Protocol #: BMX-HN-001

A Phase 1/2 Trial of Concurrent Radiation Therapy, Cisplatin, and BMX-001 in Locally Advanced Head and Neck Cancer

Sponsor: BioMimetix JV, LLC
Funding Source: National Cancer Institute – SBIR Contract to BioMimetix JV, LLC
NCT02990468

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Protocol number:	BMX-HN-001
Version:	6.0
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Version Date:	April 30, 2019
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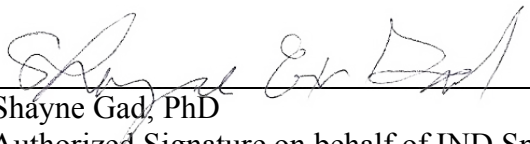

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2 List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AMRI	Albany Molecular Research, Inc.
AP	Anterior-Posterior
AST	Aspartate Aminotransferase
BED2	Biologically Equivalent Dose in 2 Gy fractions
BID	Twice daily
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CRT	Radiation Treatment and Concurrent Cisplatin
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTQA	Clinical Trials Quality Assurance
CTV	Clinical Target Volume
DLQI	Dermatology Quality of Life Index
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
EQD2	2 Gy-per-fraction Equivalent Dose
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-HN	Functional Assessment of Cancer Therapy – Head & Neck (Version 4)
GMP	Good Manufacturing Practice
GTV	Gross Tumor Volume
Gy	Gray
HIF-1	Hypoxia-inducible factor-1
HNSCC	Head and neck squamous cell carcinoma
H&P	History & Physical Exam
HRPP	Human Research Protections Program
HRQoL	Health-Related Quality of Life
IMRT	Intensity Modulated Radiotherapy
IGRT	Image-Guided Radiotherapy
kV	Kilovoltage
KPS	Karnofsky Performance Scale
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MnSOD	Manganese Superoxide Dismutase

MOS	Median Overall Survival
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MV	Megavoltage
NCI	National Cancer Institute
NFκB	Nuclear Factor Kappa B
NRG	NRG Oncology
OAR	Organs at Risk
OMWQ-HN	Oral Mucositis Weekly Questionnaire – Head & Neck
ORR	Overall Response Rate
OS	Overall Survival
PA	Posterior-Anterior
PD	Progressive Disease
PEG	Prophylactic Gastrostomy Tube
PET	Positron Emission Tomography
PFS	Progression-free Survival
PFS-6	Progression-free Survival at 6 months
p.o.	per os/by mouth/orally
PR	Partial Response
PRO	Patient-Reported Outcome
PRO-CTCAE	Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events
PRV	Planning Risk Volume
PTV	Planning Target Volume
QoL	Quality of Life
RP2D	Recommended Phase 2 Dose
RT	Radiation Therapy
SAE	Serious Adverse Event
SCCHN	Squamous Cell Carcinoma Head and Neck
SD	Stable Disease
SIB	Simultaneous Integrated Boost
SOC	Standard of Care
SOD	Superoxide Dismutase
SQ	Subcutaneous
TDP	Torsades de pointes
UAP	Unanticipated problems
ULN	Upper limit of normal
VMAT	Volumetric-Modulated Arc Therapy
XeQoLS	Xerostomia-Related Quality of Life Scale
WBC	White Blood Cells
WHO	World Health Organization

3 Schema of Clinical Trial

A Phase 1/2 Trial of Concurrent Radiation Therapy, Cisplatin, and BMX-001 in Locally Advanced Head and Neck Cancer

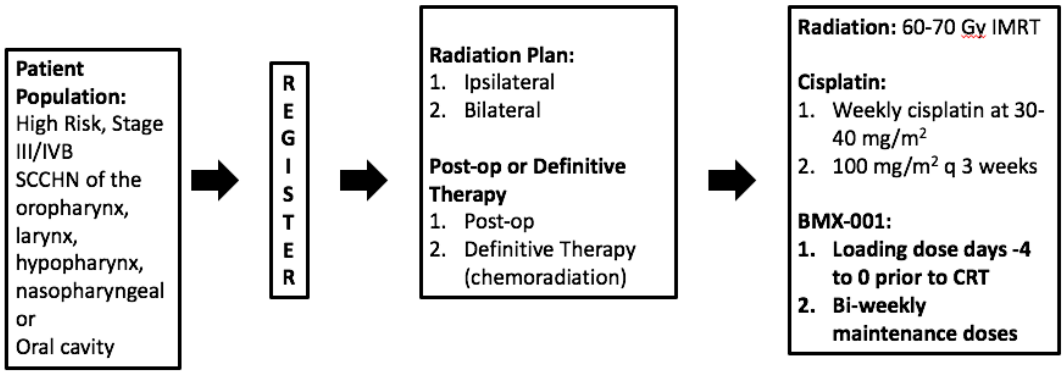

Figure 1. Schema of Clinical Trial

Patient Population: (See Section 6 for Eligibility Criteria)
Pathologically proven diagnosis of head and neck cancer (squamous cell carcinoma) requiring radiation and concurrent cisplatin chemotherapy.
Sample Size Phase 1: 6
Maximum Sample Size Phase 2: 48

Post-op in the above schema refers to subjects who have had tumor resection and are being scheduled for post-operative radiation therapy and chemotherapy.

Definitive Therapy in the above schema refers to subjects who have not undergone tumor resection but are being scheduled for primary radiation therapy and chemotherapy designed to be the definitive approach to their treatment program.

4 Introduction

4.1 Head and Neck Cancer

4.1.1 Disease

In 2013 the American Cancer Society estimated there would be 50,000 newly diagnosed cases of head and neck squamous cell carcinoma (HNSCC). Radiation therapy and concurrent cisplatin (CRT) play a prominent role in the treatment of this disease [1]. This regimen is effective in killing the tumor; however, the normal tissues in the mouth and throat are highly sensitive to radiation that can lead to severe side effects [2]. These side effects include: xerostomia (dry mouth), mucositis (inflammation and sores forming in the mouth), swelling, dysphagia, pain, infections, cavities, hair loss, and reddening of the skin. Some of these side effects may be severe enough to require feeding tube placement and detrimentally prolong the time required to complete a course of therapy. Amifostine (Ethyol®) is the only FDA approved radioprotector against radiation-induced xerostomia. Its value in preventing this side effect in a CRT setting is uncertain and it has minimal effect against mucositis.

4.1.2 Radiation-induced Damage

Radiotherapy for the treatment of head and neck cancers can produce severe therapy-induced side effects. Acute effects commonly appear within a week of starting radiotherapy and most people suffer from at least one of these unwanted side effects. The acute side effects can include: xerostomia, mucosal degradation (mucositis) and ulceration, edema, loss of taste (dysgeusia), difficulty swallowing and talking, ear aches, infections, hair loss, and radiation dermatitis. These acute problems can become so severe that radiation therapy has to be delayed, which can lead to reduced local control or at times, terminated. Long-term complications from radiation therapy directed to the head and neck region can include trismus (restriction on opening of the jaw), osteoradionecrosis, or breakdown of the mandible, loss of sensation, loss of taste, increased risk of dental caries (cavities), and decreased salivary function. Thus, quality of life can be severely compromised following the treatment of head and neck cancers. More concerning is the increase in non-cancer-related deaths in patients treated with concurrent high dose cisplatin and radiation in RTOG 91-11 as a result of long-term complications. This damage can occur anytime during radiation therapy and has been reported years after treatment. The long-term toxicities are a function of high dose radiation and volume of irradiated tissue, amplified by the addition of radio-sensitizing chemotherapy. Once the damage of normal tissue begins, it is usually progressive and irreversible. Because there is a 50-85% five year survival rate for patients treated for head and neck cancers, due in part to a rapidly increasing segment of younger patients experiencing HNSCC related to human papillomavirus infection, there are many people who are living with these long-term side effects (American Cancer Society, 2013 Statistics). Thus, the development of an effective radio-protector would improve the quality of life of many head and neck cancer patients.

4.2 BMX-001

It is well established that induction of oxidative stress after radiation therapy (RT) and chemotherapy plays a major role in tumor and normal tissue therapy responses [3,4]. Ironically, the responses in tumor tend to protect vascular endothelium and tumor cells from RT damage [5], whereas these same stresses after RT promote normal tissue damage [3,6]. A variety of approaches have been investigated to mitigate oxidative stress post irradiation, including the

free radical scavenger, amifostine [7-9]. Although this agent is approved for this use, its daily use is limited by side effects [7-9]. In addition, this agent was used primarily to protect salivary tissue rather than as a protectant against mucositis or dermatitis and with the advent of salivary sparing radiation techniques, this approach has fallen out of favor. Other agents that have been tested pre-clinically and clinically include nitroxides and genistein, but these are not currently approved for protection against normal tissue injury post-irradiation and neither provides catalytic inactivation of reactive species responsible for oxidative stress [7]. Over the past 20 years, Dr. Ines Batinic-Haberle and colleagues have developed a class of manganese (Mn) Porphyrin-based compounds that: 1) are potent anti-inflammatory agents and 2) catalytically inactivate a range of reactive oxygen species, including peroxynitrite and superoxide anion [10-12]. These properties give this class of compound the unique function of protecting normal tissues while also augmenting tumor killing in patients undergoing radiation and chemotherapy. In addition to inactivation of reactive oxygen species, these drugs inhibit transcriptional activity of stress-induced pathways by either eliminating reactive oxygen species that activate stress responses or by indirectly preventing activation. Transcription factors known to be inhibited by this class of metalloporphyrin include HIF-1 [13,14], NFκB [15], SP-1 [16] and AP-1 [10]. The most recently developed compound, BMX-001 ($MnTnBuOE\text{-}2\text{-}PyP^{5+}$), is among the most highly potent in a series of well over two dozen metalloporphyrins that have been evaluated thus far [17]. BMX-001 is lipophilic and crosses the blood-brain barrier. This drug has been licensed for commercial development and will be the lead compound for this project.

Metalloporphyrins have been shown to protect mice from total body irradiation toxicity [18] and xerostomia following parotid gland irradiation [19]. Radiation-induced lung injury was protected against by administration of metalloporphyrins in rhesus macaques [20]. Additionally, metalloporphyrins have been shown to protect against a range of CNS conditions associated with inflammation, including stroke [21] and spinal cord damage [22-24]. Relevant to this application, Dewhirst and colleagues showed protection against inflammation (mucositis) and decreased saliva production (xerostomia) after a single dose of 13 Gy RT. In this study, C57BL/6J mice were exposed to 13 Gy of irradiation with and without concurrent BMX-001. At 10 days post-RT, mice that had been treated with BMX-001 and RT had decreased mucositis as measured by an inflammation-detecting fluorescent probe, ProSense 750EX, in comparison to mice that received only RT without BMX-001. Additionally, at 6 weeks post-RT, xerostomia was not as pronounced in animals treated with BMX-001 as compared to mice that received only RT without BMX-001. Thus, saliva production ability was preserved and salivary inflammation was prevented in mice irradiated with 13 Gy and treated with BMX-001.

In tumors, Dewhirst and colleagues showed that RT and chemotherapy increase oxidative stress, driving upregulation of HIF-1 [5,25], a transcription factor that promotes endothelial and tumor cell survival and increases tumor aggressiveness [26]. Radiation creates persistent oxidative stress in surviving cells, which upregulates NFkB [27]; this transcription factor also drives treatment resistance [28]. Treatment with this new class of metalloporphyrin prevents HIF-1 and NFkB upregulation in tumors after RT and chemotherapy and improves tumor treatment responses [18]. The effect of BMX-001 has been studied on mouse flank xenografts using human hypopharnygeal squamous cell carcinoma (FaDu). In this study by Dewhirst and colleagues, FaDu tumor size was not significantly changed in the presence of BMX-001 without irradiation. However, in the presence of irradiation, BMX-001 significantly inhibited FaDu growth in nude mice. In addition, BMX-001 significantly increased the survival of the tumor bearing animals. The average time to euthanasia (tumor volume>1500 mm^3) for irradiated alone animals was 49.8

days, and mice irradiated with BMX-001 had an average survival of 63 days. Thus, BMX-001 did not protect head and neck tumor cells from radiation sensitization; in fact, BMX-001 further sensitized the head and neck tumor to irradiation and enhanced the survival of tumor bearing animals. This demonstrates that BMX-001 has differential effects in tumor tissue compared to normal tissues, with BMX-001 showing potential to protect normal tissues and sensitize tumors to RT. Thus, the rationale for this protocol is based on the demonstrated dual activity of BMX-001 to protect normal tissue while sensitizing tumors to therapy [19].

Preclinical safety toxicology studies have shown a No Observable Effect Level (NOEL) in mice of 12 mg/kg and in cynomolgus monkeys of 2 mg/kg. BioMimetix has concluded a Phase 1 dose escalation study in newly diagnosed high-grade glioma patients. This clinical trial has demonstrated no adverse effects in subcutaneous dosing up to 28 mg/subject load with half the loading dose given biweekly for 8 weeks in 12 subjects. Three subjects were enrolled and dosed with 42 mg/subject load with half the loading dose given biweekly for 8 weeks. Of these three subjects, there was one dose-limiting toxicity of grade 3 tachycardia and grade 3 hypotension. The DLT in this subject occurred with the loading dose (42 mg sc). The patient was treated with fluids and hospital admitted for observation for 24 hours during which time the hypotension and tachycardia resolved. The cardiac rhythm was a sinus tachycardia and no other cardiac toxicity was observed. The tachycardia was assumed to have resulted from hypotension occurring following the sub-cutaneous injection of BMX-001 (42 mg). After the loading dose of BMX-001 and the described DLT, the subject continued on study and experienced no tachycardia or hypotension following administration of the subsequent 16 maintenance doses (20 mg sc).

The most common related toxicity see in this Phase 1 trial was injection site reaction and all of these have been grade 1. There is no apparent toxicity to end organ tissues or bone marrow.

The completion of a Phase 1 clinical trial in patients with high-grade glioma undergoing brain radiation therapy plus chemotherapy with temozolomide has established an MTD for BMX-001. The MTD by sub-cutaneous injection is 28 mg/subject load followed by a maintenance dose of 14 mg/subject b.i.w. At the MTD, there have been no BMX-001 dose limiting toxicities observed.

Based on the completion of Phase 1 and establishment of an MTD for this treatment regimen in patients undergoing radiation therapy and chemotherapy, this clinical trial of head and neck cancer patients will proceed to a Phase 2 trial of 48 subjects with a safety lead-in of 6 subjects. The reason for the safety lead-in is to confirm safety in subjects receiving radiation therapy to the head and neck area and with chemotherapy involving cisplatin.

4.3 Study Design

This study will involve escalating doses of BMX-001 with standard of care concurrent RT and cisplatin. Patients with biopsy-proven head and neck cancer (squamous cell carcinoma) will undergo standard staging consisting of history and physical exam, contrast enhanced CT +/- PET scan and/or MRI, and QoL questionnaires. Intensity modulated radiotherapy (IMRT) will be delivered with once daily 2.0-2.1 Gy fractions for definitive intent or adjuvant post-operative patients requiring chemo-radiation for high-risk disease including evidence of positive margins or extracapsular lymph node extension. Patients undergoing definitive intent IMRT will receive 69.3-70 Gy in 33 -35 fractions. Post-operative IMRT will be delivered to a dose range of 60-66 Gy in 30-33 fractions.

Cisplatin will be delivered per investigator choice, either 100 mg/m2 IV q21 days x 2, 100 mg/m^2 IV q21 days x 3, or 30-40 mg/m^2 IV weekly x 6-7 doses. All of these dosing schedules are

acceptable as standard of care per NCCN guidelines and utilized within NCI-sponsored cooperative groups [29]. A minimum of 3 subjects and a maximum of 54 subjects with locally advanced head and neck cancers will be enrolled into this study during a 48-month period.

4.3.1 **Phase 1- Completed**

We have conducted a dose-escalation study of BMX-001 in combination with standard dose intensity modulated radiation therapy (IMRT) and concurrent cisplatin (CRT) to determine the safety of the investigational drug, BMX-001 with concurrent cisplatin and radiation therapy. Since a RP2D of 28 mg/subject load/14 mg/subject maintenance (Dose Level 3) has recently been confirmed in a Phase 1 trial of BMX-001 (with Temozolomide for chemotherapy and brain radiation as opposed to the cisplatin and head/neck radiation to be completed in this trial). This Phase 1 trial in head and neck cancer patients was only completed through Dose Levels 1 and 2. Patients with locally advanced (stage III-IVB) HNSCC for whom radiation plus cisplatin is appropriate were eligible based on inclusion and exclusion criteria. Subjects were administered BMX-001 subcutaneously as a loading dose on day -4 to 0. Starting on day 1 or 2 of CRT patients received a maintenance dose (50% of loading dose) twice weekly administered on days of radiation therapy and for one week after radiation concluded. Cisplatin was administered per institution's standard of care practice. Common standard of care practice includes dosing cisplatin at 100mg/m^2 IV q21 days starting on Day 1 of RT for 2-3 doses or dosing cisplatin at 30-40 mg/m^2 IV on Monday or Tuesday of each week of RT for 6-7 total doses. Patients received a continuous course of IMRT delivered as single daily fractions of 2.0 -2.1 Gy with a cumulative radiation dose between 60 Gy and 70 Gy depending on whether they have undergone resection or are receiving definitive radiation therapy. Planned radiation treatment volumes included at least two oral sites (buccal mucosa, floor of mouth, oral tongue, soft palate, hard palate, retromolar trigone) with each site receiving a minimum total of 50 Gy.

In order to evaluate the pharmacokinetics (PK) of BMX-001, blood samples were drawn for analysis.

Cohorts of 3 subjects have been accrued with dose escalation, beginning with 7 mg/subject load and ending with 14 mg/subject load. Following the treatment of 3 subjects at dose levels 1 and 2, and with no BMX-001 related dose limiting toxicities as defined in this protocol, the Phase 1 portion is completed.

4.3.2 **Phase 2**

We will do a safety lead-in trial for head and neck cancer patients involving 6 subjects at the 28 mg/subject loading dose given by subcutaneous injection followed by one-half the loading dose (14mg/subject) administered by subcutaneous injection biweekly during the remainder of the trial**.** We will assess safety in a lead-in cohort of 6 head and neck cancer patients being treated with cisplatin and radiation therapy. Once those 6 subjects are enrolled, we will then move to full Phase 2 open enrollment. Based on the preclinical safety toxicology studies in mice and monkey and the results of the Phase 1 BMX-001 high-grade glioma trial in humans, we anticipate that a dose of 28 mg/subject load followed by one-half the loading dose (14 mgs) twice weekly will not have dose-limiting toxicities in patients enrolled in this study. If this expectation is confirmed (meaning there are no definite BMX-001-related dose-limiting toxicities, defined as grade 3 study-drug-related adverse events), this dose will be utilized in the full Phase 2 trial enrolling an additional 42 subjects. If one or more definite BMX-001 related grade 4 or 5 DLTs occur in the 6 patient safety lead-in cohort, accrual will pause pending review by the sponsor and DSMB. Non

BMX-001 related DLTs are anticipated in this patient population due to the primary disease and treatment regimen.

This is not a randomized trial. All eligible patients enrolled will receive BMX-001.

A maximum of 48 patients will be enrolled in this Phase 2 clinical trial.

4.4 Rationale

4.4.1 Study Rationale

Patients undergoing CRT, typically with cisplatin-based regimens, can experience incapacitating acute and chronic functional disabilities in the form of dry mouth, loss of taste, mucositis or breakdown of the mucosal lining within the head and neck area, swallowing problems (dysphagia and odynophagia), and radiation dermatitis that can result in fibrosis and scarring of the skin and subcutaneous tissue. BMX-001 added to RT and cisplatin has the potential not only to benefit the survival of HN patients through improved tumor control but also to protect against the development of these types of toxicities and to prevent impairment of QoL. Therefore, we have started by performing a Phase 1 trial of BMX-001 at escalating doses in combination with standard RT, 30-35 daily fractions to 60-70 Gy, plus cisplatin at the standard of care dosing, which could be either dosing at 30-40 mg/m^2 administered IV once per week for 6-7 weeks or 100 mg/m^2 days 1 of RT and repeated q21 days for either 2 or 3 total doses. Cisplatin administration will be at the discretion of the treating team. Both regimens are considered acceptable standards within radiation oncologist-led cooperative groups such as the NRG. We hypothesize that BMX-001, when added to standard RT and cisplatin, will be safe at pharmacologically relevant doses in patients undergoing concurrent CRT for head and neck cancers. Since safety has been determined both in Dose Level 1 and Dose Level 2 for the Phase 1 portion of this study and for Dose Levels 1-3 in a separate Phase 1 safety study in patients with high-grade glioma, with establishment of an MTD, we will move to a Phase 2 expansion cohort to further study the safety and examine the effects of BMX-001 in combination with concurrent chemoradiation in the amelioration of mucositis, xerostomia, and radiation dermatitis in patients with stage III-IVb HNSCC.

4.4.2 Rationale for Selection of Dose, Regimen, and Treatment Duration

The recommended doses of BMX-001 are based on preclinical safety studies done in rats, mice, guinea pigs, dogs, and baboons, and the results of a completed Phase 1 trial in human subjects.

4.5 Quality of Life and Function Assessments

Before and during treatment for head and neck cancer, adult patients experience a decline in perceived HRQoL [30-35]. Liu defines HRQoL as “a concept that encompasses the multi-dimensional well-being of a person and reflects an individual’s overall satisfaction with life.” [31].

In order to capture fully the many aspects of HRQoL, we will utilize both objective and subjective measures to evaluate issues with fatigue and HRQoL. Subjectively, HRQoL is measured using patient-reported outcome questionnaires known as patient-reported outcomes (PROs). Four PROs will be used to assess functional status, self-reported measures of mucositis, self-reported measures of xerostomia, and self-reported measures of skin rash and discomfort: Functional Assessment of Cancer Therapy-Head & Neck (Version 4) (FACT-HN), Oral Mucositis Weekly Questinaire-Head+Neck (OMWQ-HN), Xerostomia-Related Quality of Life Scale (XeQoLS), and

Dermatology Life Quality Index (DLQI). The FACT-HN and first two questions of the OMWQ-HN measure overall HRQoL, which is the effect of disease and treatment on overall well-being. The remaining questionnaires are symptom or functional assessments. It has been shown that symptom and functional assessments provide necessary detailed information of the symptom burden on the patient that general measures of HRQoL are not sensitive enough to detect [36]. This data has also been shown to correlate poorly with toxicity scoring in some instances [37], making this information an important addition to the evaluation of treatment on well-being.

The FACT-HN version 4 is a multidimensional, self-report QoL instrument specifically designed for use with head and neck cancer patients (see Appendix B). It consists of 27 core items which assess patient function in four domains: Physical (Cronbach's $\alpha = .79$), Social/Family ($\alpha = .59$), Emotional ($\alpha = .59$), and Functional Well-Being ($\alpha = .75$), which is further supplemented by 12 site-specific items to assess for head and neck-related symptoms ($\alpha = .63$). The first four domains can be combined for a general assessment of function (FACT-G; $\alpha = .89$) [38]. Each item is rated on a 0 to 4 Likert type scale and then combined to produce subscale scores for each domain, as well as a global QoL score. Higher scores represent better QoL [39]. The FACT-HN can be completed by the patient or by an interview and has an effect size of .55 [21]. The scale's sensitivity and ability to differentiate between known groups was tested by comparing the scale to Karnofsky performance status (low KPS < 80, high KPS > 80) and treatment status (on treatment vs. off treatment for greater than 3 months) and all domains were able to distiguish between good and poor performance at the $p < .0001$ level, except the emotional domain, $p = .08$ [38]. The data also showed that 2-3 point differences on subscales appeared clinically meaningful. To determine convergent and discriminant validity, the FACT-HN was correlated with the Performance Status Scale for Head and Neck (PSS-HN), which includes 3 domains: normalcy of diet, understandability of speech, and eating in public [38]. As expected, the three scales of the PSS-HN were significantly correlated with the head and neck subsection of the FACT-HN (Spearman's $r = 0.66$, $p < 0.0001$; $r = 0.17$, $p < .05$; $r = 0.42$, $p < 0.0001$, respectively). Both diet and eating in public were also correlated with FACT-G ($r = .24$, $p < .005$; $r = .20$, $p < .05$). At least one construct from the PSS-HN was not correlated with each of the remaining constructs in the FACT-HN.

The OMWQ-HN is a 13 item functional assessment of mucositis using a Likert response format (See Appendix C). The items were developed by qualitative data provided by one on one interviews with 30 head and neck cancer patients [39]. Based on these results, questions were modified to ensure the scale was comprehensive, that there were no irrelevant questions, and for clarity of all items. The first two questions assess overall health and overall quality of life on a 7-point Likert scale. The third question quantifies overall mouth and throat soreness on a 5-point scale. The next six questions assess how much mouth and throat soreness limits certain activities on a 5-point scale. The last three questions further assess the degree of mouth and throat pain and soreness using an 11-point scale (overall Chronbach's $\alpha = .91$). All items correlated strongly (Spearman's r's > .7) except the overall health and overall QoL items and the brushing teeth item ($r < .5$). Therefore these items are not calculated into the overall OMWQ-HN score.

To evaluate validity, the OMWQ-HN was given at four timepoints with the FACT-HN and PSS-HN to 75 patients with HNC who were receiving radiotherapy with or without chemotherapy [40]. The OMWQ-HN and the FACT-HN were significantly correlated ($\eta = -0.57$), however the OMWQ-HN and the PSS-HN were not as strongly correlated (η range = -0.09 to -0.37), suggesting that

syptoms from mucositis do not readily overlap with normalcy of diet, understandability of speech, and eating in public. Three levels of pain were assessed by a Likert scale which stated "I have pain" and had three response options: not at all/a little bit, somewhat, and quite a bit/very much. There was a significant difference in scores on the OMWQ-HN depending on this variable, $F(2.62) = 38.6$, $p < .001$, $ES = .77$-$.99$. There was also significant divergence between patients who used opioid analgesics compared to those who did not, such that those who were using analgesics scored worse ($p = .002$, $ES = 0.87$). Timepoints were 24-48 hours apart, providing a test-retest correlation of .89. Sensitivity to change was shown by determining changes in the pain item and normalcy of diet item to compare OMWQ-HN scores between no change/ improved groups and worsened groups, $t(63) = -4.3$, $p < .001$, and $t(63) = -2.6$, $p = .013$, respectively. It has also been shown that the OMWQ-HN is more responsive than less symptom-focused QoL instruments in detecting early changes in symptoms related to oral mucositis [40].

The subjective impact of salivary gland dysfunction and xerostomia is assessed by collecting stimulated and unstimulated saliva production (See Section 13.1.6) and by using the Xerostomia-Related Quality of Life Scale (XeQoLS) developed at the University of Michigan (Appendix D). In its first form, the XeQoLS contained 8 questions developed through literature reviews, patient surveys, and the input of oncologists specializing in head and neck cancer, and was shown to parallel clinically measured salivary gland function [40-42]. Research showing that there were four domains to oral health-related quality of life led to the current 15 item scale that covers physical functioning (Cronbach's $\alpha = .85$), personal/psychological functioning ($\alpha = .87$), social functioning ($\alpha = .86$), and pain/discomfort issues ($\alpha = .89$). The Cronbach alpha coefficient for the total XeQoLS score was also significant ($\alpha = .96$, $p < 0.001$) [43]. Internal validity was assessed by comparing the 15 item xeQoLS to the previous 8 item version ($\alpha = .36$ to $.73$, $p < 0.001$). Correlations were significant between the scale and salivary flow ($r = -.19$ to $-.28$, $p < .05$) and there were expected between group differences when comparing those who had parotid-sparing radiotherapy compared to those that did not such that parotid-sparing provides better XeQoL [43].

The Dermatology Quality of Life Index (DLQI) is a well established 10 item questionnaire used to assess impacts of skin irritation on patients well-being and functionality (Appendix E). Although the DLQI was first developed to treat disorders of the skin, it has been validated in over 30 different skin dysfunctions and has been shown to be a valid measure for erythema, inflammation, atopic eczema, and pruritus. It is currently being used to assess radiation-induced damage in two large head and neck cancer studies, including RTOG 0920 [44,45]. The DLQI consists of 10 items and covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Scores are on a 4-point Likert scale from "not at all," to "very much," and each has an option of "not relevant," with higher scores indicating worse HRQoL. Score differences of 4 points have been shown to be statistically significant [46-50]. The scale was shown to distinguish between pre-emptive treatment vs. reactive treatment to radiation-induced skin toxicities in a colorectal cancer patient population [51].

5 Objectives

5.1 Phase 1

5.1.1 Primary Objective

To determine the safety and toxicity profile of BMX-001 in conjunction with RT and concurrent cisplatin chemotherapy for patients with locally advanced head and neck cancers.

5.1.2 Secondary Objectives

1) To assess the effect of BMX-001 in combination with RT and concurrent cisplatin in newly diagnosed HNSCC patients on overall survival (OS), progression free survival (PFS), and initial response to treatment.
2) To examine the impact on mucositis of BMX-001 in combination with RT and concurrent cisplatin in treatment of newly diagnosed patients with locally advanced head and neck cancers by evaluating the degree of oral mucositis at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, the duration of oral mucositis, and evaluation of mucositis-related patient-reported outcomes.
3) To examine the impact on xerostomia of BMX-001 in combination with RT and concurrent cisplatin by evaluating degree of xerostomia at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, the duration of xerostomia, and evaluation of xerostomia-related patient-reported outcomes.
4) To examine the impact on radiation dermatitis of BMX-001 in combination with RT and concurrent cisplatin at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, the duration of radiation dermatitis, and evaluation of radiation dermatitis-related patient-reported outcomes
5) To characterize the single-dose and repeated-dose pharmacokinetic profiles of BMX-001 when delivered in combination with RT and concurrent cisplatin.

5.1.3 Exploratory Objective

1) To describe patient-reported outcomes of health-related quality of life (HRQoL) in HNSCC patients treated with BMX-001 in combination with RT and concurrent cisplatin.

5.2 Phase 2 Endpoints

2) The primary endpoint is incidence of severe oral mucositis (grade 3 and 4).
3) The secondary endpoints are:
    1. Median duration (days) of severe oral mucositis)
    2. Median time (days) to onset of severe oral mucositis
    3. Incidence of grade >/= 2 Xerostomia at month 1 and 6 post completion of RT.

5.3 Phase 2 Objectives

1) To confirm the safety and tolerability of the MTD of BMX-001 in conjunction with RT and concurrent cisplatin in a cohort of newly diagnosed patients with locally advanced head and neck cancers.

2) To further explore efficacy based on the impact of BMX-001 on mucositis, xerostomia, and radiation dermatitis in treatment of newly diagnosed patients with locally advanced head and neck cancers by evaluating the degree of these adverse events at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, the duration of the adverse events, and evaluation of related patient-reported outcomes.

5.3.1 **Secondary Objective**

1) To assess the efficacy of BMX-001 at the MTD in a cohort of HNSCC patients based upon overall survival (OS), median progression free survival (PFS), and initial response to treatment.
2) To assess radiographic response in locally advanced HNSCC patients treated with standard RT and cisplatin with BMX-001 at the MTD.

5.3.2 **Exploratory Objectives**

3) To further describe patient-reported outcomes of HRQoL in locally advanced HNSCC with standard RT, cisplatin, and BMX-001 at the MTD.

6 Patient Selection

6.1 Inclusion Criteria

1) Pathologically confirmed (histologically or cytologically) diagnosis of squamous cell carcinoma of the oropharynx, larynx, hypopharynx, nasopharyngeal, or oral cavity with clinical or pathologic high-risk features for whom cisplatin and radiation would be considered appropriate care.
2) Treatment plan to receive a continuous course of IMRT delivered as single daily fractions of 2.0 to 2.1 Gy with a cumulative radiation dose between 60 Gy and 70 Gy depending on whether patients are considered post-operative high risk or unresectable/organ preservation high risk. Planned radiation treatment fields must include at least two oral sites buccal mucosa, retromolar trigone, floor of mouth, oral tongue, soft palate, hard palate) with a portion of each site receiving a minimum total of 50 Gy.
3) Patients who are to undergo definitive chemoradiation must have clinically or radiographically evident measurable disease at the primary site and/or at nodal stations. Tonsillectomy or local excision of the primary without removal of nodal disease is permitted, as is excision removing gross nodal disease but with intact primary site.
4) Limited neck dissections retrieving ≤ 4 nodes are permitted and considered as non-therapeutic nodal excisions. Fine needle aspirations of the neck that are positive for squamous cell carcinoma are sufficient for diagnosis pending pathology review at participating institutions.
5) For patients undergoing curative intent resection the following criteria are required:
    - Pathologically (histologically or cytologically) proven diagnosis of head and neck squamous cell carcinoma
    - Patients must have undergone gross total surgical resection within 42 days prior to registration and beginning of therapy under the clinical trial. Note: Patients may have biopsy under general anesthesia in an operating room followed by definitive ablative cancer surgery representing gross total resection.
6) Clinical or pathologic stage Stage III-IVB per AJCC, 7th edition.
7) General history and physical examination by a radiation oncologist and medical oncologist within 4 weeks prior to enrollment.
8) Examination by an ENT or head and neck surgeon, including laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) within 8 weeks prior to enrollment.
9) Axial imaging of the neck and chest- CT, MRI and/or PET/CT is acceptable, within 8 weeks prior to date of consent.
10) Age ≥ 18 years.
11) Zubrod Performance Status 0-2 within 4 weeks prior to enrollment.
12) CBC/differential obtained within 2 weeks prior to starting the study drug with adequate bone marrow function, defined as follows:
    - Hemoglobin ≥ 9.0 g/dl;
    - Platelets ≥ 100,000 cells/mm^3;
    - Absolute neutrophil count (ANC) > 1,500 cell/mm^3.

13) Adequate hepatic function as defined as follows:
    - Total bilirubin < 2x institutional ULN within 2 weeks prior to starting the study drug;
    - AST and ALT <3x institutional ULN within 2 weeks prior to starting the study drug.
14) Adequate renal function defined as follows:
    - Serum creatinine < 1.5 mg/dl within 2 weeks prior to starting the study drug or creatinine clearance rate (CCr) ≥ 50 mL/min within 2 weeks prior to starting the study drug determined by 24-hour collection or estimated by Cockcroft-Gault formula:
        - CCr male = [(140 – age) x (wt in kg)]/[(Serum Cr mg/dl) x (72)]
        - CCr female = 0.85 x (CrCl male)
15) Patient must be willing and able to follow study procedures and instructions.
16) Patient must provide study-specific informed consent within 28 days prior to starting the study drug.
17) Negative pregnancy test for women of child-bearing potential within 48 hours prior to first dose of BMX-001.
18) Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study and until 12 months following the last study treatment.

6.2 Conditions for Patient Ineligibility (Exclusion Criteria)

1) Stage I or II; T1N1 and T2N1 stage III presentations per AJCC 7th edition
2) Distant metastasis
3) Hypertension requiring 3 or more anti-hypertensive medications to control
4) Grade ≥2 hypotension at screening
5) Requirement for concurrent treatment with nitrates or other drugs that may, in the judgment of the treating investigator, create a risk for a precipitous decrease in blood pressure
6) History of syncope within the last 6 months
7) Patients receiving, or unable to stop use at least 1 week prior to receiving the first dose of BMX-001, medications listed in Section 12.2 of the protocol are not eligible.
8) Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic
9) Women who are breast feeding are not eligible
10) Prior allergic reaction to cisplatin
11) Known hypersensitivity to compounds of similar chemical composition to BMX-001
12) Grade 3-4 electrolyte abnormalities (CTCAE v 4.03) except sodium, which must be ≥126 mmol/L.
13) Prior unrelated malignancy requiring current active treatment with the exception of cervical carcinoma *in situ*, basal cell carcinoma of the skin, resected T1-2N0M0 differentiated thyroid cancers, invasive cancers with a 3-year disease-free interval, Ta bladder cancers, or low and favorable intermediate risk prostate cancer.
14) Prior history of HNSCC receiving radiation or chemo-radiation.

15) Prior systemic chemotherapy for the study cancer (including neoadjuvant chemotherapy); note that prior chemotherapy for a different cancer is allowable.
16) Prior radiotherapy that would result in overlap of radiation treatment fields with planned treatment for study cancer.
17) A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >480 milliseconds (ms) (CTCAE grade 1) using the specific/usual choice by clinical center for correction factor.
18) A history of additional risk factors for Torsades de Pointes (e.g., congestive heart failure, hypokalemia, known family history of Long QT Syndrome).
19) Severe, active co-morbidity, defined as follows:
    - Cardiovascular disease or cerebrovascular disease, for example cerebrovascular accidents or myocardial infarction ≤ 6 months prior to study enrollment, unstable angina, New York Heart Association (NYHA) Grade II or greater congestive heart failure (CHF), or serious cardiac arrhythmia uncontrolled by medication or with the potential to interfere with protocol treatment;
    - Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months prior to enrollment;
    - History or evidence upon physical/neurological examination of central nervous system disease (e.g., seizures) unrelated to cancer unless adequately controlled by medication;
    - Acute bacterial or fungal infection requiring intravenous antibiotics within 7 days of enrollment;
    - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration;
    - Patients known to be HIV positive or have active viral hepatitis.

7 Pretreatment Evaluations/Management

7.1 Informed Consent

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal Investigator or authorized key personnel with questions and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator or delegate must obtain written informed consent from the subject or a legally authorized representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent will be provided to the subject. The Principal Investigator or delegate is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator or delegate will inform the subject's primary care physician about the subject's participation in the clinical study.

7.2 Screening Examination

The screening examination will take place within 21 days prior to starting BMX-001. The screening evaluation and baseline evaluation may be combined. Standard of Care assessments (such as performance status, labs and imaging) completed per inclusion and exclusion criteria but prior to signing ICF may be utilized for eligibility purposes. An informed consent must be signed by the patient before any screening procedures take place. Subject data to be collected at the Screening Examination includes physical examination, vital signs, height (may be done at baseline), weight, laboratory studies (complete blood count with differential, complete metabolic panel and PT/aPTT), past medical history, and concomitant medications. Mucositis assessment will be done at the screening visit. Assessment of measurable disease by imaging will be done per standard of practice at each institution.

Physical, vital signs (temperature, respiratory rate, blood pressure, and pulse), height (done once at screening or baseline), weight, ECG, and mucositis must be performed at baseline (Day -4 to 0). Saliva production and questionnaires will also be done at baseline. Serum beta-HCG is measured on women of childbearing potential no more than 48 hours prior to the first dose of BMX-001.

8 Registration Procedures and Administrative Considerations

8.1 Enrollment Procedure

Once an Investigator at a participating center has verified that eligibility criteria have been met and the case has been discussed with the participating Principal Investigator, the patient is enrolled in the study.

8.2 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

8.3 Institutional Review Board and Protocol Review

Western IRB (WIRB) will be the primary IRB for this study. The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the IRB for review. Additional protocol review committees and/or scientific review committees may be used per institutional protocol. The Principal Investigator will follow each institution's policies and procedures as required to ensure activity of the protocol.

8.4 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained.

To protect privacy, every reasonable effort will be made to prevent undue access to subject's personal information during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research-related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure locations accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained in encrypted and password-protected files, which are maintained on a dedicated, HIPAA-compliant server and accessed through a secure network. Access to the electronic database will be limited to the Principal Investigator, sub-investigators, study coordinators, the statistical team, the clinical trial monitors, the data management team including the clinical trial manager, and the sponsor. Record of any changes to the electronic database will be maintained and included in the audit trail.

Upon completion of the study, research records will be archived and handled per local institutional policy. Subject names or identifiers will not be used in reports, presentations at scientific meetings or publications in scientific journals.

8.5 Protocol Amendments

All protocol amendments must be initiated by the sponsor or Principal Investigator at each participating institution and approved by the IRB prior to implementation. IRB approval is not

required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

8.6 Conflict of Interest

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting, and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

Local regulatory authorities will review and manage research-related conflicts of interest. The Principal Investigator and Sub-Investigators must report conflicts of interest annually and, when applicable, must have a documented management plan that is developed in conjunction with the local office and approved by the IRB/Institutional Ethics Committee (IEC).

9 Radiation Therapy

NOTE: FOR THIS STUDY, IMRT OR VMAT IS MANDATORY. (IGRT is required; however, margin reduction is not permitted even when IGRT is used).

Treatment plan should include a continuous course of IMRT delivered as single daily fractions of 2.0 to 2.1 Gy with a cumulative radiation dose between 60 Gy and 70 Gy. Planned radiation treatment volumes must include at least two oral mucosal sub-sites (buccal mucosa, retromolar trigone, floor of mouth, tongue, soft palate, hard palate) with a portion of each site receiving at least 50 Gy.

For post-operative irradiation, the standard of care is that radiation therapy will not be initiated until good wound healing has been achieved and will be initiated no earlier than 28 days following surgical resection of the malignancy.

9.1 Dose Specification For Clinically Measurable Disease

IMRT will be delivered in 30-35 fractions over 6 weeks, 5 fractions weekly in one plan (SIB) or 35 fractions over 7 weeks, 5 fractions weekly using sequential plans. Concomitant boost using separate IMRT plans is not allowed.

For Patients Treated with SIB Technique

Missed treatments due to holidays or logistic reasons can be compensated for by delivering an additional BID treatment during the week, OR treating on the Saturday or Sunday of that week, OR adding to the end of treatment.

The primary tumor and involved nodes (CTV1) will typically consist of a 0.5-1.5 cm expansion of the gross tumor volume (GTV) to cover potential local invasion and will be prescribed 2 Gy/ fraction, total 70 Gy.

High-risk sub-clinical disease sites, which include possible local subclinical infiltration at the primary site (primary site CTV2) and first echelon nodes, which are not clinically or radiographically involved (nodal CTV2), should be expanded by 3-5 mm to create PTV2. PTV2 should receive 1.6 Gy/fraction to a total dose of 56 Gy.

Lower-risk targets (PTV3) (such as neck nodal levels which are not first echelon nodes and are not adjacent to levels containing grossly involved nodes) will be prescribed 50-52.5 Gy (at 1.43-1.5 Gy/fraction, BED2 = approximately 40-45 Gy).

Non-uniform or larger expansions to encompass high-risk anatomical compartments may be necessary.

Either of two options is acceptable for treatment of the low neck. One option is to treat with isocentric matching AP or AP-PA fields with larynx block, matched to the inferior margin of the IMRT portals just above the arytenoids. The dose will be 2 Gy per fraction prescribed to 3 cm depth to a total dose of 44 Gy in 22 daily fractions. Whole-neck IMRT is also allowed as an alternative approach. Involved low neck nodes will receive at least 60 Gy in 30 fractions. This can be achieved by either boosting the low neck field with an additional 16 Gy in 8 fractions, by an AP or AP-PA fields, or by planning the whole neck using IMRT. In cases of gross involvement of

the vallecula or low neck, whole-neck IMRT should be considered. Whole-neck IMRT may be preferable if level VI is considered to be at risk due to gross involvement of level IV nodes.

For Patients Treated with Sequential Plans Technique

Missed treatments due to holidays or logistic reasons can be compensated for by delivering an additional BID treatment during the week, OR treating on the Saturday or Sunday of that week, OR adding to the end of treatment.

The primary tumor and involved nodes (CTV1) will typically consist of a 0.5-1.5 cm expansion of the gross tumor volume (GTV) to cover potential local invasion and will be prescribed 2 Gy/ fraction, total 70 Gy. Non-uniform or larger expansions to encompass high-risk anatomical compartments may be necessary.

High-risk subclinical disease sites, which include possible local subclinical infiltration at the primary site (primary site CTV2) and first echelon nodes, which are not clinically or radiographically involved (nodal CTV2), should be expanded by 3-5 mm to create PTV2. PTV2 should receive 2 Gy/fraction to a total dose of 60 Gy.

Lower-risk targets (PTV3) (such as neck nodal levels which are not first echelon nodes and are not adjacent to levels containing grossly involved nodes) should receive 44 Gy in 2 Gy fractions.

Either of two options is acceptable for treatment of the low neck. One option is to treat with isocentric matching AP or AP-PA fields with larynx block, matched to the inferior margin of the IMRT portals just above the arytenoids. The dose will be 2 Gy per fraction prescribed to 3 cm depth to a total dose of 44 Gy in 22 daily fractions. Whole-neck IMRT is also allowed as an alternative approach. Involved low neck nodes will receive at least 60 Gy in 30 fractions. This can be achieved by either boosting the low neck field with an additional 16 Gy in 8 fractions, by an AP or AP-PA fields, or by planning the whole neck using IMRT. In cases of gross involvement of the vallecula or low neck, whole-neck IMRT should be considered. Whole-neck IMRT may be preferable if level VI is considered to be at risk due to gross involvement of level IV nodes.

All plans must be normalized such that 95% of the volume of the PTV1 is covered with prescription dose of 70 Gy. Additionally:

- At 1 cc PTV1 volume on the DVH curve, the dose should not be > 110% of the prescribed dose.
- At a volume of 0.03 cc within the PTV1 volume on the DVH curve, the dose should not be < 95% of the prescribed dose.
- For any volume of tissue outside the PTVs that has a size of 1 cc, the dose should not be > 74 Gy for definitive radiation.
- For Resected Patients the prescribed radiotherapy dose will be 60 - 66 Gy in 2 Gy once-daily fraction size (total of 30-33 fractions) Radiotherapy should begin on a Monday, Tuesday or Wednesday. The daily dose of 2 Gy will be prescribed such that 95% of the PTV60 volume receives at least 60 Gy. PTV56 is also used, and PTV66 (given as an integrated boost) may be optionally defined. Three-dimensional conformal radiotherapy followed by a 6 Gy boost is not permitted.

9.2 Technical Factors

9.2.1 Treatment Planning/Delivery

Megavoltage energy photon beam (6 MV preferred) irradiation is required.

9.2.2 Image Guidance for IGRT

Image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g., kVOBI, ExacTrac;
- Linear-accelerator mounted kV and MV helical conebeam CT images;
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy);

9.3 Localization, Simulation, and Immobilization

Patients must have an immobilization device (e.g., Aquaplast Orfit mask) made prior to treatment planning CT scan.

The treatment planning CT scan should be performed ideally with IV contrast so that the major vessels of the neck are easily visualized and to optimally visualize the tumor. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be no greater than 0.3 cm.

Image guidance and verification should be performed at least twice weekly and more frequently if clinically indicated.

9.4 Treatment Planning/Target Volumes

9.4.1 Definition of Target Volumes for Unresected Patients (Who Receive Definitive Chemoradiation)

Planning Target Volumes (PTVs): In general, the PTV should not go outside of the skin surface; if it does exceed the skin surface, the application of bolus material over this portion of the PTV may be considered if it is judged clinically that the skin is at risk but is generally not recommended.

- PTV expansion with credentialing for daily IGRT: For those institutions that are using IGRT for margin reduction, the minimum CTV-to-PTV expansion is 3.0 mm (a larger expansion may be necessary for a target volume subject to significant intrafraction variability, such as the non-immobilized oral tongue). In general, the CTV-to-PTV expansion (with IGRT) should not exceed 5 mm.
- IMRT Dose Prescription to PTVs for the Unresected Patient: The goal is for 95% of the PTV70 to receive ≥ 2 Gy with a minimum dose (cold spot) of no less than 66.5 Gy. It is recognized that portions of the PTV70 close to the skin may receive significantly less than 66.5 Gy. This is acceptable as long as cold spots within PTV1 do not exist at a depth deeper than 8 mm beneath the skin.

For planning prioritization and priorities in dose coverage, in the final plan, PTV1 will be the highest priority target structure. PTV2 and PTV3, if applicable, will be ranked in the IMRT planning as lower priority than PTV1, although usually at a higher priority than normal structures other than spinal cord and brainstem.

9.4.2 **Definition of Target Volumes for Post-Operative Patients**

CTV60: This volume will receive 2 Gy per day. CTV60 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus regions of grossly involved lymphadenopathy. CTV60 may include the broader **operative resection bed** in the region of gross primary and nodal disease. The entire nodal regions in the involved hemi-neck may be included in CTV60 at the discretion of the investigator for perceived higher-risk cancers.

CTV60 will also include the ipsilateral pathologically positive hemineck (if both sides of the neck are proven pathologically positive, CTV60 will include both sides). This generally means encompassing nodal levels 2a, 3, and 4 for most cases. Nodal levels 1, 2b, 5a, and 5b are included in CTV60 in selected circumstances. For example, level 1 should be included for oral cavity cancer but is not mandatory for larynx cancer. Level 5a should be included for oropharynx cancer but is not mandatory for larynx cancer.

CTV56: This will include all other lesser risk regions in the operative bed (that were involved with surgery in any way) but felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV60. For example, this could apply to the broad operative bed, the contralateral hemineck being irradiated electively. This volume should not directly approach the skin < 5 mm. This volume will receive 1.85 Gy per day.

CTV66 Optional: This volume may be defined at the discretion of the treating radiation oncologist. This would include regions felt to be at particularly high risk for recurrence (eg, an area of the extracapsular extension or positive margin of resection). **Note:** This area will be receiving a daily fraction size of 2.2 Gy and thus, the volume of CTV66 should be kept **as small as possible**.

Planning Target Volumes (PTVs): In general, the PTV should not extend beyond the skin surface, except if the skin was involved with tumor. If it does extend beyond the skin surface, the application of bolus material over this portion of the PTV may be considered. It is also allowable to define 2 PTV's for a given CTV: 1) PTV for planning, which extends beyond the skin surface and is used for planning treatment segments; and 2) PTV Evaluation (PTV_Eval), which does not reach the skin surface within 2 mm and is used for evaluation of the dose volume histogram to determine if treatment goals have been met.

<u>Dose to Supraclavicular Nodal Region</u>
Regardless of whether technique 1 (Match) or technique 2 (No Match) is used, the dose to the supraclavicular nodal region may be limited to 56 Gy for the non-operated, node negative hemineck, and for an involved hemi-neck if level 4 nodes were dissected and found to be negative.

<u>IMRT Dose Prescription to PTVs in the Resected Patient</u>
The prescribed radiotherapy dose will be 60-66 Gy in 2 Gy once-daily fraction size 5 days a week. For inverse planning IMRT, the goal is for 95% of the PTV60-66 Gy to receive ≥ 2 Gy with a minimum dose (cold spot) of no less than 56 Gy. It is recognized that portions of the PTV60-66 Gy close to the skin may receive significantly less than 56 Gy.

9.4.3 **Definition of Normal Tissues/Organs at Risk (OAR)**

NOTE: Only the parts of the normal tissues/organs at risk outside the PTVs will be considered for dose optimization purposes.

Spinal Cord: The cord begins at the cranial-cervical junction (i.e., the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord for this trial is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.

Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The PRVbrainstem = brainstem + 3 mm in each dimension.

Lips and Oral Cavity: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self-explanatory. The oral cavity will be defined as a composite structure consisting of the anterior ½ to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and palate.

Parotid Glands: Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scan. Parotid gland volume may include portions of any of the CTVs if the primary or nodal volumes involved or closely approached the parotid, although they can overlap the PTVs.

Submandibular Glands: Submandibular glands will be defined in their entirety based on the treatment planning CT scan. Submandibular gland volume may include portions of any of the CTVs if the primary or nodal volumes involved or closely approached the submandibular, although they can overlap the PTVs.

Oropharynx: This will be defined as the “uninvolved” posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level).

Cervical Esophagus: This will be defined as a tubular structure that starts at the bottom of oropharynx and extends to the thoracic inlet.

Glottic/Supraglottic Larynx (GSL): This will be defined as a “triangular prism shaped” volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.

Obviously, for patients who have had a total laryngectomy, this structure is not applicable.

Mandible: This includes the entire boney structure of the mandible from TMJ through the symphysis. It is recognized that for oral cavity cancers, this may overlap with CTVs and PTVs.

Unspecified Tissue Outside the Targets: This will be defined as tissue located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

In cases of weight loss > 10% or significant shrinkage of lymphadenopathy during therapy, it is recommended that the immobilization mask will be adjusted or re-made in order to preserve adequate immobilization and that a repeated simulation CT be performed to assess the dose distributions in the current anatomy. Whether or not a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the targets should be the same as those used for the initial plan. The new CT dataset should be used for IGRT image registration when the patient's shape changes significantly.

9.4.4 **IMRT Dose Constraints to Normal Structures**

Spinal Cord: The PRVcord (as defined in Section 9.4.3) should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 50 Gy to any volume in excess of 0.01 cc. In treatment planning, the spinal cord PRV should be given the highest priority.

Brainstem: The PRVbrainstem (as defined in Section 9.4.3) should not exceed 52 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRVbrainstem should be given less priority than the PRVcord but more priority than the other critical structures listed below. Brainstem dose should be kept as low as possible in order to minimize nausea and vomiting especially since patients will be receiving cisplatin, which is highly emetogenic.

Lips: Reduce the dose as much as possible. The mean dose should be < 20 Gy.

Oral Cavity: Reduce the dose as much as possible when not registered as the primary site of disease. The mean dose should be < 30 Gy for the non-involved oral cavity. Efforts should also be made to avoid hot spots (> 60 Gy) within the non-involved oral cavity.

Parotid Glands: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a median dose of < 20 Gy and/or a mean dose of < 26 Gy. Taking into account new data suggesting monotonous improvement in saliva as dose is reduced, without a threshold the objective will be to reduce the mean doses to both parotid glands as much as possible. (Variation Acceptable: 26-30 Gy). For the parotid glands, the mean dose, median dose, and V25 Gy for each gland will be evaluated.

Contralateral or ipsilateral submandibular gland: If contralateral level Ib is not a target, aim to reduce mean contralateral submandibular gland to < 26 Gy. Ipsilateral submandibular gland sparing may also be feasible in certain cases so similar dose constraints are recommended. (Variation Acceptable: 26-30 Gy). For the submandibular glands, the mean dose, median dose, and V25 Gy for each gland will be evaluated.

Oropharynx: Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the oropharynx exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the Oropharynx exceeds 60 Gy.

Cervical Esophagus: Reduce the dose as much as possible. For oral or oropharyngeal cancer, some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 45 Gy; 2) Mean dose < 35 Gy; 3) No more than 15% of the esophagus exceeds 54 Gy. For larynx cancer, higher doses are expected and permitted. Some recommended doses (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the esophagus exceeds 60 Gy.

Glottic and Supraglottic Larynx (GSL): Reduce the dose as much as possible. The glottic larynx mean dose is recommended to be <20 Gy. If whole-neck IMRT is used under- dosage of PTV2/ PTV3 adjacent to the glottic larynx will be limited to <10% receiving < 95% prescribed dose (this under-dosage is similar to that caused by the laryngeal block inserted in the split-field IMRT.

Mandible: Reduce the dose as much as possible. Hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 66 Gy, however it is realized that this may not be possible for certain tonsil cancers and/or if there are large nodes abutting the mandible.

Unspecified Tissue Outside the Targets: No more than 1cc of unspecified tissue outside the targets can receive 74 Gy or more for patients with unresected disease. In the resected patient, for the typical case in which there is no CTV66, no more than 0.03cc or approximately 3x3x3 mm unspecified tissue can receive 66 Gy or more. When a boost is used to increase the dose to high risk regions to as much as 66 Gy, these numbers can be increased. In this case, no more than 0.03cc or approximately 3x3x3 mm of the unspecified dose should exceed the boost dose value plus 10% or 72.6 Gy.

9.5 Critical Structures

The following table outlines the various normal and critical structures. Institutional standards may be used instead.

Standard Name	Description
GTV	Primary tumor and involved nodes
CTV_7000	Primary tumor and involved nodes
PTV_7000	CTV to PTV expansion should be 5 mm minimal margin without IGRT; 3 mm minimal margin with Daily IGRT
CTV_5600	First Echelon nodal regions
PTV_5600	CTV to PTV expansion should be 5 mm minimal margin without IGRT; 3 mm minimal margin with Daily IGRT
CTV_5000	Lower risk nodal regions
PTV_5000	CTV to PTV expansion should be 5 mm minimal margin without IGRT; 3 mm minimal margin with Daily IGRT
CTV_5250	Lower risk nodal regions
PTV_5250	CTV to PTV expansion should be 5 mm minimal margin without IGRT; 3 mm minimal margin with Daily IGRT
SpinalCord	Spinal Cord
SpinalCord_05	Planning Risk Volume of 5 mm

Standard Name	Description
BrainStem	Brainstem
BrainStem_03	Planning Risk Volume of 3 mm
Parotid_L	Left Parotid
Parotid_R	Right Parotid
OralCavity	Oral Cavity
Lips	Lips
Mandible	Mandible
Pharynx	Uninvolved posterior pharyngeal wall plus adjacent constrictor muscles; should not include PTVs
Esophagus	Cervical Esophagus
Larynx	Glottic/Supraglottic Larynx
External	External border of patient used to define Unspecified Tissue
PTV_7000_8mm	Minimum dose (cold spot within PTV1 not including portion of PTV near (<8mm) skin) defined for a point that is 0.03cc in size
NonPTV_7000	Maximum dose (hot spot > 1cc outside the PTVs)

9.6 Documentation Requirements for IMRT Approach

- Pre-treatment Radiation therapy planning CT scan;
- If IGRT is not used, then orthogonal images that localize the isocenter placement of IMRT are required.
- Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, ideally should not exceed 5 treatment days at a time and 10 treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding 5 treatment days for reasons other than toxicity/ illness will be considered a protocol deviation.

All treatment plans are to be normalized to provide exactly 95% volume coverage of the PTV1 with 70 Gy for patients with unresected disease.

	Per Protocol	Variation Acceptable	Deviation Unacceptable
Total RT dose to PTV1 (to 95% of the PTV)	70 Gy	None	None
Minimum dose (“cold spot” within PTV1, not including portion of PTV near (<8 mm) skin) defined for a point that is 0.03 cc in size	66.5 Gy (equals 95% of prescribed dose)	< 66.5 but > 63 Gy	≤ 63 Gy
Maximum dose (“hot spot” > 1cc) within PTV1	≤ 77 Gy	> 77 but ≤ 82 Gy	> 82 Gy
Maximum dose (“hot spot” > 1cc outside the PTVs)	< 74 Gy	74-77 Gy	> 77 Gy

	Per Protocol	Variation Acceptable	Deviation Unacceptable
Total dose to PTV2 (to 95% of the PTV)	56 Gy	≥ 45 but < 56 Gy	< 45 Gy
Total dose to PTV3 (to 95% of the PTV)	50-52.5 Gy	≥ 40 but < 50 Gy	< 40 Gy
Total RT dose to spinal cord PRV (0.03 cc)	≤ 50 Gy	≥ 50 but ≤ 52 Gy	> 52 Gy
Definition of Spinal cord PRV	Based on case review by Primary Investigator		
Overall RT treatment time	< 47 days	48-51 days (without a medically appropriate indication for delay)	> 52 days (without a medically appropriate indication for delay).
Non-Medically Indicated Treatment Interruptions	0-2	2-4	> 4

9.7 RT Quality Assurance Reviews

RT Quality Assurance Reviews will be done with participating radiation oncology investigators with regularly scheduled discussions.

9.7.1 **Radiation Therapy / Adverse Events**

Grade 3-4 (CTCAE, v. 4.03) therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two thirds of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded, as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, headaches, loss of appetite, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: tissue necrosis, secondary cancer, mandibular osteoradionecrosis (< 5% incidence with attention to the standard dental recommendations), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

Summary of possible side effects of radiation therapy to the head and neck:

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, more than 20 and up to 100 may have:
• Sores in the mouth and/or throat which can be painful and make it very difficult to chew and or swallow foods • Mouth dryness or changes in taste and/or smell that may be permanent • Thick saliva • Hoarseness • Tanning or redness and/or irritation of the skin in the head and neck area being treated with radiation • Ear pain and/or pressure • Fatigue • Weight loss • Permanent hair loss in the area treated with radiation (face, chin, neck) • Loss of teeth or cavities in the teeth if strict dental care is not followed and/or hypersensitivity of teeth

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, from 4 to 20 may have:
• Decrease in function of the thyroid gland that may require you to take thyroid replacement medicine to prevent you from feeling tired or sleepy • Serious damage to the jawbone, voice box, skin, or other parts of the head and neck that may require a major operation to correct and, rarely, can even be life threatening • Temporary pain or scarring around nerves in the shoulder that could cause numbness and/or weakness • Breathing problems • Difficulty with swallowing and eating for which you might need a long term or permanent feeding tube; possibility of inhaling food and/or liquids into the lungs – which could also result in pneumonia. This side effect is more likely for patients receiving radiation and cisplatin (Group 1). • Serious ear infections and/or hearing loss • Loss of hearing

10 Study Drug (Cisplatin)

Refer to the package insert for detailed pharmacologic and safety information

10.1 Description

Cisplatin is a standard of care chemotherapeutic agent used to treat a myriad of malignancies, including HNSCC and salivary gland cancers. It works by binding DNA and causing crosslinks and adducts [52].

10.2 Formulation

Each vial contains 10 mg of cisplatin (DDP), 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 mL of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each mL containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.

10.3 Storage and Stability

Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

10.4 Administration

Cisplatin is an IV chemotherapeutic agent approved to treat head and neck cancers. Cisplatin will be administered per institution's standard of care practice. Common standard of care practice includes dosing cisplatin at 100mg/m^2 IV q21 days starting on Day 1 of RT for 2-3 doses or dosing cisplatin at 30-40 mg/m^2 IV on Monday or Tuesday of each week of RT for 6-7 total doses. Cisplatin will be infused per institutional guidelines. Patients who start on q21 day dosing may switch to weekly dosing if deemed necessary by the treating investigator. Per institutional guidelines, patients should receive vigorous hydration and electrolyte replacement. The use of prophylactic anti-emetics including a 5-HT3 inhibitor and dexamethasone should be used per ASCO Guidelines. A NK1 inhibitor such as aprepitant may be used per institutional guidelines.

10.5 Dose Modifications

Dose modifications of cisplatin will be performed by the treating physician per each institution's standard practice. The following are guidelines to aid in decision-making. Escalation of the cisplatin is not allowed once the dose level has been reduced.

10.5.1 **Suggested dose modifications**

Starting dose	Dose level -1	Dose level -2
40 mg/m^2 (weekly)	30 mg/m^2 (weekly)	20 mg/m^2 (weekly)

Starting dose	Dose level -1	Dose level -2
30 mg/m^2 (weekly)	20 mg/m^2 (weekly)	Discontinue cisplatin

Starting dose	Dose level -1	Dose level -2
100 mg/m^2 (q21 days)	75 mg/m^2 (q21 days)	50 mg/m^2 (q21 days)

10.5.2 **Hematologic Toxicity**

NCI CTCAE Toxicity Grade (v 4.03)	Cisplatin dose at start of subsequent week
Neutropenia	
1 (1500-1999/mm^3)	Maintain dose level
2 (1000-1499/mm^3)	Maintain dose level
3 (500-999/mm^3)	Hold dose for one week; if continues >7 days then decrease 1 dose level and resume when reaches grade 2.
4 (<500/mm^3)	Hold dose for one week; if continues >7 days then decrease 1 dose level and resume when reaches grade 2.
Neutropenic Fever (grade3 or 4)	Hold dose at least one week; if ANC ≥1500 then decrease 1 dose level.
Thrombocytopenia	
1 (75,000/mm^3 -LLN)	Maintain dose level
2 (50,000-74,999/mm^3)	Hold dose for one week; if continues >7 days then decrease 1 dose level and resume when reaches grade 1
3 (25,000-49,999/mm^3)	Hold dose for one week; if continues >7 days then decrease 1 dose level and resume when reaches grade 1
4 (<25,000/mm^3)	Hold dose for one week; if continues >7 days then decrease 1 dose level and resume when reaches grade 1

10.5.3 **Non-hematologic Toxicity**

NCI CTCAE Toxicity Grade (v 4.03)	Cisplatin dose at start of subsequent week
Renal-serum creatinine	
Cr ULN-1.5mg/dL or CrCl >50 mL/min	Maintain dose level
>1.5mg/dL and CrCl 40-50 mL/min	Decrease by 1 dose level
Cr >1.5mg/dL and CrCl <40	Hold drug until CrCl is >50mL/min the resume after decrease by 1 dose level
Fatigue Grade 3	Decrease by 1 dose level
Nausea/vomiting	
≤ Grade 2 with maximal medical management	Maintain dose level
Intolerable grade 2 with maximal medical management	Decrease by 1 dose level
≥ Grade 3 with maximal medical management	Hold drug until ≤ grade 2 then resume at one lower dose level
Mucositis in RT field	Hold drug until ≤ grade 3

Grade 4	
Hearing impairment or tinnitus	
≤ Grade 1	Maintain current dose
Grade 2	Decrease dose by one dose level
Grade 3	Hold drug until ≤ grade 1 then resume at one lower dose level
Grade 4 (hearing impairment)	Discontinue cisplatin
Other grade 4 non-hematologic AEs	Hold drug until ≤ grade 1 then resume at one lower dose level

10.6 Adverse Events

- Nephrotoxicity (kidney damage) is a major concern. The dose is reduced when there is a significant change in the patient's creatinine clearance (a measure of renal function). Adequate hydration and diuresis is used to prevent renal damage. The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species and in animal models can be ameliorated by free radical scavenging agents (e.g., amifostine). Nephrotoxicity is a dose-limiting side effect [53].
- Neurotoxicity (nerve damage) can be anticipated by performing nerve conduction studies before and after treatment. Common neurological side effects of cisplatin include visual perception and hearing disorder, which can occur soon after treatment begins [54]. While triggering apoptosis through interfering with DNA replication remains the primary mechanism of cisplatin, this has not been found to contribute to neurological side effects. Recent studies have shown that cisplatin noncompetitively inhibits an archetypal, membrane-bound mechanosensitive sodium-hydrogen ion transporter known as NHE-1 [55]. It is primarily found on cells of the peripheral nervous system, which are aggregated in large numbers near the ocular and aural stimuli-receiving centers. This noncompetitive interaction has been linked to hydroelectrolytic imbalances and cytoskeleton alterations, both of which have been confirmed *in vitro* and *in vivo*. However, NHE-1 inhibition has been found to be both dose-dependent (half-inhibition = 30 μg/mL) and reversible [56].
- Nausea and vomiting: Cisplatin is a highly emetogenic chemotherapy, but this symptom is managed with prophylactic antiemetics (ondansetron, granisetron, etc.) in combination with corticosteroids. Aprepitant combined with ondansetron and dexamethasone has been shown to be better for highly emetogenic chemotherapy than just ondansetron and dexamethasone.
- Ototoxicity (hearing loss): There is at present no effective treatment to prevent this side effect, which may be severe although doses >50 mg/m^2 may be associated with a higher risk of hearing loss. Audiometric analysis may be necessary to assess the severity of ototoxicity. Other drugs (such as the aminoglycoside antibiotic class) may also cause ototoxicity, and the administration of this class of antibiotics in patients receiving cisplatin is generally avoided. The ototoxicity of both the aminoglycosides and cisplatin may be related to their ability to bind to melanin in the stria vascularis of the inner ear or the generation of reactive oxygen species.
- Electrolyte Disturbance: Cisplatin can cause hypomagnesaemia, hypokalaemia, and hypocalcaemia. The hypocalcaemia seems to occur in those with low serum magnesium secondary to cisplatin, so it is not primarily due to the cisplatin.

- Myelotoxicity: This agent can also cause profound bone marrow suppression [57].
- Hemolytic anemia can be developed after several courses of cisplatin. It is suggested that an antibody reacting with a cisplatin-red-cell membrane is responsible for hemolysis [58].
- Other potential adverse events include: ocular disturbances, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts.

Summary of possible side effects related to cisplatin are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving cisplatin, more than 20 and up to 100 may have:
• Nausea, vomiting • Infection, especially when white blood cell count is low • Anemia, which may cause tiredness or may require blood transfusions • Bruising, bleeding • Kidney damage, which may cause swelling, may require dialysis • Hearing decrease, including ringing in ears • Change in taste

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cisplatin, from 4 to 20 may have:
• Allergic reaction, which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Confusion • Difficulty with balance • Numbness in the fingers and toes • Low blood pressure • Low magnesium in the blood, which may cause heart beat irregularities that are possible life threatening

RARE, AND SERIOUS In 100 people receiving cisplatin, 3 or fewer may have:
• Cancer of bone marrow later in life caused by chemotherapy • Seizure

10.6.1 **Risks of Phlebotomy**

Drawing blood or inserting an intravenous catheter into an arm vein may result in bruising or swelling in the area of the insertion, bleeding at the site of the needle puncture, light headedness, fainting, and very rarely, local infection, which may be severe. These risks are reduced by the fact that the blood will be drawn by a qualified physician, nurse or phlebotomist (a professional trained to draw blood).

10.7 Supply

Cisplatin is manufactured by multiple sources and commercial drug will be used in this study.

11 STUDY DRUG (BMX-001)

11.1 Names, Classification, and Mechanism of Action

BMX-001 (Figure 2) also known as MnTnBuOE-2-PyP5+ (manganese butoxyethyl pyridyl porphyrin), is a metalloporphyrin antioxidant that has anti-inflammatory, anti-oxidant, and anti-tumor functions. A series of metalloporphyrins have undergone preclinical evaluation, and BMX-001 represents one with increased catalytic potency along with high lipophilicity. This class of metalloporphyrins leads to inactivation of reactive oxygen species and in turn leads to reduction of oxidative stress. The lipophilicity of BMX-001 leads to its accumulation in the brain parenchyma, and it has been shown to cross the blood-brain barrier. Because the vasculature of most mammalian species is highly sensitive to an oxidative shift, there is a concern for blood pressure monitoring in studies of the metalloporphyrin compounds. Studies in Sprague-Dawley rats showed that intravenous delivery of metalloporphyrin could lead to transient hypotension [59]. In this same study, mice, guinea pigs, dogs, and baboons received intravenous delivery of metalloporphyrins with less effect on blood pressure. BMX-001 was patented by Duke University and has been licensed to BioMimetix JV, LLC.

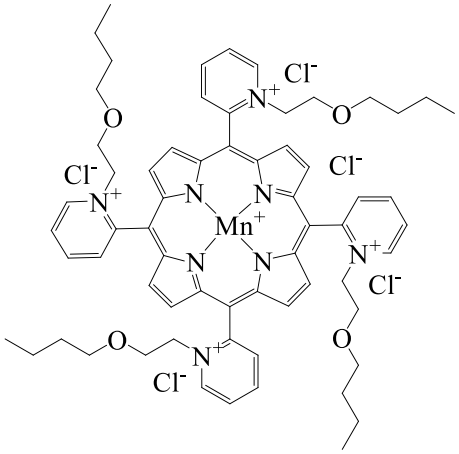

Figure 2: Chemical Structure of BMX-001

11.2 Potential Benefits

The potential benefits may include protection against mucositis and xerostomia caused by RT of the subject's head and neck cancers [19]. Because this clinical protocol is experimental, it cannot be guaranteed that subjects will receive any benefit as a result of participating in this research study. The information collected in this research may help scientists better understand the mechanisms involved in oxidative stress as it pertains to treatment of head and neck cancer. If such an understanding emerges from this research, it may benefit society by furthering the development of improved treatment methods for newly diagnosed head and neck cancers in the future.

11.3 Packaging and Labeling

11.3.1 Drug Product Formulation and Manufacture

The drug will be supplied by BioMimetix JV, LLC. The drug substance (1.2 kg of solid) was manufactured and stored according to cGMP by Albany Molecular Research, Inc. (AMRI).

BioMimetix JV, LLC, has contracted with AMRI (Glasgow) Ltd. to manufacture single dose vials of sterile BMX-001 for injection. Manufacturing will be conducted on AMRI's Flexicon FPC50W filling machine, which is dedicated for aseptic GMP manufacturing within a clean room suite. Manufacturing will include batch pre-filtration and aseptic filtration and filling in accordance with AMRI Glasgow's validated process.

BMX-001 will be formulated as a solution in 0.9% saline at 10 mg/mL, aseptically filtered and filled to 2 mL in a 5 mL Type 1 clear glass vial, sealed with a 20 mm Flurotec serum stopper and flip off aluminum overseal. A nitrogen overlay will be applied to each vial following filling and prior to stoppering.

In-process testing will include pre-filtration bioburden, post-use filter integrity test, and in-process weight checking. Release tests and specifications for BMX-001 for injection are currently under development, but will be established before manufacturing of the clinical batch commences. These will include sterility (USP <71>), bacterial endotoxins (USP <85>), particulate matter (USP <788>), appearance, color and clarity, pH, osmolality, assay, and purity.

The clinical batch of drug product will be placed on stability and tested for the duration of its use during the clinical trials.

11.3.2 **Labels for BMX-001 for Injection, 10 mg/mL**

An exemplary label for the BMX-001 for Injection, 10 mg/mL is reproduced in Figure 3.

BMX-001 for Injection, 10 mg/mL

Lot # P07715

Administer SQ, ≤1.4 mL/site.

Caution: New Drug – Limited by Federal Law to Investigational Use

Emergency contact: Dr. Shayne Gad, cell 919-618-0523 Store at RT

Figure 3: Exemplary Label for BMX-001 for Injection, 10 mg/mL

11.3.3 **Syringe and Label for Administration of BMX-001 for Injection, 10 mg/mL**

A pharmacist at the clinical study center will prepare the loaded syringe(s) and needle(s) that will be used for subcutaneous administration of the appropriate dose of BMX-001 for Injection, 10 mg/mL (from the Dosing Levels Table in Section 11.5 and 11.6) to the clinical subject. The clinical study center pharmacist will adhere to all USP 797 standards for preparation of sterile products. The subcutaneous needle will be capped and the syringe will be stored at room temperature until use, which should occur within 2 hours.

11.3.4 **Multi-Dose Kits**

The vials, labeled as described in Section 11.3.1, are packaged in paperboard cartons. The carton label includes the information indicated in Figure 4, where "XXX" is replaced by the number of vials contained in the carton.

Lot # P07715 Store at RT

BMX-001 for Injection, 10 mg/mL Multi-Dose Kit

Contents: XXX Single-Dose Units @ 20 mg each

Caution: New Drug - Limited by Federal Law to Investigational Use.

Emergency contact: Dr. Shayne Gad, cell 919-618-0523

Figure 4: Exemplary Label for Multi-Dose Kits

11.4 Supply, Receipt, and Storage

The multi-dose kits described in Section 11.3.4 will be shipped by overnight delivery to the local clinical center. These kits will be stored at room temperature, in a locked, physically secure environment, separate from other drug products, according to the local clinical center pharmacy's standard procedures for storage of investigational drug products. Drug accountability records will be maintained by the local clinical center for all clinical trial supplies.

The stability of the drug product during the course of the clinical trial will be established by long-term stability studies currently underway at AMRI (Glasgow) Ltd. At the present time, no significant drug degradation has been observed under storage conditions.

11.4.1 **Compliance and Accountability**

Drug accountability records will be maintained for all clinical trial supplies.

11.4.2 **Disposal and Destruction**

All empty and partially used clinical trial supplies will be destroyed in accordance with the institution’s requirements for an investigational agent. Disposition of all unused boxes of study drug will be carried out according to instructions provided by BioMimetix JV, LLC, at the end of the study after drug accountability is performed. The pharmacy will maintain detailed documentation of the number and identification of BMX-001 vials that are destroyed, and copies of these documents will be provided to BioMimetix JV, LLC.

11.4.3 **Dispensing and Preparation**

A pharmacist at the local investigative site will prepare the loaded syringe and needle that will be used for subcutaneous administration of the appropriate dose of BMX-001, Injection Solution 10 mg/mL, as indicated on the vial label, to the clinical subject. The BMX-001, Injection Solution 10 mg/mL will be drawn from the vial described in Section 11.3.1. The subcutaneous needle will be capped and the syringe will be stored at room temperature until use, which should occur within 2 hours.

11.5 Phase 1 Administration by Dose Escalation at levels below established MTD

The RP2D of BMX-001 has been established in a concluded Phase 1 trial with high-grade glioma patients. This head and neck cancer Phase 1 trial evaluated the two lower doses of BMX-001 and found no dose-limiting toxicities of BMX-001 in combination with cisplatin and also with radiation of the head and neck.

BMX-001 was administered subcutaneously as a loading dose before starting concurrent chemoradiation (days -4 through 0 depending on patient scheduling). After the loading dose, the maintenance dose levels were given two times per week for 8 weeks. The starting dose level was 7 mg loading dose. The BMX-001 dose was then escalated to 14 mg loading dose. After the loading dose, the BMX-001 maintenance dose was administered 7 mg twice a week.

The corresponding volumes of BMX-001, Injection Solution 10 mg/mL associated with the loading doses are as follows:

0.7 mL/subject loading dose = 7 mg/subject
1.4 mL/subject loading dose = 14 mg/subject

The corresponding maintenance doses would be equivalent to the following:

0.35 mL/subject maintenance dose = 3.5 mg/subject
0.7 mL/subject maintenance dose = 7 mg/subject

BMX-001 is administered by subcutaneous injection of a sterile 10 mg/mL solution in saline. The subcutaneous injections are at any optimum site on the torso, the upper leg or upper arm. Maintenance doses are approximately one-half the size of the loading dose and should be administered twice weekly. The first maintenance dose should be delivered either 3 or 4 days after the loading dose and subsequent maintenance doses delivered at 3 to 4 day intervals to average 2 doses per week.

Table – Dosing Levels for Groups I & II

	Group I	Group II
Loading Dose	7 mg/Subject	14 mg/Subject
Maintenance Dose		
1	3.5 mg	7 mg
2	3.5 mg	7 mg
3	3.5 mg	7 mg
4	3.5 mg	7 mg
5	3.5 mg	7 mg
6	3.5 mg	7 mg
7	3.5 mg	7 mg
8	3.5 mg	7 mg

11.6 Phase 2 Expanded

Because this Phase 2 trial involves neck radiation instead of brain and cisplatin instead of TMZ, a safety lead in studying the RP2D of 28 mg/subject load and 14 mg/subject maintenance dose will be part of Phase 2 expansion.

No more than 1.4 mL is to be administered at a single injection site. Thus a 28 mg dose will be administered in two equal portions (14 mg), taken from different vials and injected via separate syringes and needles at two different sites.

Dose Level for Phase 2	
Loading Dose	28 mg/Subject
Maintenance Dose	
1	14 mg
2	14 mg
3	14 mg
4	14 mg
5	14 mg
6	14 mg
7	14 mg
8	14 mg

11.7 Compliance and Accountability

Drug accountability records will be maintained for all clinical trial supplies. Study team staff will schedule all of the patient's appointments and a calendar may be provided to the patient.

Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 3 weeks.

11.8 Concomitant Medications

Because corticosteroids are anti-inflammatory and could interrupt oxidative stress, patients will be required to be on stable or decreasing corticosteroids dose at the time of the study enrollment. If patient is required to have additional steroids such as an allergic reaction, adrenal insufficiency, increased neurological symptoms, and/or increased intracranial pressure, then corticosteroids can be added at the discretion of the treating physician and minimal dose, if deemed medically appropriate, will be utilized to control symptoms.

11.9 Dose Modifications

If adverse events occur that require holding BMX-001, the dose will remain the same once treatment resumes.

NCI CTCAE toxicity	BMX-001 dose
Hypotension	
≤ Grade 2	Maintain current dose. For grade 2 may give IV fluids and place patient in Trandeleburg position.
≥ Grade 3	Discontinue BMX-001. Supportive care as below.
Injection site reaction	
≤ Grade 2	Administer acetaminophen 325-650 mg PO 30 minutes prior to injection.
Intolerable grade 2	Hold drug until ≤ grade 1 then resume. Supportive care as below.
≥ Grade 3	Discontinue BMX-001.

NCI CTCAE toxicity	BMX-001 dose
Other ≥ grade 3 attributable to BMX-001	Discontinue BMX-001.
Electrocardiogram QT corrected interval prolonged	
Grade 1 (Average QTc 450 - 480 ms)	Maintain current dose.
Grade 2 (Average QTc 481 - 500 ms)	Hold BMX-001 pending review by sponsor. Refer to cardiology. ECG should be re-checked in approximately 1 week after the QTc prolongation was first observed or more frequently as clinically indicated.
Grade 3 (Average QTc >= 501 ms; >60 ms change from baseline)	Discontinue BMX-001.

Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 3 weeks.

11.10 Management Guidelines for Potential BMX-001-induced Toxicities

Any toxicity associated or possibly associated with BMX-001 treatment should be managed according to standard medical practice unless as specified above. The primary anticipated toxicity is hypotension, which should resolve within 30-60 minutes.

11.10.1 **Post Drug Administration Monitoring**

Subjects should be observed for a minimum of 2 hours after administration of the initial loading dose of BMX-001 and for a minimum of 1 hour after subsequent doses. Monitoring should include evaluation of blood pressure, heart rate, and skin reaction. Blood pressure and heart rate will be measured pre-dose and then after 30 (±5), 60 (±5), and 120 (±10) minutes on the loading dose. It will be checked pre-dose, 30 (±5), and 60 (±5) minutes all other days of BMX-001 administration. The skin reaction at the injection site should be evaluated at the same time blood pressure and heart rate are monitored. Site(s) of prior drug injection will be inspected before each new drug administration.

After discharge, patient should be advised to be alert for potential symptoms of low blood pressure (i.e., dizziness, fainting, lightheadedness, blurry vision, weakness, nausea, vomiting, including exaggeration of one of the previous symptoms when transitioning from lying or sitting to standing). If these symptoms occur after discharge, the patient should lie down, elevate his/her feet and contact their health care provider if the symptoms persist.

11.10.2 **Hypotension**

If after drug therapy, the blood pressure drops > 20 mm Hg (systolic) from the pre-injection blood pressure level, place the patient in supine position and treat as follows:

Mild hypotension (systolic > 90 mm Hg and < 110 mm Hg, or postural hypotension only) observe patient with repeated measures of blood pressure and heart rate every 10 minutes and expect

resolution within 30-60 minutes. Observe patient in the outpatient setting until blood pressure returns to normal and patient has no hypotensive or postural hypotensive symptoms.

Moderate hypotension (systolic > 70 mm Hg and < 90 mm Hg) treat with i.v. fluids (normal saline or Ringer's lactate) with repeated measures of blood pressure and heart rate every 10 minutes until systolic BP > 110 mm Hg. Observe patient in the outpatient setting until blood pressure returns to normal and patient has had no hypotensive or postural hypotensive symptoms for at least 1 hour.

Severe hypotension (systolic < 70 mm Hg) treat with bolus i.v. fluids (normal saline or Ringer's lactate) with repeated measures of blood pressure and heart rate every 5 minutes until systolic BP > 110 mm Hg. If resolution is not prompt, consider evaluation for underlying cardiovascular disease (including ECG) and urgent consultation with critical care team. Observe patient until blood pressure returns to normal and patient has had no hypotensive or postural hypotensive symptoms for at least 1 hour.

11.10.3 **Local Skin Reaction**

Skin discoloration is expected due to the color of the drug product and is not an adverse reaction. For reactions such as local pain, itching or erythema, initial treatment may include cold pack, ibuprofen for pain and observation every 30 minutes times 2 and then hourly until ≤ grade 1 and patient is comfortable.

For significant edema or lipodystrophy, treat with cold pack, elevation of injection site and observation every 30 minutes times 2 and then hourly until ≤ grade 1 or patient is comfortable and stable.

For severe reactions (≥ grade 3: ulceration or necrosis; severe tissue damage) operative intervention may be indicated, seek surgical consult.

11.10.4 **Prolongation of QTc Interval and Management**

As of April 2019 there have been reports of three subjects with a QT prolongation present after a BMX-001 loading dose (28 mg/subject) that was not present at baseline. Prolongation of QTc interval has not been observed in preclinical studies of BMX-001.

In the BMX-HN-001 study, the prolonged QT interval presented in a subject at the 30 minute and 60 minute post-dose ECG.

In the BioMimetix Multiple Brain Metastases study, the prolonged QT interval presented in a subject at the 30 minute and 60 minute post-dose ECG.

In the BioMimetix Multiple Brain Metastases, the prolonged QT interval presented in a subject at the 60 minute post-dose ECG.

In all cases Electrocardiogram QT corrected interval prolonged did not exceed a grade 2 (average QTc 481 - 500 ms) according to CTCAE.

No action with regards to BMX-001 was taken due to these events and the subjects are continuing on the study and the QT prolongation appears to have resolved.

At the time of this protocol amendment, 40 subjects have received a loading dose of BMX-001 across 4 different trials. The percentage of subjects presenting with QTc prolongation after the loading dose equates to 7.5%. BioMimetix has reviewed all of the data for the subjects and there were no QTc prolongation outside of the three mentioned above.

If a subject develops prolonged QT after receiving a dose of BMX-001, the subject should be referred to cardiology for work up and the case should be reviewed with the BioMimetix Medical Monitor to determine further dosing of BMX-001 and inclusion in the study. Additionally, levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range. Finally, concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT-prolonging effects.

If the cause is not identified and the investigator believes it is appropriate, particularly if QTc remains elevated, study drug may be interrupted, and an ECG should be re-checked in approximately 1 week after the QTc prolongation was first observed or more frequently as clinically indicated. If QTc has recovered or improved and the investigator believes it is safe to do so, continuing BMX-001 therapy should be considered if previously held.

In any case, if a Grade 3 QTc interval (CTCAE) is identified, BMX-001 should be discontinued for that patient.

11.11 Dose-Limiting Toxicity (DLT)

Toxicities will be graded according to the NCI CTCAE version 4.03 criteria. DLTs will be defined as any of the following events that are at least (possibly, probably, or definitely) attributable to BMX-001 during the study. The DLT period includes from the start of BMX-001 through 4 weeks after CRT concludes.

A dose limiting toxicity is defined as an adverse event or laboratory abnormality that is:
a) assessed as unrelated to disease progression, intercurrent illness, or concomitant medications; b) occurs during and/or following the first dose of BMX-001; and c) meets any of the following criteria:

11.11.1 **Non-hematologic**

The occurrence of non-hematologic grade 3 or greater adverse events considered to be possibly, probably, or definitely related to BMX-001 during treatment with BMX-001, excluding grade 3 alopecia and elevation in alkaline phosphatase, grade 3 nausea or vomiting unless occurring despite the use of standard anti-emetics.

> 14 day delay to re-treat due to failure to resolve any grade 3 or greater non-hematologic drug-related toxicity to re-treatment criteria or pre-treatment baseline.

11.11.2 **Hematologic**

Occurrence of any of the following hematologic adverse events will be defined as DLT:

1) NCI CTCAE version 4.03 grade 3 febrile neutropenia or grade 4 neutropenia (ANC, including bands, $\leq 0.5 \times 10^9$ /l);

2) NCI CTCAE version 4.03 grade 3 thrombocytopenia (platelet count of ≤ $50x10^9$/l);
3) > 14 day delay to re-treat due to failure to resolve hematologic toxicity to re-treatment criteria.
4) Grade ≥3 anemia

11.11.3 **Other Considerations**

Inability to complete 75% of the planned radiation dose.

11.12 Adverse Events

There is a completed Phase 1 trial and ongoing Phase 2 trial for patients with newly diagnosed high grade glioma treated with concurrent radiation therapy, temozolomide, and BMX-001 (BMX-HGG study). In the Phase 1 trial, there was one dose-limiting toxicity of grade 3 tachycardia and grade 3 hypotension. The DLT in this subject occurred with the loading dose (42 mg sc). The patient was treated with fluids and hospital admitted for observation for 24 hours during which time the hypotension and tachycardia resolved. The cardiac rhythm was a sinus tachycardia and no other cardiac toxicity was observed. The tachycardia was assumed to have resulted from hypotension occurring following the sub-cutaneous injection of BMX-001 (42 mg). After the loading dose of BMX-001 and the described DLT, the subject continued on study and experienced no tachycardia or hypotension following administration of the subsequent 16 maintenance doses (20 mg sc).

The most common related toxicity see in this Phase 1 trial was injection site reaction and all of these have been grade 1. There is no apparent toxicity to end organ tissues or bone marrow.

This head and neck study is designed to determine the tolerability and safety of this agent with concurrent radiation therapy and cisplatin.

Studies have been performed using intravenous infusions of a related metalloporphyrin in multiple models including rats, mice, dogs, guinea pigs, and baboons with the finding of dose-related hypotension [59]. Metalloporphyrin compounds being evaluated are potent, catalytic antioxidants and have the potential to scavenge superoxide within the vascular system and thereby change the balance of superoxide and nitric oxide in the microvasculature. This would augment the vasodilating activity of nitric oxide and lead to hypotension [59]. This has been found in animal models to be a significant, but transient side effect and, therefore, blood pressure monitoring is essential in this proposed clinical trial of a metalloporphyrin compound. Studies of rats, mice, and monkeys have been performed with BMX-001 and have shown transient, dose-related hypotension. Hypotension is related to plasma Cmax levels and subcutaneous administration significantly reduces the risk of this toxicity in mice and primates (unpublished data per BioMimetix JV, LLC). We have designed this protocol to monitor blood pressure closely. Preliminary data suggests that the dose-limiting toxicity will be local irritation at the subcutaneous injection site. This dose-limiting toxicity is expected to be related to the concentration of the administered drug and the volume administered rather than to subject body size.

Because of the development of transient hypotension in rat models, patients will undergo blood pressure monitoring before, during, and after the BMX-001 injections. In primate studies, the primary toxicity seen was skin reaction/irritation due to subcutaneous injection. Care will be taken to limit the volume of the injections to no more than 1.4 mL per site.

A summary of the possible adverse side effects that could be associated with BMX-001 administration is below. These possible side effects are dose-dependent, and the relatively low doses of this drug planned in this study have not been associated with side effects in animals other than those related to the color of the injected drug.

The most common side effects (expected to occur in more than 30% of subjects) are:

- Red to brown discoloration of the skin at the injection site which may take up to several weeks to resolve
- Irritation at the site of the injection of the drug under the skin
- Transient tachycardia from the study drug

Less common side effects (expected to occur in 10-30% of subjects) are:

- Transient pain at the site of the injections of the drug under the skin
- Local histamine release which could be caused by the study drug. This could cause pruritus (itching), erythema (redness), edema (swelling), urticaria (welts). This is expected to resolve within a couple of hours of injection

Rare side effects (expected to occur in less than 10% of subjects) are:

- Temporary hypotension (low blood pressure)
- Malaise or “not feeling well” for a few hours
- Prolongation of the QTc interval

An additional possible side effect is:

- Light-activated skin rash in response to sun exposure
- Red to dark color of urine
- It is also possible that previously unobserved and unexpected side effects could occur.

11.13 Risk Classification

The overall risk classification of this research is unknown. Clinical trials using BMX-001 in head and neck cancer patients have not been performed.

12 Other Therapy

12.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication. These may include analgesics, anti-emetics, topical mouth rinses (Viscous lidocaine is allowed), skin creams/ointments, topical anesthetic/solution for laryngoscopy, etc. The use of amifostine as a radioprotector is not allowed. The use of granulocyte colony-stimulating factor or erythropoietin is not allowed. Any exceptions must be approved by a Principal Investigator or representative from BioMimetix JV, LLC.

12.2 Prohibited Therapies

These are prohibited during the active study drug treatment period of the study and up until the first visit following completion of chemo therapy and radiation (~1 month).

- Low-level laser treatment for OM
- Amifostine (Ethyol®)
- Benzydamine hydrochloride
- Caphosol® or similar re-mineralizing solutions
- Cevimeline hydrochloride (Evoxac®)
- Glutamine applied topically
- GM-CSF applied topically
- IL-11 (Neumega®)
- 'Magic mouthwashes' or 'Miracle mouthwashes'
- Chlorhexidine
- Hydrogen peroxide rinses
- Tetracycline
- Any other listed disallowed medications
- MuGard™
- Nitrates, phosphodiesterase type 5 (PDE 5) inhibitors (e.g., sildanefil, tadalafil, or similar agents) or other drugs that in the judgment of the treating investigator could create a risk of a precipitous decrease in blood pressure are prohibited
- Palifermin (Kepivance®) or other keratinocyte or fibroblast growth factor
- Pilocarpine hydrochloride (Salagen®)
- Povidone-iodine rinses
- Steroid rinses
- Episil® spray
- Sucralfate in suspension form (use of sucralfate tablets is not proscribed)
- Other biologic response modifiers – except systemic hematopoietic growth factors for the management of anemia or myelosuppression
- Concurrent approved or investigational anti-cancer therapy (e.g., chemotherapy, immunotherapy, targeted therapy, hormone, and biologic therapy) other than the Protocol regimen
- Other investigational agents

- Use of drugs known to lengthen QT intervals should be avoided or minimized.

13 Screening and On-Study Tests and Procedures

On-Study Tests and Procedures											
Evaluation	**Screening[a]**	**Base-line[a]**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9 and Forward[b]**
		Day -4 to 0									
Informed consent	X										
History and physical exam[b]	X	X	X	X	X	X	X	X	X	X	X
Medications[b]	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight[b]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X
Blood pressure and heart rate[c]	X	X	X	X	X	X	X	X	X	X	
CBC with differential[b]	X		X	X	X	X	X	X	X	X	X
CMP[b]	X		X	X	X	X	X	X	X	X	X
PT/aPTT	X										
Serum beta-HCG		X[j]									
ECG[d]	X	X	X			X					
Mucositis[b] (clinical score)	X	X	X	X	X	X	X	X	X	X	X
Saliva production[e] (stimulated and unstimulated)		X									X
XeQoLs, OMWQ-HN, DLQI Questionnaires		X								X	X
FACT-HN Questionnaire, PRO-CTCAE HN		X								X	X
Assessment of measurable disease by imaging[f]	X										X
Toxicity Assessment	X	Ongoing									X
BMX-001[g, h]		X	X	X	X	X	X	X	X	X	
Cisplatin[i]			X	X	X	X	X	X	X[i]		
Radiation			Daily Monday-Friday for 6-7 weeks[k]								

[a] Screening evaluation should be done within 21 days of starting BMX-001. The screening evaluation and baseline evaluation may be combined. Informed consent may be done within 28 days of starting BMX-001.

[b] Study assessments for History and Physical, medications, weight, vital signs, CBC w/ diff, CMP, and mucositis will be obtained at screening, baseline, weekly during therapy, and following therapy at clinic visits in which timing is scheduled under standard of care. Screening CBC with diff and CMP prior to the first dose of Cisplatin need not be repeated on week one for chemotherapy naïve subjects per institutional practice. Study visits following therapy (Week 9 and forward) will be under SOC and at minimum will include study data collection for the CRF at a post-therapy visit within 1 month of completion of

radiation (or within 1 month of completion of BMX-001 treatment) and at 6 and 12 months post radiation ± 1 month. Mucositis will be scored using the CTCAE version 4.03. Toxicity assessment will continue to be obtained during year 1 to identify late toxicities possibly related to SOC or with study drug. PT/aPTT will be measured once and can be done at either screening or baseline.

[c] Blood pressure and heart rate will be measured pre-dose and then after 30 (±5), 60 (±5), 120 (±10) minutes on the loading dose. It will be checked pre-dose, and post-dose at 30 (±5), and 60 (±5) minutes all other days of BMX-001 administration.

[d] Phase 2: ECG will be done at screening and will also be done pre-dose as well as at 60 (± 15) minutes after dosing on the loading day and on a maintenance dose injection day during week 1 and week 4, both pre and post dose at 60 (± 15) minutes.

[e] Saliva production will be measured on baseline and the post-therapy measurement will be obtained at clinic visit within 1 month of the end of radiation therapy and at 6 and 12 months ± 1 month. If the post-therapy measurement cannot be obtained, this will not be considered a protocol deviation.

[f] Assessment of measurable disease by imaging will be done according to SOC, i.e., during screening (up to 8 weeks prior to enrollment) and at approximately 3 and 12 months during follow-up. The 12-month (+/- 1-month post completion of radiation therapy or BMX-001 treatment) follow-up imaging for this study will be a chest x-ray and is required as part of this study protocol and is specifically for research purposes.

[g] For BMX-001, Day -4 to 0 will be the loading dose.

[h] For BMX-001, doses (50% of the loading dose) will be twice a week subcutaneously weeks 1-8.

[i] Cisplatin 100mg/m^2 IV q21 days starting Day 1 for 2-3 doses or 30-40mg/m^2 IV per institutional standard each week of treatment x 6-7 total doses.

[j] Female patients only: pregnancy test (serum beta-HCG) no more than 48 hours prior to first dose of BMX-001.

[k] Radiation therapy may extend into week 8. This is allowable and there is no limitation for radiation therapy extending into the 8th week of BMX-001 treatment.

13.1 Evaluations During Treatment

13.1.1 Treatment Period

The treatment period consists of 6-7 weeks of concurrent RT and chemotherapy with BMX-001 followed by 1-2 weeks of BMX-001 (BMX-001 extends to week 8).

Physical examinations, vital signs (temperature, respiratory rate, blood pressure, and pulse), height (screening or baseline only), and weight must be performed at:

- screening
- baseline
- every week from weeks 1-8
- at each SOC visit after completing RT for a period of 1 year

More frequent examinations may be performed.

13.1.2 **Physical Exam**

A Physical Examination (PE) will include a general physical examination of major body systems, temperature, respiratory rate, blood pressure, heart rate, body weight, and height.

Height will be measured and documented at screening or baseline only.

13.1.3 **Blood Pressure**

In Phase 1 and the 6 subject safety lead-in in Phase 2, Blood pressure and heart rate will be measured pre-dose and then after 5 (±1), 10 (±1), 15 (±2), 30 (±5), 60 (±5), and 120 (±10) minutes on the loading dose. It will be checked pre-dose, 30 (±5), and 60 (±5) minutes all other days of BMX-001 administration.

For the Phase 2 study, blood pressure and heart rate will be measured pre-dose, 30 (±5), 60 (±5) and 120 (±10) minutes on the loading dose. It will be checked pre-dose, 30 (±5), and 60 (±5) minutes post-dose on all other days of BMX-001.

Blood pressure should be measured with the following standardized techniques: patients should be seated in a chair; blood pressure measurement should begin after at least 5 minutes of rest; measurements should be taken preferably with a calibrated mercury sphygmomanometer.

13.1.4 **ECG**

ECG will be done for screening purposes and also prior to BMX-001 administration and at 60 (±15) minutes after dosing on the loading day of BMX-001 and on a BMX-001 administration day during Week 1 and Week 4 pre-dose and at 60 (±15) minutes after dosing. Results will be filed in the source for each subject.

13.1.5 **Mucositis**

Mucositis will be clinically assessed weekly during therapy and following therapy at clinic visits as listed in the table at the beginning of Section 13. Mucositis will be scored using the CTCAE version 4.03 and evaluation will also be done using the FACT-HN and the Oral Mucositis Weekly Questinaire-Head+Neck (OMWQ-HN) to be administered on screening and post therapy as listed in the table at the beginning of Section 13.

13.1.6 **Xerostomia**

Xerostomia will be assessed using the FACT-HN and the Xerostomia-Related Quality of Life Scale (XeQoLS) to be administered at baseline and post therapy as listed in the table at the beginning of Section 13.

Xerostomia will also be assessed by measurement of saliva production at baseline prior to BMX-001 administration and post therapy as listed in the table at the beginning of Section 13 using the following protocol:

Unstimulated: Clear mouth by spitting excess saliva into a disposable cup. Use a chewing motion to encourage saliva production and spit into a plastic cup for 3 minutes. The cup will be weighed after 3 minutes and compared to its tare weight to determine the volume of saliva produced.

Stimulated: Clear mouth by spitting excess saliva into a disposable cup. Use a 2x2” square of parafilm to chew on and stimulate saliva while spitting all produced saliva into a plastic cup

for 3 minutes. The cup will be weighed after 3 minutes and compared to its tare weight to determine the volume of saliva produced.

Due to institutional practices, subjects may be evaluated for Xerostomia by both the radiation oncologist and the medical oncologist. For consistency in reporting adverse events, whenever possible the clinical assessments of Xerostomia documented *by the radiation oncologist* will be entered into the CRF. When the subjects are seen by medical oncology only, the medical oncologist's clinical assessment will be used.

13.2 Re-treatment Criteria

Patients must not be experiencing a DLT in order to be retreated. Other dose modifications are specified in sections 10.5.1 (cisplatin) and 11.9 (BMX-001).

13.3 Follow-up Period

The follow-up period will consist of an approximately 24-month period following the end of RT treatment.

13.4 Early Withdrawal of Subject(s)

13.4.1 Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but are not limited to the following:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Protocol deviation
- Administrative issues
- Disease progression
- Pregnancy

13.4.2 Follow-up Requirements for Early Withdrawal

Subjects who prematurely withdraw due to toxicity or progressive disease will be followed for six months after a subject is removed from the study. End of study requirements outlined above will be conducted. Subjects withdrawn for pregnancy will be followed until the pregnancy is ended.

13.5 End of Treatment

The end of treatment will occur when the patient comes off of study for the following reasons: completion of all study tests/procedures (approximately 24 months following completion of RT), progressive disease, unacceptable toxicity, allergic reaction to chemotherapy, allergic reactions to BMX-001, non-compliance with study follow-up, or withdrawal of consent. Patients will be followed for a minimum of 30 days after End of Treatment, and also followed for any unresolved adverse events considered related to study therapy. Patient death due to progressive disease will not be reported as a SAE.

13.6 End of Study

The study will be considered complete once enrollment has been met, follow-up procedures on all subjects have been conducted, and data analysis is concluded. The study may also be terminated early for any reason by the PI or sponsor. In order to terminate the study, all data extraction and analysis must be complete. Therefore, if any articles for publication are derived from the current study, they must be submitted and accepted with no further need for additional data review prior to termination with the IRB.

Subjects that are lost to follow-up will be documented in the patient record and in the study database. In the study database, the subject will be marked as "Patient Status Unknown," along with a corresponding explanation, if any. This status may also be documented on the "Off Study Form" in the study database.

13.6.1 **Early Study Termination**

This study can be terminated at any time for any reason by the PI or sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with this protocol.

13.7 Outcomes Criteria

13.7.1 **Time-to-Event Variables**

Progression-free survival (PFS) is defined as the time between initiation of protocol treatment and the first recurrence of disease or death.

Overall survival will be defined as the time to death from the time of study enrollment.

13.7.2 **Radiographic Response**

Scans will be performed according to standard of care, which commonly would include screening or baseline, 3 months ± 2 weeks from the end of radiation therapy, and then 12 months ± 1 month from the end of radiation therapy. As part of this study protocol, the 12-month imaging (+/- 1-month post completion of radiation therapy or BMX-001 treatment) will be a chest x-ray that is required for research purposes.

The guidelines and criteria for radiographic response may be based on the RECIST 1.1 criteria and apply only to patients receiving definitive intent treatment:

- Complete Response: Disappearance of all enhancing tumor
- Partial Response: Greater than or equal to a 30% reduction in the size (sum of the largest perpendicular diameters) for all enhancing lesions taking as reference the baseline sum
- Progressive disease: At least a 20% increase in the size (sum of the largest perpendicular diameters) for all enhancing lesions, taking as reference the smallest sum recorded since the treatment started or the appearance of one or more new lesions
- Stable Disease: Evaluations that do not meet criteria for CR, PR or PD
- Not Assessable: Progression has not been documented and one or more sites have not been assessed.

If RECIST reads are not obtained per SOC per the institution, then imaging reads per the institutional standard of practice are acceptable.

Risks of the Chest X-Ray
Subjects will be exposed to radiation from the required chest X-ray. The amount of radiation from a chest X-ray is low — even lower than exposure through natural sources of radiation in the environment. The average dose of the chest x-ray is about 0.1 mSv (millisieverts) and the average annual effective dose of background radiation is about 3 mSv [61].

13.8 Quality of Life and Functional Assessments: HRQoL

The assessments of quality of life and function (XeQoLs, OMWQ-HN, DLQI, FACT-HN, and PRO-CTCAE HN) will be completed at the following time points: pre-treatment, end of treatment (during week 8) and at SOC visits following the end of therapy (this will include, at minimum, 1 month, 6 and 12 months ± 1 month after treatment). Target windows for data collection will be: 1) for end of treatment should be collected within 1 month of the last day of radiation therapy; and 2) at 6 and 12 months should be collected within ± 1 month of these time-points. However, if not possible, data should still be collected outside of these windows and analysis will account for the timing of data collection.

PRO-CTCAE HN: In addition to traditional physician obtained QoL parameters, we will incorporate a modification of the PRO-CTCAE which is a new outcome measure recently developed by the NCI designed to capture the patient's self-report of adverse events [60]. A subset of items drawn from the PRO-CTCAE system have been aggregated into a head and neck specific tool for use in this trial (PRO-CTCAE HN). The PRO-CTCAE HN measure tailored for use in this study consists of 25 items that evaluate the presence and/or severity of a range of symptoms, as well as the degree to which the symptom/toxicity interferes with usual function. Individuals respond to the questionnaire items using a 5-point Likert scale. PRO-CTCAE HN is designed to be completed by the patient without assistance from research staff similar to other quality of life measures.

All QoL/functional assessments listed below will be collected from patients at clinic visits via case report forms or by electronic data collection at the discretion of each clinical institution.

All quality of life questionnaires should be completed, even if the patient stops protocol treatment.

14 Safety Monitoring and Reporting

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. PI will review and sign off on all adverse events and problems as they occur and will report them to the IRB in accordance with HRPP policies. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

14.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of BMX-001, whether or not related to use of the BMX-001. Abnormal laboratory findings without clinical significance (based on the PI's judgment) should not be recorded as AEs, but laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

From the time the subject signs the informed consent form through the End of Treatment visit (as defined in the section titled End of Treatment), all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.03. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug
- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

14.1.1 Reporting of AEs

BioMimetix JV, LLC, should be notified of all treatment-related adverse events on a regular basis (to be agreed upon by the study team and BioMimetix JV, LLC).

14.2 Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

Reports of these should be made to Elizabeth Regan, MD, PhD, at Elizabeth.regan@bmxpharma.com, or 303-921-1880 (cell) with the Clinical Trial Manager on carbon copy.

14.2.1 **Reporting of SAEs**

Only adverse events that the Sponsor determines to be serious, unanticipated, and related or possibly/probably (i.e., more likely than not) related to the research must be reported to the appropriate IRB. Those adverse events will be submitted in the applicable IRB and sponsor, according the following guidelines:

- Report within 24 hours of learning about any subject's death that was unanticipated and more likely related to the research than unrelated;
- Report within 5 business days of learning about any serious, unanticipated, and related or possibly/probably related adverse event; that was more likely related to the research than unrelated.
- Report within 10 business days of learning about any other SAE that does not meet the above criteria.

The Sponsor must report to the FDA, in an IND safety report, any suspected adverse reaction that is both serious and unexpected. Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction (i.e., there is a reasonable possibility that the drug caused the adverse event)
- Serious
- Unexpected

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The Sponsor is required to report to the FDA all IND Safety reports in writing within 15 days (7 days for unexpected fatal or life-threatening suspected adverse reaction). The FDA Form 3500A can be found on the FDA website, www.fda.gov. All other adverse events will be reported to the FDA in the Annual Report.

The sponsor is responsible for safety reporting to the FDA and for compliance with all applicable laws and regulations pertaining to adverse events. To ensure patient safety each study treatment-related serious adverse event will also be reported to BioMimetix JV, LLC, within 24 hours by the Principal Investigator. Follow-up information on these events shall also be reported to BioMimetix JV, LLC, within 24 hours. Follow-up information may include hospital admission records, discharge summaries and autopsy reports, where applicable.

In addition, the Principal Investigator shall also make an accurate report to the reviewing Institutional Review Board (IRB) on any serious and unexpected AE per local guidelines.

14.3 External Data and Safety Monitoring Board (DSMB)

The sponsor and Principal Investigators are responsible for overseeing the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements to local and federal authorities. Additional oversight will be carried out by an external DSMB.

An external DSMB will be utilized to monitor the Phase 1/Phase 2 clinical trial of BMX-001. This DSMB will be organized to meet requirements of Western IRB, the institutional IRBs, and the NCI. We anticipate a charter with a minimum of 3 members, which may include: a radiation oncologist, a medical oncologist both with expertise in head and neck cancer, a biostatistician, and/or an ethicist or patient advocate. The DSMB will hold an initial meeting to review the final protocol before enrollment of the first patient. The responsibilities of the DSMB will be to review safety of study procedures, to maintain study integrity, to review adverse events and to review efficacy of the outcome data. The DSMB will meet either face to face or by teleconference at least semi-annually and on an ad hoc basis as indicated by any adverse events. Minutes will be kept of both open and closed meetings of the DSMB. At the end of the study, all minutes taken will be available to the clinical trial principal investigators, the NCI, and BioMimetix JV, LLC.

During Phase 2 of the trial, the sponsor will notify the DSMB within 48 hours of any reported grade 3- 5 DLT deemed probably or definitely related to BMX-001.

The DSMB's responsibilities will include evaluation of treatment outcome for evidence of tumor protection by the study drug. If the DSMB determines that there is substantial evidence of excess tumor progression in the presence of the study drug, the DSMB will have authority to recommend closure of the clinical trial.

14.4 Monitoring

BioMimetix JV, LLC, will be responsible for oversight of monitoring the trial per the trial monitoring plan and will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements.

Monitoring visits will be conducted in compliance with FDA regulations (21CFR812), SOPs, and GCP/ICH (5.18) guidelines to ensure the integrity of the data reported is accurate and the safety, rights, and well-being of the subjects are protected. The clinical trial will be monitored while the trial is active and is enrolling and overseeing patients.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or for cause. Every reasonable effort will be made to maintain confidentiality during study monitoring.

14.5 Audits

The clinical centers may conduct internal audits to evaluate compliance with the protocol and the principles of GCP. The PIs agree to allow auditors direct access to all relevant documents and to allocate his/her time and the time of the study team to the auditors in order to discuss findings and any relevant issues.

The primary purpose of the audit is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

15 Data Management and Processing

15.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the study-specific regulatory binder, which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

15.2 Case Report Forms (CRFs)

The electronic CRF (eCRF) will be the primary data collection document for the study and is developed in conjunction with statistical oversight. The CRFs will be updated in a timely manner following acquisition of new source data. Only the staff appropriately delegated by the PI are permitted to make entries, changes, or corrections in the eCRF.

An audit trail will be maintained automatically by an electronic CRF management system. All users of this system will complete user training, as required or appropriate per regulations.

15.3 Data Management Procedures and Data Verification

Users of the eCRF will have access based on their specific roles in the protocol.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data management team and the statistical team will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e., confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

15.4 Coding

All medical terms will be coded using CTCAE v.4.03, which has been harmonized to MedDRA (Medical Dictionary for Regulatory Activities) coding. Medication will be coded according to the World Health Organization Drug Dictionary.

15.5 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution;
- Accounting, reconciliation, and destruction/return of used and unused study drugs;
- Review of site study records for completeness;
- Shipment of all remaining laboratory samples to the designated laboratories;
- Submitting closure report to IRB.

15.6 Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of:

- at least two years after the date on which a New Drug Application is approved by the FDA, as an IND is involved;
- at least two years after formal withdrawal of the IND associated with this protocol, as an IND is involved;
- per institutional guidelines.

16 Statistical Methods and Data Analysis

All statistical analysis will be performed under the direction of Christopher Wichman, Ph.D., University of Nebraska Medical Center (UNMC). Any data analysis carried out independently by the investigator must be approved by the lead statistician before publication or presentation.

All patients who receive protocol treatment are expected to be included in all statistical analyses. In Phase 1, cohorts of 3 patients will be treated starting with dose level #1 and ending with dose level #2. Once three patients have undergone treatment without experiencing DLT after a monitoring period of four weeks, the dose of the subsequent group of 3 patients will be escalated. Phase 1

16.1.1 **Analysis Sets**

All patients who receive protocol treatment are expected to be included in all statistical analyses.

For purposes of determining dose escalation, we expect that all patients will be included in analyses with the possible exception of those patients receiving treatment who refuse to return for assessment and for whom information concerning toxicity cannot be garnered from other sources (e.g., primary care physician, family members, etc).

For adverse events, overall survival and progression free survival, all patients who receive BMX-001 will be included in the summaries of adverse events.

For HRQoL, all patients who receive BMX-001 will be included in the analysis with the possible exception of those patients receiving treatment who refuse to return for assessment and for whom HRQoL data are not available.

16.1.2 **Patient Demographics and Other Baseline Characteristics**

The clinical and sociodemographic characteristics of all patients treated will be summarized using descriptive statistics (e.g., means/standard deviations, percentiles, frequencies). Patient characteristics within patient subgroups defined by dose level will also be generated.

16.1.3 **Treatments**

The number of patients treated at each dose level will be summarized.

16.1.4 **Phase 1 Dose Escalation**

16.1.5 **Objectives**

16.1.5.1 **Primary Objective**

The primary objective of this Phase 1 study is to determine the maximum tolerated dose safety and toxicity profile of BMX-001 administered in conjunction with standard radiotherapy and cisplatin among patients with newly diagnosed head and neck cancer. Two dose levels were completed: 1) 7 mg/subject and 2) 14 mg/subject followed by maintenance doses given twice weekly of 1) 3.5 mg/subject and 2) 7 mg/subject. The toxicity profile will be done using the CTCAE version 4.03.

16.1.5.2 **MTD**

The MTD has been selected for studying in Phase 2 based on completed Phase 1 human trials of BMX-001.

16.1.5.3 **Secondary Objectives of Phase 1 Study**

Adverse events will be tabulated in a different manner for the manuscript summarizing the results of this study, annual reports for the Safety Oversight Committee, and the final report included within ClinicalTrials.gov.

For the manuscript, adverse events that are possibly, probably, and definitely treatment-related will be summarized. For each type of toxicity, the maximum grade experienced by each patient will be summarized with frequency distributions within each treatment group.

For ClinicalTrials.gov, serious adverse events and other adverse events will be summarized separately. These tabulations will reflect the number of patients who experience each type of toxicity regardless of grade or attribution.

CTCAE data will be collected and compared:

1. To assess the effect of BMX-001 in combination with RT and concurrent cisplatin in newly diagnosed HNSCC patients on overall survival (OS), progression free survival (PFS), and initial response to treatment.

   Kaplan-Meier methods will be used to graphically describe the distribution of overall survival (OS) and progression-free survival. OS is defined as the time interval between initiation of protocol treatment and death, with overall survival censored at last follow-up if the patient remained alive. PFS is defined as the time between initiation of protocol treatment and disease progression or death. If the patient remains alive without disease progression, then PFS will be censored at last follow-up. Median OS and PFS, as well as 6- and 12-month estimates of OS and PFS, will be estimated from the Kaplan-Meier curve.

2. To examine the impact on mucositis of BMX-001 in combination with RT and concurrent cisplatin in treatment of newly diagnosed patients with locally advanced head and neck cancers by evaluating the degree of oral mucositis at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, the duration of oral mucositis, and evaluation of mucositis-related patient-reported outcomes.

   The duration of mucositis at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, will be descriptively summarized using means and 95% confidence intervals (CIs). The evaluation of mucositis-related patient-reported outcomes at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, will be descriptively summarized using frequencies, percentages, and 95% CIs.

3. To examine the impact on xerostomia of BMX-001 in combination with RT and concurrent cisplatin by evaluating degree of xerostomia at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, the duration of xerostomia, and evaluation of xerostomia-related patient-reported outcomes.

   The duration of xerostomia at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, will be descriptively summarized using means and 95% confidence intervals (CIs). The

evaluation of xerostomia-related patient-reported outcomes at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, will be descriptively summarized using frequencies, percentages, and 95% CIs.

4. To examine the impact on radiation dermatitis of BMX-001 in combination with RT and concurrent cisplatin by evaluating degree of radiation dermatitis at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, the duration of radiation dermatitis, and evaluation of radiation dermatitis-related patient-reported outcomes.

   The duration of radiation dermatitis at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, will be descriptively summarized using means and 95% confidence intervals (CIs). The evaluation of radiation dermatitis-related patient-reported outcomes at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, will be descriptively summarized using frequencies, percentages, and 95% CIs.

5. To characterize the single-dose and repeated-dose pharmacokinetic profiles of BMX-001 when delivered in combination RT and concurrent cisplatin.

16.1.5.4 **Exploratory Objectives for Phase 1 Study**

The mean change between baseline and each follow-up assessment for HRQoL will be descriptively summarized using means and 95% CIs.

16.2 Phase 2

16.2.1 **Primary Endpoint**

1) The primary endpoint is incidence of severe oral mucositis (grade 3 and 4).

   The incidence rates of severe oral mucositis graded by CTCAE as grade 3 or 4 will be descriptively summarized and calculated.

2) The secondary endpoints are:
   1. Median duration (days) of severe oral mucositis
   2. Median time (days) to onset of severe oral mucositis
   3. Incidence of grade >/= 2 Xerostomia at month 1 and 6 post completion of RT.

16.2.2 **Objectives/Endpoint and Data Analyses**

16.2.2.1 **Primary Objectives for Phase 2**

1. To confirm the safety and tolerability of the MTD of BMX-001 in conjunction with RT and concurrent cisplatin in cohort of HNSCC patients.

   The incidence rates of adverse events (AE) will be described without regard to causality. AE incidence occurring within each cycle will be described. The frequency of overall toxicity, categorized by toxicity grades, will also be summarized. Listings of laboratory results collected at baseline and during the study will be generated and descriptive statistics summarizing changes in laboratory tests over time will be presented.

Adverse events will be tabulated in a different manner for the manuscript summarizing the results of this study, annual reports for the Safety Oversight Committee, and the final report included within ClinicalTrials.gov

For the manuscript, adverse events that are possibly, probably, and definitely treatment-related will be summarized. For each type of toxicity, the maximum grade experienced by each patient will be summarized with frequency distributions within each treatment group.

For ClinicalTrials.gov, serious adverse events and other adverse events will be summarized separately. These tabulations will reflect the number of patients who experience each type of toxicity regardless of grade or attribution.

2. To further explore efficacy based on the impact of BMX-001 on mucositis, xerostomia, and radiation dermatitis in treatment of newly diagnosed patients with locally advanced head and neck cancers by evaluating the degree of these adverse events at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, the duration of the adverse events, and evaluation of related patient-reported outcomes. Comparison against historical controls will be made.

   The duration of mucositis, xerostomia and radiation dermatitis, separately, at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, will be descriptively summarized using means and 95% confidence intervals (CIs). The evaluation of mucositis, xerostomia, and radiation dermatitis, separately, at related patient-reported outcomes at 30-39 Gy, 40-49 Gy, 50-59 Gy, and 60-70 Gy, will be descriptively summarized using frequencies, percentages, and 95% CIs.

16.2.2.2 **Secondary Objectives for Phase 2**

1. To assess the efficacy based upon overall survival (OS), median progression free survival (PFS), and initial response to treatment

   Kaplan-Meier methods will be used to graphically describe the distribution of overall survival (OS) and progression-free survival. OS is defined as the time interval between initiation of protocol treatment and death, with overall survival censored at last follow-up if the patient remained alive. PFS is defined as the time between initiation of protocol treatment and disease progression or death. If the patient remains alive without disease progression, then PFS will be censored at last follow-up. Median OS and PFS, as well as 6- and 12-month estimates of OS and PFS will be estimated from the Kaplan-Meier curve.

2. To assess radiographic response in locally advanced HNSCC patients treated with standard RT and cisplatin with BMX-001 at MTD.

   The radiographic response (CR or PR) will be assessed as defined in 12.6.2. The radiographic response rate will be tabulated and reported using frequencies and 95% confidence intervals.

16.2.2.3 **Exploratory Objectives for Phase 2**

1. To further describe patient-reported outcomes of HRQoL in locally advanced HNSCC with standard RT, cisplatin, and BMX-001 at the MTD.

16.2.3 **Interim Analysis for Phase 2**

No interim efficacy analyses are planned given the length of time to assess an individual patient's outcome and the expected rapidity of patient accrual.

16.2.4 **Sample Size Calculation for Phase 2**

In this study, patients will receive BMX-001 at the Recommended Phase 2 Dose (RP2D). The ultimate goal of this study is to determine whether BMX-001 in combination with standard RT and cisplatin treatment is worthy of further investigation. The cohort will be compared with historical controls, which will be assessed for quality.

We will focus on the occurrence and severity of mucositis, xerostomia, and radiation dermatitis in this power calculation given that the study is not a randomized study, even though we are interested in comparing groups with respect to change in mucositis and xerostomia between protocol timepoints.

We anticipate accruing 48 patients which, for statistical purposes, we assume that approximately 40 will have available measurements of mucositis, xerostomia, and radiation dermatitis. We use a conservative estimate of a proportion of 0.50 since it results in the widest CI. A sample size of 40 produces a two-sided 95% exact confidence interval (Clopper-Pearson) with a width equal to 0.324 when the sample proportion is 0.50.

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Appendix A: Functional Assessment of Cancer Therapy – Head and Neck (Version 4)

FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

Appendix B: Oral Mucositis Weekly Questionnaire – HN

OMWQ-HN

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.

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

3. How much **MOUTH AND THROAT SORENESS** did you experience in the past week? (***Circle one number***)

No soreness	0
A little soreness	1
Moderate soreness	2
Quite a lot of soreness	3
Extreme soreness	4

⇨ **If you circled 0, please stop here**

4. How much did **MOUTH AND THROAT SORENESS** limit you in each of the following activities during the past week? (***Circle one number on each line***)

	Not Limited	Limited A Little	Limited Some	Limited A Lot	Unable To Do
a. Sleeping	0	1	2	3	4
b. Swallowing	0	1	2	3	4
c. Drinking	0	1	2	3	4
d. Eating	0	1	2	3	4
e. Talking	0	1	2	3	4
f. Brushing your teeth	0	1	2	3	4

5. On a scale from 0 to 10, how would you rate your **OVERALL MOUTH AND THROAT SORENESS** during the past week? (***Circle one number***)

0	1	2	3	4	5	6	7	8	9	10
No Soreness										Worst Possible Soreness

6. On a scale of 0 to 10, what number best describes the **MOUTH PAIN** that you have experienced in the past week? (***Circle one number***)

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

7. On a scale of 0 to 10, what number best describes the **THROAT PAIN** that you have experienced in the past week? ***(Circle one number)***

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

8. Is there anything that you're going through that we haven't covered? (Please explain)

Appendix C: Xerostomia-Related Quality of Life Scale

These questions are concerned with your oral health and how it affects your life. Please answer the questions by checking the box that describes best how true each statement has been for you during **the past 7 days**:

1. My mouth/throat dryness limits the kinds or amounts of food I eat.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

2. My mouth/throat dryness causes discomfort.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

3. My mouth/throat dryness causes a lot of worry or concern.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

4. My mouth/throat dryness keeps me from socializing (going out).

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

5. My mouth/throat dryness makes me uncomfortable when eating in front of other people.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

6. My mouth/throat dryness makes me uncomfortable speaking in front of other people.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

7. My mouth/throat dryness makes me nervous.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

8. My mouth/throat dryness makes me concerned about the looks of my teeth and mouth.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

9. My mouth/throat dryness keeps me from enjoying life.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

10. My mouth/throat dryness interferes with my daily activities.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

11. My mouth/throat dryness interferes with my intimate relationships.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

12. My mouth/throat dryness has a bad effect on tasting food.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

13. My mouth/throat dryness reduces my general happiness with life.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

14. My mouth/throat dryness affects all aspects of my life.

❑ Not at all ❑ A little ❑ Somewhat ❑ Quite a bit ❑ Very much

15. If you were to spend the rest of your life with your mouth/throat dryness just the way it is now, how would you feel about this?

❑ Delighted ❑ Mostly satisfied ❑ Mixed: equally satisfied/dissatisfied ❑ Mostly dissatisfied ❑ Terrible

Appendix D: Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

Appendix E: PRO-CTCAE-HN

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

4.	In the last 7 days, what was the SEVERITY of SKIN CRACKING AT THE CORNERS OF YOUR MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, did you have any VOICE CHANGES?	
	○ Yes	○ No

6.	In the last 7 days, what was the SEVERITY of your HOARSE VOICE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

7.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

8.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

9.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

10.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

11.	In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?					
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe	○ Not applicable

12.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

13.	In the last 7 days, what was the SEVERITY of RINGING IN YOUR EARS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

14.	In the last 7 days, how OFTEN did you have PAIN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

15.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

16.	In the last 7 days, did you HAVE ANY PAIN, SWELLING, OR REDNESS AT A SITE OF DRUG INJECTION OR IV?		
	○ Yes	○ No	○ Not applicable

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe