CLINICAL STUDY PROTOCOL

Study Title: **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**

Sponsor: Stephenson Cancer Center
The University of Oklahoma Health Sciences Center
800 NE 10th Street
Oklahoma City, OK 73104

Study Products: Galunisertib
Funding Collaborator: Eli Lilly and Company (Funder ID: H9H-MC-E001)
IND Number: 133833
NCT Number: NCT03206177

STUDY CHAIRS

Principal Investigator: Kathleen Moore, MD
Stephenson Cancer Center
800 NE 10th Street, Oklahoma City, OK 73104
E-mail: Kathleen-Moore@ouhsc.edu
Translational Scientist: Resham Bhattachraya, PhD
Bio-Statistician: Kai Ding PhD

This clinical trial will be conducted in compliance with the protocol, International Conference on Harmonization Good clinical Practice Guidelines E6 (ICH-GCP), other applicable regulatory requirements and with the Declaration of Helsinki and its amendments.

Investigator Signature Page

Investigational Product Galunisertib (IND No.: 133833)

I have read and understood the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the sponsor's guidelines and all applicable government regulations and the International Conference on Harmonization Good Clinical Practice Guidelines E6 (ICH-GCP) and Good Clinical Practices (GCP) as described in the United States Code of Federal Regulations (CFR) – 21 CFR parts 50, 54, 56, and 312, and in accordance with ethical principles that have their origin in the Declaration of Helsinki.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study.

I will obtain Institutional Review Board (IRB)/Ethics Committee (EC) approval of the Protocol and Patient Informed Consent Form prior to enrollment of patients in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the Institutional Review Committee (or equivalent) and IRB/EC except when such modification is made to remove an immediate hazard to the patient.

I will ensure that a fully executed Patient Informed Consent is obtained from each patient prior to initiation of any study procedures.

I assume responsibility to report Suspected Unexpected Serious Adverse Reactions (SUSAR) to FDA and IRB/EC per the requirement contained in 21 CFR 312.64 and fax those cases to Eli Lilly and Company at 866-644-1697.

I will allow the sponsor, Lilly and its agents, as well as the United States of America (USA) Food and Drug Administration (FDA) and other regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring patient confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the sponsor and study monitor as soon as possible thereafter (no later than 1 week).

_____ _____

Investigator's Signature Date

_____

Investigator's Name

_____

Investigator's Institutional Affiliation

Sponsor Signature Page

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

Sponsor: Stephenson Cancer Center

Investigational Product: Galunisertib (IND No.: 133833)

Approved by: _____

Title: _____

Signature: _____

Date: _____

Safety Lead In: A 3-6 patient safety lead in will precede the schema below. Patients with the same eligibility criteria will receive 80mg po BID of Galunisertib along with the starting dose of paclitaxel and carboplatin based on prior exposure to pelvic radiation. The dose limiting toxicity period is cycle 1 (28 days). If 0/3 patients experience a DLT, the schema below will be activated for 20 patients. If 1/3 patients experiences a DLT, the safety lead in will be expanded to 3more patients. If 1/6 patients experiences a DLT, the below schema will be activated. If 2/3 patients have a DLT, the study will be suspended for reassessment. If 2 or more of the 6 patients experience a DLT, the study will be suspended for reassessment.

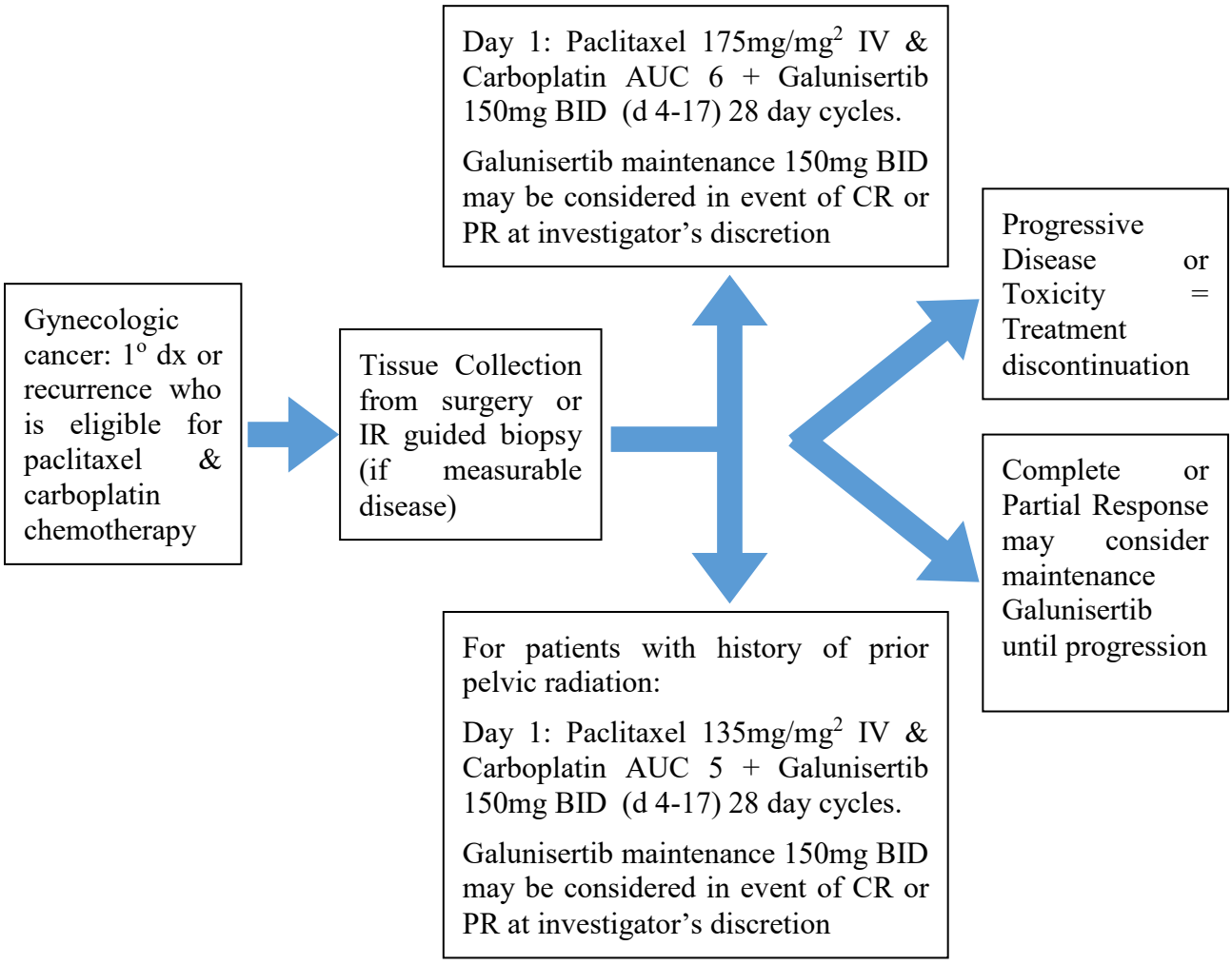

Table of Contents

1 HYPOTHESES AND OBJECTIVES

1.1 Objectives

1.1.1 Primary

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

1.1.2 Secondary

1. To determine the frequency and severity of adverse events as assessed by the CTCAE v4
2. To determine the progression free survival (PFS) and overall survival (OS) of patients receiving combination CT + GB.
3. To ascertain the pharmacokinetic profile of GB when given in a combination regimen with CT.

1.1.3 Exploratory/Correlative

1. 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.
2. To evaluate the mRNA expression Level of EMT markers along with the TGFβ1 in the GB pre-treated and post-treated patient samples

1.2 Endpoints

1.2.1 Primary

1. 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.

1.2.2 Secondary

1. Adverse event occurrence and grade
2. 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
3. Galunisertib plasma concentrations levels on Cycle 1 day 4, 8 and cycle 2 day 1

1.2.3 Exploratory

1. Correlate H-score of IHC nuclear phospho-smad2/3 before GB therapy with response rate (complete response + partial response).
2. Compare H Score of psamd2/3 staining in pretreated and post-treated patient tumor samples then correlate with the patient therapy response

2 BACKGROUND AND RATIONALE

Uterine Carcinosarcoma (UCS) is a rare, aggressive malignancy accounting for 5% of uterine cancers. It is defined by the presence of both epithelial (carcinomatous) and mesenchymal (sarcomatous) malignant cells [1]. Carcinosarcomas (CS) have been reported in a variety of organ sites including the ovary, fallopian tube, peritoneum, prostate, and breast, with uterine origin being most common. The epithelial component of UCS may include endometrioid elements but

frequently has high grade features (serous, clear cell, grade 3). Clinically, UCS tumors have a high incidence of extra-uterine spread at diagnosis and high rates of recurrence manifesting as poor progression-free survival (PFS) and overall survival (OS)[2].

Standard of care treatment for patients with UCS includes hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection. Adjuvant chemotherapy has emerged as the most active treatment. The GOG conducted a series of drug development trials with the goal of defining active regimens. Ifosfamide, cisplatin, and paclitaxel were identified as the most active single agents. Combination regimens further improved response rates, with variable effects on PFS and OS [3, 4]. A phase III trial comparing ifosfamide +/- paclitaxel in patients with advanced/recurrent UCS demonstrated an improved response rate (RR) (45% vs 29%), median PFS (5.8 vs 3.6 mo), and median OS (13.5 vs 8.4 mo) with the combination regimen [4]. A subsequent phase II trial of paclitaxel and carboplatin reported a RR of 54% (13% complete response), median PFS of 7.6 months, and median OS of 14.7 months [5]. A subsequent phase III trial comparing ifosfamide + paclitaxel to carboplatin + paclitaxel is ongoing. In a parallel trial, stage I-IV patients with no residual disease were randomized to ifosfamide + cisplatin or whole abdominal radiation therapy [5]. The results demonstrated that a 22% reduction in the relative risk of recurrence and a 29% reduction in the risk of death with chemotherapy. In addition, the results of EORTC study 55874 (observation vs pelvic radiation for stages I-II UCS and leiomyosarcoma) demonstrated better local control without impact on survival [6]. Despite these treatment improvements, <30% of patients with optimally resected, stage III-IV disease remain free of progression at 3 years [5]. For patients with bulky advanced/recurrent disease, ~15% of patients remain free of progression at 2 years, and only 20% survive 2 years[7]. Improvement upon existing treatments is greatly needed.

Historically, UCS was combined with other uterine sarcomas for treatment selection and clinical trial eligibility. There is increasing recognition that UCS are not sarcomas, but an extreme manifestation of de-differentiated endometrial cancer (EC). Several hypotheses have been advanced to explain the histiogenesis of UCS. One possible explanation for the phenotypic changes is that it may represent a model of epithelial-mesenchymal transition (EMT). EMT is a process whereby epithelial cells lose polarity and cell-cell contacts, have remodeled cytoskeletons, and acquire the ability to migrate [8-10]. These changes are associated with the activation of a mesenchymal like gene expression profile. Mesenchymal cells are able to detach, penetrate the basement membrane, infiltrate, and metastasize. Primary tumor cells undergo EMT to acquire invasive/metastatic capacity. In addition, EMT induces cancer stem-like properties and confers drug resistance to tumor cells [11, 12].

A few studies have evaluated the role of EMT in uterine carcinosarcomas. Saegusa and colleagues compared 14 cases of UCS to 13 cases of endometrial cancers and demonstrated the complete shutdown of E-cadherin expression in the mesenchymal elements[13]. In addition pAkt and nuclear B-catenin levels were increased in mesenchymal cells. Romero-Perez and colleagues compared tumor DNA microarrays between 15 UCS and 23 EC samples and demonstrated changes in the expression of genes modulating EMT including the AT-hook 2 gene (embryonic nuclear factor that mediates EMT in some tumor models) and overexpression of HMGA2 gene (which favors EMT by cooperating with the TGF-beta/Smad pathway) [14].

UCS represents an ideal model to study EMT. Morphologically, epithelial cells undergo EMT as reflected in the appearance of sarcomatous/mesenchymal populations of cells within UCS. The mesenchymal cells demonstrate many of the hallmarks (clinically and by IHC) of EMT. Metastatic

disease demonstrates epithelial components, perhaps suggesting the activation of mesenchymal to epithelial (MET) transition. However, the mechanisms underlying this EMT transformation are currently unknown.

Several candidates that may interrupt EMT and inhibit cancer stem-like cells (CSC) have been identified [10, 15, 16]. Among several growth factors that can act as inducers of EMT, transforming growth factor beta (TFG-β) has been shown to play an important role in cancer progression and metastasis [15, 17-19]. TGFβ is a multifunctional cytokine that regulates EMT and suppresses growth and proliferation in epithelial cells. Aberrations in TGF-β signaling occur frequently during tumorigenesis allowing cancer cells to proliferate, invade, and metastasize beyond their tissue of origin. Active TGFβ binds to the TGFβ type II receptor subunit (TGFβR-II), which then recruits and activates the type I receptor subunit (TGFβR-I). This active receptor complex phosphorylates and activates the receptor-activated Smads which then form complexes with Smad4, and translocates to the nucleus to modulate specific target gene expression[20]. Mani and colleagues were among the first to report a link between EMT and the acquisition of epithelial stem cell properties where TGFβ treatment of breast cancer stem cells initiated EMT and concomitant acquisition of tumor initiating and self-renewal properties[21]. TGFβ has also been shown to modulate E-cadherin expression and induce reversible epithelial to mesenchymal trans differentiation in epithelial cells [22].

Komiyama and colleagues have reported that expression of TGFß1 and its receptors is associated with biological features of ovarian cancer and cancer sensitivity to paclitaxel/carboplatin [23]. Tissues of the primary tumor were collected from 24 patients with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer who had undergone surgery and chemotherapy with paclitaxel/ carboplatin; and the expression of TGFß1, TßRI, and TßRII mRNA was evaluated. The authors found that a lower TGFß1 mRNA expression was associated with high sensitivity to paclitaxel and carboplatin [23]. In consistent with this report, studies on mice model have shown that increased TGF-β signaling could play an important role for paclitaxel-resistance and breast cancer recurrence [24].

To test the role of TGFβ in UCS, researchers at the University of Oklahoma led by Dr. Bhattachraya utilized patient tumor samples to demonstrate that the components of the TGFβ pathway are expressed and functional in UCS[25, 26]. mRNA levels of TGFβ-I, TGFβ-II, TGFβR-I and TGFβR-II were shown to be higher in recurrent compared to the non-recurrent UCS patient samples.

Additionally, TGFβ induced significant phosphorylation of i) Smad 2/3 and ii) c-Jun N-terminal kinase (JNK), iiii) nuclear localization of nuclear factor of activated T cells 1 (NFAT1) and iv) cMyc transcription in UCS. While TGFβ induced proliferation through NFAT1/cMyc, regulation of migration/invasion and EMT are currently being explored. However the TGFβ receptor 1 inhibitor (TGFβ R-1/ galunisertib.), efficiently blocks TGFβ induced proliferation, migration and EMT in UCS[15] .

Galunisertib is a small molecule selective inhibitor of the TGFβR-I kinase domain. It has been evaluated in phase I testing and 300 mg/day, 14 days on/14days off was the suggested as the phase II dose [27, 28]. A randomized phase II study comparing 160 mg vs 300 mg/day in hepatocellular carcinoma patients demonstrated manageable toxicity, evidence for biomarker response, and Pk/PD data supporting the 300 mg/day dosing in future studies [29]. Furthermore, pre-clinical studies in mice model showed that galunisertib could prevent drug resistant to paclitaxel and

enhance chemotherapy effect for mouse xenografts of human breast cancer[24]. A phase Ib study with gemcitabine found no dose limiting toxicity, and the 300 mg/day dose was advanced into a phase II study in metastatic pancreatic cancer patients [29]. A phase II study of galunisertib plus lomustine, galunisertib monotherapy, or placebo plus lomustine found that combination with lomustine did not change the PKs of galunisertib [30]. Furthermore, patients treated with galunisertib (150-mg, PO, twice a day) alone had less frequency of drug-related grade 3/4 adverse events compared with lomustine-treated patients (10% vs 26%); and galunisertib did not increase the frequency of lomustine related adverse events [30].

To date, the safety and anti-cancer effect of Galunisertib combined with paclitaxel/carboplatin regimen remains unclear. Based on the association of TGFβ signaling with EMT in UCS, we propose a Phase IB feasibility trial with this novel TGFβ inhibitor in combination with carboplatin/ paclitaxel (CT) in CS patients. In a phase II study evaluating CT in this population, 58% of patients were able to complete 6 or more cycles of CT therapy [7]. We anticipate that given the excellent tolerability of galunisertib in previous studies, and in the potential for improved disease control with this agent that 60% or more of patients will receive 4 cycles of therapy. The trial would lend support for a randomized phase II trial of CT +/- galunisertib.

2.1 Inclusion of Women and Minorities

The Stephenson Cancer Center will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire gynecologic carcinosarcoma patient population.

3 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Study 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.

3.2 Inclusion Criteria

1. 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.
2. Written informed consent/assent prior to any study-specific procedures
3. Eastern Cooperative Oncology Group (ECOG) performance status 0-2
4. Tissue available for translational study.
5. 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
6. No disease-modifying therapy, including investigational treatments, within 28 days prior to initiation of study treatment.
7. Ability to swallow tablets
8. For Women of child-bearing potential:

- 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.

9. Patient must have measurable disease before the treatment

3.3 Exclusion Criteria

1. Planned radiotherapy during or after the study chemotherapy prior to disease progression.
2. Receipt of chemotherapy or radiation within 28 days of study treatment
3. 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.
4. Active infection that would preclude receipt of chemotherapy
5. Moderate or severe cardiovascular disease with one of the following:
   - 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.
   - 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 is 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).
   - Predisposing conditions that are consistent with development of aneurysms of the ascending aorta or aortic stress (for example, family history of aneurysms, Marfan-Syndrome, bicuspid aortic valve, evidence of damage to the large vessels of the heart documented by CT scan/MRI with contrast)
6. Active pregnancy or lactation
7. Second primary malignancy for which treatment during the study period would be recommended if this cancer were not also present.
8. Prior malignancy requiring treatment within the last 3 years
9. Use of another investigational product or device within 4 weeks of study entry or during study participation.

4 SUBJECTS REGISTRATION AND ENROLLMENT

4.1 Required Protocol Specific Regulatory Documents

This protocol, the Informed Consent document, any information to be given to the patient, and relevant supporting information must be submitted to the IRB by the Principal Investigator and reviewed and approved by the IRB before the study is initiated.

4.2 Patient Registration and Enrollment

Patients must have signed and dated all applicable consents and authorization forms. Patients who signed informed consent form will be registered in Velos eResearch database system, which is sponsored by OU-SCC. The subject ID number will be generated after registration.

Patients must not start protocol treatment prior to registration. Patient will start protocol treatment only after pre-treatment evaluation is complete and eligibility criteria have been met

5 STUDY MODALITIES

5.1 Carboplatin (Paraplatin® - NSC #241240)

5.1.1 Formulation

Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL, or 600mg/60mL of carboplatin.

5.1.2 Storage

Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F). Excursions from 15 to 30°C (59 to 86°F) are permitted. Protect from light. Carboplatin multi-dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

5.1.3 Preparation

Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C / 77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

Note that carboplatin dose will be recalculated if patient has weight change of greater than or equal to 10% from baseline.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must NOT be used for the preparation or administration of carboplatin.

5.1.4 Adverse Effects

Consult the package insert for the most current and complete information.

5.1.5 Supplier

Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

5.1.6 Administration

See Section 6.1.

5.2 Paclitaxel (NSC #673089)

5.2.1 Formulation

Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi-dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

5.2.2 Storage

Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

5.2.3 Preparation

Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene lined administration sets.

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP.

All patients should be premedicated with corticosteroids, diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

5.2.4 Adverse Effects

Consult the package insert for the most current and complete information.

5.2.5 Supplier

Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts andComparisons, or the package insert for additional information.

NOTE: Docetaxel may be substituted if a patient is intolerant or has an allergic reaction to paclitaxel. Refer to the package insert for docetaxel (Taxotere, see http://products.sanofi.us/Taxotere/taxotere.pdf) for the most complete and current information for the followings:

- Docetaxel Injection Concentrate 20 mg/mL is supplied in a single use vial as a sterile, pyrogen-free, non-aqueous solution.
- Store docetaxel vials between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from light. Freezing does not adversely affect the product.
- Using only a 21 gauge needle, aseptically withdraw the required amount of Taxotere injection concentrate (20 mg docetaxel/mL) with a calibrated syringe and inject via a single

injection (one shot) into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL. If a dose greater than 200 mg of Taxotere is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL Taxotere is not exceeded.

5.3 Galunisertib

5.3.1 Formulation

The drug substance, galunisertib, is manufactured as a monohydrate and is also referred to using Lilly compound numbers LY2157299 monohydrate or LSN2232682. The nonproprietary name *galunisertib* can refer to the anhydrous or monohydrate form interchangeably. *LY2157299 r*efers specifically to the anhydrous form.

International Nonproprietary Name (INN) and Nonproprietary Name (USAN):	Galunisertib
Chemical Name (IUPAC)	4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl]quinoline-6-carboxamide monohydrate
Chemical Name (CA Index Name)	6-quinolinecarboxamide, 4-[5,6-dihydro-2-(6-methyl-2-pyridinyl)-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl]- hydrate (1:1)
Synonyms	Galunisertib LY2157299·monohydrate LSN2232682 TGF-beta R1 kinase inhibitor I TGF-β R1 kinase inhibitor I 2-(6-methyl-pyridin-2-yl)-3-(6-amido-quinolin-4-yl)-5,6-dihydro-4*H*-pyrrolo[1 ,2-*b*]pyrazole
Lilly Compound Numbers	LY2157299 monohydrate or LSN2232682
Chemical Abstracts Service (CAS) Registry Numbers	924898-09-9 (monohydrate) 700874-72-2 (anhydrous)

5.3.2 Physical and Chemical Characteristics

Molecular weight: 387.4

Molecular/Empirical formula: C22H19N5O·H2O

Description: White to practically white to light brown to light grey powder

pKa: pKa1: 3.30
pKa2: 4.43
Determined in 0.15M KCl aqueous solution/1,4-dioxane co-solvent

pH: Due to low solubility in deionised water, pH was not obtained.

Stability: Drug substance is stable at room temperature

Solubility: Practically insoluble in water and slightly soluble in ethanol at room temperature

5.3.3 Drug Product

Galunisertib is supplied for clinical trial use as nonfilm coated tablets and film coated tablets described below:

Galunisertib tablets (nonfilm-coated) are composed of galunisertib and the inactive ingredients lactose monohydrate, microcrystalline cellulose, hydroxypropyl methylcellulose, pregelatinised starch, croscarmellose sodium, and magnesium stearate. Each tablet contains galunisertib equivalent to 80 mg or 150 mg of galunisertib (anhydrous). The drug product is stable when stored at room temperature.

Galunisertib tablets (film-coated) are composed of galunisertib and the inactive ingredients mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, talc, lactose monohydrate, hypromellose, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red. Each tablet contains galunisertib equivalent to 80 mg or 150 mg of galunisertib (anhydrous). The drug product is stable when stored at room temperature.

5.3.4 Adverse Events

Approximately 700 patients and 20 healthy volunteers have been treated with galunisertib. At this time, no clear or definitive drug-related toxicity profile has emerged. Based on galunisertib's mechanism of action, the following toxicities could be expected:

- Vascular degeneration
- Aortic aneurysm
- Decrease in blood pressure
- Increase in heart rate
- Cardiac insufficiency
- Autoimmune reaction
- Birth defects
- Thrombocytopenia
- Thromboembolic events

5.3.5 Drug Supply

Galunisertib will be supplied in 150mg and 80mg tablets by Lilly.

6 TREATMENT PLAN

An original, informed consent form, indicating prior approval by the institution's Human Rights or Clinical Trials Committee for participation in this study, must be forwarded to the SCC CTO Office.

6.1 Treatment Plan

6.1.1 Paclitaxel/Carboplatin plus Galunisertib

- Paclitaxel** 175* mg/m^2 over 3 hours, IV day 1
- Carboplatin AUC 6* over 1 hour, IV day 1 (If no prior radiation therapy)
- Galunisertib 150mg po BID day 4-17 (see section 6.3)
- Cycles are 28 days

* Or, in patients with history of prior pelvic radiation, Paclitaxel 135mg/m2 over 3 hours, IV day 1; Carboplatin AUC 5* over 1 hour, IV day 1 (if no prior radiation therapy); Galunisertib 150mg po BID day 4-17 (see section 6.3). Cycles are 28 days.

** Docetaxel starting at 75 mg/m2, IV day 1 may be substituted if a patient is intolerant or has an allergic reaction to paclitaxel.

Patients will receive paclitaxel/carboplatin/galunisertib until unacceptable toxicity or progression. In the event of a complete clinical response or partial response for which the treating physician believes cytotoxic chemotherapy with paclitaxel/carboplatin may be safety suspended, patients will continue galunisertib 150mg po BID as maintenance monotherapy until progression or toxicity.

6.2 Method of Paclitaxel/Carboplatin Chemotherapy Administration

6.2.1 Pre-medications for Paclitaxel

Due to the risk of hypersensitivity reactions with paclitaxel, all patients should be pre-medicated with:

AGENT	DOSE/ROUTE	DURATION
Dexamethasone	20 mg PO **OR** 12 mg IV	-12 and 6 hours prior to paclitaxel -30 minutes prior to paclitaxel
Diphenhydramine	50 mg IV	30 minutes prior to paclitaxel
Ranitidine Or equivalent alterative	50 mg IV	30 minutes prior to paclitaxel

6.2.2 Antiemetics

It is anticipated that nausea and vomiting may be a significant side effect. Based on an updated ASCO antiemetic guidelines, adult patients who are treated with carboplatin at AUC $\geq$ 4 should be offered a three-drug combination of an NK1 receptor antagonist (like fosaprepitant), a 5-HT3 receptor antagonist, and dexamethasone[31]. Patients should receive fosaprepitant and either ondansetron, granisetron, or dolasetron prior to chemotherapy plus dexamethasone (10-20 mg IV).

For some patients the addition of lorazepam (1-2 mg IV 30 minutes prior to chemotherapy) may also be appropriate.

Note: Due to potential fosaprepitant drug interactions with oral dexamethasone[32], dose adjustment of dexamethasone should be considered.

6.2.3 BSA Calculation

If the body surface area is > 2.0m^2 then drugs should be dosed at 2.0 m^2.

6.2.4 Post pre-medication

After premedication, paclitaxel will be given at a dose of 175 mg/m^2 as a 3-hour infusion or 135mg/m2 as a 3-hour infusion for those patients with prior pelvic radiotherapy

6.2.5 Paclitaxel/Carboplatin dose

Carboplatin dosed to an AUC of 5 for patients receiving docetaxel rather than paclitaxel or with prior pelvic radiation; or AUC 6 for patients with prior radiation will be given IV over 30 minutes after paclitaxel.

The dose of carboplatin will be calculated by the formula of Calvert et al.

CALVERT FORMULA:

Carboplatin dose (mg) = (Target AUC) X (GFR + 25)

For the purposes of this protocol, GFR will be estimated based on the calculated creatinine clearance (Cockroft-Gault equation).

Dosing of paclitaxel in patients with hepatic impairment is discussed in section 7.5.4

The dose of carboplatin must be recalculated for each cycle if patient has weight change of greater than or equal to 10% from baseline.

6.2.6 Regimen

This regimen can be administered in an outpatient setting.

Regimen will be repeated every 28 days until unacceptable toxicity or progression. In the event of a complete clinical response or partial response for which the treating physician believes cytotoxic chemotherapy with paclitaxel/carboplatin may be safely discontinued, 4 cycles of combination therapy is recommended; treatment may be changed to monotherapy with galunisertib monotherapy with 28 day cycles with galunisertib alone on days 4-17.

Recommended guidelines for dose reductions/discontinuation are described in section 7.

6.3 Administration of Galunisertib

Studies must be conducted in accordance with ICH guidelines and protocols must be developed following section 6 of the ICH guidelines.

6.3.1 Administration

Galunisertib will be administered orally 150mg, bid, 14 days on and 11days off starting on day 4 and ending on 17 of a 28 day cycle.

A cycle (28 days) will be defined as an intermittent dosing regimen of 14 days of galunisertib followed by 11 days without galunisertib administration. Any missed doses should not be made up. No patient should receive more than 14 consecutive days of galunisertib dosing for safety reasons.

To date, galunisertib at the IB defined dose is well tolerated in patients. If a toxicity is observed that may be related to galunisertib, a dose reduction to 80 mg BID is permitted.

6.3.2 Recommended Guidelines for Dose Reductions/Discontinuation are as Follows:

If a patient experiences any of the following events that are considered possibly related to galunisertib, galunisertib will be omitted until the event resolves:

- Neutropenia with absolute neutrophil count (ANC) <0.5 x 10^9/L x 7 days, or ANC <1.0 x 10^9/L with a single temperature of >101ºF/38.3ºC or a sustained temperature of >100.4ºF/38ºC for more than 1 hour, or thrombocytopenia with platelet count <50,000 x 10^9/L
- Hematologic toxicity must resolve to baseline or </= grade 1 prior to resumption of galunisertib therapy.
- Non-hematologic toxicity must resolve to CTCAE Grade≤1 or baseline (with the exception of alopecia, fatigue, skin rash, nausea, vomiting, constipation, or diarrhea that can be controlled with treatment).

6.3.3 Dose reduction

If dosing is delayed for treatment-related AEs for more than 2 weeks, and the patient recovers within 28days, the patient may continue at a reduced dose of 80 mg BID (160-mg total daily dose). If recovery is >28 days, the patient must be withdrawn from study treatment. No patient will have his/her dose reduced more than once. Dose re-escalation to the previous dose is not permitted.

7 TREATMENT MODIFICATIONS

Dose modification is based on history of prior pelvic radiation therapy, interim nadir levels, and delays due to pre-treatment counts. **No dose escalation will be permitted**. Toxicity will be classified based on the current Common Toxicity Adverse Events (CTCAE) version 4.0

7.1 Paclitaxel* Dose Levels

Dose level	Dose (mg/m^2/day)	Indication
-2	110	
-1	135	Starting dose- History of prior radiation
1	175	Starting dose- No prior radiation

*Patients who experience hypersensitivity (allergic) reactions to paclitaxel may switched to docetaxel per the investigator's discretion.

Docetaxel Dose Levels

Dose level	Dose (mg/m^2)	Indication
-2	55	
-1	65	
1	75	Starting dose

7.2 Carboplatin Dose Levels

Dose level	Dose (AUC)	Indication
-2	4	
-1	5	Starting dose- for patients receiving docetaxel rather than paclitaxel or History of prior radiation
1	6	Starting dose- No prior radiation

7.3 Galunisertib Dose Levels

Dose level	Dose	Indication
-2	no second dose level reduction allowed	
-1	80 mg po bid x 14 days on, 11 days off (day 4-17)	
1	150mg po bid x 14 days on, 11 days off (day 4-17)	Starting dose

7.4 Dose Modifications-Hematologic

7.4.1 Interim Nadirs

Dose reductions are for all subsequent cycles.

Neutropenia

First Occurrence

Neutropenia CTCAE Grade	0	1	2	3 with fever	4 x 7 days or with fever
Carboplatin	No Change	No Change	No Change	Dose reduce to level -1	Dose reduce to level -1
Paclitaxel	No Change	No Change	No Change	No Change	No change
Galunisertib	No Change	No Change	No Change	Hold dosing until ANC returns to grade 1 and then resume at same dose level	Hold dosing until ANC returns to grade 1 and then resume at same dose level

Patients who experience neutropenic fever or sepsis requiring antibiotics will undergo a dose level reduction, as above.

Patients who have asymptomatic grade 4 toxicity at the lowest dose level may remain on protocol if counts recover on time and if platelet toxicity is grade 2 or less.

Galunisertib should be held until counts meet criteria for resuming of chemotherapy.

Second Occurrence

Neutropenia CTCAE Grade	0	1	2	3 with fever	4 x 7 days or with fever
Carboplatin	No Change	No Change	No Change	Add G-CSF	Add G CSF
Paclitaxel	No Change	No Change	No Change	Dose level -1	Dose level -1
Galunisertib	No Change	No Change	No Change	Hold until ANC back to grade 1 and dose reduce to dose level -1	Hold until ANC back to grade 1 and dose reduce to dose level -1

Third Occurrence

ANC Nadir Grade 3rd Occurrence	0	1	2	3 with fever	4 x 7 days or with fever
Carboplatin	No Change	No Change	No Change	Dose level -2	Dose level -2
Paclitaxel	No Change	No Change	No Change	Dose level -2	Dose level -2
Galunisertib	No Change	No Change	No Change	Hold dosing until ANC returns to grade 1and then resume at same dose level	Hold dosing until ANC returns to grade 1and then resume at same dose level

If there is a 4th occurrence of grade 3 with fever or grade 4 ANC despite two dose level reductions of carboplatin, G-CSF and one dose level reduction of Galunisertib, the patient should be removed from protocol therapy

Thrombocytopenia

First Occurrence

Thrombocytopenia CTCAE Grade	0	1	2	3 with bleeding	4
Carboplatin	No Change	No Change	No Change	No Change	No change

Paclitaxel	No Change	No Change	No Change	Hold dosing until plts return to grade 1 and then resume at same dose level	Hold dosing until plts return to grade 1 and then resume at same dose level
Galunisertib	No Change	No Change	No Change	Reduce by dose level -1	Reduce by dose level -1

Second Occurrence

Thrombocytopenia Grade	0	1	2	3 bleeding	4
Carboplatin	No Change	No Change	No Change	Reduce carboplatin to dose level -1	Reduce carboplatin to dose level -1
Paclitaxel	No Change	No Change	No Change	No change	No change
Galunisertib	No Change	No Change	No Change	Hold dosing until plts return to grade 1and then resume at one dose level reduction	Hold dosing until plts return to grade 1and then resume at one dose level reduction

A third occurrence of grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia will necessitate discontinuation of carboplatin chemotherapy. Discussion regarding continuation of paclitaxel + galunisertib or galunisertib alone will be one a case by case basis with the study PI.

No reduction below lowest dose level specified is allowed. If grade 4 neutropenia or thrombocytopenia is observed at the lowest dose levels, the Study Chair should be contacted and the patient will discontinue the study treatment.

Dosing of galunisertib should be held until hematologic parameters are within range for treatment.

If dosing is delayed for treatment-related AEs for more than 2 weeks, and the patient recovers within 28 days, the patient may continue at a reduced dose of 80 mg BID (160-mg total daily dose). If recovery is >28 days, the patient must be withdrawn from study treatment. No patient will have his/her dose reduced more than once. Dose re-escalation to the previous dose is not permitted.

7.4.2 Pre-cycle Initiation Counts

No subsequent course of therapy should be given until the ANC > 1500/mcl and the PLT count > 75,000/mcl. If dose is held due to pre-treatment myelosuppression, recheck counts weekly. If therapy is delayed 3 weeks or longer from scheduled administration, the Study Chair should be notified and the patient should be removed from study treatment.

7.5 Dose Modifications-Non-Hematologic Toxicity

7.5.1 Neurologic

Neurotoxicity (paresthesia, neuropathy, toxicity)- as detected on pre-cycle initiation evaluation.

Grade 0-1- No change, Grade 2- Hold paclitaxel until neuropathy improves to ≤ grade 1 level, then reduce paclitaxel by one dose level. Grade 3-4 requires removal of patient from study treatment.

7.5.2 Gastrointestinal

Nausea/vomiting: Increased antiemetic therapy, outpatient IV hydration, and hospital admission should be attempted prior to dose reduction.

As reported greater than 48 hours following completion of chemotherapy cycle:

Grade 0-3 toxicity- No change, Grade 4- reduce all drugs one dose level.

Other toxicity: For any Grade 3-4 toxicity not mentioned above, protocol treatment should be withheld until patient recovers to ≤ Grade 1 status. Subsequent courses of therapy should be given with a one level dose reduction of agent(s) felt to be responsible. In general, unusual toxicities should be discussed with the Study Chair.

If therapy is delayed 4 weeks or longer from scheduled administration, the Study Chair should be notified and the patient should be removed from study.

7.5.3 Cardiac

Given the cardiovascular toxicities that were observed in preclinical studies, monitoring must be performed as per the guidance below which is accordance with feedback obtained from the FDA. The specific cardiotoxicities seen in these preclinical studies were vascular degeneration and hemorrhage, resulting in development of valvular insufficiency and aneurysmal type changes in the large vessels at the base of the aorta or thoracic aorta. These changes occurred when treatment was administered continuously and at higher doses than used in humans. If moderate or severe heart valve insufficiency or new aneurysms are observed, the patient must immediately be discontinued from the treatment and the adverse event reported to Lilly within 24 hours (SAE).

General Guidance for Cardiotoxicity monitoring

Prior to Enrollment

- MRI or CT scan (with contrast) of chest will be locally assessed for enrollment and safety decisions by a physician or a person who is qualified by experience or training. The objective of this evaluation is to assess for possible aneurysms of the ascending aorta and aortic arch. Should the patient have a previous history of abdominal aneurysm, an additional abdominal MRI or CT is required. NOTE: If a chest MRI or CT scan (with contrast) is performed as part of standard screening and on-treatment tumor assessment, this same scan may be used for safety evaluation, provided that it properly assesses the great vessels of the heart.

During Study

- CT with contrast or MRI will be conducted at 6 cycles and then as clinically indicated.

30-days follow-up visit

- MRI or CT scan with contrast of chest to assess the large vessels of the heart: Perform if there was no previous post-treatment scan, if findings were observed on a previous scan, or if clinically indicated.

7.5.4 Hepatic Function

Dose adjustment of paclitaxel in patients with hepatic impairment include:

3-hour infusion:

- Transaminases <10 times ULN and bilirubin level ≤1.25 times ULN: 175 mg/m^2
- Transaminases <10 times ULN and bilirubin level 1.26 to 2 times ULN: 135 mg/m^2

- Transaminases <10 times ULN and bilirubin level 2.01 to 5 times ULN: 90 mg/m^2
- Transaminases ≥10 times ULN or bilirubin level >5 times ULN: Avoid use

8 STUDY PARAMETERS

8.1 Observations and Tests

1. Pre-study scans should be performed within 4 weeks prior to registration.
2. Initial H&P and laboratory tests can be used for C1D1 if done within 72 hours

The following observations and tests are to be performed and recorded on the appropriate form(s)[6].

PARAMETER	Prior to Study Within 28 days of enrollment	Prior to Study Within 14 days of enrollment	Weekly	Prior to each cycle	Every other cycle	30 days after last dose	Follow-up
History/ Physical/ Performance Status	X	X		X			
Vital signs/ Weight		X		X			
CT CAP [1]	X				X[2]	X[1]	
CBC/Diff/ platelets		X	X[3]	X			
Creatinine		X		X			
Urinalysis		X		X			
AST, ALT, Alkaline Phosphatase		X		X			
Eligibility Check		X					
Con-med				X			
Toxicity assessment				X		X	
Survival							X[4]
Biopsy	X[5]						

[1] MRI or CT scan with contrast of chest to assess the large vessels of the heart: Perform if there was no previous post-treatment scan, if findings were observed on a previous scan, or if clinically indicated.

[2] CT or MRI imaging and RECIST assessment will be repeated every other cycles during combination treatment, then every 4 cycles during maintenance treatment.

[3] CBC/Diff/ platelets exams will be repeated every week during combination treatment, then every cycles during maintenance treatment.

[4] The patient will be followed up every 3 month with phone check in after the last visit for duration of 2 years from date of registration.

[5] Each patient must have available tissue sample (include RNA, snap frozen and FFPE tissue) prior to treatment. For patients with a primary diagnosis, use of archival tissue from surgery or a new biopsy is acceptable. For patients with recurrence or progression, a new biopsy is required prior to receiving treatment. For patients with measurable disease, a second biopsy will be collected after cycle 1.

[6] During the COVID-19 crisis, protocol mandated visits may be performed via telemedicine or visits may be combined in order to prevent imminent safety risks to patients. Weekly laboratory visits during combination treatment with Paclitaxel/Carboplatin/Galunisertib are allowed to change to every 28 days. All such changes to the visit schedule must be clearly documented in the subject's chart. Changes in study visit schedules or missed visits must be explained in the final clinical study report.

8.2 Pharmacokinetics

For the first 6 subjects only, blood will be collected for PK testing of galunisertib levels on

- Cycle 1 day 4
  - pre-dose (within 30 minutes of dose delivery time)
- Cycle 1 day 8
  - pre-dose
  - Cycle 2 day 1
  - pre-dose

Approximately 4ml of venous blood samples will be drawn into sodium heparinized tubes at each time-point for measurement of LY2157299. Plasma samples will be used to assay for LY2157299 using a validated liquid chromatography-mass spectrometry (LC/MS) method [28, 33].

8.3 Tissue Biopsy for Pharmacodynamics

- Each patient must have available tissue sample (include RNA, snap frozen and FFPE tissue) prior to treatment.
- For patients with a primary diagnosis, use of archival tissue from surgery or a new biopsy is acceptable.
- For patients with recurrence or progression, a new biopsy is required prior to receiving treatment.
- For patients with measurable disease, a second biopsy will be collected after cycle 1

Please see lab manual for more detailed information of sample collection and shipping.

9 EVALUATION CRITERIA

9.1 Parameters of Outcome–RECIST 1.1 Criteria

9.1.1 Measurable Disease Definition

Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 10 mm when measured by CT and MRI; or ≥ 20 mm when measured by conventional techniques, including plain x-ray.

9.1.2 Baseline Documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and will be recorded and

measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the progression of the measurable dimension of the disease. Tumor within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required and each of these lesions should be followed as stable **(t**he persistence of a non-target lesion), complete response **(t**he disappearance of a non-target lesion) or progressive disease (the unequivocal progression of a non-target lesion).

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of treatment.

Measurement of the longest dimension of each target lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline.

9.1.3 Definition of Disease Progression

Progression for patients with measurable disease at baseline is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry; in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression
- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided)

Progression for patients with non-measurable disease at baseline is defined as increasing clinical, radiological, or histological evidence of disease since study entry.

9.1.4 Survival

Survival is the observed length of life from the date of study entry to death or the date of last contact.

9.1.5 Progression Free Survival

Progression free survival is the period from the date of study entry until disease progression, death, or date of last contact.

9.2 Subjective Parameters

The performance status, specific symptoms, and side effects are graded according to the CTCAE. Of particular interest will be ≥grade 3 adverse events.

9.3 Definition of Evaluable Patients

Evaluable patients will be defined as patients who receive at least four cycle of study treatment. Patients who withdraw consent before completion of four cycles will be replaced.

10 DURATION OF STUDY

Treatment may continue as long as the patient is receiving clinical benefit and not experiencing excessive toxicity or disease progression. If a complete clinical response is achieved or for patients who come on study with no measurable disease (e.g. post operative early stage) or achieve a durable partial response for which the treating physician feels discontinuation of cytotoxic chemotherapy is an option, 4 cycles of combination therapy is recommended with an option for maintenance therapy with galunisertib monotherapy until toxicity, progression.

Follow-up is required as outlined in Section 8.1 In brief, patients will be seen every 28 days (prior to each cycle of therapy) while receiving active chemotherapy and/or galunisertib maintenance. CT scans to assess response will be performed prior to every odd cycle. Patients will also be seen 30 days after last study medication is issued. Required study procedures are based on the presence or absence of galunisertib related cardiac or other toxicities and are outlined in the footnotes of section 7. Additionally, birth control must continue for 6 months after discontinuation of galunisertib. After the last visit, the patient will be followed up with phone check in every 3 month for duration of 2 years from date of registration.

A patient is considered off study therapy when the patient has progressed or died prior to completion of study therapy, a non-protocol drug or therapy (directed at the disease) is initiated or all study therapy is totally discontinued. Survival and progression data will continue to be collected.

11 STUDY MONITORING AND REPORTING PROCEDURES

In the event of an adverse event the first concern will be for the safety of the subject. Investigators are required to report to Lilly Drug Safety ANY serious treatment emergent adverse event (STEAE) as soon as possible.

A STEAE is any sign, symptom or medical condition that emerges during treatment or during a post-treatment follow-up period that (1) was not present at the start of treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect

- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

11.1 Reporting of Serious Treatment Emergent Adverse Events

All STEAEs should be recorded on a Form and emailed or faxed to the Sponsor:

Email: SCCIITreporting@ouhsc.edu

Or

Fax: 1-405-271-1416.

AND

Eli Lilly and Company

Local Safety Representative

Fax: 866-644-1697

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission)

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

The principal investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s) and sponsor institute in accordance with CFR 312.32 (IND Safety Reports).

All reportable events should be sent to the Sponsor via email/fax:

Email: SCCIITreporting@ouhsc.edu

Or

Fax: 1-405-271-1416.

In addition, the sponsor institute/principal investigator is responsible for notifying Eli Lilly and Company for AE/SAE related to Galunisertib in parallel of such events within 24 hours of the Sponsor/PI becoming aware of the event. The following reportable events must be submitted to Eli Lilly and Company

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)

11.2 MedWatch 3500a Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500a form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)

- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500a report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500a form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Occasionally Lilly may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported.

11.3 Assessing Causality

Investigators are required to assess whether there is a reasonable possibility that galunisertib combined treatment caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to galunisertib administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to galunisertib administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

11.4 SAFETY REPRORTING REQUIREMENTS FOR IND HOLDERS

In accordance with 21 CFR 212.32, sponsors of studies conducted under an IND must comply with following safety reporting requirements:

a. Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:

The Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of galunisertib. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Lilly within 7 calendar days of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

15 Calendar-Day Written Report:

The Sponsor is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of galunisertib. An unexpected adverse event is one that is not already described in the Investigator Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Lilly Drug Safety, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500a Form but alternative formats are acceptable (e.g. summary letter).

A log of the IND safety reports will be submitted annually to the OUHSC IRB at the time of Continuing Review.

b. IND Annual Reports

In accordance with the regulation 21 CFR § 312.32, the Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.32 for a list of the elements required for the annual report.

11.5 Collection and Recording Adverse Events

All adverse events (AEs) of any grade will be collected, identified using the MedDRA terminology, graded as to severity, assessed for causality, and followed until resolution.

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by patient), must be documented in the eCRF and reported in the IND annual report.

All AEs will be collected and recorded in the eCRF for each patient from the first day of dosing until 30 days after the last dose of study treatment. All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normal levels, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

11.5.1 Definitions

Adverse event: An adverse event is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

Adverse events may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

Treatment-emergent: A treatment-emergent adverse event will be defined as any new AE that begins, or any preexisting condition that worsens in severity, after at least 1 dose of study treatment has been administered.

Serious adverse event: A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - Note: This means that the patient is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - Any AE that prolongs hospitalization will be considered an SAE.
  - Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, the reason for the planned hospitalization should be captured in medical history.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s)
  - An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes.

11.5.2 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to intensity and causality with regard to study treatment as outlined in the following sections.

Intensity

Investigators should assess the severity of AEs according to CTCAE. In general, CTCAE (Version 4) severity grades are:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental activities of daily living (ADL). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

A distinction should be made between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above in Section 7.4 and 7.5. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but may not be considered an SAE.

Causality

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- **Related:** A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment should be clinically plausible.
- **Possibly related:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Unlikely related:** A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, or in which other drugs, chemicals or underlying disease provide likely explanations.
- **Unrelated:** A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

12 STATISTICAL CONSIDERATIONS

12.1 Data Analysis Plan

(a) Definition of primary outcome/endpoint:

1) Completion of 4 cycles- completion of a cycle will be defined as receiving both carboplatin/paclitaxel and taking ≥75% of the doses of GB for the cycle

(b) Definition of secondary outcomes/endpoints:

1) Adverse event occurrence and grade, as assessed by the CTCAE v4.
2) 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
3) Galunisertib serum concentrations levels on day 4, 8 and 29 (cycle 2 day 1)

(c) Exploratory:

Correlate mRNA levels of EMT markers (SNAI1, N-Cad) and TGFβ-I, TGFβR-I and TGFβR-II with response rate (complete response + partial response) and clinical benefit ratio (response rate + stable disease at 6 months)

(d) Sample size and Analytic plan for primary objective:

The % 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. 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).

# patients	Expected rate of completing 4 cycles	90% Confidence interval
25	60%	42% - 76%
	70%	52% - 85%
	80%	63% - 92%

(e) Analytic plan for secondary objectives:

1) To determine the frequency and severity of adverse events as assessed by the CTCAE v4.

- Frequency and severity of adverse events will be tabulated, by body system, type and maximum grade.

2) To determine the PFS and OS of patients receiving combination CT + GB.

- Median PFS and OS (and CIs) for patients who receive the combined regimen under study will be computed using the Kaplan-Meier curves and compared to a historical cohort of patients who received the standard care.

3) 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 impacts by co-administration of carboplatin/paclitaxel.

4) To determine if mRNA levels of TGFβ-I, TGFβ-II, TGFβR-I and TGFβR-II are associated with response to galunisertib therapy including galunisertib.

- The response rate (complete response + partial response) and clinical benefit ratio (response rate + stable disease at 6 months) will be tabulated according to high and low mRNA (divided by median mRNA levels observed) concentrations of TGFβ-I, TGFβ-II, TGFβR-I and TGFβR-II. Because of the sample size, these analyses are hypothesis generating and hypothesis testing will not be conducted.

(f) Accrual

25 patients will be enrolled over a period of 3 years.

12.2 Interim Analysis

If the main cohort is activated, an interim safety analysis will be conducted when 6 patients have received ≥ 3cycles of treatment. If a DLT occurs in 2 or more patient, 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 non-hematologic toxicity (assessed in accordance with the CTCAE Version 4.0), which cause any of the following:

Hematologic Toxicity:

- Dose delay of greater than 3 weeks due to failure to recover counts.
- Study treatment-related febrile neutropenia.
- Grade 4 neutropenia lasting > 7 days.
- Study treatment-related Grade 4 thrombocytopenia or bleeding associated with Grade 3 thrombocytopenia.

Non-Hematologic Toxicity:

- 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)
- Any drug-related death

All AEs of the 6 patients will be listed. With 6 patients, there is high probability (>0.80) to observe at least one DLT, if the true DLT rate is at least 25% (Table 1). The probability of observing ≥2 DLTs is high (≥0.77) if the true rate of DLTs is at least 40% (Table 1).

Table 1

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 DLTs	0.03	0.11	0.22	0.34	0.47	0.58	0.77	0.89

13 DATA AND SAFETY MONITORING PLAN

Safety oversight will be performed by Stephenson Cancer Center's (SCC) internal Data and Safety Monitoring Committee (DSMC). The DSMC is composed of individuals with the appropriate expertise in adult and pediatric hematology and medical oncology, radiation oncology, translational and correlative science, pharmacy, nursing and biostatistics. The DSMC operates under the rules of an approved data safety monitoring plan which complies with the National Cancer Institute (NCI) guidelines published as *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by NCI* as of January 2005 and the "*NIH Policy for Data and*

Safety Monitoring," *NIH Guide for Grants and Contracts*, http://grants.nih.gov/grants/guide/notice-files/not98-084.html.

The Data Safety Monitoring Committee is charged with oversight of participant safety, study conduct and the validity and integrity of data for clinical trials at SCC. While the focus of the DSMC is to monitor interventional investigator initiated trials (IITs) that are not subject to external monitoring, it has the authority to monitor any SCC protocol when potential concerns are identified. The DSMC also has the authority to suspend or close a study until the principal investigator addresses any issues that may cause harm or increase risks to subjects. The DSMC reports all findings to the Institutional Review Board (IRB).

Under the direction of the DSMC chair, a full board meeting is convened on a quarterly basis to review the accumulated safety data, accrual information, and additional information as stated in the DSMC plan.

13.1 DSMC Auditing

In addition to monitoring, the DSMC oversees an internal auditing process to ensure subject safety and data quality. All cancer-related clinical trials active at the SCC are eligible for audit; however, priority is placed on those clinical trials that are not monitored or audited by an outside entity. If an external entity conducts an audit of a clinical trial at the SCC, then the findings of that audit are reported to the DSMC, either through the formal audit report provided by the external auditing entity, if available, or from the PI, who will report any findings communicated during the audit process.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Quality Assurance

Stephenson Cancer Center (SCC) will be responsible for clinical monitoring all data for this study.

14.2 Electronic Case Report Forms

The Principal Investigator will develop electronic case report forms for study data entry. All study data will be stored in a HIPAA-compliant database. Only Investigator and assigned research staff will have access to study data. The electronic case report forms will be available to sponsor, IRB or regulatory authorities in even of an audit.

14.3 Record Retention

Investigator will retain all research documents and case report forms at study site.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Ethical Conduct of the Study

The study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki in addition to the requirements of the ICH E2A guidelines. This study will also comply with U.S. FDA regulations under a U.S. Investigational New Drug (IND) application in addition to local, state, and federal laws.

15.2 Informed Consent

The informed consent document will be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent document used in this study, and any changes made during the course of the study, will be prospectively approved by the local IRB.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The study site will retain the original of each patient's signed consent document.

15.3 Institutional Review Board or Ethics Committee

This protocol, the Informed Consent document, any information to be given to the patient, and relevant supporting information must be submitted to the IRB by the Principal Investigator and reviewed and approved by the IRB before the study is initiated.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB. Investigators are also responsible for promptly informing the IRB of any protocol amendments.

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB.

15.4 Confidentiality

The Sponsor and site will maintain confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent document (or separate authorization for use and disclosure or personal health information) signed by the patient, unless permitted or required by law.

16 BIBLIOGRAPHY

References

1. Amant, F., et al., *Clinical management of uterine sarcomas.* Lancet Oncol, 2009. **10**(12): p. 1188-98.
2. Major, F.J., et al., *Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study.* Cancer, 1993. **71**(4 Suppl): p. 1702-9.
3. Sutton, G., et al., *A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study.* Gynecol Oncol, 2000. **79**(2): p. 147-53.
4. Homesley, H.D., et al., *Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study.* J Clin Oncol, 2007. **25**(5): p. 526-31.
5. Wolfson, A.H., et al., *A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus.* Gynecol Oncol, 2007. **107**(2): p. 177-85.
6. Reed, N.S., et al., *Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874).* Eur J Cancer, 2008. **44**(6): p. 808-18.
7. Powell, M.A., et al., *Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study.* J Clin Oncol, 2010. **28**(16): p. 2727-31.
8. Wada, H., et al., *Molecular evidence that most but not all carcinosarcomas of the uterus are combination tumors.* Cancer Res, 1997. **57**(23): p. 5379-85.
9. Kalluri, R. and R.A. Weinberg, *The basics of epithelial-mesenchymal transition.* J Clin Invest, 2009. **119**(6): p. 1420-8.
10. Colas, E., et al., *The EMT signaling pathways in endometrial carcinoma.* Clin Transl Oncol, 2012. **14**(10): p. 715-20.
11. Cooke, V.G., et al., *Pericyte depletion results in hypoxia-associated epithelial-to-mesenchymal transition and metastasis mediated by met signaling pathway.* Cancer Cell, 2012. **21**(1): p. 66-81.
12. Thiery, J.P., et al., *Epithelial-mesenchymal transitions in development and disease.* Cell, 2009. **139**(5): p. 871-90.
13. Saegusa, M., et al., *Requirement of the Akt/beta-catenin pathway for uterine carcinosarcoma genesis, modulating E-cadherin expression through the transactivation of slug.* Am J Pathol, 2009. **174**(6): p. 2107-15.
14. Romero-Perez, L., et al., *Molecular events in endometrial carcinosarcomas and the role of high mobility group AT-hook 2 in endometrial carcinogenesis.* Hum Pathol, 2013. **44**(2): p. 244-54.
15. Connolly, E.C., J. Freimuth, and R.J. Akhurst, *Complexities of TGF-beta targeted cancer therapy.* Int J Biol Sci, 2012. **8**(7): p. 964-78.
16. Meng, F. and G. Wu, *The rejuvenated scenario of epithelial-mesenchymal transition (EMT) and cancer metastasis.* Cancer Metastasis Rev, 2012. **31**(3-4): p. 455-67.
17. Watabe, T. and K. Miyazono, *Roles of TGF-beta family signaling in stem cell renewal and differentiation.* Cell Res, 2009. **19**(1): p. 103-15.

18. Elliott, R.L. and G.C. Blobe, *Role of transforming growth factor Beta in human cancer.* J Clin Oncol, 2005. **23**(9): p. 2078-93.
19. Singh, A. and J. Settleman, *EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer.* Oncogene, 2010. **29**(34): p. 4741-51.
20. Massague, J., *TGF-beta signal transduction.* Annu Rev Biochem, 1998. **67**: p. 753-91.
21. Mani, S.A., et al., *The epithelial-mesenchymal transition generates cells with properties of stem cells.* Cell, 2008. **133**(4): p. 704-15.
22. Miettinen, P.J., et al., *TGF-beta induced transdifferentiation of mammary epithelial cells to mesenchymal cells: involvement of type I receptors.* J Cell Biol, 1994. **127**(6 Pt 2): p. 2021-36.
23. Komiyama, S., et al., *Expression of TGFss1 and its receptors is associated with biological features of ovarian cancer and sensitivity to paclitaxel/carboplatin.* Oncol Rep, 2011. **25**(4): p. 1131-8.
24. Bhola, N.E., et al., *TGF-beta inhibition enhances chemotherapy action against triple-negative breast cancer.* J Clin Invest, 2013. **123**(3): p. 1348-58.
25. Dwivedi, S.K., et al., *Role of TGF-beta signaling in uterine carcinosarcoma.* Oncotarget, 2015. **6**(16): p. 14646-55.
26. Khumar Dhar Dwivedi, S., S. McMeekin, and R. Bhattacharya, *Role of TGF-$\mathcal{B}$ signaling in Uterine Carcinosarcoma.* 2015(Accepted, In press).
27. Rodon, J., et al., *First-in-human dose study of the novel transforming growth factor-beta receptor I kinase inhibitor LY2157299 monohydrate in patients with advanced cancer and glioma.* Clin Cancer Res, 2015. **21**(3): p. 553-60.
28. Rodon, J., et al., *Pharmacokinetic, pharmacodynamic and biomarker evaluation of transforming growth factor-beta receptor I kinase inhibitor, galunisertib, in phase 1 study in patients with advanced cancer.* Invest New Drugs, 2015. **33**(2): p. 357-70.
29. Herbertz, S., et al., *Clinical development of galunisertib (LY2157299 monohydrate), a small molecule inhibitor of transforming growth factor-beta signaling pathway.* Drug Des Devel Ther, 2015. **9**: p. 4479-99.
30. Brandes, A.A., et al., *A Phase II randomized study of galunisertib monotherapy or galunisertib plus lomustine compared with lomustine monotherapy in patients with recurrent glioblastoma.* Neuro Oncol, 2016. **18**(8): p. 1146-56.
31. Hesketh, P.J., et al., *Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update.* J Clin Oncol, 2017. **35**(28): p. 3240-3261.
32. Patel, P., et al., *Aprepitant and fosaprepitant drug interactions: a systematic review.* Br J Clin Pharmacol, 2017. **83**(10): p. 2148-2162.
33. Gueorguieva, I., et al., *Defining a therapeutic window for the novel TGF-beta inhibitor LY2157299 monohydrate based on a pharmacokinetic/pharmacodynamic model.* Br J Clin Pharmacol, 2014. **77**(5): p. 796-807.