A Phase III, Open-label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection [Multikine] Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity / Soft Palate Versus Standard of Care Only

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I have read and understood the contents of this protocol entitled:

"A Phase III, Open-label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection [Multikine] Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity / Soft Palate Versus Standard of Care Only" and dated 27 June 2014.

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I have read and understood the contents of this protocol entitled:

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I understand that the information contained in this protocol is confidential and is provided to me, my staff, and the IRB/IEC for purposes of conducting a clinical trial.

I have also read and understood the contents of the Investigators' Brochure.

I agree to conduct this clinical trial in accordance with the protocol and all applicable regulatory requirements.

_____ _____

Signature of Investigator Date

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Name and Address of Investigator

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Investigator's Name City, State (or country)

TABLE OF CONTENTS

I. List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CHF	Congestive heart failure
CIZ	Cyclophosphamide, Indomethacin, Zinc
CNS	central nervous system
CRA	Clinical Research Associate
CRF	Case Report Form
CR	complete response
CTCAE	Common Toxicity Criteria for Adverse Events
CRT	Chemoradiotherapy
CSF	Colony stimulating factor
CT	Computed Tomography
CTLL-2	Cytotoxic T-lymphoid cell line
CrCl	creatinine clearance
DCFs	data clarification forms
DM	data management
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	Ethics Committee
EKG	electrocardiogram
ELISA	Enzyme Linked Immunosorbant Assay
EMEA	European Medicines Agency
EORTC 30	European Organization for Research and Treatment of Cancer QLQ (Questionnaire)
EORTC H&N 35	European Organization for Research and Treatment of Cancer Head and Neck QLQ (Questionnaire)
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FNA	fine needle aspiration
FNAB	fine needle aspiration biopsy
GCP	Good Clinical Practice
GEE	generalized estimating equations
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
H&E	Hematoxylin and Eosin
H&N	Head and Neck
HBV	hepatitis virus type B
Hct	hematocrit

List of Abbreviations (continued)

HCV	hepatitis virus type C
Hb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNC	head and neck cancer
HPV	human papilloma virus
HTLV	human T-cell Lymphotropic Virus
IC	informed consent
ICH	International Conference on Harmonization Guidelines
IHC	Immunohistochemistry
IFN-γ	Interferon gamma
IL-1,2,6,8	Interleukin type 1,2,6,8
IMRT	Intense modulated radiation therapy
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRTQA	independent radiotherapy quality assurance
IT	immunotherapy
ITT	Intent to Treat
IU	International unit
IV	intravenous
IVRS	Interactive Voice Response System
KPS	Karnofsky performance status
LD	longest diameter
LRC	Loco-regional control
MCAR	missing completely at random
mg	milligram
μM	micromolar
MHC	Major Histocompatibility Complex
MIP-1α, β	Macrophage inhibitory factor 1 alpha, 1 beta
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAT	Nucleic Acid Testing
NCI	National Cancer Institute
NK	Natural Killer cell
OS	overall survival
OSCC	Oral Squamous Cell Carcinoma
PA	posterior-anterior
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase chain reaction
PET	Positron Emission Tomography
PD	progressive disease
PFS	progression-free survival

List of Abbreviations (continued)

PHA	Phytohemaglutinin
PHI	Protected Health Information
PID	personal identification data
PO	per os (by mouth)
PORT	postoperative Radiation Therapy
PR	partial response
PT	prothrombin time
QLQ	Quality of Life Questionnaire
QOL	Quality of life
RANTES	An 8kD Protein belonging to the PF4 (Platelet Activating Factor 4) Super Family of chemoattractants, attracting CD4+, CD45RO+ T-cells and Monocytes at the inflammatory site
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCCHN	squamous cell carcinoma of the head and neck
SCR	serum creatinine
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SOC	standard of care
SOPs	standard operating procedures
STDs	sexually transmitted diseases
Th1,2	T-cell mediated immune response – Type 1, type 2
Tid	Three times daily
TNF-α, β	Tumor necrosis factor alpha, beta
TNM	tumor, lymph nodes, metastasis
TSH	Thyroid stimulating hormone
TTP	Time To Progression
US	United States
USP	United States Pharmacopeia
WBC	white blood cell

II. List of Tables

III. List of Figures

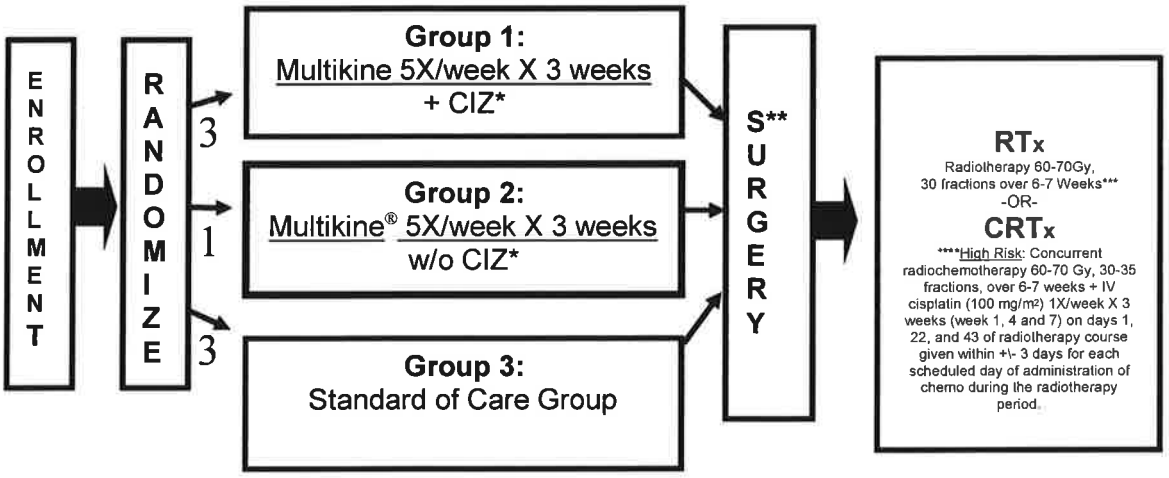
IV. Study Summary

Title	A Phase III, Open-label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection [Multikine]Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity / Soft Palate Versus Standard of Care Only
Short Title	A Phase III Study of the Effects of Multikine on Cancer of the Oral Cavity.
Protocol Number	CS001P3
Phase	III
Methodology	Open label, randomized, three group study. See Table 1.
Study Duration	45-60 months (15-18 (or 24) months accrual and 30-36 months follow-up).
Study Center(s)	Multi-center. Approximately 90 sites, globally
Objectives	The primary objective is to determine the efficacy of peri-tumoral and peri-lymphatic injection of Multikine (400 IU, as IL-2) given prior to Standard of Care (SOC) as measured by overall survival. The secondary objectives are to evaluate the effects of Multikine treatment on the cumulative incidence of loco-regional control, progression-free survival, tumor response, tumor histopathology, and quality of life, while confirming Multikine safety.
Number of Subjects	784 (completed subjects)
Diagnosis and Main Inclusion Criteria	Untreated tumors of the oral cavity to include ONLY the oral tongue (not the base of tongue), floor of mouth, cheek and soft palate that are scheduled for SOC (surgery and radiotherapy or surgery and concurrent chemo- radiotherapy). Other key inclusions: primary tumor, and if present, clinically positive lymph node(s) measurable in two dimensions, normal immune function, no immunosuppressive drugs within the past year, Karnofsky Performance Status (KPS) ≥ 70, age ≥ 18 yrs.
Study Product, Dose, Route, Multikine Regimen	Study drug name: Leukocyte Interleukin, Injection (Multikine) total daily dose: 400 IU (as IL-2); Route: one half delivered peri-tumorally, one half delivered peri-lymphatically (daily) by percutaneous injection, 5x/week for 3 weeks. Two treatment groups will get Multikine injections. Group 1 will receive Multikine preceded on Day minus 3 only by 300 mg/m^2 cyclophosphamide (I.V. bolus), 25 mg indomethacin po tid daily from Day 1 to one day prior to surgery, plus daily Zinc supplementation as found in a standard multivitamin formulation (hereinafter referred to as Multikine + *CIZ Treatment) followed by SOC (surgery of tumor and involved lymph nodes + radiotherapy or surgery + concurrent chemoradiotherapy). Group 2 will get Multikine without *CIZ (referred to as Multikine w/o *CIZ) followed by SOC. Group 3 will receive SOC only.

Duration of administration	3 weeks
Reference therapy	Standard of Care (control): surgical excision of tumor and involved lymph nodes followed by radiotherapy +/- concurrent chemotherapy.
Statistical Methodology	Statistical analysis of the Kaplan-Meier life tables, log rank tests, and proportional hazard models comparing Multikine treatment regimen (plus CIZ) plus SOC vs. SOC alone for overall survival (primary), loco-regional control and progression-free survival over a 24 month enrollment phase and a subsequent 30-36 month follow-up phase for all randomized subjects. Additional evaluations of treatment on tumor response using a longitudinal growth model and quality of life using generalized estimating equations (GEE). Further assessment of the prognosis of risk status, post-surgical therapy (radiation only, chemoradiotherapy), tumor location (tongue, floor of mouth, cheek, and soft palate), tumor stage (T1 N1-2, T2 N1-2, T3 N0-2, T4 N0-2), and geography upon treatment, including treatment interactions, using proportional hazards models.

* CIZ = Cyclophosphamide 300 mg/m^2 IV Bolus + Indomethacin 25 mg po tid + Zinc (as Multivitamin) po daily

Table 1. Methodology: Randomization and Treatment of Enrolled Subjects



* CIZ: Cyclophosphamide 300 mg/m2 (x1,IV bolus, Day -3); Indomethacin 25mg tid, po (Day 1 to approximately 24 hrs prior to surgery) + Zinc (as Multivitamin) po id (daily, from Day 1 to approximately 24 hours prior to surgery).
** Surgery: complete surgical resection of primary tumor and any positive lymph nodes.
*** Radiotherapy is to be given per protocol at a total of ≥ 60 Gy to ≤70 Gy (in 30-35 fractions over a 6-7 week period).
**** High risk subjects are defined as those with: positive surgical margins, 2 or more clinically positive nodes, or extracapsular nodal spread (any or all of the above).

1. Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 Part 312 and International Conference on Harmonization guidelines), which have their origins' and are based on the Helsinki accords, and applicable government regulations and Institutional research policies and procedures.

1.1 Background

Head and neck (H&N) carcinomas constitute 5% of all new cancers diagnosed annually worldwide and approximately 37,000 new cases annually in the United States[1]. These lesions tend to metastasize first to regional lymph nodes, and loco-regional control traditionally has been the greatest obstacle to the cure of these tumors. Approximately ninety percent of all oral cancers are primary squamous cell carcinomas (SCCHN) arising from the lining of the mouth and most commonly the tongue and floor of the mouth[2, 3, 4]. Carcinoma of the lip, tongue, and floor of the mouth represent about 65% of all oropharyngeal cancers[5]. Approximately 66% (2/3 of all H&N cancer patients) of patients with SCCHN present with locally advanced disease[6, 7], at their first visit (diagnosis), and have poor to very poor prognosis.

Although the use of current therapy (surgery, radiotherapy and chemotherapy) results in a very high (>70 – 90%) cure rate for early primary disease, review of the scientific literature for clinical trials conducted with patients having locally advanced squamous cell carcinoma of the head and neck, which have been treated with any or all available treatment modalities (surgery, radiation therapy, chemotherapy, immunotherapy and any combinations thereof) published in peer-reviewed journals between 1987 and 2006 indicates that, the median 3 year overall survival (OS) for locally advanced patients is 52% and the 5 year OS is 39%. A review of only the more recently (2004 – 2006) published clinical trials (from the same data above) indicates that, the median 3 year OS is 55% and the 5 year OS is 43%. Thus, there is a large number of locally advanced squamous cell carcinoma of the head and neck cancer patients that are not well served by the currently available treatment modalities.

Until recently the standard of care for these patients involved the surgical removal of the tumor followed by postoperative radiation therapy (PORT)[1]. However, trials conducted by the Radiation Therapy Oncology Group (RTOG)[8] and by the European Organization for Research and Treatment of Cancer (EORTC)[9] have explored the use of concurrent and sequential chemotherapy and radiotherapy regimens to improve outcomes in the head and neck cancer patient population. As a result of these and other studies, multimodality therapy is now a well-established strategy for the improved control of these tumors.

The strategy of using concurrent chemoradiotherapy (with cisplatin as the chemotherapeutic agent) following surgery in "High-Risk" patients was tested in two clinical trials for which interim analyses were recently reported by the RTOG (RTOG 9501/Intergroup) and the EORTC (EORTC trial 22931) in the New England Journal of Medicine[8, 9]. The RTOG study reported a 10% increase in the 2-year rate of local and regional control (p= 0.01). An 11% increase in the 5-year rate of disease-free survival was reported by the EORTC (p=0.02). Further the EORTC also demonstrated an increase in survival (53% in the combined-therapy group vs. 40% on the post-operative radiotherapy group alone (p=0.04). Neither trial reported a decrease in distant metastases. In addition, the incidence of severe early adverse events was significantly increased by the addition of concurrent chemoradiotherapy. Grade 3 toxicity or greater occurred in 77% of patients who received concurrent chemoradiotherapy as compared to 34% of patients who received radiotherapy alone (p=<0.001) in the RTOG study, and in 41% vs. 21% (p=0.01) in the EORTC study.

Despite the encouraging findings using the concurrent chemoradiotherapy approach following surgical resection, further improvements in treating patients with loco-regionally advanced squamous cell carcinomas of the head and neck are needed. Support for this conclusion comes from the study outcomes reported by the RTOG and EORTC [8, 9]. The estimated five-year cumulative incidence of local or regional relapses was 31% in the radiotherapy group and 18% in the combined-therapy group in the EORTC study. Similarly, local or regional recurrence as the first sign of treatment failure occurred in 61 of 210 patients who received radiotherapy (29%) and in 33 of 206 patients given combined therapy (16%).

Intra-tumoral and peri-tumoral immunotherapy with cytokines has been studied extensively in animal models. Anti-tumor responses have been associated with the development of an inflammatory response localized to the tumor mass. This therapeutic approach has also been shown to overcome tumor-induced suppression of host immune response. In animal models, the local or peri-lesional administrations of interferons, TNF and IL-2 have all shown objective regression of experimental tumors. It has been demonstrated that host reactivity is required for this response to occur, and that the effectiveness of local therapy can be abrogated by treatment with cyclosporine, a host immunosuppressant. Immunotherapy with cytokines has also been studied in and used successfully to treat human cancers.

Many human tumors have tumor-specific or tumor-associated antigens, which may be recognized by the host's defense mechanisms. Anti-tumor host defenses play an important role in the course of malignant disease. Both cell-mediated and humoral anti-tumor immunity are involved in this process. In addition, a variety of approaches to cancer treatment based on host defense mechanisms have also been developed. These are currently referred to as immunotherapy or biological therapy. Effective biological therapies approved for cancer treatment include interferon-α for malignant

melanoma, Hairy Cell Leukemia, AIDS-related Kaposi Sarcoma, and IL-2 for metastatic renal cell carcinoma and malignant melanoma.

Immunotherapy is being explored as therapy for chronic myelogenous leukemia, malignant lymphoma and carcinoid tumors, as well as for a variety of other malignancies. These treatment modalities have direct anti-tumor activity and anti-cancer effects via the modulation of host defense mechanisms. Interferon-α and IL-2 fall into the broad category of cytokines. Cytokines with known anti-tumor activity in either animal or human systems include interferon-α, -β and -γ, TNF-α, TNF-β, IL-1, IL-2 and IL-4.

In head & neck cancer subjects, injection of IL-2 at 200 units (qd/10 days) into the regional lymph node drainage (in the head & neck area) induced remission in squamous cell carcinoma[10]. When tumors from these treated subjects were examined histologically, cellular infiltrates were observed. Twelve subjects treated with 1×10^5 units of IL-2 in the peri-tumoral area before surgery exhibited marked cytotoxicity to the tumor cells[11]. In another trial, 8×10^5 units of rIL-2 were administered directly into the tumor area in 20 head & neck cancer subjects daily for 4 weeks[12]. Three responses were seen, including two complete remissions. In another study with rIL-2, four responses were observed in 46 head & neck cancer subjects[13].

Regional intra-lymphatic or intra-tumoral low-dose cytokine therapy may have important therapeutic effects. One group reported that squamous cell head & neck cancer responds to peri-lymphatic low-dose natural IL-2[14]. Others have established the rationale for local cytokine therapy and the safety of the preparation[15]. In humans, there is good evidence for the activity of local / regional cytokine therapy of cancer in a number of sites, including skin, genitalia, peritoneum, pleural cavity, brain, head & neck, liver, and bladder[16, 17, 18, 19, 20, 21, 22, 23]. These data provide a part of the rationale for the use of Leukocyte Interleukin, Injection (Multikine) in multiple solid tumors, and encourage further studies not only of recombinant IL-2, but also of mixed natural cytokine preparations, such as Multikine (an extensively characterized mixture of naturally occurring human cytokines).

The presence of both Th_1 and Th_2 type cytokines induced by a vaccination regimen is analogous to the injection of Multikine peri-tumorally and in the regional draining lymph nodes. Multikine, which contains biologically active, naturally occurring mixture of both Th_1 and Th_2 type cytokines, has induced both tumor reductions and lymphocytic infiltrations into the tumors of subjects with head & neck cancer[24]. It also appears to be effective in improving pre-cancerous cervical lesions, as determined by both visual (colposcopy) and histopathological methods[25]. These findings further support the use of Multikine as an immunotherapeutic agent for cancer.

Multikine neoadjuvant/adjuvant immunotherapy modulates both the tumor and host antitumor immune response when administered peri-tumorally[26] or both peri-tumorally

and peri-lymphatically to advanced primary oral squamous cell carcinoma (OSCC) patients, prior to conventional therapy[27]. Multikine promotes a number of putative beneficial immunologic effects:

1. induction of tumor cell entry into the pool of dividing cells increasing their sensitivity to follow-on treatment with radiotherapy,[26] chemotherapy or combined chemoradiotherapy,
2. the inversion of the CD4+/CD8+ T-cell ratio in the mononuclear cells infiltrating the tumor [27], and
3. a decrease in both the tumor and tumor-stroma macrophages [27, 28]. The reduction of Macrophages in the tumor site has recently been correlated with a marked decrease in lung-metastases of mammary tumors (and a general decrease in the tendency of mammary tumors to metastasize)[29].

In addition, in a recent Phase II trial of Multikine in advanced primary OSCC patients MHC II (HLA Class II) expression of the OSCC tumor cells was completely absent in tumors from patients responding to Multikine treatment (having >30% tumor reduction from baseline) (n=6), while the Multikine treated but non-responding group (n=11) and the disease matched pathology study historical controls (n=20) had similar HLA Class II expression on their OSCC tumor cells ($p<0.05$)[28]. MHC Class II expression on tumor cells has been correlated with poor prognosis in melanoma patients[30, 31].

These potentially beneficial immunologic effects have been achieved with no added toxicity in all clinical trials of Multikine, and support the rationale for the use of Multikine as adjuvant/neoadjuvant immunotherapy in primary OSCC of the head and neck.

Multikine (developed by CEL-SCI Corporation) contains a defined mixture of naturally derived and naturally-occurring human cytokines and chemokines with demonstrated immunomodulatory activity in-vitro and in vivo in animals and man. It has been administered as a neo-adjuvant peri-tumorally and peri-lymphatically in various dosage schedules in Phase I and Phase II clinical trials conducted in patients with advanced loco-regional squamous cell head and neck cancer (See Sec 1.4). Multikine administration was well tolerated and was found to be safe in all the studies at all the doses administered by whatever route. In addition, data from these studies suggest Multikine pre-treatment may impact the rate of tumor recurrence and/or delay the time to recurrence in patients with primary advanced disease.

Based on the clinical and pathology data collected and the fact that Multikine imparts anti-tumor immune activation, which constitutes an additional anti-tumor mechanism of action different and distinct from radiotherapy, chemotherapy, or chemoradiotherapy with little to no toxicity, Multikine has the potential to increase the effectiveness associated with follow-up radiotherapy or concurrent chemoradiotherapy in patients with primary advanced head and neck cancer.

In this Phase III trial of Leukocyte Interleukin, Injection (Multikine) in locally advanced oral squamous cell carcinoma, overall survival (OS) at 3 years is the primary end point and local regional control (LRC) at 2 years and progression-free survival (PFS) at 3 years are the secondary end points. The trial will test the hypotheses that Multikine adjuvant (or neoadjuvant) immunotherapy administered prior to surgical resection of tumor and involved lymph nodes followed by radiotherapy or chemoradiotherapy in patients with advanced squamous cell carcinoma of the oral cavity will:

- extend the time of overall and progression free survival
- enhance local/regional control
- improve quality of life

Collection of survival data for 3 years is expected to allow sufficient comparison of the treatment groups. The studies conducted by the RTOG and EORTC [8, 9] demonstrated overall survival curves whose slopes decrease in the initial 2-3 year interval and are nearly flat (after the 3 year mark) to 5 to 6 years and to 10 years.

1.2 Investigational Agent

1.2.1 Description

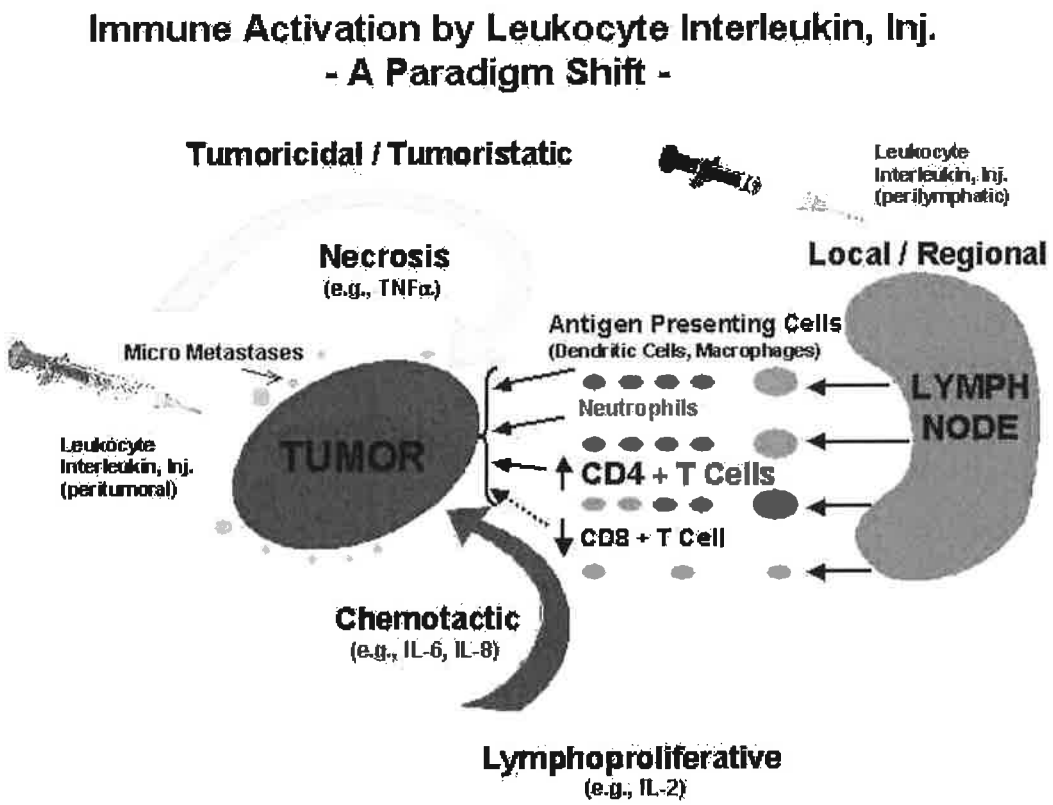
Multikine is a biological product that contains a defined mixture of naturally derived and naturally occurring human cytokines with immunomodulatory activity. It may be used as an adjuvant or neo-adjuvant immunotherapy in treating cancer, with broad-spectrum application for this disease and also for other diseases that might benefit from immunomodulation.

It has been shown that the local instillation of interleukins in the region of the tumor, or the actual transfection of interleukin genes into a tumor, markedly augments anti-tumor immune response and results in tumor regression[32].

Results of animal studies demonstrated that different interleukins have immunomodulatory and immunostimulatory activity in-vitro and in vivo[33] and the observed immunoincompetence status of patients with cancer provided the rationale for the development of Multikine. The hypothesis for the product's development is that the local/regional injection of "mixed interleukins" (Multikine) would overcome local immune-suppression (induced by the tumor), break tolerance to tumor antigens, and allow for an effective local anti-tumor immune response to occur.

Multikine's proposed mechanism of immune augmentation is depicted in Fig. 1 below:

Figure 1. Diagrammatic representation of Multikine's mode of action



CEL-SCI believes that Multikine mode of action is due to its unique and proprietary composition of matter. Multikine is a naturally derived cytokine product containing, among others, three major "families" of bioactive molecules. Each cytokine has a distinct effect on the host and the tumor, and the sum of all effects synergistically impact solid tumor destruction (i.e., regression / necrosis) in cancer patients.

Multikine, injected peri-tumorally and in the region of the local/regional draining lymph nodes contains (1) tumoricidal/tumoristatic cytokines (e.g., TNFα, TNFβ, IFNγ), (2) chemotactic cytokines and chemokines (e.g., RANTES, IL-8, MIP-1α, MIP-1β) and (3) lymphoproliferative and pro-inflammatory cytokines (e.g., IL-1, IL-2 and IL-6, TNF).

CEL-SCI and the authors of a recently published article depicting the results of a Multikine phase II trial (Timar et al, JCO, 23(15): May 2005)[28] hypothesize that Multikine mode of action is due to the combined activity of the different cytokines present which induce a cascade of events as follows:

1. tumor necrosis factors present in Multikine (such as TNF-α) attack the tumor to release tumor antigens
2. antigen presenting cells (e.g., dendritic cells) transport the newly released tumor antigens to lymph nodes
3. lymphoproliferative cytokines (present in Multikine administered peri-tumorally and peri-lymphatically, e.g., IL-1, IL-2) induce a marked polyclonal expansion of tumor specific T-cells - primarily in lymph nodes
4. Multikine (cytokines/chemokines) recruits CD4+ T-cells from local lymph nodes via chemotactic factors, and reverts the balance of intra-tumoral CD4+/CD8+ cells in favor of CD4+ T-cells, which further upregulate the antitumor immune response, resulting in tumor cell necrosis,
5. Multikine recruits neutrophils from the circulation (via GM-CSF, also present in Multikine), which propagate the destruction of the tumor cell nests
6. Multikine-derived cytokines or the de novo cytokine production by the tumor infiltrating cells induce massive local fibrosis[26, 28]

1.2.2 Manufacture

Multikine is prepared under Good Manufacturing Practices (GMP) manufacture from human peripheral blood mononuclear cells, including T-cells, B cells and macrophages. The cells are separated by centrifugation from human donor "buffy coats" obtained under contract from the American Red Cross, and subjected to tests for viruses, bacteria, and parasites, and all other tests mandated by the U.S. FDA for blood for transfusion and blood derived products (including HIV, HBV, HCV, HTLV, STDs, West Nile Virus, ALT and NAT testing). All buffy coats must be negative for all tests in order to be accepted for Multikine manufacture. In addition, all units are obtained only from repeat-donors who were not in any deferral category, either at the time of current or past donation. Viable PBMCs are cultured with PHA for 24 hours. Subsequently, the culture supernatant is aseptically harvested. The supernatant is clarified, subjected to a commercial virus exclusion process, concentrated (approximately 10 times) by ultrafiltration, and subjected to microfiltration. Subsequently, Human Serum Albumin, Inj. USP or equivalent is added, the concentrate is buffered to physiological pH and brought to a target IL-2 concentration of 200 IU/ml, then subjected to a second microfiltration (0.22 micron-rated filter). It is then aseptically dispensed into a sterile serum vial and labeled by its content of IL-2.

Product potency is measured by the incorporation of radiolabeled thymidine by a cytotoxic T-lymphoid line (CTLL-2). The final injectable agent is further tested (by ELISA) for the presence of five marker cytokines: IL-2, IL-1β, TNF-α, IFN-γ, and GM-CSF. Leukocyte Interleukin, Injection is subject to quality control tests for identity, sterility, bacterial endotoxins, pH, and total protein concentration. Each vial is inspected for particulate contamination and appearance. In addition, data is collected on the

concentrations of residual DNA, PHA and ciprofloxacin contained in each lot of the injectable drug.

Multikine is provided frozen in a borosilicate glass serum vial containing 2.2 mL of drug at 200 IU (as IL-2) per mL for peri-tumoral, intra-tumoral, peri-lymphatic or percutaneous administration. The preparation has a total protein content of 3 mg/mL.

The drug is supplied sterile and pyrogen free. DNA (approximately 20 ng/mL), PHA (approximately 0.004 µg/mL), and ciprofloxacin (approximately 2 µg/mL) are currently known to be present in the preparation. The manufacturer has assigned an expiration date of twenty-four (24) months from date of manufacture when the drug is stored at -20ºC.

1.3 Preclinical Data

Extensive studies in animal models have demonstrated antitumor effects of intra-tumoral and peri-tumoral cytokines. Alone or in combination with interferons,[34] intra-tumoral or peri-tumoral administration of tumor necrosis factor[35] and interleukin-2[10, 36] induced objective regressions of a variety of experimental tumors. In other experimental models, interleukin-1[37,38] and interleukin-4[32] inhibited tumor growth. These effects were associated with the development of an inflammatory type reaction in the tumor[39]. Host immune reactivity seems to be required for antitumor responses as the effectiveness of the local therapy can be abrogated by treatment with cyclosporine.[40] In addition to the local instillation of interleukins directly in the region of the tumor, other means of local therapy, including cell therapy with tumor cells transfected with interleukin genes also markedly augmented the antitumor immune response and resulted in tumor regression[41]. Cytokine combinations had synergistic effects on cellular immune cell activity in in-vitro models, as in the effect of IL-7 on IL-1 induced murine thymocyte proliferation[37] and the augmentation of murine CD4+ and CD8+ thymocytes by low doses of combined administration of IL-1 and IL-2.[37]

Interleukins and other cytokines are produced by antigen or mitogen stimulation of various human leukocytes. [14,25,40] Mitogen-stimulated leukocytes produced a mixture of interleukins and other cytokines that had immunomodulatory and immunostimulatory activity in-vitro[40,42]. When administered to guinea pigs, low-dose mixed interleukins had immune stimulating effects on regional lymph nodes.[43] Low-dose mixed lymphokines prolonged survival in cyclophosphamide pretreated-melanoma bearing mice[44]. The use of cyclophosphamide is based on the demonstration that cyclophosphamide pretreatment abrogates suppressor cell activity[45] and augments the response to specific immunotherapy,[46] as well as non-specific immunotherapy[47].

1.3.1 Immunopharmacology Studies

A series of in-vitro experiments and whole animal studies have been performed with IL-2. These studies demonstrate that IL-2:

1. Serves as a second signal for mitogenic action in mature T-cells but also as a regulator of proliferation and maturation of immature T-lymphocytes
2. IL-1 and IL-2 act synergistically to induce prothymocyte and immature thymocyte proliferation

Multikine contains both IL-1 and IL-2 as well as other cytokines such as gamma interferon, and it has been demonstrated that it may be more effective than recombinant IL-2 in inducing proliferation of mature functionally responsive thymocytes [42]. Studies have demonstrated that it produces the same magnitude of proliferative and differentiation affects as rDNA IL-2 in athymic nude mice at 1/10 the dose[48].

1.3.2 Efficacy Studies

In-vitro and in vivo studies in mice and in-vitro studies with Multikine with human PBMCs demonstrated significant ($p<0.01$) increases in natural killer cell (NK) and cytotoxic T-lymphocyte (CTL) responses with low doses of the drug administered by multiple routes. NK cell activity remained elevated for over 5 days following only one treatment, and multiple in vivo treatments did not lead to a depression of NK cell activity[48].

1.3.3 Toxicity Studies

Preclinical animal toxicity studies were conducted in accordance with the FDA's Good Laboratory Practice (GLP) regulations in beagle dogs, mice and guinea pigs. A repeat dose 14 day sub-acute toxicity study administered Multikine subcutaneously 5 times a week for 2 weeks at a dose as high as approximately 10 times the human dose, to beagle dogs, and was not associated with significant local or systemic toxic response. The studies undertaken in mice and guinea pigs were General Safety Tests conducted on bulk material as described in 21CFR610.11. Mixed results were obtained in these studies. While no toxicity was observed in mice, adverse effects noted in guinea pigs were determined to be the result of the presence of residual human insulin in the bulk product, which was derived from the culture medium used for in-vitro cell culture. A group of expert consulting toxicologists concluded that the adverse events noted in animals were due to the exquisite sensitivity of the species to human insulin and that, the very low level of insulin that would be present in the final drug product does not present any serious human safety concerns. In vivo human insulin titration experiments conclusively demonstrated that the effects seen were due to the residual human insulin (and not due to the investigational drug) present in the concentrated Bulk Solution used in these General Safety Tests.

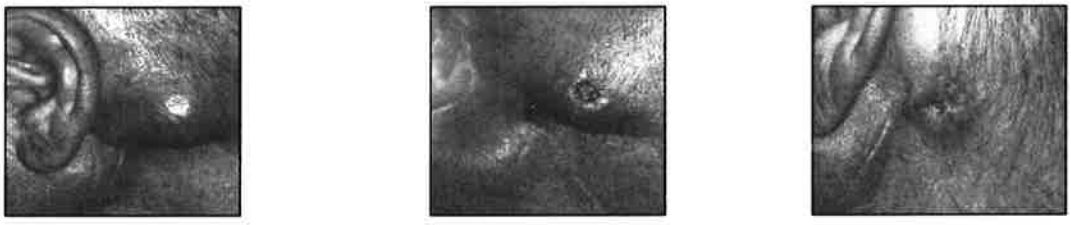
1.4 Multikine Clinical Data

To date, a number of Phase I and Phase II clinical studies have been conducted with Multikine injected into and around tumors. These studies are summarized below.

Multikine Phase I (Head & Neck – U.S.)

Hadden and co-workers completed a clinical pilot study with Multikine combined with low-dose cyclophosphamide (to reduce T suppressor activity), indomethacin (to reduce macrophage suppression via inhibition of prostaglandin synthesis), and zinc (to augment T-cell function via stimulation of thymulin production). Multikine was injected peri-tumorally and peri- or intra-lymphatically in the neck on the contra-lateral side of the measurable recurrent local metastatic head & neck squamous cell cancer. Four terminal subjects were treated; three subjects were reported by the authors to have measurable tumor regression. Biopsy of residual tumor showed increased infiltration of lymphocytes and tumor cell lyses. The fourth treated subject failed to respond. The results were achieved without demonstrable toxicity[24].

Conclusion: Three of four terminal subjects who were refractory to all conventionally available treatment (stage IV) were reported (by the authors) to have had rapid tumor regressions following Multikine administration with no Multikine treatment-related side effects. One subject, with a plum-sized metastasis behind the ear (see below) at the onset of a 21-day Multikine treatment course, had a marked (near complete) clinical response.



Day 1 Day 21 Day 42

Figure 2. Effect of Multikine treatment on tumor growth in one subject with terminal Stage IV squamous cell carcinoma.

Multikine Phase I/II (Head & Neck – Israel)

Multikine was administered peri-tumorally to subjects with head & neck cancer in an attempt to augment local/regional anti-tumor immune responses and achieve local tumor control.

Twelve subjects with previously untreated, primary (stages II to IV) squamous cell carcinoma of the oral cavity (9 subjects), facial skin (2 subjects) and a neck lymph node metastasis with an unknown primary tumor (1 subject) were given a treatment regimen that included peri-tumoral injections (10 subjects - 800 IU IL-2 equivalence and 2 subjects – 1600 IU) of Multikine daily, 5 days/week for 2 weeks, and had surgical resection of the residual tumor within one week following the last injection of Multikine. Subjects also received pretreatment with cyclophosphamide (300 mg/m^2 on Day -3 only, indomethacin, 25 mg po tid, and zinc supplementation, 50 mg po qd) for 18 days immediately following pretreatment. At the completion of the treatment regimen (before surgery), the subjects displayed one or more anti-tumor responses consisting of reduction in tumor surface dimensions, including one complete clinical response of a T2 retromolar trigone tumor and a neck lymph node metastasis with an unknown primary response and four with tumor reductions (of >50%), reduction in tumor thickness, resolution or reduction in size of tumor ulceration, subsidence of local pain and increase in tongue mobility (in tongue tumors). There were no tumor progressions or other adverse local changes, nor evidence of systemic toxicity. Recovery after operation and wound healing were normal. Microscopic examination of surgical specimens showed cellular immune infiltration into the tumor and tumor necrosis[49].

Conclusion: This well-tolerated, short-term local regimen resulted in 6/10 responders, four (4) of which had >50% tumor reduction and one (1) had a complete clinical response, while the other complete responder had a complete reduction in an affected neck node – with an unknown primary. The treatment may impact the rate of tumor recurrence and/or delay the time to tumor recurrence (see below) in subjects who are subsequently treated by surgical resection and/or radiation therapy49. Two subjects who refused surgery (following Multikine treatment) had no reported recurrence of disease 1-3 years post-treatment (personal communication, Dr. R. Feinmesser, Principal Investigator).

Multikine Phase II (Head & Neck – Poland / Czech Republic)

In a multi-center Phase II dose escalating study conducted at four centers located in Poland and the Czech Republic, 30 subjects received six (6) administrations of Multikine (×3/week) over 2 weeks, plus a one week wait period before surgical resection of the residual tumor and any effected lymph node. In contrast to the Israeli study, subjects received half of each dose peri-tumorally and half peri-lymphatically in the vicinity of the jugular lymphatic chain.

Conclusion: At the mid-dose level tested (1600 IU, as IL-2), 70% (7/10) of the subjects had tumor reductions after completion of treatment prior to surgery or radiation, 3 of whom had partial responses (reductions >50%). At the lowest dose (800 IU, as IL-2) group, 60% (6/10) of the subjects had tumor reductions, 2 of which were >50%. No partial responses were observed in the high dose (3200 IU, as IL-2) group.

Multikine Phase I (Head & Neck – US / Canada)

CEL-SCI has completed a Phase I-II multicenter, randomized, dose-response, open label trial of Multikine plus cyclophosphamide, indomethacin and zinc sulfate (CIZ) in biopsy confirmed advanced head and neck cancer patients, who had failed prior therapy. The objective of the trial was to demonstrate clinical safety, evaluate pilot efficacy and explore a possible Multikine dose-response relationship.

The study was conducted under BB-IND 5677 and Canadian IND 033575. Patients initially received monotherapy with Multikine at one of four escalating doses (200, 400, 800 or 1600 IU as IL-2) subcutaneously in a peri-tumoral, intra-tumoral, or perilymphatic location at the discretion of the investigator. Depending on their response to the therapy patients could receive up to 5 subsequent cycles of therapy consisting of Multikine in combination with cyclophosphamide injection (300 mg/m^2), oral indomethacin (25 mg po tid) and oral zinc sulfate (142 mg po qid). The first treatment course was 26 days and subsequent courses were 29 days. The last day of the previous course was also the first day of the subsequent course. During the first treatment course Multikine was administered once daily on Days 1-5 and 8-12, in subsequent courses it was administered once daily on Days 4-8 and 11-15 of each course.

One patient completed all 6 courses of therapy, three completed 5 courses, three completed 4 courses, ten completed 3 courses, fourteen completed 2 courses and all sixteen completed the initial course of treatment. One patient began treatment course 2 but did not complete it, and 1 patient who entered treatment course 4 did not complete it. Fifteen patients discontinued participation in the study, 13 because of progressive disease and 2 as a result of death.

Thirteen severe adverse events were reported during the study. None of these were attributed to the treatment regimen by investigators. Only two adverse events were considered "possibly related" to therapy: moderate hyponatremia and mild asthenia.

Seven deaths occurred during the study. The deaths were not unexpected, given the advanced nature of the patients' disease and were not drug-related. Five were related to the patient's malignancy and two were unrelated.

Currently available information indicates that none of the patients in the low dose group had a complete response or partial response, but therapy did result in decreased or

stable tumor size in about half of patients assessed after two courses of treatment. It was not possible to demonstrate a dose-response relationship for Multikine in this trial, perhaps due to small sample size.

Conclusion: Multikine when administered alone and as part of the regimen including cyclophosphamide injection, daily indomethacin and oral zinc sulfate was safely administered and well tolerated at all doses administered in this trial. A final report of the efficacy results is pending, however, given the improvement or stabilization of most patients who received two courses of therapy and the safety of Multikine when given alone or in conjunction with CIZ, additional studies are warranted in the group studied and other patient groups.

Multikine Phase II (Head & Neck – Canada)

CEL-SCI enrolled 28 patients in a multi-center, Phase II dose escalating clinical trial in subjects with previously untreated, advanced primary squamous cell carcinoma of the oral cavity.

This study was a Phase I-II trial of Leukocyte Interleukin, Injection (Multikine) in patients with head and neck cancer. The study was conducted primarily to determine the safety of a 3-week dosing regimen of Multikine in combination with cyclophosphamide, indomethacin, and zinc (CIZ) in patients with advanced disease (Multikine was given three times weekly in two of the dosing weeks), and to evaluate indications of efficacy.

The study had an open label, multicenter, ascending dose design. Following screening and at least three weeks before tumor treatment by surgical resection or the commencement of radiation therapy, each patient was given a single injection of cyclophosphamide 300 mg/m^2 IV, an 18-day regimen of indomethacin 25 mg orally three times daily, zinc sulfate monohydrate 142 mg orally daily, and alternate day peri-tumoral injections of leukocyte interleukin for a total of six injections during a two week interval. The first seven patients received the low Multikine dose 200 IU IL-2 equivalent. If safety was observed, i.e., no unacceptable toxicity as defined by the investigator or patient, the second seven patients received the Multikine dose 400 IU IL-2 equivalent, the third seven received the Multikine dose 800 IU IL-2 equivalent, and the last seven received the high Multikine dose 1600 IU IL-2 equivalent.

Patients were typical of those with advanced cancer of the head and neck. Most had a history of alcohol consumption and long term tobacco use. The mean age was 60.1 years and the majority (85.7%) were male. Most patients (89.3%) had stage II or III disease.

Almost all patients were stable in terms of primary tumor growth following treatment with Multikine. Clinically positive lymph node size changes were variable, and changes in

size did not appear to be dose-related. Tumor characteristics did not change in most patients following treatment, though pain/tenderness was decreased in those patients who did have a reduction in tumor surface area. Both the patients and medical staff assessed well-being as stable or improved, and other health assessments as stable in most patients.

Multikine was found to be safe and well tolerated. No deaths or serious adverse events occurred during the study regimen. The most common drug-related adverse events were local effects of mild severity. No clinically significant toxicity, changes in laboratory values or other safety measures occurred during the study.

Conclusion: No serious adverse events attributable to Multikine were reported in this trial. Multikine is safe for use in this patient population, and indications of potential efficacy suggest that further studies with Multikine are warranted.

Multikine Phase II (Head & Neck – Hungary)

The results of a fully enrolled, multi-center, dose escalating Phase II clinical study in advanced primary head & neck subjects conducted in Hungary are summarized as follows: Twenty-seven (27) disease matched tumor tissue samples were obtained from the National Oncology Center (Hungary), the lead center of this multi-center clinical trial, and served as the control group for a follow-on histopathology study. Multikine was administered peri-tumorally six times over a two week period to the first three groups of advanced primary OSCC patients [8 subjects – 200 IU, as IL-2 (per day), and to 12 subjects – at 400 IU/day and to 7 subjects – 800 IU/day] for a total of ten times over a two week period, peri-lymphatically plus a one-week wait period before surgical resection of the residual tumor. Preliminary safety data corroborates the lack of toxicity seen in previous studies. Furthermore, preliminary results (from one site, The National Cancer Institute, Hungary) demonstrated the lack of recurrence in the first eight (8) sequentially treated patients at 24 months + post treatment with Multikine (which was followed by surgery and radiation therapy). At the same clinical site, approximately 50% of these type of patients (undergoing surgery for the primary tumor and affected lymph nodes - followed by radiotherapy) are expected to present with recurrence of disease at 18-24 months post treatment. Histological data suggested that Multikine pre-treatment, in addition to its direct anti-tumor effect, significantly ($p<0.05$) increases the number of residual tumor cells that enter into the cell-cycle mode (Fig 3), thereby making these tumor cells more susceptible to follow-on therapy with radiation or radiation and chemotherapy[26].

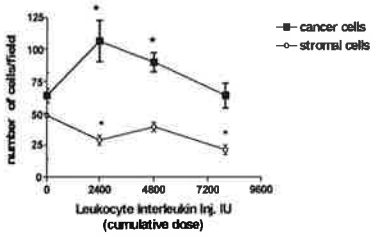
This study was expanded to include 20 additional advanced primary OSCC patients receiving the drug (800 IU/day) 1/2 peri-tumorally and 1/2 peri-lymphatically. In this later study, Multikine was administered 5x/week for 3 weeks, and 20 additional disease matched controls (selected as described above) were used for the pathology portion of the study. Safety data corroborate the lack of toxicity seen in the previous studies.

Histopathology results indicate a marked anti-tumor response resulting in necrosis, marked lymphocytic infiltration and fibrous collagen deposition in the tumor bed (Fig 4).

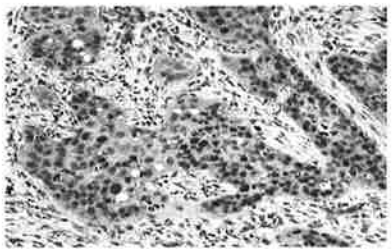
In situ HLA class II expression of OSCC tumor cells from patients responding to Multikine immunotherapy (>30% reduction) showed a complete absence of HLA II marker as compared to Multikine non-responder group ($p<0.05$). Multikine neoadjuvant immunotherapy decreased the number of macrophages in the tumor ($p<0.002$) in the Multikine responder group as compared to control (non-Multikine treatment)[28].

Conclusion: Multikine treatment induced a shift from stromal T-cells to tumor epithelial T-cell infiltrate ($p<0.05$), increased intra epithelial CD3+, CD4+, CD28+ T-cells and decreased CD8+ T-cells ($p<0.05$). As a result of tumor cell death and necrosis and CD4+ T-cell infiltration into the tumor, tumor stroma/cancer nest ratio decreased in the Multikine pre-treatment group ($p<0.005$) as compared to a control population (in this pathology study). The objective response rate in this study was 21% and the overall response was 42%[27,28]

Figure 3. Cell cycle marker (Ki67) in Multikine treated Oral Squamous Cell Carcinoma (OSCC)

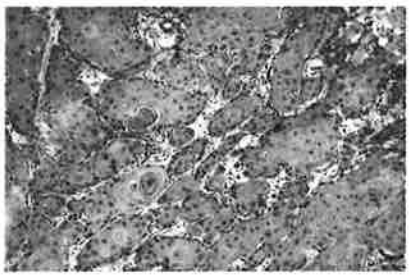


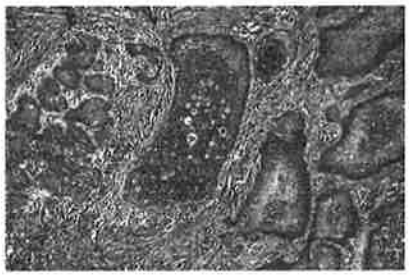
A. Morphometry of Ki-67+ cells in OSCC. Data are means+/-SEM, *p<0.05
0 = Control Untreated Grou



B. Visualization of cycling cancer cells in OSCC by Ki-67+ (Histopathology)

Figure 4. Histological appearance of necrosis in oral squamous cell carcinoma (H&E staining)





Panel A **Panel B**

Panel A: Control - Lack of necrosis in the epithelial nests of Oral Squamous Cell Carcinoma.
Panel B: Multikine treatment - Entire cancer nest is necrotic and filled with debris and leukocytes.

Multikine Phase I (Cervical Dysplasia in HIV-1 / HPV Co-infected Women - US)

In this Phase I dose escalation study, 200 IU/day (as IL-2) was administered by endocervical / peri-lesional injections (5x/wk, for 2wks, 2 wks "rest", and a repeat of the injection regimen) over a 6 week period to 5 HIV-1 / HPV co-infected subject volunteers (women) and following safety assessments of this group, Multikine was given at 400 IU/day (as IL-2) to 3 additional HIV-1/HPV co-infected study volunteers (women). All subjects tolerated the injections well without any investigational drug associated serious adverse reactions. Five of eight (5/8) showed clinical improvement by colposcopic visualization, 3/8 had improvement in PAP smear and on colposcopically guided biopsy (by pathology examination) taken 7-8 weeks after the final Multikine injection. Three of eight (3/8) remained unchanged, and 2/8 had disease progression. One patient was withdrawn from the study, due to a severe adverse reaction (severe pancreatitis), which was related (exclusively) to the anti-retroviral medication she was taking. Multikine treatment of HIV/HPV co-infected women had a direct effect on HPV virus infection of the cervix (reduction in the number of HPV viral types by 75%), as measured by PCR (tested in the first three patients enrolled in this trial).[25]

1.5 Dose Rationale and Risk/Benefits

Previous dose escalation studies in animals and humans have tested Multikine doses up to 3200 IU/day for 2 weeks when administered by peri-tumoral and peri-lymphatic injection. There was no evidence of systemic or local toxicity. Analysis of tumor tissue post treatment has shown infiltration of tumor by CD3+, CD4+ and CD25+ T-cells, tumor necrosis and a dose dependent, cell cycle activation of tumor cells in the tumor bed, which is characteristic of cells' becoming increasingly sensitive to chemotherapy and radiation therapy.

In total, over 200 patients treated with Multikine had no reported serious adverse events associated with Multikine neoadjuvant / adjuvant immunotherapy in clinical trials conducted in the US, Canada, Europe and Israel. Because antitumor activity has consistently been demonstrated at the proposed dose (between 400-800 IU, as IL-2) with concomitant activation of tumor cells in the tumor, a dose of 400 IU was chosen for this phase III study. Although not the maximum dose tested, this dose is safe, well tolerated, and achieves antitumor effects (T-cell infiltration, tumor necrosis and regression, and cell cycle activation of tumor cells). A maximum tolerated dose (MTD) is not being sought, in this trial, as this type of therapy is not anticipated to have a toxicity-based limit.

2. Study Objectives

2.1 Primary Objective

The primary objective is to compare overall survival in the Multikine + CIZ + SOC group to that in the SOC alone group for superiority of the former.

Overall survival will be accessed via a Kaplan-Meier life-table and compared using a log rank test and confirmed further with stage-, location-, and geographic-stratified log rank tests. The unstratified logrank test constitutes the primary analysis. Further details on the statistical analyses can be found in section 7.9.

2.2 Secondary Objectives

The following secondary comparisons are also planned:

(1) Overall survival in Multikine + SOC vs. SOC
(2) Progression Free Survival in Multikine + CIZ + SOC vs. SOC
(3) LRC in Multikine + CIZ + SOC vs. SOC
(4) QOL in Multikine + CIZ + SOC vs. SOC
(5) Examination of the histopathological nature of cellular tumor infiltration stimulated by Multikine injection vs SOC

2.3 Tertiary Objectives

The tertiary objectives of the study include:

(1) Equivalence between overall survival in the Multikine + CIZ + SOC vs Multikine + SOC
(2) Tumor response in Multikine + CIZ + SOC vs. SOC

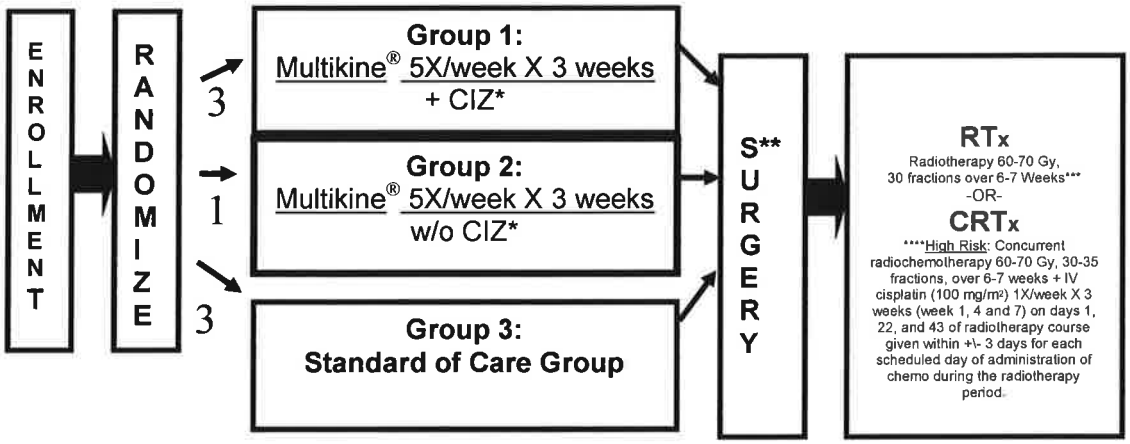
3. Study Design

3.1 General Design

This is a Phase III, open-label, randomized, multi-center study of Multikine given peri-tumorally and peri-lymphatically to subjects with cancer of the oral cavity and soft palate scheduled for surgical excision of tumor followed by radiotherapy or chemoradiotherapy. The control group will receive standard of care only (surgery followed by radiotherapy or concurrent chemoradiotherapy).

An interim safety analysis will be performed after the first 40 subjects have been treated with Multikine and completed surgery (see 8.13.1). Subsequent interim analyses will be performed to confirm sample size and to conduct futility analyses.

Figure 5. Schematic representation of subject randomization and treatment.



* CIZ: Cyclophosphamide 300 mg/m2 (x1, IV, Day -3); Indomethacin 25mg tid, po (Day 1 to approximately 24 hrs prior to surgery) + Zinc (as Multivitamin) po id daily (from day 1 to approximately 1 day prior to surgery)
** Surgery: complete surgical resection of primary tumor and any positive lymph nodes.
*** Radiotherapy is to be given per protocol at a total of ≥ 60 Gy to ≤70 Gy (in 30-35 fractions over a 6-7 week period)
**** High risk subjects are defined as those with: positive surgical margins, 2 or more clinically positive nodes, or extracapsular nodal spread (any or all of the above).

A Phase III, Open-label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection [Multikine] Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity/Soft Palate Versus Standard of Care Only

Table 2. Protocol Treatment Regimen

		Week 1	Week 2	Week 3	Week 4	Surgery Week 5-6		Radiation therapy, initiated no later than 56 days (8 weeks) post surgery +/- concurrent chemotherapy
Treatment Groups	Day -3	Days 1-5	Days 8-12	Days 15-19	Days 22-26	Days 29-38		
Multikine Treatment (Groups 1 and 2)								
Cyclophosphamide [1] **(Group 1 only)**	X							
Multivitamin with zinc supplementation[2] **(Group 1 only)**		X	X	X	X	X		
Indomethacin [3] **(Group 1 only)**		X	X	X	X	X		
Multikine Injection [4] **(Groups 1, 2)**		X	X	X				
Surgery [5] **(Groups 1 and 2)**						X		
Radiotherapy [6] **(Groups 1 and 2)**								X
Chemotherapy [7] **(Groups 1 and 2)**								X
Standard of Care Treatment (Group 3)								
Surgery [5]			X[5]					
Radiotherapy [6]								X
Chemotherapy [7]								X

Notes:
1. Cyclophosphamide given on Day –3 prior to Multikine injection. Dose: 300 mg/m^2 IV (bolus) x1.
2. Multivitamins with zinc supplementation started on Day 1, continued daily until one day prior to surgery.
3. Indomethacin 25 mg tid po with food starting on Day 1 until one day prior to surgery.
4. Multikine injection-Daily Dose: 400 IU; ½ dose peri-tumorally, ½ dose peri-lymphatically 5x/week for 3 weeks.
5. Surgery to be started between Days 29 and 38 for Multikine treated groups (1and 2), within 8-38 days of enrollment/randomization for SOC group 3 (unless otherwise indicated medically by the Investigator)
6. Radiotherapy initiated no more than 56 days (8 weeks) post surgery: 60-70Gy, 30-35 fractions; 2Gy 5x/ week for 6-7 weeks.
7. Chemotherapy: cisplatin bolus infusion, 100 mg/m^2 x3, on weeks 1,4 and 7 (or Days 1, 22, 43 of radiotherapy course given within +\- 3 days for each scheduled day of administration of chemotherapy during the radiotherapy period) to start on day one of radiotherapy if indicated (i.e. in high risk subjects).

3.1.1 Primary Study Endpoint

The primary endpoint of the study is OS. After Multikine injection (with or without CIZ) followed by SOC treatment, subjects will be monitored on a regular basis by clinical and radiographic criteria and will be followed for 30-36 months after completion of study drug + SOC until the required number of deaths are observed. Subjects will be subjected to assessments as described in Section 6.3.

3.1.2 Secondary Study Endpoints

The secondary efficacy endpoints of the study are:

1. Progression-free survival (defined as survival without tumor recurrence, new disease or distant metastases) and on the rate and distribution of distant metastases.
2. Disease progression defined as loco-regional failure, i.e. the reappearance (recurrence) of disease, progressive disease (but not distant metastases), or any new disease above the clavicle not present at baseline.
3. Quality of life assessments on subjects receiving Multikine treatment and standard of care.
4. Histopathological nature of cellular tumor infiltration stimulated by Multikine injection.

3.1.3 Tertiary Study Endpoints

1. Equivalence between overall survival in the Multikine + CIZ + SOC vs Multikine + SOC
2. Tumor response in Multikine + CIZ + SOC vs. SOC

3.1.4 Quality of Life (QOL)

3.1.4.1 Background and Rationale

It is now widely recognized that Squamous Cell Carcinoma of the Head and Neck (SCCHN) and its treatment may significantly affect patients' functioning in basic areas such as eating, speaking and socializing, all of which may, in turn, have a profound influence on overall quality of life[50, 51, 52, 53, 54]. Particularly in advanced disease, treatment is aggressive, multimodal and confers significant acute toxicity and functional impairment. Perhaps of even greater concern, are

the potential late effects, which may interfere long term, with specific functions as well as overall quality of life.[55, 56, 57]

Surgery: Treating head and neck cancer (HNC) by primary surgical resection may result in disfigurement, voice loss, and difficulty chewing and/or swallowing. In addition, some patients experience excessive drooling, choking, respiratory problems, impaired vision, and a decreased sense of taste and smell[57,58]. All of these side effects have been associated with moderate to severe distress, negative self-image and disturbed interpersonal relationships[59,60,61,62]. A review of the literature suggests that the most commonly cited late effects of surgery include (percentage reflects % of patients reporting moderate to severe problems): disfigurement (~50%); voice loss/disturbance (~50%); difficulty eating (chewing, swallowing) (30%-40%); decreased activity (~33%); pain (25%-50%); these percentages are derived from various studies[63, 64, 65, 66]of heterogeneous groups of HNC patients treated with surgery ± radiation therapy. Other data also suggest that larger tumors and more extensive surgery, which generally result from a larger tumor, confer even greater morbidity[67, 68, 69, 70, 71, 72, 73].

Radiation Therapy: Radiation therapy (RT) has long been used alone or in combination with surgery to treat HNC and both the severe acute and long-term sequelae are widely recognized. The literature documents oral toxicities and complications, functional and performance impairments, patient reported symptoms and side effects as well as consequences to QOL. The following list summarizes the most commonly cited late effects of radiation therapy and the percentage of patients reporting moderate to severe problems in that area. These percentages are derived from various studies[56,74, 75, 76, 77]of heterogeneous groups of HNC patients treated with radiation alone: xerostomia (dry mouth) >66%; difficulty eating/ swallowing 35%-68%; sticky saliva ~33%; decreased sense of taste 25%-50%; dental problems 33%; pain 15%-30%; appearance 20%-25%. In one study of 240 oro- and hypopharyngeal cancer patients treated with an aggressive investigational regimen, 25% of patients were still feeding tube dependent 2 years after treatment 77 to 95% of patients had a dry mouth after six months, while 66% had not recovered at one year; a finding, which is consistent with many radiation therapy type studies.

Adding chemotherapy to radiation regimens tends to exaggerate both the acute and long term impact of the radiotherapy[78,79,80]. Most patients recovered from acute toxicities, but some problems (e.g., dry mouth, diet restriction) persisted years after treatment cessation.

Multikine: In general, the addition of any further therapy, particularly in the induction phase, prior to scheduled definitive therapy, has the potential to: a) increase subsequent therapy related toxicities and worsen quality of life, b)

decrease subsequent toxicities by shrinking tumor (and either minimizing tumor related impairments or leading to tumor downstaging and in turn, a possible reduction in subsequent surgical resection, radiation fields or dose) or c) effecting no change in immediate or long term toxicities. In addition, one needs to address the potential impact of the additional treatment itself. As proposed in this protocol, Multikine will be administered by injection daily 5 days/week for three weeks prior to surgical resection. As presented in Section 1.4, limited data suggest that Multikine is well tolerated without substantial acute or long term side effects or sequelae. However, further data are needed to more fully document the impact of Multikine on QOL and performance both in and of itself as well as an adjunct to further therapy. Questions related to pain at the injection site, possible downstaging or possible aggravation of subsequent therapy, require further evaluation. Thus, while traditional efficacy endpoints are undeniably critical considerations, assessment of the patient's QOL and performance is important to the comprehensive evaluation of the success of this new treatment regimen.

3.1.4.2 Quality of Life Objectives

The proposed treatment regimen aims to improve overall survival, loco-regional tumor control, disease free survival and possibly impact distant metastases while minimizing performance and QOL deficits. Thus, QOL and performance assessment are also important treatment objectives. The objective is to describe these dimensions prospectively, pretreatment, through treatment, to long-term follow-up. QOL specific aims are to:

- Evaluate changes in QOL and performance as affected by Multikine treatment compared to SOC.
- Document patient's experience of treatment effects.
- Determine extensiveness and persistence of QOL and function-related treatment effects.
- Describe the pattern, timing and extent of recovery of function and QOL.

3.1.4.3 Quality of Life Assessment

Quality of life assessments will be performed for the first time prior to randomization (but following enrollment and signing of the informed consent by the subject volunteer), and then following Multikine administration up to 1 day prior to surgery and at about, 6, 12, 18, and 36 months after completion of therapy.

For SOC subjects, assessments will be at baseline prior to randomization – as above and then again prior to surgery, and at about 6, 12, 18 and 36 months after completion of therapy.

3.1.4.4 Assessment Instruments

The EORTC QLQ – C30 version 3 core questionnaire will be used in combination with EORTC QLQ-H&N35 specific to head and neck cancer. Both the core questionnaire and H&N35 are validated instruments used in multi-cultural setting. The instrument has demonstrated ability to assess the functional, performance and quality of life domains germane to SCCHN, and sensitivity to change over time.

The EORTC QLQ-C30 consists of 30 questions covering general health aspects in cancer patients. The disease-specific EORTC QLQ H&N35 consists of 35 questions covering aspects of head and neck cancer. The core questionnaire and disease-specific questionnaire in total will contain 65 questions. The instrument is self-administered by the subjects (or can be completed by subjects with the assistance of a qualified healthcare provider). Validated translations for EORTC QLQ-C30 and EORTC QLQ-H&N35 are available in most major languages such as English, Spanish, Hungarian, Ukrainian, Portuguese, French, Polish, Russian, Mandarin, Cantonese, Hebrew and many Indian languages (Bengali, Gujarathi, Hindi, Kannada, Malayalam, Marathi, Punjabi, Tamil, Telugu).

A scoring manual will be provided with details on scoring procedure for the subject's responses to the questions posed by the EORTC QLQ-C30 and EORTC QLQ-H&N35 Questionnaires.

4. Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Previously untreated primary squamous cell carcinoma of the oral cavity inclusive of the tongue (but not the base of the tongue), floor of the mouth, cheek (buccal mucosa) and soft palate only, confirmed by biopsy, with or without regional lymph nodal metastases, deemed curable by and scheduled for definitive treatment by surgical resection and postoperative radiation therapy or surgical resection and postoperative concurrent chemoradiotherapy (standard of care). Tumors in other locations (and those in other locations of the head and neck) are excluded.

- The primary tumor class must be T1, T2 or T3 and must NOT measure more than 6 cm in greatest dimension. T4 is allowed if invasion of the mandible is minimal (defined as <0.5cm as confirmed by CT,-and/or MRI with the use of CT imaging being mandatory) and can be salvaged by marginal mandiblectomy (retention of function and having intact mandible post surgery).
- The class of clinically positive lymph node(s) must be N1 or N2 and must not measure more than 6 cm in greatest dimension.
- Clinical tumor stage must be III or IV. For stage IV, only subjects treatable by surgical resection or surgical resection followed by postoperative radiation/ radiochemotherapy are eligible:

Eligible TNM Categories:

T1 N1-2 M0
T2 N1-2 M0
T3 N0-2 M0
T4* N0-2, M0

* T4 is allowed if invasion of the mandible is minimal (defined as <0.5cm as confirmed by CT, and or MRI with CT imaging mandatory) and can be salvaged by marginal mandiblectomy (retention of function and having intact mandible post surgery).

2. Primary tumor and, if present, clinically positive lymph node(s) with at least one measurable lesion as defined by the RECIST criteria (Appendix 10) and measurable in two dimensions by physical examination.
3. ≥18 years of age.
4. If female, is neither pregnant nor lactating.
5. If subject is of reproductive potential they must be willing and able to utilize effective methods of contraception (e.g. barrier methods with spermicide).
6. Hemoglobin: >9gm/dL; WBC: > 3000/mm^3; platelets: > 100,000/mm^3, bilirubin < 1.0 mg/dL; creatinine < 1.2 mg/dL.
7. No prior therapy with IL-2, IL-1 or any other biological response modifier (e.g., interferon α, β or γ, G-CSF, GM-CSF) in past one year.
8. Negative reaction to intradermal test with ciprofloxacin (a fluoroquinolone antibiotic).
9. No immune depressive drugs, e.g., corticosteroids, cyclosporine, methotrexate, or anticancer agents, in past one year. Subjects on topical corticosteroids to treat dermatological conditions covering not more than 5% of body surface area are considered eligible.
10. Life expectancy greater than six months.
11. Karnofsky score 70 or greater.

12. Able to take oral medication.
13. Able to provide informed consent.
14. Must have normal immune function, i.e., must not be known to be HIV infected or have any other disease or condition causing significant immunodeficiency.

4.2 Exclusion Criteria

1. Subjects other than those to be treated by surgery, followed by radiation therapy +/- chemotherapy and/or those for whom surgery would be scheduled prior to Day 8 from enrollment /randomization.
2. Tumor invasion of bone as detected by a suitable imaging technique MRI and/or CT or by physical examination, except for mandibular invasion (as described above for T4 Tumor).
3. Any T1N0 or T2N0 stage tumors and all tumors classified as T4, N3 and/or any TN classification with M1 or greater (Note: only M0 is allowed in this study), or in locations other than those specified in Inclusion Criteria #1 (Section 4.1).
4. Active peptic ulcer disease despite ongoing adequate medical therapy.
5. Prior surgical resection of the jugular lymph nodes on the ipsilateral neck that the injection is to be administered.
6. Any acute or chronic viral, bacterial, immune or other disease in a stage usually associated with abnormal cellular immunity (e.g., HIV infection, hepatitis, nephritis, lung disease, rheumatoid arthritis or other autoimmune disease).
7. Subjects on hemodialysis or peritoneal dialysis.
8. Prior history of asthma.
9. Prior completion of one or more courses of therapeutic irradiation, excluding such treatment of the extremities.
10. History of allergic reaction to fluoroquinolone antibiotics (e.g., ciprofloxacin, ofloxacin).
11. History of any other malignancy, excluding basal cell carcinoma of the skin and in-situ carcinoma of the cervix.
12. History of congestive heart failure (CHF) and other heart conditions that in the opinion of the investigator would cause the subject to likely be unable to participate in the study or tolerate the study's protocol regimen (including the surgical procedure).
13. The opinion of the investigator that the subject may be unable to tolerate the protocol regimen or that participation in the trial may compromise the subject's preparation for tumor treatment.
14. Failure to meet the Inclusion Criteria.

4.3 Prohibited Treatments and Medications

The following medications are prohibited during study participation:

- Any investigational agent other than Multikine.
- Routine use of hematopoietic growth factors.
- Immunotherapeutic agents.
- Chemotherapeutic agents other than those specified in the protocol.
- Radiation therapy other than that given postoperatively per this protocol.
- Surgery for cancer management or treatment other than that planned for definitive treatment of the primary head and neck cancer.
- Full-dose (therapeutic) anticoagulation therapy, aspirin >325 mg/day, or any other platelet inhibitory agent.
- Medications and treatments other than those specified in the above list, including palliative and supportive care for disease-related symptoms, are permitted during the study.

4.4 Subject Recruitment and Screening

4.4.1 Recruitment

Subjects will be recruited from oncology centers having the demonstrated expertise to treat head and neck cancer. All advertising (if any) will be reviewed and approved by the IRB/EC of that institution and a letter indicating review and approval of the advertising will be supplied. Subjects will receive and be asked to sign an informed consent that fully describes the study procedures in lay language. The subject will have an opportunity to have all questions regarding the study answered and will understand that their participation is voluntary.

4.4.2 Screening

The following assessments and tests should be performed within 2-4 weeks prior to randomization (unless otherwise specified in the Protocol):

1. Measurements of the target lesions in longest diameter (LD) by either CT/MRI or clinical examination. For clinical examination the LD should be assessed using calipers and documented by color photography including a ruler. Clinically positive regional lymph nodes will be measured in short axis.
2. Bi-dimensional measurements of the primary tumor and bi-dimensional measurement(s) of clinically positive regional lymph nodes by CT or

gadolinium – enhanced MRI scan. Note: The radiologist performing the MRI should provide an original copy of the scan(s) and a data tape or diskette to the clinical investigator for inclusion in the subject study documentation (Section 9.2). These measurements must be taken prior to biopsy.
Note: RECIST criteria (Appendix 10) will be used to evaluate the response of the tumor to Multikine treatment and for the SOC population prior to surgery and during the course of the study.

3. Punch Biopsy of the primary tumor may be obtained up to four (4) weeks prior to subject randomization in the trial. The specimens obtained must be diagnostic of squamous cell carcinoma and be sufficient to allow grading of tumor cell activity and evaluation of peripheral blood white blood cell infiltrate and other immunological markers. Tumor samples available from the biopsy (H&E slides) will have to be sent to both the local and central pathology laboratories participating in this study for examination. If these samples are unavailable or insufficient to allow the additional testing required by these laboratories then an additional biopsy must be performed at study entry. FNA biopsy will be performed on any affected clinically involved regional lymph node. Consultation with a pathologist should occur to ensure that the biopsy sample will be adequate for this evaluation. Specific instructions for sending specimens to the central pathology laboratory for this study are provided in Appendix 4 of this protocol.
4. Subjects electing to participate in the genomic microarray study described in section 6.7 will be required to provide an additional fine-needle aspiration (FNA) sample (frozen) and an additional 25-50mL of blood for collection and preparation of PBMCs for the microarray study at screening.
5. Medical history (including betel nut, tobacco and alcohol use) and physical examination.
6. Vital signs.
7. Height and body weight.
8. Chest X-ray (PA and lateral) and EKG. CT of chest may be substituted for chest X-ray.
9. Complete blood cell count (CBC), including platelets and white blood cell differential, and erythrocyte sedimentation rate (ESR) (Appendix 4).
10. Urinalysis (Appendix 4).
11. Blood chemistry tests (Appendix 4).
12. Clinical staging of the primary tumor and regional lymph nodes.
13. Photographs of the primary tumor with adjacent metric scale (color electronic media capture – Digital Photography).

14. Scoring of skin test response to ciprofloxacin.
15. Appropriate evaluations of intercurrent diseases (HIV test).
16. Review of previous and current medications.
17. Serum pregnancy test (within 3 days of start of Multikine treatment).
18. Adverse Event recording.

4.5 Withdrawal and Discontinuation of Subjects

4.5.1 Subject Discontinuation

This study will be conducted under the intent-to-treat-principle (ITT). This means that once a subject is randomized to a treatment group, he or she will remain in that treatment group and should follow his or her protocol defined sequence of visits regardless of whether the subject receives the assigned study medication, and regardless of the extent of the subject's compliance with dosing. A subject may be discontinued from study medication for a number of reasons, some of which are listed below, but this does not automatically mean the subject is discontinued from study follow-up. Reasons for discontinuing study medication include the following:

1. If a subject has documented evidence of progressive disease or symptomatic tumor progression after administration of SOC or Multikine followed by SOC.
2. If the investigator thinks a change of therapy would be in the best interest of the subject.
3. If the subject requests discontinuation, withdraws consent for any reason, or is unwilling or unable to comply with study requirements.
4. If the study drug exhibits unacceptable toxicity that does not respond to dosage modifications.
5. If a subject becomes pregnant after enrollment in the trial, or fails to use adequate birth control (for those subjects who are able to conceive).

Study personnel should make every reasonable effort to encourage subjects to continue with the follow-up schedule even if the subjects are not receiving study medication, or did not receive a full regimen of study medication.

Subjects who need to withdraw from the study for a period of time, but are willing to resume should be encouraged to do so. Likewise, subjects who are unable to attend all protocol visits but may be able to attend a subset of visits should be encouraged to do so. Subjects who miss a visit should be contacted and encouraged to continue with their treatment (if applicable) and follow-up.

The study will be closed once the targeted number of deaths are observed; this is expected to take place 30-36 months (the duration of follow-up is event driven) after SOC (as defined in this protocol) has been administered to the last enrolled subject. Investigators will collect survival information after study closure for all subjects who have been involved in the study and have not withdrawn their consent for three (3) years following randomization.

4.5.2 Study Discontinuation by the Sponsor

The sponsor has the right to terminate this study and/or any investigative site at any time. Reasons for terminating the study and/or investigative site may include the following:

1. The incidence or severity of an adverse event (AE/SAE) in this or other studies indicates a potential health hazard to subjects.
2. Subject enrollment is unsatisfactory.
3. Data recording is inaccurate or incomplete.
4. Good Clinical Practice (GCP) procedures are not being followed.

The sponsor will not have access to, or base the decision to terminate a clinic on unblinded data. Subjects from a site where enrollment has been terminated will continue to be followed under the intent-to-treat principle, at the terminated site or at an alternate site.

4.5.3 Data Collection and Follow-up for Withdrawn Subjects

All subjects must be followed for safety evaluation (Section 8) until the time of study discontinuation or study closure (Sections 4.5.1 and 4.5.2 respectively). At the time of discontinuation, all procedures and evaluations scheduled for the last visit of the study must be performed (Section 6.3 and as indicated). The reason and date of study discontinuation will be recorded for all subjects. As noted above, it is essential that all subjects be followed as long as possible, and as completely as possible even if they have not received Multikine, or have only received a partial regimen, unless they have withdrawn consent.

WHILE COLLECTING COMPLETE DATA FOR ALL STUDY ENDPOINTS IS CRUCIAL, IT MUST BE AN ESPECIALLY HIGH PRIORITY TO OBTAIN SURVIVAL DATA ON ALL SUBJECTS FOR 3 YEARS.

5. Study Drug

5.1 Description

Multikine (Leukocyte Interleukin, Injection) is provided frozen in a borosilicate glass-serum-vial containing 2.2 mL of drug at 200 IU (as IL-2) per mL for peri-tumoral, intra-tumoral, peri-lymphatic or subcutaneous administration. The preparation has a total protein content of 3 mg/mL. The drug is stored frozen in the pharmacy at –20°C until needed. The vial contents may be thawed at ambient temperature just before use, and the drug is allowed to reach ambient temperature before injection. If thawed at ambient temperature, the drug must be injected within 4 hours.

Multikine may also be thawed at refrigerator temperature (2°-8°C) one day before use, and allowed to come to ambient temperature just prior to injection - either way of thawing the drug vial, is acceptable. However, the overnight thaw at 2°-8°C temperature is preferable as the drug may be kept for up to an additional 24 hours at 2°-8°C temperature after thawing, if the subject did not arrive in the clinic – once the drug is brought to ambient temperature it must be used within 4 hours (of reaching ambient temperature) or be disposed of. See Appendix 11 for specific instructions on Drug Vial Thawing Procedure.

5.2 Treatment Regimen

Subjects randomized to one of the Multikine treatment groups are scheduled to be treated with or without CIZ. Multikine, 400 IU (2 mL) is injected each day of study drug administration, 1/2 dose (1 mL) peri-tumorally and 1/2 dose (1 mL) peri-lymphatically at the jugular lymphatic chain ipsilaterally to the injected tumor site inferior to the tip of the mastoid process in the area of the sternomastoid muscle (See Appendix 3) sequentially and during the same visit. Both injections (peri-tumorally and peri-lymphatically) are administered 5 times per week for 3 weeks. If scheduled to receive CIZ, subjects will also receive 300 mg/m^2 cyclophosphamide (IV bolus on Day –3 of first Multikine injection) and 25 mg indomethacin (tid po daily with food from Day 1 to one day prior to surgery). Additionally, a multivitamin supplement containing zinc is given from Day 1 to the day before surgery for immune system/nutritional support. These medications are to be recorded on the concomitant medication Case Report Form (CRF). At the discretion of the investigator, a local anesthetic may be administered prior to Multikine injections.

5.3 Method for Assigning Subjects to Treatment Groups

The entry criteria of eligible subjects will be reviewed upon enrollment and a study number and treatment group (Multikine +/- CIZ plus SOC or SOC alone) will be assigned via randomization. Upon acceptance, the study site will be

notified of the treatment assignment. Subjects randomized to Group1 and 2 (Multikine +/- CIZ plus SOC) must begin treatment within 7 days of study randomization.

An Interactive Voice Response System (IVRS) will be used for randomization and stratification. Randomization sequences will be computer generated and maintained by the IVRS. Subjects, who meet all eligibility requirements and complete screening evaluations, will be randomly allocated in a 3:3:1 allocation with Multikine + SOC (without CIZ) being the treatment group to be assigned least often in contrast to Multikine + CIZ + SOC and SOC alone. The IVRS will employ a dynamic randomization procedure to ensure balanced treatment assignment within the arms of the trial for each of the following stratification factors: tumor location (tongue, floor of mouth, cheek, and soft palate) and tumor stages III and IV (Table 3 below), within each country, such that each group (Multikine + SOC and SOC alone groups, respectively) will have as near to as the same number of subjects that are in each of the prospectively stratified sub-groups throughout the whole study. The dynamic algorithm (Pocock and Simon 1975: Taves 1974) [81,82] is designed to balance treatment assignment along the marginal distribution of each factor.

Table 3. TNM Categories and Corresponding Tumor Stage

	Primary Tumor			
Nodal Involvement	**T1**	**T2**	**T3**	**T4**
N0	**NE**	**NE**	Stage III	Stage IVa
N1	Stage III	Stage III	Stage III	Stage IVa
N2	Stage IVa	Stage IVa	Stage IVa	Stage IVa

Note: Stage IVb (T4b primary and all N3 disease) are not eligible.
NE = Not Eligible.

5.4 Preparation and Administration of Study Drug

Pharmacy instructions will be provided separately. Multikine is supplied sterile and pyrogen free in 5 ml vials containing 2.2 mL, 400 IU (as IL-2)/vial and is stored frozen at –20°C. Prior to use, the pharmacist will remove the vial from the freezer and place it in the refrigerator to thaw overnight (Appendix 11). After thawing of the investigational drug, the appropriate protocol and subject identification information are entered onto a label, which is then affixed to the vial, recorded on the drug accountability record and the CRF for each subject. The drug is then ready for use by the clinical staff.

When a subject is in the clinic and is being prepared (readied) to receive the injections of Multikine, the clinical staff shall prepare two separate sterile syringes each containing no less than 1 mL of Multikine® (A vial of Multikine contains approximately 2.2 mL of drug) and each syringe will have a separate sterile needle (needle size at the discretion of the administering physician.
Note: Recommended needle size smaller or equal to G-25).

Multikine is injected (one half the daily dose) 200 IU (as IL-2) into the submucosa at the peripheral margin of the tumor (peri-tumorally), and peri-lymphatically (one half the daily dose) 200 IU (as IL-2) at the jugular lymphatic chain ipsilaterally to the injected tumor site inferior to the tip of the mastoid process into the sternomastoid muscle (sequentially and at the same visit) (Appendix 3). An approximately equally subdivided volume [e.g., 1 mL (1/2 dose)] is injected in a minimum of four equally spaced sites: i.e., near either extent in the longest dimension of the tumor and near either extent at right angles to and at the midpoint of the longest dimension of the tumor [Appendix 2A: Technique of Peri-tumoral, Subepidermal Injection of Leukocyte Interleukin (Multikine), Figures 1 and 2]. When the anatomical location of the tumor does not allow injections to be made completely around the tumor (e.g., bone adherence or invasion), Multikine is injected in approximately equal volumes at a minimum of four sites around the injectable accessible portion of the tumor margin (Appendix 2B, Figure 3). If Leukocyte Interleukin, Injection (Multikine) is observed to leak out of the needle channel, the number of sites injected may be increased and volume per site reduced (e.g., 8 sites at 0.125 mL for 200 IU peri-tumoral dose, Appendix 2A, Figure 1) to ensure drug retention. Peri-lymphatic injections are administered as described in Appendix 3: Jugular Region Peri-lymphatic Administration of Multikine (200 IU peri-lymphatic).

5.5 Monitoring Subject Compliance

Except for administration of concomitant medications required per protocol (multivitamin supplementation and indomethacin self administered by subjects), all treatments are to be administered by authorized clinical staff. Compliance with concomitant medication administration by subjects will be monitored by drug accountability and notation in the CRF.

5.6 Prior and Concomitant Therapy

All concomitant medication for subjects will be recorded on appropriate case report forms. There is no prohibition on medications administered to subjects for normal medical care except administration of any immunosuppressant drugs (e.g. Cyclosporine), or administration of concomitant anticancer therapies. Corticosteroids used to control edema or inflammation post surgery or to treat

dermatological conditions topically during the protocol regimen [<5% of Body Surface Area (BSA)] are permitted as per investigator clinical judgment. Drugs for analgesia may be used during Multikine injection. Subjects may also receive nutritional support and drugs to control nausea and vomiting to be used as indicated.

Cytokines, biological response modifiers and growth factors may not be used for six (6) weeks prior to and during the protocol regimen as these may be confounding to the interpretation of the results. However, if it becomes necessary to use these agents to treat toxicity induced by radiotherapy or chemoradiotherapy as part of normal medical care of the subject, they may be used. Use of these agents will be documented including the specific indication for use in the CRF.

5.7 Packaging

Multikine is packaged in 5 ml vials containing 2 mL of Multikine (200 IU/mL) and is stored frozen at approximately –20°C (± 3 °C). It is thawed and administered as described in Appendix 11. An overage of 0.2 mL is also contained in each vial.

Multikine is packaged in bulk in 50 vial/ boxes for use in creating a "Subject Kit" (by the international drug distribution center). Packaged treatment kits contain 15 vials of drug/carton ("Subject Kit"). Two (2) extra vials are shipped for each kit (of 15 vials to be used per subject) – for a total of 17 vials per Subject Kit, shipped to the institutional pharmacy. This is done as a precautionary measure in the event of a mishap with a vial. The number of "Subjects Kits" shipped (all via courier) to the institutional pharmacy will be a sufficient quantity of study drugs to treat the number of subjects anticipated to be enrolled at each investigational site. Kits will be contained within an outer shipping carton containing cool-frozen packs (U-Teck or a validated equivalent) for shipping of drug at –20°C (or below, for shipment only, +/- 5°C allowed).

Each "Subject Kit" will be labeled with the name of the study drug, protocol number, IND number, unique subject and IVRS number and FDA mandated (if applicable) warning(s) and any specific or unique to country information mandated by country/local laws for such an investigational drug (if any) . The "Subject Kit" label will also have space for the subject's unique ID and unique IVRS number to be entered at each site.

5.8 Blinding of Study Drug

Not applicable. This is an open label Phase III study.

5.9 Receiving, Storage, Dispensing and Return/Destruction of Drugs

5.9.1 Receipt of Drug Supplies

The study drug distributor will store study drug frozen and ship the "Subject Kits" to each investigative site upon written instruction from the sponsor. Prior to drug receipt, each site must have completed a pre-study site assessment (conducted by sponsor or designee), signed a clinical trial agreement, and have IRB approval for the study protocol and informed consent.

Upon receipt of the "Subject Kits" and other supplies an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. Study drug (Multikine, "Subject Kits") must be stored at –20°C immediately upon receipt. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory at each institution. Copies of the drug receipt accountability sheets will be faxed to the sponsor or designee within 24 hours of drug receipt. The receipt of any damaged or unusable study drug in a given shipment will be documented in the study files at each participating site. The investigator must notify the study sponsor of any damaged or unusable study drug that is supplied to the investigator's site immediately by telephone and fax. Damaged drug will immediately be segregated and placed under "Quarantine" (at each site) and so labeled. Damaged or unusable supplies will be replaced via IVRS notification.

5.9.2 Storage

Multikine is stored at –20°C for long-term storage (+/- 1°C preferred, however, +/- 3°C excursions are allowed). Only transient temperature excursions are allowed and all are required to be documented on a temperature execution log. Multikine is shipped at –20°C (or lower temperature for shipment only, +/- 5°C allowed). The investigational drug is thawed just prior to use as described in Section 5.4 and administered within 4 hours.

5.9.3 Dispensing Study Drug

Study drug will be dispensed by the investigational pharmacist on a subject-by-subject basis (controlled by the IVRS system). Each subject will use one (the same) drug kit for the duration of the treatment. After a subject is enrolled, the subject's identifying information, subject ID number and subject's initials will be forwarded to the pharmacy by research personnel as described in Section 5.4

above. The pharmacist will designate a kit for treatment for a specific subject by entering the subject identifiers (given by the IVRS system) on the kit label. That kit will be used for the exclusive treatment of that subject. The pharmacist will dispense study drug on a daily basis for the subject (from the subject specific kit), as required per protocol.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of all study drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated by the investigational pharmacist at each investigative site. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug to the local/central drug depot for complete drug accountability in this study. Drug destroyed on site will be accounted for and documented in the study files and will be as per study site standard operating procedures (provided both drug and drug labels are completely destroyed). A copy of each institution's drug destruction protocol will be collected. If directed by the sponsor, study drug may also be returned to the sponsor or its designee. Separate instructions will be provided for study drug returns by the designated supplier of study drug.

6. Study Procedures

6.1 Assessment and Tests (Groups 1, 2 and 3)

1. Day minus three (-3) or the same day of treatment regimen with cyclophosphamide (if scheduled) but before cyclophosphamide administration **(Group 1 only)** and also for **Groups 2 and 3** not receiving cyclophosphamide (i.e., for all groups) at study randomization day:

    a. CBC and ESR (Appendix 4)
    b. Blood chemistry test (Appendix 4)
    c. Vital signs (Blood pressure, temperature, pulse, respiratory rate) before and 30 minutes after administration of cyclophosphamide
    d. QOL assessment (as specified in Section 3.1.4.3)
    e. Recording of Adverse Events

2. Treatment regimen Days 1-19 (**Groups 1 and 2**):

   a. Vital signs for Multikine treated group, Days 1-5, 8-12 and 15-19, before and 30 minutes after administration of Multikine
   b. Tumor measurements Day 1 and 15
   c. CBC with differential , ANC Day 1
   d. ESR Day 1
   e. Recording of Adverse Events at all visits

For Groups 1, 2 and 3:

3. Tests and examinations requested by the Principal Investigator for further evaluations of symptoms described in the Daily Health Assessment Forms and in other inquiries concerning the subjects' health status. Long term follow-up (Section 6.5)

4. Record all concomitant medications received by subjects.
   All medications [prescription, over-the-counter (OTC) medications, or herbal preparations] taken before enrolment into the study and continued after screening visit must be documented on the concomitant medication section of CRF. Medications started during study and different from protocol-specified medication must be documented on the concomitant medication section of CRF.

6.2 Administration of Protocol Required Medications and Study Drug (Groups 1, 2, 3)

6.2.1 The following medications and study drug are to be administered as per protocol to subjects randomized to the Multikine + CIZ + SOC group (Group 1):

1. Cyclophosphamide 300 mg/m^2 (USP-grade or equivalent, commercially available) administered as intravenous bolus on Day minus 3 of the protocol regimen.
2. Indomethacin, 25 mg capsule (USP-grade or equivalent, commercially available), administered orally three times daily (with food) on Days 1 through one day prior to surgery of the protocol regimen. Subjects should bring bottles to each visit for counting to monitor compliance. Unless there is a problem (i.e., <80% compliance), counts should be performed at a minimum on Days 4, 8, 11, 15, 18 and between Days 22-28. If non-compliance is noted, the reasons should be identified and efforts made to

rectify the problem. This should be documented on the subject's record and on the CRF.

3. Multivitamin tablet(s) and/or capsule(s) with zinc (commercially available), taken orally once daily on Days 1 through one day prior to surgery, and as indicated for nutritional support (amount of zinc should be >15 mg and no more than 40 mg per day).
4. Multikine 400 IU (as IL-2, total daily dose) (2.0 mL), one half (1 mL) injected peri-tumorally (200 IU) and the other half (1 mL) injected peri-lymphatically (200IU) on Days 1-5, 8-12 and 15-19 for a total of 15 daily treatments, for all subjects randomized to receive Multikine treatment (Appendix 2a, 2b and 3).
5. Cisplatin (only to those subjects as determined following surgical results – per protocol definition – "High Risk") 100mg/m^2 intravenously (IV) 1x/wk weeks 1, 4 and 7 (or Day 1, 22, 43 of start of radiotherapy course) (Table 2 and Appendix 1).

6.2.2 Study Drug Administration (Group 2)

The following medications and study drug are to be administered as per protocol to subjects randomized to Multikine + SOC (the non-CIZ) group (**Group 2**):

1. Multikine 400 IU (as IL-2, total daily dose) (2.0 mL), one half (1 mL) injected peri-tumorally (200 IU) and the other half (1 mL) injected peri-lymphatically (200 IU) on Days 1-5, 8-12 and 15-19 for a total of 15 daily treatments, for all subjects randomized to receive either Multikine treatment (Appendix 2a and 2b).
2. Cisplatin (only to those subjects as determined following surgical results – per protocol definition– "High Risk") 100mg/m^2 intravenously (IV) 1x/wk weeks 1, 4 and 7 (or Day 1, 22, 43 of start of radiotherapy course) (Table 2 and Appendix 1).

6.2.3 The following medications are given to subjects randomized to SOC only group (Group 3)

1. Cisplatin (only to those subjects as determined following surgical results – per protocol definition– "High Risk") 100mg/m^2 intravenously (IV) 1x/wk weeks 1, 4 and 7 (or Day 1, 22, 43 of start of radiotherapy course) (Table 2 and Appendix 1).

6.3 Post-Multikine Treatment Evaluations

Except for Items 9 and 10 below, which are obtained during the time specified, the following assessments and data are to be obtained between Days 21 and 28 following the first day of Multikine administration (i.e. after Multikine treatment, but prior to surgery) for subjects in the group not receiving Multikine, this evaluation will be done at baseline and or between study entry and surgery (and all evaluations will be completed before the day of surgery).

Note: All evaluations are done for all subjects whether they received Multikine treatment or not. Since there is no equivalent "experimental" treatment time period for SOC only subjects, comparable baseline assessments are required for evaluation of laboratory changes for all subjects not receiving Multikine treatment as listed below.

1. Interim medical status, including review of medical history and physical examination.
2. Vital signs and body weight.
3. CBC and ESR (Appendix 4).
4. Urinalysis (Appendix 4).
5. Blood chemistry tests (Appendix 4).
6. Appropriate evaluations of intercurrent diseases.
7. Clinical staging of the primary tumor and regional lymph nodes. Note whether there are additional positive node(s) found during the physical exam or whether there are clinical changes in the primary tumor or nodes.
8. Measurement of the primary tumor and clinically positive regional lymph node(s) documented using CT/MRI and photographs with ruler measurements. The same imaging modality used in baseline for a lesion should be consistently used during follow-up assessments. Measurements done by physical means will record bi-dimensional measurement of the primary tumor and clinically positive regional lymph node(s) and be accompanied by color photographs (color electronic camera photos are acceptable) with adjacent metric scale. RECIST criteria (Appendix 10) will be used to evaluate the response of the primary tumor to Multikine treatment and the response to SOC therapy during the course of the study.
9. Histological examination of the resected primary tumor and positive lymph nodes for the presence of squamous cell carcinoma, grading of tumor cell activity and evaluation of white blood cell infiltrate and other host responses to the tumor. It should be noted whether lymph nodes found on physical examination are confirmed positive, negative or whether there is evidence of previous tumor, but tumor cells are no

longer evident or are dead. Total number of lymph nodes removed during surgery and the number found to be positive by histologic examination should be recorded. Surgery should occur between Days 29 and 38 for Multikine treated subjects and Group 3 subjects are targeted for surgery between Days 8-38 (for subjects receiving SOC, only) from the date of enrollment/randomization, unless indicated medically otherwise.

10. Subject Compliance Assessment – final counts of indomethacin and multivitamins with zinc to assess overall subject compliance will be performed one day prior to surgery (or as necessary) and recorded on the Concomitant Drug Log.

If any result of items 1 through 5 and 7 is abnormal, appropriate examinations and tests are conducted to document the extent, duration and appropriate treatment of the abnormality and relatedness (if any) to study investigational drug or other concomitant medication.

6.3.1 Tumor measurements (to be performed at baseline and one day prior to surgery)

1. Measurement of the primary tumor and clinically positive regional lymph node(s) documented using CT/MRI or photographs with ruler (metric) measurements. The same imaging modality used at baseline for a lesion should be consistently used during follow-up assessments. RECIST criteria (Appendix 10) will be used to evaluate tumor response to treatment.
2. Color photographs of the primary tumor with adjacent metric scale.

6.4 Standard of Care

6.4.1 Dental Care

The subjects may be grouped into four Dental Care Categories in accordance with the dental care problems they present with prior to irradiation.

Dental Category 1
Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar abscess/ hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

Dental Category 2
Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedures, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas. Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

Dental Category 3
Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth which are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The subjects are instructed for dental prophylaxis and the subjects utilize custom-made fluoride carriers.

Dental Category 4
Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth Procedure
If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

6.4.2 Surgery

As a result of the RTOG and EORTC trials [8,9] the oncology community has adopted the RTOG/EORTC patient selection criteria and treatment regimens as the current SOC that is: Patients with locally advanced primary SCCHN would undergo surgery and be treated (post-operatively) with either radiotherapy or in the presence of defined post-operative risk factors (lymph node involvement,

extra capsular spread, etc.) with a prescribed concurrent radiotherapy and chemotherapy (chemoradiotherapy) regimen.

Study subjects randomized to SOC only group (**Group 3**), will be scheduled for surgery as soon as practicable but within 8 - 38 days of enrollment/randomization. Multikine treated groups (**Groups 1 and 2**) will be scheduled for surgery between Days 29-38 following enrollment/randomization (however, Groups 1 and 2 Surgery may also take place sooner, if medically indicated). Surgery will consist of complete surgical resection of tumor and involved nodes as indicated, followed by post-operative radiation therapy. To clarify, in subjects where regression of tumor or lymph nodes is observed at surgery a more sparing surgery than what was planned at randomization should **NOT** be performed. The surgical plan and its execution (wide-margin tumor resection and neck dissection) as decided on at study entry (randomization) for each subject must be strictly followed, regardless of any response which may have occurred in the time between study entry and surgery.

Note: All subjects in this trial that undergo surgery will also receive at least radiation therapy following the surgical procedure (per protocol).

Histopathological examination of excised tumor margins is necessary to confirm complete resection and assist in the determination of whether the subject is "High Risk". Subjects who are considered "High Risk" (i.e., having involvement of 2 or more lymph nodes or extracapsular nodal spread or positive tumor margins) will receive concomitant chemoradiotherapy (per protocol as described below). A general description of procedures is as follows:

6.4.2.1 T1 and T2 Disease

Complete resection of localized tumors followed by radiotherapy or chemoradiotherapy as necessary. For T2 lesions that are invasive, local excision of primary lesion followed by radiotherapy or chemoradiotherapy (for "High-Risk" only).

For oral tongue T1 disease, local excision followed by radiotherapy or chemoradiotherapy (for "High-Risk" only). For T2 disease, hemiglossectomy and selective nodal dissection.

6.4.2.2 T3 and T4 Disease

Neck dissection for subjects with cervical lymphadenopathy (or for "High-Risk" of occult metastases), followed by radiotherapy or chemoradiotherapy for "High-Risk" only.

Table 4. Summary of Surgery, Radiotherapy and Chemotherapy (SOC)

TNM Classification	Primary Surgical Treatment	Radiotherapy	Concurrent Chemotherapy*
Resectable, T3-4, N0	Excision of primary and reconstruction as indicated and unilateral or bilateral selective neck at risk dissection.	External RT 60 - 70 Gy in 30-35 fractions for 6-7 weeks	**High-Risk Subject Category** 1. Positive margins or 2. Nodal involvement (≥ 2 positive nodes) or 3. Extracapsular nodal spread
Resectable, T 1-4, N1-2	N1: excision of primary, ipsilateral comprehensive neck dissection (levels 1-5) ± contralateral selective neck dissection. Reconstruction as indicated.	External RT 60- 70 Gy in 30-35 fractions for 6–7 weeks	
	N2: excision of primary, ipsilateral or bilateral comprehensive neck dissection (levels 1-5). Reconstruction as indicated.	External RT 60 - 70Gy in 30-35 fractions for 6-7 weeks	

*Chemotherapy: cisplatin bolus iv infusion, 100 mg/m^2 × 3 weeks (on weeks 1, 4 and 7 or Days 1, 22, 43 of radiotherapy course given within ±3 days for each scheduled day of administration of chemo during the radiotherapy period) to start on Day one of radiotherapy if indicated (i.e. in "High – Risk" subjects) to start on Day one of radiotherapy if indicated (i.e. in "High -Risk" subjects).

6.4.3 Radiotherapy

Intensity modulated radiation therapy (IMRT) is the latest method of increasing the therapeutic ratio of radiation treatment. There have been no reports of prospective randomized clinical studies using IMRT, therefore IMRT's impact on clinical outcome is not known, and the technique carries with it a number of potentially difficult problems that still need to be addressed. With IMRT, it is much more difficult than with 3D conformal therapy to verify that treatment has been delivered correctly to the subject. At present, IMRT is not the standard of care for the treatment of head and neck cancers; however, selected subjects may benefit from this new technology if they are treated in centers that have expertise in IMRT.

This protocol stipulates that adjuvant radiation therapy is delivered using conventional external beam techniques with standard radiation fractionation. In instances where the investigator has reason to believe that deviation from this prescribed radiation administration schema would materially benefit the subject with improved outcome, a waiver to change the radiation therapy treatment plan would be granted by the study's medical monitor, but only on a case by case basis.

An independent Radiotherapy Quality Assurance Committee (iRTQA) will be formed and will conduct radiotherapy QA, to assure radiotherapy (RTx) quality. The committee will have responsibility for assuring that all participating institutions have the equipment, personnel and procedures necessary to administer radiation in doses that are clinically comparable to those of other participating institutions The monitoring tools to be used may include on-site dosimetry and ports reviews; remote auditing tools and adequacy of proposed radiation therapy per site anthropomorphic phantoms and reviews of benchmark and actual protocol subject treatments at time of treatment and at the end of the study. The radiation therapy committee as determined by the iRTQA (for this study) will include at minimum, a radiation oncologist (with H&N experience) and an H&N surgeon.

The iRTQA will focus on the following areas:

- *RTx Treatment* – assess the RT treatment plan and protocols, as well as training and instrumentation at each participating institution
- *RTx Adequacy* – assess the adequacy of the RT therapy at the end of the trial

6.4.3.1 Treatment

Dose: Total dose will be ≥60Gy but not exceeding 70Gy in 30 - 35 fractions: 2 Gy once a day, five days a week for six (to seven) weeks. All "High-Risk" sites (defined as microscopically involved resection margins, areas with ≥2 positive nodes, and extracapsular spread of tumor from neck nodes) shall receive 70 Gy and all sites may receive 60 Gy. A conedown boost of up to 6 Gy delivered in 3 fractions (2 Gy each) over 3 days will also be administered to the "High-Risk" site(s) only. A minimum of 54 Gy must be delivered to low risk sites; (e.g. areas requiring radiation that are distant from the region that rendered subject high-risk).

The protocol doses will be specified at the center of the target volumes (at central axis in the midplane for parallel opposed beams or at the intersection of the central axes of multiple beams). The protocol dose to the high-risk target volume will be 70 Gy in 6 weeks. To the low-risk target volume, it shall be at least 54 Gy, at 2 Gy per day, but may receive 60 - 70 Gy. For a subject who has a T1 tumor of the oral tongue that is resected without any tumor at the margins, and also has at least two involved nodes in the mid to low anterior cervical region, it is permissible to treat lateral fields which encompass the oral tongue region to 54 Gy and to treat the dissected hemi-neck to 60 -70 Gy. Alternatively, a subject who has a T3 floor of mouth lesion that is resected, but has microscopic

involvement of the margins of resection, and who also has only a single ipsilateral high cervical node containing tumor, needs to have the lateral fields directed to the primary tumor treated to 60 - 70 Gy, but could have the neck field treated to only 54 Gy. Dose non-uniformity within the target volume should be kept to within ± 5 % of the protocol dose. If larger differences are anticipated due to contour changes of the neck, then this should be reduced by the use of tissue compensators or appropriate fields reductions. The dose to clinically uninvolved "electively treated" areas of the undissected lower neck will be 44 Gy at a depth of 3 cm.

The dose to the structures anterior to the spinal cord (mid-vertebral body) is to be calculated at the central axis midplane. Posterior to the spinal cord, the dose is calculated at a point 1 cm below the skin surface.

The maximum dose to the spinal cord and the length of spinal cord irradiated must be recorded for each field. **The direct beam dose to the spinal cord must not exceed 45 Gy.** The maximum dose to spinal cord is likely to occur at the junction of upper and lower field. Details of dose calculation at the junction must be provided.

Localizing films and all images (or the electronic files) of each radiation field will be taken and made part of the subject's medical record together with a copy of the treatment prescription and initial calculations. Localization films and machine portal films will be made on all fields and repeated at the time of any field change and must be submitted in advance of therapy to the iRTQA for approval of the radiation therapy for a specific type of tumor, tumor stage and tumor location. Institutions that cannot provide electron beams portal films may substitute a Polaroid picture of the electron beam portal.

Cumulative isodose distributions 1 cm from top of the lateral fields, 1 cm from the bottom of the lateral fields, and at the center, and a copy of the treatment record indicating cumulative doses must be submitted at the completion of radiotherapy.

The entire operative bed must be included in the treatment portals. A combination of lateral opposing fields, anterior and lateral wedged fields, or several beam-directed fields will be used for the primary tumor site at the discretion of the investigator. A single anterior A-P field with a mid-line block approximately 2 cm wide will be used to treat the neck below the fields for the primary tumor. This lower neck field should abut the primary field at the skin.

Administration: Radiotherapy should begin as soon as adequate healing after surgery has been established. Normally, this will be within 24 weeks of the surgical procedure but RT must be started no later than 8 weeks (56 calendar

days) following surgery. For all groups, radiation and chemotherapy must begin on the same day post surgery.

A continuous course should be maintained if at all possible. If the radiation reaction requires an interruption of therapy, this should be kept to a minimum and reported on the CRF. Daily dose reduction to 1.8 Gy is allowed only if a treatment break has become necessary and must be fully documented on the CRF.

6.4.3.2 Primary Treatment Fields Tumors by Site

Oral Tongue, Cheek (Buccal Mucosa) and Floor of the Mouth
The primary tumor is to be radiated in the postoperative setting to a dose of 60 – 70 Gy based on institutional preference. Radiation fractions should be 2.0 Gy each. The neck should be treated in the following fashion:

- Involved nodal stations:
  - 60-66 Gy (2.0 Gy/fraction)
- Uninvolved nodal stations:
  - 44-64 Gy (1.6 – 2.0 Gy/fraction)

Adequate protection of the spinal cord is to be observed.

Soft Palate
The primary tumor is to be radiated in the postoperative setting to a dose of 60 – 70 Gy based on institutional preference. Radiation fractions should be 2.0 Gy each. The neck should be treated in the following fashion:

- Involved nodal stations:
  - 60-66 Gy (2.0 Gy/fraction)
- Uninvolved nodal stations:
  - 44-64 Gy (1.6 – 2.0 Gy/fraction)

Adequate protection of the spinal cord is to be observed.

(As recommended by the National Comprehensive Cancer Network (NCCN) Head and Neck Cancers v.1.2010) [83,]

Lower Neck Field

An undissected clinically uninvolved neck must receive at least 45 Gy at 3 cm depth. The lower border of the field will include the supraclavicular nodes and must be below the clavicles.

6.4.3.3 Radioprotective Agents

There is insufficient evidence that radioprotective agents, such as Ethyol® (amifostine), offer clinically significant protection of parotid glands. Therefore, administration of such agents is not encouraged, but their use is left up to the discretion of each investigator.

6.4.3.4 Technical Factors

Irradiation will be given with cobalt teletherapy, supervoltage energy equipment (1-6 MV), or electron beams. The treatment distance will be 80 cm or more to the isocenter. All fields are to be treated each day. The beam should be shaped with blocks to avoid unnecessary irradiation of normal structures.

6.4.3.5 Radiation Treatment Interruptions for Toxicity

Interruptions in treatment may be necessitated by skin reaction, mucositis, ulceration, edema or other acute radiotherapy complications.

In general, NCI CTC AE Grade 3 toxicity (Appendix 8) may warrant treatment interruption but this will be left to the discretion of the treating physician. NCI CTC AE Grade 4 non-hematologic toxicities will require treatment interruption until functioning has improved as evidenced by clinical examination and supportive laboratory results (as appropriate). Any hospitalization for management of an adverse event will require radiation interruption until the subject is well enough to be discharged.

Regarding hematologic toxicity, radiation therapy will be delayed for ANC < 1000/mm^3 or platelet count of < 50,000/μL. Counts will be obtained twice weekly while subject is on break and treatment resumed when counts are ANC ≥ 1000/mm^3 and platelets are ≥ 50,000/μL.

The reason for and the length of an interruption must be documented in the medical records and on the appropriate CRF.

6.4.3.6 Appropriateness of Radiation Therapy

An independent radiotherapy quality assurance committee (iRTQA) will be formed consisting of radiation oncologist(s) and head and neck surgeon(s) to review treatment plans during the trial and evaluate the adequacy of the therapy at the end of the study. All radiation treatment information (port films, dosimetry, simulation films, etc.) will be submitted to the review committee for quality control review of the technical adequacy of the treatment as delivered. The guidelines and definitions of the committee's task will be defined prospectively.

6.4.4 Chemotherapy: Cisplatin (U.S.P. or equivalent) IV Bolus Infusion

Subjects with identified "High-Risk" factors [tumor margins unclear or infiltrative, local invasion, nodal involvement ≥2 lymph nodes or extracapsular nodal spread)] will receive chemotherapy concurrently with radiotherapy.

6.4.4.1 Administration (Cisplatin)

"High-Risk" subjects will receive three courses of cisplatin (IV bolus). Each course of chemotherapy will consist of cisplatin (100 mg/m^2) given as an IV bolus infusion over 1-2 hours with pre-hydration and diuretics. Chemotherapy will be given on weeks 1, 4 and 7 (e.g., on days 1, 22, and 43 of radiotherapy plus or minus 3 days) concurrently with radiotherapy. First dose of cisplatin will be given on the same day as the first dose of radiation therapy; chemoradiotherapy must commence within 8 weeks of surgical procedure aimed at removing the H&N tumor and any involved lymph nodes.

6.4.4.2 Formulation (Cisplatin)

Cisplatin (USP or equivalent) is available in the following formulations:

- 10 mg lyophilized vial, containing Mannitol 100 mg and sodium chloride, 90 mg;
- 50 mg lyophilized vial, containing Mannitol 500 mg and sodium chloride 450 mg;
- 1 mg/mL solution of cisplatin in normal saline, 50 or 100 mL vials.

6.4.4.3 Storage (Cisplatin)

Room temperature.

6.4.4.4 Preparation (Cisplatin)

Cisplatin powder for injection is reconstituted by adding 10 or 50 mL of sterile water for injection to a vial labeled as containing 10 or 50 mg of the drug, respectively, to provide solutions containing 1 mg/mL.

6.4.4.5 Pharmacology and Pharmokinetics (Cisplatin)

The dominant mode of action appears to be the inhibition of incorporation of DNA precursors although protein and RNA synthesis are also inhibited. Cross linking of DNA has also been shown. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding which exceeds 90% of the radioactivity in the second phase. Urinary excretion is incomplete with only 27 to 45% of the radioactivity excreted in the first five days. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and standard alkylating agents. Also, there appears to be potentiation of other anti-tumor agents by cisplatin in tissue culture, animal tumor models and in early human work. Studies have shown that cisplatin has no cell cycle dependency and that cytotoxicity of this agent is similar in all stages of the cell cycle.

6.4.4.6 Toxicity (Cisplatin)

Toxicity includes nausea, vomiting, alopecia, decreased Mg and Ca, elevated SGOT and SGPT, anorexia, renal toxicity (with elevation of BUN, creatinine and impairment of endogenous creatinine clearance), ototoxicity (with hearing loss which initially is in the high frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in subjects with an abnormal or obstructed urinary excretory tract. Myelosuppression, often with delayed erythrosuppression, is expected. The nadir white cell and platelet counts occur at about two weeks with recovery generally at about three weeks after initiation of therapy. Peripheral neuropathy and acute myeloid leukemia have been reported in a few cases where long-term cisplatin was used in combination with other forms of therapy.

6.4.4.7 Supplier

Any commercially available USP or equivalent grade product.

6.4.4.8 Chemotherapy Dose Modifications (Cisplatin)

Neutropenia may occur. If on the day of scheduled treatment with cisplatin (Day 22 and 43), the absolute neutrophil count (ANC) is < 1000/mm^3, hold chemotherapy (cisplatin) treatment until ANC ≥ 1000/mm^3 then treat at 100% dose. ANC counts are to be obtained two times per week until neutrophil recovery is documented.

Thrombocytopenia may occur. If on the day of scheduled treatment with cisplatin (Day 22 and 43), the platelet count is < 75,000/µL hold treatment until platelets are ≥ 75,000/µL then treat at 100% dose. Platelet counts are to be obtained two times per week until platelet recovery is documented.

Neurotoxicity: The most typical expected neurologic toxicities attributable to cisplatin therapy are peripheral sensory (including hearing loss) and motor neuropathies. Dose adjustments for neurotoxicity are as follows:

- Grade 1 – no change
- Grade 2 – reduce cisplatin by 25%
- Grade 3/4 – omit cisplatin therapy. Cisplatin may be re-initiated at a 50% dose reduction at the next scheduled administration if neurotoxicity has resolved to Grade 2 or less.

6.4.4.9 Antiemetic Regimen for Cisplatin Administration

An antiemetic regimen for high emetic risk chemotherapy should be administered with each cisplatin dose but should be based on the standard of care within each institution where the therapy will be administered. Suggested components of this antiemetic regimen are:

- Dexamethasone IV or po given prior to chemotherapy and at daily doses for three days following cisplatin administration.
- A serotonin (5-HT3) antagonist on the day of chemotherapy
- A Neurokinin 1 antagonist (if available) on the day of chemotherapy and daily doses for two days following cisplatin administration.

- Lorazepam as needed on the day of chemotherapy and for up to 3 days following
- H2 blocker or proton pump inhibitor as needed.

6.4.4.10 Renal Toxicity

Cisplatin should be administered on the scheduled day of treatment using the following guidelines:

Creatinine		Creatinine Clearance (CrCl)	Cisplatin Dose
≤ 1.2	and/or	> 50 ml/min.	100 mg/m^2
> 1.2*		40-50 ml/min.	75 mg/m^2
> 1.2*		< 40 ml/min.	Discontinue

*If creatinine is > 1.2, creatinine clearance must be done in order to make dose adjustment.

Creatinine clearance may be estimated by Cockcroft-Gault formula as long as the creatinine is not changing rapidly; otherwise determine 24-hour urine collection. Nomogram to calculate creatinine clearance is:

$$\text{CrCl Male (mL/min)} = \frac{(140 - \text{age}) \times (\text{wt. in kg})}{(SCr) \times (72)}$$

CrCl Female = 0.85 x *(CrCl male)* where CrCl = Creatinine clearance and SCR = serum creatinine

Note: Although some subjects receiving Multikine will receive cyclophosphamide, indomethacin, and vitamins with zinc (+CIZ), subjects receiving SOC will not receive these drugs (as control) as there is no known anti-tumor benefit shown as a result of administration of the low doses of these drugs when administered alone (i.e. without an immunomodulator) to cancer subjects. SOC subjects will also not receive "mock" injections because of associated morbidity and lack of benefit.

6.4.5 Safety follow-up

Every subject (in this trial) will attend a safety evaluation follow-up visit approximately 30 days (28-35 days) following the last radiotherapy (or chemoradiotherapy) treatment. The following tests will be performed:

a. CBC and ESR (Appendix 4)
b. Blood chemistry test (Appendix 4)
c. Urinalysis (Appendix 4).
d. Vital signs (Blood pressure, temperature, pulse, respiratory rate, weight)
e. Physical Exam
f. EKG
g. Interim medical status including adverse events and inter-current illness

Appropriate monitoring and treatment of ongoing AEs will continue as standard of care.

6.5 Long-term Follow-up

Subjects will be followed-up after the completion of study drug and standard of care related procedures for a period of up to 30 to 36 months (duration of follow-up is event driven). The purpose of long-term follow-up is to assess the subject's medical condition and to determine if there is evidence of disease progression and the effect of treatment on overall survival. The first visit will occur 2 months after the last radiotherapy/chemoradiotherapy treatment. In addition, any AE elucidated by the investigator at scheduled visits during long-term follow-up will be entered in the CRF.

The following assessments will be performed every 2 months for the first year, every 3 months for the second year, then every 4 months thereafter for the third year. Subjects will be assessed for the following outcomes until death:

- Survival
- Interim Medical status including adverse events and inter-current illness
- Physical exam including performance status and weight
- Tumor measurements only if clinically indicated (as specified in Section 6.3.1)
- Progression (loco-regional, distal)
- Quality of life (Section 3.1.4.3)
- TSH levels checked every 6-12 months beginning 6 months after completion of radiation treatment.
- Toxicities including serious and unexpected adverse events.
- CT scans only if clinically indicated (as specified in Section 6.3.1)
- CBC with differential, ANC
- ESR

Unscheduled subject visits, which result in the documentation of disease progression, shall have this data recorded in the medical record and in the CRF. In addition, the assessments noted in Section 6.5 (above) will be performed.

6.6 Safety and Efficacy Intervals of Interest

The safety observation interval extends to 30 days after completion of the treatment regimen; i.e., 30 days following the last administration of radiotherapy or concurrent chemoradiotherapy. In addition, serious and unexpected adverse events will be collected through the three year follow-up interval.

Efficacy information will be collected for up to 30 to 36 months (duration of follow-up is event driven) post-randomization (for each trial subject) as follows:

1. Tumor assessments will be recorded at baseline before administration of randomized study treatment and prior to surgery. The measurable lesions will be tumor or positive lymph node(s) defined by RECIST criteria. The most appropriate imaging modality determined by the investigator will be used which can include physical examination, digital photography using rulers, X-ray, CT scan or MRI. The same imaging modality will be used for subsequent tumor assessments at scheduled follow-up visits after surgery and radiochemotherapy.

2. The histological characteristics of the resected primary tumor will be reviewed by a qualified pathologist. Clinically positive lymph node(s) will also be evaluated by the pathologist to determine whether it (they) is (are) positive, negative or show(s) evidence that it (they) was (were) previously positive, but cancer cells are either no longer present or have undergone necrosis. Tumor cell activity and host immune responses will be compared for changes in these parameters per se, and for correlations with changes in the size of the primary tumor before and one day or just prior to surgery.

   The Study definitive histological evaluations of tumor specimens (frozen and/or paraffin block) for the trial population will be conducted by a Central Pathology Laboratory. It is intended that sections obtained from all subjects participating in the trial, along with sections similarly collected and processed from untreated subjects, will be evaluated for T-cell and other white blood cell infiltrations into the tumor and in the marginal tissue around the tumor as well as other tumor cells parameter (Appendix 4).

3. Date of death and cause, if available.

6.7 Genomic Microarray – A Stand Alone collaborative study (with the US NIH/NCI) that derives its samples from the subjects of this Phase III study

For those subjects who have consented for the genomic microarray study, two samples of tumor (and any clinically involved lymph nodes) biopsy specimen (as well as PBMCs) will be collected. One sample will be collected before treatment (e.g., injection of Multikine) at time of screening (FNA or core/punch biopsy) and another sample will be collected at the time of surgery from the surgical specimen. Samples for the genomic microarray study will be obtained from patients only in those countries where the health authorities have approved of this testing. Subject participation in the genomic microarray component of the study, which requires Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approval, is optional. Refusal to participate will not result in ineligibility for the main part of the clinical study. Any subject that consents to participate in the genomic microarray study will not be identified and the samples obtained from all individuals will be blinded. In no way will the samples be traceable back to the specific individual that consented to allow their samples to be tested for genomic microarray (in the collaborative study with the US NIH/NCI).

6.7.1 Rationale for DNA Collection

Genetic differences within the population can be an important contributory factor in inter-individual variability in response to drug and can also serve as a marker for disease susceptibility and prognosis. An association between gene expression and clinical outcomes may help to identify a population subgroup that is likely to better respond to or better tolerate the drug thereby maximizing benefit and minimizing risks. Therefore; biopsy samples, as well as blood samples, will be collected in this clinical study in order to help address emerging clinical issues and to develop a safer and more effective personalized drugs in the future.

There are two parts to the genomic microarray component of this study. Part 1 allows using tumor biopsy (FNA or core/punch biopsy at study entry, and tumor samples obtained from resected tumors at surgery) and blood samples for analysis of gene expression using genomic microarray. Part 2 allows for the storage of biopsy samples for future testing. Subjects will be given the option to participate in Part 1, Part 2, both parts, or neither part of the genomic microarray study (where local regulations permit).

6.7.2 DNA Sample Disposition Procedures for Genomic Microarray Testing

Instructions on sample handling, labeling, and shipment are given in Appendix 4. The details of the subject will be blinded using unique code. A subject may withdraw consent for genomic microarray testing at any time, and still remain in the study. If a subject withdraws consent for genomic microarray testing; any biopsy sample extracted or obtained from the subject's blood will be destroyed, provided that the sample has not yet undergone conversion to the blinded format. The investigator must notify the sponsor (or designee) site contact, who will request sample destruction using the withdrawal of consent for genomic microarray testing form. The investigator will receive written confirmation from the sponsor or designee that the biopsy sample for genomic microarray can be destroyed before converting to non-identifiable blinded codes. If the sample has already undergone conversion to the non-identifiable format, then the sponsor or designee will notify the investigator in writing.

6.8 Blinding of Central Lab Specimens and Imaging Data

This study will have a number of central laboratories, where specimens or results of imaging, and lab values will be collected and analyzed for the study. These laboratories are:

(1) **A Central Pathology Laboratory** – the central pathology laboratory will receive coded samples (Paraffin embedded and frozen sections of tumor or lymph node) from all the subjects participating in this study. The samples will be coded prior to shipment to the Central Pathology Lab. The pathology lab reader will be unaware of the subject's medical history, subject's treatment arm, or clinical outcome.

(2) **A Central Imaging Center** – the central imaging center will catalogue and read all imaging (X-rays, CT, MRI, etc.) from all subjects participating in this study. All images will be coded by the Central Imaging Center prior to shipment to the central imaging radiologist(s) for reading by the central radiologist(s) who will be unaware of the subject's medical history, subject's treatment arm or clinical outcome.

(3) **A Central Laboratory Data Center** – the central laboratory data center, will house all clinical laboratory data (values) taken / recorded for each subject participating in this study. All laboratory data (values) will be coded prior to transfer to the central laboratory data center for analysis. A central Medical Monitor will evaluate all the laboratory values for all the subjects participating in this study.

Note: Blinding of all samples collected for the stand-alone genomic microarray collaborative study to be conducted at the NIH/NCI (USA) will be done at the sample collection source or at a regional "central collection" laboratory. All samples collected for the independent genomic microarray study shall be coded in such a way as to not allow any subject specific identifying information to accompany the sample to the NIH/NCI. The only information the samples will be able to be connected with is if the samples were collected before or after definitive treatment. In addition, but only at a later point (after the code has been broken) the samples will only be able to be traceable to the specific arm in the study the samples came from. **Under No Circumstance** will any sample destined for the stand-alone NIH/NCI collaborative genomic microarray study be traceable back to its specific donor.

6.9 Unblinding of Central Lab Specimens and Imaging Data

The initial data analysis for DNA microarray will occur after samples from the first 40 subjects have undergone microarray testing. The final data analysis will occur at the end of the study. The blinding code will be broken at the time of initial analysis and during final data analysis of DNA microarray results. While breaking the blinding code for DNA microarray, only details of treatment received and study visits will be revealed but the details of individual subjects will continue to remain blinded perpetually - and not be revealed at any point of time after completion of study.

Unblinding of Central Imaging data, Clinical Lab data (not DNA microarray) and Central Pathology Laboratory Data will occur at the time of statistical analysis (or at the request of the iDMC). Unblinding of Central Imaging data, Clinical Lab data and Central Pathology Data will reveal all the details of each of the subject's visits, including the treatment received, and study visit dates specific for each subject in the study, study arm, etc.

7. Statistical Considerations

7.1 Study Design

This is a Phase III open-label, multi-center, randomized study to determine the efficacy and safety of peri-tumoral and peri-lymphatic injection of Multikine (400 IU as IL-2/ daily dose for 3 weeks at 5 times per week) given prior to SOC. The following treatment groups will be enrolled:

(1) Multikine + CIZ + SOC
(2) Multikine + SOC
(3) SOC alone

7.2 Primary hypothesis and analyses

The primary hypothesis will compare overall survival in the Multikine + CIZ + SOC group to that in the SOC alone group for superiority of the former.

Overall survival will be accessed via a Kaplan-Meier life-table and compared using a log rank test and confirmed further with stage-, location-, and geographic-stratified log rank tests. The unstratified logrank test constitutes the primary analysis. Further details on the statistical analyses can be found in section 7.9.

7.3 Secondary Hypotheses and Analyses

The following secondary comparisons are also planned:

(1) Overall survival in Multikine + SOC vs. SOC
(2) Progression Free Survival in Multikine + CIZ + SOC vs. SOC
(3) LRC in Multikine + CIZ + SOC vs. SOC
(4) QOL in Multikine + CIZ + SOC vs. SOC

The Holm[84] closed-sequential procedure will be used to control the type I error probability to at most 0.05. The analysis of the secondary hypotheses is described in section 7.9.

7.4 Tertiary Hypotheses and Analyses

The following tertiary comparisons are planned:

(1) Equivalence between overall survival in the Multikine + CIZ + SOC vs. Multikine + SOC
(2) Tumor response in Multikine + CIZ + SOC vs. SOC

The equivalence between overall survival in the Multikine + CIZ + SOC vs. Multikine + SOC will be explored by constructing a 95% two-sided confidence interval to rule out a 10% 3-year overall asymptotic survival difference for Multikine+ CIZ + SOC vs. Multikine + SOC. The analysis of the tumor response is described in section 7.12.4 below.

Tumor response as assessed by dimensional analysis (e.g., physical measurement, CT scan, etc), is not expected to yield data that will reflect the efficacy of this (Multikine immunotherapy) treatment. In fact, it has been shown in Phase I and II studies that, tumor measurements were not reflective of the tumor status in subjects treated with Multikine (or in other studies with immune

stimulating drugs). The reason for that is that through relatively short period of time of drug administration prior to definitive surgical removal of the tumor (3 weeks in this study), the treatment with Multikine (an immuno-stimulatory drug) markedly increases the immune cell infiltrate into the tumor bed, such that the tumor may appear larger (by dimensional measurement). However, when the tumor is removed, at surgery, and tumor sections representative of the whole tumor are analyzed by pathology, the pathology results indicate that the tumor bulk is largely made of immune cell infiltrate and not tumor cells. Thus, physical – dimensional measurement does not necessarily reflect on the efficacy of immune-stimulating drugs, and tumor size change is not expected to be a useful measurement for assessing the efficacy of this treatment modality.

7.5 Randomization

An Interactive Voice Response System (IVRS) will be used for randomization and stratification. Subjects will be randomized in a 3:3:1 allocation with Multikine + SOC (without CIZ) being the treatment group to be assigned least often in contrast to Multikine + CIZ + SOC and SOC alone. Subjects will be stratified by country, by tumor location (tongue, floor of the mouth, check and soft palate), and tumor stage (Stage III: and Stage IVa: T4a (N0-2, T1-3N2) [see Table 3 – TNM Categories and corresponding stage permitted in this trial].

A dynamic randomization[81, 82] will be used to promote balancing across study sites within a country and globally.

7.6 Sample Size Rationale

Historical basis
Current SOC for SCCHN adopted by the oncology community [includes: post-operative concurrent chemoradiotherapy (CRTx) or radiotherapy (RTx)] is based on trials conducted by the Radiation Therapy Oncology Group (RTOG - NEJM 2004; 350(19): 1937), and the European Organization for the Research and Treatment of Cancer (EORTC – NEJM, 2004; 350(19): 1945). Both trials demonstrated improvements in the 3-year Overall Survival rates: an absolute increase of 12 % (48% vs. 60%) for the EORTC study and an absolute increase of 10% (47% vs. 57%) for the RTOG study.

This study will assume a 55% 3-year overall survival rate for SOC alone. This assumes 70-80% of the subjects will be lower risk at the time of surgery; sample sizes will be smaller if a higher percent turn out to be at high risk. As for the EORTC and the RTOG studies, a 10% absolute gain in overall survival is regarded as being clinically meaningful. The primary study goal to test Multikine + CIZ + SOC superiority vs. SOC alone will be to reject the 55% 3-year overall

survival rate for SOC alone against a 65% 3-year overall rate for Multikine + CIZ + SOC.

7.7 Assumptions and Calculations

The primary comparison will be based on 80% power and a two-sided 5% Type I error to detect a 10% absolute survival advantage at 3 years (55% vs. 65%). Assuming exponential hazards, this yields a hazard ratio of 0.721. For this comparison, the log rank test will require a total of 298 deaths. The trial will be conducted as an event-driven trial, and will conclude once a total 298 deaths have been observed.

Since death certificates should be available for virtually all subjects, the calculations assume no losses to follow-up for overall survival. A 24 month (total) recruitment period and a 30 month follow-up period yields a sample size of 336 subjects in each of the Multikine + CIZ + SOC and SOC alone groups. Under a 3:3:1 randomization, this yields 112 subjects in the Multikine + SOC group for a total estimate of 784 subjects[85].

7.8 Study Populations

The key study populations will be defined as follows:

- Intent to Treat (ITT) Population:

  All subjects who are randomized, regardless of treatment and trial group (Multikine treatment or SOC), will be included in the ITT analysis. The rationale for this is motivated by the open-label design. Thus, investigators should make all efforts to ensure that subjects are compliant, complete the protocol specified treatment regimen, follow the subsequent standard of care regimen, and may be followed for up to 36 months (duration of follow-up is event driven).

- Per Protocol Population:

  Phase II clinical studies 26 have demonstrated that objective tumor response in H&N cancer subjects requires at least 5 Multikine injections (administrations) per week for a 2 week period. Another Phase II study [28] demonstrated objective tumor responses and marked anti-tumor immune responses when subjects were given 5 injections per week for 3 weeks. These results suggest that a "minimum" number of Multikine injections may be necessary for responses to be

demonstrable. Other studies have indicated a supportive role for administration of CIZ [86, 87, 88, 89] in SCCHN. Factoring in an expected low rate of "missed" injections (possibly 1-3, over a 3 week period), the "per-protocol" subject population is defined as those subjects receiving 12 injections (administrations) over the 3 week treatment period. Therefore, the per-protocol population will be defined as follows:

(a) Multikine + CIZ + SOC Arm (**Group 1**): Eligible subjects receiving 12 Multikine injections (administrations) as randomized, having completed surgery (as defined in the protocol) and receiving at least; cyclophosphamide IV (as defined in the protocol), 2 courses of cisplatin (if as a result of surgical findings the subject is slated for the concurrent chemoradiotherapy sub-group treatment) and receiving 75% of indomethacin, 75% of scheduled radiation, and at least 75% of all other protocol required treatments.

(b) SOC Arm (**Group 3**): Eligible subjects having completed surgery (as defined in the protocol) as randomized and receiving at least two courses of cisplatin (if as a result of surgical findings the subject will receive the concurrent chemoradiotherapy as a sub-group treatment) and receiving at least 75% of all other protocol required treatments (e.g., 75% of all scheduled radiation).

(c) Multikine Treatment + SOC Arm(**Group 2**): Eligible subjects receiving 12 Multikine injections (administrations) as randomized but without administration of any CIZ components, having completed surgery (as defined in the protocol) and receiving at least 2 courses of cisplatin (if as a result of surgical findings the subject will receive the concurrent chemoradiotherapy as a sub-group treatment) and receiving at least 75% of all other protocol required treatments (e.g., 75% of all scheduled radiation).

- Safety Population:

  All subjects receiving any study therapy such as one or more injections of Multikine, any CIZ components, or surgery will be included in the safety population.

7.9 Missing Data Conventions

Subjects who are enrolled, but who do not receive Multikine treatment or surgery (for the SOC group) will be replaced. Subjects who receive Multikine but do not undergo resection will also be replaced. Data from the subjects that were replaced will be included in the efficacy analysis for only the ITT population. Subjects who are removed from the study for reasons related to drug toxicity will not be replaced.

Tumor measurement, quality of life, and Karnofsky status will be analyzed using longitudinal GEE models in the ITT analysis and in the analysis of treated per protocol subjects (see Section 7.8 for definition). Missing measurements will not be counted for treated subjects for any analyses; the actual sample sizes will be noted to be different.

If a subject cannot be contacted after several attempts by telephone and /or letter and/or due diligence, the subject will be deemed to be lost to follow-up and this will be noted in the source document and CRF.

7.9.1 Statistical Analysis Strategy

Multiple analysis strategies are to be used in this study. These address study design, study populations, data analysis, analysis confirmations, multiple endpoints, data pooling, and interim assessments.

The choice of the study population is the ITT population for the primary and secondary analyses because an open-label design is to be used. This means that all randomized subjects are to be followed to the extent that this is feasible, and included in all efficacy analyses as data permit. A per-protocol population will be analyzed in selected analysis situations for confirmation; all p-values for the per-protocol analyses will be regarded as descriptive.

Data analyses and confirmatory analyses are pre-planned to address multiple complex situations. Life-table methods allow subjects to be used as long as they have follow-up and investigators will be made aware at the time of study activation that all subjects need to be followed for at least 3 years. A log rank test for comparing treatments is the primary analysis, with supporting stratified log rank and proportional hazard models to be analyzed for confirmation; the stratified log rank and proportional hazard models are needed to address the impact of correlated baseline factors and the potential for treatment interactions. Risk factor analyses have a post hoc element since the determination is made post-surgery and the Multikine regimens may impact the SOC choice if it can affect tumor margins and positive lymph nodes pre-surgery.

Study site pooling will also be assessed. Sites with less than 14 subjects will be pooled together into a combined site in the analyses for the primary and secondary efficacy endpoints as well as the overall adverse event rate. For these endpoints, a two-sided p-value >0.05 for the global site effect will be required to pool data across sites; a site-treatment interaction will also be tested for the endpoints; in the event of significant site-treatment interactions, baseline site imbalance will be explored using proportional hazards analysis (for time to event endpoints), longitudinal model analysis (QOL domains, Karnofsky status, weight), or logistic regression (overall adverse event rate) including the tumor stage, tumor location, and geographic strata variables, treatment, site, and treatment-site interactions.

Prospective study subjects stratification will yield subgroup analyses that are planned as an exploratory analysis of the primary efficacy endpoint, OS, using tumor location (tongue, floor of mouth, cheek, and soft palate), and tumor stage (Stage III and Stage IVa [see Table 3 – TNM Categories and corresponding stage permitted in this Trial]) and country.

Further prospective subgroup analyses may be identified in the statistical analysis plan (SAP). Subsequently, subgroups may be identified on a data-driven basis, and such analyses will be considered exploratory and hypothesis generating only.

Finally, interim analyses will be used to confirm Multikine safety expectations: these safety analyses will be performed after the first 40 subjects in the trial have been dosed with Multikine and completed surgery and again after all subjects have completed the safety evaluation follow-up visit approximately 30 days (28-35 days) following the last radiotherapy (or chemoradiotherapy) treatment. Additionally, sample size assumptions and futility will also be analyzed as requested by the study iDMC (Independent Data Safety and Efficacy Monitoring Board). Sample size re-estimation will be conducted on blinded data and prior to any analysis that would require breaking the blind. No penalty is therefore applicable since the study will not be stopped for superiority, unless so determined by the iDMC in conjunction with the regulatory authority(ies) and the sponsor.

7.10 Statistical Significance

For the primary and secondary efficacy measures, a two-sided p-value of 0.05 or less will be considered to be statistically significant in comparing the Multikine treatments vs. SOC alone for superiority. A Holm[84] closed-sequential procedure

will be used to control the probability of type I error for the secondary hypotheses.

7.11 Interim Analysis

Interim analyses will be performed through the study to assess Multikine safety, sample size assumptions, and futility. The first interim analysis will be performed when 40 Multikine treated subject's complete surgery, and an additional safety analysis will be performed when all subjects have completed the 30 day safety follow-up visit (Day 28-35). Subsequent interim analyses will be performed as mutually agreed upon with the independent Data Monitoring Committee (iDMC) and sponsor; the anticipated schedule is to perform interim analyses of safety and efficacy every 6 months based on the study meeting enrollment objectives.

The iDMC will perform these semi-annual safety and effectiveness analyses during the study to assess the feasibility of continuing the study and to assess the sample size according to the primary study endpoint to see if the sample size is adequate or requires modification (reduction or increase). This sample size re-estimation will be conducted on blinded data, and prior to any unblinding. The study will not be stopped for superiority but the study may be stopped for futility (without penalty). Thus, the overall significance level of the final analysis (0.05) will be maintained.

7.12 Analysis Approach

All analyses will be conducted under a prospectively approved statistical analysis plan (SAP), which will display all database specifications and conventions in addition to all planned tables, listings, and figures. The SAP will be developed under SOPs for data analyses and the SAP will be approved and implemented prior to database lock. Any other analyses will be considered *ad hoc*.

7.12.1 Subject Disposition

All subjects entered in the study will be accounted for in the disposition summarization report. The subject disposition will include data on randomized treatment, actual treatment, site enrolment, subject eligibility, subject compliance, progress through the study, follow-up, discontinuation, data on overall qualification status of all subjects, and an account of all identified protocol violations. The number of subjects will be displayed for those who discontinue before treatment begins, do not qualify for the per protocol analyses, who progress during the study, who exhibit loco-regional recurrence, who die during the study, or who go on to other treatments.

The progress of subjects through each treatment regimen (Multikine +/-CIZ + SOC) and SOC alone (control group) and through study completion will be shown in tables and graphs. Reasons for early withdrawal from study will be displayed. The pattern of being missing completely at random (MCAR) will also be assessed.

The number of treatment visits at which Multikine is administered and the amount of each study drug delivered per visit and cumulatively will be summarized and tabulated. Subjects requiring delay and/or reduction in dose of either, study drug or radiotherapy and/or concurrent chemoradiotherapy will be displayed with reasons provided.

7.12.2 Descriptive Statistics

Descriptive statistics will be provided for items collected for all randomized subjects for the ITT, per-protocol, and safety populations as appropriate to the analysis objectives. Impacted variables will include demographic and pre-procedure subject characteristics and medical history. Treatment characteristics, post-therapy outcomes, and safety items will be displayed using descriptive statistics for each scheduled and follow-up visit.

For continuous variables, descriptive results will include mean, standard deviation, minimum, median, and maximum. Confidence bounds for the means and for the mean differences will be computed using two-sided 95% intervals calculated using a Student's t-test distribution.

Ordinal variables will be analyzed using an unpaired t-test or a Wilcoxon rank sum test to compare treatment groups and using a paired t-test or a signed rank test to compare changes from baseline within each treatment group.

Discrete outcomes will be presented as category percentages noting the numerator and denominator used to derive the percentage. Treatment groups will be compared using two-sided, 95% exact confidence intervals for proportions while individual treatment groups will be compared using Fisher's exact test.

7.12.3 Subject Demographics

A summary of subject characteristics will also be provided, including demographic information, baseline disease characteristics, pre-existing conditions, prior therapies, and concomitant medications. Other subject characteristics will be summarized as deemed appropriate.

7.12.4 Tumor Response

Tumors will be measured as described in Section 6.3.1 to allow calculation of response according to RECIST criteria (Appendix 10). Tumors treated with Multikine will be measured at baseline, (at the onset of treatment just prior to Multikine treatment), prior to the last weekly injection of Multikine, just prior to surgery, to allow evaluation of tumor size changes. Thereafter, subjects will be evaluated every 2 months after the end of therapy regimen for the first 12 months, every 3 months to 2 years, and every 4 months thereafter to 3 years (Appendix 1). If evidence of disease progression or new disease is present, CT scans and/or MRI of head/neck and chest will be performed.

Each tumor (injected peri-tumorally with Multikine) will be analyzed to include the primary tumor as well as any clinically involved lymph nodes. These tumor measurements will be used to determine tumor size changes. For each tumor, the method of measurement selected at baseline must be the same throughout the study.

Changes in tumor volume will be assessed using a longitudinal growth model including all post-baseline measurements. A log normal distribution will be used if goodness of fit assumptions warrant.

7.12.5 Progression

For subjects who progress (i.e. exhibit loco-regional failure), the pattern of progression will be examined by classifying the first evidence of progression in local and distal sites for the control group and for the Multikine treated groups.

Progression defined as loco-regional failure includes progression of tumor(s) and nodes or appearance of new disease above the clavicle (but not distant metastases) following treatment. This definition also includes the reappearance of tumor in the original tumor bed, development of cervical node metastases after the treatment regimen and new disease above the clavicle (other than distant metastases) not present at baseline. All progression of disease will be documented on each subject's CRF.

Data will be collected on progression at sites not treated with Multikine and documented in the CRF - including:

- additional nodes
- other local metastatic sites
- distant metastatic sites

The number and percent of subjects in each category as well as the timing will be displayed for each treatment group.

7.12.6 Time to Event Outcomes

Time to event outcomes include overall survival, progression-free survival, as well as loco-regional control. The time to event outcomes will be calculated from the date of randomization for all subjects and will be estimated for each treatment group in this study using the Kaplan-Meier method. Treatment groups will be compared using a stratified log rank test where stratification will be according to tumor stage, tumor location, and geography. Subjects who receive confounding anticancer therapies after treatment with Multikine and SOC (i.e. while on protocol) will be included in the overall survival analysis and censored in progression-free and loco-regional control analysis if progression was the reason for initiating new treatment.

Proportional hazards models will be used to evaluate study treatment as well as baseline covariates (tumor stage, tumor location, and geography). The respective models will include interactions between treatments and tumor stage, tumor site, and geography. Treatment will be modeled with the Multikine + CIZ + SOC as the reference group to allow simultaneous comparisons to SOC alone (primary comparison) and to Multikine + SOC (secondary comparison).

Additional analyses will be performed for the risk group assignment and for the type of therapy administered (radiotherapy, concurrent chemoradiotherapy) following surgery. The major prognostic factor for the subjects is the assignment to either the "high risk" or "low risk" group (discussed in Section 1.1) made **after** randomization, Multikine treatment and surgery. Thus, stratification at study entry for this factor cannot be performed. As described above, stratified log rank and proportional hazards models will be performed; the proportional hazards models will include tumor stage, tumor location, and geographic location as well as treatment.

7.12.7 Quality of Life

Assessment of quality of life will be based on the EORTC QLQ-C30 and EORTC QLQ-H&N35. The EORTC QLQ-C30 incorporates 30 items and consists of 5 functional scales (physical, role, cognitive, emotional, and social functioning), 3 general symptom scales (fatigue, pain, and nausea/vomiting), a global QOL scale, and 6 specific symptom scales (dyspnea, insomnia, appetite, constipation, diarrhea, and financial impact). The EORTC Quality of Life Questionnaire-Head and Neck35 (QLQ-H&N35) is a supplement module to the QLQ-C30. Most items are scored on a four-point response scale: 1 (not at all) to 4 (very much).

Questions 31 to 48 address symptoms specific for head and neck patients, e.g. pain, swallowing, taste, appearance. Questions 49 to 60 address functional items, e.g. eating, talking, social contact, sexuality. The last 5 items are answered as 'yes' or 'no' concerning analgesia, nutritional supplemental, tube feeding, and changes in weight.

Quality of Life (QOL) data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual. All scales pertaining to the EORTC QLQ-C30 and QLQ-H&N35 range from 0 to 100. A high score for a functional or global QOL scale represents a relatively high/healthy level of functioning or global QOL; whereas a high score for a symptom scale indicates a higher level of symptoms or problems. QOL data will be summarized using descriptive statistics for the multi-item subscales at baseline and at each follow-up visit. Missing data points for multi-item scales will be imputed using the method described in the scoring manual where at least half the items from a given scale were answered. In addition, changes in QOL scores at each follow-up as compared to baseline and the percentage of subjects achieving a **10 point** improvement at 6 month, 12 months, 18 months and up to 36 months will also be summarized.

Quality of life data will be assessed for the change in QOL from baseline within and between treatment groups. The comparisons between treatment groups will be performed using ANOVA (or Wilcoxon rank sum test) while the change in QOL from baseline within treatment group will be performed using a paired t-test (or a signed rank test). Two-sided test will be used with no adjustment for the Type I error. In addition, a 10 point improvement between treatments will be performed by an exact binomial test for each treatment group and using a Fisher Exact test for between group comparisons.

7.12.8 Safety

All adverse events will be reported regardless of causality. Severity of AEs will be graded by the investigator according to the NCI CTCAE version 4.0 (Appendix 8). The adverse events will be reviewed and coded by sponsor or sponsor's representative using MedDRA. Using MedDRA, each adverse event will be referred to by preferred term and system organ class. The total number of events and total number of subjects with events will also be displayed for overall safety population and also for each system organ class and preferred term. Displays will also be provided for the timing of adverse events (post-randomization, pre-surgery, post-surgery during SOC, post-SOC) to provide insight into the Multikine related adverse events distinct from adverse events related to surgery and SOC. Serious and unexpected adverse events will be summarized in a listing and described by narrative. Treatment groups will be compared at the subject level using a Fisher Exact test and will be compared at the event level using a Poisson

model for the total counts. The cumulative incidence of adverse events at the subject level will also be displayed graphically to help depict the impact of each therapeutic component. Results will also be displayed separately for the post-surgical treatment groups (radiotherapy, concurrent chemoradiotherapy) according to the randomized treatment group.

Laboratory data, including abnormal labs and clinically significant labs, will be analyzed descriptively and subjected to statistical analyses for the change from baseline through the end of treatment (pre-surgery, SOC, post-SOC). Laboratory measurements will be investigated between and within treatment groups for the pre-surgery treatment as well as for SOC using ANOVA (or a Wilcoxon rank sum test) to compare treatments and using a paired t-test (or a signed rank test) to compare changes from baseline. Shift tables will also be assessed using a Fisher Exact test to compare treatments and using a marginal homogeneity test within treatment groups. The incidence of clinically significant laboratory values, as determined by the investigators, will be summarized and compared using a Fisher Exact test.

8. Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

fatal
life-threatening
requires or prolongs hospital stay

results in persistent or significant disability or incapacity
a congenital anomaly or birth defect
an important medical event or medically significant event in the opinion of the investigator

A life-threatening adverse event is defined as any adverse experience that places the subject at immediate risk of death from the reaction as it occurred; i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization is defined as any in-patient admission (even if less than 24 hours) as a result of a precipitating, treatment-emergent adverse event. For chronic or long-term subjects, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit. Hospitalizations for administrative reasons or a non-worsening preexisting condition should not be considered adverse events (e.g. admission for workup of a persistent pretreatment lab abnormality, yearly physical exam, protocol specified admission, elective surgery, transfusion, or routine central catheter care). Preplanned treatments or surgical procedures should be noted in the baseline documentation. However, if a hospitalization due to an unknown event occurs, it should be considered as a serious adverse event. See also Section 8.7.

Prolongation of hospitalization is defined as any extension of an in-patient hospitalization beyond the stay anticipated/required for the original reason for admission, as determined by the investigator or treating physician.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for a serious adverse event are regarded as non-serious adverse events.

8.1.3 Unexpected Adverse Event

An unexpected AE is an event not previously reported in or which the nature or severity is not consistent with the current edition of the clinical

Investigator's Brochure (for investigational product) or the Summary of Product Characteristics (for authorized products).

8.1.4 Expected Adverse Events Related to Treatments in this Protocol

8.1.4.1 Medication Related Toxicities

a. Cyclophosphamide (low-dose, 300 mg/m^2, IV x 1 dose)
- Alopecia
- Nausea
- Vomiting
- Pulmonary fibrosis
- Hypersensitivity reactions
- Hemorrhagic cystitis
- Myelosuppression
- Thrombocytopenia
- Anemia

b. Indomethacin (25 mg p.o. t.i.d, during Multikine injection period)
- Anorexia
- Nausea
- Abdominal pain
- Gastritis
- Upper gastrointestinal tract ulcer
- Renal insufficiency
- Hypersensitivity reactions
- Impaired platelet function
- Bleeding tendency

c. Multivitamin with Zinc (zinc dose of 15 – 40 mg, orally during Multikine injection period)
- Abdominal discomfort
- Fatigue
- Hypersensitivity reactions

8.1.4.2 Investigational Agent -- Multikine (Leukocyte Interleukin, Injection) Possible Toxicities

- Hypersensitivity reactions

- Fever
- Chills
- Malaise
- Fatigue
- Anorexia
- Weight loss
- Injection site pain / swelling
- Infection at injection sites
- Bleeding associated with injection
- Localized erythema

8.1.4.3 Surgery Related Toxicities

- Facial nerve paralysis
- Oral incompetence
- Trismus (inability to fully open mouth)
- Nutritional deficiency
- Fatigue
- Dysphagia
- Difficulty speaking
- Difficulty swallowing
- Odynophagia
- Change in voice characteristics
- Dry mouth
- Salivary duct stenosis
- Injury to nerve and vascular structures
- Infection
- Ongoing drainage from surgical wound
- Ongoing bleeding from surgical wound
- Pain at incision site(s)
- Neck stiffness (associated with neck dissection)
- Neck weakness (associated with neck dissection)
- Shoulder weakness (associated with neck dissection)
- Depression
- Food regurgitation into nasopharynx (especially with soft palate resection)
- Anesthesia related complications including hypersensitivity reaction, myocardial infarction, cerebrovascular accident
- Post-operative venous thrombosis/pulmonary embolus
- Death

8.1.4.4 Radiation Associated Toxicities

- Facial nerve paralysis
- Oral incompetence
- Fatigue
- Dysphagia
- Difficulty speaking
- Difficulty swallowing
- Change in voice characteristics
- Dry mouth
- Salivary duct stenosis
- Injury to nerve and vascular structures
- Infection
- Neck stiffness (associated with neck radiation)
- Neck weakness (associated with neck radiation)
- Shoulder weakness (associated with neck radiation)
- Depression
- Mouth sores
- Mucositis
- Soft tissue ulceration / necrosis
- Osteonecrosis of jaw
- Dental caries
- Tooth / gum decay
- Dry skin
- Moist skin desquamation
- Burning of skin
- Skin erythema
- Trismus (inability to fully open mouth)
- Nutritional deficiency
- Halitosis
- Oral fungal infection
- Odynophagia

8.1.4.5 Cisplatin Related Toxicities

- Anorexia
- Weight loss
- Renal insufficiency
- Nausea / vomiting
- Electrolyte imbalance

- Peripheral neuropathy
- Auditory impairment
- Tinnitus
- Myelosuppression
- Thrombocytopenia
- Anemia
- Hypersensitivity reaction
- Seizure
- Visual impairment
- Fatigue

8.1.5 Severity of Adverse Events

All events will be graded according to the NCI CTCAE version 4.0 (Appendix 8) by the Investigator. For events not listed in the toxicity table, severity should be recorded as:

Grade 1	Mild adverse event
Grade 2	Moderate adverse event
Grade 3	Severe adverse event
Grade 4	Life-threatening or disabling adverse event
Grade 5	Death related to AE

8.1.6 Causal Relationship to Study Drug

The following criteria should be used in assessing the apparent causal relationship of an AE to study drug:

Definitely - The AE:
• follows a reasonable temporal sequence from drug administration
• abates upon discontinuation of the drug (de-challenge)
• is confirmed by reappearance of the reaction on repeat exposure

Probably - The AE:
• follows a reasonable temporal sequence from drug administration
• abates upon discontinuation of the drug (de-challenge)
• cannot be reasonably explained by the known characteristics of the subject's state

Possibly - The AE:
• follows a reasonable temporal sequence from drug administration

- could have been produced by either the subject's clinical state or by study drug administration

Not related - The AE:
- does not have a reasonable temporal association with the administration of study drug
- has some other obvious explanation for the event

8.2 Adverse Event Reporting Period

The study period during which adverse events must be reported is defined as the period from signing of informed consent to the end of the study treatment follow-up in each group. For this study, there will be an end of study follow-up for adverse events 30 and 60 days following the last study treatment (Multikine treatment group as well as the SOC group treatment). Particular attention should be paid to relatedness of AEs to study drug, as these AEs will be compared to those recorded for subjects receiving SOC only.

8.3 Pre-existing Conditions

A pre-existing condition is one that is present at the time of enrolment. A pre-existing condition should be recorded as an adverse event only if the frequency, intensity, or the character of the condition worsens during the study period.

8.4 Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition. Subsequent to screening, and until the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

8.5 Post-study Adverse Event

All unresolved serious adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor and its designee/agent of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor or designee should also be notified if the investigator

should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.5.1 Pregnancies

If the investigator becomes aware following administration of study drug, of a pregnancy in a female subject, which occurred prior to or subsequent to the drug's administration, the pregnancy will be reported, and follow-up assessments/reports of any possible effects of the study drug on the outcome of the pregnancy will be provided until the subject completes or withdraws from the study.

If the outcome of the pregnancy meets the criteria for immediate classification of an SAE the investigator will report the event by phone and by faxing a completed SAER form to the sponsor (or designee) within 24 hours of knowledge of the event. The investigation of the SAE will be conducted and will determine the relatedness (if any) of the study treatment regimen to pregnancy outcome, should the pregnancy result in an SAE report and investigation. (Section 8.9.4).

8.6 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
The abnormality suggests a disease and/or organ toxicity
The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.
The event is possibly, probably or definitely related to study drug.
The event is of clinical significance as determined by the investigator.

8.7 Hospitalization, Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

Hospitalization or prolonged hospitalization for diagnostic or elective a surgical procedure for a preexisting condition which does not worsen or increase in frequency during the study. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
Hospitalization or prolonged hospitalization required to allow efficacy measurements for the study.
Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.
Hospitalization for transfusion or routine central catheter care. Blood products will be reported as concomitant medications.

8.8 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.9 Reporting of Serious Adverse Events

8.9.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the sponsor or his designee within 24 hours of the event. A Serious Adverse Event (SAE) Form must be completed by the investigator or responsible site personnel and faxed to the sponsor or his designee. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone or e-mail or facsimile to:

Aptiv Solutions	**Tel:+1 508 597-6158 Fax: +1 508 416-2654 Email:**

Pharmacovigilance Marlborough, USA (For United States, Canada, Taiwan)	**Pharmacovigilance_SBO@aptivsolutions.com**
Aptiv Solutions Pharmacovigilance Glory Park, UK (For Europe,and all other regions)	**Tel: +44 (0) 870 710 7157 Fax: +44 (0) 870 710 7157 Email: safety@aptivsolutions.com**

If further follow-up is required the investigator must provide further information on the serious adverse event in the form of a written narrative or follow-up SAE reports. This should include any other diagnostic information that will assist in the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly.

8.9.2 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the EC/IRB within 10 working days or as directed by the IRB guidelines. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the clinical investigator's binder, and a copy of the EC/IRB notification will be sent by the clinical investigator to the study sponsor or designee.

8.9.3 FDA, Health Canada and other Regulatory Agencies Notification by Sponsor

The study sponsor shall notify the FDA and Health Canada by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's (or designee) original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA and Health Canada as soon as possible, but no later than 15 calendar days from the time the determination is made, and communicated to the study sponsor by the investigator.

Other regulatory agencies will be notified of SAE's per the requirements of the specific regulatory jurisdiction regulations and laws.

8.9.4 Pregnancies

If the investigator becomes aware following administration of study drug, of a pregnancy in a female subject, which occurred prior to or subsequent to the drug's administration, the pregnancy will be reported and follow-up assessments/reports of any possible effects of the study drug on the outcome of the pregnancy will be provided until the subject completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing a completed Pregnancy Report to the sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE: however, the investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days within completion of the pregnancy. The investigator should notify the sponsor (or designee) of the outcome of the pregnancy by submitting a follow-up Pregnancy Report.

If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, any congenital anomaly detected in an aborted fetus, stillbirth or neonatal death is to be documented), the investigator will report the event by phone and by faxing a completed SAER form to the sponsor (or designee) within 24 hours of knowledge of the event. The investigation of the SAE will be conducted and will determine the relatedness (if any) of the study treatment regimen to pregnancy outcome, should the pregnancy result in an SAE report and investigation.

8.10 Unbinding Procedures

Not Applicable. This is an open label Study.

The blinding and unblinding procedures for central laboratories, DNA microarray and radiology data are described in Section 6.8 and Section 6.9 respectively.

8.11 Stopping Rules

Because significant toxicity has not been observed with Multikine treatment, it is not anticipated that safety stopping rules will be implemented. However, patients in other studies examining the effects of combined radiotherapy and chemotherapy have demonstrated rates of Grade 3 and 4 toxicities significantly above those observed in patients who receive radiotherapy alone or similar

chemotherapy treatment. For this reason, an independent Data Monitoring Committee will be constituted (Section 8.13).

8.12 Medical Monitoring by Investigators

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (Section 10 - Monitoring ,Auditing and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.13 Independent Data Monitoring Committee (iDMC)

An independent data monitoring committee (iDMC) will review interim data according to the FDA Guidance: "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees". The iDMC will be formed to provide scientific and medical direction for the study.

The iDMC will focus on the following areas:

- *Efficacy* – to assess the primary efficacy measure as well as the conditional power and sample size
- *Safety* – to assess the magnitude of adverse events and monitor for safety concerns

The iDMC will consist of experts (clinical oncologists, radiologist, H&N surgeon, pathologist and biostatistician) with experience in the treatment and analysis of head and neck cancer patients who receive concurrent chemoradiotherapy. They will be provided with the Investigators Drug Brochure, study protocol and relevant literature. The iDMC will operate under a charter and will provide prospective data analysis and display specifications to conduct independent data reviews. The iDMC will make recommendations to the sponsor to continue the study as planned or to stop the study due to safety or lack of efficacy. The iDMC will meet at least semi-annually to perform safety and efficacy evaluations and to make recommendation to the sponsor. The iDMC reserves the right to request more frequent evaluations. No sample size penalty will be imposed by the iDMC evaluations since only recommendations to continue as is, to modify the sample size, or to stop for futility will be made. The sponsor retains the right to accept, modify, or reject the iDMC recommendations. The purpose of the iDMC will be to assess frequency, causality and severity of toxicities of the subjects in the protocol on a periodic basis. The iDMC will review all significant Grade 3 and 4 toxicities as well as all unexpected adverse events possibly related to the study

treatment; the iDMC will forward opinions on individual cases to the sponsor and to sponsor representative. The iDMC will determine if toxicities exceed those rates and severities normally seen with this subject population and make recommendations on the continuing progress of the study to the sponsor, medical monitor and investigators.

The iDMC will be expected to review the protocol and Investigator's Brochure in the context of the iDMCs analyses of the study data and to recommend any changes judged necessary for investigators and EC's/IRBs to adequately assess potential risks and benefits to subjects participating in the study. The iDMC will make recommendations to the sponsor for changes to the protocol or Investigator's Brochure; the sponsor will again have the final decision to implement iDMC recommendations.

The iDMC will also periodically assess the required sample size as well as the conditional power. If the new sample size is smaller than that calculated prior to the study or if there are other indicators that the results are more favorable than expected, the study will continue as planned so as not to incur the statistical penalties that would normally be associated with a traditional interim analysis involving superiority stopping; in addition, the impact on the other study endpoints will be taken into account in making a recommendation. If the new sample size is greater than that calculated prior to the study or if there are other indicators that the overall effectiveness results are not as favorable as expected, the sponsor may accept the iDMC recommendation that the study be expanded or may make the decision to terminate the trial. In the event that a decision is made to expand the sample size, the impact of the final treatment effect will be projected subject to the assumptions regarding enrollment, follow-up and underlying hazard rates.

8.13.1 Interim Safety Analysis

An interim safety analysis will be performed after the first 40 patients complete surgery following randomization to the Multikine treatment groups and have undergone surgery and again when all subjects have completed the 30 day safety follow-up visit (following all protocol treatments). This assessment will include a review of adverse events, serious adverse events, and clinically significant laboratory findings as determined by the investigators. Overall safety events will be assessed as well as safety events grouped in the time period from randomization though surgery, in the 30-day post-operative period, and from the 30-day post-operative period through 30 days following completion of chemo/radiation therapy. Descriptive statistics and tabulations of events will be presented.

The interim safety assessment will be conducted by the iDMC (Section 7.11 and 8.13). If changes in the conduct of the study are warranted as a result of the evaluation, these will be communicated to the investigators, sponsor and the regulatory authorities. If appropriate, the protocol will be amended to incorporate the recommended changes in study conduct.

9. Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) or other applicable laws in the countries participating in this study. Those regulations require a signed subject authorization informing the subject of the following:

What protected health information (PHI) will be collected from subjects in this study
Who will have access to that information and why
Who will use or disclose that information
The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data includes all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial, which are clearly marked as belonging to the study subject. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, CT/MRI, pathology slides and tissue, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study and will be supplied by the sponsor or his designee. It is intended that all sites will utilize Electronic Case Report Forms (eCRFs), but in some cases it may not be possible and it may be necessary to use Paper Case Report Forms. All data requested on the CRFs must be recorded. All missing data must be explained.

9.3.1 Electronic Case Report Form (eCRFs)

Data will be entered into the eCRF at the sites and accessed remotely by Data Management (DM). Electronic review of the data may result in queries being generated that will be accessed by the appropriate investigator or designee for prompt resolution. Resolutions will be reviewed by data monitor [which includes data analyst and clinical research associate (CRA)]. The data analyst reviews the queries once they are resolved by the site in 5 working days and CRA will review queries in their monitoring visits to the site. All data modifications resulting from review or querying of the data will be electronically tracked via electronic Data Clarification Forms (eDCFs). Any errors detected by either the clinical study monitor or the investigator after query resolution should be communicated via eDCFs. An electronic signature will be required by the PI or designee (so designated in writing by the PI).

9.3.2 Paper CRFs (CRFs)

If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D" initial and date. If the item is not applicable to the individual case, write "N/A" initial and date. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

In compliance with ICH GCPs and applicable regulatory requirements, copies of all records (e.g., informed consent documents, laboratory data slips, source documents, IND safety reports, test article dispensing records, etc.) which support CRFs of this study, must be retained in the files of the responsible

investigator for a minimum of two years following notification by the sponsor that all investigations at all sites are completed, terminated, or discontinued, or that the Food and Drug Administration has approved the New Drug Application or Biologic License Application. If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a qualified person (within the same institution) who will accept the responsibility for keeping and maintaining these records from the "departing" PI. Such assignment of responsibility will be communicated in writing naming the new custodian and its affiliation and contact information by the PI (and the Institution) to the sponsor and sponsor representative. Please note that the accepting custodian may need to file documents with the local IRB/IECs, as well as state and federal regulatory authorities.

9.5 Inspection of Records

In compliance with local regulations, US Federal regulations and ICH GCP guidelines, it is required that the investigator and institution permit the sponsor, authorized representatives of the sponsor, and representatives of the regulatory agency(ies), and the IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obliged to inform the study subject(s) and obtain their consent to permit the sponsor and agency representatives to have full access to his/her study-related records without violating the confidentiality of the subject.

10. Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored by the sponsor or its designee according to a monitoring plan to be provided separately. The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator (and the investigational clinical sites) will permit study-related audits and inspections by the EC/IRB, the sponsor, sponsor authorized

representatives, government regulatory bodies, and university compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory). Participation as an investigator in this study implies acceptance of potential inspection by the sponsor, sponsor authorized representatives, government regulatory authorities and applicable university or institutional compliance and quality assurance offices.

11. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a separate consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed and dated by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Where applicable the subject will also give consent to the use of their medical information as described by the US Health Insurance Protection Administration Act (HIPAA). As per institutional policy, a separate document may be provided or the HIPAA compliant statement may reside in the body of the consent form.

11.1 Written Informed Consent

The informed consent must contain all elements required by the FDA under 21 CFR Part 50 and ICH GCP (E6) (Section 4.8), as well as any other elements

required by state, local and institutional policies. All subjects (or legally authorized representative) must provide consent in writing after having had adequate time to ask questions and consider their participation in the study. Consent must be obtained before any protocol related procedures that are not part of the subject's normal care are applied to any subject in the trial. Written documentation of consent must be provided by signing an IRB/IEC approved informed consent document. The date and time the consent was finalized should be recorded in the subject's medical chart. The subject or their legal representative must receive a copy of a timed, dated, and signed consent form according to ICH GCP guidelines. The exact definition of legal representative should be determined for a hospital by its IRB/IEC in compliance with local and state statutes. Subjects will be informed of any significant new finding developed during the course of the research that may affect their decision to continue participation.

11.2 Genomic Microarray Study

A separate independent and stand alone genomic microarray study will be performed in conjunction with the NIH/NCI utilizing tumor specimens and peripheral blood mononuclear cells (PBMCs) obtained from a number of subjects participating in this study. The specimens will be collected at study entry and at time of surgery from subjects in this trial. To ensure subject privacy is protected NO subject specific identifying information will be attached to or be allowed to accompany any of the sample(s) shipped to the NIH/NCI. Neither will subject specific data from which the genomic microarray study results will be derived be able to be traceable back to any subject. The purpose of the genomic microarray study is to determine if subjects whose tumor display a specific genomic array will have a greater chance of being responsive to Multikine treatment than subjects whose tumor lack the same genomic array pattern. It is anticipated that the data from this study will only become available at the end of the study after all subjects have been dosed and treated and may in fact only become available during or near the end of the follow-up period of this study.

11.3 Ethics Review

The protocols and local Informed Consent (IC) forms must be reviewed and approved in writing by each of the participating institutions' IRB/IEC prior to the initiation of subject recruitment. Each of the IRB/IEC must be notified of all subsequent protocol amendments. In addition, progress reports will be submitted to the IRB/IEC by the investigator as indicated by each IRB/IEC's guidelines. A copy of each of these IRB/IEC progress reports submitted by the investigator to its local IRB/IEC will be sent to the sponsor and sponsor's representative. Each IRB/IEC must meet the FDA, and/or European Medicines Agency (EMEA), ICH,

and any additional state and/or national requirements for composition, documentation, and operational procedures.

The investigator shall provide the sponsor with the IRB/IEC's written notification of approval along with the IRB/IEC membership list and/or statement that the IRB/IEC operates in accordance with GCP.

11.4 Ethical Conduct of the Study

The study will be conducted in accordance with this protocol, the principles that have their origins in the Declaration of Helsinki, as well as ICH GCP and applicable federal, state, and local regulatory requirements. All essential documents will be archived at each participating institution.

12. Study Finances

12.1 Funding Source

This study is financed by the sponsor of the study, CEL-SCI Corporation, Vienna, VA, USA.

12.2 Financial Disclosure/Conflict of Interest

Any investigator, who participates in this study, must disclose whether they do or do not have any financial interest (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) in the study or its outcome. If an investigator has a financial interest, Form FDA 3455 must be completed and filed disclosing the financial arrangements. If there is no financial interest or arrangement, form FDA 3454 will be completed and filed.

12.3 Subject Stipends or Payments

Subjects will not receive payment for their participation in this clinical study. In accordance with country-specific rules and regulations and customs, subjects may be compensated for travel and other expenses related to participation in this trial, which otherwise may lead to financial burden (hardship) for subjects participating in the trial.

13. Publication Plan

Should any investigator desire to publish the results (including meeting abstracts) of this study, **a copy of the DRAFT manuscript will be provided to CEL-SCI**

Corporation for review and approval at least 60 days prior to the expected initial date of submission to the intended publisher. Subject names and other identifiers, such as photographs, audio or videotapes, may not be disclosed in any publication without prior written authorization from the subject. In no case can study results be presented or published by an investigator without prior written consent of the sponsor, nor can study results be published by an investigator prior to the conclusion of the study and not until sufficient follow-up of subjects is obtained, and publication is authorized in writing by CEL-SCI Corporation (the study's sponsor).

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the prior written consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14. Required Concomitant Medications

14.1 Cyclophosphamide (USP or equivalent)

The chemical name of cyclophosphamide is:

2-[bis(2-chloroethyl)-amino]tetrahydro-2H-1,3.2- oxazophosphorine 2-oxide monohydrate.

Indications for cyclophosphamide include treatment of various solid malignancies, acute and chronic leukemias, and various autoimmune diseases, including nephrotic syndrome, Lupus erythematosis, Wegener's granulomatosis and rheumatoid arthritis. The role of cyclophosphamide in this protocol is as an immunomodulator to reduce T-suppressor cell activity.

In animal tumor immunotherapy models and at least two human studies involving tumor cell vaccines the immune response to antigenic immunization is markedly augmented by pretreatment with cyclophosphamide. The presumed mechanism of action is the abrogation of T-cell suppressor (and T-reg) activity, permitting a more effective anti-tumor immune response, as a result of Multikine administration.

A dose of 300 mg/m^2 intravenously, as proposed in this protocol, is the dose which has been shown to be active in the above described immunotherapy models.[42, 44, 45, 46, 47] This is a dose well below that which is used in cancer chemotherapy. Doses of 500-600 mg/m^2 are given in combination with other

cytotoxic agents, while as a single agent doses in the range of 1000 mg/m^2 are used. To date, there have been no reports of myelosuppression in the more than 120 subjects who have received cyclophosphamide at the 300 mg/m^2 dose being evaluated in various CEL-SCI sponsored trials.

Cyclophosphamide, Inj. USP or equivalent is commercially available and is supplied as a sterile powder containing 45 mg sodium chloride, 75 mg mannitol or approximately 82 mg sodium bicarbonate per 100 mg cyclophosphamide for reconstitution prior to intravenous injection or infusion.

14.2 Indomethacin (USP or equivalent)

The chemical name of indomethacin is:

1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid.

Indomethacin is a non-steroidal anti-inflammatory (NSAID) and antipyretic agent. Indications for indomethacin include anti-inflammatory activity in rheumatoid arthritis and as an antipyretic in Hodgkin's disease. It is further indicated in the treatment of ankylosing spondylitis and osteoarthritis. Indomethacin is a potent inhibitor of prostaglandin synthesis. It has been demonstrated that monocyte and macrophage-mediated suppression of the immune response is via the synthesis and release of prostaglandins (e.g., PGE-2). The role of indomethacin in this protocol is as an inhibitor of macrophage-mediated suppressor cell activity.

Indomethacin USP or equivalent is commercially available and is supplied in capsules of 25 mg and 50 mg for oral administration. Indomethacin, 25 mg PO three times daily (with food), is utilized in this study.

14.3 Nutritional Supplementation – Multivitamins with zinc

Subjects with previously untreated, potentially curable head and neck cancers exhibit high incidences of nutritional deficiencies and impaired immune responses. Both nutritional status and immune competence have been correlated with patient survival after definitive treatment of the tumors.

Immune responses are reduced by deficiencies of certain vitamins and minerals, particularly vitamins A, B, C, D, E and zinc. These findings support the addition of nutritional supplementation with vitamins to minimize deficiencies in cancer patients that may impair immune responses and reduce survival rates after tumor treatment.

To ensure good nutritional status, a commercially available multivitamin supplement with zinc is used for self-administration by subjects receiving Multikine once daily orally.

14.4 Cisplatin IV Bolus Infusion (USP or equivalent) (Section 6.4.4)

Subjects with identified "High-Risk" factors [tumor margins unclear or infiltrative, local invasion, nodal involvement (≥2 lymph nodes or extracapsular nodal spread)] will receive chemotherapy (cisplatin, IV, bolus infusion) concurrently with radiotherapy. Concurrent chemoradiotherapy is currently adopted as the standard of care for these high risk subjects and has been shown to result in statistically significant increases in rate of local regional control, and in some cases, increases in overall survival.

If indicated, subjects will receive three courses of cisplatin IV bolus. Each course of chemotherapy will consist of cisplatin (100 mg/m^2) given as an IV bolus infusion over 1-2 hours with pre-hydration and diuretics. Chemotherapy will be given on weeks 1, 4 and 7 of radiotherapy (or Days 1, 22 and 43 of the radiotherapy course) and concurrently with radiotherapy.

APPENDIX 1. Table of Scheduled Events

A Phase III, Open-label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection [Multikine] Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity Versus Standard of Care Only

ASSESSMENT (All study groups)	**Within 2-4 wks of regimen start**	**DAY**																						
		-3	**–1 or 1**	**1**	**2-3**	**4-5**	**6-7**	**8**	**9-12**	**13-14**	**15**	**16-18**	**19**	**20**	**Between days 21-26**	**22**	**23**	**24-27**	**28**	**29-38 (Surgery)**	**Radiotherapy**	**Chemotherapy (high risk subjects)**	**Safety (Sec 6.4.5)[3]**	**Long Term Follow-up (Sec. 6.5)[4]**
Tumor punch biopsy (FNA for any involved Lymph Node)	X																							
Medical history	X														X									
Physical exam incl. vital sign (VS)	X														X							X	X	X
Height and weight	X														X							X	X	X
Urinalysis	X														X								X	
Blood chemistry (X*= TSH at RTx+ every 6-12 months following RTx)	X	X[6]	X[7]												X						X*		X	X*
Tumor staging	X														X									
Tumor measurements / photography	X			X							X				X				X					X
CT Scan / MRI (Oral Cavity and Neck region) (X* - CT scan / MRI in follow up – 1st year–3/Year, 2nd Year –2/Year, 3rd Year– 1/Year) [if medically indicated]	X																		X[8]		X			X*
HIV test	X																							
Skin test for ciprofloxacin sensitivity	X																							

ASSESSMENT (All study groups)	**Within 2-4 wks of regimen start**	**DAY**																						
		-3	**–1 or 1**	**1**	**2-3**	**4-5**	**6-7**	**8**	**9-12**	**13-14**	**15**	**16-18**	**19**	**20**	**Between days 21-26**	**22**	**23**	**24-27**	**28**	**29-38 (Surgery)**	**Radiotherapy**	**Chemotherapy (high risk subjects)**	**Safety (Sec 6.4.5)[3]**	**Long Term Follow-up (Sec. 6.5)[4]**
Concomitant medication notation (and subject compliance w/ required medications)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test		X																						
Chest X-ray (PA and lateral, or CT scan of chest)	X																							
EKG	X																						X	
CBC with differential, ANC[1] (and efore each RTx/CRTx)	X	X[6]	X[7]												X						X	X	X	X
ESR[2] (and before each RTx/CRTx)	X	X[6]	X[7]												X						X	X	X	X
Vital Signs (only) (before each RTx/CRTx)		X		X	X	X	X	X	X	X	X								X					X
Daily Health Assessments (starting Day -3) (Sec. 6.1) (Group 1&2)		X		X	X	X	X	X	X	X									X					X
Adverse Event recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Histopathological examination of tumor specimen	X																			X				
Long term follow-up (sec 6.5)																								X
QOL assessments (sec 3.1.4.3)		X																X						X
Dental Exam (if medically indicated)	X																							

ASSESSMENT (All study groups)	**Within 2-4 wks of regimen start**	**DAY**																						
		-3	**–1 or 1**	**1**	**2-3**	**4-5**	**6-7**	**8**	**9-12**	**13-14**	**15**	**16-18**	**19**	**20**	**Between days 21-26**	**22**	**23**	**24-27**	**28**	**29-38 (Surgery)**	**Radiotherapy**	**Chemotherapy (high risk subjects)**	**Safety (Sec 6.4.5)[3]**	**Long Term Follow-up (Sec. 6.5)[4]**
MULTIKINE TREATMENT REGIMEN																								
Cyclophosphamide **(Group 1 only)**		X																						
Multivitamin s with zinc(as per protocol/as indicated for nutritional support) **(Group 1 only)**				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Indomethacin **(Group 1 only)**				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Multikine Injection **(Groups 1 and 2)**				X	X	X		X	X		X	X	X											
Surgery **(Groups 1 and 2)[8]**																				X[8]				
Radiotherapy (within 8 weeks (56 days) post surgery, 60 – 70 Gy, 30 -35 fractions, 6 - 7weeks) **(Groups 1 and 2)**																					X	X		
Chemotherapy "high Risk" Subjects only [cisplatin 100mg/m ^{2} IV weeks 1,4,7 post surgery; concurrent w/ RT for high risk subjects] **(Groups 1 and 2)**																					X			
STANDARD of CARE (Group 3 Only)																								X
Surgery (after								X (Surgery may be scheduled on Days 8-38)[5]																

ASSESSMENT (All study groups)	**Within 2-4 wks of regimen start**	**DAY**																						
		-3	**–1 or 1**	**1**	**2-3**	**4-5**	**6-7**	**8**	**9-12**	**13-14**	**15**	**16-18**	**19**	**20**	**Between days 21-26**	**22**	**23**	**24-27**	**28**	**29-38 (Surgery)**	**Radiotherapy**	**Chemotherapy (high risk subjects)**	**Safety (Sec 6.4.5)[3]**	**Long Term Follow-up (Sec. 6.5)[4]**
enrollment/randomization)[5]																								
Radiotherapy (within 8 weeks (56 days) post surgery, 60 Gy – 70 Gy, 30 – 35 fractions, 6 '- 7 weeks)																					X	X		
Chemotherapy "high Risk" Subjects only [cisplatin 100mg/m ^{2} IV weeks 1,4,7 post surgery; concurrent w/ RT for high risk subjects]																					X			

1. ANC is Absolute Neutrophil Count (WBC x (% neutrophils + % bands))
2. ESR is Erythrocyte Sedimentation Rate
3. This visit occurs at Day 30 after completion of radiation +/- chemotherapy
4. First visit occurs at Day 60 after completion of radiation +/- chemotherapy
5. Surgery for SOC Group 3 only, may be scheduled on Days 8-38 (from enrollment/randomization), unless otherwise indicated medically - by the investigator
6. Group 1 only.
7. Groups 2 and 3 only.
8. Surgery for Groups 1 and 2 only may be scheduled on Days 29-38 (from Enrollment/ Randomization), unless otherwise indicated medically - by the investigator.

APPENDIX 2A. Technique for Peri-tumoral, Subepidermal Injection of Multikine

Figure 1. SURFACE VIEW

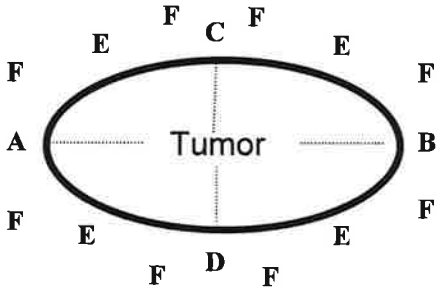
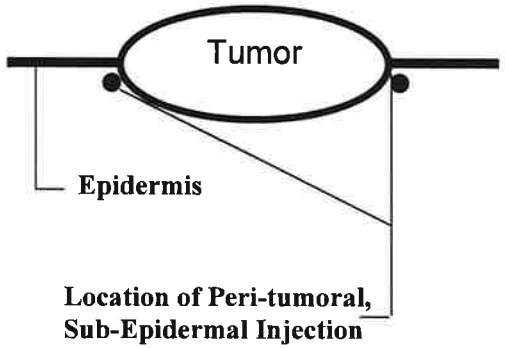


Figure 2. SAGITTAL VIEW

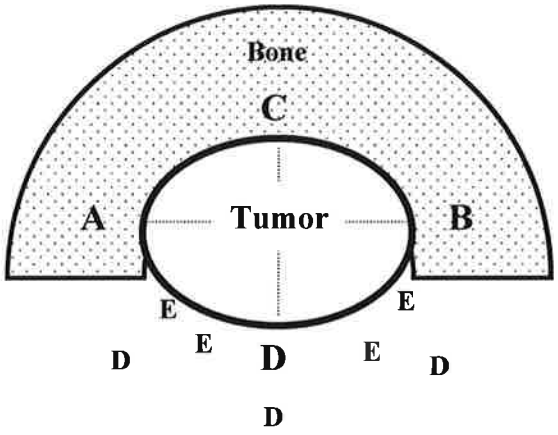


The extent of the primary tumor at its longest dimension (Fig.1, A-B) and the extent at right angles to and at the midpoint of the longest dimension (Fig.1, C-D) are determined by digital palpation. When the anatomical location of the tumor permits, one-fourth of the total dose of Multikine is injected in the region of each of the four tumor extents. For example, for the peri-tumoral Multikine dose of 200 IU (1.0 mL), 50 IU (0.25 mL) is injected in each of the four regions. Multikine is injected into the subepidermal tissue adjacent to the tumor (Fig. 2) using a 25, or smaller, gauge needle. Before injecting, aspiration is attempted to ensure against injection of Multikine into peri-tumoral blood vessels. The needle is inserted sufficiently into the subepidermal tissue to prevent leakage of Multikine out of the puncture site after the needle is withdrawn. If necessary to prevent leakage, additional peri-tumoral injection sites may be utilized (Fig. 1, E) and a second series of injection sites (Fig.1, F) adjacent to and peripheral to injection sites A-E may be required to avoid leakage from injection sites.

After completing the three-week regimen of Multikine injections, label the sketch of the primary tumor on the Case Report Form, Post Protocol Regimen, PRIMARY TUMOR, with the locations (A-F) of the injection sites.

APPENDIX 2B. Technique for Peri-tumoral, Subepidermal Injection of Multikine

Figure 3. ANATOMICAL LOCATION OF THE TUMOR PREVENTS CIRCUMFERENCIAL INJECTION OF Multikine



Note: Product is to be injected in approximately equal volumes at minimum of four sites around the injectable portion of the tumor margin.

The anatomical location of the primary tumor may prevent peri-tumoral injections of Multikine at the entire circumference of the tumor. For example, in Figure 3, proximity and adherence to bone may prevent injections of Multikine at points A-C of the circumference of the tumor. In such instances, the Multikine is injected outwardly at equidistant points in the peri-tumoral subepidermal tissues at the circumference of the tumor where the injections can be accomplished without leakage of the Multikine from the injection sites (Fig. 3, D-E).

After completing the three-week regimen of Multikine injections, label the sketch of the primary tumor on the Case Report Form, Post Protocol Regimen, PRIMARY TUMOR, with the locations (A-E) of the injection sites.

APPENDIX 3. Jugular Region Perilymphatic Administration of Multikine

PROCEDURE

The subject is positioned in an otorhinolaryngeal examination chair with the head held upright by the occipital support. The skin in the area of the mastoid process is cleansed for percutaneous puncture. At the discretion of the investigator, a local anesthetic may be administered to the proposed injection site. A 25 gauge, or smaller, needle is introduced at a point 1.5 cm inferior to the tip of the mastoid process at the area of the insertion of the sternomastoid muscle. The needle is inserted 1.5 cm and aspiration attempted to determine if a blood vessel has been punctured. If there is no evidence of blood vessel puncture, the specified dose of Multikine is injected without additional manipulation of the needle. After each injection, the side of the neck to which the injection was administered, the dose of Multikine injected and ANY DEVIATION(S) thereof are recorded on the Daily Medical Treatment Case Report Form.

Selection of Injection Site

In subjects who do not display clinical evidence of tumor metastatic to a regional lymph node, the neck on the side of tumor is injected. With a clinically positive lymph node, the neck on the side of the positive lymph node is injected, regardless of the location of the primary tumor. With midline tumors and neck lymph nodes that do not display clinical evidence of tumor metastases, one side of the neck is selected by the Principal Investigator and all injections are made on that side.

Contraindications to Injection

Injection is contraindicated if the skin of the proposed injection site shows acute or chronic infection or inflammation, dermatological disease, pre-cancerous lesion or cancer. Injection is contraindicated if the neck on the side of the proposed injection has had incisional (open) biopsy of a lymph node within the previous four weeks.

Procedure after Evidence of Blood Vessel Puncture

Multikine is not injected if there is evidence of blood vessel puncture. The needle is withdrawn and re-introduced at 1.0 cm inferior to the tip of the mastoid process; i.e., 0.5 cm superior to the previous puncture site, and inserted to a depth of 1.0 cm, compared with a 1.5 cm depth of insertion that led to puncture of a blood vessel. The performance of this procedure and any deviations are recorded on the Daily Medical Treatment Case Report Form.

APPENDIX 4. Clinical Laboratory Tests Obtained in the Protocol Regimen

BLOOD CHEMISTRY TESTS	BLOOD HEMATOLOGY TESTS	URINALYSIS
TSH		
Sodium	White Blood Cell Count	Color
Potassium	Red Blood Cell Count	pH
Chloride	Hemoglobin	Specific Gravity
Bicarbonate	Hematocrit	Protein - Urine
Glucose	Platelet Count	Glucose - Urine
Urea	(A) Neutrophils	Ketone - Urine
Creatinine	(A) Bands	Blood - Urine
Urate	(A) Lymphocytes	RBC - Urine
Calcium	(A) Monocytes	WBC - Urine
Phosphate	(A) Eosinophils	Epithelial Cells
Total Protein	(A) Basophils	Bacteria - Urine
Albumin	ESR	Mucus
Total Bilirubin		Amorphous Material
Alanine Transaminase		Crystals
Aspartate Transaminase		Casts
Alkaline Phosphatase		
Lactate Dehydrogenase		
Cholesterol		
Triglycerides		
Glutamyl Transferase		

SERUM PREGNANCY
HIV TEST

***IMMUNOHISTOCHEMISTRY/PATHOLOGY**

CD3, CD4, CD8
CD3/CD25, CD4/CD25, CD8/CD25, FOXP3
CD56/CD16, CD13
CD11b, CD45, CD45RA, CD45RO
CDR2, CD1a
HLA Class II (DP, DQ, DR)

*These determinations to be performed at a Central Pathology laboratory.

Multikine Phase-III Study: Tumor Sample Collection and Preparation Guideline and Histopathology Protocol (overview)

1. Pre-treatment phase – Biopsy Guideline

A. Primary tumor
(1) take one punch-biopsy for each 1cm of tumor size
(2) prepare freshly about 1/3 of sampled material taken for genomic studies, immerse into an Eppendorf tube containing 0.5 ml RNA-later and send ice-cold to NIH Lab (Dr. Marincola)
(3) fix the remaining 2/3 of sampled material in buffered neutral formalin and embed into paraffin. In case of more than one punched piece, embed each piece into separate paraffin blocks
(4) prepare H&E section from each paraffin block and store in local path archive one, while send the paraffin block(s) to central path lab. (Blocks will be returned after analysis).

English version of the original local path report *excluding* personal identification data (PID) must be sent electronically to the central pathology laboratory with paper copy of the original path report excluding PID.

B. Regional lymph node
In case of clinical N positivity it is recommended to confirm it by using fine needle aspiration biopsy (FNAB) technique. Cytological smears are fixed immediately by alcohol-containing fixative. Fixed smears are further processed in local pathology laboratory using HE, Giemsa or Papanicolau staining.

In case of multiple cytological smears, one representative is to be sent to the central pathology laboratory. In case of single smear it is possible to send a virtual smear after scanning via Internet to central pathology.

English version of the original local path report *excluding* PID must be sent electronically to the central pathology laboratory with paper copy of the original path report excluding PID.

2. Postoperative (Surgical) sample Preparation - Guideline

A. Primary tumor
Surgical sample kept at 4°C, has to be sent to local pathology laboratory immediately without fixation.
(1) after gross photography and marking of the resection surfaces representative sample has to be taken from fresh unfixed tumor for frozen section. After fixation and staining microscopic analysis must indicate the presence of tumor and stroma. This frozen section and the native gross photo (electronic form) must be sent to the central pathology laborarory. A parallel serial sample must be placed into Eppendorf tube

containing 0.5 ml of RNA-later and to be sent for genomic studies at NIH (prof. Marincola).
(2) after fixation of the rest of the tumor sample (buffered neutral formalin) gross photography must be prepared demonstrating the maximal diameter of the tumor (justified by ruler). One
(3) tumor block/cm and peritumoral tissue at 1 cm distance must be sampled beside resection margins. From each paraffin block an extra HE section must be prepared and sent to the central pathology laboratory for sampling review. Central pathology will select paraffin block for further analysis, which has to be sent to there. After the central pathology laboratory studies the paraffin block, these blocks will be returned to local pathology for archiving.

English version of the original local path report *excluding* PID must be sent electronically to the central pathology laboratory with paper copy of the original path report excluding PID.

B. Neck dissection (Regional lymph nodes)
Labelled and oriented neck dissection sample(s) (by surgeon) is to be fixed in buffered neutral formaline. After fixation all available lymph nodes must be analysed to define pN stage. Lymph node(s) from treated area must be labelled. Excess HE sections must be prepared from each available lymph node(s) which have to be sent to the central pathology laboratory for reviewing. Central pathology will select paraffin block for further analysis, which has to be sent to there. After the central pathology laboratory studies the paraffin block, these blocks will be returned to local pathology for archiving.

English version of the original local path report *excluding* PID must be sent electronically to the central pathology laboratory with paper copy of the original path report excluding PID.

Case-specific materials to be provided for Central Pathology Analysis – Required Samples and Information

Samples from Trial Subjects - Multikine Treated and Non-Treated (No Multikine):

- 1 fresh sample of the non-treated primary tumor in RNA-later (NIH)
- 1 paraffin block of the non-treated primary tumor (Central Path)
- 1 stained cytology smear of FNAB of clinically N+ case (Central Path)
- 1 frozen section of resected primary tumor (fixed and stained) (Central Path)
- 1 fresh sample of the resected primary tumor in RNA-later (NIH)
- All HE slides of the fixed and sampled resected primary tumor (Central Path)
- *Upon request selected paraffin block(s) is to be provided (Central Path)*
- All HE slides of the fixed and sampled lymph nodes (Central Path)
- *Upon request selected paraffin block(s) is to be provided (Central Path)*
- Electronic version of the gross photography of the native and fixed resected primary tumor (Central Path)

- English version of all the original local path reports *excluding* PID must be sent electronically to the central pathology laboratory with paper copies of the original path reports excluding PID.

It is highly advisable to use/consider the modified CAP Report forms to prepare local path reports.

Genomic Microarray Study

This Study will involve the collection and transport of tumor samples and PBMCs from a predetermined number of subjects in this study. No subject specific ID or information will be attached to any of the samples delivered to the NIH/NCI for genomic microarray testing.

- **Dr. Francesco M, Marincola (PI); Dr. Timar and Dr. Talor (Co-PIs)**
  Chief Infectious Disease and Immunogenetics Section (IDIS)
  Department of Transfusion Medicine, Clinical Center,
  Associate Director, Trans-NIH Center for Human Immunology, National Institutes of Health
  Director, CC/CHI FOCIS Center of Excellence
  Bldg 10 - Room 1N226
  Bethesda - Maryland 20892

Genomic Microarray Study

Tissue biopsies collection and storage Biopsies should be processed at the bed side.

For gene profiling analysis, punch biopsies or excisional biopsies should be collected and processed according to the following protocol:

Direct deposit punch (or FNA) biopsy immediately in 1.8ml cryo tube with the addition of 50-100ul of RNAlater (5 time of the sample volume) and keep sample at 4°C for 4hr before snap freeze and store at -80°C till RNA isolation or shipment.
For excisional biopsies, depending on the size of the biopsies, increased amount of RNAlater should be used to cover the whole tissue (5 times of the sample volume) and sample should be sliced into no more than 5mm in thickness. Store sample in RNAlater at 4°C over night before freeze at -80°C. Frozen samples should never be thawed till RNA isolation.

Ship complete frozen sample collection to:

Dr. Ena Wang (c/o Dr. F. Marincola)
9000 Rockville Pike, Building 10 room 1C711
Bethesda, MD 20892
USA
Tel: 301-451-8501
Fax: 301-420-1360

NIH will process RNA isolation; amplification and array hyb upon receiving the samples.

APPENDIX 5. Karnofsky Performance Status

Subject Ability	Percent	Status
Able to carry on normal activity; no special care is needed	**100**	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home; cares for most personal needs; a varying amount of assistance is needed	**70**	Cares for self; unable to carry on normal activity or do active work
	60	Requires occasional assistance, but is able to care for most personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	**40**	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated though death not imminent
	20	Very sick; hospitalization is necessary, active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

APPENDIX 6. American Joint Committee on Cancer (AJCC) Staging, 7th Edition 2010

AJCC STAGING

Oral Cavity
Buccal mucosa*
Floor of mouth*
Tongue (anterior two-thirds)*
*allowed in protocol

Primary Tumor (T) – Oral Cavity
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor < 2 cm in greatest dimension
T2 Tumor > 2 < 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4a Moderatelyadvanced local disease
Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose. Tumor invades adjacent structures.
T4b Very advanced local disease
Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

Oropharynx
Soft palate*
*allowed in protocol

Primary Tumor (T) - Oropharynx
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor < 2 cm in greatest dimension
T2 Tumor > 2 < 4 cm in greatest dimension or extension to lingual surface of epiglottis
T3 Tumor more than 4 cm in greatest dimension
T4a Moderatelyadvanced local disease
Tumor invades the larynx, estrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b Very advanced local disease
Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Nodal Involvement (N) (applies to both Oral Cavity and Oropharynx primary tumors)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral node, more than 3 cm, but not more than 6 cm in greatest dimension or multiple ipsilateral or bilateral or contralateral nodes, none more than 6 cm in greatest dimension
N2a Metastasis in a single ipsilateral node more than 3 cm, but not more than 6 cm in greatest dimension.
N2b Metastasis in a multiple ipsilateral nodes, none more than 6 cm in greatest dimension
N2c Bilateral or contralateral lymph node **not** more than 6 cm in greatest dimension
N3 Metastases in a lymph node more than 6 cm in greatest dimension.

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis present

Stage Groupings

Stage I	**T1 N0 M0**
Stage II	**T2 N0 M0**
Stage III	**T3 N0 M0** **T1-3 N1 M0**
Stage IVA	**T4a N0-1 M0** **T1-4a N2 M0**
Stage IVB	**Any T N3 M0** **T4b N2 M0**
Stage IVC	**Any T Any N M1**

APPENDIX 7. Management of Dental Problems in Irradiated Patients

(Adapted from RTOG protocol 95-01)

Dental Care for Irradiated Patients
Goals for a dental care program include:

1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures
The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

Dental Catergory1
Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar abscess and hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

Dental Category 2
Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

Dental Category 3
Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth, which are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

Dental Category 4

Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth

If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors

The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of fluoride carriers, custom-made mouth guards which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is moulded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results

In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation caries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay

Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis.

Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

Hypersensitivity of Teeth

Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva, and has been shown to be reduced in incidence with the fluoride treatments.

Should this problem become manifest, increasing the fluoride treatment to 10 to 15 minutes 3 times a day is recommended.

Infections

Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

Bone Necrosis

The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons including: impairment of normal metabolism, increased susceptibility to infection and severely limited repair process. Bone necrosis occurs most often after post-irradiation surgery or other traumas. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

APPENDIX 8. NCI Common Toxicity Criteria Ver. 4.0, May 28, 2009

A Booklet containing the NCI Common Toxicity Criteria Ver 4.0, May 28, 2009 will be provided to sites as part of submission package

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

APPENDIX 9.

Quality of Life Instrument – EORTC QLQ-C30 and EORTC QLQ-H&N 35

(Please see the following four pages for assessments)

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

APPENDIX 10. RECIST Response Criteria Version 1.0

At baseline, tumor lesions will be categorized as:

Measurable:	Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥10 mm with spiral CT scan.
	OR
Non-measurable:	All other lesions, including small lesions (longest diameter < 10 mm with spiral CT scan) and truly non-measurable lesions.

All measurements should be recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Lesions that are considered as truly non-measurable include the following:

- bone lesions,
- leptomeningeal disease,
- ascites,
- pleural/pericardial effusion,
- inflammatory breast disease,
- lymphangitis cutis/pulmonis,
- abdominal masses that are not confirmed and followed by imaging techniques,
- cystic lesions.

Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical Lesions

Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography - including a ruler to estimate the size of the lesion - is recommended.

Chest X-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable. It is assumed that chest radiographs are performed erect, in the postero-anterior (PA) projection, in full inspiration. However patients in trials with advanced disease may not be well enough to fulfill these criteria and such situations should be reported together with the measurements.

Note: Lesions bordering the thoracic wall are not suitable for measurements by chest X-ray, since a slight change in position of the patients can cause considerable differences in the plane in which the lesion is projected and may appear to cause a change that is actually an artifact. These lesions should be followed by CT or MRI. Similarly, lesions bordering or involving the mediastinum should be documented on CT or MRI.

CT, MRI

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. When possible, oral or IV contrast should be used to increase the differences in density between the structures. The same imaging protocol should be used for successive evaluations of the same patients [same machine (MRI), same timing for contrasts enhancement (CT), same slice thickness]. The same radiologist at an investigative site (named on FDA Form 1572) shall read all slides (as far as possible) to ensure consistency.

CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness contiguously (this applies to the chest, abdomen and pelvis). Lesions should be measured on "soft tissue" settings.

Note: Lung lesions should be imaged on both "soft tissue" and "lung" windows to ensure that small, miliary metastases are not being inadvertently overlooked.

Ultrasound

Ultrasound should not be used to measure tumor lesions for objective response evaluation. It is however a possible alternative to clinical measurements of superficial palpable nodes. Ultrasound might also be useful to detect new lesions that must be considered for the overall response assessment.

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to

validation purposes in specialized centers. However, such techniques can be useful to confirm complete pathological response.

Tumor Markers

Tumor markers alone cannot be used to assess response. However, if initially above upper normal limit, they must return to normal for a patient to be considered in complete clinical response when all tumor lesions have disappeared.

Cytology, Histology

These techniques can be used to differentiate between PR and CR in rare cases (eg after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Cytological confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. Under such circumstances, the cytological examination of the fluid collected will permit differentiation between response or stable disease.

New Techniques

New techniques to better investigate the objective tumor response (eg, PET scanning, Spiral scanning) are currently being validated. However, standard procedures and definitions to be used in the context of tumor response evaluation are not yet available. Therefore, the utilization of such techniques for objective tumor response do not form a part of this protocol.

Assessment of Overall Tumor Bulk and Measurable Disease

To assess objective response, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion with a diameter (single dimension) $\geq$ 20 mm. If the measurable disease is a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Baseline Documentation and Non-Target Lesions

Target Lesions

All measurable lesions up to a maximum of 5 lesions per organ, 10 lesions total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter [LD]) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the LD for

all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response.

Non-target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria Definitions- Evaluation of Target Lesions

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

Evaluation of Non Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level.
Incomplete Response/Stable Disease (non-CR)	Persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more new lesions, and/or unequivocal progression of existing non-target lesions.

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

Evaluation of Best Overall Response

Table 8.2.2.3: Criteria Used for Evaluation of Best Overall Response

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

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

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". In such cases, every effort should be made to document any subsequent objective progression.
- Conditions that may define "early progression, early death and inevaluability are study specific and should be clearly defined in each protocol (depending on treatment duration, treatment periodicity).
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this particular situation it is recommended to investigate the residual lesion (fine needle aspiration/biopsy) before confirming the complete response status.

Confirmatory Measurement and Duration of Response

The main goal of confirmation of objective response is to minimize the risk of over-estimation of the response rate. This aspect of response evaluation is particularly important in non-randomized trials where response is the primary endpoint. In order to be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks).

Duration of Overall Response

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

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

Duration of Stable Disease

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

Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence. In general the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

APPENDIX 11. Investigational Drug Thaw Procedure

The drug (Multikine, Leukocyte Interleukin, Injection) is stored frozen in the pharmacy at –20°C until needed. The vial contents should be thawed at ambient

temperature just before use, and the drug allowed to reach ambient temperature before injection. It must be injected within 4 hours of thawing. Multikine may also be thawed at refrigerator temperature (2-8°C) one day before use, and allowed to come to ambient temperature just prior to injection - either procedure for thawing the Drug vial may be followed. However, the overnight thaw at 2-8°C temperature is preferable as the drug may be kept for up to 24 additional hours at 2-8°C temperature if need be. Once the drug is brought to ambient temperature, it must be used within 4 hours or be disposed of. Please follow the Drug Accountability Procedure for all drug vials in this Study.

Multikine Vial Thaw Procedure

This procedure provides for the thawing of Leukocyte Interleukin, Injection. The following steps should be followed in order to minimize the loss of biological activity during thawing.

NOTICES AND PRECAUTIONS

This material is derived from human blood. Use Universal Precautions when handling.

- **DO NOT shake vial or thaw in water bath.**
- **DO NOT use the Leukocyte Interleukin, Injection vial after more than four (4) hours at ambient temperature (21-22°C) or twenty-four (24) hours at 2-8°C.**
- **DO NOT administer this drug if cold.**
- **DO NOT refreeze vial.**

Return unthawed, unused Leukocyte Interleukin, Injection vial to the pharmacy for storage and accountability by the Clinical Monitor.

PROCEDURE

1. **Thawing at Approximately 4°C (See attached Figure 1)**

Remove Leukocyte Interleukin, Injection vial from freezer (-20°C). Immediately place in 4°C (2-8°C) refrigerator for 2-24 hours.

Note: Thawing of a 2.2 mL vial will take approximately 2 hours at 2-8°C.

Keep Leukocyte Interleukin, Injection refrigerated (2-8°C) until needed for injection.

Approximately fifteen (15) minutes prior to injection, remove Leukocyte Interleukin, Injection vial from the refrigerator and place on bench top.

Note: This time (fifteen (15) minutes) of removal of vials from 2-8°C is based on approximately 21-22°C ambient temperature.

Gently swirl and use for injection when the vial temperature approximates ambient temperature.

2. **Thawing at Ambient Temperature, approximately 21-22°C (See attached Figure 2)**

Remove Leukocyte Interleukin, Injection vial from freezer (-20°C).

Place vial on bench top and allow to thaw for a period of 30 minutes to 4 hours.

Note: Thawing of a 2.2 mL vial directly removed from -20°C storage will take approximately 30 minutes at approximately 21-22°C.

Gently swirl and use for injection when the vial temperature approximates ambient temperature.

(See Figures 1 and 2 below)

Figure 1: Leukocyte Interleukin, Injection (Multikine) Vial Thaw (4°C)

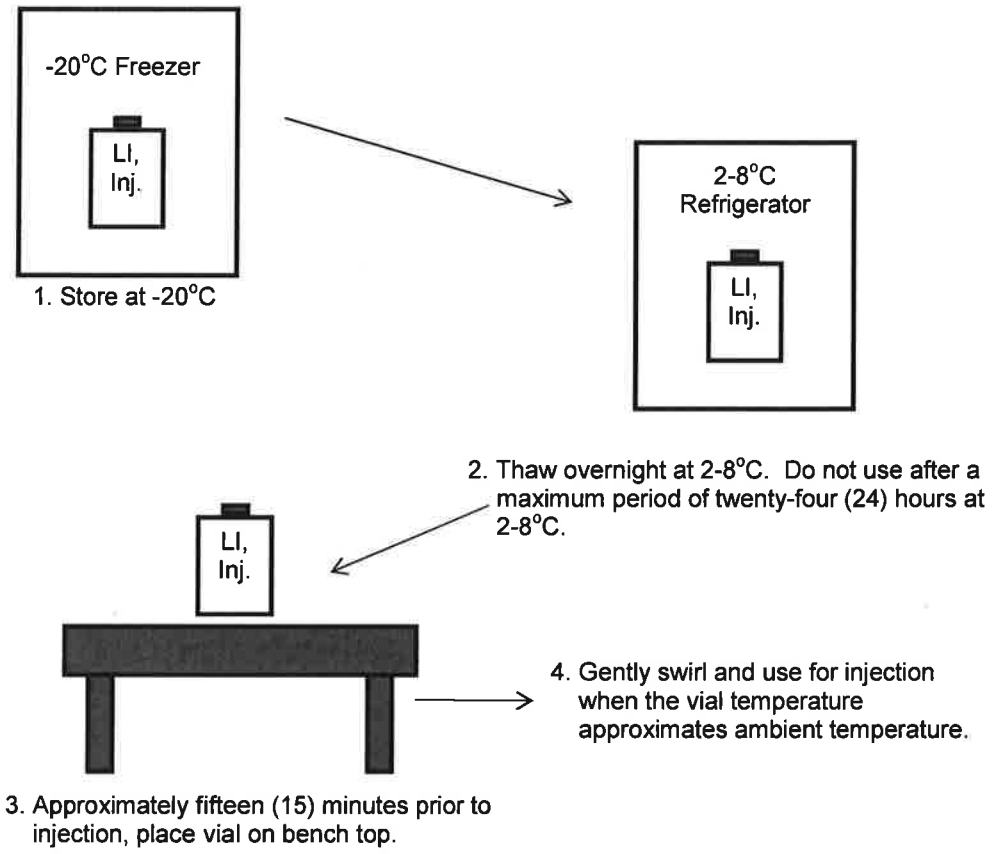
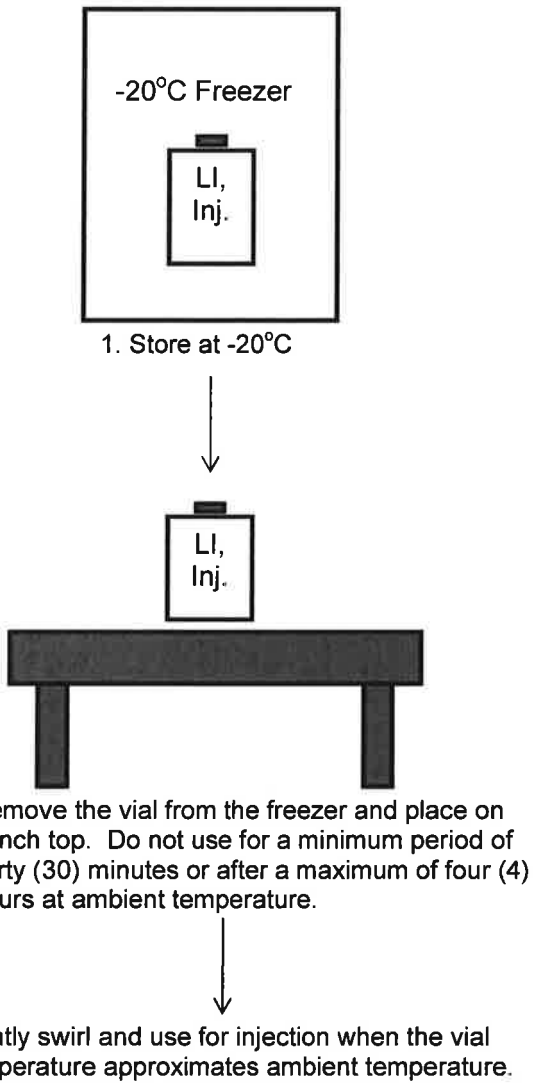


Figure 2: Leukocyte Interleukin, Injection (Multikine) Vial Thaw (amblent temperature, approximately 21-22°C)



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