USC Norris Comprehensive Cancer Center
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Protocol Title: Phase II Clinical Trial of Eribulin in Advanced or Recurrent Cervical Cancer.

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PROTOCOL NUMBER:	5C-11-2
TITLE:	Phase II Clinical Trial of Eribulin in Advanced or Recurrent Cervical Cancer
SITE:	Cervical Cancer
MODALITY:	Chemotherapy
TYPE:	Phase II
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AMENDMENTS/REVISIONS:	N/A

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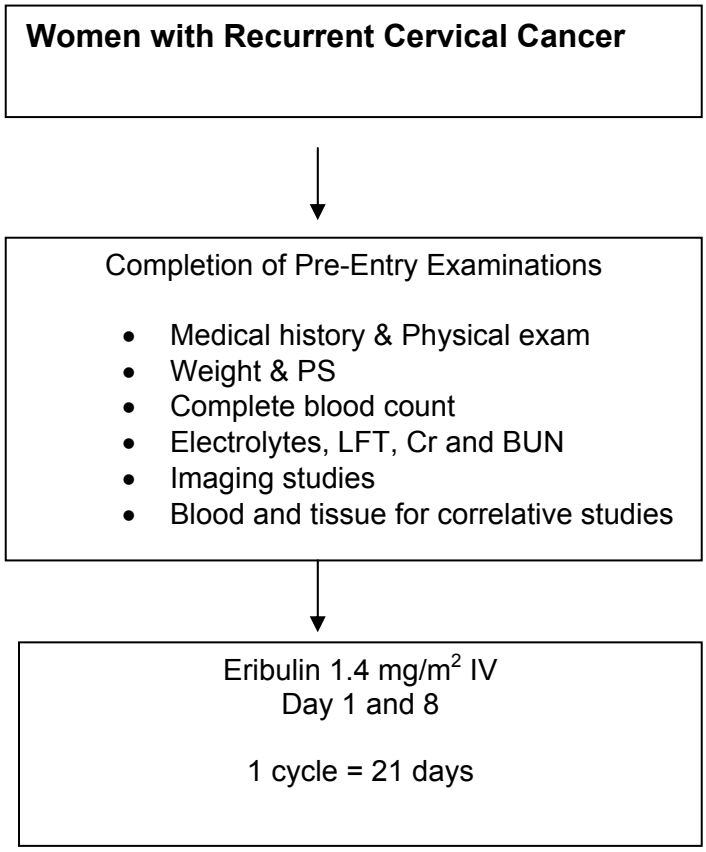
STUDY SCHEMA



This is a phase II, non-randomized, two-stage study. Fifteen patients will be treated and evaluated in the first stage; if 1 or more of the 15 patients achieve a progression free survival of 6 months an additional 15 patients will be accrued into the second stage.

Contents

1.0 BACKGROUND AND HYPOTHESES

Cervical cancer is the second most common cancer in women worldwide; and, in developing countries, it is the leading cause of death by cancer (1). Many patients present with early stage disease and subsequent treatment results in a high cure rate. However, a significant number of patients either relapse or are diagnosed with locally-advanced or metastatic disease. The prognosis of advanced cervical cancer remains poor as the 5-year relative survival rate for stage IV is 17% (2).

The treatment of advanced or recurrent cervical cancer has been improved by the introduction of new active chemotherapy agents of which cisplatin is considered the most active and is now routinely employed as part of the initial therapy (3,4). Tubulin targeting agents, such as paclitaxel and vinorelbine have also documented activity and are frequently used in the treatment of advanced or recurrent disease (5,6). However, after platinum based therapy the overall activity of these (and other chemotherapy agents) is low with response rates and 6-month progression free survival of approximately 10% at best (7). Therefore there is a huge need for the identification of active agents.

Eribulin is a synthetic analog of Halichondrin B, a natural product isolated from the marine sponge Halichondria okadai (8). Eribulin exerts its anticancer effects via a tubulin-based antimitotic mechanism, leading to G2/M (GAP 2/mitosis stages of cell cycle) cell cycle blocks, disruption of mitotic spindles, and ultimately apoptotic cell death. Among the various tubulin-targeted agents, eribulin is a mechanistically unique inhibitor of microtubule dynamics, leading to inhibition of microtubule growth in the absence of effects on microtubule shortening, and formation of non-productive tubulin aggregates. This unique pattern of inhibitory effects on microtubule dynamics is not shared by other known tubulin-targeted agents.

Eribulin inhibits cell growth in multiple human cancer cell lines, including breast, colon, prostate, ovarian, small and non-small cell lung, and pharyngeal squamous cell (head and neck cancer) carcinoma (9,10). Eribulin also exhibits potent effects in various human xenograft models including breast, head and neck, colon, pancreatic, ovarian, small cell lung and non-small cell lung cancers (9,10).

In clinical trials eribulin has documented activity in heavily pretreated breast cancer patients (11,12). In a phase III randomized trial eribulin improved the response rate and

overall survival of patients with heavily pretreated metastatic breast cancer (13). In addition, activity has been reported in previously treated nonsmall cell lung, bladder and prostate cancer, particularly in taxane naïve patients. Of note, in a phase I clinical trial a substantial response was observed in a patients with cervical cancer (14).

As important as identifying new treatments for cervical cancer is to explore why chemotherapy agents are active (or not) in particular cancers. Therefore we propose to explore the potential use of GRP 78 as a predictive marker of response to eribulin.

Cellular- and endoplasmic reticulum (ER) stress such as chemotherapy, hypoxia, and nutritional excess activates the unfolded protein response (UPR) (15-18). Maturing data point to variable glucose-regulated protein-78 (GRP78) expression levels, the critical component of the UPR, as a predictor of differential response to certain chemotherapy regimens in some tumors, particularly breast and prostate cancers. GRP78, also known as BiP, is a multifunctional Ca-binding protein that primarily resides within the ER dynamically controlling ER homeostasis, stress signaling and protein quality control. Several *in vitro* studies already demonstrate the anti-apoptotic properties of GRP78 within the tumor cell and other cells within the tumor cell microenvironment, including tumor-associated endothelial cells. GRP78 appears to also suppress doxorubicin-mediated apoptosis in part through inhibition of classic apoptosis-related mechanisms, including BAX and caspase-7 activation.

In clinical studies, a retrospective analysis of 127 breast cancer patients who received adjuvant doxorubicin-based chemotherapy, high GRP78 levels within the tumor predicted a worse clinical outcome (i.e., shorter recurrence-free survival). When the subset of patients who had received taxanes was evaluated separately, however, high GRP78 levels within the tumor actually predicted improved clinical outcome (19). This finding was subsequently upheld in a separate validation cohort, thereby providing further evidence that in breast cancer GRP78 may be an independent predictor for response to taxane-based adjuvant chemotherapy (20).

Certain tubulin classes and sub-types have recently been identified and are believed to play a role in the tumor cell's responsiveness microtubule-targeting agents, including taxanes (21). While the specific mechanism of action for eribulin is distinct from taxanes, eribulin appears to elicit its antitumor effects by exacting an irreversible mitotic block and G2M cell cycle arrest. Presently, taxane-based regimens in advanced and recurrent cervical cancer demonstrate some antitumor activity; however, the Gynecologic Oncology Group

(GOG) has demonstrated in a phase III setting that it is not definitively superior to several other cytotoxic agents, thereby highlighting the need to identify more effective regimens that interrogate novel mechanisms of cytotoxicity for recurrent/advanced cervical cancer (3). Understanding the relationship of tumoral GRP78 levels to microtubulin-associated variables such as α- or β-tubulin, certain classes of β-tubulin isotopes, and the microtubule-associated protein, Tau protein, and clinical outcomes with eribulin treatment may help identify certain subsets and profiles of patients who would benefit greatest from this class of treatment.

GRP78 in cervical cancer: The role of endoplasmic reticulum stress and cancer progression and chemoresistance has been previously described, and is an area of institutional expertise at USC Norris Cancer Center (15-18). While the body of literature about cervical cancer and endoplasmic reticulum stress is nascent, Carter and colleagues in 2004 introduced the association between endoplasmic reticulum stress, and its major mediator GRP78, and sensitivity of cervical cancer cells to cytotoxic therapies in a series of in vitro studies (22). The body of literature about GRP78 in cancer therapeutics, however, is robust and under active investigation.

Hypothesis

Hypothesis #1: We hypothesize that GRP78 levels within primary cervical tumors are associated with responsiveness to microtubule-targeting agents, such as eribulin. Specifically, primary tumors that express higher levels of GRP78 may be associated with a more favorable clinical response to eribulin, as exhibited clinically by a longer time to progression (TTP), as well as a more favorable biological and biochemical profile (i.e., increased apoptosis, decreased proliferation, higher levels of specific microtubule-associated proteins, including τ protein).

Hypothesis #2: We hypothesize that a dynamic trend of quantitative GRP78 levels in serum from recurrent cervical cancer patients undergoing treatment with eribulin treatment will be associated with responsiveness to treatment. Specifically, we hypothesize that patient who exhibit increasing levels of serum GRP78 will have an improved clinical response to eribulin treatment.

Based on the findings that cervical cancer remains one of the most common cancers in women worldwide and the lack of effective treatments for recurrent disease it is imperative to identify new therapies. Furthermore, it is essential to identify prognostic or predictive markers of response to treatment. We therefore propose to conduct a phase II clinical trial to evaluate the activity of eribulin in patients with previously treated cervical cancer and to study the potential role of GRP78 as a marker of response to treatment.

2.0 OBJECTIVES AND PURPOSE

Primary Objectives:

- To evaluate the activity of eribulin in the management of advanced or recurrent cervical cancer (PFS)

Secondary Objectives:

- To describe the toxicity profile of Eribulin in patients with advanced or recurrent cervical cancer
- To estimate the survival of patients with advanced or recurrent cervical cancer treated with Eribulin
- To evaluate potential correlative studies as predictive or prognostic makers in this patient population (GRP78 levels in tissue and blood, p53 expression, apoptosis with TUNEL assay, apoptosis-related proteins Bcl-2 and Bax using IHC, proliferation with Ki67 IHC, and expression levels of microtubule-associated variables, including τ protein, total α- and β-tubulin, and classes II-IV β-tubulin isotopes with IHC)

3.0 STUDY DESIGN

This is an open label single arm phase II clinical trial of eribulin in patients with advanced cervical cancer. Eligible patients will be treated with Eribulin 1.4 mg/m2 IV administered as a 2-5 min bolus on days 1 and 8 of a 21 day cycle.

4.0 DRUG INFORMATION

For more detailed information consult the HALAVEN™ Package Insert (Appendix A)

Names: Eribulin mesylate (E7389, HALAVEN™).

Description: HALAVEN (eribulin mesylate) Injection is a non-taxane microtubule dynamics inhibitor. Eribulin mesylate is a synthetic analogue of halichondrin B, a product isolated from the marine sponge *Halichondria okadai*. The chemical name for eribulin mesylate is 11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one, 2-[(2*S*)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-, methanesulfonate (salt). It has a molecular weight of 826.0 (729.9 for free base). The empirical formula is C40H59NO11•CH4O3S.

HALAVEN is a clear, colorless, sterile solution for intravenous administration. Each vial contains 1 mg of eribulin mesylate as a 0.5 mg/mL solution in ethanol: water (5:95).

Mechanism of Action: Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

How Supplied: Commercially available in injection, 1 mg/2 mL (0.5 mg/mL) single use vials. The drugs will be supplied by Eisai Inc**.**

Preparation: Aseptically withdraw the required amount of HALAVEN from the single-use vial and administer undiluted or diluted in 100 mL of 0.9% Sodium Chloride Injection, USP.
Do not dilute in or administer through an intravenous line containing solutions with dextrose. Do not administer in the same intravenous line concurrent with the other medicinal products.

Storage: Store at 25°C (77°F); excursions permitted to 15° – 30° C (59° -86° F). Do not freeze. Store the vials in their original cartons. Store undiluted HALAVEN in the syringe for up to 4 hours at room temperature or for up to 24 hours under refrigeration (40°F or/ 4°C). Store diluted solutions of HALAVEN for up to 4 hours at room temperature or up to 24 hours under refrigeration. Discard unused portions of the vial.

Route of Administration: Intravenous

Adverse Events and Potential Risks with a Per-Patient Incidence of at least 10%

	All Grades (%)	**≥ Grade 3 (%)**
Blood and Lymphatic System Disorders		
Neutropenia	82	57
Anemia	58	2
Nervous System Disorders		
Peripheral Neuropathy	35	8
Headache	19	< 1
General Disorders		
Asthenia/Fatigue	54	10
Mucosal Inflammation	9	1
Pyrexia	21	< 1
Gastrointestinal Disorders		
Constipation	25	1
Diarrhea	18	0
Nausea	35	1
Vomiting	18	1
Musculoskeletal and Connective Tissue Disorders		
Arthralgia/Myalgia	22	< 1
Back Pain	16	1
Bone Pain	12	2
Pain in Extremity	11	1
Investigations		
Decreased weight	21	1
Metabolism and Nutrition Disorders		
Anorexia		

	20	1
Respiratory, thoracic and mediastinal disorders		
Cough	14	0
Dyspnea	16	4
Skin and subcutaneous Disorders		
Alopecia	45	NA
Infections		
Urinary Tract Infection	10	1

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 INCLUSION CRITERIA

- Histologically confirmed diagnosis of invasive cervical cancer
- Measurable Disease (RECIST 1.1)
- 0-1 prior chemotherapy regimens for recurrent or advanced disease. Platinum based chemotherapy administered as a radiation sensitizer agent is allowed and does not count as prior therapy
- Adequate organ function defined as:
  - bone marrow (AGC $\geq$ 1,500, platelet $\geq$ 100,000),
  - renal (serum creatinine < 2.0 mg/dl)
  - hepatic function (bilirubin $\leq$ 1.5 times the upper limit of the normal range (ULN), and alkaline phosphatase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$ 3 x ULN (in the case of liver metastases, $\leq$ 5 x ULN).
- Peripheral neuropathy grade 0-2
- Recovery of all chemotherapy or radiation-related toxicities to Grade $\leq$ 1, except for alopecia and peripheral neuropathy.
- Performance status 0-2
- Signed Informed Consent
- Patients $\geq$ 18 years old

5.2 EXCLUSION CRITERIA

- Prior treatment with Eribulin
- Chemotherapy, radiation, or biological or targeted therapy within 3 weeks
- Hormonal therapy within 1 week
- Any investigational drug within 4 weeks
- Known brain metastases, unless previously treated and asymptomatic for 3 months and not progressive in size or number for 3 months

6.0 STRATIFICATION / DESCRIPTIVE FACTORS / RANDOMIZATION SCHEME

There will be no formal stratification. Descriptive factors include age, histology, number of prior lines of therapy, prior platinum as a radiation sensitizer.

7.0 STUDY AGENT ADMINISTRATION

Patients will be treated with Eribulin 1.4 mg/m^2 administered on days 1and 8, repeated every 21 days.

AGENT	DOSE	ROUTE	DAYS	ReRx INTERVAL
Eribulin	1.4 mg/m^2	i.v. bolus over 2-5 mins	1,8	3 weeks

7.1 ANCILLARY TREATMENTS

- Routine prophylactic use of granulocyte colony stimulating growth factors is not allowed. Growth factors can be used as per ASCO guidelines (23)
- Routine use of steroids, H1 or H2 blockers is not required.
- Antiemetic prophylaxis as per standard of care.

8.0 ASSESSMENT OF EFFICACY AND SAFETY AND DOSE MODIFICATIONS

8.1 GENERAL PRINCIPLES FOR DOSE DELAY AND MODIFICATIONS

- The dose of eribulin may be reduced or discontinued during any cycle in accordance with the toxicity modifications described below.
- Toxicities will be managed by treatment delay and dose reduction. Once the dose has been reduced, it cannot be increased at a later date.

8.2 RECOMMENDED DOSE DELAYS

As a general rule, participants should be assessed for peripheral neuropathy and complete blood count lab values should be obtained and reviewed prior to each dose.

- Do not administer eribulin on Day 1 or Day 8 if any of the following parameters are evident:
  - ANC < 1,000/mm^3
  - Platelets < 75,000/mm^3
  - Grade 3 or 4 non-hematological toxicities (Section 8.2 and 8.3 have additional details)

- The Day 8 dose may be delayed for a maximum of 1 week:
  - If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose
  - If toxicities resolve or improve to a ≤ Grade 2 severity by Day 15, administer eribulin at a reduced dose and initiate the next cycle no sooner than 2 weeks later

The following chart is a representation of dose modifications per event. Consult the principal investigator for additional information.

EVENT DESCRIPTION	RECOMMENDED ERIBULIN DOSE
Permanently reduce the 1.4 mg/m2 eribulin dose for any of the following: o ANC <500 cells/mm3 for >7 days o ANC <1,000 cells/mm3 with fever or infection o Platelets <25,000/mm3 o Platelets <50,000/mm3 requiring transfusion o Non-hematologic Grade 3 or 4 toxicities o Omission or delay of Day 8 dose in previous cycle for toxicity	1.1 mg/m2

EVENT DESCRIPTION	RECOMMENDED ERIBULIN DOSE
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m2	0.7 mg/m2
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m2	Discontinue eribulin

Note: if subject meets criteria to be removed from study due to toxicity but is deemed to have clinical benefit from treatment, continuation of treatment and reduction or modification of the dose can be discussed with the principal investigator.

8.3 TREATMENT REMOVAL

Patients will be removed from treatment in the event of:

- Peripheral neuropathy Grade >2 that does not improve as in Section 8.1
- Grade 3 or 4 hypersensitivity/infusion reaction.
- Inability of subject to comply with study requirements.
- Determination by the investigator that it is no longer safe for the subject to continue therapy.
- Progression of disease (as defined in Section 10.1).
- Delay of treatment ≥ 2 weeks.
- Patient may choose to withdraw her participation at any time for any reason

8.4 ADVERSE EVENT REPORTING

Any adverse events will be initially reported to Dr. Garcia at (323)865-3000 or any of the listed research personnel, who will inform the IRB within 7 days. The principal Investigator will comply with all safety reporting regulations as set forth the Code of Federal Regulations. Any correspondence to the FDA regarding adverse events or other safety issues will be simultaneously copied via facsimile or email to Eisai.

The Principal Investigator will cooperate with Eisai in all of their efforts to capture information on the safety profile of the Study Drug, including, but not limited to the following:

Notify Eisai of all serious suspected adverse drug reactions occurring in an individual who has been exposed to the Study Drug, and where the Study Drug is suspected product.

8.5 SERIOUS ADVERSE EVENT REPORTING

Where **adverse drug reaction** is defined as:

> A noxious and unintended response to a medicinal product related to any dose. A causal relationship between the medicinal product and the adverse response is at least a reasonable possibility.

And **serious** is defined as:

> A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:
>
> - Results in death
> - Is life threatening

(Note: the term life-threatening in the definition of "serious" refers to 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 or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require interventions to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

All Serious Adverse Events (SAEs) will be reported to the IRB. Also, the Principal Investigator will report SAEs via the MedWatch Form 3500A to the FDA, which can be accessed at:

http://www.accessdata.fda.gov/scripts/MedWatch/

MedWatch forms will be sent to the FDA online at the above internet address or to the following:

MEDWATCH

5600 Fishers Lane

Rockville, MD 20852-9787

FAX: 1-800-FDA-0178 (1-800-332-0178)

The notification of a serious suspected adverse drug reaction should occur as soon as possible, but no later than one business day, and should be done by fax or email via the Eisai standard serious adverse event report form (attached hereto as Appendix B). The contact details for the notification are:

Eisai Medical Services
100 Tice Blvd.
Woodcliff Lake, NJ 07677
Tel: 1-888-274-2378
Fax: 1-732-791-1111
Email: ESI_Safety@eisai.com

In addition, the Principal Investigator agrees to notify Eisai immediately of any other information that suggests a change to the safety profile of the Study Drug.

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

Parameter	Pre-Treatment[5]	Each Cycle [1]	Every 2 Cycles	Every 4 Cycles	Follow-Up (every 3 mos.) x 2 yrs	End of Study
History & Physical Exam	X	X			x	
Weight, Performance Status	X	X				
Toxicity Assessment		X Day 1 and 8				
WBC (differential), Hgb, platelets	X	X Day 1 and 8				
Electrolytes, MG, BUN, Cr	X	X				
LFT (Bilirubin, AST, ALT, Alkaline phosphatase		X				
EKG	X			X		
CXR	X		X [6]			
Radiology, x-ray or Scans for disease measurement	X		X			
Tissue collection [3]	X					
Peripheral Blood Collection for Correlative Studies		X[4]				X
Eribulin		Day 1 and 8				

[1] Within 24 hrs
[2] As clinically indicated
[3] From paraffin embedded prior biopsy
[4] Cycles 1-6
[5] Within 28 days of each cycle
[6] CXR is only required in the event that a CT of the chest is not done. Should a CXR be given in place of a CT scan, an additional CXR should be repeated every 2 cycles.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

The outcome status (in terms of toxicity, response, reason off study, progression, and survival) of all eligible patients will be reported. All eligible patients who begin treatment will be included in the analysis of response, survival and time-to-failure. Toxicities and adverse events including laboratory adverse events will be graded and summarized according to the National Cancer Institute CTCAE, v4.3 (available on the NCI website at: http://ctep.cancer.gov/forms/CTCAEv4.pdf).

Response will be evaluated according to the RECIST criteria v1.1:

Eligibility

Only patients with measurable disease (at least one measurable lesion) at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥10 mm and 2x slice thickness on CT scan. Lymph nodes must be ≥15 mm in **short axis.** Bone lesions may be measurable if there is a lytic/soft tissue component that meets minimum size criteria. CXR lesions must be ≥20 mm.

Non-measurable lesions - all other lesions, including small lesions or lesions not conventionally measurable (i.e. leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed) should be noted and followed by imaging techniques but not measured.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions
All measurable lesions up to a maximum of five lesions total (2 per organ), representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
Lymph node measurements should reflect the **short diameter**
Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete	Persistence of one or more non-target lesion(s) or/and

Response/ Stable Disease (SD):	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 (1)

Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients 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.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

10.1 ENDPOINT DEFINITIONS

10.1.1 PRIMARY EFFICACY ENDPOINT

Progression-free survival is defined as the time from first day of treatment to the first observation of disease progression or death due to any cause. If a patient has not progressed or died, progression-free survival is censored at the time of last follow-up.

10.1.2 SECONDARY EFFICACY ENDPOINTS

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started).

Overall survival is defined as the time from first day of treatment to time of death due to any cause. If a patient is still alive, survival time is censored at the time of last follow-up.

10.1.3 PRIMARY TOXICITY ENDPOINTS

The primary toxicity endpoint is any occurrence of grade 3+ hematologic and non-hematologic toxicity according to CTCAE4.3.

11.0 SPECIAL INSTRUCTIONS

To determine the association between responsiveness to eribulin and prognostic factors such as apoptosis markers, proliferation, pAkt, EGFR, and ER stress, we propose examination of primary tumor specimens using immunohistochemistry. At the time of enrollment, the original cervical tumor tissue and corresponding H&E slide from all patients will be retrieved from the pathology archive. Because of the nature of the patient population at this institution, the primary diagnosis of cervical cancer is typically made within this same institution. If sufficient tissue is remaining within the paraffin block, 20 additional unstained sections will be obtained from these paraffin blocks for immunohistochemistry. Blocks will be retrieved by the USC-Norris Translational Pathology Core under the direction of Dr. Sue Ellen Martin and the lab manager, MoLi Chen. These immunohistochemistry experiments will be performed in Dr. Yvonne Lin-Liu's laboratory in the Harlyne Norris Research Tower at the USC Norris Comprehensive Cancer Center. Scoring will be performed by a board-certified gynecologic pathologist.

In patients who undergo a biopsy or surgical procedure to demonstrate recurrent cervical cancer, the archived paraffin block will be retrieved in addition to the original tumor block, and 20 unstained sections will be obtained from the paraffin block for immunohistochemical comparison of the paired primary and recurrent tumor. The priority of immunohistochemical studies are as follows: 1) expression levels of microtubule-associated variables, including τ protein, total α- and β-tubulin, and classes II-IV β-tubulin isotopes, 2) pAkt/EGFR, 3) UPR markers (CHOP, GRP78, eIF2α), 4) p53, 5) TUNEL, Bcl-2, Bax, 6) Ki67.

For the serum studies measuring GRP78, we plan to utilize an ELISA-based tool. Serum specimens will be obtained prior to the infusion of each eribulin as described in the protocol. We will plan to obtain a maximum of 7 serial serum samples (cycles 1-6, end of study drug) in order to permit interval radiographic assessment of tumor volume as dictated in the primary treatment protocol. Serum will be collected into a separate (standard 6mL) Vacutainer at the time of standard pre-chemotherapy labs (plain red-top tube containing no anticoagulants or preservatives). Since all chemotherapy patients on protocol are seen in clinic on a designated day each week, the blood will be collected and transported to Dr. Lin-Liu's lab for processing (i.e., centrifugation, pipette-transfer into tube for -80°C storage prior to batching for assay and analysis). Specimen procurement will be performed by the USC-Norris Translational Pathology Core. The tumor volume will be ascertained by the study radiologist in accordance with the primary protocol.

12.0 DATA COLLECTION AND MONITORING

12.1. CONFIDENTIALITY OF RECORDS

The original data collection forms will be kept in secure file cabinets in the CISO.

12.2. PATIENT CONSENT FORM

At the time of registration, three signed and dated copies of the patient Informed Consent form with the Human Rights and the HIPAA authorization must be available (for patient, patient's medical chart and one for the Clinical Investigations Support Office).

12.3. REGISTRATION ELIGIBILITY WORKSHEET

At the time of registration, the information requested on the On-Study/Eligibility Worksheet Form will be completed by the Study Coordinator and reviewed by the PI.

12.4 DATA COLLECTION FORMS AND SUBMISSION SCHEDULE

All data will be collected using USC CISO data collection forms. The original data collection forms will reside at USC in secure location.

- Within two weeks of registration, the data manager will complete the On-Study Form (Form OS).
- Within two weeks of completion of each course of treatment, the data manager must complete the following:

  Treatment and Adverse Event Form

  Supplemental Data Form (if applicable)

  Flow Sheets (These are to be submitted along with each treatment form.)

Each time a patient is evaluated for response and/or new follow-up information is obtained the data manager will complete the Response/Off-Study/Follow-Up Form.

13.0 STATISTICAL CONSIDERATIONS

Study Design: This is a two-stage, single arm study to obtain preliminary evidence of efficacy of Eribulin in the treatment of recurrent cervical cancer. Current chemotherapy treatments for recurrent cervical cancer are associated with response rates and 6-month progression-free survival rates no higher than 10%. The objective of this study is to determine whether there is evidence that treatment with Eribulin will result in response and 6-month PFS rates that exceed 10%, suggesting promising activity and encouraging further study.

The primary efficacy endpoint will be 6-month progression-free survival (PFS_6). The secondary efficacy endpoint will be best overall response (BOR). A total of 30 patients who are fully evaluable for PFS_6 will be enrolled on this study. Patients who are not fully evaluable for PFS_6 will be replaced. Replaced patients will nonetheless be included in the final efficacy analysis. PFS_6 will be the endpoint for interim monitoring.

An interim analysis will occur when 15 patients have been evaluated for PFS_6, with final analysis once 30 patients have been evaluated for PFS_6. ≥1/15 patients who achieve PFS_6 are required to continue study accrual to 30 patients. ≥6/30 patients who achieve PFS_6 will be considered sufficient evidence of efficacy to warrant further study. The study will be terminated if fewer than 1/15 patients are progression-free at 6 months. The study may remain open pending the interim results on the first 15 patients, but will be suspended to enrollment if the 20^{th} patient is enrolled before the interim results are available.

Sample size justification. This design has one-sided Type I error of <0.10 (0.072) for a true PFS_6 rate of 10%, and power of at least 0.80 for a true PFS_6 rate of 26%. Hence this study has sufficient power to detect moderate and clinical important improvements in PFS_6 rate due to Eribulin treatment when compared to past experience with chemotherapy treatment of recurrent cervical cancer.

Additional efficacy analyses. Product limits estimates of 6-month PFS will be computed using all patients enrolled on the study. 95% confidence intervals will be based on Greenwood standard errors. In addition, exact 95% binomial confidence intervals will be compute for the BOR rate.

Toxicity analyses. The rate of Grade 3+ hematology and non-hematologic toxicities will be computed for course 1 and for all courses combined.

Interim Monitoring of Toxic Death. The occurrence of toxic death (TD) at any time will be a primary endpoint for safety monitoring. A population TD rate that exceeds p=0.05 will be considered unacceptable. Monitoring will be based on a Bayesian rule on the binomial frequency of TD using a Beta(1,3) prior. A posterior probability of ≥90% that the population TD rate p exceeds 0.05 will be sufficient to require that the cause and circumstances of the TDs be reviewed immediately with the study committee and with the Data and Safety Monitoring Committee to determine whether modifications to or termination of the study are warranted. Operationally this will occur if 1 TD occurs within the first 8 patients, or 2 occur

within the first 19 patients. A posterior probability of ≥97.5% that *p* exceeds 0.05, with the occurrence of at least 2 TDs, will be considered very compelling evidence that the population toxic death rate exceeds 5%, and will require immediate termination of the study unless a convincing rationale for continuing the study exists. Operationally this will occur when 2 TDs within the first 10 patients, 3 within the first 19, or 4 during the study are observed.

Analysis of correlative endpoints. The analysis of GRP78 IHC score and GRP78 serum level, as well as other correlative markers (e.g. Tau-protein, alpha- & beta-tubulin), will be analyzed via Cox regression analysis for PFS, and via logistic regression for BOR rate. The power of these analyses is difficult to determine, since there is little preliminary data on the distribution of these endpoints in tumor and serum. However, the power of these analyses can be appreciated from the following. If, for example, GRP78 IHC level is divided at the median, and BOR rate is 25% with Eribulin in this population, there will be 73% power to detect a difference in BOR rate of 5% vs 45% in the two resulting group, based on a two-sample two-sided test of proportions with 5% Type I error. Hence it is likely that only profound associations between measures of efficacy and levels of GRP78 and other correlative endpoints will be detectable. Actually analyses based on ordered categorical and continuous measures will be somewhat more powerful than this, Similar considerations apply to the other correlative endpoints that will be studied.

14.0 REGISTRATION GUIDELINE

The consent process will take place in the privacy of an examination room. The patients will be given sufficient time to review the consent form, including taking the consent form home to review.

All patients will be registered in the Cancer Center database Café. Patients will not be randomized or stratified.

15.0 STUDY MANAGEMENT

15.1 RETENTION OF RECORDS

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for at least 2 years after the investigation is completed.

15.2 DATA SAFETY AND MONITORING COMMITTEE

The *Data and Safety Monitoring Committee* (*DSMC*) at the USC Norris Comprehensive Cancer Center (NCCC) is an independent body and is responsible for the safety of study subjects through the review of new protocols to ensure an adequate adverse event reporting plan and through the real-time and periodic

monitoring of severe adverse events (SAEs) or those that require expedited reporting. The *DSMC* also performs real-time, quarterly and annual study progress and safety review, as well as efficacy/futility review as outlined in the NCCC Data and Safety Monitoring Plan (available upon request). After each review, the DSMC reports the results of each review and make recommendations to the study PI, IRB, and *CIC.*

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All patients will have signed an informed consent for participation in research activities in accord with all institutional, NCI and Federal and State regulations, and will have been given a copy of all signed documents. The study will be conducted in adherence to ICH Good Clinical Practice.

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