Protocol Title

A Phase II Study Evaluating Efficacy and Safety of Hypomethylating Agent Guadecitabine in Combination with Carboplatin in Extensive Stage Small Cell Lung Cancer

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PROTOCOL SIGNATURE PAGE

A Phase II Study Evaluating Efficacy and Safety of Hypomethylating Agent Guadecitabine in Combination with Carboplatin in Extensive Stage Small Cell Lung Cancer

VERSION DATE: 18MAR2020

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

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Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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Location of Facility (City and State)

PLEASE COMPLETE AND EMAIL A COPY TO HCRN

SYNOPSIS

TITLE	A Phase II Study Evaluating Efficacy and Safety of Guadecitabine in Combination with Carboplatin in Extensive Stage Small Cell Lung Cancer
SHORT TITLE	Phase II Study of Guadecitabine in Small Cell Lung Cancer
PHASE	II
OBJECTIVES	Primary Objective: Determine Progression Free Survival (PFS) of the combination of Guadecitabine and platinum in patients with extensive stage small cell lung cancer previously treated with platinum containing chemotherapy. Secondary Objectives: • Evaluate the toxicity profile of the combination of Guadecitabine and carboplatin in patients with extensive stage small cell lung cancer patients previously treated with platinum containing chemotherapy. • Estimate Objective Response Rate (ORR), Disease Control Rate (DCR, defined as Complete Response + Partial Response + Stable Disease), and Overall Survival (OS) of the combination of Guadecitabine and carboplatin in the above mentioned population. Exploratory Objectives: • Measure platinum induced DNA adducts in peripheral blood mononuclear cells (PBMCs) and tumor tissue on Cycle 1 Day 1 and Cycle 2 Day 5 prior to carboplatin treatment. • Methylation status change in PBMCs and tumor biopsy for global DNA and selected genes in tumor tissue on Cycle 1 Day 1 and Cycle 2 Day 5 prior to carboplatin treatment. • Analyze IHC expression of EZH2 and EZH2 target genes on Cycle 1 Day 1, Cycle 2 Day 5 prior to carboplatin treatment and at progression (optional). EZH2 expression changes will be correlated with response to Guadecitabine in combination with carboplatin. • Determine circulating tumor cell (CTC) burden prior to initiating treatment.
STUDY DESIGN	Phase II, open-label, single arm, single-stage study. A total of 34 evaluable patients will be enrolled, of which we expect 70% to be chemotherapy sensitive and 30% to be chemotherapy resistant. This study is powered for chemotherapy sensitive patients. Chemotherapy resistant patients will be enrolled but analyzed separately and descriptively only.

KEY ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria)	**Inclusion Criteria** 1. Male or female subjects, age ≥ 18 years. 2. Histological or cytological diagnosis of small cell lung cancer; extensive stage disease. 3. Patients must have received first line therapy with a platinum-based chemotherapy. Patients should not have received more than 1 prior line of chemotherapy (could have received immunotherapy which does not count as chemotherapy) 4. ECOG PS 0-1 5. Measurable disease as per RECIST v1.1. Subjects may have bone-only disease. 6. Adequate bone marrow, liver, and renal function, as assessed by the following laboratory requirements: o Hemoglobin ≥ 9.0 g/dL o Absolute neutrophil count (ANC) ≥1,500/mm3 o Platelet count ≥100,000/mm3 o Total bilirubin ≤1.5 x upper limit of normal (ULN). For subjects with Gilbert's Disease, Total bilirubin ≤3 x ULN o ALT and AST ≤2.5 x ULN. For subjects with documented liver metastases, ALT and AST ≤5×ULN o Estimated glomerular filtration rate (eGFR) ≥ 60 mL/minute/1.73 m2 as determined using the (by Cockcroft-Gault formula) 7. Male and female subjects of child- bearing potential must agree to use contraception as outlined in Section 5.4 from the screening visit through 6 months after the last dose of study drug. **Exclusion Criteria** 1. Platinum refractory disease defined as disease progression during platinum containing chemotherapy. Progression following platinum based treatment is not an exclusion. 2. Prior therapy with a hypomethylating agent. 3. Previously untreated (non-irradiated), symptomatic brain metastases. No prior treatment is required for non-symptomatic brain metastases. Previously treated symptomatic brain metastases are permitted. 4. Unstable or clinically significant concurrent medical condition, psychiatric illness or social situation that would, in the opinion of the investigator, jeopardize the safety of a subject and/or their compliance with the protocol. 5. Clinically significant acute infection requiring systemic antibacterial, antifungal, or antiviral therapy. (Suppressive therapy for chronic infections allowed, for example: Subjects with HIV/AIDS with adequate antiviral therapy to control viral

	load would be allowed. Subjects with viral hepatitis with controlled viral load would be allowed while on suppressive antiviral therapy.) 6. Hypersensitivity to (IMP) or components of the study treatment regimen. 7. Treated with any investigational drug within 3 weeks of first dose of study treatment.
STATISTICAL CONSIDERATIONS	Null Hypothesis: Median PFS with combination of Guadecitabine with carboplatin in patients with extensive stage small cell lung cancer previously treated with platinum containing chemotherapy is 3 months or less. Alternative Hypothesis: Median PFS with combination of Guadecitabine with carboplatin in patients with extensive stage small cell lung cancer previously treated with platinum containing chemotherapy is 6 months or longer. Acceptable Type I (alpha) error: 10% (one sided) Acceptable Type II (beta) error: 20% Power: 80% This study is powered for chemotherapy sensitive patients. Chemotherapy resistant patients will be enrolled but analyzed separately and descriptively only. For the chemo-sensitive group, when the sample size is 24, a non-parametric test (single-group) with a one-sided 0.10 significance level will have 80% power to detect the difference between a median survival of 3.0 months vs 6.0 months. With 24 patients in the chemo-sensitive group, we expect to enroll approximate 34 subjects total, thus we will have approximately 10 chemo-resistant patients to generate pilot data from.
TOTAL NUMBER OF SUBJECTS	N = 34
ESTIMATED ENROLLMENT PERIOD	Estimated 18 months
ESTIMATED STUDY DURATION	Estimated 12 months

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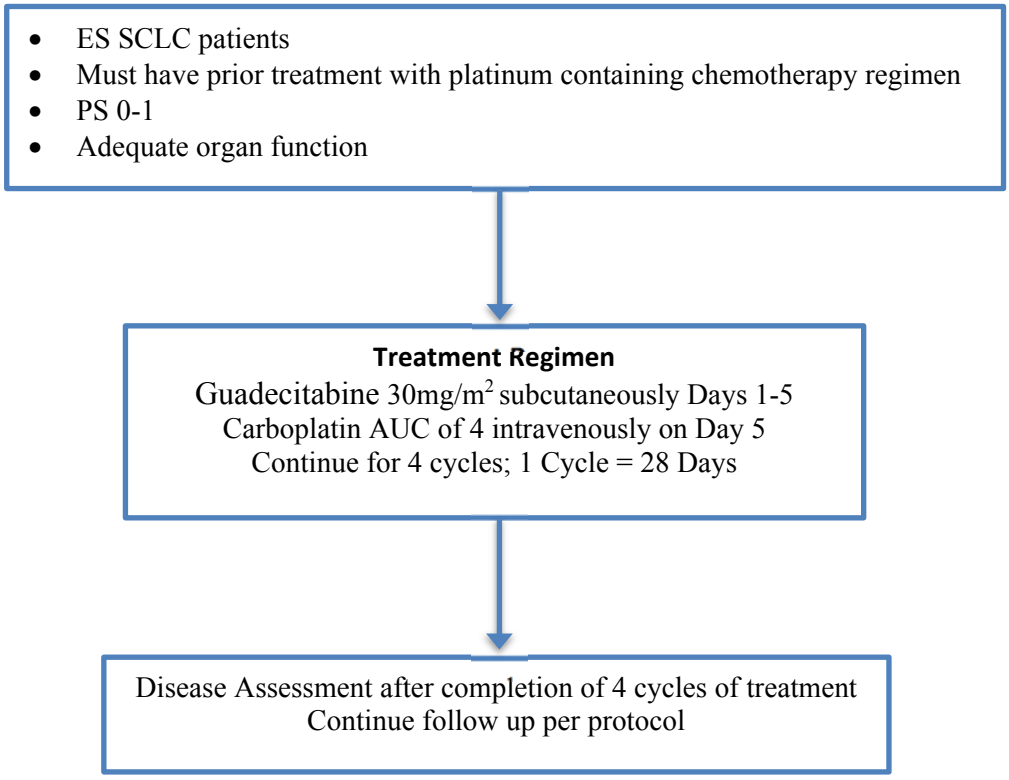
SCHEMA


ES SCLC patients
Must have prior treatment with platinum containing chemotherapy regimen
PS 0-1
Adequate organ function
Treatment Regimen
Guadecitabine 30mg/m2 subcutaneously Days 1-5
Carboplatin AUC of 4 intravenously on Day 5
Continue for 4 cycles; 1 Cycle = 28 Days
Disease Assessment after completion of 4 cycles of treatment
Continue follow up per protocol

1. BACKGROUND AND RATIONALE

1.1 SCLC General Background

Small cell lung cancer (SCLC) is an aggressive malignancy characterized by early hematogenous spread, initial chemotherapy sensitivity followed almost uniformly with rapid resistance and high genetic instability(1). The majority of patients present with extensive stage disease and platinum based chemotherapy remains the standard first line treatment(2). Chemo-sensitivity is defined as a response to initial platinum therapy that lasts ≥90 days. Chemo-resistance is defined as response to platinum therapy that lasts <90 days. Initial response rates to platinum based chemotherapy in extensive stage SCLC are 65-70%. Second line treatment options for SCLC include a number of chemotherapy agents, all with response rates of 20-30% and minimal survival benefit(3). Topotecan remains the only FDA approved second line therapy in SCLC with low response rates and minimal improvement in survival(4-6). Median survival of extensive stage SCLC patients therefore remains less than a year. SCLC has lagged behind many malignancies with limited improvements in the development of novel therapies.(7, 8)

The initial remarkable sensitivity of SCLC to platinum, including complete responses in the extensive stage setting, suggests a potential role of platinum re-sensitization in the treatment of relapsed SCLC. Platinum resistance is a complex phenomenon with multiple key pathways involved including DNA repair pathways(9). Cisplatin exerts its cytotoxicity through the formation of DNA adducts that inhibit multiple fundamental cellular processes including DNA replication and transcription(10). Adducts lead to a cascade of events that stimulate several signal transduction pathways culminating in apoptosis. Increased repair rate of cisplatin induced adducts via the nucleotide excision repair and increased tolerance of cisplatin induced adducts via the homologous recombination pathway have been tied to platinum resistance(11). In addition, epigenetic changes including alterations in DNA methylation, histone modifications and nucleosome positioning have been shown to be involved in the development of platinum resistance in lung cancer and other malignancies(12, 13). Several epigenetic disruption of distinct biological pathways were observed during the development of platinum resistance in ovarian cancer(14). The exact mechanisms of platinum resistance in SCLC are not well defined. However, epigenetics changes likely play a role both in the development of SCLC and in its response to platinum based therapy. In fact, a very recent study showed smoking induces epigenetic changes in the lungs and are potentially the first step towards the development of lung cancer. Chronic cigarette smoke induced chromatic changes that later manifested as abnormal DNA methylation(15).

1.2 DNA Methylation in SCLC

DNA methylation is an epigenetic modification involved in gene expression regulation. In cancer, the DNA methylation pattern becomes aberrant, causing an array of tumor suppressor genes to undergo promoter hypermethylation and become transcriptionally silent. In fact, DNA methylation profiles in cancer cells are unique from normal, differentiated cells(16). In cancer cells, widespread methylation occurs throughout the genome and enriched hypermethylation is focused in CpG islands. CpG islands are located in the promoters of tumor suppressor genes including some of the most commonly mutated genes in cancer in general and small cell lung cancer in particular such as retinoblastoma (Rb) gene. In a study of patients with small cell lung cancer, significant methylation differences were noted at 62 CpG sites in 52 independent genes

in the peripheral blood compared to case controls(17). DNA methylation patterns were evaluated in 18 primary SCLC tumors and 5 SCLC cell lines using a target-specific CpG island promoter array. The study identified DNA methylation peaks in 73 genes specific to SCLC with a significant representation of neuroendocrine-specifying transcription factor genes. Methylation and inactivation of tumor suppressor genes TCF21 and RB1 were described in SCLC in addition to BCL2. Methylation patterns identified 3 distinct subtypes of SCLC, yet all shared methylation of RB1 and TCF21. The chromatin modifier EZH2 was among the most significantly overexpressed genes in SCLC, expressed >12 fold higher than in normal lung. EZH2, a histone methyltransferase component of the PRC2 complex, has been implicated in dysregulation of DNA methylation in cancer through its effects on histone methylation, particularly histone H3 lysine 27 tri-methylation. *EZH2* is a known target of E2F, which is activated in SCLC by gene copy loss and loss of function mutations in *RB1*, the gene encoding the E2F repressor pRB(18). Pharmacologic inhibition of EZH2 in a SCLC patient derived xenograft using EPZ-6438 suggests hypomethylating agents might have activity in SCLC.

1.3 Hypomethylating Agents for Treatment of Cancer

Re-expression of methylation silenced tumor suppressor genes by inhibiting the DNA methyltransferases (DNMT11, DNMT3, and DNMT3B) has emerged as an effective strategy against cancer(19). The expression of DNA methyltransferase 1 (DNMT1) being high in S phase of cell cycle makes it a specific target for methylation inhibition in rapidly dividing cancer cells. The first compounds that demonstrated DNA hypomethylation activity in cancer cells were cytidine analogs such as 5-Azacyidine which has activity in the treatment of myelodysplastic syndrome and acute myelogenous leukemia. Despite the success of 5-azacytidine in hematologic malignancies multiple challenges arise due to the instability of the compound and it's *in vivo* deamination by cytidine deaminase(20). This has led to the development of Guadecitabine.

1.4 SGI-110 (Guadecitabine) and its role in platinum re-sensitization

While the FDA-approved demethylating agent decitabine is prone to deamination by cytidine deaminase, Guadecitabine (Astex Pharmaceuticals, Inc.), a dinucleotide analogue of decitabine, is more stable, less toxic, and a promising alternative to restoring silenced tumor suppression genes (TSG) expression in cancer cells by reversal of DNA methylation(21). Guadecitabine is a dinucleotide combining 5-aza-dC and deoxyguanosine that has been shown to be more stable than 5-aza-dC making it an attractive alternative. Guadecitabine is resistant to cytidine deaminase(22). Guadecitabine is currently under investigation in multiple clinical trials including high- risk myelodysplastic syndrome and acute myelogenous leukemia(23). In addition, preclinical data has demonstrated the combination of Guadecitabine with cisplatin in platinum resistant ovarian models re-sensitized ovarian cancer cells to platinum (24). This re-sensitization was not a result of inhibition of repair of platinum induced DNA as originally thought. DNA damage induced by platinum was increased by Guadecitabine as measured by inductively coupled plasma mass spectrometry analysis. A phase I trial of Guadecitabine and carboplatin in platinum resistant recurrent ovarian cancer was recently completed (25). Guadecitabine was administered once daily subcutaneously on days 1-5 followed by carboplatin IV day 8 of every 28 days cycle. The maximum tolerated dose of the combination was Guadecitabine at 30mg/m^2 SQ days 1-5 in combination with carboplatin AUC 4 on day 8. The dose limiting toxicities were grade 4 neutropenia and grade 4 thrombocytopenia. Common treatment related adverse events were neutropenia, nausea, fatigue, anemia, injection site

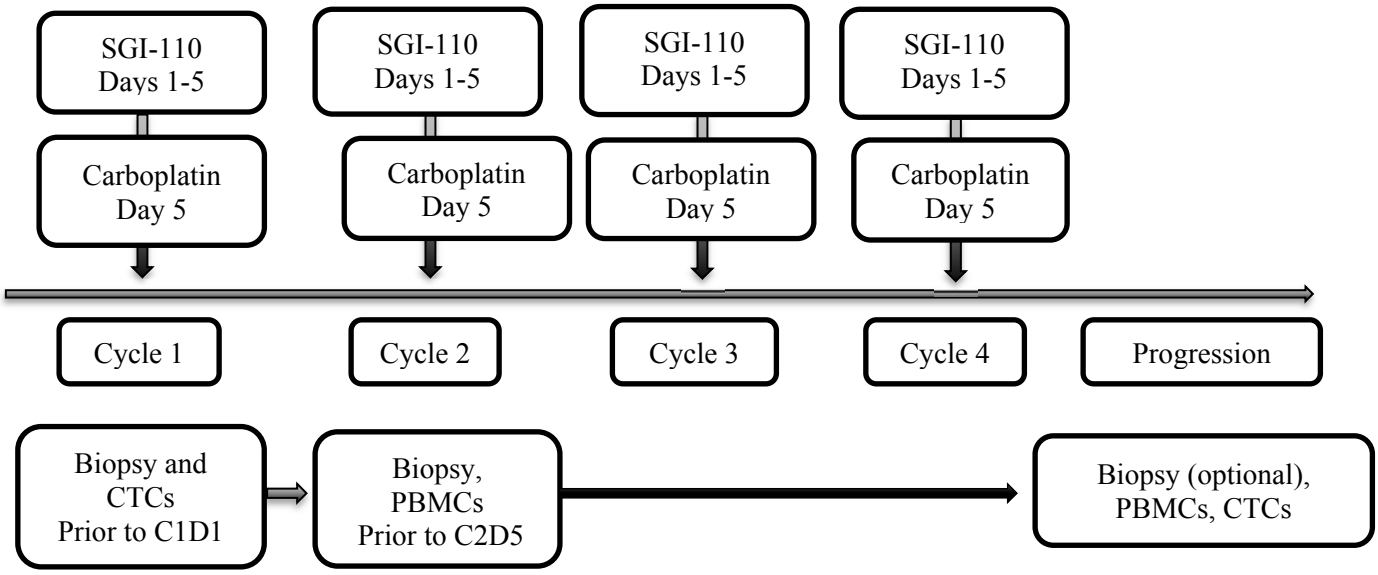
reaction, thrombocytopenia, leukopenia and vomiting. The combination of Guadecitabine and platinum is currently being investigated in platinum refractory testicular cancer and seems to be potentially promising with a response rate of 35%(26). In SCLC, re-sensitization of a platinum resistant SCLC was recently demonstrated using RRx-001, an agent that epigenetically modulates DNA methylation and histone deacetylation(27). This data provides proof of concept of the potential role of Guadecitabine in platinum re-sensitization in SCLC. A common characteristic between testicular cancer, ovarian cancer and small cell lung cancer is their initial exquisite sensitivity to platinum. Guadecitabine has been shown to prime hepatocellular carcinoma cells to oxaliplatin *in vitro(28)*. Guadecitabine is currently under investigation in combination with durvalumab/tremelimumab in SCLC. This will be the first study combining Guadecitabine with platinum in SCLC. This study is unique as guadecitabine has been mainly studied as a radio-sensitizer in acquired platinum resistance. Some of the patients on this study will be platinum resistant and guadecitabine could re-sensitize them to platinum. However, some of the patients will have low sensitivity to platinum and guadecitabine could potentially serve as an "enhancer" rather than 're-sensitizer" to platinum sensitivity in these patients.

1.5 Rationale for Combining Guadecitabine with Carboplatin

The DNA methylation changes described in SCLC in addition to the potential role of hypomethylating agents in reversal of platinum resistance suggest a potential role for hypo-methylating agents in the treatment of SCLC. EPZ-6438 (a histone methyltransferase inhibitor) profoundly inhibited SCLC growth *in vivo*(18*).* Guadecitabine had single agent activity and reduced tumor burden by 35% in a non-small cell lung cancer in an *in vivo* model. In addition Guadecitabine induced genome wide promoter region demethylation and impacted the expression of a number of EZH2-target genes(29). This finding has the potential to be pertinent in SCLC with overexpression of EZH2(30).

The goal of this study is to explore the potential for the epigenetic agent Guadecitabine in re-sensitizing SCLC patients who have progressed following a platinum based doublet regimen. Progression free survival will be the primary endpoint. A longer PFS than noted with first line platinum doublet would suggest this combination is promising in SCLC.

There are no optimal drugs for the treatment of recurrence SCLC. SCLC has been shown to respond to platinum re-challenge(31). In fact, there have been at least two studies that compared platinum re-challenge in SCLC to topotecan or Amrubicin. The response rate to platinum re-challenge was higher than topotecan and comparable to amrubicin. Re-challenging patients with platinum is therefore a reasonable treatment for recurrent SCLC(32, 33). Current evidence in ovarian cancer shows Guadecitabine re-sensitizes patients to platinum re-treatment. It is unclear if guadecitabine or hypomethylators enhance the response to a second platinum exposure. We will analyze that potential benefit in this study.



2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Determine Progression Free Survival (PFS) of the combination of Guadecitabine and platinum in patients with extensive stage small cell lung cancer previously treated with platinum containing chemotherapy.

2.1.2 Secondary Objectives

- Evaluate the toxicity profile of the combination of Guadecitabine and carboplatin in patients with extensive stage small cell lung cancer patients previously treated with platinum containing chemotherapy.
- Estimate Objective Response Rate (ORR) of the combination of Guadecitabine and carboplatin in the above mentioned population.
- Estimate disease Control Rate of the combination of Guadecitabine and carboplatin in the above mentioned population.
- Estimate Overall Survival (OS) of the combination of Guadecitabine and carboplatin in the above mentioned population.

2.1.3 Correlative/Exploratory Objectives

- Measure platinum induced DNA adducts in peripheral blood mononuclear cells (PBMCs) and tumor tissue on Cycle 1 Day 1 and Cycle 2 Day 5 prior to carboplatin treatment.
- Methylation status change in PBMCs and tumor biopsy for global DNA and selected genes in tumor tissue on Cycle 1 Day 1 and Cycle 2 Day 5 prior to carboplatin treatment.
- Analyze IHC expression of EZH2 and EZH2 target genes on Cycle 1 Day 1, Cycle 2 Day 5 prior to carboplatin treatment and at progression (optional). EZH2 expression changes will be correlated with response to Guadecitabine in combination with carboplatin.
- Determine circulating tumor cell (CTC) burden prior to initiating treatment.

2.2 Endpoints

2.2.1 Primary Endpoint

- PFS as defined as the time from Day 1 of treatment until the criteria for disease progression is met as defined by RECIST 1.1, MD Anderson (MDA) criteria or death as a result of any cause, whichever occurs first.

2.2.2 Secondary Endpoints

- Occurrence of all treatment related toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- ORR will include confirmed complete response (CR) + confirmed partial response (PR) and will be determined as per RECIST 1.1 or MDA criteria.
- DCR defined as CR + PR + Stable Disease (SD) per RECIST 1.1 or MDA criteria
- OS as defined as the time from Day 1 of treatment until death from any cause

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Male or female subjects, age ≥ 18 years.

2. Histological or cytological diagnosis of small cell lung cancer. Subjects must have extensive stage disease, defined as disease beyond the ipsilateral hemithorax, mediastinum and ipsilateral supraclavicular area and including malignant pleural or pericardial effusion or hematogenous metastases.

3. Patients must have received first line therapy with a platinum-based chemotherapy. Patients should not have received more than 1 prior line of chemotherapy (could have received immunotherapy which does not count as chemotherapy).

4. ECOG PS 0-1

5. Measurable disease as per RECIST v1.1. Subjects may have bone-only disease. **NOTE:** Bone-only subjects are eligible if their disease can be documented/evaluated by bone scans, CT or MRI. Their disease will be assessed using MD Anderson criteria.(34) **NOTE:** Previously irradiated lesions are eligible as a target lesion only if there is documented progression of the lesion after irradiation.

6. Adequate bone marrow, liver, and renal function, as assessed by the following laboratory requirements:
    - Hemoglobin ≥ 9.0 g/dL
    - Absolute neutrophil count (ANC) ≥ 1,500/mm^3
    - Platelet count ≥ 100,000/mm^3
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN). For subjects with Gilbert's Disease, total bilirubin ≤ 3 x ULN

- ALT and AST ≤ 2.5 x ULN. For subjects with documented liver metastases, ALT and AST ≤ 5×ULN
- Estimated glomerular filtration rate (eGFR) ≥ 60 mL/minute/1.73 m^2 as determined using the Cockcroft-Gault formula.

7. Women of child-bearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening.

8. Male and female subjects of child- bearing potential must agree to use contraception as outlined in Section 5.4 from the screening visit through 6 months after the last dose of study drug.

3.2 Exclusion Criteria

1. Platinum refractory disease defined as disease progression during first line platinum containing chemotherapy regimen. Progression following platinum based therapy is allowed.

2. Prior therapy with a hypomethylating agent.

3. Previously untreated (non-irradiated), symptomatic brain metastases. No prior treatment is required for non-symptomatic brain metastases. Previously treated symptomatic brain metastases are permitted.

4. Unstable or clinically significant concurrent medical condition, psychiatric illness or social situation that would, in the opinion of the investigator, jeopardize the safety of a subject and/or their compliance with the protocol.

5. Clinically significant acute infection requiring systemic antibacterial, antifungal, or antiviral therapy. (Suppressive therapy for chronic infections allowed, for example: Subjects with HIV/AIDS with adequate antiviral therapy to control viral load would be allowed. Subjects with viral hepatitis with controlled viral load would be allowed while on suppressive antiviral therapy.)

6. Hypersensitivity to (IMP) or components of the study treatment regimen.

7. Treated with any investigational drug within 3 weeks of first dose of study treatment.

8. Pregnant or breastfeeding.

9. Second malignancy currently requiring active therapy except breast or prostate cancer stable on or responding to endocrine therapy.

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system prior to starting protocol therapy. Subjects must begin therapy **within 7 business days** of registration.

Registered patients will be assigned to chemo-sensitive or chemo-resistant group based on the time of disease progression since the completion of platinum containing chemotherapy. Chemo-sensitivity is defined as a response to initial platinum therapy that lasts ≥ 90 days. Chemo-resistance is defined as response to platinum therapy that lasts < 90 days.

5. TREATMENT PLAN

This is a phase II, open-label, single arm, single-stage study. Both, chemo-sensitive and chemo-resistant patients will be enrolled and treated with 4 cycles of combination of Guadecitabine and carboplatin as detailed in the study schema. Premedication and hydration will be provided as per institutional standards for administration of carboplatin.

5.1 Drug Administration

Drug	Dose[1]	Route	Schedule[2]	Cycle Length
Guadecitabine	30 mg/m^2	Subcutaneously (SC)	Days 1-5	4 weeks (28 days)
Carboplatin	AUC 4	Intravenously (IV)	Day 5	

1 Body surface area (BSA) should be recalculated when weight changes based on institutional guidelines
2 A window of ± 3 days may be applied to all Day 1 and 5 visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

5.2 Concomitant Medications

5.2.1 Allowed Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

5.2.2 Prohibited Concomitant Medications

Drug-drug interaction studies have not been conducted with guadecitabine. *In vitro* studies suggest guadecitabine is unlikely to inhibit or induce human cytochrome p450 (CYP) enzymes and is not a substrate for CYPs, indicating that CYP-mediated drug-drug interactions with guadecitabine are unlikely to occur. Neither guadecitabine, nor the active metabolite decitabine inhibit major human drug transporters. Therefore, no specific concomitant medications are prohibited.

5.3 Supportive Care

Institutional standards should be followed for supportive care such as symptom management, hydration and transfusions. Filgrastim should be utilized based on NCCN guidelines.

5.4 Contraception

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patient of child-bearing potential

- Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + guadecitabine. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female subjects should also refrain from breastfeeding throughout this period.

Male subjects with a female partner of childbearing potential

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + guadecitabine or. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male subjects must also use a highly effective method of contraception throughout this period.

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in the table below. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without

spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action; and triphasic combined oral contraceptive pills).

Highly Effective Methods of Contraception (<1% Failure Rate)

Barrier/Intrauterine methods	Hormonal Methods
Copper T intrauterine device Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Etonogestrel implants: e.g. Implanon Intravaginal device: e.g. ethinylestradiol and etonogestrel Medroxyprogesterone injection: e.g. Depo-Provera Normal and low dose combined oral contraceptive pill Norelgestromin/ethinylestradiol transdermal system

[a] This is also considered a hormonal method

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications

Unless otherwise noted in the dose modification tables below, treatment may be delayed ≤ 2 weeks from the expected day of the next treatment for any reason. If treatment is delayed ≥ 2 weeks, subjects will proceed with the next cycle of treatment at the dose level recommended according to the tables below.

6.2 Dose Levels for Dose Reductions

Dose level	Dose of carboplatin	Dose of Guadecitabine
Starting Dose	AUC 4	30mg/m^2
Dose level (-1)	AUC 4	24mg/m^2

Dose Modification Guidance Table (applies to Day 1 for all cycles except for Cycle 1)

Neutropenia (absolute neutrophil count [ANC])			
Toxicity	**Grade**	**Stipulations**	**Suggested Action**
	G3 500 - 999/mm^3 (w/out fever [>38.3°C or 101.0°F])	≤ 14 days of interruption/delay	• hold treatments until ANC >1000/mm^3 • Prophylaxis with granulocyte colony stimulating factor (G-CSF) starting with next cycle should be considered by treating physician. In these patients GCSF support will be given on Day 6 through an on-body injector (neulasta onpro) • no change in Guadecitabine or carboplatin dose
	G3 500 - 999/mm^3 (w/out fever)	> 14 days of interruption/delay	• hold treatments until ANC >1000/mm^3 • Prophylaxis with granulocyte colony stimulating factor (G-CSF) starting with next cycle should be considered by treating physician. In these patients GCSF support will be given on Day 6 through an on-body injector (neulasta onpro) • reduce Guadecitabine by one dose level
	G3 500 - 999/mm^3 (w/ fever)		• hold treatments until ANC >1000/mm^3 • Prophylaxis with granulocyte colony stimulating factor (G-CSF) starting with next cycle should be considered by treating physician. In these patients GCSF support will be given on Day 6 through an on-body injector (neulasta onpro) • reduce Guadecitabine by one dose level
	G4 (w/out fever)	Lasting ≤ 14 days	
Any episode	G4 (w/out fever)	G4 lasting > 14 days	• discontinue subject from study

Thrombocytopenia		
Toxicity	**Grade**	**Suggested Action**
1	G3 25,000 - 50,000/mm^3	• hold treatments until plt ≥ 50,000/mm^3 • reduce Guadecitabine by one dose level
	G4 < 25,000/mm^3	• discontinue subject from study

6.3 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF)

- Documented disease progression.
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - In a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Protocol therapy is interrupted for ≥ 6 weeks.

6.4 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 28 days	Screening	On Treatment Cycle 1-4		Safety follow up visit[9]	Long-term Follow up[10]
	-28 days	Day 1 ± 3 days	Day 5 ± 3 days	30 days post last dose (± 7 days)	Every 2 months (±14 days)
REQUIRED ASSESSMENTS					
Informed Consent	X				
Medical History[1]	X				
Physical Exam	X	X		X	
Vital signs and ECOG Performance Status[2]	X	X	X	X	
AEs & concomitant medications	X	X	X	X	
LABORATORY ASSESSMENTS					
Complete Blood Cell Count with diff (CBC)	X	X[8]	X	X	
Comprehensive Metabolic Profile (CMP)	X	X[8]	X	X	
Pregnancy test (urine or serum) (WOCBP)[3]	X				
DISEASE ASSESSMENT					
CT or PET CT of chest[4]	X	Prior to C3D1		X	X
CT, PET CT or MRI of abdomen and pelvis[4]	X	Prior to C3D1		X	X
Bone Scan[4]	X	Prior to C3D1		X	X
TREATMENT EXPOSURE					
Guadecitabine		Daily D1-D5			
Carboplatin			X		
SPECIMEN COLLECTION					
Archival Tumor Tissue or Fresh Tissue[5]	X[5]	X[5]	C2D5	X	
Whole blood for somatic baseline and CTCs[6]		C1D1			
Whole blood for PBMCs[6]		C1D1	C2D5	X	
BANKING SAMPLES					
Whole blood[7]		C1D1			
Whole blood for plasma and serum[7]		C1D1		X	
FOLLOW-UP					
Survival Status, Subsequent Therapy					X

CBC with differential and platelet to include: WBC, ANC, Hgb, Hct, PLT. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase and LDH

Key to Footnotes

1: Medical History; other data to obtain during this assessment includes: diagnosis and staging to include pathology report and staging documentation. A smoking history questionnaire and trial awareness question. Prior anti-cancer treatment should be documented including medications (chemotherapy, checkpoint inhibitors, etc) radiation or surgery.

2: Vital signs to include blood pressure, temperature, pulse, oxygen saturation, weight, and height (screening only) and ECOG performance status.

3: For women of childbearing potential (WOCBP): urine or serum βhCG if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Testing is required at screening.

4: Tumor response assessment will consist of evaluation by CT or PET CT scan of chest. An MRI, CT or PET CT scan of the abdomen and pelvis may be done if there is measurable disease that is not detectable by CT or PET CT of the chest. A bone scan may be used for subjects with bone only disease or if there is suspicion of bone metastasis. Imaging will be performed at screening, prior to Cycle 3 and at the D30 safety follow up visit (± 7 days). Imaging selected for each subject should remain the same throughout the study. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated.

5: Archival tissue is required if available and should be identified at screening and shipped by C2D1. If archival tissue is not available, subjects may still be eligible. Biopsies will be obtained prior to C1D1 from 15 patients with easily accessible disease regardless of availability of archival tissue. These same 15 patients will be required to undergo a repeat biopsy prior to treatment on C2D5 if clinically feasible. These same subjects will have the option to undergo a biopsy at progression/safety visit. See Correlative Laboratory Manual (CLM) for detailed instructions.

6: Whole blood will be collected for somatic baseline and CTCs prior to treatment C1D1. Whole blood will be collected prior to treatment C1D1, C2D5 and at progression/Safety Follow Up visit for isolation of peripheral blood mononuclear cells. See CLM for detailed instructions.

7: Samples for banking for future unspecified cancer related research include: Whole blood: collected prior to treatment on Cycle 1 Day 1. Whole blood for Serum and Plasma: collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit. See CLM for detailed instructions.

8: CBC and CMP to be performed during screening for eligibility and on C1D1 prior to treatment. For the remainder of the Cycles, CBC and CMP may be performed within 4 days prior to Day 1 of treatment.

9: The safety follow-up visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (± 7 days) after the last dose of treatment. Subjects who have an ongoing Grade ≥ 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

10: Long-term follow up will occur in all subjects until documented disease progression. Radiology imaging should be performed every 2 months (± 7 days). Subjects who discontinue treatment for any reason without documented disease progression will be followed every 2 months for 1 year (± 14 days). Once disease progression is documented, subjects will enter a survival follow up period every 3 months for 1 year from the time of documented progression. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

8. BIOSPECIMEN STUDIES AND PROCEDURES

Please refer to the Correlative Laboratory Manual (CLM) for additional details on studies outlined below.

8.1 Tissue

8.1.1 Archival Tissue

Archival tissue is required if available. Archival tissue should be identified at screening, requested after registration and shipped by C2D1. If archival tissue is not available, subjects may still be eligible. This tissue will be used to analyze EZH2 expression.

8.1.2 Fresh Biopsy Tissue

For 15 patients with easily accessible disease, biopsies are required Cycle 1 Day 1 (regardless of archival tissue availability) and Cycle 2 Day 5 to assess methylation changes, EZH2 expression, and platinum-induced DNA adducts. A biopsy at progression is optional for the same 15 patients and similar analysis will be performed.

8.2 Peripheral Blood Samples

8.2.1 Somatic Baseline

Whole blood will be collected for somatic baseline prior to treatment C1D1. This sample is required.

8.2.2 Circulating Tumor Cells (CTCs)

Whole blood will be collected for CTCs prior to treatment C1D1. This sample is required and will be used to determine circulating tumor cell (CTC) burden prior to initiating treatment.

8.2.3 Peripheral Blood Mononuclear cells

Whole blood will be collected prior to treatment on C1D1, C2D5 and at progression for isolation of peripheral blood mononuclear cells. Changes in LINE1 methylation levels in PBMCs will be assessed. In addition, platinum induced DNA lesions will be quantified. DNA will be extracted and ICP-MS performed to determine global DNA lesions.

8.3 Samples for future unspecified cancer related

Subject consent will be obtained to collect additional samples for future unspecified cancer related research. Hoosier Cancer Research Network will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository until they are used up. Collection of samples is optional.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.4 Storage of Biospecimens

Any specimens remaining (leftover) once protocol described biospecimen-based studies are complete will be stored for future unspecified cancer related research. Permission to store these samples will be obtained during informed consent.

8.5 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's sequence ID assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.1 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that

lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) **NOTE**: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.8 Definitions for Response Evaluation – RECIST 1.1

9.8.1 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.2 Disease Control Rate

The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.3 Progression Free Survival

A measurement from Day 1 of treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death, whichever occurs first. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.8.4 Overall Survival

Overall survival is defined by the duration from day 1 of treatment to date of death from any cause.

9.9 Definitions for Response Criteria for patients with bone-only metastases; MD Anderson (MDA) criteria[36]

Complete Response (CR)	• Complete sclerotic fill-in of lytic lesions on XR or CT • Normalization of bone density on XR or CT • Normalization of signal intensity on MRI • Normalization of tracer uptake on SS
Partial Response (PR)	• Development of a sclerotic rim or partial sclerotic fill-in of lytic lesions on XR or CT • Osteoblastic flare - Interval visualization of lesions with sclerotic rims or new sclerotic lesions in the setting of other signs of PR and absence of progressive bony disease • ≥ 50% decrease in measurable lesions on XR, CT, or MRI • ≥ 50% subjective decrease in the size of ill-defined lesions on XR, CT, or MRI • ≥ 50% subjective decrease in tracer uptake on SS
Progressive Disease (PD)	• > 25% increase in size of measurable lesions on XR, CT, or MRI • > 25% subjective increase in the size of ill-defined lesions on XR, CT, or MRI • > 25% subjective increase in tracer uptake on SS • New bone metastases
Stable Disease (SD)	• No change • < 25% increase or < 50% decrease in size of measurable lesions • < 25% subjective increase or < 50% subjective decrease in size of ill-defined lesions • No new bone metastases
Abbreviations: XR: radiography; CT: computed tomography; SS: skeletal scintigraphy; MRI: magnetic resonance imaging.	

Measurements are based on the sum of a perpendicular, bi-dimensional measurement of the greatest diameters of each individual lesion.

10 DRUG INFORMATION

10.1 Guadecitabine; SGI-110

Guadecitabine is a potent inhibitor of DNA methylation that has been shown to induce a dose-dependent decrease of global DNA and gene-specific methylation in many different human cancer cell lines.

10.1.1 Supplier/How Supplied

Astex Pharmaceuticals will supply Guadecitabine at no charge to subjects participating in this clinical trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Preparation

Guadecitabine is available as a two-vial system, referred to as (1) Guadecitabine for Injection, 100mg and (2) Guadecitabine Diluent for Reconstitution, 3mL or 1.2mL:

- Guadecitabine for Injection, 100mg contains guadecitabine, 100mg as a dry lyophilized powder
- Guadecitabine Diluent for Reconstitution, 3mL contains 3mL of a non-aqueous diluent for constitution. 1.2mL contains 1.2mL of a non-aqueous diluent.

The diluent is comprised of 3 commonly used excipients, propylene glycol, glycerin and ethanol, which are generally recognized as safe. All 3 excipients are pharmaceutically acceptable solvents previously in drug productions approved for SC administration. Guadecitabine solution is reconstituted at a maximum concentration of 100mg/mL for SC administration.

Both product and diluent are contained in clear glass vials stoppered with a latex-free rubber stopper and capped with an aluminum flip-off seal.

10.1.3 Storage and Stability

Guadecitabine for Injection, 100mg vial is stored at 2ºC to 8 ºC in the original packaging until use. Guadecitabine Diluent for Reconstitution, 3mL is stored at 2ºC to 30 ºC, and 1.2 mL is stored at 2°C to 8°C, both in an upright position until use. Both vials are preservative free and for single use only.

10.1.4 Handling and Disposal

Occupational Safety and Health Administration (OSHA) Guidelines for handling cytotoxic drugs outlined in the American Journal of Hospital Pharmacy should be followed. As with other potentially toxic anti-cancer agents, care should be exercised in the handling and preparation of guadecitabine. The use of gloves and protective garments is recommended. Preparation should occur in a vertical laminar flow biological hood using proper aseptic technique. Reconstituted drug product is intended for SC administration at a recommended concentration of 100 mg/mL.

10.1.5 Dispensing
Guadecitabine must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Guadecitabine be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.6 Adverse Events
Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

10.2 Carboplatin
Please see product package insert for complete details regarding Carboplatin.

10.2.1 Availability
Carboplatin is commercially available.

10.2.2 Chemical Name
Carboplatin (carboplatin for injection or platinum diamine [1,1-cyclobutane- decarbozxylate (2—0,0')-,(SP-4-2)]) is a platinum compound used as a chemotherapeutic agent. It will be supplied commercially.

10.2.3 Formulation
Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Commercial supplies of carboplatin will be used in this study.

10.2.4 Preparation
Immediately before use, the contents of a carboplatin vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP. The following shows the proper diluent volumes to be used to obtain a carboplatin concentration of 10 mg/mL. Carboplatin solution can be further diluted to concentrations as low as 0.5 mg/mL with D5W or 0.9% normal saline. Carboplatin reacts with aluminum to form a precipitate and cause a 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.

10.2.5 Storage and Stability
Intact vials of carboplatin are stable for the period indicated on the package when stored at room temperature (15-30°C or 59-86°F) and protected from light. When prepared as described above, carboplatin solutions are stable for 8 hours at room temperature if protected from light. The solution should be discarded after 8 hours since no antibacterial preservative is contained in the formulation.

10.2.6 Adverse Events Associated with Carboplatin
Incidence rates of adverse events associated with carboplatin are provided in the product package insert.

11 ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v5.0 will be utilized for AE assessment. A copy of the CTCAE v5.0 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the EDC system (Documents and Information Tab).

11.1 Definitions

11.1.1 Adverse Event

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs and SUSAR's to HCRN

- SAEs will be reported from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).

- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that qualify for mandatory expedited reporting to regulatory authorities where the SAE is suspected to be caused by the study treatment and is considered unexpected (ie, not defined as expected in the current IB clinical study protocol, or approved labeling for marketed drugs). After sponsor-investigator assessment, HCRN will report to the relevant regulatory authorities and forward a formal notification describing the SUSAR to investigators, according to regulatory requirements. Each investigator must then notify his or her IRB/IEC of the SUSAR as required by local regulatory authorities and in accordance with IRB/IEC policy.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements. The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed above), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs and SUSARS to Astex

HCRN will report all SAEs to Astex Drug Safety at drugsafety@astx.com **within 1 business day** of receipt of the SAE Submission Form from a site. If the event is classified as a SUSAR, please clearly state in the notification to Astex as such, and include the date of SUSAR submission to regulatory agency. Follow-up information will be provided to Astex as it is received from site. Every quarter, Astex will provide a list of all SAEs to HCRN that were reported to Astex. HCRN will be asked to reconcile this list with the site's records, and report any discrepancies to Astex.

11.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.4 Overdose

Record the actual dose of study drug administered in the source document and on the appropriate eCRF. Record any adverse clinical signs and symptoms associated with a potential overdose on the AE eCRFs. Report signs and symptoms of a potential overdose that meet SAE criteria to HCRN on the SAE form **within 1 business day**. Treat any AE (including SAE) based on standard care for the specific signs and symptoms. HCRN will report to Astex **within 1 business day.**

11.5 Pregnancy

Report any pregnancy that occurs in a subject or male subject's female partner during the time between the first dose of study treatment and 30 days after the last dose of study treatment. Record any occurrence of pregnancy on the Pregnancy Form and send information on the baby until the baby is 1 year old to HCRN who will report the information to Astex.

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant during the time between the first dose of study treatment and 30 days after the last dose of study treatment. Any female subjects receiving (study treatment) who become pregnant must immediately discontinue study treatment. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus. Report any abortion and the reason for it, whether therapeutic, elective or spontaneous, to HCRN **within 1 business day** who will report to Astex **within 1 business day.**

11.6 HCRN Responsibilities to FDA

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to the Astex's parent IND at the time of submission. Additionally, HCRN will submit a copy of these documents to Astex and IU DSMC at the time of submission to FDA.

For protocols conducted under an IND, HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, HCRN will submit a copy of these reports to Astex and IU DSMC at the time of submission to FDA.

11.7 IND Safety Reports Unrelated to this Trial

Astex will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL METHODS

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima, and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol; however, all changes from the original analysis plan will be documented in the final study report. The statistical analysis methods are outlined below.

12.1 Study Design

This is a Phase II study evaluating the efficacy and safety of Guadecitabine in combination with carboplatin in Extensive Stage Small Cell Lung Cancer. The statistical analyses will be primarily in the chemotherapy-sensitive group. Chemotherapy-resistant patients will also be enrolled but will be described separately. Chemo-sensitivity is defined as a response to initial platinum therapy that lasts ≥ 90 days. Chemo-resistance is defined as response to platinum therapy that lasts < 90 days.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

PFS is defined as the time from Day 1 of treatment until the criteria for disease progression is met as defined by RECIST 1.1, MDA criteria or death as a result of any cause.

12.2.2 Definition of Secondary Endpoints

- Toxicities will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
- Objective response rate (CR+PR) will be assessed via RECIST 1.1 or MDA criteria.
- Disease Control Rate (CR+PR+SD > 8 weeks) will be assessed via RECIST 1.1 or MDA criteria.
- Overall survival will be defined as the time from Day 1 of treatment until death from any cause.

12.3 Sample Size and Accrual

For the chemo-sensitive group, when the sample size is 24, a non-parametric test (single-group) with a one-sided 0.10 significance level will have 80% power to detect the difference between a median survival of 3.0 months vs 6.0 months assuming an accrual period of approximately 12 months and maximum follow-up of 24 months (i.e. would allow for up to 12 months of follow-up after accrual ends). With 24 in the chemo-sensitive group, we expect to enroll approximate 34 subjects total, thus will have approximately 10 chemo-resistant patients to generate pilot data.

12.4 Assessment of Safety

The safety population will be comprised of all subjects who receive at least one dose of study drug. Safety will be assessed by the NCI CTCAE V5. Please refer to the Study Calendar for the schedule of toxicity assessment.

12.5 Assessment of Efficacy

The efficacy evaluable population will be comprised of all subjects who receive at least one dose of study drug and either undergo at least one post-baseline assessment or die before any evaluation. Efficacy will be evaluated using RECIST 1.1 or MDA criteria (for subjects with bone only disease).

12.6 Data Analysis Plans

12.6.1 Analysis Plans for Primary Objective

In the efficacy evaluable population, in the chemo-sensitive group only the primary endpoint of PFS will be separately compared to the historical control rate of 3 months using a one-sided Sign Test for censored data (35). In both the chemo-sensitive and -resistant groups, PFS overall will be estimated with a Kaplan-Meier curve and median PFS with a 95% confidence interval.

12.6.2 Analysis Plans for Secondary Objectives

In the efficacy evaluable population, Objective Response and Disease Control Rate will be estimated with 95% confidence intervals. Overall survival (OS) will be estimated with a Kaplan-Meier curve and median OS with a 95% confidence interval. Toxicities will be tabulated in the Safety Population. All analyses will be separate for the chemo-sensitive and chemo-resistant groups.

12.6.3 Analysis Plans for Exploratory Objectives

Platinum induced DNA adducts in PBMCs and tumor tissue on Cycle 2 Day 5 will be analyzed. These will be compared to platinum induced DNA lesions isolated from PBMCs of a control group of patients that have completed standard of care treatment with 4 cycles of carboplatin (+ etoposide) enrolled under a separate protocol using two-sample t-tests. LINE1 methylation levels in PBMCs and baseline tumor biopsy for global DNA methylation status and selected genes, IHC expression of EZH2 will be described with box plots and means/standard deviations or median/quartiles, as appropriate, at each time point collected and with line plots over-time if appropriate. Paired t-tests or Wilcoxon signed-rank tests will be used to compare baseline measures to post-treatment measures (for LINE1 in PBMCs, IHC expression of EZH2).

12.6.4 Other Planned Analyses

For the enrolled population (all subjects who are enrolled onto the trial), descriptive statistics will be used to characterize subject demographic and clinical characteristics, disposition, and significant protocol violations. In the safety population, concomitant medications and exposure will be described.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the Indiana University Melvin and Bren Simon Cancer Center's (IUSCC) DSMP for High Risk Safety Lead-In/Phase II Trials.

HCRN oversight activities include:

- Review and processing of all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator, including a weekly update of aggregate AE data.
- Investigators will conduct continuous review of data and patient safety. For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the sponsor investigator will notify HCRN who will notify the DSMC Chair immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.
- Notify participating sites of adverse events potentially requiring expedited reporting and subsequent DSMC recommendations for study modifications.
- Investigators will conduct continuous review of data and patient safety.
- Coordinate monthly meetings which will include representation from each accruing site.
    - These meetings should include review of data, the number of subjects and significant toxicities as described in the protocol. HCRN should maintain meeting minutes and attendance for submission to the DSMC upon request.
- Conduct the trial across all participating sites in accordance with the requirements set forth in the IUSCC DSMP.

13.2 Indiana University Melvin and Bren Simon Cancer Center's Data Safety Monitoring Committee

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study to assess toxicity, compliance, data integrity, and accrual per the Institutional DSMP. Trials managed by HCRN are not routinely audited or monitored by IUSCC; however, the IUSCC DSMC retains the right to audit HCRN trials on a for cause basis.

The IUSCC DSMC will review study data semi-annually during the active treatment and safety follow-up portion of the trial per the IUSCC DSMP.

In preparation for the IUSCC DSMC review, HCRN will provide the following:

1. Monthly Summary Reports
2. Reports of the following, if not already included in the Monthly Summary Report:
    - Adverse event summary report (including serious adverse events)
    - Study accrual patterns
    - Protocol deviations
- Audit and/or monitoring results, if applicable
- Data related to stopping/decision rules described in study design

3. HCRN weekly (Phase I) or monthly (Phase II) study update meeting minutes/ attendance

Documentation of DSMC reviews will be provided to sponsor-investigator (SI) and HCRN. The IUSCC DSMC will notify the sponsor-investigator and other regulatory bodies, as appropriate, for issues of immediate concern. The sponsor-investigator will work with HCRN to address the DSMC's concerns as appropriate.

At any time during the conduct of the trial, if it is the opinion of the sponsor-investigator that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the DSMC Chair and Compliance Officer. Alternatively, the DSMC may initiate suspension or early closure of the study at any time based on its review of the study reports.

13.2.1 IND Annual Reports

For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

13.3.1 Onsite Monitoring

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. Additional for cause visits may occur as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by Astex Pharmaceuticals or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform (EDC system), a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Astex Pharmaceuticals, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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