SGX942 (DUSQUETIDE)
IDR-OM-02-USA

A PIVOTAL, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTINATIONAL STUDY OF SGX942 (DUSQUETIDE) FOR THE TREATMENT OF ORAL MUCOSITIS IN PATIENTS BEING TREATED WITH CONCOMITANT CHEMORADIATION FOR THE TREATMENT OF SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

STATISTICAL ANALYSIS PLAN

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area-Under-the-Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CP	Conditional Power
CRT	Chemoradiation Therapy
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
HCG	Human Chorionic Gonadotropin
HNC	Head and Neck Cancer
HPV	Human Papillomavirus
ITT	Intent-to-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
n	Number
NCI	National Cancer Institute
OM	Oral Mucositis
PD	Protocol Deviation
PI	Principal Investigator
QLQ-H&N43	Quality of Life Question for Head and Neck Cancer 43
RECIST	Response Evaluation Criteria in Solid Tumors
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
RT	Radiation Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	Systeme Internationale
SOC	System Organ Class
SOM	Severe Oral Mucositis
TEAE	Treatment-Emergent Adverse Event
UOM	Ulcerative Oral Mucositis
WBC	White Blood Cell
WHO	World Health Organization
WHO Drug	World Health Organization Drug Dictionary

INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of efficacy and safety as outlined and/or specified in the study protocol. Specifications of tables, figures, and data listings are contained in a separate document (table shells).

1 STUDY OBJECTIVES

1.1 PRIMARY OBJECTIVE

- To assess the efficacy of SGX942 (dusquetide) compared to placebo in decreasing the duration of severe oral mucositis (SOM; defined as World Health Organization [WHO] Grade lesion ≥3) through 6-week post-RT in patients receiving fractionated radiation treatments and concomitant cisplatin chemotherapy, given as 80-100 mg/m^2 every third week, for the treatment of squamous cell carcinoma of the oral cavity or oropharynx.

1.2 SECONDARY OBJECTIVES

1.2.1 Clinically Important Secondary Objectives

1. To assess the impact that SGX942 has on the Area-Under-the-Curve (AUC) for SOM (WHO Grade ≥3) by time plot (severity-weighted duration)
2. To assess the impact that SGX942 has on the Area-Under-the-Curve (AUC) for ulcerative oral mucositis (UOM; defined as WHO Grade ≥2) by time plot (severity-weighted duration)
3. To assess the impact that SGX942 has on the incidence of SOM
4. To assess the impact that SGX942 has on the quality of life assessment using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3) and QLQ-H&N43 instrument
5. To assess the impact that SGX942 has on the amount of opioids used

1.2.2 Additional Secondary Objectives

- To assess the impact that SGX942 has on the cumulative number of days of RT breaks
- To assess the impact that SGX942 has on the duration of SOM; in all randomized patients receiving fractionated RT and concomitant cisplatin chemotherapy, given as 80-100 mg/m^2
- To assess the impact that SGX942 has on the duration of UOM
- To assess the impact that SGX942 has on the cumulative amount of pain reported by patients

1.3 SAFETY OBJECTIVES

- To assess the impact that SGX942 has on the Adverse Events (AE) and Serious Adverse Events (SAE)
- To assess the impact that SGX942 has on changes in safety laboratory values
- To assess the impact that SGX942 has on the Response Evaluation Criteria in Solid Tumors (RECIST) categorization of the primary tumor at 12 weeks and 12 months post chemoradiation therapy (CRT)
- To assess the impact of SGX942 on the incidence of reported presumed bacterial infections between Baseline and 6 weeks after completion of radiation therapy (RT) by total number and by severity of infection, graded using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE)

- To assess the impact of SGX942 on 12 month all-cause mortality
- To assess the impact of SGX942 on progression free survival through 12 months

2 STUDY DESIGN

Approximately 260 patients will be enrolled into this Phase 3, placebo-controlled, double-blind, multinational study to evaluate the efficacy of SGX942 compared to placebo in treating the duration of SOM in patients receiving chemoradiation therapy (CRT) for the treatment of head and neck cancer (HNC). The study sample size takes into account the recommendation of the study Data Monitoring Committee (DMC) to increase the study sample size to 260 subjects. Up to an additional 10% may be enrolled to offset the impact of study dropouts (i.e., those subjects that do not receive 55 Gy radiation) and missing data which are each expected to potentially increase during the COVID-19 pandemic.

Patients will be randomized into one of two groups (1.5 mg/kg SGX942:Placebo) at a 1:1 ratio. They will be stratified by site, presence of gastrostomy tube, and human papilloma virus (HPV) status. Patients will receive their initial blinded intravenous (IV) study drug (1.5 mg/kg SGX942 or placebo) within 3 days following the initiation of RT.

The primary efficacy outcome for this study is the duration of SOM, defined as the number of days from the first oral examination with a WHO Grade assessment of 3 or 4 through the first day that a WHO Grade of <3 is recorded with no subsequent assessments ≥3 through the 6-week post-RT visit. Oral mucositis (OM) will be evaluated using the WHO score for OM.

Patients will be screened to assess their eligibility prior to randomization. After randomization, subjects will begin treatment with study drug within 3 days following the initiation of RT.

Patients will receive study drug while undergoing CRT and continue to receive study drug for 2 weeks after the completion of their RT. Dosing will be twice weekly. Study visit days will be every third day (+/-1 day). On study visit days, patients will receive the 4-minute infusion of study drug. Study drug will not be given on the same day as chemotherapy. Study drug can be given at any time during the visit day, but must occur on the same calendar day that is the study visit day. The twice weekly study drug treatment visit calendar extends to 2 weeks post-completion of RT.

Efficacy will be further assessed at the 3 through 6 weeks post-RT completion visits. Follow-up visits will be conducted at 6 and 12 months after the last radiation dose to continue to evaluate safety and secondary endpoints.

Figure 1 summarizes the overall study design and Table 1 outlines the study schedule of procedures and assessments. The study week designations assume a 7-week CRT schedule. These times may require adjustment (as described below) if the treatment course is shorter or if treatment breaks prolong the CRT for more than 7 weeks.

Figure 1: Study Schema

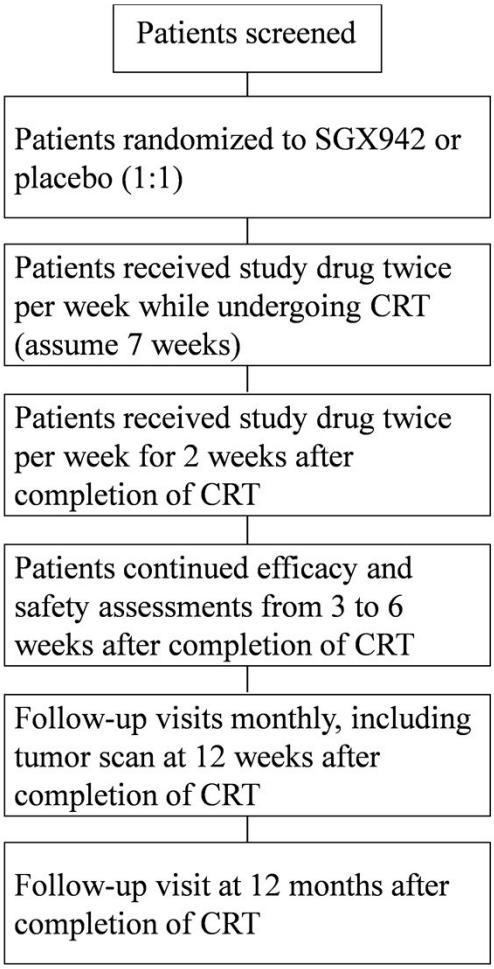


Table 1: Schedule of Events by Week

Study week	Screen	Base[2]	1w[3]	2w	3w	4w	5w	6w	7 w	8w	9w	10w	11w	12w	13w	15- 55 w	19w	59w
Post-RT[1]										1w	2w	3w	4w	5w[4]	6w	2m-11 m[5]	12w	12m
Medical History	X	X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X	X	X	X
Informed Consent	X																	
Randomization		X																
History of Pain and Opioid Use		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X		X	X
Assessment of Infections		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X			
Radiation[6]			5X	5X	5X	5X	5X	5X	5X									
Cisplatin[6]			X			X			X									
Administer Drug			2X	2X	2X	2X	2X	2X	2X	2X	2X							
WHO OM[7]		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X			
PEG Tube Use		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X			
VS[8]	X	X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X			
Physical Exam	X	X									X[13]				X			
Safety Labs[9]	X	X[12]			X			X			X[13]		X		X			
AEs		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X	X	X	X			
Tumor Scan[10]	X[11]																X	X
Serum Pregnancy	X	X[12]													X			
HPV Status	X[11]																	
Quality of Life		X				X					X[13]							

[1] Post-RT = time from the last radiation therapy treatment
[2] Baseline information needs to be obtained prior to (0 to 96 hours before) the first dose of study drug
[3] w = weeks
[4] Only to be done if WHO score is ≥2 at Week 4 Post-RT visit
[5] m = months; patient contact (clinic visit, telephone, or email) required monthly through the 12-month clinic visit
[6] Timing of radiation and chemotherapy at discretion of primary care physicians
[7] WHO OM = oral mucositis grading with WHO Oral Mucositis Grading system
[8] Vital signs to include temperature, weight, pulse, respirations, and seated blood pressure; Height will be obtained at Baseline only
[9] Safety labs = hematology and clinical chemistry panels

[10] Scan = obtain initial staging CT/PET/MRI scans (screening scan must be within 6 weeks prior to Baseline)
[11] Need to confirm that the initial diagnostic scans were CT, PET, or MRI and the tumor was tested for HPV status
[12] Repeat test required if Baseline sample >7 days from Screening
[13] To be done only on the second visit in week 2 post-RT

2.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy outcome for this study is the duration of SOM through the 6-week post-RT visit, defined as the number of days from the first oral examination with a WHO Grade assessment of ≥3 until the first time the patient has a WHO Grade of <3 is recorded with no subsequent readings ≥3. (mITT population).

2.2 SECONDARY EFFICACY ENDPOINTS

2.2.1 Hierarchical Sequential Secondary Endpoints

Multiple endpoints in this trial are expected to be clinically important. To maintain the nominal p-value, the following five secondary endpoints will be tested in a fixed sequence, hierarchical test procedure. In this procedure, a sequential comparison of the groups for each endpoint will be calculated with unadjusted p-values. If the test is statistically significant, the null-hypothesis that the groups are the same will be rejected and testing of the next endpoint will be done. Once an analysis has a p-value above the threshold, no further endpoints will be formally tested. All 5 analyses will be conducted in the mITT population.

1. Comparison of the AUC for SOM (WHO Grade ≥3) by time plot (severity-weighted duration)
2. Comparison of the AUC for UOM (defined as WHO Grade ≥2) by time plot (severity-weighted duration)
3. Comparison of the incidence of SOM
4. Comparison of the quality of life assessment using the EORTC QLQ-C30 and QLQ-H&N43 instrument
5. Comparison of the total amount of opioids used

2.2.2 Other Secondary Endpoints

- Comparison of the cumulative number of days of RT breaks (mITT population)
- Comparison of the duration of SOM; in all randomized patients receiving fractionated RT and concomitant cisplatin chemotherapy, given as 80-100 mg/m^2 (ITT population)
- Comparison of the duration of UOM (mITT population)
- Comparison of the cumulative amount of pain reported by patients (mITT population)

2.3 SAFETY ENDPOINTS

- Comparison of the incidence, type, and body system categorization of AEs
- Comparison of the incidence, type, and body system categorization of SAEs
- Comparison of the changes from Baseline for hematology parameters, clinical chemistry parameters, and vital signs
- Comparison of tumor status at 12 weeks and 12 months following completion of RT categorized using the RECIST [1.1] criteria
- Comparison of the incidence and severity of reported infections assessed by CTCAE grading
- Comparison of all-cause mortality through 12 months follow-up
- Comparison of progression-free survival through 12 months follow-up

2.4 STUDY ENDPOINT DEFINITION

2.4.1 Oral Mucositis (OM) Grading

OM will be evaluated by personnel trained in the use of the WHO Oral Mucositis Grading system which includes both physical and functional information. This grading system is widely utilized in OM clinical research trials including the SGX942 Phase 2 trial and is shown in Table 2.

Table 2: WHO Oral Mucositis Grading System

Score	Findings
0	No findings OR Pain or erythema (not both)
1	Pain and erythema AND No ulcer
2	Ulcer and/or pseudomembrane, AND Able to eat solid food AND Able to drink
3	Ulcer and/or pseudomembrane, AND Not able to eat solid food AND Able to drink
4	Ulcer and/or pseudomembrane, AND Not able to eat solid food AND Not able to drink

Only medical personnel at the site who have undergone training and certification in using the WHO Grading system will perform the OM assessments.

2.4.2 Tumor Status

The tumor response to treatment will be used as a safety endpoint. Results at 12 weeks and 12 months post-RT will be compared to the Screening results using the RECIST 1.1 system. The evaluation criteria for the target lesion (the primary head and neck carcinoma) are shown in Table 3; the criteria for non-target lesions are shown in Table 4; and the criteria for overall categorization of the tumor status are shown in Table 5. In addition, details pertaining to recurrence of disease, additional therapy, or surgery required after the active treatment phase of the trial is completed will be collected and recorded in the electronic case report form (eCRF) throughout all follow up visits until 12 months (±28 days) following the last RT treatment.

Table 3: RECIST Evaluation of the Target Lesion

Target Lesion Response	Measurement
Complete Response (CR)	All target lesions gone
Partial Response (PR)	>30% decrease from baseline
Progressive Disease	>20% increase from smallest sum of longest diameter recorded since treatment started (best response)
Stable Disease (SD)	Neither Progressive Disease nor Partial Response

Table 4: RECIST Evaluation of the Non-target Lesion

Target Lesion Response	Measurement
Complete Response (CR)	All non-target lesions gone Tumor markers gone
Stable Disease (SD)	Persistence of ≥1 non-target lesion Tumor marker level elevated
Progressive Disease	Enlargement of non-target lesions

Table 5: Overall RECIST Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	Complete Response
CR	SD	No	Partial Response
PR	Non-Progressive Disease	No	Partial Response
SD	Non-Progressive Disease	No	Stable Disease
Progressive Disease	Any	Yes or No	Progressive Disease
Any	Progressive Disease	Yes or No	Progressive Disease
Any	Any	Yes	Progressive Disease

3 STATISTICAL CONSIDERATIONS

3.1 SAMPLE SIZE CALCULATION

Sample size assessments are based on testing the hypothesis of superiority with a two-sample log rank test using the median duration of SOM, an equal allocation ratio, a 90% power (1-β), and an α level of 0.05. In the Phase 2 clinical trial, the median duration of SOM was 30 days in the placebo group and 10 days in the 1.5 mg/kg SGX942 treatment group. Because of the variability of reported results for SOM in the patient population, a conservative assumption was made that the median duration of SOM among patients receiving a minimum of 55 Gy of cumulative radiation will be 13 days in the placebo group and 8

days in the SGX942 group. Using this assumption, approximately 95 evaluable patients per arm (190 patients total) were to be randomized.

[redacted]

3.2 ANALYSIS POPULATIONS

3.2.1 Safety Population

The safety population is defined as all subjects who received at least one dose of study drug. Subjects will be analyzed based on the treatment received.

3.2.2 Intent-to-treat (ITT) Population

The ITT population is defined as all subjects who were randomized to study drug and received at least one dose of study drug. Subjects will be analyzed based on the treatment assigned.

3.2.3 Modified Intent-to-treat (mITT) Population

The mITT population is defined as all randomized subjects who received at least one dose of study drug and at least 55 Gy of cumulative radiation therapy. Subjects will be analyzed based on the treatment assigned.

3.2.4 Per Protocol (PP) Population

The PP population is defined as all randomized patients who received at least a 55 Gy cumulative dose of radiation and at least 10 doses of study drug without major or important protocol deviations. Subjects will be analyzed based on the treatment received.

Major or important protocol deviations are defined as follows:

- Received any of the following prohibited concomitant medications during the active-treatment portion of the trial (baseline through 6 weeks post-radiation treatment):
  - GM-CSF (e.g., Leukine®)
  - IL-11 (e.g., Neumega®)
  - Low level laser therapy
  - Other investigational agents for mucositis
- Had breaks in study drug administration of more than 8 days between successive doses, including any final missed doses
- Received any incorrect study drug vial treatments

3.3 METHODOLOGY AND CONVENTIONS

Safety and efficacy data will be summarized and presented by treatment group (SGX942 and placebo) in summary tables. Continuous variables will be presented by descriptive statistics including n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be tabulated by frequency count and percentage.

Unless otherwise stated, all statistical tests will be two-sided hypothesis tests performed at the 5% level of significance for main effects, and all confidence intervals will be two-sided 95% confidence intervals. All analyses will be performed using SAS® Version 9.3 or higher.

3.4 ADDITIONAL DATA HANDLING RULES AND PRESENTATION SPECIFICATIONS

The following general guidelines will apply to all statistical analyses and data presentations:

- Baseline is defined as the last available value obtained prior to the first dose of study drug, radiation and chemotherapy but within 96 hours of the initial drug treatment unless otherwise specified in this SAP.

  Systeme Internationale (SI) units will be used for laboratory value presentations.
  Age is calculated as of date that the informed consent form was signed.
  - age = the integer part of ((date of informed consent – birth date+1)/365.25)

  Body weight, height and temperatures will be converted using the following formula:
  - kg = lb/2.2
  - cm = 2.54 x in
  - °C = (5/9) x (°F – 32)

  All percentages will be rounded to one decimal place and lined up by the decimal place. The percentage will be suppressed when the count is zero.

  Any p-values will be rounded to three decimal places and will be presented as '<0.001' if they are less than 0.001 after rounding.

  For continuous variables that are recorded as "<X" or ">X", the value of "X" will be used in the calculation of summary statistics. The original values will be used for the listings.

  Decimal places will be presented as follows:
  - n: integer
  - minimum and maximum: same precision as in the database
  - mean and median: one more decimal place than minimum and maximum
  - standard deviation: two more decimal places than minimum and maximum

4 SUBJECT DISPOSITION

The following subject data will be summarized:

- Number of subjects screened
- Number of subjects randomized but not treated
- Number and percentage of subjects in each analysis population
- Number and percentage of subjects who completed or prematurely discontinued. Subjects who prematurely discontinued the study will be summarized by primary reason for discontinuation.

5 PROTOCOL DEVIATIONS

All instances of protocol non-compliance (protocol deviations [PDs]) will be tracked during study monitoring. Major PDs will be summarized by treatment group and category. Major PDs are those which may have an impact on the safety or protection of the subject, or impact the overall quality of the data. They may include, but are not limited to:

- Failure to obtain informed consent
- Failure to report an SAE
- Subject did not meet inclusion/exclusion criteria
- Drug dispensing/dosing errors

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters and important baseline characteristics will be summarized by treatment group for the Safety, PP, ITT and mITT populations. Baseline characteristics include but may not be limited to age, age group, sex, country, ethnicity, race, weight, height, body mass index (BMI), HPV status, and presence of a gastrostomy tube at randomization.

Descriptive statistics of baseline values for other parameters such as vital signs, laboratory values, and efficacy parameters will be summarized with the post-baseline values in the corresponding safety and efficacy tables.

7 MEDICAL HISTORY

Medical history will be coded using Medical Dictionary for Regulatory Affairs (MedDRA) version 20.0. Coded medical history terms will be summarized by system organ class (SOC) and preferred term (PT) for the Safety and mITT populations. At each level of summarization, subjects will only be counted once if multiple history items were recorded.

8 PRIOR AND CONCOMITANT MEDICATIONS

The World Health Organization Drug Dictionary (WHO Drug) version B3 2018 March 1st will be used to classify prior and concomitant medications by therapeutic class and generic name. Prior medication is defined as any medication taken prior to the first dose date of the study medication. Concomitant medication is defined as any medication taken between the day of first dose of the study medication or start of CRT (whichever is earliest) and 6 weeks after completion of RT. Medications taken before the first dose date and continued on or after the first dose date are categorized as both prior and concomitant medications.

Prior and concomitant medications will be summarized by the Anatomical Therapeutic Chemical (ATC) classification level 3 and generic name for the Safety and mITT populations. At each level of summarization, subjects will only be counted once if multiple drugs in that category are used.

Please see Appendix 1 for data handling conventions for any missing medication dates.

9 EFFICACY ANALYSES

Efficacy will be conducted in the mITT population unless otherwise specified. Sensitivity analyses will include the same assessments in the ITT and PP populations.

9.1 ANALYSIS OF PRIMARY ENDPOINT

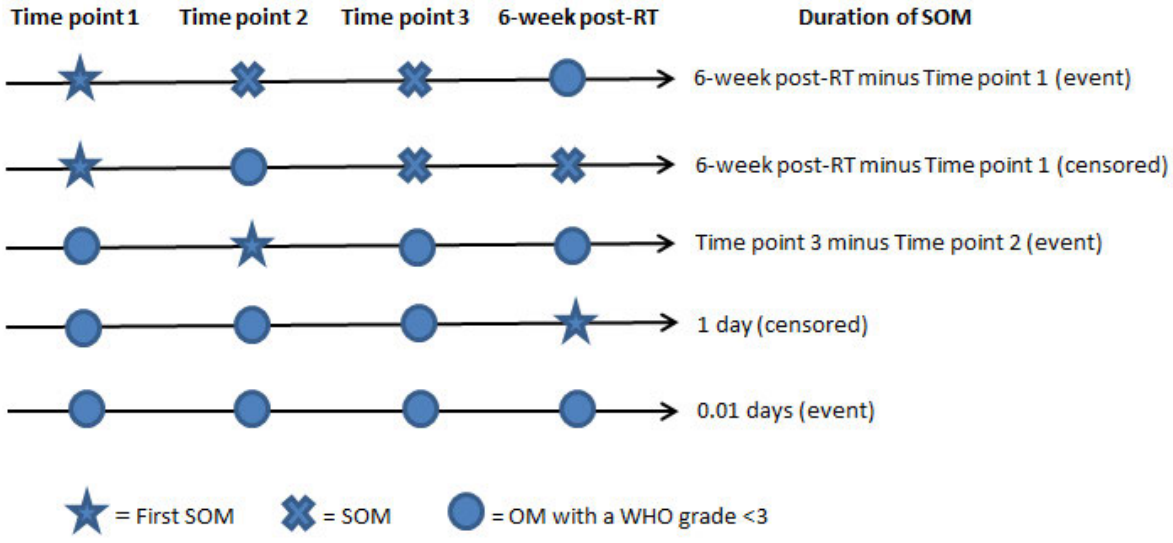
As detailed in Table 2, the clinical evaluation of mucositis will be performed and graded by trained study evaluators in accordance with the WHO Oral Mucositis Grading system at each study drug administration visit and for Week 3 through Week 6 post-RT.

SOM is defined as OM with WHO Grade ≥3. The duration of SOM is defined as the number of days from the first WHO score ≥3 to the first day with a WHO score <3 with no further occurrence of a WHO score ≥3. A log-rank test will be used to compare the duration of SOM of the two treatment groups.

Resolution of SOM is defined as the first assessment with a WHO score <3 with no further reports of a WHO grade of ≥3. If the patient has not met the requirements for resolution of SOM by the 6-week post-RT visit, he/she will be considered censored at that visit (or the point of discontinuation from the study, if the patient discontinues prior to that time point). For statistical reasons, patients who do not experience SOM will be treated as having a duration of 0.01 days.

Possible scenarios for onset of SOM are displayed below in Figure 2, along with the derivation of duration of SOM.

Figure 2: Duration of SOM (Primary Analysis)

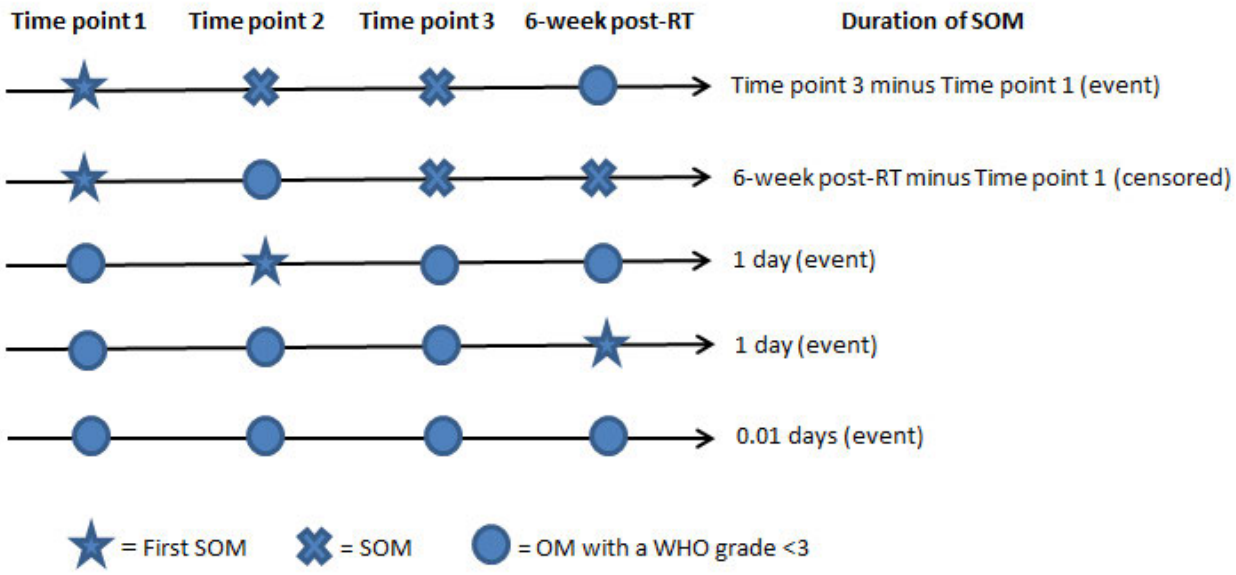


9.2 SENSITIVITY ANALYSIS OF PRIMARY ENDPOINT

The same statistical method as for primary analysis will be used for sensitivity analysis, however, duration of SOM will be calculated from the first time the patient has a SOM to the last time the patient has a SOM. For statistical reasons, patients who do not experience SOM will be treated as having a duration of 0.01 days.

Possible scenarios for onset of SOM are displayed below in Figure 3, along with the duration of SOM.

Figure 3: Duration of SOM (Sensitivity Analysis)



9.3 ANALYSES OF SECONDARY ENDPOINTS

9.3.1 Hierarchical Secondary Endpoints

Multiple endpoints in this trial are expected to be clinically important. To control type 1 error, the following five secondary endpoints will be tested in a fixed sequence, hierarchical test procedure. In this procedure, a sequential comparison of the groups for each endpoint will be calculated with unadjusted p-values. If the test is statistically significant, the null-hypothesis that the groups are the same will be rejected and testing of the next endpoint will be done. Once an analysis has a p-value above the threshold, no further endpoints will be formally tested. All 5 analyses will be conducted in the mITT population. The hierarchical orders of these endpoints are:

1. Comparison of the AUC for SOM (WHO Grade ≥3) by time plot (severity-weighted duration)
2. Comparison of the AUC for UOM (defined as WHO Grade ≥2) by time plot (severity-weighted duration)
3. Comparison of the incidence of SOM
4. Comparison of the quality of life assessment using the EORTC QLQ-C30 and QLQ-H&N43 instrument
5. Comparison of the total amount of opioids used

9.3.2 Other Secondary Endpoints

- Comparison of the cumulative number of days of RT breaks (mITT population)
- Comparison of the duration of SOM; in all randomized patients receiving fractionated RT and concomitant cisplatin chemotherapy, given as 80-100 mg/m^2 (ITT population)
- Comparison of the duration of UOM (mITT population)
- Comparison of the cumulative amount of pain reported by patients (mITT population)

9.4 ENDPOINT CALCULATIONS

The procedures for calculating these endpoints are given below.

9.4.1 Severity-weighted Duration of OM (Area-Under the OM-Time Curve)

The severity-weighted duration of OM (either SOM or UOM) will be calculated by the AUC of the OM versus time curve. This will be calculated by the formula from baseline (t_a) to the time of the last reported WHO score recorded (t_b):

$$AUC(t_b - t_a) = \sum_{i=a}^{b-1} \frac{(y_i + y_{i+1})(t_{i+1} - t_i)}{2}$$

where t_i represents the date of the i^{th} WHO assessment, and y_i represents the value of the i^{th} WHO assessment for WHO assessments for which the score is ≥3 (for SOM) or ≥2 (for UOM). The WHO score for the $(i+1)^{th}$ assessment does not need to be ≥ 3 (for SOM) or ≥2 (for UOM) but will be assigned a value of 0 if it is <3 (for SOM) or <2 (for UOM). If a patient experiences SOM or UOM at the 6-week post-RT visit (the last time point at which OM is measured), the AUC of that visit will be counted as 0. The AUC of SOM or UOM will be compared between treatment groups using a one-way ANOVA test.

9.4.2 Duration of SOM in the ITT Population

Using the same definition and statistical method as for primary endpoint, the duration of SOM will be compared between treatment groups in the ITT population.

9.4.3 Duration of UOM

UOM is defined as a WHO score ≥2. The duration of UOM is defined as the number of days from the first WHO score ≥2 to the first day with WHO score <2 with no further occurrence of WHO score ≥2. A log-rank test will be used to compare the duration of UOM between the two treatment groups.

Resolution of UOM is defined as the first assessment with a WHO score <2 with no further reports of a WHO grade of ≥2. If the patient has not met the requirements for resolution of UOM by the 6-week post-RT visit, he/she will be considered censored at that visit (or the point of discontinuation from the study, if the patient discontinues prior to that time point). For statistical reasons, patients who do not experience UOM will be treated as having a duration of 0.01 days.

9.4.4 Incidence of SOM

The incidence of SOM will be calculated as the percent of patients within each treatment group who have at least one WHO score ≥3. The incidence of patients with SOM will be compared between treatment groups using the chi-square test.

9.4.5 Quality of Life

A Quality of Life Questionnaire will be completed by each patient at Baseline, 4 weeks and end of study drug treatment (2 weeks post-RT). The EORTC QLQ-C30 (version 3) and the EORTC QLQ-H&N43 instrument will be used for these assessments. 12 multiple-item scales (fear of progression, body image, dry mouth and sticky saliva, pain in the mouth, sexuality, problems with senses, problems with shoulder, skin problems, social eating, speech, swallowing, and problems with teeth) and 7 single-

item scales (coughing, lymphoedema, neurological problems, trismus, social contact, weight loss, and problems with wound healing) will be computed and summarized by visit, including change from baseline.

9.4.6 Cumulative Treatment Break Duration

The cumulative duration of treatment breaks for each patient will be calculated by summing the actual number of treatment break days (≥3 days break) through the final RT treatment and will be compared between treatment groups using a one-way ANOVA test.

9.4.7 Incidence of UOM

The incidence of UOM will be calculated as the percent of patients within each treatment group who have at least one WHO score ≥2. The incidence of patients with UOM will be compared between treatment groups using the chi-square test.

9.4.8 Assessment of Pain

At each study visit, the patient's assessment of their pain over the previous 24 hours will be recorded by study personnel using a scale of 1-10. Descriptive statistics of pain assessments will be summarized by visit, including change from baseline. The Wilcoxon rank sum test will be used to compare the pain scale between treatment groups at each visit.

9.4.9 Amount of Opioid Medication Used

At each study visit, study personnel will record the amount of opioid medication that the patient reports having taken over the previous 24 hours. Type and usage of medication will also be collected. Descriptive statistics of the amount of opioid medication used, normalized to a calculated oral morphine equivalent, will be summarized by visit. Total opioid used will be summarized though the treatment period (baseline through 6 weeks post-radiation treatment) and compared between treatment groups. Values will be compared between treatment groups using a one-way ANOVA test. Mean ± standard deviation will be plotted for each visit.

10 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. Safety parameters include adverse events (AEs), laboratory parameters, vital signs, infections, assessment of tumor progression, and assessment of mortality and assessment of progression-free survival.

10.1 ADVERSE EVENTS

Adverse events will be coded using MedDRA version 20.0. An overall summary of AEs will present the frequency and percentage of patients with AEs, treatment-emergent AEs (TEAEs), TEAEs leading to discontinuation of study, TEAEs leading to death, and SAEs. A TEAE is defined as an AE that is new in onset or aggravated in severity or frequency following the first study drug administration and reported between randomization through the 6 week post-RT visit or 4 weeks post last study drug infusion, whichever is longer. An SAE is defined as an AE that results in any of the following outcomes:

- Death
- A life-threatening AE

- Prolongation of existing hospitalization or subsequent need for hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medical or surgical intervention to prevent one of the above

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by ***(1) SOC and PT***, ***(2) by SOC, PT, and severity***, and ***(3) by SOC, PT, and relationship to study drug***. If more than one event occurs with the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug, respectively. AEs with missing severity and relationship to the study drug will be treated as "severe" and "related" respectively. In addition, the number and percentage of patients reporting SAEs in each treatment group will be tabulated by SOC and PT. AEs that started before the first study drug administration will be included in listings but not in summaries.

If there are any missing dates for AEs, please see Appendix 1 for data handling conventions.

10.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for laboratory values (in SI units) and changes from baseline at each assessment time point will be presented by treatment group for the following laboratory parameters:

- Serum pregnancy test: human chorionic gonadotropin (HCG)
- Hematology: red blood cell count (RBC), hematocrit, hemoglobin, RBC indices, platelet count, white blood cell count (WBC), and WBC differential count
- Chemistry: serum sodium, serum potassium, serum chloride, serum bicarbonate (CO_2), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, total protein, serum creatinine, and blood urea nitrogen (BUN)

Laboratory values will be classified as "normal", "low", or "high" based on the central laboratory's normal ranges. Shift tables for each parameter will be tabulated by treatment group.

10.3 VITAL SIGNS

Descriptive statistics for vital sign values and their changes from baseline at each visit will be presented by treatment group for the following vital sign parameters:

- Heart rate
- Respiratory rate
- Temperature
- Blood pressure (seated)
- Weight

Vital sign values will be classified as "normal", "low", or "high" based on standard criteria listed in Table 6 below. Shift tables for each parameter will be tabulated by treatment group.

Table 6: Standard Criteria for Vital Signs

Vital Sign Parameter	Criteria	Observed Value
Heart Rate (beats per minute)	High	≥ 100
	Low	≤ 60
Respiratory Rate (breaths per minute)	High	≥ 20
	Low	≤ 12
Systolic Blood Pressure (mm Hg)	High	≥ 140
	Low	≤ 85
Diastolic Blood Pressure (mm Hg)	High	≥ 90
	Low	≤ 50

10.4 ASSESSMENT OF TUMOR PROGRESSION

Scans at 12 weeks and 12-months post-RT will be compared to the initial images using the RECIST 1.1 system as outlined in Tables 3, 4, and 5 and compared for overall classification as well as the target and non-target lesion evaluations. The number and percentage of patients in each overall response category will be summarized by treatment group.

10.5 INFECTIONS

Patients will be assessed at each clinical visit through the 6-week post-RT visit as to the presence of probable clinical infections. All clinical diagnoses of infections will be classified as presumed fungal, presumed viral, or presumed bacterial. The severity of each infection will be graded using the CTCAE (see protocol appendix 1).

The number and percentage of patients with any reported infections, presumed fungal infections, presumed viral infections and presumed bacterial infections will be summarized by treatment group. The incidence of patients with all reported infections and each type of infection (fungal, viral, bacterial) by severity grade (1-5) will be displayed.

10.6 ASSESSMENT OF MORTALITY

All deaths through the 12-month follow-up visit will be collected. The number of deaths in each treatment group will be compared using a standard chi-square analysis. Time to death and the cumulative probability of death will be summarized using Kaplan-Meier estimates. In addition, a log-rank test will be used to compare the survival distributions between treatment groups. Kaplan-Meier survival curves will be plotted for both treatment groups.

10.7 PROGRESSION-FREE SURVIVAL

The date that a patient's cancer progress, defined by a diagnosed with a new cancer, recurrent cancer or initiates more chemotherapy, will be collected on a monthly basis. Progression-free survival will be calculated from the time of enrollment to the earliest of date of cancer progression, death, or 12 months. If a subject drops out, withdraws or is terminates participation study early for some other reason, the subject will be censored at the last know status. Kaplan-Meier progression free survival curves with be constructed for the treatment groups and the curves compared using a log-rank test.

APPENDIX 1: DATA HANDLING CONVENTIONS

1. IMPUTATION RULES FOR START DATES

The following imputation rules apply to incomplete start dates of adverse events and medications.

Whole date is missing
The date of first study drug administration will be assigned to the missing fields.

Missing day and month
- If the year is same as the year of the first study drug administration, then the day and month of the first study drug administration will be assigned to the missing fields.
- If the year is prior to the year of the first study drug administration, then December 31 will be assigned to the missing fields.
- If the year is after the year of the first study drug administration, then January 1 will be assigned to the missing fields.

Missing month only
Treat day as missing and replace both month and day according to the above procedure.

Missing day only
- If the month and year are same as the year and month of the first study drug administration, then the date of the first study drug administration will be assigned to the missing day.
- If the month and year are before the year and month of the first study drug administration, then the last day of the month will be assigned to the missing day.
- If the month and year are after the year and month of the first study drug administration, then the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the end date, the end date will be imputed for the start date.

2. IMPUTATION RULES FOR END DATES

The following imputation rules apply to incomplete end dates of medications.

Whole date is missing
The date of last study drug administration will be assigned to the missing fields.

Missing day and month
- If the year of the incomplete end date is the same as the year of the last study drug administration, then the day and month of the last study drug administration will be assigned to the missing fields.

- If the year of the incomplete end date is prior to the year of the last study drug administration, then December 31 will be assigned to the missing fields.
- If the year of the incomplete end date is after the year of the last study drug administration, then January 1 will be assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure.

Missing day only

- If the month and year of the incomplete end date are the same as the month and year of the last study drug administration, then the day of the last study drug administration will be assigned to the missing day.
- If the month and year are before the year and month of the last study drug administration, then the last day of the month will be assigned to the missing day.
- If the month and year are after the year and month of the last study drug administration, then the first day of the month will be assigned to the missing day.

3. DERIVATION RULES OF NUMERIC VALUES OF CLINICAL LABORATORY PARAMETERS

If a character string (">x", "<x" or "=x") is reported for a parameter of the numerical type, the numeric part of the value ("x") will be derived and used in the statistical analyses. However, the actual values as reported in the database will be presented in data listings.

4. MISSING DATA FOR SOM DURATION CALCULATIONS

As noted above (Section 9.1), the primary analyses will examine the duration of SOM and censor the patient's data when missing. For clarity, censored visits will carry forward the last WHO score recorded for the subject through to discontinuation. For sensitivity analyses, the data will be analyzed assuming that the SOM remains at the last recorded WHO grade for the entire trial (irrespective of early study termination) and, again, assuming that the SOM was 0 throughout the trial period.

5. ANALYSIS ADJUSTMENTS DUE TO IMPACT OF COVID-19 PANDEMIC

Reference is made to the FDA Guidance for Industry, "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency," June 2020. While many of the patients were in the treatment portion of their participation, the COVID-19 pandemic interrupted normal clinical operations with an impact on patient retention, the number and degree of protocol deviations, the ability to obtain protocol specified measurements, the ability to ship clinical specimens, and decreased the availability of clinical research personnel to perform protocol related activities. The ultimate impact of this unprecedented disruption in the clinical trial and the resulting number of dropouts, missing data, and partial data remains unclear at this time, Currently, the protocol specifies a last-value forward method of handling missing data and all patients in the mITT population are included in the analyses even if the final 4-6 weeks of experimental therapy is not delivered. To address the impact of the pandemic on this study, we will:

- Drop patients at specific sites in which the COVID-19 activities created extensive problems with documentation, data collection and/or patient enrollment and compliance;
- Terminate the trial early; and

- Conduct sensitivity analyses on primary, secondary and safety analyses to understand the potential impact of the pandemic (with an assigned "start date" to the pandemic of January 1, 2020 based on the onset of disease potentially impacting participating European sites).