Phase II Trial of Mitomycin C in Patients with Incurable p16 Positive Oropharyngeal and p16 Negative Head and Neck Squamous Cell Carcinoma (HNSCC) Resistant to Standard Therapies

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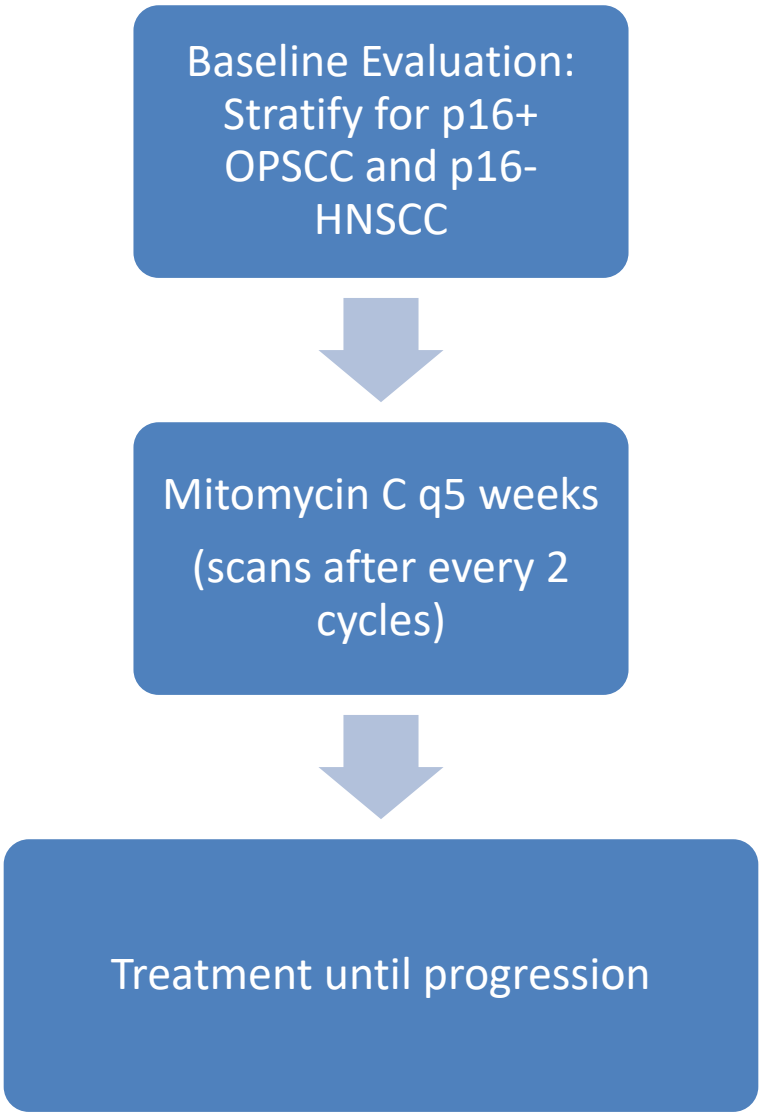
SCHEMA



Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
B-HCG	Beta human chorionic gonadotropin
CBC	Complete blood count
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HRPO	Human Research Protection Office (IRB)
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IULN	Institutional upper limit of normal
IV	Intravenous (i.v.)
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
OPSCC	Oropharyngeal squamous cell carcinoma
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PHI	Protected health information
PI	Principal investigator
PR	Partial response

QASMC	Quality Assurance and Safety Monitoring Committee
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RNA	Ribonucleic acid
RR	Response rate
SAE	Serious adverse event
SCC	Siteman Cancer Center
SD	Stable disease
SQ	Subcutaneous
TRR	Tumor response rate
UPN	Unique patient number
WUSM	Washington University School of Medicine

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1.0 BACKGROUND AND RATIONALE

1.1 Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer. Fifty thousand new cases are diagnosed each year. Most patients present with locally advanced disease stage (III, IVa, and IVb) and are treated with multimodality therapy. Human papilloma virus (HPV; p16+)-related oropharyngeal squamous cell carcinoma (OPSCC) represents 15% of all new cases of HNSCC. Such patients have an excellent prognosis with recurrence rates of only 10-20%. However, patients with HPV-unrelated (p16-)/smoking-induced HNSCC have a substantially poorer prognosis, and 50% or more of these patients will experience death due to disease recurrence. Patients with incurable HNSCC have a poor prognosis and limited therapy options, resulting in major unmet need.

1.2 Incurable HNSCC

1.2.1 First Line Therapy

Patients with recurrent, incurable HNSCC have a median overall survival (OS) of 10.1 months, median progression-free survival (PFS) of 5.6 months, and an overall tumor response rate (RR) of 36% when treated with the current standard first line chemotherapy regimen of cis/carboplatin, 5-FU, and cetuximab.[1,2] This was established in a landmark study called the EXTREME trial, during which Vermorken et al randomly assigned patients with untreated incurable HNSCC to receive a regimen of PF (platin [cisplatin 100 mg/m^2 or carboplatin AUC 5] on Day 1 plus 5-FU 1000 mg/m^2/day for 4 days) on a 3-week cycle either alone or with concurrent cetuximab for a maximum of 6 cycles.[1] The trial showed a significant improvement in all major efficacy parameters including OS (7.4 vs 10.1 mos), PFS (3.3 vs 5.6 mos), and RR (20% vs 36%) with the addition of cetuximab to chemotherapy. In addition to promoting the institution of the new standard of care therapy for incurable HNSCC, the EXTREME trial led to a new Food and Drug Administration (FDA) approved indication for cetuximab.

1.2.2 Second Line Therapy

Paclitaxel has substantial single agent activity as first line treatment of incurable HNSCC with tumor RR of 40%.[3,4] However, the efficacy of paclitaxel alone in patients with incurable HNSCC that progressed with platin, 5-FU, and cetuximab is unknown.

Docetaxel also has substantial single agent activity as first line treatment in incurable HNSCC with RR of 42%.[4] However, the efficacy of docetaxel in patients with incurable HNSCC that progressed with platin, 5-FU, and cetuximab is unknown.

Methotrexate has been used in the treatment of incurable HNSCC; however, the

efficacy of this agent in patients with HNSCC that progressed with platin, 5-FU, and cetuximab is also unknown.

1.2.3 PD-L1 in HNSCC

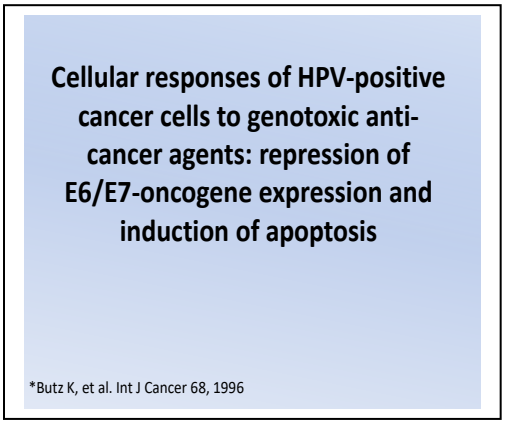
Expression of PD-L1 is frequent (80%) in HNSCC.[5] Clinical trials showed an OS benefit with nivolumab, a PD-1 inhibitor, in platin-resistant RM-HNSCC.[6] Regulatory agencies approved nivolumab and pembrolizumab in 2016 for this indication. However, the benefit of PD-1 inhibitors was also modest. The tumor response rate of these agents was 13-18%,[5,6] the median PFS was 2.0 months and the median OS was only 7.5 months.[6] These data point to the observation that only a small subset of patients with RM-HNSCC benefit from PD-1 inhibitors.

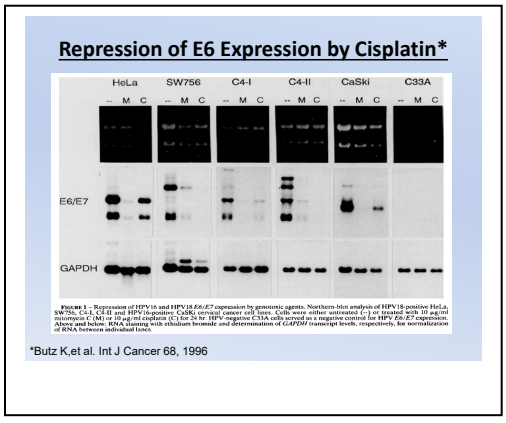
1.3 Mitomycin C

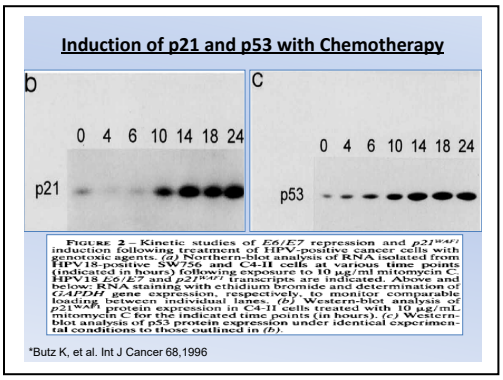
1.3.1 In HNSCC

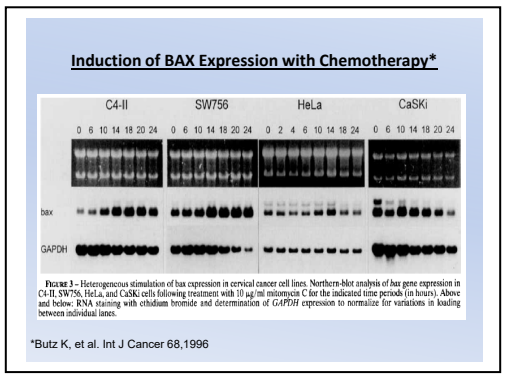
Although mitomycin C is not currently considered a standard option in the treatment of incurable HNSCC, there is a body of data supporting its efficacy in preclinical experiments[7] and in combination with radiation as a radiosensitizer for curable disease and in combination with other chemotherapy in incurable disease.[8]

Preclinical experiments demonstrated repression of E6 expression and induction of apoptosis in HPV SCC cell lines exposed to mitomycin C.[7]







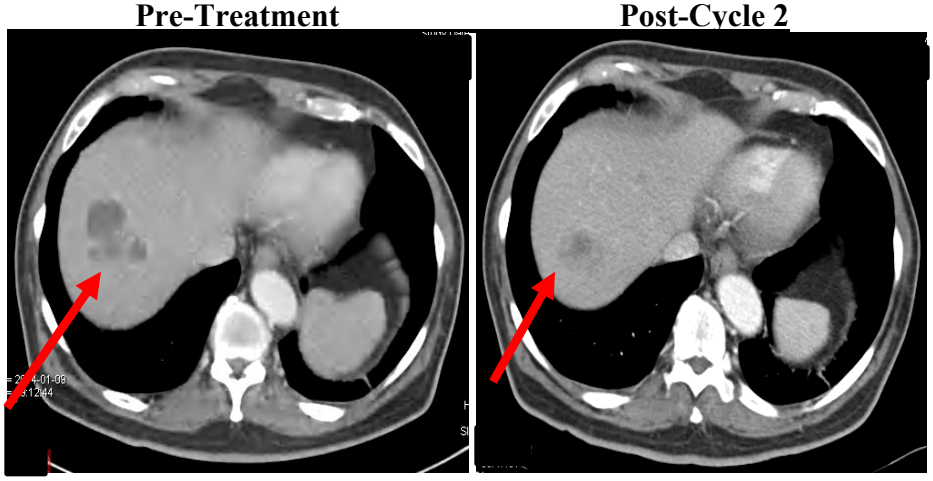


In patients with curable HNSCC, several studies have added mitomycin C to radiation as a radiosensitizer;[9] however, the independent effect of mitomycin C on efficacy is not clear. In patients with incurable HNSCC, studies have combined mitomycin C with other chemotherapy; however, the independent effect of mitomycin C is not clear.[8]

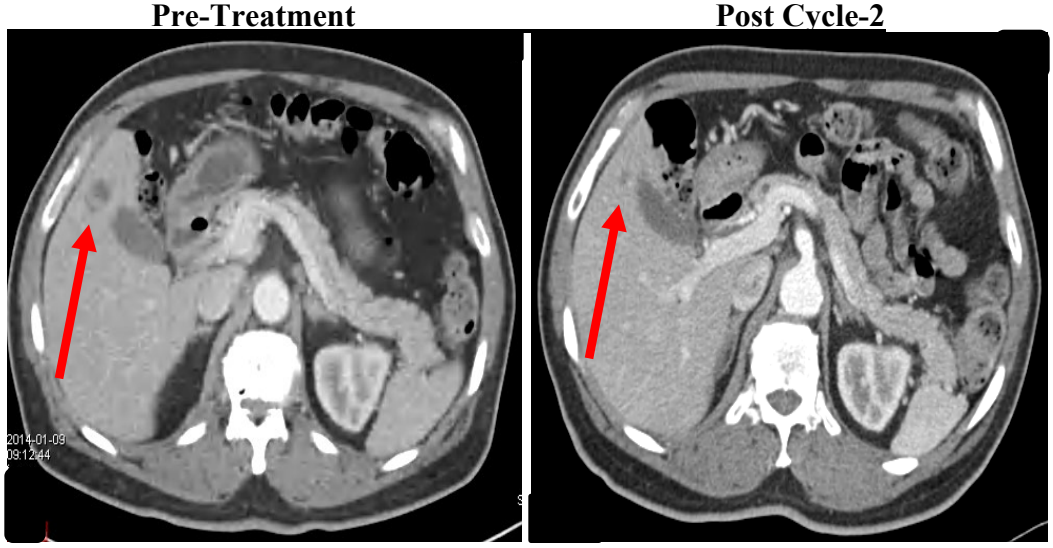
1.3.2 Patients with Incurable HNSCC Treated with Single Agent Mitomycin C

We have treated two patients with incurable HNSCC with mitomycin C. Each patient's cancer had progressed on prior platin, 5-FU, cetuximab, and taxane. Mitomycin C was administered at either 20 mg/m^2 (Case 1) or 10 mg/m^2 (Case 2) q6 wks. Both patients' cancer responded to mitomycin C. Case 1 is shown below:

Pre-Treatment **Post-Cycle 2**



Pre-Treatment **Post Cycle-2**



Case 1 was given 20 mg/m^2 of mitomycin C q6 weeks; however, this patient experienced prolonged grade 4 thrombocytopenia after Cycle 2 during which the

patient's cancer progressed. Therefore, a lower dose of mitomycin C (10 mg/m^2) was used for Case 2. This patient did not experience grade 3 or 4 hematologic toxicity with Cycle 1. Although Case 2 has not undergone full radiologic assessment of tumor response assessment yet, the large fungating neck mass has dramatically decreased in size based on direct visual examination.

1.3.3 In Anal SCC

Anal SCC is also caused by HPV infection. Most patients are treated with definitive chemoradiation, the current standard regimen being mitomycin C, 5-FU, and radiation.[10] Randomized trials have established the critical importance of mitomycin C in the CRT regimen. RTOG 87-04/ ECOG 1289 demonstrated that mitomycin C/5-FU/RT was superior to 5-FU/RT alone.[11] RTOG 98-11 demonstrated that mitomycin C/5-FU/RT was superior to cisplatin/5-FU/RT.[12,13] These studies highlight the effectiveness of mitomycin C in the treatment of HPV induced anal SCC, and provide rationale for investigating this agent in other HPV induced mucosal SCC such as those of the oropharynx.

1.3.4 In Cervical SCC

Cervical SCC is initiated by high risk HPV serotypes. Several studies have included mitomycin C in the treatment of incurable cervical SCC; however, the independent effects of mitomycin C in these studies is unclear.[8]

1.4 Study Rationale

In incurable HNSCC, no standard second line therapy exists following disease progression on platin/5-FU/cetuximab, although most would deliver a taxane, even though no prospective data exists to support the benefit of this approach.

No agent is known to have efficacy in patients with incurable HNSCC that progressed with prior platin, 5-FU, cetuximab and taxane. Herein lies the unmet need to be addressed by this trial. Based on the preclinical and clinical data presented, we propose that mitomycin C will have anti-tumor activity in these patients. Since the biology of p16 positive OPSCC and p16 negative HNSCC are distinctly different, we will stratify patients into two groups based on p16 status. A two stage Simon schema will be used for each group (p16+ OPSCC and p16- HNSCC). The primary endpoint is tumor response rate as assessed by RECIST 1.1 criteria.

Amendment #7: As of October 2020, accrual to the p16+ cohort continues based on activity observed in Simon Stage 1; the p16- cohort was closed after Simon Stage 1 due to inactivity. However, accrual to the trial has been slower than expected. Since the trial opened, a key impediment to accrual was the interim FDA approval of immunotherapy for HNSCC, adding an additional line of standard treatment prior to patients going on to this trial. In an effort to increase the pace of accrual to this trial, we propose changing the current inclusion requirement of disease progression on prior platinum, cetuximab, taxane

and 5-FU to disease progression on prior platinum and immunotherapy. The rationale for this amendment is that platinum and immunotherapy are the only agents that improved OS when given as monotherapy; whereas, monotherapy with either cetuximab, taxane, and 5-FU do not yield an OS benefit and have a low response rate (<5%) in this setting.

1.5 Correlative Studies Background

Tumor biopsies and blood will be obtained, if possible, for planned immunohistochemistries of smad4, BRCA1, and Rad51, which are known to be reduced in HNSCC and whose loss confers sensitivity to mitomycin C. Other studies may be performed as indicated.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the tumor response rate of patients with incurable HNSCC that progressed following platin, 5-FU, cetuximab and taxane who are treated with mitomycin C, stratified for p16+ OPSCC and p16- HNSCC. Post October 2020: To determine the tumor response rate of patients with incurable p16+ OPSCC HNSCC that progressed following platin, and immunotherapy who are treated with mitomycin C.

2.2 Secondary Objectives

1. To determine progression-free survival (PFS) of these patients, stratified for p16+ OPSCC and p16- HNSCC.
2. To evaluate the instances of grades 3 and 4 adverse events (using CTCAE version 3.0) on this trial.
3. To determine the overall survival (OS) of these patients, stratified for p16+ OPSCC and p16- HNSCC.

2.3 Exploratory Objectives

1. To evaluate tumor tissue and blood for immunohistochemical analyses relating to response to mitomycin C.
2. To characterize the quality of life of patients on this trial.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed incurable HNSCC of the oral cavity, oropharynx, larynx, hypopharynx, and/or Level 1-3 neck node with non-cutaneous SCC and unknown primary. “Incurable” is defined as metastatic disease or a local or

regional recurrence in a previously irradiated site that is unresectable (or patient declines resection).

2. Progression following platin and immunotherapy given for incurable disease.

3. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan, as ≥ 20 mm by chest x-ray, or ≥ 10 mm with calipers by clinical exam per RECIST 1.1.

4. Tissue available (either initial diagnostic or recurrent tissue specimen) for p16 testing (if p16 status is already known, this criterion may be waived).

5. At least 18 years of age.

6. ECOG performance status ≤ 3 (see Appendix A).

7. Adequate hematologic, renal, and hepatic function as defined below:
   a. Absolute neutrophil count ≥ 1,000/mcl
   b. Platelets ≥ 75,000/mcl
   c. Total bilirubin ≤ 1.5 mg/dL
   d. AST(SGOT)/ALT(SGPT) ≤ 2.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN, unless bone metastasis is present in the absence of liver metastasis
   e. Creatinine below ULN (males 0.7-1.30 mg/dl; females 0.6-1.10 mg/dl) OR creatinine clearance ≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

8. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry, for the duration of study participation, and for 1 month after completing treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

9. Patients who have known HIV positivity must be on a 3-drug antiviral regimen that does not include zidovudine, and must have a CD4 count >100/mm3 and virus load <5000 copies/ml, and are placed on a regimen to prevent PCP reactivation during treatment.

10. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Other active malignancy with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only, carcinoma *in situ* of the cervix, or synchronous H&N primaries.

2. Currently receiving any other investigational agents.

3. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4. Pregnant and/or breastfeeding. Patient must have a negative pregnancy test within 7 days of start of study treatment.

5. Known active central nervous system (CNS) metastases. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 28 days prior to treatment.

6. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to mitomycin C or other agents used in the study.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

This is a phase II trial of mitomycin C, given in 5 week cycles. Tumor response assessment using RECIST criteria will occur after every two cycles of chemotherapy. Treatment will be discontinued for disease progression, unacceptable AE, or patient or physician decision.

Tissue will be requested for p16 analysis IHC stain. This may be either an initial diagnostic or recurrent tissue specimen. p16+ is defined as ≥ 70% of tumor cells staining for p16; p16- is defined as < 70% tumor cells staining for p16.

5.1 Premedication Administration

Standard anti-emetics will be given before mitomycin C.

5.2 Agent Administration

The regimen consists of:

1. Mitomycin C 10 mg/m^2 IV will be given on Day 1 Q5 weeks.
2. Pegfilgrastim 6 mg SQ will be given on Day 2 of each cycle.

Pegfilgrastim will be administered as per routine care, and may be given during an office visit on Day 2 using a prefilled syringe or using the on-body injector, which will be applied to the back of the patient's upper arm or to the patient's abdomen in the clinic on Day 1 and will administer the injection approximately 27 hours after application.

5.3 Evaluability

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 28-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they come off study prior to completion of cycle 2 due to adverse event(s), patient withdrawal, or early death and have not had an assessment of tumor response.

5.4 General Concomitant Medication and Supportive Care Guidelines

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Concurrent treatment with bisphosphonates and denosumab is allowed. Erythropoietin and G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines. Palliative radiation therapy is acceptable for bone metastases provided the bone lesion is not a target lesion.

5.5 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 7 days prior to the first dose of mitomycin C.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 1 month following the last dose of study treatment.

If a patient is suspected to be pregnant, all study drugs should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 1 month after the last dose of study treatment, the investigator must be notified in order to facilitate outcome follow-up.

5.6 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue indefinitely until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up

- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.7 Duration of Follow-up

Patients will be followed for progression and survival every 3 months indefinitely until death. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications for Mitomycin C

Nadir After Prior Dose		Percentage of Prior Dose To Be Given
Neutrophils/mm^3	**Platelets/mm^3**	
>1000	>50,000	100%
>500	20,000–50,000	75%
<500	<20,000	50%

Dosing will not be re-escalated after reduction, and there is no limit to the number of dose reductions a patient may have during the course of his/her participation on trial. There is no minimum dose. Patients may be dose-reduced until dosing cannot physically be further reduced or until progression.

No repeat dosage should be given until absolute neutrophil count has returned to 1000/mm^3 and a platelet count to 75,000/mm^3. Dosing between cycles may be delayed for up to 5 weeks. If a patient requires a delay of more than 5 weeks s/he must come off study.

Mitomycin C will not be re-dosed following the diagnosis of Hemolytic Uremic Syndrome (HUS).

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below. Please refer to Appendix D for definitions and Appendix E for a grid of reporting timelines.

Adverse events will be tracked from start of study treatment through 28 days following the last day of study treatment. All adverse events must be recorded on the toxicity tracking case report form (CRF).

Refer to the data submission schedule in Section 12 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the changes.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Sponsor-Investigator is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 PHARMACEUTICAL INFORMATION

8.1 Mitomycin C

8.1.1 Mitomycin C Description

Mitomycin (also known as mitomycin-C) is an antibiotic isolated from the broth of Streptomyces caespitosus which has been shown to have antitumor activity. The compound is heat stable, has a high melting point, and is freely soluble in organic solvents.

Mitomycin is a blue-violet crystalline powder with the molecular formula of $C_{15}H_{18}N_4O_5$, and a molecular weight of 334.33. Its chemical name is 7-amino-9α-methoxymitosane and it has the following structural formula.

8.1.2 Clinical Pharmacology

Mitomycin selectively inhibits the synthesis of deoxyribonucleic acid (DNA). The guanine and cytosine content correlates with the degree of mitomycin-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed.

In humans, mitomycin is rapidly cleared from the serum after intravenous administration. Time required to reduce the serum concentration by 50% after a 30 mg bolus injection is 17 minutes. Clearance is effected primarily by metabolism in the liver, but metabolism occurs in other tissues as well. The rate of clearance is inversely proportional to the maximal serum concentration because, it is thought, of saturation of the degradation pathways.

Approximately 10% of a dose of mitomycin is excreted unchanged in the urine.

8.1.3 Supplier

Mitomycin for Injection is available commercially.

8.1.4 Dosage Form and Preparation

Mitomycin for Injection is a sterile dry mixture of mitomycin and mannitol, which when reconstituted with Sterile Water for Injection provides a solution for intravenous administration. Each vial contains either mitomycin 5 mg and mannitol 10 mg, or mitomycin 20 mg and mannitol 40 mg, or mitomycin 40 mg and mannitol 80 mg. Each mL of reconstituted solution will contain 0.5 mg mitomycin and have a pH between 6.0 and 8.0.

8.1.5 Storage and Stability

Mitomycin C should be stored at controlled room temperature at 15°C-30°C and protected from light. Reconstituted mitomycin C should be used within 24 hours.

8.1.6 Administration

Mitomycin C will be given IV at a dose of 10 mg/m^2 on Day 1 Q5 weeks.

9.0 CORRELATIVE STUDIES

9.1 Archived Tumor Tissue

9.1.1 Collection of Specimen(s)

Previously collected formalin-fixed paraffin embedded tissue (15 slides per case) will be requested for immunohistochemical analyses. This may be archival tissue from a previous pre-treatment diagnostic biopsy, tissue collected under HRPO# 201102323 ("Analysis of Histological, Genomic, Molecular, and Clinical Factors in Head and Neck Cancer: The Tissue Acquisition Protocol (TAP)") to which participants in this study will be encouraged to enroll, or tissue collected under the auspices of this protocol should archival or previously banked tissue be unavailable. If biopsies are performed as part of this protocol, collection will be performed as follows. Tissue samples will be obtained by simple excision (1-2 cm^3 portion of tissue) or 4 mm or greater dermatology biopsy punch. Specimens should be fixed in 10% buffered formalin.

Tissue for p16 testing is required. Tissue collection is highly encouraged for correlative testing, but is not required for trial participation.

9.1.2 Handling of Specimen(s)

Archived tissue should be delivered to the study team at Campus Box 8056.

9.2 Blood for Future Research

For patients not enrolled in HRPO# 201102323, 20 mL of anticoagulated blood will be collected in three EDTA purple top tubes prior to initiation of treatment and again at progression/recurrence. Samples will be spun and processed for peripheral white blood cells. Residual red blood cells will be removed by hypotonic lysis. Nucleated cells will be washed in phosphate buffered saline, divided into approximately 20 x 10^6 cells/aliquot, spun down, and the supernatant removed. Cell pellets will be labeled with a unique specimen ID number, snap frozen in liquid nitrogen, and stored under liquid nitrogen vapor in an inventoried storage unit at the Siteman Cancer Center Tissue Procurement Core Facility.

9.3 Quality of Life Assessments

QOL assessments will be performed at screening, every 5 weeks, and at the end of treatment visit.

QOL assessment tools will include EORTC QLQ-C30 (Appendix B) and Cognitive Failures Questions (CFQ) (Appendix C).

10.0 STUDY CALENDAR

Screening evaluations are to be conducted within 28 days prior to start of protocol therapy.

	Screening	Treatment[1]			EOT[2]	Follow-Up[3]
		W1D1	W1D2	W3		
Informed consent	X					
H&P, ECOG PS, weight	X	X		X	X	
CBC	X	X		X	X	
CMP	X	X			X	
BMP				X		
B-hCG[4]	X					
CT or MRI of neck and chest (abdomen/pelvis only if disease in area)	X	X[5]			X	X[6]
Mitomycin-C		X				
Neulasta			X[8]			
QOLs	X	X			X	
Research blood draw	See Section 9.2					
Archival tumor tissue for correlatives	X[9]					
Archival tumor tissue for p16 testing[10]	X					
AE assessment		X----------X[7]				

1. Indefinite number of cycles – q 5 weeks
2. Defined as date patient comes off study (due to progression, adverse event, patient/physician decision, etc)
3. Every 3 months (+/- 1 month)
4. Women of childbearing potential only; must be within 7 days of first dose of study treatment
5. Scans to be repeated after every 2 cycles
6. Only if off study for reason other than progression, scan until progression
7. Date of first treatment until 28 days post treatment
8. May be given in clinic using a pre-filled syringe or at home using the on-body injector
9. Optional
10. Or separate confirmation of p16 status

11.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

For phase I dose escalation studies, the Principal Investigator will review all patient data at least monthly (or before each dose-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). For phase II or dose expansion cohorts of a phase I study, the Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy (phase I studies only if efficacy is objective of the protocol)
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Power analysis and/or interim analysis (if described in the protocol)
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

12.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment
Treatment Form	Every cycle
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 3 months
Tumor Measurement Form	Baseline End of every even-numbered cycle End of treatment
QOL Form	Baseline Every cycle End of treatment
Correlative Studies Form	Baseline
SAE Form	See Section 7.0 for reporting requirements
Progression Form	Time of progression
Death Form	Time of death

12.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment must be captured in the Toxicity Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

13.0 MEASUREMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response at the end of every even-numbered cycle (every 10 weeks). In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter

(unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

13.2 Disease Parameters

Measurable disease: 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).

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.

Non-measurable disease: 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 patient, these are preferred for selection as target lesions.

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.

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.

13.3 Methods for Evaluation of Measurable Disease

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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the

initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

13.4 Response Criteria

13.4.1 Evaluation 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.

13.4.2 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 patient 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 treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

13.4.3 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 progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

13.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.4.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of first radiologic confirmation of progression or death, whichever occurs first.

13.4.6 Response Review

For trials where the response rate is the primary endpoint, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

14.0 STATISTICAL CONSIDERATIONS

14.1 Hypothesis

A novel regimen of mitomycin C will result in tumor responses in patients with incurable p16+ OPSCC and p16- HNSCC.

14.2 Study Endpoints

The primary endpoint is tumor response rate in p16+ OPSCC and p16- HNSCC. Secondary endpoints are progression free survival (PFS), occurrence of grade 3-4 adverse events by CTCAE 3.0, and overall survival (OS). Exploratory endpoints of quality of life measured by the EORTC-QLQ-30 and Cognitive Failures Questions (CFQ).

14.3 Statistical Design

Tumor response rate (TRR) will be evaluated separately in p16- HNSCC patients and in p16+ OPSCC patients using two optimal two-stage Simon designs. In both cases, the expected TRR is 10%. A TRR of 30% is considered a clinically significant increase. In each study arm a maximum of 35 patients will be enrolled, 12 in the first stage. If at least 2 tumor responses are observed in the first stage, an additional 23 patients will be enrolled in the second stage. The trial will conclude that there is evidence of increased efficacy if at least 6 tumor responses are observed among the 35 patients in both stages. The probability of termination after the first stage is .66 if the true TRR is 10%. Power is .90 at a .10 significance level.

We did not see at least 2 tumor responses in the p16- HNSCC group, so there will not be a second stage of enrollment for that patient population.

14.4 Analysis Plan for Time to Event and Adverse Events Endpoints

All grade AEs, all serious (Grades 3-4) AEs, and all Grade 5 (treatment-related deaths) AEs will be analyzed using descriptive statistics and compared to historical controls using one-sample tests for difference of proportions.

PFS and OS will be described in each study group using Kaplan-Meier or Cox proportional hazards models to estimate medians and hazard ratios with 95% confidence intervals.

14.5 Analysis Plan for Quality of Life Endpoints

The exploratory quality of life endpoints will include the EORTC-QLQ-C30, which has a total score, one general QOL and one “within the last week” subscale, as well as a single general health item and a single overall QOL item. The CFQ has 3 subscales describing perception, memory and motor function.

Mean or median quality of life will be documented in the two study groups. Patient-specific and clinical significance of observed differences will be a matter for discussion at the end of the study; the study does not intend to determine a minimal important difference. The study does use current empirical guidelines for the EORTC-QLQ-30 global score with the understanding that both the magnitude and variance of scores vary considerably from patient to patient, from one time point to another and by such factors as disease condition, age and comorbidity. For the CFQ, a change of 1 standard deviation will be considered a perceptible difference.

Tables and histograms will be used to explore change in the subscales and summary scales in each study group. Scale and subscale scores may be used as independent variables in models of TRR, OS or PFS using chi-square, Kaplan-Meier and Cox proportional hazards methods. Spearman's rank correlation or, where there are a large number of tied scores, Kendall's tau-b will be used to explore correlation (redundancy) between QOL (sub)scales prior to modeling.

15.0 REFERENCES

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: EORTC QLQ-C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	**A Little**	**Quite a bit**	**Very Much**
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	**1**	**2**	**3**	**4**
2. Do you have any trouble taking a long walk?	**1**	**2**	**3**	**4**
3. Do you have any trouble taking a short walk outside of the house?	**1**	**2**	**3**	**4**
4. Do you need to stay in bed or a chair during the day?	**1**	**2**	**3**	**4**
5. Do you need help with eating, dressing, washing yourself or using the toilet?	**1**	**2**	**3**	**4**
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	**1**	**2**	**3**	**4**
7. Were you limited in pursuing your hobbies or other leisure time activities?	**1**	**2**	**3**	**4**
8. Were you short of breath?	**1**	**2**	**3**	**4**
9. Have you had pain?	**1**	**2**	**3**	**4**
10. Did you need to rest?	**1**	**2**	**3**	**4**
11. Have you had trouble sleeping?	**1**	**2**	**3**	**4**
12. Have you felt weak?	**1**	**2**	**3**	**4**
13. Have you lacked appetite?	**1**	**2**	**3**	**4**
14. Have you felt nauseated?	**1**	**2**	**3**	**4**
15. Have you vomited?	**1**	**2**	**3**	**4**
16. Have you been constipated?	**1**	**2**	**3**	**4**
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?				
18. Were you tired?				
19. Did pain interfere with your daily activities?				
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?				
21. Did you feel tense?				
22. Did you worry?				
23. Did you feel irritable?				
24. Did you feel depressed?				

25. Have you had difficulty remembering things?				
26. Has your physical condition or medical treatment interfered with your family life?				
27. Has your physical condition or medical treatment interfered with your social activities?				
28. Has your physical condition or medical treatment caused you financial difficulties?				

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						**Excellent**

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						**Excellent**

APPENDIX C: COGNITIVE FAILURES QUESTIONNAIRE

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the past 6 months. Please circle the appropriate number.

	Very Often	Quite Often	Occasion-ally	Very rarely	Never
1. Do you read something and find you haven't been thinking about it and must read it again?	**4**	**3**	**2**	**1**	**0**
2. Do you find you forget why you went from one part of the house to the other?	**4**	**3**	**2**	**1**	**0**
3. Do you fail to notice signposts on the road?	**4**	**3**	**2**	**1**	**0**
4. Do you find you confuse right and left when giving directions?	**4**	**3**	**2**	**1**	**0**
5. Do you bump into people?	**4**	**3**	**2**	**1**	**0**
6. Do you find you forget whether you've turned off a light or a fire or locked the door?	**4**	**3**	**2**	**1**	**0**
7. Do you fail to listen to people's names when you are meeting them?	**4**	**3**	**2**	**1**	**0**
8. Do you say something and realize afterwards that it might be taken as insulting?	**4**	**3**	**2**	**1**	**0**
9. Do you fail to hear people speaking to you when you are doing something else?	**4**	**3**	**2**	**1**	**0**
10. Do you lose your temper and regret it?	**4**	**3**	**2**	**1**	**0**
11. Do you leave important letters unanswered for days?	**4**	**3**	**2**	**1**	**0**
12. Do you find you forget which way to turn on a road you know well but rarely use?	**4**	**3**	**2**	**1**	**0**
13. Do you fail to see what you want in a supermarket (although it's there)?	**4**	**3**	**2**	**1**	**0**
14. Do you find yourself suddenly wondering whether you've used a word correctly?	**4**	**3**	**2**	**1**	**0**
15. Do you have trouble making up your mind?	**4**	**3**	**2**	**1**	**0**
16. Do you find you forget appointments?	**4**	**3**	**2**	**1**	**0**
17. Do you forget where you put something like a newspaper or a book?	**4**	**3**	**2**	**1**	**0**
18. Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	**4**	**3**	**2**	**1**	**0**
19. Do you daydream when you ought to be listening to something?	**4**	**3**	**2**	**1**	**0**
20. Do you find you forget people's names?	**4**	**3**	**2**	**1**	**0**

21. Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	**4**	**3**	**2**	**1**	**0**
22. Do you find you can't quite remember something although it's "on the tip of your tongue"?	**4**	**3**	**2**	**1**	**0**
23. Do you find you forget what you came to the shops to buy?	**4**	**3**	**2**	**1**	**0**
24. Do you drop things?	**4**	**3**	**2**	**1**	**0**
25. Do you find you can't think of anything to say?	**4**	**3**	**2**	**1**	**0**

APPENDIX D: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term “research” encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX E: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Serious AND unexpected suspected adverse reaction		
Unexpected fatal or life-threatening suspected adverse reaction		
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	