

Phase II Trial of Eribulin for Locally Advanced Refractory or Metastatic Salivary Gland Cancers

Current Version Date: 12/18/2012

Principal Investigator: Renato Martins, MD

Co-Investigators: Christina Baik, MD
Laura Chow, MD
Bernardo Goulart, MD
Ted Gooley, PhD
Sarah G. Wallace

TABLE OF CONTENTS

1. Background	4
1.1 Salivary Gland Carcinoma	
1.2 Systemic therapy for advanced refractory and metastatic SGC	
1.3 Eribulin	
2. Rationale	5
3. Trial Objectives	5
4. Trial Design	5
5. Subject Selection	5
5.1 Inclusion Criteria	
5.2 Exclusion Criteria	
6. Trial Treatments	7
6.1 Drug Supplies	
6.1.1 Formulation and Packaging	
6.1.2 Preparation and Dispensing	
6.2 Treating the Patient	
6.2.1 Conditions prior to administering treatment	
6.2.2 Eribulin administration	
6.2.3 Dose Modifications	
6.3 Concomitant Medications	
7. Trial Procedures	9
7.1 Screening Visit	
7.2 Day 1 of each Cycle	
7.3 End of Treatment Visit	
7.4 Thirty Day Post Treatment Visit	
7.5 Subject Withdrawal	
8. Assessments	10
8.1 Efficacy Assessments	
8.1.1 Definition of Measurable Disease	
8.1.2 Baseline Documentation of Tumor Burden	
8.1.3 Response Criteria	
8.2 Time to Event Measures	
9. Adverse Event Reporting	12
9.1 Adverse Events	
9.2 Definition of an Adverse Event	
9.3 Serious Adverse Events	
9.4 Adverse Event Reporting Requirements	

10. Data analysis/Statistical Methods	13
10.1 Sample Size Determination	
10.2 Efficacy Analysis	
10.3 Analysis of Other Endpoints	
APPENDIX 1 Schedule of Assessments	14
11. References	15

1. Background

1.1 Salivary Gland Carcinoma

Salivary gland cancers (SGC) are rare neoplasms, constituting approximately 5% of head and neck cancers, with an overall incidence of 1-3 per 100,000 persons. There are multiple histological subtypes including adenoid cystic carcinoma, mucoepidermoid carcinoma, and adenocarcinoma. The biologic behavior of these cancers is quite variable [Laurie]. Initial therapy for patients who present with localized disease consists of surgery and/or radiation therapy. Neutron beam radiotherapy has been demonstrated to have superior efficacy to conventional radiotherapy for the treatment of localized disease [Griffin]. As the University of Washington is one of only a few neutron facilities operating worldwide, it has become a referral center for the treatment of this rare neoplasm. Despite optimal treatment, many patients progress either locally or with distant metastatic disease. Due to the rare nature of this disease, conducting clinical trials is difficult; therefore there is limited clinical trial data to guide systemic therapeutic treatments.

1.2 Systemic therapy for advanced refractory and metastatic SGC

There is no current standard of care for palliative chemotherapy in patients with advanced SGC. A recent review cited 12 small trials reporting the use of chemotherapy for salivary gland carcinomas [Laurie]. In general, objective responses to any cytotoxic agent or regimen are infrequent and stabilization of disease is more commonly observed. Agents with activity include cisplatin, mitoxantrone, vinorelbine, epirubicin, and paclitaxel. Combination chemotherapy also appears to be effective. The only randomized clinical trial done in this cancer demonstrated a higher response rate with cisplatin and vinorelbine compared to vinorelbine alone [Airoldi]. Data is insufficient to conclude that combination chemotherapy is superior to single agent therapy and combination therapy certainly has more toxicity. Despite scientific rationale for the use of molecular targeted agents such as imatinib (c-kit) [Hotte], gefitinib (EGFR), and trastuzumab (HER2) [Agulnik], the results of these agents in phase II clinical trials have been disappointing.

1.3 Eribulin

Eribulin mesylate 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*.

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 antimetabolic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

In 2010, the Food and Drug Administration approved eribulin mesylate under the trade name HALAVEN for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

2. Rationale

Patients with locally advanced refractory or metastatic salivary gland cancers have limited treatment options.

This trial has the potential to benefit patients with salivary gland cancers by improving treatment options. Due to the relative rarity of this disease, this has been an underserved population and is difficult to conduct adequately powered clinical trials. Additionally, pharmaceutical companies have not pursued drug development in this disease since it is not considered commercially viable.

3. Trial Objectives

Primary:

- Evaluate the response rate of eribulin per RECIST criteria in patients with locally advanced refractory or metastatic SGC.

Secondary:

- Determine the safety and toxicity of eribulin in patients with locally advanced refractory or metastatic SGC.
- Evaluate the duration of response and time-to-progression.

Exploratory:

- Evaluate overall survival.

4. Trial Design

This is an open-label, single-center, phase II study of eribulin for patients with locally advanced refractory or metastatic SGC.

Patients will receive eribulin 1.4 mg/m² administered intravenously (IV push) over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. Treatment will be continued until disease progression, unacceptable toxicity or withdrawal of patient consent.

5. Subject Selection

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

- Patients must have histologically or cytologically documented salivary gland cancers. Patients that do not have a salivary gland primary must have one of the following histologies - adenoid cystic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma).
- Patients must have recurrent and/or metastatic disease that is progressive and not amenable to surgery or curative radiotherapy occurring within 6 months of study entry, as evidenced by: at least a 20% increase in radiographically or clinically measurable disease, appearance of any new lesions, or deterioration in clinical status.
- Age \geq 18 years.
- ECOG performance status of 0, 1, or 2.
- Patients with measurable disease per RECIST 1.1 criteria [Eisenhauer].
 - At least one lesion of \geq 1.5 cm in long-axis diameter for nonlymph nodes or \geq 1.5 cm in short-axis diameter for lymph nodes which is serially measurable according to RECIST 1.1 using either computerized tomography (CT) or magnetic resonance imaging (MRI).
 - Lesions that have had radiotherapy must show evidence of progressive disease (PD) based on RECIST 1.1 to be deemed a target lesion.
- Patients must have normal organ and marrow function as defined below:
 - absolute neutrophil count \geq 1,500/ μ L
 - platelets \geq 100,000/ μ L
 - creatinine clearance \geq 40 mL/min
 - bilirubin \leq 1.5 ULN
 - Alkaline phosphatase \leq 3 ULN. If total ALP is $>$ 3 x ULN (in the absence of liver metastasis) or $>$ 5 x ULN in subjects with liver metastasis AND the subject is known to have bone metastases, then liver ALP iso-enzyme should be used to assess liver function rather than total ALP.
 - AST and ALT \leq 3 X ULN,
- Women of child-bearing potential (WOCP) and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for the duration of study participation.
- Life expectancy of $>$ 12 weeks.
- Signed and dated informed consent document indicating that the patient has been informed of all the pertinent aspects of the trial prior to enrollment.

5.2 Exclusion Criteria

Subjects presenting with any of the following will not be included in the trial:

- Patients with symptomatic CNS metastases must have stable disease after

treatment with surgery or radiation therapy.

- Second primary malignancy that is clinically detectable or clinically significant at the time of consideration for study enrollment
- Radiotherapy within 14 days of study treatment.
- Major surgery within 21 days of study treatment. Minor surgery within 2 weeks of study treatment. Placement of vascular access device and biopsies allowed and is not considered major or minor surgery.
- Treatment with any chemotherapy or investigational agents within 4 weeks of the start of study treatment. Subjects must have recovered from toxicities of prior therapy.
- Patients with peripheral neuropathy \geq grade 2
- Significant cardiovascular impairment: congestive heart failure >Class II according to the New York Heart Association (NYHA), unstable angina or myocardial infarction within 6 months of enrollment, or serious cardiac arrhythmia (> grade 2).
- Concomitant severe or uncontrolled medical disease.
- Significant psychiatric or neurologic disorder which would compromise participation in the study
- Pregnant or breast-feeding females.

6. *Trial Treatments*

All patients enrolled will receive treatment with eribulin.

6.1 Drug Supplies

6.1.1 Formulation and Packaging

Eribulin mesylate will be supplied by Eisai in single-use vials at a concentration of 1 mg/2 mL (0.5 mg/mL) solution in ethanol: water (5:95). Eribulin is a clear, colorless, sterile solution for intravenous administration.

6.1.2 Preparation and Dispensing

Aseptically withdraw the required amount of eribulin mesylate 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.

Store undiluted eribulin mesylate 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 eribulin mesylate for up to 4 hours at room temperature or up to 24 hours under refrigeration.

Discard unused portions of the vial.

6.2 Treating the Patient

6.2.1 Conditions patients must meet prior to administering any treatment on Day 1 and 8 of each cycle

Prior to receiving any study treatment on Day 1 or 8 of each cycle, the patient must have all of the following criteria met:

- Neutrophils are $\geq 1.0 \times 10^9/L$,
- Platelets $\geq 75 \times 10^9/L$,
- No grade 3 or 4 non-hematological toxicities.

The Day 8 dose may be delayed for a maximum of 1 week.

- If toxicities do not resolve or improve to \leq Grade 2 severity by Day 15, omit the dose.
- If toxicities resolve or improve to \leq Grade 2 severity by Day 15, administer eribulin at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Blood tests should be performed before starting any study treatment administration and if the above criteria are not met, treatment should be delayed until the criteria for start of treatment are met. If a delay of > 3 weeks (one cycle) is required, the patient should be removed from the study and continue to be treated in accordance with the Investigator's standard clinical practice.

6.2.2 Eribulin administration

Patients will receive eribulin 1.4 mg/m^2 administered intravenously (IV push) over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. Treatment will be continued until disease progression, unacceptable toxicity or patient withdraws consent.

Guidelines for dose modification and dose interruption of study drug are described in Table 6-1.

6.2.3 Dose Modifications

Any dose reduction or dose delay of study drug is based upon the severity of toxicity, as graded by NCI Clinical Toxicity Criteria (NCI-CTCAE, version 4.0). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycles.

All toxicity-related causes for dose reductions or dose delays, must be recorded as an AE. Please refer to Table 6-1 for recommended study drug dose adjustments. Patients requiring a delay in study treatment > 3 weeks or > 2 dose reductions, will be discontinued from study treatment.

Table 6-1 Recommended Dose Reductions of Eribulin

Event Description	Recommended Dose
Permanently reduce the dose for any of the following: <ul style="list-style-type: none"> • ANC <500/mm³ for >7 days • ANC <1,000 /mm³ with fever or infection • Platelets <25,000/mm³ • Platelets <50,000/mm³ requiring transfusion • Non-hematologic Grade 3 or 4 toxicities • Omission or delay of Day 8 dose in previous cycle for toxicity • Creatinine clearance 30-50 mL/min • ECG > 480 hold drug until QTc value is within protocol specified range. 	1.1 mg/m ²
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m²	0.7 mg/m ²
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m² or a Creatinine clearance <30 mL/min	Discontinue eribulin

6.3 Concomitant Medications

Concomitant therapies considered as supportive care are acceptable while participating in this study including granulocyte colony stimulating factors (GCSF), palliative radiation and bisphosphonates for bone metastasis. Patients that require palliative radiation should wait 7-14 days before resuming eribulin therapy.

7. Trial Procedures

Prior to undergoing any study-specific procedure, patients must read and sign the current Institutional Review Board (IRB)-approved informed consent form.

The schedule of assessments is presented in Table 1 (Visit Schedule) in the Protocol Summary.

Assessments outlined in the visit schedule include the following components:

7.1 Screening Visit

The screening visit will occur up to 30 days prior to initiating study treatment.

- Medical History - SGC diagnosis, prior SGC treatment history, and demographics.
- Physical examination - examination of major organ systems, ECOG performance status, body weight and vital signs (i.e., blood pressure, heart rate).
- Laboratory Evaluations will be obtained up to 14 days prior the first dose of eribulin
 - Hematology (CBC with platelets and absolute neutrophil count)
 - Blood chemistry (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, LDH, albumin, bilirubin, AST, ALT, total protein, alkaline phosphatase, magnesium)

- Pregnancy test - serum or urine pregnancy test performed for all women of childbearing potential
- CT scan for known sites of involvement.
- ECG If < 450, no further monitoring. If > 450, needs ECG prior to second dose of eribulin. If > 480, eribulin needs to be held until QTc value is within protocol specified range.

7.2 Day 1 of each Cycle

Day 1 will occur every 21 days (+/- 4 days)

- Physical examination - examination of major organ systems, ECOG performance status, body weight and vital signs (i.e., blood pressure, heart rate).
- Laboratory Evaluations
 - Hematology (CBC with platelets and absolute neutrophil count)
 - Blood chemistry (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, LDH, albumin, bilirubin, AST, ALT, total protein, alkaline phosphatase, magnesium)
- Adverse Event Assessment
- CT scan for known sites of involvement after every 2 cycles (i.e. after cycle 2, 4, 6, etc. Once patients have completed 4 cycles of therapy, they can have CT scans after every 3 cycles.)

7.3 End of Treatment Visit

Patients will undergo the following assessments when all study treatment is discontinued:

- Physical examination - examination of major organ systems, ECOG performance status, body weight and vital signs (i.e., blood pressure, heart rate).
- Laboratory Evaluations
 - Hematology (CBC with platelets and absolute neutrophil count)
 - Blood chemistry (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, LDH, albumin, bilirubin, AST, ALT, total protein, alkaline phosphatase, magnesium)
- Adverse Event Assessment

7.4 Thirty Day Post Treatment Visit

Patients will undergo evaluation for toxicity 30 days (+/- 6 days) after the last dose of study treatment. Patients will undergo the following assessments:

- Physical examination - examination of major organ systems, ECOG performance status, body weight and vital signs (i.e., blood pressure, heart rate).
- Laboratory Evaluations
 - Hematology (CBC with platelets and absolute neutrophil count)
 - Blood chemistry (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, LDH, albumin, bilirubin, AST, ALT, total protein, alkaline phosphatase, magnesium)
- Adverse Event Assessment

7.5 Subject Withdrawal

Patients will be removed from study if they present with disease progression, as defined by radiological RECIST 1.1 criteria. Subjects will also be removed from study if they require more than two dose level reductions. Subjects will also be removed from study if they require more than 3 weeks to recover from adverse events. Patients may withdraw consent at any time.

8. Assessments

The schedule of assessments is presented in Appendix 1. The description of assessments is provided in Section 7.

8.1 Efficacy Assessments

Patients will have their tumors assessed for response by conventional imaging methods (typically CT scans), which will be performed at baseline (at least 30 days prior to the first study drug dose) and then at least every 2 cycles (~ every 6 weeks) after initial dose. Once patients have completed 4 cycles of therapy, they can have CT scans after every 3 cycles.

8.1.1 Definition of Measurable Disease

Measurable disease: the presence of at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with spiral CT scan for non-lymph nodes or ≥ 1.5 cm in short-axis diameter for lymph nodes

Non-measurable disease: all other lesions, including small lesions (longest diameter < 10 mm with spiral CT scan).

8.1.2 Baseline Documentation of Tumor Burden

- Target lesions: All measurable lesions should be identified and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter (SLD). The baseline SLD will be used as the reference by which to characterize the objective tumor response.
- Non-target lesions: 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.

8.1.3 Response Criteria

Radiological response will be defined as per the RECIST criteria. Treatment outcomes will be defined as:

- Complete response (CR): complete resolution of all tumor lesions.
- Partial response (PR): at least a 30% decrease in the sum of the longest diameter of the target lesions (primary tumor and lymph nodes).
- Stable disease (SD): patients with changes that would not qualify as partial responses or progressive diseases.
- Progressive disease (PD): at least a 20% increase in the sum of the longest diameter of the target lesions.

8.2 Time-to-Event Measures

The following definitions for time-to-event measures will apply:

- Duration of Tumor Response is measured from the date of the first objective assessment of PR or CR to the first date of disease relapse or death from any cause.
- Time to Progression is measured from the date of enrollment to the first date of radiographic progression of disease per RECIST 1.1 criteria.

9. Adverse Event Reporting

9.1 Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Cancer Consortium IRB to any event that seems unusual in accordance with IRB policy. The investigator is responsible for the appropriate medical care of patients during the study. The investigator remains responsible to follow, through an appropriate health care option, adverse events that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event resolves or stabilizes. Frequency of follow-up is left to the discretion of the investigator.

Safety measurements that will be used in the study include physical examinations and clinical laboratory tests (hematology and blood chemistries). The adverse event will be graded for toxicity using the NCI CTC version 4.0. Toxicity assessment will occur at each monthly treatment visit, see Schedule of Events, Appendix 1. Any adverse events leading to a treatment interruption or dose reduction along with all adverse events that are grade 3 and higher will be recorded in the CRF.

9.2 Definition of an Adverse Event

The definitions of adverse events (AEs) and serious adverse events (SAEs) are given below.

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), or signs (e.g., tachycardia, enlarged liver).

9.3 Serious Adverse Events

An event that fulfills at least one of the following criteria will be designated a serious adverse event (SAE). SAEs will be reported to the Cancer Consortium IRB per Cancer Consortium policy/procedure.

- Results in death
- Requires initial inpatient hospitalization or prolongation of existing hospitalization
- Is immediately life-threatening
- Results in severe or permanent disability or incapacity
- Is a congenital abnormality or birth defect
- Any other important medical event that may jeopardize the subject or requires medical intervention to prevent one of the outcomes listed above.

Any events that are unequivocally due to progression of disease should not be reported as a serious adverse event.

9.4 Adverse Event Reporting Requirements

Adverse events will be collected after the patient has taken the first dose of study drug. After discontinuation from treatment, patients must be followed for all existing AEs for 30 calendar days after the last dose of study drug or until another anti-cancer therapy is initiated.

Prior to beginning study treatment, study site personnel will note the occurrence and nature of each patient's medical condition(s). During the study, site personnel will again note any change in the condition(s) and/or the occurrence and nature of any adverse events. Toxicities are to be graded according to the NCI CTC version 4.0.

A description of the event, including its date of onset and resolution, any action taken should be provided along with the investigator's assessment of causality. An event that is due to unequivocal progression of disease should not be reported as an AE. Any adverse events leading to a treatment interruption or dose reduction along with all grades 3 and higher adverse events must be recorded on a case report form (CRF).

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has initiated study therapy and until 30 days after the patient has stopped study treatment must be reported to Eisai within 24 hours of learning of its occurrence. Any SAEs experienced after this 30-day period should only be reported to Eisai if the investigator suspects a causal relationship to the study drug.

10. Data Analysis/Statistical Methods

10.1 Sample Size Determination

This is an open-label single-arm phase II study. We will utilize the optimal two-stage Simon design, which minimizes the expected number of patients enrolled under the null hypothesis and given various other assumptions [Simon]. The null hypothesis is that the true response rate is 5% and the alternative hypothesis is that the true response rate is 20%. If we additionally set the significance level to 0.05 (or less) and the power to be at least 80% ($p_0 = 0.05$, $p_1 = 0.20$, $a = 0.05$, $b = 0.20$), then Simon's design dictates that 10 subjects be treated in the first stage. If there are no responses among these 10, the study will be terminated due to lack of efficacy (i.e., this will be considered reasonably strong evidence against the alternative hypothesis that the response rate is 20% or more). If at least one response is observed among these 10, an additional 19 subjects will be recruited for a total of 29 subjects. If 3 or fewer responses are seen among the 29 (an observed response rate of 10.3% or less), the regimen will be deemed to be not sufficiently efficacious for further study. Four or more responses among the 29 will be viewed as sufficient evidence to deem the regimen as potentially efficacious (i.e., reasonably strong evidence that the true response rate is greater than 5%). The expected number of patients to be enrolled under the null hypothesis that the true response rate is 5% is 17.6, and the probability of terminating early in this scenario (after the first stage, i.e., if no responses are seen in the first 10 patients) is 0.60.

10.2 Efficacy Analysis

The primary endpoint will be overall response rate. As noted above, 4 or more observed responses among 29 patients would be considered potentially efficacious and would justify further study. Responses include both complete and partial responses, as defined by RECIST 1.1 criteria. Duration of response and time to progression will be reported as median values. The disease control rate (DCR), defined as the stable disease + partial response rate will be calculated. Toxicity rates will be described as the overall percentage of patients experiencing Grade 3 or higher toxicity.

10.3 Analysis of Other Endpoints

Demographic characteristics such as patient age, gender, tumor type, and ECOG performance status will be tabulated. All continuous data will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum values). All categorical data will be summarized using frequencies and percentages.

Study drug administration will be described in terms of the total number of months administered, the median (range) of months administered, dose intensity, dose modifications, and reasons for the deviations from planned therapy.

Appendix 1. Schedule of Assessments

Procedure	Screening		Every 21 days		End of tmt	30 day post ⁵ tmt
	within 30 days	within 7 days	Day 1	Day 8		
Physical Exam	X		X	X	X	X
Medical History	X					
Pregnancy Test		X				
Hematology ¹	X		X	X	X	X
Serum Chemistries ²	X		X	X	X	X
EGG	X	X ⁴				
CT scans ³	X		X		X	
Eribulin			X	X		
AE Assessment			X	X	X	X

¹ Serum chemistries include sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, LDH, albumin, bilirubin, AST, ALT, total protein, alkaline phosphatase, magnesium.

² CBC with platelets and absolute neutrophil count.

³ CT scan for known sites of involvement after every 2 cycles of combined therapy. After 4 cycles of therapy scans may be repeated after every 3 cycles.

⁴ If > 450, needs ECG prior to second dose of eribulin.

⁵ 30 day follow-ups can be done at patients' local physician

13. References

- Airoldi M, Pedani F, Succo G, Gabriele AM, Ragona R, Marchionatti S, Bumma C. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. *Cancer*. 2001 Feb 1;91(3):541-7.
- Agulnik M, Cohen EW, Cohen RB, Chen EX, Vokes EE, Hotte SJ, Winkquist E, Laurie S, Hayes DN, Dancey JE, Brown S, Pond GR, Lorimer I, Daneshmand M, Ho J, Tsao MS, Siu LL. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. *J Clin Oncol*. 2007 Sep 1; 25(25):3978-84.
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009 Jan;45(2):228-47.
- Hotte SJ, Winkquist EW, Lamont E, MacKenzie M, Vokes E, Chen EX, Brown S, Pond GR, Murgu A, Siu LL. Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: a Princess Margaret Hospital phase II consortium study. *J Clin Oncol*. 2005 Jan 20;23(3):585-90.
- Griffin TW, Pajak TF, Laramore GE, Duncan W, Richter MP, Hendrickson FR, Maor MH. Neutron vs photon irradiation of inoperable salivary gland tumors: results of an RTOG-MRC Cooperative Randomized Study. *Int J Radiat Oncol Biol Phys*. 1988 Nov;15(5):1085-90.
- Laurie SA, Licitra L. Systemic therapy in the palliative management of advanced salivary gland cancers. *J Clin Oncol*. 2006 Jun 10;24(17):2673-8.
- Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989 Mar;10(1):1-10.