cellceutix

CLINICAL PROTOCOL

CTIX-KEV-201

A Phase 2 study of Kevetrin (thioureidobutyronitrile) in Subjects with Platinum-Resistant/Refractory Ovarian Cancer

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PROTOCOL SYNOPSIS

Name of Sponsor/Company: Cellceutix Corporation

Name of Finished Product: Kevetrin

Name of Active Ingredient: Thioureidobutyronitrile

Title of Study:

A Phase 2 study of Kevetrin (thioureidobutyronitrile) in Subjects with Platinum-Resistant/Refractory Ovarian Cancer

Study Centers:

Approximately 3 sites in the United States

Number of Subjects Planned:

Approximately 10 study participants with platinum-resistant/refractory ovarian cancer

Study Duration per subject:

Approximately 10 weeks: 4 weeks for screening, a 3-week Kevetrin cycle, followed by a 3-week follow-up

Phase of Development:

Phase 2

Primary Objective(s):

- To evaluate safety and tolerability of two different treatment regimens of Kevetrin when administered to subjects with platinum-resistant/refractory ovarian cancer
- To evaluate changes in biomarkers and molecular signatures related to cell proliferation and cell death from tumor tissue, ascites fluid, and peripheral blood after treatment with Kevetrin to subjects with platinum-resistant/refractory ovarian cancer

Secondary Objectives:

- To evaluate the objective tumor response to treatment with Kevetrin when administered to subjects with platinum-resistant/refractory ovarian cancer
- To evaluate the pharmacokinetics of Kevetrin after administration to subjects with platinum-resistant/refractory ovarian cancer

Design and Methodology:

This is an open label, dose-escalation trial to study the safety, biomarker changes (including modulation of p53), objective tumor response changes, and pharmacokinetics following administration of two different treatment regimens of Kevetrin over a 3-week period to subjects with platinum-resistant/refractory ovarian cancer. Following the 3 weeks of Kevetrin dosing, subjects are to be followed up for 3 weeks after completion of Kevetrin treatment. Standard of care treatment, as medically appropriate and per local

guidelines, outside of this study protocol can commence after the collection of the post-Kevetrin treatment biomarker samples (collected on Day 21±1 day).

The patient population recruited into this study includes those ovarian cancer patients that have platinum resistant/refractory disease, defined as disease progression/relapse within 6 months following the last administered dose of platinum therapy (resistant), or lack of response or disease progression while receiving the most recent platinum based therapy (refractory), respectively. Patients may or may not have had additional treatment (e.g., Doxil) prior to entry in this study.

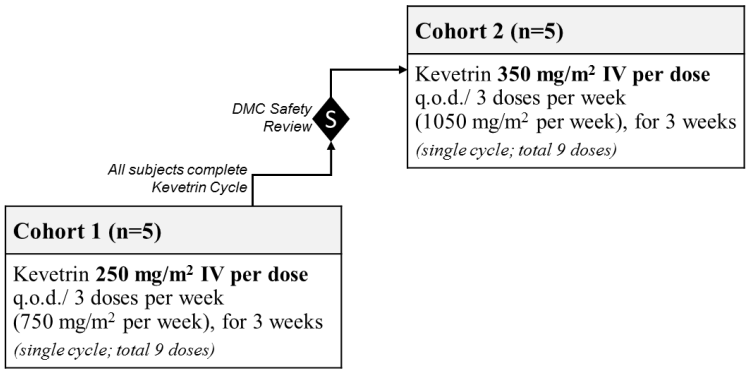
A total of approximately 10 study participants are planned to be enrolled in two cohorts of approximately 5 subjects per cohort, with enrollment in a sequential, dose-escalating fashion. Investigators and subjects will be aware of the treatment cohort into which they are recruiting. Cohort details and the planned doses are listed below:

Cohort 1 (n=5) **Kevetrin Cycle**
Kevetrin 250 mg/m^2 IV per dose every other day (q.o.d.)/ 3 doses per week (750 mg/m^2 per week), for 3 weeks (single cycle; total 9 doses)
Follow-up
For 3 weeks after Kevetrin treatment ends

Cohort 2 (n=5) **Kevetrin Cycle**
Kevetrin 350 mg/m^2 IV per dose every other day (q.o.d.)/ 3 doses per week (1050 mg/m^2 per week), for 3 weeks (single cycle; total 9 doses)
Follow-up
For 3 weeks after Kevetrin treatment ends

Cohorts 1 and 2 will be conducted in a sequential fashion, with safety data from cohort 1 evaluated by an independent Data Monitoring Committee (DMC). The DMC will make appropriate recommendations based on the available safety data as regards the intent of progressing to the higher dose cohort 2.

Study Design Schematic



If 2 of the 5 subjects in cohort 1 experience a dose-limiting toxicity (DLT) adverse event, the DMC will consider reducing the Kevetrin dose regimen for cohort 2 by 25%.

Dependent on the DLT adverse events experienced, the dose in cohort 1 may be repeated, or reduced. If no new or unexpected safety concerns are identified by the DMC safety review, enrollment of subjects to cohort 2 with a higher dose regimen of Kevetrin will commence.

If a subject experiences a DLT adverse event during treatment with Kevetrin, treatment with Kevetrin will be stopped and the subject will be appropriately followed-up to document the course of the abnormality until returned to a normal or baseline level, or until the adverse event/abnormality is deemed clinically stable. For any DLT adverse event, the Investigator must immediately notify the Medical Monitor by telephone and follow-up in writing.

For this study, a DLT adverse event is defined as follows, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03:

Hematologic toxicity:

- Grade 3 or 4 febrile neutropenia or Grade 4 neutrophil count decreased of ≥ 7 days' duration
- Grade 4 thrombocytopenia or grade 3 thrombocytopenia complicated by hemorrhage

Nonhematologic toxicity:

- Any grade ≥ 3 nonhematologic toxicity unless there is clear alternative evidence that the adverse event was not caused by Kevetrin
- Grade 3 diarrhea, nausea, or vomiting may be excluded from DLT classification provided that the maximum time limit for supportive measures is 48 hours

A subject studied under this clinical protocol will commence with a screening period of up to 4 weeks, a treatment cycle with Kevetrin (3 weeks), followed by a 3-week follow-up.

Safety and tolerability will be assessed by ascertainment of AEs, physical examinations, and results of clinical laboratory testing, and vital signs assessments. Tumor measurement assessments, by computed tomography (CT) scan, will be taken pre- and post-Kevetrin treatment. Tumor biopsies and ascites fluid (if available), and blood samples for biomarkers will also be collected pre- and post-Kevetrin treatment. Serial blood samples for determination of plasma Kevetrin concentrations will be collected on Study Days 1 and 5, from 2 hours pre-infusion out to 24 hours post-infusion completion.

Any discontinuation of study treatment (Kevetrin) is to be reported by the Investigator to the Medical Monitor. Any subject that discontinues study treatment is to be followed up for (approximately) 3 weeks after the end of treatment. Subjects who withdraw from the study or discontinue treatment for reasons other than a demonstrated intolerance to Kevetrin or a DLT may trigger additional subjects to be enrolled, to obtain 5 completed subjects in each cohort.

Inclusion Criteria:

1. Evidence of a personally signed and dated written informed consent to participate in the clinical study
2. Non-pregnant female adults at least 18 years of age at time of informed consent

3. Histologically confirmed serous epithelial ovarian cancer with peritoneal metastases
4. Platinum resistant/refractory disease, defined as disease progression/relapse within 6 months following the last administered dose of platinum therapy (resistant), or lack of response or disease progression while receiving the most recent platinum based therapy (refractory), respectively
5. Measurable disease, as determined by radiologist evaluator, with at least 1 unidimensional measurable lesion (target lesion) by RECIST v.1.1 that has not previously been irradiated or biopsied
6. Presence of non-target lesions that have not previously been irradiated or biopsied; to allow for collection of needle-biopsies at Screening and after completion of Kevetrin treatment
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
8. Adequate hematologic and organ function as confirmed by laboratory values at Screening:
    a. Bone marrow function: Absolute neutrophil count (ANC) ≥ 1500 cells/μL (with no evidence that this ANC was induced or supported by granulocyte colony stimulating factors)
    b. Hemoglobin ≥ 9 g/dL (with no RBC transfusions within 7 days of Screening)
    c. Platelets ≥ 100,000 cells/μL (with no evidence that this platelet count was induced or supported by a platelet-stimulating agent)
    d. Renal function: creatinine ≤ 1.5 x ULN
    e. Hepatic function: total bilirubin ≤ 1.5 x ULN; ALT and AST ≤ 3 x ULN; alkaline phosphatase ≤ 2.5 x ULN
    f. Neurologic function: neuropathy (sensory and motor) ≤ CTCAE Grade 1
    g. Coagulation status: prothrombin time (PT) ≤ 1.5 ULN or INR within normal limits; and partial thromboplastin time (PTT) ≤ 1.2 × ULN
9. Women of child-bearing potential are required to use effective contraception throughout the study period. Effective contraception methods include:
    a. Total abstinence (if this is the usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. (Subject must agree to use contraception should they become sexually active while on the study.)
    b. Surgical sterilization (hysterectomy and/or bilateral oophorectomy) or tubal ligation at least six weeks before start of study treatment.
    c. Male partner sterilization, occurring at least 6 months prior to screening. For female subjects on the study, the vasectomized male partner should be their sole partner.

d. Double barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

e. Oral*/ injected/ implanted/ transdermal hormonal contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), e.g., hormone vaginal ring.

f. Intrauterine device or intrauterine system.

*Stable oral contraception use (on the same pill) for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 consecutive months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical hysterectomy and/or bilateral oophorectomy or tubal ligation at least six weeks ago.

10. Estimated life expectancy of at least 6 months, in the Investigator's opinion
11. Willing and able to comply with scheduled visits, study assessments and laboratory tests, and other study procedures

Exclusion Criteria:

1. Unwilling to allow removal of tumor biological samples for analysis, i.e., biopsies of tumor lesions, and/or collection of ascites fluid from abdominal ascites (if present)
2. Non epithelial tumor, including malignant mixed Müllerian tumors without high grade serous component, or ovarian tumors with low malignant potential (i.e., borderline tumors)
3. Known presence of central nervous system metastases
4. Presence of tumor metastases causing significant pleural disease/effusion unilaterally or bilaterally (significant pleural effusion is defined by need for thoracentesis more frequently than once every 21 days)
5. Presence of ascites that requires paracentesis more frequently than once every 21 days.
6. A history of another primary cancer that has been active or treated within the past 3 years prior to start of study treatment, with the exception of adequately treated/resected: basal cell or squamous cell skin carcinoma or actinic keratoses; or carcinoma in situ of the breast or of the cervix; or non-invasive malignant colon polyps
7. Persistent toxic effects with severity of CTCAE grade 2 or greater (excluding alopecia) caused by previous treatment
8. History of arterial or deep venous thromboembolism within the 12 months prior to enrollment
9. Clinically significant cardiac disease, including:

a. Myocardial infarction or unstable angina < 6 months prior to enrollment
b. New York Heart Association (NYHA) Grade II or greater congestive heart failure
c. Cardiac arrhythmia requiring medication (does not include asymptomatic atrial fibrillation with controlled ventricular rate)

10. Electrocardiogram (ECG) obtained at Screening which shows QTc prolongation or other medically relevant abnormalities which may affect subject safety or interpretation of study results
11. At a higher than average risk, in the Investigator's opinion, of bowel perforation (e.g., symptoms of partial or complete bowel obstruction, recent (within 6 months) history of fistula or bowel perforation, requirement for total parenteral nutrition and continuous hydration)
12. Active or chronic recurrent systemic infections that require continuous antimicrobial therapy during the Kevetrin study period
13. Past medical history of infection with HIV, hepatitis B or hepatitis C
14. Ongoing or recent history of any other uncontrolled and/or clinically significant systemic disease or condition which, in the Investigator's medical opinion, should exclude participation in the study
15. Less than 3 weeks between major surgery and planned start of study treatment; major incisions must have healed
16. Less than 4 weeks since last treatment for ovarian cancer
17. Any investigational or experimental therapy or procedure or participation in any interventional trial within 4 weeks or 5 half-lives (whichever is longer) prior to start of study treatment
18. Women of child-bearing potential who are pregnant or nursing (lactating)
19. Previous participation in a clinical study of Kevetrin
20. History of alcohol or substance abuse, unless in full remission for more than 6 months prior to start of study treatment
21. Any other severe acute or chronic medical or psychiatric condition or test abnormality(ies) that, in the Investigator's opinion, puts the subject at significant risk, could confound the study results, or may interfere significantly with the subject's participation in the study

Test Product, Dose, and Mode of Administration:

Kevetrin (thioureidobutyronitrile) will be supplied by the Sponsor in 5 mL glass vials, with each vial containing 200 mg Kevetrin (lyophilized).

Kevetrin will be reconstituted in water for injection (WFI) and placed in a non-PVC infusion bag containing 250mL of 0.9% Sodium Chloride Injection USP (Braun L8002 or equivalent, provided by the site). A low sorbing (PVC-free) IV infusion set equipped with an in-line

0.2-µm pore size filter (CareFusion / Alaris 11532269 or equivalent, provided by the site) will be attached to the non-PVC bag.

Cohort 1: Kevetrin 250 mg/m^2 IV per dose every other day (q.o.d.)/ 3 doses per week (750 mg/m^2 per week), for 3 weeks

Cohort 2: Kevetrin 350 mg/m^2 IV per dose every other day (q.o.d.)/ 3 doses per week (1050 mg/m^2 per week), for 3 weeks

Nine (9) doses of Kevetrin are to be divided and administered every other day (q.o.d.) as three doses split over each 7-day period, for a single (21-day) treatment cycle.

Doses 1, 2, and 3 are each separated by approximately 48 hours; Dose 4 is administered approximately 72 hours after Dose 3. Doses 5 and 6, and doses 8 and 9 are administered approximately 48 hours after doses 4 and 7, respectively. The separation between doses 6 and 7 is approximately 72 hours.

Each Kevetrin dose is to be administered intravenously over a duration of no less than 180 minutes (3 hours). A pre-medication regimen is recommended for administration within 30 to 60 minutes prior to initiation of each Kevetrin infusion.

Data Analysis:

Details of the statistical methodology for summary and analyses of the data collected in this study will be prepared separately from this protocol in a statistical analysis plan (SAP).

All statistical analyses will be performed using SAS version 9.3 or higher.

Safety endpoints: AEs, SAEs, dosing compliance, any discontinuations from Kevetrin treatment due to toxicities, and changes in laboratory values, vital signs, ECGs, and ECOG performance status, and incidence of clinical laboratory, blood pressure, heart rate, temperature and respiration rate, and ECG abnormalities.

Biomarker endpoints:

- Change from baseline in tumor tissue markers and/or cellular markers (in cells separated from ascites fluid) including, but not limited to, changes in transcriptional and translational pathways leading to anticancer activitiy such as p53signaling pathway, miRNA-34a, and other tumor activity markers.
- Change from baseline in ascites fluid markers and/or plasma markers, including CA-125, CCL2, miRNA-25, miRNA-27a, and miRNA-1274b.

Tumor measurement endpoints:

- Number of subjects in each RECIST response category (complete response, partial response, stable disease or progressive disease)
- Number of subjects with confirmed objective tumor response according to RECIST
- Change from baseline in tumor size (defined as sum of the longest diameters as measured among all target lesions)

All safety data, demographic and baseline characteristics, will be summarized descriptively through appropriate data tabulations, descriptive statistics, and categorical summaries.

Biomarker and tumor measurement endpoints will be summarized with descriptive statistics by cohort and visit. Summary statistics for continuous variables will include N, mean, standard deviation, minimum, median, maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

Pharmacokinetic parameters will be estimated from those subjects with a sufficient number of plasma concentrations to allow for such estimation.

Interim analyses may be conducted to support decision making concerning the current clinical study, the Sponsor's clinical development projects in general or in case of any safety concerns. As this is an open label study, safety and efficacy data (individual and aggregate) will be reviewed by the Sponsor on an ongoing basis throughout the study.

A planned interim analyses for investigating safety will be conducted after completion of cohort 1. Safety data will be provided to an independent DMC for review. The DMC will make appropriate recommendations based on the available safety data as regards the intent of progressing to the higher dose cohort 2. A full review by the Sponsor of all data from participants in cohort 1 after cohort completion will also be conducted.