3.4.3.1 Handling of Partial Dates

All start and end dates, when applicable, for safety, efficacy, and exposure to study treatment must be complete dates (i.e., day, month and year must be present). Dates associated with prior medications, prior therapies, and other historical data, whether complete or not, that typically are not involved in direct calculations affecting safety or efficacy will be listed as recorded on the case report form (CRF).

When defining TEAEs, if a partial date is adequate to determine when the onset date of an event occurred relative to first dose of study treatment, then the partial date will be used. If a partial date does not provide enough information to determine the onset date relative to first dosing date, then the adverse event (AE) will be assumed as treatment emergent. AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study treatment.

The following rules provide an algorithm to impute a complete AE start date when determining if an AE is treatment-emergent in the scenario where the start date is missing or partially missing.

- AE start date is missing day and month:
  - If the year is the same as the year of the treatment start date, the day and month of the treatment start date will be assigned to the missing fields.

- If the year is prior to the year of the treatment start date, December 31 will be assigned to the missing fields.
- If the year is after the year of the treatment start date, January 1 will be assigned to the missing fields.

- AE start date is missing day only:
  - If the month and year are the same as the month and year of the treatment start date, the day of the treatment start date will be assigned to the missing day.
  - If the year is before the year of the treatment start date, or if both years are the same but the month is before the month of the treatment start date, the last day of the month will be assigned to the missing day.
  - If the year is after the year of the treatment start date, or if both years are the same but the month is after the month of the treatment start date, the first day of the month will be assigned to the missing day.
- AE start date is completely missing:
  - If the AE end date is complete and after the treatment start date, the treatment start date will be assigned to the missing AE start date.
  - If the AE end date is complete and before the treatment start date, the AE end date will be assigned to the missing AE start date.
  - Otherwise, the AE start date will be assigned to the treatment start date.

[Note: If the AE end date is complete and the imputed AE start date is after the AE end date per the above rules, the AE start date will be imputed as the AE end date.]

Similarly, the same principles as TEAE apply when defining whether a medication is concomitant.

For durations using historical data, the following rules apply:

- Missing months will be imputed as July and missing days will be imputed as the 15th.

  [Note: If the above rule results in a negative duration and only the day is missing, the day will be imputed as the first of the month. If the month is missing, the month will be imputed as the month of first dose of study treatment, and day will be imputed as the first of the month.]

3.4.4 Analysis Visit Windows

No visit windowing will be performed in the analyses. Assessments will be summarized under the visit as entered in the database.

3.4.5 Descriptive Statistics

Summaries will be presented by each dose level and overall unless stated otherwise.

Qualitative variables, such as binary, ordinal, and categorical variables, will be presented as frequencies and percentages. Percentages will be rounded to one decimal place.

Continuous variables will be presented with the number of non-missing values, mean, standard deviation, median, minimum, and maximum values. Minimum and maximum will be displayed with the same accuracy as the original data; mean and median will be rounded to one additional decimal place compared to the original data; standard deviation will be rounded to two additional decimal places compared to the original data.

If data are available for less than three participants, no summary statistics other than number of non-missing values, minimum, and maximum will be presented. The remaining summary statistics will be presented as "NC" (Not Calculable).

3.4.6 Graphical Presentation

Data may be presented graphically where appropriate.

3.4.7 Analysis Software

Analyses will be performed using SAS® version 9.4 or higher.

3.5 Analysis of Efficacy Variables

3.5.1 Time-to-Event Variables

The proportion of events and censored observations will be summarized with frequency and percentage. Medians of DoR and PFS along with the 95% CIs will be calculated from the Kaplan-Meier (KM) analysis. Q1 and Q3 will also be displayed.

The CIs will be calculated using the Brookmeyer and Crowley method after applying the log-log transformation (Kalbfleisch et al, 1980).

KM curves will be produced to provide a visual description of the differences between the dose levels.

Sample SAS code is provided in Appendix A: Sample SAS Code.

3.5.2 Analysis of Response Rate

The ORR, CBR, and DCR will be summarized with frequency and percentage with a 95% CI by Clopper-Pearson.

Sample SAS code is provided in Appendix A: Sample SAS Code.

4 Trial Population

4.1 Participant Disposition

Participant disposition will be summarized by frequency and percentage for all participants.

The following categories will be tabulated:

- Participants screened
- Participants assigned to AC699
- Participants who received AC699

  - Participants with ongoing AC699 treatment at data cut-off
  - Participants who discontinued AC699, and reasons for discontinuation (from CRF)
- Participants ongoing study at data cut-off
  - Participants who discontinued study, and reasons for discontinuation (from CRF)
- Participant inclusion to analysis sets: Full, Safety, and Efficacy.

Participants in each analysis set will be summarized by frequency for all participants.

Participant disposition data will be listed, inclusive of treatment discontinuation, study discontinuation, eligibility, and analysis set inclusion.

4.2 Baseline Participant Characteristics

Participants with missing categorical data will be tabulated as a missing category and will be included in the denominator for percentages overall.

Baseline participant characteristics will be listed, inclusive of demography, clinical characteristics, medical history, and disease characteristics. Tables will be presented as applicable.

4.2.1 Demographic Characteristics

The following demographic characteristics will be summarized:

- Age (years) at Informed Consent, calculated as *the difference in years between the Date of Informed Consent and the Year of Birth,* summarized continuously and categorically: 18 – <50, ≥50 - <65, ≥65
- Sex (Female, Male)
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)

4.2.2 Clinical Characteristics

The following baseline clinical characteristics will be summarized:

- ECOG performance status
- ECOG performance status at post-baseline assessments
- ECHO screening outcome
- Tumor (radiographic) assessments
- Laboratory test (HIV, HBV, and HCV) outcome
- Vital signs including weight and height

4.2.3 Medical History

Ongoing medical history will be summarized by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or higher.

4.2.4 Disease Characteristics

The following baseline participant disease characteristics will be summarized:

- Time from initial diagnosis of disease to enrollment (months), calculated as (*Date of First Dose of AC699 – Date of Initial Diagnosis + 1) / 30.4375* (refer to section 3.4.3.1 for date imputation rules if date of initial diagnosis is partial)
- ESR1 mutation status

4.3 Prior Anticancer Therapy

Prior anticancer therapies (including systemic therapy, radiation, and procedures) will be summarized separately by frequency and percentage of participants who received each.

Systemic therapies will be coded and subcategorized by class using the World Health Organization (WHO) Drug Dictionary Global September 2021 or higher. Radiation and surgeries will be coded using MedDRA version 25.0 or higher.

All prior anticancer therapies will be listed.

4.4 Prior and Concomitant Medications

All medications will be coded using the WHO Drug Dictionary Global September 2021 or higher. Prior medications are those taken before the start of study treatment. Concomitant medications are those taken after the start of study treatment, including those that started prior to study treatment but were taken on/after start of study treatment. A given medication may be both prior and concomitant. Transfusions can be prior or concomitant medication but will not be considered as a procedure.

The frequency and percentage of participants who received concomitant medications will be summarized by Anatomical Therapeutic Chemical Classification and preferred name.

All prior and concomitant medications will be listed.

4.5 Concomitant Procedures

All concomitant procedures will be listed and coded using MedDRA version 25.0 or higher.

4.6 Subsequent Anticancer Therapy

Anticancer therapy initiated after patient's discontinuation from the study treatment will be summarized by frequency and percentage of participants.

- Participants who received subsequent systemic therapy(ies)
- Participants who received subsequent procedure(s)
- Participants who received subsequent radiation

All subsequent anticancer therapies will be listed.

5 Efficacy Analysis

All efficacy data will be presented in listings. Tables and figures will be presented as applicable. All efficacy analyses will be performed using the EFF as a whole and subdivided by ESR1 mutational status.

The secondary endpoints are ORR, CBR, DoR, DCR, PFS.

The exploratory endpoints are as follows:

1. Change of ERα expression in tumors from baseline to post-treatment in paired biopsies.
2. Correlation between circulating tumor cell count at baseline and post-treatment and anti-tumor activity (ORR, CBR, DOR, DCR, and PFS)
3. Correlation between estrogen receptor gene 1 mutational status and anti-tumor activity (ORR, CBR, DOR, DCR, PFS).
4. Correlation between circulating tumor DNA levels at baseline and post-treatment and anti-tumor activity (ORR, CBR, DOR, DCR, PFS).

5.1 Endpoint Foundations

5.1.1 Objective Tumor Response

Tumor response will be evaluated using RECIST 1.1 criteria (Eisenhauer, et al 2009), every 8 weeks (± 5 days) for the first year of treatment, and then once every 16 weeks (± 5 days) thereafter or until disease progression (as determined by the investigator).

The response categories are as follows:

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
- Progressive disease (PD)

Not Evaluable (NE)

The overall response to each assessment will be determined by the Investigator.

5.1.2 Time-to-Event Variables

Time-to-event variables are defined as:

Time-to-Event (months) = (End Date – Start Date + 1) / 30.4375

DOR = (Earliest Date of Progression or Death – Date of First Documented CR of PR + 1)/30.4375.

Start Dates

For all time to event variables other than DoR, the date of first dose of AC699 will be used as the start date.

The start date for DoR will be the date of first PR or CR, which has been subsequently confirmed.

End Dates

For DoR and PFS, the following rules will be used to derive the end dates for these endpoints:

- Events always take precedence to Censoring
- If multiple event dates are applicable, the earliest date will be used.
- If multiple censoring dates are applicable, the latest date will be used.

Table 2 shows data sources that can be used to determine end dates.

Table 2: Data Sources for End Dates

Date	Data Source
Date of Death	Death CRF
Date of Progression	Using RECIST 1.1 criteria, the earliest of the dates from the components that triggered the overall PD response from the Target Lesions, Non-target Lesions and New Lesions CRFs.
Date of Last Evaluable Tumor Assessment	The latest data from the Target Lesions, Non-Target Lesions, and New Lesions CRFs reflecting the overall response, where the overall response is evaluable (i.e., not missing or NE), prior to further subsequent anticancer therapy if initiated.
Date of Subsequent Anticancer Therapy	The earliest date is from the Subsequent Systemic Therapy, Subsequent Radiation, and Subsequent procedure CRFs.

5.1.3 Participant Follow-up

Participants are expected to be followed from the date of first dose of AC699 until the end of the study or death, whichever occurs first. Participants who discontinue the study treatment will continue to be followed up for disease progression (after the 30-day safety follow-up) through the end of the whole study as per the Protocol section 7.4.3: follow-up visits will be performed every 8 weeks (± 5 days) for the first year after treatment ends and then every 16 weeks (±5 days) thereafter until disease progression based on RECIST 1.1 or another withdrawal criterion is met:

- Start of a new anti-cancer therapy
- Lost to follow-up

- Death
- Patient withdrawal
- End of the whole study

5.2 Endpoints

5.2.1 Best Overall Response

Best overall response (BOR) is defined as per RECIST 1.1 and will be calculated as the best response recorded from date of first dose of AC699 up until evidence of progression per RECIST 1.1.

The frequency and percentage of participants with each response will be summarized.

Confirmation of response is required (i.e., consecutive CRs, consecutive PRs or 1 CR and PR at least 4 weeks apart).

See Table 3 for scenarios of overall response.

Table 3: Best Overall Response with Confirmation of CR and PR Required

Overall Response		BEST Overall Response
Initial	**Subsequent**	
CR	CR	CR
CR	PR	SD, PD, or PR*
CR	SD	SD if minimum criteria for SD duration met, otherwise PD
CR	PD	SD if minimum criteria for SD duration met, otherwise PD
CR	Missing	SD if minimum criteria for SD duration met, otherwise NE
PR	PR	PR
PR	CR	PR
PR	SD	SD
PR	PD	SD if minimum criteria for SD duration met, otherwise PD
PR	Missing	SD if minimum criteria for SD duration met, otherwise NE

Abbreviations: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

*If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since the disease must have reappeared after CR). Best response would depend on whether minimum duration of SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

When SD is believed to be the BOR, SD must have met the minimum interval of 7 weeks (8 weeks - 1 week for early assessments within window) since start of AC699. If it does not

meet the minimum interval and there are no subsequent assessments indicating the participant had a PD, the BOR would be NE.

If a CR or PR cannot be confirmed, the BOR is dependent on the subsequent timepoint response. If the subsequent timepoint response is NE or there is no subsequent timepoint response, the BOR would be SD provided the minimum criteria for SD duration is met, otherwise NE. The unconfirmed responses (unconfirmed CR and unconfirmed PR) will be summarized as a sub-category of SD, and SD not meeting the minimum interval of 7 weeks (8 weeks – 1 week for early assessments within window) will be summarized as a sub-category of NE.

5.2.2 Objective Tumor Response

The following endpoints, along with their 95% CI, will be presented based on the objective tumor response:

- ORR = proportion of participants with a BOR of confirmed CR or PR.
- CBR = proportion of participants with a confirmed CR, or PR or a SD for ≥ 6 months according to the RECIST 1.1 criteria, where duration of SD is defined the date of last SD assessment - the start date of study drug.
- DCR = proportion of patients with a best overall response of CR, PR, or SD (where SD is >= 6 months).

The denominator will be the number of participants in the EFF analysis set, and includes participants with a BOR of NE.

5.2.3 Duration of Response

Only participants with measurable disease whose BOR is CR or PR will be included in the analysis.

DoR (months) is defined as the time from first documentation of response (CR or PR, subsequently confirmed) to the first documentation of disease progression or death due to any cause. Participants who have neither progressed nor died will be censored.

Refer to **Table 4** for the event/censoring rules and dates to be used.

5.2.4 Progression-Free Survival

PFS (months) is the time from date of first dose of AC699 to the first documentation of disease progression or death due to any cause. Participants who have neither progressed nor died will be censored.

Refer to **Table 4** for the event/censoring rules and dates to be used.

Table 4: Progression Situations and Event/Censoring Rules

Situation	Date of Event or Censoring	Outcome
No baseline assessment	Date of first dose of AC699	Censored

Situation	Date of Event or Censoring	Outcome
Progression documented between scheduled visits, or after one missed or non-evaluable assessment	Date of progression (see **Table 2**)	Event
No progression	Date of last evaluable tumor assessment (see **Table 2**)	Censored
Treatment discontinuation for undocumented progression (e.g., clinical progression based on investigator claim)	Date of last evaluable tumor assessment (see **Table 2**)	Censored
Treatment discontinuation for adverse event or other reason	Date of last evaluable tumor assessment (see **Table 2**)	Censored
Further anticancer therapy started	Date of last evaluable tumor assessment (see **Table 2**)	Censored
Death before first PD assessment	Date of last evaluable tumor assessment (see **Table 2**)	Event (PFS)
Death before the next scheduled tumor assessment, or after one missed tumor assessment	Date of death (see **Table** 2)	Event (PFS)
Death, or progression after two or more missed tumor assessments	Date of last evaluable tumor assessment (see **Table 2**)	Censored

The rule to determine whether there are at least two missing tumor assessments is based on the interval between the last evaluable tumor assessment date and the event date. If the interval is greater than twice the protocol-specified interval between the tumor assessment plus the protocol-allowed time window around the assessment, then the number of missing assessments is two or more.

For the first 52 weeks, tumor assessments are to be performed every 8 weeks (± 5 days); therefore, the threshold will be 18 weeks. After the first 52 weeks, tumor assessments are to be performed every 16 weeks (± 5 days); therefore, the threshold will be 34 weeks.

6 Safety Analysis

All safety data will be presented in listings. Tables and figures will be presented as applicable.

6.1 Exposure to Study Treatments

Exposure to AC699 will be summarized in the following ways:

- Total Treatment Duration (days), calculated as *Date of Last AC699 Dose – Date of First AC699 Dose + 1.*
- Actual Duration of Exposure (days) calculated as (*Date of Last AC699 Dose – Date of First AC699 Dose + 1, excluding days where AC699 dose was interrupted, and the participant successfully returned to receiving AC699 or a full AC699 dose was missed.*
- Relative Dose Intensity (RDI) (%)

The number of participants with dose interruptions, dose modifications (increased, not changed, reduced, interrupted, withdrawn), and intra-patient dose-escalation together with the reason of interruption/modification will be summarized by frequency and percentage.

Note: Dose interruptions will be summarized up until the last dose where participant received the study treatment. If the last dosing record(s) show an interruption, those will not be included in the summary.

Any overdoses will be listed.

6.1.1 Relative Dose Intensity (%)

$$RDI\ (\%) = 100\% * \frac{Actual\ Dose\ Intensity\ (ADI)}{Planned\ Dose\ Intensity\ (PDI)}$$

Where ADI and PDI are defined below:

6.1.1.1 Dose Calculations

- $PDI\ \left(\frac{mg}{day}\right) = \frac{\sum_{j=1}^{m} Planned\ Dose\ (mg)_j}{\sum_{j=1}^{m-1} Planned\ Cycle\ Length\ (days)_j + Last\ Cycle\ Length\ (days)}$

  [Note: Planned Dose is the initial per-protocol dose assigned to the participant.]

- $ADI\ \left(\frac{mg}{day}\right) = \frac{\sum_{j=1}^{m} Actual\ Dose\ (mg)_j}{\sum_{j=1}^{m} Actual\ Cycle\ Length\ (days)_j}$

Where j =1, 2, 3, m are the indices for the cycle, and the cycle length is defined as follows:

Except for last cycle,;

Cycle Length (days) = 28

Since participants may discontinue the study treatment at any time, the last cycle may not be a complete cycle of treatment, therefore it needs special attention.

Last Cycle Length (days) = (min [Date of Last AC699 Dose, Date of Death, Date of Data Cut-off] – Date of First AC699 Dose in Last Cycle + 1)

6.2 Adverse Events

A TEAE is defined as an AE with an onset or worsening grade on or after the first dose of study treatment up to 30 days after the end of treatment or up to the start of other anticancer

therapy (which occurs earlier). AEs will be graded using the National Cancer Institute - Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 where applicable and coded using MedDRA version 25.0 or higher.

An overall summary of on treatment AEs will present the frequency and percentage of participants by the following categories:

- Any TEAEs
- Any AC699-related TEAEs
- Any grade ≥3 TEAE
- Any AC699-related grade ≥3 TEAE
- Any TEAE leading to death
- Any AC699-related TEAE leading to death
- Any treatment-emergent serious adverse events (SAE)
- Any AC699-related treatment-emergent SAEs
- Any TEAE leading to discontinuation of AC699
- Any TEAE leading to interruption of AC699
- Any TEAE leading to reduction of AC699

Additional summaries for all of the above categories, will present the frequency and percentage of participants experiencing at least one event by MedDRA SOC and MedDRA preferred term (PT).

Additional summaries for the following categories will present the frequency and percentage of participants experiencing at least one event by MedDRA SOC, MedDRA PT, and worst CTCAE grade:

- Any TEAEs
- Any AC699-related TEAEs

Specific listings, with all relevant information, will be provided for TEAEs, SAEs, TEAEs with an outcome of death, and TEAEs leading to discontinuation of AC699.

6.3 Participant Deaths

Death and primary cause of death will be summarized by frequency and percentage.

All death data will be provided in listings.

6.4 Laboratory Parameters

Descriptive statistics for each lab parameter (chemistry, hematology, urinalysis, and coagulation) at baseline, each scheduled post-baseline assessment, and changes from baseline to scheduled post-baseline assessments will be presented.

Abnormal laboratory values will be graded according to CTCAE version 5.0, if applicable. Clinical descriptions will not be considered when grading; grading will only be based on numeric results and thresholds.

A shift table will be presented for each laboratory parameter to display the shift from baseline to the maximum post-baseline CTCAE grade within 30 days post-treatment, inclusive of unscheduled post-baseline assessments. For parameters that can be graded in either direction

(both high and low), the shift in both directions will be presented. For parameters that cannot be graded per CTCAE, shift tables based on the normal ranges will be presented for both the minimum and maximum values within 30 days post-treatment. Normal lab ranges will be based on local lab ranges.

A listing of potential Hy's Law cases will be provided (defined as alanine or aspartate aminotransferase > 3 × upper limit of normal with concurrent total bilirubin > 2 × upper limit of normal without findings of cholestasis [alkaline phosphatase <2 × upper limit of normal]).

All lab data will be provided in listings. Urinalysis will not be summarized and only listed.

6.5 Electrocardiogram Assessments

12-lead electrocardiogram (ECG) QTcF assessments are collected in triplicate. The values will be averaged for each visit/timepoint prior to analysis. Descriptive statistics for the average of the QTcF assessments at baseline, each scheduled post-baseline assessment, and change from baseline to each scheduled post-baseline assessment will be presented.

Maximum observed QTcF (msec) results post-baseline and maximum change from baseline will be tabulated by the following categories:

- Maximum Observed QTcF
  - >480 - ≤500
  - >500
- Maximum Change from Baseline QTcF
  - >60

All ECG data will be provided in listings.

6.6 Vital Signs

Descriptive statistics for weight (kg), pulse rate (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and temperature (C) at baseline, each scheduled post-baseline assessment, and changes from baseline to scheduled post-baseline assessments will be presented. In the event there is more than one assessment per scheduled timepoint, the average of the records will be used in the summary.

All vital signs data will be provided in listings.

6.7 ECOG Performance Status

All ECOG data will be summarized as well as provided in listings.

6.8 Physical Examinations

All physical examination data will be summarized as well as provided in the listing.

6.9 Other Safety Parameters

Additional safety parameters including hepatoxicity – liver assessment, and post-menopausal status will be listed only.

7 Other Analyses

7.1 Pharmacokinetic Analysis

Plasma concentrations of AC699 will be summarized descriptively at each timepoint.

Plasma concentrations of AC699 will be used to calculate the PK parameters. These parameters will be listed by individual patient and summarized by descriptive statistics (means, medians, ranges, standard deviations, and coefficients of variation as appropriate) by cohort.

7.2 Pharmacodynamic Analysis

Change of ERα expression in tumors from baseline to post-treatment if tumor tissue is available from paired biopsies will be presented. Biomarker and biopsy data will be listed.

The following biomarker data will be evaluated at baseline and post-baseline assessments:

- ERα expression in tumors
- Circulating tumor cell counts
- Estrogen receptor gene 1 mutational status
- Circulating tumor DNA

For each of the above, actual and change from baseline values will be summarized with descriptive statistics at each timepoint and will be evaluated for correlation to anti-tumor activity in ORR, CBR, DOR, DCR, and PFS.

All biomarker data will be listed.

8 Changes from Analyses Specified in the Protocol

Not applicable.

9 References

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10 Appendices

Appendix A: Sample SAS Code

10.1 Time-to-Event Analysis

To obtain the median, CI, and Q1 and Q3 estimates in SAS,

```
proc lifetest data=<DATASET NAME> method=km conftype=loglog
alpha=<ALPHA>;
        by trtp;
        time aval*cnsr(1);
        ods output quartiles=<DATASET NAME>;
        run;
```

10.2 Analysis of Response Rate

To obtain the CI in SAS by Clopper-Pearson,

```
proc freq data=<DATASET NAME>;
        by trtp;
        tables orr/binomial(level="1") alpha=<ALPHA>;
        weight count/zeros;
        exact binomial;
        ods output binomial=<DATASET NAME>;
        run;
```