STATISTICAL ANALYSIS PLAN

Feasibility IB Trial of Paclitaxel/Carboplatin + Galunisertib. (A Small Molecule Inhibitor of the Kinase Domain of Type 1 TGF-B Receptor) in Patients with Newly Diagnosed, Persistent or Recurrent Carcinosarcoma of the Uterus or Ovary

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Study Products:	Galunisertib

Abbreviations

cOR	Clinical response
CR	Complete response
CT	Carboplatin/paclitaxel
EOS	End of study
GB	Galunisertib
OS	Overall survival
pCR	Pathological complete response
PFS	Progression free survival
PR	Partial response
SAP	Statistical analysis plan

Contents

1. **Objectives**
    a. **Primary Objectives**
        i. To determine the feasibility of delivering 4 cycles of carboplatin/paclitaxel (CT) in combination with galunisertib (GB) to patients with gynecologic carcinosarcoma.

    b. **Major Secondary Objectives**
        i. To determine the frequency and severity of adverse events as assessed by the CTCAE v4.
        ii. To determine the progression free survival (PFS) and overall survival (OS) of patients receiving combination CT + GB.
        iii. To ascertain the pharmacokinetic profile of GB when given in a combination regimen with CT.

    c. **Exploratory Research Objectives**
        i. To determine if H-score criteria (% of cells and intensity) of IHC nuclear phospho-smad2/3 levels after cycle 1 are associated with response to galunisertib therapy.
        ii. To evaluate the mRNA expression Level of EMT markers along with the TGFβ1 in the GB pre-treated and post-treated patient samples.

2. **Endpoints**
    a. **Primary**
        i. Completion of 4 cycles of CT + GB- completion of a cycle will be defined as receiving both carboplatin/paclitaxel and taking ≥75% of the doses of GB for the cycle.
    b. **Secondary**
        i. Adverse event occurrence and grade.
        ii. PFS- duration of time from enrollment to RECIST progression or death from any cause, censored at last disease assessment or loss to follow-up; and OS – duration of time from enrollment to death from any cause, censored at date last known alive or loss to follow-up.
        iii. Galunisertib plasma concentrations levels on Cycle 1 day 4, 8 and cycle 2 day 1.
    c. **Exploratory**
        i. Correlate H-score of IHC nuclear phospho-smad2/3 before GB therapy with response rate (complete response + partial response).
        ii. Compare H Score of psamd2/3 staining in pretreated and post-treated patient tumor samples then correlate with the patient therapy response.

3. **Design information**
    a. **General statistical considerations**
        i. This is a single arm, phase Ib study. A total of 25 evaluable patients will be enrolled at the Stephenson Cancer Center. 36 patients are expected to be enrolled in the trial, with a 30% dropout rate. The primary goal of this study is to determine the feasibility of CT and Galunisertib as a treatment for gynecological carcinoma.
        ii. An evaluable patient is a patient who completed four cycles, defined as receiving both carboplatin/paclitaxel and taking >=75% of the doses of GB for the cycle.

Patients who come off the treatment for disease progression but did not experience toxicity requiring termination of treatment will be included among those patients completing the target goal of treatment of 4 cycles.

iii. Study accrual is expected to last three years.

b. Sample Size and Power

i. The primary purpose of this study is to determine the feasibility of CT and Galunisertib as a treatment option for patients with gynecological carcinoma. The percentage of patients completing four cycles will be calculated and a 90% confidence interval will be constructed for the completion rate. With 25 patients and an expected completion rate of 60%, the lower bound of the two-sided exact Clopper-Pearson 90% confidence interval (CI) would be 42%, which provides sufficient evidence that the combined regimen is feasible for inclusion in a randomized Phase II study. The following table provides 90% confidence intervals when the expected completion rate ranges from 60% to 80%, with a sample size of 25. Patients who come off the treatment for disease progression but did not experience toxicity requiring termination of treatment will be included among those patients completing the target goal of treatment of 4 cycles. Assuming 30% of the enrolled patients will drop out, we will enroll 36 patients to reach the targeted sample size (n = 25).

Patiens (N)	Expected rate of completing four cycles	90% Confidence Interval
25	60%	42-76%
	70%	52-85%
	80%	63-92%

4. Study Populations

Inclusion and exclusion criteria are sometimes modified during the duration of the protocol. Before beginning analysis, the statistical team will review the criteria in the SAP to confirm it is up to date with the current criteria.

Target population: Women with a primary diagnosis of uterine, ovarian, fallopian tube or peritoneal carcinosarcoma, Stage I-IV or recurrent or progressive disease eligible for treatment with CT.

a. Inclusion Criteria

i. Women ≥ 18 years old with a diagnosis of primary, recurrent or progressive uterine, ovarian, fallopian tube or peritoneal carcinosarcoma, for whom treatment with combination paclitaxel and carboplatin is recommended.

ii. Written informed consent/assent prior to any study-specific procedures.

iii. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

iv. Tissue available for translational study.

v. Adequate bone marrow, renal, and hepatic function as defined by ANC > 1500 cells/mcl, platelets > 100,000/mcl, creatinine < 2.0 x ULN, bilirubin < 1.5 times institutional normal, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels < 2.5 x ULN.
vi. No disease-modifying therapy, including investigational treatments, within 28 days prior to initiation of study treatment.
vii. Ability to swallow tablets.
viii. For Women of child-bearing potential:
    1. Willingness to use a highly effective method of contraception during the study and for 6 months following the last dose of galunisertib. Negative beta human chorionic gonadotropin pregnancy test documented within 7 days prior to initiation of study drug.
ix. Patient must have measurable disease before the treatment

b. Exclusion Criteria

i. Planned radiotherapy during or after the study chemotherapy prior to disease progression.
ii. Receipt of chemotherapy or radiation within 28 days of study treatment.
iii. Have had a major surgical procedure or a significant traumatic injury within 28 days prior to study treatment; Minor procedures such as biopsy within 7 days prior to study treatment are allowed.
iv. Active infection that would preclude receipt of chemotherapy.
v. Moderate or severe cardiovascular disease with one of the following:
    1. Myocardial infarction within 6 months prior to study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension.
    2. Major ECG abnormalities (e.g. Q-QS wave abnormalities, left ventricular hypertrophy, Wolff-Parkinson-White syndrome, complete bundle branch block, intraventricular block, atrial fibrillation, atrial flutter or major ST-T changes) not responding to medical treatments. Major abnormalities documented by ECHO with Doppler (for example, moderate or severe heart valve function defect) that are not stable for at least 6 months. Note: Left ventricular [LV] ejection fraction <50% is allowed only if clinically stable for at least 6 months (evaluation based on the institutional lower limit of normal).
    3. Predisposing conditions that are consistent with development of aneurysms of the ascending aorta or aortic stress (for example, family history of aneurysms, MarfanSyndrome, bicuspid aortic valve, evidence of damage to the large vessels of the heart documented by CT scan/MRI with contrast).
vi. Active pregnancy or lactation.
vii. Second primary malignancy for which treatment during the study period would be recommended if this cancer were not also present.
viii. Prior malignancy requiring treatment within the last 3 years.
ix. Use of another investigational product or device within 4 weeks of study entry or during study participation.

5. Analysis Populations

The analysis populations are defined as below.

a. **Safety population:** All patients who receive at least one dose of combination CT and Galunisertib will be included in the analyses of compliance and safety.
b. **Evaluable population:** Evaluable patients will be defined as patients who complete four cycles of CT and take >=75% of GB for the cycle or patients who experience disease progression while on treatment.

   Patients who withdraw due to toxicity will not be included in the efficacy analysis but will be included in the safety analyses.

6. Interim Analysis

a. An interim dose limiting toxicity (DLT) analysis will be conducted when 6 patients have received ≥ 3cycles of treatment. If a DLT occurs in 2 or more patients, the dose of GB will be decreased to a lower level (level -1) at 80mg, PO, BID and an additional analysis will then be conducted after 6 patients have completed ≥ 3cycles. DLT is defined as either hematologic or nonhematologic toxicity (assessed in accordance with the CTCAE Version 4.0), which cause any of the following:
b. Hematologic Toxicity:
   i. Dose delay greater than 3 weeks due to failure to recover counts.
   ii. Study treatment-related febrile neutropenia.
   iii. Grade 4 neutropenia lasting >7 days.
   iv. Study treatment-related Grade 4 thrombocytopenia or bleeding associated with Grade 3 thrombocytopenia.
c. Non-Hematologic Toxicity
   i. Study treatment-related Grade 3 or Grade 4 non-hematological toxicity (excluding alopecia, fatigue, hypersensitivity reaction), (if controlled w/ medications exclude nausea, vomiting, constipation, diarrhea, hypokalemia, hypomagnesemia, hypocalcemia, hypophosphatemia).
   ii. Any drug-related death.
d. All AEs of the 6 patients will be listed. With 6 patients, there is a high probability (>0.80) to observe at least one DLT, if the true DLT rate is at least 25% . The probability of observing ≥2 DLTs is high (≥0.77) if the true rate of DLTs is at least 40%.

True AE rate:	5%	10%	15%	20%	25%	30%	40%	50%
Probability of observing >=1 DLT	0.26	0.47	0.62	0.74	0.82	0.88	0.95	0.98
Probability of observing >=2 DLT	0.03	0.11	0.22	0.34	0.47	0.58	0.77	0.89

7. Statistical Analysis Methods

a. The percent of patients completing 4 cycles will be calculated and a 90% confidence interval constructed for the completion rate. With 25 patients and an expected completion rate of

60%, the lower bound of the two-sided exact Clopper-Pearson 90% confidence interval (CI) would be 42%, which provides sufficient evidence that the combined regimen is feasible for inclusion in a randomized Phase II study.

b. Progression-Free Survival (PFS) is defined as the time in months from study entry to the date of death or the first documented date of progression, whichever comes first. For patients who did not die and did not have progression, the PFS is censored at the last documented tumor assessment. Survival curve for PFS will be generated using the Kaplan-Meier method. Median PFS with 95% CI will be computed.
c. Overall survival (OS) is defined as time in months from study entry to the date of death from all causes. Patients who are still alive at EOS are censored on the date they were last known to be alive. Survival curve for OS will be generated using the Kaplan-Meier method. Median OS with 95% CI will be computed.
d. Objective response (complete response + partial response) rate will be reported with 95% CI using the Clopper-Pearson method.
e. To ascertain pharmacokinetic profile of GB when given in a combination regimen with CT, Galunisertib levels will be drawn cycle 1 day 4: pre-dose and 2 and 6 hours post dose; Day 8 and day 29: pre-dose for the first 6 patients. Levels over time will be summarized descriptively, as quartiles and range, and graphically using boxplots for example. These will be compared to previous phase I data describing the pharmacokinetics of galunisertib to determine if it is significantly impacted by co-administration of carboplatin/paclitaxel.
f. Exploratory analysis will correlate mRNA levels of EMT markers (SNAI1, N-Cad) and TGFβ-I, TGFβR-I and TGFβR-II with response status (complete response + partial response vs. stable disease + progressive disease) and clinical benefit status (response rate + stable disease at 6 months). The response rate and clinical benefit ratio will be tabulated according to high and low mRNA (divided by median mRNA levels observed) concentrations of TGFβI, TGFβ-II, TGFβR-I and TGFβR-II. H Score of psamd2/3 staining in pretreated and post-treated patient tumor samples will be summarized and then correlate with the patient therapy response status. Because of the sample size, these analyses are hypothesis generating and hypothesis testing will not be conducted.

8. Safety Analyses

a. Adverse Events

i. Severity of AEs will be graded according to the CTCAE Version 4.0.
ii. Frequency and severity of adverse events will be tabulated by body system, type and maximum grade. Serious adverse events will be listed.

9. Handling of Missing Data

Every effort will be made to collect information at all defined visits including at early withdrawal or dropout. Reasons for missing data will be summarized. However, there will be no imputation of missing data.